MONOGRAPH OF

FLIGHT ATTENDANT

MEDICAL RESEARCH

INSTITUTE

FUNDED RESEARCH

2002-2023

FOREWORD

David Sidransky, MD, Chairman, FAMRI's Medical Advisory Board, Johns Hopkins School of Medicine

Presented here is FAMRI's 2023 Monograph, which contains synopses of its funded projects beginning in 2001. FAMRI has awarded almost 600 grants, including five Centers of Excellence and twenty Distinguished Professors, resulting in over 4300 publications. The progress is inspiring and sets the stage for significant discoveries and better prevention, earlier detection, treatment, and cures of tobacco-related diseases.

FAMRI's rich history, which made this research possible, is a story that always merits telling as an example of what can be accomplished with vision and selfless dedication.

For decades Flight Attendants were involuntarily exposed to secondhand tobacco smoke (SHS) while at their workplace in aircraft cabins. As they became aware of their health hazards caused by exposure to tobacco smoke, they began to seek remedies, although they realized that they had formidable adversaries in the tobacco industry that had at that time never lost a lawsuit brought by people who sought redress for the health consequences of smoking. The history of FAMRI, along with videos relating its accomplishments, can be found in this website at www.famri.org .

Although the tobacco industry attorneys tried to deny the harmful health effects of smoking, they took refuge in the notion that there was no scientific evidence for health effects of exposure to tobacco smoke. In 1964, the Advisory Committee on Smoking and Health presented data to Surgeon-General Luther Terry that undermined such notion. Big Tobacco also underestimated a hardy band of Flight Attendants who knew better. They saw themselves as "canaries in the coal mines" calling attention to the growing scientific evidence for the harmful effects of exposure to SHS which were clearly established in 1986 in Dr. C. Everett Koop's Surgeon-General's Report, "The Health Consequences of Involuntary Smoking". The Flight Attendants persisted in their creative efforts to curb the tobacco industry's influence through litigation and legislation. By 1988 Congress had banned smoking on domestic flights of less than two hours; and again in 1990 for flights under six hours. Despite these successes, legal action was more difficult because the resources of the tobacco industry discouraged attorneys from acting. Fortunately, the Flight Attendants persevered, and in 1991 they found their way to attorneys Susan and Stanley Rosenblatt in Miami, Florida, who were willing to take the risk of bringing the industry to trial. After years of preparation, a Settlement in the Class Action was reached in 1997, the year when smoking on all domestic airlines was completely banned. Smoking on foreign carriers ended in 2000.

The combined perseverance and creativity of the Flight Attendants and their attorneys, along with their witnesses, made legal history. Four months into the jury trial, and after extensive negotiations with Class Counsel, the tobacco industry agreed to a settlement that provided many benefits to Flight Attendants, including $300 million allocated for the establishment of a research entity. The Rosenblatts, with court approval, formed FAMRI,

and pursuant to the settlement, they then selected the Board of Trustees, consisting of a majority of Flight Attendants.

The Medical Advisory Board (MAB), which I chair, is composed of distinguished scientists and physicians who are devoted to medical research and share FAMRI's vision of making an impact in the fight against diseases caused by unwilling exposure to tobacco smoke. These members include W. Jarrard Goodwin, MD, University of Miami Miller School of Medicine; David W. Kennedy, MD, Perelman School of Medicine, University of Pennsylvania; Mark W. Geraci, MD, University of Pittsburgh School of Medicine; and Rama Mallampalli, MD, University of Ohio School of Medicine.

Under the leadership of our first Chairman, Julius B. Richmond, MD, (1921-2008), former US Surgeon General under President Jimmy Carter and former Professor Emeritus at Harvard Medical School, the MAB took on an important role in helping to shape the structure of FAMRI's mission and the goals of its peer-reviewed research grant program. Dr. Richmond was a consummate spokesperson and ambassador of FAMRI's research endeavors. The program continues to emphasize basic and applied research into the diseases caused by SHS exposure and has successfully funded a large cadre of young scientists, as well as innovative approaches, screening programs for early detection, and other notable endeavors. Indeed, it is clear to me that lives have been saved through the screening programs at two of the Centers.

Through the work of the scientists and physicians it funds, FAMRI is making important contributions to improving public health in general and particularly that of non-smoking Flight Attendants who have developed, or are at risk of developing, the diseases of smokers. FAMRI funding has also started many new careers in the study of involuntary smoke exposure, and these investigators will perpetuate FAMRI as they continue to explore and contribute to the scientific and medical literature in this field for decades to come. The research has increased our understanding in many areas, such as the therapeutic potential of stem cells and the effects of genetic predisposition and defects in DNA repair on disease. The research has also led to the development of methods for detecting and targeting cancers early. These are just a few of many other basic scientific and translational findings that have emerged through FAMRI support. Such research provides new avenues for detecting and treating the maladies caused by tobacco exposure.

We remain very much indebted to the Flight Attendants for their courage in bringing their suit and to the remarkable legal skills and commitment of their attorneys to improving the public's health. The Flight Attendants and the attorneys who constitute the Board have carried on the tradition of the intrepid group that pursued legal action by supporting this invaluable program by approving grants surpassing $300 million.

FAMRI has lost several crucial people over the years since it was established. We lost Julius Richmond in 2008, and Flight Attendant Board members Bland Lane and Kathleen Cheney in 2007 and 2014, respectively. Both Flight Attendants died due to conditions caused by SHS exposure. In 2021, FAMRI lost Susan Rosenblatt after three years of battling a rare blood disorder. Susan was the ultimate force that formed FAMRI and crafted our united vision to bring it to fruition.

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FAMRI BOARD GOVERNANCE

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* Bland Lane (1928-2007) Flight Attendant Trustee and Class Representative

* Kathleen S. Cheney (1945-2014), Flight Attendant Trustee

Administration

Stanley M. Rosenblatt, CEO

Elizabeth A. Kress, MJ, Executive Director

Marti Gammon, Administrative Assistant

Rachel Gdanski, Program Assistant

INTRODUCTION

Elizabeth A. Kress, Executive Director of FAMRI

Flight Attendant Medical Research Institute, Inc. (FAMRI) has funded scientific work showing the health risks of secondhand tobacco smoke (SHS) exposure for more than 20 years. The large body of work chronicled here emerged from this funding, which has been instrumental in the elimination of tobacco smoking from many public places, resulting in improved public health and environmental conditions, both nationally and on the world stage. FAMRI was formed from a settlement of a class action lawsuit, known as the Broin Trial, brought in 1991 on behalf of non-smoking Flight Attendants who suffered health effects from their exposure to tobacco smoke in their workplace-airline cabins, which were essentially "flying ashtrays". Among other concessions, the Settlement banned smoking immediately on all domestic flights and on all international flights two years thereafter.

At a similar time in history, 46 U.S. states and 5 territory attorneys general brought a lawsuit against the tobacco industry that transformed tobacco control. The money awarded by the Master Settlement Agreement (MSA) served as compensation for taxpayer money that had been spent in connection with tobacco-related diseases and the loss to local economies. The MSA has been erroneously perceived as involving smoking on airlines, but the fact is that the flying public enjoys smoke-free environments due to the settlement of the Broin litigation, which also provided for the establishment of FAMRI, a research foundation to study the diseases caused by exposure to tobacco smoke, the work of which is reported herein. Read more about the Broin Trial under the menu tab "RESOURCES – Broin Trial History and Testimony Excerpts" on FAMRI's website www.famri.org.

Despite the vast body of knowledge published from the research demonstrating that exposure to SHS is detrimental to overall health, inclusion of patients' biographical data on tobacco smoke exposure history is scant in the electronic health record (EHR). The inclusion of this information would facilitate earlier diagnoses and treatments, ultimately leading to reduced health care costs and improved general health of the population. Some progress along these lines has occurred, but so much more could be achieved.

Questions regarding patients' exposure to secondhand tobacco smoke on EHR intake forms are crucial. These questions should include biographical information on the length and depth of such exposure. People continue to need to know the dangers, not only of smoking cigarettes, but also to the dangers inherent in exposing innocent bystanders. Further, the public needs to be made aware of these dangers so that patients can inform their health care providers of their life-long exposure as another way to enhance the chance of earlier and better diagnoses and treatments.

FAMRI continues to honor Susan Rosenblatt's vision for funding novel scientific research to find early diagnoses and cures for diseases caused from exposure to tobacco smoke. Susan, who co-founded FAMRI with her husband and law partner, Stanley Rosenblatt, was a FAMRI Trustee who succumbed to a rare blood cancer in 2021.

FAMRI IMPACT ON NON-SMOKING ACHIEVEMENTS: AN UPDATE

Elizabeth A. Kress, Executive Director of FAMRI

What has been FAMRI's impact on society worldwide regarding the science of secondhand tobacco smoke exposure? After formation in 2000, FAMRI's program began funding scientific studies in 2001, which expanded changes on how tobacco smoke exposure, especially on the non-smoker, is viewed, even by smokers. Internal Revenue Code Restrictions about advocacy by private foundations and conditions of the Broin Case Settlement Agreement restricts FAMRI from funding advocacy; however, FAMRI has contributed immensely to the understanding of the perils of secondhand smoke exposure via the formation of its research program.

The formation of this $300,000,000 research entity, FAMRI, was a key part of the Settlement, which began funding in 2001. By 2003, scientific evidence began to emerge that has had a significant impact on the elimination of cigarette smoke in public places. This evidence, which continues to be a catalyst for change, provides the public health sector and advocacy groups with the proof needed to effect changes in laws regarding smoking in public places. Prior to FAMRI funding, the scientific literature was devoid of studies into the effects of tobacco smoke on the non-smoker; now it contains more than 4,000 FAMRI-supported peer reviewed articles in prestigious journals.

Examples of FAMRI's Impact

Smoking in cars

The Julius B. Richmond Center FAMRI Center for Children at the American Academy of Pediatrics presented data from one of its initiatives about the harm children suffer from exposure to tobacco smoke while in cars. Like the Flight Attendants in smoke filled airplanes, children are individuals with no choice and no voice on the assault to their health from exposure to tobacco smoke. The report showed that legislation in some states had been passed permitting Departments of Children and Families to eliminate smoking in cars, housing, day care centers, etc., to protect foster children from being exposed. A scientist in attendance queried as to why the law didn't protect all children rather than just those in foster care. The reason is that States are *in loco parentis* of foster children with a mandate to keep them safe from harm. Using the Julius Richmond Center data, the scientist then advocated that his state enact a law to protect all children from such harm; this law was passed.

Housing and Age for buying Tobacco Products.

FAMRI's scientists provided the necessary data to bring about a ban on smoking in public housing and for laws to increase the age to purchase tobacco products from 18 to 21.

Centers of Excellence Life Saving Scans

Two FAMRI Centers of Excellence had screening programs for Flight Attendants for early detection of lung and heart diseases. Accounts from two individuals were presented at a FAMRI Annual Symposium. They had been screened at the FAMRI IELCAP Center and reported how the early detection of lung cancer and heart disease had saved their lives.

Another individual who participated in the screening program at University of California San Francisco had a similar experience. His screening revealed an early diagnosis of heart disease.

Internationally

Very soon after information from FAMRI-supported studies became available through the published literature (2004), Ireland went totally smoke free in all public places, including pubs and the exterior of the buildings. Many other countries internationally have followed the example of Ireland.

These are but a few examples of how scientific discoveries by FAMRI researchers have made differences in the world and saved lives.

SYNOPSES OF FAMRI-SUPPORTED RESEARCH 2002-2022

FAMRI CENTERS OF EXCELLENCE

FAMRI has provided funding for five Centers of Excellence since funding began in 2002. The FAMRI Center of Excellence at the Weizmann Institute of Science and the Drug Discovery Core at the FAMRI Center of Excellence at the Sidney Kimmel Comprehensive Cancer Center remain active.

FAMRI CENTER OF EXCELLENCE AT THE WEIZMANN INSTITUTE OF SCIENCE: CARE

Directors: Zvi Livneh, PhD and Varda Rotter, PhD (2004-2022); Zvi Livneh, PhD (2004-present)

The FAMRI Center for Advanced Research on Lung Cancer (CARE) was established in 2004 and is based at the Weizmann Institute of Science and the Sheba Medical Center in Israel. The long-term goals of the Center have been to elucidate the molecular genetic bases for lung cancer development and provide clues towards better diagnosis, prognosis, and therapy.

Much attention is naturally directed these days to the COVID-19 pandemic, yet tobacco-smoke related diseases are still a central health issue, and a major cause of mortality that needs to be addressed. Since smoking is considered a risk factor for SARS-CoV-2 infection, samples and clinical data were collected from COVID-19 patients in Sheba Medical Center and will be used to study the relationships among smoking, infection, and disease severity.

FAMRI SUPPORTED RESEARCH

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PRESENTATIONS AND ABSTRACTS

Cohen-Saban N, Dahan R. Effect of FcγR pathways in the therapeutic antitumor activity of human anti-PD-L1 antibodies. Presented at Next Gen Immunology. Rehovot, Ha Merkaz, Israel, Feb 2-5, 2020.

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FAMRI has funded a number of other Centers in the past as noted below.

FAMRI CENTER OF EXCELLENCE AT THE SIDNEY KIMMEL COMPREHENSIVE CANCER CENTER, JOHNS HOPKINS MEDICAL INSTITUTIONS

Directors: Charles Rudin, MD (2005-2013); Philip Cole, MD and Julie Brahmer, MD (2013-2018); Jun Liu, MD, PhD (2018-present)

The Johns Hopkins FAMRI Center of Excellence (HFCOE) was founded in 2005 and was dedicated to biomedical discovery and translation related to cigarette smoke-related disease. The HFCOE supported research in four core facilities and a variety of developmental projects. The core facilities conducted research in drug discovery, *in vivo* animal model analysis, clinical studies, and population-based exposures and outcomes. Some developmental projects included studies on telomeres and fibrosis, head and neck cancer therapies, epigenetics in lung cancer, and chemoprotection against asthma. Some of the achievements of the HFCOE researchers include the investigation of the antifungal drug itraconazole in patients with lung cancer and development of a protein small molecule conjugate for the potential treatment of immune/inflammatory lung diseases. They also discovered a new angiogenesis factor and identified some novel molecular mechanisms in pulmonary fibrosis.

The FAMRI Drug Discovery Core (DDC) was part of the original Center and continues today. The DDC provides support for the Johns Hopkins Drug Library (JHDL) Screening Center, led by Dr. Jun Liu, and the Johns Hopkins Synthetic Core Facility, led by Dr. David Meyers. Each of these components provides critical technology and resources for the FAMRI-related goals in immunology, inflammation, and stem cell translational research.

FAMRI SUPPORTED RESEARCH

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FAMRI-IELCAP CENTER OF EXCELLENCE MOUNT SINAI MEDICAL CENTER

Co-Directors: Claudia I. Henschke, PhD, MD, David Yankelevitz, MD; 2006

The FAMRI-IELCAP Screening Center began in 2005 and offered free scans to non-smoking flight attendants to screen for diseases caused by exposure to tobacco smoke, particularly among never-smoking Flight Attendants. Thirty-four sites were located throughout the United States. The grant for the Center of Excellence ended in 2018, but the need to scan Flight Attendants remained a high priority for FAMRI. In 2019, The Mount Sinai Health System was designated as the central point for continuing to the scans and provided free screenings to current and former never-smoking Flight Attendants, who flew pre-smoking ban. The screening ended in 2021 with the onset of the COVID epidemic.

FAMRI SUPPORTED RESEARCH

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THE JULIUS B. RICHMOND CENTER OF EXCELLENCE AT THE AMERICAN ACADEMY OF PEDIATRICS

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The Julius B. Richmond Center of Excellence (RCE) at the American Academy of Pediatrics (AAP) was established in 2006 and is dedicated to the elimination of children's exposure to tobacco products and SHS. The object of the Administrative Core is to eliminate SHS exposure by optimizing interactions among investigators, collaborators, and other stakeholders to maximize the reach of the AAP RCE activities and projects. The Core has coordinated RCE research and education initiatives and worked to create a healthy environment for children and adults through the translation of research, education of clinicians and the general public, and promotion of evidence-based policies to eliminate exposure to SHS.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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Gottlieb M. Understanding the spectrum of legal and regulatory approaches to smoke-free homes, and Understanding the Prevent all Cigarette Trafficking Act of 2009 on panel entitled Tobacco Sales Regulations. Presented at the Annual Meeting of the Southeastern Psychological Association. New Orleans, LA, Oct 13, 2009.

Gottlieb MA, Cheyne A, Dorfman L, Daynard RA, Friedman LC, Wilking C. Food Industry's Front of Package Labeling: Cautionary Tales from Tobacco Control. Presented at the 139th APHA Annual Meeting and Exposition, Washington, DC, Oct 29-Nov 2, 2011.

Gottlieb MA, Davidson P, Daynard RA. Acting on FDA's authority to limit nicotine in smoked tobacco products: is it a viable pathway to a smoke-free society? Presented at the 138th APHA Annual Meeting. Denver, CO, Nov 6-10, 2010.

Gottlieb MA, Daynard RA, DiFranza JR, Davidson PA. FDA authority to limit nicotine in smoked tobacco products: opportunities and obstacles for a smoke-free society. Presented at the Society for Research on Nicotine and Tobacco 2010 Annual Meeting. Baltimore, MD, Feb 24-27, 2010.

Gottlieb MA. Role of legal-medical partnerships to reduce exposure of children to tobacco smoke. Presented at the World Conference on Tobacco or Health. Mumbai, India, Mar 8-12, 2009.

Groner J, Huang H, Boettner B, Kuck J, Nagaraja H, Bauer JA. Secondhand smoke exposure and endothelial stress in children and adolescents. Presented at the2011 Pediatric Academic Societies' & Asian Society for Pediatric Research Joint Meeting. Denver, CO, Apr 30-May 3, 2011.

Groner J, Huang H, Eastman N, Lewis LM, Kuck J, Schanbacher BL, Hoffman R, Bauer JA. Oxidative stress in youth and adolescents exposed to secondhand smoke. Presented at the 2013 Pediatric Academic Societies Annual Meeting. Washington, DC, May 4-7, 2013.

Groner J. Childhood antecedents of adult heart disease – tobacco smoke exposure and obesity. Presented at the 53rd Annual Meeting of the Midwest Society for Pediatric Research. Columbus, OH, Oct 5, 2012.

Groner J. Electronic Cigarettes and Vaping—What you and your patients don't know can hurt them. Presented at the Science Symposium, Pediatric Academic Societies annual meeting. San Francisco, CA, May 6-9, 2017.

Groner JA, Huang H, Nicholson L, Bauer, JA. Secondhand smoke exposure and pre-clinical cardiovascular risk in toddlers. Presented at the Pediatric Academic Societies annual meeting. San Francisco, CA, May 6-9, 2017.

Groner JA. A Seminar on Vaping. Presented at the Central Ohio Breathing Association, 2019.

Groner JA. E-cigarettes and Juul. Presented at the Central Ohio Pediatric Society, 2019.

Groner JA. Smoking Cessation and Facts on E-cigarettes. Lecture for Pediatric Residents, Nationwide Children's Hospital Fast Facts. 2019.

Gundel L, Martins-Green M, Jennifer Logue J, Winickoff JP. Thirdhand cigarette smoke: chemistry, exposure, toxicity, risk assessment and policy implications. Presented at the 2014 SRNT Annual Meeting. Washington, DC, Feb 5-8, 2014.

Hahn A, Groner J, Eaton A. Target Tobacco – A pilot quality improvement project at Nationwide Children's Hospital. Presented at the Pediatric Academic Societies' Meeting. Vancouver, BC, Canada, May 1-4, 2010.

Hahn A, Groner J, Eaton A. Target Tobacco – A quality improvement project at Nationwide Children's Hospital. Presented at the Celebration of Educational Scholarship' at the Ohio State University College of Medicine, Center for Education and Scholarship. Columbus, OH, Nov 17, 2010.

Hahn A, Groner JA, Eaton A. Target Tobacco – A Pilot Quality Improvement Project at Nationwide Children's Hospital - Update 2010. Presented at the APA Region V Meeting. Grand Rapids, MI, Mar 10, 2011.

Harris C, Buffington A, McMillen R. State-wide tobacco reporting and progress system (TRAPS). Presented at the National Conference on Tobacco or Health. Austin TX, Mar 22-24, 2017.

Harris DL, Gorzkowski JA, Kaseeska KR, Bocian AB, Moreno M, Pbert L, Klein JD. Are young smokers in greater need of screening around risky social media use? Platform presentation at the 2015 Annual Meeting of the Pediatric Academic Societies. San Diego, CA, Apr 25-28, 2015.

Hart R, Jones S, McMillen R. The impact of research on local policies: engaging and informing communities and policy-makers on the benefits of smoke free air. Presented at the 19th Annual Conference of the National Association of Local Boards of Health. Coeur d'Alene, ID, Sept 7-9, 2011.

Hecht S, Breysse P, Travers M, Avila Tang, Erika Hepp L. Assessment of secondhand smoke workshop: learning from the experts - what works best & why. Presented at the 15th World Conference on Tobacco or Health. Singapore, Mar 20-24, 2012.

Hipple B, Lando HA, Klein JD, Winickoff JP. Tobacco as a global pediatric disease. Presented at the World Conference on Tobacco or Health. Mumbai, India, Mar 8-12, 2009.

Hipple B, Nabi-Burza E, Shaefer R, Gorzkowski J, Drehmer J, Yuen N, Ossip D, Winickoff J. Training child healthcare practices to address family tobacco use: a qualitative analysis of training call data. Presented at the Society for Research on Nicotine and Tobacco Europe 16th Annual Congress. Maastricht, Netherlands, Sep 10-12, 2015.

Holstein J, Moss A, Lowary M, O'Hara K, Wilson KM. Barriers and motivators to smoking cessation for caregivers of inpatient pediatric patients. Presented at the Pediatric Hospital Medicine Meeting. Seattle WA, Jul 25-28, 2019.

Houston T, Shaefer R, and Klein J. Physicians as active members in the tobacco control movement. Presented at the National Conference on Tobacco or Health. Kansas City, MO, Aug 15-17, 2012.

Jenssen BP, Klein JD, Best D, Kamara S, Sesselberg T. Eliminating children's exposure to tobacco and secondhand smoke: evaluating dissemination of best practices. Presented at the Poster Symposium, Pediatric Academic Societies' Meeting. Honolulu, HI, May 3-6, 2008.

Jenssen BP, Klein JD, Salazar LF, DiClemente RJ, Daluga NA. Pro-smoking media use by adolescents on the Internet: A Content Analysis. Presented at Pediatric Academic Societies' Meeting. Honolulu, HI, May 3-6, 2008.

Kaseeska K, Klein JD, Gorzkowski J, Unger R, Levy S, Craig J, McMillen R, Pearson S, Wilson K, Shone L. Feasibility pilot of a brief counseling intervention for adolescent marijuana users. Disseminated to the Pediatric Academic Societies Conference 2020 Meeting Program Guide. Apr 30, 2020. Link: https://plan.core-apps.com/pas2020/abstract/d1991d636c602c4c6e6882f767603eb6

Kaseeska, KR, Gorzkowski, JA, Whitmore Shaefer RM, Harris DL, Wasserman RC, Klein JD. Delivery of preventive counseling and confidential care to adolescents. Presented at the 2015 Annual Meeting of the Pediatric Academic Societies. San Diego, CA, Apr 25-28, 2015.

King K, Herman M, Martynenko M, Fryer GE, Jr, Weitzman M. Utilization of health care by children with asthma living with smokers. Presented at the Pediatric Academic Societies' Meeting. Honolulu, HI, May 3-6, 2008.

King K, Martynenko M, Herman M, Fryer GE, Jr, Weitzman M. Who exposes children to secondhand smoke in their homes? Presented at the Pediatric Academic Societies' Meeting. Honolulu, HI, May 3-6, 2008.

Klein JD. Tobacco and marijuana issues. Presented on ECHO Chicago: Adolescent Health Online Course. Chicago, IL, 2019.

Klein J, Gorzkowski J, Wilson K, Tanski S, Tait V. Strengthening tobacco control capacity in global settings: engaging child health leaders [abstract]. Presented at the 144th Annual Conference of the American Public Health Association. Atlanta, GA, Nov 10-14, 2017.

Klein J, McGrath-Morrow S. Tobacco and children, who is winning? Asthma in childhood. Presented at the Chinese Pediatric Society 18th Annual Meeting. Changsha, China, 2013.

Klein JD (moderator), Gottlieb M, Allen CE. Tobacco and secondhand smoke: chapter successes and lessons learned. Presented at the Annual Leadership Forum. Chicago, IL, Mar 12-15, 2009.

Klein JD, Etzel R. Comprehensive children's tobacco control: The AAP Julius B. Richmond Center of Excellence. Presented at the International Pediatric Association (IPA) 2010 Meeting. Johannesburg, South Africa, Aug 4-9, 2010.

Klein JD, Graff Havens C. Comparing telephone and online survey reliability. Presented at the Pediatric Academic Societies' Meeting. Honolulu, HI, May 3-6, 2008.

Klein JD, McMillen RC, Winickoff JP. Are we asking the right questions about secondhand smoke? Presented at the Pediatric Academic Societies' Meeting. Honolulu, HI, May 3-6, 2008.

Klein JD, Sesselberg T, Pbert L, Steffes J, Harris D, Sutter E, Gotlieb E, Davis J, Slora E, Wasserman R. Successful recruitment and distance training of clinicians in an adolescent smoking cessation pilot study in AAP PROS practices. Presented at the Annual Meeting of the Southeastern Psychological Association. New Orleans, LA, Oct 13, 2009.

Klein JD, Sesselberg T, Pbert L, Steffes J, Harris D, Sutter E, Gottlieb E, Davis J, Slora E, Wasserman R. Successful recruitment and distance training of clinicians in an adolescent smoking cessation pilot study in AAP PROS practices. Presented at the Pediatric Academic Societies' Annual Meeting. Baltimore, MD, May 2-5, 2009.

Klein JD. E-Cigarettes. Presented at the Illinois Chapter of American Academy of Pediatrics (ICAAP) Annual Educational Conference, Northern Illinois University. Naperville, IL, Mar 6, 2020.

Klein JD. Keynote Presentation: Tobacco and adolescents. Presented at the 29th International Pediatric Association Congress. Panama City, Panama, Mar 17-21, 2019.

Klein JD. The Flight Attendant Medical Research Institute Centers of Excellence Program. Presented at the World Conference on Tobacco or Health. Mumbai, India, Mar 8-12, 2009.

Klein, J. Children and Tobacco 2017: Who is winning? Visiting Professorship presentation at UCSF-San Francisco General Hospital. San Francisco, CA, Nov 2017.

Klein, J. Product preferences among light and regular adolescent e-cigarette users: results from the first waves of the PATH Study [abstract]. Presented at the Robert Wood Johnson National Clinical Scholars Program Annual Meeting. New Haven, CT, Nov 2017.

Klein, J. Taking on big tobacco – cultivation of the child and adolescent market. Presented at the International Congress of Pediatrics 2013 (ICP). Melbourne, Australia, Aug 24-29, 2013.

Krugman J, Boykan R, Gorzkowski J. Pediatric residents' perspective on residency education and role of the ehr in addressing tobacco smoke exposure. Presented at the 2019 AAP National Conference and Exhibition. New Orleans, LA, Oct 25-29, 2019.

Lee M, Wilson K. Pediatric tobacco issues APA special interest group. Presented at the 2011 Pediatric Academic Societies' & Asian Society for Pediatric Research Joint Meeting. Denver, CO, Apr 30-May 3, 2011.

Levy DE, Adamkiewicz G, Araujo AB, Rigotti NA, Spengler JD, Winickoff JP. Airborne nicotine in non-smokers' homes in public housing. Presented at the 2014 SRNT Annual Meeting. Washington, DC, Feb 5-8, 2014.

Levy DE, Araujo AB, Adamkiewicz G, Winickoff JP, Rigotti NA. Changes in nonsmoker's self-reported tobacco smoke exposure after a smoking ban in public housing: a natural experiment. Presented at the 2014 SRNT Annual Meeting. Washington, DC, Feb 5-8, 2014.

Lewis L, Huang H, Schanbacher B, Kuck J, Eastman N, Hoffman RP, Bauer JA. Oxidative stress in youth and adolescents exposed to secondhand smoke. Presented at the 53rd Annual Scientific Meeting. Midwest Society for Pediatric Research. Columbus OH, Oct. 4-5, 2012.

Li D, Shi H, Xie Z, Rahman I, McIntosh S, Bansal-Travers M, Winickoff J, Drehmer J, Ossip D. Home smoking and vaping policies among US adult cigarette smokers, vapers, and dual users – results from the Population Assessment of Tobacco and Health (PATH) Study, Wave 3. Presented at the Society for Research on Nicotine and Tobacco Annual Meeting, New Orleans, LA, Mar 11-14, 2020.

Liu Y, Romanos E, Fryer GE, Jr, Miyoshi T, Weitzman M. Secondhand smoke exposure is associated with increased rates of childhood obesity. Presented at the Pediatric Academic Societies' Meeting. Honolulu, HI, May 3-6, 2008.

Madoka H, Chen G, Collaco J, McGrath-Morrow S. Effects of E-cigarette exposure on early postnatal alveolar development in neonatal mice. Presented at the 2014 American Thoracic Society Meeting. San Diego, CA, May 16-21, 2014.

Madoka H, Chen G, Collaco J, McGrath-Morrow S. Effects of E-cigarette exposure on early postnatal alveolar development in neonatal mice. Presented at the 2014 PAS/ASPR Joint Meeting.Vancouver, CA, May 3-6, 2014.

Mahabee-Gittens E, Collins BN, Murphy SA, Woo H, Chang Y, Dempsey J, Weiley V, Winickoff JP. The parent-child dyad and parents who quit smoking successfully. Presented at the Pediatric Academic Societies Annual Meeting. Washington DC, May 4-7, 2013.

McClelland E, Colvin L, Valentine N, McMillen R. Trends in poly-tobacco use among Mississippi secondary students. Presented at the 59th Annual Meeting of the Southeastern Psychological Association. Atlanta, GA, Mar 13-16, 2013.

McClelland E, McMillen R, Huell, Bryant J. Social Climate Survey of Tobacco Control: Identifying support for tobacco control policies in Mississippi. Presented at the National Conference of Tobacco or Health. Austin, TX, Mar 22-24, 2017.

McClelland E, Valentine N, McMillen R. JUUL Awareness, trial, and continued use among undergraduate students in Mississippi. *J Mississippi State Med Assoc*. 2019:60;44-50.

McClelland E, Valentine N, McMillen R. JUUL Awareness, trial, and continued use among undergraduate students in Mississippi. Presented at the 2019 National Conference on Tobacco OR Health. Minneapolis, MN, Aug 27-29, 2019.

McGrath-Morrow SA, Collaco JM. Secondhand smoke exposure increases length of time on supplemental oxygen in preterm infants with bronchopulmonary dysplasia. Presented at the Pediatric Academic Societies Meeting. Boston, MA, May 1, 2012.

McGrath-Morrow, S. Health effects of e-cigarettes. Symposium presentation at the 2018 Society for Research on Nicotine and Tobacco Meeting. Baltimore, MD, Feb 21-24, 2018.

McMillen R, Gorzkowski J, Wilson K, Klein J, Winickoff J. Smokefree homes are associated with better health and fewer ER visits, Presented at the PAS Annual Meeting. Toronto, Canada, May 5-8, 2018.

McMillen R, Gorzkowski J, Wilson K, Tanski S, Klein JD, Winickoff JP. Who uses pod-based e-cigarettes? Adult smokers trying to quit or nonsmoking young adults? Presented at the 2019 Pediatric Academic Societies Conference. Baltimore, MD, Apr 29, 2019.

McMillen R, Gottlieb M, Tanski S, Wilson K, Winickoff JP, Klein J. Household rules about e-cigarette use and beliefs about harm to children. Presented at AAP National Conference and Expo. San Francisco, CA, Oct 22-25, 2016.

McMillen R, Hill A, Cothron A. Dewey defeats Truman, revisited: address-based, cell phone, and internet panel sampling frames: A comparison of data quality from the social climate survey of tobacco control. Presented at the 2009 MSU College of Arts & Sciences Research Showcase. Mississippi State, MS, Oct 22, 2009.

McMillen R, Huell M**.** Harrah's New Orleans: Six months after implementation of a smoke-free ordinance. Presented at 143rd Annual Conference of APHA. Denver, CO, Oct 30, 2016.

McMillen R, Klein J, Tanski S, Winickoff J, Best D. Changes in children's exposure to secondhand smoke: 10 years after the master settlement agreement with the tobacco industry. Presented at the Pediatric Academic Societies' Annual Meeting. Baltimore, MD, May 2-5, 2009.

McMillen R, Klein J. Social climate survey of tobacco control: A mixed-mode approach. Presented at the European Survey Research Association Meeting.Lausanne, Switzerland, Jul 18-22, 2011.

McMillen R, Klein J. The social climate of tobacco control, 2000-2008: It's getting better, but not for everybody. Presented at the Annual Meeting of the Southeastern Psychological Association. New Orleans, LA, Oct 13, 2009.

McMillen R, Klein JD, Hill A. Social Climate Survey of Tobacco Control: A mixed-mode approach. Presented at the 138th APHA Annual Meeting. Denver, CO, Nov 6-10, 2010.

McMillen R, Klein JD, Wilson K, Winickoff JP, Tanski S. E-Cigarette use is associated with future cigarette initiation among never-smokers and relapse among distant former smokers: results from two waves of the PATH study. Presented at the 2018 Society for Research on Nicotine and Tobacco conference. Baltimore, MD, Feb 21-24, 2018.

McMillen R, Klein, J. Social Climate Survey of Tobacco Control: A mixed-mode approach. Presented at the 2011 European Survey Research Association Meeting. Lausanne, Switzerland, Jul 18-22, 2011.

McMillen R, Maduka J, Winickoff J. Ever use of emerging tobacco products by cigarettes smoking status and other characteristics. Presented at the 139th Annual Conference of the American Public Health Association. Washington DC, Oct. 29-Nov. 2, 2011.

McMillen R, Mahan G. Predictors of tobacco counseling among Mississippi pediatricians. Presented at the 2013 AAP National Conference & Exhibition. Orlando, FL, Oct 25-29, 2013.

McMillen R, McClelland E, Valentine N. Surveillance informing policy and practice. Presented at the National Conference of Tobacco or Health. Austin TX, Mar 22-24, 2017.

McMillen R, Mohanty S, Edwards J, Klein JD. Applying the social media tracking and analysis system to social science research. Presented at the World Association for Public Opinion Research 67th Annual Conference. Nice, France, Sep 4-6, 2014.

McMillen R, O'Connor K, Groner J, Klein J. Trends in tobacco counseling: Results from the AAP Periodic Survey of Fellows. Presented at the Pediatric Academic Societies Meeting. Boston, MA, May 1, 2012.

McMillen R, O'Connor K, Winickoff J, Wilson K. Factors associates with counseling parents about tobacco smoke exposure: A national pediatrician survey. Presented at the Pediatric Academic Societies Meeting. Boston, MA, Apr 28-May 1, 2012.

McMillen R, Shaefer R, Wilson K, Gottleib M, Klein J, Winickoff J. Use of electronic cigarettes by former smokers. Presented at the 141st Annual Conference of the American Public Health Association. New Orleans, LA, Nov 15-19, 2014.

McMillen R, Shaefer R, Wilson K. Use of electronic cigarettes among parents. Presented at the 2014 PAS/ASPR Joint Meeting, Vancouver. CA, May 3-6, 2014.

McMillen R, Tanski S, Klein J, Winickoff J. Are we asking the right questions about smoking and secondhand smoke? Presented at the Pediatric Academic Societies' Annual Meeting. Baltimore, MD, May 2-5, 2009.

McMillen R, Tanski S, Wilson K, Klein J, Winickoff J. Product preferences among light and regular adolescent e-cigarette users: results from the first waves of the PATH study. Presented at the 144th Annual Conference of the American Public Health Association. Atlanta, GA, Nov 10-14, 2017.

McMillen R, Tanski S, Wilson K, Shaefer RM, Klein JD, Winickoff JP. Susceptibility to electronic cigarette use among current nonsmokers. Presented at the 141st Annual Conference of the American Public Health Association. New Orleans, LA, Nov 15-19, 2014.

McMillen R, Valentine N, McClelland E, Gorzkowski J. Smoke-free ordinances and policies protect youth, but ordinances appear to have little impact on non-combustible tobacco use. Presented at the 2019 AAP National Conference and Exhibition. New Orleans, LA, Oct 25-29, 2019.

McMillen R, Wheeler G. Advocacy for tobacco prevention: why it matters and how to do it. Presented at the American Academy of Pediatrics Advocacy Institute Meeting. Schaumburg, IL, Mar 10-12, 2010.

McMillen R, Whitmore Shaefer R, Tanski S, Gottlieb M, & Wilson K. (2015). Support for e-cigarette regulations that protect children and adolescents: Results from a nationally representative survey. Platform presentation at the Pediatric Academic Societies' Annual Conference, San Diego, CA, Apr 25-28, 2015.

McMillen R, Wilson K, Gorzkowski J, Winickoff J, Klein J. E-Cigarette use and motivation for use predicts future cigarette smoking among youth. Presented at the PAS Annual Meeting, Toronto, Canada, May 5-8, 2018.

McMillen R, Wilson K, Groner J, Winickoff J. Possible misconceptions in self-reported tobacco smoke exposure. Presented at the National Conference on Tobacco or Health, Kansas City, MO, Aug 15-17 2012.

McMillen R, Wilson K, Tanski S, Klein JD, Winickoff JP. US adult attitudes and practices about smoking restrictions and child exposure to tobacco smoke, 2000-2015. Presented at the Pediatric Academic Societies' Annual Conference. San Francisco, CA, May 6-9, 2017.

McMillen R, Wilson K, Torok M, Rosas Gutierrez M. Tobacco smoke incursions in multi-unit housing among Spanish and English speaking Hispanics. Presented at the 2015 Society for Research on Nicotine and Tobacco Annual Meeting. Philadelphia, PA, Feb 25-28, 2015.

McMillen R, Wilson K, Winickoff J, Gottlieb M, Klein J. Predictors of Public Support for Smoke-Free Outdoor Public Places. Presented at the 2011 Pediatric Academic Societies' & Asian Society for Pediatric Research Joint Meeting. Denver, CO, Apr 30-May 3, 2011.

McMillen R, Wilson K, Winickoff JP, Klein JD, Tanski S. Three year trends in the use of emerging tobacco products among parents. Presented at the 2013 AAP National Conference & Exhibition. Orlando, FL, Oct 25-29, 2013.

McMillen R, Winickoff J, Wilson K, Gottlieb M, Klein J. Predictors of public support for smoke-free multi-unit housing. Presented at the 2011 Pediatric Academic Societies' & Asian Society for Pediatric Research Joint Meeting. Denver, CO, Apr 30-May 3, 2011.

McMillen R, Winickoff JP, Gottlieb M, Tanski S, Wilson K, Klein J. Public support for Smokefree Public Housing. Presented at the APHA 143rd Annual Conference. Denver, CO, Oct 30, 2016.

McMillen R, Winickoff JP, Tanski S, Wilson K, Klein J. Beliefs about potential harms and smoking cessation potential of e-cigarettes. Presented at the APHA 143rd Annual Conference. Denver, CO, Oct 30, 2016.

McMillen R, Winickoff JP, Wilson K, Shaefer R, Klein L. Electronic cigarette use and willingness to use approved nicotine replacement for cessation. Presented at the 2014 Society for Research on Nicotine and Tobacco Annual Meeting. Seattle, WA, Feb 5-8, 2014.

McMillen R. Before and after: a look at Mississippi's only smoke-free casino. Presented at the 2012 National Conference on Tobacco or Health. Kansas City, MO, Aug 15-17, 2012.

McMillen R. Economic effects of smoke-free ordinances in Mississippi communities. Presented at the 2012 National Conference on Tobacco or Health. Kansas City, MO, Aug 15-17, 2012.

McMillen R. Evaluation and surveillance. Presented at the Annual Meeting of the Southeastern Psychological Association. New Orleans, LA, Oct 13, 2009.

McMillen R. Mississippi, 1999-2008: the good, the bad, and the ugly. Presented at the Annual Meeting of the Southeastern Psychological Association. New Orleans, LA, Oct 13, 2009.

McMillen R. Parents are not Aware of Their Adolescents' Cigarette and E-Cigarette Use. Disseminated to the Pediatric Academic Societies Conference 2020 Meeting Program Guide. Apr 30, 2020. Link: https://plan.core-apps.com/pas2020/abstract/d1991d636c602c4c6e6882f76741c421

McMillen R. Presented at the 2019 Annual Meeting of the Mississippi Public Health Association. Jackson, MS, Oct 17-18, 2019.

McMillen R. Presented at the 2020 Vaping Summit, hosted by EnrichMS and funded by the Mississippi State Department of Health. Feb 5, 2020.

McMillen R. Presented at the University and College Tobacco-Free Collaborative hosted by the BlueCross BlueShield of Mississippi Foundation. Aug 20, 2019.

McMillen R. Secondhand smoke and quitlines. Presented at the annual meeting of the North American Quitline Consortium, Kansas City, MO, Aug 13-14, 2012.

McMillen R. The Mississippi experience, 1998 to 2018. Presented at the 2019 National Conference on Tobacco OR Health. Minneapolis, MN, Aug 27-29, 2019.

McMillen R. The social climate survey of tobacco control, 2000-2010. Presented at the Center for Tobacco Control Research and Education (CTCRE), University of California, San Francisco. San Francisco, CA, Mar 2011.

McMillen RC, Gottlieb MA, Shaefer RM, Winickoff J, Klein J. Three year trends in the use of emerging tobacco products. Presented at the 141st Annual American Public Health Association Meeting. Boston, MA, Nov 2-6, 2013.

McMillen RC, Maduka J, Winickoff J. Ever use of emerging tobacco products by cigarette smoking status and other characteristics. Presented at the 139th APHA Annual Meeting and Exposition. Washington, DC, Oct 29-Nov 2, 2011.

McMillen RC, Tanski SE, Winickoff JP, Valentine N. Attitudes about smoking in the movies. Presented at the Legacy/AMA Alliance SmokeFree Movies event. Washington, DC, Feb 12, 2007.

McMillen RC, Winickoff JP, Tanski SE, Klein JD, Weitzman M. Changes from 2000 to 2006 in U.S. Adult attitudes and practices regarding children's exposure to secondhand smoke. Presented at the Pediatric Academic Societies' Meeting. Toronto, Canada, May 5-8, 2007.

McMillen, R. Using databases in tobacco research. Presented at the Pediatric Tobacco Issues Special Interest Group at the 2017 Pediatric Academic Societies Annual Conference. San Francisco, CA, May, 2017.

McMillen, R. Vaping update. Presented at the 2019 Mississippi Thrive! Child Health and Development Summit. 2019.

Metzger MJ, Halperin AC, Tanski S. Maternal smoking during pregnancy and infant infectious disease morbidity and mortality. Presented at the 2013 AAP National Conference & Exhibition. Orlando, FL, Oct 25-29, 2013.

Moreno A, Eastman N, Huang H, Kuck J, Groner J, Bauer J. Evidence of vascular endothelial injury in young children exposure to secondhand smoke. Presented at the 2014 PAS/ASPR Joint Meeting. Vancouver, CA, May 3-6, 2014.

Moreno A, Eastman N, Huang H, Kuck J, Groner J, Bauer JA. Evidence of vascular endothelial injury in young children exposed to secondhand smoke. Presented at the Nationwide Children's Hospital Annual Research Retreat. Columbus, OH, Oct. 23, 2013.

Moreno A, Kuck J, Huang H, Bauer J, Groner JA. Vascular injury in young children exposed to secondhand smoke. Presented at the Children's Hospital Research Institute 2013 Research Retreat. Oct 23, 2013,

Moreno A, Kuck J, Huang H, Bauer J, Groner JA. Vascular injury in young children exposed to secondhand smoke. Presented at the Pediatric Academic Societies meeting.Vancouver, British Columbia, May 3-6, 2014.

Moreno M, Kaseeska KR, Gorzkowski JA, Wright MW, Harris DL, Shone LP, Bocian AB, Davis JB, Oldendick R, Klein JD. (2015) Clinician delivery of a media use screening and intervention. Platform presentation at the 2015 Annual Meeting of the Pediatric Academic Societies. San Diego, CA, Apr 25-28, 2015.

Nabi E, Steffes J, Hipple B, Chang Y, Klein J, Ossip D, Regan S, Wasserman R, Friebely J, Slora E, Winickoff J. Missed opportunities to help parents with smoke-free home and cars. Presented at Pediatric Academic Societies' Meeting. Vancouver, BC, Canada, May 1-4, 2010.

Nabi E. Weiley V, Regan S, Dempsey J, Drehmer J, Friebely J, Hall N, Ossip D, Rigotti N, Slora E, Winickoff J. Parents smoking in their cars with children. Presented at the 2011 Pediatric Academic Societies' & Asian Society for Pediatric Research Joint Meeting. Denver, CO, Apr 30-May 3, 2011.

Nabi-Burza E, Wasserman R, Chang Y, Finch S, Ossip D, Woo H, Winickoff JP. Do parents who smoke quit spontaneously? Presented at the Pediatric Academic Societies Annual Meeting. Washington, DC, May 4-7, 2013.

Nwaigwe CA, Shaefer RM, Brishke JK, Murray L, Klein J. Communities putting prevention to work: engaging leaders in tobacco control. Presented at the 139th APHA Annual Meeting and Exposition, Washington, DC, Oct 29-Nov 2, 2011.

Ossip D, Chang Y, Nabi E, Drehmer J, Hipple B, Winickoff J. What factors are associated with smokefree homes among smoking parents? Presented at the 2011 Pediatric Academic Societies' & Asian Society for Pediatric Research Joint Meeting. Denver, CO, Apr 30-May 3, 2011.

Ossip DJ, Woo H, Chang Y, Nabi-Burza E, Rigotti N, Winickoff JP. Do parents who smoke want their child's pediatrician to address their smoking – and does it occur? Presented at

the Annual Meeting of the North American Quitline Consortium. Kansas City, MO, Aug 13-14, 2012.

Ossip DJ, Woo H, Chang Y, Nabi-Burza E, Rigotti N, Winickoff JP. Do parents who smoke want their child's pediatrician to address their smoking – and does it occur? Presented at the SRNT 19th Annual International Meeting. Boston MA, Mar 13-16, 2013.

Parks MJ. Reducing disparities in smoke-free rules among households with children. Presented at IRT-CAPC 2018 Research Day, Department of Pediatrics, University of Minnesota. Minneapolis, MN, Jul 2019.

Parks MJ. Reducing disparities in smoke-free rules among households with children. Webinar presentation for Bureau of Health Workforce, National Research Service Award Program Webinar Series, 2019.

Parks MJ. Reducing socioeconomic disparities in comprehensive smoke-free rules among households with children. Presented at First Friday Meeting, Department of Pediatrics, University of Minnesota. Minneapolis, MN, 2019.

Patwardhan P, McMillen R, Winickoff J. Consumer opinions on tobacco sales in pharmacies and grocery stores. Presented at the National Conference on Tobacco or Health, Kansas City, MO, Aug 15-17 2012.

Pearson J, McMillen R, Tanski S, Gottlieb M, Winickoff J. Public reaction to FDA regulation of menthol and nicotine. Presented at the National Conference on Tobacco or Health, Kansas City, MO, Aug 15-17 2012.

Pennywitt J, Eastman N, Huang H, Kuck J, Moreno A, Bauer J, Groner J. What should pediatricians be asking parents regarding secondhand smoke exposure? Survey versus objective measures. Presented at the 2014 PAS/ASPR Joint Meeting. Vancouver, BC, Canada, May 3-6, 2014.

Pennywitt J, Eastman N, Huang H, Kuck J, Moreno A, Bauer JA, Groner J. What should pediatricians be asking parents regarding secondhand smoke exposure? Survey versus objective measures. Presented at the Nationwide Children's Hospital Annual Research Retreat. Columbus, OH, Oct. 23, 2013.

Phillips RM, Merritt TA, Goldstein MR, Job JS, Rudatsikira EM. Prevention of smoking relapse in mothers of Infants in the neonatal intensive care unit. Presented at the Pediatric Academic Societies' Annual Meeting, AAP Presidential Plenary Presentation. Vancouver, BC, Canada, May 1-4, 2010.

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FAMRI-BLAND LANE CENTER OF EXCELLENCE ON SECONDHAND SMOKE AT THE UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

Co-Directors: Rita Redberg, MD; Neal Benowitz, MD (2002-2012); Rita Redberg, MD (2012-2019)

The FAMRI-Bland Lane Center of Excellence on Secondhand Smoke was established in 2002 and ended in 2018. The Center included a research project of lung health effects of cabin SHS exposure on Flight Attendants that includes resting pulmonary function testing and exercise testing, a children's biomarkers' study, an Analytical Chemistry Core, and an Administrative and Leadership Core. The Center evaluated lung and cardiovascular function in Flight Attendants. A FAMRI-funded study emerged from the Center entitled

"Flight Attendant Cardiopulmonary Health Study". Warren Gold, MD is the PI and Mehrdad Arjomandi, MD, PhD, acts as Co-PI.

FAMRI SUPPORTED RESEARCH

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RESEARCH BY TOPIC AREA

SINUSITIS

Completed Research

TRANSLATION AND DEVELOPMENT OF A GLYCOSAMINOGLYCAN-BASED THERAPY FOR SINUSITIS

Jeremiah Alt, MD, PhD; University of Utah; CIA 2017

Chronic rhinosinusitis (CRS) is a prevalent disease with well-known symptoms of nasal congestion and infectious discharge. CRS also has an impact on a patient's quality of life; it

can lead to increased depression, sleep dysfunction, and poor cognition. This substantial reduction in quality of life is associated with enormous health care costs. CRS is a chronic inflammatory condition caused by inflammatory immune cells infiltrating the sinonasal mucosa, which results in impaired sinus drainage and infection. Glycosaminoglycans (GAGs) are compounds that have anti-inflammatory properties. Preliminary studies show that a semi-synthetic GAG (SAGE) efficiently penetrates the sinuses, and effectively prevents sinus inflammation by blocking neutrophils and mast cell activation and infiltration in the sinonasal mucosa. The hypothesis is that SAGE can prevent the development and progression of CRS by inhibiting these processes, thereby reducing inflammation and associated infections.

FAMRI SUPPORTED RESEARCH

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EXCHANGE PROTEINS DIRECTLY ACTIVATED BY CAMP, A NOVEL PROTEIN CONTRIBUTING TO VIRUS-INDUCED SINUSITIS

Xiaoyong Bao, PhD; University of Texas Medical Branch at Galveston; CIA 2017

Around 90% of the episodes of acute sinusitis result from viral infection. Current treatments are inadequate and lead in some cases to chronic sinusitis or more serious/complicated diseases. There is a significant contribution of viral infection to sinusitis, thus there is a need to develop therapeutic strategies against viral infection and associated sinus inflammation. Preliminary studies have revealed that a protein called EPAC has a role in regulating the replication of sinusitis-inducing viruses and inflammation. EPAC is an exchange factor directly activated by cAMP. An EPAC-specific inhibitor, ESI-09, was used to treat airway epithelial cells from the lower respiratory tract, pre- or post-infection, followed by the investigation of its effects on RSV replication. It was found that, in ESI-09 pre-treated cells, the production of infectious progeny virus was significantly decreased. A549 cells treated with ESI-09 after 2 h of RSV infection showed a remarkable reduction of RSV titer. Results from this project will elucidate molecular pathways by which respiratory viruses induce sinusitis and other acute and chronic lung diseases exacerbated by upper respiratory tract viral infection.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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THE IMPACT OF CXCL11 ON SINUSITIS IN ACTIVE AND PASSIVE SMOKERS

Robert Foronjy, MD; SUNY Downstate Medical Center; CIA 2017

Cigarette smoke enhances the binding of c-Src to HuR and of HuR to CXCL11 mRNA in airway epithelial cells. Silencing c-Src or HuR increases CXCL11 expression in these cells. The hypothesis of this study is that cigarette smoke downregulates CXCL11 and Treg responses in the upper airway epithelium by triggering c-Src to induce HuR-mediated degradation of CXCL11 mRNA. This is supported by the fact that the specific Src inhibitor AZD0530 significantly enhances CXCL11 protein expression in the airways of smoke-exposed mice *in vivo*, and intranasal CXCL11 protein administration augmented lung Treg responses in smoke-exposed mice. This suggests that increasing CXCL11 or inhibiting c-Src could enhance Treg responses to counter damaging inflammation in CRS. The investigators will use adeno-associated viral vectors to manipulate CXCL11 expression in the upper airways to determine the impact on Treg responses and tissue injury in a smoke/sinusitis model in mice, and will address how the loss of c-Src or HuR expression in the upper airway epithelium alters CRS symptoms and pathology. Primary nasal epithelial cells will be isolated from non-smokers, smokers, and passive smokers to determine how c-Src and HuR modulate CXCL11 expression in the nasal epithelium of tobacco smoke-exposed humans. Insights into a pathway that regulates the severity of smoke-related sinusitis could lead to treatments that decrease injurious inflammatory responses in CRS.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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PULMONARY SURFACTANT LIPIDS INHIBIT RHINOVIRUS-INDUCED SINUSITIS

Mari Numata-Nakamura, MD, PhD; Interim PI, Dennis R. Voelker, PhD; National Jewish Health; CIA 2017

The chief instigators of sinusitis are viruses, predominantly members of the rhinovirus family. These are not only associated with acute and chronic sinusitis, but also cause serious exacerbations of chronic lung diseases such as asthma and COPD. Vaccine development has been hindered by the diversity of rhinoviruses. Two lipids (POPG and PI) normally found in the lower lung have been shown to act against three major classes of rhinoviruses. The lipids attenuate the inflammation elicited by the viruses, and block infection of nasal cells and lower airway cells. The focus of this study is to elucidate the mechanism of action of the lipids and determine how the lipids interact with the viruses and the cells that become infected. Because these lipids are natural compounds already present in the lung, they are expected to be safe when used therapeutically in nasal and sinus compartments and airways. The hope is that these lipids can be moved to clinical trials to determine efficacy in treating sinusitis and chronic lung diseases such as COPD.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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TARGETING EOSINOPHILS FOR THE TREATMENT OF SINUSITIS

Patrick Geraghty, PhD; SUNY Downstate Medical Center; CIA 2017

Sinusitis is reported by nearly 30 million adults annually in the United States. Most episodes of sinusitis are caused by upper respiratory tract viral infection that is linked to asthma, allergic rhinitis, and exposure to cigarette smoke. Eosinophilic inflammation is observed in a subset population of chronic rhinosinusitis (CRS) patients and eosinophil numbers are associated with CRS severity and polyp development; the impact of blocking eosinophilic inflammation in CRS is unknown. Dr. Geraghty and colleagues directly targeted eosinophils for the treatment of CRS. An exposure model induced a CRS-like phenotype with increased eosinophil infiltration, circulating IgE, and collagen deposition in the nasal cavities. Depletion of eosinophils resulted in reduced collagen deposition and circulating IgE. Eosinophils play an important role in immune responses against respiratory syncytial virus (RSV) infection, with eosinophil depleted mice being more susceptible to RSV infection. To investigate this, the team will perform extensive profiling of gene expression changes in the nasal and sinus tissue. The team has also tested the activation status of eosinophils from non-smokers, smokers, and CRS subjects in the presence of RSV infected nasal epithelial cells. Overall, the data suggest that targeting eosinophils using depletion antibodies is a plausible method to treat established CRS. In addition, the data suggest that unique inflammation and protease signaling could contribute to disease progression.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR-DELTA AS A THERAPEUTIC TARGET IN SMOKE-EXACERBATED RHINOSINUSITIS

Raju Reddy, MD; University of Pittsburgh; CIA 2017

Chronic rhinosinusitis is currently treated with nasal steroid sprays, which are not always effective and may lead to adverse effects. Both active and passive tobacco smoke exposure are known to be risk factors for developing CRS, and cigarette smoke exposure has been shown to worsen a mouse model of the disease. Peroxisome proliferator-activated receptor-delta (PPAR-delta) is an intracellular protein with anti-inflammatory properties whose role in CRS has not been studied. PPAR-delta levels are decreased in cells from the nasal passages of CRS patients; exposure to cigarette smoke replicates this effect in laboratory studies. Treating the cells with a PPAR-delta activator inhibits this response. Thus PPAR- delta activators might prove useful for treating CRS. The ability of PPAR-delta activators to block the inflammatory responses of nasal cells will be investigated, with special focus on nuclear factor kappa B (NF-kappaB). The nasal cell-specific mechanism will be investigated. A mouse model of smoke-exacerbated CRS will be used to determine PPAR-delta's role in the disease in living organisms. A mouse strain completely lacking PPAR-delta has been developed which will be used to show if CRS is worse in these animals. These models will be used to investigate therapeutic mechanisms based on this pathway.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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NOVEL ANTI-INFLAMMATORY THERAPY FOR SMOKE-ASSOCIATED CHRONIC RHINOSINUSITIS

Matthias Salathe, MD; University of Kansas Medical Center Research Institute, Inc.; CIA 2017

Mucociliary clearance (MCC) is a major host defense mechanism in the nose and paranasal sinuses. This mechanism is dysfunctional in patients with smoking-associated upper respiratory tract diseases such as chronic rhinosinusitis (CRS). Over 40% of CRS cases are caused by SHS exposure. Flight Attendants exposed to SHS when smoking was allowed in airplanes disproportionally suffer from CRS. Effective MCC requires an adequate nasal surface liquid volume for mucus hydration, appropriate mucin composition, and proper ciliary beating. Dr. Salathe and his team have accumulated data showing that cigarette smoke exposure greatly increases inflammation.

Losartan is a clinically approved and widely used angiotensin II receptor blocker. The investigators showed that if this drug is given orally for 8 weeks, there is decreased inflammation in upper airways of smokers compared to nonsmokers. They found that exposure of human bronchial epithelial cells (HBECs) from COPD donors to cigarette smoke did not lead to an increase in levels of NOTCH1 compared to nonsmokers and "healthy" smokers. Other investigators have shown that a polymorphism in the gene that encodes tumor protein p53 leads to an increase in mucous cells with higher expression of MUC5AC, SPDEF, and Bcl-2. When the team examined the p53 genotype in HBECs a correlation was found between the p53 polymorphism and NOTCH1; i.e., the p53-RR variant was associated with decreased levels of NOTCH1. The investigators hypothesize that the p53- RR variant predisposes smokers to cigarette smoke-induced mucociliary dysfunction due to overproduction of MUC5AC and reduced expression of NOTCH1, which impairs the repair of the airway epithelium. The team will determine if losartan treatment can improve mucociliary function and epithelial repair after tobacco smoke exposure in CRS.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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PRESENTATIONS AND ABSTRACTS

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COGNITIVE FUNCTION AND CHRONIC RHINOSINUSITIS: EXPLORING THE IMPACT OF SECONDHAND SMOKE EXPOSURE ON TREATMENT OUTCOMES

Zachary Soler, MD; Charleston Research Institute; CIA 2015

Dr. Soler and colleagues previously demonstrated that patients with chronic rhinosinusitis (CRS) have greater cognitive dysfunction than appropriately matched controls, manifested

by blunted reaction times and increased general fatigue. The investigators are determining the degree to which SHS exposure affects change in cognitive function after comprehensive medical treatment and after surgical treatment of CRS by measuring local cytokine expression before and after treatment. This investigation is designed as a multi-arm, prospective outcomes study that will enroll subjects over a 3-year period and follow outcomes up to 6 months post treatment. Efforts in Year 2 have been primarily focused on patient enrollment and execution of study assessments. Preliminary results from an interim analysis demonstrate 1) that the study is adequately powered to show statistically significant improvements in cognitive measures, and 2) improvements in objective cognitive testing parameters occur after medical treatment of CRS.

FAMRI SUPPORTED RESEARCH

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PRESENTATIONS AND ABSTRACTS

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SMOKE, CELLULAR AGING, AND CHRONIC RHINOSINUSITIS

Daniel Frank, PhD; University of Colorado, Denver; CIA 2014

Drs. Frank and Ramakrishnan investigated the detrimental effects of SHS on the sinuses in chronic rhinosinusitis (CRS). The investigators completed a study examining the natural variation in bacterial community composition and diversity between different sites of the upper airways. The primary conclusions include: 1) interpersonal variation of the upper airway microbiome greatly outweighs niche-specific differences and 2) the middle meatus is a fair representation of the underlying sinuses and may be considered for use as a simple

single site for sampling in longitudinal studies or in subjects who have not undergone sinus surgery. A preliminary analysis of cigarette smoking history and the sinus microbiome in association with other clinical and demographic factors was performed in a total of 101 subjects (70 CRS, 31 non-CRS). Subjects were categorized as self-reported former plus current cigarette smokers. Analysis of middle meatus microbiota identified substantial changes in sinus bacterial colonization in smokers and non-smokers. A diverse range of bacterial taxa differed significantly in abundance or prevalence between never- and ever-smokers. Because most of the "ever-smokers" were self-reported former smokers, these results suggest that disruption of the sinonasal environment may persist long after smoking cessation.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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Hauser L, Ir D, Kingdom T, Robertson CE, Frank DN, Ramakrishnan VR. Evaluation of bacterial transmission to the paranasal sinuses through sinus irrigation. Presented at the American Rhinologic Society Combined Society Meeting. Boston, MA, Apr 23-24, 2015.

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NITRIC OXIDE IN SMOKE-EXPOSED HUMAN AIRWAY MUCOSA

Johnny L. Carson, PhD; University of North Carolina at Chapel Hill; CIA 2013

Dr. Carson and colleagues used a device capable of measuring very small concentrations of nitric oxide (NO) gas in very small samples of cultured human airway epithelium. Previous data clearly pointed to modified NO dynamics as a component of potential adverse health effects among individuals exposed to tobacco smoke, including those exposed to SHS. The investigators demonstrated marked modification of ciliary function associated with both tobacco smoke and e-cigarette vapor exposure. The experiments point to comparable changes in function resulting from both types of exposure. Based on these experiments aimed at elucidating NO-associated changes in cell physiology as a result of tobacco smoke or e-cigarette vapor, the investigations suggest that in terms of documented modification of ciliary function and the potential for peroxynitrite-mediated cytotoxicity, commercial claims promoting the reduced risk of adverse health effects associated with e-cigarette use lack credibility.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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CIGARETTE SMOKE, VIRAL INFECTIONS & NK CELLS

Ilona Jaspers, PhD; University of North Carolina at Chapel Hill; CIA 2013

Using a newly developed method for CD56+ NK/ILC1 cell enrichment, the investigators determined the phenotype and gene expression profile of the resident CD56+ NK/ILC1 cell population in the nasal mucosa and compared those data to matched peripheral blood (PB) CD56+ NK/ILC1 cell in healthy nonsmokers and CS-exposed subjects. Based on surface markers and gene expression profiles, it was shown that 1) NLF and PB CD56+ NK/ILC1 cells significantly differ in their phenotype, with NLF CD56+ NK/ILC1 cells expressing multiple markers of tissue residency, 2) NLF CD56+ NK/ILC1 cells are more likely to be responsible for cytokine signaling and immune system orchestration than their PB circulating cytotoxic counterparts, and 3) smoking only moderately affected gene expression profiles in NLF and PB CD56+/NK cells. These data indicate that in humans, resident NLF CD56+ NK/ILC1 cells are functionally distinct from PB CD56+NK/ILC1 cells. Preliminary data from the NEC–NK cell co-culture model suggest that differences in NK cell phenotypes may be derived from direct interactions with underlying epithelial cells and are modified by CS exposure in those cells. Further, nasal influenza infection may induce complex changes in peripheral blood NK cell activation, and broccoli sprout homogenate increases virus-induced peripheral blood NK cell granzyme B production, an effect that may be important for enhanced antiviral defense responses.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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Jaspers I. Tobacco products-it's not just cigarettes anymore. Presented at the University of North Carolina at Chapel Hill Pediatrics Grand Rounds. Chapel Hill, NC, Nov 2015.

Jaspers I. Tobacco-induced health effects: it's not just cigarettes anymore. Presented at the University of Arizona. Tucson, AZ, Jan 11, 2016.

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Jaspers I. Viral infections: observations from right under your nose. Presented at the Center in Molecular Toxicology, Vanderbilt School of Medicine. Nashville, TN, Jan 2013.

Jaspers I. What is really going up in smoke: antiviral host defense responses in the respiratory mucosa. Presented at the Lovelace Respiratory Research Institute. Albuquerque, NM, Feb 2015.

EFFECTS OF STS ON MUCOCILIARY CLEARANCE AND SINUSITIS

Lawrence Ostrowski, PhD; University of North Carolina at Chapel Hill; CIA 2012

The effects of tobacco smoke exposure on mucociliary clearance and its different components (e.g., cilia, mucus) were explored in a mouse model; however, in mice exposed to smoke by a variety of different protocols, a significant effect on any aspect of mucociliary clearance was not detected. The mice used were relatively resistant to the effects of tobacco smoke inhalation, and may not be a suitable model for studies of this type. Therefore, future studies on the relationship between tobacco smoke exposure and chronic rhinosinusitis would require a more appropriate model.

SMOKE IMPAIRED EPITHELIAL FUNCTION IN SINUSITIS

Rodney Schlosser, MD; Charleston Research Institute; CIA 2012

Dr. Schlosser and his team investigated several actions of cigarette smoke that may lend themselves to therapeutic interventions in chronic rhinosinusitis (CRS). One such mechanism for smoke-induced inflammation in CRS appears to be impairment of the activation by human sinonasal epithelial cells (HSNECs) of 25 hydroxy vitamin D3 (25VD3), which leads to a local deficiency of active vitamin D. The investigators found a major impact of smoke exposure upon local and systemic vitamin D activation and several mechanisms by which it exerts its proinflammatory effects. Smoke exposure is associated with impaired local vitamin activation by HSNECs. This likely is associated with increased fibrosis, HSNF proliferation, and impaired quality of life. Supplementation with 1,25VD3 appears to have therapeutic potential, through actions upon HSNEC production of local cytokines, as well as HSNF proliferation. Further studies are needed to confirm *in vivo* efficacy of 1,25VD3 in treating smoke exacerbated CRS.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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SHS, SINUSITIS, AND COGNITION

Zachary Soler, MD; Charleston Research Institute; CIA 2012

Dr. Soler and colleagues investigated the hypothesis that patients with SHS-exacerbated chronic rhinosinusitis experience significant cognitive dysfunction that can be identified by patient-reported evaluations and objective testing. The investigators worked to identify mechanisms through which SHS-induced cognitive dysfunction occurs, such as chronic inflammation, disrupted sleep quality, and depression.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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INDUCTION OF BACTERIAL BIOFILMS BY TOBACCO SMOKE

Noam Cohen, MD, PhD; Philadelphia Research & Education Foundation; CIA 2011

Dr. Cohen and colleagues determined whether chronic tobacco smoke exposure confers microbial alterations leading to a biofilm phenotype. Patients with biofilms in their sinuses have worse sinusitis and require more medicines and surgery than non-biofilm sinusitis patients, because these infections are refractory to treatment. The investigators determined if chronic tobacco smoke exposure induces bacterial biofilm formation and increased bacterial adherence to respiratory epithelium in order to define the molecular mechanisms of tobacco-induced biofilm formation.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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NASAL EPITHELIAL GROWTH DYSFUNCTION BY SECONDHAND SMOKE IN CHRONIC SINUSITIS

Jean Kim, MD, PhD; Johns Hopkins Medical Institutions; CIA 2011

Dr. Kim and colleagues studied whether VEGF, a well-known ubiquitous growth factor, is responsible for nasal epithelial growth from healthy individuals and whether SHS exposure results in impairment of nasal epithelial cell growth and survival due to impairment of VEGF function. The human nasal epithelium expresses a large family of VEGF ligands and receptors that are important to cell growth and survival. The investigators showed that cigarette smoke exposure inhibits and harms these processes in healthy human nasal airway epithelial cells. They also demonstrated that TH2 immune effector pathways propagate aberrant hyperplastic epithelial cell growth in chronic rhinosinusitis with nasal polyposis. Elevation in human peripheral blood eosinophils is a biomarker for hyperplastic nasal polyp growth.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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TOBACCO SMOKE EXPOSURE EFFECTS ON SINONASAL MUCOSA

Diego A. Preciado, MD, PhD; Children's National Medical Center; CIA 2011

Pediatric CRS is characterized by an increased amount of mucous-producing glands in the sinonasal tissues at the microscopic level. When mucin proteins are chronically overproduced in the airway, a thick fluid is produced, accompanied by stagnation and infection. Dr. Preciado and colleagues tested the hypothesis that tobacco smoke exposure induces an increase in mucous gland formation and an increase in the expression of MUC5B.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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PRESENTATIONS AND ABSTRACTS

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NRF2 AND TOBACCO SMOKE EXACERBATED CHRONIC SINUSITIS

Muragappan Ramanathan, Jr., MD; Johns Hopkins Medical Institutions; YCSA 2011

Dr. Ramanathan and colleagues generated allergic inflammation in the sinuses of normal mice and mice that lack antioxidant production. The investigators exposed mice to cigarette smoke to determine if they have decreased antioxidant levels. In clinic visits, the team characterized patients with sinusitis that are exposed to SHS by measuring inflammation and antioxidant levels. The investigators determined that cigarette smoke exposure primarily affects sinonasal epithelial cells by causing barrier dysfunction, and that enhancing Nrf2 can ameliorate this effect. The data support the possibility of Nrf2-enhancing drugs as a therapeutic modality to combat cigarette smoke-induced sinusitis.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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Ramanathan M Jr, London NR Jr, Tharakan A, Surya N, Sussan TE, Rao X, Lin SY, Toskala E, Rajagopalan S, Biswal S. Airborne Particulate matter induces nonallergic eosinophilic sinonasal inflammation in mice. *Am J Respir Cell Mol Biol* 2017;57(1):59-65.

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ORIGIN AND EFFECTS OF ACQUIRED CILIARY DEFECTS

Johnny L. Carson, PhD; University of North Carolina at Chapel Hill; CIA 2010

Dr. Carson and his colleagues showed that active heavy smokers exhibit significant increases in *in vivo* nasal NO levels relative to individuals exposed to SHS and nonsmokers. Although NO is an important mediator of normal physiologic function, if present in excess, it has potential pathophysiologic effects through the formation of highly reactive peroxynitrite and irreversible combination with tyrosine to form 3-nitrotyrosine. The investigators are studying whether exposure to components of SHS affect early ciliogenic events during ciliated cell differentiation to provoke the formation of functionally deficient ciliary defects and phenotypic modification of the airway mucosa. The team propagated nasal epithelium from nonsmokers in the presence of an NO donor to create an environment of excessive NO production. They used these cultures to evaluate expression of molecular markers of ciliogenesis, to assess ciliary ultrastructure, and to document changes in phenotypic patterns that represent an *in vitro* correlate of *in vivo* epithelial remodeling in the presence of SHS exposure. The research team is also cultured nasal epithelial cells in the presence of 3-nitrotyrosine during known temporal windows of differentiation to assess ciliogenic patterns and phenotypic modifications.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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PRESENTATIONS AND ABSTRACTS

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TOBACCO SMOKE-INDUCED OXIDATION AND CILIARY DYSFUNCTION

Gregory E. Conner, PhD; University of Miami Miller School of Medicine; CIA 2010

Dr. Conner and colleagues are investigating the mechanistic relationship of smoke-induced oxidative changes in cystic fibrosis transmembrane conductance regulator (CF TR) function and decreased mucociliary clearance. The team is investigating whether reactive oxygen species (ROS) found in SHS contribute to changes in airway surface liquid volume via an oxidant-mediated mechanism, by first elevating intracellular cyclic adenosine monophosphate levels that increase CF TR activity and then, after chronic ROS exposure like that seen following chronic SHS exposure, by decreasing CF TR activity and messenger RNA.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Conner GE, Ivonnet P, Gelin M, Whitney P, Salathe M. H2O2 stimulates cystic fibrosis transmembrane conductance regulator through an autocrine prostaglandin pathway, using multidrug-resistant protein-4. *Am J Respir Cell Mol Biol.* 2013;49(4):672-679.

PRESENTATIONS AND ABSTRACTS

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SECOND HAND SMOKE PROMOTES ANTIBIOTIC RESISTANCE AND VIRULENCE IN UPPER AIRWAY BACTERIA: A NOVEL MECHANISM FOR SECONDHAND SMOKE INDUCED AIRWAY DISEASES

Ritwij Kulkarni, PhD; Columbia University; Louisiana State University; YCSA 2010

Dr. Kulkarni and colleagues studied whether genotoxic and mutagenic chemicals in cigarette smoke (CS) affect the normal microflora of the upper respiratory tract, resulting in the emergence of virulent pathogens that are refractory to available antibiotic treatments. The research team has determined that exposure to CS augments the formation of an *S. aureus* biofilm and its adherence to respiratory epithelium. At the molecular level, CS-mediated induction of staphylococcal biofilms is accompanied by downregulation of the quorum sensing agr regulon that is involved in biofilm dispersal and modulation of bacterial response to oxidative stress. Pretreatment with an anti-oxidant N-acetyl cysteine

abrogates CS-mediated biofilm induction, indicating an important role for reactive oxygen species in this process.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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Kulkarni R, Randis TM, Antala S, Wang A, Amaral FA, Ratner AJ. Beta H/C of group B streptococci enhances host inflammation but is dispensable for establishment of urinary tract infection. *PLoS One* 2013; 8(3): e59091.

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PRESENTATIONS AND ABSTRACTS

Kulkarni R, Antala S, Wang A, Amaral FA, Rampersaud R, Ratner AJ. Cigarette smoke induces biofilm formation in Staphylococcus aureus. Presented at the American Society for Microbiology Annual Meeting. San Francisco, CA, Jun 16-19, 2012.

Kulkarni R, Antala S, Wang A, Ratner AJ. Cigarette smoke exposure modulates bacterial antibiotic resistance and virulence factors. Presented at the Microbial Pathogenesis and Host Response meeting at Cold Spring Harbor Laboratory. Cold Spring Harbor, NY, Sept 13-17, 2011.

EFFECTS OF SECOND HAND SMOKE ON DENDRITIC CELL REGULATION AND FUNCTION IN CHRONIC RHINOSINUSITIS

Jennifer Mulligan, PhD; Charleston Research Institute; YCSA 2010

Dr. Mulligan and her team observed that in the sinus mucosa there is an increased presence of dendritic cells (DCs) and DC chemokines in patients with chronic rhinosinusitis with nasal polyps (CRSwNP) and allergic fungal rhinosinusitis (AFRS) compared to control and CRS subjects without nasal polyps (CRSsNP). The investigators have also shown that there

are increased numbers of circulating DCs in CRSwNP and AFRS as compared to control and CRSsNP subjects. These studies suggest that the Th2 skewing observed in CRSwNP and AFRS are DC-mediated.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Ayers CM, Schlosser RJ, O'Connell BP, Atkinson C, Mulligan RM, Casey SE, Bleier BS, Wang EW, Sansoni ER, Kuhlen JL, Mulligan JK. Increased presence of dendritic cells and dendritic cell chemokines in the sinus mucosa of chronic rhinosinusitis with nasal polyps and allergic fungal rhinosinusitis. *Int Forum Allergy Rhinol*. 2011;1(4):296-302.

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SECOND HAND SMOKE- INDUCED VITAMIN D DEFICIENCY PROMOTES AIRWAY INFECTION AND PROVIDES A NOVEL THERAPEUTIC TARGET

Adam J. Ratner, MD, MPH; Columbia University; CIA 2010

Dr. Ratner and his team have shown that antimicrobial peptides are important to epithelial defense against microbial products and that the active form of vitamin D can regulate epithelial production of these mediators. The team determined whether SHS exposure induces vitamin D deficiency and whether this predisposes SHS-exposed patients to respiratory infections, including chronic rhinosinusitis. The team used a combination of *in vitro*, *in vivo*, and population data to assess the validity and the importance of SHS-induced alterations in vitamin D metabolism to airway infections, and they determined the potential for vitamin D supplementation as a treatment for SHS-induced respiratory diseases.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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TOBACCO MEDIATED SINONASAL CILIARY DYSFUNCTION

Noam Cohen, MD, PhD; Philadelphia Research & Education Foundation; CIA 2009

Dr. Cohen demonstrated that SHS exposure not only diminishes the ability of the nose and sinuses to respond to environmental challenges (dust, bacteria, viruses, pollen) but also impairs the ability of new forming cells to grow hair-like projections (cilia). These results suggest that exposure to SHS may significantly contribute to the development and persistence of chronic sinusitis. Using sinus tissue obtained from patients undergoing sinus surgery, as well as mouse nasal cells growing in culture, Dr. Cohen and his team further investigated the effects of SHS exposure on the function and regeneration of the hair-like projections responsible for keeping the nose and sinuses clean.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Cohen NA, Zhang S, Sharp DB, Tamashiro E, Chen B, Sorscher EJ, Woodworth BA. Cigarette smoke condensate inhibits transepithelial chloride transport and ciliary beat frequency. *Laryngoscope* 2009;119(11):2269-2274.

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Zhao KQ, Cowan AT, Lee RJ, Goldstein N, Droguett K, Chen B, Zheng C, Villalon M, Palmer JN, Kreindler JL, Cohen NA. Molecular modulation of airway epithelial ciliary response to sneezing. *FASEB J* 2012;26(8):3178-3187.

SECONDHAND TOBACCO SMOKE EXACERBATION OF ALLERGIC RHINITIS

M. Boyd Gillespie, MD; Charleston Research Institute; CIA 2008

Dr. Gillespie and colleagues investigated whether SHS exposure triggers local release of neurogenic mediators that augment the classic Th2 adaptive response of allergic and non-allergic rhinosinusitis (AR) and lead to increased dendritic cell (DC) maturation and recruitment. The team found that cigarette smoke extract stimulates epithelial cells to secrete factors that result in increased DC maturation, which is most pronounced in Th2 subsets of rhinosinusitis that are both allergic and non-allergic. In addition, nerve growth factor was shown to be increased and brain derived neurotrophic factor was shown to be decreased in allergic rhinosinusitis tissue.

It was not possible to identify definitive differences in innate immunity, specifically neurogenic inflammatory mediators, induced by SHS, however, the investigators were able to identify a definite mechanism by which SHS causes inflammation in rhinosinusitis with *in vivo* clinical data and *in vitro* mechanistic studies, which demonstrated that SHS impairs vitamin D metabolism that affects innate immunity by causing HSNRCs to secrete proinflammatory cytokines and recruitment of APCs.

FAMRI SUPPORTED RESEARCH

PRESENTATIONS AND ABSTRACTS

Coffey C, Mulligan RM, Gillespie MB, Schlosser RJ. Mucosal expression of nerve growth factor and brain-derived neurotrophic factor in chronic rhinosinusitis. Presented at the American Rhinologic Society Meeting. Philadelphia, PA, Apr 15-19, 2009.

PATHOGENESIS OF CHRONIC RHINOSINUSITIS IN RELATION TO SECONDHAND CIGARETTE SMOKE AND ABNORMAL EPITHELIAL INNATE IMMUNITY

Daniel L. Hamilos, MD; Massachusetts General Hospital; CIA 2008

Dr. Hamilos and colleagues investigated chronic rhinosinusitis (CRS) by using *in vitro* cultures of primary nasal epithelial cell (PNEC) to study the behavior of epithelial cells from patients with chronic rhinosinusitis without nasal polyposis (CRSsNP), CRS with nasal polyposis, and healthy controls. They found that primary nasal epithelial cells from patients with CRSsNP have an exaggerated response to stimulation with cigarette smoke extract (CSE) plus double-stranded RNA (dsRNA), a stimulus mimicking a viral infection. CRSsNP patients produce excessive RANTES, a chemokine involved in recruitment of lymphocytes and eosinophils into sinus tissue. This team found that NP patients have an exaggerated response to CSE and dsRNA with respect to production of TGF-b1 and activin-A. These results show that cigarette smoke exposure exacerbates viral infection and contributes to chronic rhinosinusitis.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Yamin M, Holbrook EH, Gray ST, Harold R, Busaba N, Sridhar A, Powell KJ, Hamilos DL. Cigarette smoke combined with Toll-like receptor 3 (TLR3) signaling triggers exaggerated

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SECONDHAND SMOKE AND SINUSITIS: EFFECT OF SIDESTREAM SMOKE ON SINUS OSTIAL PATENCY

Dennis Shusterman, MD, MPH, John Balmes, MD; University of California, San Francisco; CIA 2008

Drs. Shusterman and Balmes showed that nasal exposure to chemical irritants produces transient airflow obstruction, particularly among individuals with pre-existing allergic rhinitis. They speculated that SHS-induced nasal mucosal swelling could contribute to the development of sinusitis, since mucosal swelling likely affects sinus ostial patency. Analysis of nasal nitric oxide (NO) samples taken under quiet conditions from normal controls was consistent with the para-nasal sinuses acting as a reservoir of nasal NO and with osteomeatal complex patency acting as a significant factor in NO diffusion.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Shusterman D. The effects of air pollutants and irritants on the upper airway. *Proc Am Thorac Soc* 2011;8(1):101-105.

PRESENTATIONS AND ABSTRACTS

Shusterman D, Weaver E, Goldberg A, Schick S, Wong H, Balmes J. Evaluation of the nasal NO response to humming as an index of osteo-meatal patency: A comparison with sinus CT measurements [abstract]. J All & Clin Immunol 2011;127(2):AB121.

REVERSAL OF TOBACCO-RELATED CHRONIC SINUSITIS

Bradford A. Woodworth, MD; University of Alabama at Birmingham; YCSA 2008

Dr. Woodworth and colleagues investigated whether exposure to SHS induces chronic rhinosinusitis (CRS) by inhibiting mucociliary function. The investigators examined the relationships among SHS exposure, zinc deficiency, and CRS in human subjects by correlating zinc levels and SHS exposure to CRS signs and symptoms. They also investigated the mechanism of action by which SHS exerts influence on the major apical epithelial Cl-channel cystic fibrosis transmembrane conductance regulator (CF TR) and examined the ability of the powerful CF TR activator resveratrol to reverse the deleterious effects of SHS.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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Zhang S, Smith N, Schuster D, Azbell C, Sorscher EJ, Rowe SM, Woodworth BA. Quercetin increases cystic fibrosis transmembrane conductance regulator-mediated chloride transport and ciliary beat frequency: Therapeutic implications for chronic rhinosinusitis. *Am J Rhinol Allergy* 2011;25(5):307-312.

LABORATORY STUDIES OF HUMAN NASAL EPITHELIUM

Johnny L. Carson, PhD; University of North Carolina at Chapel Hill; CIA 2007

Dr. Carson's goal was to determine if exposure of human ciliated airway epithelial cells to components of tobacco smoke contributes to evident development and structural anomalies of cilia and to epithelial remodeling resulting in measurable dysfunction. This follows on findings of previous FAMRI-supported research documenting accelerated ciliary beat frequencies (CBF) in freshly acquired nasal epithelium of human subjects having variable histories of lifestyle tobacco smoke exposure. These studies showed that nasal

epithelium deriving from tobacco smoke-exposed subjects and subsequently cultured in an air-liquid interface system retains physiologic and phenotypic characteristics of the epithelial layer *in vivo* even through rounds of proliferative expansion. Stable epigenetic factors are operative that influence mucociliary function and phenotype commitment, even in the absence of continuing exposure.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Carson JL, Lu T-S, Brighton L, Hazucha M, Jaspers I, Zhou H. Phenotypic and physiologic variability in nasal epithelium cultured from smokers and non-smokers exposed to secondhand tobacco smoke. *In vitro Cell Dev Biol Anim* 2010;46(7):606-612.

TOBACCO SMOKE EXPOSURE, INNATE IMMUNITY, AND CHRONIC SINUSITIS

Andrew P. Lane, MD; Johns Hopkins Medical Institutions; CIA 2007

Dr. Lane's previous work demonstrated that the function of the local immune system within the nose is diminished in patients with chronic sinusitis. In this study, the researchers investigated whether tobacco smoke exposure impacts the innate immune function of the nasal lining, thereby predisposing individuals to sinusitis. They examined immune gene expression in nasal tissue obtained from patients with varying degrees of SHS exposure, and used a cell culture model to determine the effect of tobacco smoke on sinus epithelial cells derived from patients and controls. The results indicate that the tobacco smoke component acrolein suppresses expression of antimicrobial products produced by epithelial cells *in vitro*. The investigators focused on the expression of multiple epithelial cell gene targets involved in the innate and the adaptive immune system of the nose and sinuses. They determined whether a subject's history of smoke exposure is associated with an impaired ability of their sinus epithelial cells to respond to bacterial stimuli. Failure of nasal mucosal immunity to eliminate pathogens is an important underlying factor in the development of chronic sinusitis among smoke-exposed individuals.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Heinecke L, Proud D, Sanders S, Schleimer RP, Kim J. Induction of B7-H1 and B7-DC expression on airway epithelial cells by the Toll-like receptor 3 agonist double-stranded RNA and human rhinovirus infection: *in vivo* and *in vitro* studies. *J Allergy Clin Immunol* 2008;121:1155-1160.

Kim J, Myers AC, Chen L, Pardoll DM, Truong-Tran QA, Lane AP, McDyer JF, Fortuno L, Schleimer RP. Constitutive and inducible expression of b7 family of ligands by human airway epithelial cells. *Am J Respir Cell Mol Biol*. 2005;33(3):280-289.

Lalaker A, Nkrumah L, Lee WK, Ramanathan M, Lane AP. Chitin stimulates expression of acidic mammalian chitinase and eotaxin-3 by human sinonasal epithelial cells *in vitro*. *Am J Rhinol Allergy* 2009;23(1):8-14.

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Reh DD, Ramanathan M Jr, Sultan B, Wang Y, May L, Lane AP. The role of hepatocyte growth factor/c-Met in chronic rhinosinusitis with nasal polyps. *Am J Rhinol Allergy* 2010;24(4):266-270.

Reh DD, Wang Y, Ramanathan M Jr, Lane AP. Treatment-recalcitrant chronic rhinosinusitis with polyps is associated with altered epithelial cell expression of interleukin-33. *Am J Rhinol Allergy* 2010;24(2):105-109.

EVALUATING CD137 AS A NOVEL TREATMENT IN A NEW TOBACCO-EXACERBATED MODEL OF CHRONIC SINUSITIS

Rodney J. Taylor, MD, MPH; University of Maryland; CIA 2007

Dr. Taylor's goal was to develop a murine model of allergy-mediated CRS and a model of tobacco-exacerbated CRS. By using mice with well-described sinus anatomy, the investigators endeavored to create the models using a known allergen and immunogen, ovalbumin, that results in a localized allergic reaction that will occur in the sinuses and nasal cavity leading to mucosal thickening and infiltration of eosinophils and other chronic inflammatory cells.

CLINICAL PHASE I/IIA TRIAL FOR TESTING THE EFFICACY OF MRX-4 IN ALLERGIC RHINITIS

Saul Yedgar, PhD; Hebrew University of Jerusalem; 2007

Dr. Yedgar's team designed a synthetic nonsteroidal anti-inflammatory drug prototype, which consists of secretory phospholipase A2 (sPLA2)-inhibiting lipids (PLA2Is) that incorporate into the cell membrane linked to glycosaminoglycans (GAGs) and prevent PLA2I internalization. The investigators explored the involvement of sPLA2 in experimental allergic bronchitis (EAB) in mice and in metaplasia (mucus over-secretion) of human tracheal epithelial cells, which is a major pathological manifestation of respiratory system diseases. They found that the development of EAB was accompanied by enhanced expression of sPLA2-X and cyotosolic PLA2-IVc in lung homogenates, but both were suppressed upon treatment with nebulized PLA2I with amelioration of broncho-constriction and airway remodeling and suppression of the airway-constricting eicosanoids cysteinyl-leukotrienes and thromboxane B2. They also found that mucin secretion by IL-13-stimulated human airway epithelial (HAE) cells was accompanied by elevated expression of PLA2, especially sPLA2-X.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Mruwat R, Yedgar S, Lavon I, Ariel A, Krimsky M, Shoseyov D. Phospholipase A2 in experimental allergic bronchitis: a lesson from mouse and rat models. *PLoS One* 2013;8(10):e76641.

SECONDHAND TOBACCO SMOKE EXPOSURE INCREASES BIOFILMS FORMATION AND SUBSEQUENT CILIARY DYSFUNCTION

James N. Palmer, MD; University of Pennsylvania; CIA 2006

Dr. Palmer determined whether tobacco smoke exposure allows bacterial biofilms to grow faster in the sinuses, and, if they grow faster, whether more biofilms in the sinuses mean the cilia will stop working. Dr. Palmer grew sinus linings from sinus surgery patients in a Petri dish and treated some of the specimens with cigarette smoke condensate and bacteria that form biofilms to determine if more biofilms will form (and whether the cilia stop working) in those exposed to cigarette smoke. Cigarette smoke exposure may cause ciliary damage and decrease the defenses of the sinonasal mucosa because of increased biofilm accumulation.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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Shaari J, Palmer JN, Chiu AG, Judy KD, Cohen AS, Kennedy DW, Cohen NA. Regional analysis of sinonasal ciliary beat frequency. *Am J Rhinol* 2006;20(2):150-154.

Woodworth BA, Antunes MB, Bhargave G, Palmer JN, Cohen NA. Murine tracheal and nasal septal epithelium for air-liquid interface cultures: a comparative study. *Am J Rhinol* 2007;21(5):533-537.

Woodworth BA, Tamashiro E, Bhargave G, Cohen NA, Palmer JN. An *in vitro* model of *Pseudomonas aeruginosa* biofilms on viable airway epithelial cell monolayers. *Am J Rhinol* 2008;22(3):235-238.

PRESENTATIONS AND ABSTRACTS

Schipor I, Cryer JE, Cohen AS, Palmer JN, Cohen NA. Physiologic sequelae of biofilm and non-biofilm forming *Pseudomonas aeruginosa* sinusitis. Presented at the Combined Otolaryngology Spring Meeting. Boca Raton, FL, Apr 2005.

EFFECTS OF SECONDHAND TOBACCO SMOKE ON SINONASAL IMMUNITY

Rodney J. Schlosser, MD; Charleston Research Institute; CIA 2006

Dr. Schlosser and colleagues found increased surfactant proteins (SP)-A, B, and D gene expression and protein production in certain types of sinusitis associated with Th1 adaptive immune responses, although this did not appear to be affected by smoke exposure. The research team's *in vitro* tissue explant model was used to demonstrate an increased inflammatory response as measured by IL-8, PGE2, and GMCSF with increasing exposure to cigarette smoke extract. These inflammatory responses are abolished by superoxide dismutase, indicating that tobacco smoke causes inflammation via production of free radicals. Additionally, activation of the complement pathway occurs in some subsets of chronic rhinosinusitis, and complement-deficient mice are protected from the pro-inflammatory effects of smoke exposure. The normal protective dynamic ciliary response of upper airway epithelium is abolished in cells exposed to smoke. These results demonstrate that tobacco smoke exposure increases complement activation and free radical production, and inhibits protective ciliary action, but it does not appear to affect opsonization with surfactant proteins.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Ahn CN, Wise SK, Lathers DM, Mulligan RM, Harvey RJ, Schlosser RJ. Local production of antigen-specific IgE in different anatomic subsites of allergic fungal rhinosinusitis patients. *Otolaryngol Head Neck Surg* 2009;141:97-103.

Bleier BS, Debnath I, Harvey RJ, Schlosser RJ. Temporospatial quantification of fluorescein-labeled sinonasal irrigation delivery. *Int Forum Allergy Rhinol*. 2011;1(5):361-365.

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Wise SK, Ahn CN, Schlosser RJ. Localized immunoglobulin E expression in allergic rhinitis and nasal polyposis. *Curr Opin Otolaryngol Head Neck Surg* 2009;17:216-222.

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Woodworth BA, Wood R, Baatz JE, Schlosser RJ. Sinonasal surfactant protein A1, A2, and D is elevated in cystic fibrosis: A preliminary report. *Otolaryngol Head Neck Surg* 2007;137(1):34-38.

Woodworth BA, Wood R, Bhargave G, Cohen NA, Baatz JE, Schlosser RJ. Surfactant protein B detection and gene expression in chronic rhinosinusitis. *Laryngoscope* 2007;117(7):1296-1301.

PRESENTATIONS AND ABSTRACTS

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Schlosser RJ, Mulligan RM, Atkinson CA. Alterations in complement pathway gene and protein expression in chronic rhinosinusitis. Presented at the American Rhinologic Society Meeting. Philadelphia, PA, Apr 15-19, 2009.

Skinner ML, Schlosser RJ, Neal JG, Woodworth BA, Hall J, Newton D, Baatz JE. Innate and adaptive mediators in cystic fibrosis and allergic fungal rhinosinusitis. Presented at the American Rhinologic Society Meeting. Chicago, IL, May 19-20, 2006.

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Woodworth BA, Wood R, Bhargave G, Cohen NA, Baatz JE, Schlosser RJ. Surfactant protein B detection and gene expression in chronic rhinosinusitis. Presented at the Trio-logic Society Combined Sections Meeting Program. Marco Island, FL, Feb 14-15, 2007.

TOBACCO SMOKE AND GENE EXPRESSION IN SINUS MUCOSA

Vladimir Vincek, MD, PhD; University of Miami Miller School of Medicine; CIA 2004

Dr. Vincek's goal was to determine the effect of SHS and firsthand smoking on development and worsening of chronic rhinosinusitis (CRS), and to elucidate and understand the

complexity of the various factors leading to the development of CRS. Dr. Vincek hypothesized that tobacco smoke exposure causes changes in the gene expression pattern of histologically normal upper respiratory mucosa and stroma that lead to CRS development.

CLINICAL AND LABORATORY STUDIES OF HUMAN NASAL EPITHELIUM

Johnny L. Carson, PhD; University of North Carolina at Chapel Hill; CIA 2004

Dr. Carson found that active smokers and individuals exposed to SHS in domestic and/or occupational settings exhibited a statistically significant persistent increase in their baseline ciliary beat frequency (CBF). Individuals exposed to SHS with demonstrably lower levels of tobacco smoke exposure relative to active smokers had baseline CBFs comparable to those of active smokers with significantly higher cotinine. He investigated the cellular mechanisms that might account for this observation and established a collaboration for further studies.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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PRESENTATIONS AND ABSTRACTS

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Carson JL. Human ciliopathies: an overview of the first one hundred years. Presented at the Joint Meeting of the Microscopy Society of America, Microbeam Analysis Society, and International Metallographic Society. Albuquerque, NM, Aug 3-7, 2008.

CONTRIBUTION OF SECONDHAND TOBACCO SMOKE TO SINUSITIS

Noam Cohen, MD, PhD; Philadelphia Research & Education Foundation; CIA 2004

Dr. Cohen has pursued this line of research with a number of grants; please see above.

FAMRI SUPPORTED RESEARCH

EPITHELIUM AND IMMUNOMODULATION IN CHRONIC RHINOSINUSITUS

Jean Kim, MD, PhD; Johns Hopkins Medical Institutions; CIA 2004

Dr. Kim and colleagues sought to test the hypothesis that disease exacerbation induces the expression of B7 homolog. They found no appreciable difference in B7 homolog mRNA expression between chronic rhinosinusitis (CRS) subjects without SHS exposure and CRS subjects with SHS exposure. They exposed sinonasal epithelial cells derived from nasal scrapings and the BEAS2B cell line to relevant stimuli and assessed expression of B7 homologs and other T cell regulators. Selective induction of B7-H1 and B7-DC by cytokines, rhinovirus, and dsRNA was observed *in vitro* from human primary nasal epithelial cells in culture and *in vivo* from nasal scrapings of epithelial cells. Respiratory viral infection was shown to induce costimulatory molecules on human nasal airway epithelial cells, but no differences in levels of costimulatory molecule expression between CRS subjects with and without SHS exposure were observed.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Kim J, Myers AC, Chen L, Pardoll D, Truong-Tran Q, McDyer J, Lane A, Fortuno L, Schleimer RP. Constitutive and inducible exression of B7 family of ligands by human airway epithelial cells. *Am J Respir Cell Mol Biol* 2005;33:280-289.

Lee HS, Myers A, Kim J. Vascular endothelial growth factor drives autocrine epithelial cell proliferation and survival in chronic rhinosinusitis with nasal polyposis. *Am J Respir Crit Care Med* 2009;180:1056-1067.

Schleimer RP, Kato A, Peters A, Conley D, Kim J, Liu MC, Harris KE, Kuperman DA, Chandra R, Favoreto S Jr., Avila PC, Grammer LC, Kern RC. Epithelium, inflammation, and immunity in the upper airways of humans: Studies in chronic rhinosinusitis. *Proc Am Thorac Soc* 2009;6:288-294.

PRESENTATIONS AND ABSTRACTS

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Oh YJ, Kim JH, Ryoo S, Sikka G, Berkowitz D. Genetic deficiency of arginase II reduces endothelial dysfunction and atherosclerosis in ApoE-knockout mice [abstract]. *Circulation* 2009;120:S1073.

CHRONIC SINUSITIS AND THE AIRLINE CABIN ENVIRONMENT

Andrew P. Lane, MD; Johns Hopkins Medical Institutions; CIA 2004

Dr. Lane and colleagues developed a cell culture model for studying the effect of the airline cabin environment on human sinonasal cells and established a technique for harvesting and growing cells from tissues derived from sinus surgery patients. They determined conditions where epithelial cells differentiated into polarized cells such as those found in the human nose. Cell viability and expression patterns of inflammatory mediators were assessed and it was demonstrated that conditions of airline cabins such as low humidity

and low oxygen levels do not, in and of themselves, cause changes in these parameters. The team successfully characterized the novel innate immune properties of sinonasal epithelial cells that are thought to play a critical role in the development of chronic sinusitis, which include immune receptors and anti-microbial proteins. There is a difference in the expression of these factors between normal controls and sinusitis patients that may contribute to the disease process. The team examined how exposure to SHS impacts the immune activity of these cultured cells *in vitro*. Decreased amounts of immune mediators were observed in standard cultured epithelial cells in the presence of acrolein for example, but cells grown in an air-liquid interface were remarkably resistant.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Lane AP, Truong-Tran QA, Myers A, Bickel C, Schleimer RP. Serum amyloid A, properdin, complement 3, and toll-like receptors are expressed locally in human sinonasal tissue. *Am J Rhinol* 2006;20(1):117-123.

Lane AP, Truong-Tran QA, Schleimer RP. Altered expression of genes associated with innate immunity and inflammation in recalcitrant rhinosinusitis with polyps. *Am J Rhinol* 2006;20(2):138-144.

Lee WK, Ramanathan M Jr, Spannhake EW, Lane AP. The cigarette smoke component acrolein inhibits expression of the innate immune components IL-8 and human betadefensin 2 by sinonasal epithelial cells. *Am J Rhinol* 2007;21(6):658-663.

Ramanathan M Jr, Lane AP. A comparison of experimental methods in molecular chronic rhinosinusitis research. *Am J Rhinol* 2007;21(3):373-377.

Ramanathan M Jr, Lee WK, Dubin MG, Lin S, Spannhake EW, Lane AP. Sinonasal epithelial cell expression of toll-like receptor 9 is decreased in chronic rhinosinusitis with polyps. *Am J Rhinol* 2007;21(1):110-116.

Ramanathan M Jr, Spannhake EW, Lane AP. Chronic rhinosinusitis with nasal polyps is associated with decreased expression of mucosal interleukin 22 receptor. *Laryngoscope* 2007;117(10):1839-1843.

Vandermeer J, Sha Q, Lane AP, Schleimer RP. Innate immunity of the sinonasal cavity: expression of messenger RNA for complement cascade components and toll-like receptors. *Arch Otolaryngol Head Neck Surg* 2004;130(12):1374-1380. Erratum in: *Arch Otolaryngol Head Neck Surg* 2005;131(5):406.

PRESENTATIONS AND ABSTRACTS

Lui C, Dubin M, Martin B, Lane AP. Effect of smoking on maximal medical therapy for chronic sinusitis [abstract]. Presented at the 52nd annual meeting of the American Rhinologic Society. Toronto, Canada, Sept 16, 2006.

BOOK CHAPTERS, ETC.

Schleimer RP, Sha Q, Vandermeer J, Lane AP, Kim J. Epithelial responses in airway inflammation and immunity. *Clin Exp Allergy Rev* 2004;4:176-182.

CORRELATION OF CHRONIC SINUSITIS AND TOBACCO SMOKE

Jeffrey S. Wolf, MD; University of Maryland; CIA 2004

Dr. Wolf and colleagues conducted a prospective study with 90 patients with severe CRS who were scheduled for sinus surgery after failing maximal medical therapy. During surgery, maxillary sinus mucosa was biopsied and evaluated for ciliary ultrastructure, mitochondrial DNA, and presence of cotinine. Further measures included a blinded grading of sinus CT scans, a validated questionnaire about tobacco smoke exposure and severity of sinus-related disease, and serum cotinine. They found a correlation between quality of life and tobacco smoke exposure. There were significant increases in sinusitis symptom severity in active smokers, asthmatics, patients with environmental allergies, and those with cotinine in their serum. There were multiple individual correlations between independent variables and sinonasal outcome test 20 (SNOT-20) scores. Serum cotinine level, the number of cigarettes smoked per day, and the number of secondhand cigarettes exposed to per day; all significantly correlated with a diminished quality of life. The team found a five-variable predictive model of total SNOT score ($R2 = 0.366$, $p = 0.0019$).

MOLECULAR MECHANISMS OF SPATIOTEMPORAL REGULATION OF LEUKOCYTE CHEMOTAXIS AND ITS DYSREGULATION INVOLVED IN CHRONIC SINUSITIS

Jin Zhang, PhD; Johns Hopkins Medical Institutions; YCSA 2004

Dr. Zhang determined the molecular mechanisms controlling cell polarization and directional movement in leukocyte chemotaxis, and identified the molecular component changes involved in chronic sinusitis. The data showed that the phosphoinositide pathway is needed to mediate leukocyte chemotaxis. This involves two kinases, phosphoinositide-3 kinase (PI3K) and protein kinase B (Akt), and a phosphatase and tensin homologue deletion on chromosome 10 (PTEN). The approach for investigating this was a combination of live-cell imaging, protein engineering, and chemical and molecular biology.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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Herbst K, Allen MD, Zhang J. The cAMP-dependent protein kinase inhibitor H-89 attenuates the bioluminescent signal produced by Renilla luciferase. PLoS One 2009;4(5):e5642.

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Sample V, Newman RH, Zhang J. The structure and function of fluorescent proteins. Chem Soc Rev 2009; 38(10):2852-2864.

Vincent P, Gervasi N, Zhang J. Real-time monitoring of cyclic nucleotide signaling in neurons using genetically-encoded FRET probes. Brain Cell Biol 2008;36:3-17.

PATHOGENESIS OF CHRONIC SINUSITIS IN RELATIONSHIP TO TOBACCO SMOKE EXPOSURE

Daniel L. Hamilos, MD; Massachusetts General Hospital; CIA 2003

A 1-hour pulse exposure to cigarette smoke extract (CSE) was shown to have a significant effect on epithelial cell viability and it induces multiple genes of importance to epithelial innate immunity and inflammatory response; HC and CRS primary epithelial cells (PNTEC) appear to be equally sensitive to the effects of CSE on cellular viability. PNTECs show a similar pattern of basal gene expression with the exception of expression of the chemokine MCP-3, which was shown to be expressed > 2-fold in CRS subjects. Studies of mRNA induction in response to inflammatory stimuli suggest that CRS patients may be less responsive to normal inflammatory stimuli from microbial organisms. This was particularly true for the chemokine GRO-alpha, which showed a significantly reduced level of expression in response to the panel of stimuli; for most mRNA species, combined stimulation with CSE and TNF-ALPHA or LPS provided additive gene induction, which suggests that CSE may exaggerate epithelial responses to viral and bacterial infection and allergic inflammation.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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EMPHYSEMA

Completed Research

DDT-CD74: A NOVEL SIGNALING PATHWAY THAT MAY PROTECT AGAINST EMPHYSEMA

Maor Sauler, MD; Yale University; YCSA 2015

Emphysema characterized by lung tissue destruction is the hallmark histologic finding of COPD and is often due to chronic cigarette smoke exposure (CSE) in susceptible individuals. However, there is a great variation in disease susceptibility among at-risk individuals. Dr. Sauler and colleagues identified macrophage migration inhibitory factor (MIF) as a protein that affects disease susceptibility and showed that plasma concentrations of MIF are lower in individuals with COPD. Genetic deletion of MIF or its receptor CD74 in mice results in spontaneous emphysema characterized by DNA damage, cellular senescence, and increased susceptibility to apoptosis. D-dopachrome tautomerase (DDT) is a homologue of MIF and the only other known binding partner of CD74 in the lung. Lungs of patients with COPD have increased CD74 compared to "healthy smokers" and never smokers, as do lung endothelial cells from mice exposed to cigarette smoke. Studies to determine changes in DDT expression *in vitro* and with treatment by HDAC inhibitors in response to CS exposure are ongoing, with the emphasis on mechanisms of DNA repair.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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DJ-1 IMPAIRMENT IN ATII CELLS IN EMPHYSEMA

Beata Kosmider, PhD; Temple University; CIA 2014

Dr. Kosmider and her team studied the mechanism of alveolar type II (ATII) cell injury in pulmonary emphysema. The major risk factor for emphysema is exposure to SHS and cigarette smoke, and it is caused by the destruction of alveolar wall septa. ATII cells make and secrete pulmonary surfactant, and they proliferate to restore the epithelium after damage to the more sensitive alveolar type I cells. The team used murine and human primary ATII cells to expand preliminary data indicating the impairment of the antioxidant defense system in ATII cells after exposure to cigarette smoke. DJ-1 regulates the antioxidant defense system and CR6-interacting Factor 6 (CRIF-1) modulates its activation. Dr. Kosmider and her colleagues studied the protective role of the DJ-1-CRIF-1 pathway in ATII cells isolated from control organ donors and emphysema patients. Primary human ATII cells provide a unique approach for studying cellular and molecular mechanisms of disease pathophysiology. The results suggest a protective role of DJ-1 against emphysema development and ATII cell injury by CS. Targeting DJ-1 may provide potential therapeutic target against disease development.

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MODELING COPD AND NOVEL RAGE TRANSGENIC MICE

Paul R. Reynolds, PhD; Brigham Young University; CIA 2012

The investigators have broadened the understanding of the environmental impact of receptors for advanced glycation end products (RAGE)-mediated inflammation by assessing the array of particulates that induce deleterious RAGE signaling in isolated primary epithelium, primary macrophages, and the lungs of animals exposed to diesel particulates. They showed that RAGE abrogation lessens SHS-induced lung inflammation and that RAGE silencing protects mouse pups from SHS-mediated defects *in utero* and during early post-natal life. Transgenic upregulation of RAGE in the proximal lung lessens the abundance of pro-inflammatory mediators in SHS-exposed mice. RAGE may be a key driver of SHS-induced inflammation in a variety of susceptible tissues. Targeting RAGE may offer therapeutic value in lessening the impact of smoke exposure.

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ALTERED GLUTATHIONE BIOSYNTHESIS IN CIGARETTE SMOKE-INDUCED EMPHYSEMA

Christopher Franklin, PhD; University of Colorado, Denver; CIA 2011

Dr. Franklin and colleagues studied the role of glutamate cysteine ligase (GCL) in CS-induced emphysema. The team determined if alpha, beta-unsaturated aldehydes present in cigarette smoke (CS) post-translationally modify GCL subunits, leading to suppressed GCL activity in response to exposure. The investigators determined whether compromised GSH biosynthetic capacity enhances susceptibility to the CS-induced oxidative stress and apoptosis that is associated with emphysema. They characterized the role of acrolein- and CSE-mediated adduction of GCLC and GCLM and determining the functional effects of acrolein- and CSE-mediated adduction of the CGL subunits. They investigated the molecular mechanism(s) mediating these effects, and determined whether GSH biosynthetic capacity dictates sensitivity to acrolein- and CSE-induced oxidative stress and apoptotic cell death in cultured lung epithelial cells.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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THE ROLE OF MMP-13 IN EMPHYSEMA DEVELOPMENT

Monica Goldklang, MD; Columbia University; YCSA 2011

Dr. Goldklang and colleagues investigated whether matrix metalloproteinase-13 (MMP-13) is an essential collagenase in the development of emphysema. This study demonstrated the importance of MMP-13 in COPD exacerbations and identified this protease as a possible mediator of lung destruction following viral disease exacerbations. MMP-13 expression in the lungs is upregulated early following influenza infection in the smoke-influenza model system of COPD exacerbations. In addition, loss of MMP-13 protects from air space enlargement in the smoke-influenza model system. Human data support this conclusion, with serum MMP-13 levels remaining elevated in smokers suffering from COPD exacerbations. Therefore, it is possible that targeting MMP-13 activity with specific inhibitors may be a viable treatment option to prevent lung function decline in the setting of virally induced COPD exacerbations.

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CIGARETTE SMOKE INDUCES XOR MEDIATED APOPTOSIS

Bo Kim, MD; Johns Hopkins Medical Institutions; YCSA 2011

Dr. Kim and colleagues provided evidence for a novel mechanism of CS-induced pulmonary EC apoptosis where xanthine oxidoreductase (XOR) is necessary for DNA damage, ataxia telangiectasia mutated (ATM) activity, and increased p53 expression that leads to cell death. They demonstrated that cigarette smoke exposure is sufficient to upregulate XOR expression/activity, resulting in a pro-apoptotic signal that is probably secondary to XOR's ability to generate ROS. This XOR- and p53-dependent apoptotic pathway may be critical in emphysema development and progression. They also identified a regulatory role for p35/CDK5 for XOR and potential modifiers of ROS-mediated injury. Further, these studies established a role for macrophage migration inhibitor factor (MIF), a pleiotropic cytokine, in controlling ROS responses to cigarette smoke exposure by regulating p38-depedent XOR activity, and directly links MIF as a direct inhibitor of apoptosis signal-regulating kinase 1 (ASK1), upstream of p38 in CS-induced EC injury. In a murine model, tobacco smoke exposure was associated with lower levels of paraoxonase activity despite no differences in HDL-cholesterol levels compared to control mice. This suggests that tobacco smoke exposure primarily acts directly to reduce paraoxonase levels rather than indirectly via reduction in HDL-cholesterol levels.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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INFLAMMASOME ACTIVATION AS A MODULATOR OF CIGARETTE-SMOKE INDUCED EMPHYSEMA IN MICE

Thomas Sussan, PhD; Bloomberg School of Public Health; YCSA 2010

Dr. Sussan and colleagues investigated the effects of the IL-1 receptor and toll-like receptors in the pulmonary response to household air pollution (HAP). A growing body of evidence suggests that HAP is a major risk factor for COPD, especially in developing countries. The team determined that HAP induces inflammation and alveolar destruction, and this is partially mediated by IL-1. A study was completed that demonstrated that Nrf2 plays an important role in deterioration of skeletal muscle in a mouse model of muscular dystrophy. Muscle wasting is a major co-morbidity of COPD, and decreased exercise capacity is a stronger predictor of COPD-related mortality than decreased lung function. The investigators determined that aquaporin V is an important mediator of susceptibility to cigarette smoke induced emphysema, via enhanced epithelial barrier function and that Nrf2 attenuates asthma via antioxidant cytoprotective responses and enhanced airway epithelial barrier function This demonstrates that Nrf2 can improve airway epithelial function by reducing oxidative stress and inflammation and improving the epithelial barrier to prevent exogenous agents from penetrating the airway wall.

FAMRI SUPPORTED RESEARCH

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TLR-MEDIATED EMPHYSEMA: ROLE OF AGING AND GENDER

Patty J. Lee, MD; Yale University; CIA 2009

Dr. Lee and her colleagues found that an innate immune receptor in the lung, toll-like receptor 4 (TLR4), is a critical determinant of COPD and survival during cigarette smoke exposure. In addition, they found that the functioning of this receptor decreases with age, which may explain why COPD manifests as a person ages. They also showed that a cytokine, macrophage migration inhibitory factor (MIF), is intimately related to TLR4 function and that inadequate MIF levels correlate with low TLR4 function and COPD, indicating that MIF is either a key biologic marker for, or a cause of, COPD. The team developed small molecules that restore MIF pharmacologically. In addition, they established a multi-investigator, multi-disciplinary research, and translational infrastructure at Yale to study smoke- and age-related COPD. A biorepository with clinical data, lung function, and blood/cell samples from over 200 young and older people (75 have COPD) has been established and serves as a resource for collaborations to investigate cause and treatment of COPD.

FAMRI SUPPORTED RESEARCH

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ROLE OF ADIPONECTIN IN THE PROTECTION OF EMPHYSEMA

Rubin M. Tuder, MD; University of Colorado, Denver; CIA 2009

Dr. Tuder and colleagues examined the systemic impact of SHS exposure on lung involvement in emphysema. They determined if SHS exposure-disrupted expression of anti-inflammatory and anti-apoptotic molecules in adipose tissue affects alveolar damage. The investigators analyzed the role of adiponectin (APN) in bleomycin-induced lung injury in the presence of SHS exposure. The cross-talk between systemic organs, including fat and muscular tissue, and the lung is part of the alveolar maintenance program. The team determined if adipocytokine APN opposes lung inflammation, alveolar cell apoptosis, and defective apoptotic cell clearance caused by SHS exposure and if it modifies lung responses to lung injury caused by bleomycin. They used lung and serum samples of patients with emphysema and smokers/nonsmokers with interstitial lung disease to see if there is decreased expression of APN. In addition, the team studied whether enhancement of APN levels protects the lung against SHS-induced alveolar damage and tested whether reduced levels of APN increase the alveolar injury and airspace enlargement caused by SHS exposure.

FAMRI SUPPORTED RESEARCH

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TARGETING Nrf2 FOR INTERVENING EMPHYSEMA

Shyam Biswal, PhD; Johns Hopkins Medical Institutions; CIA 2008

Dr. Biswal and his team discovered a host factor, nuclear factor-erythroid 2 p45-related factor 2 (Nrf2) that plays a critical role in determining susceptibility to cigarette smoke-induced emphysema, allergen-induced asthma, and pulmonary pneumonia in mouse models. Dr. Biswal and colleagues tested the hypothesis that increasing Nrf2 activity enhances the expression of antioxidant and cytoprotective pathways thereby intervening in the progression of pulmonary emphysema. They used a genetic approach to determine if increasing Nrf2 activity can intervene in CS-induced emphysema and they generated mice with increased Nrf2 activity and its antioxidant target genes. Their studies indicated that a triterpenoid compound, 1-[2-cyano-3-,12-dioxooleana-1,9(11)dien-28-oyl]imidazole is a potent activator of Nrf2 in mice and leads to an increase in antioxidant pathways that inhibit inflammation.

FAMRI SUPPORTED RESEARCH

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ROLE OF CYCLIC GUANOSINE MONOPHOSPHATE IN TOBACCO SMOKE-INDUCED LUNG ENDOTHELIAL DYSFUNCTION AND EMPHYSEMA

David B. Pearse, MD; Johns Hopkins Medical Institutions; CIA 2008

Oxidant-induced pulmonary endothelial cell apoptosis has been implicated in the pathogenesis of cigarette smoke (CS)-induced emphysema. Tidal ventilation generates endothelial nitric oxide and cyclic guanosine monophosphate (cGMP), which has been shown to protect other cell types from oxidant injury. Dr. Pearse and his group investigated whether physiologic levels of cyclic stretch would protect against cigarette smoke extract

(CSE)- and reactive oxygen species (ROS)-induced apoptosis in mouse lung microvascular endothelial cells (MLMVECs) via a cGMP-dependent mechanism. MLMVECs pretreated with 8p-CPT-cGMP scavenged significantly more hydrogen peroxide compared to untreated cells. The data show that physiologic levels of cyclic stretch increase MLMVEC antioxidant capacity and decrease CSE- and reactive oxygen species (ROS)induced apoptosis via a cGMP-dependent mechanism.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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SYNERGISTIC EFFECTS OF CIGARETTE SMOKE AND PMNS IN COPD

Rachel L. Zemans, MD; National Jewish Health; YCSA 2008

Dr. Zemans and colleagues used *in vitro* and *in vivo* models of polymorphonuclear neutrophil (PMN) transepithelial migration to identify pathways involved in epithelial repair. PMNs were induced to transmigrate across a cultured lung epithelial monolayer in the physiologic basolateralto-apical direction, which resulted in rapid and extensive epithelial injury. The injury phase was followed by a period of repair. PMN transmigration induced upregulation of beta-catenin signaling and beta-catenin transcriptional activation in alveolar type II epithelial cells. Inhibition of beta-catenin signaling through lentiviral small interfering RNA delayed repair of the injury epithelium. The data show that beta-catenin signaling is enhanced in lung epithelial cells in response to PMN transmigration and is critical to epithelial repair after PMN-mediated injury, such as is seen in COPD. Epithelial monolayers were exposed to SHS after PMN transmigration. SHS exposure exacerbated injury and delayed repair of the lung epithelium after PMN transmigration. Moreover, SHS exposure downregulated beta-catenin signaling.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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THE ROLE OF THROMBOSPONDIN-1 IN EMPHYSEMA

Michael E. Ezzie, MD; Ohio State University; YCSA 2007

Dr. Ezzie and colleagues tested whether loss of thrombospondin-1 (TSP-1) activity contributes to the development of emphysema. Investigation of the effect of smoking on mice that lack TSP-1 was used to determine if these mice develop emphysema more readily than wild-type mice when exposed to smoke. The emphysema model mice undergo nine months of smoke exposure. The team investigated the physiologic state of the model by lung function testing, morphometric analysis, and analysis of the inflammatory state compared to controls. They also collected lung samples from smokers with varying degrees of COPD and analyzed them for expression of TSP-1. They found changes in TSP-1 expression in the lung tissue from the COPD patients.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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RAGE-MEDIATED EFFECTS OF PULMONARY INFLAMMATION AND EMPHYSEMA

Paul R. Reynolds, PhD; Brigham Young University; YCSA 2007

Dr. Reynolds and colleagues demonstrated upregulation of the receptor for advanced glycation end-products (RAGE) and its ligands by cigarette smoke extract (CSE) in rat R3/1 cells, a type I-like alveolar epithelial cell line. They demonstrated that R3/1 cells exposed to 25% CSE for two hours have induced activation of Ras, which controls several intracellular signaling networks. Conversely, cells treated with siRNA for RAGE (siRAGE) resulted in decreased Ras activation. Furthermore, Ras was significantly diminished in lungs from

RAGE knockout mice exposed to chronic tobacco smoke when compared to smoke-exposed wild type controls. Elevated NF-kappa B activation was observed following CSE stimulation, and decreased NF-kappa B activation was observed in cells transfected with siRAGE prior to exposure. Transfection with a Ras dominant-negative vector confirmed a link between elevated Ras expression and NF-kappa B activation.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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EXHALED SMOKE-INDUCED LUNG ENDOTHELIAL APOPTOSIS via PEROXYNITRITE-BAX SIGNALING

Jianliang Zhang, PhD; University of Florida; CIA 2007

Dr. Zhang and colleagues used a cell model to investigate the molecular mechanisms underlying exhaled smoke-induced cell death and dysfunction. Exposure of lung vascular endothelial cells to saline buffer-conditioned mainstream smoke results in extensive cell death, including apoptosis. Peroxynitrite formed from excessive superoxide reaction with nitric oxide can modify a number of proteins, including the pro-apoptosis protein, Bax. The

investigators focused on the link between peroxynitrite-induced modification of Bax and apoptosis of the lung endothelium.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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NEUROPILIN-1 AND EMPHYSEMA

Patrice M. Becker, MD; Johns Hopkins Medical Institutions; CIA 2006

Neuropilin-1 (Nrp-1) was independently cloned from neurons as a receptor for class 3 semaphorins (Sema 3), and from endothelium as a novel vascular endothelial growth factor (VEGF) receptor. Dr. Becker demonstrated that conditional deletion of epithelial Nrp-1 in the lungs of adult mice promotes the development of cigarette smoke-induced airspace enlargement and alveolar epithelial programmed cell death. Additional *in vitro* experiments support a role for Nrp-1 in resistance of pulmonary epithelial cells to cigarette smoke-induced apoptosis, and are consistent with published reports that both VEGF- and Sema 3-induced Nrp-1 signaling regulate apoptotic cell death in other cell types. The investigators evaluated whether Nrp-1 deletion exacerbates cigarette smoke-induced epithelial cell death and airspace remodeling by altering ligand-specific signaling.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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A NOVEL ANTI-INFLAMMATORY ROLE FOR ADAM15 IN EMPHYSEMA

Caroline A. Owen, MD, PhD; Brigham and Women's Hospital; CIA 2006

Dr. Owen and colleagues showed that cigarette smoke exposure upregulates the expression of a disintegrin and metallopeptidase domain 15 (ADAM15) on the surface of macrophages and CD8+ T cells *in vitro* and in lungs *in vivo*. Exposure of wild-type (WT) mice and mice genetically deficient in ADAM15 (ADAM15$^{-/-}$mice) to SHS for 1 to 24 weeks resulted in higher lung macrophage and CD8+ T cell counts, higher lung levels of proinflammatory mediators, greater weight loss, higher mortality, and greater airspace enlargement in ADAM15$^{-/-}$mice than WT mice. ADAM15$^{-/-}$alveolar macrophages and CD8+ T cells have reduced rates of apoptosis and necrosis than do WT cells in response to cigarette smoke exposure. Thus, ADAM15 appears to protect the lung from cigarette smoke-induced inflammation and airspace enlargement, at least in part, by reducing the survival of destructive leukocytes.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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MOLECULAR PHENOTYPE OF EARLY EMPHYSEMA

Russell Bowler, MD, PhD; National Jewish Health; YCSA 2005

Oxidants in tobacco smoke play a role in the pathogenesis of emphysema but only a minority of exposed individuals develop clinically evident COPD or emphysema. Data indicate that tobacco smoke is associated with induction of antioxidants, and that COPD correlates with oxidative stress and antioxidant response, which damage lung proteins. Development of centrilobular emphysema (CLE) and panlobular emphysema (PLE) may have distinct antioxidant properties. Dr. Bowler used high-resolution CT scans to determine affected lung segments in asymptomatic smokers in the early stages of emphysema. This can be used to direct bronchoscopy to the affected regions, allow assessment for CLE versus PLE, determine which patients are at higher risk for developing early emphysema, and what role oxidative stress plays.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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IDENTIFICATION OF PATHOGENIC CD4+ T CELLS IN THE LUNGS OF PATIENTS WITH SEVERE EMPHYSEMA

Andrew K. Sullivan, MD, Philip L. Simonian, MD, Michael Falta, MD, PhD; University of Colorado, Denver; YCSA 2005

Inflammation in lung airways and tissue resulting from cigarette smoke exposure persists long after cessation of exposure. Reports have correlated the number of T cells in the lung with emphysema severity. The hypothesis of Dr. Falta's research was that CD4+ T cell clones build up in the lungs of patients with severe emphysema in response to altered protein expression resulting from prolonged proteolytic and oxidative damage and may be the cause of the persistent inflammation. T cells that share the same T cell receptors (i.e., those that respond to the same protein antigen) as those from emphysematous lung were identified. An immortalized T cell hybridoma line from these cells was grown to large numbers to determine receptor specificity. The hybridoma lines allowed identification of proteins responsible for T cell accumulation and activation in inflammation-damaged lungs. CD4+ T cells specific to the antigen were determined in blood and bronchoalveolar fluid of patients with and without emphysema. The number of specific T cells in blood could be a key marker for development of emphysema.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Sullivan AK, Simonian PL, Falta MT, Mitchell JD, Cosgrove GP, Brown KK, Kotzin BL, Voelkel NF, Fontenot AP. Oligoclonal CD4+ T cells in the lungs of patients with severe emphysema. *Am J Respir Crit Care Med* 2005;172:590-596.

CHRONIC BRONCHITIS

Completed Research

ROLE OF K+ CHANNELS AND ATP IN CHRONIC BRONCHITIS

Matthias Salathe, MD; University of Miami Miller School of Medicine; CIA 2014

Dr. Salathe and colleagues used human cells that represent the airway surface exposed to mainstream tobacco smoke or SHS to study the mechanism by which the clearing of phlegm is hindered. The investigators delineated the IFN-gamma-mediated mechanisms of decreased adenosine triphosphate (ATP) release in normal human bronchial epithelial cells (NHBE) cells. They also showed the effects of cigarette smoke on cystic fibrosis transmembrane conductance regulator (CFTR) and big potassium channel (BK) activities, as well as air-surface liquid (ASL) volume in the absence or presence of different inhibitors. Cigarette smoke stimulates both Smad3 and p38 phosphorylation via TGF-b eta signaling, which in turn decreases CFTR and BK channel functions. This causes ASL volume loss, resulting in mucociliary dysfunction. Inhibitors ameliorated CFTR and BK activities and thereby improved ASL volume loss.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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OXIDATION AND pH CHANGE IN SMOKE EXPOSED EPITHELIA

Gregory E. Conner, PhD; University of Miami Miller School of Medicine; CIA 2013

Dr. Conner and his team have shown that hydrogen peroxide (H_2O_2) production and proton secretion may be altered by exposure to cigarette smoke. The investigators showed that dual oxidase 2 (Duox2) mRNA and activity are regulated during infection and inflammation and that upregulation by IFN gamma during inflammation may result in high levels of H_2O_2 at the airway surface. IFN gamma is upregulated in COPD, as is Duox2, suggesting relevance to inflammatory airway disease. The role of hydrogen voltage gated channel 1 (HVCN1) in Duox-mediated H_2O_2 synthesis was investigated by using short hairpin RNA (shRNA) expression to knockdown Duox1 and Duox2. Duox1 knockdown resulted in loss of Zn2+ inhibition while Duox2 knockdown had no effect. A small molecule inhibitor (5-chloro-2-guanidinobenzimidazole, (ClGBI) was used to investigate the sensitivity of Duox activity to inhibition of HVCN1 by Zn2+. ClGBI inhibited both baseline and adenosine triphosphate (ATP)-stimulated activity. Lentiviral mediated knockdown of Duox1 revealed that the remaining H_2O_2 synthesis due to Duox2 activity was sensitive to ClGBI. The team also studied regulation Duox by Ca^{2+} and confirmed that lowered H_2O_2 synthesis is concomitant

with changes in intracellular calcium concentration. Thus Zn^{2+} inhibition of Duox1, while sparing Duox2, is related to changes in Ca^{2+} signaling. DuoxA1 or DuoxA2 were expressed in human embryonic kidney cell line 293 (HEK293), which was used to study the effect of Zn^{2+} and ClGBI on Duox1 and Duox2. These inhibitors blocked both enzymes in a similar fashion. HVCN1 was shown to be required for full expression of Duox NADPH oxidase H_2O_2 synthesis. Cigarette smoke exposure resulted in an increase of HVCN1 transcripts, suggesting that more proton channels are being expressed following exposure and suggesting the possibility of increased proton transfer to the airway lumen leading to lower airway lumen pH.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Gerovac BJ, Valencia M, Baumlin N, Salathe M, Conner GE, Fregien NL. Submersion and hypoxia inhibit ciliated cell differentiation in a notch dependent manner. *Am J Respir Cell Mol Biol* 2014;51(4):516-525.

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TOBACCO SMOKE AND HMGB1 IN RSV BRONCHIOLITIS

Yashoda Madaiah Hosakote, PhD; University of Texas Medical Branch at Galveston; YCSA 2013

Dr. Hosakote and colleagues have shown that respiratory syncytial virus (RSV) and tobacco smoke-induced oxidative stress promotes the translocation of high mobility group B1 (HMGB1) from the cell nuclei to the extracellular space and that Treatment of RSV-infected and tobacco smoke exposed AECs with antioxidants significantly inhibited extracellular release of HMGB1 from the cells. They showed that active replication by virus was required to trigger HMGB1 release from airway epithelial cells (AECs) and that RSV infection-induced cytokines and chemokines do not promote HMGB1 release from AECs. HMGB1 was released only by AECs and that secreted HMGB1 activates innate immune cells to promote inflammatory response and RSV infection of AECs hyperacetylates and phosphorylates nuclear protein HMGB1 for its active secretion. Nrf2 gene silencing and knockdown reduced RSV and tobacco smoke-induced HMGB1 release with increased mRNA and significantly increased HDAC1 and NFκB expression. HMGB1 gene silencing increased residual HMGB1 release from the cells and worsens the inflammation in RSV infection, whereas treatment with rHMGB1 significantly reduced the viral load. HMGB1 knockdown significantly reduced Nrf2, catalase, and HDAC1 expression with increased NFκB phosphorylation, suggesting that HMGB1 downregulation results in increased cellular oxidative stress. Cigarette smoke exposure enhances RSV-induced HMGB1 secretion and increases RSV-induced NF-kB and p38 MAPK phosphorylation upon HMGB1 gene silencing. HDAC1 gene silencing enhances RSV-induced HMGB1 release with reduced cellular HMGB1 as well as increased Nrf2 and NFkB expression, suggesting that HDAC1 inhibition enhances RSV and tobacco smoke-induced inflammation. Cigarette smoke exposure enhances RSV-induced HMGB1 secretion and increases RSV-induced NF-kB and p38 MAPK phosphorylation upon HMGB1 gene silencing. HDAC1 gene silencing enhances RSV-induced HMGB1 release with reduced cellular HMGB1 as well as increased Nrf2 and NFkB expression, suggesting that HDAC1 inhibition enhances inflammation. Recombinant (rHMGB1) and secreted HMGB1 (sHMGB1) activates human primary macrophages to induce proinflammatory mediator release. RSV viral replication was significantly increased in cells treated with HMGB1 monoclonal antibody (mAb) whereas RSV replication was significantly decreased with rHMGB1 treatment of RSV-infected and HMGB1 mAb treated cells. HMGB1 gene silencing increased RSV replication, which was decreased with rHMGB1 treatment and cigarette smoke exposure, suggesting that cigarette smoke-induced oxidative stress activates antiviral response. HMGB1 gene silencing and tobacco smoke exposure of AECs downregulates HMGB1 expression and RSV-induced HMGB1 secretion is mediated via the NFκB pathway.

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THE ROLES OF MACROPHAGES IN LUNG INFLAMMATION

Yogesh Saini, PhD; Louisiana State University; YCSA 2012

Dr. Saini and colleagues are investigating the roles of macrophages in the initiation and the course of lung inflammation in beta-ENaC mice. The beta-ENaC mouse model recapitulates many features of chronic bronchitis, including impaired mucus clearance and airway inflammation. The lung disease in beta-ENaC is due to the increased Na+ absorption (by overexpression of the Scnn1b transgene) that leads to airway surface liquid dehydration, thickening of mucus, and airway inflammation. The characterization of pathophysiology of lung disease in beta-ENaC mice has revealed a high number of macrophages with altered morphology, persistent neutrophilic and transient eosinophilic infiltrates, and airway mucus obstruction. The investigators are studying whether the initiation and the course of airway inflammation in beta-ENaC mouse is determined by macrophage activation patterns in the lung.

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CALPAIN IN AIRWAY AND LUNG VASCULAR REMODELING

Yunchao Su, MD, PhD; Augusta University; CIA 2012

Dr. Su and colleagues have found that calpain mediates H_2O_2-induced collagen synthesis and proliferation of bronchial and pulmonary artery smooth muscle cells (BSMCs and PASMCs) and that phosphorylation of calpain-2 contributes to a H_2O_2-induced increase in calpain activity and collagen synthesis. Calpains comprise a family of calcium-dependent non-lysosomal neutral cysteine endopeptidases that act via limited proteolysis of substrate proteins in mammalian cells, including BSMCs and PASMCs. Calpain was shown to mediate H_2O_2-induced collagen synthesis and proliferation of BSMCs and PASMCs via activation of intracellular TGF beta 1. Further, calpain was shown to play an important role in airway and lung vascular remodeling in mice exposed to tobacco smoke.

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SMOKE-INDUCED MUCOCILIARY DYSFUNCTION

Matthias Salathe, MD; University of Miami Miller School of Medicine; CIA 2011

Dr. Salathe and colleagues examined proteins called pannexins that form channels to the outside of the cells and allow ATP secretion onto the airway surface. Tobacco smoke detrimentally slows ciliary beat and dries out the surfaces of the cells lining the airway lumen. The investigators focused on a specific channel that facilitates chloride secretion from airway epithelial cells, and examined in detail how these two channels become dysfunctional in tobacco smoke-associated airway diseases.

FAMRI SUPPORTED RESEARCH

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CILIA REPAIR IN SMOKING RELATED CHRONIC BRONCHITIS

Andreas Schmid, MD; University of Miami Miller School of Medicine; YCSA 2010

Dr. Schmid and colleagues investigated the influence of different Wnt pathway elements in a model of direct cigarette smoke exposure. Overexpression and short hairpin RNA (shRNA) knock out of different frizzled receptors, Wnt proteins, and inhibitors were used to dissect the influence of Wnt elements on ciliogenesis during repair from smoking-related airway epithelial injury. This process is characterized by proliferation and re-differentiation of epithelial cells, and is regulated by developmental signaling mechanisms including retinoic acid (RA) and Wnt. During repair, cells build cilia after intercellular junctions are formed, cell polarity is established, and a certain cell density is reached. This process is preceded by the construction of an apical actin web. Basal bodies dock to this web and Dvl and Vangl2 are attached. Over the time course of ciliogenesis, the expression of several Wnt proteins and frizzled receptors is dynamic and appears to be dependent on the presence of RA.

FAMRI SUPPORTED RESEARCH

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EPITHELIAL BARRIER DISRUPTION IN CHRONIC BRONCHITIS

Maria Monzon-Medina, PhD; University of Miami Miller School of Medicine; YCSA 2009

Dr. Monzon-Medina and her team investigated whether hyaluronan fragments (sHAs) generated by SHS exposure bind layilin, a cell surface HA receptor, triggering a cascade of events that results in Rho activation and loss of epithelial barrier integrity in primary cultures of normal human bronchial epithelial cells. The team expanded preliminary data indicating that sHA induces epithelial barrier disruption and that sHA-induced epithelial disruption is mediated by a layilin-radixin interaction. They determined if HA-induced disruption of epithelial integrity is mediated by RhoA and downstream signaling and defining the role of sHA in epithelial barrier disruption in NHBE cells exposed directly to SHS using the VITROCELL® VC 10® smoking robot.

FAMRI SUPPORTED RESEARCH

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TOBACCO SMOKE AND OXIDATIVE STRESS IN RSV BRONCHIOLITIS

Antonella Casola, MD; University of Texas Medical Branch at Galveston; CIA 2008

Dr. Casola and colleagues showed that respiratory syncytial virus (RSV) infection induces reactive oxygen species (ROS) production *in vitro* and oxidative injury in lungs *in vivo*. Furthermore, they showed that oxidative-driven inflammatory events in RSV-infected epithelial cells are exacerbated by exposure of cells to tobacco products. The investigators determined whether RSV infection of airway epithelial cells modified the expression and/or activities of antioxidant enzymes (AOE). A549 cells (a human alveolar type II-like epithelial cell line), and small airway epithelial (SAE) cells (normal human cells derived from terminal bronchioli), were infected with RSV and F2-8 isoprostanes and total and reduced glutathione (GSH and GSSG) were measured. RSV infection induced an increase of lipid peroxidation products and a decrease in the GSH/GSSG ratio. There was a decrease in super oxide dismutase (SOD 1), SOD 3, catalase, and GST expression with a concomitant increase of SOD 2 in RSV-infected cells compared to uninfected cells. Total SOD activity was increased, but catalase, glutathione peroxidase (GPx), and GST activities were decreased following RSV infection.

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REDOX REGULATION OF SMOKE INDUCED INFLAMMATION

Robert F. Foronjy, MD; Columbia University; CIA 2008

Dr. Foronjy and colleagues determined that superoxide dismutase 1 (SOD1) and gluathione peroxidase 1 (GPX1) expression in the lungs of mice increases protein phosphatase 2A (PP2A) activity, decreases AP-1 activation, and prevents smoke-induced inflammation and emphysema formation. The team found that the increased PP2A activity in GPX1 transgenic mice occurred without affecting PP2A protein or mRNA levels. The investigators showed that GPX1 transgenic mice were completely resistant to cigarette smoke-induced inflammation and did not develop air space enlargement in response to chronic cigarette smoke exposure. It appears that the increased PP2A activity detected within the lungs of the GPX1 mice protected them against the damaging effects of cigarette smoke in the lung. The investigators also found that inhibiting PP2A completely negated the anti-inflammatory effects of GPX1 expression.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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NEUROTROPHINS IN CIGARETTE SMOKE INDUCED AIRWAY HYPERREACTIVITY

Y. S. Prakash, MD, PhD; Mayo Clinic; CIA 2008

Dr. Prakash and colleagues determined whether thymic stromal lymphopoietin (TSLP) represents an important link between cigarette smoke exposure and inflammatory signaling in the airways. The investigators examined the expression and function of TSLP and its receptor (TSLP-R) in human airway smooth muscle (ASM) under normal conditions and following exposure to cigarette smoke extract (CSE). Western blot analysis showed significant expression of TSLP and TSLP-R, with increased expression of both by exposure to 1% or 2% CSE. In parallel experiments, the investigators evaluated the effects of CSE exposure on intracellular Ca2+ ([Ca2+]i) responses to agonist stimulation, which are important in determining bronchoconstriction. The [Ca2+]i responses to histamine were increased with overnight CSE exposure. Exposure to TSLP also resulted in elevated responses that were blunted by a functional TSLP antibody. The enhancing effects of CSE on [Ca2+]i responses were also blunted by a functional TSLP antibody. These effects were associated with CSE- and TSLP-induced changes in STAT5 phosphorylation.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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Aravamudan B, Thompson M, Pabelick C, Prakash YS. Brain-derived neurotrophic factor induces proliferation of human airway smooth muscle cells. *J Cell Mol Med* 2012;16(4):812-823.

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Prakash YS, Sathish V, Thompson MA, Pabelick CM, Sieck GC. Asthma and sarcoplasmic reticulum Ca2+ reuptake in airway smooth muscle. *Am J Physiol Lung Cell Mol Physiol* 2009;297:L794.

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Sathish V, Delmotte PF, Thompson MA, Pabelick CM, Sieck GC, Prakash YS. Sodium-calcium exchange in intracellular calcium handling of human airway smooth muscle. *PLoS One* 2011;6(8):e23662.

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PRESENTATIONS AND ABSTRACTS

Abcejo AJ, Venkatachalem S, Aravamudan B, Meuchel L, Thompson MA, Pabelick C, Prakash YS. TrkB Mediated Brain-Derived Neurotrophic Factor (BDNF) Effects on human airway smooth muscle [abstract]. *Am J Respir Crit Care Med* 2012;185:A4142.

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Aravamudan B, Thompson MA, Pabelick CM, Prakash YS. Signaling mechanisms involved in cigarette smoke-induced alterations in airway smooth muscle mitochondrial morphology

and dynamics. Presented at the American Thoracic Society International Conference. Philadelphia, PA, May 17-22, 2013.

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Vassallo R, Sathish V, Suri H, Sanyal B, Thompson M, Prakash Y. Human airway smooth muscle cells express thymic stromal lymphopoietin receptors [abstract]. *Am J Respir Crit Care Med* 2011;183:A2579.

SIDE-STREAM TOBACCO SMOKE AND NITRIC OXIDE MODIFICATION AND CALPAINS IN AIRWAY EPITHELIAL REPAIR

Yunchao Su, MD, PhD; University of Florida, Augusta University; CIA 2008

Dr. Su and colleagues found that exposure of bronchial epithelial cells (BECs) to side-stream tobacco smoke (STS) or nitric oxide (NO) resulted in a dose-dependent inhibition of cell proliferation. The reduction of monolayer wound repair was not caused by increased cell death. Incubation of BECs with NOC-18 caused an increase in the level of nitrosylated calpain and a decrease in calpain activity. Overexpression of calpastatin, an intracellular-specific calpain inhibitor resulted in a dramatic decrease in calpain activity and in monolayer wound repair and proliferation of BECs. Exposure of mice to STS for 4 weeks caused an increase in the amount of nitrosylated calpain in bronchial epithelium, but not in the wall of blood vessels. Exposure of mice to STS for 4 weeks also caused denudation of epithelial cells in the lungs. These results indicate that STS- and NO-induced inhibition of airway epithelial repair is caused by decreased calpain activity due to nitrosylation of calpain.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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PRESENTATIONS AND ABSTRACTS

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Han W, Wang W, Mohammed K, Su Y. Wnt/.-catenin mediates .-Defensins-induced increases in proliferation and collagen synthesis of lung fibroblasts. Presented at the American Thoracic Society International Conference. San Diego, CA, May 16-21, 2009.

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BOOK CHAPTERS, ETC.

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THE ROLE OF BRONCHIO-ALVEOLAR STEM CELLS IN CIGARETTE SMOKE RELATED EMPHYSEMA

Shivraj Tyagi, PhD; Brigham and Women's Hospital; CIA 2008

Dr. Tyagi and colleagues assessed fibroblast growth factor receptor (FGFR)3/(FGFR)4 deficient mice for temporal changes in lung growth, airspace morphometry, and genome-wide gene expression. There is a failure of secondary crest elongation in the compound mutant mice. Changes in elastic fiber gene expression were shown to result in temporal increases in elastin deposition with the loss of typical spatial restriction. No abnormalities in elastic fiber gene expression were observed in isolated mesenchymal cells from the compound mutant mice, indicating that abnormal elastogenesis is not cell-autonomous. The team identified molecular alterations involving aberrant expression of numerous extracellular matrix (ECM) molecules from RNAs derived from the lung tissue of 56 subjects with varying degrees of airflow obstruction. They identified a gene expression biomarker for COPD, which was validated in an independent data set. They also identified two genes whose expression levels in both lung tissue and peripheral blood are associated with lung function. In further studies, autologous lung-derived mesenchymal stem cells (LMSC) were transplanted endoscopically into sheep with experimental emphysema to assess their capacity to regenerate functional tissue.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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Hoffman A, Paxson JA, Mazan MR, Davis AM, Tyagi SR, Murthy S, Ingenito EP. Lung derived mesenchymal stromal cell post-transplantation survival, persistence, paracrine signaling, and repair of elastase injured lung. *Stem Cells Dev* 2011;10:1779-1792.

Ingenito EP, Tsai L, Murthy S, Tyagi S, Mazan M, Hoffman A. Autologous lung-derived mesenchymal stem cell transplantation in experimental emphysema. *Cell Transplant* 2012;21(1):175-189.

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GOBLET CELL HYPERPLASIA IN CHRONIC BRONCHITIS

Yohannes Tesfaigzi, PhD; Lovelace Respiratory Research Institute; CIA 2007

Dr. Tesfaigzi and colleagues found that exposure to cigarette smoke (CS) reduces expression of the pro-apoptotic protein Bik, and that Bik protein levels are reduced in primary normal human bronchial epithelial cells in culture as well as in the lungs of C57Bl/6 mice that were exposed to CS compared to controls exposed to filtered air. This reduction was sustained in mice that were exposed to CS and allowed to recover in filtered air for 8 weeks. The reduction in Bik expression by CS was associated with an increased number of epithelial cells per millimeter basal lamina and increased expression of Muc5ac

mRNA levels, both immediately after exposure and following 8 weeks of recovery. Analysis of airway cells obtained by bronchial brushings showed that Bik mRNA levels were reduced in chronic bronchitis compared to non-diseased controls. CS treatment did not affect Bik promoter activity but significantly shortened Bik mRNA half-life from 3.1 to 1.4 hours, suggesting that CS reduces Bik expression by destabilizing Bik mRNA. CS exposure reduced Bik expression in wild-type mice, and $bik^{-/-}$ mice showed epithelial cell hyperplasia similar to that observed in bik+/+ mice in response to exposure. However, when Bik expression was restored, metaplasia was significantly reduced compared to cultures infected with the mutant Bik as control. CS exposure activated ERK1/2 in a dose-dependent manner, and Bik caused cell death by interacting with and inhibiting nuclear translocation of activated ERK1/2.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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PRESENTATIONS AND ABSTRACTS

Contreras AU, Tesfaigzi Y. Modulation of histone deacetylase activity regulates Bmf transcription and protein stability to cause cell death in hyperplastic mucous cells [abstract]. *Am J Respir Crit Care Med* 2011;183:A1356.

Mebratu YA, Schuyler M, Schwalm K, Tesfaigzi Y. Bik reduces cigarette smoke-induced epithelial cell hyperplasia by interacting with activated ERK1/2 and cleaving the death associated protein kinase [abstract]. Presented at the American Thoracic Society International Conference. Denver, CO, May 13-18, 2011.

CILIARY DYSFUNCTION IN SECOND HAND TOBACCO SMOKE-INDUCED BRONCHITIS

Matthias Salathe, MD; University of Miami Miller School of Medicine; 2006 CIA

Ciliary beat frequency (CBF) is increased by cyclic adenosine monophosphate (cAMP) through activating axonemal protein kinase A (PKA). There is no transmembrane adenylyl cyclase (tmAC) found along the airway ciliary membrane. On the other hand, cAMP is produced by soluble adenylyl cyclase (sAC), expressed along the axoneme in human airway epithelial cells in response to changes in the carbon dioxide/bicarbonate ratio. The human sAC gene comprises 33 exons, all of which are included in the testicular mRNA that encodes a 187 kDa protein containing two putative catalytic domains. Dr. Salathe and colleagues identified alternatively spliced sAC mRNAs using sAC exon specific primers for RNAs isolated from normal human epithelial (NHBE) cells. The variants include mRNAs without exons 5 and 14, and another variant that is missing exons 3 to 6. Each of these splice

variants changes the coding region and predicts smaller sAC isoforms containing only the second catalytic domain. The identification of alternatively spliced sAC mRNAs may explain the origins of multiple sAC proteins observed in western blots and supports the hypothesis that multiple sAC isoforms may be differentially localized.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Manzanares D, Monzon ME, Savani RC, Salathe M. Apical oxidative hyaluronan degradation stimulates airway ciliary beating via RHAMM and RON. *Am J Respir Cell Mol Biol* 2007;37:160-168.

Nlend MC, Schmid A, Sutto Z, Ransford GA, Conner GE, Fregien N, Salathe M. Calcium-mediated, purinergic stimulation and polarized localization of calcium-sensitive adenylyl cyclase isoforms in human airway epithelia. *FEBS Lett* 2007;581:3241-3246.

Ransford GA, Fregien N, Qiu F, Dahl G, Conner GE, Salathe M. Pannexin 1 contributes to ATP release in airway epithelia. *Am J Respir Cell Mol Biol* 2009;41:525-534.

Salathe M. Regulation of mammalian ciliary beating. *Ann Rev Physiol* 2007;69:401-422.

Schmid A, Bai G, Schmid N, Zaccolo M, Ostrowski LE, Conner GE, Fregien N, Salathe M. Real-time analysis of cAMP-mediated regulation of ciliary motility in single primary human airway epithelial cells. *J Cell Sci* 2006;119:4176-4186.

Schmid A, Sutto Z, Nlend MC, Horvath G, Schmid N, Buck J, Levin LR, Conner GE, Fregien N, Salathe M. Soluble adenylyl cyclase is localized to cilia and contributes to ciliary beat frequency regulation via production of camp. *J Gen Physiol* 2007;130:99-109.

PRESENTATIONS AND ABSTRACTS

Ivonnet P, Conner GE, Salathe M. Hydrogen peroxide-induced CF TR activity is modulated by soluble adenylyl cyclase [abstract]. *Am J Respir Crit Care Med* 2009;179:A1207.

Manzanares D, Valencia Gattas M, Ivonnet P, Conner GE, Salathe M. Maxi-K (BK) channels contribute to nucleotide-stimulated chloride secretion and mucociliary transport in normal and cystic fibrosis airway cells [abstract]. *Am J Respir Crit Care Med* 2009;179:A1208.

Valencia Gattas M, Salathe M, Conner GE. Duox2 expression regulates basal hydrogen peroxide production in airway epithelial cells [abstract]. *Am J Respir Crit Care Med* 2009;179:A4171.

PROTEIN FINGERPRINT OF AIRWAY INFLAMMATION INDUCED BY VIRAL INFECTION AND SECONDHAND TOBACCO SMOKE EXPOSURE

Roberto P. Garofalo, MD; University of Texas Medical Branch at Galveston; CIA 2005

Dr. Garofalo and colleagues investigated whether exposure to SHS exacerbates airway disease by enhancing or modifying the pattern of production of cytokines and other immunomodulatory and/ or inflammatory protein mediators triggered by viral infection. Nasopharyngeal secretions were obtained from infants during the acute phase of antigen/culture-positive respiratory syncytial virus (RSV) infection of different clinical severities. The team examined the profile of mucosal cytokines in these infants and

determined whether pattern of expression and/or abundance is affected by exposure to SHS and analyzed whether distinct protein patterns at the airway mucosal site can discriminate among infants with different severities of the RSV illness or exposure to SHS.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Castro S, Kolli D, Guerrero-Plata A, Garofalo RP, Casola A. Cigarette smoke condensate enhances respiratory syncytial virus-induced chemokine release by modulating NF-kappa B and interferon regulatory factor activation. *Toxicol Sci* 2008;106:509-518.

Hosakote YM, Liu T, Castro SM, Garofalo RP, Casola A. Respiratory syncytial virus (RSV) induces oxidative stress by down regulation of antioxidant enzymes in the lung. *Am J Respir Cell Mol Biol* 2009;41(3):348-357.

Hosakote YM, Jantzi P, Schiblisky P, Esham D, Casola A, Garofalo RP. Viral-mediated inhibition of antioxidant enzymes contributes to the pathogenesis of severe RSV bronchiolitis. *Amer J Resp Critic Care Med* 2011;183:1550-1560.

SMOKE-INDUCED DYSREGULATION OF AIRWAY AQUAPORINS

Landon S. King, MD; Johns Hopkins Medical Institutions; CIA 2004

Aquaporin 5 (AQP5) is one of a family of water specific membrane channel proteins that determine water permeability. They have been shown to be dynamically regulated by pathophysiologically relevant stimuli. Dr. King and colleagues investigated whether cigarette smoke alters the expression and distribution of AQP5 in lung epithelium and contributes to altered secretions and pathogenesis of chronic bronchitis. The team investigated this by 1) exposing the lung epithelial cell lines to cigarette smoke and examining AQP5 abundance; 2) determining the effects of cigarette smoke condensate on AQP5 subcellular distribution in cultured cells; and 3) assessing differential gene expression in tracheal cells from wild-type and AQP5-null mice exposed to cigarette smoke. The findings show that the expression patterns of several proteins predicted to contribute to the generation and biophysical properties of the lung surface airway layer are altered within a few hours of cigarette smoke extract exposure.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Sidhaye VK, Chau E, Breysse P, King LS. Septin-2 mediates airway epithelial barrier function in physiologic and pathologic conditions. *Am J Respir Cell Mol Biol* 2011;45(1):120-126.

Sidhaye VK, Güler AD, Schweitzer KS, D'Alessio F, Caterina MJ, King LS**.** Transient receptor potential vanilloid 4 regulates aquaporin-5 abundance under hypotonic conditions. *Proc Natl Acad Sci U S A* 2006;103(12):4747-4752.

MATRIX-INDUCED EPITHELIAL ACTIVATION IN BRONCHITIS

Maureen Horton, MD; Johns Hopkins Medical Institutions; YCSA 2003

Dr. Horton and colleagues defined the ability of fragments of the extracellular matrix component hyaluronan (HA) to promote epithelial cell-induced inflammation. The team

determined that HA fragments employ innate immune Toll-like receptor-2 (TLR-2) to mediate its effects. Blocking TLR-2 inhibits HA fragment-induced inflammation and disease, and TLR-2-deficient animals are protected from noninfectious lung injury. HA fragments induce IL-8 and inducible protein 10 gene expression in airway epithelial cells by different signaling pathways, mitogen-activated protein kinase (MAPK), and nuclear factor-kappa B, respectively. Broken down extracellular matrix, in the form of HA fragments, appears to employ the same activating receptors as infectious agents, thus provides a mechanism by which HA can promote the chronic inflammation of bronchitis in the absence of infection.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Boodoo S, Spannhake EW, Powell JD, Horton MR. Differential regulation of hyaluronan-induced IL-8 and IP-10 in airway epithelial cells. *Am J Physiol Lung Cell Mol Physiol* 2006;291(3):L479-486.

Eberlein M, Scheibner KA, Black KE, Collins SL, Chan-Li Y, Powell JD, Horton MR. Anti-oxidant inhibition of hyaluronan fragment-induced inflammatory gene expression. *J Inflamm* (Lond) 2008;5:20.

Heikamp EB, Patel CH, Collins S, Waickman A, Oh MH, Sun IH, Illei P, Sharma A, Naray-Fejes-Toth A, Fejes-Toth G, Misra-Sen J, Horton MR, Powell JD. The AGC kinase SGK1 regulates TH1 and TH2 differentiation downstream of the mTORC2 complex. *Nat Immunol* 2014;15(5):457-464.

Horton MR, Danoff SK, Lechtzin N. Thalidomide inhibits the intractable cough of idiopathic pulmonary fibrosis. *Thorax* 2008;63(8):749.

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Scheibner KA, Boodoo S, Collins S, Black KE, Chan-Li Y, Zarek P, Powell JD, Horton MR. The adenosine a2a receptor inhibits matrix-induced inflammation in a novel fashion. *Am J Respir Cell Mol Biol* 2009;40(3):251-259.

Scheibner KA, Lutz MA, Boodoo S, Fenton MJ, Powell JD, Horton MR. Hyaluronan fragments act as an endogenous danger signal by engaging TLR2. *J Immunol* 2006;177(2):1272-1281.

Zarek PE, Huang CT, Lutz ER, Kowalski J, Horton MR,Linden J, Drake CG, Powell JD. A2A receptor signaling promotes peripheral tolerance by inducing T-cell anergy and the generation of adaptive regulatory T cells. *Blood* 2008;111:251-259.

SECOND HAND TOBACCO SMOKE WORSENS RSV BRONCHIOLITIS BY CYSTEINYL LEUKOTRIENE

Jesse P. Joad, MD; University of California, Davis; CIA 2002

Dr. Joad and colleagues determined whether SHS exposure increases urinary cysteinyl leukotriene E4 (uLTE4) in well infants and in those hospitalized for respiratory syncytial virus (RSV) bronchiolitis. They also determined if SHS exposure increases length of hospital stay for those with RSV bronchiolitis and if infants with parent(s) with asthma have higher

uLTE4. High SHS exposure and RSV significantly increased uLTE4. The SHS-induced increase in uLTE4 was seen in infants with no parental asthma but not in those with parental asthma. Length of hospital stay positively correlated with uLTE4. SHS exposure may increase the severity of bronchiolitis RSV-infected infants by enhancing production of cysteinyl leukotrienes in infants with no parental asthma.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Kott KS, Salt BH, McDonald RJ, Jhawar S, Bric JM, Joad JP. Effect of secondhand cigarette smoke, RSV bronchiolitis and parental asthma on urinary cysteinyl LTE4. *Pediatr Pulmonol* 2008;43:760-766.

SMOKE AND SUSCEPTIBILITY TO RESPIRATORY INFECTION

Lester Kobzik, MD; Harvard University; CIA, 2002

Dr. Kobzik investigated whether cigarette smoke downregulates levels of class A receptors, such as macrophage receptor with collagenous structure (MARCO), mediators of initial binding of unopsonized bacteria and environmental particles, on human alveolar macrophages. He also determined if cigarette smoke-mediated decreased expression of MARCO results in a decreased ability to bind and kill bacteria and if the effect of cigarette smoke particulates on MARCO levels is mediated by oxidant-mediated pathways that can be ameliorated by antioxidants. Secondhand and mainstream tobacco smoke exposure showed decreases in expression of one of the major scavenger receptors on human alveolar macrophages as well as a decrease in bacterial ingestion.

FAMRI SUPPORTED RESEARCH

PRESENTATIONS AND ABSTRACTS

Haley KJ, Manoli SE, Tantisira KG, Litonjua AA, Nguyen P, Kobzik L, Weiss ST. Maternal smoking causes abnormalities of the vitamin D receptor [abstract]. *Am J Respir Crit Care Med* 2009;179:A5874.

NONINVASIVE ASSESSMENT OF THE LOWER RESPIRATORY TRACT IN RESPONSE TO SECONDHAND TOBACCO SMOKE

Richard A. Robbins, MD, PhD; Carl T. Hayden VA Medical Center; CIA 2002

Dr. Robbins and colleagues collected exhaled breath condensate (EBC), bronchoalveolar lavage (BAL), and sputum from 35 subjects: 15 smokers, 10 non-smokers, 4 former smokers, and 6 non-smokers heavily exposed to SHS. The samples were collected from the same individuals on the same day. Total protein was elevated in sputum compared to BAL or EBC. Sputum contained a higher percentage of neutrophils compared to BAL. The neutrophils were elevated in smokers' sputum and BAL compared to non-smokers. Individuals exposed to SHS were intermediate between the smokers and non-smokers. Similarly, protein was elevated in the sputum, BAL, and EBC of the smokers compared to the non-smokers and those exposed to SHS; protein was only higher in BAL of those exposed to SHS compared to non-smokers.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Garey KW, Neuhauser MM, Robbins RA, Danziger LH, Rubinstein I. Markers of inflammation in exhaled breath condensate of young healthy smokers. *Chest* 2004;125:22-26.

Numanami H, Koyama S, Nelson DK, Hoyt JC, Freels JL, Habib MP, Amano J, Haniuda M, Etsuro Sato E, Robbins RA. Serine protease inhibitors modulate smoke-induced chemokine release from human lung fibroblasts. *Am J Resp Cell Mol Biol* 2003;29:613-619.

PRESENTATIONS AND ABSTRACTS

Garcia A, McHugh M, Ballering JG, Hoyt JC, Hayden JM, Robbins RA. Neutrophils, protein and LTB4 are increased in sputum compared to bronchoalveolar lavage and exhaled breath condensate [abstract]. *Am J Resp Crit Care Med* 2005;171:A844.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Completed Research

TRISTETRAPROLIN IN CONTROL OF INFLAMMATION

Qiang Ding, PhD; University of Alabama at Birmingham; CIA 2015

Persistent inflammation plays a major role in COPD pathogenesis. The mechanisms leading to the persistent inflammation in COPD have not been completely defined. Tristetraprolin (TTP) is an AU-rich element (ARE)-binding protein. Preliminary data demonstrate that TTP controls the expression of several pro-inflammation mediators, including tumor necrosis factor (TNF-alpha), IL-8 (CXCL1/KC), and IL1-beta. TPP negatively regulates the expression of these mediators by promoting their mRNA degradation. Expression of pro-inflammation mediators plays important role in tobacco smoke-induced emphysema. TTP functions as an anti- inflammation regulator in response to SHS exposure. Preliminary data demonstrate that TTP function is impaired by cigarette smoke (CS) exposure, and that impaired TTP function results in increased and prolonged expression of pro-inflammatory mediators. The hypothesis is that CS exposure inhibits the function of TTP as an mRNA destabilizing protein. This results in increased mRNA stability and protein expression of pro-inflammation mediators, thereby contributing to persistent inflammation and lung injury induced by CS exposure. The investigators are studying the role of TTP as a negative regulator of pro-inflammatory mediator expression induced by CS exposure, and determining the role of p38 MAPK in TTP-downregulation induced by CS exposure as well as the mechanisms involved. They will investigate the effect of loss and gain of TTP on pro-inflammatory mediator expression and on lung epithelial cell death/survival *in vivo*. The findings of this project should provide insights regarding the mechanism by which SHS exposure induces persistent inflammation. The long-term goal to design therapeutic interventions that limit the persistent inflammation induced by SHS exposure.

FAMRI SUPPORTED RESEARCH

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INFLAMMASOME SIGNALING IN COPD AND EMPHYSEMA

Sanjay Batra, PhD; Southern University Baton Rouge; YCSA 2013

Cytosolic NOD-like receptors (NLRs) belong to a family of pattern recognition receptors that initiate pro-inflammatory signaling pathways and have not been extensively studied in terms of their role in CS-mediated responses such as those seen in COPD. The investigators are determining the role of NLRP10 in regulating inflammatory responses upon CS-exposure using *in vivo* and *in vitro* experiments to elucidate phenomena that are NLRP10-mediated.

FAMRI SUPPORTED RESEARCH

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ROLE OF LOWER AIRWAY DYSBIOSIS IN THE DEVELOPMENT OF COPD

Benjamin Wu, MD; New York University School of Medicine; YCSA 2016

Dr. Wu is investigating the role of microbes in COPD. Tobacco exposure is the best-known risk factor in the development of COPD, but the roles of SHS exposure and microbes in the early stages of disease are not well understood. Dr. Wu has conducted studies that show that a distinct lung microbiome (called a pneumotype) consisting of supraglottic predominant taxa (pneumotype SPT) is associated with increased markers of inflammation. The use of culture-independent techniques reveal that the lungs contain a complex microbial community (microbiome) containing microbes normally found in the oral cavity (human oral commensals). This unique lung microbiome consisting of human oral commensals is associated with upregulated TH17 inflammation. Thus, a disrupted lung microbiome with human oral commensals (dysbiosis) may enhance inflammation caused by SHS exposure. The investigators hypothesize that during SHS exposure, enrichment of

the lower airway microbiome with human oral anaerobes is required for the transition from a healthy subject status to a Th17 inflammatory COPD phenotype. The investigators are exploring causative mechanisms among the microbiota, inflammation, and SHS exposure. Dysbiosis exposure is required for Th17 inflammation on a smoke exposure background. This observation may explain why sub-populations of COPD patients have difficult to treat symptoms. Dysbiosis with SHS exposure may represent a potential target for treatment of COPD.

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SHARED SUSCEPTIBILITY TO COPD AND CVD

Robert Reed, MD; University of Maryland; YCSA 2013

There is a need for pharmacologic therapies improving survival in COPD. A better understanding of the genetic susceptibilities leading to COPD will facilitate both the development and testing of new therapeutic agents. Susceptibilities to COPD and cardiovascular disease (CVD) appear to overlap, and these conditions co-exist in excess of that which can be explained by common risk factors including tobacco exposure. The

mortality risk significantly increases in patients with combined COPD and CVD compared to the mortality risk of each individual condition. The common susceptibilities are poorly understood and remain a barrier to the optimal treatment of each condition. The investigators have undertaken a translational genetic study to examine the hypothesis that multiple gene variants act in synergy via a pathway of endothelial dysfunction and monocyte/macrophage recruitment and activation to result in increased susceptibility to both COPD and CVD. Identification of a common pathway would facilitate development of future therapies for both conditions and could be used to genetically personalize future clinical trial designs.

FAMRI SUPPORTED RESEARCH

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MIF-CD74 IN COPD

Patty J. Lee, MD; Yale University; CIA 2016

Dr. Lee and colleagues have identified an innate immune protein, macrophage migration inhibitory factor (MIF), and its receptor, CD74, as endogenous protective molecules that determine susceptibility to COPD. They found that MIF expression decreases with age and/or chronic tobacco smoke exposure. Further, they have shown that the genetic loss of MIF-CD74 leads to COPD in mice. The team reported lower MIF levels in people with COPD compared to those without COPD; these findings have been confirmed in two other human COPD cohorts. In this study, the investigators are investigating whether MIF-CD74 is critical in protecting against cigarette smoke-induced COPD, and if MIF-CD74 augmentation can be therapeutic.

FAMRI SUPPORTED RESEARCH

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BIOMARKERS OF ELASTIN DEGRADATION IN PROLONGED SECONDHAND SMOKE EXPOSURE

Gerard M. Turino, MD; Mehrdad Arjomandi, MD; Icahn School of Medicine at Mount Sinai/San Francisco General Hospital Foundation

It is recognized from the alpha-1 antitrypsin deficiency (AATD) genetic cause of pulmonary emphysema that increased degradation of body and lung elastin leads to pulmonary emphysema even in non-smokers. Two amino acids, desmosine and isodesmosine (DI) are present in the body and lung only in elastic tissue. DI can be measured in body fluids such as plasma, urine, and sputum as evidence of the degree of elastin degradation by elastases. Prior published studies have demonstrated increased levels of DI in plasma of individuals exposed to SHS. Flight Attendants working through the 1960s to 1980s were occupationally exposed to SHS. An evaluation of the current clinical health status and levels of biomarkers in plasma can provide insights into the long-term risks of exposure to SHS. Preliminary measurements of DI in plasma indicate elevations above normal in most of 27 plasma samples from former Flight Attendants. The investigators are measuring plasma levels of DI in approximately 100 Flight Attendants per year for 3 years to relate levels of biomarkers to the current clinical health status and pulmonary function.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Mustra Rakic J, Zeng S, Rohdin-Bibby L, Van Blarigan EL, Liu X, Ma S, Kane JP, Redberg RF, Turino GM, Oestreicher Stock E, Arjomandi M. Elastin degradation and lung function

deterioration with remote secondhand tobacco smoke exposure in never-smokers. *Chronic Obstr Pulm Dis*. 2022;9(3):377-393.

PRESENTATIONS AND ABSTRACTS

Arjomandi M, Stock E, Zeng S, Weldemichael L, Nishihama M, Hunt C, Ching W, Bibby LR, Liu X, Ma S, Redberg R, Turino G. Elastic degradation markers are elevated in never-smokers with history of prolonged exposure to secondhand tobacco smoke and are inversely associated with lung function. Presented at the American Thoracic Society Virtual Conference. Aug 5-Nov 10, 2020.

THE EFFECT OF CHLORHEXIDINE ON THE ORAL AND LUNG MICROBIOTA

Christine Wendt, MD; Minnesota VA Medical Center; CIA 2016

The lower respiratory tract in patients with COPD often contain bacteria even during periods of stable disease. This microbiota may be a key factor in the pathogenesis of COPD. Current culture-independent methods to describe the microbiota rely on the analysis of the bacterial 16S rRNA gene, which provides a sensitive method of determining which bacterial species are present in complex environmental mixtures. The investigators hypothesize that COPD patients have an altered lung microbiota that reflects the oral microbiota, which contributes to disease manifestation. The benefit of oral decontamination in the treatment of COPD remains unknown. Chlorhexidine is a cationic polybiguanide used as a topical broad-spectrum antiseptic and is shown to decrease respiratory infection associated with oral intubation. The investigators are determining if twice-daily chlorhexidine oral rinse decreases the microbiota biomass in the COPD lung and oral cavity as measured in induced sputum and oral wash in a randomized, double blind, placebo controlled pilot trial. Participants were drawn from patient populations that include those with COPD, those who are non-edentulous, and current or ex-smokers who have symptoms of chronic bronchitis and a history of at least one COPD exacerbation requiring treatment in the past year. Using these criteria, the investigators are targeting those most at risk for exacerbation. They are determining if chlorhexidine oral rinse 1) decreases lung and oral microbiota diversity and taxonomic composition, 2) decreases inflammatory markers, 3) changes respiratory health status, and 4) is safe and well tolerated.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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TARGETING HISTONE H3.3 RECEPTORS AS A NOVEL APPROACH TO PREVENT COPD PROGRESSION

Carlos Barrero, MD; Temple University; YCSA 2015

Dr. Barrero and colleagues have shown via proteomics that aberrant extracellular histone H3.3 (H3.3) is increased in the lungs of patients with COPD and plays a critical role in the progression of the disease. Cigarette smoke exposure causes accumulation of the hyperacetylated H3.3 isoform, which is resistant to proteasomal degradation in COPD patients. The investigators overexpressed H3.3 in bronchoepithelial cells and used these cells to identify inositol 1,4,5 trisphosphate receptor type 3 as the most probable H3.3 receptor. A murine model for COPD has been developed that is being used to investigate the role of H3.3 and its complex in the pathogenesis of COPD.

FAMRI SUPPORTED RESEARCH

PRESENTATIONS AND ABSTRACTS

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NEUTROPHIL REGULATION OF INSULIN/IGF-1-MEDIATED CELLULAR SENESCENCE IN COPD

Alyssa Gregory, PhD; University of Pittsburgh; YCSA 2015

Dr. Gregory and colleagues have demonstrated that the abundantly- expressed neutrophil proteinase, neutrophil elastase (NE), degrades insulin receptor substrate-1 (IRS-1) an important adapter protein in the insulin/IGF-1 signaling pathway, a critical regulator of cellular proliferation and senescence. The investigators have conducted cigarette smoke (CS) exposure studies on a number of different mouse strains. SVEV/129 wild type mice were found to be resistant to emphysema, but ablation of IRS-1/-2 resulted in emphysema six months after CS exposure. This finding suggests that loss of an intact IGF-1 signaling pathway increases susceptibility to smoke. Further, treating C57Bl/6 wild type mice with daily intraperitoneal injections of recombinant IGF-1 protects against the development of emphysema. These complimentary experiments demonstrate that IGF-1 signaling is protective in the animal model of emphysema.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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MOLECULAR MECHANISMS OF VIRAL DISEASE ENHANCEMENT BY TOBACCO SMOKE EXPOSURE

Maria Antonieta Guerrero-Plata, PhD; Louisiana State University; CIA 2015

Exposure to SHS is a major cause of mortality and morbidity among children. It is associated with an increase in frequency and severity of lower respiratory tract infections (LRTI), bronchiolitis, asthma, pneumonia, sepsis, and COPD. Maternal smoking during pregnancy and exposure of infants to cigarette smoke is associated with adverse health effects in childhood, including higher susceptibility to respiratory viral infection, suggesting that the *in utero* and postnatal periods are crucial determinants for future susceptibility to infection. The aim of this study is to dissect the mechanisms responsible

for increased severity to respiratory infection, which is clinically important for the design of treatment strategies. The innate immune system is the first line of host defense against pathogens and plays a critical role in the recognition and response to respiratory viral infections via pattern recognition receptors (PRR). These receptors trigger inflammatory and antiviral responses in the lung of infected hosts. Previous data have shown that cigarette smoke alters the production of type I IFN as well as the expression and activation of TLR7 in response to respiratory syncytial virus (RSV) in human plasmacytoid dendritic cells. RSV is the most important cause of LRTI among young infants and there is a direct correlation of exacerbation when children are previously exposed to SHS. The hypothesis is that prenatal exposure to tobacco smoke affects the ability of the innate immune system to fight respiratory viral infections by interfering with the innate immune system in the lung. The hypothesis will be tested in an established mouse model of *in utero* SHS exposure. The investigators will determine the effect of SHS on the expression of PRR in response to viral infection. They will also identify the altered molecules in the cytokine signaling pathways, the effect on the proinflammatory response to viral infection, and the effect of combined *in utero* and postnatal tobacco smoke exposure on the expression on antiviral immune response. This should help to elucidate critical aspects of the complex interplay between smoke exposure and increased respiratory viral disease and lead toward human translational research to develop new treatment strategies for SHS-related diseases.

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METABOLIC REPROGRAMMING IN PATIENTS WITH COPD

Xiangming Ji, PhD; Georgia State University; YCSA 2015

Dr. Ji and colleagues are testing the hypothesis that cigarette smoking induces metabolic reprogramming in the airway epithelium and promotes the development of COPD. They identified key metabolic alterations associated with COPD disease progression. They performed shotgun proteomic analysis to identify the overexpression of metabolic enzymes regulating glucose consumption, lactate production, glutamine reductive carboxylation, and pentose phosphate pathway from brushings of the airways of patients with different severity of disease. The observations were verified using metabolic flux analysis in an *in vitro* model of long-term exposure of bronchial airway epithelial cells to cigarette smoke condensate (CSC). Further, the team characterized the metabolomics profile of these cells upon CSC exposure with gene expression analysis (Nanostring) and liquid chromatography-mass spectroscopy to uncover as series of metabolic dysregulations. The preliminary data suggest that metabolic reprogramming happens early in the pathogenesis of the disease. What remains unknown is how these alterations regulate the development of COPD as a phenotype. Currently the investigators are studying the molecular pathogenesis of COPD by focusing on the early detection and prevention by targeting specific metabolic pathways.

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NITRIC OXIDE COUPLING AND BH4 AVAILABILITY ROLES IN MUSCLE DYSFUNCTION WITH COPD

Gwenael Layec, PhD; Anthony Donato, PhD; University of Utah; YCSA 2015

COPD is characterized by the progressive development of inflammation-induced airflow limitation, parenchymal destruction, and other systemic manifestations. It is of particular interest that skeletal muscle dysfunction is a frequent and clinically relevant systemic consequence of COPD that predicts morbidity and mortality, independent of the severity of lung function impairment. Oxidative stress has been suggested to play a major role in the

development of limb dysfunction with COPD. In other diseased states that are characterized by chronic oxidative stress (e.g., aging and cardiovascular disease), dysfunctional O2 transport and muscle metabolism in the periphery have been linked to a lower nitric oxide (NO) bioavailability and nitric oxide synthase (NOS) uncoupling induced by a deficit in tetrahydrobiopterin (BH4). Evidence of BH4 deficit-induced NOS uncoupling on the development of peripheral dysfunction with COPD is still lacking; therefore, the goal of this project is to address this gap by elucidating the role of BH4 bioavailability and NOS coupling on peripheral O2 transport and use in patients suffering from COPD, with the prospective that BH4 supplementation may be able to restore peripheral function and improve quality of life. Accordingly, the investigators are exploring whether the severity of peripheral dysfunction during exercise in patients with COPD is related to the level of oxidative stress, as well as BH4 and NO bioavailability. They will examine the effects of acute and chronic alterations in NO bioavailability on the level of oxidative stress, with the ultimate goal of restoring vascular function, overall functional capacity, and improvement of quality of life in patients with COPD. The team is using a comprehensive approach combining *in vivo* measurements of O2 transport and consumption in exercising muscle, and *in vitro* methods utilizing molecular techniques to assess the level of oxidative stress.

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NOVEL PROTECTIVE ACTIVITIES FOR ADAM8 IN COPD CAUSED BY SECOND-HAND TOBACCO SMOKE (SHS)

Francesca Polverino, MD; University of Arizona Health Sciences Center; YCSA 2015

Dr. Polverino has shown that levels of a proteinase with a disintegrin and a metalloproteinase (MP) domain-8, (ADAM8), are reduced in the lungs of SHS-exposed mice and humans. SHS-exposed Adam8-/- mice have increased airway remodeling, higher lung macrophage counts, and more emphysema than SHS-exposed wild type mice. This study is designed to provide new knowledge about the biology and activities of ADAM8 for a foundation for future studies directed at developing and testing the efficacy of therapies aimed at boosting ADAM8 levels in the lung. This strategy may lead to an increase the anti-inflammatory reserve of the lung, which may limit progression of disease and reduce COPD morbidity and burden of symptoms due to SHS exposure.

FAMRI SUPPORTED RESEARCH

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PROTECTIVE EFFECT OF BMP4 IN AIRWAY AND LUNG VASCULAR REMODELING OF SHS-INDUCED COPD

Yunchao Su, MD, PhD; Augusta University; CIA 2015

A key feature of pathological alteration in COPD is airway and pulmonary vascular remodeling. In remodeling, inflammatory mediators and growth factors are released in great abundance from activated inflammatory cells or structural cells such as epithelial, endothelial, and smooth muscle cells. These inflammatory mediators activate calpain in bronchial and pulmonary artery smooth muscle cells (BSMCs and PASMCs), leading to intracrine transforming growth factor beta one (TGF B1) activation, cell proliferation, and collagen synthesis in airway and pulmonary vascular remodeling. Bone morphogenetic protein 4 (BMP4), a protein in the TGF beta superfamily, regulates growth, differentiation, and apoptosis in BSMCs and PASMC. In preliminary experiments, the investigators found that BMP4 inhibits platelet-derived growth factor (PDGF)- and interleukin-6 (IL-6)-induced calpain activation, collagen synthesis, and cell proliferation. BMP4 levels are much lower in lungs of tobacco smoke (TS)-exposed mice and COPD patients. The hypothesis is that BMP4 exerts a protective effect in airway and lung vascular remodeling of COPD. The investigators are determining whether BMP4 antagonizes PDGF- and IL-6-induced collagen synthesis and hyperproliferation of BSMCs and PASMCs via the BMP receptor- PKA pathway; They are also determining whether the suppressive effect of BMP4 on PDGF- and IL-6-induced collagen synthesis and hyperproliferation is caused by a PKA-mediated inhibition of the calpain-intracrine TGF beta signaling pathway in BSMCs and PASMCs, and they are investigating whether BMP4 reduces airway and lung vascular remodeling in an animal model of SHS-induced COPD. An understanding of the mechanistic insight of the protective effect of BMP4 should provide a strong rationale for manipulating BMP and calpain activities in the treatment of COPD.

FAMRI SUPPORTED RESEARCH

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COMPONENTS OF SECONDHAND SMOKE IN COPD

Alison Bauer, PhD; University of Colorado, Denver; CIA 2014

Polycyclic aromatic hydrocarbons (PAHs) are major toxicants in secondhand and thirdhand smoke exposure. Little is known about the non-genotoxic low molecular weight (LMW) PAHs (e.g., fluoranthene) despite their high concentrations in SHS and thirdhand smoke, and their potential role in inflammatory lung diseases, such as COPD. Preliminary data demonstrated that LMW PAHs and cigarette smoke condensate activated p38 mitogen activated protein kinase (p38 MAPK) followed by the induction of inflammatory markers

associated with COPD development, and dysregulation of gap junctional intercellular communication (GJIC, a crucial mechanism in maintaining tissue homeostasis) in mouse and human lung epithelial cells, properties indicative of early COPD events. Further, p38 MAPK is activated in several cell types in COPD patients and is a current target for therapy, although liver toxicity and compensatory mechanisms may limit utility. PAHs are key constituents of air pollution and are a contributor to lung diseases such as COPD. These studies provided an improved understanding of how the nongenotoxic LMW PAHs contribute to the early stages of COPD, identified potential new therapeutic targets (e.g., GJIC), and provided additional data to improve risk assessment for PAHs.

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CIGARETTE SMOKE IMPAIRS ALPHA-1-ANTITRYPSIN FUNCTION

Hong Wei Chu, MD; National Jewish Health; CIA 2014

Studies were performed to determine the effects of alpha 1-antitrypsin in virus- and bacteria- mediated infection and inflammation in the absence or presence of cigarette smoke (CS) exposure. Alpha 1-antitrypsin treatment prevents the increase of rhinovirus load in CS-exposed normal and COPD airway epithelial cells, which is associated with reduced viral receptor ICAM-1 expression. The data suggest that alpha 1-antitrypsin has a therapeutic effect of during human rhinovirus infection. Alpha 1-antitrypsin treatment in normal and COPD airway epithelial cells significantly reduced pro-inflammatory cytokine IL-8 production induced by CS exposure and human rhinovirus infection. COPD cells are less responsive to the anti-inflammatory effect of alpha 1-antitrypsin than normal cells. Mechanistically, alpha 1-antitrypsin exerted the anti-inflammatory function in part by reducing caspase-1 activity in normal cells, but not in COPD cells. In mice, alpha 1-antitrypsin significantly reduced rhinovirus-induced lung neutrophilic inflammation. The weaker anti-inflammatory effect of alpha 1-antitrypsin in COPD cells suggests the need of a combinational therapy of alpha 1-antitrypsin with other anti-inflammatory drugs, such as corticosteroids, to more effectively reduce lung inflammation during acute exacerbations of COPD. The investigators also found that alpha 1-antitrypsin significantly reduced lung inflammation and bacterial load in mice with cystic fibrosis-like lung disease. These results suggest a therapeutic role for alpha 1-antitrypsin in lung infections with pathogens such as *Pseudomonas aeruginosa* that are often seen in patients with cystic fibrosis and COPD.

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ROLE OF OCTN1 IN TOBACCO-RELATED COPD

Carsten Ehrhardt, PhD; Trinity College Dublin; CIA 2014

The investigators performed molecular biological studies that confirmed expression of organic cation transporter novel 1 (OCTN1) in mouse lungs and human respiratory epithelial cells. They also studied uptake and transport using the OCTN1 substrate ergothioneine (ESH) to determine functional activity of OCTN1 in human respiratory epithelial cells. Measurements of cytotoxicity cellular reactive oxidative stress (ROS) showed that cellular uptake of ESH by OCTN1 protects human respiratory epithelial cells from cigarette smoke extract-related insults. SHS exposure studies provided evidence that *Octn1* knock out mice develop more signs of emphysema and airway inflammation than control animals. *In vitro* studies using human respiratory epithelial cells showed that exposure to ESH at physiological levels resulted in upregulation of a number of antioxidant enzymes. Exposure of these cells to electrophilic toxicants formed ESH conjugates, a sign of a cellular detoxification mechanism. Genetic analysis of COPD patient samples from the University Medical Center Groningen biobank showed that the gene encoding OCTN1 is an expression quantitative trait locus and that there are several polymorphisms in this gene that are associated with development of COPD. A correlation was established between OCTN1 mRNA and lung function using bronchial brushings from an Irish COPD patient cohort.

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PROTECTIVE EFFECTS OF COG133 IN COPD

Robert F. Foronjy, MD; SUNY Downstate Medical Center; CIA 2014

Dr. Foronjy and colleagues have previously shown that protein phosphatase 2A (PP2A) counters the damage done by cigarette smoke in the lung. In this study, they used PP2A knockout mice that do not express PP2A within the airways to show that apolipoprotein E COG 133 mimetic peptide (COG 133) treatment decreases lung inflammation and activates PP2A in cigarette smoke-exposed mice. Further, COG 133 counters keratinocyte-derived protein expression in macrophages from smoke-exposed mice and c-Jun N-terminal kinase activation is decreased. The loss of PP2A expression in mice enhances cigarette smoke-induced immune cell infiltration into the airways. PP2A and PTP1B activity is decreased in primary HBE cells isolated from COPD donors compared to healthy subjects and MMP-2 expression and activity in primary HBE cells is decreased by COG133 administration in

every donor. The impact of COG133 on cigarette smoke-induced emphysema will be determined in newly funded studies.

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NEUTROPHIL DEATH IN TOBACCO-INDUCED COPD

Hongbo R. Luo, PhD; Children's Hospital at Harvard University; CIA 2014

Previous studies from this group demonstrated that inhibition of inositol hexakisphosphate kinase 1 (InsP6K1) is a causal mediator of cigarette smoke-induced upregulation of phosphotidylinositol(3,4,5)P3/protein kinase B [PtdIns(3,4,5)P3/Akt] signaling and delay of neutrophil spontaneous death. Inositol hexakisphosphate kinase 1 (InsP6K1) activity was enhanced during neutrophil death, and cigarette smoke exposure inhibited cellular InsP6K1 activity. The function of the Akt pathway and its regulation by InsP6K1 in controlling *in vivo* neutrophil death and the severity of inflammation-induced lung damage was investigated in a mouse CS-induced COPD model. Inhibiting Akt signaling augments neutrophil death, while disruption of InsP6K1 intrinsically inhibits neutrophil death in CS-induced COPD. Inhibiting PI3K/Akt signaling significantly decreased the accumulation of lung neutrophils and alleviated pulmonary inflammation and damage, while disruption of InsP6K1 led to elevated neutrophil accumulation and enhanced pulmonary inflammation in CS-induced COPD. CS-induced upregulation of PtdIns(3,4,5)P3/Akt signaling is likely mediated by InsP6K1 phosphorylation by casein kinase 2. These results provide insight into the physiological functions of Akt and InsP6K1 in modulating *in vivo* neutrophil death in COPD, but also further solidify Akt, InsP6K1, and related pathways as legitimate therapeutic targets for the treatment of CS-induced COPD.

FAMRI SUPPORTED RESEARCH

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NOVEL F BOX ANTI-INFLAMMATORIES FOR COPD

Rama Mallampalli, MD; University of Pittsburgh; CIA 2014

The hypothesis of this study is that F-box protein 3 (FBXO3), transcriptionally upregulated in response to bacterial pathogens, impairs the ability of F-Box and Leucine Rich Repeat Protein 2 (FBXL2) to limit inflammasome and metalloproteinase (MMP) activation. As a corollary to this hypothesis, a preclinical development of a F-box antagonist may be capable of reducing both the severity of inflammation and the bacterial burden in a COPD model by inhibiting activity of the target, FBXO3-ApaG, which activates inflammasomes or MMPs that are pro-inflammatory. The research emerging from this study has in part helped lead to a better understanding of the molecular pathways implicated in ubiquitin-mediated inflammation in COPD, which will lead to the design of newer drugs targeting ubiquitin-related proteins like Fbxo3 to limit inflammation.

FAMRI SUPPORTED RESEARCH

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CFTR, A NOVEL DRUG TARGET FOR COPD

Sammeta Raju, PhD; University of Alabama at Birmingham; YCSA 2014

Dr. Raju set out to determine the total contribution of acrolein to SHS-induced cystic fibrosis transmembrane conductance regulator (CFTR) abnormalities. However, the original research plan had to be changed due to the inability to recapitulate mucus clearance defects in mice after 4 weeks of exposure to smoke. Further, owing to the increased cellular toxicity of acrolein modifying antioxidants, the prime focus of the project shifted to the nicotine receptor α-7nAChR. As suggested by *in vitro* (human bronchial epithelial cells), *ex vivo* (freshly isolated human and ferret trachea) and *in vivo* (smoke and nicotine exposed rats) studies, cigarette smoke decreases CFTR function via decreased nicotine receptor α-7nAChR signaling. More importantly, α-7nAChR agonists correct cigarette smoke effects on CFTR ion transport and mucociliary evidence. To further advance the pharmacologic benefits of α-7nAChR agonists on mucus clearance in COPD therapy, the investigators are generating mechanistic insights into how α-7nAChRs function in airway epithelium. Towards this goal, animal models with genetic deletion and insertion of disease relevant mutations in α-7nAChR genes will be crucial.

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METABOLIC DYSFUNCTION IN THE PATHOGENESIS OF COPD

Anju Singh, PhD; Johns Hopkins Bloomberg School of Public Health; CIA 2014

Dr. Singh and colleagues built on their previous findings to determine if hypoxia inducible factor-1A (HIF1A)-dependent metabolic reprogramming promotes inflammation, impairs alveolar macrophage (AM) function, and promotes emphysema. They showed that activated HIF1a signaling upregulates glucose flux through glycolysis, promotes inflammation, mucus production, and extracellular matrix degradation, culminating in tissue damage and emphysema development. They also showed that blocking HIF1a signaling attenuates inflammation and matrix degradation, and protects against emphysema development. Activation of HIF1a signaling in inflammatory cells essential for driving inflammation, matrix degradation by metalloproteinases, and emphysema development. Selective activation of HIF1a signaling in clara cells of the lungs leads to baseline increase in the pulmonary inflammation whereas loss of HIF1a signaling has no impact on baseline inflammation in the lungs. Comparison of the pulmonary inflammation induced by cigarette smoke (CS) exposure and elastase revealed that elastase induces robust pulmonary inflammation as compared to CS. HIF1a signaling is essential for the bacterial phagocytosis and killing. HIF1a-deficient macrophages demonstrated impaired killing of *S. pneumoniae*. Stable isotope-resolved metabolomics analysis of murine air- and CS- exposed lung and liver tissues using revealed that chronic CS exposure results in systemic alteration in glucose metabolism.

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VIRUS AND COPD EXACERBATION

Yin Chen, PhD; University of Arizona Health Sciences Center; CIA 2013

Autophagosomes appear to support viral growth and substantially enhance inflammation. Dr. Chen and colleagues showed that cigarette smoke-induced autophagy is mediated through the classical autophagy pathway that depends on ATG5, ATG7 and BECLIN1. CC16, a potent anti-inflammatory protein, is a novel diagnostic and therapeutic target for COPD. Retinoids modulate CC16 level *in vitro* and *in vivo* and have the potential to be further developed for treating COPD. Human rhinovirus, the major viral pathogen for COPD exacerbation, can replicate in monocytes/macrophages in the presence of airway epithelium. Thus, replicating-virus-bearing inflammatory cells may be a novel target for treating COPD exacerbation.

FAMRI SUPPORTED RESEARCH

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A NOVEL THERAPY OF MUCUS HYPERSECRETION IN COPD

Y. Peter Di, PhD, MBA; University of Pittsburgh; CIA 2013

The investigators showed that extracellular signal-regulated kinase 2" (ERK2) and p38 signaling pathways contribute to cigarette smoke and electronic-cigarette smoke exposure-associated regulation. A panel of genes, including CYP4F11 and SDCBP2, and MUC13 that are associated with differential expression in COPD patients showed noticeable expression differences between samples from COPD patients and normal subjects; their expression

was regulated by epigenetic-associated mechanisms. Blockade of the transcription factor Sp1 did not sufficiently rescue the phenotype of cigarette smoke exposure-induced mucus-hypersecretion, probably due to the function of Sp1as a global gene regulator. Additional repressor genes may have been also suppressed that decreased the efficacy of Sp1 inhibition on smoke exposure- induced mucus-hypersecretion. Bacterial infection-induced exacerbation in COPD patients could potentially be prevented by better control of infection status. The antimicrobials identified by this group could be effective in killing COPD-related multidrug resistant pathogens and preventing bacterial biofilm formation.

FAMRI SUPPORTED RESEARCH

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TLR4-MEDIATED EMPHYSEMA: ROLE OF AGING

Patty J. Lee, MD; Yale University; CIA 2013

Dr. Lee and colleagues determined that Toll-like receptor 4 (TLR4) and macrophage migration inhibitory factor (MIF) are key regulators of aging- and cigarette smoke exposure-related emphysema in experimental mouse models and in people. The team has identified new mechanisms by which TLR4 and MIF work in the lungs and identified the lung endothelium as a key target. Subsequent studies to test MIF small agonists as a prevention and/or therapy against emphysema/COPD are underway.

FAMRI SUPPORTED RESEARCH

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MODIFIED LIPOPROTEINS IN COPD AND LUNG INFECTIONS

Mathieu Morissette, PhD; Institut universitaire de cardiologie et de pneumologie de Québec, Laval University; YCSA 2013

Dr. Morissette and colleagues found that smoking elicits a systemic drive to increase reverse lipid transport. In animal models, it happens as quickly as 1 hour after a single exposure. The investigators previously showed that promoting reverse lipid transport can protect the lung from cigarette smoke-induced damage. A systemic increase in reverse lipid transport is largely controlled by the liver. This suggests that the lung can send a signal very rapidly to the liver to increase reverse lipid transport. The hypothesis is that cigarette smoke exposure disrupts pulmonary lipid export mechanisms, leading to a systemic increase of reverse lipid transport by the liver. Moreover, the liver would be instrumental in limiting smoking-induced lung damage and an injured liver would lead to exacerbated lung pathology. A well-characterized mouse model of cigarette smoke exposure is being used to investigate the impact of acute and chronic cigarette smoke on the pulmonary and liver transcriptome as well as the change in HDL-associated proteins, the main class of

molecules responsible for promoting reverse lipid transport. The relationship between the lung and the liver is being studied by exposing mice with acute liver injury to cigarette smoke.

FAMRI SUPPORTED RESEARCH

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NOVEL ACTIVITIES FOR ADAM9 IN COPD

Caroline A. Owen, MD, PhD; Francesca Polverino, MD; Brigham and Women's Hospital; CIA 2013

The investigators are studying the activities of a disintegrin and a metalloproteinase domain-1 (ADAM9) in SHS-induced COPD development. Preliminary data link the ubiquitously expressed ADAM9 to COPD pathogenesis. *Adam9*$^{-/-}$ mice are protected from SHS-induced emphysema development but not from SHS-induced lung inflammation. The human ADAM9 protein is a potent extracellular matrix (ECM) degrading protein *in vitro* and COPD patients are found to have high levels of plasma ADAM9 when compared to healthy controls. The investigators are studying whether mouse protein Adam9 promotes SHS-induced emphysema development by degrading lung ECM proteins (especially lung elastin). They are also conducting studies in humans to determine if ADAM9 protein expression is increased in blood and lung samples from SHS- exposed humans and COPD

patients and if this expression correlates positively with the amount of SHS exposure and COPD severity.

FAMRI SUPPORTED RESEARCH

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PULMONARY GM-CSF TO REVERSE HARMFUL EFFECTS OF SECONDHAND SMOKE

Homayoun Shams, DVM, PhD; University of Texas Health Center at Tyler; CIA 2013

Dr. Shams and his group investigated strategies to harness efferocytosis by alveolar macrophages (AMs) to provide protection through maintenance of lung homeostasis. Boosting efferocytosis can be used against multiple pulmonary infections, including those which are refractory to drugs and those for which vaccines are not available. The team showed that inhalational delivery of granulocyte-macrophage colony-stimulating factor (GM-CSF) and bacille Calmette-Guerin markedly increases efferocytic activity of AMs, which protects mice against lethal influenza A viral infection. Increased efferocytosis of AMs was shown to be critical in repair of lung and airway damage due to SHS exposure and other insults.

FAMRI SUPPORTED RESEARCH

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ROLE OF PAI-1 IN TOBACCO SMOKE-INDUCED LUNG INJURY

Sreerama Shetty, PhD; University of Texas Health Center at Tyler; CIA 2013

Using a mouse model system, Dr. Shetty and his team investigated the molecular nature of lung injuries stemming from SHS exposure. The investigators showed that preventing p53 from binding to the endogenous PAI-1 mRNA in alveolar epithelial cells (AECs) by either suppressing p53 expression or blockading p53 interactions with the PAI-1 mRNA mitigates apoptosis and lung injury. This link between p53-mediated induction of PAI-1 expression and AEC apoptosis offers a therapeutic approach for reversing lung epithelial damage caused by SHS exposure. Lung sections from COPD patients were analyzed to confirm the molecular findings in humans.

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MATRIX ELASTIN AS A BIOMARKER FOR COPD

Gerard Turino, MD; St. Luke's-Roosevelt Hospital Center; CIA 2013

Studies of elastin degradation by liquid chromatography with tandem mass spectrometry (LC-MS-MS) analysis have resulted in development of a specific and sensitive method for measurement of desmosine (DES) and isodesmosine (IDS), two crosslinking molecules of elastin, as effective biomarkers for elastin degradation. This analytical method has been shown to effectively detect biomarkers for clinical characterization of COPD and detection of exposure to SHS and cigarette smoke. The DES and IDS measurements can be applied successfully for evaluation of drug efficacy in COPD and in alpha-1 antitrypsin augmentation therapies. Successful chemical synthesis of DES and IDS molecules further improved the LC-MS/MS as an accurate methodology for elastin degradation detection.

FAMRI SUPPORTED RESEARCH

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SECONDHAND CIGARETTE SMOKE AND EFFEROCYTOSIS

R. William Vandivier, MD; University of Colorado, Denver; CIA 2013

Dr. Vandivier and colleagues performed genome-wide association studies to identify novel pathways involved with COPD pathogenesis and progression. These studies suggest a potential role for neuroendocrine signaling via serotonin (5-HT) in the normal decline of lung function and susceptibility to COPD. This addresses the hypothesis that the 5-HT pathway is a novel target in COPD, setting the stage for therapeutic development. COPD is initiated by mainstream and SHS exposure, which lead to accumulation of inflammatory cells/mediators, oxidants, proteases and apoptotic cells that cause tissue and airway disease. 5-HT increases inflammatory mediators, oxidants, proteases, and decreases efferocytosis, suggesting that the exposure may contribute to COPD pathogenesis through these established pathways. Efferocytosis is a key mechanism regulating resolution of inflammation that has been shown to be impaired in COPD and by exposure to mainstream or SHS. It has been shown that 5-HT is increased in the serum of COPD patients, and that cell sources of 5-HT are increased and activated in stable and exacerbated COPD. This group has shown that 1) SHS exposure increases 5-HT in mouse lung lavage, 2) mouse and human alveolar macrophages (AMs) express proteins critical to 5-HT signaling, including 5-HT2c receptor, 5-HT transporter, and transglutaminase-2 (TG-2), and that 3) human AMs respond to 5-HT by activating the RhoA/Rho kinase (ROCK) pathway, which inhibits efferocytosis.

FAMRI SUPPORTED RESEARCH

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CIGARETTE SMOKE INCREASES GDF15 TO IMPAIR LUNG INNATE IMMUNITY

Qun Wu, MD, PhD; University of Colorado, Denver; National Jewish Health; YCSA 2013

The primary goal of this study is to test whether targeting cellular senescence can reduce respiratory viral infection and virus-induced inflammation. Previous research findings highlight an essential contribution of growth differentiation factor 15 (GDF15) in promoting airway epithelial senescence upon cigarette smoke (CS) exposure and facilitating human rhinovirus (HRV) infection by inhibiting antiviral type III interferon (e.g., IFN-gamma 1) production in human airway epithelial cells. Over-expressing human GDF15 in mice enhances lung inflammatory responses to HRV infection and is associated with increased lung senescence. The hypothesis of the is study is that cellular senescence induced by excessive GDF15 promotes HRV infection and worsens virus-induced inflammation via impaired antiviral IFN- gamma 1 production and increased HRV replication. The investigators are defining the pro-senescence function of GDF15 and its role in promoting HRV infection *in vivo* and elucidating the mechanism by which GDF15-induced senescence enhances HRV infection and inflammation *in vitro*.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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PROOF OF CONCEPT TRIAL OF A NOVEL THERAPY FOR COPD

Shyam Biswal, PhD; Johns Hopkins Bloomberg School of Public Health; CIA 2012

Dr. Biswal and colleagues completed a parallel, placebo-controlled, phase 2, randomized trial that was conducted at three US academic medical centers. Patients who met GOLD criteria for COPD and were able to tolerate bronchoscopies were randomly assigned to receive placebo or sulforaphane at 25 μmoles or 150 μmoles daily by mouth for four weeks. The primary outcomes were changes in Nrf2 target gene expression in alveolar macrophages and bronchial epithelial cells. Secondary outcomes included measures of oxidative stress and airway inflammation, and pulmonary function tests. Between July 2011 and May 2013, 89 patients were enrolled and randomized. Sulforaphane was absorbed in the patients as evident from their plasma metabolite levels. Changes in Nrf2 target gene expression relative to baseline ranged from 0.79 to 1.45 and there was no consistent pattern among the three groups; the changes were not statistically significantly different from baseline. Changes in measures of inflammation and pulmonary function tests were not different among the groups. Sulforaphane was well tolerated at both dose levels. Sulforaphane administered for four weeks at doses of 25 μmoles and 150 μmoles to patients with COPD did not stimulate the expression of Nrf2 target genes or have an effect on levels of other anti- oxidants or markers of inflammation. The conclusion of this study is that sulforaphane is unable to effectively activate the Nrf2 target in patients with COPD for enhancing the effect of steroids.

FAMRI SUPPORTED RESEARCH

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NALP6 IS CRITICAL TO SMOKE-INDUCED INFLAMMATION

Shanshan Cai, PhD; Louisiana State University; YCSA 2012

In order to determine if cellular influx and cytokine/chemokine expression in the lungs is mediated by the inflammasome NLRP6, the investigators used C57BL6 (wild-type) mice and NLRP6-deficient mice and exposed them to filtered air or subacute SHS levels. There was an increased recruitment of leukocytes to the lungs of WT mice in response of SHS-exposure but not in the NLRP6 -/- mice. There was also a significant reduction in total leukocyte (especially neutrophil) counts in the lungs as well as peripheral blood of SHS-exposed WT mice after *Klebsiella pneumoniae* infection as compared to their air-exposed counterparts. An increase in reactive oxygen species was observed in smoke-exposed WT neutrophils. However, the production was suppressed when the neutrophils were infected with *K. pneumoniae*. Additionally, cigarette smoke extract inhibited the killing ability of neutrophils from WT mice. In contrast, these effects were not evident in NLRP6-deficient mice. These findings highlight the immunomodulatory potential of SHS components and implicate NLRP6 in augmenting leukocyte maturation and recruitment to the lungs following SHS exposure.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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EPITHELIAL HER2 ACTIVATION BY CIGARETTE SMOKE

James Finigan, MD; National Jewish Health; CIA 2012

Dr. Finigan and colleagues have shown that IL-1 beta leads to shedding of the ligand neuregulin-1 (NRG-1) from the epithelium, resulting in paracrine activation of the epidermal growth factor receptor HER2. They have also shown that IL-1 beta-mediated increases in airway epithelium IL-6 are HER2 dependent and that CS induces NRG-1 shedding and HER2 activation in airway epithelial cells *in vitro* and *in vivo*, suggesting that the NRG-1-HER2 axis participates in CS-mediated airway inflammation. The team studied the mechanisms of epithelial HER2 activation by CS exposure and defining a requirement for HER2 activation in CS-induced airway inflammation. They also examined the role of HER2 activation in CS-mediated pulmonary inflammation *in vivo*, and investigated whether HER2 activation is a critical regulator of CS-induced inflammation in airway epithelial cells, using *in vitro* and *in vivo* CS exposure models, primary airway epithelial cells, and targeted transgenic animals.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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PTP1B REGULATES CIGARETTE SMOKE/RSV ACTIVATED TLRS

Patrick Geraghty, PhD; SUNY Downstate Medical Center; YCSA 2012

Dr. Geraghty and colleagues have shown that respiratory syncytial virus (RSV) infections in COPD contribute to loss of lung function and disease progression. Their studies dissected the ramifications of tobacco smoke and exposure and RSV infection in the pathogenesis of COPD. They showed that tobacco smoke inhalation alone reduces viral clearance from the lung and that repeat infection with RSV alone can induce a COPD like phenotype. Together RSV infection and tobacco smoke exposure represent a serious exacerbation of COPD. Proteases induced by exposure and viral infection enhance airway resistance and lung damage. Protease inhibitors can reduce viral load, inflammation and airway resistance, which may represent an approach to minimizing lung damage in COPD patients.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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ALTERED PROGENITOR-PROGENY RELATIONSHIP IN COPD

Moumita Ghosh, PhD; National Jewish Health; YCSA 2012

Dr. Ghosh and colleagues concluded that airway progenitor cells are crucial for maintaining and repairing a healthy airway; malfunction of these cells plays a pivotal role in COPD pathogenesis. These findings will be extended by 1) identifying people who are at the earliest stages of disease or pre- COPD, 2) identifying signaling pathways or molecules that are responsible for progenitor cell exhaustion and therefore can be therapeutically targeted, and 3) using of cell-based therapy for COPD.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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SUPPRESSION OF NEUTROPHIL IMMUNITY BY SMOKE

Sambithamby Jeyaseelan, DVM, PhD; Louisiana State University; CIA 2012

NETs are extracellular lattices of decondensed chromatin decorated with antimicrobial proteins and enzymes that trap and kill microbes. Dr. Jeyaseelan and colleagues have evidence that *Hemophilus influenzae* and *Staphylococcus aureus* infection induces NET formation in naïve bone marrow neutrophils and that extracellular bacterial clearance is DNase dependent. Further, they have shown that SHS exposure in mice attenuates clearance of *H. influenzae* and *S. aureus* and reduces the generation of reactive oxygen

species (ROS) in mouse lungs, and that neutrophil depletion in mice attenuates bacterial-induced ROS generation in the lungs. An ROS inhibitor was shown to abolish NETosis in naïve neutrophils in response to *H. influenzae* and *S. aureus*. The team further investigated whether SHS exposure promotes bacterial colonization and suppresses host antibacterial immunity by impairing NET formation.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Balamayooran G, Batra S, Theivanthiran B, Cai S, Pacher P, Jeyaseelan S. Intrapulmonary G-CSF rescues neutrophil recruitment to the lung and neutrophil release to blood in Gram-negative bacterial infection in MCP-1-/- mice. *J Immunol.* 2012;189(12):5849-5859.

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ROLE OF NLRX1 IN COPD PATHOGENESIS

Min-Jong Kang, MD, PhD; Yale University; YCSA 2012

Cigarette smoke (CS) exposure and viruses play key roles in the inflammation and remodeling in COPD, and the MAVS-RIG-I-like helicase (M-RLH) and inflammasome-dependent innate immune pathways are important mediators of these responses. The M-RLH pathway is inhibited at baseline and requires dysinhibition to engender its tissue effects. NLRX1 is an inhibitor of the M-RLH pathway and other innate immune responses. However, the mechanisms that inhibit this pathway at baseline and allow for its activation after CS- exposure have not been defined. In addition, the regulation and roles of the M-RLH pathway in CS-induced inflammation and remodeling responses and in human COPD have not been addressed. The investigators demonstrated that NLRX1 expression is significantly decreased in three COPD cohorts. This suppression correlates with disease severity and inversely with pulmonary function, quality of life, and prognosis. CS exposure inhibited murine NLRX1, and null mutations of NLRX1 augmented CS-induced inflammation, alveolar destruction, protease induction, structural cell apoptosis, and inflammasome activation. In contrast, null mutations of MAVS abrogated this CS-induced inflammation and remodeling. Furthermore, restoration of NLRX1 ameliorated CS-induced alveolar destruction significantly. Thus, CS exposure inhibits NLRX1, which facilitates CS-induced and MAVS-dependent inflammatory, remodeling, protease expression, cell death, and inflammasome responses.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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ALTITUDE AND SMOKE-INDUCED INFLAMMATION

Jordan Metcalf, MD; University of Oklahoma Health Science Center; CIA 2012

Dr. Metcalf and colleagues tested the hypothesis that cabin altitude exposure exacerbates lung inflammation in those exposed to cigarette smoke. They found that modest cigarette smoke exposure results in increased bronchoalveolar lavage (BAL) cellularity. There is a trend toward increased cellularity with altitude exposure in nonsmokers, which may suggest that cabin altitude alone triggers airway inflammation similar to that seen with cigarette smoke, though to a lesser degree. Modest cigarette smoke exposure causes

immunosuppression of the innate immune antiviral response through epigenetic modification and SHS exposure is likely to cause these adverse effects as well.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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OXYGEN (35) IMPAIRS MURINE MACROPHAGE FUNCTION

Neil Aggarwal, MD, Venkataramana Sidhaye, MD; Johns Hopkins Medical Institutions; YCSA 2011

The research team investigated whether low concentrations of oxygen that are beneficial to hypoxemic COPD patients may impair alveolar macrophage function and clearance of bacteria. One key observation is that exposure of macrophages in culture to low-dose (35-40%) oxygen following cigarette smoke (CS) exposure appears to modulate phagocytic receptor expression. In addition, following exposure to CS and 35-40% oxygen, these macrophages phagocytose *Pseudomonas* bacteria more efficiently than macrophages exposed to CS or air alone. Marked changes were noted in macrophage cell surface phagocytic and scavenger receptor expression in response to cigarette smoke and 40% oxygen. Dectin-1 is a type II transmembrane receptor involved in beta- glucan-derived fungal pathogen immune responses and is critical for clearance of fungal pathogens via recognition of beta-glucans. Dectin-1 expression was increased following oxygen exposure in CS-exposed macrophages, and this increase strongly correlates with increased bacterial uptake by macrophages. With the strong correlation between macrophage Dectin-1 expression and *Pseudomona*s phagocytosis among MH-S macrophages in culture, oxygen-induced upregulation of Dectin-1 may contribute to clearance of *Pseudomonas* via beta-glucan recognition and binding. Oxygen may improve bacterial phagocytosis through upregulation of cell surface phagocytic and scavenger receptors. These findings suggest

that oxygen-induced modulation of macrophage function is complex and likely associated with both the underlying lung substrate and the level of supplemental oxygen that is administered. The investigators also analyzed epithelial responses to CS exposure, with better understanding of what happens to the epithelium following acute and repetitive CS exposure. They found that there are significant actin cytoskeletal modifications that occur that alter the way epithelia form a monolayer and preserve tissue integrity after repetitive smoke exposure. These changes are seen in epithelium from patients with COPD, even when the cells are cultured *in vitro* for several weeks. This remarkable transformation of the epithelium is likely to impact the interactions seen between the epithelium and macrophages, potentially influencing phagocytic ability. Mechanisms modulating these interactions are a clear next step in the understanding of CS on infection and inflammation.

FAMRI SUPPORTED RESEARCH

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Singer BD, Mock JR, D'Alessio FR, Aggarwal NR, Mandke P, Johnston L, Damarla M. Flow-cytometric method for simultaneous analysis of mouse lung epithelial, endothelial, and hematopoietic lineage cells. *Am J Physiol Lung Cell Mol Physiol.* 2016;310(9):L796-801.

AIRWAY SPLUNC1 and BACTERIAL INFECTION IN COPD

Hong Wei Chu, MD; National Jewish Health; CIA 2011

Dr. Chu investigated the effect of cigarette smoke (CS) exposure on the expression of a protein called short palate lung and nasal epithelium clone 1 (SPLUNC1) in the airway epithelium, which may affect susceptibility to infections. The influence of SPLUNC1 in acute exacerbations of COPD (AECOPD) was investigated by applying recombinant SPLUNC1 and/or a neutrophil elastase (NE) inhibitor to SPLUNC1-deficient mice or to air-liquid interface cultures of NE-exposed airway epithelial cells from healthy controls and from

patients with COPD. The findings guided future therapies that restore SPLUNC1 antimicrobial functions during AECOPD.

FAMRI SUPPORTED RESEARCH

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EFFECTS OF SMOKING CESSATION AND VITAMIN D ON PROGRESSION OF COPD

Margaret A. Crane-Godreau, PhD; Geisel School of Medicine at Dartmouth; CIA 2011

Dr. Crane and colleagues investigated whether vitamin D can arrest or reverse the progression of COPD-like disease in inbred FVB female mice following removal from cigarette smoke (CSE) treatment. They also investigated whether high dose vitamin D supplementation during CSE can alter the course of CSE-induced lung diseases in this model system.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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THE THERAPEUTIC POTENTIAL OF Src ANTAGONISTS IN COPD

Robert F. Foronjy, MD; St. Luke's-Roosevelt Hospital; CIA 2011

Dr. Foronjy and colleagues determined how the redox status of the lung influences Src kinase activity and tyrosine phosphorylation of protein phosphatase (PP2A). The team studied how tyrosine phosphorylation of PP2A affects lung inflammation and protease expression in response to cigarette smoke exposure and investigated if inhibition of Src kinase activity *in vivo* increases lung PP2A activity and prevents the damaging effects of

acute and chronic exposure. These experiments may lead to the use of Src antagonists, which have been shown to be well tolerated in humans, as effective treatments for COPD patients.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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CIGARETTE SMOKE IMPAIRS FABP5-MEDIATED BACTERIAL CLEARANCE

Fabienne Gally, PhD; National Jewish Health; YCSA 2011

COPD is associated with important chronic comorbid diseases, including obesity, cardiovascular disease, diabetes, and hypertension. FABP5 has been shown to play a role in the development of obesity, insulin resistance, and atherosclerosis. The investigators have shown that fatty acid binding protein 5 (FABP5) mRNA levels from human smokers with COPD are significantly lower than those from smokers without COPD. The data show an association between the FABP5 gene and COPD exacerbations. It appears that decreased FABP5 expression leads to increased COPD exacerbations. CS exposure modulates the expression of FABP5 in primary human airway epithelial cells, contributing to their sensitivity to bacterial infection. These results agree with previous observations that CS exposure alters the innate immune system, in particular the airway epithelium host defenses. The susceptibility of smokers and COPD patients to CS- dependent diseases may be related to FABP5 expression in airway epithelial cell and its modulation of PPAR gamma

activity during bacterial infection. The investigators have previously shown that bacterial infection and cigarette smoke exposure differentially regulate FABP5 expression. LPS increases FABP5 transcript expression in a dose-dependent manner in BEAS-2B lung epithelial cells. c-Jun, a subunit of the activator protein 1 (AP-1) transcription factor, binds to a consensus sequence in the FABP5 promoter region. Cigarette smoke impairs c-Jun binding to the FABP5 promoter, providing a molecular mechanism underlying the observation that CS exposure negatively affects FABP5 expression. These results suggest that LPS-induced FABP5 upregulation may be part of an effective innate host response aimed at protecting lung tissue against bacterial infection-induced inflammation. Mouse models constructed by this group support *in vitro* findings that show that FABP5 expression is reduced in WT mice exposed to CS and increased following bacterial infection, which results in impaired bacterial clearance in WT mice exposed to CS. FABP5$^{-/-}$ mice are more sensitive to P. aeruginosa infection. However, in the presence of CS, bacterial loads are reduced in FABP5$^{-/-}$ mice due to heightened inflammation. Treatment with anti-Gr1 antibody increases the bacterial loads in FABP5$^{-/-}$ mice but not in WT mice. It also greatly reduced inflammatory cell recruitment to the airways but increased the levels of inflammatory cytokines and chemokines in both WT and FABP5$^{-/-}$ mice. FABP5$^{-/-}$ mice exposed to cigarette smoke and infected with *P. aeruginosa* may recapitulate an episode of exacerbation with heightened levels of inflammatory cells and cytokines.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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TOBACCO INDUCED EPIGENETIC ALTERATIONS IN COPD

Mohammad O. Hoque, DDS, PhD; Johns Hopkins Medical Institutions; CIA 2011

Preliminary data indicate that exposure to tobacco smoke is associated with induction of epigenetic alterations. The hypothesis of this study is that altered methylation patterns due to this exposure lead to changes in expression of genes that participate in the development and progression of COPD. The investigators are comparing methylation patterns of genes from subjects with GOLD stage I, II, and III COPD to those of never-smokers and smokers without disease. Immunohistochemistry is being used to investigate the protein expression of selected biological targets. A panel of hypo and/or hypermethylated genes is being screened to determine biological functions in the pathogenesis of COPD. The investigators

hope to identify epigenetically modified genes that can be used as non-invasive biomarkers for early detection of disease.

ROLE OF Cyr61 IN CIGARETTE SMOKING INDUCED COPD

Yang Jin, MD, PhD; Brigham and Women's Hospital; CIA 2011

Dr. Jin and colleagues investigated how cigarette smoke exposure induces COPD and severe stage emphysema. The team focused on the mechanism(s) of the pathogenesis of COPD using protein Cyr61, which modulates lung tissue remodeling and repair. The effect of CS exposure on regulation of Cyr61 expression and secretion and the functional role of Cyr61 in CS-induced lung cell apoptosis *in vitro* and emphysema *in vivo* were investigated, as well as the mechanisms by which Cyr61 mediates CS-induced lung epithelial cell apoptosis.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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E-PROSTANOID 2 SIGNALING IN CIGARETTE SMOKE-INDUCED IMMUNE SUPPRESSION

Peter Mancuso, PhD; University of Michigan; CIA 2011

Dr. Mancuso and colleagues studied the prostaglandin EP2 receptor, which mediates the immunosuppressive effects of prostaglandin E2 (PGE2) during pneumococcal pneumonia, an infection common among smokers and COPD patients. The team also investigated the role of PGE2EP2 signaling during CS-exposure and pneumococcal pneumonia and defined the effects of CS-exposure on the dynamics of EP2 expression and PGE2-EP2 signaling or blockage of alveolar macrophage effector functions. They also assessed the ability of an EP2 receptor antagonist to ameliorate established pneumococcal pneumonia in normal mice exposed to CS.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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Stolberg VR, Martin B, Mancuso P, Olszewski MA, Freeman CM, Curtis JL, Chensue SW. Role of CC chemokine receptor 4 in natural killer cell activation during acute cigarette smoke exposure. *Am J Pathol.* 2014;184(2):454-463.

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PRESENTATIONS AND ABSTRACTS

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SMOKE INDUCED UNFOLDED PROTEIN RESPONSE IN COPD

Anna Blumental-Perry, PhD; Mercer University School of Medicine; YCSA 2010

Dr. Blumental-Perry and colleagues investigated problems with protein folding and induction of stress signaling connected to the protein folding machinery as an early event

in response to CS exposure. They identified protein disulphide isomerase (PDI) as an endoplasmic reticulum resident target of CS. PDI is a protein implicated as a factor in the pathogenesis of different diseases. An increase in PDI usually confers protection from the stress of exposure, but the team found that CS modifies the protein and renders it less active and less efficient in performing its protective function. Moreover, the modified protein has the potential to facilitate cell death. The team addressed the question of whether the ratio of modified-by-smoke PDI to functional PDI increases as disease progresses. They also tested the correlation between the age-related failure of the protective mechanisms seen in COPD and the ability of individual cells to function with inefficient PDI.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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Vedagiri K, Reynolds CE, Kenche H, Degar A, Blumental-Perry A. Unfolded protein response as a driving force of tissue loss during virally induced exacerbations of chronic obstructive pulmonary disease. Presented at the FASEB Summer Research conferences: From Unfolded Proteins in the ER to Disease. Saxtons River, VT, Jun 16-21, 2013.

CIGARETTE SMOKE INDUCES ENDOGENOUS OXIDANT INJURY

Russell Bowler, MD, PhD; National Jewish Health; CIA 2010

Dr. Bowler and colleagues studied whether oxidative stress is responsible for the observed persistence of free radicals in COPD patients. The team created a knock-in mouse that contains a single nucleotide polymorphism (SNP) in the gene (SOD3) that encodes the antioxidant protein ECSOD. This is identical to the human SNP (R213G) that is associated with a lower risk of COPD. These mice have a similar phenotype to humans (i.e., a significant increase in plasma EC-SOD) as well as low levels of EC-SOD in tissues and high levels of EC-SOD in other biologic fluids such as bronchoalveolar lavage fluid (BALF). The *in vivo* studies suggest that the high levels of EC-SOD in BALF are responsible for the protection from lung inflammation and oxidative and nitrative injury, and that enhanced EC-SOD activity promotes resolution of inflammation through a reduction in proinflammatory cytokines and enhanced clearance of apoptotic cells (efferocytosis). The team also developed antioxidant therapies based on SOD activity.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Bahmed K, Messier EM, Zhou W, Tuder RM, Freed CR, Chu HW, Kelsen SG, Bowler RP, Mason RJ, Kosmider B. DJ-1 Modulates Nuclear Erythroid 2-Related Factor-2-Mediated Protection in Human Primary Alveolar Type II Cells in Smokers. *Am J Respir Cell Mol Biol.* 2016;55(3):439-449.

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Sorheim IC, DeMeo DL, Washko G, Litonjua A, Sparrow D, Bowler R, Bakke P, Pillai SG, Coxson HO, Lomas DA, Silverman EK, Hersh CP, International CGNI. Polymorphisms in the superoxide dismutase-3 gene are associated with emphysema in COPD. *COPD.* 2010;7(4):262-268.

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ROLE OF MMP-12 IN COPD EXACERBATIONS

McGarry Houghton, MD; University of Pittsburgh; Fred Hutchinson Cancer Research Center; CIA 2010

Dr. Houghton and colleagues identified an antimicrobial peptide residing within the carboxyterminal domain (CTD) of macrophage elastase (matrix metalloproteinase-12 or MMP-12). They generated a model of acute bacterial COPD exacerbation by combining a cigarette smoke exposure protocol with the agarose plug model of bacterial airway infection. Gene-targeted mice were used to dissect the contributions of inflammatory cell-derived proteinases on infection vs. tissue destruction in COPD/emphysema. The team optimized the MMP-12 CTD bacterial killing peptide by changing residues to enhance both solubility and bacteriocidal properties and tested it in *in vivo* models of infection.

TARGETING c-JUN TO REGENERATE EPITHELIUM IN COPD

Sekhar Reddy, PhD; University of Illinois at Chicago; CIA 2010

Dr. Reddy and colleagues investigated the mechanisms by which loss of c-Jun contributes to progressive emphysema. They found that targeted deletion of Jun in type II epithelial cells increased the level of apoptosis in the lungs at 1.5 months of age, and the number of apoptotic cells increased gradually with age. This was accompanied by an inflammatory response at 3 months, leading to a gradual loss of lung alveoli in 8- and 12-month-old mice. The investigators analyzed cytokine expression and found increased levels of TNF alpha and IL-13 in BAL fluids from Jundeficient mice as compared to wild-type mice; both of

these cytokines have been implicated in emphysema. Genetic disruption of surfactant protein D (SP-D) causes progressive emphysema, accompanied by inflammation. The investigators also analyzed SP gene expression in the lungs of these mice, which revealed strikingly lower levels of SP-A, SP-C, and SP-D in the lungs of Jundeficient mice. The data suggest that deregulation of Jun/AP-1-regulated surfactant gene expression contributes in part to the progression of emphysema, and that loss of c-Jun promotes cell death accompanied by dysregulated cytokine and surfactant gene expression, contributing to the development of emphysema.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Rajasekaran S, Reddy NM, Zhang W, Reddy SP. Expression profiling of genes regulated by Fra-1/AP-1 transcription factor during bleomycin-induced pulmonary fibrosis. *BMC Genomics.* 2013;14:381.

Rajasekaran S, Vaz M, Reddy SP. Fra-1/AP-1 transcription factor negatively regulates pulmonary fibrosis in vivo. *PLoS One.* 2012;7(7):e41611.

Reddy NM, Vegiraju S, Irving A, Paun BC, Luzina IG, Atamas SP, Biswal S, Ana NA, Mitzner W, Reddy SP. Targeted deletion of Jun/AP-1 in alveolar epithelial cells causes progressive emphysema and worsens cigarette smoke-induced lung inflammation. *Am J Pathol.* 2012;180(2):562-574.

Vaz M, Machireddy N, Irving A, Potteti HR, Chevalier K, Kalvakolanu D, Reddy SP. Oxidant-induced cell death and Nrf2-dependent antioxidative response are controlled by Fra-1/AP-1. *Mol Cell Biol.* 2012;32(9):1694-1709.

Vaz M, Reddy NM, Rajasekaran S, Reddy SP. Genetic disruption of Fra-1 decreases susceptibility to endotoxin-induced acute lung injury and mortality in mice. *Am J Respir Cell Mol Biol.* 2012;46(1):55-62.

BOOK CHAPTERS, ETC.

Reddy NM, Qureshi W, Potteti HR, Kalvakolanu D, Reddy SP. Regulation of mitochondrial functions by transcription factor Nrf2. In: Natarajan V, Parinandini N, eds. Mitochondrial Function in Lung Health and Disease. New York, NY: Humana Press, 2014.

CIGARETTE SMOKE EXPOSURE AND HIGH FAT DIET IN COPD

Steven D. Shapiro, MD; University of Pittsburgh; CIA 2010

Cigarette smoking and high fat diet are two lifestyle factors that contribute greatly to morbidity and mortality in the United States. Despite the fact that many persons indulge in both of these habits, the causes of these diseases have only been considered in isolation. Dr. Shapiro and colleagues studied the impact of cigarette smoking in conjunction with high fat diet on the development of COPD/emphysema. Additionally, they focused on the development of pulmonary hypertension associated with COPD.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Tsuji T, Kelly NJ, Takahashi S, Leme AS, Houghton AM, Shapiro SD. Macrophage elastase suppresses white adipose tissue expansion with cigarette smoking. *Am J Respir Cell Mol Biol.* 2014;51(6):822-829.

THE ROLE OF REDOX ENZYMES IN ACROLEIN TOXICITY

Page Spiess, PhD; University of Vermont; YCSA 2010

Dr. Spiess and colleagues investigated whether acrolein alters specific redox enzymes by adduction of highly reactive amino acid residues within the enzymes' active sites. They characterized morphological changes in airway epithelial cells that correlate with the formation of acrolein-adducted proteins along with effects on redox enzyme systems. Using *in vitro* and *in vivo* mouse models exposed to acrolein vapor at concentrations found in SHS, the investigators found that acrolein adduction of redox enzymes contributes significantly to morphological changes in pulmonary epithelial cells following exposure. The identification of acrolein-protein adducts was compared with morphological and functional outcomes to find a biomarker of acrolein exposure. Acrolein adduction of specific redox enzymes was studied to determine if the biochemical alterations in the enzymes contribute to changes in activity that cause functional and morphological changes.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Spiess PC, Deng B, Hondal RJ, Matthews DE, van der Vliet A. Proteomic profiling of acrolein adducts in human lung epithelial cells. *J Proteomics.* 2011;74(11):2380-2394.

CIGARETTE SMOKE IMPAIRS REMOVAL OF APOPTOTIC CELLS (EFFEROCYTOSIS) THROUGH RHO-A-DEPENDENT AND INDEPENDENT MECHANISMS

R. William Vandivier, MD; University of Colorado, Denver; CIA 2010

Dr. Vandivier and colleagues investigated the effect of CS on efferocytosis *in vivo* and *ex vivo* using acute, subacute, and long-term mouse exposure models. Acute and subacute CS exposure suppressed efferocytosis by alveolar macrophages in a dose-dependent, reversible, and cell-type independent manner, while more intense CS-exposure had an irreversible effect. In contrast, CS did not alter ingestion through the Fc gamma receptor. At 24 hours post exposure, the inhibitory effect of CS on apoptotic cell clearance depended on oxidants, because the effect was blunted in oxidant-resistant ICR mice, and was prevented by genetic or pharmacologic antioxidant strategies *in vivo* and *ex vivo*. At the same time point, CS inhibited efferocytosis through oxidant-dependent activation of the RhoA/Rho kinase pathway by a number of mechanisms, including 1) CS activation of RhoA, 2) antioxidant prevention of CS RhoA activation, and 3) reversal of the suppressive effect of CS on apoptotic cell clearance *in vivo* and *ex vivo* by inhibitors of the RhoA/Rho kinase pathway. In contrast, CS exposure inhibited efferocytosis immediately post exposure in a RhoA/Rho kinase independent manner. The ability of CS to inhibit efferocytosis was TNFa-dependent at 24 hours post exposure, but was TNFa-independent immediately post exposure.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Kearns MT, Dalal S, Horstmann SA, Richens TR, Tanaka T, Doe JM, Boe DM, Voelkel NF, Taraseviciene-Stewart L, Janssen WJ, Lee CG, Elias JA, Bratton D, Tuder RM, Henson PM, Vandivier RW. Vascular endothelial growth factor enhances macrophage clearance of apoptotic cells. *Am J Physiol Lung Cell Mol Physiol.* 2012;302(7):L711-718.

ROLE OF FRA-1 TRANSCRIPTION FACTOR IN COPD

Michelle Vaz, PhD; Johns Hopkins Bloomberg School of Public Health173; YCSA 2010

Dr. Vaz and colleagues investigated the role of the Fra-1 transcription factor in mediating cigarette smoke (CS)-induced lung inflammatory responses and in the development of COPD. *In vitro* experiments suggest that Fra-1 plays a vital role in regulating the expression of cigarette smoke-induced inflammatory cytokines as well as proteases that are known to play important roles in the pathogenesis of COPD. Results obtained from the *in vivo* experiments using a mouse model with a conditional deletion of fra-1 in macrophages/myeloid cells show that deletion of Fra-1 in macrophages decreases cigarette smoke-induced lung macrophage-mediated inflammation in mice. However, the lack of Fra-1 expression in macrophages alone is not sufficient to attenuate the lung morphological changes typical of CS-induced emphysema. Fra-1 has a similar pro-inflammatory role in lung epithelial cells too. Fra-1 can modulate the expression of cigarette smoke-induced cytokines by regulating the acetylation of these genes. Fra-1 enhances chronic CS-induced inflammatory gene expression by increasing histone acetylation at promoters of inflammatory genes. This is mediated via increased recruitment of histone acetyl transferases such as p300 at the promoters of these genes. Additionally, Fra-1 possibly enhances CS condensate-induced inflammatory gene expression by decreasing recruitment of deacetylases to promoters of inflammatory genes. Fra-1 can also enhance the development of COPD by altering the methylation status of genes involved in the development of COPD.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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Vaz M, Machireddy N, Irving A, Potteti HR, Chevalier K, Kalvakolanu D, Reddy SP. Oxidant-induced cell death and Nrf2-dependent antioxidative response are controlled by Fra-1/AP-1. *Mol Cell Biol.* 2012;32(9):1694-1709.

Vaz M, Rajasekaran S, Potteti HR, Reddy SP. Myeloid-specific Fos-related antigen-1 regulates cigarette smoke-induced lung inflammation, not emphysema, in mice. *Am J Respir Cell Mol Biol.* 2015;53(1):125-134.

Vaz M, Reddy NM, Rajasekaran S, Reddy SP. Genetic disruption of Fra-1 decreases susceptibility to endotoxin-induced acute lung injury and mortality in mice. *Am J Respir Cell Mol Biol.* 2012;46(1):55-62.

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PRESENTATIONS AND ABSTRACTS

Vaz M, Biswal S, Reddy SP. Loss of Fra-1 mitigates cigarette smoke-induced pro-inflammatory cytokine expression in cultured macrophages and lung macrophagic inflammation in mice [abstract]. Presented at a mini-symposium at the American Thoracic Society International Conference, Philadelphia, PA, May 18-23, 2012.

AUTOPHAGY IN COPD

Augustine M. K. Choi, MD; Brigham and Women's Hospital; CIA 2009

Dr. Choi's data strongly suggest that autophagy is a major cellular and tissue response to tobacco smoke exposure *in vitro* and *in vivo*, which is also observed in human COPD lung specimens. The autophagic responses may contribute to tobacco-induced apoptosis and pathogenesis of emphysema. Dr. Choi and colleagues determined whether autophagy plays a critical role in pulmonary responses to cigarette smoke exposure *in vitro* and *in vivo*, and if it regulates tobacco smoke-induced apoptosis and pathogenesis of emphysema. They also determined whether Egr-1 acts as a critical factor that regulates the regulation and function of autophagy in emphysema.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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Cloonan SM, Choi AM. Mitochondria: commanders of innate immunity and disease? *Curr Opin Immunol.* 2012;24(1):32-40.

DeMeo DL, Mariani T, Bhattacharya S, Srisuma S, Lange C, Litonjua A, Bueno R, Pillai SG, Lomas DA, Sparrow D, Shapiro SD, Criner GJ, Kim HP, Chen Z, Choi AM, Reilly J, Silverman EK. Integration of genomic and genetic approaches implicates IREB2 as a COPD susceptibility gene. *Am J Hum Genet.* 2009;85(4):493-502.

Haspel J, Shaik RS, Ifedigbo E, Nakahira K, Dolinay T, Englert JA, Choi AM. Characterization of macroautophagic flux in vivo using a leupeptin-based assay. *Autophagy.* 2011;7(6):629-642.

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Ryter SW, Lee SJ, Choi AM. Autophagy in cigarette smoke-induced chronic obstructive pulmonary disease. *Expert Rev Respir Med.* 2010;4(5):573-584.

Ryter SW, Nakahira K, Haspel JA, Choi AM. Autophagy in pulmonary diseases. *Annu Rev Physiol.* 2012;74:377-401.

van der Toorn M, Rezayat D, Kauffman HF, Bakker SJ, Gans RO, Koeter GH, Choi AM, van Oosterhout AJ, Slebos DJ. Lipid-soluble components in cigarette smoke induce mitochondrial production of reactive oxygen species in lung epithelial cells. *Am J Physiol Lung Cell Mol Physiol.* 2009;297(1):L109-114.

Wang XM, Kim HP, Nakahira K, Ryter SW, Choi AM. The heme oxygenase-1/carbon monoxide pathway suppresses TLR4 signaling by regulating the interaction of TLR4 with caveolin-1. *J Immunol.* 2009;182(6):3809-3818.

PRESENTATIONS AND ABSTRACTS

An CH, Smith LA, Choi AMK, Haley KJ. Prenatal tobacco exposure and abnormalities in postnatal autophagy-associated proteins [abstract]. American Thoracic Society International Conference. New Orleans, LA, May 14-19, 2010.

CIGARETTES AND RIG-LIKE HELICASE INNATE IMMUNITY

Jack A. Elias, MD; Yale University; CIA 2009

Dr. Elias and colleagues used RNAseL null mice to demonstrate that the Rig-like helicase (RLH) pathway plays a critical role in the responses induced by cigarette smoke (CS) and viruses/viral pathogen-associated molecular patterns (PAMPs). The team also demonstrated that CS and respiratory syncytial virus (RSV) interact to augment inflammation. In addition, the investigators showed that RSV nucleic acid clearance is delayed via the RLH pathway in the lungs of mice exposed to CS. The data indicate that CS exposure and withdrawal differentially affect pulmonary epithelial progenitor populations and bronchoalveolar stem cells (BASCs) in the murine lung. The data also suggest that there may be a common origin of lung cancer in COPD relating to CS-induced abnormalities in progenitor cells. The team demonstrated that viral PAMPs abrogate the cytoprotective effects of VEGF in the lung, and developed an experimental system to elucidate the mechanisms of VEGF augmentation of metastatic disease. The role of IL-15 was investigated using a CS exposure model and an IL-15 transgenic mouse. It was found that IL-15 is induced by exposure to CS and virus/viral PAMPs and that IL-15 augments virus-induced tissue responses and the accumulation of CD8 cells. An increase in tissue inflammation was seen in CS exposed mice infected with pneumococcus. Lung-targeted IL-18 transgenic mice were generated and evaluated to investigate the role of IL-18 in the effects of CS and viruses. These mice have a COPD-like phenotype that includes alveolar destruction with emphysema, airway remodeling with sub-epithelial fibrosis, tissue inflammation, and vascular remodeling with medial hypertrophy.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Kang MJ, Choi JM, Kim BH, Lee CM, Cho WK, Choe G, Kim DH, Lee CG, Elias JA. IL-18 induces emphysema and airway and vascular remodeling via IFN-gamma, IL-17A, and IL-13. *Am J Respir Crit Care Med.* 2012;185(11):1205-1217.

Lee BJ, Moon HG, Shin TS, Jeon SG, Lee EY, Gho YS, Lee CG, Zhu Z, Elias JA, Kim YK. Protective effects of basic fibroblast growth factor in the development of emphysema induced by interferon-gamma. *Exp Mol Med.* 2011;43(4):169-178.

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Lee CG, Ma B, Takyar S, Ahangari F, Delacruz C, He CH, Elias JA. Studies of vascular endothelial growth factor in asthma and chronic obstructive pulmonary disease. *Proc Am Thorac Soc.* 2011;8(6):512-515.

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Sohn MH, Kang MJ, Matsuura H, Bhandari V, Chen NY, Lee CG, Elias JA. The chitinase-like proteins breast regression protein-39 and YKL-40 regulate hyperoxia-induced acute lung injury. *Am J Respir Crit Care Med.* 2010;182(7):918-928.

HUMAN ALVEOLAR TYPE II CELL INJURY BY CIGARETTE SMOKE

Beata Kosmider, PhD; National Jewish Health; YCSA 2009

Dr. Kosmider and colleagues investigated molecular mechanisms of ATII cell protection against injury by CS exposure in humans and validated the results *in vivo*. Higher *ex vivo* levels of ROS, DNA damage, oxidative stress, and apoptosis were detected in freshly isolated ATII cells from smokers in comparison with those from non-smokers. These results were confirmed in ATII cells exposed to CS *in vitro*. ATI-like cells were found to have higher sensitivity to injury by CS exposure than ATII cells. High inflammation and low levels of Nrf2 and glutathione were observed in lung tissue obtained from patients with emphysema compared to controls. The team developed a method of mouse ATII cell isolation and purification using magnetic MicroBeads, and used it to study the protective role of N-acetylcysteine (NAC) against injury by CS *in vivo* and *in vitro*. They showed that NAC decreased injury of ATII cells in Nrf2 KO mice through ROS scavenging activities and abolished ATII cell damage in wild-type mice. The results indicate that CS-induced ex-vivo, *in vitro*, and *in vivo* ATII cell injury is caused by impaired antioxidant defense systems regulated by Nrf2, as well as unbalanced oxidant-induced cell damage.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Gally F, Kosmider B, Weaver MR, Pate KM, Hartshorn KL, Oberley-Deegan RE. FABP5 deficiency enhances susceptibility to H1N1 influenza A virus-induced lung inflammation. *Am J Physiol Lung Cell Mol Physiol.* 2013;305(1):L64-72.

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Messier EM, Mason RJ, Kosmider B. Efficient and rapid isolation and purification of mouse alveolar type II epithelial cells. *Exp Lung Res.* 2012;38(7):363-373.

Wei Y, Gong J, Thimmulappa RK, Kosmider B, Biswal S, Duh EJ. Nrf2 acts cell-autonomously in endothelium to regulate tip cell formation and vascular branching. *Proc Natl Acad Sci U S A.* 2013;110(41):E3910-3918.

PRESENTATIONS AND ABSTRACTS

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Gally F, Kosmider B, Weaver MR, Pate KM, Hartshorn KL, Oberley-Deegan RE. FABP5 deficiency enhances susceptibility to H1N1 influenza A virus-induced lung inflammation, Presented at the Society for Free Radical Biology and Medicine, 17th Annual Meeting. 2012, San Diego, CA, Nov 15-18, 2012.

Kosmider B, Chu HW, Mason RJ. Human primary alveolar cell injury induced by cigarette smoke. Presented at the 49th Annual Meeting and ToxExpo of the Society of Toxicology. Salt Lake City, UT, Mar 7-11, 2010.

Kosmider B, Messier E, Chu HW, Mason RJ. Expression of Nrf2-modulated genes in response to cigarette smoke. Presented at the Thomas L. Petty Aspen Lung Conference, 54th Annual Meeting. Aspen, CO, Jun 9, 2011.

Kosmider B, Messier E, Chu HW, Mason RJ. Expression of Nrf2-modulated genes to cigarette smoke. Presented at the Medicine Office of Research Retreat, National Jewish Health. Denver, CO, 2012.

Kosmider B, Messier E, Chu HW, Mason RJ. Nrf2 protects human and mouse alveolar epithelial cells against injury by cigarette smoke. Presented at the 51st Annual Meeting and ToxExpo of the Society of Toxicology. San Francisco, CA, Mar 11-15, 2012.

Kosmider B, Messier E, Chu HW, Mason RJ. Nrf2 response to cigarette smoke in human alveolar cells. Presented at the Basic Science Section, National Jewish Health. Denver, CO, 2011.

Kosmider B, Messier E, Chu HW, Mason RJ. Response of Nrf2-modulated genes to cigarette smoke. Presented at the Society of Toxicology 50th Annual Meeting and Tox- Expo. Washington, DC, Mar 6-10, 2011.

Kosmider B, Messier EM, Bowler RP, Tuder RM, Kleeberger SR, Chu HW, Mason RJ. High DNA damage in alveolar type II cells in emphysema. Presented at Lung Development, Cancer and Disease. Taos, NM, Feb 5-10, 2013.

Kosmider B, Messier EM, Chu HW, Mason RJ. Expression of Nrf2-regulated genes and apoptosis in response to cigarette smoke [abstract]. *Proc Am Thorac Soc* 2012;9(2):81.

Kosmider B, Messier, Chu HW, Mason RJ. Expression of Nrf2-modulated genes to cigarette smoke. Presented at the Medicine Office of Research Retreat, National Jewish Health. Denver, CO, 2012.

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Kosmider B. DJ-1 pathway protects alveolar type II cells from cigarette smoke-induced injury. Presented at Research Retreat, National Jewish Health. Denver, CO, Dec 19, 2013.

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Kosmider B. Human alveolar type II cell injury by cigarette smoke. Presented at the FAMRI site visit, National Jewish Health. Denver, CO, Aug 8, 2012.

Kosmider B. Isolation and purification of mouse alveolar type II cells. Presented at National Jewish Health, Denver, CO, Oct 3, 2012.

Messier EM, Jones K, Mason RJ, Bowler RP, Tuder RM, Kosmider B. Dysregulated miRNAs in alveolar type II cells in emphysema. Presented at the Medicine Office of Research Retreat, National Jewish Health. Denver, CO, Jun 26, 2014.

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Messier EM, Mason RJ, Tuder RM, Zhou W, Edwards M, Bowler R, Freed C, Chu HW, Kosmider B. The impairment of the DJ-1 pathway in alveolar type II cells in emphysema. Presented at the Medicine Office of Research Retreat, National Jewish Health. Denver, CO, Jan 21, 2014

Messier EM, Tuder RM, Bowler RP, Chu HW, Mason RJ, Kosmider B. Human alveolar type II cell injury in emphysema. Butcher Program, BioFrontiers Institute, Westminster, CO, Nov 1, 2013.

REGULATION OF TOBACCO SMOKE INDUCED AIRWAY INJURY

Sreerama Shetty, PhD; University of Texas Health Center at Tyler; CIA 2009

Dr. Shetty and colleagues investigated whether passive or SHS exposure promotes apoptosis of airway and alveolar epithelial cells (AECs) through induction of plasminogen activator inhibitor-1 (PAI-1) expression via posttranscriptional messenger RNA (mRNA) stabilization by p53. The team found that apoptosis of the airway epithelium was evident after 20 weeks of SHS exposure in C57B6 mice, and that PAI-1 and p53 expression were induced by SHS exposure in a peribronchial and subpleural distribution. They also found that SHS-induced apoptosis of AECs is blocked in p53- and PAI-1-deficient mice. Inhibition of SHS-induced p53 binding to PAI-1 mRNA suppressed PAI-1 induction in AECs; these cells also resisted apoptosis.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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NRF2- A THERAPEUTIC TARGET FOR COPD EXACERBATION

Rajesh Thimmulappa, PhD; Johns Hopkins Bloomberg School of Public Health; YCSA 2009

Dr. Thimmulappa and colleagues demonstrated that besides regulation of antioxidant and antiinflammatory responses, Nrf2 improves innate immune functions, including antibacterial defenses. They determined if an increase Nrf2 activity can improve innate immune anti-bacterial defenses and lung bacterial clearance and attenuate inflammation in CS-exposed mice. They investigated whether pharmacological activation of Nrf2 by sulforaphane improves bactericidal activity and inhibits inflammatory response in alveolar macrophages from patients with COPD. A Phase II clinical trial was started to test whether sulforaphane improves antioxidant, antiinflammatory, and anti-bacterial defenses in patients with COPD.

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MECHANISM OF PROTEASOMAL PATHWAY IN COPD AND EMPHYSEMA

Neeraj Vij, PhD; Johns Hopkins Medical Institutions, Central Michigan University; YCSA 2009

OPD is a complex lung disorder, which challenges the concept of single gene or pathway connection. Several pathogenetic mechanisms for cigarette-smoke (CS)-induced disordered

alveolarization and morphometric changes (emphysema) in COPD are described that include inflammatory- oxidative stress response pathways. One specific question asked by Dr. Vij and colleagues was why are smokers or elderly-subjects susceptible to COPD-emphysema? A reasoned hypothesis is that personal and environmental insults such as tobacco smoke exposure or biomass-smoke and/or age-dependent pathogenetic changes result in the clinical expression of COPD. Ubiquitin-mediated proteolysis is an inherent homeostatic mechanism to balance the optimal inflammatory-oxidative stress response, although CS exposure and/or age-related changes in proteostasis can compromise this response, which results in pathogenesis of chronic or fatal lung disease. Another goal of this study was to expand on the understanding of the proteostasis mechanisms that regulate aggresome-formation and pathogenesis of SHS induced COPD-emphysema. The investigators showed that the VCP/p97-retrograde translocation protein-complex may play a critical role in determining susceptibility to COPD- emphysema by regulating compensatory pathways that control pathogenesis of emphysema in COPD subjects. They observed that the VCP-retrograde translocation complex can regulate proteasomal degradation of I kappa B (endogenous inhibitor of NF kappa B-mediated inflammatory response), Nrf2 (a transcription factor that regulates the expression of antioxidant genes), and HDAC2 (a histone deacetylase that regulates glucocorticoid resistance). Moreover, it was shown that CS/SHS exposure may result in cytosolic accumulation of ubiquitinated-proteins (aggresomes) that can induce alveolar apoptosis and inflammation; this is a potential mechanism for initiating the loss of alveolar structures in COPD. The investigators suggest that CS induced aggresomes may cause pathophysiological-imbalance involved in the pathogenesis of COPD and point the way to intervention strategies targeting aggresomes for treating SHS-induced COPD- emphysema.

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HOST DEFENCE FUNCTIONS OF AIRWAY EPITHELIAL CELLS IN COPD

Hong Wei Chu, MD; National Jewish Health; CIA 2008

Dr. Chu's studies revealed that SHS exposure increases *Mycoplasma pneumoniae*, *Moraxella catarrhalis*, and nontypeable *Haemophilus influenzae* (NTHi) bacterial load on airway epithelial cells and decreases antimicrobial peptide beta-defensin 2. Several pathways may be involved in the increased bacterial load; one possible pathway is the fatty acid-binding protein 5 (FABP-5). FABP-5 messenger RNA levels from human smokers with COPD are shown to be significantly lower than those from smokers without COPD. Another possible pathway involves prostaglandin E2 (PGE2) production. Dr. Chu's group has tested the effects of modifying FABP-5 and PGE2 pathways on the restoration of host defense functions of human primary airway epithelial cells exposed to whole SHS and infected with bacteria. In addition, the effects of beta 2-agonists on host defense against bacterial infection in primary human bronchial epithelial cells have been investigated.

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PUBLICATIONS

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REGULATORS OF CIGARETTE-INDUCED ENDOTHELIAL CELL APOPTOSIS

Rachel Damico, MD, PhD; Johns Hopkins Medical Institutions; YCSA 2008

Dr. Damico and colleagues demonstrated that macrophage migration inhibitory factor (MIF) antagonizes lipopolysaccharide (LPS)-induced apoptosis of human pulmonary endothelial cells (HPEC) and plays a critical role in the expression of the apoptosis inhibitor, FLICE-like inhibitory protein (FLIPshort). MIF also possesses oxidoreductase activity and may modify the redox status of the cell. The group investigated the role of MIF in HPEC responses to CS exposure and characterized the molecular determinants of endothelial survival and apoptosis. HPEC were exposed to cigarette smoke extract (CSE) for increasing time periods and analyzed for protein expression and presence of apoptotic cells. There was significant activation/phosphorylation of p38 MAP kinase and its downstream effectors, MK2 and heat shock protein 27 (HSP27), which was accompanied by dephosphorylation of protein kinase B. Furthermore, exposure to CSE induced apoptosis. Phosphorylation of HSP27 correlated with induction of apoptosis. These results suggest that phosphorylation of HSP27 may be necessary for CSE-mediated apoptosis.

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SECONDHAND TOBACCO SMOKE EXPOSURE AND SUSCEPTIBILITY TO RESPIRATORY VIRAL INFECTION

Adriana Elisa Kajon, PhD; Lovelace Respiratory Research Institute; CIA 2008

Dr. Kajon investigated the effects of SHS exposure on viral infectivity in lung epithelial cells using an *in vitro* system designed to assess the effect of sidestream cigarette smoke and adenovirus, a prevalent human respiratory virus. Dr. Kajon's work demonstrated that SHS exposure of polarized Calu-3 airway epithelial cells results in increased viral entry from the apical surface that correlates with increased abundance of the coxsackievirus and adenovirus receptor. In addition, the level of cellular glycogen synthase kinase 3 beta was found to be downregulated in SHS-exposed cells compared to air exposed controls, providing a possible lead into the molecular mechanisms underlying the observed increased susceptibility to viral infection.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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HAEMOPHILUS INFLUENZAE TOLERANCE: A MECHANISM FOR CHRONIC COLONIZATION IN COPD

Tricia LeVan, PhD; University of Nebraska; CIA 2008

Dr. LeVan showed that *Haemophilus influenzae* strains isolated from COPD subjects are responsible for decreased cilia beating in lung bronchial epithelial cells. This decrease is a result of activation of PKC-epsilon, and can result in impairment of *H. influenzae* clearing in the lung. She also showed that *H. influenzae* strains isolated from subjects with transient exacerbation of COPD are more susceptible to human beta-defensin and less susceptible to the antibiotic ceftriaxone than strains that chronically colonize the COPD airway. These results suggest that strains that colonize COPD subjects are differentially susceptible to innate anti-microbial compounds and antibiotics and are likely to contribute to chronic colonization in COPD subjects. Repeat exposure of bronchial epithelial cells to *H. influenzae* induces a moderate tolerant response within 72 hours of exposure as indicated by a decrease in the proinflammatory cytokines, IL6 and IL8. Bronchial epithelial cells may continue to elicit a continued inflammatory response, albeit at much lower levels, when exposed to chronic *H. influenzae* colonization. These results suggest that both monocytes and bronchial epithelial cells have the capability of microbial tolerance and may contribute to chronic bacterial colonization in COPD subjects.

FAMRI SUPPORTED RESEARCH

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NONINVASIVE MEASUREMENT OF ALVEOLAR SURFACE AREA

Samuel Patz, PhD; Brigham and Women's Hospital; CIA 2008

Dr. Patz's group used a noninvasive MRI method that provides a quantitative map of alveolar surface area per unit volume of gas (SA/Vgas). Their results indicate this method can detect subtle changes in lung function and architecture. Early subclinical changes in pulmonary function associated with either active smoking or exposure to SHS may be able to be detected with this method. Quantitative images of SA/Vgas acquired over the entire lung will potentially provide unique information.

FAMRI SUPPORTED RESEARCH

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IMMUNE RESPONSES TO SECONDHAND CIGARETTE SMOKE EXPOSURE

Laimute Taraseviciene-Stewart, PhD; University of Colorado, Denver; CIA 2008

Dr. Taraseviciene-Stewart's team developed a rat model of SHS-induced emphysema where rats developed emphysema after a 2-month period of chronic SHS exposure. Anti-endothelial cell antibodies (AECA) were formed and apoptosis of lung endothelium was observed in this model. Circulating AECA has been found in COPD patients. While the numbers of circulating CD25 / CD4 T regulatory (Treg) cells in the rat model appeared to be augmented, their immune responses were marked by impaired macrophage function, increased levels of pro-inflammatory cytokine IL-18 and decreased levels of endogenous neutralizer IL-18 binding protein. The team demonstrated that endothelial cell death caused by SHS exposure is mediated by IL-18 via down-regulation of vascular endothelial growth factor receptors VEGFR1 and VEGFR2.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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SECONDHAND TOBACCO SMOKE AND AIRWAY INFECTION

Veena Antony, MD; University of Florida; CIA 2007

Dr. Antony conducted *in vivo* studies using a model of RSV infection in inducible nitric oxide synthase (iNOS) transgenic and control mice and demonstrated that iNOS$^{-/-}$mice did not show the increases in vascular endothelial growth factor (VEGF) and increases in airway epithelial permeability seen in iNOS / mice. Respiratory syncytial virus (RSV) caused the development of a breach in airway epithelial integrity, resulting in altered shape, paracellular gap formation between epithelial cells, and leakage of protein. Bronchial airway epithelial cells (BAEpC) stimulated by RSV demonstrated significant increases in VEGF in these studies. It is likely that RSV infection increases airway permeability leading to loss of integrity of the airway epithelium and disruption of airway epithelial junctional proteins in SHS-exposed BAEpC. RSV induces airway epithelial cells to release VEGF through a nitric oxide hypoxia inducible factor-1 alpha-mediated pathway.

FAMRI SUPPORTED RESEARCH

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INFLUENCE OF ARHGEF1 ON PULMONARY IMMUNITY

John M. Hartney, PhD; University of Colorado, Denver; YCSA 2007

Arhgef1 is Rho guanine nucleotide exchange factor (GEF) that is important in integrating signaling from activated G-protein coupled receptors to RhoA. Mice deficient for Arhgef1 spontaneously develop pulmonary inflammation and pathology similar to human COPD. Using adoptive transfer of leukocytes, Dr. Hartney and colleagues established that Arhgef1-deficient leukocytes are sufficient to induce pulmonary pathology, inflammation, and elevated matrix metallopeptidase 9 (MMP9) production. Subsequent *in vitro* studies showed that Arhgef1-deficient macrophages exhibit exaggerated MMP9 production that is dependent on thromboxane receptor signaling. Investigations using human primary cells revealed that alveolar macrophages and peripheral blood monocytes from COPD patients express reduced levels of Arhgef1 and exhibit exaggerated MMP9 production when stimulated. Treatment of patient cells with a thromboxane receptor antagonist attenuated MMP9 production.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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CXCL5 IS CENTRAL TO CIGARETTE SMOKE-INDUCED NEUTROPHIL INFLUX

Sambithamby Jeyaseelan, DVM, PhD; Louisiana State University; YCSA 2007

Dr. Jeyaseelan and colleagues investigated the role of chemokine ligand 5 (CXCL5), which is produced by alveolar type-II epithelial cells in response to lipopolysaccharide (LPS). LPS is one of the active ingredients in cigarette smoke. The team investigated the role of CXCL5 in neutrophil influx in the lungs to elucidate the effects associated with neutrophil accumulation in response to SHS exposure. Viable and fertile Cxcl5 gene-deficient mice ($Cxcl5^{-/-}$) were generated. These mice express similar levels of messenger RNA, chemokine KC protein, and macrophage-inflammatory protein- 2 as normal littermate controls, despite the absence of CXCL5. Impaired neutrophil influx was observed in $Cxcl5^{-/-}$mice at 8 hours and 24 hours when compared with their littermate controls (Cxcl5 /) after an *in vivo* Escherichia coli LPS challenge. The team conducted experiments to determine the role of CXCL5 in lung inflammation in mice in response to SHS exposure. A correlation was established between human epithelial cell-derived neutrophil-activating protein-78 (ENA-78) levels in bronchoalveolar lavage fluid and neutrophil accumulation in COPD patients.

FAMRI SUPPORTED RESEARCH

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REDUCED NEUTROPHIL DEATH IN TOBACCO-INDUCED COPD

Hongbo R. Luo, PhD; Children's Hospital Boston; CIA 2007

Exaggerated neutrophil accumulation in the lungs plays a major role in the pathogenesis of cigarette smoke-induced COPD. One mechanism leading to the massive neutrophil accumulation is cigarette smoke-induced delay of neutrophil spontaneous death in the lungs. Dr. Luo and colleagues have showed that deactivation of the phosphatidylinositol 3,4,5-trisphosphate/protein kinase B (PtdIns(3,4,5)P3/Akt) pathway, a well known survival signal, is a causal mediator of neutrophil spontaneous death. They further revealed that Akt deactivation is inhibited in tobacco-induced COPD. They have evidence that the reduced neutrophil death is mediated by blockage of Akt deactivation, which is due to inhibition of InsP6K1 and subsequent reduction of InsP7 level. The team is investigated the involvement of Akt and InsP6K1 in neutrophil death in the lungs *in vivo* using a cigarette-induced COPD animal model. In addition, they began to dissect the molecular mechanisms by which InsP6K1 activity is regulated in neutrophil death and by cigarette smoke.

FAMRI SUPPORTED RESEARCH

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DOES SECONDHAND CIGARETTE SMOKE MODULATE VITAMIN E UPTAKE IN LUNG TISSUE?

Giuseppe Valacchi, PhD; University of Siena; CIA 2007

Dr. Valacchi and colleagues investigated the role of the scavenger receptor B1 (SR-B1) in altering vitamin E delivery in the lung. They explored the effects of SHS exposure on components of tocopherol-based antioxidant defense by analyzing the levels of SR-B1 receptor before and after SHS exposure in lung tissues and after isolation of type II cells. The effects were analyzed for modulation by vitamin E dietary manipulation of SRB1 levels. Upon lung exposure to SHS and its attendant oxidative stress, a positive feedback loop is induced that increases vitamin E consumption while decreasing expression of SR-B1, a key means of antioxidant delivery. This combination results in reduced lung vitamin E, thereby rendering it vulnerable to further insult.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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Sticozzi C, Pecorelli A, Lim Y, Maioli E, Pagnin E, Davis PA, Valacchi G. Modulation of skin oxidative stress and inflammatory markers by environmental stressors. Differences between young and old. *J Dermatol Sci.* 2012;65(3):226-228.

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AGING & COPD: PHAGOCYTE FUNCTION IN THE PATHOGENESIS OF EMPHYSEMA

R. William Vandivier, MD; University of Colorado, Denver; CIA 2007

Dr. Vandivier and colleagues determined the effect of cigarette smoke (CS)-impaired efferocytosis on the development of emphysema and examined the therapeutic potential of drugs known to enhance efferocytosis. They found that CS activates RhoA through an oxidant-dependent mechanism, because MnTBAP prevented CS from activating RhoA at 24 hours. They also found that inhibition of RhoA or Rho kinase *ex vivo* prevented CS-impaired efferocytosis and that inhibition of Rho kinase *in vivo* prevented CS-impaired efferocytosis. Multiple instillations of apoptotic cells were shown to induce a perivascular inflammatory response composed of mononuclear cells. The effect of statins and PPAR gamma-agonists on CS-suppressed efferocytosis and aleveolar destruction was examined. The investigators extended the study to include liver X receptors. Two liver X receptor agonists were shown to increase efferocytosis and prevent CS-impaired efferocytosis *ex vivo*.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Borges VM, Vandivier RW, McPhillips KA, Kench JA, Morimoto K, Groshong SD, Richens TR, Graham BB, Muldrow AM, Van Heule L, Henson PM, Janssen WJ. TNFalpha inhibits apoptotic cell clearance in the lung, exacerbating acute inflammation. *Am J Physiol Lung Cell Mol Physiol.* 2009;297(4):L586-595.

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Vandivier RW, Richens TR, Horstmann SA, deCathelineau AM, Ghosh M, Reynolds SD, Xiao YQ, Riches DW, Plumb J, Vachon E, Downey GP, Henson PM. Dysfunctional cystic fibrosis

transmembrane conductance regulator inhibits phagocytosis of apoptotic cells with proinflammatory consequences. *Am J Physiol Lung Cell Mol Physiol.* 2009;297(4):L677-686.

PRESENTATIONS AND ABSTRACTS

Dalal SA, Tuder RM, Voelkel NF, Lee CG, Elias JA, Henson PM, Vandivier RW. Role of vascular endothelial growth factor (VEGF) in the phagocytosis of apoptotic cells by macrophages: implications in obstructive airways disease [abstract]. Presented at the American Thoracic Society International Conference. San Diego, CA, May 15-20, 2009.

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Vandivier RW, Richens TR, Linderman DJ, Xiao YQ, Boe DM, Morimoto K, Bowler RP, Day BJ, Janssen WJ, Henson PM. Cigarette smoke impairs clearance of apoptotic cells through oxidant-dependent activation of RhoA. Presented at the Society of Leukocyte Biology International Meeting. Denver, CO, Nov 6-9, 2008.

CELL-BASED THERAPY FOR CIGARETTE SMOKE-RELATED LUNG DISEASE

Andrew A. Wilson, MD; Boston University; YCSA 2007

Dr. Wilson and his team developed a lentiviral system capable of selectively targeting alveolar macrophages and allowing the inducible overexpression of genes or interfering RNAs that can modulate lung inflammation or elastolysis. They showed that this system transduces alveolar macrophages *in vivo*, resulting in long-term expression of human alpha1-antitrypsin (AAT) in mouse epithelial lining fluid at levels that could be protective in patients deficient in this protein. The team demonstrated that overexpression of AAT partially protects these animals from developing emphysema after treatment with intratracheal elastase. They tested this technique to see if it confers similar protection from cigarette smoke-mediated injury. The team adapted this system to allow real-time *in vivo* tracking of nuclear factor (NF)-kappa B activation and to knock down NF-kappa B gene expression. They used it to test the effects of macrophage-specific NF-kappa B knockdown on emphysema pathogenesis in the setting of cigarette smoke exposure.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Wilson AA, Kwok LW, Hovav AH, Ohle SJ, Little FF, Fine A, Kotton DN. Sustained expression of alpha1-antitrypsin after transplantation of manipulated hematopoietic stem cells. *Am J Respir Cell Mol Biol.* 2008;39(2):133-141.

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Wilson AA, Murphy GJ, Hamakawa H, Kwok LW, Srinivasan S, Hovav AH, Mulligan RC, Amar S, Suki B, Kotton DN. Amelioration of emphysema in mice through lentiviral transduction of long-lived pulmonary alveolar macrophages. *J Clin Invest.* 2010;120(1):379-389.

CIGARETTE SMOKE AND MECHANICAL STRETCH IN COPD

James C. Lavelle, MD; University of Colorado, Denver; YCSA 2006

Dr. Lavelle investigated the effects of mechanical stretch and cigarette smoke exposure on lung epithelial cells with respect to injury, repair, and propagation of emphysema by alveolar cell apoptosis. A549 and Calu-3 alveolar epithelial type-II-like cells subjected to injurious strain results show plasma membrane disruptions and initiation of multiple signaling cascades. Cells exposed to cigarette smoke extract are less able to repair stretch-induced membrane breaks. Cyclic strain results in rapid activation of the low molecular weight guanosine triphosphatase, RhoA, and leads to nuclear factor kappa B- and activator protein 1-dependent elaboration of proinflammatory cytokines such as IL-8. These events are blocked by pharmacologic inhibition of Rho with *Clostridium botulinum* C3 exoenzyme. Dr. Lavelle investigated the transcriptional program elicited by stretch, and examined the effects of stretch and cigarette smoke extract on the structure and function of the actin cytoskeleton, with special attention to the role of RhoA activation in the repair of stretch-induced plasma membrane disruptions affected by cigarette smoke extract. The inflammatory milieu induced by stretch and the deleterious effect of cigarette smoke on plasma membrane repair synergy may contribute to alveolar cell apoptosis and the development of emphysema.

FAMRI SUPPORTED RESEARCH

PRESENTATIONS AND ABSTRACTS

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Lavelle JC, Malcolm KC, Worthen GS, Downey GP. RhoA and NF kappa B dependent secretion of IL-8 induced by mechanical stretch of Calu-3 cells. Presented at the American Thoracic Society International Meeting. San Diego, CA, May 15-20, 2009.

Lavelle JC, Malcolm KC, Worthen GS. Mechanical stretch induces a pro-fibrotic, antiapoptotic phenotype in human lung fibroblasts. Presented at the American Thoracic Society International Meeting. San Diego, CA, May 19-24, 2006.

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PPAR GAMMA AND SUSCEPTIBILITY TO SMOKE-INDUCED COPD

Thomas J. Mariani, PhD; Brigham and Women's Hospital, University of Rochester; CIA 2006

Dr. Mariani and colleagues used airway epithelial cell PPAR gamma-deficient mice to investigate the impact of airspace enlargement on the physiomechanical properties of the

lung. There were no significant differences in surfactant quantity/function or in elastin and collagen content between targeted animals and littermate controls. Radial alveolar counts were significantly reduced in the targeted animals. Chronic cigarette smoke exposure increased whole lung PPAR gamma mRNA levels in mice *in vivo*. Cigarette smoke condensate (CSC) increased PPAR gamma protein and mRNA levels in lung epithelial cells *in vitro*, and induced expression of pro-inflammatory chemokines including Ccl5, Cxcl-2, -5, -10, -15; a subset of which (Ccl5, Cxcl-10,-15) was attenuated by co-treatment with the PPAR gamma activator rosiglitazone (ROSI). The investigators developed a line of mice with a targeted deletion of PPAR gamma in the airway epithelium that resulted in exaggerated Cxcl10 expression in response to cigarette smoke exposure, which was associated with increased lung macrophage accumulation and emphysema susceptibility. Conversely, treatment of mice exposed to CSC with ROSI-attenuated Cxcl10 expression was associated with reduced lung macrophage accumulation. Both CS and ROSI were capable of increasing PPAR gamma expression and PPAR gamma-mediated transcriptional activity from a peroxisome proliferator response element in lung epithelial cells *in vitro*. The investigators also observed that ROSI was necessary for promoting PPAR gamma NF-kappa B- and PPAR gamma-mediated NF-kappa B transcriptional repression *in vitro*.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Chu EK, Cheng J, Foley JS, Mecham BH, Owen CA, Haley KJ, Mariani TJ, Kohane IS, Tschumperlin DJ, Drazen JM. Induction of the plasminogen activator system by mechanical stimulation of human bronchial epithelial cells. *Am J Respir Cell Mol Biol.* 2006;35(6):628-638.

Simon DM, Arikan MC, Srisuma S, Bhattacharya S, Andalcio T, Shapiro SD, Mariani TJ. Epithelial cell PPARgamma is an endogenous regulator of normal lung maturation and maintenance. *Proc Am Thorac Soc.* 2006;3(6):510-511.

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PRESENTATIONS AND ABSTRACTS

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Srisuma S, Bhattacharya S, Mariani TJ. SERPINE2 is a direct target of FGF signaling; a potential mechanism for airspace homeostasis and repair [abstract]. *Am J Respir Crit Care Med* 2010;181:A4945.

Srisuma S, Mariani TJ. A Role of SERPINE2 in pulmonary homeostasis in mice [abstract]. *Am J Respir Crit Care Med* 2008;177:A967.

CAN WE PREVENT SEVERE COPD EXACERBATIONS?

Ryan Michael McGhan, MD; Denver Health & Hospital Authority; YCSA 2006

Dr. McGhan used observational data to examine the effectiveness of medications in reducing severe exacerbations and death in COPD. Inhaled medications (such as corticosteroids and bronchodilators) and treatments for COPD, including 5-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors and beta-blockers were of particular interest. He examined predictors of the risk of rehospitalization and death in a cohort of Veterans Administration patients hospitalized for severe COPD exacerbation. It was found that nonwhite race is associated with lower rates of death and rehospitalization, while older age is associated with an increased risk of death and rehospitalization. Co-morbidities also influenced the risk of death and rehospitalization.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

McGhan R, Radcliff T, Fish R, Sutherland ER, Welsh C, Make B. Predictors of and death after a severe exacerbation of COPD. *Chest.* 2007;132(6):1748-1755.

PRESENTATIONS AND ABSTRACTS

McGhan R, Radcliff T, Fish R, Sutherland ER, Welsh C, Kramer A, Lee T, Make B. Predictors of or death in VA patients with a history of a severe exacerbation of COPD [abstract]. *Proc Am Thorac Soc* 2006;3:A852.

SMOKING IMPAIRS ALPHA 1-ANTITRYPSIN'S PRO-SURVIVAL EFFECT IN THE LUNG

Irina Petrache, MD; Indiana University; CIA 2006

Dr. Petrache's data indicate that alpha-1-antitrypsin (A1AT) acts as a pro-survival molecule and prevents emphysema by binding to and inhibiting active caspase-3, which protects alveolar cells against apoptosis. The group determined that cigarette smoke inhibits the uptake of human A1AT in primary murine lung endothelial cells by actions on the endothelial cells and on the protein. They showed that A1AT modified by cigarette smoke has decreased caspase-3 inhibitory activity. Furthermore, cigarette smoke exposure impaired the biophysical interaction of A1AT with the active caspase-3 protein *in vitro*. Exposure of mice to cigarette smoke impaired the uptake of A1AT *in vivo*. The data from a translational study of the effect of cigarette smoke-induced post-translational changes of circulating A1AT on its antiapoptotic function reveal that A1AT functions as a protector against lung destruction by quenching neutrophil elastase and preventing apoptosis.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Clauss M, Voswinckel R, Rajashekhar G, Sigua NL, Fehrenbach H, Rush NI, Schweitzer KS, Yildirim AO, Kamocki K, Fisher AJ, Gu Y, Safadi B, Nikam S, Hubbard WC, Tuder RM, Twigg HL, 3rd, Presson RG, Sethi S, Petrache I. Lung endothelial monocyte-activating protein 2 is a mediator of cigarette smoke-induced emphysema in mice. *J Clin Invest.* 2011;121(6):2470-2479.

Petrache I, Fijalkowska I, Medler TR, Skirball J, Cruz P, Zhen L, Petrache HI, Flotte TR, Tuder RM. alpha-1 antitrypsin inhibits caspase-3 activity, preventing lung endothelial cell apoptosis. *Am J Pathol.* 2006;169(4):1155-1166.

Petrache I, Hajjar J, Campos M. Safety and efficacy of alpha-1-antitrypsin augmentation therapy in the treatment of patients with alpha-1-antitrypsin deficiency. *Biologics.* 2009;3:193-204.

Sohrab S, Petrusca DN, Lockett AD, Schweitzer KS, Rush NI, Gu Y, Kamocki K, Garrison J, Petrache I. Mechanism of alpha-1 antitrypsin endocytosis by lung endothelium. *FASEB J.* 2009;23(9):3149-3158.

Tuder RM, Petrache I. Molecular multitasking in the airspace: alpha1-antitrypsin takes on thrombin and plasmin. *Am J Respir Cell Mol Biol.* 2007;37(2):130-134.

PRESENTATIONS AND ABSTRACTS

Lockett A, Petrusca DN, Kamocki K, Adamowicz J, Gu Y, Rush NI, Fisher A, Presson RG, Schweitzer KS, Petrache I. Clathrin-mediated alpha-1 antitrypsin internalization by primary lung endothelial cells. Presented at the ATS International Conference. San Diego, CA, May 15-20, 2009.

Petrache I. Mechanisms of serpin involvement in lung cellular apoptosis. Presented at the ATS International Conference. Toronto, Canada, May 16-21, 2008.

Sohrab S, Petrusca DN, Petrache I. Effect of cigarette smoke extract on the alpha-1 antitrypsin (A1AT) internalization by primary lung endothelial cells *in vitro* [abstract]. *AJRCCM* 2008;177:A967.

Sohrab S, Smith PA, Gu Y, Kamocki K, Petrache I. Alpha-1 antitrypsin (A1AT) polymerization and cigarette smoke exposure impair the uptake of human A1AT by primary lung endothelial cells. Presented at the Fourth Annual Respiratory Disease Young Investigators Forum. Pittsburgh, PA, 2007.

ELASTIN FRAGMENT INHIBITION AS A THERAPY FOR COPD

Steven D. Shapiro, MD; University of Pittsburgh; CIA 2006

Dr. Shapiro and colleagues investigated the inflammatory cell cascades in COPD, and the interactions among elastin, innate immunity, and adaptive immunity. They examined the actions of CD8 T cells following smoke exposure, and found that mainstream and SHS exposure blunt dendritic cell function resulting in impaired T cell activation. This finding helps explain the increased risk of airway infections in people exposed to SHS. They also investigated the complex innate and adaptive inflammatory network induced by cigarette smoke exposure.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Houghton AM, Quintero PA, Perkins DL, Kobayashi DK, Kelley DG, Marconcini LA, Mecham RP, Senior RM, Shapiro SD. Elastin fragments drive disease progression in a murine model of emphysema. *J Clin Invest.* 2006;116(3):753-759.

Maeno T, Houghton AM, Quintero PA, Grumelli S, Owen CA, Shapiro SD. CD8+ T Cells are required for inflammation and destruction in cigarette smoke-induced emphysema in mice. *J Immunol.* 2007;178(12):8090-8096.

Robbins CS, Franco F, Mouded M, Cernadas M, Shapiro SD. Cigarette smoke exposure impairs dendritic cell maturation and T cell proliferation in thoracic lymph nodes of mice. *J Immunol.* 2008;180(10):6623-6628.

SERINE PROTEASE INHIBITOR E2 AND COPD

Sorachai Srisuma, MD, PhD; Mahidol University, Bangkok; YCSA 2006

Dr. Srisuma identified a significant increase in an alveolar mean linear intercept at maturity in unchallenged serine proteinase inhibitor clade E member 2 (SERPINE2) $^{-/-}$ mice This change in airspace size persisted in aged SERPINE2$^{-/-}$ mice and in SERPINE2$^{-/-}$ mice exposed to cigarette smoke for 6 months. However, SERPINE2 expression was not induced by smoke exposure and SERPINE2$^{-/-}$ mice did not demonstrate increased susceptibility to smoke-induced emphysema, as defined by the magnitude of airspace enlargement. RNA was isolated from the lungs of SERPINE2$^{-/-}$ mice for gene expression profiling. Stringent analyses identified a small number of dysregulated genes, including reduced expression of SERPINE2 and CLIC5, and increased expression of PDE4B. Deficiency of CLIC5 has been previously shown to result in congenital airspace enlargement in mice, while inhibition of PDE4 protein activity can modify disease progression in mice.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Bhattacharya SD, Tyagi SR, Srisuma, DeMeo, S, DL, Shapiro SD, Bueno R, Silverman EK, Reilly JJ, Mariani TJ. Peripheral blood gene expression profiles in COPD subjects. *J Clin Bioinforma.* 2011;1:12.

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PRESENTATIONS AND ABSTRACTS

Bhattacharya S, Srisuma S, Demeo DL, Shapiro SD, Bueno R, Silverman EK, Reilly JJ, Mariani TJ. Molecular biomarkers for quantitative and discrete COPD phenotypes. *Am J Respir Cell Mol Biol.* 2009;40(3):359-367.

Bhattacharya S, Tyagi S, Srisuma S, Demeo DL, Shapiro SD, Bueno R, Silverman EK, Reilly JJ, Mariani TJ. Peripheral blood gene expression profiles in COPD subjects. *J Clin Bioinforma.* 2011;1(1):12.

ROLE OF NICOTINE IN COPD PROGRESSION

Diane L. Carlisle, PhD; Magee Women's Health Corporation at the University of Pittsburgh; YCSA 2005

Dr. Carlisle identified the signaling pathways initiated by low-dose nicotine exposure, and established their contribution to the changes in differentiation that occur as the lung tries to heal from tobacco exposure. Cultured airway fibroblasts treated with nicotine were

shown to express signaling pathways associated with cell growth and apoptosis. Signaling secondary to nicotine occurs in doses as low as 1 nM, well within the range of the 1-10 nM concentration of nicotine found in the serum of non-smokers exposed to SHS. The investigator determined that stem cells express nicotine receptors, which persist during differentiation. Analysis of global gene expression changes in cells after directed differentiation in the presence or absence of nicotine was performed. Ingenuity pathway analysis indicated that specific networks of genes are changed in their expression patterns as a result of nicotine exposure during the differentiation process. These data provide additional evidence that nicotine plays a major role in development of COPD by activating signaling pathways that predispose differentiating cells towards abnormal phenotypes.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Carlisle DL, Liu X, Hopkins TM, Swick MC, Dhir R, Siegfried JM. Nicotine activates cell-signaling pathways through muscle-type and neuronal nicotinic acetylcholine receptors in non-small cell lung cancer cells. *Pulm Pharm & Ther.* 2007;20:629-641.

PRESENTATIONS AND ABSTRACTS

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Carlisle DL, Brekosky J, Foley J, Ben-Yehudah A, Redinger C, Mich-Basso J, Castro C, Navara C, Schatten G. Expression of nicotinic markers during stem cell differentiation. Presented at the American Society for Cell Biology 47th Annual Meeting. Washington, DC, Dec 1-5, 2007.

Carlisle DL, Kinney T, Brekosky J, Foley J, Ben-Yehudah A, Redinger C, Mich-Basso J, Castro C, Navara C, Schatten G. Directed differentiation of NHP embryonic stem cells into fibroblasts: Comparison with cultured lung fibroblasts. Presented at the 2008 ISSCR Annual Meeting. Philadelphia, PA, Jun 11-14, 2008.

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Carlisle DL, Liu X, Tavlarides MC, Hopkins TM, Siegfried JM. Nicotine promotes survival of NSCLC cells in the presence of anti-tumor agents. *Proc Amer Assoc Cancer Res* 2005;46:A5243.

Easley IV CA, Ben-Yehudah A, Redinger CJ, McFarland D, Varum ST, Eisinger VM, Carlisle DL, Donovan PJ, Schatten GP. Activation of mTOR-mediated protein translation induces differentiation in pluripotent human embryonic stem cells. Presented at the American Society for Cell Biology. San Diego, CA, Dec 5-9, 2009.

Liu X, Carlisle DL, Gaither-Davis A, Tavlarides MC, Siegfried JM. Gastrin-releasing peptide induces non-small cell lung carcinoma cell survival through the Akt pathway [abstract]. *Proc Amer Assoc Cancer Res* 2005;46:A156.

EFFECTS OF CIGARETTE SMOKE AND *MYCOPLASMA PNEUMONIAE* ON VEGF EXPRESSION BY HUMAN PRIMARY SMALL AND LARGE AIRWAY EPITHELIAL CELLS

Hong Wei Chu, MD; National Jewish Health; CIA 2005

Dr. Chu and his team studied the role of cigarette smoke on the role of macrophage host defense function against *Mycoplasma pneumoniae*. They used a culture of large airway epithelial cells to determine the regulation of a novel antimicrobial substance, short palate, lung, and nasal epithelium clone 1 (SPLUNC1). These findings contributed significantly to the understanding of the detrimental effects of cigarette smoke exposure on public health.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Baqir M, Chen CZ, Martin RJ, Thaikoottathil J, Case SR, Minor MN, Bowler R, Chu HW. Cigarette smoke decreases MARCO expression in macrophages: implication in Mycoplasma pneumoniae infection. *Respir Med.* 2008;102(11):1604-1610.

Chu HW, Thaikoottathil J, Rino JG, Zhang G, Wu Q, Moss T, Refaeli Y, Bowler R, Wenzel SE, Chen Z, Zdunek J, Breed R, Young R, Allaire E, Martin RJ. Function and regulation of SPLUNC1 protein in Mycoplasma infection and allergic inflammation. *J Immunol.* 2007;179(6):3995-4002.

Martin RJ, Wexler RB, Day BJ, Harbeck RJ, Pinkerton KE, Chu HW. Interaction between cigarette smoke and mycoplasma infection: a murine model. *COPD.* 2006;3(1):3-8.

PERIPHERAL BLOOD MONONUCLEAR CELL PROFILING IN TOBACCO EXPOSURE: SUSCEPTIBILITY MARKERS FOR COPD

Michael G. Edwards, PhD; University of Colorado, Denver; YCSA 2005

Dr. Edwards used Affymetrix U133 Plus 2.0 arrays to examine differences in global gene expression from peripheral blood mononuclear cells (PBMCs) isolated from current and former smokers with and without COPD. Analysis of the microarray data reveals more than the expected numbers of transcripts that are significantly different between smokers and non-smokers, males and females, and subsets of individuals with and without COPD. He identified thirteen transcripts whose expression shows a significant correlation to two standard pulmonary tests that are used to assess the severity of COPD. In order to identify genes specific to COPD, Dr. Edwards eliminated those transcripts differentially expressed in the disease state of four other publicly available PBMC array studies from the COPD expression profile; ulcerative colitis, Crohn's disease, severe acute respiratory syndrome infection, and endotoxin challenge. This reductive approach produced a list of 177 transcripts from an original list of 585 whose expression is altered in the COPD patients. A functional pathway analysis of the COPD-unique transcripts reveals that genes involved in inflammatory/immune processes are overrepresented. Expression profiling to identify molecular biomarkers of COPD in an easily sampled biological fluid (blood), may aid in the early detection and prevention of the disease.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Moré JM, Voelker DR, Silveira LJ, Edwards MG, Chan ED, Bowler RP. *BMC Pulm Med.* 2010;10:53.

PRESENTATIONS AND ABSTRACTS

Edwards MG, Gruber MP, Coldren CD, Bowler RP, Geraci MW. Peripheral Blood mononuclear cell profiling in tobacco exposure: susceptibility markers for COPD [abstract]. *Proc Am Thorac Soc* 2011;8(2):204.

PAI-1 AND AIRWAY REMODELING IN SECONDHAND TOBACCO SMOKE EXPOSURE

Steven Idell, MD, PhD; University of Texas Health Center at Tyler; CIA 2005

Dr. Idell and colleagues addressed the hypothesis that SHS exposure induces excessive plasminogenactivator inhibitor-I (PAI-I) expression by airway epithelial cells to promote pathophysiologicairway remodeling characteristic of COPD. Fibrinolytic pathways, and PAI-I in particular,are central to the pathogenesis of repair following acute lung injury. He and his team found thatairway epithelial cells elaborate PAI-I, that PAI-I is altered in lung epithelial cells in culture byexposure to cigarette smoke extract, and that PAI-I is induced in the lung epithelium of mice thatwere exposed to SHS for 20 weeks. These studies show that regulation of PAI-I at the posttranscriptional level of mRNA stability contributes to disordered fibrinolysis in the SHS-exposed airway and that PAI-I contributes to the pathogenesis of SHS-induced airway injury via regulation of programmed cell death of the airway epithelium. The team used cultured human bronchial epithelial cells and primary cultures of human small airway epithelial cells to determine how SHS regulates expression of PAI-I in airway epithelial cells and exposed mice to SHS for 20 weeks to determine whether PAI-I expression was altered in the lungs after exposure to SHS.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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ELASTIN DEGRADATION IN PULMONARY DISEASES

Yong Y. Lin, PhD; Mount Sinai St. Luke's-Roosevelt Hospital Center; 2005

Studies of elastin degradation by mass spectrometry resulted in development of a specific and sensitive methodology for measurement of desmosine and isodesmsoine, two

crosslinking molecules of elastin, as effective biomarkers of elastin degradation. This analytical method has been successfully applied in clinical characterization and evaluation of drug efficacy for COPD as well as for detection of exposure to cigarette smoke and exposure to SHS. The investigators synthesized desmosine, which will facilitate research on molecular biochemistry of elastin structure and its degradation as well as study of the pathogenesis of elastin degradation.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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PRESENTATIONS AND ABSTRACTS

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BIOLOGY OF IL-13 AND 5-LO IN THE PATHOGENESIS OF COPD

Yun M. Shim, MD; University of Virginia; YCSA 2005

Dr. Shim characterized expression and localization of IL-13, Th2 inflammatory cytokines, and leukotrienes in COPD and normal control patients. The study population included emphysematous smokers, nonemphysematous smokers, and individuals who never smoked. The same population was used to determine expression and localization of the enzymes that produce leukotrienes in COPD. The direct effects of cigarette smoke on induction of IL-13 and Th2 inflammatory cytokines and leukotriene production were determined using peripheral whole blood. In addition, the role of leukotrienes in the pathogenesis of emphysema was investigated in the IL-13 transgenic knock-in murine model and IL-13-independent elastase-induced murine emphysema model.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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Shim YM, Kim SH, Burdick MD, Strieter RM. LTB4 receptor 1 as a protective gene in the murine modeling of pulmonary emphysema [abstract]. The American Thoracic Society International Conference. New Orleans, LA, May 14-19, 2010.

GENETIC EPIDEMIOLOGY OF PULMONARY FUNCTION AND COPD

Jemma B. Wilk, DSc; Boston University; YCSA 2005

Genome-wide association studies were performed to identify genetic variants associated with the spirometric lung function measures, forced expiratory volume in 1 second (FEV1) and its ratio to forced vital capacity (FEV1/FVC). Dr. Wilk and her collaborators identified

nine genes or regions associated with these lung function measures. The HHIP region was first identified in studies of the Framingham Heart Study (FHS) cohort, and later replicated. To improve power to detect additional loci, the FHS cohort was included in a meta-analysis for the CHARGE consortium, and the combined sample of over 20,000 participants was used to identify eight additional loci: GPR126, ADAM19, AGER (RAGE), FAM13A, PTCH1, PID1, HTR4, and the INTS12GSTCD-NPNT region.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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RISK FACTORS FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Francine L. Jacobson, MD; Brigham and Women's Hospital; CIA 2004

Dr. Jacobson performed CT scans on normal never-smokers with significant exposure to SHS, never-smokers without SHS exposure, and patients with severe COPD. She found subtle changes in never-smokers exposed to SHS who have normal lung function. These

include small airway thickening and subtle loss of lung parenchyma. Although too subtle to consider the individuals abnormal, the changes in lung structure are similar to the dramatic changes seen in patients with severe early onset COPD.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Hersh CP, Hansel NN, Barnes KC, Lomas DA, Pillai SG, Coxson HO, Mathias RA, Rafaels NM, Wise RA, Connett JE, Klanderman BJ, Jacobson FL, Gill R, Litonjua AA, Sparrow D, Reilly JJ, Silverman EK, Investigators I. Transforming growth factor-beta receptor-3 is associated with pulmonary emphysema. *Am J Respir Cell Mol Biol.* 2009;41(3):324-331.

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AGING AND COPD: CELLULAR SENESCENCE IN EMPHYSEMA

Sarah McKinley, MD; University of Colorado, Denver; YCSA 2004

Exposure to cigarette smoke is the primary cause of COPD. Emphysema may represent premature aging of the lung due to stress on the lung's normal maintenance program caused by exposure to cigarette smoke. Signs of premature aging at the level of the cell are present in lung tissue samples from patients with emphysema when compared to normal lung tissue samples. Oxidative stress is important in development of cellular aging and hence emphysema. This project represented a novel approach to the evaluation of the origins of emphysema.

THE EFFECT OF PLTP INDUCTION IN SMOKERS

Robert F. Foronjy, MD; Columbia University; YCSA 2003

Dr. Foronjy determined that phospholipid transfer protein (PLTP) activity, measured in sputum from COPD patients, correlates with disease severity and progression. His results revealed that there is a marked decrease in PLTP activity in the lung lavage of COPD patients. He continued these studies to determine the cause and biological significance of the decrease in PLTP activity and to explore how the decrease in PLTP activity affects the composition and function of lung surfactants.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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Foronjy RF, Sun J, Lemaitre V, D'Armiento JM. Transgenic expression of matrix metalloproteinase-1 inhibits myocardial fibrosis and prevents the transition to heart failure in a pressure overload mouse model. *Hypertens Res.* 2008;31(4):725-735.

Foronjy RF, Wallace A, D'Armiento J. The pharmokinetic limitations of antioxidant treatment for COPD. *Pulm Pharmacol Ther.* 2008;21(2):370-379.

Ghio AJ, Hilborn ED, Stonehuerner JG, Dailey LA, Carter JD, Richards JH, Crissman KM, Foronjy RF, Uyeminami DL, Pinkerton KE. Particulate matter in cigarette smoke alters iron homeostasis to produce a biological effect. *Am J Respir Crit Care Med.* 2008;178(11):1130-1138.

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BOOK CHAPTERS, ETC.

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BIOMARKERS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Robert E. Walter, MD; Boston University; YCSA 2003

Dr. Walter utilized the multigenerational, multi-cohort Framingham Heart Study (FHS) to better understand the mechanisms underlying the development of COPD resulting from chronic tobacco smoke exposure. The FHS has a wide range of longitudinal measures including lung function and tobacco smoke exposure. The genetic information and the variety of biomarkers of inflammation, oxidant stress, and endothelial function measured at various points offer a unique opportunity to explore the mechanisms, including gene-by-environmental interactions, linking cigarette smoke to pulmonary disease.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Levitzky YS, Guo CY, Rong J, Larson MG, Walter RE, Keaney JF, Jr., Sutherland PA, Vasan A, Lipinska I, Evans JC, Benjamin EJ. Relation of smoking status to a panel of inflammatory markers: the framingham offspring. *Atherosclerosis.* 2008;201(1):217-224.

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PRESENTATIONS AND ABSTRACTS

Walter RE, Guo CY, Chen T, Lee TA, Weiss KB, O'Connor GT. Chronic obstructive pulmonary disease in the Framingham Heart Study. Presented at the American Thoracic Society. San Diego, CA, May 19-24, 2006.

AIRWAY DISEASES AND LUNG INJURY

Completed Research

LRP1 IN SMOKE-INDUCED LUNG INFLAMMATION

Itsaso Garcia-Arcos, PhD; SUNY Downstate Medical Center; YCSA 2014

Genetic variations of low-density lipoprotein related protein 1 (LRP1) are associated with decreased lung function in COPD patients. The hypothesis of this study is that LRP1 is essential for epithelial and surfactant function in the lung and that its loss would render the

lung more sensitive to COPD. The investigators have created tamoxifen-inducible club cell-specific LRP1 knockout mice (Club-LRP1$^{-/-}$), which show an increase in lung inflammation. Deletion of LRP1 also enhanced airway hyperreactivity after SHS exposure. The proteome signature of club cells reflects their roles in xenobiotic detoxification and in cytoskeleton signaling. Cells isolated from Club-LRP1$^{-/-}$ mice showed deep alterations in their proteome signature: xenobiotic detoxification and cytoskeletal signaling pathways are repressed, and these lungs have more permanent protein oxidative damage than WT after smoke exposure. In addition, there are significantly fewer glutathione reserves in lungs from Club-LRP1$^{-/-}$ than in those from WT mice, before and after smoke exposure. The investigators are determining the cause for the glutathione depletion and delineating the upstream factors that originate the deficiency. Therapeutic options are also being investigated. LRP1 loss may compromise migratory ability and re-epithelization after injury. Data show that LRP1 expression is higher in airway epithelium from COPD patients than from non- smokers, thus LRP1 may serve a protective function against smoke-induced inflammation.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Agudelo CW, Kumley BK, Area-Gomez E, Xu Y, Dabo AJ, Geraghty P, Campos M, Foronjy R, Garcia-Arcos I. Decreased surfactant lipids correlate with lung function in chronic obstructive pulmonary disease (COPD). *PLoS One.* 2020;15(2):e0228279.

Agudelo CW, Samaha G, Garcia-Arcos I. Alveolar lipids in pulmonary disease. A review. *Lipids Health Dis.* 2020;19(1):122.

Garcia-Arcos I, Geraghty P, Baumlin N, Campos M, Dabo AJ, Jundi B, Cummins N, Eden E, Grosche A, Salathe M, Foronjy R. Chronic electronic cigarette exposure in mice induces features of COPD in a nicotine-dependent manner. *Thorax.* 2016;71(12):1119-1129.

Garcia-Arcos I, Park SS, Mai M, Alvarez-Buve R, Chow L, Cai H, Baumlin-Schmid N, Agudelo CW, Martinez J, Kim MD, Dabo AJ, Salathe M, Goldberg IJ, Foronjy RF. LRP1 loss in airway epithelium exacerbates smoke-induced oxidative damage and airway remodeling. *J Lipid Res*. 2022;63(4):100185.

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PRESENTATIONS AND ABSTRACTS

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SECONDHAND SMOKE EXPOSURE IMPAIRS IMMUNITY TO LUNG INFECTION

Yasmin Thanavala, PhD; Roswell Park Alliance Foundation; CIA 2014

Long-term exposure to SHS is associated with increased susceptibility to respiratory infection and can cause COPD, chronic bronchitis, and emphysema. Even brief SHS exposure causes lung inflammation that can damage lung cells and make lung tissue more susceptible to infection with bacteria or viruses. COPD patients are particularly vulnerable to respiratory infections with bacterial and viral pathogens, causing a rapid decline in lung function. These infections exacerbate inflammation, contributing to a vicious cycle that can result in progressive decline in lung function, disability, and even death. The only current therapies for infection in COPD patients are antibiotics, bronchodilators and corticosteroids. Corticosteroids suppress inflammation to relieve symptoms, but suppress the body's ability to fight off the infection. The overall goal this study was to understand the processes by which SHS exposure contributes to immune suppression and chronic inflammation, and to test new therapies that can restore normal immune function and break the cycle. A mouse model was developed to examine the impact of chronic SHS exposure on chronic infection with nontypeable *Haemophilus influenzae* (NTHI), a bacterial pathogen commonly found in COPD exacerbations. The investigators evaluated how chronic SHS exposure impacts pulmonary inflammation and the development of adaptive immunity to chronic NTHI infection, and examined if prophylactic vaccination could help in mitigating SHS-induced defects in adaptive immunity to combat and alleviate future bouts

of acute infection. The results established that chronic SHS exposure worsens NTHI-mediated pulmonary inflammation and diminishes the generation of adaptive immunity. Moreover, SHS exposure impairs bacterial clearance from the lungs of mice, resulting in augmented inflammation and increased lung damage. Chronic exposure to SHS is an important pulmonary inflammatory insult that worsens lung immunity to respiratory infections and reduces the efficacy of prophylactic vaccination. This study established that chronic SHS exposure worsens bacterial infection-induced pulmonary inflammation and compromises the host's ability to mount effective immune responses to infection, thus facilitating pulmonary damage that increases the susceptibility to further respiratory infections. This has critical implications for people who are either chronically exposed to SHS or who are current or former smokers. This inability to mount a strong immune response likely facilitates subsequent bouts of infection by the same pathogen or long-term pathogen colonization. Colonization with new strains of respiratory pathogens is a key finding in COPD patients with frequent acute exacerbations. In addition, respiratory infections seen in children exposed to SHS at home are frequently observed. The results of this study demonstrate that involuntary SHS exposure has the potential to induce a variety of defects which play an important role in the pathophysiology of various diseases, especially human respiratory disorders.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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ASTHMA EXACERBATION INDUCED BY SECOND HAND SMOKE

Rosanna Malbran Forteza, MD; University of Miami Miller School of Medicine; CIA 2013

Dr. Forteza and colleagues built on their previous award to unravel the mechanisms asthma exacerbation in individuals exposed to SHS.

PRESENTATIONS AND ABSTRACTS

Forteza RM. The hyaluronan receptor layilin (LAYN) serves as the extracellular sensor linking radixin to the apical actin cytoskeleton in polarized airway epithelial cells. Presented at the American Thoracic Society Meeting. San Diego, CA, May 16-21, 2014.

TSLP AND CIGARETTE SMOKE-INDUCED AIRWAY REMODELING

Robert Vassallo, MD; Mayo Clinic; CIA 2013

Dr. Vassallo and his team studied the specific mechanisms by which the protein thymic stromal lymphopoietin (TSLP) affects changes in airway smooth muscle cells that promote airway remodeling (excessive narrowing of the airways due to thickening of the smooth muscle layer and deposition of excessive proteins) in asthma and COPD. *In vitro* and *in vivo* experiments were conducted to determine the expression and regulation of the heterodimeric TSLP receptor on airway smooth muscle cells (ASM) and the effect of cigarette smoke exposure and oxidative stress on receptor expression, as well as the

mechanisms by which cigarette smoke and TSLP promote proliferation of ASM cells *in vitro* and the expression of TSLP and its receptor in a mouse model of asthma. The studies confirmed preliminary observations that human ASM cells express TSLP-R as well as IL-7R alpha. This heterodimeric TSLP receptor is functional: the effects of TSLP on ASM cells can be blocked by antibodies targeting the receptor. The investigators identified that smoking induces TSLP-R in ASM cells and that smokers have higher levels of TSLP-R than non-smoker ASM cells. They also showed that TSLP-R and IL-7R alpha expression is increased in asthmatic ASM cells. Certain inflammatory mediators like TNF alpha as well as IL-13 induce TSLP-R expression on ASM, suggesting a feedback inflammatory loop in asthmatic ASM cells. The investigators looked at key signaling events that affect cell proliferation in airway remodeling and identified a number of factors involved in this process.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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SMOKING, MITOCHONDRIAL DYSFUNCTION AND ASTHMA

Bharathi Aravamudan, PhD; Mayo Clinic Rochester; YCSA 2012

Dr. Aravamudan and colleagues studied the mechanisms by which cigarette smoke (CS) exposure alters airway smooth muscle (ASM) cell mitochondrial dynamics and the role that the alteration plays in the effects of CS exposure. Exposure to CS extract (CSE) results in a dramatic shift in ASM morphology, where mitochondria get fragmented. Cytoplasmic signaling and transcriptional mechanisms were found to underlie CSE-induced fission-fusion changes in ASM mitochondria. CS exposure impairs adenosine triphosphate (ATP) production and respiratory capacity. There is a strong correlation between mitochondrial morphology and mitochondrial function, which is regulated by CS exposure in such a way

that proliferation, not apoptosis, of ASM is favored. Quantitative PCR analysis on the RNA from epithelial and ASM layers isolated from CS-exposed mice show that proteins driving cell proliferation and autophagy are upregulated, while those involved in apoptosis are downregulated. CS exposure seems to impair the expression of enzymes essential for oxidative phosphorylation.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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Aravamudan B, Thompson MA, Pabelick CM, Sieck GC, Vassallo R, Prakash YS. Cigarette smoke induces dysregulation of mitochondrial morphology and function in human airway smooth muscle. Presented at the Mitochondrial Symposium. Birmingham, AL, Mar 2-4, 2015.

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A 3-GENE SIGNATURE IN SMOKING EXPOSURE AND ASTHMA

Jose Gomez-Villalobos, PhD; Yale University; YCSA 2012

Dr. Gomez-Villalobos and colleagues performed an analysis in a population of asthmatics at the Yale Center for Asthma and Airways Disease, using a computational approach

integrating micro-array data from alveolar macrophages after bronchoscopic sampling of controls, asthmatics, and smokers. Preliminary results show that several members of the IL-18 family had similar expression at baseline and following 24-hour stimulation with cigarette smoke extract. *IL18R1* and *IL18RAP* are members of the family with highest average expression and are most frequently found in PBMCs of both controls and subjects with asthma. The team investigated whether gene expression of *P2RY14*, *HCAR3*, and *CHI3L1* in the airway macrophages of asthmatics is associated with the degree of SHS exposure and if their expression follows a specific temporal pattern after exposure to smoke. Only *P2RY14* was found to be expressed above background and the investigators are in the process of identifying the cell subsets associated with it.

FAMRI SUPPORTED RESEARCH

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EPIGENOMIC ALTERATIONS ASSOCIATED TO SHS IN ASTHMA

Rafael Guerrero-Preston, DrPH; Johns Hopkins Medical Institutions, CIA 2012

Dr. Guerrero-Preston addressed the role of SHS-driven epigenomic alterations in asthma with a profiling study nested in a longitudinal intervention for inner city asthmatic adults residing with a smoker, in Baltimore, MD. Genome-wide tools are used to examine the association of asthma with SHS driven global DNA hypomethylation and promoter hypermethylation in peripheral blood cells after controlling for particulate matter and air nicotine exposure.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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AIRWAY EPITHELIAL CONTROL OF ASTHMA SEVERITY

Matthew Poynter, PhD; University of Vermont; CIA 2012

Dr. Poynter and colleagues demonstrated that airway epithelial NF-kappa B activation promotes allergic sensitization to an innocuous inhaled antigen and promotes mixed Th2/Th17 allergic responses against previously tolerized antigens. Airway epithelial NF-kappa B activation induces expression of serum amyloid A (SAA), an inflammatory mediator elevated in the sputum and nasal lavage fluid of severe asthmatics. In mice, SAA causes an allergic asthma phenotype with a mixed Th2/Th17 response and augments methacholine hyperreactivity. SAA also prolongs the lifespan of dendritic cells (DCs) and diminishes expression of the pro-apoptotic molecule Bim, facilitating a prolonged capacity for DCs to stimulate CD4 T cells and induce DC secretion of mediators that promote interleukin 17 production. The team investigated whether airway epithelial-derived products, including SAA, affect pulmonary DC activities that allow for allergic sensitization and the ability to overcome inhalational tolerance, resulting in the development of severe disease. Initial results indicate that exosomes from visceral adipose tissue contain a large number of citrullinated peptides, which are often associated with autoimmune diseases.

FAMRI SUPPORTED RESEARCH

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IMPACT OF SHS ON CHILDREN WITH SICKLE CELL DISEASE

Robyn Cohen, MD, MPH; Drexel University, Boston Medical Center; CIA 2011

Dr. Cohen and colleagues set up a cross sectional study looking at the association between SHS exposure and clinical and biomarker outcomes of disease severity among children with sickle cell anemia. Data were collected from 199 children and adolescents with sickle cell anemia, age 5-19 years. The collected data included urine samples for biomarkers of SHS exposure and oxidative stress. Plasma was collected for biomarkers of allergic and nonallergic inflammation, vascular activation, and adhesion molecules. Questionnaire data was collected separately from parents and children regarding SHS exposure. Respiratory symptom and medical history questionnaires were also provided that included lung function testing and retrospective medical record reviews. The primary aims included evaluation of the association between SHS exposure and 1) lung function, 2) rates of pain and acute chest syndrome, and 3) oxidative stress. Secondary aims of the study included evaluation of the association between SHS exposure and 1) respiratory symptoms and 2) plasma biomarkers of inflammation, vascular activation, and adhesion. Data analysis is currently ongoing. Preliminary results suggest that the distribution of urine cotinine (SHS exposure) levels in a primarily African American cohort of children with sickle cell anemia is comparable to the distribution of cotinine levels in otherwise healthy African American children

in the general population, suggesting that renal and hepatic manifestations of sickle cell anemia do not affect nicotine metabolism. Despite a previous study showing that reported SHS exposure was moderately associated with lower airway obstruction in children in sickle cell anemia, analyses using cotinine levels as the biomarker of exposure of suggest that this association is weaker than originally demonstrated. In the cohort studied here the association between SHS exposure and airway obstruction was strongest among children who did NOT have a co-existing diagnosis of asthma. Earlier data showed the association was strongest between early life exposure (*in utero* smoke exposure and exposure from birth-age 2 years) rather than current reported exposure; the biomarker data is consistent with that finding. This suggests that there is a critical period during which SHS exposure affects lung development, which affects lung function in school age children and adolescents. SHS exposure did not appear to be associated with oxidative stress in children with sickle cell anemia. However, preliminary analyses suggest that SHS exposure is associated with an increase in wheezing among children with sickle cell anemia. This seems to be true for children with and without an asthma diagnosis. This is an important finding because wheezing symptoms have been positively associated with hospitalizations for pain and acute chest syndrome. Further analysis of the data will include 1) associations between SHS exposure and rates of hospitalization for pain and acute chest crises occurring within 3 years of the sample collection and 2) associations between SHS exposure and plasma biomarkers of allergic and non-allergic inflammation, vascular activation, and adhesion molecules.

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SECONDHAND SMOKE AND MYELOID CELLS IN ASTHMA

Jessy Deshane, PhD; University of Alabama at Birmingham; YCSA 2011

Dr. Deshane and colleagues investigated whether SHS exposure impairs the ability of myeloid-derived regulatory cells (MDRC) to control airway hyper-responsiveness (AHR) and lung inflammation in asthma. Myeloid -cells have been shown to play an essential role in the first day after antigen challenge as drivers of inflammation during asthma, and subpopulations of these cells can suppress or worsen asthmatic inflammation by producing free radicals. The investigators demonstrated that MDRCs are key regulators of allergic airway inflammation, and showed that MDRC function and associated mechanistic pathways are important targets for asthma therapy.

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NOVEL STRATEGIES FOR RESPIRATORY DISEASE OUTCOMES

Tulay Koru-Sengul, PhD; University of Miami Miller School of Medicine; CIA 2011

Dr. Koru-Sengul and colleagues performed a comprehensive comparative analysis of methods for data analysis that includes biomarkers with a detection limit. The methods were compared with each other under different scenarios by conducting Monte Carlo simulation studies based on data from the available population-based National Health and Nutrition Examination Survey (NHANES) III and the continuous NHANES 1999-2010 surveys. Further analyses into the effects of low levels of SHS exposure and chronic respiratory disease outcomes were performed, based on the guidelines established by the initial analysis for measurement of serum cotinine or urinary NNAL.

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C/EBP ALPHA: NOVEL THERAPEUTIC TARGET FOR ASTHMA

Elena Levantini, PhD; Beth Israel Deaconess Medical Center; CIA 2011

Dr. Levantini and colleagues determined how much of the transcription factor C/EBP alpha is normally present in healthy epithelial, muscle, and immune cells, and compared it to the levels in the same cells of patients with asthma. C/EBP alpha is involved in controlling the growth of these cells, and when its function is diminished, asthma tends to develop. The drug CDDO can be used to cure types of leukemia where the C/EBP alpha protein is produced at low levels by increasing C/EBP alpha activity. This led the team to investigate the efficacy of CDDO for the treatment of asthma.

FAMRI SUPPORTED RESEARCH

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ESTROGEN, CIGARETTE SMOKE, AND AIRWAY DISEASE

Venkatachalem Sathish, PhD; Mayo Clinic, North Dakota State; YCSA 2011

The investigators explored the mechanisms of altered estrogen signaling in bronchial epithelium induced by cigarette smoke exposure. They demonstrated that cigarette smoke extract (CSE) exposure (24 hr) significantly increased estrogen receptor alpha and beta (ER alpha, ER beta) expression in human bronchial epithelial cells (BEC) and airway smooth muscle cells (ASM). Studies using human BEC found that acute 17 beta-estradiol (E_2) exposure activates endothelial nitric oxide synthase (eNOS) phosphorylation, producing nitric oxide (NO) and inducing bronchodilation. CSE blunts E_2 mediated eNOS phosphorylation and NO production of epithelium. Estrogens reduce ASM calcium concentration, which aids bronchodilation. Cigarette smoke exposure interferes with this bronchodilatory role. ER expression and signaling is increased in CSE/inflamed ASM, with a greater, beneficial role for ER beta in reducing contractility and remodeling.

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PUBLICATIONS

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IMMUNE FUNCTION OF ALVEOLAR EPITHELIAL CELLS

Min Wu, MBBS, PhD; University of North Dakota; CIA 2011

Dr. Wu and colleagues investigated the molecular mechanisms that make passive and active smokers more susceptible to *Pseudomonas aeruginosa* (PA) infection, an outcome that is strongly associated with bronchitis, sinusitis, asthma, and COPD. Conventional antibiotics and vaccines are ineffective against PA. The main clinical hurdle is a lack of detailed understanding of the host defense mechanism. Although alveolar macrophages (AM) are the first line of host defense in the lower respiratory tract, their immunity against PA is often insufficient. Alveolar epithelial type II cells (AECII) form the barriers of alveolar spaces and produce surfactants to maintain lung integrity. In addition, AECII may perform immunologic functions via secretion of cytokines that may enhance AM's activity. The investigators have shown that both AECII and AM participate in innate immunity against PA. AECII were shown to have a crucial role in enhancing the immunity of AM when exposed to a conditioned-medium from PA-infected AECII. It was found that AECII-derived monocyte chemoattractant protein (MCP-1/CCL2) was a main factor in the activation of AM. Secretion of MCP-1 may be regulated by ceramide-containing lipid rafts, which are membrane microdomains involved in regulating various cellular functions. These two immune factors form a unified and potent anti-infection force. Mouse and human AMs activated by AECII-secreted cytokines are more effective in bacterial clearance than un-activated controls, whereas cigarette smoke exposure will dampen the human AM's bacterial clearance. It is necessary to understand these difficult research areas in order to develop novel therapeutics for infections in smoking-related diseases, including COPD and chronic bronchitis.

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COMPLEMENT MEDIATED EXACERBATION OF ASTHMA BY SHS

Gary Gilkeson, MD; Charleston Research Institute; CIA 2010

Dr. Gilkeson and colleagues investigated whether SHS exposure worsens the activation of the complement system in the lungs—a part of the human immune system. The complement system has been shown to be over-activated in asthma patients. The team tested targeted inhibitors of the complement system in models of asthma under conditions of SHS exposure. The inhibitors were designed to inhibit the complement system and provide protection from the development and worsening of asthma in patients exposed to SHS.

FAMRI SUPPORTED RESEARCH

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MECHANISMS OF SYNERGY BETWEEN CIGARETTE SMOKE AND RSV

Charles S. Dela Cruz, MD, PhD; Yale University; CIA 2009

Dr. Dela Cruz and colleagues showed that cigarette smoke (CS) exposure augments respiratory syncytial virus (RSV)-induced inflammatory and airway remodeling changes in mice. RSV infection in CS-exposed mice resulted in an inflammatory response and development of alveolar emphysema that was more severe than that seen in non-CS-exposed mice, or mice only infected with RSV. The team characterized the role of the mitochondrial antiviral signaling (MAVS) pathway, the regulation of antiviral molecules, the roles of type I and II interferons in the MAVS pathway, and the roles of negative regulators of the MAVS signaling pathway. They also characterized the roles of resistin-like molecule-a (RELM-a) and its binding partner, Bruton's tyrosine kinase (Btk), through expression analysis and experimental systems that delete the expression of either RELM-a or Btk.

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SMOKING AND THE PATHOGENESIS OF ASTHMA

Joseph DiDonato, PhD; Cleveland Clinic Foundation; CIA 2009

Dr. DiDonato and his team showed that there is a dramatic increase in protein carbamylation in the asthmatic airways of humans and in a mouse model of asthma following allergen challenge. In addition to the leukocyte peroxidase, myeloperoxidase (MPO), the studies demonstrated that eosinophil peroxidase (EPO) is more efficient than MPO at promoting protein carbamylation at normal plasma levels of thiocyanate. Furthermore, the studies showed that protein carbamylation in lung tissues co-localizes with EPO in lung biopsies from human asthmatic subjects. EPO-catalyzed protein carbamylation was shown to induce multiple asthma-associated phenotypes, including induction of airway epithelial cell apoptosis, mucin 5AC expression, and mucin accumulation. Protein carbamylation may serve as a mechanism linking tobacco smoke exposure and asthma pathogenesis in humans.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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SECONDHAND SMOKE-INDUCED ASTHMA EXACERBATIONS

Rosanna Malbran Forteza, MD; University of Miami Miller School of Medicine; CIA 2009

Dr. Forteza and her team showed that exposure to reactive oxygen species (ROS) results in increases of airway hyperreactivity (AHR) that is induced at least in part by bradykinin (BK); the bronchoalveolar lavage of asthmatic individuals and smokers contains increased amounts of BK. These findings are consistent with the fact that BK induces AHR in asthmatics but not in normal subjects. The enzyme responsible for BK generation in the airways is tissue kallikrein (TK) that is normally bound and inhibited by hyaluronan (HA), present at the apical surface of airway epithelium. HA depolymerization by ROS or hyaluronidases (Hyal) results in TK activation and BK generation. The investigators found that ROS exposure induces HA cleavage and TK activation that continues for at least 24 hours. In contrast, when HA is exposed to ROS in a cell free system, the HA cleavage is short lived (60 min) suggesting that additional mechanisms exist in airway epithelium that sustain HA depolymerization and TK activation. The investigators found that Hyal-2 that is GPI-anchored to the apical membrane of airway epithelial cells is induced by ROS.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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MOLECULAR CONTROL OF CILIATED CELL MAINTENANCE

Nevis Fregien, PhD; University of Miami Miller School of Medicine; CIA 2009

Dr. Freigen investigated the impact of cigarette smoke on human airway ciliated cells, which play an important role in the protection of the airway from inhaled noxious and infectious agents. He and his colleagues found that cigarette smoke inhibits the differentiation of ciliated epithelial cells and causes an acute reduction in the number of ciliated cells in differentiated cultures of human airway epithelial cells. They showed that the loss of ciliated cells is due to the lack of tight junction formation and the downregulation of FoxJ1 gene expression. This reduction can be completely hampered by inhibiting epidermal growth factor receptor (EGFR) signaling using gefitinib. The researchers also showed that treatment with gefitinib leads to the recovery of ciliated cells after cessation of smoking, suggesting that inhibiting EGFR signaling may provide a therapeutic approach for reversing smoke-induced damage to the airway epithelium.

FAMRI SUPPORTED RESEARCH

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EFFECTS OF CIGARETTE SMOKE ON AIRWAY EPITHELIAL BARRIER FUNCTION

Venkataramana Sidhaye, MD; Johns Hopkins Medical Institutions; YCSA 2008

Dr. Sidhaye's data suggest that changes in aquaporin-5 expression regulate paracellular permeability in response to physiologic stresses such as shear stress. Aquaporin-5 is known to be the primary determinant of transmembrane water permeability. Alterations in epithelial permeability have been linked to the pathogenesis of reactive airway disease with increased subepithelial exposure to luminal allergens. The addition of cigarette smoke to the inspired airstream increases epithelial permeability and a disruption of the protective mechanisms created by shear stress. These studies indicate that cigarette smoke extract leads to disruption of the shear-induced epithelial paracellular permeability. Human small nucleotide polymorphisms in AQP5 have been correlated with susceptibility to reactive airways and COPD.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Chau E, Galloway JF, Nelson A, Breysse PN, Wirtz D, Searson PC, Sidhaye VK. Effect of modifying quantum dot surface charge on airway epithelial cell uptake *in vitro*. *Nanotoxicology.* 2013;7(6):1143-1151.

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TOBACCO ALDEHYDES AND ALLERGIC AIRWAY INFLAMMATION

Albert van der Vliet, PhD; University of Vermont; CIA 2008

These studies indicated that acrolein inhalation enhances airways eosinophilia and Th2 cytokine production in allergic mice. The data suggest that acrolein inhalation alters alveolar macrophage activation by infectious stimuli in favor of alternative macrophage activation that is associated with Th2-mediated immune responses. Dr. van der Vliet and colleagues demonstrated that acrolein may be among the major components of cigarette smoke that are responsible for redox changes. Likewise, acrolein can directly modify critical proteins involved in inflammatory signaling, including nuclear factor kappa B (NF kappa B) and c-Jun-N-terminal kinase (JNK). The team found that concentrations of acrolein that inhibit Th1 cytokine production or nitric oxide response also inhibit activation of these signaling pathways, and are associated with direct acrolein modification of NF kappa B and JNK, most likely by direct alkylation of their cysteine residues. Thioredoxin reductase (TrxR) was found to be one of the main cellular targets for acrolein.

The impact of acrolein on TrxR enzymatic activity was characterized and a unique selenocysteine residue in the active site was shown to be the main target for acrolein.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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CIGARETTE SMOKE EXPOSURE AND INFLUENZA VIRUS INFECTION IN HUMAN LUNG

Wenxin Wu, PhD; University of Oklahoma Health Sciences Center; CIA 2008

This study focused on how cigarette smoke extract (CSE) alters the influenza-induced proinflammatory response and suppresses host antiviral activity in human lung using a lung organ culture model. Dr. Wu and colleagues determined that treatment with 2-20% CSE did not induce cytotoxicity as assessed by lactate dehydrogenase (LDH) release. However, CSE treatment inhibited influenza-induced IP-10 mRNA and protein. Induction of mRNA for the major anti-viral cytokine IFN-beta was also decreased by CSE, which also blunted viral-mediated retinoic acid-inducible gene I (RIG-I) mRNA and protein. Inhibition of viral-mediated RIG-I induction by CSE was prevented by the antioxidants N-acetyl-cysteine and glutathione. These findings show that CSE suppresses anti-viral and innate immune responses in the influenza-infected human lung though oxidative inhibition of viral-mediated induction of RIG-I, which may play a role in the enhanced susceptibility of smokers to serious lung influenza infection.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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IMPACT OF TOBACCO SMOKE EXPOSURE ON ACUTE LUNG INJURY

Carolyn Calfee, MD; University of California, San Francisco; YCSA 2007

Dr. Calfee and colleagues studied the association between cigarette smoke exposure and acute lung injury (ALI) in two large cohorts: 1) severely injured trauma patients at a county hospital; and 2) medical and surgical intensive care unit (ICU) patients at a large tertiary care center. The investigators found that both active and passive cigarette smoke exposures are highly prevalent in critically ill ICU patients, with rates notably higher than in the general population. They also found that active smoking and SHS exposures above the median level in the cohort are associated with a nearly 3-fold increase in the odds of developing ALI in patients at high risk for ALI following severe blunt trauma. The team analyzed the data from patients in the medical-surgical ICU cohort and measured

biomarkers of lung epithelial and endothelial injury to gain insight into the mechanisms by which cigarette smoke exposure enhances susceptibility to ALI. The team worked on developing a cohort of ICU-bound critically ill patients enrolled in the emergency department, in order to study early ALI (when intervention may be most promising) and to lay the groundwork for future studies of the impact of cigarette smoke exposure on critical illness outcomes such as septic shock and acute kidney injury.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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SECONDHAND TOBACCO SMOKE EXACERBATES ALLERGIC ASTHMA

Julie A. Wilder, PhD; Lovelace Respiratory Research Institute; CIA 2006

Dr. Wilder and colleagues studied the effects of SHS exposure on the development of allergic asthma in mice. The team showed that chronic exposure to SHS increases sensitivity of muscles surrounding the airways in the lung, increasing the probability of airway constriction upon inhalation of an allergen. They discovered that chronic SHS exposure of young adult mice heightens the ability of allergen-specific immune cells to migrate to the lung in response to inhaled allergens, compared to those in mice exposed to allergen alone. SHS exposure inhibits the movement of allergen-specific cells to the lung; the team sought to understand the ways in which SHS heightens, while initially inhibiting, allergic asthmatic inflammation. The role that T regulatory cells in the lungs and draining

lymph nodes play following inhaled SHS and allergen was investigated. The data showed that these cells are not increased in abundance in the presence of SHS, thus do not explain the inhibitory effect of SHS on cell migration to the lung.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Singh SP, Gundavarapu S, Pena-Philippides J, Rir-sima-ah J, Mishra NC, Wilder J, Kurup V, Sopori ML. Prenatal secondhand cigarette smoke promotes Th2 polarization and impairs goblet cell differentiation and airway mucus formation*. J Immunol.* 2011;187(9):4542-4552.

COMPARATIVE STUDIES OF HUMAN BUCCAL CELLS OF SMOKERS AND NON-SMOKERS

John L. Pauly, PhD; Roswell Park Alliance Foundation; CIA 2005

A comprehensive review of the literature regarding changes in human buccal cells (HBC) that are associated with the use of smoking and smokeless tobacco was completed. Clinicopathological studies correlated HBC changes with oral cancer. A high-throughput technology was developed to use HBC as biomarkers of tobacco exposure and as surrogate biomarkers of tobacco-associated oral disease. A relatively large population of HBC can be collected in a noninvasive manner with a toothbrush and purified. The HBC were analyzed successfully with a single laser cytometer (FAC-ScanÔ) and a multispectral cytometer (FACSAriaÔ). Cytometry revealed that the buccal cells expressed a high level of autofluorescence that was displayed over a broad spectrum; autofluorescence of HBC collected from the left and right cheek was consistent, illustrating sample collection and assay procedure reproducibility. HBC autofluorescence differed significantly among 69 adult subjects; and a statistical difference ($p = 0.018$) among current, former, and never smokers was seen. This research suggests that buccal cell autofluorescence is a reasonable candidate biomarker of tobacco smoking.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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PASSIVE SMOKE EXPOSURE IN ASTHMATICS: RELATIONSHIP TO MATRIX METALLOPROTEASES

Jeanine M. D'Armiento, MD, PhD; Columbia University; CIA 2004

Asthmatic patients exposed to active tobacco smoke or SHS have more severe airway inflammation and remodeling compared to asthmatics that have not been exposed. Dr. D'Armiento and her colleagues conducted studies that included 1) measurement and comparison of biomarkers of airway remodeling such as metalloproteinases and their inhibitors with inflammation (cytokine levels) in the induced sputum of mild and moderate asthmatic patients exposed to SHS, active tobacco smoke, and no smoke; and 2) comparison of airflow obstruction reversibility, hyper-responsiveness, and asthma quality of life among asthmatics exposed to passive smoking, active smoking, and no smoking.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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ENVIRONMENT TOBACCO SMOKE-INDUCED LUNG CELL DEATH via THE NITRIC OXIDE-CYTOCHROME C OXIDASE SIGNALING

Jianliang Zhang, PhD; University of Florida; CIA 2004

Dr. Zhang showed that SHS contributes to the development of pulmonary emphysema, a deadly disease associated with lung alveolar wall destruction. Exposure of lung vascular endothelial cells to conditioned mainstream cigarette smoke resulted in extensive cell death compared to control cells that are exposed to air or unlit cigarettes. Exhaled smoke can induce apoptosis. Nitric oxide (NO) derived from smoke and/or from smoke-stimulated cells plays a key role in exhaled smoke-induced lung cell death and dysfunction. NO inhibits mitochondrial cytochrome c oxidase, the terminal enzyme of the mitochondrial respiratory

chain. Inhibition of the enzyme can enhance the leak of reactive oxygen species such as superoxide from mitochondria. Excessive superoxide reacts with tobacco smoke-derived or tobacco smoke–stimulated NO to form peroxynitrite, which can modify proteins, including the pro-apoptotic protein Bax.

FAMRI SUPPORTED RESEARCH

PRESENTATIONS AND ABSTRACTS

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LUNG CANCER SUSCEPTIBILITY AND CHEMOPREVENTION

Shyam Biswal, PhD; Johns Hopkins Bloomberg of Public Health; YCSA 2002

Dr. Biswal used genomic DNA from lymphoblastoid cells derived from the Caucasian panel (100 individuals) and the African-American panel (100 individuals) from the Coriell repository to sequence all exons of the Nrf2 gene to determine the frequency of known single nucleotide polymorphisms to associate the differences in Nrf2 activity in the population and associate the differences in Nrf2 with lung cancer. The team showed that Nrf2 is a strong candidate gene for susceptibility to COPD and asthma. These data contain valuable information about susceptibility to several cigarette-smoke induced lung diseases.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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FUNCTIONAL STUDIES OF HUMAN LUNG MACROPHAGES

John L. Pauly, PhD; Roswell Park Alliance Foundation; CIA 2002

Dr. Pauly and his colleagues developed a method for isolating a large population of normal lung macrophages from surgical specimens. They used these macrophages in studies to define the production of pro-inflammatory cytokines in response to different stimuli. The team used a modified high-throughput Luminex100 Multi-Analate Profiling (LabMAP) assay system to identify and measure the diverse set of cytokines, which included interleukins 1, 6, 8, and 10, as well as granulocyte-macrophage colony-stimulating factor macrophage inflammatory proteins, and tumor necrosis factor alpha. Tobacco-associated fluorescence was found to interfere with FACS-based schemes for phenotypic analysis of surface membrane markers on lung macrophages isolated from smokers. This fluorescence is attributable to the polycyclic aromatic hydrocarbons found in cigarette smoke.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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PRESENTATIONS AND ABSTRACTS

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CANCER: LUNG

Completed Research

LUNG CANCER RISK ASSESSMENT AMONG PEOPLE EXPOSED TO SECONDHAND TOBACCO SMOKE

Claudia I. Henschke, PhD, MD; Mount Sinai Health System; CIA 2020

Secondhand tobacco smoke (SHS) exposure is a risk factor for the development of lung cancer. More than 20% of lung cancers (the most frequent cause of cancer death) occur in never-smokers, and this group of 20% has more deaths than nearly any other cancer. Screening for lung cancer with low dose CT scans has been recommended for people with extensive smoking histories, but current guidelines do not recommend screening for those with SHS exposure. Dr. Henschke and colleagues have used CT scans in people with SHS exposure with lung damage to demonstrate that the risk of lung cancer in this population is equal to that of a high risk smoker. They also shown that there are additonal beneficial findings from the same CT scan, including the ability to assess risk of heart disease. The present study is designed to evaluate a large population of people exposed to SHS who have already had CT scans, and based on the extent of their exposure as well as other risk factors, develop a risk model to determine the probability that an individual may develop lung cancer. The team will determine how this model can be improved to further define the risk. The aim is to develop a method for identifying candidates who should remain in a screening program, leading to earlier treatment and cure.

NICOTINE/ACETYLCHOLINE SIGNALING IN LUNG CANCER

Piyali Dasgupta, PhD; Joan C. Edwards School of Medicine at Marshall University; YCSA 2009

Lung adenocarcinoma (LAC) forms the majority of human non-small cell lung cancers (NSCLCs). Dr. Dasgupta and colleagues showed that human LAC cell lines and tumors expressed all the proteins of the cholinergic pathway; choline acetyltransferase (ChAT), vesicular acetylcholine transferase (VAChT), choline transporter 1 (CHT1), acetylcholinesterase (AChE), and nicotinic acetylcholine receptors (nAChRs). They tested the levels of expression of these proteins in human LAC tissues isolated from smokers via collaboration with the University of Kentucky Clinical and Translational Science Awards program. The team observed that out of all the cholinergic proteins, ChAT levels were significantly increased in the LAC tumor samples isolated from smokers, compared to LAC samples isolated from never smokers and was dependent on the pack-years smoked by the patient. They found that ChAT was expressed at low levels in LAC tumors isolated from never smokers and at higher levels in LAC tumors isolated from patients who smoked between 10-40 pack-years, with a maximum in patients who smoked 80-100 pack-years. Therefore, ChAT appears to be potential molecular target for LAC in smokers.

FAMRI SUPPORTED RESEARCH

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MCL-1 IS A NOVEL SIGNALING TARGET OF NICOTINE IN HUMAN LUNG CANCER CELLS

Xingming Deng, MD, PhD; Emory University; CIA 2009

Mcl-1, a major antiapoptotic protein of the Bcl-2 family, is extensively expressed in small cell (SCLC) and non-small cell lung cancer (NSCLC) cells. Dr. Deng and colleagues showed

that nicotine-induced Mcl-1 phosphorylation at threonine 163 (T163) enhances Mcl-1's antiapoptotic activity. By *in silico* screening of the NCI compound database, the team identified two small molecule Mcl-1 inhibitors (SMMI-1 and -2), which block nicotine-stimulated Mcl-1 phosphorylation at T163 and potently induce apoptosis of lung cancer cells. Nicotine can induce Stat3 phosphorylation in association with upregulation of Mcl-1. The team investigated whether nicotine-induced Mcl-1 phosphorylation regulates Mcl-1 protein turnover and its survival, leading to chemoresistance of human lung cancer cells. They determined if inhibition of Mcl-1 phosphorylation by SMMI or PD98059 affects Mcl-1's stability and antiapoptotic activity, and whether nicotine-activated Stat3 regulates Mcl-1 transcription in nicotine-induced survival signaling. They determined whether SMMI represses lung tumor growth in xenograft animal models, and evaluated the anti-lung cancer efficiency of SMMI *in vivo*.

FAMRI SUPPORTED RESEARCH

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INFLAMMATORY ROLE FOR LKB1 TUMOR SUPPRESSOR IN LUNG CANCER

Edward Ratovitski, PhD; Johns Hopkins Medical Institutions; CIA 2009

Dr. Ratovitski and his colleagues showed that the cigarette smoking induces LKB1/PEA-3/ delta Np63-dependent transcriptional regulation of inflammatory molecules, such as COX-2/ PTGS. Using mainstream smoke extract (MSE) and sidestream smoke extract (SSE) as models for primary and secondhand tobacco smoking, they found that both downregulate protein levels for LKB1, and upregulate protein levels for PEA 3 and COX-2 in a dose-dependent manner. The team found that the C/EBP beta, NF-kappa B, NF-Y (CHOP), PEA 3 (ETS), and delta Np63 proteins bind to a specific region (-550 to -130) of the COX-2 promoter while forming multiple protein complexes in lung cancer cells exposed to MSE and SSE. This defines a link between various transcription factors occupying the COX-2 promoter and cellular responses to cigarette smoke exposure involving delta Np63 alpha. The data define a role for cooperation among various chromatin components in regulation of COX-2 expression and strengthen the observation that the inflammatory process plays a central role in tumorigenesis of epithelial cells, which is exacerbated by exposure to tobacco smoke.

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INFLAMMATION AND STEM CELLS IN SMOKE INDUCED LUNG CANCER

Rebecca Toonkel, MD, May-Lin Wilgus, MD; Columbia University; YCSA 2009

Dr. Wilgus took over the grant from Dr. Toonkel. She and her colleagues developed two murine models of chronic lung inflammation; a model of intranasal exposure to exogenous lipopolysaccharide and a transgenic model expressing IL-1 beta in the lung. They used these models in tagged bone marrow transfer studies from reporter mouse donors to track bone marrow-derived progenitor cell (BMPC) contributions to tumors induced by SHS exposure to test the hypothesis that chronic inflammation and BMPCs promote SHS-associated lung carcinogenesis.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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TOLERANCE OF TOBACCO SMOKE-INDUCED DNA DAMAGE IN LUNG

Laura Barkley-Elliman, PhD; Galway University; YCSA 2008

Benzo[a]pyrene (B[a]P) is a carcinogenic component of cigarette smoke that is metabolized within cells to B[a]P diol epoxide (BPDE), which covalently binds DNA to form bulky adducts. Dr. Barkley-Elliman and colleagues showed that E3 ligase Rad18 is phosphorylated in response to BPDE-induced DNA damage, and that this phosphorylation *in vivo* requires the checkpoint kinase, Chk1. They identified five *in vivo* Rad18 phosphorylation sites; one of which is phosphorylated directly by the c-jun N-terminal kinase and indirectly by Chk1. In addition, phosphorylation at this specific site is required for appropriate trans-lesion synthesis (TLS) polymerase recruitment to BPDE adducts. The team studied whether Rad18 E3 ligase activity and subsequent DNA polymerase kappa recruitment are regulated by Chk1. They also studied the effect of phosphorylation site mutations on the subcellular localization of Rad18, proliferating cell nuclear antigen-directed ubiquitination, interaction with TLS polymerases, and recovery from the S phase checkpoint. They investigated whether Rad18 phosphorylation sites are mutated in lung cancer to give loss-of-function or gain-of-function phenotypes that perturb TLS.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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THERAPEUTIC TARGETS IN K-RAS-INDUCED LUNG CANCER

Daniela S. Bassères, PhD; Universidade de São Paulo; YCSA 2008

Dr. Bassères and colleagues identified and tested therapeutic targets in K-Ras-mediated lung cancer. There is a well-established relationship between cigarette smoke exposure and K-Ras mutations. The team investigated a critical downstream effector of oncogenic K-Ras, the transcription factor nuclear factor B (NF- kappa B) and its activation by K-Ras, which involves two important therapeutic targets: aurora kinases and IkB kinase (IKK). The team determined the function and relative importance of NF-kappa B and IKK and aurora kinases in K-Ras-transformed human cells and determined the therapeutic efficacy of targeting of their pathways in K-Ras-induced lung cancer in situ. An RNA interference approach was used to inhibit expression of the p65 NF-kappa B subunit of IKK or aurora kinases A and B, and the oncogenic properties of the transformed cells were analyzed. A K-Ras-induced lung cancer mouse model was used to evaluate the effects of pharmacological inhibition of IKK and aurora kinases on lung tumor growth and overall survival.

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ALLELIC IMBALANCE AND MIRNA REGULATION BY TOBACCO SMOKE IN NSCLC

Shahnaz Begum, PhD; Johns Hopkins Medical Institutions; YCSA 2008

Dr. Begum and colleagues determined whether there are distinct patterns of allelic imbalance that correspond to deregulated micro RNA (miRNA) expression in primary lung cancers. They correlated these allelic imbalances and deregulated miRNAs in lung adenocarcinoma in smokers, non-smokers, and passive smokers, using single nucleotide polymorphism array hybridization for over 250,000 markers. They generated a genome-wide map of loss of heterozygosity (LOH) in these samples, and compared classification by allelic imbalance/LOH with classification by deregulated miRNA to validate adenocarcinoma classification to aid in the identification of lung cancer-associated deregulated genes (oncogenes and tumor suppressor genes).

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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DEVELOPMENT OF STRUCTURE-BASED SMALL MOLECULE ANTI-LUNG CANCER DRUG(S) BY TARGETING BAX

Xingming Deng, MD, PhD; Emory University; CIA 2008

Dr. Deng and colleagues discovered that nicotine-activated AKT phosphorylates Bax at serine 184 (Ser184), which abolishes the proapoptotic activity of Bax. In contrast, protein phosphatase 2A-mediated dephosphorylation of Bax at Ser184 activates its proapoptotic function, suggesting that the Ser184 site is critical in regulating its proapoptotic activity. The investigators chose the Ser184 residue as a docking site for screening of small molecules that may activate Bax using the computerized DOCK suite of programs (version 6.1) and a database of 300,000 small molecules from the National Cancer Institute (NCI) filtered to follow the Lipinski rules. Thirty-six of the compounds determined to have the highest affinity for the Bax Ser184 site were obtained from NCI and tested for their effects on apoptosis. Three of the 36 compounds potently induce apoptosis of various human lung cancer cells; SMBA1, SMBA2, and SMBA3. Treatment of lung cancer cells with SMBA1, 2, or 3 blocks nicotine-induced Bax phosphorylation in association with enhanced apoptotic cell death. Importantly, a combination of SMBA1, 2, or 3 with a chemotherapeutic drug such as cisplatin significantly enhances chemosensitivity of lung cancer cells as compared to drug alone. It appears that SMBA(s) may activate the proapoptotic function of Bax by binding to the Ser184 site, which leads to apoptosis. The SMBAs may have potent anti-tumor effects *in vivo*.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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GENDER DIFFERENCES IN THE EFFICACY OF ANTIANGIOGENIC THERAPIES: THE ROLE OF EGFR/ESTROGEN RECEPTOR INTERACTIONS IN NSCLC

Matthew H. Herynk, PhD; University of Texas M. D. Anderson Cancer Center; YCSA 2008

Dr. Herynk investigated whether the epidermal growth factor receptor (EGFR) and estrogen receptor (ER) pathways cooperatively interact to increase angiogenesis and enhance EGFR dependence. He examined the role of estrogen and EGFR-mediated signaling *in vitro* by measuring the production of cytokines and angiogenic factors in NSCLC cell lines

and endothelial cells derived from normal lung and lung tumors. Using reverse phase protein arrays and multiplex bead analysis, he and his team analyzed differentially activated signal transduction pathways and secreted angiogenic factors following modulation of estrogen receptor signaling. They examined the role of estrogen signaling in the therapeutic efficacy of VEGF or dual EGFR/VEGFR inhibitors by modulating estrogen signaling in an *in vivo* xenograft model of NSCLC. These studies helped to explain the molecular mechanisms underlying gender-specific differences in angiogenesis and the responsiveness to antiangiogenic therapies.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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PRESENTATIONS AND ABSTRACTS

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TETRAVALENT VACCINE AGAINST SCLC: A PILOT TRIAL

Lee M. Krug, MD; Memorial Sloan-Kettering Cancer Center; CIA 2008

Dr. Krug and his team conducted a pilot clinical trial of an antibody-inducing tetravalent vaccine against SCLC. In this trial, 10 patients with limited or extensive stage SCLC and a complete or partial remission after first-line chemotherapy and radiation therapy were enrolled. The primary endpoints were safety and immunogenicity. The individual conjugates of the tetravalent vaccine were prepared under contract by GMP facilities or in the Clinical Grade Production Facility at the Memorial Sloan-Kettering Cancer Center.

HEDGEHOG SIGNALING IN SMALL CELL LUNG CANCER STEM CELLS

Craig D. Peacock, PhD; Johns Hopkins Medical Institutions; YCSA 2008

Dr. Peacock and colleagues investigated whether conventional chemotherapy in small cell lung cancer (SCLC) effectively kills differentiated cancer cells while sparing undifferentiated cancer stem cells, which could regenerate the entire tumor in a chemoresistant form. The investigators focused on the role of embryonic signaling pathways in promoting tumor regeneration through the regulation of self-renewal. They demonstrated a requirement of Hedgehog (Hh) signaling in the self-renewal of SCLC and shown that Hh pathway antagonists can block recurrence following chemotherapy *in vivo*. The team showed that Hh signaling occurs through non-canonical pathways in SCLC and they performed basic and pre-clinical studies to address the mechanism and significance of this observation.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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EPHA2 KINASE AS A TARGET FOR TREATMENT AND EARLY DETECTION OF LUNG CANCER

Bingcheng Wang, PhD; Case Western Reserve University; CIA 2008

Dr. Wang and colleagues showed that tumor suppressor gene EphA2 homozygous knockout mice but not their wild type littermates spontaneously develop lung tumors, and display markedly increased susceptibility to chemically induced lung carcinogenesis. EphA2 is consistently upregulated in tumors arising in wild type mice. The overexpression

is robust and occurs very early, even in preneoplastic lesions. However, the overexpressed EphA2 is poorly activated in mouse tumors, suggesting that its tumor suppressor activities have been functionally silenced during tumorigenesis. The team found that the loss of tumor suppressor activities is correlated with loss of ligand expression; similar observations were made in human lung cancer. In human NSCLC cells *in vitro*, the latent tumor suppressor function can be reawakened by stimulation with ephrin-A1, a ligand for EphA2. This causes suppression of ERK1/2 and Akt kinase activities and inhibition of cell migration and proliferation. Systemic administration of ephrin-A1-Fc leads to selective homing of the ligand to tumors that overexpress the dormant EphA2, resulting in activation.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Fu W, McCormick T, Qi X, Luo L, Zhou L, Li X, Wang BC, Gibbons HE, Abdul-Karim FW, Gorodeski GI. Activation of P2X(7)-mediated apoptosis Inhibits DMBA/TPA-induced formation of skin papillomas and cancer in mice. *BMC Cancer.* 2009;9:114.

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SMOKING, POLYMORPHISMS, AND LUNG CANCER PROGNOSIS

Zhaoxi (Michael) Wang, MD, PhD; Harvard School of Public Health; CIA 2008

Dr. Wang and colleagues investigated whether SHS exposure (before diagnosis and continuous SHS exposure after diagnosis) is associated with shorter survival in a large population of lung cancer patients. In addition, they investigated whether genetic polymorphisms of genes involved in several biological pathways, e.g., tobacco smoke metabolism, DNA repair, and cell cycle regulation modify the association between smoking and the survival of lung cancer patients. The team used various statistical techniques to adjust for important covariates that have been shown to be associated with lung cancer survival, including clinical stage and performance status. This study resulted in a better idea of how the combination of SHS exposure and constitutive host factors influences the effect of cancer therapy and provided easily measurable markers to help clinicians plan patient-specific therapy.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Huang YT, Heist RS, Chirieac LR, Lin X, Skaug V, Zienolddiny S, Haugen A, Wu MC, Wang Z, Su L, Asomaning K, Christiani DC. Genome-wide analysis of survival in early-stage non-small-cell lung cancer. *J Clin Oncol.* 2009;27(16):2660-2667.

Ter-Minassian M, Asomaning K, Zhao Y, Chen F, Su L, Carmella SG, Lin X, Hecht SS, Christiani DC. Genetic variability in the metabolism of the tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) to 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL). *Int J Cancer.* 2012;130(6):1338-1346. (Laboratory of Dr. Zhaoxi Wang).

REGULATION OF NON-SMALL CELL LUNG CANCER BY NOTCH

Douglas W. Ball, MD; Johns Hopkins Medical Institutions; CIA 2007

Dr. Ball's data for both small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) illustrate the heterogeneity of the capacity of individual cancer cells within a tumor to initiate new tumors. Using direct xenograft models for SCLC, Dr. Ball and colleagues identified two key markers of enhanced tumor-initiating capacity, CD133/ prominin 1 and aldehdye dehdrogenase (ALDH1A1). Both of these markers are positively regulated by the neuroendocrine bHLH transcription factor achaete-scute homolog 1 (ASCL1), as identified by microarray and confirmed by quantitative PCR, fluorescence activated cell sorting, and chromatin immunoprecipitation. ASCL1 expression and action are antagonized by the Notch signaling pathway. High levels of Notch pathway signaling activity are found in a spectrum of NSCLC cell lines and NSCLC tumors using tissue microarrays. A broad range of Notch pathway activity concordant with expression of CD133 and ALDH1A1 was found in NSCLC direct xenograft tumor models.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Jiang T, Collins BJ, Jin N, Watkins DN, Brock MV, Matsui W, Nelkin BD, Ball DW. Achaete-scute complex homologue 1 regulates tumor-initiating capacity in human small cell lung cancer. *Cancer Res.* 2009;69(3):845-854.

USING NOVEL TUMOR MODELS AND NOVEL THERAPEUTICS TO DEFINE TUMOR PROGENITORS IN SMALL LUNG CANCER

Christine L. Hann, MD, PhD; Johns Hopkins Medical Institutions; YCSA 2007

Dr. Hann and colleagues targeted the Bcl-2 protein, a central apoptotic inhibitor that is upregulated in 70-90% of small cell lung cancer (SCLC) patients. The investigators demonstrated a dramatic regression in SCLC cell line xenografts treated with ABT-737, a potent small molecule inhibitor of Bcl-2. These preclinical studies were expanded to include a newer primary xenograft model system that may better reflect patient tumor biology. For primary SCLC xenografts that express very low levels of Bcl-2, ABT-737 treatment alone did not have antitumor efficacy; however, when co-administered with the chemotherapy agent etoposide, ABT-737 caused statistically significant decreases in tumor growth. Treatment of two primary SCLC xenografts that express high levels of Bcl-2 with ABT-737 alone caused a near arrest of tumor growth. The addition of etoposide did not

enhance the antitumor effect of ABT-737 in these particular xenografts. A third Bcl-2-expressing primary SCLC xenograft demonstrated intermediate sensitivity to ABT-737 treatment, which was enhanced with etoposide. To define mechanisms that may contribute to ABT-737 resistance, the investigators characterized an ABT-737-resistant derivative cell line and found that both Bcl-2 expression and Bcl-2:BIM heterodimers are decreased. Expression profiling revealed 85 genes with changes in expression associated with acquired resistance. Dr. Hann's team validated eight of these genes, all of which are implicated in tumorigenesis.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Gandhi L, Camidge DR, Ribeiro de Oliveira M, Bonomi P, Gandara D, Khaira D, Hann CL, McKeegan EM, Litvinovich E, Hemken PM, Dive C, Enschede SH, Nolan C, Chiu YL, Busman T, Xiong H, Krivoshik AP, Humerickhouse R, Shapiro GI, Rudin CM. Phase I study of Navitoclax (ABT-263), a novel Bcl-2 family inhibitor, in patients with small-cell lung cancer and other solid tumors. *J Clin Oncol.* 2011;29(7):909-916.

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Hann CL, Rudin CM. Fast, hungry and unstable: finding the Achilles' heel of small-cell lung cancer. *Trends Mol Med.* 2007;13(4):150-157.

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PRESENTATIONS AND ABSTRACTS

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Connis N, Gardner E, Poirier JT, Kamat CD, Cope L, Rudin CM, Hann CL. ABT737/263. Presented at the 13th Annual Targeted Therapies for the Treatment of Lung Cancer (IASLC). Santa Monica, CA, Feb 20-23, 2013.

Connis N, Gardner E, Poirier JT, Kamat CD, Cope L, Rudin CM, Hann CL. Bcl-2 and mTOR inhibitors in SCLC. Presented at the NCI Workshop on Small Cell Lung Cancer, Bethesda, MD. Jul 1, 2013.

COMBINATION AD.P53-DC IMMUNOTHERAPY/CHEMOTHERAPY FOR SCLC

Terri B. Hunter, PhD, Hatem Soliman, MD; H. Lee Moffitt Cancer Center at the University of South Florida; YCSA 2007

Dr. Soliman and colleagues determined mechanisms of increased efficacy of combination chemotherapeutic/immunotherapy treatment in SCLC patients. They determined that SCLC cells are relatively insensitive to killing by biologically relevant doses of Paclitaxel (PA) *in*

vitro. They also determined that PA increases expression of the pro-survival protein Bcl-xl in SCLC cells, identifying an active mechanism of resistance of SCLC to PA treatment. Thus, they tested obataclax mesylate (GX), a pan-Bcl-2 family inhibitor that inhibits pro-survival members of the Bcl family (Bcl-2, Bcl-xl, Mcl-1) by competitively inhibiting BH3-binding of pro-apoptotic proteins. The investigators hypothesized that inhibiting Bcl-family members with GX would enhance the tumoricidal activity of PA. The team determined that GX and PA synergize to kill SCLC tumor cells *in vitro*.

TARGETING EPIGENETIC CHANGES IN METASTATIC LUNG CANCER

Rosalyn Juergens, MD; Johns Hopkins Medical Institutions; YCSA 2007

Studies by Dr. Juergens and her group showed that combined inhibitions of DNA methyl transferases (DNMTs) and histone deacetylases (HDACs) synergistically induce re-expression of tumor suppressor genes that are epigenetically silenced in cancer. The investigators tested the efficacy of combined epigenetic targeting in patients with advanced recurrent NSCLC using the DNMT inhibitor 5AC and the HDAC inhibitor entinostat on a schedule that is well tolerated and associated with significant activity in patients with hematologic malignancies. The team completed the Phase I and II portions of a clinical trial. They observed that toxicities are mild. There were four patients with excellent responses: one patient had a complete response that lasted 14 months, one patient showed a partial response, and two patients had prolonged stable disease for over 14 months. Epigenetic therapy offers an alternate strategy in the fight against lung cancer.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Juergens RA, Wrangle J, Vendetti FP, Murphy SC, Zhao M, Coleman B, Sebree R, Rodgers K, Hooker CM, Franco N, Lee B, Tsai S, Delgado IE, Rudek MA, Belinsky SA, Herman JG, Baylin SB, Brock MV, Rudin CM. Combination epigenetic therapy has efficacy in patients with refractory advanced non-small cell lung cancer. *Cancer Discovery*. 2011;1:598-607.

PRESENTATIONS AND ABSTRACTS

Juergens RA, Vendetti F, Coleman B, Sebree R, Rudek MA, Belinsky SA, Brock MV, Herman JG, Baylin SB, Rudin CM. A Phase II trial of 5-azacitidine (5AC) and entinostat (SNDX-275) in relapsed advanced lung cancer (NSCLC): An interim analysis. *J Thorac Oncol* 2009;4:S306.

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Juergens RA. Targeting epigenetic changes in non-small cell lung cancer. PhD Dissertation in the Graduate Training Program in Clinical Investigation at the Johns Hopkins University Bloomberg School of Public Health. Baltimore, MD, Apr 2012.

Wrangle JM, Mohammad HP, Abukhdeir A, Juergens RA, Harbom K, Rodgers K, Shin J, Zahnow CA, Baylin S, Herman J, Rudin CM, Brock MV. Predicting sensitivity to azacytidine in non-small cell cancer lines by absence of activating mutations [abstract]. American Society of Clinical Oncology. Chicago, IL Jun 1-5, 2012.

MEK-INDUCED GROWTH ARREST IN SMALL CELL LUNG CANCER CELLS

Jong-In Park, PhD; Medical College of Wisconsin; YCSA 2007

Dr. Park investigated whether the ability of small cell lung cancer (SCLC) cells to arrest in response to Ras/Raf activation depends on a growth arrest-specific intracellular signaling complex of the MAP kinases, MEK/ ERK, and whether non-small cell lung cancer (NSCLC) cells, in which Ras/Raf has opposing effects, have lost the ability to form this complex. The investigators studied the biochemical characteristics of ERK required to mediate growth arrest signaling and identified the components of growth arrest-specific MEK/ ERK complexes using tandem affinity purification and proteomics mass spectrometry techniques. ERK has been found to be able to utilize its noncatalytic activity to mediate growth arrest signaling. This finding supports the hypothesis that formation of specific intracellular signaling complexes of MEK/ERK is important in directing the pathway signaling toward growth arrest.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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DEVELOPING NRF2 INHIBITORS FOR CANCER CHEMOTHERAPY

Anju Singh, PhD; Johns Hopkins Medical Institutions; YCSA 2007

Dr. Singh and colleagues screened a library of FDA-approved drugs to identify inhibitors of nuclear factor erythroid-2-related factor 2 (Nrf2) and identified several drugs as putative inhibitors. Nrf2 is a redox-sensitive transcription factor that regulates the expression of antioxidants, xenobiotic detoxification enzymes, and efflux proteins. It also confers cytoprotection against a broad spectrum of drugs and electrophiles. Loss-of-function mutations in the Nrf2 inhibitor Kelch-like ECH-associated protein (KEAP1) result in gain of Nrf2 function in lung and prostate cancer. The drugs uncovered in the screen were evaluated for their Nrf2 inhibitory activity.

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NICOTINE INDUCED SRC SIGNALING IN LUNG METASTASIS

Hong-Gang Wang, PhD; University of Pennsylvania; CIA 2007

Dr. Wang investigated the metastatic spread of breast cancer to the lung caused by cigarette smoke exposure and explored the possible chemotherapeutic benefit of dasatinib, a dual Src/Bcr-Abl inhibitor, in the prevention of this metastasis. Anoikis is a mechanism that induces apoptosis by activating the death effector Bax in cells detached from their normal extracellular matrix environment; therefore, it plays an inhibitory role in metastatic dissemination of cancers. Nicotine is known to activate the tyrosine kinase Src, and activated Src has been shown to inhibit Bax-dependent anoikis. Findings from Dr. Wang and colleagues suggest that Src blocks anoikis by altering the relative expression of the Bcl-2 family members Mcl-1 and Bim through the PI3K/ Akt and Erk1/2 pathways. Src is also able to prevent anoikis, even when Akt and Erk1/2 signaling is inhibited. Further evaluation of the role of Src in this process revealed that Bif-1, a protein that associates with and activates Bax, is directly phosphorylated by Src at Tyr80, which prevents the association of Bax with Bif-1 and impairs the anoikis response. Loss of Bif-1 expression suppresses apoptosis as well as autophagy.

FAMRI SUPPORTED RESEARCH

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THE ROLE OF THE TRANSCRIPTION FACTOR C/EBP ALPHA IN NORMAL LUNG DEVELOPMENT AND IN MURINE MODELS OF LUNG CANCER AND TOBACCO-DAMAGED AIRWAY EPITHELIUM

Elena Levantini, PhD; Beth Israel Deaconess Medical Center; YCSA 2006

Dr. Levantini and collaborators showed that C/EBP alpha is detected in bronchoalveolar stem cells, which are linked to adenocarcinoma initiation. Data from two lung conditional models support the hypothesis that C/EBP alpha is a lung tumor suppressor; the conditional models develop adenocarcinoma. Furthermore, the data indicate that Gli-1, a transcriptional effector of the sonic hedgehog pathway, is highly active only in C/EBP alpha-deleted pulmonary cells that may represent cells of origin of lung adenocarcinomas in the murine models. Dr. Levantini also observed that C/EBP alpha excision results in upregulation of Bmi-1, and that tumor initiation strictly depends on Bmi-1 gene dosage, because C/EBP alpha lung-deleted mice carrying only one functional Bmi-1 allele escape tumorigenesis. C/EBP alpha negative human adenocarcinomas show elevated Bmi-1 expression, consistent with the observation that C/EBP alpha acts as tumor suppressor in lung cells by directly inhibiting Bmi-1 transcription. Pharmacological inhibition of Bmi-1 impairs the ability of C/EBP alpha null adenocarcinoma cells to form tumors in xenografts. Overall, the data reveal that loss of C/EBP alpha increases the susceptibility to lung cancer development and identify Bmi-1 as a critical therapeutic target in patients carrying abnormal C/EBP alpha function.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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LUNG ADENOCARCINOMA PROGRESSION: MARKERS AND MEDIATION BY CIGARETTE SMOKE EXPOSURE

Charles A. Powell, MD; Columbia University; CIA 2006

Dr. Powell and colleagues focused on understanding the importance of regulation on activation, normally expressed and secreted (RANTES) signaling in type II receptor for transforming growth factor beta (TBRII)-deficient lung adenocarcinoma cells and developed murine models to study the function of TBRII *in vivo*. They concluded that inhibition of the signaling of RANTES, a member of the interleukin-8 superfamily of cytokines, via CCR5 blockade in tumor cells, reduces lung adenocarcinoma progression and metastasis *in vivo*. The team developed murine models of chronic inflammation that overexpress interleukin 1B in the lung along with a pharmacologic delivery of lipopolysaccharide into the lungs and showed that chronic lung inflammation promotes smoke-associated tumorigenesis and contributes to the tumor immune response. In additon it partially inhibits progression. The investigators concluded that loss of TBRII *in vivo* promotes tumor progression, invasion, and metastasis.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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ANALYSIS OF DNA REPAIR CAPACITY TO PREDICT AND TARGET CHEMORESISITANT SMALL CELL LUNG CANCER

John Turchi, PhD; Indiana University School of Medicine, CIA 2006

Dr. Turchi and colleagues developed a solid phase assay that can be used to ascertain DNA repair protein expression and activity from cell and biological samples. Assessment of DNA repair capacity can be used to determine potential utility of cisplatin-based therapies in the context of both non-small cell lung cancer and small cell lung cancer treatment. The investigators demonstrated the efficacy of proteins involved in DNA metabolism responsible for chromosome stability and maintenance in tumor xenograft models of non-small cell lung cancer.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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TGF BETA SIGNALING IN LUNG CANCER: A THERAPEUTIC TARGET

Pran Datta, PhD; Vanderbilt University Medical Center; CIA 2005

Dr. Datta determined the molecular mechanism of TGF beta RII downregulation in primary lung cancer. He also determined if restoration of TGF beta signaling re-establishes tumor suppressor function or tumor-promoting effects of TGF beta and investigated the radiation-sensitizing effects of the histone deacetylase inhibitor MS-275 *in vitro* and *in vivo* in human lung cancer preclinical models. He and his colleagues observed that TGF-beta-induced tumor suppressor function is restored in TGF beta-resistant lung cancer cells by exogenous expression of TGF betaRII or by the treatment with histone deacetylase inhibitors (HDI). Using proteomics and biochemical methods, Dr. Datta's group identified a region of the TGF betaRII promoter required for activation by HDI and proteins involved in the regulation of TGF betaRII expression.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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BOOK CHAPTERS, ETC.

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NICOTINE REGULATION OF BAX'S PROAPOPTOTIC FUNCTION IN HUMAN LUNG

Xingming Deng, MD, PhD; University of Florida; CIA 2005

Dr. Deng continued his 2002 study and concluded that nicotine induces the phosphorylation of Bax via activation of the P13K/AKT pathway. Bax is extensively expressed in human lung cancer treatment. Nicotine induces Bax phosphorylation exclusively at the ser 184 site in its c-terminal region and inactivates its proapoptotic function and lessens chemoresistance in human lung cancer cells.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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EFFECTS OF PTHrP ON LUNG CANCER SURVIVAL IN WOMEN

Randolph Hastings, MD, PhD; VA San Diego Healthcare System; CIA 2005

Dr. Hastings found that tumors in males make less parathyroid related protein (PTHrP) than those found in females, which may be a phenomenon related to testosterone levels. He determined the effect of PTHrP on lung cancer survival and confirmed the observation that PTHrP is a sex-dependent survival factor for NSCLC. He investigated the effects of androgen suppression on lung cancer PTHrP, PTHr1, and lung cancer growth in athymic mice that had been implanted with orthotopic lung cancers that produce PTHrP; some of the mice were orchiectomized to reduce testosterone levels. The results show that androgen suppression can reduce tumor growth and that the mechanism involves PTHrP signaling.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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PPAR GAMMA AGONIST MEDIATED SUPPRESSION OF PGE2 IN HUMAN NSCLC

Saswati Hazra, PhD; University of California, Los Angeles; YCSA 2005

Dr. Hazra and colleagues utilized human telomerase reverse transcriptase- and cyclin-dependent kinase 4-immortalized human bronchial epithelial cells (HBECs) expressing mutant KrasV12 to generate profiles of miRNA, gene expression, and protein expression of the K-ras mutated and vector control HBECs. The investigators found that the miRNA miR-125a-3p was significantly suppressed in K-ras-mutated HBECs compared to the controls. They demonstrated that both K-ras-mutated HBECs and NSCLC cell lines expressed low levels of miR-125a-3p and found that miR-125a-3p expression downregulated tumor-promoting factors such as growth-regulated oncogene-alpha (Gro-alpha), hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), granulocyte macrophage colony-stimulating factor (GM-CSF), and G-CSF. Suppression of Gro-. and HGF, but not VEGF, was regulated at the level of mRNA expression. Over-expression of miR-125a-3p downregulated Gro-alpha and suppressed proliferation of K-ras-mutated HBECs. An association was found between the use of rosiglitazone and a reduced risk of lung cancer. The investigators found that rosiglitazone upregulates miR-125a-3P by 15-fold in K-rasmutated HBECs compared to 1.8-fold in the control cells.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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A TRANSGENIC ANIMAL MODEL TO CONTROL THE ANGIOGENIC SWITCH IN LUNG CANCER

Douglas A. Arenberg, MD; The University of Michigan; CIA 2004

Dr. Arenberg and colleagues produced a transgenic mouse that permits precise control of the timing and nature of the angiogenic switch in the context of chemically induced lung cancer tumorigenesis. This transgenic model was used to test the hypothesis that evolution of a given angiogenic strategy suppresses the development of other angiogenic strategies during tumor development; demonstrating that tumors use only one such strategy at a time. The results suggest that migration inhibitory factor (MIF) expression during tumor growth accelerates tumor development and alters the angiogenic phenotype of the resulting tumors compared to controls.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Keshamouni VG, Arenberg DA, Reddy RC, Newstead MJ, Anthwal S, Standiford TJ. PPAR-gamma activation inhibits angiogenesis by blocking ELR+CXC chemokine production in non-small cell lung cancer. *Neoplasia.* 2005;7(3):294-301.

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PRESENTATIONS AND ABSTRACTS

McClelland M, Gray A, Carskadon S, Zhao L, Arenberg D. Angiogenic strategies in non-small cell lung cancer. Presented at the American Association for Cancer Research Conference: Molecular Pathogenesis of Lung Cancer. San Diego, CA, Feb 2005.

McClelland M, Gray A, Carskadon S, Zhao L, Arenberg D. Macrophage migration inhibitory factor (MIF)-dependent induction of angiogenic CXC chemokines in an animal model of NSCLC Presented at the American Association for Cancer Research Conference: Molecular Pathogenesis of Lung Cancer. San Diego, CA, Feb 2005.

METHYLATION IN LUNG CANCERS OF SMOKERS AND NONSMOKERS

William P. Bennett, MD; City of Hope; CIA 2004

Dr. Bennett and colleagues developed a methylation signature in DNA exposed to incinerated tobacco. The group analyzed the methylation status in promoter regions of the following genes: CDH13; p16/CDKN2A; and RassF1A from 30 smokers and eight non-smokers. They found that 40% of the tumors from smokers have more methylation in p16/CDKN2A and RassF1A than any of the eight non-smokers, that smokers have more moderate to high-level methylation than nonsmokers in p16/CDKN2A and RassF1A; that non-smokers have more low-level methylation than smokers, and that smokers and non-smokers have comparable amounts of methylation in CDH13. These results can be used to define a tobacco exposure signature based on methylation rates at hotspot CpG sites, and can be used to identify lung cancers in individuals exposed to SHS.

FAMRI SUPPORTED RESEARCH

PRESENTIONS AND ABSTRACTS

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SECONDHAND TOBACCO SMOKE AND LUNG CANCER RISK

Olga Y. Gorlova, PhD; University of Texas M.D Anderson Cancer Center; YCSA 2004

Dr. Gorlova identified several lung cancer risk factors for never smokers. They are overall and workplace SHS exposure, dust exposure, and family history of young-onset cancer (less than 50 years of age). She noted that hay fever that occurs without asthma is associated with decreased lung cancer risk. In addition, a significantly elevated risk of overall cancer such as young-onset lung cancer, breast, and testicular cancer, was demonstrated among the first-degree relatives of never smokers with lung cancer. It was found that a suboptimal DNA repair capacity (DRC) conferred a significantly increased lung cancer risk in never smokers, which was exacerbated by SHS exposure. An almost four-fold lung cancer risk was observed in SHS-exposed individuals with suboptimal DRC. Relatives of probands (cases and controls) with lowest DRC (below the first quartile) were more likely to be diagnosed with lung cancer compared with relatives of probands with the most proficient DRC (above the third quartile). Relatives of probands with suboptimal (below the control median) versus proficient DRC had an earlier age at diagnosis of lung cancer, although the only statistically significant difference was in female relatives. The roles of genetic susceptibility and smoking history in the initiation, clonal expansion, and malignant transformation processes in lung carcinogenesis were studied in never smokers and smokers that utilized the two-stage clonal expansion stochastic model framework. The results show that individuals with a suboptimal DRC have enhanced transition rates to key events in carcinogenesis.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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Gorlova OY, Weng SF, Zhang Y, Amos CI, Spitz MR. Aggregation of cancer among relatives of never-smoking lung cancer patients. *Int J Cancer.* 2007;121(1):111-118.

Gorlova OY, Weng SF, Zhang Y, Amos CI, Spitz MR, Wei Q. DNA repair capacity and lung cancer risk in never smokers. *Cancer Epidemiol Biomarkers Prev.* 2008;17(6):1322-1328.

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PRESENTATIONS AND ABSTRACTS

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Wu X, Lin J, Etzel CJ, Schabath MB, Gorlova OY, Zhang Q, Dong Q, Amos CI, Spitz MR. Interplay between mutagen sensitivity and epidemiological factors in modulating lung cancer risk. Presented at the American Association for Cancer Research, 97th Annual Meeting. Washington, DC, Apr 1-5, 2006.

DEVELOPMENT OF STEM CELL MODEL SYSTEMS OF LUNG CANCER AND TOBACCO-DAMAGED AIRWAY EPITHELIUM

Balazs Halmos, MD, MS; Columbia University; YCSA 2004

Dr. Halmos identified the DUSP6 gene as a key negative feedback regulator of oncogenic EGFR and ERK signaling. He also identified a low number of oncogenic EGFR mutations in African-American patients with non-small cell lung cancer. Strides were made toward identifying novel mechanisms of acquired resistance to small molecule EGFR tyrosine kinase inhibitors, such as erlotinib and gefitinib. The role of the larger class of dual-specificity phosphatases in lung carcinogenesis, with a particular focus on the DUSP7 gene was studied. Translational studies were performed in the clinic to determine the best clinical use of EGFR inhibitors in patients with non-small cell lung cancer and the contributions of EGFR inhibitors in the cancer stem cell population as mediators of resistance.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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Kobayashi S, Ji H, Yuza Y, Meyerson M, Wong KK, Tenen DG, Halmos B. An alternative inhibitor overcomes resistance caused by a mutation of the epidermal growth factor receptor. *Cancer Res.* 2005;65(16):7096-7101.

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THE IMPLICATION OF POTENTIAL TUMOR SUPPRESSION FUNCTION OF DAXX IN C-MET-DEPENDENT LUNG MALIGNANCY

Alexander M. Ishov, PhD: University of Florida; CIA 2004

Dr. Ishov's hypothesis was that DAXX may inhibit c-Met gene activation by recruiting negative regulators of gene expression. Downregulation or inactivation of DAXX can release this repression, leading to an increase in c-Met gene expression, resulting in oncogenic

transformation of cells and lung tumor progression. Elucidation of ways to regulate c-Met protein production should lead to strategies for blocking lung malignancies.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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PPAR-GAMMA IN TUMOROGENESIS AND THERAPY OF NON-SMALL CELL LUNG CANCER

Venkateshwar Keshamouni, PhD; University of Michigan; YCSA 2004

Dr. Keshamouni investigated the role of PPAR-gamma in the initiation and progression of NSCLC tumors and developed new strategies to target it for therapy. Dr. Keshamouni demonstrated that chemotherapeutic drugs induce PPAR-gamma expression and synergize with PPAR-gamma ligands in the treatment of lung cancer.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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THE SMALL MOLECULE INHIBITORS OF BCL-2 AS NOVEL THERAPEUTICS FOR LUNG CANCER

Charles M. Rudin, MD, PhD; Johns Hopkins University Sidney Kimmel Comprehensive Cancer Center; CIA 2004

Aberrant expression of B-cell lymphoma protein 2 (Bcl-2), an apoptotic inhibitor, is common in small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), and is accompanied with an increase in resistance to chemotherapy and radiation. Through the use of human lung cancer xenografts in mice, Dr. Rudin and colleagues explored the clinical development of a novel set of cytotoxic agents that function via inhibition of critical anti-apoptotic pathways upregulated in lung cancer and other malignancies. They demonstrated that ABT-737, a very potent small molecule inhibitor of Bcl-2, is highly effective against SCLC *in vitro* and *in vivo* even in the absence of standard cytotoxic chemotherapy.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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TARGETING MYC FOR THE TREATMENT OF LUNG CANCER

Catherine M. Shachaf, PhD; Stanford University; YCSA 2004

Dr. Shachaf and collaborators used genetically-altered mice that can activate or inactivate MYC expression to demonstrate that atorvastatin reverses and prevents the onset of MYC-induced tumorigenesis, but fails to reverse or prevent tumorigenesis in the presence of constitutively activated K-Ras (G12D). Atorvastatin treatment resulted in the inactivation of the Ras and extracellular signal-regulated kinase (ERK)1/2 signaling pathways associated with dephosphorylation and inactivation of the MYC protein. Correspondingly, tumors with a constitutively activated G12D did not exhibit dephosphorylation of ERK1/2 and MYC. Inhibiting 3-hydroxy-3-methyl-glutaryl-CoA reductase caused atorvastatin to induce changes in phosphoprotein signaling that prevents MYC-induced lymphomagenesis. The investigators demonstrated that there is a precise threshold level of expression required for maintaining the tumor phenotype, whereupon there is a switch from a program of proliferation to a state of proliferative arrest and apoptosis. They showed that changes in expression occur at or near the MYC threshold, including factors implicated in the regulation of the Gap 1/synthesis, Gap 2/mitosis cell cycle checkpoints, and death receptor/apoptosis signaling. The team developed composite organic-inorganic nanoparticles and a unique method to detect DNA amplifications and deletions in single cells by FACS. This should help determine how different cell populations respond to therapy.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Gentles AJ, Alizadeh AA, Lee SI, Myklebust JH, Shachaf CM, Shahbaba B, Levy R, Koller D, Plevritis SK. A pluripotency signature predicts histologic transformation and influences survival in follicular lymphoma patients. *Blood.* 2009;114(15):3158-3166.

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PRESENTATIONS AND ABSTRACTS

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TARGETING THE ESTROGEN RECEPTOR RECEPTOR FOR LUNG CANCER THERAPY

Laura A. Stabile, PhD; University of Pittsburgh; YCSA 2004

The goal of this study was to determine if a combination of drugs that target the pathways of both the estrogen receptor (ER) and the epidermal growth factor receptor (EGFR) might decrease lung cancer growth *in vitro* and *in vivo*. Fulvestrant and gefitinib together showed more of a decrease in tumor size in a mouse model than either drug alone. The investigators demonstrated that estrogen can increase vascular endothelial growth factor (VEGF) secretion in lung cancer cells, and that an EGFR/VEGFR inhibitor, AZD6474, or vandetanib in combination with fulvestrant showed very promising results. A Phase I clinical trial examining the safety of fulvestrant and gefitinib was completed with no major adverse effects. Dr. Stabile and colleagues showed that ER beta is responsible for the genomic and nongenomic actions of estrogen in the lung, and a nonnuclear estrogen receptor, GPR30, is expressed in the lung and may be responsible for some of the actions of estrogen. It appears to be more highly expressed in cells from nonsmoking lung cancer patients compared to smokers. GPR30 expression was not correlated with lung cancer survival; however, high cytoplasmic ER beta expression was found to be a negative prognostic factor for overall survival.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Hershberger PA, Stabile LP, Kanterewicz B, Rothstein ME, Gubish CT, Land S, Shuai Y, Siegfried JM, Nichols M. Estrogen receptor beta (ERbeta) subtype-specific ligands increase transcription, p44/p42 mitogen activated protein kinase (MAPK) activation and growth in human non-small cell lung cancer cells. *J Steroid Biochem Mol Biol.* 2009;116(1-2):102-109.

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Stabile LP, Lyker JS, Gubish CT, Zhang W, Grandis JR, Siegfried JM. Combined targeting of the estrogen receptor and the epidermal growth factor receptor in non-small cell lung cancer shows enhanced antiproliferative effects. *Cancer Res.* 2005;65(4):1459-1470.

PRESENTATIONS AND ABSTRACTS

Siegfried JM, Stabile LP, Hershberger PA, Nichols M, Schiller JH. Targeting the estrogen receptor for lung cancer therapy. Proceedings of the American Association for Cancer Research. 2005;46:SY26.A197:C197

Stabile LP, Lyker JS, Gubish CT, Siegfried JM. Targeting the estrogen receptor and the epidermal growth factor receptor for lung cancer therapy. *Proc Am Assoc Cancer Res* 2004;45:2423.

EPIGENETIC CONTROL OF HUMAN PROSTACYCLIN SYNTHASE

Robert S. Stearman, PhD; University of Colorado, Denver; CIA 2004

Prostacyclin synthase, the key enzyme responsible for producing the eicosanoid prostacyclin, is significantly decreased in human lung cancer. Murine studies showed that high prostacyclin synthase expression has a protective effect in various lung cancer models. Dr. Stearman examined genetic and epigenetic mechanisms that could account for the deficiency of prostacyclin synthase in human lung cancer. His results suggested that DNA methylation causes silencing and can significantly affect prostacyclin synthase expression.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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PATTERNS OF GENE EXPRESSION IN EARLY LUNG LESIONS

Scott Wadler, MD (1946-2007), Maureen Lane, PhD; Weill Medical College, Cornell University; CIA 2004

This project was assigned to Maureen Lane, PhD on Dr. Wadler's death in 2007. Drs. Wadler and Lane had shown that early lung lesions exhibit distinct genetic profiles and cluster into distinct groups. These groups include normal, benign, three distinct subclasses

of lung adenocarcinoma, and one subclass of metastatic adenocarcinoma. One of the subgroups of adenocarcinomas exhibits a gender bias toward women. This may play a role in treatment strategies for patients that express the genes associated with this group. Early lung samples obtained by guided fine needle aspirates (FNA), a relatively non-invasive method, were profiled. FNAs can be routinely used to obtain good quality specimens for molecular analysis using gene expression arrays.

FAMRI SUPPORTED RESEARCH

PRESENTATIONS AND ABSTRACTS

Lane ME, Yankelevitz DF, Henschke CI, Vazquez MF, Xiang Z, Kimmel M, Kramer A, Wadler S. Patterns of gene expression in pulmonary fine needle aspirates (FNA) with diverse radiographic appearances exhibit distinct patterns of gene expression. *Proc Amer Assoc Cancer Res* 2004;45:5589.

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Wadler S, Yankelevitz DF, Henschke CI, Vazquez MF, Xiang M, Kramer A, Campagne F, Lane ME. Gene expression patterns in early lung adenocarcinomas exhibit a gender bias. Presented at the 14th International Conference on Screening for Lung Cancer. Silver Spring, MD, Apr, 2006.

TRANSCRIPTIONAL REGULATION OF PUMA IN LUNG CANCER

Jian Yu, PhD; University of Pittsburgh; YCSA 2004

Dr. Yu and colleagues identified a novel p53 target and B-cell lymphoma 2 (Bcl-2) family protein p53 upregulated modulator of apoptosis (PUMA), which induces profound apoptosis in cancer cells. Using lung cancer lines and gene-targeted cancer cell lines, Dr. Yu's group demonstrated that p53-mediated PUMA transcription is essential for apoptosis induced by common chemotherapeutic drugs and radiation. Reintroduction of PUMA results in extensive apoptosis, growth suppression, and chemosensitization in cancer cells derived from lung, esophagus, and head and neck cancers *in vitro* and *in vivo*. Several transcription factors were found to regulate PUMA induction in p53-deficient cancer cells in response to targeted cancer therapies, including selective EGFR tyrosine kinase inhibitors. These findings were translated into cell-based assays for small molecule compound library screening and additional mechanistic studies.

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BOOK CHAPTERS, ETC.

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SMOKING, POLYMORPHISMS, AND LUNG CANCER PROGNOSIS

Wei Zhou, MD, PhD; Harvard School of Public Health; YCSA 2004

Dr. Zhou investigated the interactive roles of SHS and mainstream smoke (MSS) by looking at a number of genetic polymorphisms in clinical outcomes of a cohort of non-small cell lung cancer (NSCLC) patients to investigate whether SHS and MSS are associated with

poorer prognosis in both earlier and more advanced stages of cancer. The investigator examined whether polymorphisms of interest might modify the association between SHS and MSS and NSCLC prognosis. Results demonstrate that smoking cessation is associated with improved survival in early stage NSCLC, and the longer the duration since smoking cessation, the better the survival outcome. Results show SHS exposure before diagnosis results in poorer survival in early stage NSCLC patients.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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Miller DP, Park S, Gitin E, Zhou W, Liu G, Wain JC, Lynch TJ, Christiani DC. DNA repair polymorphisms, secondhand tobacco smoke and lung cancer risk. Presented at the Annual Meeting of the American Association for Cancer Research. Anaheim, CA, Apr 16-20, 2005.

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REGULATION OF NON-SMALL CELL LUNG CANCER BY NOTCH

Douglas W. Ball, MD; Johns Hopkins Medical Institutions; CIA 2003

Please see the synopsis under Dr. Ball's 2007 award.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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ROLE OF IRF-5 AS A TUMOR SUPPRESSOR IN A NON-SMALL CELL LUNG CANCER (NSCLC)

Betsy J. Barnes, PhD; Johns Hopkins Medical Institutions, University of Medicine and Dentistry of New Jersey; YCSA 2003

Dr. Barnes investigated the relationship between interferon regulatory factor 5 (IRF-5) expression and the tumor suppressor gene p53 in human NSCLC to illuminate novel IRF-5-based therapies for lung cancer. The majority of NSCLC expresses mutant non-functional p53 or lacks IRF-5 expression. She examined expression of IRF-5 and p53 in multiple human cancers and investigated the IRF-5 tumor suppression potential in the growth regulation of lung cancers where IRF-5 and/ or p53 are not expressed.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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Schoenemeyer A, Barnes BJ, Mancl ME, Latz E, Goutagny N, Pitha PM, Fitzgerald KA, Golenbock DT. The interferon regulatory factor, IRF5, is a central mediator of toll-like receptor 7 signaling. *J Biol Chem.* 2005;280(17):17005-17012.

THE ROLE OF HMG-I/Y IN THE PATHOGENESIS OF LUNG CANCER

Raka Bhattacharya, PhD; Johns Hopkins Medical Institutions; YCSA 2003

Dr. Bhattacharya and colleagues defined the role in lung cancer of Id1, a helix-loop-helix transcription factor. The team demonstrated that over-expression of Id1 is associated with highly aggressive and less differentiated tumor types, with poor prognosis and a propensity for tumor metastasis. Tumors in patients at Johns Hopkins with aggressive lung cancer who have been exposed to tobacco smoke have elevated levels of Id1 when compared to the surrounding normal tissue. The data show that Id1 expression is found at an early stage of the disease with metastasis to the lymph nodes. The investigators have shown that most non-small lung cancer (NSCLC) cells and small cell lung cancer (SCLC) cells express elevated levels of Id1 when grown in media containing fetal bovine serum; this serum responsiveness in many of the lung cancer cell lines suggests growth factor dependent Id1 expression.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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IDENTIFICATION OF NEW MOLECULAR TARGETS IN LUNG CANCER

Pierre P. Massion, MD (1963-2021); Vanderbilt University Medical Center; CIA 2003

Dr. Massion and collaborators identified molecular abnormalities in invasive and preinvasive lung cancers. They identified amplified and deleted genomic regions in invasive squamous, adeno, large, and small cell lung cancers using array-comparative genomic hybridization and potential targets in preinvasive lung cancer using matrix-assisted laser desorption/ionization mass spectrometry. They characterized eight tissue microarrays from a total of 360 lung cancers for validation of biomarkers in a high-throughput fashion. Dr. Massion passed away in April, 2021.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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Rahman SM, Shyr Y, Yildiz PB, Gonzalez AL, Li H, Zhang X, Chaurand P, Yanagisawa K, Slovis BS, Miller RF, Ninan M, Miller YE, Franklin WA, Caprioli RM, Carbone DP, Massion PP. Proteomic patterns of preinvasive bronchial lesions. *Am J Respir Crit Care Med.* 2005;172(12):1556-1562.

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ROLE OF ALDHs IN THE PATHOGENESIS AND BIOLOGY OF LUNG CANCER

Jan Moreb, MD; University of Florida; CIA 2003

Dr. Moreb demonstrated that aldehyde dehydrogenase (ALDH)1A1 and ALDH3A1 are highly expressed in squamous cell lung cancer, adenocarcinoma (AdenoCA), and non-small cell lung cancer, but very little expression is detected in small cell lung cancer. Atypical pneumocytes were shown to have significantly higher levels of expression of ALDH-1A1 and ALDH-3A1 than normal pneumocytes, which is suggestive of upregulation during malignant transformation to AdenoCA. Similar levels of expression were observed in bronchial epithelium. Expression of these enzymes in normal pneumocytes is seen in cigarette smokers. Small interfering RNAs (siRNAs) specifically inhibit ALDH-1A1 or ALDH-3A1 and result in increased 4-hydroperoxycyclophosphamide toxicity in the A549 lung cancer cell line. An Aldefluor assay was adapted to measure ALDH activity and real-time changes in ALDH activity in viable cells treated with siRNA or chemotherapy. Lentiviral vectors had great efficacy and specificity in the inhibition of either enzyme. Differences in gene transcription were determined between wild-type A549 cells and lenti 1+3 cells. A number of genes were categorized that are either repressed or induced two-fold when compared with normal cells.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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DEVELOPMENT OF A TUMOR VACCINE FOR LUNG CANCER

Scott Antonia, MD; H. Lee Moffitt Cancer Center; CIA 2002

Dr. Antonia's group created a human bystander cell line that expresses both GM-CSF and CD40 ligand (GM.CD40L). They completed a phase I trial involving patients with solid tumors, testing GM.CD40L cells admixed with autologous tumor cells. The vaccine was safe, and the vaccine sites of these patients were densely infiltrated with activated (CD86 positive) DCs and T cells. Twenty-three patients were treated with the cytoxan/ATRA/GM.CD40L vaccine combination. There were no serious adverse events attributed to the treatment. Several patients had CTC Grade 2 fatigue and headache that were attributed to the cytoxan and ATRA treatment. No toxicity was reported that was attributed to the vaccine. Three of the 23 patients had stable disease as their best clinical response. No patient achieved a partial response or complete response. According to the protocol, because there was no patient who developed an objective response by the time of the interim analysis, the study was terminated. A significant reduction was observed in the T cell responsiveness to stimulation with an agonistic anti-CD3 monoclonal antibody as measured in gamma-interferon ELISPOT assays. This shows that a general immunosuppression was induced along with the investigational treatment, most likely from systemic administration of cytoxan and/or ATRA.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Hunter TB, Manimala NJ, Luddy KA, Catlin T, Antonia SJ. Paclitaxel and TRAIL synergize to kill paclitaxel-resistant small cell lung cancer cells through a caspase independent mechanism mediated through AIF. *Anticancer Res.* 2011;31(10):3193-3204.

THE ROLE OF BC1-2 IN NICOTINE-INDUCED SURVIVAL SIGNALING AND CHEMORESISTANCE IN HUMAN LUNG CANCER CELLS

Xingming Deng, MD, PhD; University of Florida; CIA 2002

Dr. Deng determined whether phosphorylation of Bcl-2 is required for nicotine-induced lung cancer survival and chemoresistance and whether inhibition of nicotine-induced Bcl-2 phosphorylation enhances chemosensitivity in human lung cancer cells. He found that nicotine-induced survival may occur by a mechanism involving multisite phosphorylation of Bad, which may lead to the development of human lung cancer and/or chemoresistance.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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NUCLEOLAR EXPRESSION OF PTHrP AND OUTCOME IN NON-SMALL CELL LUNG CANCER (NSCLC)

Randolph H. Hastings, MD, PhD, Leonard J. Deftos, MD; VA San Diego Healthcare System and the University of California, San Diego; CIA 2002

Dr. Deftos reported data suggesting that parathyroid-hormone-related protein (PTHrP), a growth factor produced by many lung cancers, may predispose lung cancer cells to apoptosis if transported to the cell nucleolus. PTHrP isoform 1-173 expression and nucleolar PTHrP were evaluated for their efficacy as favorable prognostic signs for non-small cell lung cancer treatment in both patient and cell culture studies. PTHrP expression is present in two-thirds of cancer patients, and PTHrP immunoreactivity appears to be a positive prognostic factor for stage 1-2 lung cancer patients.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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Hastings RH, Montgrain PR, Quintana R, Rascon Y, Deftos LJ, Healy E. Cell cycle actions of parathyroid hormone-related protein in non-small cell lung carcinoma. *Am J Physiol Lung Cell Mol Physiol.* 2009;297(4):L578-585.

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LOH AND GENE EXPRESSION PROFILES IN LUNG CARCINOMA

Matthew Meyerson, MD, PhD; Dana-Farber Cancer Institute; CIA 2002

Dr. Meyerson observed loss of heterozygosity (LOH) and gene expression profiles in lung carcinoma using single nucleotide polymorphism (SNP) arrays to determine whether there are distinct patterns that correspond to gene expression-derived lung adenocarcinoma classes. In addition, tyrosine kinase genes were sequenced from non-small cell lung cancer (NSCLC) tissue and matched normal tissue. Somatic mutations of the estrogen growth factor receptor (EGFR) gene were found in 15 out of 58 unselected tumors from Japan and 1 out of 61 from the United States. Treatment with the EGFR kinase inhibitor gefitinib caused NSCLC regression more frequently in Japan, as well as in certain US cancer samples with EGFR gene mutations. The results suggest that EGFR gene mutations might predict sensitivity to gefitinib, and it may be necessary to identify differences within ethnic subgroups rather than assume equality in responses to drug therapies.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Jackman DM, Yeap BY, Sequist LV, Lindeman N, Holmes AJ, Joshi VA, Bell DW, Huberman MS, Halmos B, Rabin MS, Haber DA, Lynch TJ, Meyerson M, Johnson BE, Janne PA. Exon 19 deletion mutations of epidermal growth factor receptor are associated with prolonged survival in non-small cell lung cancer patients treated with gefitinib or erlotinib. *Clin Cancer Res.* 2006;12(13):3908-3914.

Janne PA, Borras AM, Kuang Y, Rogers AM, Joshi VA, Liyanage H, Lindeman N, Lee JC, Halmos B, Maher EA, Distel RJ, Meyerson M, Johnson BE. A rapid and sensitive enzymatic method for epidermal growth factor receptor mutation screening. *Clin Cancer Res.* 2006;12(3 Pt 1):751-758.

Janne PA, Li C, Zhao X, Girard L, Chen TH, Minna J, Christiani DC, Johnson BE, Meyerson M. High-resolution single-nucleotide polymorphism array and clustering analysis of loss of heterozygosity in human lung cancer cell lines. *Oncogene.* 2004;23(15):2716-2726.

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THE MOLECULAR EPIDEMIOLOGY OF SECONDHAND TOBACCO SMOKE-ASSOCIATED LUNG CANCER

David P. Miller, ScD; Harvard School of Public Health; YCSA 2002

Dr. Miller collected samples and assessed the SHS exposure in a case control study comprising individuals with non-small cell lung cancer (NSCLC) and controls. Different genotypes were determined and genes, direct smoke exposure, and SHS exposure were correlated. The exposure to SHS in this population was not only associated with lung cancer, but individuals with exposure earlier than 25 years of age had a greater lung cancer risk than for those whose exposure occurred after they were 25.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Asomaning K, Miller DP, Liu G, Wain JC, Lynch TJ, Su L, Christiani DC. Second hand smoke, age of exposure and lung cancer risk. *Lung Cancer.* 2008;61(1):13-20.

Liu G, Zhou W, Park S, Wang LI, Miller DP, Wain JC, Lynch TJ, Su L, Christiani DC. The SOD2 Val/Val genotype enhances the risk of nonsmall cell lung carcinoma by p53 and XRCC1 polymorphisms. *Cancer.* 2004;101(12):2802-2808.

Liu G, Zhou W, Wang LI, Park S, Miller DP, Xu LL, Wain JC, Lynch TJ, Su L, Christiani DC. MPO and SOD2 polymorphisms, gender, and the risk of non-small cell lung carcinoma. *Cancer Lett.* 2004;214(1):69-79.

Miller DP, De Vivo I, Neuberg D, Wain JC, Lynch TJ, Su L, Christiani DC. Association between self-reported environmental tobacco smoke exposure and lung cancer: modification by GSTP1 polymorphism. *Int J Cancer.* 2003;104(6):758-763.

Zhou W, Heist RS, Liu G, Asomaning K, Miller DP, Neuberg DS, Wain JC, Lynch TJ, Christiani DC. Second hand smoke exposure and survival in early-stage non-small-cell lung cancer patients. *Clin Cancer Res.* 2006;12(23):7187-7193.

Zhou W, Park S, Liu G, Miller DP, Wang LI, Pothier L, Wain JC, Lynch TJ, Giovannucci E, Christiani DC. Dietary iron, zinc, and calcium and the risk of lung cancer. *Epidemiology.* 2005;16(6):772-779.

PRESENTATIONS AND ABSTRACTS

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Miller DP, Park S, Gitin E, Zhou W, Liu G, Wang Z. ERCC2 Asp312Asn polymorphism modifies the association between secondhand tobacco smoke and lung cancer risk. Presented at the Annual Meeting of the American Association for Cancer Research. Orlando, FL, Mar 27-31, 2004.

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Zhou W, Heist R, Liu G, Miller DP, Neuberg DS, Asomaning K, Wain JC, Lynch TJ, Christiani D. Secondhand tobacco smoke exposure and survival in early stage non-small cell lung cancer patients. Presented at the Annual Meeting of the American Association for Cancer Research. Washington, DC, Apr 1-5, 2006.

CYCLOPAMINE INHIBITS HEDGEHOG SIGNALING AND GROWTH IN LUNG CANCER CELLS

D. Neil Watkins, MD, PhD; Johns Hopkins Medical Institutions; YCSA 2002

Dr. Watkins' studies showed that hedgehog (Hh) pathway activation is a frequent event in lung cancer, and follows two distinct paradigms. In Gorlin's syndrome, mutations in the tumor suppressor patched (Ptch) cause medulloblastoma and basal cell carcinoma (BCC). The Gorlin's type tumors manifest clonally deregulated Hh signaling and activation of the smoothened (Smo) protein in every cell in the tumor. This leads to activation of the Gli transcription factors and activation of Hh signaling. The data show that there are two distinct types of non-Gorlin's tumors. In the small cell lung cancer (SCLC) group, Ptch, Smo, and Hh ligands Shh are expressed, and differential levels of Hh gene expression concentrate in the pathway in the tumor stem cell compartment. By contrast, non-small cell lung cancers (NSCLCs) express high levels of Hh ligands, but do not express Smo and do not demonstrate evidence of cell-autonomous pathway activation.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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Koskimaki JE, Karagiannis ED, Tang BC, Hammers H, Watkins DN, Pili R, Popel AS. Pentastatin-1, a collagen IV derived 20-mer peptide, suppresses tumor growth in a small cell lung cancer xenograft model. *BMC Cancer.* 2010;10:29.

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Peacock CD, Wang Q, Gesell GS, Corcoran-Schwartz IM, Jones E, Kim J, Devereux WL, Rhodes JT, Huff CA, Beachy PA, Watkins DN, Matsui W. Hedgehog signaling maintains a

tumor stem cell compartment in multiple myeloma. *Proc Natl Acad Sci U S A.* 2007;104(10):4048-4053.

Peacock CD, Watkins DN. Cancer stem cells and the ontogeny of lung cancer. *J Clin Oncol.* 2008;26(17):2883-2889.

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Watkins DN, Peacock CD. Hedgehog signalling in foregut malignancy. *Biochem Pharmacol.* 2004;68(6):1055-1060.

BOOK CHAPTERS, ETC.

Watkins DN, Berman DM, Baylin SB, Beachy PA. Invention disclosure: "Use of Hedgehog pathway in small cell lung cancer". 2003.

PKC-EPSILON EXPRESSION ON THE OUTCOME OF CHEMOTHERAPY

Lei Xiao, PhD; University of Florida; CIA 2002

Dr. Xiao investigated the relationship between expression of a protein kinase C (PKC)-epsilon isoform and patient response to lung cancer chemotherapy. The results showed that PKC-epsilon negative lung cancer patients may have a better prognosis.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Bae KM, Wang H, Jiang G, Chen MG, Lu L, Xiao L. Protein kinase C epsilon is over-expressed in primary human non-small cell lung cancers and functionally required for proliferation of non-small cell lung cancer cells in a p21/Cip1-dependent manner. *Cancer Res.* 2007;67(13):6053-6063.

CANCER: BREAST

Completed Research

UNIVERSITY OF MIAMI BREAST CANCER PROGRAM

Director: Joyce Slingerland, MD, PhD; University of Miami Miller School of Medicine; 2015, 2017, 2018

FAMRI funded the following ten exploratory investigations in breast cancer.

NOVEL TRANSCRIPTIONAL REPROGRAMMING MECHANISM DRIVING TRIPLE NEGATIVE BREAST CANCER DEVELOPMENT

Karoline J. Briegel, PhD; University of Miami Miller School of Medicine; 2018

Basal subtype triple-negative (ER-/PR-/HER2-) breast cancer (hereafter TNBC) is the deadliest breast cancer. It cannot be treated with hormonal therapy or Herceptin.

Resistance to chemotherapy and radiation is rapid, and most TNBC patients relapse and die within 3-5 years after diagnosis.Clinically aggressive TNBC are highly undifferentiated, metastatic tumors with basal cell lineage identity. It has been established that TNBC originate from highly differentiated, luminal breast tumor cells.

The investigators sought to identify novel transcriptional mechanisms that drive luminal-to-basal de- differentiation underlying TNBC development. They investigated LBH, a regulator of mammary lineage determination and differentiation. LBH ihas been shown to be critically required for normal mammary gland development by promoting an undifferentiated, basal mammary stem cell state and apparently represses luminal lineage differentiation. LBH is frequently overexpressed in poor prognosis TNBC (>50%) but not in good prognosis luminal breast cancers. LBH may promote luminal-to-basal dedifferentiation in breast cancer. LBH-mediated luminal-to-basal lineage changes are accompanied by downmodulation of the luminal-specific isoform (TAp63) of the epithelial transcription factor, TRP63, whereas LBH upregulates the basal lineage-specific isoform, Np63.

DISSECTING THE IMMEDIATE RESPONSE TO ESTROGEN OF BREAST CANCER CELLS

Lluis Morey, PhD; University of Miami Miller School of Medicine; 2018

Dr. Morey will address the role of RING1B, the main E3-ligase of the Polycomb Repressive Complex 1 (PRC1), as a positive regulator of estrogen-induced ER target gene expression in ER+ breast cancers. Preliminary data show that RING1B levels are elevated in ER+ breast cancer and that RING1B is recruited to ER target genes that are associated with cancer-related pathways in the T47D breast cancer line. In addition, the recruitment of RING1B to ER target genes is associated with FOXA1 recruitment and gene activation, as opposed to the canonical repressive function of PRC1. RING1B appears to be required for estrogen-induced gene expression. The hypothesis is that RING1B regulates ERa and FOXA1 recruitment to chromatin of upon estrogen (E2) administration in ER+ breast cancer cells. Here he will determine how the chromatin is opened up by Ring1/Foxa1 to accommodate ER binding after estrogen administration. The PI has developed a state-of-the art auxin-inducible/degron-mediated degradation of RING1B in T47D cells to examine the immediate (primary) effects of RING1B depletion on ER-mediated gene regulation.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Chan HL, Morey L. Emerging Roles for Polycomb-Group Proteins in Stem Cells and Cancer. *Trends Biochem Sci.* 2019;44(8):688-700.

IMPROVING THE THERAPEUTIC INDEX OF BREAST CANCER IMMUNOTHERAPY BY RADIATION-INDUCED APTAMER TARGETING;

Adrian Ishkanian, MD, MSc, Brian Marples, PhD; University of Miami Miller School of Medicine; 2017

Triple-negative breast cancer (TNBC) is cancer that tests negative for estrogen receptors, progesterone receptors, and excess HER2 protein. There is currently no existing therapy has been successful for patients diagnosed with TNBC. Novel strategies targeting the TNBC

tumor microenvironment and/or tumor cells are needed to improve clinical outcomes for this patient group. Radiotherapy (RT) can produce excellent local tumor control in non-TNBC tumors, as well as eliciting a systemic immune control of distant non-irradiated tumor lesions, a response known as the abscopal effect. While this effect is enhanced using checkpoint blockade or costimulatory antibodies, objective responses remain suboptimal, partly due to the dose limiting toxicity of the immunomodulatory antibodies. Since RT induces the secretion of stress products in the tumor microenvironment, the investigators hypothesize that targeting immune modulatory drugs to such products will reduce immunomodulation toxicity and broaden the scope of tumor targeted immunotherapy. Using an oligonucleotide aptamer platform, the team has shown that the therapeutic index of 4-1BB aptamer can be significantly improved through RT-induced VEGF mediated tumor targeting. The experimental concept will be extended by directly targeting the existing therapeutic PD-1 monoclonal antibody (mAb) using this novel platform. The hypothesis is that irradiated tumors express epitopes that can be selectively targeted by oligonucleotide aptamers to improve the therapeutic index of therapeutic immunomodulatory mAbs.

ROLE OF FANCA IN BREAST CANCER DEVELOPMENT

Yanbin Zhang, PhD; University of Miami Miller School of Medicine; 2017

Chromosomal instability is a significant factor in driving human breast tumorigenesis. It enables cells to acquire additional capabilities required for cancer development and progression. Chromosomal instability complexity is associated with aggressive behavior and poor prognoses. Dr. Zhang will investigate the molecular mechanisms of chromosomal instability and delineate role of Fanconi anaemia, complementation group A (FANCA) in sporadic breast cancer. Preliminary data indicate that FANCA catalyzes error-prone DNA single-strand annealing. In addition, FANCA expression causes epithelial-mesenchymal transition in MCF-7 cells, and its expression level inversely correlates with breast cancer distant metastasis free survival. Knockout of FANCA in MDA-MB-231 cells strongly inhibits breast cancer formation in mice. The hypothesis of this study is that overexpression of FANCA tips the balance of DNA repair in the favor of an error-prone pathway promoting chromosomal instability and eventually leading to the development of breast cancer, in particular basal-like breast cancer.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Benitez A, Liu W, Palovcak A, Wang G, Moon J, An K, Kim A, Zheng K, Zhang Y, Bai F, Mazin AV, Pei XH, Yuan F, Zhang Y. FANCA Promotes DNA Double-Strand Break Repair by Catalyzing Single-Strand Annealing and Strand Exchange. *Mol Cell*. 2018;71(4):621-628 e624.

STEM CELL-MEDIATED VIROTHERAPY FOR BREAST CANCER

Noriyuki Kasahara, MD, PhD; University of Miami Miller School of Medicine; 2017

The investigators propose a strategy using retroviral replicating vectors (RRV) for gene therapy of late-stage metastatic breast cancer, a disease with a dismal prognosis. RRV can replicate selectively within tumors, and by engineering RRV to deliver a prodrug activator ('suicide') gene, the majority of infected cancer cells can be killed simultaneously upon

administration of a non-toxic prodrug that is converted to an active chemotherapeutic drug directly within the infected tumor cells. Since there are no adverse systemic effects such as myelotoxicity, the immune system remains intact and capable of subsequently developing effective anti-tumor immunity. A collaboration was established with Tocagen Inc. to develop RRV encoding the yeast cytosine deaminase (CD) prodrug activator ('suicide') gene (RRV-CD; 'Toca 511'), which is now being evaluated in multi-center Phase I dose escalation trials in patients with recurrent glioma. The investigators propose to apply RRV to systemic malignancies that metastasize to the central nervous system CNS, such as breast cancer. The team has reported that RRV-CD showed therapeutic benefit after locoregional delivery in murine syngeneic breast cancer models. To further improve the efficiency of vector delivery and intratumoral dissemination, the investigators will evaluate the use of tumor-homing human mesenchymal stem cells (MSC) engineered to serve as RRV virus producer cells. The efficiency of gene delivery and tumor transduction using this approach will be evaluated using MSC producing RRV expressing a reporter gene. The therapeutic efficacy of this approach will be evaluated using MSC producing the clinical RRV expressing the CD suicide gene in human breast cancer xenograft models of CNS metastasis in immunodeficient mice..

CIRCULATING CANCER ASSOCIATED FIBROBLASTS AS PROGNOSTIC BIOMARKERS IN METASTATIC BREAST CANCER

Marc Lippman, PhD; University of Miami Miller School of Medicine; 2017

Despite the advances in the treatment of metastatic breast cancer (MBC), noninvasive tests that could serve as liquid biomarkers with prognostic implications are lacking. One such biomarker is the circulating tumor cells (CTCs) which have prognostic implications in patients with MBC. However, CTCs are present even in the circulation of non-metastatic patients. Therefore, there continues to be a medical need to develop better markers of metastasis. Cancer associated fibroblasts (CAFs) are a subpopulation of fibroblasts found in the tumor microenvironment. The reciprocal signaling between tumor cells and CAFs promotes carcinogenesis, invasion, and metastasis. CAFs are involved in breast cancer initiation by over-expression of TGF-beta and hepatocyte growth factor, which promote tumor progression and invasion by secreting extra cellular matrix (ECM) degrading proteases-matrix metalloproteinases. CAFs promote angiogenesis and can induce epithelial–mesenchymal transition (EMT). Recent studies in mouse models have shown that metastatic cells can bring their own stromal components from the primary site to the site of metastasis, and that these co-traveling stromal cells can provide an early growth advantage to the accompanying metastatic cancer cells. The investigators have shown that CAFs can be identified in the peripheral circulation from patients with metastatic breast cancer. CTCs are detected in both early stage and metastatic breast cancer making it difficult to use their presence or number as a standalone biomarker for metastasis. A companion biomarker, such as circulating CAFs could enhance the early detection of MBC and prove to be an efficient biomarker for disease metastasis.

EPIGENETIC ROLE OF VITAMIN C IN PREVENTING BREAST CANCER

Gaofeng Wang, PhD; University of Miami Miller School of Medicine; 2017

The onset of breast cancer is the consequence of a combination of genetic and environmental risk factors. Dr. Wang and colleagues recently found that vitamin C, a micronutrient, is essential for a group of enzymes termed ten-eleven translocation (TET) to generate 5-hydroxymethylcytosine (5hmC) in DNA. The discovery of TET enzymes is a significant finding in epigenetics that provides a mechanistic basis for active DNA demethylation. 5hmC is very low or undetectable in cancers including breast cancer. The loss of 5hmC changes the functions of many genes, which could contribute to the transformation of healthy breast cells into cancerous breast cells. Previous studies have shown that increasing the amount of TET enzymes in breast cancer decreases malignancy. While increasing TET level in patients might not be clinically feasible, finding a means to therapeutically restore normal 5hmC content may help revert the malignant phenotype and yield a novel therapy for breast cancer. In preliminary studies, the investigators found that the vitamin C transporter is low in some cases of human breast cancer, indicating that a local vitamin C deficiency may be responsible for the reduced level of 5hmC. Treatment of one breast cancer cell line with vitamin C decreased invasiveness, inhibited cell growth, and increased 5hmC content. Based on these findings, the team will determine if vitamin C treatment can prevent the onset and progression of breast cancer by reestablishing the normal profile of 5hmC.

MECHANISTIC CONSEQUENCES OF KAT3 LOSS IN BREAST CANCER

Nanette H. Bishopric, MD; University of Miami Miller School of Medicine; 2015

The investigators used genomic information from the Cancer Genome Atlas (TCGA) to query the role of EP300 in ER-, p53-mutant and triple-negative human cell lines. This analysis showed that heterozygous loss of EP300 is frequent in breast cancer and that there is no significant correlation between ER, PR or HER2 status, or PAM50 subtype, and loss of EP300. This implies that loss of EP300 occurs in breast cancer of all varieties, either as an epiphenomenon or as an early event in all tumors. Additionally, there is no correlation with gain of CREBBP, implying that CREBBP gain does not compensate for EP300 loss in most tumors. Loss of EP300 strongly correlates with expression of genes that drive the epithelial-mesenchymal transition (EMT) as well as with expression of target genes in breast cancer and in all cancers. These data strongly support the hypothesis that EP300 is a unique, non-redundant tumor suppressor in breast cancer, and that heterozygous loss of EP300 is a critical event in the evolution of breast cancer. The investigators confirmed the relationship between EP300 expression and expression of miR-let-7c and miR- let-7g, which suggests that miR-let-7 may underlie in part the tumor suppressor activity of EP300. They discovered that the mechanisms for regulating let-7 are highly cell type-specific.

GENETIC ANALYSIS OF THE ROLE OF GATA 3 IN BREAST TUMORIGENESIS

Xin-Hai Pei, MD, PhD; University of Miami Miller School of Medicine; 2015

Basal-like breast cancers frequently lack the expression of ER and are more aggressive and associated with poor prognosis. Most basal-like breast cancers express significantly

reduced GATA3 expression. Deficiency of Gata3 in mice results in basal-like breast cancers with epithelial-mesenchymal transition (EMT) features, providing the first genetic evidence that Gata3 may suppress basal-like tumorigenesis and EMT. Dr. Pei characterized p18;Gata3 compound mutant mice and found that 1 of 2 $p18^{-/-}$; $G3^{f/+}$; MC and 3 of 6 $p18^{-/-}$; $G3^{+/-}$mice developed mammary tumors, which were heterogeneous in cell shape and expression of Gata3, Ck5, Ck8, and EMT markers. Loss of p18 results in luminal tumorigenesis, and further loss of GATA3 transforms luminal tumors to basal-like tumors with an EMT feature. A GATA3 overexpressing MDA-MB-231 cell line was generated and transplanted into mammary fat pads of immunodeficient mice. MDA-MB-231-GATA3 tumors were significantly smaller than MDA-MB-231-control tumors. Immunohistochemical analysis of control tumors revealed a strong staining of the transcription factor TWIST1, whereas MDA-MB-231-GATA3 tumors expressed high levels of GATA3, but non-detectable TWIST1, indicating that GATA3 suppresses TWIST1. These data support the hypothesis that GATA3 suppresses TWIST1 and inhibits basal-like breast cancer development.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Liu S, Chan HL, Bai F, Ma J, Scott A, Robbins DJ, Capobianco AJ, Zhu P, Pei XH. Gata3 restrains B cell proliferation and cooperates with p18INK4c to repress B cell lymphomagenesis. *Oncotarget.* 2016;7(39):64007-64020.

IDENTIFICATION OF SMALL MOLECULE EPIGENETIC MODULATORS OF CD 24 SUBPOPULATIONS IN TRIPLE NEGATIVE BREAST CANCER CELLS

Claes Wahlested, MD, PhD; University of Miami Miller School of Medicine; 2015

Triple negative breast cancer (TNBC) lacks estrogen and progesterone receptor expression and HER2 amplification and is the deadliest form of the disease, often presenting in younger women. It cannot be treated with hormonal therapy or Herceptin; chemotherapy and radiation resistance invariably emerge rapidly. Increasing evidence suggest that tumor initiating cells (TIC) mediate cancer therapy resistance and metastasis, which are responsible for cancer relapse and deaths in breast cancer patients. Breast TICs have been identified by expression of the surface marker profile, $CD44^{+}CD24^{neg/low}$ ESA^{+}, and these can generate tumors from as few as 100 cells in xenograft models. Distinct subsets of TICs have been identified in the deadliest form of TNBC cell lines and patient derived cultures. While all cells in these TNBC lines are $CD44^{+}$, CD24 expression defines two subsets of TICs: $CD24^{neg}$ and $CD24^{+}$. Cells with low level $CD24^{+}$ (hereafter $CD24^{+}$) are more aggressive than $CD24^{neg}$ cells. Both $CD24^{neg}$ and $CD24^{+}$ populations have self-renewing and tumor-initiating properties. Most strikingly, only the $CD24^{+}$ population can spontaneously metastasize from an orthotopic tumor xenograft. $CD24^{+}$ cells show greater motility and invasion, and preferential expression of gene profiles are observed in breast cancers metastatic to lung, brain and bone. Notably, the $CD24^{+}$ cells are chemo- and radiation-resistant. Upon paclitaxel, doxorubicin, or radiation treatment, >80% of $CD24^{neg}$ cells die and the majority of cells that survive are $CD24^{+}$. Thus, identifying drugs that selectively kill the metastatic and chemo-resistant $CD24^{+}$ population in the deadliest form of breast cancers has the potential to reduce the incidence of mortality. The investigators showed that pan-HDAC

inhibitors such as Veronistat and selective HDAC6 inhibitor ACY-1215 (Rocilinostat) selectively target the most aggressive $CD24^+$ cells in TNBCs.

CYP2A13: A NEW LINK BETWEEN SMOKING AND BREAST CANCER

Jun-Yan Hong, PhD; Rutgers, The State University of New Jersey; CIA 2009

Dr. Hong and colleagues demonstrated that the cytochrome P450 2A13 (CYP2A13) protein is selectively expressed in human breast ductal cells. The team investigated whether CYP2A13mediated metabolic activation of tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3pyridyl)-1-butanone (NNK) in breast ductal cells plays an important role in the development of breast cancer. They established a transgenic mouse model with mammary epithelial cell-specific expression of human CYP2A13 and demonstrated the *in vivo* role of CYP2A13 in the development of tobacco smoking-related breast cancer by induction of mammary cancer in NNK-treated CYP2A13 humanized mice.

ROLE OF TRANSCRIPTION FACTOR TBX2 IN BREAST CANCER

Karoline J. Briegel, PhD; University of Miami Miller School of Medicine; CIA 2008

Dr. Briegel and colleagues found that abnormal transcription factor TBX2 expression in mammary epithelial cells causes hyperplasia and secondary tumor formation. In addition, MMTV-TBX2 transgenic mice exhibit defects in mammary gland development reminiscent of p53 pathway mouse mutants. These defects suggest that both p53-dependent as well as p53-independent mechanisms are perturbed by TBX2 overexpression. The investigators also found that ectopic expression of TBX2 in non-malignant mammary epithelial cells induces epithelial-mesenchymal transition (EMT), a morphogenetic program linked with tumor invasion and metastasis. RNAi-mediated knockdown of TBX2 in metastatic human breast carcinoma cells leads to EMT reversal and reduces tumor cell invasiveness *in vitro*. Immunohistochemical analysis of TBX2 expression in primary human breast cancers shows that TBX2 is aberrantly overexpressed in invasive breast tumors and lymph node metastasis. Exposure to secondhand tobacco smoke has been shown to induce EMT.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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PRESENTATIONS AND ABSTRACTS

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DISCOVERY AND CHARACTERIZATION OF NOVEL TUMOR SUPPRESSOR GENES IN BREAST CANCER USING GENOME-WIDE GENETIC AND EPIGENETIC ANALYSIS AND DEVELOPMENT OF MOLECULAR MARKERS FOR HIGH RISK PATIENTS WITH TOBACCO EXPOSURE

Timothy A. Chan, MD, PhD; Memorial Sloan-Kettering Cancer Center; YCSA 2008

Dr. Chan and colleagues developed a microarray approach that enables rapid and accurate identification of genes silenced by hypermethylation, which they used to identify genes silenced in this way in breast cancer. The resultant dataset was compared to a database of genes mutated in breast cancer (CAN genes). In all, 11 genes were found to be subject to both mutation and cancer-specific methylation. Because exposure to tobacco smoke is a strong risk factor for poor outcome in patients with breast cancer, these genes were evaluated as prognostic biomarkers in breast cancer patients with this risk. The molecular details of the tumor suppressive function of the most promising and clinically significant gene (PTPRD) were studied using gene overexpression, RNAi studies, and biochemical analysis. Data from this study could lead to use of genes as predictors of clinical prognosis and targets for therapy.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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TRANSLATIONAL CONTROL AND BREAST CANCER DEVELOPMENT

Ronald B. Gartenhaus, MD; University of Maryland; CIA 2008

Dr. Gartenhaus showed that expression of the oncogene MCT-1 can transform immortalized breast epithelial cells and increase the tumor forming ability in nude mice of cells from the MCF7 breast cancer cell line. He demonstrated that increased levels of MCT-1 are able to modify a cell's translational profile, and he identified the repertoire of translated mRNAs required for *in vivo* transformation and progression. The MCT-1 protein modifies mRNA translational profiles through its interaction with DENR, a cell density-regulated protein containing the translation initiation factor SUI1 domain. Dr. Gartenhaus demonstrated that two RNA-binding proteins, HuR and AUF1, bind to the 3' untranslated region of DENR. He examined the effect of associations of structurally related mRNAs and ribonucleoprotein complexes on the translation of the DENR transcript and identified and profiled endogenously clustered mRNAs associated with the two proteins.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Mazan-Mamczarz K, Hagner PR, Corl S, Srikantan S, Wood WH, Becker KG, Gorospe M, Keene JD, Levenson AS, Gartenhaus RB. Post-transcriptional gene regulation by HuR promotes a more tumorigenic phenotype. *Oncogene.* 2008;27(47):6151-6163.

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TELOMERE DYSFUNCTION AND BREAST CANCER DETECTION

David P. Gilley, PhD; Indiana University; CIA 2008

Dr. Gilley and his team used telomere dysfunction markers in breast tumor tissue and circulating DNA for early breast cancer detection. They developed a PCR-based method to detect and analyze chromosome fusions from genomic DNA using cell lines with known percentages of end-to-end chromosome fusions. The team discovered that there are relatively short fragments of previously identified fragile DNA sites and other non-telomeric DNAs within these telomere-to-telomere fusion junctions. The discovery of these

DNA sequences at this location provides important clues regarding the mechanisms responsible for generating the junctions. Using this detection assay, Dr. Gilley and colleagues found that these chromosome fusions are present in over 90% of the tested tumor tissue from early breast tumorigenesis. Identifying these chromosome fusion junctions in the early stages of breast tumorigenesis should provide a useful diagnostic tool for detection, prevention, and treatment of breast cancer.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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MECHANISM OF SECONDHAND CIGARETTE SMOKE-INDUCED TRANSFORMATION OF NORMAL HUMAN BREAST EPITHELIAL CELLS

Satya Narayan, PhD; University of Florida; CIA 2008

Dr. Narayan and colleagues investigated whether adenomatous polyposis coli (APC)-mediated blockages of polymerase-beta (Pol-beta) activity cause accumulation of mutations in normal breast epithelial cells exposed to cigarette smoke condensate (CSC) and benzo(a)pyrene (B[a]P). They also determined if this exposure stimulates a mutator phenotype in conjunction with Pol-beta mutations and investigated whether the blockage causes transformation of normal breast epithelial cells exposed to CSC and B(a)P as indicated by anchorage-independent growth and xenograft assays. They determined whether the invasive characteristics of CSC- and B[a]P-transformed normal breast epithelial cells are increased in culture and associated with the expression of NF-kappa B. In addition to identifying an etiologic basis for SHS-induced breast carcinogenesis, the studies were useful in pinpointing events leading to the development of aggressive tumors.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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SECONDHAND SMOKE AND ITS ROLE IN BREAST CANCER

Cynthia Zahnow, PhD; Johns Hopkins Medical Institutions; CIA 2008

Dr. Zahnow and colleagues used *in vitro* and *in vivo* models to demonstrate that both SHS and mainstream cigarette smoke can transform human mammary epithelial cells and lead to tumorigenesis. They characterized progressive epigenetic changes in chronically exposed human mammary epithelial cells and correlated these changes with transformation. They cultured cigarette smoke treated cells in soft agar to test for anchorage-independent growth and performed transmembrane assays of migration and invasion. Further, they used xenograft studies to assess tumorigenic and metastatic potential in mice. Molecular markers for epithelial-mesenchymal transition (EMT) were validated by PCR, immunocytochemistry, and western blot analysis. Epigenetic changes in Wnt signaling and other regulatory pathways were conducted. The data suggest that chronic exposure of mammary epithelial cells to cigarette smoke leads to EMT, anchorage-independent growth, regulation of Wnt signaling, and an increase in the cancer stem cell population.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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TARGETING NRF2/ARE BY HDAC INHIBITION IN BREAST CANCER

Qun Zhou, MD, PhD; University of Maryland; YCSA 2008

Dr. Zhou and colleagues characterized the role of estrogen receptor alpha (ER alpha) in regulation of nuclear factor erythroid-derived 2-related factor-2 (Nrf2)-dependent gene transcription. Their studies revealed that ER alpha is an inhibitory regulator of Nrf2 function in breast cancer cells. They also found that ER alpha suppresses Nrf2 levels and inhibits Nrf2 binding at the promoter, leading to suppression of NQO1 transcription. Nrf2

binds to the antioxidant response element (ARE) found in Phase II enzyme gene promoters such as NQO1, which are necessary to activate Nrf2dependent gene expression. The team identified acetylated proteins in human breast cancer cells, and showed that treatment with the histone deacetylase inhibitor, suberoylanilide hydroxamic acid (SAHA), induces lysine acetylation of sequestosome 1 (SQSTM1) at the C terminal ubiquitination binding domain in human breast cancer cells. SQSTM1 mediates the Nrf2/ARE pathway. Acetylated SQSTM1 disrupts the association between Nrf2 and Keap1, leading to activation of Nrf2 function. The investigators also demonstrated that SAHA induction of acetylated SQSTM1 prevents transformation of normal mammary epithelial cells.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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ROLE OF SECOND HAND TOBACCO SMOKE IN BREAST CANCER ANGIOGENESIS AND METASTASIS

Shalom Avraham, MD, PhD; Beth Israel Deaconess Medical Center; CIA 2007

Dr. Avraham showed that specific targeted knockdown of VEGFR-1 expression by sVEGFR-1 siRNA significantly decreased the survival of breast cancer cells. VEGFR-1 was found to be expressed internally in breast cancer cells and colocalized with lamin A/C. VEGFR-1 is expressed mainly in the nuclear envelope in breast cancer cell lines and primary breast cancer tumors. In addition, Dr. Avraham observed that breast cancer cells stably transfected with VEGFR-1 are dramatically resistant to doxorubicin and cisplatin chemotherapy treatments and have increased invasion capabilities. Exposure to SHS resulted in significantly increased resistance to these chemotherapy treatments. The results suggest that the VEGF-VEGFR-1 autocrine survival system may confer a chemotherapy resistance of breast cancer cells that is exacerbated by exposure to SHS.

CHEMICAL GENETIC VALIDATION OF POLO-LIKE KINASE-1 AS A BREAST CANCER DRUG TARGET

Mark E. Burkard, MD, PhD; University of Wisconsin; YCSA 2007

Dr. Burkard and his team developed human cell lines containing modified polo-like kinase 1 (Plk1) that are resistant to drug inhibition. They used them to distinguish the effects due to specific Plk1 inhibition from off-target effects to evaluate the relative specificities of several proposed therapeutic agents, to uncover previously unknown functions of Plk1, and establish therapeutic implications. Because kinase-targeted drugs affect many cellular enzymes, it is important to identify which targets mediate their effects. Thus, the investigators used the model systems to determine the phosphorylation of Plk1 that is required for cytokinesis of human cells. When Plk1 is inhibited, human cells fail to execute the initial steps of cytokinesis. Time-lapse video microscopy of fluorescently-labeled human cells revealed that, with moderate Plk1 inhibition, cells display a variety of

phenotypes of mitotic dysfunction, many unassociated with mitotic arrest. Understanding these phenotypes is crucial for determining what Plk1 inhibition can be achieved pharmacologically and what the effects are on normal cells when such inhibitors are used for treatment of breast cancer.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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PRESENTATIONS AND ABSTRACTS

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NICOTINE: SIGNALING AND MITOGENESIS IN THE BREAST

Chang-Yan Chen, MD, PhD; Beth Israel Deaconess Medical Center; Northeastern University; CIA 2007

Dr. Chen and colleagues investigated the effect of the cooperation of 4-(methylnitrosamino)- 1-(3-pyridyl)-1-butanone (NNK) and nicotine on cell growth and apoptosis. They demonstrated that short-term nicotine exposure moderately activates mitogenic signaling pathways such as the protein kinase C, extracellular signal-regulated protein kinase, and Akt pathways, and provides mediocre protection against cisplatin-mediated apoptosis. In contrast, NNK strongly stimulates mitogenic signaling and renders the cells highly resistance to cisplatin. The investigators also found that pre-ligation of nicotinic acetylcholine receptors by nicotine interferes with NNK-mediated mitogenic signaling and resistance to cisplatin, the magnitude of which was similar to nicotine exposure alone. A week after exposure to nicotine or nicotine plus NNK, Bcl-2 expression was augmented and accompanied by an increased resistance to cisplatin-induced apoptosis. In comparison, long-term NNK treatment provided little protection from cisplatin. The investigators also showed that the combination treatment promoted more cells to grow in an anchorage-independent fashion than NNK exposure alone.

FAMRI SUPPORTED RESEARCH

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ROLE OF PBRS IN BREAST CANCER INDUCED BY SECONDHAND TOBACCO SMOKE

Salil K. Das, ScD; Meharry Medical College; CIA 2007

Dr. Das and colleagues developed a smoke exposure model system for human breast cell lines, which is a modified version of the Cultex® cell culture smoke exposure system. Cells were exposed to direct and SHS generated from research grade cigarettes in a Tobacco and Health Research Institute mainstream and sidestream smoke exposure system. The sham control group comprised cells that were exposed to the same environmental conditions without smoke exposure. The investigators determined that both direct and SHS exposure caused significant activation of AP-1 transcription factors associated with an increase in the protein level of Fos. In addition, an up-regulation of cyclin D1 and proliferating-cell nuclear antigen was observed, along with activation of metalloproteinase. Both direct and SHS exposure caused a significant activation of the AP-1 signaling pathway in all three breast cell lines tested. Furthermore, Dr. Das and colleagues have demonstrated that both direct and SHS smoke exposure caused upregulation in the expression of peripheral benzodiazepine receptors associated with angiogenic signaling.

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SECONDHAND TOBACCO SMOKE AND HMG-IY IN BREAST CANCER

Francescopaolo Di Cello, PhD; Johns Hopkins Medical Institutions; YCSA 2007

Dr. Di Cello and colleagues studied whether estrogen agonists induced by SHS-exposure activate molecular pathways that promote the development of breast cancer. They focused on the high mobility group A (HMGA) gene family, which encodes chromatin binding proteins that regulate gene expression. It has been shown that HMGA genes are overexpressed in metastatic breast cancer cells and high-grade lung cancers. The team investigated whether HMGA1a (formerly HMG-I), which is induced by estrogen, is also induced by SHS. HMGA genes are oncogenic in cultured cells derived from normal breast or lung tissue; inhibiting these genes can block the transformed phenotype in cancer cells. The

investigators determined if HMGA gene expression and SHS exposure correlate with more aggressive breast cancer and if breast cancer growth can be inhibited by blocking expression of HMGA genes.

FAMRI SUPPORTED RESEARCH

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HOW SECONDHAND TOBACCO SMOKE AFFECTS BREAST TUMOR DORMANCY IN THE LUNG

Stuart S. Martin, PhD; University of Maryland; CIA 2007

Dr. Martin and collaborators showed that circulating breast tumor cells produce unique extensions of their surfaces called microtentacles (McTNs). McTNs are supported by stabilized tubulin, and contribute to the persistence of circulating tumor cells in lung capillaries. The investigators have identified two major mechanisms that increase levels of McTNs in breast tumor cells, both of which are upregulated by exposure to nicotine. The first is expression of the tubulin-stabilizing protein, tau, and the second is the epithelial-to-mesenchymal transition that occurs during wound healing. In addition, the investigators used whole-animal bioluminescence imaging to determine how SHS exposure affects lung physiology and influences the retention and survival of circulating tumor cells.

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TARGETING THE SRC ONCOGENE IN BREAST CANCER THERAPY

Joyce Slingerland, MD, PhD; University of Miami Miller School of Medicine; CIA 2007

Dr. Slingerland and colleagues investigated interactions among a number of anti-cancer drugs. Anastrozole alone caused an incomplete cell cycle arrest in estrogen receptor (ER)-positive human breast cancer cells stably transfected with the aromatase gene (MCF-Arom5). The Src inhibitor AZD0530 alone had no effect on the cell cycle, but it enhanced the antiproliferative effect of anastrozole on cultured MCF-AROM5 cells. When AZD0530 was combined with anastrozole, it took 10-fold less anastrozole to arrest these cells; AZD0530 alone at this dosage did not affect cell proliferation. Treatment with anastrozole alone stimulated Src and MAPK activity, whereas treatment with anastrozole and AZD0530 together inhibited their activities. The two drugs together caused a greater p27 increase and cyclin E-Cdk2 inhibition than either drug alone. The investigators also observed synergy between anastrozole and AZD0530 *in vivo* in MCF-AROM5 xenograft tumors in athymic mice. Without androstenedione, tumor growth was minimal; in contrast, tumor volume increased rapidly with androstenedione treatment. While daily oral AZD0530 had no effect on tumor growth, it was significantly delayed by the combination of AZD0530 and anastrozole. The investigators compared the effects of ER blockade with tamoxifen or fulvestrant with or without AZD0530, and found that ER blockers together with Src inhibition cooperate to reduce tumor growth and prevent the emergence of resistance to AZD0530. These targeted therapies do not enhance tumor stem cell recruitment in the same way that chemotherapy does.

FAMRI SUPPORTED RESEARCH

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A2A RECEPTOR ANTAGONISM AS A NOVEL MEANS TO ENHANCE VACCINE THERAPY FOR THE TREATMENT AND PREVENTION OF BREAST CANCER

Jonathan D. Powell, MD, PhD; Johns Hopkins University Medical Institutions; CIA 2006

Dr. Powell and colleagues demonstrated that A2a engagement of T-cells not only inhibits T-cell function but promotes the generation of T-cell tolerance and T-regulatory cells. The tumor microenvironment contains high concentrations of adenosine, thus the investigators proposed that tumor-derived adenosine acts to inhibit immune function and promote tumor-specific T-cell tolerance. Data using A2a receptor (A2aR) null mice indicate that such mice mount more robust antitumor responses, leading to an enhanced ability to reject tumor challenge. In addition, these mice respond better to tumor-specific vaccines as treatment for pre-existing tumors. These data suggest that A2aR mice are resistant to anergy induction *in vivo* and develop fewer antigen-specific Lag-3+ regulatory T-cells. The team showed that A2aR antagonists given in the peri-vaccine period can enhance antitumor immunity. Studies were performed to employ whole cell vaccines with breast cancer stem cells with A2aR antagonists as a means of preventing the development of breast cancer.

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ACTIVATION OF DDX3 BY BENZO[A]PYRENE DIOL EPOXIDE, A COMPONENT OF SECONDHAND TOBACCO SMOKE IN TRANSFORMATION OF HUMAN BREAST CELLS: A POTENTIAL MECHANISM FOR NEOPLASTIC TRANSFORMATION

Venu Raman, PhD; Johns Hopkins Medical Institutions; CIA 2006

This work is an extension of Dr. Raman's 2003 award. He and his group identified a gene (DDX3) that is upregulated by cigarette smoke exposure and has been validated as a

contributing factor for the maintenance of an aggressive cancer phenotype. The team designed a small molecule inhibitor (proprietary fused diimidazodiazepine ring molecule-RK-33) for the target gene that shows promise in decreasing lung tumor growth in two preclinical mouse lung cancer models, which led to Patent Cooperation Treaty (PCT) applications PCT/US2009/005273 and PCT/US2012/028475.

FAMRI SUPPORTED RESEARCH

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AN MVA VACCINE TARGETING P53 IN BREAST CANCER

Joshua Ellenhorn, MD; City of Hope National Medical Center; CIA 2005

Dr. Ellenhorn generated and evaluated a vaccine using recombinant DNA technology with modified vaccinia virus Ankara (MVA), which was used to generate a vaccine that contains p53 (MVAp53). Immune cells exposed to MVAp53 can be stimulated in a way that leads to the development of cytotoxic T cells (CTL) capable of destroying p53 overexpressing cells. Dr. Ellenhorn and colleagues recruited cancer patients for involvement in a clinical trial. Trial subjects had blood drawn, and the mutant cells from each patient's blood were exposed to their own MVAp53-infected cells. After stimulation with MVAp53 and repeat stimulation with fragments of p53 protein, p53-recognizing CTLs were generated. The resulting CTLs could recognize and destroy cancer cells that contain abundant p53. Although cancer patients often have suppressed immune systems, the investigators were able to generate p53-recognizing CTL from 11 of the 17 patients who were recruited to the clinical trial. In additional studies, the ability of MVAp53 to be combined with other p53 containing vaccines was evaluated. This approach has the potential to boost p53 specific immunotherapy.

FAMRI SUPPORTED RESEARCH

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Lowe TE, Ellenhorn JD, Wong C, Somlo G. Increased abdominal girth in a 29-year-old breast cancer patient with extensive liver metastasis and presumed chemotherapy induced amenorrhea. A case report and review of the literature. *Breast Cancer Res Treat.* 2007;106(3):305-306.

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ONCOGENIC ROLE OF RHBDF1 IN BREAST CANCER

Luyuan Li, PhD: University of Pittsburgh; CIA 2005

Dr. Li's studies have shown that the human rhomboid family-1 (RHBDF1) gene expression level is significantly elevated in clinical specimens of invasive ductal carcinoma of the breast, and the protein is readily detectable in human breast cancer or head and neck cancer cell lines. Silencing the RHBDF1 gene with short interfering RNA (siRNA) in the breast cancer cell-line MDAMB- 435 and the head and neck squamous cell cancer cell-line 1483 caused apoptosis to the former and autophagy to the latter. The treatment also led to downmodulation of activated AKT and extracellular signal-regulated kinases. Furthermore, the RHBDF1 gene in established MDAMB- 435 or 1483 xenograft tumors can be silenced by using intravenously administered histidine-lysine polymer nanoparticle-encapsulated siRNA. This treatment resulted in marked inhibition of tumor growth.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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EPOXYGENASE MECHANISMS OF BREAST CANCER PROGRESSION

David A. Potter, MD, PhD; University of Minnesota Twin Cities; CIA 2005

Dr. Potter showed that CYP3A4 regulates the growth and adhesion of the MCF7 breast cancer line. Part, but not all, of the effect of CYP3A4 on the MCF7 line may be mediated through epoxyeicosatrienoic acids. CYP3A4 overexpression increases the relative abundance of anti-apoptotic 14,15-EET and decreases pro-apoptotic 8,9-EET. These data suggest that the ratio of EETs may be important. CYP3A4 knock down inhibits c-Src and STAT3 phosphorylation, while CYP3A4 over-expression has the opposite effect, thus it is likely that CYP3A4 is a regulator of c-Src and STAT3 signaling. Compensatory activation of the pAkt pathway occurs with knock down, despite the lack of constitutive activation of Akt in the MCF7 line. The compensatory Akt response suggests that CYP3A4 is functioning as a gene promoting the transformed phenotype. Because CYP3A4 knock down exhibited no

effect on adhesion, but still resulted in downregulation of c-Src, STAT3, and FAK phosphorylation, it appears that CYP3A4 primarily acts on c-Src, which is upstream of FAK and STAT3.

FAMRI SUPPORTED RESEARCH

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HDGF, A NEW POTENTIAL TARGET FOR BREAST CANCER THERAPY

Jun Yang, PhD; Johns Hopkins Medical Institutions; YCSA 2005

Dr. Yang and collaborators identified hepatoma-derived growth factor (HDGF) as a nuclear-targeted mitogen overexpressed in human breast cancer. They found that HDGF is necessary for tumor cell growth *in vitro* and in a nude mouse model. Additionally, they showed that the migration ability of a breast tumor cell line was decreased dramatically when the HDGF protein level was knocked down, implying that it plays an important role in breast tumor metastasis. Women smokers have decreased serum estrogen levels and estrogen receptor-negative breast tumors usually have increased HDGF expression levels. The investigators showed that estrogen receptors directly regulate HDGF gene expression and provided evidence that different estrogen receptor isoforms play different roles on HDGF gene expression. An animal model that overexpresses HDGF protein in mammary

tissue was generated and used to determine whether HDGF is essential for breast tumor formation.

FAMRI SUPPORTED RESEARCH

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ENVIRONMENTAL AND GENETIC RISK FACTORS OF BREAST CANCER

Yun-Ling Zheng, PhD, MPH; Georgetown University; CIA 2005

Dr. Zheng and colleagues investigated the association between mutagen sensitivity and risk of breast cancer using bleomycin as the mutagen. High bleomycin sensitivity was associated with an increased risk of breast cancer, which increased with a greater number of bleomycin-induced chromosomal breaks. The association between bleomycin sensitivity and breast cancer risk was greater for women who were black, premenopausal, and who were ever smokers. These data also suggest that bleomycin sensitivity may modulate the effect of tobacco smoke exposure on breast cancer risk. Among women with hypersensitivity to bleomycin, ever smokers had a 1.6-fold increased risk of breast cancer. Increased bleomycin sensitivity is significantly associated with an increased risk of breast cancer in both pre- and post-menopausal women.

FAMRI SUPPORTED RESEARCH

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COMBINATORIAL TREATMENT MODALITIES OF ANTI-ANGIOGENIC AND ANTI-HIF THERAPY IN INVASIVE BREAST CANCERS

Alexy Bazarov, PhD; University of California, San Francisco; YCSA 2004

Dr. Bazarov and colleagues specifically inhibited hypoxia inducible factor (HIF) HIF-1 alpha and/or HIF-2 alpha expression in a breast cancer cell line and in breast cancer stem cells obtained from primary tumors. The investigators monitored the effects of induced HIF suppression on the establishment and maintenance of tumors after injection into host animals. In addition, the team investigated whether suppression of HIF-2 alpha counteracts the tumor promoting effects of a component of tobacco smoke, nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, and they determined if HIF-2 alpha expression correlates with breast stem cell markers and poor prognosis among smokers

and nonsmokers. Expression was analyzed of HIF-2 alpha, Oct-4, human telomerase reverse transcriptase, estrogen receptor-alpha, progesterone receptor, and Her-2 proteins in human breast tumors of different types and grades.

FAMRI SUPPORTED RESEARCH

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Mukhopadhyay R, Costes SV, Bazarov AV, Hines WC, Barcellos-Hoff MH, Yaswen P. Promotion of variant human mammary epithelial cell outgrowth by ionizing radiation: an agent-based model supported by in vitro studies. *Breast Cancer Res.* 2010;12(1):R11.

PROMOTER HYPERMETHYLATION AS A MOLECULAR MARKER FOR BREAST CANCER

Hetty E. Carraway, MD; Johns Hopkins Medical Institutions; YCSA 2004

Dr. Carraway developed methods to detect tumor-specific DNA methylation changes and to examine sentinel lymph node biopsies for tumor-specific methylation changes that can be clinically prognostic. Results show that methylation found in sentinel lymph nodes is abnormal. The study was expanded to establish testing that shows that normal lymph nodes lack abnormal methylation. This provides a means to determine which patients are likely to suffer a breast cancer recurrence by examining the methylation pattern in histologically negative nodes.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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Guo M, Ren J, Brock MV, Herman JG, Carraway HE. Promoter methylation of HIN-1 in the progression to esophageal squamous cancer. *Epigenetics.* 2008;3(6):336-341.

ACTIVATION OF CUBGP1 IN BREAST BY SECONDHAND TOBACCO SMOKE (SHS)

Cynthia Zahnow, PhD; Johns Hopkins Medical Institutions; CIA 2004

Dr. Zahnow demonstrated that the chronic exposure of non-malignant mammary epithelial cell lines (MCF10A and MCF12A) or breast cancer cells (MCF7) to main stream cigarette smoke or particulate matter from SHS leads to transformation and increased invasiveness, increased migration, gene expression changes, and an increased basal phenotype. IGF-1 signaling mediates cell survival and tumorigenesis via its actions to increase the LIP/LAP ratio; the transcription factor, CCAAT enhancer binding protein-beta (C/EBP beta), is expressed as several distinct protein isoforms (LAP1, LAP2, LIP) that have opposing actions in cellular proliferation and differentiation. Increases in the ratio of LIP/LAP are associated with aggressive metastatic breast cancer. The data demonstrate that IGF-I signaling leads to an increase in the LIP/LAP ratio via a post-transcriptional mechanism that is independent of EGFR/ErbB1 activation. The team also demonstrated that IGF-I-induced elevations in LIP/LAP expression are biologically active and that the resultant transcriptional activity is governed by increases in the dominant-negative isoform, LIP. The data also showed that Akt, but not Erk1/2 activity, is a critical regulator of IGF-I-mediated LIP expression.

NOVEL DRUG DEVELOPMENT FOR BREAST CANCER

Saeed R. Khan, PhD; Johns Hopkins Medical Institutions; YCSA 2003

Dr. Khan investigated the value of the mouse double minute 2 (MDM2) oncogene as a drug target for breast cancer therapy by using boronic-chalcone analogs to inhibit its expression. Results demonstrated that certain chalcones preferentially inhibit growth of human breast cancer cell lines compared to normal epithelial cells.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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Rudek MA, Zhao M, Smith NF, Robey RW, He P, Hallur G, Khan S, Hidalgo M, Jimeno A, Colevas AD, Messersmith WA, Wolff AC, Baker SD. In vitro and in vivo clinical pharmacology of dimethyl benzoylphenylurea, a novel oral tubulin-interactive agent. *Clin Cancer Res.* 2005;11(23):8503-8511.

Yamada R, Kostova MB, Anchoori RK, Xu S, Neamati N, Khan SR. Biological evaluation of paclitaxel-peptide conjugates as a model for MMP2-targeted drug delivery. *Cancer Biol Ther.* 2010;9(3):192-203.

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Kahn SR. US provisional patent application 60/444,429 "Novel boronic chalcone derivatives and uses thereof". Filed Feb 3, 2003.

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MECHANISMS OF SECONDHAND SMOKING-INDUCED BREAST CARCINOGENESIS

Satya Narayan, PhD; University of Florida; CIA 2003

Dr. Narayan and colleagues reported that cigarette smoke condensate (CSC) transforms the normal human breast epithelial cell line, MCF10A, *in vitro*. The results showed that adenomatous polyposis coil (APC) gene expression is increased in MCF10A after treatment with CSC. The investigators also showed that APC interacts with DNA polymerase beta (pol-beta) and blocks pol beta-mediated strand-displacement synthesis of the long-patch repair pathway. These results show that CSC-induced increase in the level of APC compromises the DNA repair capacity of breast epithelial cells. Thus CSC-induced levels of APC interact with pol-beta and block pol-beta-mediated long-patch base excision repair, resulting in the accumulation of mutations that cause initiation of transformation of normal breast epithelial cells.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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excision repair and increases sensitivity to methylmethane sulfonate. *J Biol Chem.* 2005;280(8):6942-6949.

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ESTROGEN RECEPTOR SIGNALING IN NORMAL AND CANCEROUS BREAST EPITHELIAL CELLS

Ben-Ho Park, MD, PhD; Johns Hopkins Medical Institutions; YCSA 2003

Dr. Park focused on clarifying the mediators of estrogen receptor (ER) signaling as related to breast carcinogenesis. This allowed for the identification of pathways that link SHS exposure and breast cancer; the risk of breast cancer due to exposure to SHS is primarily seen in premenopausal women. A normal breast epithelial line was engineered to overexpress ER alpha to create a hormonally-responsive ER positive nontumorigenic breast cell line. The results showed that over-expression of ER in normal human breast epithelial cells leads to an agonistic response to estrogen that can be blocked by antiestrogen compounds such as tamoxifen. Moreover, somatic cell deletion of the p21

gene reversed the response of tamoxifen from antagonistic to agonistic. Because loss of p21 expression can be found in many early breast cancer lesions, not only can abnormal estrogen signaling cause breast cancer, but hormonal preventive drugs may have a harmful effect on early cancerous breast tissues. The isogenic p21 knockout cell lines can be used to test drugs that can overcome this form of tamoxifen resistance.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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DECIPHERING GENETIC ALTERATIONS CAUSED BY SECONDHAND TOBACCO SMOKE EXPOSURE IN THE PATHOGENESIS OF BREAST CANCER

Venu Raman, PhD; Johns Hopkins Medical Institutions; CIA 2003

Dr. Raman has identified a gene that plays a pivotal role in transforming normal mammary epithelial cells to their associated tumor phenotype. The gene encodes the DEAD-box

protein 3 (DDX3), and it belongs to a family of RNA helicases. It has been demonstrated that its over-expression contributes to hepatocellular carcinoma and is important in facilitating human immunodeficiency virus (HIV) replication. DDX3 is induced in normal mammary epithelial cells by benzo[a]pyrene diol epoxide (BP[a]DE), a component present in secondhand tobacco smoke. Dr. Raman and colleagues demonstrated that the overexpression of this protein in normal mammary epithelial cells can augment cellular motility and invasive properties. In addition, overexpression of this gene transforms normal cells so that they resemble highly invasive breast carcinomas. Detection of this gene product can be used as a prognostic marker for breast cancers and can be targeted for therapy by chemotherapeutic agents.

THE ROLE OF WT 1 IN THE PATHOGENESIS OF BREAST CANCER

David M. Loeb, MD, PhD; Johns Hopkins Medical Institutions; YCSA 2002

Dr. Loeb and colleagues identified Wilms' tumor protein (WT1) target genes important for proliferation and cell death, and determined the effect of expressing WT1 in mammary epithelial cells. The investigators utilized a breast tumor bank to correlate WT1 expression with expression of putative target genes and clinical outcome. The results demonstrated that different forms of WT1 have distinct effects on mammary epithelial cells, and one form promotes the changes typically seen in cancer cells. The team has also identified a number of potential WT1 target genes, including ribosomal protein S6 kinase, vascular-endothelial growth factor, and the cell survival-promoting gene, Bfl-1.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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CANCER: HEAD AND NECK

Completed Research

STAT3 AND THE TUMOR MICROENVIRONMENT IN HEAD AND NECK CANCER

Young J. Kim, MD, PhD; Johns Hopkins Medical Institutions; CIA 2009

Dr. Kim and colleagues characterized the paracrine influence of STAT3-activated human HNSCC cell lines on the trafficking and immunosuppressive behavior of human leukocytes *in vitro*. They investigated the immunoregulatory role of STAT3 in human HNSCS in the context of an immunocompetent human immune system using humanized NOD-SCID/Il-2Rg$^{-/-}$ mice reconstituted with human hematopoietic stem cells.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Albesiano E, Davis M, See AP, Han JE, Lim M, Pardoll DM, Kim Y. Immunologic consequences of signal transducers and activators of transcription 3 activation in human squamous cell carcinoma. *Cancer Res.* 2010;70(16):6467-6476.

DEVELOPMENT OF PKC EPSILON INHIBITORS FOR TREATING HEAD AND NECK CANCER

Quintin Pan, PhD; Ohio State University Research Foundation; YCSA 2008

Dr. Pan and colleagues identified protein kinase Ce (PKCe) as a critical causative factor in establishing an aggressive phenotype in HNSCC. The team investigated the specificity and efficacy of HN1-PKCe, a bifunctional HNSCC homing PKCe inhibitory peptide as a treatment for HNSCC. The HN1-PKCe peptide was designed by merging two technologies and was synthesized as a capped peptide with two functional motifs; HN1 (HNSCC cell homing) and PKCe (specific PKCe inhibitory), connected by a linker. HN1-PKCe preferentially internalized in a dose- and time-dependent manner into two HNSCC cell lines, UMSCC1 and UMSCC36. Consistent with these *in vitro* observations, systemic injection of HN1-PKCe resulted in selective delivery of HN1-PKCe into UMSCC1 xenografts in nude mice. HN1-PKCe blocked the translocation of active PKCe in UMSCC1 cells, confirming HN1-PKCe as a PKCe inhibitor. HN1-PKCe inhibited cell invasion and cell motility in UMSCC1 cells, reduced the levels of phosphorylated-signal transducer and activator of transcription 3 (STAT3), and retarded the growth of UMSCC1 xenografts in nude mice.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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USE OF PDE5 INHIBITORS FOR THE IMMUNE THERAPY OF HNSCC

Paolo Serafini, PhD; University of Miami Miller School of Medicine; YCSA 2008

Dr. Serafini and colleagues demonstrated that the two head and neck squamous cell carcinoma (HNSCC) immune suppressive host cell populations, myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs), can be inhibited by phosphodiesterase type 5 (PDE5) inhibitors; sildenafil (Viagra), or tadalafil (Cialis). In mice, PDE5 inhibition can enhance intratumoral T cell infiltration and activation to reduce outgrowth and prime a spontaneous antitumor response. There is *in vitro* T cell proliferation when sildenafil is added to peripheral blood mononuclear cells from HNSCC patients. The team found that intereukin 4 alpha receptor (IL4R alpha) expression is

associated with tumor recurrence, but no correlation with CD4+Foxp3+ tumor-infiltrating T cells was seen. Analysis taking sub-cellular localization into account showed that FOXP3 expression in the cytoplasm of CD4+ cells is associated with a favorable prognosis, whereas nuclear localization of FOXP3 is correlated with an increased risk of recurrence. The team showed that tadalafil and sildenafil blocks MDSC suppressive mechanisms by limiting Treg expansion and promoting spontaneous anti-tumor immunity in murine tumor models. They evaluated whether a presurgical PDE5 blockade is sufficient to restore favorable tumor micro- and macro-environments in a clinical trial. Analyses indicated that MDSC and Treg are downregulated by the PDE5 blockade in the peripheral blood and the tumor, and tumor specific immunity is enhanced. T cell proliferation and a higher infiltration of activated CD8+ T cells is observed after tadalafil treatment and a drastic reduction of IL4R alpha expression in the tumor-infiltrating myeloid cell compartment, suggesting a loss of MDSCs suppressive activity *in vivo*.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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DETECTION OF PREMALIGNANT LESIONS IN THE ORAL CAVITY INDUCED BY TOBACCO RELATED CARCINOGENS

Yuman Fong, MD; Memorial-Sloan Ketttering Cancer Center; CIA 2007

Dr. Fong's group and other investigators have shown that genetically engineered herpes simplex viruses (HSVs) selectively infect and kill many different types of cancers while sparing normal tissues. The team investigated one such virus (NV1066) that carries the gene for green fluorescent protein that could be used to identify and kill premalignant lesions caused by tobacco-related carcinogens before they progress to invasive cancers. To investigate this, the team used sensitivity to carcinogenesis (SENCAR) mice that manifest progressive carcinogenesis in the oral cavity. Tobacco-related carcinogens that promoted the development of dysplasia and ultimately squamous cell carcinoma were applied to the buccal, palatal, and tongue mucosa. The investigators tested the ability of the herpes virus to infect tumors at all stages and tested the ability for such infection to retard and arrest the transformation process. Further, the team investigated the mechanism underlying the phenomenon that certain engineered herpes viruses selectively infect and kill a wide variety of cancers, as well as the timing of this selectively in the transformation process. These studies amassed preclinical data that can be used to evaluate the efficacy of these oncolytic herpes viruses for early diagnosis and for definitive treatment of cancer.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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ROLES OF DNA PROMOTER HYPERMETHYLATION IN HEAD AND NECK CANCER CISPLATIN RESISTANCE

Zhongmin Guo, MD, PhD; Indiana University; YCSA 2007

Dr. Guo and colleagues performed genome-wide scanning of hypermethylated genes in several isogenic cisplatin-resistant cell models and identified a panel of candidate genes whose methylation may associate with cisplatin resistance in head and neck cancer. The team demonstrated the abnormal methylation of the Gpx3 gene and reciprocal overexpression of the Gpx1 gene in cisplatin resistant HNSCC cell lines and tumors. They identified an additional gene, neurofilament light peptide (NEFL), whose methylation silencing plays a role in chemoresistance. Cell lines with NEFL methylation had a reduction or a complete silencing in gene expression, and 5aza-dC demethylation restored its expression. Quantitative analysis of NEFL methylation in tumors retrospectively collected from a panel of HNSCC patients with recorded responses to cisplatin-based chemotherapy revealed that NEFL promoter methylation strongly correlates with HNSCC chemoresistance and predicts a reduced survival rate in patients who received cisplatin-based chemotherapy. Reduced expression of the NEFL gene was shown to contribute to cisplatin resistance via derepression of the mTOR oncogenic pathway in HNSCC cells. The team elucidated a molecular mechanism for de-regulation of antioxidant systems in HNSCC cells and identified SerpinB2 as a molecular target associated with development of HNSCC chemoresistance.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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EPIGENETIC ALTERATIONS IN PROGRESSION OF ESOPHOGEAL SQUAMOUS CELL CARCINOMA BY TOBACCO SMOKING

Myoung Sook Kim, PhD; Johns Hopkins Medical Institutions; YCSA 2007

Dr. Kim and colleagues identified promoters of a number of tumor suppressor genes (TSGs) that are methylated due to exposure to cigarette smoke. A major cause of esophageal cancer is exposure to tobacco smoke, and carcinogens in tobacco smoke damage genes that control the growth of cells, causing them to grow abnormally or to reproduce too rapidly. Evidence indicates that promoter methylation of TSGs occurs more frequently in cancers from smokers than non-smokers, suggesting that a tobacco signature could emerge from distinctive patterns of gene promoter methylation.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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OPTIMIZING FUSION HYBRIDS FOR CANCER IMMUNOTHERAPY

Walter T. Lee, MD; Duke University; YCSA 2007

Dr. Lee and his team investigated development of an immunotherapy vaccine based on dendritic cell (DC)-tumor fusion hybrids. They studied whether vaccination with these allogeneic tumor-DC fusion hybrids would be effective against autologous tumors expressing shared tumor-associated antigens (TAAs). They sought to optimize the components of the DC-tumor fusion hybrids and provide an immune environment that results in improved immunotherapy and clinical applicability. They investigated methods to skew DC maturation *in vivo* using toll-like receptor (TLR) agonists for effective immunotherapy and for developing an allogeneic tumor-DC fusion model that targets shared TAAs. *In vivo* results supporting the use of TLR agonists with fusion cells were observed and *in vitro* studies were performed to further analyze the effects. Experiments using allogeneic tumor-DC fusion vaccines showed immune responses against tumors sharing target antigens.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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SECONDHAND TOBACCO SMOKE AND ALCOHOL IN HEAD AND NECK CANCER

Michael McClean, ScD; Boston University; YCSA 2007

Dr. McClean and colleagues evaluated whether polymorphisms involved in carcinogen metabolism and DNA repair genes modify the effect of the tobacco-alcohol interaction with respect to head and neck squamous cell carcinoma (HNSCC). They also explored the extent to which epigenetic alterations confer susceptibility to HNSCC and/or affect survival. They identified human papillomavirus (HPV) as an independent risk factor for HNSCC. They also found that tobacco and alcohol are associated with increased HNSCC risk in HPV seronegative individuals but not in the HPV seropositive individuals, suggesting that HPV-related HNSCC is etiologically distinct from HNSCC associated with tobacco and alcohol. Additionally, they found that HPV seropositive cases experience significantly better survival rates than HPV seronegative cases, suggesting a worse prognosis for HNSCC associated with tobacco and alcohol. The investigators created a dataset for evaluating the effect of SHS exposure on HNSCC risk and survival by tumor site and HPV status.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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THE RECEPTOR TYROSINE KINASE C-MET AS A NOVEL THERAPEUTIC TARGET IN HEAD AND NECK CANCER

Tanguy Seiwert, MD; University of Chicago; YCSA 2007

Dr. Seiwert and colleagues identified mutations in a receptor tyrosine kinase, c-MET, in head and neck squamous cell carcinoma that occurred in 12% of tested tumors. All of these mutations clustered in the juxta-membrane (JM) and ligand binding semaphorin (SEMA) domains of c-MET. The research team analyzed samples from matched primary tumors from smokers, lymph node metastases, and distant metastases and correlated them with epidemiological tobacco exposure data to evaluate the frequency in HNSCC and its correlation with tobacco use. They also examined the biological role of mutations in JM, SEMA, and thymidine kinase *in vitro* and *in vivo* and compared viability, signaling, migration, and *in vivo* metastasis formation. They also determined the influence of tobacco smoke extract and NNK on keratinocytes in culture short term and long term. Further, they tested two c-MET inhibition strategies *in vitro* and *in vivo* using buccal swabs from patients treated in a Phase I study with the c-MET inhibitor PF-02341066. They were evaluated before and after drug administration of phosphorylated c-MET.

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ROLE OF EGR3 IN SMOKING INDUCED CANCER

Sanjai Sharma, MD; West Los Angeles VA Medical Center; YCSA 2007

Dr. Sharma and colleagues performed microarray profiling following paralysis of the nonsense mediated decay pathway (NMD) to identify unregulated RNAs that might contain premature termination codons (PTCs) in head and neck cancer cells (HNSCC). They identified an E-cadherin RNA transcript with a PTC. The E-cadherin gene codes for a tumor suppressor in HNSCC. An alternatively spliced E-cadherin transcript was found that did not include exon 11, which resulted in a frame-shift that caused a PTC in exon 12. This aberrant transcript has a short half-life and is rapidly degraded by the NMD pathway. The researchers found that non-tumorigenic keratinocytes also express the aberrant splice product, albeit 2-6 fold less that in the tumorigenic HNSCC cell lines. Upregulated expression of the aberrant E-cadherin transcript was detected in primary human head and neck cancer tissues when compared to adjacent normal tissues, and it undergoes rapid degradation. The amount of aberrantly spliced products can be modulated by siRNA silencing of the splicing factor, SFRS2 (SC35), which is overexpressed in HNSCC cell lines versus non-malignant cells. The investigators are studying aberrant splicing and upregulated expression of splice factors as potential mechanisms of E-cadherin downregulation in HNSCC.

FAMRI SUPPORTED RESEARCH

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SMOKING-GENE-ENVIRONMENT INTERACTIONS IN ESOPHAGEAL ADENOCARCINOMA

Rihong Zhai, MD, PhD; Harvard School of Public Health; YCSA 2007

Dr. Zhai and colleagues showed that genetic variants in cancer-associated genes, particularly angiogenic and inflammatory genes, contribute to esophageal adenocarcinoma (EA) risk through interactions with environmental factors, including tobacco smoke exposure, unhealthy body mass index, and reflux. The team used integrated analytic approaches, including logistic regression, multifactor dimensionality reduction, random forest, and classification and regression tree analysis to explore gene-environment interactions in EA risk. They found that gene-environment interaction patterns differ

significantly between different genes and environmental factors, providing support for personalized preventive strategies.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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TOBACCO-INDUCED MITOCHONDRIAL ALTERATIONS IN UPPER AERODIGESTIVE MUCOSA

Joseph A. Califano, MD; Johns Hopkins Medical Institutions; CIA 2006

Dr. Califano and colleagues developed a cell line model to compare the effects of acute versus chronic cigarette-smoke-extract (CSE) exposure on mitochondria in minimally transformed oral keratinocytes (OKF6). The cells were treated with varying concentrations of CSE for 6 months and analyzed monthly by flow cytometry for mitochondrial-membrane-potential (MMP), cytochrome-c release, caspase-3 activation, and viability. After 6 months of CSE-treatment, the cells were increasingly resistant to CSE-mediated and valinomycin-induced cell death. In addition, chronic CSE-treatment caused chronic depolarization of MMP, cytochrome c release, and caspase activation. Cells grown in the presence of only CSE vapor exhibited the same resistance and chronic baseline apoptotic activation. Mitochondrial DNA sequencing revealed that chronic CSE treated cells had more amino acid-changing mutations than were found in acutely treated cells. CSE treatment of normal cells selects for apoptotic dysfunction as well as mitochondrial mutations. These findings suggest that chronic tobacco exposure induces carcinogenesis via selection of apoptosis resistance and mitochondrial mutations.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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ANALYSIS OF SERUM PEPTIDES ASSOCIATED WITH SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK (HNSCC)

Radoslav Goldman, PhD; Georgetown University; CIA 2006

Dr. Goldman and collaborators identified peptides associated with HNSCC in a case-control study and evaluated their behavior after therapeutic intervention. The team developed methods for enrichment of the low molecular weight fraction of serum, which allows high-throughput analysis of peptides by MALDITOF/TOF MS, screening of peptide biomarker candidates and their identification by TOF/TOF sequencing. Similar MS methods can be applied to the analysis of glycans, a common peptide modification. The analysis of peptides and glycans is facilitated by computational methods for selection of the best combination of biomarkers for disease classification. To improve the depth of coverage, the investigators used high temperature fractionation of the enriched peptides prior to MS analysis, and established an optimal protocol for analyzing blood samples collected from patients after treatment, which can be used to examine newly diagnosed HNSCC cases, as well as controls matched for age, gender, and smoking history. Samples collected sequentially from the same person showed how the markers change with treatment.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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ERYTHROPOIETIN SIGNALING IN HEAD AND NECK CANCER

Stephen Y. Lai, MD, PhD; University of Pittsburgh, University of Texas M. D. Anderson Cancer Center; YCSA 2005

Dr. Lai and collaborators showed that erythropoietin (EPO) and its receptor (EPOR) are expressed in HNSCC cell lines and tissue specimens, and that expression levels are increased in metastatic HNSCC specimens as compared to paired primary HNSCC specimens. Signaling through the EPO/EPOR complex in HNSCC also promotes tumor invasion and metastasis. Dr. Lai focused upon the regulation of signaling pathways activated by EPO/EPOR and the relationship between EPOR expression and patient prognosis. Given the use of EPO in cancer and treatment-associated anemia, the characterization of EPO/EPOR expression and signaling in HNSCC has direct patient care impact. Characterization of the EPO/EPOR complex in solid tumors has led to changes in patient care guidelines from the FDA, the European Medicines Agency (EMEA), and the National Comprehensive Cancer Network (NCCN). Understanding the role of EPO/EPOR in HNSCC may alter the clinical use of EPO and lead to the development of targeted therapies.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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TARGETING THE INK4A/ARF LOCUS IN HEAD AND NECK CANCERS

James Rocco, MD, PhD; Massachusetts General Hospital; CIA 2004

Dr. Rocco's team characterized the chain of events that couple tobacco-smoke exposure to increased expression of p16 and cellular senescence at the molecular level. They determined whether a change in epigenetic modifications of the histone proteins that are associated with the promoter region of the CDKN2A gene that codes for p16 precedes the smoke-induced increase in p16 expression. They also predicted that the loss of transcriptional repression, mediated by the C-terminal binding protein, will couple the effect of cigarette smoke exposure to the altered epigenetic regulation of p16 expression.

FAMRI SUPPORTED RESEARCH

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ROLE OF EGFR AND ITS DOWNSTREAM TARGETS IN HEAD AND NECK CANCERS OF SMOKING PATIENTS

Alexey Fomenkov, PhD; Johns Hopkins Medical Institutions; CIA 2003

Dr. Fomenkov found that head and neck squamous cell carcinomas (HNSCC) from patients affected by primary or secondhand tobacco smoke exposure displayed induced tyrosine autophosphorylation of a tyrosine in the epithelial growth factor receptor (EGFR) and activated the phosphoinositol 3-kinase/ protein kinase B (PI3K/Akt) signaling pathway. He did profiling analysis of genes induced and downregulated in human tumor samples of primary smokers and secondhand tobacco smokers and found that the oncogenic p63 gene was dramatically induced. He and his team also showed that p63 transcription regulator of epithelial stratification is a downstream target of the EGFR pathway, and expression is specifically modulated by PI3K/Akt pathway rather than by Ras/ErkI/MAPK pathway. The team found that p63 regulates the transcription of genes for proteins specifically involved in cell adhesion and that p63 physically and functionally associates with members of RNA

transcription/splicing machinery. They showed that p63 function is regulated by a specific proteasome-dependent degradation mechanism through association with RACK1 and stratifin. The team extensively investigated the effects of cisplatin treatment on p63 in HNSCC cell lines.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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ADENOVIRAL GENE TRANSFER OF FRNK AND P53 FOR TREATMENT OF HEAD AND NECK CANCER: *IN VITRO* STUDIES

Lori J. Kornberg, PhD; University of Florida; CIA 2003

Dr. Kornberg's study demonstrated that focal adhesion kinase (FAK), a tyrosine kinase that mediates intracellular signals produced by the integrin family of adhesion receptors, is overexpressed in oral and laryngeal cancers. She developed an epithelial cell line that overexpresses FAK-related non-kinase (FRNK), an FAK inhibitor, for study of these cancers. The data suggest that expression of p53 and FRNK render cancer cells exquisitely sensitive to anticancer drugs.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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CHROMOSOMAL INSTABILITY IN HEAD AND NECK CANCER

Joseph A. Califano, MD; Johns Hopkins Medical Institutions; CIA 2002

Dr. Califano and colleagues investigated the status of chromosomal instability (CIN) in HNSC primary tumors and cell lines. The data show that ongoing instability in chromosomal number and structure are consistent features of primary HNSC and cell lines and that spindle assembly checkpoint impairment occurs in HNSC cell lines and may contribute to chromosomal instability. The team delineated the integrity of homologous recombination and nonhomologous end joining repair activities in HNSC. The results implicate impaired homologous recombination in HNSC cell lines when compared to control cell lines. A genetic progression model for HNSC was established that implies the presence of transcriptional dysregulation as a consequence of accumulation of genetic alterations. A transcriptional progression model of HNSC transcriptional shows that the majority of alteration occurs prior to the development of malignancy, and identifies key targets of transcriptional dysregulation during progression from a normal to a premalignant state, and from a premalignant to a malignant state. The team identified gene products whose expression patterns are altered in HNSC and are involved in chromosomal instability.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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MARKERS AND MECHANISMS FOR HEAD AND NECK CANCER

Elizabeth Franzmann, MD; University of Miami Miller School of Medicine; YCSA 2002

Dr. Franzmann established molecular markers that identify HNSCCs at an early stage and determined the role these molecules play in tumor growth and metastases. Analysis was done on salivary soluble CD44 expression in HNSCC patients and normal controls to determine its potential as a screening tool. The data show that soluble CD44 levels are significantly elevated in HNSCC patients compared to controls, suggesting that soluble CD44 could be used as a marker for early HNSCC. Further work has established that this marker can distinguish HNSCC from benign diseases of the mouth, nose, and throat. The marker also appears to detect lesions that are precancerous. Since precancer is a reversible state, the marker can be used for the early detection of HNSCC. Additional work in Dr. Franzmann's laboratory has shown that certain members of the CD44 family of proteins are expressed at high levels in HNSCC tissues compared to controls. Such overexpression of these isoforms in cell lines results in increased tumor cell growth and migration, thus these CD44 proteins are potential targets for therapy.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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Franzmann E, Lokeshwar, U.S. Provisional patent application number 11/090,705 "Soluble CD44: A Potential Molecular Marker for Head and Neck Cancer". Filed Mar 28, 2005.

Franzmann E, Singal, U.S. Provisional patent application number 60/845,526. "Hypermethylation of CD44 promoter in Head and Neck Squamous Cell Carcinoma". Filed Sep 19, 2006.

CANCER: BLADDER

Completed Research

METHYLATION MARKERS OF BLADDER CANCER RECURRENCE

George Netto, MD; Johns Hopkins Medical Institutions: CIA 2009

Dr. Netto and his colleagues used quantitative methylation-specific PCR and genetic markers for sensitive detection of low-grade urothelial tumors. Point mutations in the promoter of the telomerase reverse transcriptase (TERT) gene increase telomerase expression and have been shown to occur in melanomas and a small number of other tumors. The team surveyed 1,230 tumors of 60 different types and found that tumors could be divided into types with low (<15%) and high (≥15%) frequencies of TERT promoter mutations. The nine TERT-high tumor types almost always originated in tissues with relatively low rates of self renewal, including melanomas, liposarcomas, hepatocellular carcinomas, urothelial carcinomas, squamous cell carcinomas of the tongue, medulloblastomas, and subtypes of gliomas (including 83% of primary glioblastoma, the most common brain tumor type). TERT mutations provide a biomarker that may be useful for the early detection of urinary tract and liver tumors and aid in the classification and prognostication of brain tumors.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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RESISTANCE IN BLADDER CELLS

Aditi Chatterjee, PhD; Johns Hopkins Medical Institutions; YCSA 2008

Dr. Chatterjee and colleagues looked for evidence that chronic cigarette smoke condensate vapor exposure affects adenylate kinase 3 expression and renders cells resistant to cisplatin, which is one of the most commonly used antineoplastic agents for the treatment of advanced bladder cancer. The team investigated the relationship between cigarette

smoke exposure and cisplatin resistance and its reversal in bladder and lung cells. Resistance to cisplatin during treatment is common and constitutes a major obstacle to treatment. Cellular mechanisms of cisplatin resistance are multifactorial and contribute to severe limitations in the use of this drug.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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CIGARETTE SMOKE IMPAIRMENT OF BLADDER CANCER TREATMENT

Warren D. W. Heston, PhD; Cleveland Clinic; CIA 2008

Dr. Heston and colleagues developed a bladder cancer (BCa) mouse model for testing the effects of SHS on treatment regimens used in humans. The team demonstrated cure rates in mice with BCa using intravesical gene therapy with IL-2 that are equivalent to those seen using *Bacillus Calmette–Guérin* (BCG). This approach has prolonged immunological memory that protects the cured mice from re-challenge of the tumor, which BCG does not. IL-2 treatment, however, is limited in the percentage cures observed because it has the propensity to adversely increase immunosuppressive cells. A similar suppression was observed with smoking. Sunitinib, an anti-angiogenic agent, has been shown to reverse immune suppression. It may be that SHS exposure has a deleterious effect on current treatments for BCa, thus the team examined the role of SHS exposure on the response of BCa to BCG treatment, the role of cytokine gene therapy alone and with sunitinib, and the efficacy of these treatments combined with SHS exposure.

FAMRI SUPPORTED RESEARCH

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GENOMIC ANALYSIS OF URINE TO DETECT BLADDER CANCER

Charles J. Rosser, MD, MBA; Orlando Health Cancer Institute; CIA 2008

Dr. Rosser and colleagues identified a panel of eight biomarkers for the detection of bladder cancer (BCa) in voided urine samples. The investigators validated the diagnostic signatures from 308 subjects (102 BCa and 208 with varying urologic disorders). The urinary concentrations of eight biomarkers (IL-8, MMP-9, MMP-10, PAI-1, VEGF, ANG, CA9, APOE) were assessed by enzyme-linked immunosorbent assay. The levels of seven of the eight biomarkers were significantly elevated in subjects with BCa relative to subjects without BCa. Only CA9 was not increased in BCa subjects. The investigators found that the

combination of IL8, PA-1, and MMP-9 is the most accurate subset of biomarkers for the diagnosis of BCa. By comparison, the sensitivity of voided urinary cytology in this cohort was 39% and the sensitivity of Urovysion was 54%. The diagnostic signature was further validated from previous gene expression array and proteomics analyses that possess a high sensitivity in detecting BCa in voided urine. The result of this study is a validated panel of biomarkers that can detect BCa with very high accuracy in voided urine samples.

FAMRI SUPPORTED RESEARCH

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THE GPI TRANSAMIDASE COMPLEX SUBUNITS AS ONCOGENES IN BLADDER CANCER

Barry Trink, PhD (1950-2019); Johns Hopkins Medical Institutions; CIA 2007

Building on a previous FAMRI funded study, Dr. Trink and colleagues examined in depth the role of the subunits PIG-U, PIG-T, and GPAA1 in human cancer. They studied their activation in the progression of transitional cell carcinoma in bladder cancer and elucidated the role of the complex of GPI anchoring subunits in bladder cancer. Using a translational approach, they evaluated toxicity of proaerolysin in non-tumor and orthotopic bladder tumor-bearing mice to establish whether a therapeutic index can be achieved. Cigarette smoke exposure is a major cause of bladder cancer; thus, the team investigated the relationship between tobacco exposure and expression of these specific subunits.

FAMRI SUPPORTED RESEARCH

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THE EFFECT OF ADENYLATE KINASE 3 ON TOBACCO SMOKE-INDUCED CISPLATIN SPECTRAL AND SPATIAL ANALYSIS OF URINE CYTOLOGY

Edward Uchio, MD; Yale University; YCSA 2007

Dr. Uchio and colleagues used spectral information from the entire color spectrum as well as conventional spatial relationships, by incorporating the complex computer modeling GENetic Imagery Exploitation (PATHOGENIE) developed at Los Alamos, to improve the diagnosis of transitional cell carcinoma (TCC) of the bladder in voided urine samples. The standard for diagnosing TCC of the bladder at the time of this study involved visualization by cystoscopy and surgical removal by transurethral resection of the bladder tumor. Voided urine cytology obtained during this evaluation was used in monitoring for TCC recurrences due to its simplicity. However, a negative result did not obviate visualization by cystoscopy. To test the GENIE algorithm, voided urine cytology specimens from two different institutions were analyzed with it to provide spectral and spatial information. This algorithm was found to be more efficacious than a cytopathologist on specimens that were first categorized as atypical and subsequently found to be unequivocal by biopsy.

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GENETIC AND EPIGENETIC ALTERATIONS IN BLADDER CANCER BY TOBACCO SMOKE

Mohammad O. Hoque, DDS, PhD; Johns Hopkins Medical Institutions; YCSA 2006

Dr. Hoque and colleagues determined whether there are distinct patterns of chromosomal loss and methylation in smokers and non-smokers. The team demonstrated that bladder cancer can be detected by observing the methylation of a panel of genes isolated from urine sediment. Stratification of tumor stage was shown to be possible by profiling methylation markers, and tissue inhibitor of metalloproteinases-3 methylation was shown to be an independent prognostic factor for bladder cancer survival, stage, and metastasis.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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ROLE OF SHS ON SOMATIC ALTERATIONS IN BLADDER CANCER

Carmen J. Marsit, PhD; Harvard University; Brown University; YCSA 2006

Dr. Marsit and colleagues examined the somatic molecular profile of individuals to determine how tobacco exposure, lifestyle, and genetics interact to lead to bladder cancer. The investigators focused on how primary and SHS exposures affect epigenetic alterations;

specifically, hypermethylation and global hypomethylation, in the context of bladder cancer. The investigators used a high-throughput approach to examine the DNA methylation status of over 1,400 loci in more than 350 primary bladder tumor samples and identified two loci whose methylation is strongly associated with invasive bladder cancer, and are significant predictors of poor patient survival. The investigators also examined epigenetic alterations outside of the target tissue and showed that hypomethylation of the LINE1 repetitive element, which is detectable in peripheral blood-derived DNA, correlates with an increased risk of bladder cancer; especially in women. Further, the investigators identified profiles of gene-specific methylations that can be detected in peripheral blood and can serve as sensitive and specific markers of bladder cancer.

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Marsit CJ. Clinical Significance of epigenetic profiles in bladder cancer. Presented at the Program in Epidemiology Seminar Series in the Department of Community Health, Brown University. Providence, RI, Nov 2009.

DEVELOPING DMAPT, A NF-KAPPA B INHIBITOR FOR BLADDER CANCER

Harikrishna Nakshatri, PhD; Indiana University; CIA 2006

Dr. Nakshatri and colleagues developed a compound called LC-1, which inhibits bladder cancer cell growth both *in vivo* and *in vitro*. This drug was originally developed as an inhibitor of NF-kappa B, but these investigators observed that key proteins involved in epigenetic gene silencing are also LC-1 targets. LC-1 reduced the levels of epigenetic regulators such as polycomb protein EZH2, histone deacetylase HDAC1, and CtBP-1. It also increased histone H4lys20 trimethylation. Loss of histone H4lys20 trimethylation is a hallmark of a variety of cancers; LC-1 reverses this loss. LC-1 reduced the levels of SUV39h1 and histone H3K9 trimethylase, which correlates with reduced levels of histone H3K9 methylation. Histone H3K9 trimethylation is associated with repressive chromatin, a modification often observed in cancers. LC-1-treated cells displayed elevated levels of the tumor suppressor p21 and the proapoptotic protein Bim. The team investigated which of the above effects of LC-1 is independent of NF-kappa B inhibition. LC-1 effectively reduces CXCL-1 expression; overexpression of CXCL-1 is linked to metastatic progression of bladder cancer. Its expression is dependent on NF-kappa B.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Shanmugam R, Kusumanchi P, Appaiah H, Cheng L, Crooks P, Neelakantan S, Peat T, Klaunig J, Mathews W, Nakshatri H, Sweeney CJ. A Water Soluble parthenolide analogue suppresses *in vivo* tumor growth of two tobacco carcinogen associated cancers, lung and bladder cancer, by targeting NF-kappa B and generating reactive oxygen species. *Int J Cancer.* 2011;128(10):2481-2494.

PRESENTATIONS AND ABSTRACTS

Shanmugam R, Kusumanchi P, Crooks P, Klaunig J, Jordan C, Nakshatri H, Sweeney CJ. An orally bioavailable parthenolide analogue inhibits both subcutaneous and metastatic xenograft growth in lung and bladder cancer cell lines and is independent of p53 status [abstract]. *AACR* 2008;2008:2315.

A MARKER FOR BLADDER CANCER IN INVOLUNTARY SMOKERS

Robert H. Getzenberg, PhD; Johns Hopkins Medical Institutions; CIA 2005

Dr. Getzenberg hypothesized that the presence of a bladder cancer-specific nuclear matrix protein, BLCA-4, is sensitive and specific for the diagnosis of early bladder cancer and has potential as a screening tool in high-risk populations such as SHS-exposed individuals and smokers. He determined if urine BLCA-4 correlates with the presence of bladder cancer in SHS-exposed individuals in a sensitive and specific fashion, and whether smoking confounds the measurement of BLCA-4 in urine. Exposure to cigarette smoke increases the risk for developing bladder cancer but the survival rate is high if the tumors are detected early. Consequently, the ability to screen high-risk populations for the presence of low-grade bladder tumors has potential to improve the health management of this population group.

MARKERS OF RESPONSE TO INTRAVESICAL THERAPY TO BLADDER CANCER THERAPY

Ashish Kamat, MD; University of Texas M. D. Anderson Cancer Center; YCSA 2005

Dr. Kamat and colleagues evaluated the hypothesis that the presence of cytogenetically abnormal cells at defined time points during intravesical immunotherapy with bacillus *Calmette-Guérin* (BCG) is predictive of clinical tumor recurrence. A prospective clinical trial was conducted on patients undergoing BCG therapy. The patients had urine samples collected and assayed by a fluorescence *in situ* hybridization (FISH) assay and correlated to clinical outcomes. The findings suggested that patterns of the FISH assay at early time points during intravesical immunotherapy can help identify patients at risk for tumor recurrence. These data can be used to counsel patients regarding alternative strategies or they can be incorporated into prospective trial designs that evaluate novel therapies.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Kamat AM, Dickstein RJ, Messetti F, Anderson R, Pretzsch SM, Gonzalez GN, Katz RL, Khanna A, Zaidi T, Wu X, Grossman HB, Dinney CP. Use of fluorescence *in situ* hybridization to predict response to Bacillus Calmette-Guérin therapy for bladder cancer: results of a prospective trial. *J Urol.* 2012;187(3):862-867.

PRESENTATIONS AND ABSTRACTS

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Kamat A. Prospective clinical trial to evaluate markers of response to intravesical therapy for bladder cancer: preliminary results of FISH data. Presented at the American Urological Association National Annual Meeting. San Francisco, CA, May 29-Jun 3, 2010.

FUNCTIONAL ROLE OF CDC91L1-CONTAINING COMPLEX IN HUMAN BLADDER CANCERS

Edward Ratovitski, PhD; Johns Hopkins Medical Institutions; CIA 2005

Dr. Ratovitski and his collaborators discovered that the expression of the gene for CDC91L1 is affected by a common genomic amplification in bladder cancer at chromosomal location 20q11-13. This gene codes for phosphatidylinositol glycan anchor biosynthesis, class U (PIG-U), which is a part of a glycosylphosphatidylinositol (GPI)-anchoring complex of several proteins that modify other membranal proteins. The team evaluated the protein-protein interactions caused by overexpression of a number of GPI proteins to determine their roles in tumor formation, apoptosis, and cell proliferation of human cancer cells (e.g., bladder and breast). PIG-U was found to form several different protein-protein complexes with paxillin, mitogen-activated protein kinase 6 (MEK6), or human leukocyte antigen B-associated transcript 3 (BAT-3) in bladder and breast cancer cells. It also plays an important role in tumorigenesis, cell adhesion, and apoptosis. Dr. Ratovitski examined PIGU modifications mediated by association of PIG-U with MEK6 as well as interactions between PIG-U and paxillin and their effects on cell migration. In addition, he examined the association of PIG-U with BAT-3 and its effect on BAT-3-mediated apoptosis.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Carvalho AL, Chuang A, Jiang WW, Lee J, Begum S, Poeta L, Zhao M, Jeronimo C, Henrique R, Nayak CS, Park HL, Brait MR, Liu C, Zhou S, Koch W, Fazio VM, Ratovitski E, Trink B, Westra W, Sidransky D, Moon CS, Califano JA. Deleted in colorectal cancer is a putative conditional tumor-suppressor gene inactivated by promoter hypermethylation in head and neck squamous cell carcinoma. *Cancer Res.* 2006;66(19):9401-9407.

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Trink B, Osada M, Ratovitski E, Sidransky D. p63 transcriptional regulation of epithelial integrity and cancer. *Cell Cycle.* 2007;6(3):240-245.

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HEDGEHOG SIGNALING LINKS CANCER AND INJURY REPAIR IN BLADDER EPITHELIUM

Sunil S. Karhadkar, MBBS; Johns Hopkins Medical Institutions; YCSA 2004

Dr. Karhadkar investigated the role of sonic hedgehog (Hh) signaling in repairing bladder injury and estimated the number of bladder cancer patients that might benefit from therapy with drugs that block it. He tested the ability of such therapy to treat bladder cancer, and established a working model to study the return of urothelial barrier function, which is an important measure of the efficacy of repair. The data show localization of induction of Hh signaling in response to bladder injury.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Beachy PA, Karhadkar SS, Berman DM. Mending and malignancy. *Nature.* 2004;431(7007):402.

Beachy PA, Karhadkar SS, Berman DM. Tissue repair and stem cell renewal in carcinogenesis. *Nature.* 2004;432(7015):324-331.

CLONING OF A PUTATIVE ONCOGENE ON 20q11

Barry Trink, PhD (1950-2019); Johns Hopkins Medical Institutions; CIA 2003

Dr. Trink and colleagues cloned and characterized PIG-U, a human oncogene for human bladder cancer, which is implicated the glycosylphosphatidylinositol (GPI) anchoring pathway in the development of human cancers. PIG-U is one of five subunits making up the transamidase complex involved in the GPI anchoring pathway. The team showed that activation of at least three of these subunits can be oncogenic. The investigators studied activation of the subunits in the progression of transitional cell carcinoma (TCC) in bladder cancer. Aerolysin, a cytolytic toxin, binds to GPI-anchored proteins on the target cells and

becomes active upon proteolysis and causes cell lysis. The investigators have shown that cells overexpressing the subunits have increased sensitivity to proaerolysin. Human bladder cells were subjected to tobacco smoke and the expression of these subunits was measured in order to determine the relationship between tobacco smoke exposure and oncogenic potential.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Guo Z, Linn JF, Wu G, Anzick SL, Eisenberger CF, Halachmi S, Cohen Y, Fomenkov A, Hoque MO, Okami K, Steiner G, Engles JM, Osada M, Moon C, Ratovitski E, Trent JM, Meltzer PS, Westra WH, Kiemeney LA, Schoenberg MP, Sidransky D, Trink B. CDC91L1 (PIG-U) is a newly discovered oncogene in human bladder cancer. *Nat Med.* 2004;10(4):374-381.

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Wu G, Osada M, Guo Z, Fomenkov A, Begum S, Zhao M, Upadhyay S, Xing M, Wu F, Moon C, Westra WH, Koch WM, Mantovani R, Califano JA, Ratovitski E, Sidransky D, Trink B. DeltaNp63alpha up-regulates the Hsp70 gene in human cancer. *Cancer Res.* 2005;65(3):758-766.

ADENOVIRAL BLADDER CANCER GENE THERAPY

Ronald Rodriguez, MD, PhD; Johns Hopkins Medical Institutions; CIA 2002

Dr. Rodriguez discovered that bladder cancer cells downregulate the expression of the adenoviral receptor. This downregulation was reversed by histone deacetylase inhibitor 1 (HDACI).

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Sachs MD, Ramamurthy M, Poel H, Wickham TJ, Lamfers M, Gerritsen W, Chowdhury W, Li Y, Schoenberg MP, Rodriguez R. Histone deacetylase inhibitors upregulate expression of the coxsackie adenovirus receptor (CAR) preferentially in bladder cancer cells. *Cancer Gene Ther.* 2004;11(7):477-486.

Sachs MD, Rauen KA, Ramamurthy M, Dodson JL, De Marzo AM, Putzi MJ, Schoenberg MP, Rodriguez R. Integrin alpha(v) and coxsackie adenovirus receptor expression in clinical bladder cancer. *Urology.* 2002;60(3):531-536.

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CANCER: GASTRIC

Completed Research

GASTRIC CANCER: MOLECULAR PATHOGENESIS AND BIOMARKER DISCOVERY

Florin M. Selaru, MD; Johns Hopkins Medical Institutions; YCSA 2008

Dr. Selaru and colleagues performed microRNA (miR) arrays on gastric tissues from smokers with gastric cancer (GC), non-smokers with gastric cancer, smokers with normal stomach, and nonsmokers with normal stomach. The team identified miR species differentially expressed in GC vs. normal gastric cells and showed that miR-21 is generally overexpressed in GC. Moreover, they showed that the levels of miR-21 are higher in smokers than in non-smokers. Tissue inhibitor of metalloproteinases 3 (TIMP3) was found to be upregulated in miR-21 inhibitor-treated cells. These findings suggest that miR-21 may exert its oncogenic properties in gastric cancer cells in part through TIMP3 inhibition.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Agarwal R, Mori Y, Cheng Y, Jin Z, Olaru AV, Hamilton JP, David S, Selaru FM, Yang J, Abraham JM, Montgomery E, Morin PJ, Meltzer SJ. Silencing of claudin-11 is associated with increased invasiveness of gastric cancer cells. *PLoS One.* 2009;4(11):e8002.

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Kan T, Sato F, Ito T, Matsumura N, David S, Cheng Y, Agarwal R, Paun BC, Jin Z, Olaru AV, Selaru FM, Hamilton JP, Yang J, Abraham JM, Mori Y, Meltzer SJ. The miR-106b-25 polycistron, activated by genomic amplification, functions as an oncogene by suppressing p21 and Bim. *Gastroenterology.* 2009;136(5):1689-1700.

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BOOK CHAPTERS, ETC.

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CANCER: OVARIAN

Completed Research

ANTIBODIES FOR SMOKING-RELATED MUCINOUS OVARIAN CANCER

Shu-Wing Ng, PhD; Brigham and Women's Hospital; CIA 2006

Dr. Ng and colleagues identified 35 auto-antibodies that are significantly elevated in cancer plasma samples compared with healthy controls, as well as six auto-antibodies that segregated smoking from non-smoking patients. Functional annotation of the antibody targets identified nine target antigens involved in the integrin and Wnt signaling pathways. Immunohistochemistry of archived ovarian specimens showed significant overexpression of eight of the nine target antigens in mucinous ovarian tumor tissues. Dr. Ng and colleagues devised methods to validate the auto-antibody data and to understand the mechanisms by which the immune system reacts to tobacco exposure.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Tang L, Yang J, Ng SK, Rodriguez N, Choi PW, Vitonis A, Wang K, McLachlan GJ, Caiazzo RJ, Jr., Liu BC, Welch WR, Cramer DW, Berkowitz RS, Ng SW. Autoantibody profiling to identify biomarkers of key pathogenic pathways in mucinous ovarian cancer. *Eur J Cancer.* 2010;46(1):170-179.

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CANCER: CERVICAL

Completed Research

SYNERGY OF HPVs AND TOBACCO SMOKE IN CERVICAL CANCER

Hans-Ulrich Bernard, PhD; University of California, Irvine; CIA 2007

Dr. Bernard and colleagues investigated the impact of nicotinic acetylcholine signaling on the biology of cervical cells, and the consequences of recombination of papilloma virus and cellular DNA, presumably stimulated by nitrosamines. They showed that cervical epithelia express a subset of the 16 potential subunits of nicotinic acetylcholine signaling and that the proliferation of cervical cells accelerates under the influence of nicotine. Similarly, the motility of cervical epithelial cells increases by the same pathway. The investigators also investigated details of this molecular mechanism, including calcium transport and kinase cascades. They showed that as cervical neoplasia progresses, papilloma viruses are sequentially and frequently chromosomally recombined rather than remaining episomal. The team demonstrated that methylation of the papilloma virus DNA can serve as a

biomarker to differentiate between patients whose infection progresses and those whose infection does not.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Calleja-Macias IE, Kalantari M, Bernard HU. Cholinergic signaling through nicotinic acetylcholine receptors stimulates the proliferation of cervical cancer cells: an explanation for the molecular role of tobacco smoking in cervical carcinogenesis? *Int J Cancer.* 2009;124(5):1090-1096.

Kalantari M, Chase DM, Tewari KS, Bernard HU. Recombination of human papillomavirus-16 and host DNA in exfoliated cervical cells: a pilot study of L1 gene methylation and chromosomal integration as biomarkers of carcinogenic progression. *J Med Virol.* 2010;82(2):311-320.

Kalantari M, Garcia-Carranca A, Morales-Vazquez CD, Zuna R, Montiel DP, Calleja-Macias IE, Johansson B, Andersson S, Bernard HU. Laser capture microdissection of cervical human papillomavirus infections: copy number of the virus in cancerous and normal tissue and heterogeneous DNA methylation. *Virology.* 2009;390(2):261-267.

Kalantari M, Villa LL, Calleja-Macias IE, Bernard HU. Human papillomavirus-16 and -18 in penile carcinomas: DNA methylation, chromosomal recombination and genomic variation. *Int J Cancer.* 2008;123(8):1832-1840.

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ENHANCING CISPLATIN EFFICIENCY WITH A COPPER CHELATOR

Douglas Hanahan, PhD; University of California, San Francisco; CIA 2005

Dr. Hanahan determined whether cervical cancer therapy with the pharmacological agent tetrathiomolybdate (TM), which reduces systemic copper levels, increases the transport of cisplatin into tumors, thereby improving antitumor efficacy while reducing the dose and attendant toxicity required for maximal efficacy. Modulating copper levels could improve cisplatin responses with less toxicity in cervical and other cancers where secondhand tobacco smoke exposure is causally linked, and modulating copper levels with TM may inhibit the tumor-related angiogenesis that sustains cervical and other forms of human cancer. The data suggest that TM treatment reduces systemic copper levels in mice (with anti-angiogenic effects) and increases cisplatin transport into mouse cervical cancers, but not into normal tissues.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Ishida S, McCormick F, Smith-McCune K, Hanahan D. Enhancing tumor-specific uptake of the anticancer drug cisplatin with a copper chelator. *Cancer Cell.* 2010;17(6):574-583.

GENETIC PREDISPOSITION TO SECOND HAND TOBACCO SMOKE IN CERVICAL DISEASES

Ramin Mirhashemi, MD; Torrance Memorial Medical Center; CIA 2003

Dr. Mirhashemi identified specific genes that play a role in the pathogenesis of invasive cervical cancer. Cervical cancer propensity is the function of a differential bioactivation of environmental carcinogens in the population, and women with invasive cervical cancer share certain xenobiotic metabolism gene polymorphisms not present in healthy women. Individuals exposed to secondhand tobacco smoke are at higher risk for developing cervical cancer if they carry specific polymorphisms in xenobiotic genes.

CANCER: PROSTATE

Completed Research

GENERATION OF OPTIMIZED PROSTATE SPECIFIC CRAD VIRUS

Naser Uddin Höti, PhD; Johns Hopkins Medical Institutions; YCSA 2009

Dr. Höti and colleagues found that cellular p21/Waf-1-a cyclin-dependent kinase inhibitor is a potent factor inhibiting adenoviral replication. Knocking down p21/Waf-1 not only helped in viral titers and viral DNA replication, but also induced the androgen-dependent promoters used to drive the adenoviral immediate early gene used for tumor specificity. The group focused on the development of more efficient prostate specific adenovirus vectors. They compared the efficacy of an engineered prostate-specific adenovirus that carries a p21/Waf-1 small hairpin RNA *in vitro* and *in vivo* and found that it is as potent as wild type adenovirus and more specific in tumor cell lysis of the prostate tumor. The group also focused on improvement of the viral replication that can overcome cellular-induced repression. There is an absolute requirement for androgen to stimulate the androgen receptor for trans-activating the androgen-dependent promoter driving viral replication. An alternative approach is needed for patients that have undergone total androgen ablation therapy. To overcome these problems, the team constructed conditionally replicating adenoviruses with a point mutation in the androgen receptor ligand-binding domain, which alters specificity of binding, such that androgens and nonsteroidal anti-androgens are able to activate the virus to maximal effect. When this virus is combined with bicalutamide and low dose rate radiation it exerts a profound impact on cell death and viral replication. The synergy of these viruses was evaluated in an androgen-independent disease model and in combination with high versus low dose radiation studies in animal models.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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Hoti N, Johnson TJ, Chowdhury WH, Rodriguez R. Loss of Cyclin-Dependent Kinase Inhibitor Alters Oncolytic Adenovirus Replication and Promotes More Efficient Virus Production. *Cancers* (Basel). 2018;10(6).

Hoti N, Yang S, Aiyetan P, Kumar B, Hu Y, Clark D, Eroglu AU, Shah P, Johnson T, Chowdery WH, Zhang H, Rodriguez R. Overexpression of Exportin-5 Overrides the Inhibitory Effect of miRNAs Regulation Control and Stabilize Proteins via Posttranslation Modifications in Prostate Cancer. *Neoplasia.* 2017;19(10):817-829.

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Johnson TJ, Khan ZU, Mustafa S, Desai K, Höti NU. A single therapeutic miRNA rescues the oncolysis of androgen activated prostate specific virus in androgen independent cell model. *J Cancer Ther.* 2012;3:1012-1019.

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Khan M, Khan Z, Uddin Y, Mustafa S, Shaukat I, Pan J, Hoti N. Evaluating the Oncogenic and Tumor Suppressor Role of XPO5 in Different Tissue Tumor Types. *Asian Pac J Cancer Prev*. 2018;19(4):1119-1125.

PRESENTATIONS AND ABSTRACTS

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Höti N. Improving replication kinetics by using a single shRNA p21/Waf-1 construct in backbone of prostate specific CRAd. Presented at the American Association for Cancer Research 2010 Meeting. Washington, DC, Apr 17-21, 2010.

SMALL PEPTIDE THERAPY ON METASTATIC PROSTATE CANCER

Jer-Tsong Hsieh, PhD; University of Texas Southwestern; CIA 2008

Dr. Hsieh and colleagues used a cell permeable peptide (CPP) sequence to analyze the underlying mechanism CPP-specific uptake by prostate cancer (PCa). They also explored the application of a unique CPP-oligoarginine peptide as a delivery vehicle and molecular imaging agent to detect PCa lesions. To specifically target molecular defects in androgen-independent PCa (AIPCa) cells, small peptide motifs from tumor suppressor proteins such as differentially expressed in ovarian carcinoma-2/disabled-2 (DOC-2/DAB2) and its interactive protein DAB2IP, were synthesized and their effects were examined in preclinical animal models. The route of CPP uptake and the potential application of molecular imaging capabilities was determined using positron emission tomography.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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Hsieh JT, Zhou J, Gore C, Zimmern P. R11, a novel cell-permeable peptide, as an intravesical delivery vehicle. *BJU Int.* 2011;108(10):1666-1671.

Kong Z, Raghavan P, Xie D, Boike T, Burma S, Chen D, Chakraborty A, Hsieh JT, Saha D. Epothilone B confers radiation dose enhancement in DAB2IP gene knock-down radioresistant prostate cancer cells. *Int J Radiat Oncol Biol Phys.* 2010;78(4):1210-1218.

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PRESENTATIONS AND ABSTRACTS

Zhou J, Gore C, Hsieh, JT, Zimmerm P. Developing bladder specific targeting agent using cell permeable peptide. Presented at the 104th Annual Meeting of American Urologic Association. Chicago, IL, Apr 25-30, 2009.

NDRG1 MODULATION TO DECREASE PROSTATE CANCER INVASION

Sushant K. Kachhap, PhD; Johns Hopkins Medical Institutions; YCSA 2008

Dr. Kachhap and colleagues investigated the N-myc downregulated gene 1 (NDRG1) product as an anti-metastatic tool specifically in prostate cancer (PCA). They are investigating the pathways regulated by NDRG1 in PCA with the aim of pharmacologically targeting NDRG1-deficient advanced PCA. Stable NDRG1 knockdown (NDRG1KD) PCA cells exhibit a collective migration phenotype in a three-dimensional extracellular matrix. The team determined whether this highly invasive phenotype is due to increased integrin signaling that regulates actin dynamics in NDRG1KD cells. Their findings demonstrate that NDRG1KD PCA cells exhibit differential levels of several integrins, decreased focal adhesion complexes, increased activation of cdc42GTPase, and an increase in filopodial extensions, a feature of invasive cells. The team investigated the role of NDRG1 in regulation of actin dynamics via the integrin signaling pathway and the role of integrin beta1 signaling in NDRG1-deficient PCA cells. They determined whether activation of cdc42GTPase plays a central role in invasion of NDRG1deficient PCA cells. They investigated pharmacological and genetic inhibition of the integrin/cdc42/actin pathway as a way to decrease PCA invasion.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Fu C, van der Zwan A, Gerber S, Van Den Berg S, No E, Wang WC, Sheibani N, Carducci MA, Kachhap S, Hammers HJ. Screening assay for blood vessel maturation inhibitors. *Biochem Biophys Res Commun*. 2013;438(2):364-369.

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inhibition in prostate cancer is mediated through the E2F1 transcription factor. *PLoS One*. 2010;5(6):e11208.

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Kortenhorst MS, Zahurak M, Shabbeer S, Kachhap S, Galloway N, Parmigiani G, Verheul HM, Carducci MA. A multiple-loop, double-cube microarray design applied to prostate cancer cell lines with variable sensitivity to histone deacetylase inhibitors. *Clin Cancer Res*. 2008;14(21):6886-6894.

Lin J, Haffner MC, Zhang Y, Lee BH, Brennen WN, Britton J, Kachhap SK, Shim JS, Liu JO, Nelson WG, Yegnasubramanian S, Carducci MA. Disulfiram is a DNA demethylating agent and inhibits prostate cancer cell growth. *Prostate*. 2011;71(4):333-343.

Mendonca J, Sharma A, Kim HS, Hammers H, Meeker A, De Marzo A, Carducci M, Kauffman M, Shacham S, Kachhap S. Selective inhibitors of nuclear export (SINE) as novel therapeutics for prostate cancer. *Oncotarget*. 2014;5(15):6102-6112.

Paller CJ, Wissing MD, Mendonca J, Sharma A, Kim E, Kim HS, Kortenhorst MS, Gerber S, Rosen M, Shaikh F, Zahurak ML, Rudek MA, Hammers H, Rudin CM, Carducci MA, Kachhap SK. Combining the pan-aurora kinase inhibitor AMG 900 with histone deacetylase inhibitors enhances antitumor activity in prostate cancer. *Cancer Med*. 2014;3(5):1322-1335.

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Wissing MD, Mendonca J, Kim E, Kim E, Shim JS, Kaelber NS, Kant H, Hammers H, Commes T, Van Diest PJ, Liu JO, Kachhap SK. Identification of cetrimonium bromide and irinotecan as compounds with synthetic lethality against NDRG1 deficient prostate cancer cells. *Cancer Biol Ther*. 2013;14(5):401-410.

Wissing MD, Mendonca J, Kortenhorst MS, Kaelber NS, Gonzalez M, Kim E, Hammers H, van Diest PJ, Carducci MA, Kachhap SK. Targeting prostate cancer cell lines with polo-like kinase 1 inhibitors as a single agent and in combination with histone deacetylase inhibitors. *FASEB J*. 2013;27(10):4279-4293.

CANCER

Saeed Khan, PhD, Aniriban Maitra, MD; Johns Hopkins Medical Institutions; CIA 2008

Dr. Maitra and colleagues designed biodegradable polymeric nanoparticles that enable encapsulation of cyclopamine and other small molecule hedgehog (Hh) inhibitors. These

nanoparticles have variable release kinetics, ranging from short-term to sustained release of the nano-encapsulated drug *in vivo*. The nanoparticles are amenable to targeting by addition of surface ligands or antibodies directed against prostate cancer cells.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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Chenna V, Hu C, Pramanik D, Aftab BT, Karikari C, Campbell NR, Hong SM, Zhao M, Rudek MA, Khan SR, Rudin CM, Maitra A. A polymeric nanoparticle encapsulated small-molecule inhibitor of Hedgehog signaling (NanoHHI) bypasses secondary mutational resistance to Smoothened antagonists. *Mol Cancer Ther.* 2012;11(1):165-173.

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Kumar SK, Roy I, Anchoori RK, Fazli S, Maitra A, Beachy PA, Khan SR. Targeted inhibition of hedgehog signaling by cyclopamine prodrugs for advanced prostate cancer. *Bioorg Med Chem.* 2008;16(6):2764-2768.

Lim KJ, Bisht S, Bar EE, Maitra A, Eberhart CG. A polymeric nanoparticle formulation of curcumin inhibits growth, clonogenicity and stem-like fraction in malignant brain tumors. *Cancer Biol Ther.* 2011;11(5):464-473.

Pramanik D, Campbell NR, Karikari C, Chivukula R, Kent OA, Mendell JT, Maitra A. Restitution of tumor suppressor microRNAs using a systemic nanovector inhibits pancreatic cancer growth in mice. *Mol Cancer Ther.* 2011;10(8):1470-1480.

Xu Y, Chenna V, Hu C, Sun HX, Khan M, Bai H, Yang XR, Zhu QF, Sun YF, Maitra A, Fan J, Anders RA. Polymeric nanoparticle-encapsulated hedgehog pathway inhibitor HPI-1 (NanoHHI) inhibits systemic metastases in an orthotopic model of human hepatocellular carcinoma. *Clin Cancer Res.* 2012;18(5):1291-1302.

BOOK CHAPTERS, ETC.

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CIGARETTE SMOKE AND IMPAIRED SELENOPROTEIN PRODUCTION

Charles B. Foster, MD; Cleveland Clinic; CIA 2007

Dr. Foster and colleagues developed two reporter assays to characterize cellular signaling pathways regulating selenoprotein production and stability. One reporter measures how efficiently the amino acid selenocysteine is incorporated into an artificial selenoprotein,

and the other measures the stability of an artificial selenoprotein. In the presence of selenium, inducers of the PI3K pathway such as the cytokine IL-13 enhance L-seryl-tRNA incorporation efficiency, increase the level of the antioxidant selenoprotein glutathione peroxidase 1, and protect HEK293 cells against hydrogen peroxide or cigarette smoke-induced cell death. In contrast to HEK293 cells, supplemental selenium does not afford prostate cancer cells enhanced protection against inducers of oxidative stress.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Banerjee S, Yang S, Foster CB. A luciferase reporter assay to investigate the differential selenium-dependent stability of selenoprotein mRNAs. *J Nutr Biochem.* 2012;23(10):1294-1301.

INHIBITION OF HEDGEHOG SIGNALING BY CYCLOPAMINE PRODRUG FOR PROSTATE OPTIMIZING THERAPY OF SMOKING-RELATED CANCERS BY MODULATING NUCLEOTIDE METABOLISM

Paula J. Hurley, PhD; Johns Hopkins Medical Institutions; YCSA 2007

Dr. Hurley and colleagues identified the gene for high endothelial venule protein (Hevin) as a gene that is dynamically regulated during prostate development and is disrupted in prostate cancer. The investigators showed that Hevin expression is significantly reduced in several human prostate cancer cell lines, in primary human prostate cancers, in mouse models of prostate cancer, and especially in more aggressive murine and human cancers and cell lines. They also showed that Hevin regulates prostatic cell proliferation, adhesion, and migration, and that Hevin modulates growth factors involved in Akt activation in the prostate.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Huang Z, Hurley PJ, Simons BW, Marchionni L, Berman DM, Ross AE, Schaeffer EM. Sox9 is required for prostate development and prostate cancer initiation. *Oncotarget.* 2012;3(6):651-663.

Hurley PJ, Marchionni L, Simons BW, Ross AE, Peskoe SB, Miller RM, Erho N, Vergara IA, Ghadessi M, Huang Z, Gurel B, Park BH, Davicioni E, Jenkins RB, Platz EA, Berman DM, Schaeffer EM. Secreted protein, acidic and rich in cysteine-like 1 (SPARCL1) is down regulated in aggressive prostate cancers and is prognostic for poor clinical outcome. *Proc Natl Acad Sci U S A.* 2012;109(37):14977-14982.

Ross AE, Emadi A, Marchionni L, Hurley PJ, Simons BW, Schaeffer EM, Vuica-Ross M. Dimeric naphthoquinones, a novel class of compounds with prostate cancer cytotoxicity. *BJU Int.* 2011;108(3):447-454.

Ross AE, Marchionni L, Phillips TM, Miller RM, Hurley PJ, Simons BW, Salmasi AH, Schaeffer AJ, Gearhart JP, Schaeffer EM. Molecular effects of genistein on male urethral development. *J Urol.* 2011;185(5):1894-1898.

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BOOK CHAPTERS, ETC.

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Hurley PJ, Schaeffer EM. Invention disclosure: "SPARCLI and metastatic prostate cancer". 2012.

THE ROLE OF DNA METHYLATION AS A PREDICTOR OF BIOCHEMICAL RELAPSE AFTER RADICAL PROSTATECTOMY AND NKX3.1 GENE SILENCING IN PROSTATE CANCER: IMPORTANCE AND MECHANISMS

Joshi J. Alumkal, MD; Johns Hopkins Medical Institutions, Oregon Health and Sciences Center; YCSA 2006

Dr. Alumkal and colleagues developed treatments for advanced prostate cancer. The efforts focused on targeting the androgen receptor (AR). Diets high in cruciferous vegetables are associated with lower prostate cancer risk, and sulforaphane is an isothiocyanate compound in these foods that has anti-tumor activity in pre-clinical models. The investigators studied whether the effect of sulforaphane in prostate cancer was at least partially mediated by effects on the AR pathway. They demonstrated that sulforaphane treatment suppressed AR signaling and that this effect was mediated by inhibition of histone deacetylase enzymes. These results served as the basis for a clinical trial to study the effects of sulforaphane treatment in men with recurrent prostate cancer.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Alumkal JJ. Through the looking glass. *Blood.* 2009;114(16):3363-3364.

Alumkal JJ, Zhang Z, Humphreys EB, Bennett C, Mangold LA, Carducci MA, Partin AW, Garrett-Mayer E, DeMarzo AM, Herman JG. Effect of DNA methylation on identification of aggressive prostate cancer. *Urology.* 2008;72(6):1234-1239.

Gao L, Alumkal J. Epigenetic regulation of androgen receptor signaling in prostate cancer. *Epigenetics.* 2010;5(2):100-104.

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Gao L, Schwartzman J, Gibbs A, Lisac R, Kleinschmidt R, Wilmot B, Bottomly D, Coleman I, Nelson P, McWeeney S, Alumkal J. Androgen receptor promotes ligand-independent prostate cancer progression through c-Myc upregulation. *PLoS One.* 2013;8(5):e63563.

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PRESENTATIONS AND ABSTRACTS

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CANCER: THYROID

Completed Research

BRAF MUTATION AND OTHER COMMON GENETIC AND EPIGENETIC ALTERATIONS IN THYROID CANCER: RELATIONSHIP WITH SMOKING AND CLINICAL APPLICATIONS

Michael M. Xing, MD, PhD; Johns Hopkins Medical Institutions; CIA 2004

Dr. Xing and collaborators hypothesized that smoking causes a higher incidence of certain genetic and epigenetic alterations in thyroid cancer such as BRAF and Ras mutations, as well as gene methylation leading to adverse pathological and clinical consequences. The team determined whether smoking causes specific genetic/epigenetic alterations in thyroid cancer, with predilection to a particular subtype and specific clinicopathological characters, and applied the information to thyroid cancer diagnostic and prognostic evaluation. The most common genetic and epigenetic alterations in thyroid cancer involve BRAF (Ras regulated kinase), Ras mutations, and aberrant gene methylation. Smoking is

linked with mutations in Ras, nodular goiter, and Grave's disease. Both nodular goiter and Grave's disease are associated with an increased risk of thyroid cancer.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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CANCER: LYMPHOMA

Completed Research

TRANSFORMED FOLLICULAR LYMPHOMA: SMOKE RELATED?

Ronald B. Gartenhaus, MD; Northwestern University, University of Maryland; CIA 2002

Dr. Gartenhaus made a comparison of p53 mutations in transformed follicular lymphoma from non-smokers and smokers and between the presence of a mutator phenotype in transformed follicular lymphoma from nonsmokers and smokers. The results show no

association between p53 status and smoking in transformed follicular lymphoma, but do show a trend towards a higher rate of mutation in a DNA repair mismatch enzyme (MLH-1) and in a gene associated with genetic instability in a hereditary form of colon cancer (MSH-2) in smokers as compared to non-smokers.

CANCER: ANGIOGENESIS

Completed Research

REGULATION OF TUMOR ANGIOGENESIS BY COMBOSTATIN

Sudhakar Akulapalli, PhD; Boys Town National Research Hospital; YCSA 2007

Dr. Akulapalli and colleagues developed a fusion protein called combostatin, comprising the functional regions from known antiangiogenic molecules; endostatin type XVIII collagen noncollagenous (NC1) domain, and a1 and a3 type IV collagen NC1 domains. It was found that combostatin has more antitumorogenic activity than any of its parent molecules. Combostatin blocks formation of new blood vessels in solid tumors, which is a prerequisite for tumor growth. Combostatin inhibits the important pro-inflammatory molecule cyclo-oxygenase (COX-2) and inhibits activation of metalloproteinase-2 (MMP-2). A number of studies using one of the parent molecules of combostatin, (a3(IV)NC1) showed that regulation of COX-2 is dependent on integrin a3b1. The investigators focused on understanding the functional nature of the parent molecules by *in vitro* and *in vivo* studies.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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CANCER: MULTIPLE

Completed Research

SMOKING'S IMPACT ON EPIGENETIC REGULATION OF P16

James Rocco, MD, PhD; Massachusetts General Hospital; CIA 2009

Dr. Rocco and colleagues characterized the chain of events that couple tobacco smoke exposure to increased expression of p16 and cellular senescence in primary cells from human target tissues adversely affected by chronic smoke exposure. The team identified C-terminal binding protein (CtBP) as a critical regulator of p16 expression, capable of integrating a diverse set of upstream signals. They also investigated how tobacco smoke exposure affects CtBP and its repression of p16 in these cells, and characterized the

epigenetic regulation at the p16 promoter in each of the primary cell types to show how this epigenetic regulation is affected by exposure. They showed that the increased p16 expression after functional loss of CtBP-mediated repression is associated with epigenetic modification at the p16 promoter. These results should allow an evaluation of whether changes in epigenetic control of p16 could provide a permanent mark of past exposure of primary cells to the stresses of cigarette smoke.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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Nichols AC, Finkelstein DM, Faquin WC, Westra WH, Mroz EA, Kneuertz P, Begum S, Michaud WA, Busse PM, Clark JR, Rocco JW. Bcl2 and human papilloma virus 16 as predictors of outcome following concurrent chemoradiation for advanced oropharyngeal cancer. *Clin Cancer Res.* 2010;16(7):2138-2146.

TARGETING THE ATR KINASE IN SECONDHAND TOBACCO SMOKE-RELATED CANCERS

Fred Bunz, MD, PhD; Johns Hopkins Medical Institutions; CIA 2008

Dr. Bunz and his colleagues conducted studies that yielded genetic tools to study cancer biology and provided strategies for rational cancer therapy. They developed and refined efficient methods to edit genes in cultured human cancer cells. As a result of these efforts, methods to study human genes are more versatile, simpler, and accessible to medical scientists than those previously available. The technology developed by these investigators has been increasingly utilized to analyze the human genome and thereby understand how genetic alterations cause cancer. These studies allowed understanding of some of the unique sensitivities to therapeutics that are unmasked by alterations in p53, a tumor suppressor gene that is inactivated in half of all cancers. The team exploited genetic tools to alter p53 and the complex signaling pathways that function upstream and in parallel with p53. The team explored how the ATR-Chk1 signaling pathway functions during unperturbed cell growth and after a cell is exposed to therapy that causes DNA damage or DNA replication stress. By systematically comparing cells with normal and experimentally mutated genes, the team devised strategies that employ existing anticancer therapeutics.

FAMRI SUPPORTED RESEARCH

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FUNCTIONAL ANALYSIS OF THE MMSET ONCOGENE IN TRANSLOCATION 4;14 MULTIPLE MYELOMA

Josh Lauring, MD, PhD; Johns Hopkins Medical Institutions; YCSA 2007

Dr. Lauring and colleagues investigated the function of the multiple myeloma (MM) SET domain (MMSET)-containing protein in translocation (4;14) in MM, a tobacco smoke-related blood cell cancer. The chromosomal translocation t(4;14) juxtaposes the immunoglobulin heavy chain enhancer sequences with MMSET and fibroblast growth

factor receptor 3 (FGFR3) genes. This translocation defines approximately 20% of MM cases and confers the worst prognosis of all MM subtypes. The aberrant overexpression of FGFR3 is found in approximately 70% of the cases, but the remainder do not over express FGFR3, suggesting that dysregulation of the MMSET locus is the primary and unifying oncogenic event in all t(4;14) MM cases. The team demonstrated that translocation-mediated overexpression of MMSET is critical for the growth, adhesion, and tumorigenicity of MM cells. A number of adhesion proteins and growth factors are downregulated with loss of MMSET expression, which could represent MMSET target genes responsible for the pathogenesis or poor prognosis. The team also demonstrated that oncogenic dysregulation of MMSET leads to global transcriptional changes by modifying the histone code. The investigators focused on the recurrent, poor-prognosis 8p11–12 amplicon in breast, lung, and pancreatic cancers to identify driver genes that confer aggressive tumor behavior, such as Wolf-Hirschhorn syndrome candidate 1-like gene 1, a MMSET homolog located within the 8p11–12 amplicon, and over-expressed in amplified tumors. The team also investigated the histone methyltransferase activity of MMSET, which is essential for stimulating myeloma cell growth.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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SENSITIVITY OF TOBACCO-INDUCED CANCER TO HERPES VIRAL ONCOLYSIS/SELECTIVE HERPES VIRAL TARGETING OF TOBACCO-RELATED CANCERS

Richard J. Wong, MD; Memorial Sloan-Kettering Cancer Center; CIA 2007

Replication-competent oncolytic herpes viruses have a remarkable ability to selectively infect tobacco-induced cancers while preserving adjacent normal tissues, which may be due to the differential expression of herpes viral receptors on cancer cells. Dr. Wong's goal was to determine if the herpes viral receptor status of squamous cell carcinoma is useful as a determinant of sensitivity to oncolytic herpes simplex virus therapy. This was based on the hypotheses that: 1) cancers of the lung and head and neck caused by tobacco smoke

exposure have elevated expression of herpes viral receptors compared to normal tissues allowing for increased susceptibility to herpes viral infection and lysis; and 2) an assessment of herpes viral receptor expression in each malignancy allows prediction of tumor response to herpes oncolytic viral therapy.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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USURPING SIGNALING CHARACTERISTICS OF BREAST, CERVICAL AND PROSTATE CANCER TO TARGET THEM WITH A "SIGNAL-SMART" VIRUS

Faris Farassati, PhD, PharmD; University of Minnesota, University of Kansas Medical Center; YCSA 2006

Dr. Farassati and colleagues generated an oncolytic herpes virus to target cancer cells with increased activation of the Ras signaling pathway (Signal-Smart 1 or SS1 virus). The research team showed that SS1 was capable of specifically targeting cells with an overactivated Ras/ERK/ ELK pathway. They also showed that certain transcription factors downstream of Ras pathway (i.e., phospho-ELK) can be used as molecular indicators for targeting tumors with oncolytic herpes. The team obtained results from targeting the SC mouse model for cancer with SS1 that demonstrates significant induction of tumors. The

investigators studied the role of the immune system in boosting the oncolytic effects of SS1 *in vivo*.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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SOMATIC CELL KNOCK-IN OF A MUTANT K-RAS GENE FOR UNDERSTANDING AND TARGETING RAS-INDUCED CANCERS RELATED TO SECONDHAND TOBACCO SMOKE

Hiroyuki Konishi, MD, PhD, Ben-Ho Park, MD, PhD; Johns Hopkins Medical Institutions; CIA 2006

The analysis of Dr. Park's K-ras gene-targeted cell models revealed that the mutation of a single K-ras allele does not confer remarkable oncogenic properties that have been seen in conventional cell models with the ectopic overexpression of mutant K-ras. In addition, the heterozygous K-ras mutation was only found in a half of cancer cell lines harboring mutant K-ras analyzed in this study; and the remaining half demonstrated K-ras homozygous mutation, copy number gain, or amplification accompanied by its deregulated expression. These data suggest that a sole K-ras mutation does not provide sufficient oncogenic properties to accomplish full cellular transformation, and other oncogenic events in addition to K-ras mutation are required for cancer development. The gain, amplification, and overexpression of mutant K-ras itself are likely to serve as cooperative oncogenic

events supplementing K-ras mutation as demonstrated in this study. The examination of K-ras downstream activity in K-ras gene-targeted cell clones as well as various cancer cell lines further suggested that multiple oncogenic signals cooperate with K-ras pathway to activate oncogenic effector molecules and thereby achieve cellular transformation.

FAMRI SUPPORTED RESEARCH

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TARGETING THE TROP-2 RECEPTOR PATHWAY IN CANCER

Loren Michel, MD; Washington University; YCSA 2006

Dr. Michel and colleagues identified an essential role for Trop-2 in tumor formation and invasion. Tumor cells in which Trop-2 production is blocked by RNA interference are no longer able to grow as tumors, suggesting that targeting Trop-2 can be effective in treating cancer. The investigators found that Trop-2 is expressed in approximately one-third of primary breast tumors. No direct correlation between Trop-2 and prognosis has been found; however, when breast cancer cells based on high versus low levels of Trop-2 expression are purified, only cells expressing high levels are tumorigenic and invasive. This suggests that the more aggressive fraction of tumor cells is that which expresses high levels of Trop-2. Consistent with these observations, it has been reported that poly-clonal antibodies against Trop-2 can block tumor cell invasion. There is a monoclonal antibody against Trop-2 that has antitumor properties. When human tumor cell xenografts growing in mice are treated with this antibody, tumors either decrease or fail to increase in size.

FAMRI SUPPORTED RESEARCH

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THE ROLE OF CDK5 IN CANCER AND METASTASIS

Barry Nelkin, PhD; Johns Hopkins Medical Institutions; CIA 2006

Dr. Nelkin showed that CDK5 kinase is active in SCLC and in several other types of cancer. Inhibition of CDK5 activity results in invasion, and a 79% decline in spontaneous metastasis. This suggests that inhibition of CDK5 could be therapeutically beneficial in limiting metastasis in cancers associated with tobacco smoke exposure. Dr. Nelkin examined the steps of metastasis affected by CDK5 activity in a xenograft model *in vivo* using intravital imaging and experimental metastasis. Dr. Nelkin and his team explored whether CDK5 act as inducing factors for HGF/SF and CXCL12/SDF-1, which promote metastasis. They hypothesized that inhibition of CDK5 can sensitize cancer cells to chemotherapeutic agents by altering normal cytoskeletal function. They also hypothesized that NNK, a component of cigarette smoke shown to activate cell motility and invasion, acts through a CDK5-dependent pathway. They investigated the molecular pathway by which NNK promotes metastasis, examined whether inhibition of CDK5 can block NNK-induced SCLC cell migration and invasion, and determined whether NNK treatment results increased CDK5 activity in SCLC cells. CDK5 was defined as a potential therapeutic target in cancer, and cigarette smoke exposure was implicated in the activation of CDK5. The work started with this study went on to Phase I clinical development: Dinaciclib and Akt Inhibitor MK2206 in treating patients with pancreatic cancer that cannot be removed by surgery (NCT01783171).

FAMRI SUPPORTED RESEARCH

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THE ROLE OF LYSINE HISTONE METHYLTRANSFERASE SET 7/9 IN BREAST CANCER

Nickolai A. Barlev, PhD; Tufts-New England Medical Center Hospitals; CIA 2005

Dr. Barlev and collaborators discovered a mechanism by which p53 is upregulated in response to DNA damage through lysine methylation. They investigated the molecular mechanisms of p53 activation by lysine methylation in response to SHS exposure using a mammary cell model system. In addition, they found that lysine methylation is not only required for activation of p53, but is also necessary for global DNA repair.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Ivanov GS, Ivanova T, Kurash J, Ivanov A, Chuikov S, Gizatullin F, Herrera-Medina EM, Rauscher F, 3rd, Reinberg D, Barlev NA. Methylation-acetylation interplay activates p53 in response to DNA damage. *Mol Cell Biol.* 2007;27(19):6756-6769.

Morgunkova A, Barlev NA. Lysine methylation goes global. *Cell Cycle.* 2006;5(12):1308-1312.

THE IMPACT OF SWI/SNF COMPLEX IN CANCER

David N. Reisman, MD, PhD; University of Michigan; CIA 2005

Dr. Reisman's hypothesis was that loss of the activity of the chromatin remodeling complex SWI/ SNF is a pivotal event in development of smoking-related cancers. The loss abrogates key cellular growth controls such as the functions of tumor suppressor proteins Rb and p53 and it negatively influences important signaling pathways that are targets for clinical intervention. He determined the epigenetic mechanism underlying biological response modifier (BRM) suppression and identified novel drugs that can restore BRM expression. He also investigated the mechanism of brahma-related gene 1 (BRG1) loss, defined how loss of BRM affects cancer development, and determined how loss of BRG1 can be used as a biomarker to guide clinical decision making.

FAMRI SUPPORTED RESEARCH

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Brena RM, Morrison C, Liyanarachchi S, Jarjoura D, Davuluri RV, Otterson GA, Reisman D, Glaros S, Rush LJ, Plass C. Aberrant DNA methylation of OLIG1, a novel prognostic factor in non-small cell lung cancer. *PLoS Med.* 2007;4(3):e108.

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BASE EXCISION REPAIR IN SHS CAUSED DNA DELETIONS AND CANCER

Robert Schiestl, PhD; University of California, Los Angeles; CIA 2005

It has been difficult to produce lung tumors in experimental animals with side stream or even mainstream cigarette smoke. Dr. Schiestl hypothesized that such difficulty may be due to the extreme variation of humans in genetic cancer-predisposing factors and that only people with polymorphisms in oxidative DNA damage repair genes have the highest risk for smoking-induced cancer. Dr. Schiestl showed that sidestream cigarette smoke causes an elevated frequency of DNA deletions *in vivo* in mice. He and his colleagues have shown that such deletion events are increased by environmental and genetic cancer-predisposing factors. Besides mechanistic insight into the genetic control of sidestream smoke-induced lung cancer, this study provided an animal model for smoke-induced cancer, which could be used for further studies on mechanisms and intervention. It may also provide justification for determining whether people exposed to SHS that develop cancer are more likely to have mutations in genes important in DNA repair.

SENSITIVITY OF TOBACCO-INDUCED CANCER TO HERPES VIRAL ONCOLYSIS

Richard J. Wong, MD; Memorial Sloan-Kettering Cancer Center; CIA 2004

Please see the synopsis of Dr. Wong's 2007 award.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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Yu Z, Li S, Brader P, Chen N, Yu YA, Zhang Q, Szalay AA, Fong Y, Wong RJ. Oncolytic vaccinia therapy of squamous cell carcinoma. *Mol Cancer.* 2009;8:45.

ROLES OF THE CHECKPOINT KINASES IN THE RESPONSES OF HUMAN CANCER CELLS TO DNA DAMAGE

Fred Bunz, MD, PhD; Johns Hopkins Medical Institutions; YCSA 2003

The majority of people with cancers caused by smoking or SHS exposure are treated with radiation therapy, used alone or in combination with chemotherapy or surgery. Dr. Bunz tested molecular targets that may increase the sensitivity of cancer cells to ionizing radiation and DNA damaging drugs. One promising molecular target is the ATR kinase. This DNA-damage induced enzyme is involved in the basic response of cells to radiation and other forms of anticancer therapy. The investigators showed that the genetic inhibition of ATR kinase activity causes cancer cells to become highly sensitive to widely used therapeutic agents. The team determined the sensitivity of DNA damage signaling-deficient xenograft tumors to the effects of ionizing radiation and identified small molecules that specifically inhibit ATR kinase activity. They identified a drug, BAY11-7082, that inhibits NF- kappa B signaling as an inhibitor of ATR. This potently inhibits ATR-dependent phosphorylation of Chk1 and can recapitulate some of the phenotypic effects of ATR-deficiency. Further, the group showed that NF-kappa B pathways are aberrantly regulated in ATR-deficient cancer cells.

FAMRI SUPPORTED RESEARCH

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INHIBITORS OF HISTONE ACETYLTRANSFERASE (HAT) AS NOVEL THERAPIES FOR HPV-ASSOCIATED MALIGNANCIES

Rhoda M. Alani, MD; Johns Hopkins Medical institutions; YCSA 2002

Dr. Alani determined the role of histone acetyltransferase (HAT) in the development of human papillomavirus (HPV)-associated malignancies such as cervical and head and neck cancers and developed HAT inhibitors (HATIs) as HPV-related tumor therapies. Dr. Alani worked on developing a series of HAT inhibitors that could inhibit oncogenic HPV activation with minimal toxicity. She also worked on determining the effects of HATIs on cell cycle progression and viability in HPV-positive and HPV-negative cell lines and identifying HPV-specific cell inhibitors. The precise mechanism of action of HPV-specific HATIs and their ability to affect cell cycle regulatory proteins was also investigated. Access to pure HATI compounds was facilitated by the chemistry therapy core of the Johns Hopkins Medical Institutions FAMRI Center of Excellence.

FAMRI SUPPORTED RESEARCH

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EARLY DETECTION OF CANCER BY HYPERMETHYLATION

Paul Cairns, PhD; Fox Chase Cancer Center at Drexel University; YCSA 2002

Dr. Cairns screened matched tumor and sediment DNA from urine specimens taken from kidney cancer patients for the hypermethylation status of six normally unmethylated tumor suppressor genes. Results revealed hypermethylation of at least one gene. There was a difference in suppressor gene hypermethylation patterns between clear cell and non-clear cell tumors, suggesting that this panel of suppressor genes may be useful in differential kidney cell cancer diagnosis. This study provided a path to an early noninvasive urine diagnostic test for renal cancer. Hypermethylation of at least one out of three suppressor genes was found in a number of bladder cancers. Additionally, gene hypermethylation was detected in urine DNA of patients, including some with negative cytology. Dr. Cairns concluded that methylation-specific PCR may enhance early detection of bladder cancer via a noninvasive urine test. Dr. Cairns found promoter methylation in tumor suppressor and cancer genes in 93 out of 100 kidney cancer tumors of various pathologic types. No hypermethylation was noted in 15 samples from normal kidney or ureteral tissue. Hypermethylation of the tumor suppressor gene VHL was found to be specific for clear cell tumors. Promoter hypermethylation probably plays an important part in kidney tumor genesis and the hypermethylation profile may provide molecular markers for diagnostic and prognostic approaches to renal cancer.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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MRN-TARGETED CHEMOSENSITIZATION FOR ORAL CANCER

Daqing Li, MD; University of Maryland, University of Pennsylvania; YCSA 2002

Dr. Li and colleagues hypothesized that targeted impairment of function of the native cellular repair machinery MRN complex, which is involved in DNA replication, DNA repair, and signaling to the cell cycle checkpoints, could sensitize tumor cells to cisplatin. They designed a dominant negative vector containing a mutant Rad50 gene that significantly downregulates MRN expression and disrupts MRN function. Combination cisplatin and mutant Rad50 therapy produced significant tumor cytotoxicity *in vitro* with a corresponding increase in DNA damage and telomere shortening. In cisplatin-resistant human squamous cell cancer xenografts, combination therapy caused dramatic tumor regression with increased apoptosis. These findings support the use of targeted Rad50 disruption as a novel chemosensitizing approach for cancer therapy in the context of chemoresistance. This strategy has the potential to be applicable to several types of chemoresistant malignant tumors.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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MODULATION OF TUMOR RESPONSE TO RETINOIDS

Roberto Pili, MD; Johns Hopkins University Medical Institutions; CIA 2002

Dr. Pili hypothesized that: 1) retinoid resistance in tumors is associated with epigenetic loss of expression of retinoic acid receptor beta (RAR-beta 2); 2) retinoid resistant tumors with epigenetic changes at RAR-beta 2 may benefit from a combined therapy with RAR-beta 2 agonists and chromatin remodeling drugs; and 3) loss of RAR-beta 2 expression due to epigenetic changes is a general phenomenon occurring in epithelial precancerous lesions. He demonstrated that the histone deacetylase inhibitor (HDACI) MS-275 appears to revert resistance due to epigenetic silencing of RAR-beta 2 in human epithelial cell carcinoma cells and has greater antitumor efficacy in combination with 13-cis retinoic acid. The combination of HDACIs and retinoids may provide a therapeutic approach in patients with epithelial cell cancer.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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CANCER: TREATMENT

Completed Research

TARGETING CANCER STEM CELLS BY ONCOLYTIC VIRUSES: TOWARDS HUMAN TRIALS

Faris Farassati, PhD; PharmD; Kansas City VA Medical Center Foundation; CIA 2016

Oncolytic viruses are a novel family of anti-cancer agents. Signal-Smart 2 and Signal-Smart 3 (SS2 and SS3) oncolytic viruses are genetically modified versions of Herpes Simplex Virus-1 transcriptionally targeted against cancer stem cells. These agents are programmed to infect and destroy a fraction of tumor cells that act as the stem cell backbone of a tumor, hence they are called cancer stem cells (CSCs). According to the CSC model for tumor development, a fraction of cells within each tumor play the role of stem cells and give rise to all other kinds of cells needed to maintain tumor integrity. An effective therapy must be able to destroy CSCs. There are no pharmacological agents currently available for specific targeting of CSCs. And the lack of such a feature in current chemotherapy agents leads to eventual tumor relapse. The SS2 and SS3 viruses are designed to attack CSCs and therefore they do not need to infect each and every tumor cell. In this study the investigators will review toxicology and biodistribution studies as the last pre-clinical steps needed before applying for Phase I human trials. They will also explore the use of nano technology to advance the specificity and pharmacokinetics of these viruses.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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MODULATION OF STEREOTACTIC BODY RADIATION THERAPY TO IMPROVE THERAPEUTIC RATIO

Debabrata Saha, PhD; University of Texas Southwestern; CIA 2008

Dr. Saha and colleagues focused on the development of a tumor model in rodent lung that demonstrates successful targeting of lung tumors using image-guided stereotactic body radiation therapy (SBRT). To validate the image guided delivery of SBRT dose to the lung tumor, the investigators used a method of detecting anionic phospholipids such as phosphatidylserine (PS), that are externalized on tumor endothelial cells in response to radiation. The exposed PS in the tumor was detected by the monoclonal antibody-bavituximab that binds to PS. This model will enable the designing and testing of new strategies for treating non-small cell lung cancer patients.

FAMRI SUPPORTED RESEARCH

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LUNG CANCER IMMUNOTHERAPY

Luis Raez, MD; University of Miami Miller School of Medicine; CIA 2006

Dr. Ruiz and collaborators had previously conducted a phase I trial for advanced (stage IIIB/IV) non-small cell lung cancer (NSCLC) patients using a vaccine of allogeneic NSCLC tumor cells (AD100) transfected with B7.1 (CD80) and HLA Al or A2 (B7). They saw strong, tumor-specific CD8 CTL responses as measured by IFN-gamma ELI-spots. Median survival

of metastatic disease patients increased from an expected 8 months to >18 months. The investigators proposed to conduct a randomized phase II immunotherapy vaccination (AD100-B7.1-HLA A1) study of 60 patients with stages IIIB/IV NSCLC that had responded to first-line chemotherapy with stable disease, partial response, or complete response. (Under 2007 treatment guidelines, such patients would not be treated further until their disease progressed). The other aim of the study was to conduct correlative studies of the immune response to B7-vaccination as compared to that in randomized controls to elucidate the immunological parameters that must accompany a CD8 response to allow prediction of increased time to progression of disease.

TUMOR VACCINE AFTER NONMYELOABLATIVE ALLOGENEIC STEM CELL TRANSPLANTATION FOR KIDNEY CANCER

Ephraim J. Fuchs, MD; Johns Hopkins Medical Institutions; CIA 2003

Dr. Fuchs and collaborators found that significant anti-tumor responses can be obtained by the infusion of allogenic T cells following the administration of high dose cyclophosphamide, with or without tumor cell vaccine. It seemed reasonable that a transient graft-versus-host reaction mediated by donor CD4+ T cells would be sufficient to unmask functional anti-tumor immunity among host T cells. This research involved a trial of cyclophosphamide administration followed by the infusion of purified CD4+ T cells from a partially human leukocyte antigen (HLA) mismatched donor to treat locally advanced or metastatic kidney cancer to determine the maximally tolerated dose of semi-unified CD4+ T cells administered one day after cyclophosphamide treatment.

DEVELOPMENT OF NOVEL HUMAN IMMUNOLOGY ASSAYS FOR HPV VACCINE TRIALS

Chien-Fu Hung, PhD; Johns Hopkins Medical Institutions; YCSA 2003

Dr. Hung hypothesized that human patients receiving an increased number of human papilloma-virus (HPV) DNA vaccinations will exhibit greater HPV-specific CD8+T cell activity and a rapid expansion of HPV-specific CD8+T cells, which may lead to a strong therapeutic effect against cervical cancer. Dr. Hung also hypothesized that patients with different immunological genetics may generate different HPV-specific CD8+ T cell immune responses after DNA vaccination. Using blood samples taken at three different stages from patients receiving the HPV DNA vaccine regimen as part of an ongoing clinical trial, Dr. Hung characterized the quantitative and qualitative differences among the T cells from patients with different immunological genetics.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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Peng S, Trimble C, Wu L, Pardoll D, Roden R, Hung CF, Wu TC. HLA-DQB1*02-restricted HPV-16 E7 peptide-specific CD4+ T-cell immune responses correlate with regression of HPV-16-associated high-grade squamous intraepithelial lesions. *Clin Cancer Res.* 2007;13(8):2479-2487.

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APOPTOSIS OF EFFECTOR T CELLS IN CANCER: IMPLICATIONS FOR IMMUNE THERAPY

Robert L. Ferris, MD, PhD; University of Pittsburgh; YCSA 2003

Based on evidence that HNSCC has been shown to interfere with T cell survival and function, Dr. Ferris hypothesized that tumor antigen-specific T cells are preferentially targeted for early apoptosis, leading to host tolerance to the tumor. This investigation included a mechanistic study of the dynamic basis for T cell depletion in patients with HNSCC, its *in vivo* kinetics, and therapeutic strategies for preventing early death of circulating immune cells in a prospective series of patients. The results suggest abnormally high T-lymphocyte apoptosis in cancer. The investigators initiated a Phase 1 clinical trial where they directly labeled T cells from HNSCC patients with deuterated water to compare cell life to the T cell lifespan in healthy controls. Biomarker analyses from accrued patients and healthy controls were conducted.

FAMRI SUPPORTED RESEARCH

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COX-2 REGULATION IN RESPONSE TO COMBINED THERAPY

Debabrata Saha, PhD; University of Texas Southwestern; YCSA 2003

Dr. Saha demonstrated that cyclin dependent kinase (CDK) inhibitor prevents the induction of cyclooxygenase-2 (COX-2) expression under stress conditions such as inflammatory response and ionizing radiation. Ionizing radiation enhances inflammatory response to lung cancer cells via the induction of cytokine release, and CDK-inhibitor blocks IL-1beta-induced expression and steady-state mRNA levels of COX-2. CDK2 inhibition blocks IL-1beta-induced binding to the NF-IL6 element of the COX-2 promoter and inhibits transcription of the COX-2 gene. Dr. Saha and colleagues reported that a CDK inhibitor, SNS-032, sensitized radioresistant tumor cells to ionizing radiation. They demonstrated a modulation of DNA double-strand break repair due partially to the radio-sensitization effects of SNS-032. Inhibition of COX-2 has been shown to increase radiosensitivity, thus the investigators used a syngeneic model of Chinese hamster ovarian cell lines to demonstrate a DNA-PKcs-dependent differential modulation of cellular radiosensitivity by celecoxib, a specific COX-2 inhibitor. These effects can be attributed to alterations in signaling cascades downstream of DNA-PK toward cell survival. The team investigated the role of phosphorylation and posttranslational modification of the key signaling molecules that regulate COX-2 expression in response to chemoradiation and CDK inhibitors using proteomics and mass spectrometry.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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CARDIOVASCULAR AND VASCULAR

Ongoing Research

OCCULT CARDIOVASCULAR DISEASE WITH CHRONIC EXPOSURE TO SECONDHAND TOBACCO SMOKE

Mehrdad Arjomandi, MD; San Francisco General Hospital Foundation & University of California San Francisco; 2020

Dr. Arjomandi and his team will examine whether prolonged exposure to SHS causes occult cardiovascular disease with sequela of reduced cardiovascular reserve and predisposition to adverse health outcomes. The main hypothesis is that prolonged exposure to SHS, even when remote, is associated with subclinical cardiovascular disease as determined by abnormal cardiac structure and function, abnormal vascular structure and function, and abnormal circulatory inflammatory mediators, which generate vascular ageing and hypertensive response to exertion. The investigators further hypothesize that management of the hypertensive response to exercise using an angiotensin-converting enzyme receptor blocker can reduce the response and improves exercise capacity. This has the potential to improve long-term health outcomes.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Arjomandi M, Zeng S, Barjaktarevic I, Barr RG, Bleecker ER, Bowler RP, Buhr RG, Criner GJ, Comellas AP, Cooper CB, Couper DJ, Curtis JL, Dransfield MT, Han MK, Hansel NN, Hoffman EA, Kaner RJ, Kanner RE, Krishnan JA, Paine R, 3rd, Peters SP, Rennard SI, Woodruff PG, Investigators S. Radiographic lung volumes predict progression to COPD in smokers with preserved spirometry in SPIROMICS. *Eur Respir J*. 2019;54(4).

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Zeng S, Arjomandi M, Tong Y, Liao ZC, Luo G. Developing a Machine Learning Model to Predict Severe Chronic Obstructive Pulmonary Disease Exacerbations: Retrospective Cohort Study. *J Med Internet Res.* 2022;24(1):e28953.

PRESENTATIONS AND ABSTRACTS

Arjomandi M , Stock E, Nishihama M, Weldemichael L, Zeng S, Hunt C, Ching W, Rohdin-Bibby L, Ma S, Liu X, Redberg R, Turino GM. Elastin degradation markers are elevated in never-smokers with past history of prolonged exposure to secondhand tobacco smoke and are inversely associated with their lung function [abstract]. *Am J Resp Crit Care Med* 2020;201:A6138.

Completed Research

SHS EXACERBATES CEREBROVASCULAR SIGNAL TRANSDUCTION AND INFARCT SIZE

Lars Edvinsson, MD, PhD; Lund University; CIA 2013

Vascular plasticity plays an important role in the pathophysiology of ischemic cerebrovascular diseases. Dr. Edvinsson and his colleagues investigated the mechanisms behind alterations of vasoconstrictor receptors and proinflammatory mediators after exposure to SHS. They have demonstrated that expression of the contractile endothelin- and serotonin-receptors are upregulated in cerebral arteries as a response to SHS exposure *in vivo*. The upregulation is mediated by the Raf/ MEK/ERK1/2 pathway. Much research has been focused on counteracting endothelin receptor activation by antagonists and inhibiting transcription signaling and mapping of the time frame for optimal prevention of organ damage after ischemia. The team investigated the involvement of calcium-calmodulin-dependent protein kinase II and extracellular signal-regulated kinase1/2 (ERK1/2) on inflammatory mediators and found crosstalk, which suggests a role in cerebrovascular inflammation. The role of transcription factor Sp1 in vasodilatation has been investigated as well as the involvement of transcription factor STAT3 in local inflammation in late cerebral ischemia. The data have made it clear that SHS exposure strongly exacerbates the expression of the contractile receptors in vascular smooth muscle cells in coronary arteries as well as cerebral arteries. The use of the MEK/ERK1/2 inhibitor was shown to be successful in reducing vascular damage and improving the outcome of ischemic disease days and weeks after different types of stroke. A human clinical trial with this inhibitor is planned.

FAMRI SUPPORTED RESEARCH

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SHS AND ATHEROSCLEROSIS

Anna Kurdowska, PhD; University of Texas Health Science Center at Tyler; CIA 2012

Dr. Kurdowska and colleagues have demonstrated that both endothelial cell (EC) apoptosis and levels of metalloproteinase-9 (MMP-9) are increased in the aortic tissue from mice exposed to SHS relative to non-exposed animals. Additionally, *in vitro* experiments have demonstrated that MMP-9 has a direct effect on EC activation and apoptosis. The team has shown that long term treatments with either MMP-9-directed siRNA (to minimize cell specific MMP-9 expression in neutrophils and ECs), or a small molecule inhibitor that indirectly limits MMP-9 production leads to the reduction of atherosclerotic changes and

the improvement of overall vascular health. The animal model of atherosclerosis used for these studies may also serve as a model for COPD, and the team has noted that specific indicators of pulmonary inflammation, airway remodeling, and reduced lung elasticity are decreased in treated animals. The team found that plasma levels of urokinase and alpha-2-macroglobulin, an effective MMP-9 inhibitor, are decreased in SHS exposed animals relative to controls.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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TREATMENTS OF EXPOSURE TO SECONDHAND SMOKE

Lars Edvinsson, MD, PhD; Lund University; CIA 2011

Dr. Edvinsson and colleagues used a large patient cohort in Denmark to investigate a population-based multi-factorial life-style intervention of 5 years duration to show the sustained benefits of smoking abstinence. The group, run by Dr. Pisinger, was also involved in amassing a large consortium to examine major causes of death among middle-aged adults and to examine the benefits of smoking cessation among older adults. This comprehensive study showed that cigarette smoking is a strong risk factor for premature mortality and cessation can be beneficial, even at advanced ages; therefore, programs to support smoking cessation should be a public health priority. The investigators also examined the difference in receptor expression and function in the lungs of smokers vs. non-smokers. in addition, they examined the effects of knocking out a gene that is related to surfactant protein D (SP-D) in mice. SPD is important in particle clearance in the lung; when it is knocked out in mice, the mice develop emphysema. Changes in contractility were investigated in these knock out mice compared to normal mice. The speculation from these studies is that emphysema induces the observed vascular changes. Inhibition of disease progression contractile receptors can reduce tissue damage, pointing a way toward treating SHS-induced disease.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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CARDIOVASCULAR EFFECTS OF SECONDHAND TOBACCO SMOKE (SHS) IN CONSTRUCTION WORKERS

Jennifer Cavallari, ScD, CIH; Harvard School of Public Health, University of Connecticut Health Center; YCSA 2009

Dr. Cavallari and colleagues examined the acute cardiovascular effects of SHS and workplace exposures among non-smoking, union, boilermaker construction workers. This study helped to elucidate the mechanisms and time course of cardiovascular and autonomic response to SHS exposures. Cardiovascular autonomic and inflammation responses may contribute to the pathophysiological pathways that link SHS exposure with adverse cardiovascular outcomes. Short term SHS exposure may be associated with significantly lower heart rate variability (HRV) and higher levels of inflammatory markers. Exposure-associated declines in HRV were observed immediately following exposure, but higher levels of an inflammatory marker, c-reactive protein (CRP) were not observed until 18 hours following exposure. The team also observed negative associations between short

(15 minutes) and longer (240 minutes) term PM2.5 and HRV that indicate adverse effects of SHS exposure on the cardiovascular system.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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ENGINEERED CARDIAC PATCH WITH CARDIAC PROGENITORS

Nicolas Christoforou, PhD; Duke University; YCSA 2009

Dr. Christoforou and colleagues investigated whether, following a heart attack, the replacement of the damaged tissue with functional tissue and the long-term prevention of heart failure requires delivery of a cell source capable of forming cells of the heart within a 3-dimensional matrix that enables long-term retention, survival, and function. They examined the cell fate of human embryonic stem cell - and induced pluripotent stem cell-derived cardiac progenitor cells in an engineered electromechanically functional biosynthetic tissue with respect to cardiomyogenesis, vascularization, electrocoupling, electrical propagation, and active force generation. Both *ex vivo* and *in vitro* biosynthetic tissues were assembled. The team tested if this will guide the growth and differentiation of the cardiac progenitors into a functional vascularized cardiac tissue, and they determined if it is feasible to use the assembled cardiac tissue patch to determine cardiac progenitor cell fate.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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Chen J, Lee EJ, Jing L, Christoforou N, Leong KW, Setton LA Differentiation potential of human induced pluripotent stem cells (iPSCs) to nucleus pulposus-like cells *in vitro*. *Global Spine J* 2012;02-S4.18.

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ROLE OF HEAT SHOCK PROTEIN 90 IN TOBACCO SMOKE-INDUCED HEART DISEASE

Kathleen L. Gabrielson, DVM, PhD; Johns Hopkins Medical Institutions; CIA 2008

Dr. Gabrielson showed that 3-month exposures to tobacco smoke in mice resulted in more pathological changes than 5-month exposures, suggesting a non-linear nature of activation and/or depression of molecular mechanisms. For instance, a decrease in expression of endothelial nitric oxide synthase (eNOS) was observed in post-myocardial infarction (MI) hearts of mice exposed to tobacco smoke for 3 months compared to their age-matched controls. In the hearts of mice exposed to tobacco smoke for 5 months, eNOS levels were close to those of control mice. Remaining fractional shortening was lower in mice exposed for 3 months, but not 5 months, compared to control mice. It has been shown before that after MI, newly formed myofibroblasts express vascular endothelial growth factor (VEGF) and VEGF receptor 2 (VEGFR2). These increases play a significant role in tissue repair and remodeling. The data show that there is an increase in expression of VEGFR2 in the left ventricle adjacent to infarction and in the septum after MI induction in control mice. In 3- and 5-month exposed mice, VEGFR2 expression remains at the level of expression in the hearts of mice that did not undergo MI. These findings suggest that tobacco smoke exposure either directly or indirectly affects the protective activation of the eNOS and the VEGF pathways. This could lead to more extensive damage and less effective healing of the post-infarction wound, which may result in a significant post-MI decline of cardiac function and a worse long-term outcome.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Sussan TE, Rangasamy T, Blake DJ, Malhotra D, El-Haddad H, Bedja D, Yates MS, Kombairaju P, Yamamoto M, Liby KT, Sporn MB, Gabrielson KL, Champion HC, Tuder RM, Kensler TW, Biswal S. Targeting Nrf2 with the triterpenoid CDDO-imidazolide attenuates cigarette smoke-induced emphysema and cardiac dysfunction in mice. *Proc Natl Acad Sci U S A.* 2009;106(1):250-255.

EFFECTS OF SECONDHAND CIGARETTE SMOKE (SHS) EXPOSURE ON ADIPONECTIN, mTOR, AND VASCULAR DISEASE

Kathleen A. Martin, PhD; Geisel School of Medicine at Dartmouth, Yale University; CIA 2008

Dr. Martin and colleagues studied the links among SHS exposure, cardiovascular disease, and dysregulation of adiponectin, a cardioprotective hormone implicated in diabetes. Their data indicated that SHS exposure inhibits synthesis of adiponectin in mice. They further showed that SHS exposure induces vascular smooth muscle cells (VSMC) to dedifferentiate from a quiescent, contractile phenotype, to a dedifferentiated phenotype known to contribute to the pathogenesis of vascular disease. The team showed that the mammalian target of rapamycin (mTOR) cellular signaling pathway suppresses VSMC differentiation. Their experiments revealed elevated mTOR activity in VSMC in mice exposed to SHS. Notably, adiponectin directs signals through activated protein kinase, which can suppress mTOR activity. The team hypothesized that cigarette smoke exposure contributes to vascular disease in part by promoting VSMC dedifferentiation, and that this dedifferentiation is due to SHS inhibition of adiponectin expression, resulting in elevated mTOR activity.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Ding M, Carrao AC, Wagner RJ, Xie Y, Jin Y, Rzucidlo EM, Yu J, Li W, Tellides G, Hwa J, Aprahamian TR, Martin KA. Vascular smooth muscle cell-derived adiponectin: a paracrine regulator of contractile phenotype. *J Mol Cell Cardiol.* 2012;52(2):474-484.

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PRESENTATIONS AND ABSTRACTS

Davey JC, Wagner RJ, Jin Y, Rzucidlo EM, Hwa J, Rodeheffer M, Crane-Godreau M, Martin KA. Secondhand cigarette smoke-exposure dysregulates white and brown adipose tissue in young healthy female mice [abstract]. Cleveland Clinic Obesity Summit Meeting. Cleveland, OH, Oct 4-5, 2012.

LONG-TERM VASCULAR EFFECTS OF SECONDHAND TOBACCO SMOKE

Matthew L. Springer, PhD; University of California, San Francisco; CIA 2008

Dr. Springer and colleagues developed a way to monitor the changes in the ability of rat blood vessels to react to increased blood flow by flow-mediated dilation (FMD). They used this to study the effects of different levels and times of SHS exposure on the decrease in vascular function and on the length of time that the vessels need to recover their full function. Exposure of rats to SHS at levels comparable to those found in bars that allow smoking substantially impairs FMD, but the effect becomes less pronounced with progressively lower levels. However, impairment of FMD is observed after only one minute of exposure. These results were compared to changes in components of the serum that

influence the ability of endothelial cells to produce nitrous oxide. A firmer understanding of the deleterious effects of limited passive smoking provides supportive information for the crafting of health initiatives to protect the public from the hazards of SHS exposure, and contributes to the prevention of SHS-related diseases.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Pinnamaneni K, Sievers RE, Sharma R, Selchau AM, Gutierrez G, Nordsieck EJ, Su R, An S, Chen Q, Wang X, Derakhshandeh R, Aschbacher K, Heiss C, Glantz SA, Schick SF, Springer ML. Brief exposure to secondhand smoke reversibly impairs endothelial vasodilatory function. *Nicotine Tob Res.* 2014;16(5):584-590.

NICOTINE AND THE PATHOBIOLOGY OF ANEURYSM

Vincent Lemaitre, PhD; Columbia University; CIA 2007

Dr. Lemaitre found that interstitial collagenase-1 (MMP-1) is induced by cigarette smoke extract (CSE) in human aortic endothelial cells in culture and that the mTOR/p70S6K signaling pathway in aortic endothelial cells is inhibited. Gene array analysis of smoke-treated endothelial cells revealed a marked increase in diacylglycerol kinase gamma 90kDa expression. Dr. Lemaitre and colleagues analyzed the activation status of the mTOR/p70S6K pathway in endothelial cells treated with cigarette smoke and found that that CSE resulted in the loss of phosphorylated p70S6K at residue Thr 389, a specific target of the mTOR complex 1. The influence of cigarette smoke on the development of atherosclerosis was examined using the ApoE knockout mouse model, comparing the lesions of smoke-exposed animals to room air exposed controls. MMP-1 was induced in vascular cells. The consequences of an induction of MMP-1 in the vascular wall and in atherosclerotic lesions could include increased inflammation, decreased collagen content, aneurysm formation due to medial degradation, impaired angiogenesis, and initiation of vascular injury due to matrix disruption. *In vivo*, smoke exposure induced dramatic changes in atherosclerotic lesions of ApoE knockout mice with increased necrosis and decreased collagen, supporting the *in vitro* observation. These data demonstrate that smoke exposure decreases collagen deposition, probably through collagenase upregulation, and increases necrosis in the plaque.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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SMALL DIAMETER BLOOD VESSEL REGENERATION BY BIOMIMETIC ENGINEERING

Feng Zhao, PhD; Duke University; YCSA 2007

Dr. Zhao and colleagues developed an aligned human mesenchymal stem cells (hMSC) sheet on nanoimprinted poly(dimethylsiloxan) (PDMS) surface with the hypothesis that the aligned hMSCs will provide a mechanically strong and immunosuppressive and antithrombotic cell sheet for the construction of tissue-engineered blood vessels (TEBVs) in the regeneration of functional vascular tissues. The aligned hMSC sheet was fabricated on nanopatterned PDMS surfaces coated with thermally responsive hydroxybutyl chitosan (HBC) polymer. A well-aligned hMSC cell sheet, which showed no platelet adhesion property, was produced upon the dissolution of the HBC coating under 17^{o}C. hMSCs were expanded on the nanograted PDMS surfaces under physiologically relevant low oxygen tension to extensively stimulate extracellular matrix protein expression and vascular endothelial growth factor secretion. The team constructed a small diameter TEBV using the aligned hMSC sheets, and matured it in a rotating wall vessel bioreactor system. A preliminary animal study in an athymic rat femoral artery model resulted in remodeling of the vascular graft as well as the infiltration of endothelial cells into the hMSC-based TEBV.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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Zhu A, Zhao F, Ma T. Photo-initiated grafting of gelatin/N-maleic acyl-chitosan to enhance endothelial cell adhesion, proliferation and function on PLA surface. *Acta Biomater.* 2009;5(6):2033-2044.

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Zhao F, Leong KW. Cell sheet engineering of small-diameter blood vessel from aligned human mesenchymal stem cells. Presented at the Southern Biomedical Engineering Conference. Baltimore, MD, Apr 30 to May 2, 2010.

SECONDHAND TOBACCO SMOKE (SHS) AND CARDIOVASCULAR DYSFUNCTION IN CHILDREN

Judith Groner, MD; Children's Research Institute, Ohio State University; CIA 2006

Drs. Groner and Bauer investigated the effects of SHS exposure on inflammation, endothelial stress, endothelial repair defined as prevalence of endothelial progenitor cells (EPCs), and endothelial function in children of ages 2-5 years, (toddlers) and 9-14 years (youths). They investigated the relationship of SHS exposure on these endpoints in groups who already have one major risk factor for CVD in adulthood: obesity. Endothelial function was measured by venous occlusion plethysmography on the older age group and serum from both groups was analyzed for markers of inflammation. SHS exposure was determined by questionnaire and by hair sampling. The investigators observed that the most important independent determinants of child hair nicotine were the presence of maternal smoking and age (the toddler age group had higher hair nicotine). Presence of a smoking ban in the home was not an independent predictor of hair nicotine level. Both obese/high SHS-exposed toddlers and obese/high-SHS exposed youth had higher levels of inflammation markers when compared to other toddlers or youths, respectively. Obese subjects with higher SHS exposure had the highest levels of inflammation.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Groner JA, Huang H, Nicholson L, Kuck J, Boettner B, Bauer JA. Secondhand smoke exposure and hair nicotine in children: age-dependent differences. *Nicotine Tob Res.* 2012;14(9):1105-1109.

Groner JA, Joshi M, Bauer JA. Pediatric precursors of adult cardiovascular disease: noninvasive assessment of early vascular changes in children and adolescents. *Pediatrics.* 2006;118(4):1683-1691.

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Groner JA, Huang H, Nicholson L, Frock D, Schroeder C, Foley S, Bauer JA. Secondhand smoke exposure and endothelial progenitor cell prevalence in children. Platform presentation, Society for Research on Nicotine and Tobacco Annual Meeting. Feb 28, 2008, Portland OR.

Groner JA, Huang H, Nicholson L, Frock D, Schroeder C, Foley S, Bauer JA. Presented at the American Heart Association 48th Cardiovascular Epidemiology and prevention Conference. Colorado Springs, CO, Mar 14, 2008.

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Groner JA, Joshi M, Huang H, Bauer J. Cardiovascular effects of passive smoking in children and adults. In: Frank Columbus, ed. Passive Smoking and Health Research, Nova Publications, 2007.

EXACERBATION OF VIRAL MYOCARDITIS BY TOBACCO SMOKE AS A CAUSE OF HEART FAILURE

James P. Morgan, MD, PhD; Caritis St. Elizabeth's Medical Center; CIA 2006

Dr. Morgan and colleagues tested the hypothesis that exposure to tobacco smoke exacerbates the severity of viral myocarditis generated in 4-week old, male BALB/c mice by intraperitonial injection of encephalomyocarditis virus (EMCV). Four groups were studied: 1) control (C, no smoke and no virus); 2) smoke only (S, exposure to cigarette smoke for 90 minutes/day); 3) virus only (V); and 4) pre-exposure to smoke for 1 week before plus 2 weeks following virus injection (S+V). The investigators found that if viral inoculation was preceded by tobacco smoke exposure, mortality increased more than 2-fold compared with virus alone. In addition, the mRNA level of atrial natriuretic factor (ANF) was significantly higher in S+V than among any of the other three groups. Analysis of cardiac function by pressure-volume loop measurement showed virus significantly decreased cardiac function compared with that of controls and further deterioration was observed in the S+V group. Furthermore, the S+V group had a significantly decreased level of connexin 43 and increased virus loading. An increased rate of apoptosis was found to be associated with increased activation of apoptosis inducing factor in hearts exposed to S+V compared to those exposed to V alone. These results suggest that pre-exposure to smoke significantly exacerbates the severity of viral myocarditis, most likely through increased viral load and increased cardiomyocyte cell death.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Bae S, Ke Q, Koh YY, Lee W, Choi JH, Kang PM, Morgan JP. Exacerbation of acute viral myocarditis by tobacco smoke is associated with increased viral load and cardiac apoptosis. *Cancer J Physiol Pharmacol.* 2010;88(5):568-575.

BOOK CHAPTERS, ETC.

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EFFECTS OF SECONDHAND TOBACCO SMOKE (SHS) ON SUSCEPTIBILITY OF VENTRICULAR MYOCYTES TO ISCHEMIC INJURY

William H. Barry, MD; University of Utah; CIA 2005

Dr. Barry demonstrated that exposure to cigarette smoke extract (CSE) increased the percentage of myocytes undergoing contracture and increased susceptibility to the mitochondrial permeability transition (MPT). Exposure to CSE increased mitochondrial Ca2+ uptake, which was completely inhibited by the free radical scavenger Tiron; Tiron had no significant effect on mitochondrial Ca2+ uptake in the absence of CSE. The nicotine concentration in 0.1 % CSE is similar to that observed in arterial blood in humans after smoking. Experiments in paced adult ventricular myocytes exposed to 2.0 mM CN-0 glucose have shown that 0.1 % CSE increases Ca2+ loading. This effect is prevented by the inhibitor of the late Na+ current, Ranolazine, and by Tiron. Increased myocyte Na+ and Ca2+ loading exacerbates angina in patients with coronary artery disease; these findings provided an experimental basis for the observation that exposure to cigarette smoke decreases the angina threshold in coronary artery disease patients. Thus, CSE has direct effects on myocyte mitochondrial Ca2+ homeostasis, and increases susceptibility to the MPT. The MPT is triggered by mitochondrial Ca2+ overload and increased mitochondrial free radicals and contributes to the development of irreversible myocyte injury during ischemia/reperfusion. These direct myocyte effects account for increased infarct size produced *in vivo* by exposure to CS.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Yamada S, Zhang XQ, Kadono T, Matsuoka N, Rollins D, Badger, T, Rodesch CK, Barry WH. Aqueous extract of cigarette smoke has direct toxic effects on cardiac myocytes at clinically relevant concentrations. *Toxicol Appl Pharmacol.* 2009;236:71-77.

EFFECT OF SMOKING ON MODEL ABDOMINAL AORTIC ANEURYSMS

John Curci, MD; Washington University; YCSA 2005

Dr. Curci and colleagues demonstrated that exposure to tobacco smoke results in exacerbation of aneurysm formation in a mouse model of abdominal aortic aneurysm (AAA). AAA is a potentially fatal disease affecting nearly 9% of the male population over 55 years old.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Bergoeing MP, Arif B, Hackmann AE, Ennis TL, Thompson RW, Curci JA. Cigarette smoking increases aortic dilatation without affecting matrix metalloproteinase-9 and -12 expression in a modified mouse model of aneurysm formation. *J Vasc Surg.* 2007;45(6):1217-1227.

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Hackmann AE, Rubin BG, Sanchez LA, Geraghty PA, Thompson RW, Curci JA. A randomized, placebo-controlled trial of doxycycline after endoluminal aneurysm repair. *J Vasc Surg.* 2008;48(3):519-526; discussion 526.

Jin J, Arif B, Garcia-Fernandez F, Ennis TL, Davis EC, Thompson RW, Curci JA. Novel mechanism of aortic aneurysm development in mice associated with smoking and leukocytes. *Arterioscler Thromb Vasc Biol.* 2012;32(12):2901-2909.

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PRESENTATIONS AND ABSTRACTS

Arif B, Jin J, Curci JA. Tobacco smoke exposure interferes with normal arterial injury response. Presented at the Annual Conference of Arteriosclerosis, Thrombosis and Vascular Biology. Washington DC, Apr 29-May 1, 2009.

Kittel J, Arif B, Pagano M, Curci JA. Effect of tobacco smoke on arterial cell populations and stimulated cytokine responses. Presented at the Academic Surgical Congress. Fort Meyers, FL, Feb 3-6, 2009.

ALTERATION IN EXPRESSION OF VASCULAR G-PROTEIN COUPLED RECEPTORS AS A NOVEL MECHANISM RESPONSIBLE FOR CARDIOVASCULAR MORBIDITY BY CIGARETTE SMOKING

Lars Edvinsson, MD, PhD; Lund University; CIA 2005

Dr. Edvinsson's team has investigated the role and expression of different vasoregulatory compounds and receptor subtypes under pathophysiological conditions. They found that the microvascular response to the endogenous vasodilator peptide brain natriuretic peptide was significantly reduced in subjects with heart failure. A markedly reduced microvascular response in smokers that affected both endothelial and smooth muscle responses was seen by laser Doppler methodology. Cigarette smoke causes adherence of platelets and macrophages to the vessel walls, thus the team investigated the effect of increased atherogenic lipoproteins on the expression of vasoconstrictive receptors. Dr. Edvinsson and co-workers found that low density lipoprotein (LDL) induces upregulation of vasoconstrictive endothelin type B receptor through the ERK1/2 and p38 MAPK signaling pathways and also that apolipoprotein B impairs nitric oxide-mediated

endothelial vasodilatation. They also found morphological damage to the vascular endothelium. Taken together these results show that smoking and SHS exposure induce reduced vasodilatation and increased vasoconstriction. These both contribute to cardiovascular morbidity, and with an increase in LDL, adds to a spiral of damage of the microcirculation due to exposure to cigarette smoke.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Bondesson S, Pettersson T, Erdling A, Hallberg IR, Wackenfors A, Edvinsson L. Comparison of patients undergoing enhanced external counterpulsation and spinal cord stimulation for refractory angina pectoris. *Coron Artery Dis.* 2008;19(8):627-634.

Cao YX, Xu CB, Luo GG, Edvinsson L. Up-regulation of alpha1A-adrenoceptors in rat mesenteric artery involves intracellular signal pathways. *Basic Clin Pharmacol Toxicol.* 2006;98(1):61-67.

Chen QW, Edvinsson L, Xu CB. Role of ERK/MAPK in endothelin receptor signaling in human aortic smooth muscle cells. *BMC Cell Biol.* 2009;10:52.

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Edvinsson L. Cerebrovascular endothelin receptor upregulation in cerebral ischemia. *Curr Vasc Pharmacol.* 2009;7(1):26-33.

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Granstrom BW, Xu CB, Nilsson E, Vikman P, Edvinsson L. Smoking particles enhance endothelin A and endothelin B receptor-mediated contractions by enhancing translation in rat bronchi. *BMC Pulm Med.* 2006;6:6.

Haanes KA, Edvinsson L. Characterization of the contractile P2Y14 receptor in mouse coronary and cerebral arteries. *FEBS Lett.* 2014;588(17):2936-2943.

Jamali R, Edvinsson L. Involvement of protein kinases on the upregulation of endothelin receptors in rat basilar and mesenteric arteries. *Exp Biol Med (Maywood).* 2006;231(4):403-411.

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PRESENTATIONS AND ABSTRACTS

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ENDOTHELIAL PROGENITOR CELL NUMBER AND FUNCTION, INFLAMMATION, AND ENDOTHELIAL DYSFUNCTION AFTER EXPOSURE TO SECONDHAND TOBACCO SMOKE (SHS): A PUTATIVE MECHANISM OF THE CARDIOVASCULAR COMPLICATIONS OF TOBACCO SMOKE

Andrew Lee, MD; University of California, San Francisco; YCSA 2005

Dr. Lee and colleagues studied the short-term effects of acute SHS exposure on endothelial cell progenitor (EPC) number and function. Healthy non-smokers were exposed to 30 minutes of SHS in a controlled exposure chamber and blood samples drawn at regular intervals were assessed for level and migration capacity of EPCs. Flow-mediated dilation of the brachial artery was evaluated as a measure of endothelial function. The level of EPCs increased significantly after short exposures to SHS, accompanied by a reduction in endothelial function.

TREATING VASCULAR DISEASE BY TARGETING ELASTIN SIGNALING

Dean Y. Li, MD, PhD; University of Utah; CIA 2005

Dr. Li and colleagues identified novel matrix and matrix-bound proteins that regulate vascular guidance and stability. The group showed that netrins promote vascular and neurovascular regeneration. This has direct application to individuals who are exposed to cigarette smoke and who have an increased risk of developing peripheral vasculopathy and neuropathy. The team also showed that the slit proteins (key regulators of axon guidance, axonal branching, and cell migration) play a central role in vascular stability and reducing vascular eye disease, the number one cause of blindness in patients exposed to cigarette smoke.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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THROMBOGENIC EFFECTS OF SMOKE AND NICOTINE ON PLATELETS AND ENDOTHELIUM

Danny Bluestein, PhD; State University of New York at Stony Brook; CIA 2004

Dr. Bluestein hypothesized that SHS exposure significantly increases cardiovascular risk by predisposing platelets to activation in areas of elevated arterial flow stress. He developed an assay for platelet activation state (PAS) that can be used to establish thrombogenic potential of platelets subjected to SHS and has used this assay to demonstrate that sidestream smoke from high-tar and low-tar cigarettes is equally potent, although the mainstream smoke from each of these showed differences, and pure nicotine was found to inhibit platelet activation under static and arterial flow. Dr. Bluestein studied cigarette extract effects on susceptibility of platelets to activation under flow stress conditions and examined the effect of smoke on endothelial cells under flow stress conditions in the presence of normal and nicotine-free smoke extracts, measuring standard markers of endothelial cell activation. He evaluated the combined effect of smoke and nicotine, and investigated the possibility that exposure to total cigarette smoke, not pure nicotine, may be the initiating factor in platelet adhesion.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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THE EFFECT OF SECONDHAND TOBACCO SMOKE ON THE RISK OF DEVELOPING ATRIAL FIBRILLATION IN PATIENTS WITH PACEMAKERS AND DEFIBRILLATORS

Byron K. Lee, MD; University of California, San Francisco; YCSA 2004

Dr. Lee and his collaborators sought to characterize the association between smoking and the pathophysiology of atrial fibrillation (AF) by analyzing data from the Study of Physical Performance and Age-related Changes in Sonomans (SPPARCS) project to determine such association. The SPPARCS project was a community-based longitudinal study of physical activity and fitness in people approximately 55 years of age that live in or near the city of Sonoma, California. Over 2,000 patients were followed for up to 8 years. Detailed smoking histories and medical histories were obtained and electrocardiograms (ECGs) were done every two years. Patients were deemed to have AF if they had AF on any of these ECGs. In the model (adjusted for potential confounders including age, hypertension, congestive heart failure, and coronary artery disease), previous smokers had a 71% greater chance of having AF compared to non-smokers ($p = 0.03$). History of hypertension and congestive heart failure also were associated with the development of AF. Notably, the increase in risk of AF in smokers is persistent even if one has quit smoking for more than 40 years.

IMPACT OF PASSIVE SMOKING AND EARLY ATHEROSCLEROSIS IN CHILDREN WITH TYPE I DIABETES MELLITUS (ImPasSE)

Petru Liuba, MD, PhD; Lund University; YCSA 2004

Dr. Liuba hypothesized that: 1) SHS additively interacts with type 1 diabetes mellitus (DM-1) with negative consequences on vasculature and myocardial function; 2) that vascular changes in diabetic patients exposed to SHS evolve more rapidly toward more advanced lesions than those in smoke-free diabetic patients; and 3) that the putative interplays may be present already in nondiabetic children with a diabetes-susceptible human leukocyte antigen HLA group (DQ2/8). The arterial changes were evaluated by ultrasound assessment of brachial artery endothelial function and carotid artery intima-media thickness. Microvascular function was assessed by laser Doppler iontophoresis. Myocardial function was assessed by transthoracic ultrasound and by assessment of heart rate variability. Results revealed that nearly 20% of DM-1 patients are constantly exposed to SHS in their home environment. Patients with both high recurrence of respiratory infections and exposure to tobacco smoke are more prone to atherogenic changes in the carotid artery than those with either one or none of these risk factors. In addition, SHS exposure adversely influences heart rate variability, particularly in individuals with genetic HLA-related susceptibility to diabetes. The study underscored the significant influence of

diabetes-risk HLA (DQ 2/8) on the development of atherosclerosis and microvasculopathy. The research team demonstrated that the plasma level of vitamin C, which is known to be affected by SHS exposure, indirectly correlates with the degree of arterial and microvascular damage in children with DM-1.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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CARDIOVASCULAR EFFECTS OF SECONDHAND SMOKE (SHS) DURING PREGNANCY

Dana McGlothlin, MD; University of California, San Francisco; CIA 2003

Dr. McGlothlin hypothesized that SHS exposure impairs fetal blood flow during exercise in pregnant women. To study this, pregnant women exercised in the echocardiography laboratory and their umbilical arterial endothelial dilatory function was tested for abnormalities. The study design was changed after the first year from a longitudinal cohort to a cross-sectional study because of recruitment difficulties for first-trimester pregnant women and retention for the duration of pregnancy. The change involved pregnant women in the third trimester and the hypothesis remained in place.

EFFECT OF SIDE-STREAM CIGARETTE SMOKE ON LUNG ENDOTHELIAL ANGIOGENESIS INDUCED BY EPIDERMAL GROWTH FACTOR

Yunchao Su, MD, PhD; University of Florida; CIA 2004

Dr. Su hypothesized that sidestream cigarette smoke extract inhibits epidermal growth factor angiogenic effect and that this inhibition is caused by decreased calpain (a calcium activated protease) activity involving actin cytoskeleton reorganization. Dr. Su involved other FAMRI grantees in this research.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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PRESENTATIONS AND ABSTRACTS

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PERIPHERAL VASCULAR HEMODYNAMICS AND VENTRICULAR MECHANICS IN PASSIVE SMOKERS

Theodore P. Abraham, MD; Johns Hopkins Medical Institutions; CIA 2003

Passive smokers are presumed to have higher systolic blood pressure, lower systemic vascular compliance, and impaired ventricular relaxation when compared to non-smokers. Healthy nonsmokers with and without SHS exposure were compared as a pilot study to launch a larger study to evaluate long-term biological effects and the positive effects of cessation of SHS exposure on the cardiovascular system.

FAMRI SUPPORTED RESEARCH

PRESENTATIONS AND ABSTRACTS

Dimaano VL, Wang J, Gerstenblith G, Capriotti A, Ju H, Benowitz N, Correti M, Abraham T. High C reactive protein levels indicate secondhand smoke induces vascular inflammation in young, healthy adults: Implications for future coronary artery disease. Presented at the American Society of Echocardiography Scientific Sessions. Toronto, Canada, Jun 7-11, 2008.

THE EFFECT OF SECONDHAND TOBACCO SMOKE (SHS) ON EXERCISE CAPACITY AND CLINICAL OUTCOMES IN PULMONARY ARTERIAL HYPERTENSION

Teresa De Marco, MD; University of California, San Francisco; CIA 2003

Dr. De Marco demonstrated that SHS exposure is prevalent among patients treated for pulmonary arterial hypertension (PAH). At baseline, SHS exposure was associated with greater exercise capacity. This observation suggests that patients with poor exercise

capacity may avoid or have limited ability to participate in social situations where SHS exposure is common. Despite having lower exercise capacity at baseline, patients without SHS exposure demonstrated a greater, albeit non-significant, response to PAH therapy in terms of 6-minute walk distance at 6 and 12 months as compared to those with SHS exposure.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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Weeks SG, Glantz SA, De Marco T, Rosen AB, Fleischmann KE. Secondhand smoke exposure and quality of life in patients with heart failure. *Arch Intern Med.* 2011;171(21):1887-1893.

PRESENTATIONS AND ABSTRACTS

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PASSIVE SMOKING AND OUTCOMES IN CONGESTIVE HEART FAILURE

Kirsten Fleischmann, MD, MPH; University of California, San Francisco; CIA 2003

Dr. Fleischmann assessed the relationship of exposure to SHS to death, nonfatal myocardial infarction, and re-hospitalization for heart failure. She found that a substantial number of patients with heart failure in a large university clinic reported SHS exposure and that the clinical event rates in these patients were high. This strongly indicates that exposure to passive smoking affects several domains of health-related quality of life detrimentally. Dr. Fleischmann conducted a long-term follow-up to determine whether SHS exposure significantly increases the risk of these clinical events.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Ren X, Hsu PY, Dulbecco FL, Fleischmann KE, Gold WM, Redberg RF, Schiller NB. Remote second-hand tobacco exposure in flight attendants is associated with systemic but not pulmonary hypertension. *Cardiol J.* 2008;15(4):338-343.

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PRESENTATIONS AND ABSTRACTS

Hsu PYF, Dulbecco FL, Redberg RF, Fleischmann KE, Schiller NB. Doppler pulmonary vascular resistance response during supine exercise in healthy subjects. Presented at the

14th Annual Scientific Sessions of the American Society of Echocardiography. Las Vegas, Nevada, Jun 11-14, 2003.

SECONDHAND TOBACCO SMOKE PLATELET ACTIVATION AND CARDIOVASCULAR RISK

Danny Bluestein, PhD; State University of New York at Stony Brook; CIA 2002

Please see text above under Dr. Bluestein's 2004 award.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Ramachandran J, Rubenstein D, Bluestein D, Jesty J. Activation of platelets exposed to shear stress in the presence of smoke extracts of low-nicotine and zero-nicotine cigarettes: the protective effect of nicotine. *Nicotine Tob Res.* 2004;6(5):835-841.

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PRESENTATIONS AND ABSTRACTS

Bluestein D, Rubenstein D, Jesty J. The effects of mainstream and sidestream cigarette smoke and nicotine on platelet activation under arterial and coronary flow conditions. Presented at the World Congress on Medical Physics and Biomedical Engineering. Sidney, Australia, 2003.

Ramachandran J, Rubenstein D, Jesty J, Bluestein D. Cardiovascular risk in low-nicotine cigarettes: platelet activation and the effect of nicotine Presented at the BMES 2004 Conference. Philadelphia, PA, 2004.

Ramachandran J, Rubenstein D, Jesty J, Bluestein D. Effects of low-nicotine cigarette smoke on platelet activation under normal coronary flow conditions Presented at the Annual Fall BMES Meeting. Nashville, TN, 2003.

Rubenstein D, Jesty J, Bluestein D. The effects of mainstream and secondhand cigarette smoke extracts and nicotine on platelet activation under normal coronary flow conditions. Annual Fall BMES Meeting. Nashville, TN, 2003.

Schulz-Heik K, Ramachandran J, Bluestein D, Jesty J. Platelet-platelet interactions under shear stress: the extent of activation depends on platelet count. Presented at the 2004 BMES Conference. Philadelphia, PA, 2004.

INFLAMMATION

Completed Research

ROLE OF FABP5 IN CIGARETTE SMOKE-INDUCED INFLAMMATION

Fabienne Gally, PhD; National Jewish Health; CIA 2016

Dr. Gally's objective is to understand the mechanism by which cigarette smoke interferes with monocyte/macrophage function, leading to persistent lung inflammation and COPD disease progression.Her team has characterized Fatty Acid Binding Protein 5 (FABP5), which plays a central role in modulating pulmonary inflammation. This protein is highly expressed in monocytes, but its expression is reduced by cigarette smoke exposure. The hypothesis of this study is that cigarette smoke dysregulates FABP5 expression in monocytes, thus modulating their function and predisposing them to excessive inflammation. The investigators are determining whether modifying FABP5 *in vitro* and *in vivo* alters cigarette smoke-induced inflammation, and they are characterizing the alteration of the expression of FABP5 in individuals exposed to cigarette smoke or in patients with COPD. They are identifying genetic alterations that decrease FABP5 function and contribute to disease susceptiblity. The hope is that FABP5 can be used as a target to attenuate the inflammation commonly involved in chronic lung diseases such as COPD.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Rao D, Perraud AL, Schmitz C, Gally F. Cigarette smoke inhibits LPS-induced FABP5 expression by preventing c-Jun binding to the FABP5 promoter. *PLoS One.* 2017;12(5):e0178021.

Rao DM, Phan DT, Choo MJ, Weaver MR, Oberley-Deegan RE, Bowler RP, Gally F. Impact of fatty acid binding protein 5-deficiency on COPD exacerbations and cigarette smoke-induced inflammatory response to bacterial infection. *Clin Transl Med.* 2019;8(1):7.

THE ROLE OF FIBROBLAST GROWTH FACTOR RECEPTOR SIGNALING IN INFLAMMATION IN CHRONIC BRONCHITIS

Stefanie Krick, MD, PhD; University of Alabama at Birmingham; YCSA 2016

Chronic bronchitis caused by SHS exposure, is characterized by chronic inflammation leading to mucociliary dysfunction. The inflammation is associated with upregulation of cytokines such as IL-1b and TGF-b1 and a decrease in airway surface liquid volume. Fibroblast growth factors (FGFs) are ubiquitously expressed proteins that play a key role in the pathogenesis of diseases associated with chronic inflammation in the kidney and the heart. A member of the FGF family, FGF23, is a bone-derived hormone that regulates serum phosphate levels by targeting the kidney and parathyroid glands. Recent data demonstrate upregulation of serum FGF23 levels in smokers and patients with COPD. Mammals have four FGF receptor isoforms (FGFR1-4). Classic FGF23 signaling occurs via FGFR1 and its co-receptor α-klotho; however, there appears to be alternative signaling via an a- klotho independent mechanism through FGFR4 leading to activation of calcineurin/nuclear factor of activated T-cells (NFAT). Dr. Krick has preliminary data that indicate that FGFR4 is

upregulated in bronchial epithelial cells after tobacco smoke exposure, and that FGF23 can activate FGFR4 signaling in these cells. Furthermore, she found that there is a smoke-mediated downregulation of α-klotho, which supports alternative signaling of FGF23 via FGFR4/calcineurin/NFAT thereby inducing pro-inflammatory effects.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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RAGE AND SAGE: MODELING SECONDHAND SMOKE-INDUCED COPD AND THERAPEUTIC MODALITIES

Paul R. Reynolds, PhD; Brigham Young University; CIA 2016

Dr. Reynolds and colleagues identified the receptor for advanced glycation end-products (RAGE) as a smoke- induced pattern recognition receptor with potent pro-inflammatory characteristics. Further research demonstrated that RAGE is increased in the lung following first and secondhand tobacco smoke exposure and that transgenic mice that conditionally upregulate RAGE manifest characteristics of a smoker's lung in the absence of tobacco smoke exposure. Semi-synthetic glycosaminoglycan ethers (SAGEs) are potent modulators of inflammation in numerous animal models of human disease, and are in preclinical development for periodontitis, oral mucositis, and bladder inflammation. SAGEs significantly inhibit interactions between RAGE and the ligands necessary for signaling. The investigators will assess the biology of RAGE in the context of tobacco smoke exposure. They have a collection of animal models that tightly control RAGE expression; including RAGE null mice, pulmonary-specific transgenic mice that upregulate RAGE, and mice harboring phosphorylation-deficient RAGE alleles. There is significant clinical translational potential for lessening tobacco smoke-induced inflammation and pulmonary remodeling. The investigators hypothesize that RAGE expression by pulmonary epithelium induces

COPD by orchestrating widespread inflammation and parenchymal tissue loss. Further, the investigators hypothesize that SAGEs can be used as a novel translational therapy for RAGE-mediated COPD.

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THERAPEUTIC EFFECTS OF CSP7 ON PASSIVE TOBACCO SMOKE-INDUCED LUNG INJURY

Sreerama Shetty, PhD; The University of Texas Health Science Center at Tyler; CIA 2016

In this study the investigators are using a range of molecular and interventional approaches, including transgenic mice, to determine if interleukin-17A (IL-17A) increases microRNA-34a and p53 to promote apoptosis in progenitor type II alveolar epithelial cells (A2ECs); this is central to the pathogenesis of SHS exposure-induced lung injury. They are investigating whether inhibition of an IL-17A-induced microRNA-34a-p53-positive feedback by CSP7 (a seven amino acid peptide derived from caveolin-1) mitigates SHS exposure induced lung injury. They are determining how IL-17A augments miR-34a-p53-positive feedback in A2ECs and A2EC apoptosis during SHS-induced lung injury and whether blockade of IL-17A-induced miR-34a and p53 in A2ECs by CSP7 can reduce the severity of SHS-induced lung injury.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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GENE SILENCING IN CHRONIC BRONCHITIS AND COPD

Hoshang Unwalla, PhD; Florida International University; CIA 2016

Defective mucociliary clearance (MCC) in chronic bronchitis and COPD is attributed in part to decreased cystic fibrosis transmembrane conductance regulator (CFTR) function and expression. Beta-2-adrenergic receptor agonists are widely used bronchodilators for the symptomatic management of COPD. These not only bronchodilate but can activate CFTR to improve airway surface hydration, ciliary beat frequency, and epithelial permeability. However, these beneficial effects are suppressed in COPD patients and in individuals exposed to cigarette smoke due to decreased CFTR expression. Preliminary data suggest that TGF-beta signaling that is upregulated in COPD and smokers is directly involved in repression of CFTR mRNA. Dr. Unwalla and colleagues are examining miRNA-mediated posttranscriptional silencing of CFTR mRNA by TGF-beta and they are testing aptamer-siRNAs designed to overcome TGF-beta1-mediated CFTR suppression. The long-term goal

of this study is to improve dysfunctional mucociliary clearance in tobacco-related lung disease by beta-2-agonists by restoring physiologic CFTR expression.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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IMMUNOLOGY

Completed Research

NOVEL APPROACH TO OVERCOME CRS-INDUCED IMMUNE DYSFUNCTION

Ilona Jaspers, PhD; University of North Carolina at Chapel Hill; CIA 2017

Dr. Jaspers and colleagues have demonstrated that exposure to cigarette smoke (CS) causes immune dysfunction in the nasal mucosa as marked by reduced antiviral immune responses and decreased Natural Killer (NK) cell function. Chronic rhinosinusitis (CRS) has variable etiologies, manifestations, and progression, but is usually accompanied by bacterial infections, chronic inflammation, and overall immune dysfunction of the nasal mucosa. In particular, CRS without nasal polyps (CRSsNP) is marked by pro-inflammatory neutrophilic inflammation of the nasal mucosa. Persistent presence of inflammatory cells, such as neutrophils, depends on the increased recruitment as well as decreased resolution and removal of these cells. NK cells are emerging as playing important roles in regulating the activation, apoptosis, and resolution of inflammatory cells, such as neutrophils. The hypothesis is that enhancing NK cell function could revert the chronic pro-inflammatory status in the nasal mucosa of patients with CRS. The team has demonstrated that socioemotional intervention, based on an ancient practice known as “loving-kindness meditation” (LKM), enhances leukocyte gene expression profiles consistent with decreased inflammation and enhanced NK cell function. LKM teaches individuals skills to self-generate warm and empathic positive emotions, which in turn results in measurable biological responses and increased psychosocial measures. Teaching socially- meaningful positive emotions through LKM may shift nasal mucosal and systemic immune responses towards less inflammation and greater NK cell function, thus providing a novel approach for counterbalancing the pathophysiology associated with CRS. Patients suffering from CRSsNP are participating in a study to determine the effects of LKM intervention on symptoms associated with CRS. These data are being correlated with nasal mucosal immune markers to determine how LKM intervention in CRS changes peripheral blood and nasal NK cell function and gene expression. Integrating objective measurements of biomarkers assessing nasal mucosal immune status and NK cell function with clinical CRS symptom scores may provide evidence to support the adoption of non-surgical and non-

steroidal interventions as a low-cost, novel, and promising intervention into clinical practice.

MECHANISMS REGULATING CIGARETTE SMOKE-INDUCED SLE

Betsy J. Barnes, PhD; Rutgers, The State University of New Jersey, The Feinstein Institute for Medical Research; CIA 2013

Autoimmune diseases are considered to be influenced by both genetic and environmental factors. One of the major environmental risk factors identified for chronic autoimmune diseases is active and/or passive cigarette smoking (CS). CS has been causally linked to the development of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), among others. In RA, CS has been shown to interact with genetic factors to create a significant combined risk. Less is known of the mechanisms (genetic and/or biological) by which smoking increases SLE risk. With regard to autoimmune disease, smoking can have opposing effects that make it difficult to predict and/or understand its contribution to disease risk and severity. CS is known to modulate the immune system through many mechanisms, including the induction of an inflammatory response, immune suppression, alteration of cytokine balance, induction of apoptosis, and DNA damage that results in the formation of anti-double stranded DNA antibodies. A primary goal of this study was to determine whether a known genetic risk factor for SLE, variants of the interferon regulatory factor 5 (*IRF5*) gene, synergizes with CS to induce chronic inflammation that will lead to SLE onset and/or severity. IRF5 expression was shown to be significantly decreased in healthy donors that smoke cigarettes as compared to those that do not. SLE patients already have elevated IRF5 expression as compared to healthy donors; however, patients who smoke had reduced expression compared those who did not. Keep in mind that these are lifetime smokers. The investigators examined the initial effect of CS on IRF5 expression and activation by *ex vivo* culture. IRF5 activation is also normally elevated in SLE patients; however, in SLE patients who smoke, IRF5 activation was decreased to the levels of healthy donors. Together, these data suggest that IRF5 is an immune responder to CS that over time (lifetime of smoking) leads to reduced IRF5 expression and activation. *Ex vivo* analysis of IRF5 expression and function showed that initial exposures of cells to CS media caused a significant increase in IRF5 expression, activation, and IL6 production. Increased cell apoptosis was detected in IRF5-expressing cells, but when the IRF5 inhibitor was added to media, CS-induced apoptosis was significantly reduced. These data support the fact that IRF5 is important for the initial response of the immune system to CS.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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REGULATION OF CS-INDUCED PATHOGENIC T CELLS

Michael T. Borchers, PhD; University of Cincinnati; CIA 2012

Dr. Borchers and colleagues demonstrated that long-term CS exposure has many effects on adaptive immune function such as enhancing the number and activation of T cells producing pro-inflammatory mediators and the development of autoreactive T cells. The investigators examined the cellular and molecular mechanisms involved in the generation of CS-induced pathogenic T cell populations to yield a better understanding of the development of COPD pathology, chronic exacerbations in response to infection, and the increased susceptibility to autoimmune disorders. The ability of regulatory T cells to prevent local and systemic autoimmune pathologies in preclinical studies suggests a potential for therapeutic strategy in patients with overactive T cells. The team sought to identify specific CS-induced alterations in T cell functions that represent the critical first steps necessary to advance the therapeutic options for patients.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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CX3CR1 AND LUNG INFLAMMATION BY SHS

Janet S. Lee, MD; University of Pittsburgh; CIA 2012

Dr. Lee and her colleagues determined if a cell type identified by the surface expression of the chemokine receptor, CX3CR1, promotes the abnormal inflammatory signature characteristic of COPD by increasing the production of mediators such as tumor necrosis factor alpha and interleukin 6, resulting in amplification of inflammation and tissue damage seen after cigarette smoke exposure. The investigators examined how cigarette smoke alters the behavior of lung mononuclear phagocytes in response to bacterial pathogen signals in a cell culture model. They used genetically altered mice that do not express CX3CR1 and compared their responses in a cigarette smoking model in the presence of secondhand tobacco smoke and a bacterial pathogen challenge. The team also determed the function of the CX3CR1 cell type in human COPD lungs.

FAMRI SUPPORTED RESEARCH

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Xiong Z, Pinilla Vera M, Lechner EJ, Horne W, Kolls J, Barge S, Woodske M, Donahoe MP, Ray P, Lee JS. Scavenger receptors as homeostatic markers in airspace mononuclear phagocytes of healthy volunteers (ID 53500). Presented at the Poster Discussion Session: B21-Airway Host Defense, American Thoracic Society International Conference. San Diego, CA. May 16-21, 2014.

Zhao Y, Xiong Z, Hulver M, Sayeed S, Yu M, Lechner EJ, Ray A, Ray P, Lee JS. Thrombospondin-1 negatively regulates neutrophil bacterial killing and pulmonary host defense against *Klebsiella pneumoniae* (ID 53709 C93). Presented at the Mini-Symposium: Advances in acute lung injury and mucosal immunity, American Thoracic Society International Conference. San Diego, CA. May 16-21, 2014.

Zhao Y, Xiong Z, Lechner EJ, Klenotic PA, Hulver M, Chan Y, Mangalmurti N, Rosengart MR, Ray P, Ray A, Silverstein RL, Lee JS. Thrombospondin-1 triggers CD36-dependent macrophage IL-10 production by facilitating apoptotic cell recognition and promotes resolution of experimental lung injury. Presented at the Mini-Symposium: C93-Resolution

of Lung Injury and Inflammation at the American Thoracic Society International Conference. Philadelphia, PA, May 17-22 2013.

REVERSING THE EFFECTS OF SHS ON MUCOSAL IMMUNITY

Homayoun Shams, DVM, PhD; University of Texas Health Center at Tyler; CIA 2010

Dr. Shams and colleagues investigated an approach to combat flu by boosting the host immune response. They found that SHS exposure increased the mortality of flu in mice, and that local administration of granulocyte-macrophage colony-stimulating factor (GM-CSF), a natural substance produced by immune cells, induces resistance to lethal doses of H1N1 and other flu strains. Their data show that the mortality of flu in mice that express high levels of GM-CSF in the lung is 0%, compared to 100% in normal mice, and found that pulmonary delivery of GM-CSF to normal mice abrogated mortality from flu. The team investigated whether the increased susceptibility to flu is due to impaired T cell functions, and if GM-CSF can correct these effects. Recombinant GM-CSF has been approved by the FDA to stimulate white blood cell recovery following bone marrow transplantation, treatment of fungal infections, and replenishment of white blood cells following chemotherapy. However, it has never been used to prevent or treat flu infections. These studies may accelerate the development of effective strategies to prevent, control, and treat flu, including flu exacerbated by SHS exposure.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Feng Y, Kong Y, Barnes PF, Huang FF, Klucar P, Wang X, Samten B, Sengupta M, Machona B, Donis R, Tvinnereim AR, Shams H. Exposure to cigarette smoke inhibits the pulmonary T-cell response to influenza virus and Mycobacterium tuberculosis. *Infect Immun.* 2011;79(1):229-237.

Guo J, Feng Y, Barnes P, Huang FF, Idell S, Su DM, Shams H. Deletion of FoxN1 in the thymic medullary epithelium reduces peripheral T cell responses to infection and mimics changes of aging. *PLoS One.* 2012;7(4):e34681.

Huang FF, Barnes PF, Feng Y, Donis R, Chroneos ZC, Idell S, Allen T, Perez DR, Whitsett JA, Dunussi-Joannopoulos K, Shams H. GM-CSF in the lung protects against lethal influenza infection. *Am J Respir Crit Care Med.* 2011;184(2):259-268.

ADJUVANT EFFECTS OF CIGARETTE SMOKE CONSTITUENTS

Robert Vassallo, MD; Mayo Clinic; CIA 2010

Dr. Vassallo and his colleagues have shown that oxidative SH) components alter dendritic cell function in ways that facilitate the development of aberrant immune responses associated with asthma and allergy. They also observed that smoking increases asthmatic response following inhalational challenge with *Alternaria*, a ubiquitous environmental fungus associated with asthmatic exacerbations and death. The investigators determined the contribution of SHS-induced oxidative stress as a promoter of *Alternaria*-induced asthmatic responses in murine lungs. They also determined the role of oxidative stress in the induction of proallergic dendritic cell activation and the effect of SHS-induced oxidative stress on relevant molecular changes in dendritic cells that result in enhanced capacity to

induce asthmatic responses. The team investigated whether antagonism of oxidative stress *in vivo* can reverse the oxidative stress imbalance and airway inflammatory responses in *Alternaria* and SHS-challenged mouse models.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Lee J, Taneja V, Vassallo R. Cigarette smoking and inflammation: cellular and molecular mechanisms. *J Dent Res.* 2012;91(2):142-149.

Sathish V, Vanoosten SK, Miller BS, Aravamudan B, Thompson MA, Pabelick CM, Vassallo R, Prakash YS. Brain-derived neurotrophic factor in cigarette smoke-induced airway hyperreactivity. *Am J Respir Cell Mol Biol.* 2013;48(4):431-438.

Vassallo R, Ryu JH. Smoking-related interstitial lung diseases. *Clin Chest Med.* 2012;33(1):165-178.

PRESENTATIONS AND ABSTRACTS

Burkholder D, Kiel A, Venkatachalem S, Thompson MA, Vassallo R, Pabelick CM, Prakash YS, Wylam ME. Cigarette smoke enhances TRPC and CD38 expression in human airway smooth muscle [abstract]. *FASEB J* 2011;25:864.7

Vassallo R, Sathish V, Suri H, Sanyal B, Thompson M, Prakash Y. Human airway smooth muscle cells express thymic stromal lymphopoietin receptors [abstract]. *Am J Respir Crit Care Med* 2011;183:A2579.

Vassallo R, Walters P, Grill DE. Extracts from presumed "reduced harm" eclipse cigarettes induce equivalent or greater cellular toxicity in antigen presenting cells. Presented at the American Thoracic Society annual meeting. Philadelphia, PA, May 17-22, 2013.

Walters P, Taneja V, Vassallo R. Cigarette smoke modulates systemic dendritic cell function *in vivo*. Presented at the Autoimmunity 2012 meeting. Granada, Spain, May 9-13, 2012.

CYTOTOXIC T CELL EXPANSIONS IN SMOKE-INDUCED LUNG DISEASE

Michael T. Borchers, PhD; University of Cincinnati; CIA 2009

Dr. Borchers and colleagues defined the effects of CS exposure on pulmonary immunity and examined the role of cytotoxic T cells in COPD pathogenesis. The investigators examined the mechanisms involved in CS-induced CD8 T cell expansions and determine whether these populations are pathogenic. Long-term exposure to CS may induce persistent T cell expansions that directly contribute to pulmonary remodeling; CD8-deficient mice fail to develop airspace enlargement in COPD models. The team demonstrated that chronic CS exposure, in the absence of infection or tumors, causes oligoclonal expansions of CD8 T cells, which persist following exposure cessation. The team studied the processes driving persistent CD8 T cell expansions as a result of chronic CS exposure and defined the pathological capacity of expanded CD8 T cell populations in a mouse model of CS-induced COPD. They also identified the origin of expanded T cell populations in the lung and examined whether these expanded T cell populations play a causative role in the development of pulmonary pathology.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Eppert BL, Motz GT, Wortham BW, Flury JL, Borchers MT. CCR7 deficiency leads to leukocyte activation and increased clearance in response to pulmonary Pseudomonas aeruginosa infection. *Infect Immun.* 2010;78(5):2099-2107.

Motz GT, Eppert BL, Wesselkamper SC, Flury JL, Borchers MT. Chronic cigarette smoke exposure generates pathogenic T cells capable of driving COPD-like disease in Rag2-/- mice. *Am J Respir Crit Care Med.* 2010;181(11):1223-1233.

Motz GT, Eppert BL, Wortham BW, Amos-Kroohs RM, Flury JL, Wesselkamper SC, Borchers MT. Chronic cigarette smoke exposure primes NK cell activation in a mouse model of chronic obstructive pulmonary disease. *J Immunol.* 2010;184(8):4460-4469.

Wortham BW, Eppert BL, Motz GT, Flury JL, Orozco-Levi M, Hoebe K, Panos RJ, Maxfield M, Glasser SW, Senft AP, Raulet DH, Borchers MT. NKG2D mediates NK cell hyperresponsiveness and influenza-induced pathologies in a mouse model of chronic obstructive pulmonary disease. *J Immunol.* 2012;188(9):4468-4475.

SHS AND INFLUENZA-INDUCED IMMUNE RESPONSES

Ilona Jaspers, PhD; University of North Carolina Chapel Hill; CIA 2009

In a previous FAMRI-funded study, Dr. Jaspers and colleagues showed that exposure to SHS increases the susceptibility to influenza virus in humans, and that these effects are associated with suppression of interferon-dependent antiviral immune responses at the level of the epithelium. In this study, the investigators determined the mechanisms by which exposure to SHS modifies nasal antiviral immune responses. Comparisons of live attenuated influenza virus-induced responses in the nasal mucosa from smokers and non-smokers revealed that natural killer cell function is suppressed in smokers as compared to non-smokers. In subsequent studies focusing on mucosal immune phenotypes it was demonstrated that the recruitment of gamma/delta T lymphocytes was decreased in smokers, further supporting the notion that mucosal innate immune defense responses are suppressed in the context of viral infections.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Horvath KM, Brighton LE, Herbst M, Noah TL, Jaspers I. Live attenuated influenza virus (LAIV) induces different mucosal T cell function in nonsmokers and smokers. *Clin Immunol.* 2012;142(3):232-236.

Horvath KM, Brighton LE, Zhang W, Carson JL, Jaspers I. Epithelial cells from smokers modify dendritic cell responses in the context of influenza infection. *Am J Respir Cell Mol Biol.* 2011;45(2):237-245.

Horvath KM, Herbst M, Zhou H, Zhang H, Noah TL, Jaspers I. Nasal lavage natural killer cell function is suppressed in smokers after live attenuated influenza virus. *Respir Res.* 2011;12:102.

Kesic MJ, Simmons SO, Bauer R, Jaspers I. Nrf2 expression modifies influenza A entry and replication in nasal epithelial cells. *Free Radic Biol Med.* 2011;51(2):444-453.

Noah TL, Zhou H, Jaspers I. Alteration of the nasal responses to influenza virus by tobacco smoke. *Curr Opin Allergy Clin Immunol.* 2012;12(1):24-31.

Rager JE, Bauer RN, Muller LL, Smeester L, Carson JL, Brighton LE, Fry RC, Jaspers I. DNA methylation in nasal epithelial cells from smokers: identification of ULBP3-related effects. *Am J Physiol Lung Cell Mol Physiol.* 2013;305(6):L432-438.

PRESENTATIONS AND ABSTRACTS

Jaspers I. Antiviral host defenses in the nose: Role of the epimmunome. Presented at the James Hogg Research Centre, University of British Columbia. Vancouver, Canada, Feb 2012.

Jaspers I. Cigarette smoke and influenza: basic and translational studies. Presented at the University of North Carolina at Chapel Hill Pediatric Grand Rounds. Chapel Hill, NC, Feb 2009.

Jaspers I. How smoking may affect your ability to fight influenza. Presented at the University of North Carolina at Chapel Hill Pathology Grand Rounds. Chapel Hill, NC, Jan 2010.

Immune Disease Institute Jaspers I. Translational research approaches to investigate the effects of smoking on influenza infections. Presented at the Translational Medicine Symposium, University of North Carolina at Chapel Hill. Chapel Hill, NC, Apr 2010.

LUNG ACTIVATION OF CX3CL1 BY SECONDHAND SMOKE EXPOSURE

Janet S. Lee, MD; University of Pittsburgh; 2009 CIA

Dr. Lee and colleagues investigated the role of a small protein, CX3CR1, in recruitment of mononuclear phagocytes, inflammatory cytokine responses, and tissue destruction in lungs following cigarette smoke exposure. The team showed that alveolar macrophages increased transmembrane ligand CX3CL1 expression. Soluble CX3CL1 is detectable in the airspaces, but cx3cr1GFP/ GFP and cx3cr1GFP/+ mice did not recruit CX3CR1+ cells into airspaces exposed to cigarette smoke. An intact CX3CL1-CX3CR1 pathway is not essential for recruitment of mononuclear phagocytes into the lungs, but functional CX3CR1 is required for a subset of tissue-bound mononuclear phagocytes to produce tumor necrosis factor alpha and interleukin 6 in response to cigarette smoke *in vivo*, amplify divergent populations of CD11b+ cells regardless of CX3CR1 expression, and contribute directly to tissue-destructive emphysema. The team identified a cell-type in mice defined by CX3CR1 expression and implicated in cell survival whose population expands and elaborates type 1 signature cytokines in response to cigarette smoke exposure *in vivo*.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Bon JM, Leader JK, Weissfeld JL, Coxson HO, Zheng B, Branch RA, Kondragunta V, Lee JS, Zhang Y, Choi AM, Lokshin AE, Kaminski N, Gur D, Sciurba FC. The influence of radiographic phenotype and smoking status on peripheral blood biomarker patterns in chronic obstructive pulmonary disease. *PLoS One.* 2009;4(8):e6865.

Xiong Z, Leme AS, Ray P, Shapiro SD, Lee JS. CX3CR1+ lung mononuclear phagocytes spatially confined to the interstitium produce TNF-alpha and IL-6 and promote cigarette smoke-induced emphysema. *J Immunol.* 2011;186(5):3206-3214.

ROLE OF SERPINB1 IN CIGARETTE SMOKE-INDUCED DEFECTIVE ANTIMICROBIAL DEFENSE

Charaf Benarafa, DVM, PhD; Immune Disease Institute, Universität Bern; YCSA 2008

Dr. Benarafa and colleagues observed that although cigarette smoke can induce emphysema in mice compared to controls, no difference was observed in the severity of emphysema between serpinB1 deficient mice and wild type, suggesting that this gene is not essential for regulating the extent of the protease-mediated damage following chronic smoke exposure. The studies demonstrated that serpinB1 and alpha 1-antitrypsin proteins vary in their biological functions: alpha serpinB1 has a central role in protecting neutrophil survival and antimicrobial defenses; and
alpha 1-antitrypsin regulates proteases in the onset and development of emphysema. The investigators unveiled new mechanisms by which sustained subacute inflammation induced by SHS alter the development of bone marrow-derived monocytes and neutrophils with opposite effects on bacterial clearance kinetics from the lungs and the upper airways.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Benarafa C. The SerpinB1 knockout mouse a model for studying neutrophil protease regulation in homeostasis and inflammation. *Methods Enzymol.* 2011;499:135-148.

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PRESENTATIONS AND ABSTRACTS

Basilico P, Cremona TP, Benarafa C. Cigarette smoke exposure induces systemic inflammation with an acute effect on myelopoiesis and lung bacterial clearance. Presented at the American Thoracic Society International Conference. San Diego, CA, May 16-21, 2014.

Basilico P, Cremona TP, Benarafa C. Increased myelopoiesis induced by cigarette smoke transiently improved the kinetics of lung bacterial clearance in mice. Presented at the European Respiratory Society – Lung Science Conference. Estoril, Portugal, Mar 21-23, 2014.

Basilico P, Cremona TP, Benarafa C. Systemic inflammation induced by cigarette smoke exposure transiently increases myelopoiesis and lung bacterial clearance in serpinB1-/- mice. Presented at the 7th International Symposium on Serpin Biology, Structure and Function. Leogang, Austria, Mar 28-Apr 2, 2014.

Basilico P, Cremona TP, Benarafa C. Systemic inflammation induced by cigarette smoke exposure transiently increases myelopoiesis and lung bacterial clearance in serpinB1-/-

mice. Presented at the 48th Annual Meeting of the European Society for Clinical Investigation. Utrecht, The Netherlands, Apr 30-May 3, 2014.

Basilico P, Oevermann A, Benarafa C. Secondhand cigarette smoke exposure induces lasting upper airway colonization and increases severity of otitis media after *S. pneumoniae* infection in mice. Presented at the European Respiratory Society – Lung Science Conference. Estoril, Portugal, Mar 21-23, 2014.

Cremona TP, Basilico P, Häfliger P, Frei E, Benarafa C. Impact of cigarette smoke exposure on *Pseudomonas aeruginosa* clearance in wild-type and serpinB1-/-mice. Presented at the American Thoracic Society International Conference. Philadelphia, PA, May 17-22, 2013.

Cremona TP, Basilico P, Häfliger P, Frei E, Benarafa C. Impact of cigarette smoke exposure on *Pseudomonas aeruginosa* clearance in wild-type and serpinB1-/-mice. Presented at the Joint Annual Meeting of the Swiss Society for Allergology and Immunology and the Swiss Respiratory Society. Bern, Switzerland, Apr 17-19, 2013.

Cremona TP, Benarafa C. Impact of cigarette smoke exposure on Pseudomonas clearance in serpinB1-/- mice. Presented at the 10th International Summer School. Sigriswil, Switzerland, Aug 21-23, 2011.

Cremona TP, Tschanz SA, Benarafa C. Deficiency in neutrophil protease inhibitor serpinb1 is not associated with increased susceptibility to cigarette smoke-induced emphysema in mice. Presented at the American Thoracic Society International Conference. Philadelphia, PA, May 17-22, 2013.

Cremona TP, Tschanz SA, Benarafa C. Role of neutrophil protease inhibitor serpinB1 in cigarette smoke-induced emphysema in mice. Presented at the Joint Annual Meeting of the Swiss Society for Allergology and Immunology and the Swiss Respiratory Society. Bern, Switzerland, Apr 17-19, 2013.

SECONDHAND CIGARETTE SMOKE (SCS), IMMUNITY AND ALLOGRAFT REJECTION

Zhenhua Dai, MD, PhD; University of Texas Health Science Center at Tyler; CIA 2008

Dr. Dai and colleagues showed that SHS exposure increases memory T cell number and hinders allograft survival induced by the CD40/CD154 costimulatory blockade. The team investigated whether SHS exposure shortens allograft survival by suppressing regulatory T cell (Treg) development and promoting memory T cell recall, and they investigated the impact of SHS exposure on the function of memory CD4+ and CD8+ T cells. They studied whether SHS suppresses the generation and function of CD4+CD25+FoxP3+ Treg cells, and examined whether targeting memory T cells and administering Treg cells suppresses allograft rejection related to SHS exposure. Using a murine cardiac transplant model, the team found that SHS exposure hinders long-term allograft survival by suppressing the expression and activity of indoleamine 2,3-dioxygenase, which favors long-term allograft survival and tolerance.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Wan F, Dai H, Zhang S, Moore Y, Wan N, Dai Z. Cigarette smoke exposure hinders long-term allograft survival by suppressing indoleamine 2,3-dioxygenase expression. *Am J Transplant.* 2012;12(3):610-619.

PRESENTATIONS AND ABSTRACTS

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THE INFLUENCE OF SECONDHAND CIGARETTE SMOKE (SCS) ON THE INNATE IMMUNE FUNCTION OF NASAL EPITHELIAL CELLS.

James A. Jukosky, PhD; Geisel School of Medicine at Dartmouth; YCSA 2008

Dr. Jukosky and colleagues demonstrated that innate immune protection provided by nasal epithelial cells is altered by tobacco smoke exposure. They also demonstrated nasal epithelial cell secretion of CCL20, (a protein that has antimicrobial and signaling functions), is suppressed by tobacco smoke exposure. The team tested the production of other related antimicrobial and signaling molecules in volunteers with no tobacco smoke exposure, prior tobacco smoke exposure (6 months to 5 years ago), current SHS exposure, and subjects with current primary tobacco smoke exposure (smokers) to determine if exposure alters constitutive production and induction of innate immune molecules by lipotechoic acid. They studied the nasal secretions of the volunteers to determine if cigarette smoke exposure alters steady-state levels of the same innate immune molecules in the nasal passage.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Crane-Godreau MA, Maccani MA, Eszterhas SK, Warner SL, Jukosky JA, Fiering S. Exposure to Cigarette Smoke Disrupts CCL20-Mediated Antimicrobial Activity in Respiratory Epithelial Cells. *Open Immunol J.* 2009;2:86-93.

INNATE IMMUNITY AND TOBACCO SMOKE

Maria Antonieta Guerrero-Plata, PhD; University of Texas Medical Branch at Galveston, Louisiana State University; YCSA 2007

Dr. Guerrero-Plata and colleagues investigated whether exposure to SHS affects the ability of the immune system to fight respiratory viral infections by interfering with the production of innate immune molecules, such as interferon type I, or by interfering with the activation and recruitment of specialized cells called plasmacytoid dendritic cells, to the sites of infection. The team investigated the clinical relevance of the innate immune response in the context of co-exposure to viral respiratory pathogens and SHS and dissected the molecular and cellular basis of this interaction.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Banos-Lara Mdel R, Ghosh A, Guerrero-Plata A. Critical role of MDA5 in the interferon response induced by human metapneumovirus infection in dendritic cells and *in vivo*. *J Virol.* 2013;87(2):1242-1251.

Castro SM, Chakraborty K, Guerrero-Plata A. Cigarette smoke suppresses TLR-7 stimulation in response to virus infection in plasmacytoid dendritic cells. *Toxicol In Vitro.* 2011;25(5):1106-1113.

Guerrero-Plata A. Dendritic cells in human Pneumovirus and Metapneumovirus infections. *Viruses.* 2013;5(6):1553-1570.

Guerrero-Plata A, Kolli D, Hong C, Casola A, Garofalo RP. Subversion of pulmonary dendritic cell function by paramyxovirus infections. *J Immunol.* 2009;182(5):3072-3083.

Lancelin W, Guerrero-Plata A. Isolation of mouse lung dendritic cells. *J Vis Exp.* 2011(57).

PRESENTATIONS AND ABSTRACTS

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Baños-Lara RM, Guerrero-Plata A. Critical Role of MDA5 in the interferon response induced by human metapneumovirus infection in dendritic cells. Presented at the International RSV Symposium. Santa Fe, NM, Sept 27-30, 2012.

Baños-Lara RM, Guerrero-Plata A. Specific helicase activation in human dendritic cells by paramyxovirus infection. Presented at Phi Zeta Research Emphasis Day, Louisiana State University. Baton Rouge, LA, Sept 28, 2011.

Baños-Lara RM, Guerrero-Plata A. Specific helicase activation in human dendritic cells by paramyxovirus infection.Keystone Symposia. Presented at Innate Immunity: Sensing the Microbes and Damage Signals. Keystone, CO, Mar 04-09, 2012.

Baños-Lara RM, Guerrero-Plata A. Specific helicase activation in human dendritic cells by paramyxovirus infection. Presented at the Gordon Research Conferences: Biology of Acute Respiratory Infection. Ventura, CA, Mar 11-16, 2012.

Baños-Lara RM, Guerrero-Plata A. Type III IFN induction by hMPV infection in human epithelial cells. Presented at the American Thoracic Society International Conference. Philadelphia, PA, May 17-22, 2013.

Castro S, Garofalo RP, Guerrero-Plata A. Inhibition of dendritic cell activation by cigarette smoke extract. Presented at the 48th Annual Meeting. Society of Toxicology. Baltimore, MD, Mar 15-19, 2009.

Castro S, Garofalo RP, Guerrero-Plata A. Mechanisms of inhibition of viral-induced interferon production in human dendritic cells by cigarette smoke extract. Presented at the 2009 Annual McLaughlin Colloquium on Infection and Immunity. Galveston, TX, Feb 26, 2009.

Castro S, Guerrero-Plata A. Cigarette smoke suppresses the anti-viral capacity of dendritic cells. Presented at the American Association of Immunologists. Baltimore, MD, May 07-11, 2010.

Castro S, Guerrero-Plata A. Inhibition of viral-induced dendritic cell function by cigarette smoke extract. Presented at the American Thoracic Society International Conference. San Diego, CA, May 15-20, 2009.

Castro S, Guerrero-Plata A. Cigarette smoke suppresses TLR-7 stimulation in response to virus infection in plasmacytoid dendritic cells [abstract]. The Keystone Symposia, Dendritic Cell and the Initiation of Adaptive Immunity. Santa Fe, NM, Feb 12-17, 2011.

Guerrero-Plata A, Castro S, Liu T, Casola A, Garofalo RP. Mechanisms of type I interferon induction by human metapneumovirus in human dendritic cells. Presented at the Keystone Symposia: Dendritic Cells/Immune Pattern Recognition. Banff, Alberta, Canada. Mar 29-Apr 03 2009.

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Guerrero-Plata A, Kolli D, Ivanciuc T, Casola A, Garofalo RP. Respiratory syncytial virus and human metapneumovirus impair the antigen presentation capacity of pulmonary dendritic cells. Presented at the Annual Meeting of the American Society for Virology. Ithaca, NY, Jul 12-15, 2008.

Guerrero-Plata A, Kolli D, Ivanciuc T, Casola A, Garofalo RP. Trafficking of dendritic cell subsets to the lung controls viral replication and pathology in human metapneumovirus infection. Presented at the XIV International Congress of Virology. Istanbul, Turkey, Aug 10-15, 2008.

Lancelin W, Castro S, Wakamatsu N, Guerrero-Plata A. Plasmacytoid dendritic cells control lung inflammation and cell trafficking in human metapneumovirus infection. Presented at the Phi Zeta Research Emphasis Day, Louisiana State University. Baton Rouge, LA, Sep 29, 2010.

Lancelin W, Chakraborty K, Zhou Z, Wakamatsu N, Guerrero-Plata A. Role of pulmonary dendritic cells in human metapneumovirus infection. Presented at the SE Regional IDeA Meeting. New Orleans, LA, Sep 22-24, 2011.

Lancelin W, Guerrero-Plata A. Plasmacytoid dendritic cells regulate humanmetapneumovirus pathogenesis. Presented at the VII Biannual Mexican Congress of Virology. Tuxtla Gutierrez, Chiapas, Mexico, Sep 26-30, 2011.

Lancelin W, Wakamatsu N, Guerrero-Plata A. Regulation of human paramyxovirus pathogenesis by pulmonary dendritic cells [abstract]. The American Association of Immunologists Meeting. San Francisco, CA, May 13-17, 2011

Mendoza A, Banos-Lara MR, Guerrero-Plata A. Type III interferon response of airway epithelial cells to human metapneumovirus infection. Presented at the Summer Undergraduate Research Forum. Louisiana State University, Baton Rouge, LA, Jul 27, 2012.

SUPPRESSION OF AIRWAY IMMUNITY BY SECONDHAND TOBACCO SMOKE (SHS)

Adam J. Ratner, MD, MPH; Columbia University; CIA 2007

Dr. Ratner and his colleagues demonstrated that SHS exerts a specific immunosuppressive effect on the cells of the upper airway, inhibiting the local response to bacterial products. They hypothesized that this ultimately leads to bacterial overgrowth and the excessive inflammation that is the hallmark of chronic rhinosinusitis (CRS). The group has examined the effects of SHS on the three most important components of epithelial defense of the upper airway: epithelial innate immune signaling, epithelial barrier function, and ciliary beat frequency. In each of these areas, they investigated specific molecular mechanisms of SHS-induced immune suppression, with a focus on finding potential targets for therapeutic intervention.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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Hsiao YS, Parker D, Ratner AJ, Prince A, Tong L. Crystal structures of respiratory pathogen neuraminidases. *Biochem Biophys Res Commun.* 2009;380(3):467-471.

Kulkarni R, Rampersaud R, Aguilar JL, Randis TM, Kreindler JL, Ratner AJ. Cigarette smoke inhibits airway epithelial cell innate immune responses to bacteria. *Infect Immun.* 2010;78(5):2146-2152.

Lehrer RI, Jung G, Ruchala P, Wang W, Micewicz ED, Waring AJ, Gillespie EJ, Bradley KA, Ratner AJ, Rest RF, Lu W. Human alpha-defensins inhibit hemolysis mediated by cholesterol-dependent cytolysins. *Infect Immun.* 2009;77(9):4028-4040.

Parker D, Martin FJ, Soong G, Harfenist BS, Aguilar JL, Ratner AJ, Fitzgerald KA, Schindler C, Prince A. Streptococcus pneumoniae DNA initiates type I interferon signaling in the respiratory tract. *MBio.* 2011;2(3):e00016-00011.

Parker D, Soong G, Planet P, Brower J, Ratner AJ, Prince A. The NanA neuraminidase of Streptococcus pneumoniae is involved in biofilm formation. *Infect Immun.* 2009;77(9):3722-3730.

PRESENTATIONS AND ABSTRACTS

Kulkarni R, Aguilar JL, Ratner AJ. Cigarette smoke components alter the airway epithelial innate immune response to microbial products. Presented at the American Society for Microbiology Annual Meeting. Boston, MA, Jun 1-5, 2008.

Kulkarni R, Ratner AJ. Cigarette smoke alters epithelial immune responses to microbial products. Presented at the American Society for Microbiology Annual Meeting. Philadelphia, PA, May 17-21, 2009.

ROLE OF PROBIOTICS IN INTESTINAL INFLAMMATION

Sang Hoon Rhee, PhD; University of California, Los Angeles; YCSA 2007

Dr. Rhee and colleagues studied the role of the probiotic bacteria, *Bacillus polyfermenticus*, in maintaining intestinal physiology. The researchers investigated the effect of *B. polyfermenticus* in mice with induced colitis. Mice with induced colitis and treated with *B. polyfermenticus* showed reduced mortality and severity of colitis (weight loss, diarrhea, and mucosal damage) when compared to mice treated with colitis-inducing agents alone. *B. polyfermenticus* also reduced the expression of a number of inflammatory molecules and enhanced the expression of the anti-inflammatory cytokine interleukin-10 in the inflamed mouse colon. *B. polyfermenticus* suppressed apoptosis both *in vivo* in inflamed colonic mucosa and *in vitro* in colonic epithelial cells stimulated with apoptosis-inducing agents. Treating colonic epithelial cells with *B. polyfermenticus*-conditioned medium (BPCM) enhanced cell proliferation and induced the phosphoinositide 3-kinases/protein kinase B signaling pathway, suggesting that this bacterium can promote epithelial cell proliferation. BPCM also promoted the migration of colonic epithelial cells. These data suggest that *B. polyfermenticus* ameliorates colonic inflammation by suppressing apoptosis and promoting epithelial cell proliferation and migration.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Choi YJ, Im E, Chung HK, Pothoulakis C, Rhee SH. TRIF mediates Toll-like receptor 5-induced signaling in intestinal epithelial cells. *J Biol Chem.* 2010;285(48):37570-37578.

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Im E, Choi YJ, Kim CH, Fiocchi C, Pothoulakis C, Rhee SH. The angiogenic effect of probiotic Bacillus polyfermenticus on human intestinal microvascular endothelial cells is mediated by IL-8. *Am J Physiol Gastrointest Liver Physiol.* 2009;297(5):G999-G1008.

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THE IMPACT OF SECONDHAND TOBACCO SMOKE (SHS) ON T CELL IMMUNE RESPONSE: IMPLICATIONS FOR UPPER AND LOWER AIRWAYS DISEASE

Stephen M. Canfield, MD, PhD; Columbia University; CIA 2006

Dr. Canfield and his group analyzed total immunoglobulin E (IgE) as well as IgEs specific to dust mite, cockroach, mouse, and cat in a cohort of 501 children aged four. From these analyses, the investigators showed that total IgE levels among children correlate well with levels in both mother and father, and this correlation is strengthened among children living in a home with at least one smoker. Inclusion of SHS in a linear regression model relating parental and child total IgE strengthened the correlations with a magnitude of effect similar to inclusion of national origin. Inclusion of SHS exposure and national origin simultaneously produced an additive effect. These results show an exacerbating influence of SHS on the allergic susceptibility of the children and provided insight into the mechanism of the SHS effect on allergic susceptibility.

SECOND HAND TOBACCO SMOKE AND INFLUENZA-INDUCED RESPONSES IN NASAL EPTHELIUM

Ilona Jaspers, PhD; Hamner Institutes for the Health Sciences; CIA 2006

Exposure to SHS has been associated with increased susceptibility to infection with respiratory viruses. The objectives of this project were to determine whether exposure to SHS enhances the susceptibility to influenza virus infections *in vivo* and whether the effect is mediated by SHS-induced oxidative stress. The completed study was subdivided into two interdependent studies; one determined the effects of SHS exposure on influenza infections in healthy human volunteers *in vivo* and one used an *in vitro* model of differentiated human nasal epithelial cells to confirm and expand the *in vivo* findings and to examine potential cellular mechanisms mediating the effects of SHS on influenza virus infections. Dr. Jaspers and colleagues completed studies comparing experimental live attenuated influenza vaccine infections in healthy non-smoking and healthy non-smoking/SHS-exposed volunteers. The studies were conducted over two seasons in a population of volunteers that was large enough for statistical analysis.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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Noah TL, Zhou H, Monaco J, Horvath K, Herbst M, Jaspers I. Tobacco smoke exposure and altered nasal responses to live attenuated influenza virus. *Environ Health Perspect.* 2011;119(1):78-83.

SECONDHAND CIGARETTE SMOKE (SCS) AND IMMUNITY TO TUBERCULOSIS

Homayoun Shams, DVM, PhD; The University of Texas Health Science Center at Tyler; CIA 2006

Dr. Shams and colleagues determined whether SCS enhances susceptibility to pulmonary tuberculosis and expanded the studies to include influenza A virus, which induces acute pneumonia. The experiments demonstrated that the effects of SCS exposure on IFN-gamma production by T cells are not limited to *M. tuberculosis* and have sequelae that affect vaccination strategies.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Klucar P, Barnes PF, Kong Y, Howard ST, Pang X, Huang F, Tvinnerereim AR, Samten B, Shams H. Vaccination strategies to enhance local immunity and protections against *Mycobacterium tuberculosis*. *Vaccine.* 2009;27(12):1816-1824.

ALTERATIONS IN DENDRITIC CELL-MEDIATED IMMUNITY CAUSED BY SMOKING

Robert Vassallo, MD; Mayo Clinic; YCSA 2005

Dr. Vassallo's research focused on the effect of cigarette smoking and nicotine on dendritic cell (DC) function; DCs are a critical component of the immune system. Dr. Vassallo showed that cigarette smoke-induced oxidative stress is a major mechanism by which cigarette smoke preferentially inhibits DC production of IL-12p70 and IL-23 through the induction of ERK-dependent signaling pathways. He also showed that cigarette smoke-induced pro-inflammatory DC response through nicotinic stimulation and oxidative stress result in the induction of diverse inflammatory responses relevant to the recruitment of immune cells in inflamed airways. He established a mouse model of chronic cigarette smoke exposure. Measurement of blood nicotine levels in these mice exposed to high concentration of smoke is similar to that observed in heavy cigarette smokers.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Carmona EM, Vassallo R, Vuk-Pavlovic Z, Standing JE, Kottom TJ, Limper AH. Pneumocystis cell wall beta-glucans induce dendritic cell costimulatory molecule expression and inflammatory activation through a Fas-Fas ligand mechanism. *J Immunol.* 2006;177(1):459-467.

Kobayashi T, Iijima K, Radhakrishnan S, Mehta V, Vassallo R, Lawrence CB, Cyong JC, Pease LR, Oguchi K, Kita H. Asthma-related environmental fungus, Alternaria, activates dendritic cells and produces potent Th2 adjuvant activity. *J Immunol.* 2009;182(4):2502-2510.

Kroening PR, Barnes TW, Pease L, Limper A, Kita H, Vassallo R. Cigarette smoke-induced oxidative stress suppresses generation of dendritic cell IL-12 and IL-23 through ERK-dependent pathways. *J Immunol.* 2008;181(2):1536-1547.

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Smelter DF, Sathish V, Thompson MA, Pabelick CM, Vassallo R, Prakash YS. Thymic stromal lymphopoietin in cigarette smoke-exposed human airway smooth muscle. *J Immunol.* 2010;185(5):3035-3040.

Vassallo R, Kroening PR, Parambil J, Kita H. Nicotine and oxidative cigarette smoke constituents induce immune-modulatory and pro-inflammatory dendritic cell responses. *Mol Immunol.* 2008;45(12):3321-3329.

Vassallo R, Tamada K, Lau JS, Kroening PR, Chen L. Cigarette smoke extract suppresses human dendritic cell function leading to preferential induction of Th-2 priming. *J Immunol.* 2005;175(4):2684-2691.

Vassallo R, Walters PR, Lamont J, Kottom TJ, Yi ES, Limper AH. Cigarette smoke promotes dendritic cell accumulation in COPD; a Lung Tissue Research Consortium study. *Respir Res.* 2010;11:45.

ONTOGENY OF CYTOKINE IMMUNE RESPONSES: ROLE OF SECONDHAND TOBACCO SMOKE (SHS)

Deborah A. Gentile, MD; Allegheny-Singer Research Institute; CIA 2004

Dr. Gentile compared subjects with and without exposure to SHS (determined by serum cotinine levels). The number of dendritic cells and CD4+CD25+ cells in those individuals without exposure was significantly higher than in those who had been exposed to SHS. No significant differences were seen in CD8+CD38+ lymphocytes or cytokine production in the two groups, but there were age-related decreases in the absolute numbers of CD4+CD25+ cells, CD8+CD38+ lymphocytes, and dendritic cells. CD8+ cells that produce interleukin (IL) 4 and IL13 also decreased in number with respect to age. However, interferon (IFN) gamma from CD8+ cells and cytokines from CD4+ cells and dendritic cells did not decrease as a function of age. These results indicate that there is a differential immune response in children related to both age and to exposure to SHS.

FAMRI SUPPORTED RESEARCH

PRESENTATIONS AND ABSTRACTS

Gentile D, Koehrsen J, Patel A, Skoner DP. Association between secondhand smoke exposure (SSE) and increased IL-13 production from CD4+ cells during early childhood. *J Allergy Clin Immunol* 2006;117(2)S257.

Koehrsen JM, Gentile DA, Patel A, Kwon Y, Schad C, Schaffner T, Skoner DP. Alterations of immune cell phenotypes in young children with second-hand smoke exposure (SSE). *J Allergy Clin Immunol* 2008;121(2)S59.

Patel A, Gentile DA, Koehrsen JM, Skoner DP, Varga M, Schad CA, Schaffner TJ. Association between second hand smoke exposure (SSE) and T-Helper Type 2 (TH2) cytokine production during early childhood. *J Allergy Clin Immunol* 2007;119(1) S45.

SECONDHAND TOBACCO SMOKE AND THYROID DISEASE

Ruth M. Belin, MD, Rachel Chong, MD; Johns Hopkins Medical Institutions; CIA 2002

This award was originally granted to Dr. Ruth Belin and then transferred to Dr. Chong who studied abnormal cortisol responses to stress. Abnormal hypothalamic-pituitary-adrenal (HPA) function is a fundamental endocrine abnormality identified in individuals exposed to tobacco smoke. This abnormality may play an important role in insulin resistance, cardiovascular events, and decreased bone mineral density in persons subjected to SHS exposure. The endogenous opioid system is one of several neurotransmitter systems modulating the HPA axis response to stress. The cold pressor test (CPT), a pain stressor that activates both endogenous opioid and HPA axis activity, was used to elicit cortisol responses among young adults to determine whether individual differences in the mu-opioid receptor gene are associated with differences in cortisol response to the CPT. It was found that Caucasians have a more robust HPA axis response to the Trier Social Stress Test (TSST) compared with African Americans, even after controlling for several socioeconomic and psychological factors. There were no differences in subjective response to the TSST to explain the difference in the HPA axis response.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Belin RM, Astor BC, Powe NR, Ladenson PW. Smoke exposure is associated with a lower prevalence of serum thyroid autoantibodies and thyrotropin concentration elevation and a higher prevalence of mild thyrotropin concentration suppression in the third National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab.* 2004;89(12):6077-6086.

BOOK CHAPTERS, ETC.

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VISION

Completed Research

ROLE OF SMOKING IN AGE-RELATED MACULAR DEGENERATION

Maria Marin-Castaño, MD, PhD; University of Miami Miller School of Medicine; CIA 2008

Dr. Marin-Castaño and colleagues postulated that cigarette smoke, oxidative damage to the retinal pigment epithelium (RPE), and inflammation are involved in the pathophysiology of age-related macular degeneration (AMD). The team examined the expression of proinflammatory monocyte chemoattractant protein-1 (MCP-1), proangiogenic vascular endothelial growth factor (VEGF), and antiangiogenic pigment epithelial-derived factor (PEDF) in RPE from smoker patients with AMD as well as the effects of hydroquinone (HQ), a major pro-oxidant in cigarette smoke on MCP-1, VEGF, and PEDF gene expression in cultured ARPE-19 cells and RPE/choroids from C57BL/6 mice. The results suggest that impaired RPE-derived MCP-1-mediated scavenging macrophage recruitment and phagocytosis might lead to incomplete clearance of proinflammatory debris and infiltration of proangiogenic macrophages that might promote accumulation and progression to choroidal neovascularization in Flight Attendants and other SHS-exposed patients with dry AMD. The investigators also evaluated the expression of the nicotinic acetylcholine receptor (nAchR) in RPE and determined the effects of nicotine on RPE-derived VEGF and PEDF expression in the context of SHS exposure. The results revealed a contribution of the RPE cells to the proangiogenic effects of nicotine at concentrations found in the plasma of those exposed to SHS, such as Flight Attendants.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Pons M, Marin-Castano ME. Cigarette smoke-related hydroquinone dysregulates MCP-1, VEGF and PEDF expression in retinal pigment epithelium in vitro and in vivo. *PLoS One.* 2011;6(2):e16722.

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PRESENTATIONS AND ABSTRACTS

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Marin-Castaño ME, Alcazar O, Pons M. Regulation of monocyte chemoattractant protein-1 (MCP-1), growth factors, and pigment epithelium-derived factor in response to transient and repetitive non lethal oxidative injury in human retinal pigment epithelial cells. Presented at the Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting. Fort Lauderdale, FL, May 2-6, 2010.

Marin-Castaño ME, Pons M, Cousins SW, Alcazar O. Regulation of MCP-1 by cigarette smoke components and angiotensin II in human REP cells. Presented at the Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting. Fort Lauderdale, FL, May 3-7, 2009.

Marin-Castaño ME, Pons M. Nicotine regulates VEGF and PEDF in passive smokers with AMD. Presented at the Association for Research in Vision and Ophthalmology Annual Meeting. Fort Lauderdale, FL, May 1-5, 2011.

Marin-Castaño ME. Smoking and eye diseases. Presented at the International Society for the Prevention of Tobacco Induced Diseases. Vienna, Austria, Sep 21-23, 2011.

Pons M, Alcazar O, Cousins SW, Csaky K, Marin-Castaño ME. Cigarette smoke-related hydroquinone induces F-actin reorganization and Hsp27 phosphorylation through p38 and ERK1/2 in Retinal Pigment Epithelium. Presented at the Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting. Fort Lauderdale, FL, May 2-6, 2010.

Pons M, Marin-Castaño ME. Cigarette smoke-related hydroquinone deregulates MCP- 1, VEGF and PEDF in retinal pigment epithelium *in vitro* and *in vivo*. Presented at the Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting. Fort Lauderdale, FL, May 1-5, 2011.

BOOK CHAPTERS, ETC.

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Pons M, Marin-Castaño ME: Involvement of Cigarette Smoke-Related Hydroquinone in the Pathogenesis of Age-Related Macular Degeneration. In: Gokden F, Lazzarotto A, eds. Hydroquinone: Production, Uses and Health Effects. New York, NY: Nova Science Publishers Inc, 2011.

Pons M, Marin-Castaño ME. Involvement of cigarette smoke-related hydroquinone in the pathogenesis of age-related macular degeneration. In: Gokden F, Lazzarotto A, eds. Hydroquinone: Production, Uses and Health Effects. Hauppauge, NY: Nova Science Publishers, Inc, 2011.

GENE PROFILING SECONDHAND TOBACCO SMOKE AND MACULAR DEGENERATION

George Inana, MD, PhD; University of Miami Miller School of Medicine; CIA 2007

The cause of age-related macular degeneration (AMD) is not known, but genetic and environmental factors, especially tobacco smoke exposure, are leading factors. Dr. Inana and colleagues obtained a data bank of genes that show changes in expression in AMD through a custom gene expression profiling strategy called CHANGE. These genes are candidates for causal involvement in AMD that can be compared with genes that are induced by tobacco smoke exposure. The deleterious effect of SHS exposure was dramatically demonstrated in an animal model. A 6-week exposure to SHS resulted in a global suppression of gene expression in the mitochondrial genes that are responsible for respiration and energy production for the cell, signaling serious trouble for the cells. Suppression of other important genes was also observed.

A ROLE FOR CATHEPSIN B IN SECONDHAND TOBACCO SMOKE-RELATED VASCULAR DISEASES

Eunok Im, PhD; Schepens Eye Research Institute, Harvard University, University of California, Los Angeles; YCSA 2006

The vascularized form of age-related macular degeneration (AMD) is tightly associated with SHS exposure. Regulators of vessel formation will aid in finding early diagnostic tools and ways to prevent disease progression. Dr. Im discovered that cathepsin B (a lysosomal cysteine protease) inhibits angiogenesis by suppressing pro-angiogenic factors such as vascular endothelial cell growth factor and generating anti-angiogenic factors such as endostatin. These findings reveal cathepsin B as a modulator of angiogenesis. Dr. Im set out to elucidate the mechanism by which cathepsin B modulates pro- and anti-angiogenic factors, and to develop effective approaches to control SHS-induced angiogenesis. The molecular dissection of angiogenesis should enable better treatment and control of diseases arising from SHS exposure.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Im E, Kazlauskas A. Src family kinases promote vessel stability by antagonizing the Rho/ROCK pathway. *J Biol Chem.* 2007;282(40):29122-29129.

Im E, Kazlauskas A. PtdIns-4,5-P2 as a potential therapeutic target for pathologic angiogenesis. *Expert Opin Ther Targets.* 2007;11(4):443-451.

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Im E, Motiejunaite R, Aranda J, Park EY, Federico L, Kim TI, Clair T, Stracke ML, Smyth S, Kazlauskas A. Phospholipase Cgamma activation drives increased production of autotaxin in endothelial cells and lysophosphatidic acid-dependent regression. *Mol Cell Biol.* 2010;30(10):2401-2410.

Im E, Pothoulakis C. [Recent advances in Saccharomyces boulardii research]. *Gastroenterol Clin Biol.* 2010;34 Suppl 1:S62-70.

INFLAMMATION, SMOKING, AND BLINDNESS FROM OCULAR NEOVASCULARIZATION

Scott W. Cousins, MD; University of Miami Miller School of Medicine, Duke University; CIA 2004

Neovascular acute macular degeneration (AMD) is caused by exposure to cigarette smoke. Dr. Cousins' research tested the hypothesis that tobacco smoke-related nicotine acts upon circulating monocytes to induce partially activated monocytes in the blood. The monocytes are recruited to the eye in areas of choroidal neovascularization and lead to increasingly severe neovascularization via tumor necrosis factor alpha production. The relationships between neovascular AMD, blood cotinine levels, and partial activation of blood monocytes were evaluated in a human case-control study of passive and active smokers versus non-smokers. If this relationship holds, blood monocyte activation status could serve as a biomarker for risk of AMD progression. A similar study in mice evaluated the capacity of

passive and active cigarette smoke (or nicotine) to affect bone marrow progenitor cells, causing them to differentiate into activated monocytes after smoking cessation. Mice exposed to cigarette smoke suffered more severe pathology in the bone marrow stem cells than those not exposed. These results carry the implication that Flight Attendants and others exposed to SHS may have long-term changes in bone marrow stem cells predisposing them to vascular diseases, including atherosclerosis and macular degeneration, long after cessation of the cigarette smoke exposure.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Espinosa-Heidmann DG, Suner IJ, Catanuto P, Hernandez EP, Marin-Castaño ME, Cousins SW. Cigarette smoke-related oxidants and the development of sub-RPE deposits in an experimental animal model of dry AMD. *Invest Ophthalmol Vis Sci.* 2006;47(2):729-737.

NEUROLOGICAL EFFECTS

Completed Research

EFFECTS OF SECONDHAND SMOKING ON THE DEVELOPMENT OF NEURODEGENERATIVE SIGNS

Seyha Seng, PhD; Beth Israel Deaconess Medical Center; YCSA 2009

Dr. Seng and colleagues examined whether SHS contributes to altered function of neural progenitor cells (NPC) and neurocognitive deficit in dementia and neurodegenerative diseases. The team showed that SHS exposure impairs neurogenesis by inhibiting proliferation of human NPCs, promoting cellular apoptosis, and decreasing cell survival. The impairment may be associated with deregulation of three key molecules, ADORA2A, CDK5RAP1, and PAX6. The team observed alteration of expression of ABC1, ACHE, APBA1, CTSC, and GNGs, which are molecules linked to Alzheimer's and Parkinson's diseases, in SHS-treated NPC. In addition, SHS decreased glutathione synthetase levels in NPC, which may deregulate glutathione homeostasis in NPC. This is a pathologic event contributing to initiation and progression of neurodegenerative disease.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Birrane G, Li H, Yang S, Tachado SD, Seng S. Cigarette smoke induces nuclear translocation of heme oxygenase 1 (HO-1) in prostate cancer cells: nuclear HO-1 promotes vascular endothelial growth factor secretion. *Int J Oncol.* 2013;42(6):1919-1928.

Li H, Sekine M, Seng S, Avraham S, Avraham HK. BRCA1 interacts with Smad3 and regulates Smad3-mediated TGF-beta signaling during oxidative stress responses. *PLoS One.* 2009;4(9):e7091.

Li H, Wood JT, Whitten KM, Vadivel SK, Seng S, Makriyannis A, Avraham HK. Inhibition of fatty acid amide hydrolase activates Nrf2 signalling and induces heme oxygenase 1 transcription in breast cancer cells. *Br J Pharmacol.* 2013;170(3):489-505.

Seng S, Avraham HK, Birrane G, Jiang S, Avraham S. Nuclear matrix protein (NRP/B) modulates the nuclear factor (Erythroid-derived 2)-related 2 (NRF2)-dependent oxidative stress response. *J Biol Chem.* 2010;285(34):26190-26198.

Seng S, Avraham HK, Birrane G, Jiang S, Li H, Katz G, Bass CE, Zagozdzon R, Avraham S. NRP/B mutations impair Nrf2-dependent NQO1 induction in human primary brain tumors. *Oncogene.* 2009;28(3):378-389.

Xue J, Yang S, Seng S. Mechanisms of Cancer Induction by Tobacco-Specific NNK and NNN. *Cancers (Basel).* 2014;6(2):1138-1156.

Yang S, Long M, Tachado SD, Seng S. Cigarette smoke modulates PC3 prostate cancer cell migration by altering adhesion molecules and the extracellular matrix. *Mol Med Rep.* 2015;12(5):6990-6996.

PRESENTATIONS AND ABSTRACTS

Birrane G, Li H, Yang S, Tachado S, Seng S. Cigarette smoke induces nuclear translocation of HO-1 enhancing the secretion of VEGF in prostate cancer cells. Presented at 18th World Congress on Advances in Oncology and 16th International Symposium on Molecular medicine. Oct 10-12, 2013, Crete, Greece.

Birrane G, Li H, Yang S, Tachado S, Seng S. Cigarette smoke induces nuclear translocation of HO-1 enhancing the secretion of VEGF in prostate cancer cells [abstract]. *Int J Mol Med* 2013;32:S42.

PERINATAL NICOTINE, CARBON MONOXIDE AND NEURODEVELOPMENT

J. Timothy O'Neill, PhD; Uniformed Services University of the Health Sciences; CIA

Dr. O'Neill and colleagues examined whether nicotine and carbon monoxide (CO) are synergistic by studying migration in the neocortex during the perinatal exposure of mice to nicotine and CO. They investigated the consequences of perinatal nicotine and CO on the development of the neocortex. Maternal smoking has been associated with several neurological disorders including autism and attention deficit disorder.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Trentini JF, O'Neill JT, Juliano SL. Carbon monoxide: A quiescent toxin to neuronal migration in the developing brain. *Archives of Ibadan Medicine.* 2011;11:22-26.

PRESENTATIONS AND ABSTRACTS

O'Neill JT, Kehl ML, Johnson KP, Cravedi K, Barry ES, Grunberg NE. Perinatal exposure to low levels of carbon monoxide impairs neurobehavioral function in adult mice [abstract]. *Abstracts2ViewTM E-PAS* 2013:3826.426.

MECHANISMS OF ENVIRONMENTAL TOBACCO SMOKE-INDUCED NERVOUS SYSTEM MALFORMATIONS AND CANCERS

Annie W. Chan, MD; Massachusetts General Hospital; CIA 2008

Dr. Chan and colleagues investigated whether stem cells, which play critical roles in the functioning and maintenance of biological systems such as the nervous system, are particularly vulnerable to toxic effects of SHS. The team also investigated the molecular mechanisms by which SHS exposure affects abnormal differentiation and tumorigenesis of neural stem cells, and identifying targets for treatment. They developed methods for improved diagnosis and therapies specifically for SHS-induced nervous system malformation and neoplasia, and provided a framework for understanding how dysregulation of normal stem and progenitor cells leads to development of cancer in general.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Cole BK, Curto M, Chan AW, McClatchey AI. Localization to the cortical cytoskeleton is necessary for Nf2/merlin-dependent epidermal growth factor receptor silencing. *Mol Cell Biol.* 2008;28(4):1274-1284.

Johannessen CM, Johnson BW, Williams SM, Chan AW, Reczek EE, Lynch RC, Rioth MJ, McClatchey A, Ryeom S, Cichowski K. TORC1 is essential for NF1-associated malignancies. *Curr Biol.* 2008;18(1):56-62.

McBride SM, Ali NN, Margalit DN, Chan AW. Active tobacco smoking and distant metastasis in patients with oropharyngeal cancer. *Int J Radiat Oncol Biol Phys.* 2012;84(1):183-188.

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Wong HK, Shimizu A, Kirkpatrick ND, Garkavtsev I, Chan AW, di Tomaso E, Klagsbrun M, Jain RK. Merlin/NF2 regulates angiogenesis in schwannomas through a Rac1/semaphorin 3F-dependent mechanism. *Neoplasia.* 2012;14(2):84-94.

TOBACCO SMOKE AND EARLY HUMAN NEUROBEHAVIOR

Kimberly Yolton, PhD; Cincinnati Children's Hospital Medical Center; CIA 2007

Dr. Yolton and colleagues investigated the impact of prenatal and postnatal tobacco smoke exposure on development and behavior from the newborn period to age 2 years in a sample of infants whose exposure to tobacco smoke during pregnancy resembled nationally-reported rates. The team found that high levels of prenatal tobacco smoke exposure were associated with lower motor and cognitive development scores at years 1 and 2 in black children. When accounting for postnatal SHS exposure, the significant relationship between prenatal exposure and lower motor scores at 1 year and lower cognitive scores at 2 years among black children remained, but the relationship with lower motor development at 2 years was attenuated. No statistically significant associations were

found in white children. The investigators analyzed the infant data collected shortly after birth to determine the optimal time for a neurobehavioral examination to determine effects of prenatal exposures. Latent profile analysis was employed for structural equation modeling analysis of the impact of prenatal and postnatal tobacco smoke exposure on neurobehavioral outcomes.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Sucharew H, Khoury JC, Xu Y, Succop P, Yolton K. NICU Network Neurobehavioral Scale profiles predict developmental outcomes in a low-risk sample. *Paediatr Perinat Epidemiol.* 2012;26(4):344-352.

Xu Y, Yolton K, Khoury J. Earliest appropriate time for administering neurobehavioral assessment in newborn infants. *Pediatrics.* 2011;127(1):e69-75.

Yolton K, Khoury J, Hornung R, Dietrich K, Succop P, Lanphear B. Environmental tobacco smoke exposure and child behaviors. *J Dev Behav Pediatr.* 2008;29(6):450-457.

Yolton K, Khoury J, Xu Y, Succop P, Lanphear B, Bernert JT, Lester B. Low-level prenatal exposure to nicotine and infant neurobehavior. *Neurotoxicol Teratol.* 2009;31(6):356-363.

CHILDHOOD SECONDHAND TOBACCO SMOKE EXPOSURE: DELAYED NEUROPSYCHIATRIC EFFECTS

Adriaan W. Bruijnzeel, PhD; University of Florida; YCSA 2006

Dr. Bruijnzeel and his colleagues investigated whether SHS exposure leads to the development of nicotine dependence. They established an automated setup for exposing freely moving rats to tobacco smoke. The team used the intracranial self-stimulation procedure (ICSS) to determine if administration of a nicotinic acetylcholine receptor (nAChR) antagonist leads to elevations in ICSS thresholds, if administration of a nicotinic receptor antagonist leads to an increase in somatic withdrawal signs, and if exposure to tobacco smoke affects self-administration of nicotine in rats. The results show that the nAChR antagonist mecamylamine elevated the ICSS thresholds of the rats chronically exposed to smoke but did not affect the brain reward thresholds of the controls, and it induced more somatic withdrawal signs in smoke-exposed rats than in controls. Nicotine self-administration was decreased one day after the last exposure and returned to control levels five days later. Exposure to tobacco smoke led to an increase in alpha 7 nAChR levels in the CA2/3 region, hilus of dentate gyrus, and stratum oriens, and increased alpha 4 beta 2 nAChR levels in the dentate gyrus. An increase in nAChRs is a hallmark feature of the development of nicotine dependence. These studies suggest that SHS exposure can lead to the development of nicotine dependence, and they indicate that people who are exposed to SHS undergo brain changes similar to active smokers.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Bruijnzeel AW. kappa-Opioid receptor signaling and brain reward function. *Brain Res Rev.* 2009;62(1):127-146.

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EFFECTS OF PASSIVE SMOKING AND NICOTINE ON THE DEVELOPMENT OF CNS BODY IMAGE AND MOTOR SKILL

Jens Schouenborg, MD; Lund University; CIA 2005

Body constitution is adaptively laid down in the spinal cord of the fetus. Cholinergic mechanisms are important for plasticity and learning, thus Dr. Schouenborg and colleagues determined whether SHS and nicotine exposures disturb mechanisms that tune the central nervous system sensorimotor systems, resulting in lifelong defects in motor ability and sensory capacity. The results show that nicotine exposure during development distorts the body image in the spinal cord and significantly alters the sensitivity in the nociceptive withdrawal reflexes in a dose dependent manner, indicating interventions at multiple sites. The distortion of the spinal body image is still present in the adult mice after only 1 week of exposure to nicotine. Since the sensorimotor circuits in the spinal cord serve as building blocks in higher order systems, it is likely that the impaired body representation will be reflected in impaired motor skill. The data show that nicotine exposure during early development can cause permanent damage in sensorimotor systems.

REPRODUCTIVE TRACT EFFECTS

Completed Research

GENE/TOBACCO INTERACTIONS AND OVARIAN FUNCTION

Corrine Kolka Welt, MD; Massachusetts General Hospital; CIA 2009

Dr. Welt and her team compared CGG repeat lengths in the 5' untranslated region of the FMR1 gene in women who have ovarian dysfunction-related infertility and in women with infertility from other causes. The investigators demonstrated that the frequency of premutation and intermediate alleles were higher in women with ovarian dysfunction than in women with other causes of infertility. Furthermore, the allele with the greatest number of CGG repeats was longer in women with ovarian dysfunction than in women with other causes of infertility. There was no effect of cigarette smoke exposure on follicle-stimulating hormone (FSH) or estradiol levels or response to treatment. The location of the pathologic effect of the FMR1 gene was examined, and ubiquitin staining intranuclear inclusions were identified in the stroma of the ovaries of women who carry the fragile X premutation. The investigators also demonstrated that genetic variants associated with early age at menopause are underrepresented in women with polycystic ovary syndrome (PCOS). These women have an increased follicle number compared to controls and higher levels of anti-Mullerian hormone. The interaction between cigarette smoking and SHS exposure on ovarian function was examined in these women. The data demonstrate that smokers have higher systolic and diastolic blood pressures and triglycerides and women with PCOS have higher triglycerides, waist circumference, fasting glucose, HOMA-IR, and lower HDL compared to controls.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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PRESENTATIONS AND ABSTRACTS

Welt CK. Relationship between smoking and parameters of metabolic syndrome in women with polycystic ovary syndrome and controls. Presented at the 94th Annual Meeting of the Endocrine Society. Houston TX, Jun 23-26, 2012.

EFFECT OF SECONDHAND TOBACCO SMOKE ON RESPIRATORY AND REPRODUCTIVE TRACT EPITHELIAL CELL PRODUCTION AND RELEASE OF CCL20

Margaret Crane-Godreau, PhD; Geisel School of Medicine at Dartmouth; YCSA 2006

Dr. Crane-Godreau and colleagues developed a mouse model that was used to show that chronic SHS exposure has a profound effect on barrier and secretory functions of the uterine epithelium, including diminished expression and production of CCL20, an antimicrobial and signaling peptide essential for competent innate immune protection. Moreover, levels of granulocyte macrophage colony-stimulating factor, chemokine (C-X-C motif) ligand 1, interleukin 9, and CCL3 are all lower in secretions from lipopolysaccharide-stimulated uterine epithelial cell cultures as compared to those from control mice.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Xia L, Crane-Godreau M, Leiter JC, Bartlett D, Jr. Gestational cigarette smoke exposure and hyperthermic enhancement of laryngeal chemoreflex in rat pups. *Respir Physiol & Neurobiol.* 2009;165:161-166.

PRESENTATIONS AND ABSTRACTS

Crane-Godreau MA, Jukosky JA, Fiering SF. Effects of cigarette smoke exposure on changes in gene expression in the uteri, bladders and lungs of FVB mice. Presented at the Society for Mucosal Immunology International Meeting. Boston, MA, Jun 2009.

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Crane-Godreau MA. Cigarette smoke exposure suppresses immune protection at the mucosa. Presented at the University of Vermont Medical School, Department of Obstetrics and Gynecology Research Seminar Series. Burlington, VT, Mar 13, 2008.

Crane-Godreau MA. Environmental influences on the changes in the lung--insights from vitamin D deficient and cigarette smoke exposed models. Presented at the Immunology and Cancer Immunotherapy Research Program (ICIP) Seminar, NCCC. Lebanon, NH, Mar 2009.

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Crane-Godreau MA. The cigarette smoke exposed-vitamin D deficient mouse model- new insights on lung pathology. Presented at the Veterans Administration Hospital Research Seminar. White River Junction, VT, Dec 2009.

Crane-Godreau MA. Vitamin D deficiency and cigarette smoke exposure induce COPD like disease in the mouse. Presented at the Dartmouth Medical School Endocrine Conference. Lebanon, NH, Feb 2011.

Maccani MA, Fiering SN, Eszterhas SK, Crane-Godreau MA. Tobacco smoke inhibits airway antimicrobial defense. Presented at the New England Immunology Conference. Woods Hole, MA, Oct 2006.

PREGNANCY AND PERINATAL EFFECTS

Completed Research

EFFECTS OF PRENATAL CS EXPOSURE ON ALLERGIC ASTHMA

Neerad C. Mishra, PhD; Lovelace Respiratory Research Institute; CIA 2009

Exposure to SHS exacerbates the development of allergic asthma in young children, particularly those of smoking mothers. The reason for this increase is not clear; however, epidemiological studies suggest that exposure to cigarette smoke (CS) during pregnancy is a risk factor in the offspring's development of childhood asthma and atopy. Previously Dr, Mishra and colleagues demonstrated that in utero exposure to CS increased the airway hyper-responsiveness (AHR) to methacholine; however, the effects of prenatal CS exposure on allergic responses have not been examined. Moreover, the mechanism by which in utero CS exposure affects lung function and elevates the risk of childhood asthma is largely unknown. Immune cells, such as lymphocytes and macrophages express alpha 7-nicotinic acetylcholine receptors (alpha 7nAChR) and several muscarinic acetylcholine receptors (mAChRs). Nicotinic and muscarinic receptors are also found on airway smooth muscle cells and lung parenchyma. Lymphocytes also express acetylcholine (ACh) synthetase, and upon activation, produce ACh. The investigators observed that while postnatal exposure to CS or nicotine (NT) suppresses immune and inflammatory responses, prenatal exposure activates the immune system and increases AHR. Moreover, while the CS/NT-induced immunosuppression is associated with activation of alpha 7nAChR, preliminary results suggest that activation of mAChRs results in immunostimulation. Because ACh is the only known physiological ligand for these receptors, the relative density and/or activation

status of nAChRs and mAChRs might determine the course of the immune response. Based on this, the researchers hypothesize that postnatal exposure primarily activates nAChRs, leading to suppression of immune and inflammatory responses; however, in utero CS exposure downregulates the density and/or tolerizes nAChRs. This loss of nAChRs function increases the access of ACh produced during an immune/inflammatory response toward mAChRs. The overstimulation of mAChRs encourages immune and inflammatory responses and higher AHR to allergens and methacholine. The investigators studied whether prenatal exposure to CS increases the intensity of allergic asthma and its Th2 correlates in offspring in order to ascertain the status of nAChRs and mAChRs on lung parenchymal and immune cells.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Singh SP, Gundavarapu S, Pena-Philippides JC, Rir-Sima-ah J, Mishra NC, Wilder JA, Langley RJ, Smith KR, Sopori ML. Prenatal secondhand cigarette smoke promotes Th2 polarization and impairs goblet cell differentiation and airway mucus formation. *J Immunol.* 2011;187(9):4542-4552.

Singh SP, Mishra NC, Rir-Sima-Ah J, Campen M, Kurup V, Razani-Boroujerdi S, Sopori ML. Maternal exposure to secondhand cigarette smoke primes the lung for induction of phosphodiesterase-4D5 isozyme and exacerbated Th2 responses: rolipram attenuates the airway hyperreactivity and muscarinic receptor expression but not lung inflammation and atopy. *J Immunol.* 2009;183(3):2115-2121.

Singh SP, Razani-Boroujerdi S, Pena-Philippides JC, Langley RJ, Mishra NC, Sopori ML. Early postnatal exposure to cigarette smoke impairs the antigen-specific T-cell responses in the spleen. *Toxicol Lett.* 2006;167(3):231-237.

SMOKING AND INTRAUTERINE GROWTH RESTRICTION

Alice Wang, MD; Boston Medical Center; YCSA 2009

Dr. Wang and colleagues investigated whether fetal growth restriction and shallow placentation affected by tobacco smoke exposure harbor a shared dysregulation of vascular growth and angiogenesis factors. They determined if placental development is regulated by hepatocyte growth factor (HGF) and hepatocyte growth factor activator inhibitor (HAI-1). The data suggest that maternal serum levels of HAI-1 may serve as a biomarker of intrauterine growth restriction (IUGR) later in pregnancy. *In vitro* data suggest that carbon monoxide (CO) may reduce HAI-1 levels. The team is investigating whether human fetal growth restriction is due to altered HGF signaling in the placenta that leads to impaired angiogenesis and trophoblast invasion. HAI-1 may be an important target of smoking-induced effects on fetal growth and placentation. The team sought to identify potential biomarkers in the HGF/HAI-1 pathway associated with IUGR, to define the role of HAI-1 in placental angiogenesis and trophoblast invasion, and to characterize the effect of CO and other components in cigarette smoke on the placental expression and production of growth and angiogenesis factors associated with IUGR.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Powe CE, Ecker J, Rana S, Wang A, Ankers E, Ye J, Levine RJ, Karumanchi SA, Thadhani R. Preeclampsia and the risk of large-for-gestational-age infants. *Am J Obstet Gynecol.* 2011;204(5):425 e421-426.

Wang A, Holston AM, Yu KF, Zhang J, Toporsian M, Karumanchi SA, Levine RJ. Circulating anti-angiogenic factors during hypertensive pregnancy and increased risk of respiratory distress syndrome in preterm neonates. *J Matern Fetal Neonatal Med.* 2012;25(8):1447-1452.

Wang A, Rana S, Karumanchi SA. Preeclampsia: the role of angiogenic factors in its pathogenesis. *Physiology (Bethesda).* 2009;24:147-158.

Wang A, Zsengeller ZK, Hecht JL, Buccafusca R, Burke SD, Rajakumar A, Weingart E, Yu PB, Salahuddin S, Karumanchi SA. Excess placental secreted frizzled-related protein 1 in maternal smokers impairs fetal growth. *J Clin Invest.* 2015;125(11):4021-4025.

FETAL-POSTNATAL SMOKE EXPOSURE: RESPONSE TO RSV INFECTION

Edward G. Barrett, PhD; Lovelace Respiratory Research Institute; CIA 2007

Dr. Barrett and colleagues used a mouse model to examine *in utero* exposure to SHS to determine if such exposure increases the severity of neonatal RSV infection. Offspring from female BALB/c mice exposed *in utero* to SHS and infected with RSV had significantly higher levels of bronchoalveolar lavage (BAL) macrophages at 6 days post-infection (PI) than RSV infected offspring exposed to air and offspring exposed to SHS only. Independent of *in utero* SHS exposure, RSV infection significantly decreased histone deacetylase activity in lung tissue at 2, 4, and 6 days PI, while *in utero* SHS exposure had no effect on HDAC activity. Alterations in HDAC activity could be a mechanism that regulates the expression of the inflammatory mediators involved in RSV infection. *In utero* SHS exposure affects how offspring respond to a subsequent respiratory infection later in life; this suggests that the *in utero* period is a crucial determinant for future susceptibility to infection.

FAMRI SUPPORTED RESEARCH

PRESENTATIONS AND ABSTRACTS

Day KC, Shinnick SS Harrod KS, Barrett EG. *In utero* second hand smoke increases RSV induced inflammation while RSV alone decreases HDAC activity in a neonatal mouse model [abstract]. *Am J Respir Crit Care Med* 2009;177:A3260.

Day KC, Shinnick SS, Harrod KS, Barrett EG. Effects of nicotine exposure on respiratory viral infections in a neonatal mouse model [abstract]. *Am J Respir Crit Care Med* 2009;177:A3261.

Day KC, Shinnick SG, Tipper JL, Harrod KS, Barrett EG. Maternal allergic status influences offspring's immune response to infection [abstract]. *Am J Respir Crit Care Med* 2008;177:A434.

SECONDHAND TOBACCO SMOKE AND SIDS: A LARYNGEAL CONNECTION?

Donald Bartlett, Jr., MD; Geisel School of Medicine at Dartmouth; CIA 2007

Dr. Bartlett found that the laryngeal chemoreflex (LCR) (i.e., apnea in response to intralaryngeal water, milk, gastric contents, or other fluids) is exaggerated in neonatal piglets and rats that are warmed 1–3ºC above their normal body temperature. Pregnant rats were exposed to artificially generated cigarette smoke or to nicotine, and the rat pups were examined to see whether the effect of high body temperature on the duration of the LCR is enhanced. The influence of hyperthermia on the LCR duration as a function of age in rat pups not exposed to cigarette smoke was determined. The hyperthermic exaggeration of the LCR is most striking in the youngest rats, aged 5 days or less, and disappears by 20 days of age. Subsequent findings with maternal smoke exposure during pregnancy showed an exaggeration of reflex apnea in the youngest animals. Gestational treatment with nicotine results in a similar prolongation of the LCR. These results indicate that maternal exposure to cigarette smoke prolongs laryngeal reflex apnea in the offspring, and is due, at least in part, to gestational nicotine exposure.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Xia L, Crane-Godreau M, Leiter JC, Bartlett D, Jr. Gestational cigarette smoke exposure and hyperthermic enhancement of laryngeal chemoreflex in rat pups. *Respir Physiol Neurobiol.* 2009;165(2-3):161-166.

Xia L, Leiter JC, Bartlett D, Jr. Laryngeal apnea in rat pups: effects of age and body temperature. *J Appl Physiol (1985).* 2008;104(1):269-274.

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EFFECTS OF SECONDHAND TOBACCO SMOKE ON PLACENTAL STEM CELL DIFFERENTIATION

Teresa M. Erb, MD; Magee Women's Health Corporation; YCSA 2007

Dr. Erb focused on four aims: 1) to produce a minimal media for maintenance of viable, differentiation-competent human embryonic stem cells (hESCs); 2) to determine the paracrine requirements for selective trophectoderm (TE) differentiation from hESCs in a defined minimal media; 3) to evaluate morphological transformation of hESCs to TE; and 4) to determine the requirement of histone deacetylases for TE formation from hESCs. The study conclusions provided information regarding the growth factors necessary for the differentiation of hESCs.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Erb TM, Schneider C, Mucko SE, Sanfilippo JS, Lowry NC, Desai MN, Mangoubi RS, Leuba SH, Sammak PJ. Paracrine and epigenetic control of trophectoderm differentiation from human

embryonic stem cells: The role of bone morphogenic protein 4 and histone deacetylases. *Stem Cells Dev.* 2011;20(9):1601-1614.

PRESENTATIONS AND ABSTRACTS

Erb TM, Mucko SE, Sammak PJ. Differentiation to trophectoderm from human embryonic stem cells and the role of histone deacetylases--a platform for pre-implantation epigenetic studies [abstract]. *Fertil Steril* 2009;92(3):S172-S172.

Erb TM, Rodriguez-Collazo P, Mucko SE, Leuba S, Sammak PJ. Centromeric heterochromatin assembly during human embryonic stem cell differentiation: Implications for aneuploidy [abstract]. *Fertil Steril* 2009;92(3):S171-S171.

EFFECTS OF SECONDHAND TOBACCO ON THE IMMATURE LUNG

Kathleen J. Haley, MD; Brigham and Women's Hospital; CIA 2007

Dr. Haley and colleagues investigated the effects of secondhand tobacco toxin exposure on the developing lung. The studies showed that this toxin exposure during development perturbs major signaling pathways, such as the vitamin A pathway and the vitamin D pathway. Additional studies showed that secondhand tobacco toxins cause abnormalities in RUNX transcription factors and T regulatory cells, which are important mediators of the immune response that are regulated by the vitamin A pathway. Even though the exposure to secondhand tobacco toxins occurs during development, the defects in the signaling pathways persist well into postnatal period. Dr. Haley's studies also showed that secondhand tobacco toxin exposure causes abnormalities in several autophagy effector proteins.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Haley KJ, Lasky-Su J, Manoli SE, Smith LA, Shahsafaei A, Weiss ST, Tantisira K. RUNX transcription factors: association with pediatric asthma and modulated by maternal smoking. *Am J Physiol Lung Cell Mol Physiol.* 2011;301(5):L693-701.

Haley KJ, Sunday ME, Porrata Y, Kelley C, Twomey A, Shahsafaei A, Galper B, Sonna LA, Lilly CM. Ontogeny of the eotaxins in human lung. *Am J Physiol Lung Cell Mol Physiol.* 2008;294(2):L214-224.

Manoli SE, Smith LA, Vyhlidal CA, An CH, Porrata Y, Cardoso WV, Baron RM, Haley KJ. Maternal smoking and the retinoid pathway in the developing lung. *Respir Res.* 2012;13:42.

PRESENTATIONS AND ABSTRACTS

An CH, Smith LA, Choi AMK, Haley KJ. Prenatal tobacco exposure and abnromalities in postnatal autophagy-associated proteins. Presented at the American Thoracic Society International Conference. New Orleans, LA , May 14-29, 2010.

Haley KJ, Manoli SE, Tantisira KG, Litonjua AA, Nguyen P, Kobzik L, Weiss ST. Maternal smoking causes abnormalities of the vitamin D receptor [abstract]. *Am J Respir Crit Care Med* 2009;179:A5874.

Haley KJ, Weiss ST, Tantisira KG. Maternal smoking causes abnormalities in RUNX1 expression [abstract]. *Am J Resp Crit Care Med* 2009;179:A1667.

Lu J, Zhang Y, Nguyen P, Fedulov A, Cernadas M, Kobzik L, Haley KJ. Maternal smoking causes postnatal T regulatory cell abnormalities. Presented at the American Thoracic Society Meeting. Philadelphia, PA, May 17-22, 2013.

SECONDHAND TOBACCO SMOKE AND NEONATES AND PREDISPOSITION TO COPD

Sharon A. McGrath-Morrow, MD; Johns Hopkins Medical Institutions; CIA 2007

Dr. McGrath-Morrow used a mouse model to determine if neonatal hyperoxia exacerbates adult lung sensitivity to cigarette smoke exposure and causes greater lung abnormalities than either exposure alone. Mice exposed to neonatal oxygen alone had significant increases in mean chord length (Lm) and decreased elastance compared to controls. The oxygen + cigarette smoke (CS; 6-month exposure) mice had similar increases in mean Lms as oxygen alone mice, similar increases in resistance and time constants as CS alone mice, but significantly larger residual volume and total lung capacity than all groups of mice tested. Surfactant protein C transcript and protein expression were found to be significantly decreased in the oxygen + CS mice compared to all other groups. Based on these findings, the investigators conclude that neonatal lung injury can exacerbate sensitivity to cigarette smoke exposure, increasing the risk of developing structural and functional lung abnormalities in the adult.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

McGrath-Morrow S, Lauer T, Yee M, Neptune E, Podowski M, Thimmulappa RK, O'Reilly M, Biswal S. Nrf2 increases survival and attenuates alveolar growth inhibition in neonatal mice exposed to hyperoxia. *Am J Physiol Lung Cell Mol Physiol.* 2009;296(4):L565-573.

McGrath-Morrow S, Rangasamy T, Cho C, Sussan T, Neptune E, Wise R, Tuder RM, Biswal S. Impaired lung homeostasis in neonatal mice exposed to cigarette smoke. *Am J Respir Cell Mol Biol.* 2008;38(4):393-400.

McGrath-Morrow SA, Lauer T, Collaco JM, Yee M, O'Reilly M, Mitzner W, Neptune E, Wise R, Biswal S. Neonatal hyperoxia contributes additively to cigarette smoke-induced chronic obstructive pulmonary disease changes in adult mice. *Am J Respir Cell Mol Biol.* 2011;45(3):610-616.

Yee M, Chess PR, McGrath-Morrow SA, Wang Z, Gelein R, Zhou R, Dean DA, Notter RH, O'Reilly MA. Neonatal oxygen adversely affects lung function in adult mice without altering surfactant composition or activity. *Am J Physiol Lung Cell Mol Physiol.* 2009;297(4):L641-649.

Yee M, White RJ, Awad HA, Bates WA, McGrath-Morrow SA, O'Reilly MA. Neonatal hyperoxia causes pulmonary vascular disease and shortens life span in aging mice. *Am J Pathol.* 2011;178(6):2601-2610.

LOW LEVEL PRENATAL TOBACCO EXPOSURE AND INFANT WHEEZE

Adam Spanier, MD, PhD, MPH; Cincinnati Children's Hospital, Pennsylvania State University; YCSA 2007

Dr. Spanier and colleagues characterized the relationship of prenatal tobacco exposure with infant wheezing. They used a birth cohort study of 398 mother-infant dyads and measured exposure by maternal report and serum cotinine levels. Of 367 children with respiratory outcomes, 26% were reported to have any tobacco exposure during pregnancy and 12% were reported to have maternal smoking exposure; however, 61% of mothers had measurable cotinine during pregnancy. Higher maternal prenatal cotinine level was associated with increased odds of wheeze in adjusted models. When reported maternal smoking and any other exposure was used instead of cotinine, the association between tobacco exposure and wheeze was weaker. One quarter of mothers reported any tobacco exposure during pregnancy, but over 60% were shown to be exposed based upon cotinine levels. Prenatal tobacco exposure and infant wheeze were only significantly associated when a biomarker of exposure was used. Consequently, at current levels of prenatal tobacco exposure there is exposure misclassification when relying upon reported exposures, with the potential to miss significant associations.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Howrylak JA, Spanier AJ, Huang B, Peake RW, Kellogg MD, Sauers H, Kahn RS. Cotinine in children admitted for asthma and readmission. *Pediatrics.* 2014;133(2):e355-362.

Lin C, Rountree CB, Methratta S, LaRusso S, Kunselman AR, Spanier AJ. Secondhand tobacco exposure is associated with nonalcoholic fatty liver disease in children. *Environ Res.* 2014;132:264-268.

Spanier AJ, Fiorino EK, Trasande L. Bisphenol A exposure is associated with decreased lung function. *J Pediatr.* 2014;164(6):1403-1408 e1401.

Spanier AJ, Kahn RS, Hornung R, Lierl M, Lanphear BP. Associations of Fraction of Exhaled Nitric Oxide with Beta Agonist Use in Children with Asthma. *Pediatr Allergy Immunol Pulmonol.* 2011;24(1):45-50.

Spanier AJ, Kahn RS, Kunselman AR, Hornung R, Xu Y, Calafat AM, Lanphear BP. Prenatal exposure to bisphenol A and child wheeze from birth to 3 years of age. *Environ Health Perspect.* 2012;120(6):916-920.

Spanier AJ, Kahn RS, Kunselman AR, Schaefer EW, Hornung R, Xu Y, Calafat AM, Lanphear BP. Bisphenol a exposure and the development of wheeze and lung function in children through age 5 years. *JAMA Pediatr*. 2014;168(12):1131-1137.

Spanier AJ, Kahn RS, Xu Y, Hornung R, Lanphear BP. Comparison of biomarkers and parent report of tobacco exposure to predict wheeze. *J Pediatr.* 2011;159(5):776-782.

MATERNAL SMOKING: FETUSES IN WITHDRAWAL?

Laura Stroud, PhD; The Miriam Hospital, Brown University; CIA 2007

Dr. Stroud examined the possibility of a fetal withdrawal syndrome from exposure to maternal smoking using ultrasound technology and a population of smoking and nonsmoking mothers matched for socioeconomic status, alcohol use, race, and age of life. The research team amassed a large number of statistics on this population and their children. Characterizing the effects of exposure to maternal cycles of daytime smoking and overnight abstinence on the developing fetus has implications for early identification and targeted intervention efforts to protect high-risk offspring and for intervention efforts to help pregnant smokers quit.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Bublitz MH, Stroud LR. Maternal smoking during pregnancy and offspring brain structure and function: review and agenda for future research. *Nicotine Tob Res.* 2012;14(4):388-397.

Lester BM, Miller RJ, Hawes K, Salisbury A, Bigsby R, Sullivan MC, Padbury JF. Infant neurobehavioral development. *Semin Perinatol.* 2011;35(1):8-19.

Salisbury AL, Ponder KL, Padbury JF, Lester BM. Fetal effects of psychoactive drugs. *Clin Perinatol.* 2009;36(3):595-619.

Stroud LR, Papandonatos GD, Rodriguez D, McCallum M, Salisbury AL, Phipps MG, Lester B, Huestis MA, Niaura R, Padbury JF, Marsit CJ. Maternal smoking during pregnancy and infant stress response: test of a prenatal programming hypothesis. *Psychoneuroendocrinology.* 2014;48:29-40.

Stroud LR, Paster RL, Papandonatos GD, Niaura R, Salisbury AL, Battle C, Lagasse LL, Lester B. Maternal smoking during pregnancy and newborn neurobehavior: effects at 10 to 27 days. *J Pediatr.* 2009;154(1):10-16.

PRESENTATIONS AND ABSTRACTS

Bublitz MH, Borrelli B, Dunsiger S, Wagner T, Papandonatos GD, Niaura R, Salsibury A, Lester B, Stroud LR. Child sexual abuse history predicts greater weekly drinking and smoking over pregnancy. Presented at North American Society of Obstetrics and Gynecology. Providence, RI, Apr 22-25, 2012.

Crespo F, Lense M, Salisbury A, Stroud LR. Maternal smoking and fetal neurobehavior: A pilot study. Presented at the 11th International Conference on Toxicology. Montréal, Canada, Jul 14-21, 2007.

Lense M, Stroud LR, Niaura R, Shenassa E, Lipsitt L, Paster R, LeWinn K, Buka S. Markers of fetal nicotine exposure and neonatal neurobehavior: The National Collaborative Perinatal Project. Presented at the 14th Annual Society for Research on Nicotine and Tobacco Meeting. Portland, OR, Feb 27 to Mar 1, 2008.

Marcello D, Lense M, Salisbury A, Stroud LR. Links between fetal and infant response in smoking-exposed and unexposed offspring: A pilot. Presented at the 38th Annual

International Society for Research on *Psychoneuroendocrinology* Conference. Madison, WI, Aug 19-22, 2007.

Stroud LR, Bublitz MH, McCallum M, Salisbury A, Padbury J, Marsit C. Methylation of placental glucocorticoid receptor gene (NR3C1) as a mediator of links between maternal smoking and infant neurobehavior. Presented at the New York Academy of Sciences Behavioral Epigenetics Conference. Boston, MA, Oct 29-30, 2010.

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Svenson AE, Stroud LR, Lester B, Lagasse L, Salisbury A, Niaura R. Does breastfeeding moderate the influence of smoking during pregnancy on newborn behavior? Presented at the Annual Mental Health Sciences Research Day, Brown Medical School. Providence, RI, 2008.

SECOND HAND TOBACCO SMOKE AND SEX DIFFERENCES IN AIRWAY DEVELOPMENT

Laura S. Van Winkle, PhD; University of California, Davis; CIA 2007

Dr. Van Winkle and her team determined the sex differences in the pattern of male and female postnatal airway epithelial differentiation. they also determined how SHS exposures during postnatal lung development affect antioxidant enzymes and how postnatal SHS exposure changes susceptibility to acute toxicity. They characterized oxidant and antioxidant enzyme systems and determined how they mature differently in male versus female mice. Female mice take longer to achieve adult levels of the enzyme systems, and their patterns of airway growth are different than males with less regular dispersion of Clara and ciliated cells. It had been shown that male and female mice have differential expression of the lung antioxidant enzyme glutathione S transferase pi (GSTpi) when exposed to sidestream smoke from birth to adulthood. The investigators examined the response of the developing lung acutely and after 2 days of recovery in filtered air in 4-week old postnatal mice. They found that SHS exposure in the postnatal mouse decreases expression of Clara cell secretory protein more than fivefold with a decreased expression of GSTpi and peroxiredoxin 6. Only the GSTpi expression decrease persists in the absence of SHS exposure, indicating that this enzyme system is slower to return to a steady state following cessation of exposure. There is an increase in glutamate cysteine ligase that wanes with time post-smoke exposure, indicating a possible tolerizing effect. These studies

indicate that SHS exposure changes the expression pattern of key protective mechanisms in the airways of the very young.

FAMRI SUPPORTED RESEARCH

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Van Winkle LS, Murphy SR, Edwards PC, Walby WF, Hyde DM, Schelegle ES. Effects of postnatal exposure history on airways: use of airway explant cultures to evaluate responses to acute oxidant stress [abstract]. *Am J Respir Crit Care Med* 2009;179:A4976.

ALTERED GENE EXPRESSION IN VASCULAR ENDOTHELIAL CELLS IN RESPONSE TO OXIDATIVE STRESS FROM SECONDHAND SMOKE

Mark L. Martinez, MD; University of Utah; YCSA 2006

Dr. Martinez' studies focused on the effects of SHS exposure on the endothelial cells that line the human vasculature in all parts of the body, including the umbilical vessels. The data indicate that the production of endothelin-1 (the most potent vascular constrictor in humans) is regulated by the RNA binding protein, T cell intracellular antigen 1-related protein (TIAR), and that abnormal regulation of TIAR through the formation of stress granules due to oxidant stress such as SHS exposure in endothelial cells is responsible for vascular injury and dysregulated vascular tone.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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CAUSES OF PERINATAL AND INFANT MORTALITY DUE TO FETAL NICOTINE EXPOSURE

Hugo Lagercrantz, MD, PhD; Karolinska Institutet; CIA 2005

Unborn fetuses exposed to tobacco products are at an increased risk of abortion, fetal death, and sudden infant death syndrome-related fatalities. Dr. Langercrantz described the developmental changes in reflex blood pressure regulation and heart rate in normal healthy infants, as well as in those infants at risk secondary to maternal use of tobacco products during pregnancy. The research methods included evaluation of the infant baroreflex by tilt table examination as well as induction of mild hypercapnia. Abnormal results may indicate delay or alteration in the cardiovascular stabilizing reflexes of the infant.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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MATERNAL EXPOSURE TO SECONDHAND TOBACCO SMOKE AND PREGNANCY OUTCOMES

John D. Meeker, MS, ScD; University of Michigan; YCSA 2005

In this epidemiological study, Dr. Meeker used archived data acquired from over 2500 couples who had taken part in a study of factors influencing *in vitro* fertilization (IVF) results. These data include medical and lifestyle questionnaires, SHS exposure self-assessment, results of IVF treatment, and urine cotinine measurements. This extensive database was used to investigate the association between SHS exposure and IVF results, adjusting for confounders. The dependent variables include a number of oocytes retrieved, percent of fertilized oocytes that develop into normal appearing zygotes, and embryo implantation rates. The percent of treatment cycles that result in clinical pregnancy and live birth, birth length and weight, preterm birth, and clinical pregnancy loss were also assessed. Archived follicular fluid was used to measure cotinine levels as a measure of direct oocyte exposure. The results show that there is an increased risk of miscarriage in women who were exposed to SHS as children.

FAMRI SUPPORTED RESEARCH

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Meeker JD, Rossano MG, Protas B, Diamond MP, Puscheck E, Daly D, Paneth N, Wirth JJ. Cadmium, lead, and other metals in relation to semen quality: human evidence for molybdenum as a male reproductive toxicant. *Environ Health Perspect.* 2008;116(11):1473-1479.

Meeker JD, Rossano MG, Protas B, Diamond MP, Puscheck E, Daly D, Paneth N, Wirth JJ. Multiple metals predict prolactin and thyrotropin (TSH) levels in men. *Environ Res.* 2009;109(7):869-873.

Meeker JD, Rossano MG, Protas B, Padmanahban V, Diamond MP, Puscheck E, Daly D, Paneth N, Wirth JJ. Environmental exposure to metals and male reproductive hormones: circulating testosterone is inversely associated with blood molybdenum. *Fertil Steril.* 2010;93(1):130-140.

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ROLE OF ERK IN AHR IN PRENATAL TOBACCO SMOKE EXPOSURE

Shashibushan P. Singh, PhD; Lovelace Respiratory Research Institute; CIA 2005

Dr. Singh and colleagues reported that maternal exposure to mainstream cigarette smoke (CS) markedly increases the risk for childhood allergic asthma in a murine model of bronchopulmonary aspergillosis. The investigators also reported that CS increases airway hyperreactivity (AHR) after acute intratracheal administration of *Aspergillus fumigatus* extract. Compared with controls, mice exposed prenatally to SHS exhibit increased lung inflammation, atopy, and airway resistance. They also produce a number of proinflammatory cytokines; interleukin (IL)-4, IL-5, IL-6, and IL-13, but not IL-2 or interferon-gamma. These changes, which occur only after allergen treatment with *A. fumigatus* extract, correlate with marked upregulated lung expression of M1, M2, and M3 muscarinic receptors and the phosphodiesterase-4D5 (PDE4D5) isozyme. The PDE4-selective inhibitor rolipram attenuates the increase in AHR, muscarinic receptors, and PDE4D5, but fails to downregulate lung inflammation, T helper cell-2 cytokines, or serum

immunoglobulin E levels. Thus, the fetus is extraordinarily sensitive to SHS exposure, and allergic asthma is induced after postnatal exposure to allergens.

FAMRI SUPPORTED RESEARCH

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THE ROLE OF GPR56 IN LUNG DEVELOPMENT AND SMOKING-RELATED LUNG DISEASE

Zhaohui Jin, MD; Children's Hospital of Boston at Harvard University; YCSA 2004

Exposure to mainstream smoke SHS has been associated with alterations in pulmonary function at birth and greater incidence of respiratory illnesses after birth, including asthma, sudden infant death, and lung cancer. Dr. Jin and colleagues hypothesized that G protein-coupled receptor 56 (GPR56) might be the target of nicotine and NNK during fetal lung development. GPR56 and its putative ligands may play an important role in tumor metastasis by regulating cell migration.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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SECOND HAND TOBACCO SMOKE EXPOSURE, MATERNAL STRESS, AND ADVERSE BIRTH OUTCOMES

Edmond Shenassa, ScD; The Miriam Hospital Brown University; YCSA 2004

Epidemiologic evidence suggests that exposure to SHS or its metabolites may be linked with gastrointestinal dysregulation among infants, specifically infantile colic (IC). The investigators examined whether exposure to SHS predicts elevated risk of IC. They established whether exposure to SHS predicts increased plasma motilin levels among infants and examined whether these levels predict infant risk of IC.

FAMRI SUPPORTED RESEARCH

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EFFECT OF SECONDHAND TOBACCO SMOKE ON FETAL BODY SIZE AND BRAIN SIZE

Hamisu M. Salihu, MD; University of Alabama at Birmingham, University of South Florida; YCSA 2003

The main purpose of this project was to estimate the association between prenatal tobacco smoke exposure and fetal and brain growth trajectories using ultrasound measurements. The results of the study added substantially to current knowledge regarding the relationship between SHS exposure and fetal morbidity *in utero*.

FAMRI SUPPORTED RESEARCH

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HORMONAL CHANGES

Completed Research

TOBACCO SMOKE EXPOSURE ASSOCIATIONS WITH HORMONAL CHANGES AND THE RISK OF SPONTANEOUS ABORTION

Offie P. Soldin, PhD, MBA (1952- 2014); Georgetown University; CIA 2009

Dr. Soldin and colleagues determined if there is an association between tobacco smoke exposure and inflammation in women of reproductive age. They found that active smoking and SHS exposure are associated with significant differences in the levels of several steroid hormones, thyroid hormones, and thyroid-stimulating hormone. Additionally, they examined associations between highly sensitive C-reactive protein (hsCRP), an acute marker of inflammation, and found positive correlations between tobacco smoke exposure and inflammation. The investigators recruited women who have suffered from a spontaneous abortion and compared their hormone levels to women who maintained successful pregnancies, matched for age, race, and gestation week to determine associations between tobacco smoke exposure with hormonal changes and the risk of spontaneous abortion. The team investigated whether changes in steroid hormones associated with tobacco smoke exposure are responsible for pregnancy outcome. Serum steroid hormone levels in both cases and controls were within the normal ranges for pregnancy, however, in the miscarriage group cortisol levels were higher and estrogen and progesterone levels were lower than in controls. The team investigated the relationships among free thyroid hormone levels, SHS exposure, and pregnancy outcomes. The differences were minor, but they may indicate that subclinical differences in thyroid function can contribute to adverse pregnancy outcomes.

FAMRI SUPPORTED RESEARCH

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SECONDHAND SMOKE AS AN ENDOCRINE DISRUPTOR

T. John Wu, PhD; Uniformed Services University of the Health Sciences; CIA 2007

Dr. Wu and colleagues investigated whether exposure to endocrine disruptors, including estrogen, mimics that act on the estrogen receptor (ER) and components of SHS, may result in an increase in vulnerability to stress. They tested whether exposure to SHS components in neonatal female rats can result in an increased behavioral vulnerability to stress via an estrogen pathway. The investigators determined the ability of neonatal SHS exposure to alter cognitive performance and emotional behavior subsequent to stress exposure in the adult using behavioral tests that index hallmark depressive symptoms in humans. Expression of ER underlying stress and estrogen signaling in female rats exposed to SHS during the neonatal age was also investigated.

SMOKE AND EARLY MENOPAUSE: MECHANISMS AND MODEL SYSTEMS

Diego H. Castrillon, MD, PhD; University of Texas Southwestern; CIA 2006

Dr. Castrillon and colleagues investigated whether the result of tobacco smoke exposure is an acceleration of ovarian aging via direct damage to the primordial follicle. The investigators developed a model system to clarify the major mechanisms by which SHS results in ovarian damage, and subjected female mice to SHS using a custom-fitted automated cigarette-smoking machine. Adult female mice were exposed to SHS for 16 or 22 weeks to mimic the impact of chronic SHS exposure and detailed histologic analyses of ovaries from SHS-treated and control female mice were performed. Decreased numbers of primordial follicles were evident at 16 and 22 weeks, demonstrating a direct toxic effect on primordial follicles. The team also determined if an increased rate of oocyte death contributes to, or is the primary mechanism, driving SHS-associated primordial follicle depletion. The investigators used counts of inflammatory cells to determine if such cells are recruited to SHS-damaged ovaries and therefore contribute to the observed SHS damage or response.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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TOBACCO SMOKE EXPOSURE AND GENETIC DISPOSITION ASSOCIATIONS WITH HORMONAL CHANGES IN WOMEN

Offie P. Soldin, PhD, MBA (1952-2014); Georgetown University; CIA 2006

Dr. Soldin and colleagues examined the associations between genetic polymorphisms in genes of the steroid hormone pathway and hormone concentrations in premenopausal women.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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PRESENTATIONS AND ABSTRACTS

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SPERMATOGENESIS

Completed Research

SECONDHAND SMOKE AS A POTENTIAL CAUSE OF SPERMATOGENIC FAILURES AND MALE INFERTILITY

Margarita Vigodner, PhD; Stern College, Yeshiva University; YCSA 2008

Dr. Vigodner and colleagues showed that exposure of mice to SHS induces an increased level of oxidative stress in testicular cells. The team employed DNA arrays to monitor gene

expression in testis of mice that were exposed to SHS for 24 weeks. The results revealed significant changes in differential expression of several genes. Candidate genes were characterized to better understand how SHS affects testicular gene expression. In addition, the investigators studied a post-translation modification, sumoylation, which is the covalent modification by small ubiquitin-like modifiers (SUMO proteins), and its role in oxidative stress, including SHS-induced stress. Their results show that SHS-induced stress has a dramatic effect on sumoylation in male germ cells, even before other pathways are activated; stress-induced changes in sumoylation may adversely affect spermatogenesis. A short exposure of human sperm to cigarette smoke extract caused protein desumoylation. The team identified several proteins as targets of SUMO in human sperm that have been implicated in sperm activation, capacitation, and acrosome reaction.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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PRESENTATIONS AND ABSTRACTS

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FUNCTIONAL CHARACTERIZATION OF SCCRO

Bhuvanesh Singh, MD; Memorial Sloan-Kettering Cancer Center; CIA 2006

Dr. Singh and colleagues focused on the functional characterization of squamous cell carcinoma-related oncogene (SCCRO), using developmental and biochemical models. SCCRO- /- mice have severe defects in spermatogenesis. It was found that while azoospermia is present at the end of the first round of spermatogenesis, gross defects in testicular mass are first detected at 3 months and progressively worsen with increasing age. Histopathological analysis suggested that the first round of sperm development

proceeds normally until about 5.5 weeks of age, at which time abnormal sperm begin to appear in the seminiferous vesicles. The testis are progressively filled with seminiferous tubules containing Sertoli cells, representing ~20% of all seminiferous tubules by 3 months and ~50% by 6 months. The sperm is grossly abnormal, with two predominant phenotypes seen, including sperm heads separated from the tail and those with multiple flagella and a markedly enlarged head. Scanning and transmission electron microscopy showed that the sperm have gross defects in mitochondrial arrangement, with detachment from the annulus and exposure of axonemes.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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KIDNEY DISEASE

Completed Research

ROLE OF NICOTINE AS MEDIATOR OF THE EFFECTS OF TOBACCO IN THE PROGRESSION OF CHRONIC KIDNEY DISEASE

Edgar Jaimes, MD; University of Alabama at Birmingham; CIA 2008

In the previous study, Dr. Jaimes and colleagues observed that human mesangial cells are endowed with nicotine acetylcholine receptors (nAChRs) and that nicotine promotes mesangial cell proliferation and extracellular matrix production (ECM) via increased generation of reactive oxygen species (ROS) (see below). The *in vivo* data suggest that nicotine worsens glomerular injury in an animal model of nephritis. They hypothesized that nicotine plays a major role in the pathogenesis of CKD by promoting mesangial cell proliferation and ECM deposition in the glomerulus and that COX-2-derived prostaglandins and ROS play a major role as mediators of these effects. They identified the role of nicotine exposure as a risk factor in the progression of glomerulosclerosis and investigated the effects of nicotine administration in vivo on proteinuria, glomerular injury, and ECM deposition in the 5/6 nephrectomy model of chronic kidney disease. In addition, they determined the effects of nicotine on glomerular production of ROS and cortical COX-2 expression, as well as the effects of COX-2 inhibition on renal injury in the 5/6 nephrectomy animals who received nicotine. The team investigated the mechanisms that mediate the growth-promoting effects of nicotine in the glomerular mesangium. COX-2-derived prostaglandins and cytokines such as TGF-beta and platelet derived growth factor may participate as mediators of ECM production and mesangial cell proliferation in response to nicotine.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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MECHANISMS OF ENDOTHELIAL DYSFUNCTION IN SMOKERS

Edgar Jaimes, MD; University of Miami Miller School of Medicine; YCSA 2003

Dr. Jaimes and colleagues determined that cigarette smoke and stable aldehydes present in large amounts in tobacco increase the generation of reactive oxygen species (ROS) via activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase in human pulmonary artery endothelial cells. They also determined that cigarette smoke induces the generation of ROS in human pulmonary artery smooth muscle by activating NADPH oxidase and xanthine oxidase. Increases in ROS were shown to be induced by cigarette smoke and to mediate the development of endothelial dysfunction. These results showed that human mesangial cells have nicotine receptors and that nicotine promotes mesangial hypertrophy and proliferation via increased generation of ROS. Nicotine was found to worsen renal injury in an animal model of acute nephritis that closely resembles acute glomerulonephritis in humans. Thus, the generation of ROS induced by stable compounds in cigarette smoke plays a major role in the pathogenesis of accelerated vascular injury in smokers. The investigators established the presence of nicotine receptors in the kidney and implicated nicotine as a mediator of renal injury in smokers.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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ARTHRITIS

Completed Research

INVESTIGATION OF ACTIVE AND SECONDHAND TOBACCO SMOKE AS TRIGGERS OF ARTHRITIS

Lars Klareskog, MD, PhD; Karolinska Institutet; CIA 2009

A large proportion of rheumatoid arthritis (RA) cases (25-40%) are caused by exposure to cigarette smoke in countries such as Sweden. Dr. Klareskog's research was directed at understanding the role of exposure to smoke (both active and passive smoking) in the etiology of RA. It is known that smoking is a risk factor for RA. This project is based on previous FAMRI-funded project (see below). In this continuation of the work, the investigators described in more detail which type of smoking habits induce which type of

immune reaction and investigated the genetic context in which this can occur. The investigators used a case control study of 3200 incident RA cases and 3600 matched controls to define the effects of exposure to smoke in precisely defined genetic contexts. The investigators placed emphasis on immunity to an array of citrullinated auto-antigens (both peptides and larger protein fragments). Studies were done to elucidate pathogenic potentials of such immunity. In addition, the longitudinal studies, which comprise a database of epidemiological investigation of RA from a 10-year clinical course, enabled the research team to closely determine effects of smoke exposure. They were also able to determine genotype and immunophenotype with regard to disease course, response to therapy, and risk for co-morbidities (in particular, cardiovascular disease) over time. The studies provided new understanding on how smoke exposure can cause certain types of RA, how smoke exposure can affect disease course, and may provide direction in the understanding of response to therapy.

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Klareskog L, Catrina AI, Paget S. Rheumatoid arthritis. *Lancet.* 2009;373(9664):659-672.

Klareskog L, Gregersen PK, Huizinga TW. Prevention of autoimmune rheumatic disease: state of the art and future perspectives. *Ann Rheum Dis.* 2010;69(12):2062-2066.

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Stolt P, Yahya A, Bengtsson C, Kallberg H, Ronnelid J, Lundberg I, Klareskog L, Alfredsson L, Group ES. Silica exposure among male current smokers is associated with a high risk of developing ACPA-positive rheumatoid arthritis. *Ann Rheum Dis.* 2010;69(6):1072-1076.

TOBACCO-CAUSED RHEUMATOID ARTHRITIS; GENES, MECHANISMS, AND SPECIFIC THERAPY

Lars Klareskog, MD, PhD; Karolinska Institutet; CIA 2004

A large case-control study of rheumatoid arthritis patients was used to determine the risk of arthritis development secondary to exposure to cigarette smoke in a potential dose dependent manner. An addition to the epidemiological portion of the study included data on SHS exposure. The investigators used animal models to describe the molecular pathways that are triggered by cigarette smoke exposure, which may be involved in the etiology of arthritis. This work was continued in another FAMRI grant (see above).

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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SKIN AND SHS

Completed Research

NICOTINIC RECEPTORS ALTER GENE EXPRESSION IN KERATINOCYTES

Sergei A. Grando, PhD, DSc; University of California, Irvine; CIA 2005

Dr. Grando and his team investigated the contribution of nicotine and tobacco smoke-induced alterations on the growth regulation of epidermal keratinocytes. The investigators sought to identify the long-term effects of nicotine and SHS on attainment of a specific cell state in cultured keratinocytes, and to determine the ACh metabolism and signaling in these cells. The signaling pathway that mediates cholinergic regulation of chemotaxis and galvanotropism was studied to elucidate the physiological mechanisms determining keratinocyte lateral migration. Results suggest that keratinocyte galvanotaxis is essentially chemotaxis toward the concentration gradient of ACh created by the highly positively charged field. Modifiers of the Ras/Raf-1/mitogen activated protein kinase kinase-1/extracellular signal-regulated kinase (MEK1/ERK) signaling pathway were shown to alter choline-directed chemotaxis and galvanotropism, suggesting the same signaling steps were engaged. Additionally, a7 nicotinic and M1 muscurinic receptors work together to orient a keratinocyte to the direction of its migration. Both seem to use the Ras/Raf-1/MEK1/ERK pathway, leading to upregulated sedentary integrin expression necessary for stabilization of the out pouching at the keratinocyte's leading edge. This study demonstrated that the Ras/Raf-1/MEK1/ ERK pathway is involved in the reorientation of keratinocytes that is needed for chemotaxis and galvanotaxis.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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PRESENTATIONS AND ABSTRACTS

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PASSIVE CIGARETTE SMOKE IN THE PATHOGENESIS OF SKIN CANCER

Barry Starcher, PhD; University of Texas Health Center at Tyler; CIA 2004

Chronic exposure to sunlight, i.e., ultraviolet B (UVB) irradiation, is the most common cause of nonmelanoma skin tumors. The effects of passive cigarette smoke superimposed on UVB irradiation on tumor development, skin pathology, and matrix changes in skin tumor in hairless SKH-1 mice were studied. Groups of 10 mice were exposed to 0.1 Joules per square centimeter of UVB five times a week for 20 weeks and/or exposure to passive cigarette smoke from 40 cigarettes a day over the same time period. UVB exposure resulted in an average of four large squamous cell tumors and 15 papillomas per mouse, whereas exposing the mice to both UVB + passive cigarette smoke completely prevented the skin tumor formation. Oxidative DNA damage was investigated and there were no significant changes in the levels of DNA adducts among control, smoke, UV, and UV + smoke groups, with the exception of 8-oxyguanine, which was significantly reduced in the presence of passive cigarette smoke. Immunohistochemistry results revealed that tumor necrosis factor receptor 2, glycogen synthase kinase 3 beta, nuclear factor kappa B/p65, the monoclonal antibody KI-67, and cyclooxygenase 2 were markedly upregulated by UVB exposure, whereas passive smoke exposure combined with the UVB irradiation completely

blocked the expression of these proteins. The results suggest that passive smoke exposure prevents UVB-induced tumors in mice by altering the NF-kappa B signaling pathway of tumorigenesis.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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PRECOCIOUS SKIN AGING DUE TO SECONDHAND SMOKE

Sergei A. Grando, PhD, DSc; University of California, Davis; CIA 2002

Please see text above under Dr. Grando's 2005 Award.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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DISEASE PREVENTION

Completed Research

PREVALENCE OF SMOKE-FREE CAMPUSES IN U.S. HOSPITALS AND BEST PRACTICES FOR IMPLEMENTATION

Sharon Milberger, ScD, PhD; Henry Ford Health System; CIA 2007

Dr. Milberger's team developed and administered an online survey to 4,494 US hospitals to establish baseline rates of existing smoke-free campuses and to correlate the adoption of such policies with rates of inpatient cessation counseling. Almost 43% of the hospitals responded to the survey. Of the participating hospitals, 45.2% reported having a smoke-free campus environment (i.e., smoking prohibited on all hospital property, indoors and outside, as well as designated no-smoking areas). More private nonprofit hospitals (57%) adopted such standards than for-profit hospitals (31.1%). Psychiatric hospitals (31.5%) are significantly less likely than general hospitals (48.5%) to have implemented a smoke-free campus. Similarly, teaching hospitals (38.4%) are less likely than nonteaching hospitals (50.9%) to have implemented a smoke-free campus. In Phase II of the study, in-depth phone interviews were conducted with a random sample of 182 of the 865 hospitals from the initial survey with smoke-free campuses. Data collected on planning, development, implementation, lessons learned, obstacles faced and how they were addressed, enforcement, and recommendations were analyzed. Based on the findings, it was determined that while hospitals were able to locate resources to assist them in developing and implementing their initiatives, they did not focus on enforcement and maintenance; organizations expressed interest in ways to address these areas. In Phase III the team conducted on-site meetings with ten hospitals that exhibited promising practices in this area.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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PRESENTATIONS AND ABSTRACTS

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EXPRESSION PROFILING OF BLOOD IN LUNG CANCER CHEMOPREVENTION

Christopher D. Coldren, PhD; University of Colorado, Denver; YCSA 2004

Dr. Coldren and colleagues demonstrated that the gene expression profiles from circulating peripheral blood mononuclear cells (PBMCs) can provide important biomarkers for the development of lung cancer as an adjunct to an ongoing clinical trial testing iloprost (a prostacyclin analog) for prevention of lung cancer in high-risk current and former smokers. The team collected PBMC gene expression data on the upper and lower quartile of iloprost trial enrollees prior to medication administration, and used the follow-up data and gene expression profiles to identify biomarkers for the early detection of lung cancer. Dr. Coldren and colleagues amassed a nearly complete set of RNA samples to construct a cohort for the final array experiment based on the degree of dysplasia change. This project enabled a grant from the American Cancer Society to expand the study in an additional cohort of individuals with newly identified lung nodules.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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BOOK CHAPTERS, ETC.

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LAW AND THE PREVENTION OF TOBACCO-RELATED DISEASE

Stephen P. Teret, JD, MPH; Johns Hopkins Bloomberg School of Public Health; CIA 2004

Dr. Teret examined how the Americans with Disabilities Act can be used to regulate smoking and SHS exposure in public places and the workplace and how it can affect the

appropriateness of class action lawsuits against the tobacco industry. He also investigated possible lessons for tobacco litigation that can be learned from lawsuits against other product manufacturers and legal issues that may be raised by the possibility that one or more tobacco companies could enter bankruptcy as a result of litigation.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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DIAGNOSTIC TECHNIQUES AND MEASUREMENT

Completed Research

IN VIVO MAPPING OF CILIARY BEAT FREQUENCY USING ULTRA HIGH SPEED FOURIER DOMAIN OPTICAL COHERENCE TOMOGRAPHY

Brian J. F. Wong, MD, PhD; University of California, Irvine Medical Center; CIA 2015

Ciliary beat frequency (CBF) is an important measurement of mucosal function in the upper aerodigestive tract, and is an excellent overall functional measure of respiratory airway health. It is difficult to measure and requires specialized hardware such as a phase contrast microscope and direct sampling of respiratory mucosa. Several groups have reported the *ex vivo* measurement and imaging of CBF using air-space laboratory bench optical coherence tomography imaging systems (OCT), which rely on light to generate high-resolution cross-sectional images of living tissue. Dr. Wong and colleagues have developed fundamental OCT imaging technology and imaging probes, catheters, and endoscopes. They also developed Doppler OCT and polarization sensitive OCT. They performed studies of OCT technology in upper airway imaging and the head and neck. In this study, the investigators focused on the development of a clinical high-speed, high resolution, Fourier domain OCT imaging system with the specific objective of imaging CBF *in vivo*. They worked on designing and constructing an OCT endoscope with the form factor of a conventional nasal endoscope that will allow a clinician to image and determine CBF in specific regions of the nose. They evaluated and refined the system in *ex vivo* fresh tissue models and *ex vivo* clinical specimens. Further, they evaluated the device in a pilot study consisting of subjects with no history of tobacco use or exposure and compared the results to those from a cohort of individuals with known chronic tobacco use.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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PRESENTATIONS AND ABSTRACTS

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HAIR AND TOENAIL NICOTINE AND POPULATION TOBACCO EXPOSURE

Wael K. Al-Delaimy, MD, PhD; University of California, San Diego; CIA 2009

Dr. Al-Delaimy and colleagues studied mean hair and toenail nicotine levels and their variability in a healthy general population in California with a range of SHS exposure, to assess the possibility of nicotine dependence among nonsmokers exposed to SHS. In 2014, they extended the study to Jordan, a country with high SHS exposure, and 600 nonsmokers and 100 smokers were recruited from around the country to determine the same variables in the healthy general population with a range of tobacco exposure. The investigators examined age and gender levels, including age- and gender-specific median and quartiles, for hair and toenail nicotine levels and they correlated self-reported exposure of active and involuntary smoking to biomarker levels in this heavily exposed population. Variables such as the number of cigarettes smoked or frequency of hookah use and duration of use at home, presence of home bans, presence of smokers at home, and other variables were assessed for the ability to predict toenail and hair nicotine levels, which will assist in identifying the short- and long-term exposure variables that best predict useful biomarkers and the ones that contribute to misclassification. The heavy exposure to SHS in Jordan enabled the determination of the hair and toenail nicotine levels relevant to categories of addiction among smokers, which can be compared with levels in nonsmokers to determine the possibility of nicotine dependence among the heavily exposed nonsmokers in this population.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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PRESENTATIONS AND ABSTRACTS

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ANALYZER FOR DETECTING EXPOSURE TO SECONDHAND SMOKE

Z. Hugh Fan, PhD; University of Florida; YCSA 2009

Dr. Fan and his colleagues developed a hand-held analyzer based on lab-on-a-chip technology that is capable of detecting SHS exposure and demonstrated its efficacy in a mouse model. The team developed two platforms; plastic microfluidic devices and paper-based analytical devices that can be optimized for clinical applications. The platforms could be low-cost alternatives to existing laboratory diagnostics. In addition, these platforms can be used at the point of care; rapid sample-to-answer analysis can help physicians make

quick and efficient clinical decisions. The team showed that it is feasible to use these devices to detect a panel of SHS biomarkers through separation or detection strategies with different labels, and that false positives and false negatives can be avoided by measuring a panel of biomarkers. This approach is more accurate than a single biomarker-based approach.

FAMRI SUPPORTED RESEARCH

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Liu K, Gu P, Hamaker K, Fan ZH. Characterization of bonding between poly(dimethylsiloxane) and cyclic olefin copolymer using corona discharge induced grafting polymerization. *J Colloid Interface Sci.* 2012;365(1):289-295.

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Xu X, Fan ZH. Concentration and determination of cotinine in serum by cation-selective exhaustive injection and sweeping micellar electrokinetic chromatography. *Electrophoresis.* 2012;33(16):2570-2576.

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Fan ZH. Fabrications and applications of laminated paper-based analytical devices (LPAD). Presented at the 7th International Conference on Microtechnologies in Medicine and Biology. Marina Del Rey, CA, Apr 10-12, 2013.

Fan ZH. Microfluidic platforms for biomarker detection. Presented at the CSIRO Cutting Edge Symposium: Lab-on-a-chip sensing platforms - interfacing physics with chemistry and biology. Melbourne, Australia, Jul 17-18, 2014.

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AIR FILTRATION SYSTEMS, SECONDHAND TOBACCO SMOKE AND RESPIRATORY DISEASE

Chris A. Pritsos, PhD; University of Nevada, Reno; CIA 2008

Dr. Pritsos and colleagues monitored the impact of filters commonly used by businesses to protect employees and customers from exposure to SHS. They determined the levels of tobacco smoke pollution, carbon monoxide (CO), and particulate matter (PM) 1.0, 2.5, and 10 microns in chambers with and without the various air filters. They accessed filter efficiency and compared them with inflammatory and oxidative parameters following exposure. The results showed that even with MERV 8 filters, which are the most efficient air filtration system used by businesses, at least 40% of the PM is not filtered out. Significant levels of PM 1.0 and 2.5, which are the most damaging to lungs, remained in the air after filtration. In addition, CO levels were not significantly reduced. These studies showed that air filters commonly used by businesses are not effective in reducing exposure to SHS. The team exposed C57/BL6 and BALB/C mice to SHS +/- air filters and monitored the impact on SHS-induced oxidative stress and inflammation in the lungs. Unexposed alveolar macrophages (AMs) of C57/BL6 mice showed greater cytokine response after lipopolysaccharide (LPS) stimulation than the AM of BALB/C mice. Following exposure, however, the C57/BL6 SHS-exposed AM had a decreased LPS-induced inflammatory response compared to unexposed counterparts, whereas the BALB/C SHS-exposed AM had an equivalent or greater inflammatory response. These results suggest that C57/BL6 mice and not BALB/C mice may express an endotoxin tolerance similar to that observed in human smokers.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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Muthumalage T, Hunter K, Redelman D, Pritsos K, Pritsos C. Commonly used air filters do not substantially reduce exposure to secondhand smoke constituents. Presented at the 50th Annual Meeting of the Society of Toxicology. Washington, DC, Mar 6-10 2011.

Muthumalage T, Pritsos K, Hunter K, Pritsos C. Effect of commercially used air filters on environmental tobacco smoke constituents and cytokine-mediated inflammatory response. Presented at the 51st Annual Meeting of the Society of Toxicology. San Francisco, CA, Mar 11-15, 2012.

HUMAN EXPOSURE ANALYSIS FOR POLLUTANTS FROM SECONDHAND SMOKE

Lynn Hildemann, PhD; Stanford University; 2007

Dr. Hildemann and colleagues optimized the SidePak™ real-time monitors that measure fine airborne particles so that they would reflect accurate particle mass concentrations for a range of environmental conditions (e.g., relative humidity) and for different types of particles (e.g., SHS versus ambient particles). Further, the investigators assessed the proximity effect of exposure under controlled indoor conditions and found that exposure to pollutants from an indoor emission source (e.g., a cigarette) is typically 2–6 times as high as the "well mixed room" prediction for someone located 1 meter or less from the source. Besides distance from the source, the proximity effect has been found to vary significantly with how the breathing height compares to the source height and with the ventilation rate in the room. The investigators extended the study of the proximity effect to "real world" conditions in a large-scale covert field survey of 44 casinos. The data show that the average airborne particle levels in smoking slot machine areas are 9 times as high as outdoors. In nonsmoking slot machine areas, the airborne particle levels depended on how well the area is separated from the smoking areas. Nonsmoking areas in the same room as smoking areas had concentrations 5 times as high as outdoors, whereas those areas that are located in a separate room with a closed door had concentrations much closer to outdoor levels.

FAMRI SUPPORTED RESEARCH

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MISSIVE STS PALMTOP: AN INTELLIGENT AID TO HELP PHYSICIANS IDENTIFY AND ELIMINATE STS EXPOSURE

Justin D. Pearlman, MD, PhD; Geisel School of Medicine at Dartmouth; CIA 2007

Dr. Pearlman and colleagues developed the IHealEMR© application for the iPhone, which captures information during a patient interview, and suggests key SHS questions in appropriate places. It covers the full range of Review of Systems (ROS) questions, integrates with legacy EMR software, reduces oversight errors and is easy to use. IHealEMR© increases productivity. It automatically generates a chart note and letters to patient and referring physician so a physician can focus on clinical issues. SHS exposure is covered within the diagnostic dialog supplied by IHealEMR© a physician uses to screen and diagnose every patient. The SHS questions in IHealEMR© probe patient SHS exposure and rate exposure severity and impact on patient health. The IHealEMR© application documents connections between SHS exposure and disease and facilitates efficient management of exposure without compromising physician productivity. Field trials were conducted that confirmed that physicians found value in and want to use IHealEMR© because it captures patient responses rapidly without typing, assures that physicians follow clinical best practices, works with their legacy Electronic Medical Record (EMR) or paper systems, and saves time by automatically generating a chart note and visit documentation for patients and referring physicians, eliminating time taken to write and edit. The project proceeded in six steps: 1) telephone interviews with national SHS experts; 2) face to face interviews with specialists in tertiary and primary care to identify their current rate of SHS behaviors; 3) Usability and acceptance interviews to test and fine-tune IHealEMR© user interface mockup; 4) Development of IHealEMR© iPhone application to ensure physicians to ask SHS questions during patient interviews; 5) building a knowledge base of SHS Best Practices; and 6) pilot testing IHealEMR© in three neighborhood healthcare clinics.

FAMRI SUPPORTED RESEARCH

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SCREENING AND DIAGNOSIS OF LARYNGEAL CANCER WITH OCT

Brian J. F. Wong, MD, PhD; University of California, Irvine Medical Center; CIA 2007

Dr. Wong and colleagues expanded their previous study using the optical computed tomography (OCT) device that they developed to image tobacco-related head and neck cancers. Patients can be imaged in an office-based setting where they can go for a revision under fiber optic examination and the lab can obtain OCT information of the different laryngeal tissues for various purposes, such as monitoring progress of disease or as a guide for surgical biopsies. A third generation swept-source OCT device attached to the rigid office-based endoscope system was developed, which allows for a faster image acquisition rate that decreases artifacts caused by the tremor of the examiner. Good images were successfully obtained from volunteers and *In vivo* OCT images of the dynamic vibration of the human vocal folds provided high-resolution cross-sectional images.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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A DISPOSABLE DEVICE TO MEASURE SECONDHAND SMOKE EXPOSURE

Zhiyong Cui, PhD; Geisel School of Medicine at Dartmouth; YCSA 2006

Dr. Cui planned to develop a disposable device with appropriate sensitivity for measuring the cotinine level of children in order to detect SHS exposure. The device would take advantage of the highly specific immunochemical reactions between antigens and antibodies of cotinine. Two commercial disposable products that were available at the time of this study, AccuSign® Nicotine and QuickScreen, did not have the sensitivity to detect the levels of cotinine that would be present in children exposed to SHS.

FAMRI SUPPORTED RESEARCH

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SIMULATION OF SECONDHAND TOBACCO SMOKE DEPOSITION IN THE AIRWAYS

Jeffrey J. Heys, PhD; Arizona State University , Montana State University; YCSA 2006

Dr. Heys and colleagues developed a higher-order mathematical model of airflow and particle transport in the human airways to better understand the movement and deposition of inhaled particles, both destructive and therapeutic. They also developed accurate computational geometries of patient-specific airways to understand the relationship between airborne particles and smoking. The investigators validated the mathematical models by measuring the deposition of radio labeled tobacco smoke and radio labeled polystyrene particles in rats. The team conducted *In vivo* experiments that show strong agreement with the simulation predictions.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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DETECTION OF PASSIVE SMOKE EXPOSURE IN CHILDREN AND ADULTS USING ORAL BASED RAPID TEST TECHNOLOGY.

Sam Niedbala, PhD; Lehigh University; CIA 2006

A 20-minute test that detects low levels of nicotine breakdown products that employs small amounts of saliva was developed. The test is noninvasive and easy to use, thus can assist physicians and researchers in identifying those at risk for illness caused by SHS exposure. The investigators looked for reagents that can rapidly identify the lowest possible level of nicotine metabolites from a viscous oral fluid sample. A variety of derivatives were developed for use as haptens, which were coupled to carrier proteins under a variety of conditions to optimize analytical sensitivity. Additionally, these conjugates were used as immunogens to generate antibodies. Evaluation of candidate hapten conjugates were subjected to a number of tests to qualify them for further study. Once qualified, reagents were tested for feasibility in a lateral flow format. Work with various human gland fluids following a small dose of nicotine ingestion suggests that oral fluids to be tested may be collected from either the parotid or submandibular oral glands.

FAMRI SUPPORTED RESEARCH

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ADVANCES IN MONITORING EXPOSURE TO SECONDHAND TOBACCO SMOKE IN THE AIR AND IN THE BODY

Mark J. Travers, PhD; Roswell Park Alliance Foundation; YCSA 2006

Dr. Travers and colleagues validated a method to measure exposure to tobacco smoke pollution (TSP) using a continuous fine particle monitor. It was validated against existing gold standard methods and against biological markers of TSP exposure. This method has resulted in a large data set, including data on air quality, as determined by real-time fine particle concentrations, the presence of smoking and smoke-free air policies, and physical

descriptions of hospitality venues in over 3,000 places in the US and over 60 countries. The team has trained hundreds of researchers on the use of this method via in-person trainings, Webinars, a Web site (www.tobaccofreeair.org), and training videos on DVD and the Web. This method is now one of the most common ways of measuring TSP-derived particulate matter to show the efficacy of smoke-free air policies, and serves as the foundation on which decisions relating to the health effects of SHS exposure can be based. The investigators used and validated the measure of TSP exposure in microenvironments where exposure occurs and expanded its use to more geographic areas of the world, including developing countries. Further, the team used the method to evaluate the emissions of alternative smoking products and to disseminate the findings.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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THE MACRONOME AS A TOOL FOR EARLY CANCER DIAGNOSIS

Samuel R. Denmeade, MD; Johns Hopkins Medical Institutions; CIA 2005

Dr. Denmeade employed proteomics-based strategies to analyze body fluids for changes in protein profiles and the presence of individual proteins that may be useful as tumor biomarkers. Proteases meet the requirements for reliably secreted biomarkers and potential therapy targets. Alpha-2- macroglobulin (A2M) is a broad-spectrum protease inhibitor that covalently binds proteases. Dr. Denmeade investigated the macronome (the population of A2M-bound proteases) to map circulating protease changes specific to bladder cancer, which is often not detected until the cancer is at an advanced stage. The technique was validated by A2M capture of proteases *In vitro* from media conditioned with a bladder cancer cell line. The macronome technique was tested in a mouse model and in human bladder cancer patients.

FAMRI SUPPORTED RESEARCH

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DEVELOPMENT OF A NONINVASIVE DIAGNOSTIC METHOD FOR DETECTING GENETICALLY ALTERED CELLS PRESENT IN ORAL MUCOSA OF HIGH RISK PATIENTS

AND IN PREMALIGNANT ORAL LESIONS BY USING MULTIPARMETRIC CELL SCANNING SYSTEM WHICH COMBINES MORPHOLOGY AND FLUORESCENT *IN-SITU*

Abraham Hirshberg, MD, DMD; Tel Aviv University; CIA 2005

Dr. Hirshberg developed a noninvasive diagnostic tool for detecting genetically-altered cells in premalignant oral lesions and in normal-looking oral mucosa in high-risk patients, using a technique that combines morphological observations and fluorescent *in situ* hybridization (FISH). He used oral brush samples to collect cells from suspicious lesions and from normal-appearing mucosa of high-risk patients to analyze ploidy. Dr. Hirshberg showed direct correlations among the presence of aneuploid cells in brush samples from oral leukoplakia, the severity of the histopathologic diagnosis, and the outcome of the patients. All samples obtained from cancerous lesions contained a significant proportion of aneuploid cells. This method is easy to perform, reproducible, and highly sensitive. Aneuploid cells can be detected in early stages of oral carcinogenesis. The supplement of a brush sample and the combined morphological and FISH analysis increase the specificity in predicting the nature of a suspicious oral lesion in order to guide treatment and improve outcome.

FAMRI SUPPORTED RESEARCH

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Hirshberg A, Yarom N, Amariglio N, Yahalom R, Adam I, Stanchescu R, Ben-Dov I, Taicher S, Rechavi G, Trakhtenbrot L. Detection of non-diploid cells in premalignant and malignant oral lesions using combined morphological and FISH analysis - a new method for early detection of suspicious oral lesions. *Cancer Lett*. 2007;253(2):282-290.

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A NEW METHOD TO DETECT EARLY CHANGES OF EMPHYSEMA IN PERSONS EXPOSED TO SECONDHAND CIGARETTE SMOKE

Talissa Altes, MD; University of Virginia; CIA 2004

Dr. Altes studied the use of diffusion helium MRI as a method to detect early changes of emphysema in persons exposed to SHS. Diffusion MRI makes images of the size and morphology of the distal airspaces of the lung using hyperpolarized helium-3 (^{3}He) as the contrast agent. This technique appears to be very sensitive in determining early changes in

emphysema. Dr. Altes and colleagues found that 67% of active smokers, 27% of healthy people with a high exposure to SHS, and only 4% of healthy people with a low exposure to SHS had changes in their lungs that could be detected using hyperpolarized ^{3}He MRI. This demonstrates that SHS is damaging to the lung and provides a dose-response relationship between cigarette smoke exposure and changes in the lung.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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ECG-GATED MULTIDETECTOR CT OF AORTIC DISTENSIBILITY

Joel Fletcher, MD; Mayo Clinic; CIA 2004

Dr. Fletcher optimized electrocardiogram (ECG)-gated multidetector CT technology and developed software algorithms that can automatically and reproducibly calculate regional changes in aortic pulsatility in patients with abdominal aortic aneurysm (AAA). He tested the hypothesis that aortic aneurism distensibility is an independent risk factor for AAA rupture or a candidate for intervention. One hundred patients with AAA who are likely to be followed by CT scanning and unlikely to undergo immediate surgery were recruited. These individuals underwent time-resolved ECG-gated multidetector CT angiography at baseline and 1-year follow up. Novel aortic distensibility software was used to create aortic pulsatility maps and quantitate maximum aortic distensibility associated with each AAA. This information was compared to clinical outcome to determine if aneurism distensibility can predict rupture.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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EARLY DETECTION AND SCREENING OF SMOKING-RELATED CANCERS BY USE OF GREEN FLUORESCENT PROTEIN EXPRESSING HERPES SIMPLEX VIRUS

Yuman Fong, MD; Memorial-Sloan Ketttering Cancer Center; CIA 2004

Dr. Fong and colleagues used viruses designed to infect cancer cells for early detection to see if these viruses can reverse the process of cancer formation. The investigators demonstrated that fluorescence-assisted viral detection of cancer is possible and can be used to improve early diagnosis of cancer and its treatment. In animal and in human studies, the team was able to detect one tumor cell in the background of one million normal cells (50 times improvement over traditional cytology). The fluorescence that is indicative of cancer cells can be read by personnel with rudimentary training or by automated techniques. This can lead to rapid and high throughput detection of many cancers including lung, oral, pancreatic, and stomach. This technique also uses viruses that can be produced in a relatively inexpensive way. This could be used for cytologic screening of patients, even in rural areas of developing nations where cigarette smoking is still popular and produces cancer.

FAMRI SUPPORTED RESEARCH

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FUNCTIONAL MRI INVESTIGATION OF IMPAIRED LEPTIN REGULATION DUE TO SECONDHAND TOBACCO SMOKE

Yijun Liu, PhD; University of Florida; CIA 2004

Dr. Liu investigated whether the functional regulation of leptin in the brain is impaired due to SHS exposure, leading to elevated blood leptin levels, which may contribute to SHS-related conditions in cerebrovascular and cardiovascular diseases. Dr. Liu correlated functional MRI with biochemical measurements of leptin, insulin, and counter-regulatory hormones such as epinephrine and norepinephrine in groups of SHS-exposed individuals, chronic smokers, and non-smokers.

ADVANCED CARDIOVASCULAR IMAGING CENTER

Justin D. Pearlman, MD, PhD; Geisel School of Medicine at Dartmouth; 2003

Dr. Pearlman assessed the feasibility of characterizing tumor angiogenesis noninvasively for early accurate cancer diagnosis using MRI-based analysis that can visualize and characterize microvascular development *in vivo*. A three-dimensional robotic microscope was developed as a method for characterizing the effects of early cancers on microvascular changes. Additionally, a dynamic MRI was developed to evaluate pulmonary vasculature in and around early cancer nodules to distinguish them from inflammatory nodules and benign lesions such as scar tissue.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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QUANTIFYING HUMAN EXPOSURE TO SECONDHAND TOBACCO SMOKE

Paul Switzer, PhD; Stanford University; 2003

The investigators demonstrated that SHS respirable particle concentration in public places when smoking occurred exhibited a variation in concentrations depending on the distance from the smoker and the position of the individual with respect to the wind. Peak and average outdoor SHS levels near smokers rivaled indoor tobacco smoke concentrations when active smoking was occurring. Thus, outdoor SHS presented a nuisance or hazard under certain conditions comparable to indoor exposure to SHS. In indoor measurements it was shown that closing a door between rooms effectively prevented transport of air pollutants. When doors were left open, the reduction in average concentrations was only

20-50%. An indoor air model accurately predicted the observed percent reduction in average concentrations. Modeling exposure in multicompartment homes indicated that the multicompartment nature of these dwellings causes substantial variation in nonsmoker SHS exposure. The two most effective strategies in reducing SHS exposure in homes were isolation of the smoker in a closed room with an open window and a ban on smoking whenever the nonsmoker was at home. The use of open windows to supply ventilation, or the operation of portable filtration devices in smoking rooms provided moderate exposure reductions. Closed doors, by themselves, were not effective.

FAMRI SUPPORTED RESEARCH

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OPTICAL DIAGNOSIS OF EARLY LARYNGEAL CANCER

Brian J. F. Wong, MD, PhD; University of California, Irvine Medical Center; CIA 2003

Dr. Wong constructed an optical coherence tomography (OCT)-based device for use in a physician's office to image and differentiate early laryngeal cancers from benign laryngeal diseases. OCT is a non-contact imaging modality that uses light to construct high-resolution (7 micron) cross-sectional images of tissue to depths of up to 1- 2mm. All upper aerodigestive tract tobacco related diseases were included in the study of 150 patients. These data comprised the core of a proposal to the NIH to accelerate the clinical implementation of the technology.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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PRESENTATIONS AND ABSTRACTS

Guo S, Xie T, Peavy GM, Wong BJF, Chen Z. Three-dimensional structural and local birefringence imaging of the bovine meniscus by use of OCT and PSOCT. *Proceedings Vol 6079, Domain Optical Methods and Optical Coherence Tomography in Biomedicine X; 60792D* Presented at SPIE BiOS. San Jose, CA, Feb 20, 2006.

RISK OF CORONARY HEART DISEASE AMONG WOMEN EXPOSED TO SECONDHAND SMOKE

Wael K. Al-Delaimy, MD, PhD; University of California, San Diego; YCSA 2002

Dr. Al-Delaimy assessed the associations among SHS exposure, coronary heart disease (CHD), and lung cancer using toenail nicotine levels as a biomarker of exposure. The study was based on data collected from the large Nurses Health Study and Health Professionals follow-up study. The team's results show that toenail nicotine biomarkers reflect additional risk for CHD not previously captured by questionnaires alone. Furthermore, toenail biomarkers are related to SHS exposure even after adjusting for other factors, such as age and active smoking. Toenail nicotine levels are predictive of CHD among women, independent of other risk factors, even after adjustment for history of cigarette smoking. The toenail nicotine biomarker was shown to be a strong predictor of lung cancer independent of smoking history. This suggests that studies of lung cancer risk that are based only on smoking history have underestimated the adverse effects of smoking.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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Al-Delaimy WK, Stampfer MJ, Manson JE, Willett WC. Toenail nicotine levels as predictors of coronary heart disease among women. *Am J Epidemiol.* 2008;167(11):1342-1348.

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EXPOSURE TO SHS/MOLECULAR STUDIES

Completed Research

TOBACCO SMOKE BIOAEROSOL

Lennart P. Larsson, PhD; Lund University; CIA 2010

Dr. Larsson and colleagues characterized the production of inflammatory mediators in cell cultures challenged with SHS that contained varying concentrations of smoking-produced endotoxin and other microbiological compounds. They also determined endotoxin, peptidoglycan, fungal biomass, (1-->3)-beta-D-glucan, and mycotoxins in mainstream cigarette smoke, SHS, and water-pipe smoke by using biological and chemical-analytical assays. In addition, they determined whether smoking results in an increase in the concentration of airborne viable microorganisms. The study provided information about the associations between exposure to SHS and the development of respiratory disease. Public awareness that smoking entails inhaling of microorganisms and toxic microbial products may help to keep non-smokers from starting to smoke.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Larsson L, Pehrson C, Dechen T, Crane-Godreau M. Microbiological components in mainstream and sidestream cigarette smoke. *Tob Induc Dis.* 2012;10(1):13.

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PRESENTATIONS AND ABSTRACTS

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Szponar B, Pehrson C, Larsson L. Biological components of tobacco smoke aerosol. Presented at the Workplace and Indoor Aerosols Conference. Lund, Sweden, Apr 19-20, 2012.

EARLY DETECTION OF LUNG CANCER IN AFRICAN AMERICANS EXPOSED TO SECONDHAND SMOKE

Feng Jiang, MD, PhD; University of Maryland; CIA 2008

Dr. Jiang and colleagues evaluated the efficacy of combining computerized tomography (CT) and genetic analysis of sputum for noninvasive diagnosis of stage I non-small cell lung cancer (NSCLC) in African American nonsmokers exposed to SHS. The investigators optimized a panel of genes by using an *in situ* mini-chip for measuring changes of the signatures in sputum of a case-control cohort of 49 NSCLC patients, 49 patients with COPD, and 49 healthy smokers. The team then validated the genes in an independent cohort of 69 NSCLC patients and 65 subjects without cancer. The results were compared with those of sputum cytology. Fifteen genes showed significant differences of their copy number changes in sputum between NSCLC and both COPD and healthy subjects. A logistic regression model with the best prediction was built on the basis of the following six genes: ENO1, FHIT, HYAL2, SKP2, p16, and 14-3-3 epsilon. The composite of the six genes produced 86.7% sensitivity and 93.9% specificity in distinguishing stage I NSCLC patients from the individuals without cancer. Furthermore, the genes had higher sensitivity (86.9%) in identification of squamous cell carcinoma (SCC) than in adenocarcinoma of the lungs (80.8%; $P < 0.05$). Validation of the genes in the independent cohort confirmed their diagnostic power, which showed higher accuracy for lung SCCs than for sputum cytology.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Jiang F, Qiu Q, Khanna A, Todd NW, Deepak J, Xing L, Wang H, Liu Z, Su Y, Stass SA, Katz RL. Aldehyde dehydrogenase 1 is a tumor stem cell-associated marker in lung cancer. *Mol Cancer Res.* 2009;7(3):330-338.

Jiang F, Todd NW, Li R, Zhang H, Fang H, Stass SA. A panel of sputum-based genomic marker for early detection of lung cancer. *Cancer Prev Res (Phila).* 2010;3(12):1571-1578.

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Li T, Su Y, Mei Y, Leng Q, Leng B, Liu Z, Stass SA, Jiang F. ALDH1A1 is a marker for malignant prostate stem cells and predictor of prostate cancer patients' outcome. *Lab Invest.* 2010;90(2):234-244.

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TOBACCO SMOKE ENDOTOXIN

Lennart P. Larsson, PhD; Lund University; CIA 2007

Dr. Larsson and his colleagues demonstrated that cigarette mainstream smoke contains large amounts of potent bacterial constituents such as endotoxins and peptidoglycans as well as fungal (e.g., mold) components. These substances stem from microorganisms in the tobacco. Endotoxin causes severe respiratory disease upon inhalation, and peptidoglycan is proinflammatory; both types of toxins interact with the immune system through Toll-like receptors. The investigators found that: 1) ten different brands of American cigarettes purchased in the US were similar in microbial load to cigarettes of international brands purchased in Europe and Asia; 2) there were no detectable microbial components in

sidestream smoke unlike in mainstream and SHS; 3) that smoking indoors resulted in a 90-fold and 658-fold increase in air concentrations of endotoxin and fungal material, respectively; and 4) that less fungal material but more bacterial toxins were found in mainstream water-pipe smoke than in mainstream cigarette smoke. The investigators determined whether these last differences depend upon different combustion conditions or different compositions of the tobacco used. It is clear that SHS is rich in biologically potent bacterial and fungal components.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Larsson L, Szponar B, Ridha B, Pehrson C, Dutkiewicz J, Krysinska-Traczyk E, Sitkowska J. Identification of bacterial and fungal components in tobacco and tobacco smoke. *Tob Induc Dis.* 2008;4:4.

PRESENTATIONS AND ABSTRACTS

Larsson L Pehrson C, Szponar B. Bacterial and fungal components in tobacco smoke. Presented at 14th World Conference on Tobacco or Health. Mumbai, India, Mar 8-12, 2009.

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Pehrson C, Ridha B, Szponar B, Larsson L. Microbial marker patterns in smoke and tobacco of cigarettes purchased in six different countries. Presented at the American Academy of Allergy Asthma and Immunology annual meeting. Philadelphia, PA, Mar 14-18, 2008.

SECONDHAND TOBACCO SMOKE-INDUCED HEART AND BRAIN INJURY

Kevin K. Wang, PhD, Mark S. Gold, MD; University of Florida; CIA 2006

Dr. Wang and colleagues showed that SHS perturbs brain biochemistry in a rat model, and results in central nervous system injury due to the extensive amounts of gaseous free radicals (e.g., superoxide anions, nitrogen oxides, reactive aldehyde species, nitric oxide, and peroxynitrite). SHS induces a prominent increase in the glia marker, glial fibrillary acidic protein, suggesting that increased reactive gliosis is an inflammatory response. The investigators analyzed body fluids, including cerebrospinal fluid and serum for neuronal markers, e.g., alpha II spectrin and ubiquitin carboxyl-terminal esterase L1 proteins, which can serve as potential biomarkers for SHS exposure. Dr. Wang's group also showed that SHS exposure promotes rapid overactivation of proteases and increased cellular oxidative stress in cardiac tissue. The data show further that cardiac tissue exposed to SHS increases the expression of glycogen phosphorylase BB protein, which is a diagnostic marker of acute coronary syndromes, and markers such as light chain 3-I (LC3-I) and LC3-II, which are indicative of autophagic induction. This was coupled with pronounced cardiomyopathy represented by cardiac hypertrophy and interstitial fibrosis. The team used a semi-quantitative proteomics technique to analyze the mechanism by which SHS induces cardiac injury.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Fuller BF, Gold MS, Wang KK, Ottens AK. Effects of environmental tobacco smoke on adult rat brain biochemistry. *J Mol Neurosci.* 2010;41(1):165-171.

Guingab-Cagmat J, Bauzo RM, Bruijnzeel AW, Wang KK, Gold MS, Kobeissy FH. Methods in tobacco abuse: proteomic changes following second-hand smoke exposure. *Methods Mol Biol.* 2012;829:329-348.

Guingab-Cagmat JD, Stevens SM, Jr., Ratliff MV, Zhang Z, Gold MS, Anagli J, Wang KK, Kobeissy FH. Identification of tyrosine nitration in UCH-L1 and GAPDH. *Electrophoresis.* 2011;32(13):1692-1705.

CARBON MONOXIDE HYPOXIA IN TOBACCO SMOKE INDUCED DISEASE

J. Timothy O'Neill, PhD; Uniformed Services University of the Health Sciences; CIA 2005

Dr. O'Neill's laboratory used chronic carbon monoxide (CO) hypoxia as a model of cigarette smoking in mice to examine cardiovascular adaptive changes. Mice were exposed to 0, 100, or 500 ppm CO for 30 days. Blood pressure dropped in the group with the highest CO and stayed lower than those with low CO or no CO exposure. Weight of the 500 ppm group fell for the first week of exposure but returned to normal thereafter. At day 30, total hemoglobin was significantly elevated from 18.4 to 20.7 and 30.0 gms % by 100 ppm and 500 ppm, respectively. Carboxyhemoglobin was also increased by CO exposure from 4.5 to 17.2 and 53.4%, respectively. Two hypoxia inducible factor 1 alpha-regulated proteins, vascular endothelial growth factor and erythropoietin, were also found to increase in brain and kidney with increased CO exposure. These data suggest that mice adapt to chronic CO hypoxia by increasing hemoglobin and microvascular proliferation rather than by cardiac output to maintain tissue oxygenation. The increase in erythropoietin in the brain is neuroprotective.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Trentini JF, O'Neill JT, Poluch S, Juliano SL. Prenatal carbon monoxide impairs migration of interneurons into the cerebral cortex. *Neurotoxicology.* 2016;53:31-44.

PRESENTATIONS AND ABSTRACTS

O'Neill JT, Trentini J, Li A, Halim N, Ren M, Xing G, Thaker J, Verma A. Cardiovascular (CV) adaptation to chronic mild carbon monoxide (CO) hypoxia in mice [abstract]. FASEB J 2007;21:A1287-A1288.

LDL OXIDATION BY SECONDHAND TOBACCO SMOKE

JeanClare Seagrave, PhD; Lovelace Respiratory Research Institute; CIA 2005

Dr. Seagrave's specific aims were 1) to determine the capacity of SHS to oxidize low-density lipoprotein (LDL) in the vascular compartment of a physiologically relevant *in vitro* model; 2) to determine the relationships among SHS exposure, increased levels of oxidized LDL, atherogenesis, and the potential for an antioxidant-rich diet to reduce LDL oxidation and

progression of atherosclerotic lesions using an atherosclerosis-susceptible strain of mice; and 3) to evaluate the oxidation of LDL in an isolated-perfused rat lung model.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Pickett G, Seagrave J, Boggs S, Polzin G, Richter P, Tesfaigzi Y. Effects of 10 cigarette smoke condensates on primary human airway epithelial cells by comparative gene and cytokine expression studies. *Toxicol Sci.* 2010;114(1):79-89.

ORGANISMAL EFFECT OF TOBACCO SMOKE ON TELOMERASE NULL MICE

Kwok-Kin Wong, MD, PhD; Dana-Farber Cancer Institute; CIA 2005

Dr. Wong's hypothesis was that when exposed to SHS, mice engineered to have critically short dysfunctional telomeres would be predisposed to accelerated organ failure and higher frequency of tumorigenesis in the lung and other organs. He chronically exposed cohorts of wild-type mice, telomerase-null mice with long telomeres, and telomerase-null mice with shortened telomeres, to SHS. These mice were analyzed for level of inflammation, cell proliferation, and apoptosis in various organs.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Engelman JA, Chen L, Tan X, Crosby K, Guimaraes AR, Upadhyay R, Maira M, McNamara K, Perera SA, Song Y, Chirieac LR, Kaur R, Lightbown A, Simendinger J, Li T, Padera RF, Garcia-Echeverria C, Weissleder R, Mahmood U, Cantley LC, Wong KK. Effective use of PI3K and MEK inhibitors to treat mutant Kras G12D and PIK3CA H1047R murine lung cancers. *Nat Med.* 2008;14(12):1351-1356.

Girnun GD, Chen L, Silvaggi J, Drapkin R, Chirieac LR, Padera RF, Upadhyay R, Vafai SB, Weissleder R, Mahmood U, Naseri E, Buckley S, Li D, Force J, McNamara K, Demetri G, Spiegelman BM, Wong KK. Regression of drug-resistant lung cancer by the combination of rosiglitazone and carboplatin. *Clin Cancer Res.* 2008;14(20):6478-6486.

Huang YT, Lin X, Liu Y, Chirieac LR, McGovern R, Wain J, Heist R, Skaug V, Zienolddiny S, Haugen A, Su L, Fox EA, Wong KK, Christiani DC. Cigarette smoking increases copy number alterations in nonsmall-cell lung cancer. *Proc Natl Acad Sci U S A.* 2011;108(39):16345-16350.

Ji H, Li D, Chen L, Shimamura T, Kobayashi S, McNamara K, Mahmood U, Mitchell A, Sun Y, Al-Hashem R, Chirieac LR, Padera R, Bronson RT, Kim W, Janne PA, Shapiro GI, Tenen D, Johnson BE, Weissleder R, Sharpless NE, Wong KK. The impact of human EGFR kinase domain mutations on lung tumorigenesis and in vivo sensitivity to EGFR-targeted therapies. *Cancer Cell.* 2006;9(6):485-495.

Ji H, Ramsey MR, Hayes DN, Fan C, McNamara K, Kozlowski P, Torrice C, Wu MC, Shimamura T, Perera SA, Liang MC, Cai D, Naumov GN, Bao L, Contreras CM, Li D, Chen L, Krishnamurthy J, Koivunen J, Chirieac LR, Padera RF, Bronson RT, Lindeman NI, Christiani DC, Lin X, Shapiro GI, Janne PA, Johnson BE, Meyerson M, Kwiatkowski DJ, Castrillon DH,

Bardeesy N, Sharpless NE, Wong KK. LKB1 modulates lung cancer differentiation and metastasis. *Nature.* 2007;448(7155):807-810.

Ji H, Wang Z, Perera SA, Li D, Liang MC, Zaghlul S, McNamara K, Chen L, Albert M, Sun Y, Al-Hashem R, Chirieac LR, Padera R, Bronson RT, Thomas RK, Garraway LA, Janne PA, Johnson BE, Chin L, Wong KK. Mutations in BRAF and KRAS converge on activation of the mitogen-activated protein kinase pathway in lung cancer mouse models. *Cancer Res.* 2007;67(10):4933-4939.

Ji H, Zhao X, Yuza Y, Shimamura T, Li D, Protopopov A, Jung BL, McNamara K, Xia H, Glatt KA, Thomas RK, Sasaki H, Horner JW, Eck M, Mitchell A, Sun Y, Al-Hashem R, Bronson RT, Rabindran SK, Discafani CM, Maher E, Shapiro GI, Meyerson M, Wong KK. Epidermal growth factor receptor variant III mutations in lung tumorigenesis and sensitivity to tyrosine kinase inhibitors. *Proc Natl Acad Sci U S A.* 2006;103(20):7817-7822.

Kobayashi S, Ji H, Yuza Y, Meyerson M, Wong KK, Tenen DG, Halmos B. An alternative inhibitor overcomes resistance caused by a mutation of the epidermal growth factor receptor. *Cancer Res.* 2005;65(16):7096-7101.

Li D, Ambrogio L, Shimamura T, Kubo S, Takahashi M, Chirieac LR, Padera RF, Shapiro GI, Baum A, Himmelsbach F, Rettig WJ, Meyerson M, Solca F, Greulich H, Wong KK. BIBW2992, an irreversible EGFR/HER2 inhibitor highly effective in preclinical lung cancer models. *Oncogene.* 2008;27(34):4702-4711.

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Perera SA, Maser RS, Xia H, McNamara K, Protopopov A, Chen L, Hezel AF, Kim CF, Bronson RT, Castrillon DH, Chin L, Bardeesy N, Depinho RA, Wong KK. Telomere dysfunction promotes genome instability and metastatic potential in a K-ras p53 mouse model of lung cancer. *Carcinogenesis.* 2008;29(4):747-753.

Shimamura T, Ji H, Minami Y, Thomas RK, Lowell AM, Shah K, Greulich H, Glatt KA, Meyerson M, Shapiro GI, Wong KK. Non-small-cell lung cancer and Ba/F3 transformed cells harboring the ERBB2 G776insV_G/C mutation are sensitive to the dual-specific epidermal growth factor receptor and ERBB2 inhibitor HKI-272. *Cancer Res.* 2006;66(13):6487-6491.

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NICOTINE REGULATION OF MANGANESE SUPEROXIDE DISMUTASE

Richard J. Rogers, MD; University of Florida; YCSA 2004

Dr. Rogers's hypothesis was that nicotine alters the transcription of basal and inflammatory mediator-inducible expression of manganese superoxide dismutase (MnSOD), a mitochondrial enzyme serving as a crucial antioxidant within all aerobic organisms. Additional hypotheses were that nicotine alters basal and inducible MnSOD gene expression via a nicotinic acetylcholine receptor-mediated pathway, and that nicotine affects MnSOD expression by altering important protein-DNA interactions on the regulatory region of the MnSOD gene.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Drake TJ, Medley CD, Sen A, Rogers RJ, Tan W. Stochasticity of manganese superoxide dismutase mRNA expression in breast carcinoma cells by molecular beacon imaging. *Chembiochem.* 2005;6(11):2041-2047.

Medley CD, Drake TJ, Tomasini JM, Rogers RJ, Tan W. Simultaneous monitoring of the expression of multiple genes inside of single breast carcinoma cells. *Anal Chem.* 2005;77(15):4713-4718.

EXPOSURE TO SHS/POPULATION STUDIES

Completed Research

IDENTIFYING SHS EXPOSURE IN HOSPITAL PATIENTS

Nancy Rigotti, MD; Massachusetts General Hospital; CIA 2012

Dr. Rigotti and colleagues used the opportunity of a system-level change in hospital practice, the hospital electronic medical record (EMR), to achieve the goal of embedding SHS exposure documentation into routine hospital practice. Massachusetts General Hospital, a 900-bed hospital in Boston, was transitioning its inpatient records from paper to EMR. Dr. Rigotti and her team succeeded in adding a question to identify SHS exposure to the template that doctors and nurses will use to admit every patient. The investigators evaluated the impact of this change on SHS documentation rates and built on it with an intervention to encourage nurses to advise patients to adopt smoke-free home policies. Results of this study can be used to compare the impact of the system change on individuals with COPD and asthma versus other diagnoses. Because EMRs are being rapidly adopted nationwide, this project has the potential for broad dissemination to US hospitals.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Kruse GR, Rigotti NA. Routine screening of hospital patients for secondhand tobacco smoke exposure: a feasibility study. *Prev Med.* 2014;69:141-145.

Rigotti NA, Clair C. Managing tobacco use: the neglected cardiovascular disease risk factor. *Eur Heart J.* 2013;34(42):3259-3267.

PRESENTATIONS AND ABSTRACTS

Kruse GR, Ives Erickson J, Rigotti NA. Implementation of a routine assessment of smoke free homes among hospitalized patients. Presented at the 2014 Annual Meeting of the Society for Research in Nicotine and Tobacco. Seattle, WA, Feb 5-8, 2014.

REDUCING SMOKE EXPOSURE IN CHILDREN FACING SURGERY

David Warner, MD; Mayo Clinic; YCSA 2009

Dr. Warner and colleagues developed and test piloted a brief practice-based intervention that can be used by surgical providers (e.g., surgeons, anesthesiologists, and perioperative nurses) to reduce SHS exposure of children who are scheduled for procedures requiring general anesthesia. The team learned that both parental and clinician interest is high in reducing SHS exposure of children undergoing surgery. They also learned that in this setting, parents are much more likely to be receptive to mitigation procedures rather than insistence that they quit smoking for good, a fact incorporated in the intervention approach. The intervention has been implemented in the clinical practice at Mayo Clinic Rochester, and its effectiveness is being evaluated. This intervention has the potential to be disseminated throughout the country, with great benefit to children undergoing surgery.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Shi Y, Warner DO. Pediatric surgery and parental smoking behavior. *Anesthesiology.* 2011;115(1):12-17.

Warner DO, Campbell EB, Hathaway JC, Shi Y, Flick R, Harrison TE, Hinds RF, Klesges RC, Vickers KS. Reducing secondhand smoke exposure of children undergoing surgery. *Am J Health Behav.* 2014;38(6):924-932.

REDUCING SECONDHAND TOBACCO SMOKE EXPOSURE AMONG YOUNG CHILDREN

Abu S. Abdullah, MD, PhD, MPH, MFPH; Boston University, Guangxi Medical University; CIA 2008

Dr. Abdullah examined the effectiveness of a smoking hygiene intervention (SHI) delivered by a community health worker (CHW) to reduce SHS exposure and improve respiratory health among young children in urban settings in Shanghai, China. Baseline data on SHS exposure and health status of young children was obtained as well as smoking status of parents and other household members. Effectiveness data was generated for CHW-delivered SHI, and culturally appropriate biochemical measures to assess children's exposure to household SHS were developed. The first part of the study was a pre-intervention baseline assessment; the second, a randomized controlled trial among households in urban Shanghai. Participants included families with a child aged below 5 years and at least one smoker in the household. All smokers in the intervention group received CHW-delivered SHI and educational pamphlets on hazards of SHS. The SHI comprises behavioral counseling on the health hazards of SHS for children and brief advice to quit or to adopt a no smoking practice around children. The control group received no intervention for reducing SHS or quitting smoking, but received a placebo education pamphlet on child development issues. The control group subjects received the same SHI

as the intervention group upon completion of the follow up assessment. The main outcome measures were subject-reported improvement of smoking hygiene practices within the household and reduction in children's cotinine concentrations in urine at 6-month follow up.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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Xia X, Pin-pin Z, Abdullah AS, Hua F. Application and development of protection motivation theory in individual behavior change. *Chinese Journal of Health Education* 2009;25(11):853-855.

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SECONDHAND SMOKE EXPOSURE AND PEDIATRIC ILLNESS IN THE US

Hillel R. Alpert, ScM; Harvard School of Public Health; CIA 2008

Dr. Alpert and his colleagues analyzed data from the 2001-2006 National Health and Nutrition Examination Survey for 11,657 non-smokers aged <15 years. Residence/housing was categorized as multi-unit housing (MUH) or detached. Household SHS exposure was defined as ≥1 smoker in the home. The number of ambulatory or emergency visits in the past year due to wheezing was self-reported. A multivariate Poisson regression model was fitted to assess the effect of household SHS exposure and housing type on hospital visits on account of wheezing, adjusting for pre-existing asthma, general health condition, sex, age, race/ethnicity, household reference-person education, and poverty index ratio. Household SHS exposure-housing type interaction was assessed using the likelihood-ratio test. The research team found that children exposed to household SHS had 1.89 times the rate of hospital visits due to wheezing compared to non-exposed children. The rate of hospital visits among children in MUH was 1.62 times that of children in detached houses. The effect of SHS exposure on hospital visits in children in MUH was higher compared to children in

detached houses. Overall, the effect of household SHS exposure on hospital visits due to wheezing was significantly higher in MUH children compared to those in detached housing.

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SMOKE-FREE AIR LAWS, EXPOSURE, AND HEALTH IN ADOLESCENTS

Gregory N. Connolly, DMD, MPH; Harvard School of Public Health; CIA 2008

Dr. Connolly examined the association between SHS exposure of children in the home and SHS-related pediatric diagnoses and symptoms in all US health care settings, as well as the association between SHS exposure of children in the home and health services utilization for treatment of SHS-related pediatric diagnoses and symptoms in all US health care settings. He used a cross-sectional observational design involving secondary data analysis of existing national and state-level data sets. The outcome measures were SHS-related pediatric diagnoses and symptoms and health services utilization for treatment of SHS-related pediatric diagnoses and symptoms. The exposure measurements were percentage of households with an adult smoker and any children, percentage of households with smoking restrictions, percentage of households with an adult smoker and any children and smoking allowed, percentage of children exposed to SHS in the home, percentage of population coverage with comprehensive smoke-free workplace laws, and percentage of coverage with smoke-free day care center regulations.

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SMOKE-FREE AIR LAWS, EXPOSURE, AND HEALTH IN ADOLESCENTS SMOKE IN MULTIUNIT HOUSING

Andrew Hyland, PhD; Roswell Park Alliance Foundation; CIA 2008

Dr. Hyland and colleagues evaluated the impact of an informational packet on the benefits of implementing a smoke-free policy among multi-unit housing (MUH) operators in two counties of New York State. MUH operators in these intervention communities receiving the informational packet were more likely to report interest in adopting a smoke-free initiative and were less likely to report concerns about adopting such a program compared to a control group of MUH operators from the rest of New York State. However, the rate of adoption of smoke-free initiatives over the intervention period was comparable between the groups. The team also examined SHS transfer between smoke-permitted and smoke-free units in eleven MUH buildings, and found evidence of SHS transfer from smoke-permitted units. Many factors were found to be determinants of SHS transfer from smoke-permitted units to adjacent smoke-free units, including ventilation and proximity between units. National assessments mirrored many of the findings from the state assessment.

FAMRI SUPPORTED RESEARCH

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FETAL AND INFANT EXPOSURE TO SHS AND ITS ROLE IN CHRONIC DISEASE

Manolis Kogevinas, MD, PhD, Leda Chatzi, MD, PhD; University of Crete; CIA 2008

Dr. Chatzi and colleagues measured the extent of SHS exposure in Greek pregnant women to determine how it is related to adverse pregnancy outcomes and predisposition to acute and chronic disease. The team also investigated whether the effects of prenatal SHS exposure can be modified by adherence to the Mediterranean diet. Almost all Greek women report exposure to SHS. The analysis revealed that less educated women and those married to less educated husbands had significantly higher cotinine levels. Cotinine levels during pregnancy were strongly influenced by the husband's smoking status, and women who quit smoking once pregnant had significantly lower NNAL levels in comparison to women who continued to smoke. The study showed that educational interventions are needed to inform pregnant women of the importance of smoke free households and cars, and of the fact that exposure to SHS can be interpreted as direct exposure to cancer causing agents.

FAMRI SUPPORTED RESEARCH

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SECONDHAND TOBACCO SMOKE, PEDIATRIC HEALTHCARE USE, AND SPENDING

Douglas Levy, PhD; Harvard Medical School; YCSA 2008

Dr. Levy used the nationally representative Medical Expenditures Panel Survey to evaluate the short-term effect of household SHS exposure on pediatric healthcare utilization, health expenditures, number of days of school children miss, and the number of workdays adults miss to care for others. He also focused on SHS exposure in public housing. Pilot studies were conducted including cotinine measurement and questionnaire testing in residents of public housing, setting the stage for a large-scale assessment of how smoke-free policies in public housing affect SHS exposure in non-smoking households. This work provides an

evidence base for policy makers, housing authorities, and landlords considering the implementation of residential smoke-free policies.

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A WELL-BABY CLINIC-BASED INTERVENTION TO PROTECT INFANTS FROM EXPOSURE TO SECONDHAND TOBACCO SMOKE

Laura Rosen, PhD; Tel Aviv University; YCSA 2008

Tobacco smoke exposure (TSE) harms children. The very young are often captive smokers in homes in which others smoke. Past programs to protect young children from TSE have shown limited effectiveness. The primary goal of this project is to develop and test a parent-oriented, theory-based intervention which will reduce the TSE of young children. Secondary goals are to increase knowledge of measurement of TSE in young children, explore the relationship between early TSE and child illnesses, and investigate parental perceptions of child exposure and perceptions. The study includes three phases. The developmental phase included systematic reviews, a qualitative study with 65 parents and 15 professionals, consultations with experts worldwide, and development of an intervention program. During the second phase, a pilot study was run with 29 families to test feasibility and acceptability of program components and research procedures using a one-group (uncontrolled) before–and–after study. Dr. Rosen and colleagues are conducting the Phase III randomized controlled trial (RCT). The goal is to test the effectiveness of the developed intervention. Concurrent with the Phase III RCT, the investigators are conducting a small cohort study (n=20) of TSE in children aged 0-7 from nonsmoking families. Those families do not receive an intervention or take part in the RCT. The intervention program focuses on enhancing parental perceptions of child TSE, provision of information on risk, and recommendations for techniques to minimize exposure. The program includes motivational interviews with parents in their homes, follow-up phone calls, personalized biochemical feedback of child exposure level (hair nicotine) and home air quality, self-help materials (brochure, magnets), use of digital media (via a Facebook platform), a website (www.parents.org.il), and a video of Patty Young describing effects of tobacco smoke on flight attendants. The qualitative study has yielded important information on parental willingness to provide child biomarker samples, and a conceptual model about parental perceptions of child exposure to tobacco smoke. Results from the pilot study are promising. The RCT will provide high quality information on effectiveness. An effective program could serve as a prototype for interventions in other countries struggling with the problem of young child TSE.

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RCT OF A FAMILY INTERVENTION TO REDUCE SHS EXPOSURE IN CHILDREN

Sophia Siuchee Chan, PhD; University of Hong Kong; CIA 2007

Dr. Chan conducted a random controlled trial to evaluate the effectiveness of a proactive multistep theory-based family smoking cessation intervention to protect infants under 18 months from household SHS exposure and to help smoking fathers quit. Families in the intervention group received three telephone smoking cessation counseling sessions to smoking fathers, one face-to-face counseling with two telephone follow-ups, support and reinforcement for non-smoking mothers to implement household no-smoking policies, and other preventive measures to reduce SHS exposure. These families also received an additional face-to-face family counseling session to encourage the spouses to work together to improve the household smoking hygiene and protect their infants. Families in the control group received usual care plus a self-help booklet on smoke-free homes and brief smoking cessation tips. This proactive family intervention was effective in helping fathers to quit smoking and in reducing the hospitalization rate of infants. However, the intervention for empowering mothers to implement household no-smoking policy was not strong enough to minimize household SHS exposure of infants and nonsmoking mothers.

FAMRI SUPPORTED RESEARCH

PRESENTATIONS AND ABSTRACTS

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THE EFFECTS OF SECONDHAND SMOKE ON CYSTIC FIBROSIS

Garry R. Cutting, MD; Johns Hopkins Medical Institutions; CIA 2007

Dr. Cutting and colleagues demonstrated that people with cystic fibrosis (CF) who are exposed to any SHS in the home have worse lung function than CF patients who were not exposed. In addition, they observed that certain genetic variants of an inflammatory gene (transforming growth factor beta) can drastically accelerate the decline in lung function from SHS exposure. Because actual SHS exposure can be difficult to quantify in the clinical setting, Dr. Cutting's team examined the effect of SHS on lung function compared to other environmental modifiers of CF lung disease, such as air pollution, climate, access to healthcare, and socioeconomic status. They identified the role of climate in significantly altering lung function and studied whether climate confounds the relationship between SHS and lung function. The team also collected genetic data and conducted genome-wide analyses to look for genetic variants that ameliorate or worsen the effects of SHS exposure.

FAMRI SUPPORTED RESEARCH

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A MULTIPLE STAKEHOLDER STUDY REGARDING THE IMPACT OF SECONDHAND SMOKE IN MULTIUNIT HOUSING

Andrew Hyland, PhD; Roswell Park Alliance Foundation; CIA 2007

Dr. Hyland and colleagues expanded a global research network exploring SHS exposure and the impact of smoke-free air initiatives. This network includes developed and developing countries and researchers in all six WHO regions. The research team funded and/or

collaborated with international partners in over 65 countries to complete air quality studies on exposure to SHS. The tools that were developed and disseminated for SHS exposure studies are now a critical part of most smoke-free air debates and are used to ensure that effective smoke-free air initiatives are implemented that truly protect public health. This network has been able to determine what the relative contribution of SHS to indoor air pollution versus other sources of pollution in different regions of the world is, especially in developing nations, and what the health and economic impacts of smoke-free regulations are in developing or non-western countries. This research has contributed to surveys in Mexico to assess SHS attitudes and beliefs before and after Mexico City's smoke-free legislation. Further, the studies were part of a supplement of Nicotine and Tobacco Research on SHS issues. Data on the economics of smoke-free procedures were presented in Madrid to inform the process of strengthening Spanish smoke-free initiatives.

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ADULT HEALTH CONSEQUENCES OF PRENATAL AND POSTNATAL SECONDHAND TOBACCO EXPOSURE

Stephen L. Buka, ScD; Harvard School of Public Health; CIA 2006

Dr. Buka used data from a well-defined cohort of approximately 2000 individuals followed from the prenatal stage through age 40 to prospectively examine the relationship between chemically validated *in utero* tobacco exposure and adult health outcomes. The design of the study controlled for the potential confounding effects of factors such as parental socioeconomic status, a major limitation of much prior research. Secondary data analysis was performed on a long-term prospective study, the New England cohorts of the National Collaborative Perinatal Project.

PSE RATES AND CORRELATES: KOREANS/KOREAN AMERICANS

Suzanne C. Hughes, PhD, MPH; San Diego State University; YCSA 2006

Dr. Hughes examined the extent and determinants of SHS exposure among Korean Americans and Koreans; the males in this population have high smoking rates. She conducted a feasibility pilot study of a SHS intervention that was designed to 1) estimate and compare the prevalence and correlates of SHS exposure among Korean Americans and native Koreans for cultural comparison; 2) assess physiological, emotional, sociocultural, and other aspects of SHS exposure; 3) explore the role of home smoking bans on SHS exposure using cross-sectional data; 4) examine whether home smoking bans reduce SHS exposure using a longitudinal design; and 5) design and pilot test a culturally tailored intervention to reduce SHS exposure. Longitudinal analyses of baseline follow-up data for the California sample was performed. A faith-based intervention was designed based on results from telephone surveys, focus groups, and key informant interviews. This faith-based intervention was test piloted in 12 Korean churches. This research should enhance the understanding of SHS exposure among immigrant groups, and could facilitate the development and implementation of culturally appropriate interventions.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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HOOKAH USE AND SECONDHAND TOBACCO SMOKE

Nada Kassem, DrPH; San Diego State University; YCSA 2006

Dr. Kassem and colleagues compared SHS contamination in homes of five types of households of hookah smokers with children 4 years or younger. The households included 1) frequent smokers of only hookah who smoke inside their homes; 2) frequent smokers of only hookah who smoke outdoors at their homes; 3) occasional smokers of only hookah who smoke inside their homes; 4) occasional smokers of only hookah who smoke outdoors at their homes; and 5) nonsmokers. The households were visited for data collection on days that coordinated with hookah smoking. During a 7-day period, the researchers interviewed the hookah smokers on hookah smoking behavior and collected five environmental samples (three air samples and two surface samples) per home in living rooms and bedrooms to measure nicotine contamination of indoor air and household surfaces. Three urine samples per child were collected and urine levels of cotinine and two carcinogens, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and 3-(hydroxypropyl)mercapturic acid, were measured to determine levels of SHS exposure in the children. The results of the study can inform estimates on health risks for children living in homes of hookah smokers and identify points of intervention for health promotion programs tailored to hookah smokers.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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PRESENTATIONS AND ABSTRACTS

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SECONDHAND TOBACCO SMOKE AND WORKER HEALTH

David J. Lee, PhD; University of Miami Miller School of Medicine; CIA 2006

Dr. Lee and his colleagues extended earlier work using cotinine as an objective tobacco smoke exposure biomarker and found that US workers are reasonably accurate when reporting their smoking status, but are less accurate when reporting SHS exposures. The team has also documented significant population-level reductions in serum cotinine levels from 1990–2002 in all major nonsmoking US worker groups examined, with the most dramatic reductions occurring in blue collar workers; this provides objective documentation of the effects of workplace smoking restrictions across the nation. The team has also examined a variety of health outcomes possibly related to SHS exposure including 1) higher levels of homocysteine, which is associated with increased risk of coronary heart disease; 2) risk of depression and depressive symptoms; 3) early menopause; 4) hearing loss; and 5) sleep disorders. The investigators continued work on the challenging task of accurately assessing SHS exposure. This study focused on the use of salivary and hair cotinine and nicotine exposure biomarkers to validate a set of self-reported SHS exposure questions for use in health surveys when the collection of biological samples is not feasible.

FAMRI SUPPORTED RESEARCH

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SECONDHAND TOBACCO SMOKE EXPOSURE AMONG BAR AND NIGHTCLUB EMPLOYEES

Ana Navas-Acien, MD, PhD; Johns Hopkins Bloomberg School of Public Health; CIA 2006

Dr. Navas-Acien and her team assessed SHS exposure of bar and nightclub employees in more than 20 countries. The study was conducted in major cities worldwide, including Baltimore City. In each city, 10 bars and nightclubs and up to five employees per bar or nightclub were selected. Air and hair nicotine concentrations were analyzed by gas chromatography at the Johns Hopkins Bloomberg School of Public Health. In most countries, bar and nightclub workers were exposed to high levels of SHS. Countries such as Uruguay, where there are smoke-free initiatives, showed an extraordinary decrease in SHS exposure compared to baseline measures conducted in 2002. By objectively documenting airborne and personal exposure to SHS in bars and nightclubs worldwide, the investigators helped to achieve smoke-free public places that protect all workers from exposure to SHS.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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SECONDHAND TOBACCO SMOKE IN MEXICAN AMERICAN HOUSEHOLDS

Alexander V. Prokhorov, MD, PhD; University of Texas M.D. Anderson Cancer Center; CIA 2006

Dr. Prokhorov and colleagues completed a randomized controlled trial of reducing SHS and adopting tobacco-free air standards through Project Clean Air-Safe Air (CASA). The experimental intervention comprised a series of three illustrated storybooks (fotonovelas) designed to address the needs of Mexican American households and to measure SHS exposure of nonsmokers over time compared to the Standard-Care (SC) pamphlet. Results

at 6-month follow-up revealed a strong initial impact of this program in terms of subjectively measured SHS exposure, knowledge, and health perception. At 12 months, intervention households continued to be favorably influenced by the customized fotonovelas, resulting in greater numbers of households that became completely free of SHS exposure.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Prokhorov AV, Hudmon KS, Marani SK, Bondy ML, Gatus LA, Spitz MR, Wilkinson AV, Hammond SK, Koehly LM. Eliminating second-hand smoke from Mexican-American households: outcomes from Project Clean Air-Safe Air (CASA). *Addict Behav.* 2013;38(1):1485-1492.

REDUCING SHS: CARDIAC AND ASTHMA OUTCOMES

Ellen Hahn, PhD, RN; University of Kentucky; CIA 2004

Dr. Hahn evaluated the effects of a community initiative in Lexington, Kentucky, to reduce the effect of exposure to SHS on cardiac and asthma outcomes, including the rate of hospital and emergency department (ED) discharges, length of stay, and total hospital costs. Differences in event rates between, before, and after changes in smoke-free environments were determined. The models based on the negative binomial distribution assumption fit the data well. Relative risks (RR), 95% confidence intervals for RR's, and corresponding tests of significance for the period variable were determined. The results of this study indicate that the risk of asthma ED visits declined by 18% after the clean air initiative and that there was a 22% decline in the risk of acute myocardial infarction (AMI) events during the same period for females when all 72 months are included in the model; the RR for AMI for males between the two time periods was stable. This is the first study that has considered differential effects of smoke-free initiatives for males and females.

FAMRI SUPPORTED RESEARCH

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DEVELOPMENT AND IMPLEMENTATION OF SMOKING RESTRICTIONS

Lisa A. Bero, PhD; University of California, San Francisco; CIA 2003

Dr. Bero developed a timeline and regulatory history for initiatives banning smoking on airlines by conducting a systematic review to identify all governmental standards that restricted or banned smoking on airlines in the United States and abroad. She determined 1) US federal regulatory proceedings pertaining to smoking restrictions on passenger aircraft and their outcomes from 1969 to 1985; 2) all federal attempts to restrict airline smoking from 1969 through 2000; 3) the adoption of smoking restrictions on aircraft in the context of other important events; and 4) international initiatives restricting airline smoking. Dr. Bero performed an assessment of the relative roles of research evidence and other factors restricting smoking on airlines using the 1987 legislation banning smoking on flights of 2 hours or less and the 1989 extension to most domestic flights. All available legislative debates, hearings, committees, and conference reports on each of the initiatives were compiled and all key factors that contributed to the enactment of the airline smoking bans were outlined. The extensive timelines that were developed and the thorough identification of tobacco industry activities over the 30-year period provided an understanding of the context in which these two bans were enacted. This information makes it possible to discern the relative importance of the factors that went into the enactment of the smoking bans.

FAMRI SUPPORTED RESEARCH

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SERUM COTININE AND MIDDLE EAR DISEASE IN CHILDREN AND ADOLESCENTS: THE NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY III

David J. Lee, PhD; University of Miami Miller School of Medicine; CIA 2003

In this study Dr. Lee and colleagues used data collected as part of the NHANES III completed in 1994 to determine the prevalence of middle ear dysfunction and its

association with cotinine levels in adolescents and young children. The study was aimed at defining the exact nature of the association of middle ear disease in children and association with exposure to SHS. The results were able to definitively inform pediatricians and other health care providers about the need to limit exposure of adolescents and young people to cigarettes and were instrumental in setting public standards regarding SHS exposure in young people.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Arheart KL, Lee DJ, Fleming LE, LeBlanc WG, Dietz NA, McCollister KE, Wilkinson JD, Lewis JE, Clark JD, 3rd, Davila EP, Bandiera FC, Erard MJ. Accuracy of self-reported smoking and secondhand smoke exposure in the US workforce: the National Health and Nutrition Examination Surveys. *J Occup Environ Med.* 2008;50(12):1414-1420.

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PRESENTATIONS AND ABSTRACTS

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SECONDHAND TOBACCO SMOKE AND HEAD AND NECK CANCER

Edward Peters, DMD, ScD; Louisiana State University; YCSA 2003

A joint venture between the Louisiana State University Health Science Center School of Public Health and the Coalition for Tobacco Free Louisiana was conducted to determine if indoor air was less polluted in venues where smoking is prohibited or does not occur compared to places where smoking is present. Two 3-month sampling frames were employed, the last 3 months of 2006 and the second quarter of 2007. Air monitoring was conducted with TSI SidePak AM510 personal aerosol monitor to sample and record the levels of respirable suspended particles (RSP). The differences in the average RSP were measured in places with and without presence of tobacco smoke, and a time-weighted average fine particulate matter with a diameter smaller than 2.5 microns (PM 2.5) level for each venue was calculated. The mean RSP levels of all venues were compared to those that may be classified as smoke-free and those that are not. A comparison between smoke-free and not smoke-free for each venue type was made and contrasted using the Mann-Whitney Test. Descriptive statistics, such as venue volume, number of patrons, and the average smoker density (number of lighted cigarettes/ 100 m3), were estimated. In addition, time plots to show the level of PM 2.5 throughout the duration of sampling for each region of the state were developed.

FAMRI SUPPORTED RESEARCH

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CHANGING PEDIATRIC PRACTICE TO ADDRESS SECONDHAND TOBACCO SMOKE EXPOSURE

Jonathan P. Winickoff, MD, MPH; Massachusetts General Hospital; YCSA 2003

Dr. Winickoff and colleagues developed and tested a pediatric office system to enhance the delivery of evidence-based tobacco control services with a resulting decrease in childhood exposure to SHS and the diseases caused by it. The three phases of the research study included 1) an exploratory study consisting of the preliminary adaptation of an evidence-based tobacco control strategy to the pediatric outpatient setting; 2) a qualitative study using focus groups from eight pediatric practices to elicit pediatrician and key staff responses, barriers, and solutions to implementing the proposed strategy; and 3) an intervention study examining the feasibility and efficacy of implementation within the pediatric office setting the tobacco control system developed in Phase 1 and refined in Phase 2. The study was designed to justify a larger trial with randomization at the practice level, which was funded by National Cancer Institute/National Institute of Drug Abuse/ Agency for Healthcare Research and Quality.

FAMRI SUPPORTED RESEARCH

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ECONOMIC, BEHAVIORAL, AND DISEASE IMPACT OF CLEAN AIR

Andrew Hyland, PhD; Roswell Park Alliance Foundation; YCSA 2002

Dr. Hyland performed studies to assess the economic, behavioral, and health impact of smoke-free regulations. Economic studies were conducted to assess changes in employment and other business indicators in jurisdictions that have implemented smoke-free regulations. Dr. Hyland and colleagues worked with several leading national organizations to disseminate the information gleaned from these studies with the goal of generating interest in promoting efforts to eliminate SHS exposure in the workplace.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Abrams SM, Mahoney MC, Hyland A, Cummings KM, Davis W, Song L. Early evidence on the effectiveness of clean indoor air legislation in New York State. *Am J Public Health.* 2006;96(2):296-298.

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Hyland A, Goldstein R, Brown A, O'Connor R, Cummings KM. Happy Birthday Marlboro: the cigarette whose taste outlasts its customers. *Tob Control.* 2006;15(2):75-77.

Hyland A, Puli V, Cummings KM, Sciandra R. New York's smoke free regulations: Effects on employment and sales in the hospitality industry. . *Cornell Hotel and Restaurant Administration Quarterly.* 2003;44:9-16.

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Jones SC, Travers MJ, Hahn EJ, Robertson H, Lee K, Higbee C, Hyland A. Secondhand smoke and indoor public spaces in Paducah, Kentucky. *J Ky Med Assoc.* 2006;104(7):281-288.

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Abrams SM, Mahoney MC, Hyland A, Cummings KM. A cross-sectional study of secondhand smoke exposure in western New York, 2003. Presented at the 10th Annual Society for Research on Nicotine and Tobacco Meeting. Scottsdale, AZ, Feb 18-21, 2004.

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Hyland A. Multi-city air monitoring study: public policy and exposure to secondhand smoke, 2005. Presented at the Society on Nicotine and Tobacco. Prague, Czech Republic, Mar 20-23, 2005.

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Travers MJ, Hyland A. Indiana Air Monitoring Study, December 2004-Jan 2005. Report prepared for Indiana Tobacco Prevention and Cessation, 2005.

Travers MJ, Hyland A. Michigan Air Monitoring Study: Ann Arbor: Report prepared for Tobacco-Free Michigan, 2005.

Travers MJ, Hyland A. New Jersey Air Monitoring Study, August 18th to September 27th 2005. Report prepared for New Jersey G.A.S.P. and the American Cancer Society, 2005.

Travers MJ, Hyland A. Wisconsin Air Monitoring Study, October 13th to November 6th 2005. Report prepared for Friends of Clean Air Works, 2005.

SECONDHAND TOBACCO SMOKE EXPOSURE AND HEALTH IN A BLUE-COLLAR POPULATION

Francine Laden, ScD; Brigham and Women's Hospital; YCSA 2002

Dr. Laden sent detailed questionnaires covering SHS history and respiratory symptoms to 4,500 trucking company workers who had answered an initial smoking history questionnaire; 2300 workers responded with information regarding SHS exposure. The analysis of this information suggests that the prevalence of adverse health outcomes, including respiratory symptoms and allergies, is greater in non-smokers exposed to recent secondhand tobacco smoke compared to nonsmokers who are not exposed.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Chiu YH, Hart JE, Smith TJ, Hammond SK, Garshick E, Laden F. Nicotine contamination in particulate matter sampling. *Int J Environ Res Public Health.* 2009;6(2):601-607.

Chiu YH, Hart JE, Spiegelman D, Garshick E, Smith TJ, Dockery DW, Hammond SK, Laden F. Workplace secondhand smoke exposure in the U.S. trucking industry. *Environ Health Perspect.* 2010;118(2):216-221.

Chiu YH, Spiegelman D, Dockery DW, Garshick E, Hammond SK, Smith TJ, Hart JE, Laden F. Secondhand smoke exposure and inflammatory markers in nonsmokers in the trucking industry. *Environ Health Perspect.* 2011;119(9):1294-1300.

Jain NB, Hart JE, Smith TJ, Garshick E, Laden F. Smoking behavior in trucking industry workers. *Am J Ind Med.* 2006;49(12):1013-1020.

Laden F, Chiu YH, Garshick E, Hammond SK, Hart JE. A cross-sectional study of secondhand smoke exposure and respiratory symptoms in non-current smokers in the U.S. trucking industry: SHS exposure and respiratory symptoms. *BMC Public Health.* 2013;13:93.

PRESENTATIONS AND ABSTRACTS

Jain N, Hart JE, Garshick E, Laden F. Variation of smoking behavior in unionized trucking industry workers [abstract]. *Am J Resp Crit Care Med* 2005;171: A442.

INFLUENCE OF SHS ON HEALTH STATUS IN YOUTH

David J. Lee, PhD; University of Miami Miller School of Medicine; CIA 2002

Dr. Lee re-interviewed 5,949 respondents to the Florida Anti-tobacco Media Evaluation surveys in three follow-up surveys (FSS) conducted in 1999, 2000, and 2001. Dr. Lee and his team selected at random 800 FSS participants from within each of three *a priori*-determined exposure categories: 1) non-smoking parents; 2) parents who consistently smoked during their pre- and teenage years; and 3) parents who quit smoking during some of their pre- and teenage years. Assessments were made by telephone interviews with respect to tobacco-related disease symptoms such as respiratory symptoms, eye irritation, earaches, difficulty exercising, dry skin, sore throat, taste, and smell impairments. Standard CDC tobacco smoking histories were also collected. The investigators determined if never smokers who were consistently exposed to SHS during adolescence reported more tobacco-related disease symptoms than never smokers who were not exposed. The investigators documented the subtle health consequences of SHS exposure in a large number of young adults exposed to this toxic agent. A broad inventory of tobacco-related disease symptoms was developed that helps to identify a set of sentinel items that may be used to screen for early evidence of tobacco-related illness in young adults. The study findings can be used to counsel smoking parents on the potential long-term effects their smoking practices have on their children.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Lee DJ, Arheart KL, Trapido E, Soza-Vento R, Rodriguez R. Accuracy of parental and youth reporting of secondhand smoke exposure: the Florida youth cohort study. *Addict Behav.* 2005;30(8):1555-1562.

Lee DJ, Gaynor JJ, Trapido E. Secondhand smoke and earaches in adolescents: the Florida Youth Cohort Study. *Nicotine Tob Res.* 2003;5(6):943-946.

PRESENTATIONS AND ABSTRACTS

Lee DJ, Arheart K, Trapido E, Sly D, Rodriguez R, Soza R. Secondhand smoke exposure determined by salivary cotinine and reported earaches in adolescents: A pilot investigation. Presented at the 12th World Conference on Tobacco or Health. Helsinki, Finland, Aug 2003.

THE USE OF SIMULATION MODELS TO PREDICT AND UNDERSTAND PUBLIC HEALTH PROBLEMS

David Levy, PhD; Pacific Institute for Research and Evaluation; 2002 CIA

Dr. Levy and colleagues examined the direct effect of clean indoor air regulations and home smoking bans on SHS exposure. They used the 1998/1999 Tobacco Use Supplement to the US Current Population Survey to examine the responses of 43,613 homes where two or more adults responded to the home ban question. The results demonstrated that 12% of households gave inconsistent results regarding the home smoking ban. Discrepancies varied systematically by race, socioeconomic status, and smoking behavior. The inconsistent reports suggested that children living with smokers were at particular risk. The conclusion from these studies was that analyses of home smoking bans should not rely on individual reports, especially in homes with smokers and children. Home and work smoking bans were examined at the national and state levels utilizing the Current Population Survey's 1992/1993 and 1998/1999 tobacco use supplements. Since previous evidence suggested that strict bans were more effective, the analysis was limited to bans where no smoking was allowed at any time or in any place. There was a considerable increase in home and working bans between the early and late 1990s. By the end of the study period, 65% of the population over 15 years of age was employed in places with smoking bans and over 60% lived in homes with such bans. States with stricter bans by 1999 tended to have higher cigarette taxes, stricter clean air laws, and more media campaigns. The study demonstrated that lower smoking rates were associated with higher numbers of home and work smoking bans.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Levy DT, Romano E, Mumford EA. Recent trends in home and work smoking bans. *Tob Control.* 2004;13(3):258-263.

Mumford EA, Levy DT, Romano EO. Home smoking restrictions. Problems in classification. *Am J Prev Med.* 2004;27(2):126-131.

AIRWAY RESISTANCE AND CYTOGENETIC ABNORMALITIES ASSOCIATED WITH TOBACCO SMOKE EXPOSURE

Martin Mahoney, MD, PhD; Roswell Park Alliance Foundation; CIA 2002

On July 24, 2003, New York State enacted a statewide Clean Indoor Air Law (CIAL), which eliminated smoking in nearly all indoor public places, creating an opportunity to compare exposures among hospitality and non-hospitality workers before and after enactment. Dr. Mahoney interviewed a group of non-smokers recruited from the western New York State region to assess exposures to SHS. The number of hours of SHS exposure reported during the 4 days prior to the baseline interview decreased from 7.0 hours pre-law to 3.0 hours post-law and there was a significant reduction of SHS exposure among non-casino hospitality workers. There was no significant change in reported exposures among casino workers or among non-hospitality workers. Since tribally-owned casinos are exempt from the CIAL and still allow smoking, no real change in SHS exposure among casino workers

was anticipated. These results provide clear evidence of a substantial reduction in work site SHS exposure among hospitality workers.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Abrams SM, Mahoney MC, Hyland A, Cummings KM, Davis W, Song L. Early evidence on the effectiveness of clean indoor air legislation in New York State. *Am J Public Health.* 2006;96(2):296-298.

Paszkiewicz GM, Timm EA, Jr., Mahoney MC, Wallace PK, Sullivan Nasca MA, Tammela TL, Hutson A, Pauly JL. Increased human buccal cell autofluorescence is a candidate biomarker of tobacco smoking. *Cancer Epidemiol Biomarkers Prev.* 2008;17(1):239-244.

Song LG, Davis W, Abrams SM, Hemiup J, Kazim AL, Cummings KM, Mahoney MC. Sensitive and rapid method for the determination of urinary cotinine in non-smokers; an application for studies assessing exposures to second hand smoke (SHS). *Anal Chim Acta.* 2005;545:200-208.

PRESENTATIONS AND ABSTRACTS

Abrams S, Mahoney M, Hyland A, Cummings KM. Clean indoor air laws protect hospitality workers: evidence from New York State. Presented at the National Conference on Tobacco or Health. Chicago, IL, May 4-6, 2005.

Abrams SM, Mahoney MC, Hyland A, Cummings KM. A cross-sectional study of secondhand smoke exposure in western New York, 2003. Presented at the 10th Annual Society for Research on Nicotine and Tobacco Meeting. Scottsdale, AZ, Feb 18-21, 2004.

IMPACT OF SECONDHAND TOBACCO SMOKE ON RESPIRATORY HEALTH OF NON-SMOKING ADULTS

Archana Mishra, MD; Research for Health in Erie County, Inc.; YCSA 2002

Dr. Mishra investigated the relationship between SHS and respiratory health in adult non-smokers using data from two cross-sectional studies. Prevalence of self-reported SHS exposure at work and home was compared with self-reported exposure during an initial 16-year-old survey in adult non-smokers, and the validity of the questionnaires was determined indicating SHS exposure by assessing the relationship between self-reported measures and urinary cotinine adjusted for creatinine. Dr. Mishra also determined the association between SHS exposure and pulmonary function tests in the adult population and the association between SHS exposure and respiratory symptoms. Analysis of the association between SHS exposure and self-report of obstructive airway disease in non-smoking adults and comparison of gender differences in reported respiratory symptoms and pulmonary function measures in individuals exposed to SHS was performed. Lifetime SHS exposure places adults at risk for respiratory symptoms. An additive deleterious effect of SHS exposure on lung function was seen by a decline in forced expiratory volume in current smokers with high versus low SHS exposure.

EDUCATION

Ongoing Research

ELIMINATION OF PEDIATRIC TOBACCO AND SECONDHAND SMOKE EXPOSURE

Debra Waldron, MD, MPH; American Academy of Pediatrics; CIA 2022

There is no safe level of exposure to tobacco smoke, including exposure to secondhand tobacco smoke (SHS). Tobacco smoke stays in a room long after a cigarette has been extinguished, and this smoke can be inhaled by children, causing illnesses such as ear and respiratory infections. Exposed children are also at risk of serious illnesses as they age, such as lung cancer, heart attacks, and stroke. In order to protect children from the diseases related to SHS exposure, it is important to be sure that doctors, scientists, and policymakers understand the impact of SHS and work to eliminate SHS exposure in children. Dr. Waldron and colleagues will create educational resources and clinical tools to convey the dangers of SHS exposure. Doctors will be trained to ask families questions about SHS exposure, and will encourage families not to smoke in their homes, cars, or anywhere around their children. Information and tools will be given to public health partners to support policies and laws that prevent people from smoking in places where children spend time. Meetings will be held at the Richmond Center to provide education and training, and the investigators will work to make sure that scientific knowledge about the dangers of SHS exposure is shared with a wide audience.

Completed Research

ENGAGING PEDIATRICIANS FOR ENQUIRY ON SECONHAND SMOKE EXPOSURE

Abu Abdullah, MD, PhD, MPH, FFPH; American Academy of Pediatrics

The high prevalence of smoking in adults in China results in many children being exposed to SHS. Although both the American Academy of Pediatrics and the American Academy of Family Physicians recommended that practitioners assess their patients' exposure to SHS and provide exposure reduction counseling including the adverse effects of SHS on child health; similar recommendations in many developing countries are either scarce or non-existent. Sick children who visit pediatricians' offices represent a vulnerable subset of children. Pediatricians rarely use these opportunities to counsel families about the effects of second hand smoke.

The goals were to adapt an in-person training module, clinical effort against second hand smoke exposure (CEASE) to pediatric settings in China, and to test the feasibility and efficacy of CEASE training to address the SHS exposure of children in the home and car.

COPD AND STRENGTH OF SMOKE-FREE LAWS

Ellen Hahn, PhD, RN; University of Kentucky; CIA 2010

Dr. Hahn and colleagues determined the impact of the strength and extent of coverage of smoke- free laws on hospitalization and mortality for COPD in Kentucky, a rural tobacco-growing state with high rates of smoking and COPD. The team analyzed hospital discharges and mortality from COPD to investigate the differential effects of smoke free initiatives on

COPD hospitalizations and mortality. The investigators determined differences in rates by the strength of the community initiatives and by the extent of coverage of these initiatives. The Kentucky Hospital Association hospitalization database was used for all Kentucky hospitals for a 9.5-year period and was queried for hospital discharge diagnosis by the International Classification of Diseases, 9th revision, (codes 491,492, 496); dates of service; disposition; gender; age; and county of residence. Poisson regression was used to determine the impact of strength and extent of coverage of the initiative on the monthly-adjusted COPD rates for each county.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Hahn EJ, Rayens MK, Adkins S, Simpson N, Frazier S, Mannino DM. Fewer hospitalizations for chronic obstructive pulmonary disease in communities with smoke-free public policies. *Am J Public Health.* 2014;104(6):1059-1065.

Hahn EJ, Rayens MK, Burkhart PV, Moser DK. Smoke-free laws, gender, and reduction in hospitalizations for acute myocardial infarction. *Public Health Rep.* 2011;126(6):826-833.

PRESENTATIONS AND ABSTRACTS

Hahn EJ, Rayens MK, Frazier S, Mannino D, Adkins S, Hopkins E. Fewer hospitalizations for chronic obstructive pulmonary disease in communities with smoke-free public policies. Presented at the Southern Nursing Research Society. New Orleans, LA, Feb 22-25 2012.

SECONDHAND SMOKE: PREVALENCE, VALIDATION, AND EFFECTS

David J. Lee, PhD; University of Miami Miller School of Medicine; CIA 2009

Dr. Lee and colleagues estimated the prevalence of SHS exposure in a representative sample of Florida adults via self-report measures and tobacco exposure biomarkers in a cost-effective fashion. They also validated self-reported SHS exposures and examined the effects of exposure misclassification on associations with self-reported respiratory symptoms. Results from this study will be used to improve public health in Florida and to determine if and how self-reported SHS exposure questions should be used in documenting studies of tobacco associated health outcomes.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Bandiera FC, Arheart KL, Caban-Martinez AJ, Fleming LE, McCollister K, Dietz NA, Leblanc WG, Davila EP, Lewis JE, Serdar B, Lee DJ. Secondhand smoke exposure and depressive symptoms. *Psychosom Med.* 2010;72(1):68-72.

Bandiera FC, Caban-Martinez AJ, Arheart KL, Davila EP, Fleming LE, Dietz NA, Lewis JE, Fabry D, Lee DJ. Secondhand smoke policy and the risk of depression. *Ann Behav Med.* 2010;39(2):198-203.

Davila EP, Lee DJ, Fleming LE, LeBlanc WG, Arheart K, Dietz N, Lewis JE, McCollister K, Caban-Martinez A, Bandiera F. Sleep disorders and secondhand smoke exposure in the U.S. population. *Nicotine Tob Res.* 2010;12(3):294-299.

Fabry DA, Davila EP, Arheart KL, Serdar B, Dietz NA, Bandiera FC, Lee DJ. Secondhand smoke exposure and the risk of hearing loss. *Tob Control.* 2011;20(1):82-85.

Koru-Sengul T, Clark JD, Fleming LE, Lee DJ. Toward improved statistical methods for analyzing Cotinine-Biomarker health association data. *Tob Induc Dis.* 2011;9(1):11.

Koru-Sengul T, Clark JD, 3rd, Ocasio MA, Wanner A, Fleming LE, Lee DJ. Utilization of the National Health and Nutrition Examination (NHANES) Survey for Symptoms, Tests, and Diagnosis of Chronic Respiratory Diseases and Assessment of Second hand Smoke Exposure. *Epidemiology (Sunnyvale).* 2011;1(2).

PRESENTATIONS AND ABSTRACTS

Major BT, Ocasio MA, Arheart KL, Cabán-Martinez AJ, Hu JJ, Dietz N, Fleming LE, Huang Y, Cohen K, Fleming LE, Lee DJ. Secondhand smoke: prevalence, validation and effects. Presented at the Society for Research on Nicotine and Tobacco. Houston, TX, Mar 13-16, 2012.

Major BT, Ocasio MA, Arheart KL, Caban-Martinez AJ, Murray M, Forrest J, Hu J, Dietz N, Fleming LE, Lee DJ. Secondhand smoke: prevalence, validation and effects. Presented at the Second Annual Delta Omega, Beta Sigma Chapter Poster Competition. Miami, FL, Apr 4, 2011.

Major BT, Ocasio MA, Cabán-Martinez AJ, Arheart KL, Forrest J, Jordan M, Cohen K, Huang Y, Clark TC, Dietz N, Hu JJ, Fleming LE, Lee DJ. Secondhand smoke: prevalence, validation and effects. Presented at the American Public Health Association Conference. Washington DC, Oct 29- Nov 2, 2011.

Ocasio MA, Cabán Martinez A, Asfar T, Koru-Sengul T, Arheart KL, Fleming LE, Clarke TC, Austin SB, Lee DJ. Disparities in Tobacco Exposure by Sexual Orientation: Results from the National Health and Nutrition Examination Survey, 2001-2010. Presented at the American Public Health Association Annual Meeting. San Francisco, CA, Oct 27-31, 2012.

Ocasio MA, Cabán-Martinez AJ, Koru-Sengul T, Clark JD, Arheart KL, LeBlanc WG, Fleming LE, Lee DJ. Tobacco smoke exposure among lesbian, gay and bisexuals: Results from the National Health and Nutrition Examination Survey, 2001-2010. Presented at the 2012 Society for Research on Nicotine and Tobacco 18th Annual Meeting. Houston, TX, Mar 13-16, 2012.

Parris D, Koru-Sengul T, Dietz NA, Trapido EJ, Lee DJ. Is smoking related to stage of diagnosis of prostate cancer? Presented at the Society for Research on Nicotine and Tobacco Annual International Meeting. Boston, MA, Mar 13-16, 2013.

HOSPITALIZATION FOR CORONARY HEART DISEASE: A TIME TO ADDRESS SHS EXPOSURE

Nancy Rigotti, MD; Massachusetts General Hospital; CIA 2009

Dr. Rigotti and colleagues explored whether hospital admission for coronary heart disease (CHD) can be used as a time to intervene with nonsmokers who are exposed to SHS. The prevalence of biochemically-detectable SHS exposure in blood samples collected from a random sample of hospitalized CHD patients was assayed for the frequency at which

hospital personnel recorded SHS exposure in the hospital chart. In adults admitted to Massachusetts General Hospital (MGH), 11.8% of all patients and 14.5% of nonsmokers had biochemical evidence of SHS exposure, which was almost never assessed by the clinicians. The team prospectively surveyed nonsmokers hospitalized with CHD to determine the prevalence of SHS exposure (self-report and cotinine level), awareness of the risks of SHS exposure, and SHS reduction efforts. One-quarter of hospitalized nonsmokers with CHD reported past 30-day SHS exposure. Adult children were more likely than spouses to be the household smoker living with an exposed patient. Nearly one-half of nonsmokers with CHD were unaware of the cardiac risk of SHS, and health care providers rarely addressed SHS exposure. These data identify a need to educate nonsmoking cardiac patients about the risk of SHS and ways to minimize exposure. The team developed an intervention to encourage hospitalized nonsmokers to adopt smoke free home and car policies, using a pamphlet about the risks of SHS. A question about SHS exposure and a prompt to advise a smoke free home was added to the standard admission form used by nurses in the MGH cardiac inpatient units. Nurses were trained to provide the SHS handout to all patients admitted. The team is surveying nonsmoking cardiac inpatients to assess whether they have been asked about SHS exposure, given the SHS pamphlet, and advised to have a smoke free home and car. These data are being compared to data collected prior to the start of the intervention. Preliminary data indicate that nurses are adopting the intervention and an increased number of patients report having been advised to have a smoke free home and car. However, improvement is needed to increase nurses' rate of intervention delivery, therefore a monthly in-service training for staff was offered and a monthly incentive for 3 months was provided for each unit that achieves a predetermined rate of advising nonsmokers about SHS.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Japuntich SJ, Eilers MA, Shenhav S, Park ER, Winickoff JP, Benowitz NL, Rigotti NA. Secondhand tobacco smoke exposure among hospitalized nonsmokers with coronary heart disease. *JAMA Intern Med.* 2015;175(1):133-136.

Rigotti NA, Park ER, Streck J, Chang Y, Reyen M, McKool K, Winickoff JP. An intervention to address secondhand tobacco smoke exposure among nonsmokers hospitalized with coronary heart disease. *Am J Cardiol.* 2014;114(7):1040-1045.

PRESENTATIONS AND ABSTRACTS

Eilers M, Japuntich J, Shenhav S, Reyen M, Winickoff J, Park E, Rigotti NA. Secondhand smoke exposure patterns among patients hospitalized with coronary heart disease. Presented at the 2011 Annual Meeting of the Society for Research on Nicotine and Tobacco. Toronto, ON, Canada, Feb 16-19, 2011.

Rigotti NA, Lewandrowski K, Lewandrowski E, Reyen M, Richards A, Shenhav S, Chang Y. Secondhand smoke exposure among adults admitted to an acute-care general hospital: A comparison of serum cotinine screening and chart review. Presented at the 2011 Annual Meeting of the Society for Research on Nicotine and Tobacco. Toronto, ON, Canada, Feb 16-19, 2011.

Rigotti NA, Lewandrowski L, Lewandrowski E, Reyen M, Richards AE, Shenhav S, Chang Y, Benowitz N. Prevalence of tobacco smoking among adults admitted to an acute-car general hospital: a comparison of results from serum cotinine screening and chart review. Presented at the16th Annual Society for Research on Nicotine and Tobacco Conference. Baltimore, MD, Feb 24-27, 2010.

Rigotti NA, Streck J, Chang Y, McKool K, Reyen M, Park ER, Winickoff JP. A nursedelivered intervention to address secondhand smoke exposure among nonsmokers hospitalized with coronary heart disease. Presented at the 2014 Annual Meeting of the Society for Research in Nicotine and Tobacco. Seattle, WA, Feb 5-8, 2014.

BAR INTERVENTIONS TO DECREASE YOUNG ADULT SMOKING

Pamela Ling, MD, MPH; Public Health Institute, San Francisco; CIA 2010

Dr. Ling addressed the prevention of diseases caused by mainstream and SHS by developing an intervention to block tobacco industry marketing to young adults (age 18-25). Almost all tobacco prevention efforts concentrate on preventing children and adolescents from experimenting with cigarettes despite the fact that the transition from experimentation to regular smoking and addiction often occurs during young adulthood. The tobacco industry has invested millions of dollars in sophisticated marketing research on young adults. Because the Master Settlement Agreement restricts marketing to youth, young adults have become an even more important focus of industry marketing efforts, which often emphasize events at “adult only” venues (bars, nightclubs and casinos), which are exempt from these restrictions. Successfully competing with industry promotion in these venues will prevent transitions to regular smoking among young adults, by preventing long term morbidity and mortality from active smoking and preventing them from exposing others to SHS. This study builds on insights from Dr. Ling's previous study, which used previously secret tobacco industry market research to identify vulnerable segments of the young adult population and messages that reduce the likelihood of smoking. These insights were used to develop and evaluate a novel intervention promoting a smoke free lifestyle among young adults attending bars and nightclubs in San Diego, Albuquerque, and Oklahoma City. The intervention emphasizes strong smoke free aspirational identities and popularizes smoke free environments. A significant decrease in smoking was observed in these cities over the course of the pilot interventions.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Berg CJ, Ling PM, Guo H, Windle M, Thomas JL, Ahluwalia JS, An LC. Using Market Research to Characterize College Students and Identify Potential Targets for Influencing Health Behaviors. *Soc Mar Q.* 2010;16(4):41-69.

Cortese DK, Ling PM. Enticing the New Lad: Masculinity as a Product of Consumption in Tobacco Industry-Developed Lifestyle Magazines. *Men Masc.* 2011;14(1):4-30.

Fallin A, Neilands TB, Jordan JW, Hong JS, Ling PM. Wreaking "havoc" on smoking: social branding to reach young adult "partiers" in Oklahoma. *Am J Prev Med.* 2015;48(1 Suppl 1):S78-85.

Jiang N, Lee YO, Ling PM. Young adult social smokers: their co-use of tobacco and alcohol, tobacco-related attitudes, and quitting efforts. *Prev Med.* 2014;69:166-171.

Jiang N, Lee YO, Ling PM. Association between tobacco and alcohol use among young adult bar patrons: a cross-sectional study in three cities. *BMC Public Health.* 2014;14:500.

Jiang N, Ling PM. Impact of alcohol use and bar attendance on smoking and quit attempts among young adult bar patrons. *Am J Public Health.* 2013;103(5):e53-61.

Kalkhoran S, Neilands TB, Ling PM. Secondhand smoke exposure and smoking behavior among young adult bar patrons. *Am J Public Health.* 2013;103(11):2048-2055.

Ling PM, Lee YO, Hong J, Neilands TB, Jordan JW, Glantz SA. Social branding to decrease smoking among young adults in bars. *Am J Public Health.* 2014;104(4):751-760.

Mejia AB, Ling PM. Tobacco industry consumer research on smokeless tobacco users and product development. *Am J Public Health.* 2010;100(1):78-87.

Mejia AB, Ling PM, Glantz SA. Quantifying the effects of promoting smokeless tobacco as a harm reduction strategy in the USA. *Tob Control.* 2010;19(4):297-305.

Schane RE, Ling PM, Glantz SA. Health effects of light and intermittent smoking: a review. *Circulation.* 2010;121(13):1518-1522.

Song AV, Ling PM. Social smoking among young adults: investigation of intentions and attempts to quit. *Am J Public Health.* 2011;101(7):1291-1296.

PRESENTATIONS AND ABSTRACTS

Grana R, Ling PM. E-cigarettes and quitting behavior among bar-going young adult smokers of California. Presented at the American Public Health Association Annual Meeting. San Francisco, CA, Oct 27-31, 2012.

Grana RA, Jordan J, Ling PM. Smoking cessation intervention with young adults in bars and clubs. Presented at the 139th American Public Health Association Annual Meeting. Washington, DC, Oct 29-Nov 4, 2011.

Holmes L, Jordan JW, Ling PM. Peer crowd segmentation and young adult tobacco use. Presented at the American Public Health Association Annual Meeting. Denver CO, Nov 1, 2016.

Holmes L, Ling PM. Alternative tobacco product use among young adult bar patrons: A six city study. Presented at the APHA 142nd Annual Meeting & Expo. New Orleans, LA, Nov 15-19, 2014.

Holmes LM, Ling PM. Secondhand Smoke Exposure in the Workplace: A Lingering Hazard for Young Adults in California. Presented at the American Public Health Association Meeting. Chicago, IL, Nov 3, 2015.

Jiang N, Lee YO, Ling PM. Association between tobacco and alcohol use among young adults attending bars. Presented at the Society for Research on Nicotine and Tobacco Annual Meeting. Toronto, Ontario, Canada, Feb 16-19, 2011.

Jiang N, Lee YO, Ling PM. Co-use of alcohol and tobacco among young adult social smokers. Presented at the American Public Health Association Annual Meeting. San Francisco, CA, Oct 27-31, 2012.

Jiang N, Ling PM. Co-use of tobacco and alcohol and quit attempts among young adult bar patrons. Tobacco Related Diseases Research Program Conference. Sacramento CA, Apr 10-12, 2012.

Jiang N, Ling PM. Does tobacco marketing promote co-use of tobacco and alcohol and undermine quit attempts? Presented at the American Public Health Association Annual Meeting. San Francisco, CA, Oct 27-31, 2012.

Jiang N, Ling PM. Tobacco and alcohol use among young adults attending bars. Presented at the 139th American Public Health Association Annual Meeting. Washington, DC, Oct 29-Nov 4, 2011.

Jordan JW, Djakaria M, Ling PM. Reducing young adult tobacco use in California, Nevada and New Mexico; A promising new model. Presented at the APHA 142nd Annual Meeting & Expo. New Orleans, LA, Nov 15-19, 2014.

Kalkhoran S, Ling PM. Secondhand smoke exposure and association with smoking behavior among young adults in bars. Presented at the Society for General Internal Medicine Annual Meeting. Orlando, FL, May 9-12, 2012.

Lee YO, Ling PM. Young adult social smoking in bars and clubs. Presented at the Society for Research on Nicotine and Tobacco Annual Meeting. Toronto, Ontario, Canada, Feb 16-19, 2011.

Ling PM, Jordan J, Neilands TB, Glantz SA. Targeting trendsetters to reduce smoking among young adults in bars. Presented at the 139th American Public Health Association Annual Meeting. Washington, DC, Oct 29-Nov 4, 2011.

Ling PM, Jordan JA. Wreaking "havoc" on smoking: social branding to reach young adult "partiers" in Oklahoma. Presented at the TSET/OTRC Symposium. Oklahoma City, OK, May 2015.

Ling PM, Ramo D, Thrul J. Technology and tobacco use: reaching the “Hard to Reach”. Presented at the Association of Health Care Journalists. Oct, 2016.

Ling PM, Strader T, Paulson S, Jordan J. From changing norms to changing policy: young adult tobacco use prevention in Oklahoma. Presented at the National Cancer Institute Research to Reality webinar. Sep, 13, 2016.

Ling PM. Countering young adult tobacco marketing in bars. Presented at the Centers for Disease Control and Prevention, Office on Smoking and Health. May 21, 2016.

Ling PM. Novel interventions to reduce smoking among young adults. Presented at University of Otago, Dunedin, Wellington, and Auckland. New Zealand, Jul 2014.

Ling PM. Tobacco marketing strategies targeting youth and young adults. Presented at the Alameda County Tobacco Control Coalition. Oakland, CA, Dec 2, 2014.

Ling, PM, Jordan, J, Neilands TB, Glantz SA. Sustaining reduced smoking among young adults in bars. Presented at the World Conference on Tobacco or Health. Singapore, Mar 20-24, 2012.

Ling, PM. Selling sin or sainthood? Reducing tobacco use among young adult bar patrons. Plenary speaker, 38th Annual AMERSA National Conference. San Francisco CA, Nov 6, 2014.

Ling, PM. Who's at risk? Pragmatic market segmentation strategies to understand young adult tobacco use. Presented at the Agents of Change summit. Feb 2016.

Lisha NE, Neilands TB, Jordan JW, Holmes LM, Ling PM. Using a social prioritization index to predict young adult smoking. Presented at the American Public Health Association Meeting. Chicago, IL, Nov 1, 2015.

Stevenson T, Lee YO, Ling PM. Dual and poly-tobacco use of snus, spit tobacco and hookah among young adults in bars. Presented at the National Summit on Spit and Smokeless Tobacco. Austin, TX, May 10-12, 2011.

Veffer JR, Ling PM. Beyond the brotherhood: Smokeless marketing strategies to recruit new users. Presented at the National Summit on Spit and Smokeless Tobacco. Austin, TX, May 10-12, 2011.

EVALUATING THE CHARACTERISTICS THAT INFLUENCE PERSUASIVENESS OF SECONDHAND TOBACCO SMOKE ADVERTISEMENTS

Maansi Bansal-Travers, PhD; Roswell Park Alliance Foundation; YCSA 2008

Dr. Bansal-Travers conducted a number of studies with the goal of examining how different characteristics of television ads depicting the adverse effects of toxic smoke pollution (TSP) influence different target audiences. These ads focused on issues related to TSP exposure and were independently coded by trained coders for three main characteristics: main theme (e.g., health effects; social norms), target audience (parents; general audience), and execution style (e.g., personal testimonial; negative visceral image). Several in-person focus groups were conducted in New York and South Carolina to evaluate attitudes and beliefs about health risks from TSP exposure, tobacco use behavior, and policies in the home and car related to tobacco use. Those same ads were then evaluated in New York and South Carolina using a Web-based survey to compare the responses among adults living with at least one smoker and at least one child under the age of 18. This second study was done to examine differences in perceptions and responses to ads between in-person and Web-based survey modalities, since Web-based ads are an increasing prevalent method for education and communication. As an extension of this work, two national surveys were completed using Web-based survey methods with adults and youth (13-17 years) in the US. Updated ads were tested in these surveys and were also coded for main theme, target audience, and execution style. In all studies, participants were followed up approximately one week later to evaluate recall of ads seen, tobacco use behavior, quit attempts, and changes to home and car tobacco use policies. The lessons learned have been applied to several areas in tobacco control. Originally the focus was on TSP from cigarettes and television advertising educating smokers, particularly parents, about the risks to health, the principle concepts of education, communication, and TSP exposure information research have been expanded through work related to snus (a moist powder tobacco

product) and electronic nicotine delivery systems, particularly e-cigarettes. Results and conclusions drawn from this research regarding effective messaging, including theme of message and execution style, have been applied to several studies evaluating health warning labels for both cigarettes and other tobacco products. For example, Dr. Bansal-Travers has conducted several studies evaluating health warning labels, including format, text, and graphic that should be included to best communicate the risks from tobacco use for cigarettes and other products. In addition, she has worked with co-investigators to complete studies evaluating perceptions of snus and use of snus indoors when smoking is prohibited, as well as studies examining increasing trends in use of e-cigarettes and dual use with cigarettes to maintain nicotine addiction while trying to decrease TSP exposure.

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HEALTH IMPACT STUDY OF SMOKEFREE POLICIES IN LATIN AMERICA

Ernesto Sebrié, MD MPH; Roswell Park Alliance Foundation; YCSA 2008

Dr. Sebrié and colleagues tested whether the 2006 comprehensive smoke free policy adopted in Uruguay is associated with a reduction in acute myocardial infarction (AMI) hospital admissions in the four-year time period after the adoption of the law, and whether a comprehensive smoke free law implemented in Panama in 2008 is associated with a similar health outcome. The team also determined if the 2006 comprehensive smoke free policy in Uruguay is associated with a reduction in asthma visits to hospital emergency rooms. The team evaluated the effectiveness of pictorial-based health warning labels printed on cigarette packages to raise awareness on SHS exposure and increase public support for implementation of a comprehensive smoke free policy in Bolivia. This was the first study conducted in Latin America to evaluate the impact of a comprehensive smoke free initiative on heart and respiratory diseases and to assess the effectiveness of health warnings to increase public support for smoke free policies.

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EVALUATING ONLINE CLINICAL OFFICE-SYSTEMS TRAINING TO ADDRESS SECONDHAND TOBACCO SMOKE EXPOSURE OF CHILDREN

Jonathan P. Winickoff, MD, MPH; Massachusetts General Hospital; CIA 2008

Dr. Winickoff and colleagues developed and tested a rapidly deployable online system to train pediatric offices in addressing children's exposure to SHS. The course, "Help Every Family Quit Smoking," is available through the American Academy of Pediatrics PediaLink™ online learning center (pedialink.org). To test the feasibility and efficacy of the online training tool for implementing an office system to address children's SHS exposure, two pediatric practices in the Boston area were recruited and randomized to control for intervention status. The pediatricians at the intervention practice completed the PediaLink™ training and used the enhanced Web site to support their office system change. The primary outcome for this study was a change in the rates of asking and advising parents about smoking and smoke-free home and cars before and after the intervention. Exit surveys of parents showed that receiving the intervention increased overall rates of parental reports of being asked about: 1) smoking, 2) smoke-free home and car rules, 3) whether a household member smokes, and 4) being advised to have a smoke-free home and car.

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Winickoff JP, Van Cleave J, Oreskovic NM. Tobacco smoke exposure and chronic conditions of childhood. *Pediatrics.* 2010;126(1):e251-252.

SECOND HAND TOBACCO SMOKE EMISSIONS OF REDUCED EXPOSURE PRODUCTS

Gregory N. Connolly, DMD, MPH; Harvard School of Public Health; CIA 2007

Two so-called low smoke smell (LSS) products, which utilize differing design technologies (i.e., perfume additives to mask odor and potassium/calcium additives to increase burn temperature), were compared with a conventional cigarette on machine yield mainstream and sidestream emissions and human sensory perceptions of SHS. Mirage and Vogue cigarettes produced less overall SHS compared with the Marlboro Lights control. Yield analyses suggested that LSS products yielded lower emissions on some gas phase constituents (e.g., carbonyl, phenolic, and volatile organic compounds). Particulate phase polycyclic aromatic hydrocarbon compounds were similar between LSS brands and control. However, after controlling for weight of tobacco, sidestream smoke machine yields were similar for all brands, suggesting no substantial reduction in sidestream emissions, despite suggestions to the contrary by the manufacturers. Human sensory perceptions of LSS cigarette smoke were generally positive and not greatly different than the Marlboro Lights control.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Karabela M, Vardavas CI, Tzatzarakis M, Tsatsakis A, Dockery D, Connolly GN, Behrakis P. The relationship between venue indoor air quality and urinary cotinine levels among semiopen-air cafe employees: what factors determine the level of exposure? *J Aerosol Med Pulm Drug Deliv.* 2011;24(1):35-41.

Kennedy RD, Millstein RA, Rees VW, Connolly GN. Tobacco industry strategies to minimize or mask cigarette smoke: opportunities for tobacco product regulation. *Nicotine Tob Res.* 2013;15(2):596-602.

Rees VW, Kreslake JM, O'Connor RJ, Cummings KM, Parascandola M, Hatsukami D, Shields PG, Connolly GN. Methods used in internal industry clinical trials to assess tobacco risk reduction. *Cancer Epidemiol Biomarkers Prev.* 2009;18(12):3196-3208.

Saade G, Seidenberg AB, Rees VW, Otrock Z, Connolly GN. Indoor secondhand tobacco smoke emission levels in six Lebanese cities. *Tob Control.* 2010;19(2):138-142.

Van Hemelrijck MJ, Kabir Z, Connolly GN. Trends in lung cancer death rates in Belgium and The Netherlands: a systematic analysis of temporal patterns. *J Community Health.* 2009;34(3):188-194.

Van Hemelrijck MJ, Michaud DS, Connolly GN, Kabir Z. Secondhand smoking, 4-aminobiphenyl, and bladder cancer: two meta-analyses. *Cancer Epidemiol Biomarkers Prev.* 2009;18(4):1312-1320.

SECONDHAND TOBACCO SMOKE COUNSELING FOR PARENTS OF HOSPITALIZED PEDIATRIC PATIENTS

Alan C. Geller, MPH, RN; Boston University
Harvard School of Public Health; CIA 2007

Dr. Geller evaluated current SHS assessment and counseling practices of hospital-based pediatric nurses and developed a systems-change demonstration project to enhance assessment and counseling of the smoking parents/caregivers of hospitalized children. Developmental work was done before conducting surveys with members of the Society of Pediatric Nurses and mailing the survey to members. Data from the national surveys were used to identify the barriers, propose improvements to data recording systems, and develop innovative systems' approaches and intervention strategies for improving nurse-parent/caregiver communication for SHS exposure reduction. The completed survey enabled assessment of the frequency with which pediatric nurses perform the 5As (ask, advise, assess, assist, and arrange) with parents and caregivers.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Geller AC, Brooks DR, Woodring B, Oppenheimer S, McCabe M, Rogers J, Timm A, Resnick EA, Winickoff JP. Smoking cessation counseling for parents during child hospitalization: a national survey of pediatric nurses. *Public Health Nurs.* 2011;28(6):475-484.

Kells M, Rogers J, Oppenheimer SC, Blaine K, McCabe M, McGrath E, Woodring B, Geller AC. The teachable moment captured: a framework for nurse-led smoking cessation interventions for parents of hospitalized children. *Public Health Nurs.* 2013;30(5):468-473.

PRESENTATIONS AND ABSTRACTS

Geller A. Smoking cessation and second-hand smoke counseling reduction for parents of hospitalized pediatric patients. Presented at the Society of Pediatric Nurses Annual Meeting. Orlando, FL, Apr 2007.

Geller A. Smoking cessation and second-hand smoke counseling reduction for parents of hospitalized pediatric patients. Presented at Children's Hospital. Boston, MA, Nov 2009.

Kells M. Smoking cessation and second-hand smoke counseling reduction for parents of hospitalized pediatric patients. Presented at Division of Adolescent Medicine, Children's Hospital. Boston, MA, Jan 2012 (Laboratory of Alan Geller).

Kells M, Oppenheimer S, Geller AC, Woodring BC, Rogers J, McCabe M. Smoking cessation for parents at a large children's hospital. Presented at the Society of Pediatric Nurses Meeting. Houston TX, Apr 15-18, 2010.

Rogers J. Smoking cessation and second-hand smoke counseling reduction for parents of hospitalized pediatric patients. Presented at the Symposium on Tobacco use initiatives at Children's Hospital. Boston, MA, Nov 2011.

INCREASING SECONDHAND SMOKE AWARENESS, COMPETENCY and SCREENING AMONG MEDICAL PROFESSIONALS: EXPANDING THE MEDICAL CURRICULUM

Mark S. Gold, MD; University of Florida; CIA 2007

Dr. Gold's team delivered educational intervention to second-year students at the University of Florida College of Medicine. Students from the Class of 2009 were administered the SHS Competency Exam, serving as a no treatment, no pre-test control group, and students from the Class of 2010 were pre-tested at the beginning of their second year and post-tested at the beginning of their third year, serving as a no treatment control group. Students in the Class of 2011 served as the treatment group and were pre-tested at the beginning of their second year. They were administered the full educational intervention and then post-tested at the beginning of their third year. Results indicated that beginning second-year medical students knew little more than members of the general public regarding SHS exposure, scoring an average of 63% on the SHS Competency Exam. After completing their second year of medical school, the control group showed no improvement in their scores. However, students who receive the educational intervention significantly improved their scores the beginning of their third year. The course was updated to include new research findings and clinical practices to combat SHS exposure and related conditions; a section with information on the effects of thirdhand smoke was also included. Case library and an online lecture and instructional video series (via YouTube) were submitted to MedEdPORTAL, a peer-reviewed free online publication service for dissemination of the materials.

FAMRI SUPPORTED RESEARCH

PRESENTATIONS AND ABSTRACTS

Fuller BF, Ottens AK. Secondhand smoke induced heart and brain injury. Presented at the Society for Neuroscience 38th Annual Meeting Chicago, IL, Oct 17-21, 2009.

Kobeissy FH, Bruijnzeel A, Buchanan M, Gjymishka A, Wang K, Gold MS. Secondhand smoke induced molecular effects in adult rat brain. Presented at the Society for Neuroscience 38th Annual Meeting. Chicago, IL, Oct 17-21, 2009.

RESEARCH AND EDUCATION ON SMOKE-FREE AIR FOR PETS AND FAMILIES

Ronald M. Davis, MD (1956-2008), Sharon Milberger, ScD, PhD; Henry Ford Health System; CIA 2006

Dr. Sharon Milberger continued Dr. Davis' initial work. The aim was to assess whether pet health conditions may be linked to SHS exposure and to determine whether knowledge about the effects of SHS on the health of pets can be a persuasive motivator for smokers to change their smoking behaviors. The investigators developed a World Wide Web-based survey for pet owners across Southeast Michigan, and obtained responses from over 3,000 pet owners in Michigan and beyond. Significant associations were found between selected health conditions in pets and exposure to SHS in the home. An intervention phase was started to determine if cognizance of the effects of SHS on pets' health would motivate smoking cessation and the adoption of smoke-free environments.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Milberger S, Davis RM, Holm AL. Pet owners' attitudes and behaviors related to smoking and secondhand smoke: A pilot study. *Tob Control.* 2009;18(2):156-158.

HOUSEHOLD SMOKING BANS: A COMPREHENSIVE ANALYSIS

Nancy Rigotti, MD; Massachusetts General Hospital; CIA 2006

Dr. Rigotti studied whether adolescents living in households where smoking is banned are more likely to develop anti-smoking attitudes and less likely to progress to smoking. A related question about the impact of smoke-free homes on youth behaviors was also investigated. It was shown that the presence of complete household smoking bans significantly decreases adolescents' exposure to SHS at home and increases the likelihood that youths will develop anti-smoking attitudes. The study supported the notion that home smoking bans have potential to promote anti-smoking norms and to prevent adolescent smoking. Further, a household smoking ban in the parental home appears to lead youths to prefer smoke-free living quarters once they leave home. Smoke-free homes appear to be transmitted across generations.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Albers AB, Biener L, Siegel M, Cheng DM, Rigotti N. Household smoking bans and adolescent antismoking attitudes and smoking initiation: findings from a longitudinal study of a Massachusetts youth cohort. *Am J Public Health.* 2008;98(10):1886-1893.

Albers AB, Biener L, Siegel M, Cheng DM, Rigotti NA. Impact of parental home smoking policies on policy choices of independently living young adults. *Tob Control.* 2009;18(3):245-248.

Thomson CC, Hamilton WL, Siegel MB, Biener L, Rigotti NA. Effect of local youth-access regulations on progression to established smoking among youths in Massachusetts. *Tob Control.* 2007;16(2):119-126.

SECONDHAND TOBACCO SMOKE AWARENESS, COMPETENCY AND PRACTICE: PHYSICIANS AND MEDICAL STUDENTS

Mark S. Gold, MD; University of Florida; CIA 2004

Although health care professionals are ideally positioned to screen for SHS exposure, many may not ask about it. This study was designed, pilot-tested, and implemented as a ten-item SHS competency exam to assess knowledge of SHS-related health issues among health science students and physicians, such as asking the question about exposure to tobacco smoke, the components in exhaled smoke, smoke-related diseases, effective tests of exposure, and how to quantify exposure. Dr. Gold found that 58% of physicians said they check every patient, every visit for tobacco smoking status but only 34.5% ask patients about SHS exposure. This low rate was attributed to a relative lack of competency, which was made apparent by the poor performance observed on the competency exam. It is difficult to re-educate health providers who have had no training in SHS exposure. A standard patient case and extensive continuing medical education course was developed as a consequence. Medical curriculum and focused remediation were developed to help students and health care providers understand SHS exposure and its role in disease.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Gold MS, Graham NA. A 13-year-old boy with persistent coughing, wheezing. *Psych Annals.* 2005;35(6):461-467.

PRESENTATIONS AND ABSTRACTS

Gold MS, Frost-Pineda K, Graham NA, Watson RT. Physician awareness, competency, and practice secondhand smoke survey. Presented at the 29th National Conference for the Association for Medical Education and Research in Substance Abuse. Bethesda, MD, Oct 27-29, 2005.

Rodriguez L, Gold J, Watson R, Frost-Pineda K, Gold MS**.** Second hand smoke (SHS): Health professional students competency and intent to screen. Presented at the 36th Annual Medical-Scientific Conference of the American Society of Addition Medicine. Dallas, TX, Apr 14-17, 2005.

BOOK CHAPTERS, ETC.

10-credit continuing medical education (CME) course for practicing professionals: "Smoking and Secondhand Smoke" was released in early 2007 and has been disseminated to over a million physicians, nurses and social workers across the nation via CME Resource in Sacramento, CA.

REVERSING TOBACCO MARKET RESEARCH ON YOUNG ADULTS

Pamela Ling, MD, MPH; University of California, San Francisco; YCSA 2004

Dr. Ling used previously secret tobacco industry market research to identify vulnerable segments of the young adult population and messages that reduce the likelihood of smoking. She found that concern about the effects of SHS on others, tobacco industry de-normalization, and certain personality characteristics were associated with smoking. These

insights were used to develop and evaluate an intervention promoting a smoke-free lifestyle among young adults attending bars and nightclubs in San Diego and two other cities. The message strategy emphasizes strong smoke-free identities and popularizes smoke-free environments. These interventions in different geographical and social environments enabled the development and implementation of the first evidence-based strategies to reduce smoking and SHS exposure among young adults in social venues. The resulting information improves approaches to young adult-targeted messaging for public health campaigns and clinical patient counseling to block the transition from experimentation to established addicted smokers.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Anderson SJ, Dewhirst T, Ling PM. Every document and picture tells a story: using internal corporate document reviews, semiotics, and content analysis to assess tobacco advertising. *Tob Control.* 2006;15(3):254-261.

Anderson SJ, Ling PM. "And they told two friends...and so on": RJ Reynolds' viral marketing of Eclipse and its potential to mislead the public. *Tob Control.* 2008;17(4):222-229.

Anderson SJ, Ling PM, Glantz SA. Implications of the federal court order banning the terms "light" and "mild": what difference could it make? *Tob Control.* 2007;16(4):275-279.

Anderson SJ, Pollay RW, Ling PM. Taking ad-Vantage of lax advertising regulation in the USA and Canada: reassuring and distracting health-concerned smokers. *Soc Sci Med.* 2006;63(8):1973-1985.

Braun S, Mejia R, Ling PM, Perez-Stable EJ. Tobacco industry targeting youth in Argentina. *Tob Control.* 2008;17(2):111-117.

Cortese DK, Lewis MJ, Ling PM. Tobacco industry lifestyle magazines targeted to young adults. *J Adolesc Health.* 2009;45(3):268-280.

Hafez N, Ling PM. Finding the Kool Mixx: how Brown & Williamson used music marketing to sell cigarettes. *Tob Control.* 2006;15(5):359-366.

Ling PM, Glantz SA. Tobacco industry consumer research on socially acceptable cigarettes. *Tob Control.* 2005;14(5):e3.

Ling PM, Haber LA, Wedl S. Branding the rodeo: a case study of tobacco sports sponsorship. *Am J Public Health.* 2010;100(1):32-41.

Ling PM, Neilands TB, Glantz SA. The effect of support for action against the tobacco industry on smoking among young adults. *Am J Public Health.* 2007;97(8):1449-1456.

Ling PM, Neilands TB, Glantz SA. Young adult smoking behavior: a national survey. *Am J Prev Med.* 2009;36(5):389-394 e382.

Ling PM, Neilands TB, Nguyen TT, Kaplan CP. Psychographic segments based on attitudes about smoking and lifestyle among Vietnamese-American adolescents. *J Adolesc Health.* 2007;41(1):51-60.

Mars SG, Ling PM. Meanings & motives. Experts debating tobacco addiction. *Am J Public Health.* 2008;98(10):1793-1802.

Schane RE, Glantz SA, Ling PM. Nondaily and social smoking: an increasingly prevalent pattern. *Arch Intern Med.* 2009;169(19):1742-1744.

Schane RE, Glantz SA, Ling PM. Social smoking implications for public health, clinical practice, and intervention research. *Am J Prev Med.* 2009;37(2):124-131.

Song AV, Ling PM, Neilands TB, Glantz SA. Smoking in movies and increased smoking among young adults. *Am J Prev Med.* 2007;33(5):396-403.

PRESERVATION OF DOCUMENTS

Completed Research

TOBACCO INSTITUTE AND COUNCIL FOR TOBACCO RESEARCH COLLECTION DEVELOPMENT

Anthony Brown, BS; Roswell Park Alliance Foundation; 2003

Approximately one-half of the Tobacco Institute (TI) and Council for Tobacco Research (CTR) collection that was released to New York State following the 1998 Master Settlement Agreement was digitally captured. These scanned documents can be viewed at http://roswelldocs.com . About 3,200 VHS and audiocassettes from the TI audiovisual archives were transferred to archival DVDs. Over 2,100 videos have been transferred and placed online through the Legacy Library at University of California, San Francisco. Further, a Web site http://tobaccovideos.com , containing more than 650 cigarette commercials and tobacco industry videos, was created for online viewing. A youth-focused interface (http://roswelldocs.com/ashes/ashestoashes.html) was created for students. In addition, a dynamic tobacco issue timeline allows for guests to move through time with key events, links, and resources. The timeline is available at http://hendersonit.net/hendersonit/timeline . More than 6,000 historical artifacts collected by FAMRI Distinguished Professor Alan Blum, MD, were transferred and cataloged.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Cummings KM, Brown A, O'Connor R. The cigarette controversy. *Cancer Epidemiol Biomarkers Prev.* 2007;16:1070-1076.

FAMRI-GUILFORD DIGITAL LIBRARY OF DOCUMENTS

Karen Butter, MLS; University of California, San Francisco; 2003

This project supported scanning, optical character recognition, indexing, and creation of an online repository for 6.7 million pages of British American Tobacco (BAT) Company documents to allow free public access via the Internet. These documents contain invaluable scientific research data on SHS exposure, and evidence as to how the tobacco companies fought tobacco-control efforts, including efforts to protect people from SHS exposure worldwide. The BAT Document Archive was launched in October 2004.

FLIGHT ATTENDANT STUDIES

0ngoing Research

DEEP IMPACT OF SECONDHAND CIGARETTE SMOKE ON SYMPTOMATIC FLIGHT ATTENDANTS WITH PRESERVED LUNG FUNCTION -- I.E. SYMPTOMATIC NON-OBSTRUCTIVE COPD

R. William Vandivier, MD; University of Colorado, Denver; 2020

Dr. Vandivier and colleagues will focus on the hypothesis that SHS-induced, symptomatic non- obstructive COPD (SNO-COPD) impairs progenitor-mediated epithelial repair and alters the airway microenvironment. To achieve this goal, the team will compare SHS-exposed and non-exposed individuals using a smartphone application and a monitor to examine daily activity (Actigraph activity monitor), and by examining stem/progenitor function and the environment in the nasal passage. The overall aim is to come to a comprehensive understanding of the extent to which SHS-induced SNO-COPD impairs quality of life and to connect these factors to biologic mechanisms of disease. Identifications of cellular and molecular mechanisms can be used to develop novel therapies for the millions of people who have been exposed to substantial amounts of SHS over a lifetime.

In light of the current pandemic, the investigators will also perform SARS CoV-2 testing for all Flight Attendants.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Breathett K, Liu WG, Allen LA, Daugherty SL, Blair IV, Jones J, Grunwald GK, Moss M, Kiser TH, Burnham E, Vandivier RW, Clark BJ, Lewis EF, Mazimba S, Battaglia C, Ho PM, Peterson PN. African Americans Are Less Likely to Receive Care by a Cardiologist During an Intensive Care Unit Admission for Heart Failure. *JACC Heart Fail.* 2018;6(5):413-420.

Diaz Del Valle F, Zakrajsek JK, Min SJ, Koff PB, Bell HW, Kincaid KA, Frank DN, Ramakrishnan V, Ghosh M, Vandivier RW. Impact of Airline Secondhand Tobacco Smoke Exposure on Respiratory Health and Lung Function Decades After Exposure Cessation. *Chest*. 2022;S0012-3692(22):00416-00420.

Kiser TH, Burnham EL, Clark B, Ho PM, Allen RR, Moss M, Vandivier RW. Half-Dose Versus Full-Dose Alteplase for Treatment of Pulmonary Embolism. *Crit Care Med.* 2018;46(10):1617-1625.

Sottile PD, Kiser TH, Burnham EL, Ho PM, Allen RR, Vandivier RW, Moss M, Colorado Pulmonary Outcomes Research G. An Observational Study of the Efficacy of Cisatracurium Compared with Vecuronium in Patients with or at Risk for Acute Respiratory Distress Syndrome. *Am J Respir Crit Care Med.* 2018;197(7):897-904.

Completed Research

FAMRI-SUPPORTED FLIGHT ATTENDANT SCREENINGS

Claudia I. Henschke, PhD, MD; Icahn School of Medicine at Mount Sinai; 2018

Dr. Henschke and colleagues developed a new paradigm of screening for lung cancer. This provides a earlier diagnosis than previous methods, hence a greater probablity of cure.

FAMRI-BLAND LANE CLINIC ON SECOND HAND SMOKE AT UCSF

Rita F. Redberg, MSc, MD; University of California, San Francisco; 2018

For the last fourteen years, the FAMRI Bland Lane Clinic at UCSF has provided complete medical evaluations of flight attendants exposed to secondhand smoke (SHS). The Clinic has developed a personalized approach for evaluation of flight attendants (FAs), which includes diagnosis and prevention of diseases related to SHS exposure. The Clinic's services have been developed and refined from years of experience and feedback from FAs who were exposed to SHS before the smoking ban. The clinical evaluation includes a complete physical exam, an EKG, ankle and arm blood pressure measurements, and a breathing test to screen for heart and lung diseases. Suspicious conditions conditions that require treatment are referred to specialists. The Clinic has developed a valuable database for determining the effects of SHS exposure on flight attendant health.

LONG-TERM EFFECTS OF HIGH-INTENSITY SECONDHAND SMOKE ON FLIGHT ATTENDANT SINUS MORBIDITY: THE FLIGHT ATTENDANT SINUS HEALTH STUDY

Daniel Frank, PhD; University of Colorado, Denver; CIA 2017

Chronic rhinosinusitis (CRS) is an inflammatory disorder of the nasal sinuses that afflicts 12- 16% of the US population. CRS is exacerbated by mainstream cigarette smoke, SHS, and infections. Flight attendants who flew before smoking was banned on airlines were exposed to SHS in concentrations that were 14-fold higher than typical workers of the time. Decades later, "pre-ban" flight attendants have diagnosed sinus disease, but the impact of this on their lives is still not understood. The goal of this study is to better understand, recognize, and treat SHS-induced sinus disease. As part of the Colorado FAMRI Research Collaborative, Dr. Frank and colleagues are performing the Initiative to Measure and PRomote Quality of Life for Flight Attendants with ObstructiVE Lung Disease – The IMPROVE Study, which will investigate the long-term effects of SHS-exposure on obstructive lung disease in pre- and post-ban flight attendants. Preliminary results suggest that pre-ban flight attendants have a higher prevalence of physician-diagnosed sinus problems compared to post-ban flight attendants The IMPROVE study will be used to perform the Flight Attendant Sinus Health Study, a detailed investigation of sinus health in this unique group of highly exposed people. The overall hypothesis is that high-intensity SHS exposure causes specific, long-lasting physiological, microbiological, and immunological defects in the upper airways. To date however, no studies have reported on associations between long-term SHS exposure and sinonasal microbiology, or the impact on sinonasal inflammation and health. The investigators will determine the effects of SHS-exposure on sinonasal health and healthcare and determine how SHS exposure alters upper airways microbiota. They will also determine the molecular mechanisms underlying SHS-induced sinonasal disease.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Diaz Del Valle F, Zakrajsek JK, Min SJ, Koff PB, Bell HW, Kincaid KA, Frank DN, Ramakrishnan V, Ghosh M, Vandivier RW. Impact of Airline Secondhand Tobacco Smoke Exposure on Respiratory Health and Lung Function Decades After Exposure Cessation. *Chest*. 2022;S0012-3692(22):00416-00420.

Vickery TW, Armstrong M, Kofonow JM, Robertson CE, Kroehl ME, Reisdorph NA, Ramakrishnan VR, Frank DN. Altered tissue specialized pro-resolving mediators in chronic rhinosinusitis. *Prostaglandins Leukot Essent Fatty Acids*. 2021;164:102218.

PRESENTATIONS AND ABSTRACTS

Diaz del Valle F, Zakrajsek J, Bell HW, Ramakrishnan VR, Frank DN, Vandivier RW. Long-term impact of remote environmental tobacco smoke exposure on respiratory symptoms and quality of life. Presented at the Thomas L. Petty Lung Conference. Aspen, CO, Jun 6-9, 2018.

Zakrajsek JK, Bell HW, Diaz del Valle F, Frank DN, Zamora MR, Lee JS, Phang TL, Ginde AA, Kiser TH, Abrams ME, Tallieu SS, Gerber AN and Vandivier RW. Recovery following COPD exacerbations associated with respiratory failure. Presented at the Thomas L. Petty Lung Conference. Aspen, CO, Jun 6-9, 2018.

REDUCED EXERCISE CAPACITY IN FLIGHT ATTENDANTS EXPOSED TO SECONDHAND SMOKE: PATHOGENESIS AND CONSEQUENCES.

Warren M. Gold, MD, Mehrdad Arjomandi, MD; University of California, San Francisco; 2015

Long-term exposure to SHS is associated with COPD. The investigators found that many SHS-exposed Flight Attendants had curvilinear flow-volume tracings, decreased airflow at mid- and low-lung volumes, and air trapping. In addition, they found over half of these individuals had decreased diffusing capacity, which did not increase appropriately with exertion, suggesting an overall limited pulmonary capillary bed availability. These findings implicate the presence of an obstructive ventilatory defect, which is consistent with COPD. In a preliminary study, the team found that exercise capacity was associated with the severity of air trapping. These findings suggest that many people at risk for COPD (but without spirometric COPD) have abnormal lung volumes on exhalation resulting in air trapping, and air trapping in these individuals is associated with functional limitations that may have important health consequences. The investigators will examine the hypothesis that the exercise capacity in never- smoking SHS-exposed Flight Attendants is limited by progressive airflow limitation (dynamic hyperinflation) that they develop with exertion, and that both dynamic hyperinflation and exercise capacity will improve with the use of inhaled bronchodilators.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Arjomandi M, Zeng S, Geerts J, Stiner RK, Bos B, van Koeverden I, Keene J, Elicker B, Blanc PD, Gold WM. Lung volumes identify an at-risk group in persons with prolonged secondhand tobacco smoke exposure but without overt airflow obstruction. *BMJ Open Respir Res.* 2018;5(1):e000284.

Barjaktarevic IZ, Buhr RG, Wang X, Hu S, Couper D, Anderson W, Kanner RE, Paine Iii R, Bhatt SP, Bhakta NR, Arjomandi M, Kaner RJ, Pirozzi CS, Curtis JL, O'Neal WK, Woodruff PG, Han MK, Martinez FJ, Hansel N, Wells JM, Ortega VE, Hoffman EA, Doerschuk CM, Kim V, Dransfield MT, Drummond MB, Bowler R, Criner G, Christenson SA, Ronish B, Peters SP, Krishnan JA, Tashkin DP, Cooper CB, SubPopulations N, InteRmediate Outcome Measures In CS. Clinical Significance of Bronchodilator Responsiveness Evaluated by Forced Vital Capacity in COPD: SPIROMICS Cohort Analysis. *Int J Chron Obstruct Pulmon Dis*. 2019;14:2927-2938.

Blagev DP, Collingridge DS, Rea S, Carey KA, Mularski RA, Zeng S, Arjomandi M, Press VG. Laboratory-based Intermountain Validated Exacerbation (LIVE) Score stability in patients with chronic obstructive pulmonary disease. *BMJ Open Respir Res*. 2020;7(1).

Blagev DP, Collingridge DS, Rea S, Horne BD, Press VG, Churpek MM, Carey KA, Mularski RA, Zeng S, Arjomandi M. The Laboratory-Based Intermountain Validated Exacerbation (LIVE) Score Identifies Chronic Obstructive Pulmonary Disease Patients at High Mortality Risk. *Front Med (Lausanne)*. 2018;5:173.

Blagev DP, Collingridge DS, Rea S, Press VG, Churpek MM, Carey K, Mularski RA, Zeng S, Arjomandi M. Stability of Frequency of Severe Chronic Obstructive Pulmonary Disease Exacerbations and Health Care Utilization in Clinical Populations. *Chronic Obstr Pulm Dis*. 2018;5(3):208-220.

Chen J, Weldemichael L, Zeng S, Giang B, Geerts J, Ching WC, Nishihama M, Gold WM, Arjomandi M. Actigraphy informs distinct patient-centered outcomes in Pre-COPD. *Respir Med*. 2021;187:106543.

Putcha N, Barr RG, Han MK, Woodruff PG, Bleecker ER, Kanner RE, Martinez FJ, Smith BM, Tashkin DP, Bowler RP, Eisner MD, Rennard SI, Wise RA, Hansel NN, Investigators S. Understanding the impact of second-hand smoke exposure on clinical outcomes in participants with COPD in the SPIROMICS cohort. *Thorax.* 2016.

Zeng S, Arjomandi M, Luo G. Automatically Explaining Machine Learning Predictions on Severe Chronic Obstructive Pulmonary Disease Exacerbations: Retrospective Cohort Study. *JMIR Med Inform*. 2022;10(2):e33043.

Zeng S, Dunn M, Gold WM, Kizer JR, Arjomandi M. Remote exposure to secondhand tobacco smoke is associated with lower exercise capacity through effects on oxygen pulse, a proxy of cardiac stroke volume. *BMJ Open Respir Res*. 2022;9(1).

Zeng S, Tham A, Bos B, Jin J, Giang B, Arjomandi M. Lung volume indices predict morbidity in smokers with preserved spirometry. *Thorax*. 2019;74(2):114-124.

PRESENTATIONS AND ABSTRACTS

Arjomandi M, Zeng S, Blanc PD, Gold WM. Increasing the resolution of chronic obstructive pulmonary disease definition. lessons from a cohort with remote but extensive exposure to secondhand tobacco smoke. *Ann Am Thorac Soc* 2018;15(Supplement_2):S122-S123.

Zeng S, Tham A, Bos B, Jin J, Arjomandi M. Back to the Box: Using Lung Volumes to Predict Susceptibility to Develop Chronic Obstructive Pulmonary Disease among Smokers. *Ann Am Thorac Soc.* 2018;15(Supplement_4):S286-S287.

INITIATIVE TO MEASURE AND PROMOTE QUALITY OF LIFE FOR FLIGHT ATTENDANTS WITH OBSTRUCTIVE LUNG DISEASE: THE IMPROVE STUDY

R. William Vandivier, MD; University of Colorado, Denver; 2015

The Colorado FAMRI Screening Center is evaluating pre-ban Flight Attendants to assess SHS exposure, quality of life, respiratory symptoms, and healthcare utilization. To do this, the IMPROVE Study is in the process of enrolling 380 pre-ban and 190 post-ban flight attendants over 5 years The investigators will examine the effect of remote airline-associated SHS exposure on the development of early lung function abnormalities that occur before COPD can be diagnosed (i.e. pre-COPD) and how this relates to symptoms, healthcare use and quality of life.

FOLLOW-UP SURVEY OF THE 2007 FLIGHT ATTENDANT HEALTH STUDY

Eileen McNeely, PhD; Harvard School of Public Health; 2013; CIA 2015

Dr. McNeely and colleagues are evaluating the health impact of occupational exposures to SHS in the largest Flight Attendant cohort in the US. The first findings from this study showed 3.5 times the prevalence of chronic bronchitis in this group when compared to a matched US population. In addition, higher rates of cardiac disease were seen in female Flight Attendants. This study was repeated in 2014-15, enlarging the sample to 10,000 Flight Attendants, and taking into consideration healthy worker effects to estimate historical airplane cabin exposures to SHS. The team is investigating current health problems in the cohort and changes in cardiopulmonary conditions over time as they relate to airplane cabin exposures to SHS.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

McNeely E, Mordukhovich I, Staffa S, Tideman S, Coull B. Legacy health effects among never smokers exposed to occupational secondhand smoke. *PLoS One*. 2019;14(4):e0215445.

McNeely E, Mordukhovich I, Staffa S, Tideman S, Gale S, Coull B. Cancer prevalence among flight attendants compared to the general population. *Environ Health.* 2018;17(1):49.

McNeely E, Mordukhovich I, Tideman S, Gale S, Coull B. Estimating the health consequences of flight attendant work: comparing flight attendant health to the general population in a cross-sectional study. *BMC Public Health.* 2018;18(1):346.

McNeely E, Staffa SJ, Mordukhovich I, Coull B. Symptoms related to new flight attendant uniforms. *BMC Public Health.* 2018;17(1):972.

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Wu AC, Donnelly-McLay D, Weisskopf MG, McNeely E, Betancourt TS, Allen JG. Airplane pilot mental health and suicidal thoughts: a cross-sectional descriptive study via anonymous web-based survey. *Environ Health.* 2016;15(1):121.

IMPACT OF VITAMIN D ON SEVERITY OF COPD SYMPTOMS IN FLIGHT ATTENDANTS

Margaret A. Crane-Godreau, PhD; Geisel School of Medicine at Dartmouth; CIA 2014

Dr. Crane-Godreau and colleagues are working with SHS-exposed Flight Attendants with tobacco-induced respiratory dysfunction to investigate the physiologic interplay of this dysfunction with cardiovascular, autonomic nervous system, and immune system functions and comorbidities, especially as they are related to Vitamin D levels in collaboration with another FAMRI-funded project, "Validating an Intervention for Flight Attendants with COPD" (see below). Flight Attendants from the Northeastern US have participated in Phase I testing; Phase II testing and training continued into early 2017.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Crane-Godreau MA, Clem KJ, Payne P, Fiering S. Vitamin D Deficiency and Air Pollution Exacerbate COVID-19 Through Suppression of Antiviral Peptide LL37. *Front Public Health*. 2020;8:232.

Jukosky J, Gosselin BJ, Foley L, Dechen T, Fiering S, Crane-Godreau MA. In vivo Cigarette Smoke Exposure Decreases CCL20, SLPI, and BD-1 Secretion by Human Primary Nasal Epithelial Cells. *Front Psychiatry*. 2015;6:185.

Payne P, Crane-Godreau MA. The preparatory set: a novel approach to understanding stress, trauma, and the bodymind therapies. *Front Hum Neurosci*. 2015;9:178.

Payne P, Fiering S, Leiter JC, Zava DT, Crane-Godreau MA. Effectiveness of a Novel Qigong Meditative Movement Practice for Impaired Health in Flight Attendants Exposed to Second-Hand Cigarette Smoke. *Front Hum Neurosci.* 2017;11:67.

Payne P, Fiering S, Zava D, Gould TJ, Brown A, Hage P, Gaudet C, Crane-Godreau M. Digital Delivery of Meditative Movement Training Improved Health of Cigarette-Smoke-Exposed Subjects. *Frontiers in Public Health*. 2018;6:282.

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PRESENTATIONS AND ABSTRACTS

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Payne P, Crane-Godreau M. Mechanisms of the effects of meditation practice on health. Presented at the International Symposium of Contemplative Sciences. Boston, MA, Oct 30-Nov 2, 2014.

Payne P, Crane-Godreau M. Resilience through bodymind practices: neuro-immune implications. Visiting Professorship presentation to DHMC Anesthesiology Department. Hanover, NH, Feb 20, 2015.

Payne P, Crane-Godreau M. The neurobiology of mind body science: trauma gives us a window. Keynote presentation at the 8th Annual C. Everett Koop Addiction Medicine Symposium. Hanover, NH, Dec 11, 2014.

BOOK CHAPTERS, ETC.

Crane-Godreau M, Payne, P. Flight attendant respiratory and comorbidities testing and training series, Phase I: Northern New England. Burlington, VT, Feb-Jul 2015.

Crane-Godreau M, Payne, P. Flight attendant respiratory and comorbidities testing and training series, Phase I: Boston Regional Hub. Woburn, MA, Jul 2015-Jan 2016.

Crane-Godreau M, Payne, P. Flight attendant respiratory and comorbidities testing and training series, Phase I: NY. New York, NY, May 2015-Jan 2016.

VALIDATING AN INTERVENTION FOR FLIGHT ATTENDANTS WITH COPD

Steven N. Fiering, PhD; Geisel School of Medicine at Dartmouth; CIA 2014

Dr Fiering and colleagues are conducting a study of an adapted form of meditative movement as an intervention designed to improve respiratory health and quality of life for Flight Attendants with respiratory disease associated with in-flight exposure to SHS. Flight Attendants from the Northeastern US have participated in Phase I testing. Phase II testing and training continued into early 2017. This study builds on other FAMRI-funded projects, and includes the investigation of effects of SHS on the immune system and lung disease, especially COPD. Potential cancer treatments are being explored in mice. Anthony Brown of the Roswell Park Alliance Foundation provides communications support for this project and the one described above.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Baker I, Fiering SN, Griswold KE, Hoopes PJ, Kekalo K, Ndong C, Paulsen K, Petryk AA, Pogue B, Shubitidze F, Weaver J. The Dartmouth Center for Cancer Nanotechnology Excellence: magnetic hyperthermia. *Nanomedicine* (Lond). 2015;10(11):1685-1692.

Crane-Godreau MA, Clem KJ, Payne P, Fiering S. Vitamin D Deficiency and Air Pollution Exacerbate COVID-19 Through Suppression of Antiviral Peptide LL37. *Front Public Health*. 2020;8:232.

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Lizotte PH, Wen AM, Sheen MR, Fields J, Rojanasopondist P, Steinmetz NF, Fiering S. In situ vaccination with cowpea mosaic virus nanoparticles suppresses metastatic cancer. Nat *Nanotechnol*. 2016;11(3):295-303.

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Fiering SN. *In situ* vaccination to treat cancer. Presented at the International Society of Hyperthermia Annual Meeting. Orlando, FL, Apr 25, 2015.

Fiering SN. *In situ* vaccination to treat cancer with viral-like nanoparticles. Presented at Norris Cotton Cancer Center Grand Rounds. Dartmouth Hitchcock Medical Center, Lebanon NH, Feb 12, 2016.

Fiering SN. *In situ* vaccination to treat cancer with viral-like nanoparticles. Presented at Stanford University celebrate for endowed chair for Lee Herzenberg. Palo Alto, CA, Dec. 7 2015.

COMMUNICATIONS AND DISSEMINATION SUPPORT FOR THE FLIGHT ATTENDANT MEDICAL RESEARCH INSTITUTE

Andrew Hyland, PhD; Roswell Park Alliance Foundation; 2010

The aim of this study is to provide FAMRI and grantees with scientific dissemination support through various media, print, social media, and web development to support the dissemination and recruitment of Flight Attendants into FAMRI studies. The investigators plan to provide a report on the SHS exposure in the US, develop a video illustrating FAMRI H-Index and impact on SHS science, and collect and report on hospital patient intake interviews for future analysis.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Cummings KM, Brown A, Douglas CE. Consumer acceptable risk: how cigarette companies have responded to accusations that their products are defective. *Tob Control*. 2006;15 Suppl 4:iv84-89.

FAMRI DISTINGUISHED PROFESSORS

BLAND LANE INTERNATIONAL DISTINGUISHED PROFESSOR

ENHANCED EXPRESSION OF VASCULAR G-PROTEIN COUPLED RECEPTORS IN ARTERIAL SMOOTH MUSCLE CELLS INDUCED BY CIGARETTE SMOKE

Lars Edvinsson, MD, PhD; Lund University; 2008

Dr. Edvinsson and his team explored the molecular mechanisms responsible for the cardiovascular morbidity and mortality that are associated with SHS exposure. In particular they showed that lipid soluble cigarette smoke particles (DSP) rather than nicotine in normal levels or water-soluble smoke particles may cause an enhanced number of contractile receptors in smooth muscle cells of arteries and bronchioles (endothelin ETA and ETB receptors, and thromboxane A2 receptors). These receptors mediate enhanced tone and proliferation and build-up of atherosclerotic plaque and cause thickening of vessel walls and reduced perfusion of tissues. These studies unraveled the signal transduction involved and suggested that interaction with the Raf/MEK/ERK pathway of mitogen-activated protein kinase system may have an important role in disease expression associated with exposure to cigarette smoke. It is suggested that the enhanced pulmonary and cardiovascular morbidity and mortality following active or passive smoking may be modified by interaction with this intracellular signal system.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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Dimitrijevic I, Andersson C, Rissler P, Edvinsson L. Increased tissue endothelin-1 and endothelin-B receptor expression in temporal arteries from patients with giant cell arteritis. *Ophthalmology.* 2010;117(3):628-636.

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Edvinsson ML, Andersson SE, Xu CB, Edvinsson L. Cigarette smoking leads to reduced relaxant responses of the cutaneous microcirculation. *Vasc Health Risk Manag.* 2008;4(3):699-704.

Ghorbani B, Holmstrup P, Edvinsson L, Kristiansen KA, Sheykhzade M. LPS from Porphyromonas gingivalis increases the sensitivity of contractile response mediated by endothelin-B (ET(B)) receptors in cultured endothelium-intact rat coronary arteries. *Vascul Pharmacol.* 2010;53(5-6):250-257.

Lei Y, Cao Y, Zhang Y, Edvinsson L, Xu CB. Enhanced airway smooth muscle cell thromboxane receptor signaling via activation of JNK MAPK and extracellular calcium influx. *Eur J Pharmacol.* 2011;650(2-3):629-638.

Lei Y, Zhang Y, Cao Y, Edvinsson L, Xu CB. Up-regulation of bradykinin receptors in rat bronchi via I kappa B kinase-mediated inflammatory signaling pathway. *Eur J Pharmacol.* 2010;634(1-3):149-161.

Nilsson D, Wackenfors A, Gustafsson L, Ugander M, Ingemansson R, Edvinsson L, Malmsjo M. PKC and MAPK signalling pathways regulate vascular endothelin receptor expression. *Eur J Pharmacol.* 2008;580(1-2):190-200.

Sandhu H, Ansar S, Edvinsson L. Comparison of MEK/ERK pathway inhibitors on the upregulation of vascular G-protein coupled receptors in rat cerebral arteries. *Eur J Pharmacol.* 2010;644(1-3):128-137.

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Xie YH, Wang SW, Zhang Y, Edvinsson L, Xu CB. Up-regulation of G-protein-coupled receptors for endothelin and thromboxane by lipid-soluble smoke particles in renal artery of rat. *Basic Clin Pharmacol Toxicol.* 2010;107(4):803-812.

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Xu CB, Sun Y, Edvinsson L. Cardiovascular risk factors regulate the expression of vascular endothelin receptors. *Pharmacol Ther.* 2010;127(2):148-155.

Zhang Y, Edvinsson L, Xu CB. Up-regulation of endothelin receptors induced by cigarette smoke--involvement of MAPK in vascular and airway hyper-reactivity. *ScientificWorldJournal.* 2010;10:2157-2166.

Zheng JP, Zhang Y, Edvinsson L, Hjalt T, Xu CB. NF-kappaB signaling mediates vascular smooth muscle endothelin type B receptor expression in resistance arteries. *Eur J Pharmacol.* 2010;637(1-3):148-154.

THE DR. WILLIAM CAHAN DISTINGUISHED PROFESSORS

GETTING PHYSICIANS TO ASK THE RIGHT QUESTIONS

William Grossman, MD; University of California, San Francisco; 2008

Dr. Grossman's FAMRI project had the primary objective of improving clinical attention to tobacco use and SHS exposure in cardiology. Even though these are major contributors to cardiovascular disease, cardiology training programs often do not provide comprehensive training in addressing them in clinical practice. Dr. Grossman conducted studies on the development and evaluation of an evidence-based model curriculum for improving clinical attention in cardiology to tobacco use and exposure for evaluating primary and secondary exposures by collecting blood cotinine samples from patients seen in the cardiology unit at UCSF. A questionnaire for self-reporting was also utilized. Additionally, exposure levels in this insured patient population were compared to published cotinine levels on 114 cardiology patients from the public county hospital in San Francisco.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Heiss C, Amabile N, Lee AC, Real WM, Schick SF, Lao D, Wong ML, Jahn S, Angeli FS, Minasi P, Springer ML, Hammond SK, Glantz SA, Grossman W, Balmes JR, Yeghiazarians Y. Brief secondhand smoke exposure depresses endothelial progenitor cells activity and endothelial function: sustained vascular injury and blunted nitric oxide production. *J Am Coll Cardiol.* 2008;51(18):1760-1771.

Prochaska JJ, Benowitz NL, Glantz SA, Hudmon KS, Grossman W. Cardiology Rx for Change: improving clinical attention to tobacco use and secondhand smoke exposure in cardiology. *Clin Cardiol.* 2011;34(12):738-743.

Prochaska JJ, Grossman W, Young-Wolff KC, Benowitz NL. Validity of self-reported adult secondhand smoke exposure. *Tob Control.* 2015;24(1):48-53.

PRESENTATIONS AND ABSTRACTS

Prochaska JJ, Grossman W. Improving clinical attention to tobacco use and secondhand smoke in cardiology. Presented at the UCSF Annual "It 's About a Billion Lives" Symposium. San Francisco, CA, Feb 25, 2011.

ASSESSMENT OF FLIGHT ATTENDANTS' EXPOSURE TO SECOND HAND SMOKE FOR EPIDEMIOLOGIC STUDIES

S. Katherine Hammond, PhD; University of California at Berkeley; 2008

Dr. Hammond and her team assessed lifetime exposure to SHS, especially related to Flight Attendants. The frequent and long-term exposure to high concentrations of SHS in aircraft cabins places pre-smoking ban Flight Attendants at high risk for SHS related diseases. Most epidemiologic studies of SHS exposure rely on an assessment through a questionnaire during admission and one source (e.g., the smoking status of a spouse). This can be problematic for chronic diseases in which the relevant exposure occurs decades prior to the manifestation of disease. The case of the causal association of SHS with breast cancer is informative; studies with poor exposure assessment found little association, while studies

that evaluated lifetime exposure were more likely to find a nexus. To mitigate the current method to acquire data, Dr. Hammond and colleagues developed a tool that can be implemented on the internet, as well as with paper and pencil, which could quickly capture the most important aspects of SHS exposure throughout an individual's life. This tool is intended for use in epidemiologic studies of SHS exposure and disease; especially for studies of SHS and breast cancer.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Chiu YH, Hart JE, Smith TJ, Hammond SK, Garshick E, Laden F. Nicotine contamination in particulate matter sampling. *Int J Environ Res Public Health.* 2009;6(2):601-607.

Chiu YH, Hart JE, Spiegelman D, Garshick E, Smith TJ, Dockery DW, Hammond SK, Laden F. Workplace secondhand smoke exposure in the U.S. trucking industry. *Environ Health Perspect.* 2010;118(2):216-221.

Johnson KC, Miller AB, Collishaw NE, Palmer JR, Hammond SK, Salmon AG, Cantor KP, Miller MD, Boyd NF, Millar J, Turcotte F. Active smoking and secondhand smoke increase breast cancer risk: the report of the Canadian Expert Panel on Tobacco Smoke and Breast Cancer Risk (2009). *Tob Control.* 2011;20(1):e2.

Liu R, Bohac DL, Gundel LA, Hewett MJ, Apte MG, Hammond SK. Assessment of risk for asthma initiation and cancer and heart disease deaths among patrons and servers due to secondhand smoke exposure in restaurants and bars. *Tob Control.* 2014;23(4):332-338.

Liu R, Dix-Cooper L, Hammond SK. Modeling flight attendants' exposure to secondhand smoke in commercial aircraft: historical trends from 1955 to 1989. *J Occup Environ Hyg.* 2015;12(3):145-155.

Liu R, Hammond SK, Hyland A, Travers MJ, Yang Y, Nan Y, Feng G, Li Q, Jiang Y. Restaurant and bar owners' exposure to secondhand smoke and attitudes regarding smoking bans in five Chinese cities. *Int J Environ Res Public Health.* 2011;8(5):1520-1533.

Liu R, Jiang Y, Li Q, Hammond SK. An assessment of health risks and mortality from exposure to secondhand smoke in Chinese restaurants and bars. *PLoS One.* 2014;9(1):e84811.

Liu R, Jiang Y, Li Q, Hammond SK. Assessing exposure to secondhand smoke in restaurants and bars 2 years after the smoking regulations in Beijing, China. *Indoor Air.* 2014;24(4):339-349.

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Satran C, Drach-Zahavy A, Hammond SK, Baron-Epel O. Implementing the ban on smoking in Israeli pubs: measuring airborne nicotine and enforcement by local authorities. *Glob Health Promot.* 2014;21(2):7-14.

PRESENTATIONS AND ABSTRACTS

Collishaw NE, Boyd NF, Cantor KP, Hammond SK, Johnson KC, Millar J, Miller AB, Miller M, Palmer JR, Salmon AG, Turcotte F. Canadian Expert Panel on Tobacco Smoke and Breast Cancer Risk. Toronto, Canada: Ontario Tobacco Research Unit, OTRU Special Reports Series, April 2009.

Satran C, Drach-Zahavy A, Hammond SK, Baron-Epel O. Enforcement of the ban on smoking in public places. *Int J Behav Med* 2010;17(suppl):314.

Schick SF, Sleiman M, Hammond SK, Perrino C, van den Vossenberg G, Farraro K, Balmes J, Jenkins BM. Cigarette smoke deposition in an experimental chamber: Implications for thirdhand smoke build-up on room surfaces. Presented at the American Thoracic Society International Conference. Denver, CO, May 13-18, 2011.

Schick SF, Sleiman M, Hammond SK, Perrino C, van den Vossenberg G, Farraro K, Balmes J, Jenkins BM. Cigarette smoke deposition in an experimental chamber: Implications for thirdhand smoke build-up on room surfaces [abstract]. *Am J Respir Crit Care Med* 2011;183:A4028.

ADVERSE IMPACT OF SECOND HAND TOBACCO SMOKE EXPOSURE ON SOCIETY

K. Michael Cummings, PhD; Roswell Park Alliance Foundation, Medical University of South Carolina; 2005

Dr. Cummings received his Distinguished Professor Award at Roswell Park Cancer Institute; he is currently at the Medical University of South Carolina. There are two primary objectives to this project: 1) promoting adoption of smoke-free policies by documenting the levels of tobacco smoke pollution in common public indoor venues in different countries around the world; and 2) informing the public about the tactics and efforts used by the tobacco industry to misrepresent scientific information about the health risks of smoking and SHS exposure.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Alberg AJ, Shopland DR, Cummings KM. The 2014 Surgeon General's report: commemorating the 50th Anniversary of the 1964 Report of the Advisory Committee to the US Surgeon General and updating the evidence on the health consequences of cigarette smoking. *Am J Epidemiol.* 2014;179(4):403-412.

Bauer JE, Hyland A, Li Q, Steger C, Cummings KM. A longitudinal assessment of the impact of smoke-free worksite policies on tobacco use. *Am J Public Health.* 2005;95(6):1024-1029.

Borland R, Yong HH, Cummings KM, Hyland A, Anderson S, Fong GT. Determinants and consequences of smoke-free homes: findings from the International Tobacco Control (ITC) Four Country Survey. *Tob Control.* 2006;15 Suppl 3:iii42-50.

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Connolly GN, Carpenter CM, Travers MJ, Cummings KM, Hyland A, Mulcahy M, Clancy L. How smoke-free laws improve air quality: a global study of Irish pubs. *Nicotine Tob Res.* 2009;11(6):600-605.

Cummings KM, Brown A, Douglas CE. Consumer acceptable risk: how cigarette companies have responded to accusations that their products are defective. *Tob Control*. 2006;15 Suppl 4:iv84-89.

Cummings KM, Fong GT, Borland R. Environmental influences on tobacco use: evidence from societal and community influences on tobacco use and dependence. *Annu Rev Clin Psychol.* 2009;5:433-458.

Cummings KM, Proctor RN. The changing public image of smoking in the United States: 1964-2014. *Cancer Epidemiol Biomarkers Prev.* 2014;23(1):32-36.

Hyland A, Higbee C, Borland R, Travers M, Hastings G, Fong GT, Cummings KM. Attitudes and beliefs about secondhand smoke and smoke-free policies in four countries: findings from the International Tobacco Control Four Country Survey. *Nicotine Tob Res.* 2009;11(6):642-649.

Jatoi I, Cummings KM, Cazap E. Global tobacco problem getting worse, not better. *J Oncol Pract.* 2009;5(1):21-23.

Kahler CW, Borland R, Hyland A, McKee SA, Thompson ME, Cummings KM. Alcohol consumption and quitting smoking in the International Tobacco Control (ITC) Four Country Survey. *Drug Alcohol Depend.* 2009;100(3):214-220.

King BA, Hyland AJ, Borland R, McNeill A, Cummings KM. Socioeconomic variation in the prevalence, introduction, retention, and removal of smoke-free policies among smokers: findings from the International Tobacco Control (ITC) Four Country Survey. *Int J Environ Res Public Health.* 2011;8(2):411-434.

King BA, Travers MJ, Cummings KM, Mahoney MC, Hyland AJ. Prevalence and predictors of smoke-free policy implementation and support among owners and managers of multiunit housing. *Nicotine Tob Res.* 2010;12(2):159-163.

Koong HN, Khoo D, Higbee C, Travers M, Hyland A, Cummings KM, Dresler C. Global air monitoring study: a multi-country comparison of levels of indoor air pollution in different workplaces. *Ann Acad Med Singapore.* 2009;38(3):202-206.

McKee SA, Higbee C, O'Malley S, Hassan L, Borland R, Cummings KM, Hastings G, Fong GT, Hyland A. Longitudinal evaluation of smoke-free Scotland on pub and home drinking behavior: findings from the International Tobacco Control Policy Evaluation Project. *Nicotine Tob Res.* 2009;11(6):619-626.

Paoletti L, Jardin B, Carpenter MJ, Cummings KM, Silvestri GA. Current status of tobacco policy and control. *J Thorac Imaging.* 2012;27(4):213-219.

Song LG, Davis W, Abrams SM, Hemiup J, Kazim AL, Cummings KM, Mahoney MC. Sensitive and rapid method for the determination of urinary cotinine in non-smokers; an application

for studies assessing exposures to second hand smoke (SHS). *Anal Chim Acta.* 2005;545:200-208.

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Van Deusen A, Hyland A, Travers MJ, Wang C, Higbee C, King BA, Alford T, Cummings KM. Secondhand smoke and particulate matter exposure in the home. *Nicotine Tob Res.* 2009;11(6):635-641.

PRESENTATIONS AND ABSTRACTS

Cummings KM, Goldstein R, Brown A. Those who seek the truth: Tobacco litigation in the United States. Presented at the 16th World Conference on Tobacco or Health. Abu Dhabi, United Arab Emirates, Mar 17-21, 2015.

Cummings, KM. 50-year Surgeon General Report. Presented at IASLC 16th World Lung Cancer Conference. Denver, CO, Sep 2015.

Cummings, KM. 50-year Surgeon General Report. Presented at NCTOH Annual Meeting. Bethesda, MD, Oct 2015.

Cummings, KM. 50-year Surgeon General Report. Presented at the 21st Annual Family Medicine Update: Tobacco & Disease Pre-Conf. Little Rock, AR, Oct 2017.

Cummings, KM. 50-year Surgeon General Report. Presented at the AAHB Annual Meeting. Charleston, SC, Mar 2014.

Cummings, KM. 50-year Surgeon General Report. Presented at the AACR Frontiers in Cancer Prevent Research. National Harbor, MD, Oct 2013.

Cummings, KM. 50-year Surgeon General Report. Presented at the APHA Annual Meeting. New Orleans, LA, Nov 2014.

Cummings, KM. 50-year Surgeon General Report. Presented at the ASCO Annual Meeting. Chicago, IL, May 2014.

Cummings, KM. 50-year Surgeon General Report. Presented at the Dartmouth-Hitchcock Medical Center. Lebanon, NH, May 2016.

Cummings, KM. 50-year Surgeon General Report. Presented at the National Press Club. Washington, DC, Jan 2014.

Cummings, KM. 50-year Surgeon General Report. Presented at the Scientific Retreat on Tobacco Related Research. Charleston, SC, Oct 2014.

Cummings, KM. 50-year Surgeon General Report. Presented at the South Carolina Tobacco Free Collaborative/Cancer Alliance. Columbia, SC, Oct 2013.

Cummings, KM. 50-year Surgeon General Report. Presented at the SRNT Annual Meeting. Seattle, WA, Feb 2014.

Cummings, KM. 50-year Surgeon General Report. Presented at the Vernberg Distinguished Lecture Series, University of South Carolina. Columbia, SC, Apr 2014.

Cummings, KM. 50-year Surgeon General Report. Presented at Tobacco Merchants Association 99th Annual Meeting. Williamsburg, VA, May 2014.

Cummings, KM. A Century of Cigarettes. Presented at Johnson & Johnson. Fort Washington, PA, Nov 2013.

Cummings, KM. A Century of Cigarettes. Presented at the AACR Annual Meeting. San Diego, CA, Apr 2014.

Cummings, KM. A Century of Cigarettes. Presented at the AACR Annual Meeting. Chicago, IL, Mar 2012.

Cummings, KM. A Century of Cigarettes. Presented at the AACR Frontiers in Cancer Prevention Research. National Harbor, MD, Oct 2013.

Cummings, KM. A Century of Cigarettes. Presented at the APHA Annual Meeting. New Orleans, LA, Nov 2014.

Cummings, KM. A Century of Cigarettes. Presented at the ASCO Annual Meeting. Chicago, IL, Jun 2012.

Cummings, KM. A Century of Cigarettes. Presented at the ASPO Annual Meeting. Washington, DC, Mar 2012.

Cummings, KM. A Century of Cigarettes. Presented at the CADCA National Leadership Forum. National Harbor, MD, Feb 2013.

Cummings, KM. A Century of Cigarettes. Presented at the CTOH Annual Meeting. Kansas City, MO, Aug 2012.

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Cummings, KM. Framework Convention on Tobacco Control (FCTC). Presented at the Johns Hopkins Institute for Global Tobacco Control Innovations. Baltimore, MD, Nov 2014.

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Cummings, KM. The Evolving Cigarette. Presented at the AAHB Annual Meeting. Greenville, SC, Mar 2019.

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Cummings, KM. The Evolving Cigarette. Presented at the MultiCare Health System Great American Smokeout Event. Tacoma, WA, Nov 2017.

Cummings, KM. The Evolving Cigarette. Presented at the NCTOH Annual Meeting. Austin, TX, Mar 2017.

Cummings, KM. The Evolving Cigarette. Presented at the Roswell Park Cancer Inst. Tobacco Treatment Specialist Training Program. Sep 2018.

Cummings, KM. The Evolving Cigarette. Presented at the Say What! Texas Tobacco-Free Conference. San Marcos, TX, Jul 2017.

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Cummings, KM. The Evolving Cigarette. Presented at the The E-Cigarette Summit – Science, Regulation and Public Health. Washington, DC, May 2017.

Cummings, KM. The Evolving Cigarette. Presented at the University of Arkansas at Pine Bluff. Pine Bluff, AK, May 2017.

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BOOK CHAPTERS, ETC.

Connolly GN, Carpenter CM, Travers MJ, Cummings KM, Hyland A, Mulcahy M, Clancy L. How smoke-free laws improve air quality. Released as a live webcast, Mar 16, 2006.

Cummings KM, Borland R, Braak D. Public Health and Nicotine. In: Brady K, Levin FR, Galanter M, Kleber HD, eds.The American Psychiatric Association Publishing Textbook of Substance Use Disorder Treatment, Washington DC: American Psychiatric Association Publishing, 2021.

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Ostrow P, Cummings KM. Stop targeting kids. DVD. Buffalo, NY: Roswell Park Cancer Institute, 2009.

CURTAILING SECOND HAND TOBACCO SMOKE EXPOSURE WORLDWIDE

Richard A. Daynard, JD, PhD; Northeastern University Law School; 2005

Dr. Daynard has made contributions to the field of tobacco research leading to the curtailing of SHS exposure worldwide. Dr. Daynard's research was based on critically important and time-sensitive issues stemming from the World Health Organization (WHO)-

sponsored Framework Convention on Tobacco Control (FCTC) Treaty, which became effective February 27, 2005, and was ratified by over 140 nations. Dr. Daynard focused on research for non-governmental organizations (NGOs) in relevant countries to reduce exposure to SHS to the greatest extent possible, resulting in long-term reduction in diseases caused by such exposure.

LEGAL ACTION AND EDUCATION AGAINST TOBACCO SMOKE POLLUTION

John F. Banzhaf, III, JD; George Washington University; 2004

Professor Banzhaf was instrumental in getting Flight Attendant representatives before Congress to reveal the unhealthy work conditions of airline cabins because of their exposure to SHS. He initiated methods that required OSHA to propose a rule banning smoking in virtually all work places. Professor Banzhaf developed new approaches for educating and protecting non-smokers from exposure to SHS and its health dangers. These approaches included organization of three world conferences on nonsmokers' rights and annual contests among law students to research, develop, and report to others new legal and law-related proposals to protect and advance nonsmokers' rights.

FAMRI SUPPORTED RESEARCH

BOOK CHAPTERS, ETC.

Organization of the following three conferences:

Second world conference on non-smokers rights. Washington, DC, Apr 8-10, 2005.

Third world conference on non-smokers rights. Washington, DC, Apr 1-3, 2006.

Fourth world conference on non-smokers rights. Washington, DC, Apr 7-8, 2007.

IMPACT OF STATE, NATIONAL AND INTERNATIONAL CLEAN IN-DOOR AIR LAWS ON THE ECONOMY AND HEALTH OF HOSPITALITY WORKERS

Gregory N. Connolly, DMD, MPH; Harvard School of Public Health; 2004

Dr. Connolly examined the effect on air quality of the 2004 Massachusetts initiative banning smoking in all workplaces, and the economic effect on the state's bar and restaurant business, tourism, and lottery sales. This research has been replicated in other states. In 2006 his study examined and compared indoor air quality in a global sample of smoke-free and smoking-permitted Irish pubs. The results of the study indicated that the level of air pollution inside Irish pubs located in smoke-free cities was 93% lower than the level found in pubs in cities that permit smoking, which demonstrates that statistics aid in creating smoke-free environments worldwide.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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Rees VW, Connolly GN. Measuring air quality to protect children from secondhand smoke in cars. *Am J Prev Med.* 2006;31(5):363-368.

PRESENTATIONS AND ABSTRACTS

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Hyland A, Travers MJ, Higbee C, Cummings KM, Dresler C, Carpenter C, Connolly G. A 24-country comparison of levels of indoor air pollution in different workplaces. Presented at the 2006 World Conference on Tobacco or Health. Washington, DC, Jul 12-15, 2006.

BOOK CHAPTERS, ETC.

Connolly GN, Carpenter CM, Travers MJ, Cummings KM, Hyland A, Mulcahy M, Clan-cy L. How smoke-free laws improve air quality. Released as a live Webcast, Mar 16, 2006.

GENETIC SUSCEPTIBILITY TO LUNG CANCER

Margaret R. Spitz, MD, MPH; University of Texas M.D. Anderson Cancer Center; 2004

Dr. Spitz' s overall research goal was to further the understanding of the molecular mechanisms underlying individual differences in susceptibility to cancer caused by exposure to tobacco smoke and to extend the findings from the individual projects in FAMRI's Center of Excellence at the Weizmann Institute. Dr. Spitz developed and tested a panel of *in vitro* functional assays for determining susceptibility to lung cancer, including the comet assay, telomere length measurements, cell cycle control, and DNA repair capacity assays. Her collaboration with the Weizmann FAMRI Center combined a basic foundation in science with the rigor of high throughput assay development and validation to augment the molecular epidemiology undertakings. Rapid screening of individuals for risk using minimally invasive procedures can be used to identify high-risk subgroups.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

D'Amelio AM, Jr., Cassidy A, Asomaning K, Raji OY, Duffy SW, Field JK, Spitz MR, Christiani D, Etzel CJ. Comparison of discriminatory power and accuracy of three lung cancer risk models. *Br J Cancer*. 2010;103(3):423-429.

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Engels EA, Wu X, Gu J, Dong Q, Liu J, Spitz MR. Systematic evaluation of genetic variants in the inflammation pathway and risk of lung cancer. *Cancer Res*. 2007;67(13):6520-6527.

Etzel CJ, Lu M, Merriman K, Liu M, Vaporciyan A, Spitz MR. An epidemiologic study of early onset lung cancer. *Lung Cancer*. 2006;52(2):129-134.

Gorlov IP, Meyer P, Liloglou T, Myles J, Boettger MB, Cassidy A, Girard L, Minna JD, Fischer R, Duffy S, Spitz MR, Haeussinger K, Kammerer S, Cantor C, Dierkesmann R, Field JK, Amos CI. Seizure 6-like (SEZ6L) gene and risk for lung cancer. *Cancer Res*. 2007;67(17):8406-8411.

Gorlova OY, Zhang Y, Schabath MB, Lei L, Zhang Q, Amos CI, Spitz MR. Never smokers and lung cancer risk: a case-control study of epidemiological factors. *Int J Cancer*. 2006;118(7):1798-1804.

Gu J, Gong Y, Huang M, Lu C, Spitz MR, Wu X. Polymorphisms of STK15 (Aurora-A) gene and lung cancer risk in Caucasians. *Carcinogenesis*. 2007;28(2):350-355.

Kachroo S, Tong L, Spitz MR, Xing Y, Merriman K, Zhu DK, Fueger J, Amos CI, Etzel CJ. Trends in prevalence of prognostic factors and survival in lung cancer patients from 1985 to 2004 at a tertiary care center. *Cancer Detect Prev*. 2008;32(2):101-108.

Li G, Zhai X, Zhang Z, Chamberlain RM, Spitz MR, Wei Q. MDM2 gene promoter polymorphisms and risk of lung cancer: a case-control analysis. *Carcinogenesis*. 2006;27(10):2028-2033.

Lin X, Gu J, Lu C, Spitz MR, Wu X. Expression of telomere-associated genes as prognostic markers for overall survival in patients with non-small cell lung cancer. *Clin Cancer Res*. 2006;12(19):5720-5725.

Mahabir S, Forman MR, Barerra SL, Dong YQ, Spitz MR, Wei Q. Joint effects of dietary trace metals and DNA repair capacity in lung cancer risk. *Cancer Epidemiol Biomarkers Prev*. 2007;16(12):2756-2762.

Mahabir S, Schendel K, Dong YQ, Barrera SL, Spitz MR, Forman MR. Dietary alpha-, beta-, gamma- and delta-tocopherols in lung cancer risk. *Int J Cancer*. 2008;123(5):1173-1180.

Mahabir S, Spitz MR, Barrera SL, Beaver SH, Etzel C, Forman MR. Dietary zinc, copper and selenium, and risk of lung cancer. *Int J Cancer*. 2007;120(5):1108-1115.

Mahabir S, Spitz MR, Barrera SL, Dong YQ, Eastham C, Forman MR. Dietary boron and hormone replacement therapy as risk factors for lung cancer in women. *Am J Epidemiol*. 2008;167(9):1070-1080.

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Spitz MR, Amos CI, Dong Q, Lin J, Wu X. The CHRNA5-A3 region on chromosome 15q24-25.1 is a risk factor both for nicotine dependence and for lung cancer. *J Natl Cancer Inst*. 2008;100(21):1552-1556.

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Gu J, Spitz MR, Roth JA, Wu X. Aberrant promoter methylation profile associated with survival in patients with non-small cell lung cancer [abstract]. The American Association for Cancer Research, 97th Annual Meeting. Washington, DC, Apr 1-5, 2006.

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Wang L, Shi Q, Guo Z, Qiao Y, Spitz MR, Wei Q. A novel assay to measure the capacity to repair N7-guanine site-specific DNA damage [abstract]. The American Association for Cancer Research, 97th Annual Meeting. Washington, DC, Apr 1-5, 2006.

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Yang H, Spitz MR, Liu J, Gu J, Lu C, Stewart DJ, Wu X. ATM haplotype-tagging SNPs predict non-small cell lung cancer risk in Caucasians [abstract]. The American Association for Cancer Research, 97th Annual Meeting. Washington, DC, Apr 1-5, 2006.

HISTORY AND POLICY STUDIES IN TOBACCO CONTROL

Allan M. Brandt, PhD; Harvard College; 2003

Dr. Brandt's FAMRI research resulted in his history of the 20th Century pandemic of public health entitled The Cigarette Century. The book brings to fruition a decade of research on the social and cultural history of cigarette smoking and associated diseases in the twentieth century. His study traces the dramatic rise of cigarette consumption, new scientific approaches that expose the serious harm caused by smoking, and the half-century of denials by the tobacco companies of the harmfulness of their product. Included are the approaches to regulating tobacco use and the history of litigation against the tobacco companies. The study traces the transformation in the success of the litigation that accounts for the shifts in legal and public perception of the harms of smoking and the corporate responsibility for the diseases generated by cigarette smoke.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Brandt AM. Inventing conflicts of interest: a history of tobacco industry tactics. *Am J Public Health*. 2012;102(1):63-71.

Gardner MN, Brandt AM. "The doctors' choice is America's choice": the physician in US cigarette advertisements, 1930-1953. *Am J Public Health*. 2006;96(2):222-232.

BOOK CHAPTERS, ETC.

Brandt A. Difference and Diffusion: Cross-Cultural Perspectives on the Rise of Anti-Tobacco Policies. In: Feldman E, Bayer R, eds. Unfiltered: Conflicts over Tobacco Policy and Health. Cambridge: Harvard University Press, 2004.

Brandt A. From Analysis to Advocacy: Crossing Boundaries as a Historian of Health Policy. In: Huisman F, Warner JH, eds. Locating Medical History: the Stories and Their Meanings. Baltimore: Johns Hopkins University Press, 2004.

Brandt A. From Nicotine to Nicontrol: Addiction, Cigarettes and American Culture. In: Tracy SW, Acker CJ, eds. Altering American Consciousness: Essays on the History of Alcohol and Drug Use in the United States. Amherst: University of Massachusetts Press, 2004.

Brandt A. The Culture of Consumer Confidence: Engineering Smoking in the Twentieth Century Smoke: A Global History of Smoking. London: Reaktion Books, 2005.

HEALTH ASSESSMENT OF FLIGHT ATTENDANTS PREVIOUSLY EXPOSED TO SECOND HAND TOBACCO SMOKE

Richard D. Hurt, MD; Mayo Clinic; 2003

Dr. Hurt has been active in initiatives throughout Minnesota for smoke-free environments. Dr. Hurt's work involved health assessment of Flight Attendants (FAs) previously exposed to SHS, and he has assessed candidate genes to determine factors for predisposition towards development of tobacco-caused diseases. FAs who were exposed to SHS and confined to the cabin space of airlines continue to suffer a range of SHS-related adverse health effects. Exposed FAs that stopped working due to health problems reported a higher incidence of sinusitis, pneumonia, middle ear infections, hay fever, and allergies when

compared to FAs who did not stop work due to health problems. SHS exposure in airline cabins clearly contributed to these health problems.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Ebbert JO, Croghan IT, Schroeder DR, Murawski J, Hurt RD. Association between respiratory tract diseases and secondhand smoke exposure among never smoking Flight Attendants: a cross-sectional survey. *Environ Health.* 2007;6:28.

PROMOTE KNOWLEDGE ABOUT NEW TECHNOLOGIES AND APPROACHES TO THE EARLY DIAGNOSIS OF LUNG CANCER AND RELATED DISORDERS

Thomas L. Petty, MD (1932-2009); National Lung Health Education Program; 2003

Dr. Petty promoted knowledge about new technologies and approaches to the early diagnosis and treatment of patients with lung cancer and chronic obstructive pulmonary disease (COPD). He believed that unsuspected lung cancer patients could be detected in a primary care outpatient practice by use of spirometry, which is an effective means of identification and assessment of progress. Dr. Petty was Editor-in-Chief of Lung Cancer Frontiers, a newsletter dedicated to advancing knowledge about lung cancer; it can be seen on line at www.lungcancerfrontiers.org .

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Bechtel JJ, Kelley WA, Coons TA, Klein MG, Slagel DD, Petty TL. Lung cancer detection in patients with airflow obstruction identified in a primary care outpatient practice. *Chest.* 2005;127(4):1140-1145.

REDUCING THE RISKS OF SECOND HAND TOBACCO SMOKE: A GLOBAL APPROACH

Jonathan Samet, MD; University of Southern California; 2003

Dr. Samet is currently at the University of Southern California; he received his award while at Johns Hopkins School of Public Health. Dr. Samet's research was used to assess exposures of women and children to SHS globally. A common protocol was used to generate a global profile of SHS exposure among women and children to estimate the associated risks. The study characterized exposure to SHS using questionnaires, passive nicotine monitors, and analysis of hair samples for the presence and level of nicotine.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Blanco-Marquizo A, Goja B, Peruga A, Jones MR, Yuan J, Samet JM, Breysse PN, Navas-Acien A. Reduction of secondhand tobacco smoke in public places following national smoke-free legislation in Uruguay. *Tob Control.* 2010;19(3):231-234.

Jones MR, Wipfli H, Shahrir S, Avila-Tang E, Samet JM, Breysse PN, Navas-Acien A, Investigators FBS. Secondhand tobacco smoke: an occupational hazard for smoking and non-smoking bar and nightclub employees. *Tob Control.* 2013;22(5):308-314.

Kim S, Wipfli H, Navas-Acien A, Dominici F, Avila-Tang E, Onicescu G, Breysse P, Samet JM, Investigators FHS. Determinants of hair nicotine concentrations in nonsmoking women and children: a multicountry study of secondhand smoke exposure in homes. *Cancer Epidemiol Biomarkers Prev.* 2009;18(12):3407-3414.

Kim SR, Wipfli H, Avila-Tang E, Samet JM, Breysse PN. Method validation for measurement of hair nicotine level in nonsmokers. *Biomed Chromatogr.* 2009;23(3):273-279.

Rudin CM, Avila-Tang E, Harris CC, Herman JG, Hirsch FR, Pao W, Schwartz AG, Vahakangas KH, Samet JM. Lung cancer in never smokers: molecular profiles and therapeutic implications. *Clin Cancer Res.* 2009;15(18):5646-5661.

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A BOOK DOCUMENTING FLIGHT ATTENDANT EXPOSURE TO SECOND HAND TOBACCO SMOKE IN AIRLINE CABINS

Alan Blum, MD; University of Alabama at Birmingham; 2002

Dr. Blum has carefully documented the fight for clean indoor air, with a specific focus on Flight Attendants in the origins of non-smokers' rights issues. Dr. Blum has used his

extensive historical records to create smoking-related exhibitions for a number of museums.

FAMRI SUPPORTED RESEARCH

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SECOND HAND TOBACCO SMOKE IN THE WORK PLACE

David M. Burns, MD; University of California, San Diego; 2002

Dr. Burns has written extensively on the study of SHS exposure in the work place and has contributed to a number of US Surgeon General's Reports. Dr. Burns was senior editor for the landmark 1979 Surgeon General's Report written by Julius B. Richmond, MD, (1916 – 2008), which was the first report to describe the health dangers of SHS exposure. Dr. Burns has studied how this exposure varies by location and correlated it with individual state initiatives and job categories. Dr. Burns has used a vast amount of available data to establish disease risk models for estimating lung cancer and all cause mortality from smoking behaviors.

FAMRI SUPPORTED RESEARCH

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INVESTIGATE SMOKING POLICIES AMONG A NATIONAL SAMPLE OF AIRPORTS IN THE UNITED STATES, LINKING PASSIVE SMOKING AND DISEASE AND FACTORS THAT AFFECT THE ADOPTION (OR NON-ADOPTION) OF CLEAN INDOOR AIR POLICIES

Ronald M. Davis, MD (1956 – 2008); Henry Ford Health System; 2002

Before his untimely death, Dr. Davis and his co-investigators had completed a national survey of airport smoking restrictions, which was published in Morbidity and Mortality Weekly Report, a publication of the US Centers for Disease Control and Prevention. He conducted a case-control study to confirm the causal nexus between SHS exposure and chronic sinusitis, chronic non-allergic rhinitis, and chronic allergic rhinitis. Dr. Davis and his colleagues worked with groups that support local and statewide initiatives to reduce exposure to SHS. They also worked with leaders at Henry Ford Health System to establish smoke-free campuses for the system's hospitals and ambulatory medical centers.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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SCIENTIFIC IMPACT OF SECOND HAND TOBACCO SMOKE

Stanton A. Glantz, PhD; University of California, San Francisco; 2002

Dr. Glantz's work related to SHS includes 1) biological effects on the heart, blood, and the vascular system; and 2) activities the tobacco industry used to counter the effects of smoking on growing public awareness of dangers caused by SHS. Dr. Glantz's research revealed that the effect of active smoking is a 100% to 200% increase in risk of harm and being married to a smoker or working in a smoke-filled environment is associated with about a 30% increased risk of a heart attack compared to those who are non-exposed. A comparison of the biological effects of smoke on factors that affect cardiovascular function have consistently revealed that the effects of SHS exposure are approximately 80% that of active smoking, with effects appearing at low doses. Dr. Glantz also used tobacco industry documents released as a result of litigation to understand the industry's secret efforts to undermine the science that establishes the link between SHS exposure with disease.

FAMRI SUPPORTED RESEARCH

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BIOMARKERS OF TOBACCO-SPECIFIC CARCINOGEN UPTAKE

Steven S. Hecht, PhD; University of Minnesota; 2002

Dr. Hecht focused on improved methods for quantifying 4-(methylnitrosamino)-1- (3-pyridyl)- 1-butanol (NNAL) and its glucuronides in human urine; markers that are used to investigate human uptake of carcinogens from SHS. NNAL and its glucuronides are metabolites of the tobacco-specific lung carcinogen 4-(methylnitrosamino)-1-(3- pyridyl)-1-butanone (NNK). Total NNAL is an effective biomarker for SHS exposure. Dr. Hecht developed a highly sensitive and rapid method for the analysis of total NNAL in urine, which can be used in large clinical and epidemiologic studies. The method was used in a study on non-smoking hospitality workers who were exposed to SHS in the workplace. The study indicated that working day exposure was greater than non-working days and may have important health effects on non-smoking employees. Dr. Hecht has also examined the impact of clean indoor air laws in Washington and Oregon and demonstrated that non-smoking workers exposed to workplace SHS have elevated levels of NNK, nicotine, and cotinine in their bodies, associated with hours of workplace exposure. This is further evidence that all workers should be protected from workplace exposure to SHS.

FAMRI SUPPORTED RESEARCH

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SCIENTIFIC STUDY REGARDING SECOND HAND TOBACCO SMOKE IN THE HOSPITALITY INDUSTRY

James Repace, MSc; Tufts University; 2002

James Repace explored a diverse set of projects ranging from exposure of Flight Attendants in the smoky skies, of workers and patrons in smoky restaurants, bars, and hotels, to levels of smoke in outdoor cafes, on cruise ships at sea, and on college campuses. In addition, he investigated the precision and accuracy of multiple types of monitors for SHS measurements. He has shown that it would take tornado-like levels of ventilation or air cleaning to control tobacco smoke pollution in hospitality venues to be within acceptable levels of lung cancer and heart disease mortality risk, as defined by federal guidelines for minimum risk from hazardous air pollution. He developed a set of physical and pharmacokinetic equations for SHS exposure that make it possible to inter-correlate atmospheric markers such as respirable particles, nicotine, and carbon monoxide, with each other and with biomarkers such as hair nicotine, and cotinine from serum, saliva, or urine. In collaboration with others he has used this methodology to estimate levels of fine particle air pollution in bars and compared them to the federal air quality index for outdoor air pollution alerts. This exposure analysis methodology is available to students of public, occupational, and environmental health via a key chapter in the CRC Press textbook on exposure analysis.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

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Repace J. Flying the smoky skies: secondhand smoke exposure of flight attendants. *Tob Control.* 2004;13 Suppl 1:i8-19.

Repace J, Al-Delaimy WK, Bernert JT. Correlating atmospheric and biological markers in studies of secondhand tobacco smoke exposure and dose in children and adults. *J Occup Environ Med.* 2006;48(2):181-194.

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Repace JL. Human exposure to secondhand smoke. In: Ott W, Steinemann A, eds. Human Exposure Analysis, Part II. Inhalation – Occurrence, Sources, and Quantitative Levels of Exposure. Boca Raton, FL: CRC Press, 2006.

SCIENTIFIC STUDY OF TOBACCO USE AMONG YOUNG ADULTS

Nancy Rigotti, MD; Massachusetts General Hospital; 2002

Dr. Rigotti conducted a study to advance knowledge about the extent and impact of strategies to reduce SHS exposure and discourage tobacco use among young adults in US colleges. She used retrospective data to show that college student tobacco use has declined since its peak in 1997-1999. These analyses show strong student support for the full spectrum of tobacco control programs on college campuses, including the institution of smoke-free housing that have been recommended by the American College Health Association. Dr. Rigotti created a tobacco control research training program at Massachusetts General Hospital's Tobacco Research and Treatment Center, and she developed interventions for pediatricians to use while addressing parents about their children's exposure to SHS. She conducted longitudinal analyses that measure the impact of

household smoking education on adolescent exposure to SHS and rate of smoking initiation.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Albers AB, Siegel M, Cheng DM, Biener L, Rigotti NA. Relation between local restaurant smoking regulations and attitudes towards the prevalence and social acceptability of smoking: a study of youths and adults who eat out predominantly at restaurants in their town. *Tob Control*. 2004;13(4):347-355.

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Skeer M, Cheng DM, Rigotti NA, Siegel M. Secondhand smoke exposure in the workplace. *Am J Prev Med.* 2005;28(4):331-337.

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Thomson CC, Rigotti NA. Hospital- and clinic-based smoking cessation interventions for smokers with cardiovascular disease. *Prog Cardiovasc Dis*. 2003;45(6):459-479.

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Winickoff JP, Tanski SE, McMillen RC, Klein JD, Rigotti NA, Weitzman M. Child health care clinicians' use of medications to help parents quit smoking: a national parent survey. *Pediatrics*. 2005;115(4):1013-1017.

STUDY OF EFFECTS OF SECOND HAND TOBACCO SMOKE ON WORKERS AND THE PUBLIC

Michael B. Siegel, MD, MPH; Boston University School of Public Health; 2002

Dr. Siegel has used the health effects of SHS exposure to assess the impact of local clean indoor air initiatives in Massachusetts. He focused on three major outcomes: 1) exposure to SHS among adults and youths in bars and restaurants; 2) smoking-related attitudes and social norms among youths and adults; and 3) changes in smoking behaviors among adults and youths. He used a baseline telephone survey on a large sample with a two-year follow-up. In addition, the local restaurant and bar smoking regulations in 351 towns in Massachusetts were analyzed and classified. These two databases were merged that show that smoke-free restaurant regulations can be effective in reducing exposure of the public to SHS, although weak regulations are not adequate to protect the public. Dr. Siegel's research demonstrates that workplace smoking initiatives and local smoke-free bar and restaurant standards have a substantial impact on reducing SHS exposure. These strategies appear to change social norms regarding smoking, particularly the perceived prevalence of smoking in the community and the perceived level of social acceptability of smoking. As a result, workers are protected from SHS exposure, and the effect on preventing initiation of youth smoking is significant.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Albers AB, Siegel M, Cheng DM, Biener L, Rigotti NA. Relation between local restaurant smoking regulations and attitudes towards the prevalence and social acceptability of smoking: a study of youths and adults who eat out predominantly at restaurants in their town. *Tob Control.* 2004;13(4):347-355.

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ACKNOWLEDGEMENT

The FAMRI Trustees acknowledge and thank Maggie Chamberlin, PhD, Editor; consultant with American Institute of Biological Sciences, for producing the 2022 edition of this monograph describing FAMRI-funded research, with the invaluable help of Marti Gammon of FAMRI.