2016 MONOGRAPH OF FLIGHT ATTENDANT MEDICAL RESEARCH INSTITUTE FUNDED RESEARCH
FOREWORD

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

This publication contains updated synopses of projects funded by FAMRI from 2002 to the present.

The rich history of FAMRI, which made this research possible, 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) in their work place—aircraft cabins. As they became aware of their health hazards caused by exposure to tobacco smoke, they began to seek remedies. They realized that they had formidable adversaries in the tobacco industry that had never lost a lawsuit brought by people who sought redress for the health consequences of smoking at that time.

Up until 1964 the tobacco industry tried to deny the harmful health effects of smoking, but the data presented to Surgeon-General Luther Terry by his Advisory Committee on Smoking and Health undermined their effectiveness. Still there was scant scientific evidence for health effects of exposure to tobacco smoke. A hardy band of Flight Attendants, also known as the “canaries in the coal mines”, called attention to the growing scientific evidence for the harmful effects of exposure to SHS which were clearly established in the 1986 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 banned smoking on domestic flights. Despite these successes, legal action was more difficult because the resources of the tobacco industry discouraged attorneys from taking action. Fortunately, the Flight Attendants persevered and they found their way to attorneys Susan and Stanley Rosenblatt in 1991, who were willing to take the risk of bringing the industry to trial. After years of preparation, the case came to trial in 1997.

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, Stanley and Susan Rosenblatt, 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 who were involved in the underlying litigation.

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, Hospital of
University of Pennsylvania; Mark W. Geraci, MD, Indiana University School of Medicine; and Rama Mallampalli, MD, University of Pittsburgh.

Under the leadership of our first Chairman, Julius B. Richmond, MD, (1921-2008), US Surgeon General during the Carter administration and former Professor Emeritus at Harvard Medical School, the MAB took on an important role in helping to shape FAMRI’s structure and 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, innovative approaches, and several Centers of Excellence. Indeed, lives have been saved.

Through the work of the scientists and physicians it funds, FAMRI is making important contributions to improving public health in general and that of non-smoking Flight Attendants who have developed or are at risk of developing the diseases of smokers. FAMRI has also started many new careers in the study of involuntary smoke exposure, and these investigators will continue to explore and contribute to the scientific and medical literature in this field for decades to come. The research has increased understanding on many levels, including the therapeutic potential of stem cells, new targeted biologic approaches to healing the upper and lower airways, and how genetic predisposition and defects in DNA repair affect smoke-induced diseases. Such research provides avenues for treating and possibly curing these maladies.

Based on data gleaned from results of peer-reviewed publications in prestigious medical journals, the overall impact of FAMRI published research continues to rank among the top academic institutions in both the US and Europe.

In conclusion, we remain very much indebted to the Flight Attendants for their courage in bringing their suit and to their attorneys for their remarkable legal skills and commitment 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.
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**To Develop a Digital Library Containing Key Tobacco Events, Studies, Documents, and Promotions for Tobacco Research**

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- **Follow-up Survey of the 2007 Flight Attendant Health Study**

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INTRODUCTION

Elizabeth A. Kress, Executive Director of FAMRI

FAMRI is a not-for-profit, private foundation formed with Court approval under the laws of the State of Florida.

It all started with a daring act of courage by Patty Young and a handful of Flight Attendants who fought the system to stop smoking on airplanes, their work place. The act continued when Patty Young sought justice for many years for the damages she suffered from the exposure to tobacco smoke, but no lawyer would accept her case. Then Patty suggested that another injured Flight Attendant contact Susan and Stanley Rosenblatt, attorneys in Miami, Florida, who ultimately dared to ignore the tobacco industry’s success in winning cases brought by smokers for their damages. “No one wins against Big Tobacco”, they were told. In 1991 the Rosenblatts devised a new way to seek justice by bringing a class-action lawsuit in Miami-Dade, Florida, on behalf of never-smoking Flight Attendants against the tobacco industry. Tobacco threw one stumbling block after another to keep the case from getting to Court, but the Rosenblatts prevailed and presented the case before a jury in 1997. Four months later after lengthy negotiations, tobacco agreed to a settlement. With other valuable concessions for Flight Attendants (and the final death knell for smoking on flights), tobacco agreed to endow three hundred million dollars to form a nonprofit research foundation whose purpose is to sponsor scientific and medical research with respect to the early detection and cure of diseases associated with cigarette smoking.

FAMRI has invested more than $300,000,000 in excess of 300 individual projects and five centers of excellence, resulting in over 4,000 research publications, which rank favorably among those from the top academic institutions globally. FAMRI has changed the world.

FAMRI’s origin through litigation is a creative and compelling example of having the courage to dare and drive change.
The FAMRI-Bland Lane Center of Excellence on Secondhand Smoke at UCSF has been conducting research on SHS since 2002. The Center includes a clinic that evaluates lung and cardiovascular function in Flight Attendants, 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 Bland Lane Center clinic offers medical evaluation and pulmonary function testing at the UCSF Mission Bay location to all non-smoking Flight Attendants who were exposed to SHS. In addition, cardiopulmonary exercise testing is performed on eligible Flight Attendants at Parnassus. This testing allows Flight Attendants to benefit from FAMRI’s work. Further, extensive clinical data on health histories, occupational histories, SHS exposure, and medical evaluations on Flight Attendants is being collected, which aids in understanding the determinants of health and disease in Flight Attendants. In order to expand geographic diversity and offer more choices for flight attendant health, a satellite clinic has been established at Cedars-Sinai in Los Angeles. For more information please go to the following urls:

www.tobacco.ucsf.edu/

www.Facebook.com/FAMRI.Bland.Lane

FAMRI SUPPORTED RESEARCH

PUBLICATIONS


Bernert JT, Jacob P III, Holiday DB, Benowitz NL, Sosnoff CS, Doig MV, Feyerabend C, Aldous KM, Sharifi M, Kellogg MD, Langman LJ. Interlaboratory comparability of


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**PRESENTATIONS AND ABSTRACTS**


**FAMRI CENTER OF EXCELLENCE AT THE WEIZMANN INSTITUTE OF SCIENCE**

**Director: Varda Rotter, PhD**

https://weizmann.ac.il/FAMRI/

The FAMRI Center for Advanced Research on Lung Cancer (CARE) is based at the Weizmann Institute of Science and the Sheba Medical Center in Israel. The long-term goals of the Center are to elucidate the molecular genetic basis for lung cancer development and provide clues towards better diagnosis, prognosis, and therapy. The investigators are focusing on the understanding of the molecular mechanisms that underlie the development of lung pathologies as a result of exposure to tobacco smoke. They are investigating the contribution of transposable genetic elements, DNA repair, epigenetics, and inflammation as factors that influence disease development. In addition they are investigating stem cell-based therapy. The information gleaned from these areas can be used to investigate COPD as well. For complete details on the research being conducted at this Center please see https://weizmann.ac.il/FAMRI/.

http://www.weizmann.ac.il/FAMRI/publications.html

**FAMRI SUPPORTED RESEARCH PUBLICATIONS**


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Liberman N, Marash L, Kimchi A. The translation initiation factor DAP5 is a regulator of cell survival during mitosis. *Cell Cycle* 2009;8:204-209.


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**PRESENTATIONS AND ABSTRACTS**


**BOOK CHAPTERS, ETC.**

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**FAMRI CENTER OF EXCELLENCE AT THE SIDNEY KIMMEL COMPREHENSIVE CANCER CENTER JOHN HOPKINS MEDICAL INSTITUTIONS**

**Directors: Philip A. Cole, MD, PhD, and Julia Brahmer, MD**

A new Web site is under construction.

The Johns Hopkins FAMRI Center of Excellence was founded in 2005 and remains committed to highlighting the harms and ridding society of the scourge of cigarette smoke exposure. Since its inception, the Hopkins FAMRI COE has been committed to a broad portfolio of research and dissemination covering the spectrum of health issues related to smoke exposure, from COPD, to sinusitis, to cancer, to development of public health initiatives.

A new Web site is under construction for in depth information about the progress and projects of the Hopkins Center of Excellence.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**


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### PRESENTATIONS AND ABSTRACTS


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Hammers H, Paesante S, Rudek M, Pili R. Combination of the VEGF receptor tyrosine kinase sunitinib and the mTOR inhibitor rapamycin leads to tumor regression in the


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

Director: Jonathan D. Klein, MD, MPH

http://www2.aap.org/richmonddcenter/
The Julius B. Richmond Center of Excellence (Richmond Center) at the American Academy of Pediatrics (AAP) is dedicated to the elimination of children’s exposure to tobacco products and secondhand tobacco smoke (SHS). The Richmond Center seeks to ensure that all clinicians “ask the right questions” about non-smokers’ exposure, and that clinicians have the evidence and tools to address this issue in their practices and in their communities. The Richmond Center Administrative Core is housed at AAP headquarters in Elk Grove Village, IL, with research projects at multiple academic partner sites. Children, as well as non-smokers continue to be exposed to SHS in single family homes, cars, daycare facilities, restaurants, outdoor venues, and multi-unit home settings. The bench-to-bedside approach encompasses basic science projects, efficacy and effectiveness trials in practice-based research networks, and population and health services’ studies. The Richmond Center monitors and reports on the social climate of tobacco control in the US and provides answers to questions about multi-unit housing, emerging tobacco products, trends in tobacco counseling, clean indoor air initiatives, smoke-free rules in homes and cars, and public perceptions about FDA regulation of tobacco and nicotine products. Investigators at the Richmond Center have developed a nanotechnology-based sensor to measure real-time SHS exposure for use in practice and research. Current research projects also include studies on the effects of SHS exposure on airway development, on the hospitalization course of patients with bronchiolitis and other infections, on the development of asthma, and on vascular endothelial status. A set of standardized measures of exposures has been developed and is maintained. The Richmond Center provides information for clinical interventions, medical education, and continuing professional development; its presence at the AAP allows for rapid translation of research into public health initiatives and practice.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS


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**PRESENTATIONS AND ABSTRACTS**


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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.


**BOOK CHAPTERS, ETC.**

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FAMRI-IELCAP CENTER OF EXCELLENCE MOUNT SINAI MEDICAL CENTER

Director: Claudia I. Henschke, PhD, MD

http://www.ielcap.org/getting-screened/famri

The FAMRI-IELCAP Center of Excellence is dedicated to assessing the extent of exposure to SHS and the effect of this exposure on pulmonary, cardiovascular, and other diseases. It has a low-dose CT scanning program that is being used to address the potential benefits of this scanning for never-smokers who have been exposed to SHS. The Center’s approach to evaluation of screening is focused on how to diagnose disease earlier and how to translate early diagnosis into early treatment. All of the investigators share the common goal of developing and testing new methods that will improve the detection and diagnosis of early lung cancer and the prognostic indicators of cure. The present collaborative effort provides a structured and unique platform to continue the interaction and coordination among the 38 Center members and participating FAMRI-IELCAP sites in the United States in an efficient way. Screening sites are found in the following cities: Berkeley, California; Concord, California; Rancho Mirage, California; Redwood City, California; Greenwich, Connecticut; Norwich, Connecticut; Deerfield Beach, Florida; Miami, Florida (2); Atlanta, Georgia; Chicago, Illinois; Mount Vernon, Illinois; Silver Spring, Maryland; Lewiston, Maine; Fenton, Missouri; St. Charles, Missouri; Omaha, Nebraska; Galloway, New Jersey; Livingston, New Jersey; Long Branch, New Jersey; Morristown, New Jersey; Neptune, New Jersey; Paramus, New Jersey; Summit, New Jersey; New York, New York (2); Oceanside, New York; Poughkeepsie, New York; Rockville Centre, New York; Staten Island, New York; White Plains, New York; Charlotte, North Carolina; Toledo, Ohio; Albany, Oregon; Sayre, Pennsylvania; Oak Ridge, Tennessee; Dallas, Texas; and Seattle, Washington.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS


**PRESENTATIONS AND ABSTRACTS**


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FAMRI SUPPORTED RESEARCH

SINUSITIS

Ongoing Research

COGNITIVE FUNCTION AND CHRONIC RHINOSINUSITIS: EXPLORING THE IMPACT OF SECOND HAND 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. The investigators are enrolling patients undergoing medical and surgical treatment of CRS into a prospective cohort study in order to accomplish these goals.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS


SMOKE, CELLULAR AGING, AND CHRONIC RHINOSINUSITIS

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

Drs. Frank and Ramakrishnan are investigating whether the detrimental effects of SHS on the sinuses in chronic rhinosinusitis (CRS) involve 1) accelerated cellular aging and cell death within the tissue lining the sinuses; 2) associated deficiencies in immune function in the sinuses; and 3) disrupted sinus microbiomes, characterized by decreased amounts of protective microbes and increased amounts of pathogens (e.g., S. aureus) that contribute to tissue destruction and chronic inflammation. They are testing the relative importance of these factors in causing or contributing to CRS through carefully controlled human subjects’ research and experimentation.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS


**PRESENTATIONS AND ABSTRACTS**


Ramakrishnan VR. Bacterial microbiome and TH17 cytokines in CRS. 2015 Presented at the American College of Allergy and Immunology (ACAAI) annual meeting. San Antonio, TX, Nov 5-9, 2015.


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 are using 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 team is focusing on three aspects of NO dynamics in airway cells as they relate to tobacco smoke exposure. They are examining 1) the distribution of cell types among lifestyle smokers and non-smokers comparing NO production as a function of cell type and state of differentiation; 2) the role of secretory materials; and 3) the depth of airway secretions on NO production and modification. The team is also experimentally exposing healthy cells from non-smokers to tobacco smoke in an experimental model to clearly characterize the contribution of the different NO-relevant enzymes on NO dynamics in smokers and non-smokers.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS


PRESENTATIONS AND ABSTRACTS


CIGARETTE SMOKE, VIRAL INFECTIONS & NK CELLS
Ilona Jaspers, PhD; University of North Carolina at Chapel Hill; CIA 2013

In previous FAMRI-funded studies, Dr. Jaspers and colleagues developed and optimized experimental protocols to assess the effects of ex vivo viral stimulation on markers of cytolytic function, cytokine profiles, and immunophenotypes in non-smoking and cigarette smoke (CS)-exposed subjects. The team has demonstrated that the immunophenotypes of peripheral blood and nasal NK cells are vastly different and that CS exposure further alters these differences. In the current study, responses to viral challenges are being determined in these subjects using peripheral blood and nasal lavage natural killer (NK) cells. Nasal epithelial cells (NEC) from subjects are being co-cultured with autologous NK cells in order to determine the function and phenotype of NK cells in the context of a viral infection and CS exposure. Initial data suggest that infection with influenza increases the expression of the cytotoxic NK cell marker CD16 on NK cells co-cultured with NEC from non-smokers, while co-cultures with NEC from smokers do not, suggesting that signals from CS-exposed epithelial cells have a suppressive effect on NK cells. The data also suggest that the expression of the NK cell ligand, MICA/B, important during NK cell maturation, is reduced in NEC from CS-exposed subjects. Further, the team is developing experimental parameters to assess whether supplementation with nutritional antioxidants can modify NK cell function or alleviate the effects of CS on antiviral activity at the level of the epithelium. Initial data from this study indicate that nutritional antioxidant supplementation enhances peripheral blood NK cell function associated with reduced markers of viral replication in the nasal passages.

FAMRI SUPPORTED RESEARCH PUBLICATIONS


EFFECTS OF STS ON MUCOCILIARY CLEARANCE AND SINUSITIS
Lawrence Ostrowski, PhD; University of North Carolina at Chapel Hill; CIA 2012

Dr. Ostrowski and colleagues are investigating the effects of chronic sidestream tobacco smoke (STS) exposure on key components of the mucociliary clearance system in the upper airways. They are examining the effect of chronic STS exposure
on the establishment of bacterial sinusitis to advance the understanding of the increased susceptibility to chronic sinusitis. The investigators are establishing a murine model of STS-induced bacterial sinusitis for studies designed to evaluate new treatment strategies.

**SMOKE IMPAIRED EPITHELIAL FUNCTION IN SINUSITIS**

**Rodney Schlosser, MD; Charleston Research Institute; CIA 2012**

Dr. Schlosser and his team are investigating 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 will determine if SHS induces sinonasal inflammation by impairing HSNEC activation of vitamin D by altering toll like receptor (TLR) expression, increased pro-inflammatory cytokine production, and increased immune infiltrate in CRS. Smoke exposure is known to increase HSNEC expression of certain TLRs, priming them for a pro-inflammatory response.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**


Carroll WW, O'Connell BP, Schlosser RJ Gudis DA, Karnezis TT, Lawrence LA, Soler ZM, Mulligan JK. Fibroblast levels are increased in chronic rhinosinusitis with nasal polyps and are associated with worse subjective disease severity. *Int Forum Allergy Rhinol* [Epub 2015 Sep 15].


Sansoni ER, Sautter NB, Mace JC, Smith TL, Yawn JR, Lawrence LA, Schlosser RJ, Soler ZM, Mulligan JK. Vitamin D3 as a novel regulator of basic fibroblast growth


**PRESENTATIONS AND ABSTRACTS**


**NRF2 AND TOBACCO SMOKE EXACERBATED CHRONIC SINUSITIS**

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

Dr. Ramanathan and colleagues are generating allergic inflammation in the sinuses of normal mice and mice that lack anti-oxidant production. The investigators will expose mice to cigarette smoke to determine if they have decreased anti-oxidant levels. The team is also characterizing patients with sinusitis that are exposed to SHS by measuring inflammation and anti-oxidant levels during clinic visits. The investigators will study the ability of a natural compound found in broccoli sprouts to reduce or prevent smoke-associated inflammation in the nose and sinuses in both the mouse models and patients.

**NASAL EPITHELIAL GROWTH DYSFUNCTION BY SECONDHAND SMOKE IN CHRONIC SINUSITIS**

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

Dr. Kim and colleagues are studying 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.
FAMRI SUPPORTED RESEARCH

PUBLICATIONS


**Completed Research**

**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


**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


PRESENTATIONS AND ABSTRACTS

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


**SHS INDUCES BACTERIAL DRUG RESISTANCE AND VIRULENCE**

Ritwij Kulkarni, PhD; 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**


**PRESENTATIONS AND ABSTRACTS**


**EFFECTS OF SHS ON DC FUNCTIONS IN CRS**

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**


Carroll WW, O’Connell BP, Schlosser RJ, Gudis DA, Karnezis TT, Lawrence LA, Soler ZM, Mulligan JK. Fibroblast levels are increased in chronic rhinosinusitis with nasal polyps and are associated with worse subjective disease severity. *Int Forum Allergy Rhinol* 2016;6(2):162-168.


**PRESENTATIONS AND ABSTRACTS**


**VITAMIN D DEFICIENCY LINKS SHS AND SINUSITIS**

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**


**PRESENTATIONS AND ABSTRACTS**


**TOBACCO SMOKE 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.

**PRESENTATIONS AND ABSTRACTS**


**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 is propagating nasal epithelium from nonsmokers in the presence of an NO donor to create an environment of excessive NO production. They are using 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 culturing 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**

Carson JL, Brighton LE, Collier AM, Bromberg PA. Correlative ultrastructural investigations of airway epithelium following experimental exposure to defined air pollutants and lifestyle exposure to tobacco smoke. *Inhal Toxicol* 2013;25(3):134-140.


PRESENTATIONS AND ABSTRACTS

Carson JL. Human ciliopathies: the first 100 years. Presented at University of Wisconsin Department of Pediatrics Grand Rounds, Madison WI, Dec 01, 2011.


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


**ROLE OF SECRETORY PHOSPHOLIPASE A2 (sPLA2) IN RESPIRATORY DISORDERS**

**Saul Yedgar, PhD; Hebrew University of Jerusalem; 2008**

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 cytosolic 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 cysteinyll-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**


**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


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


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.

FAMRI SUPPORTED RESEARCH
PUBLICATIONS
PRESENTATIONS AND ABSTRACTS


CLINICAL AND 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


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

Dennis Shusterman, MD, MPH and 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

PRESENTATIONS AND ABSTRACTS

Shusterman D, Weaver E, Goldberg A, Schick S, Wong H, Balmes J. Evaluation of the

**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**


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.

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 may cause ciliary damage and decrease the defenses of the sinonasal mucosa because of increased biofilm accumulation.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS


**PRESENTATIONS AND ABSTRACTS**


**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 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**


**PRESENTATIONS AND ABSTRACTS**


**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 causes changes in the gene expression pattern of histologically normal upper respiratory mucosa and stroma that lead to CRS development.
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 worse quality of life. The team found a five-variable predictive model of total SNOT score (R^2 = 0.366, p = 0.0019).

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


**PRESENTATIONS AND ABSTRACTS**


**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**


**LABORATORY STUDIES OF HUMAN NASAL EPITHELIUM**

Johnny L. Carson, PhD; University of North Carolina; 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


PRESENTATIONS AND ABSTRACTS


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

PUBLICATIONS


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


PRESENTATIONS AND ABSTRACTS


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 responses; 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**


**EMPHYSEMA**

**Ongoing 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. The investigators found that DDT is differentially expressed in the lungs of patients with COPD and that DDT null mice develop spontaneous emphysema. DDT may promote both antioxidant and DNA repair processes that protect against the genotoxic effects of CSE. In this study, the investigators are characterizing the role of the CD74 signaling pathway on DNA damage and repair processes in the lung and determine the key cell type(s) responsible for spontaneous emphysema in the DDT and CD74 knockout mice. They are also determining the therapeutic potential of DDT as a treatment for COPD.

**DJ-1 IMPAIRMENT IN ATII CELLS IN EMPHYSEMA**

Beata Kosmider, PhD; Temple University; CIA 2014

Dr. Kosmider and her team study 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 is using 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 isolated ATII cells from wild-type and DJ-1 KO mice exposed for a short time to cigarette smoke. They found high oxidative stress and inflammatory response in DJ-1 KO mice. They are investigating whether these mice are more susceptible to...
emphysema development. The team will validate the results in ATII cells isolated from excess tissue obtained from lung volume reduction surgery of patients with severe emphysema. Control ATII cells will be obtained from non-smoker and smoker organ donors. The investigators will use these results to define the protective roles of CRIF-1, DJ-1, and downstream signaling in cigarette smoke-induced lung injury.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**


**PRESENTATIONS AND ABSTRACTS**


**MODELING COPD AND NOVEL RAGE TRANSGENIC MICE**

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

Dr. Reynolds and colleagues are characterizing the roles of receptors for advanced glycation endproducts (RAGE) in the progression of COPD using targeted, transgenic, and wild type mice exposed to first and secondhand tobacco smoke. They are investigating whether smoke-induced RAGE expression orchestrates the inflammatory signaling and alveolar cell death observed in COPD. The team generated a conditional RAGE overexpressing transgenic mouse model, which constitutes a powerful non-smoking model of COPD pathogenesis.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**


**PRESENTATIONS AND ABSTRACTS**


Nelson MB, Tippetts T, Winden DR, Reynolds PR, Bikman B. RAGE activation reduces cardiomyocyte mitochondrial function in a ceramide-dependent manner [abstract]. *Diabetes* 2014;63(S1):447-P.


Tippetts T, Winden DR, Wagner M, Condie T, Reynolds PR, Bikman B. 2014. Ceramide is necessary for cigarette smoke-induced reduced heart mitochondrial function [abstract]. *Diabetes* 2014;63(S1):1855-P.


**THE ROLE OF MMP-13 IN EMPHYSEMA DEVELOPMENT**

*Monica Goldklang, MD; Columbia University; YCSA 2011*

Dr. Goldklang and colleagues are investigating whether matrix metalloproteinase-13 (MMP-13) is an essential collagenase in the development of emphysema. The team is studying the regulation of macrophage MMP-13 induction by cigarette smoke and determining if MMP-13 knockout mice are protected from passive cigarette smoke-induced emphysema. The team is identifying specific targets that can be utilized to prevent smoking-related emphysema and the progress of lung disease.

**RESEARCH**

**PUBLICATIONS**


**CIGARETTE SMOKE INDUCES XOR MEDIATED APOPTOSIS**

*Bo Kim, MD; Johns Hopkins University; YCSA 2011*

Dr. Kim and colleagues have demonstrated that C57/Bl6 mice exposed to cigarette smoke (CS) have increased pulmonary xanthine oxidoreductase (XOR) activity and protein levels compared to filtered-air-exposed controls. In addition, the researchers have demonstrated that primary pulmonary human lung microvascular endothelial cells (ECs) exposed to CS extract undergo increased rates of caspase-dependent apoptosis that are reliant on XOR activity, reactive oxygen species production, and p53 function/expression. Exogenous XOR is sufficient to increase p53 expression and induce apoptosis, suggesting that XOR is an upstream mediator of p53 in CS-induced EC apoptosis. In addition, XOR activation results in DNA
double-strand breaks that activate the enzyme ataxia telangiectasia mutated, which phosphorylates histone H2AX and upregulates p53. These results suggest that CS exposure increases XOR expression, and the enzyme is both sufficient and necessary for p53 induction and CS-induced EC apoptosis.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS


PRESENTATIONS AND ABSTRACTS


INFLAMMASOME AS A MODULATOR OF EMPHYSEMA IN MICE

Thomas Sussan, PhD; Johns Hopkins Medical Institutions; YCSA 2010

Dr. Sussan and colleagues are investigating the role of nuclear factor erythroid 2-related factor 2 (Nrf2), a key transcription factor that mediates an adaptive response to counteract oxidative stress in inflammasome activation. They are using inflammasome knockout mice to investigate the role of inflammasome in driving inflammation and emphysema due to SHS exposure. The team has determined that SHS exposure causes oxidative stress and results in elevated secretion of interleukin 1b in bronchoalveolar lavage (BAL) fluid and increased activity of caspase-1 in alveolar macrophages. The team is also investigating whether Nrf2 protects from inflammasome activation by decreasing oxidative stress in the lungs of SHS-exposed mice. They will use mice with enhanced Nrf2 (by disruption of its inhibitor, Keap1, in lungs and myeloid cells), which were generated in their laboratory. The
investigators have determined that the Nrf2-deficient mice exhibit elevated activation of the inflammasome in BAL and alveolar macrophages following exposure to SHS and that macrophages from Keap1-deficient mice exhibit decreased activation of caspase-1.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**


**Completed Research**

**ALTERED GLUTATHIONE BIOSYNTHESIS IN CIGARETTE SMOKE-INDUCED EMPHYSEA**

**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**


**PRESENTATIONS AND ABSTRACTS**


**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**

**PUBLICATIONS**


Pastukh VM, Zhang L, Ruchko MV, Gorodnya O, Bardwell GC, Tuder RM, Gillespie MN. Oxidative DNA damage in lung tissue from patients with COPD is clustered in functionally significant sequences. *Int J Chron Obstruct Pulmon Dis* 2011;6:209-217.


**ROLE OF TLR4, AGING, AND GENDER IN EMPHYSEMA**

**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**

**PUBLICATIONS**


**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-dioxoleana-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**

**PUBLICATIONS**


**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


PRESENTATIONS AND ABSTRACTS


Stephens RS, Servinsky LE, Pearse DB. cGMP-mediated antioxidant signaling: a role for the c-Abl tyrosine kinase. 5th International Conference on cGMP Generators, Effectors and Therapeutic Implications. BMC Pharmacology 2011;11(Suppl 1):70.

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 basolateral-to-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


**PRESENTATIONS AND ABSTRACTS**


**THE ROLE OF THROMBOSPONDIN-1 IN EMPHYSEMA**

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

Dr. Ezzie and colleagues tested whether loss of 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**


Ezzie ME, Piper MG, Montague C, Newland CA, Opalek JM, Baran C, Ali N, Brig-stock D, Lawler J, Marsh CB. Thrombospondin-1 deficient mice are not protected from

**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**


Reynolds PR, Allison CH, Willnauer CP. TTF-1 regulates alpha 5 nicotinic acetylcholine receptor (nAChR) subunits in proximal and distal lung epithelium. *Resp Res* 2010;11:175.


**PRESENTATIONS AND ABSTRACTS**


Kasteler SD, Reynolds PR, Hoidal JR. Downstream effects of receptors for advanced glycation end products (RAGE) in pulmonary epithelial cells exposed to cigarette smoke. Presented at the ATS International Meetings. Toronto, Canada, May 16-21, 2008.


FAMRI Supported Research


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


PRESENTATIONS AND ABSTRACTS

Lodhi S, Palma N, Patel J, Zhang J. Hypoxia-induced upregulation of CX3CL1/fractalkine expression is mediated through PI3K/Akt- and p38 MAPK-


**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**


**PRESENTATIONS AND ABSTRACTS**


**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**

Campbell EJ, Owen CA. The sulfate groups of chondroitin sulfate- and heparan sulfate proteoglycans in neutrophil plasma membranes are novel binding sites for neutrophil elastase and cathepsin G. *J Biol Chem* 2007;282:14645-14654.


**PRESENTATIONS AND ABSTRACTS**

Cala LF, Owen CA. ADAM15 is a novel neutrophil proteinase that contributes to pericellular proteolysis. Presented at the American Thoracic Society meeting. Toronto, Canada, May 16-21, 2008.

Cala LF, Owen CA. Biology of ADAM15 in human neutrophils [abstract]. Society for Leukocyte Biology 2007;A4:1S.

Craig VJ, Owen CA. Matrix metalloproteinase-8 (MMP-8) has potent anti-inflammatory activities during bleomycin-mediated acute lung inflammation in mice [abstract]. *Proc Am Thor Soc* 2012;D29S.

Knolle M, Owen CA. Anti-inflammatory role for ADAM8 in asthma [abstract]. Society for Leukocyte Biology. 2007;A39:4S.


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


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

**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**

CHRONIC BRONCHITIS

Ongoing 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 are using 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. Preliminary results show that TGF-beta 1 is responsible for the failure of clearing phlegm and that the inhibition of TGF-beta 1 can prevent mucus build up in cell culture. TGF-beta 1 negatively influences a potassium channel that is critical for maintaining sufficient water in the airway. The team is testing medications that are currently used for other indications to see whether they can prevent mucus build up in vitro. The successful medications will be tested in patients who suffer from chronic bronchitis or COPD.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS


PRESENTATIONS AND ABSTRACTS


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) infection induces severe oxidative damage by downregulation of antioxidant enzymes in lung epithelial cells, which is exacerbated by exposure to SHS. It has been shown that extracellular high mobility group box 1 protein (HMGB1) can act as a danger signal that mediates the activation of innate and adaptive immune responses through a receptor for advanced glycation end products (RAGE) and Toll-like receptors 2 and 4, which are involved in inflammatory processes. The team has shown that RSV-infected airway epithelial cells exposed to cigarette smoke condensate (CSC) have an increase in HMGB1 protein expression in the secretome with concomitant decrease in cell lysates. The investigators are studying the effects of RSV infection enhanced by the exposure to tobacco smoke on the molecular mechanisms that induce the release of HMGB1 and associated signaling, and the elevated levels of secreted HMGB1 from airway epithelial cells associated with inflammation.

FAMRI SUPPORTED RESEARCH

PRESENTATIONS AND ABSTRACTS


**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 are examining the relationships between endogenous hydrogen peroxide production and acid secretion in the bronchial tree, and how tobacco smoke exposure changes the mechanisms that control them, using fluorescent molecules that respond to changes in cell cultures. The team has shown that hydrogen peroxide production and proton secretion may be altered by exposure to cigarette smoke. Changes in levels of gene expression are being determined in a model system designed to resemble the epithelia in the bronchial lumen.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**


**PRESENTATIONS AND ABSTRACTS**


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.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS


PRESENTATIONS AND ABSTRACTS


CALPAIN IN AIRWAY AND LUNG VASCULAR REMODELING

Yunchao Su, MD, PhD; Georgia Regents University; CIA 2012

Dr. Su and colleagues have found that hydrogen peroxide (H$_2$O$_2$) activates calpain in bronchial and pulmonary artery smooth muscle cells (BSMCs and PASMCs) and that calpain mediates cell proliferation and collagen-I synthesis. Calpain is 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. The investigators have demonstrated that the specific calpain inhibitor, MDL28170, prevented H$_2$O$_2$-induced increases in intracellular active TGF beta, cell proliferation, and protein levels of collagen-I in BSMCs and PASMCs. Moreover, reactive oxygen species formation and calpain activation are higher in smooth muscle cells of bronchi and pulmonary arteries in mice exposed to tobacco smoke for 24 weeks. Importantly, calpain knockout attenuates thickening of smooth muscle layers and collagen deposition in airway and pulmonary vessels in a mouse model of tobacco smoke-induced COPD. This project provides a strong rationale for targeting calpain in airway and pulmonary vascular smooth muscle for intervention in SHS-induced COPD.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS


**PRESENTATIONS AND ABSTRACTS**


Han W, Su Y. Knockout of calpain inhibits right ventricular hypertrophy and fibrosis in chronic hypoxic pulmonary hypertension. Presented at the Keystone Symposia. Snowbird, UT, Apr 7-12, 2013.


BOOK CHAPTERS, ETC.


Completed Research

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

PUBLICATIONS


PRESENTATIONS AND ABSTRACTS


CILIAR REPAIR IN SMOKING RELATED CHRONIC BRONCHITIS

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

Dr. Scmidt and colleagues investigated the influence of different Wnt pathway elements in a model of direct cigarette smoke exposure. Overexpression and 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

PUBLICATIONS


**PRESENTATIONS AND ABSTRACTS**


**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**

**PUBLICATIONS**


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


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.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**


**TOBACCO SMOKE EXPOSURE CAUSES NITROSYLATION OF CALPAIN AND IMPAIRMENT OF BRONCHIAL EPITHELIAL REPAIR IN CELL CULTURE AND MURINE MODELS**

Yunchao Su, MD, PhD; Georgia Regents 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


PRESENTATIONS AND ABSTRACTS


BOOK CHAPTERS, ETC.

**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 glutathione 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**


**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+]) 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**


**PRESENTATIONS AND ABSTRACTS**


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.


PRESENTATIONS AND ABSTRACTS


ALTERNATIVELY SPLICED VARIANTS OF SOLUBLE ADENYLYL CYCLASE
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


**PRESENTATIONS AND ABSTRACTS**


**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**


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


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


**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 2003

Dr. Robbins and colleagues collected exhaled breath condensate (EBC), bronchoalveolar lavage (BAL), and sputum from 35 subjects: 15 smokers, 10 nonsmokers, 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**


**PRESENTATIONS AND ABSTRACTS**


**SMOKE AND SUSCEPTIBILITY TO RESPIRATORY INFECTION**

Lester Kobzik, MD; Harvard Medical School; 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. Sidestream and mainstream smoke 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**


**EFFECT OF SECONDHAND CIGARETTE SMOKE, RSV BRONCHIOLITIS AND PARENTAL ASThma ON URINARY CYSTEINYL LTE4**

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

Dr. Joad and colleagues determined whether SHS exposure increases urinary cysteinyll 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 cysteinyll leukotrienes in infants with no parental asthma.

**CHRONIC OBSTRUCTIVE PULMONARY DISEASE**

**Ongoing Research**

**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. Extracellular H3.3 induces cytotoxicity upon interaction with the structural lung cell surface, subsequently promoting a self-sustaining cell death process that contributes to COPD progression. The investigators observed that this process can be blocked *in vitro* by using antibodies against H3.3, suggesting that the apoptosis generated by H3.3 can be inhibited by an interaction with its receptor on the lung cell surface or by blocking the signaling cascade after the initial interaction. The team is currently exploring the ability of H3.3 to be used as an early marker and as a therapeutic target for COPD progression. Dr. Barrero and his collaborators have identified five putative H3.3 receptors and are investigating *in vitro* the role of these receptors in H3.3 toxicity by identifying interacting membrane partners involved in triggering cell death. The team is evaluating neutralizing antibodies to prevent H3.3 lung toxicity *in vivo*, and screening for compounds that can block H3.3 cytotoxicity in a high throughput assay, with the long-term goal of prevention and treatment of COPD.

**FAMRI SUPPORTED RESEARCH**

**PRESENTATIONS AND ABSTRACTS**


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

Alyssa Gregory, PhD; University of Pittsburgh; YCSA 2015

COPD is increasingly gaining recognition as a disease characterized by accelerated aging of the lung microenvironment, and the effects of cigarette smoke exposure mirror those that occur with age, including excessive infiltration by myeloid cells, presence of oxidative stress, and shortening of telomeres. It has been demonstrated that neutrophil elastase (NE), degrades insulin receptor substrate-1 (IRS-1), which is a critical regulator of cellular proliferation and senescence. The investigators are
determining the influence of insulin-like growth factor 1 (IGF-1) signaling axis on the development of emphysema in mice, and examining the contribution of NE-mediated disruption of insulin/IGF signaling pathways to the induction of senescence in lung epithelial cells in vitro. They are correlating expression levels of IGF-1, IRS-1, and NE in patient tissues with COPD disease status.

**METABOLIC REPROGRAMMING IN PATIENTS WITH COPD**

**Xiangming Ji, PhD; Vanderbilt University; YCSA 2015**

Dr. Ji and colleagues are testing the hypothesis that cigarette smoke exposure induces metabolic reprogramming in the airway epithelium and promotes the development of COPD. Chronic inflammation, disruption of innate immunity by downregulation of the polyimmunoglobulin receptor (pIgR), and mucus cell proliferation have been implicated as biological alterations in the pathogenesis of COPD. Preliminary proteomic analysis of the airway epithelium from patients with different risks of COPD suggests that early metabolic reprogramming of bronchial epithelial cells may hold clues to the understanding of the progression of COPD. The investigators are studying the metabolic reprogramming occurring in the airway epithelium of patients with COPD, as well as the roles of key regulating enzymes on tobacco smoke-induced COPD phenotypes, including cytokine production, mucus hypersecretion, and loss of poly-immunoglobulin receptor (pIgR) expression in an in vitro model. They are also determining if these phenomena are regulated by metabolic reprogramming of rate-limiting enzymes.

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

**Gwenael Layec, PhD; University of Utah; YCSA 2015**

Limited exercise capacity acts as a marker of well-being and a prognostic tool in COPD patients. However, leg discomfort is a frequent exercise-limiting symptom invoked by these patients during cycling exercise, thus peripheral oxygen (O₂) transport and muscle O₂ utilization capacity appear to be impaired. It is unclear which peripheral component of the O₂ cascade limits overall muscle aerobic capacity. The goal of this project is to determine whether mitochondrial function in vivo is limited by convective O₂ delivery or if it is limited by the capacity of mitochondria to synthesize ATP. The investigators are using phosphorus magnetic resonance spectroscopy, near-infrared spectroscopy, and Doppler ultrasound to examine the effect of superimposing reactive hyperaemia on O₂ delivery and mitochondrial function in the calf muscle of patients with moderate to severe COPD. Preliminary results indicate that an increase in convective O₂ delivery does not improve mitochondrial function in the plantar flexor muscles of the patients with COPD, thereby suggesting that the peak rate of mitochondrial ATP synthesis is limited by intrinsic mitochondrial capacity and not O₂ availability. The loss of mitochondrial reserve capacity can lead to a greater susceptibility to mitochondrial damage and a deterioration of mitochondrial bioenergetic function.

**FAMRI SUPPORTED RESEARCH**
PUBLICATIONS

PRESENTATIONS AND ABSTRACTS
Layec G. Metabolic abnormalities with COPD: Is it only physical deconditioning? Presented at the UVRL colloquium. Presented at the University of Utah. Salt Lake City, UT, Jan 2016.


ADAM8: A NOVEL PROTEINASE THAT PROTECTS AGAINST SECONDHAND SMOKE-INDUCED COPD
Francesca Polverino, MD; Brigham and Women’s Hospital; 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 higher lung macrophage counts, more emphysema, and more small airway remodeling than SHS-exposed WT mice. Dr. Polverino hypothesizes that ADAM8 has anti-inflammatory activities in the murine lung, and is investigating the mechanisms by which SHS exposure limits emphysema development in mice. She is studying plasma and lung samples from human subjects exposed or not to SHS to delineate the roles of ADAM8 in human emphysema pathogenesis, and is investigating the effects of SHS exposure on its expression.

FAMRI SUPPORTED RESEARCH
PUBLICATIONS

PROTECTIVE EFFECT OF BMP4 IN AIRWAY AND LUNG VASCULAR REMODELING OF SHS-INDUCED COPD
Yunchao Su, MD, PhD; Georgia Regents University; CIA 2015
Inflammatory mediators in COPD activate calpain in bronchial and pulmonary artery smooth muscle cells (BSMCs and PASMCs), leading to intracrine TGF beta1 activation, cell proliferation, and collagen synthesis in airway and pulmonary vascular remodeling. In preliminary experiments, Dr. Su and colleagues found that bone morphogenetic protein 4 (BMP4) inhibits platelet-derived growth factor
(PDGF)- and interleukin-6 (IL-6)-induced calpain activation, collagen synthesis, and cell proliferation in BSMCs and PASMCs. BMP4 levels are much lower in lungs of tobacco smoke-exposed mice and COPD patients. The investigators hypothesize that BMP4 exerts protective effect in airway and lung vascular remodeling of COPD. They are testing this hypothesis using a multidisciplinary approach to determine whether BMP4 antagonizes PDGF- and IL-6-induced collagen synthesis and hyperproliferation of BSMCs and PASMCs via the BMP receptor-PKA pathway and 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. The team is investigating whether BMP4 reduces airway and lung vascular remodeling in an animal model of SHS-induced COPD. Their hope is to identify BMP4 as a protective agent in COPD, which may lead to an effective therapy for airway and lung vascular remodeling in SHS-associated COPD.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**


**MOLECULAR MECHANISMS OF VIRAL DISEASE ENHANCEMENT BY TOBACCO SMOKE EXPOSURE**

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

Dr. Guerrero-Plata and colleagues are investigating the mechanisms responsible for increased severity to respiratory infection due to SHS exposure. 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), which trigger inflammatory and antiviral responses in the lung of infected hosts. The investigators 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 causes lower respiratory tract infections among young infants and there is direct correlation of exacerbation of the disease when children are exposed to SHS. The investigators are determining whether prenatal exposure to tobacco smoke interferes with components of the innate immune system in the lung. They are examining the effect of SHS exposure on the expression of PRR in response to viral infection. They are also defining the altered molecules in the cytokine signaling pathways and their effects on the proinflammatory response to viral infection. They are investigating the effect of combined in utero and postnatal tobacco smoke exposure on the expression on antiviral immune response.
TRISTETRAPROLIN IN CONTROL OF INFLAMMATION
Qiang Ding, PhD; University of Alabama at Birmingham; CIA 2015

Dr. Ding and colleagues are studying the mechanisms leading to the persistent inflammation seen in COPD. The investigators have demonstrated that tristetraprolin (TTP), an adenylate-uridylate rich element-binding protein, controls the expression of several pro-inflammation mediators, including tumor necrosis factor (TNF-alpha). TPP negatively regulates the expression of multiple pro-inflammatory mediators by promoting their mRNA degradation, and may have a role in the persistent inflammation induced by cigarette smoke (CS) exposure. TTP functions as an anti-inflammation regulator in response to SHS exposure, and the investigators have shown that TTP function is impaired by this exposure, which results in increased and prolonged expression of a number of inflammation mediators. They hypothesize that CS exposure inhibits the function of TTP as an mRNA destabilizing protein, which could increase mRNA stability and protein expression of pro-inflammatory mediators, thereby contributing to persistent inflammation and lung injury. The investigators are defining the role and mechanisms of TTP as a negative regulator of expression of TNF-alpha, IL-8, and COX-2, and are determining the role of p38 MAPK in TTP downregulation induced by CS exposure. Further, they are investigating the effect of loss and gain of TTP on pro-inflammatory mediator expression and on lung epithelial cell death/survival in vivo.

FAMRI SUPPORTED RESEARCH
PRESENTATIONS AND ABSTRACTS


METABOLIC DYSFUNCTION IN THE PATHOGENESIS OF COPD

Anju Singh, PhD; Johns Hopkins Medical Institutions; CIA 2014

Dr. Singh and colleagues are building 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 are also determining if attenuation of glycolytic flux or lactate production by small molecule inhibitors of glycolysis/HIF1A or activation of pentose phosphate pathway (PPP) flux can restore metabolic balance and reduce inflammation in human bronchial epithelial cells and macrophages. They are investigating whether glucose flux is upregulated through glycolysis and if PPP flux is attenuated in alveolar macrophages and bronchial epithelial cells isolated from COPD patients.
NOVEL F BOX ANTI-INFLAMMATORIES FOR COPD

Rama Mallampalli, MD; University of Pittsburgh; CIA 2014

Dr. Mallampalli and collaborators have designed, synthesized, and tested actions of a drug, BC1261, that acts on the molecular target FBXO3, which reduces inflammation and prevents lung injury in a cigarette smoke mouse model of COPD. They are investigating the FBXO3 protein further to assist in an optimal drug design that can be tested in mice exposed to cigarette smoke and mice infected with bacteria to determine if lung inflammation and bacterial burden can be effectively reduced.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS


CIGARETTE SMOKE IMPAIRS ALPHA-1-ANTITRYPSIN FUNCTION

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

The objective of this study is to discover effective treatments to prevent and treat acute exacerbations of COPD (AECOPD) by eliminating the excessive lung inflammation that worsens COPD symptoms. The investigators have shown that alpha-1-antitrypsin (A1AT) effectively reduces airway epithelial inflammation when the cells are not exposed to cigarette smoke, but when the airway epithelial cells are exposed to cigarette smoke, A1AT loses its inflammation inhibitory function. They are using a human airway epithelial cell culture model to test if A1AT's anti-inflammatory function is less effective in cells from COPD patients than those from normal subjects. They are determining how A1AT inhibits inflammation, and investigating how cigarette smoke damages that function. A mouse cigarette smoke exposure model is being used in combination with bacterial or viral infection to test if A1AT can overcome the damaging effects of cigarette smoke.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS


**COMPONENTS OF SECONDHAND SMOKE IN COPD**

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

Dr. Bauer and colleagues are focusing on low molecular weight polycyclic aromatic hydrocarbons (LMWPAHs), which are found in high concentrations in SHS and thirdhand smoke. They are investigating what regulates the p38 mitogen activated protein kinase (p38 MAPK) pathway during the early stages of COPD development using LMW PAHs in lung cells in culture and an animal model to discover targets for diagnostics and therapy.

**FAMRI SUPPORTED RESEARCH**

**PRESENTATIONS AND ABSTRACTS**


**PROTECTIVE EFFECTS OF COG133 IN COPD**

*Robert F. Foronjy, MD; SUNY Downstate; 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 are using PP2A knockout mice that do not express PP2A within the airways to determine if inhaled COG133 will prevent disease development in the control mice but not in the smoke-exposed PP2A knockout mice. To determine if COG133 is effective when smoke related disease is already established, the investigators are exposing mice to tobacco smoke for a two-month period of time prior to initiating treatment with COG133. Since COG133 is a potent activator of PP2A in the lung, it is expected that COG133 treatment during the additional two-month period of exposure will slow, prevent, or reverse the progression of COPD.
FAMRI SUPPORTED RESEARCH

PUBLICATIONS


PRESENTATIONS AND ABSTRACTS


ROLE OF OCTN1 IN TOBACCO-RELATED COPD

Carsten Ehrhardt, PhD; Trinity College Dublin; CIA 2014

Dr. Ehrhardt and collaborators are investigating the role of the ergothioneine transporter (OCTN1) in COPD. They hypothesize that people with a defective OCTN1 who are lacking ergothioneine in their lungs have a higher chance of developing COPD compared to people who have fully functioning OCTN1. They are using
cultures of lung cells and a strain of mice lacking functional OCTN1 to investigate this and they are determining whether COPD patients have a higher frequency of OCTN1 mutations than healthy individuals.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS


PRESENTATIONS AND ABSTRACTS


Ehrhardt C. Arzneistoffabsorption in der Lunge-mehr als nur Diffusion. Presented at the Institut für Pharmazie, Martin Luther-Universität Halle-Wittenberg, Halle (Saale), Germany, Apr 24, 2015.

Ehrhardt C. Drug transporters in the lung - expression and interactions with inhaled medicines. Presented at the Faculty of Pharmacy, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University, Kanazawa, Japan, Apr 15, 2015.


Ehrhardt C. Recent advances in drug transporter research in the lungs. Department of Pharmaceutics and Therapeutics, Graduate School of Biomedical & Health Sciences, Hiroshima University. Hiroshima, Japan, Nov 9, 2015.

Ehrhardt C. Spielen Arzneistofftransporter im Lungeneptihel eine biopharmazeutische Rolle? Presented at the Institut für Pharmazeutische Technologie. Technische Universität, Braunschweig, Germany, Jun 18, 2014.


Ehrhardt C. The role of drug transporters in inhalation biopharmaceutics. Presented at the University of Toyama Graduate School of Medicine and Pharmaceutical Sciences. Toyama, Japan, Apr 13, 2015.


Ehrhardt C. Wo geht’s lang? Wege der Arzneistoffabsorption in der Lunge. Presented at the Institut für Pharmazeutische Technologie und Biopharmazie, Philipps-Universität Marburg, Germany, Sep 02, 2014.


Nickel S, Selo MA, Clerkin CG, Reynolds PR, Kato Y, Nakamichi N, Talbot BN, Walsh JJ, Ehrhardt C. OCTN1-mediated uptake of ergothioneine protects from tobacco


**CFTR, A NOVEL DRUG TARGET FOR COPD**

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

Dr. Raju and colleagues are determining the total contribution of acrolein to SHS-induced cystic fibrosis transmembrane conductance regulator (CFTR) abnormalities. They are studying the mechanisms of acrolein modifications on CFTR protein, the impact on ion transport and mucus clearance, and they are validating new drugs capable of correcting mucus transport defects in chronic bronchitis by blocking the effects of acrolein on the CFTR channel.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**


**PRESENTATIONS AND ABSTRACTS**


**NEUTROPHIL DEATH IN TOBACCO-INDUCED COPD**

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

Dr. Luo and colleagues are identifying and characterizing cellular events that mediate reduced neutrophil spontaneous death in cigarette smoke-induced COPD. They hypothesize that the reduced neutrophil spontaneous death in tobacco-induced COPD is mediated by blockage of protein kinase B (Akt) deactivation, which
is due to inhibition of inositol hexakisphosphate kinase 1 (InsP6K1) and subsequent reduction of inositol pyrophosphate (InsP7). They are investigating the involvement of Akt and InsP6K1 in neutrophil death in the lungs in vivo using a cigarette-induced COPD animal model and they are also investigating the molecular mechanisms that regulate InsP6K1 activity in neutrophil death.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**


Luo HR, Mondal S. Molecular control of PtdIns(3,4,5)P3 signaling in neutrophils. *EMBO Rep* 2015;16(2):149-163.

**MODIFIED LIPOPROTEINS IN COPD AND LUNG INFECTIONS**

Mathieu Morissette, PhD; McMaster University; YCSA 2013

Dr. Morissette and colleagues are exploring causes of the lung inflammation and increased risk of pulmonary infection associated with cigarette smoke exposure in both human subjects and animal models. The team is investigating new therapies that could reduce lung inflammation and normalize the risk of lung infection.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**


**SHARED SUSCEPTIBILITY TO COPD AND CVD**

Robert Reed, MD; University of Maryland; YCSA 2013

Epidemiologic data and Dr. Reed’s own data suggest that the association between cardiovascular disease and diseases of the airway is present even in people who do not smoke. Dr. Reed is investigating several mechanisms that may account for this observation in the Amish population. Amish men smoke primarily pipes and cigars and Amish women’s exposure is essentially entirely in the form of SHS, thus this population is ideal for studies of susceptibility to this toxic substance.

**FAMRI SUPPORTED RESEARCH**
PUBLICATIONS


Crowley ND, Verceles AC, Reed RM. Sore throat... don’t forget Lemierre’s syndrome. *BMJ Case Rep* 2015 Jan 9;2015. pii: bcr2014208225.


Naderi N, McCurdy MT, Reed RM. Holt-Oram: when the key to a broken heart is in the hand. *BMJ Case Rep* 2014 Apr 10;2014. pii: bcr2014203851.


Reed RM, Reed AW, McArdle PF, Miller M, Pollin TI, Shuldiner AR, Steinle NI, Mitchell, BD. Vitamin and supplement use in the old order Amish: sex-specific prevalence and associations with use. *J Acad Nutr Diet* 2014;S2212-2672(14)01353-01357.


**BOOK CHAPTERS, ETC.**


CIGARETTE SMOKE INCREASES GDF15 TO IMPAIR LUNG INNATE IMMUNITY

Qun Wu, MD, PhD; National Jewish Health; YCSA 2013

Dr. Wu and colleagues are studying the induction of growth differentiation factor 15 (GDF15) in airway epithelial cells by cigarette smoke exposure. They will determine if this induction impairs lung host defense against bacteria.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Wu Q, Jiang D, Minor M, Chu HW. Electronic cigarette liquid increases inflammation and virus infection in primary human airway epithelial cells. *PLos One* 2014;9(9):e108342.

PRESENTATIONS AND ABSTRACTS


INFLAMMASOME SIGNALING IN COPD AND EMPHYSEMA

Sanjay Batra, PhD; Louisiana State University; YCSA 2013

Dr. Batra and colleagues are investigating whether cigarette smoke enhances inflammation and cell injury via the activation of the NOD-like receptor protein 10 (NLRP10), and if the activation of NLRP10 involves interaction with other cytosolic NLR proteins that lead to inflammation and emphysema. The team has demonstrated that cigarette smoke exposure induces upregulation of NALP10 protein in human airway epithelial cells, human alveolar macrophages, and mouse lungs. NLRP10 has been shown to be the most potent inducer of cytokines in the NLRP family. The role of NALP10 in smoke-induced lung inflammation and emphysema in subacute and chronic CS exposure is being studied, and the associations between the severity of COPD and active caspase-1, IL-1 beta, and IL-18 are being explored.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS


PRESENTATIONS AND ABSTRACTS
FAMRI Supported Research


A NOVEL THERAPY OF MUCUS HYPERSECRETION IN COPD

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

Dr. Di and colleagues are investigating whether targeted regulation of Sp1, a transcription factor, will alleviate cigarette smoke (CS)-induced MUC5AC upregulation and mucus hypersecretion. The team has shown that phosphorylation and methylation are involved in CS-induced Sp1-DNA binding mediated mucin expression. They are examining how CS exposure affects phosphorylation, DNA methylation, and histone modification leading to increased mucus hypersecretion in human primary cultured normal bronchial epithelial (NHBE) cells and in COPD patients. They are also determining the optimal pharmacological intervention of CS-induced Sp1 activation and mucus hypersecretion using CS-exposure mouse models.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS


PRESENTATIONS AND ABSTRACTS

Di PY. Effects of cigarette smoke on mucociliary clearance, lung microbiome, and respiratory infection. Presented at the 32nd Annual Meeting of the Mountain West Society of Toxicology. Tucson, AZ, Sep 4-5, 2014.


Di PY. Pathogenesis of air pollution-associated lung diseases. Presented at the Department of Physiology, Medical College, Qingdao University, Qingdao, China, Jun 26, 2014.

**VIRUS AND COPD EXACERBATION**

**Yin Chen, PhD; University of Arizona; CIA 2013**

Autophagosomes appear to support viral growth and substantially enhance inflammation. Dr. Chen and colleagues are investigating whether tobacco smoke exposure increases the number of autophagosomes in three experimental models, including human COPD samples. If autophagosomes do increase in number, then targeting their formation could become an effective method for treating COPD exacerbation.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**


**SECONDHAND CIGARETTE SMOKE AND EFFEROCYTOSIS**

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

Dr. Vandivier and colleagues are investigating how serotonin (5-HT) may regulate the development of COPD from SHS exposure. Studies show that 5-HT is increased in the blood of COPD patients, and that 5-HT-containing platelets are increased and activated in COPD. The group has shown that 5-HT is increased in SHS-exposed animals and that it impairs efferocytosis by lung macrophages through activation of RhoA and its downstream effector, Rho kinase. The team is determining whether 5-HT contributes to the development of COPD by impairing efferocytosis by lung macrophages and preventing the normal resolution of inflammation. The mechanism for 5-HT-mediated RhoA activation may occur through one of its receptors or by RhoA serotonylation, a mechanism by which 5-HT activates RhoA.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**


**NOVEL ACTIVITIES FOR ADAM9 IN COPD**

**Caroline A. Owen, MD, PhD; Brigham and Women’s Hospital; CIA 2013**

Dr. Owen and colleagues are doing studies that will lead to the development of a diagnostic test that allows earlier detection of lung diseases caused by SHS exposure, such as emphysema. The team is focusing on the role of the ADAM family of proteinases in the development of emphysema in individuals exposed to SHS. Exposure to cigarette smoke causes white blood cells in the lung to release proteinases that digest structural proteins in the lung and damage lung cells, resulting in loss of tissue and function. The team has shown that ADAM9 is produced in high amounts by white blood cells linked to emphysema, and they are investigating how ADAM9 specifically contributes to emphysema development.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**


Craig VJ, Polverino F, Laucho-Contreras ME, Shi Y, Liu Y, Osorio JC, Tesfaigzi Y, Pinto-Plata V, Gochuico BR, Rosas IO, Owen CA. Mononuclear phagocytes and airway


PRESENTATIONS AND ABSTRACTS


**TLR4-MEDIATED EMPHYSEMA: ROLE OF AGING**

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

Dr. Lee and colleagues hypothesize that Toll-like receptor 4 (TLR4) signaling is necessary to maintain normal lung homeostasis and prevent age- and cigarette smoke-induced emphysema/COPD. The investigators found that TLR4 responsiveness is decreased in older adults and linked to macrophage migration inhibitory factor (MIF), which is a unique regulatory cytokine that is released upon TLR4 stimulation. In collaboration with Dr. Richard Bucala, who identified and cloned functional human MIF gene polymorphisms, they found that low circulating MIF levels and reduced TLR4 expression are associated with cigarette tobacco smoke-related COPD. This suggests that insufficient TLR4-MIF signaling may determine susceptibility to COPD. A FAMRI-supported biorepository of smokers of all ages with and without COPD was used to identify TLR4- and MIF-regulated mechanisms in the lungs that are responsible for injury and repair responses during aging and during cigarette smoke exposure, which are two of the most prevalent risk factors for COPD.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**


**BOOK CHAPTERS, ETC.**


**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 team have shown that SHS exposure reduces host immunity to influenza A virus (IAV) and increases mortality in a mouse model. They have also shown that overexpression of granulocyte-macrophage colony-stimulating factor (GM-CSF) in the lungs protects against community acquired pneumonia such as influenza and primary and secondary necrotizing pneumonia due to *Staphylococcus aureus*. Mortality due to primary and secondary *S. aureus* pneumonia after IAV infection in SPC-GM transgenic mice that overexpress GM-CSF only in the lung was 0%, compared to 100% in wild-type mice. Recently, his team has identified that exposure to SHS impairs efferocytosis of alveolar macrophages (AMs) and that the impairment is due to downregulation of CD16/32 receptors. They have also shown that pulmonary treatment of SHS-exposed mice with inhalation GM-CSF restores efferocytosis of AMs, reduces the inflammation and allows the homeostasis of SHS-exposed and IAV-infected lungs.
FAMRI SUPPORTED RESEARCH

PUBLICATIONS


MATRIX ELASTIN AS A BIOMARKER FOR COPD

Gerard Turino, MD; Columbia University; CIA 2013

Dr. Turino and colleagues are developing a biomarker for COPD that is based on measurement of amino acids specific for elastic tissue degradation in the body and the lung. Amino acids desmosine and isodesmosine exist only in matrix elastin and can be measured specifically and sensitively in plasma, urine, and sputum by mass spectrometry and can indicate changes in the systemic balance between elastase activity and elastase inhibition brought on by the systemic inflammatory state. The lung tissue fragments may contribute to the chronic inflammatory state of the lung and autoimmune mechanisms seen in COPD.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS


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

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

Dr. Shetty and colleagues have shown that tobacco smoke exposure-induced lung injury involves lung epithelial cell damage, lung inflammation, and abnormal fibrin turnover. These changes are clinically relevant in patients with COPD and are associated with symptoms of chronic cough and shortness of breath. Influenza A virus (IAV) infection alone results in 200,000 hospitalizations and 40,000 deaths on an annual basis in the US; people exposed to tobacco smoke are seven times more likely to be infected with IAV. The investigators are studying how p53, a protein that causes lung epithelial cell death, regulates PAI-1, which is an inhibitor of the blood clot dissolution system that influences the viability of the airway and alveolar epithelium. Misregulation of this protein is implicated in increased severity and susceptibility to IAV infection.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS


**PRESENTATIONS AND ABSTRACTS**


**NALP6 IS CRITICAL TO SMOKE-INDUCED INFLAMMATION**

Shanshan Cai, PhD; Louisiana State University; YCSA 2012

Dr. Cai and colleagues have demonstrated that the NALP6 inflammasome is expressed in neutrophils, macrophages, and epithelial cells in human COPD lungs. NALP6 is upregulated in human bronchial epithelial cells and macrophages and mouse airway epithelial cells and macrophages following cigarette smoke (CS) extract challenge. The investigators are elucidating the role of NALP6 in CS-induced lung inflammation and emphysema following 1.5 month (subacute) and 6 month (chronic) CS exposure. They are exploring whether the protein products of inflammasome activation are elevated in COPD patients and smokers without COPD.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**


Cai S, Batra S, Del Piero F, Jeyaseelan S. NLRP12 modulates host defense through IL-17A-CXCL1 axis. *Mucosal Immunol* [Epub 2015 Sep 9].


**PRESENTATIONS AND ABSTRACTS**


**PTP1B REGULATES CIGARETTE SMOKE/RSV ACTIVATED TLRS**

*Patrick Geraghty, PhD; SUNY Downstate; YCSA 2012*

Dr. Geraghty and colleagues have shown that combined cigarette smoke exposure and respiratory syncytial virus (RSV) infection enhances lung injury in mice, accompanied by increased apoptosis, protease production, inflammation, airway remodeling, and reduced phosphatase responses. The team have identified that smoke exposure subdues protein tyrosine phosphatase (PTP1B) responses, which contribute to lung damage. Loss of PTP1B activity enhances expression of S100A9, a damage-associated molecular pattern molecule that contribute to loss of lung function. Dr Geraghty is investigating how S100A9 signaling impacts lung injury and whether targeting S100A9 represents a potential approach to minimizing lung damage in COPD patients.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**


**PRESENTATIONS AND ABSTRACTS**

Geraghty P. Protein tyrosine phosphatase 1B protects the lung during respiratory syncytial viral infection. Presented at the Briscoe Lung Club, Cornell University, New York, NY, Dec 4, 2014.
Geraghty P. An animal model approach to investigate the impact of viral exacerbations on chronic obstructive pulmonary disease progression. Presented at Queen’s University. Belfast, Northern Ireland, United Kingdom, Sep 12, 2014.


ALTERED PROGENITOR-PROGENY RELATIONSHIP IN COPD

Moumita Ghosh, PhD; National Jewish Health; YCSA 2012

Dr. Ghosh and colleagues are investigating epithelial cell progenitor/progeny relationships and how they affect tobacco smoke-induced lung disease. Three progenitor pools maintain the proximal airway epithelium; tissue stem cells (TSC), basal progenitors, and secretory progenitors. In the normal epithelium, the basal progenitor self-renews, whereas the secretory progenitor self-renews and generates ciliated cells. After injury, basal progenitors give rise to both secretory and ciliated cells. The research team has data that indicate that injury alters the source of ciliated cells in the airway. Repeated cigarette smoke-mediated injury transforms secretory progenitors to non-mitotic mucus-producing cells. The team is determining whether a functional epithelium can be restored by TSC and basal progenitors after smoking cessation.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS


**PRESENTATIONS AND ABSTRACTS**


**ROLE OF NLRX1 IN COPD PATHOGENESIS**

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

Dr. Kang and colleagues are comparing the responses of otherwise healthy mice exposed to a mimic of flu virus with or without CS exposure and the mechanism(s) of these exaggerated responses to explain why CS-exposed individuals are more prone to viral infections. The team has conducted studies that show that virus-infected CS-exposed mice suffer from high respiratory inflammation and lung destruction. Some of the signaling pathways that mediate the exaggerated immune responses have been identified, which may point to the mechanisms by which viruses and cigarette smoke interact to increase lung inflammation and damage. These results suggest that the anti-viral responses are hyperactive in CS-exposed lungs in mice. The team is investigating whether lung damage is due to the virus itself or the process of trying to clear the virus.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**


**PROOF OF CONCEPT TRIAL OF A NOVEL THERAPY FOR COPD**

Shyam Biswal, PhD; Johns Hopkins Medical Institutions; CIA 2012

Dr. Biswal and colleagues showed that a pharmacological compound, sulforaphane, enhances the activity of histone deacetylase-2 (HDAC2) in COPD patients. Sulforaphane enables corticosteroids to effectively inhibit inflammation. The team is focusing on developing a proof of concept clinical trial in COPD patients with sulforaphane to test the approach of restoring the efficacy of corticosteroids to inhibit inflammation. The investigators are treating COPD patients with sulforaphane or placebo, then testing the responsiveness of their isolated inflammatory cells to corticosteroids. The results should establish a proof of concept for designing a large-scale clinical trial using a combination of sulforaphane and corticosteroids to treat COPD progression and exacerbation.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**


**ALTITUDE AND SMOKE-INDUCED INFLAMMATION**

Jordan Metcalf, MD; University of Oklahoma; CIA 2012

Dr. Metcalf and colleagues are testing the hypothesis that cabin altitude exposure exacerbates lung inflammation in those exposed to cigarette smoke. The team is investigating whether lung inflammation is accentuated in otherwise healthy smokers in response to altitude exposure, and if the presence of COPD further augments this inflammatory response to cabin altitudes over similarly exposed smokers without COPD. The investigators are studying the inflammatory response to cigarette smoke, the potential cellular sources of that response, and whether there is an increased level of risk associated with altitude exposure routinely
incurred by air passengers and Flight Attendants. They have also examined whether smoke and/or altitude exposure impairs immune responses to influenza virus.

**FAMRI SUPPORTED RESEARCH**

**PRESENTATIONS AND ABSTRACTS**


**OXYGEN (35%) IMPAIRS MURINE MACROPHAGE FUNCTION**

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

Dr. Aggarwal and colleagues are investigating whether low concentrations of oxygen that are beneficial to hypoxic COPD patients may impair alveolar macrophage function and clearance of bacteria. The team is dissecting the underlying mechanisms in a murine model, and determining the effects of low-dose oxygen after cigarette smoke exposure on macrophage function. They are also determining the role of Toll-like receptor 4 signaling in oxygen-induced impairment of macrophage function, and if cell-cell signals can restore this function.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**


CIGARETTE SMOKE IMPAIRS FABP5-MEDIATED BACTERIAL CLEARANCE

Fabienne Gally, PhD; National Jewish Health; YCSA 2011

Dr. Gally and colleagues have shown that fatty acid binding protein 5 (FABP5) is an important anti-inflammatory factor in respiratory infections, which are linked to COPD disease pathogenesis, which in turn are exacerbated by cigarette smoke (CS) exposure. The data indicate that CS exposure decreases FABP5 expression and that overexpression of FABP5 in primary airway epithelial cells protects against bacterial infection and subsequent inflammation. The investigators showed that FABP5 mRNA is decreased in peripheral blood mononuclear cells (PBMCs) of COPD patients as compared to non-COPD patients, in particular among patients that reported flare-up, bronchitis, or pneumonia. It appears that CS exposure contributes to a sustained inflammation in response to bacterial infection by decreasing FABP5 expression. To demonstrate the involvement of FABP5 in COPD, FABP5−/− mice and wild type (WT) controls were subjected to air or CS exposure and inoculated with *P. aeruginosa* or saline. Air-exposed FABP5−/− mice have increased *P. aeruginosa* bacterial load as compared to WT mice. However, CS-exposed FABP5−/− mice have significantly lower bacterial load than WT mice and increased inflammatory cell numbers and cytokines, which correlates with increased neutrophil numbers. The findings suggest that FABP5 confers antimicrobial immunity during COPD exacerbation.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS


PRESENTATIONS AND ABSTRACTS


TOBACCO INDUCED EPIGENETIC ALTERATIONS IN COPD

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

Dr. Hoque and colleagues are investigating the epigenetic alterations of COPD by using Illumina gene expression and methylation arrays to identify a set of signatures that represent epigenetic regulation of COPD pathogenesis. Genes with promoter hypermethylation that are involved in the pathogenesis of COPD will be identified and the timing of methylation changes that occur during COPD progression will be determined. Non-invasive markers for prognosis and early detection are crucial.
because of the large number of people who suffer from COPD due to exposure to SHS.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**


**PRESENTATIONS AND ABSTRACTS**


ROLE OF FRA-1 TRANSCRIPTION FACTOR IN COPD

Michelle Vaz, PhD; Johns Hopkins Medical Institutions; YCSA 2010

Dr. Vaz and colleagues are determining the role of the Fra-1 transcription factor in mediating CS-induced lung inflammatory responses and in the development of COPD. The investigators observed that the induction of inflammatory cytokines following exposure to cigarette smoke condensate (CSC) was markedly lower in macrophages that lack Fra-1 as compared to Fra-1 expressing macrophages. Experimental emphysema was induced in SHS-exposed mice lacking Fra-1 specifically in macrophages. CS-induced lung inflammation in mice lacking Fra-1 in macrophages was significantly lower than that observed in their wild-type counterparts. Further, Fra-1 was found to play a role in the epigenetic regulation of inflammatory gene expression. The team is studying the role of Fra-1 in epigenetic effects on genes that are deregulated in COPD.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS


**PRESENTATIONS AND ABSTRACTS**


**COPD AND SEVERE EMPHYSEMA**

**Neeraj Vij, PhD; Central Michigan University; YCSA 2009**

Dr. Vij and colleagues are studying the proteostasis mechanisms that regulate pathogenesis of CS induced COPD-emphysema. They identified specific proteostasis mechanisms that may play a critical role in determining susceptibility to COPD-emphysema by regulating compensatory pathways that control pathogenesis of emphysema in COPD subjects. Their data suggest that CS exposure controls accumulation of peri-nuclear ubiquitinated protein aggregates (aggresome-bodies) that induces alveolar apoptosis and inflammation as a potential mechanism for the initiation of the loss of alveolar structures in COPD. They found that CS induced acquired-CFTR dysfunction and autophagy-impairment as a mechanism for aggresome-formation. The investigators also evaluated therapeutic efficacy of compounds to correct the CS-induced autophagy-impairment in COPD-emphysema. The potential of aggresome-bodies as prognostic marker for tobacco smoke induced COPD-emphysema disease severity is under investigation.

**FAMRI SUPPORTED RESEARCH**
PUBLICATIONS


**PRESENTATIONS AND ABSTRACTS**


Calfee CS, Ware LB, Glidden DV, Eisner MD, Parsons PE, Thompson BT, Matthay MA. Combining multiple plasma biomarkers improves risk prediction in patients with ALI [abstract]. Am J Respir Crit Care Med 2009;179:A4626. 1


Vij N. Pathogenesis of chronic obstructive lung diseases: mechanisms and therapeutic strategies. Presented at Internal Medicine Grand Rounds, Division of Internal Medicine, St Mary’s and CMED Health, Central Michigan University. Mt Pleasant, MI, May 21, 2015.


Vij N. Proteostasis and inflammatory mechanisms in chronic obstructive lung disease: Challenges and therapeutic strategies. Presented at the Division of
Pulmonary, Allergy & Critical Care Medicine and at the University of Alabama Lung Health Center, University of Alabama. Birmingham, AL, Apr 1, 2010.

Vij N. Signature interdisciplinary programs in allergy, immunology & infectious disease (sipaiid) invited lecture, ubiquitin mediated proteasomal degradation and chronic airway disease pathogenesis. Presented at the University of South Florida. Tampa, FL, May 7, 2009.


BOOK CHAPTERS, ETC.

Vij N. http://wcmu.org/news/?p=13884
Vij N. http://issuu.com/cmlife/docs/2-18-2015_e/1

Newly Funded

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 will determine 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 will be 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 will be able to target those most at risk for exacerbation. They will determine 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.

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 will investigate whether MIF-CD74 is critical in protecting against cigarette smoke-induced COPD, and if MIF-CD74 augmentation can be therapeutic.

**ROLE OF LOWER AIRWAY DYSBIOSIS IN THE DEVELOPMENT OF COPD**

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

Dr. Wu will investigate 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 (pneumotypeSPT) is associated with increased markers of inflammation. He hypothesizes that a disruption of the host microbiome may enhance the damage and inflammation from SHS exposure by enrichment of the oral anaerobes required for the transition from a healthy subject status to a COPD phenotype. He will determine the nature of the contribution of a disrupted lower airway microbiome to a smoke-induced inflammatory process. He will also test if the transfer of SHS-altered microbiota is sufficient to induce airway inflammation, and he will determine if there are direct causative links among airway microbiota, airway inflammation, and the effects of SHS exposure.

**Completed Research**

**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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**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**


Cai S, Batra S, Del Piero F, Jeyaseelan S. NLRP12 modulates host defense through IL-17A-CXCL1 axis. *Mucosal Immunol* [Epub 2015 Sep 9].


PRESENTATIONS AND ABSTRACTS


**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**


**PRESENTATIONS AND ABSTRACTS**


**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**


**PRESENTATIONS AND ABSTRACTS**


**THE THERAPEUTIC POTENTIAL OF Src ANTAGONISTS IN COPD**

**Robert F. Foronjy, MD; Mount Sinai 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**


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


PRESENTATIONS AND ABSTRACTS


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.
PUBLICATIONS


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

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


PRESENTATIONS AND ABSTRACTS


Degar A, Pandit K, Kaminski N, Perry Y, D'Souza MJ, Blumental-Perry A. Cigarette smoke exposure alters mitochondria function by regulating expression of


Kenche H, Brown JA, Blumental-Perry A. One time cigarette smoking (CS) results in oxidation of protein disulfide isomerase (PDI) and induction of unfolded protein response (UPR) [abstract]. Am J Respir Crit Care Med 2012;185;A1262.


**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**


**ROLE OF MMP-12 IN COPD EXACERBATIONS**

**McGarry Houghton, MD; 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.

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


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**


**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**


BOOK CHAPTERS, ETC.


APPROACHES TO CONTROL THE RIG-1-LIKE HELICASE (RLH) PATHWAY

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 subepithelial fibrosis, tissue inflammation, and vascular remodeling with medial hypertrophy.

FAMRI SUPPORTED RESEARCH
PUBLICATIONS


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


**PRESENTATIONS AND ABSTRACTS**


**REGULATION OF TOBACCO SMOKE INDUCED AIRWAY INJURY**

Shreerama 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**


**PRESENTATIONS AND ABSTRACTS**


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


**PRESENTATIONS AND ABSTRACTS**


Kosmider B. Application of transcription factor activation profiling plate array i and phosphokinase array kit to study human alveolar cell response to cigarette smoke


Kosmider B. Human alveolar epithelial cell injury induced by cigarette smoke, Presented at the Basic Science Section Seminar, National Jewish Health. Denver, CO, Apr 20, 2011.


**NRF2- A THERAPEUTIC TARGET FOR COPD EXACERBATION**

**Rajesh Thimmulappa, PhD; Johns Hopkins Medical Institutions; 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.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**


**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**

**PUBLICATIONS**

PRESENTATIONS AND ABSTRACTS


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.

FAMRI SUPPORTED RESEARCH
PUBLICATIONS


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.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS


**PRESENTATIONS AND ABSTRACTS**


Damico RL. Apoptosis and pulmonary pathobiology. Presented at the Division of Pulmonary and Critical Care Medicine, Brown University Medical School, Providence, RI. 2010.
Damico RL. Cell fate and pulmonary vascular disease. Presented at the Lung Research Conference, Division of Pulmonary and Critical Care Medicine, Johns Hopkins University, Baltimore, MD, 2009.


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

**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**


**PRESENTATIONS AND ABSTRACTS**


**BOOK CHAPTERS, ETC.**


**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**

**PUBLICATIONS**


**PRESENTATIONS AND ABSTRACTS**


**BOOK CHAPTERS, ETC.**

Patz S, Muradyan I, Hrovat MI, Dabaghyan M, Washko GR, Hatabu H, Butler JP. Noninvasive measurement of alveolar surface area with magnetic resonance imaging. Lung Health Professional, Nov 2011, COPD Foundation. (www.lunghealthprofessional.org)


**AGING AND 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 alveolar 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**


PRESENTATIONS AND ABSTRACTS


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

PUBLICATIONS


PRESENTATIONS AND ABSTRACTS


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


**CXCL5 IS CENTRAL TO CIGARETTE SMOKE-INDUCED NEUTROPHIL INFUX**

**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**

**PUBLICATIONS**


**PRESENTATIONS AND ABSTRACTS**


**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**


**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 metalloproteinase 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**


**PRESENTATIONS AND ABSTRACTS**


**BOOK CHAPTERS, ETC.**


REDUCED NEUTROPHIL DEATH IN TOBACCO-INDUCED COPD

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

PUBLICATIONS


CIGARETTE SMOKING 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**


**CAN WE PREVENT SEVERE COPD EXACERBATIONS?**

**Ryan Michael McGhan, MD; Alaska Hospitalist Group; 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**


**PRESENTATIONS AND ABSTRACTS**

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


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


PRESENTATIONS AND ABSTRACTS


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.


**PPAR GAMMA AND SUSCEPTIBILITY TO SMOKE-INDUCED COPD**

*Thomas J. Mariani, PhD; 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**


PRESENTATIONS AND ABSTRACTS


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.

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


**PRESENTATIONS AND ABSTRACTS**


**ELASTIN DEGRADATION IN PULMONARY DISEASES**

**Yong Y. Lin, PhD and Gerard Turino, MD; 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 isodesmosine, 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**

Cantor JO, Armand G, Turino GM. Lung hyaluronan levels are decreased in alpha-1 antiprotease deficiency COPD. *Resp Med* 2015;109, 656-659


**PRESENTATIONS AND ABSTRACTS**


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


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


**PRESENTATIONS AND ABSTRACTS**


**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


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 plasminogen activator inhibitor-1 (PAI-1) expression by airway epithelial cells to promote pathophysiological airway remodeling characteristic of COPD. Fibrinolytic pathways, and PAI-1 in particular, are central to the pathogenesis of repair following acute lung injury. He and his team found that airway epithelial cells elaborate PAI-1, that PAI-1 is altered in lung epithelial cells in culture by exposure to cigarette smoke extract, and that PAI-1 is induced in the lung epithelium of mice that were exposed to SHS for 20 weeks. These studies show that regulation of PAI-1 at the posttranscriptional level of mRNA stability contributes to disordered fibrinolysis in the SHS-exposed airway and that PAI-1 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-1 in airway epithelial cells and exposed mice to SHS for 20 weeks to determine whether PAI-1 expression was altered in the lungs after exposure to SHS.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS


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**


**PRESENTATIONS AND ABSTRACTS**


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


RISK FACTORS FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Francine L. Jacobson, MD; Harvard Medical School; 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**


**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**


**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


PRESENTATIONS AND ABSTRACTS


AIRWAY DISEASES AND LUNG INJURY

Ongoing Research

SECONDHAND SMOKE EXPOSURE IMPAIRS IMMUNITY TO LUNG INFECTION

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

Dr. Thanavala and colleagues developed a mouse model to elucidate the connections among tobacco smoke exposure, chronic pulmonary infection, and changes in adaptive immunity. They are investigating the combined effect of SHS exposure and chronic infection on inflammation as well as innate and adaptive immune responses and have shown that both high and low dose SHS exposures augment pulmonary inflammation to non-typeable Haemophilus influenzae (NTHI), a respiratory pathogen often found in COPD patients. Because SHS exposure increases NTHI-mediated chronic respiratory inflammation, the team is investigating whether this inflammatory insult affects the generation and function of NTHI-specific adaptive immunity. Increased numbers of neutrophils, T cells, B cells and dendritic cells (DCs) were also observed, thus the investigators measured antibody responses and found that total anti-P6 antibody levels were significantly decreased in the sera of SHS-exposed mice and found that even though these mice had increased numbers of T cells, B cells, and DCs in the lungs, their function was impaired, leading to an inefficient adaptive immune response resulting in increased inflammation.
**LRP1 IN SMOKE-INDUCED LUNG INFLAMMATION**

*Itsaso Garcia-Arcos, PhD; SUNY Downstate; YCSA 2014*

Dr. Garcia-Arcos and colleagues are investigating the mechanism of action of low density lipoprotein receptor related protein 1 (LRP1) in the lung as an anti-inflammatory target against COPD, using an *in vitro* model of epithelial cells, with and without the expression of LRP1 and exposed to cigarette smoke extract. The activation of inflammatory cascades is being assessed, and the interactions of LRP1 with other proteins, such as membrane receptors, and the intracellular processing of LRP1 subunits are being studied.

**FAMRI SUPPORTED RESEARCH**

**PRESENTATIONS AND ABSTRACTS**


**TSLP AND CIGARETTE SMOKE-INDUCED AIRWAY REMODELING**

*Robert Vassallo, MD; Mayo Clinic; CIA 2013*

Dr. Vassallo and his team are studying 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. The team is using cell culture approaches and an animal model of chronic asthma to investigate these mechanisms. The findings will be used to form the conceptual foundation upon which clinical trials of targeted therapies may be developed for patients with cigarette smoke-induced lung diseases.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**


Vassallo R, Luckey D, Behrens M, Madden B, Luthra H, David C, Taneja V. Cellular and humoral immunity in arthritis are profoundly influenced by the interaction


ASTHMA EXACERBATION INDUCED BY SECONDHAND SMOKE

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

Dr. Forteza and colleagues have investigated the mechanisms involved in asthma exacerbation in individuals exposed to SHS using cultures of human airway epithelial cells and sidestream smoke generated by a smoking robot that mimics real life exposure to SHS. Samples obtained from asthmatics exposed to cigarette smoke were used to confirm that the findings made with the cells are relevant to the disease.

FAMRI SUPPORTED RESEARCH

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.

A 3-GENE SIGNATURE IN SMOKING EXPOSURE AND ASTHMA

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

Dr. Gomez-Villalobos and colleagues have 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. The data from sputum induction in asthmatics has been stratified by prior SHS exposure, and several candidate genes that may play a role at the intersection between SHS and asthma have been identified, including genes for the purinergic receptor P2Y (P2RY14), the nicotinic acid receptor 2 (HCAR3), and the CHI3L1 gene, which is associated with asthma severity. The team is investigating if the 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. The team is also determining if these genes are associated with a specific clinical asthma phenotype.

FAMRI SUPPORTED RESEARCH
PUBLICATIONS


PRESENTATIONS AND ABSTRACTS


SMOKING, MITOCHONDRIAL DYSFUNCTION AND ASTHMA

Bharathi Aravamudan, PhD; Mayo Clinic Rochester; YCSA 2012

Dr. Aravamudan and colleagues are investigating whether cigarette smoke (CS), acting via reactive oxygen species (ROS), modulates mitochondrial fission vs. fusion by increasing mitochondrial fragmentation. The team is determining if these changes result in impaired mitochondrial calcium buffering (thus enhancing bronchoconstriction) and altered balance between airway smooth muscle (ASM) proliferation vs. death, which is relevant to remodeling.


**PRESENTATIONS AND ABSTRACTS**


EPGENOMIC ALTERATIONS ASSOCIATED TO SHS IN ASTHMA
Rafael Guerrero-Preston, DrPH; Johns Hopkins Medical Institutions, CIA 2012

Dr. Guerrero-Preston is addressing the role of secondhand tobacco smoke 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.

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 is investigating 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.

FAMRI SUPPORTED RESEARCH
PUBLICATIONS


Martin RA, Ather JL, Daggert R, Hoyt L, Alcorn JF, Suratt BT, Weiss DJ, Lundblad LK, Poynter ME. The endogenous Th17 response in NO2-promoted allergic airway
disease is dispensable for airway hyperresponsiveness and qualitatively distinct from Th17 adoptive transfer. *PLoS One* 2013;8(9):e74730.


**PRESENTATIONS AND ABSTRACTS**


Burgess EJ, Boyson JE Poynter ME. Marker or mediator? Discerning the function of serum amyloid A during inflammatory disease. Presented at the Northern New York Local Section of the American Chemical Society 5th Annual Undergraduate and Graduate Chemistry and Biology Research Symposium, SUNY. Plattsburgh, NY, Apr 26, 2014.


Poynter ME. The airway epithelium in allergic and intrinsic asthma. Presented at the Department of Comparative Veterinary Sciences seminar series, Louisiana State University School of Veterinary Medicine. Baton Rouge, LA, Dec 10, 2015.


**ESTROGEN, CIGARETTE SMOKE AND AIRWAY DISEASE**

Venkatachalem Sathish, PhD; Mayo Clinic; YCSA 2011

Dr. Satish and colleagues are exploring the mechanism of estrogen action on the airway and its disruption by cigarette smoke exposure. Cigarette smoking and SHS
exposure are associated with increased prevalence of airway diseases such as asthma, bronchitis, rhinitis, and sinusitis. Women may be biologically more susceptible to exposure than men when it comes to incidence of and complications from smoking-related airway diseases. The team is investigating the mechanisms by which sex steroids normally modulate airway tone, to develop a better understanding of gender differences in smoking-induced diseases.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**


**PRESENTATIONS AND ABSTRACTS**


Sathish V, Townsend MA, Aravamudan B, Pabelick CM, Prakash YS. Airway smooth muscle-derived BDNF potentiates inflammation effects on airway remodeling [abstract]. *Am J Respir Crit Care Med* 2014;189;A5317.


**BOOK CHAPTERS, ETC.**


**SECONDHAND SMOKE AND MYELOID CELLS IN ASTHMA**

Jessy Deshane, PhD; University of Alabama at Birmingham; YCSA 2011

Dr. Deshane and colleagues are investigating whether SHS exposure reduces the ability of myeloid-derived regulatory cells (MDRC) to regulate asthmatic inflammation. 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 are isolating MDRC from non-smoking subjects; from blood and from lungs using bronchoalveolar lavage. Biomarkers and fluorescent molecules are being used to identify subtypes of MDRC that make free radicals and cytokines. The investigators are also testing the effect of SHS exposure on the ability of similar types of cells cultured from bone marrow of mice to regulate inflammatory responses and affect experimental asthma.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**

Trevor JL, Deshane JS. Refractory asthma: mechanisms, targets and therapy. Allergy 2014;69(7):817-827.


PRESENTATIONS AND ABSTRACTS


IMPACT OF SHS ON CHILDREN WITH SICKLE CELL DISEASE

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

Dr. Cohen and colleagues are examining the impact of SHS exposure on a young cohort with sickle cell anemia and are evaluating the impact of SHS exposure by testing the association between reported and objective measures of exposure. The investigators are doing studies to identify a modifiable risk factor for health problems and death among patients with sickle cell disease. If SHS exposure is associated with an increase in morbidity, the investigators will develop and test an intervention strategy to reduce SHS exposure and asthma-related morbidity in families with sickle cell disease.

IMMUNE FUNCTION OF ALVEOLAR EPITHELIAL CELLS

Min Wu, MBBS, PhD; University of North Dakota; CIA 2011

Dr. Wu and colleagues are investigating the molecular mechanism that makes passive and active smokers more susceptible to Pseudomonas aeruginosa (PA) infection, an outcome that is strongly associated with bronchitis, sinusitis, asthma,
and COPD. The team is focusing on alveolar macrophages (AM), which constitute the first line of host defense against bacteria in the lung. The team is also investigating the immune function of alveolar epithelial type II cells (AECII) in PA clearance. AM function is unable to suppress PA infection, particularly in passive smokers, thus the investigators are identifying which AECII-secreted cytokines boost anti-microbial defense against PA. They are also defining the mechanism that controls the secretion of immunity-boosting cytokines by AECII and determining the role of cytokine-activated AM in bacterial clearance.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**


**Completed Research**

**C/EBP ALPHA: NOVEL THERAPEUTIC TARGET FOR ASTHMA**

Elena Levantini, PhD; Harvard Medical School; 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**

**PUBLICATIONS**


PRESENTATIONS AND ABSTRACTS


Levantini E. Out of the ashes. A research career soars with Flight Attendant’s Funding. Giving matters Presented at the Beth Israel Deaconess Medical Center. 2012.

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.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS


Koru-Sengul T, Clark JD, Ocasio MA, Wanner A, Fleming LE, Lee DJ. Utilization of the National Health and Nutrition Examination Survey (NHANES) for symptoms,


**PRESENTATIONS AND ABSTRACTS**


Koru Sengul T, Clark JD, Fleming LE, Lee DJ. A Comparison of techniques for analyzing left-censored biomarker data with application to secondhand smoking research. Presented at the Annual Zubrod Memorial Lecture and Cancer Research Poster Session. Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, Miami, FL. May 13, 2011.


Koru-Sengul T. Out of sight, not out of mind: Missing data. Presented at the Biostatistics Clinic, Biostatistics Collaboration and Consulting Core Division of Biostatistics at the Department of Epidemiology and Public Health, Miller School of Medicine, University of Miami. Miami, FL, Sept 13, 2011.


**COMPLEMENT MEDIATED EXACERBATION OF ASTHMA BY SHS**

Gary Gilkeson, MD; Medical University of South Carolina; 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**

**PUBLICATIONS**


**PRESENTATIONS AND ABSTRACTS**


Casey S, Qiao F, Williamson T, Gilkeson G, Tomlinson S, Atkinson C. Complement anaphylatoxins, C3a and C5a, enhanced pro-inflammatory cytokine production


**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**


**PRESENTATIONS AND ABSTRACTS**


**SMOKING AND THE PATHOGENESIS OF ASTHMA**

*Joseph DiDonato, PhD; Cleveland Clinic; 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 smoking and asthma pathogenesis in humans.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**

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

PUBLICATIONS


PRESENTATIONS AND ABSTRACTS

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.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS


**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 studies indicate 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**


**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**


Hansel NN, Sidhaye V, Rafaei NM, Gao L, Gao P, Williams R, Connet JE, Beaty TH, Mathias RA, Wise RA, King LS, Barnes KC. Aquaporin 5 polymorphisms and rate of


**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 the major anti-viral cytokine IFN-beta mRNA 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**


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


Duan M, Yturralde O, Calfee CS. Biomarkers of tobacco exposure are more sensitive than smoking history in critically ill adults. Am J Respir Crit Care Med 2009;179:A5873.


PRESENTATIONS AND ABSTRACTS


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 that 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.

**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-Scan®) and a multispectral cytometer (FACSAria®). 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**


**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**


**SECONDHAND 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 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 pro-apoptotic protein Bax.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**


**PRESENTATIONS AND ABSTRACTS**


**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 Lumimx100 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**
FAMRI Supported Research

PUBLICATIONS


PRESENTATIONS AND ABSTRACTS


LUNG CANCER SUSCEPTIBILITY AND CHEMOPREVENTION

Shyam Biswal, PhD; Johns Hopkins Medical Institutions; 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


**CANCER: LUNG**

**Completed Research**

**INFLAMMATORY ROLE FOR LKB1 TUMOR SUPPRESSOR IN LUNG CANCER**

Edward Ratovitski, PhD; Johns Hopkins Medical Institutions School of Medicine; 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.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**


**MCL-1 IS A NICOTINE TARGET 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**

**PUBLICATIONS**


INFLAMMATION AND STEM CELLS IN SMOKE INDUCED LUNG CANCER

May-Lin Wilgus, MD; Baylor College of Medicine; YCSA 2009

Dr. Wilgus and 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


**PRESENTATIONS AND ABSTRACTS**


**BOOK CHAPTERS, ETC.**


**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**

**PUBLICATIONS**


PRESENTATIONS AND ABSTRACTS


BOOK CHAPTERS, ETC.


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.
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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PUBLICATIONS


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**


**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) are 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**


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


PRESENTATIONS AND ABSTRACTS


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


**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**


**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.

**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**


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 SCLC and 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 aldehyde dehydrogenase (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


DEVELOPING NRF2 INHIBITORS FOR CANCER CHEMOTHERAPY

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

FAMRI SUPPORTED RESEARCH

PUBLICATIONS


**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 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 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**


**PRESENTATIONS AND ABSTRACTS**


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
PUBLICATIONS

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 inhibition of DNA methyl transferases (DNMTs) and histone deacetylases (HDACs) synergistically induces 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, 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


**PRESENTATIONS AND ABSTRACTS**


**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 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 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


COMBINATION AD.P53-DC IMMUNOTHERAPY/CHEMOTHERAPY FOR SCLC
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.

ANALYSIS OF DNA REPAIR CAPACITY TO PREDICT AND TARGET CHEMORESITANT 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


BOOK CHAPTERS, ETC.
LUNG ADENOCARCINOMA PROGRESSION: MARKERS AND MEDIATION BY CIGARETTE SMOKES 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 and partially inhibits progression. The investigators concluded that loss of TBRII in vivo promotes tumor progression, invasion, and metastasis.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS


PRESENTATIONS AND ABSTRACTS

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; Harvard Medical School; 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.

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**PRESENTATIONS AND ABSTRACTS**


Levantini E. C/EBP alpha acts as tumor suppressor in lung by inhibiting the protooncogene Bmi-1. Presented at the BIDMC Pulmonary Division Research Seminar Series Beth Israel Deaconess Medical Center. Boston, MA, Jan 31, 2013.


Levantini E. Runx1 regulates human CD34 expression in hematopoietic stem cells. Presented at the Beth Israel Deaconess Medical Center, Center for Life Science Building. Boston, MA, May 12, 2009.


**TGF BETA SIGNALING IN LUNG CANCER: A THERAPEUTIC TARGET**

**Pran Datta, PhD; Vanderbilt University; 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**


**BOOK CHAPTERS, ETC.**


**NICOTINE REGULATION OF BAX'S PROAPOPTOTIC FUNCTION IN HUMAN LUNG**

Xingming Deng, MD, PhD; Emory University; 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**


**THE ROLE OF MICRO RNA 125A-3P IN THE PATHOGENESIS OF LUNG CANCER**

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-ras-mutated HBECs compared to 1.8-fold in the control cells.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**


PRESENTATIONS AND ABSTRACTS


EFFECTS OF PTHrP ON LUNG CANCER SURVIVAL IN WOMEN

Randolph Hastings, MD, PhD; Veterans Medical Research Foundation; 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


**PATTERNS OF GENE EXPRESSION IN EARLY LUNG LESIONS**

**Scott Wadler, MD (1946-2007); 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 adenocarcinomas, and one subclass of metastatic adenocarcinomas. 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**

**PUBLICATIONS**


**PRESENTATIONS AND ABSTRACTS**


METHYLATION ANALYSIS OF LUNG CANCERS FROM SMOKING AND NONSMOKING WOMEN

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
PUBLICATIONS


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


**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**


**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**

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; 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


PRESENTATIONS AND ABSTRACTS


THE SMALL MOLECULE INHIBITORS OF BCL-2 AS NOVEL THERAPEUTICS FOR LUNG CANCER

Charles M. Rudin, MD, PhD; University of Chicago; 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), 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


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.

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PUBLICATIONS


TRANSGENIC ANIMAL MODEL TO CONTROL THE ANGIGENIC SWITCH IN LUNG CANCER

Douglas A. Arenberg, MD; University of Michigan; CIA 2004

Dr. Arenberg’s lab 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


PRESENTATIONS AND ABSTRACTS


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. Reinroduction 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.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**


**PRESENTATIONS AND ABSTRACTS**


BOOK CHAPTERS, ETC.


SMOKING, POLYMORPHISMS, AND LUNG CANCER PROGNOSIS

Wei Zhou, MD, PhD; Harvard Medical School; 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


**PRESENTATIONS AND ABSTRACTS**


TARGETING THE ESTROGEN RECEPTOR AND EPITHELIAL GROWTH FACTOR 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


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


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


THE ROLE OF HMG-1/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**


**ROLE OF IRF-5 AS A TUMOR SUPPRESSOR IN A NON-SMALL CELL LUNG CANCER (NSCLC)**

Betsy J. Barnes, PhD; Rutgers, The State University 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**


**IDENTIFICATION OF NEW MOLECULAR TARGETS IN LUNG CANCER**

Pierre P. Massion, MD; Vanderbilt University; 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.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**


**ROLE OF ALDEHYDE DEHYDROGENASES 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


PKC-EPISILON 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


NUCLEOLAR EXPRESSION OF PTHrP AND OUTCOME IN NON-SMALL CELL LUNG CANCER (NSCLC)

Leonard Deftos, MD, JD; 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


Pache JC, Burton DW, Deftos LJ, Hastings RH. A carboxyl leucine-rich region of parathyroid hormone-related protein is critical for nuclear export. *Endocrinology* 2006;147:990-998.


**THE ROLE OF BC1-2 IN NICOTINE-INDUCED SURVIVAL SIGNALING AND CHEMORESISTANCE IN HUMAN LUNG CANCER CELLS**

**Xingming Deng, MD, PhD; Emory University; 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**


**DEVELOPMENT OF A TUMOR VACCINE FOR LUNG CANCER**

**Scott Antonia, MD; University of South Florida; 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.

**LOH AND GENE EXPRESSION PROFILES IN LUNG CARCINOMA**

**Matthew Meyerson, MD, PhD; Harvard Medical School; 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


THE MOLECULAR EPIDEMIOLOGY OF SECONDHAND TOBACCO SMOKE-ASSOCIATED LUNG CANCER

David P. Miller, ScD; Harvard Medical School; YCSA 2002

Dr. Miller collected samples and assessed the secondhand tobacco smoke (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


**PRESENTATIONS AND ABSTRACTS**


**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 (Ptc) 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, Ptc, 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


CANCER: BREAST

Ongoing Research

UNIVERSITY OF MIAMI BREAST CANCER PROGRAM

Director: Joyce Slingerland, MD, PhD; University of Miami Miller School of Medicine; 2014

FAMRI has funded three exploratory investigations in breast cancer.

MECHANISTIC CONSEQUENCES OF KAT3 LOSS IN BREAST CANCER

Nanette H. Bishopric, MD

High-throughput sequencing of cancer genomes has revealed that a single breast cancer cell may harbor a thousand separate mutations; a few of which are mutations that enforce the growth of the tumor, allowing cancer cells to mutate to escape normal growth controls and to metastasize to other parts of the body. Dr. Bishopric and colleagues have used in silico analysis of very large cancer data sets from the Cancer Genome Atlas (TCGA) consortia to demonstrate the importance of EP300 loss across multiple breast cancer subtypes, which may play a role in the earliest steps of mammary epithelial transformation. The team is performing *in vitro* studies...
in primary human mammary epithelial cells rather than in existing breast cancer lines, with the hope that this approach will provide more robust information.

**GENETIC ANALYSIS OF THE ROLE OF GATA 3 IN BREAST TUMORIGENESIS**

**Xin-Hai Pei, MD, PhD**

Dr. Pei characterized p18;Gata3 compound mutant mice and found that 1 of 2 p18/−; G3/−; MC and 3 of 6 p18/−; G3+/− mice developed mammary tumors, which were heterogeneous in cell shape and expression of Gata3, Ck5, Ck8, and epithelial-mesenchymal transition (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.

**ID OF SMALL MOLECULE EPIGENETIC MODULATORS OF CD 24 SUBPOPULATIONS IN TRIPLE NEGATIVE BREAST CANCER CELLS**

**Claes Wahlested, MD, PhD**

Triple-negative breast cancers (TNBC) are highly aggressive tumors with visceral metastasis, poor prognosis, and a high tendency to develop chemoresistance. They do not express the typical breast cancer receptors: estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER2). Dr. Wahlested is investigating therapeutic compounds that can serve to target TNBCs.

**Completed Research**

**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 CYP2A13-mediated metabolic activation of tobacco-specific nitrosamine 4-(methylamino)-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.
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


Li H, Baldwin BR, Zahnow CA. LIP expression is regulated by IGF-1R signaling and participates in suppression of anoikis. Mol Cancer 2011;10:100.


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
etiological basis for SHS-induced breast carcinogenesis, the studies were useful in pinpointing events leading to the development of aggressive tumors.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS


PRESENTATIONS AND ABSTRACTS


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 Nrf2-dependent 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


PRESENTATIONS AND ABSTRACTS


Zhou Q, Eades G, Yao, Y. Epigenetic activation of miR-200a targets the Nrf2-dependent chemoprevention pathway in breast cancer [abstract]. Presented at American Association for Cancer Res Conference. Chicago IL, Mar 31-Apr 4, 2012.

BOOK CHAPTERS, ETC.


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. RNA-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


**PRESENTATIONS AND ABSTRACTS**


**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 nontelomeric 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**


**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


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


Meng S, Arbit T, Veeriah S, Mellinghoff IK, Rohle D, Vivanco I, Chan TA. 14-3-3s and p21 synergize to determine DNA damage response following Chk2 inhibition. *Cell Cycle* 2009;8:2238-2246.


**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**

**PUBLICATIONS**


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 (HMG-A) gene family, which encodes chromatin binding proteins that regulate gene expression. It has been shown that HMG-A genes are overexpressed in metastatic breast cancer cells and high-grade lung cancers. The team investigated whether HMG-A1α (formerly HMG-I), which is induced by estrogen, is also induced by SHS. HMG-A 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 HMG-A gene expression and SHS exposure correlate with more aggressive breast cancer and if breast cancer growth can be inhibited by blocking expression of HMG-A genes.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS


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 videomicroscopy 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


Lera RF, Burkard ME. The final link: tapping the power of chemical genetics to connect the molecular and biologic functions of mitotic protein kinases [review]. Molecules 2012;17(10): 12172-12186.


PRESENTATIONS AND ABSTRACTS


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.

FAMRI SUPPORTED RESEARCH
PUBLICATIONS


PRESENTATIONS AND ABSTRACTS


NICOTINE: SIGNALING AND MITOGENESIS IN THE BREAST
Chang-Yan Chen, MD, PhD; Beth Israel Deaconess Medical Center; 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 resistant 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**

**PUBLICATIONS**


THE EFFECTS OF SECONDHAND SMOKING ON SENSITIVITY TO CHEMOTHERAPEUTIC TREATMENT IN BREAST CANCER CELLS

**Shalom Avraham, MD, PhD; Harvard Medical School; 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.

**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 metallocproteinase. 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.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**


Mukherjee S, Das SK. Activation of metallocproteinase in breast epithelial cells by direct and secondhand cigarette smoke. FASEBJ 2009;23:695.3.


Schaeffer MW, Sinha Roy S, Mukherjee S, Nohr D, Wolter M, Biesalski HK, Ong DE, Das SK. Qualitative and quantitative analysis of retinol, retinyl esters, tocopherols and selected carotenoids out of various internal organs from different species by HPLC. *Anal Methods* 2010;2:1320-1332.


**PRESENTATIONS AND ABSTRACTS**

Das SK, Mukherjee S. Molecular mechanism of breast cancer development by cigarette smoke exposure. Presented at the International Heart Congress. Chongqing, China, Apr 22-23, 2011.

Das SK. Peripheral benzodiazepine receptor, a biomarker for breast cancer. Presented at the 96th Indian Science Congress. Shillong, Meghalaya, India, Jan 3-7, 2009.


**BOOK CHAPTERS, ETC.**


**ACTIVATION OF DDX3 BY BENZO[APYRENE 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

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**


**PRESENTATIONS AND ABSTRACTS**


**A2A RECEPTOR ANTAGONISM AS A NOVEL MEANS TO ENHANCE VACCINE THERAPY FOR THE TREATMENT AND PREVENTION OF BREAST CANCER**

Jonathan D. Powell, MD, PhD; Columbia University; 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.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**


**AN MVA VACCINE TARGETING P53 IN BREAST CANCER**

**Joshua Ellenhorn, MD; City of Hope; 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**

**PUBLICATIONS**


**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**

**PUBLICATIONS**


**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**

**PUBLICATIONS**


**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**

**PUBLICATIONS**


**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 downregulation 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 histidinelysine polymer nanoparticle-encapsulated siRNA. This treatment resulted in marked inhibition of tumor growth.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**


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-1alpha and/or HIF-2alpha 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-2alpha counteracts the tumor promoting effects of a component of tobacco smoke, nitrosamine 4-(methylamino)-1-(3-pyridyl)-1-butanone, and they determined if HIF-2alpha expression correlates with breast stem cell markers and poor prognosis among smokers and nonsmokers. Expression was analyzed of HIF-2alpha, 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

PUBLICATIONS


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 mainstream 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.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**


**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**


**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**


FAMRI Supported Research


BOOK CHAPTERS, ETC.


**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**


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.

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


Jaiswal AS, Balusu R, Armas ML, Kundu CN, Narayan S. Adenomatous polyposis coli (APC) interacts with flap endonuclease 1 (Fen-1) and blocks its cleavage activity in base excision repair. Proc Am Assoc Cancer Res 2006;1068A.


**PRESENTATIONS AND ABSTRACTS**


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.

CANCER: HEAD AND NECK

Ongoing Research

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

PUBLICATIONS


**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**

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


PRESENTATIONS AND ABSTRACTS


DEVELOPMENT OF PKC EPSILON INHIBITORS FOR TREATING HEAD AND NECK CANCER

Quintin Pan, PhD; Ohio State University; 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


EPGENETIC ALTERATIONS IN PROGRESSION OF ESOPHAGEAL 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


PRESENTATIONS AND ABSTRACTS

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 juxtamembrane (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.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS


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**


and female odds ratios by BMI, cigarette smoking, and alcohol consumption for cancers of the oral cavity, pharynx, and larynx in pooled data from 15 case-control studies. *Cancer Cause Control* 2011;22(9):1217-1231.


**PRESENTATIONS AND ABSTRACTS**


**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**


DETECTION OF PREMALIGNANT LESIONS IN THE ORAL CAVITY INDUCED BY TOBACCO RELATED CARCINOGENS

Yuman Fong, MD; Memorial-Sloan Kettering Cancer Center; CIA 2007

Dr. Fong’s group and other investigators have shown that genetically engineered herpes simplex viruses (HSV) 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**


**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 result 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**


**SMOKING-GENE-ENVIRONMENT INTERACTIONS IN ESOPHAGEAL ADENOCARCINOMA**

Rihong Zhai, MD, PhD; Harvard Medical School; 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 smoking, 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**


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


BOOK CHAPTERS, ETC.

CHRONIC CIGARETTE SMOKE EXTRACT TREATMENT SELECTS FOR APOPTOTIC DYSFUNCTION AND MITOCHONDRIAL MUTATIONS IN MINIMALLY TRANSFORMED ORAL KERATINOCYTES

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


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

PUBLICATIONS


ERYTHROPOIETIN SIGNALING IN HEAD AND NECK CANCER

Stephen Y. Lai, MD, PhD; 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


**ROLE OF EPIDERMAL GROWTH FACTOR RECEPTOR (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/Erk1/ 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**


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


Kornberg LJ, Grant MB. Adenoviruses increase endothelial cell proliferation, migration, and tube formation: partial reversal by the focal adhesion kinase inhibitor, FRNK. *Microvasc Res* 2007;73(3):157-162.


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**


**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**


**PRESENTATIONS AND ABSTRACTS**


**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**


GENOMIC ANALYSIS OF URINE TO DETECT BLADDER CANCER
Charles J. Rosser, MD, MBA; University of Texas M.D. Anderson Cancer Center Orlando; 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
PUBLICATIONS


**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**

**PUBLICATIONS**


THE EFFECT OF ADENYLATE KINASE 3 ON TOBACCO SMOKE-INDUCED CISPLATIN 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


**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.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**


**BOOK CHAPTERS, ETC.**

THE GPI TRANSAMIDASE COMPLEX SUBUNITS AS ONCOGENES IN BLADDER CANCER

Barry Trink, PhD; 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

PUBLICATIONS


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


**PRESENTATIONS AND ABSTRACTS**


Demokan S, Chang X, Chuang A, Brait M, Hoque MO, Sidransky D, Koch W, Califano J. Methylation of the KIF1A and EDNRB genes is a frequent event in head and neck
ROLE OF SHS ON SOMATIC ALTERATIONS IN BLADDER CANCER

Carmen J. Marsit, PhD; Geisel School of Medicine at Dartmouth; YCSA 2006

Dr. Marsit and colleagues examined the somatic molecular profile of individuals to determine how 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 cancer. Presented at the Annual Meeting of the American Association for Cancer Research. San Diego, CA, Apr 12-16, 2008.


profiles of gene-specific methylations that can be detected in peripheral blood and can serve as sensitive and specific markers of bladder cancer.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**


Maccani MA, Avissar-Whiting M, Banister CE, McGonnigal B, Padbury JF, Marsit CJ. Maternal cigarette smoking during pregnancy is associated with downregulation of miR- 16, miR-21, and miR-146a in the placenta. *Epigenetics* 2010;5(7).


**PRESENTATIONS AND ABSTRACTS**


**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**


**PRESENTATIONS AND ABSTRACTS**


**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**


**PRESENTATIONS AND ABSTRACTS**

Kamat A. Optimizing responses to Bacillus Calmette Guérin for non-muscle invasive bladder cancer: role of inflammation and cytokine biomarkers. Presented at the


**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 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 modifies 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 PIG-U 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**


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.

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, 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

THE GPI TRANSAMIDASE COMPLEX SUBUNITS AS ONCOGENES IN BLADDER CANCER

**Barry Trink, PhD; 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**


**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 SUPPOR TED RESEARCH

PUBLICATIONS


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


**PRESENTATIONS AND ABSTRACTS**


**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**

**BOOK CHAPTERS, ETC.**


**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


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

GENETIC SUSCEPTIBILITY TO CERVICAL CANCER IN SECONDHAND TOBACCO SMOKERS

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**

Naseruddin 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**


**PRESENTATIONS AND ABSTRACTS**


**NDRG1 MODULATION TO DECREASE PROSTATE CANCER INVASION**

**Sushant K. Kachhap, PhD; Johns Hopkins Medical Institutions; YCSA 2007**

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**


**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**


**PRESENTATIONS AND ABSTRACTS**


**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**


**INHIBITION OF HEDGEHOG SIGNALING BY CYCLOPAMINE PRODRUG FOR PROSTATE CANCER**

**Aniriban Maitra, MBBS; 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**


**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


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; 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


**PRESENTATIONS AND ABSTRACTS**


**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 such as BRAF and Ras mutations, and gene methylation in thyroid cancer 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**


Xing M. BRAF mutation is not a germline mutation in familial papillary thyroid cancer. *Clin Endocrinol* 2005;63:263-266.

**CANCER: LYMPHOMA**

**Completed Research**

**TRANSFORMED FOLLICULAR LYMPHOMA: SMOKE RELATED?**

Ronald B. Gartenhaus, MD; 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**

Akulapalli Sudhakar, PhD; Boys Town National Research Hospital; YCSA 2007

Dr. Sudhakar and colleagues developed a fusion protein called combostatin, comprising the functional regions from known antiangiogenic molecules; endostatin type XVIII collagen noncollagenous (NC1) domain, and α1 and α3 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(V)NC1) showed that regulation of COX-2 is dependent on integrin α3β1. The investigators focused on understanding the functional nature of the parent molecules by *in vitro* and *in vivo* studies.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**


**PRESENTATIONS AND ABSTRACTS**


Sudhakar A. Angioinhibitory mechanisms of type IV collagen derived endogenous angioinhibitors. Presented at University of Nebraska Medical Center, Department of Biochemistry and Molecular Biology. Omaha, NE, Feb 22, 2010.

Sudhakar A. Regulation of tumorangiogenesis by extra cellular matrix derived angioinhibitors. Presented at the Department of Biochemistry, University of Hyderabad. Hyderabad, India, Mar 5, 2010.


BOOK CHAPTERS, ETC.


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**


**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 previously available methods. 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**

**PUBLICATIONS**


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**


**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.


**SIGNAL-SMART 1 (SS1) VIRUS TARGETS SHS RAS OVER ACTIVATED CELLS IN A CELL SPECIFIC MANNER**

Faris Farassati, PhD, PharmD; University of Kansas; 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 demonstrate 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**


**PRESENTATIONS AND ABSTRACTS**


Farassati F. Molecular targeting of prostate cancer. Presented at the Nevada Cancer Institute, Prostate Cancer Research Core. Las Vegas, NV, 2011.


Farassati F. Targeting cancer stem cells with oncolytic viruses. Sixth International Conference on Oncolytic Viruses as Cancer Therapeutics. Las Vegas, NV, Mar, 2011.


Farassati F. Targeting head & neck cancer with oncolytic viruses. Presented at Yale University, Department of ENT. New Haven, CT, Jul 18, 2014.

Farassati F. Transcriptional Targeting of CD133+ Cancer stem cells by oncolytic viruses. Presented at the Seventh International Meeting on Replicating Oncolytic Virus Therapeutics. Quebec City, Quebec, Canada, Jun 15-18, 2013.


BOOK CHAPTERS, ETC.


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

PUBLICATIONS

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

PUBLICATIONS

PRESENTATIONS AND ABSTRACTS

SOMATIC CELL KNOCK-IN OF A MUTANT K-RAS GENE FOR UNDERSTANDING AND TARGETING RAS-INDUCED CANCERS RELATED TO SECONDHAND TOBACCO SMOKE
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

PUBLICATIONS


**THE IMPACT OF SWI/SNF COMPLEX IN CANCER**

**David N. Reisman, MD, PhD; University of Florida; 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 brahmarelated 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**

**PUBLICATIONS**


**THE ROLE OF LYSINE HISTONE METHYLTRANSFERASE SET 7/9 IN BREAST CANCER**

**Nickolai A. Barlev, PhD; Tufts-New England Medical Center; CIA 2005**

Dr. Barlev and collaborators discovered a mechanism, through lysine methylation, by which p53 is upregulated in response to DNA damage. 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**


**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 sidestream 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**


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. They 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 potentely 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

PUBLICATIONS


Wilsker D, Petermann E, Hellday T, Bunz F. Essential function of Chk1 can be uncoupled from DNA damage checkpoint and replication control. Proc Natl Acad Sci U S A 2008;105:20752-20757.

BOOK CHAPTERS, ETC.

MODULATION OF TUMOR RESPONSE TO RETINOIDS

Roberto Pili, MD; Roswell Park Alliance Foundation; 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


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


MRN-TARGETED CHEMOSENSITIZATION FOR ORAL CANCER

Daqing Li, MD; University of Pennsylvania; YCSA 2002

Dr. Li and colleagues hypothesized that targeted impairment of the native cellular repair machinery MRN complex function 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


**PRESENTATIONS AND ABSTRACTS**


**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

PUBLICATIONS


CANCER: TREATMENT

Newly funded

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 nanotechnology to advance the specificity and pharmacokinetics of these viruses.

Completed Research

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

PUBLICATIONS


**LUNG CANCER IMMUNOTHERAPY**

*Luis Raez, MD; University of Miami; 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 A1 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 MYELOABLATIVE ALLOGENIC 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

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
PUBLICATIONS


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 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 cyclooxygenase-2 (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


**CARDOVASCULAR AND VASCULAR**

**Ongoing 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 are investigating 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 kinase 1/2 (ERK1/2) on inflammatory mediators and found cross-talk, 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 investigators are determining how early the MEK-ERK1/2 inhibition affects stroke-induced changes in arterioles and interactions with neurons and glia cells.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**


**SHS AND ATHEROSCLEROSIS**

Anna Kurdowska, PhD; University of Texas Health Science Center; 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**

**CARDIOVASCULAR EFFECTS OF SECONDHAND TOBACCO SMOKE (SHS) IN CONSTRUCTION WORKERS**

**Jennifer Cavallari, ScD, CIH; University of Connecticut; YCSA 2009**

Dr. Cavallari and colleagues are examining the acute cardiovascular effects of SHS and workplace exposures among non-smoking, union, boilermaker construction workers. The team investigated whether levels of inflammatory cytokines or adhesion molecules differed by participant characteristics such as age, body mass index, and statin use. The team also investigated whether levels of inflammatory cytokines or adhesion molecules differed by urinary cotinine levels. Further, the team investigated whether lower heart rate variability during the measurement period was associated with higher levels of inflammatory cytokines or adhesion molecules. However, no significant (p<0.05) associations or trends were observed. Previously, Dr. Cavallari’s team identified increases in post-shift inflammatory markers, including white blood cells, platelets, and neutrophils following exposure to SHS. The team also demonstrated changes in heart rate variability indices associated with SHS-related fine particulate matter (PM$_{2.5}$) moving averages of different durations between 15-240 minutes.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**


**PRESENTATIONS AND ABSTRACTS**


**Completed Research**

**TREATMENTS OF EXPOSURE TO SECONDHAND SMOKE**

**Lars Edvinsson, MD, PhD; Lund University; 2011**

Sustained benefits due to smoking abstinence were seen in a large Danish patient cohort 5 years after discontinuation of a multi-factorial life style intervention. A study was undertaken to investigate whether surfactant protein D (SP-D) is important in the cardiovascular response to SHS. Mice lacking the SP-D gene were shown to develop severe emphysema and lung damage when compared to controls. SHS exposure results in enhanced transcription of G protein-coupled contractile receptors in vascular beds such as heart and brain. The signaling pathway Ras-Raf-MEK-ERK1/2 plays a crucial role, and the investigators showed that treatment with Raf or MEK inhibitors can block or reverse this process.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**

Ahnstedt H, Stenman E, Cao L, Henriksson M, Edvinsson L. Cytokines and growth factors modify the upregulation of contractile endothelin ET(A) and ET(B) receptors in rat cerebral arteries after organ culture. *Acta Physiol (Oxf)* 2012;205(2):266-278.


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


Jing L, Christoforou N, Leong KW, Setton LA, Chen J. Differentiation potential of human induced pluripotent stem cells (iPSCs) to nucleus pulposus-like cells *in vitro*. *Global Spine J* 2012;02-S4.18.


**PRESENTATIONS AND ABSTRACTS**


BOOK CHAPTERS, ETC.


EFFECTS OF SECONDHAND CIGARETTE SMOKE (SCS) EXPOSURE ON ADIPONECTIN, mTOR, AND VASCULAR DISEASE

Kathleen A. Martin, PhD; Yale University; CIA 2008

Dr. Martin and colleagues studied the links among SCS exposure, cardiovascular disease, and dysregulation of adiponectin, a cardioprotective hormone implicated in diabetes. Their data indicated that SCS exposure inhibits synthesis of adiponectin in mice. They further showed that SCS 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 SCS. 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 SCS inhibition of adiponectin expression, resulting in elevated mTOR activity.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS


PRESENTATIONS AND ABSTRACTS


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

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 the worst long-term outcome.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS


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**


**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 (TEBV) 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°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


PRESENTATIONS AND ABSTRACTS


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 and John A. Bauer, PhD; Ohio State University; CIA 2006

Drs. Groner and Bauer investigated the effects of SHS exposure on inflammation, endothelial stress, endothelial repair as 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**


**PRESENTATIONS AND ABSTRACTS**


**BOOK CHAPTERS, ETC.**

EXACERBATION OF VIRAL MYOCARDITIS BY TOBACCO SMOKE THROUGH INCREASED VIRAL LOAD AND CARDIAC APOPTOSIS

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 intraperotinal 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


BOOK CHAPTERS, ETC.


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


**PRESENTATIONS AND ABSTRACTS**


**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.
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.

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


**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**


Lindstedt I, Xu CB, Zhang Y, Edvinsson L. Increased perfusion pressure enhances the expression of endothelin (ETB) and angiotensin II (AT1, AT2) receptors in rat mesenteric artery smooth muscle cells. *Blood Press* 2009;18:78-85.


Nilsson D, Wachenfors A, Gustafsson L, Edvinsson L, Paulsson P, Ingemansson R, Malmsjö M. Increased ET(A) and ET(B) receptor contraction in the left internal mammary artery from patients with hypertension. *J Hum Hypertens* 2008;226-229.


PRESENTATIONS AND ABSTRACTS


IMPACT OF PASSIVE SMOKING AND EARLY ATHEROSCLEROSIS IN CHILDREN WITH TYPE I DIABETES MELLITUS

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**


**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.

**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.
EFFECT OF SIDE-STREAM CIGARETTE SMOKE ON LUNG ENDOTHELIAL ANGIOGENESIS INDUCED BY EPIDERMAL GROWTH FACTOR
Yunchao Su, MD, PhD; Georgia Regents University; 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


SECONDHAND TOBACCO SMOKE (SHS) PLATELET ACTIVATION AND CARDIOVASCULAR RISK and 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
PERIPHERAL VASCULAR HEMODYNAMICS AND VENTRICULAR MECHANICS IN PASSIVE SMOKERS
Theodore P. Abraham, MD; Johns Hopkins Medical Institutions; CIA 2004
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

SHS 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


PRESENTATIONS AND ABSTRACTS
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


PRESENTATIONS AND ABSTRACTS


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


PRESENTATIONS AND ABSTRACTS


INFLAMMATION

Newly Funded
ROLE OF FABP5 IN CIGARETTE SMOKE-INDUCED INFLAMMATION

Fabienne Gally, PhD; National Jewish Health; CIA 2016

Dr. Gally’s objective is to understand the mechanisms 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 the host to excessive inflammation. The investigators will determine if modifying FABP5 in vitro and in vivo alters cigarette smoke-induced inflammation, and they will characterize the alteration of the expression of FABP5 in individuals exposed to cigarette smoke or in patients with COPD. They will identify genetic alterations that decrease FABP5 function and contribute to disease susceptibility. The hope is that FABP5 can be used as a target to attenuate the inflammation commonly involved in chronic lung diseases such as COPD.
THERAPEUTIC EFFECTS OF CSP7 ON PASSIVE TOBACCO SMOKE-INDUCED LUNG INJURY

Sr eerama Shetty, PhD; The University of Texas Health Science Center at Tyler; CIA 2016

In this study the investigators will use 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 will determine if 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 will determine how IL-17A augments miR-34a-p53-positive feedback in A2ECs and A2EC apoptosis during SHS-induced lung injury and determine whether blockade of IL-17A-induced miR-34a and p53 in A2ECs by CSP7 can reduce the severity of SHS-induced lung injury.

RAGE AND SAGE: MODELING SECONDHAND SMOKE-INDUCED COPD AND THERAPEUTIC MODALITIES

Paul R. Reynolds, PhD; Brigham Young University; CIA 2016

Dr. Reynolds and colleagues will continue their studies of the receptor for advanced glycation end-products (RAGE) as a smoke-induced pattern recognition receptor with potent pro-inflammatory characteristics, which is increased in the lung following tobacco smoke exposure. The investigators have developed a mouse model that conditionally up-regulates RAGE and manifests characteristics of a smoker’s lung in the absence of smoke. Semi-synthetic glycosaminoglycan ethers (SAGEs) are potent modulators of inflammation that significantly inhibit interactions between RAGE and its ligands. In this study, the team will assess the biology of RAGE in the context of chronic tobacco smoke exposure. The investigators will use a collection of animal models that tightly control RAGE expression including RAGE null mice, pulmonary-specific transgenic mice that up-regulate RAGE, and mice harboring phosphorylation deficient RAGE alleles. They will demonstrate whether RAGE is required for smoke-induced COPD pathogenesis and elucidate the efficacy of SAGEs in targeting RAGE signaling involved in the progression of COPD.

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 will examine miRNA-mediated posttranscriptional silencing of CFTR mRNA by TGF-beta and they will test 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.

THE ROLE OF FGF RECEPTOR SIGNALING IN INFLAMMATION IN CHRONIC BRONCHITIS

Stefanie Krick, MD, PhD; University of Miami Miller School of Medicine; YCSA 2016

Dr. Krick and her team will investigate the roles of fibroblast growth factors (FGFs) and receptors (FGFRs) in chronic bronchitis and COPD. Fibroblast growth factor signaling has been thought to be confined to chronic inflammation in the kidney and the heart; however, Dr. Krick has preliminary data that suggest that this signaling may be involved in the pathogenesis of lung diseases such as chronic bronchitis and COPD. For instance, her team has shown that there is an upregulation of serum FGF23 levels in smokers and patients with COPD, and that FGFR4 is upregulated in bronchial epithelial cells after smoke exposure. Further, FGF23 can activate FGFR4 signaling in these cells. In this study the investigators will determine if smoking increases FGFR4 signaling in bronchial epithelial cells. They will test whether FGF23 in combination with tobacco smoke exposure can induce inflammation and mucociliary dysfunction. They will elucidate the FGF23-induced signaling pathway and will evaluate whether specific FGFR4 inhibition can prevent tobacco smoke-induced changes in cells.

IMMUNOLOGY

Ongoing Research

MECHANISMS REGULATING CIGARETTE SMOKE-INDUCED SLE

Betsy J. Barnes, PhD; Rutgers, Feinstein Institute for Medical Research; CIA 2013

Dr. Barnes and her team have shown that interferon regulatory factor 5 (IRF) might be a genetic determinant that works coordinately with cigarette smoke exposure to precipitate clinical systemic lupus erythematosus (SLE) in at-risk individuals. The team is using a variety of complementary molecular and immunological approaches in human primary immune cells from smoking and nonsmoking healthy donors and SLE patients to determine if this is the case. They are complimenting these experiments with mechanism-based experiments in a genetically susceptible mouse model of murine lupus, using novel inhibitors that target IRF5 activation.
**Completed Research**

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 indentify 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**


**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 determined the function of the CX3CR1 cell type in human COPD lungs.
FAMRI SUPPORTED RESEARCH

PUBLICATIONS


PRESENTATIONS AND ABSTRACTS


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 secondhand tobacco smoke (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


ADJUVANT EFFECTS OF CIGARETTE SMOKE CONSTITUENTS

Robert Vassallo, MD; Mayo Clinic; CIA 2010

Dr. Vassallo and his colleagues have shown that oxidative insert secondhand tobacco smoke (SHS) 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**


**PRESENTATIONS AND ABSTRACTS**


**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


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 called 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

**SHS AND INFLUENZA-INDUCED IMMUNE RESPONSES**

Ilona Jaspers, PhD; Hamner Institutes for Health Sciences; 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**


**ROLE OF SERPINB1 IN CIGARETTE SMOKE-INDUCED DEFECTIVE ANTIMICROBIAL DEFENSE**

Charaf Benarafa, DVM, PhD; 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


#### PRESENTATIONS AND ABSTRACTS


**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 SCS exposure. They also demonstrated nasal epithelial cell secretion of CCL20, (a protein that has antimicrobial and signaling functions), is suppressed by SCS exposure. The team tested the production of other related antimicrobial and signaling molecules in volunteers with no SCS exposure, prior SCS exposure (6 months to 5 years ago), current insert secondhand tobacco smoke exposure, and subjects with current primary SCS 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**


**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 SCS exposure increases memory T cell number and hinders allograft survival induced by the CD40/CD154 costimulatory blockade.
The team investigated whether SCS exposure shortens allograft survival by suppressing regulatory T cell (Treg) development and promoting memory T cell recall, and they investigated the impact of SCS exposure on the function of memory CD4+ and CD8+ T cells. They studied whether SCS 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 SCS exposure. Using a murine cardiac transplant model, the team found that SCS 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


PRESENTATIONS AND ABSTRACTS


INNATE IMMUNITY AND TOBACCO SMOKE

**Maria Antonieta Guerrero-Plata, PhD; Louisiana State University; YCSA 2007**

Dr. Guerrero-Plata and colleagues investigated whether exposure to insert secondhand tobacco smoke (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


4. Guerrero-Plata A, Kolli D, Hong C,


**PRESENTATIONS AND ABSTRACTS**


Castro S, Guerrero-Plata A. Cigarette smoke suppresses TLR-7 stimulation in response to virus infection in plasmacytoid dendritic cells [abstract]. The Keystone


**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


PRESENTATIONS AND ABSTRACTS


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**


**SHS AND INFLUENZA-INDUCED RESPONSES IN NASAL EPITHELIUM**

Ilona Jaspers, PhD; Hamner Institutes for 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 secondhand tobacco smoke (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**


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.

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 \textit{M. tuberculosis} and have sequelae that affect vaccination strategies.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS


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


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.
SECONDHAND TOBACCO SMOKE (SHS) AND THYROID DISEASE
Rachel Ying Vun 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.


VISION

Completed Research

ROLE OF SMOKING IN AGE-RELATED MACULAR DEGENERATION
Maria Marin-Castaño, MD, PhD; University of Miami; 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**


**PRESENTATIONS AND ABSTRACTS**


BOOK CHAPTERS, ETC.


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; 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


INFLAMMATION, SMOKING, AND BLINDNESS FROM OCULAR NEOVASCULARIZATION

Scott W. Cousins, MD; 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

**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**


**PRESENTATIONS AND ABSTRACTS**


**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**


**PRESENTATIONS AND ABSTRACTS**


**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**


**TOBACCO SMOKE AND EARLY HUMAN NEUROBEHAVIOR**

**Kimberly Yolton, PhD; Cincinnati Children’s Hospital; 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**


**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**


**BOOK CHAPTERS, ETC.**

Gold MS, Wang DQ, Bruijnzeel AW. Implications of secondhand smoke in pediatric and adult health. Primary Care Reports, May 1, 2005.
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

Pau CT, Keefe CC, Welt CK. Cigarette smoking, nicotine levels and increased risk for metabolic syndrome in women with polycystic ovary syndrome. *Gynecol Endocrinol* 2013;29:551-555.


**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**


**PRESENTATIONS AND ABSTRACTS**


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.

Crane-Godreau MA. Setting the stage for cancer--looking for early changes in gene expression in cigarette smoke exposed mice. Presented at the American Cancer Society Meeting. Lebanon, NH, Jul 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.


PREGNANCY AND PERINATAL EFFECTS

Ongoing Research

SMOKING AND INTRAUTERINE GROWTH RESTRICTION

Alice Wang, MD; Beth Israel Deaconess Medical Center; YCSA 2009

Dr. Wang and colleagues are investigating whether fetal growth restriction and shallow placentation affected by tobacco smoke exposure harbor a shared dysregulation of vascular growth and angiogenesis factors. They are determining 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 is identifying potential biomarkers in the HGF/HAI-1 pathway associated with IUGR, defining the role of HAI-1 in placental angiogenesis and trophoblast invasion, and characterizing...
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**


**Completed Research**

**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**


**PRESENTATIONS AND ABSTRACTS**


**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**


**PRESENTATIONS AND ABSTRACTS**


**EFFECTS OF SECONDHAND TOBACCO ON THE IMMATURE LUNG**

**Kathleen J. Haley, MD; Harvard Medical School; 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**


**PRESENTATIONS AND ABSTRACTS**


**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**


SECONDHAND TOBACCO SMOKE AND NEONATES AND PREDISPOSITION TO COPD AND DURABLE EFFECTS OF NEWBORN CIGARETTE SMOKE EXPOSURE ON THE ADULT LUNG

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


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 1–3°C 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**


**THE RELATIONSHIP OF PRENATAL TOBACCO EXPOSURE AND INFANT WHEEZE: A COMPARISON OF PARENT-REPORTED EXPOSURE AND SERUM COTININE**

**Adam Spanier, MD, PhD, MPH; 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


SHS 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: 1) sex differences in the pattern of male and female postnatal airway epithelial differentiation; 2) how SHS exposures during postnatal lung development affect antioxidant enzymes; and 3) 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**

**PUBLICATIONS**


**PRESENTATIONS AND ABSTRACTS**


**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**

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. Lagercrantz 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


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

PUBLICATIONS


Singh SP, 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;183:2115-2121.

**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**

**PUBLICATIONS**


Meeker JD, Rossano MG, Protas B, Padmanabhan 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.

**BOOK CHAPTERS, ETC.**


**EXPOSURE TO SECONDHAND TOBACCO SMOKE AND INFANTILE COLIC**

*Edmond Shenassa, ScD; 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**

**PUBLICATIONS**


**PRESENTATIONS AND ABSTRACTS**


Wen X, Shenassa ED, Paradis A. Maternal smoking, breastfeeding, and risk of childhood overweight: Findings from a historical national cohort. Presented at the


BOOK CHAPTERS, ETC.

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

BOOK CHAPTERS, ETC.

EFFECT OF SECONDHAND TOBACCO SMOKE ON FETAL BODY SIZE AND BRAIN SIZE
Hamisu M. Salihu, MD; 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
PUBLICATIONS


**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 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

PUBLICATIONS


**PRESENTATIONS AND ABSTRACTS**

Chung SH, Mackmbi KH, Soldin OP. Where there's smoke, there's fire: The associations between cigarette tobacco smoke and inflammation in women of reproductive age. Presented at the Georgetown University Medical Center Research Day. Washington, DC, May 12, 2011.

Chung SH, Makambi KH, Soldin OP. Cigarette tobacco smoke exposure and inflammation are associated with thyroid hormone changes. Presented at the 81st Annual Meeting of the American Thyroid Association. Indian Wells, CA, Oct 26-30, 2011.

Chung SH, Makambi KH, Soldin OP. The association between tobacco smoke exposure, inflammation and hormones in women of reproductive age. Presented at the American Society of Preventive Oncology Meeting. Washington, DC, Mar 3-6, 2012.


Lu X, Makambi KH, O'Mara D, Soldin OP. The association between genetic polymorphisms (SNPS), serum TSH, and thyroid hormone levels among smokers, secondhand smokers, and nonsmokers [abstract]. American Thyroid Association Annual Meeting. Quebec City, Canada, Sep 19-23, 2012.

Soldin OP, Aschner M. Chronic manganese alters thyroid and estrogen levels in rats’ blood. Presented at the Society of Toxicology. Washington DC, Mar 9, 2011.

Soldin OP, Makambi KH, Soldin SJ, O’Mara DM. Steroid hormone levels associated with passive and active smoking. Steroids 2011 76(7):653-659.


BOOK CHAPTERS, ETC.


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.

**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**


OP, Goughenour BE, Gilbert SZ, Landy HJ, Soldin SJ. Thyroid hormone levels associated with active and passive cigarette smoking. *Thyroid* 2009;19(8):817-823.


**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**


**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**


Shrivastava V, Pekar M, Grosser E, Im J, Vigodner M. SUMO proteins are involved in the stress response during spermatogenesis and are localized to DNA double-strand breaks in germ cells. Reproduction 2010;139:999-1010.


PRESENTATIONS AND ABSTRACTS


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


**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


BOOK CHAPTERS, ETC.


MECHANISMS OF ENDOTHELIAL DYSFUNCTION IN SMOKERS

Edgar Jaimes, MD; University of Alabama at Birmingham; 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.
**PUBLICATIONS**


**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 effect disease course, and may provide direction in the understanding of response to therapy.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**


**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**


**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 1) identify the long-term effects of nicotine and SHS on attainment of a specific cell state in cultured keratinocytes; and 2) 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 muscarinic 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


PRESENTATIONS AND ABSTRACTS


FAMRI Supported Research


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 (UV) B irradiation, is the most common cause of nonmelanoma skin tumors. The effects of passive cigarette smoke superimposed on UVB irradiation on tumor development, skin pathlogy, 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


**PRECOCIOUS SKIN AGING DUE TO SECONDHAND SMOKE**

Sergei A. Grando, PhD, DSc; University of California, Irvine; CIA 2002

Please see text above under Dr. Grando’s 2005 Award.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**


DISEASE PREVENTION

Completed Research

PREVALENCE OF SMOKE-FREE CAMPUSES IN U.S. HOSPITALS AND BEST PRACTICES FOR IMPLEMENTATION

Sharon Milberger, ScD, and Amanda Holm, MPH; 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 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


PRESENTATIONS AND ABSTRACTS


LAW AND THE PREVENTION OF TOBACCO-RELATED DISEASE

Stephen P. Teret, JD, MPH; Johns Hopkins Medical Institutions; 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


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


Marek L, Ware KE, Fritzshe A, Hercule P, Helton WR, Smith JE, McDermott LA, Coldren CD, Nemenoff RA, Merrick DT, Helfrich BA, Bunn PA, Heasley LE. Fibroblast


**BOOK CHAPTERS, ETC.**


**DIAGNOSTIC TECHNIQUES AND MEASUREMENT**

**Ongoing 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 are focusing 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 are 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 are evaluating and refining the system in *ex vivo* fresh tissue models and *ex vivo* clinical specimens. Further, they are evaluating the device in a pilot study consisting of subjects with no history of tobacco use or exposure and comparing the results to those from a cohort of individuals with known chronic tobacco use.
**Completed Research**

**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**

**PUBLICATIONS**


PRESENTATIONS AND ABSTRACTS


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**


**PRESENTATIONS AND ABSTRACTS**


**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**

PRESENTATIONS AND ABSTRACTS
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.

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


**PRESENTATIONS AND ABSTRACTS**


**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 humidities) 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

PUBLICATIONS


SIMULATION OF SECONDHAND TOBACCO SMOKE DEPOSITION IN THE AIRWAYS

Jeffrey J. Heys, PhD; 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


**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**

**PUBLICATIONS**


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

Agbenyikey W, Wellington E, Gyapong J, Travers MJ, Breysse PN, McCarty KM, Navas-Acien A. Secondhand tobacco smoke exposure in selected public places (PM2.5 and air nicotine) and non-smoking employees (hair nicotine) in Ghana. Tob Control 2011;20:107-111.


**BOOK CHAPTERS, ETC.**


**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**

**PUBLICATIONS**


**BOOK CHAPTERS, ETC.**


**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**

**PUBLICATIONS**


**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**

**PUBLICATIONS**


**PRESENTATIONS AND ABSTRACTS**


Wolf M, Shani T, Primov-Fever A, Amariglio N, Rechavi G, Trakhtenbrot L, Hirshberg A. Detecting cytogenetically altered cells taken by brush biopsy technique in


BOOK CHAPTERS, ETC.


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

PRESENTATIONS AND ABSTRACTS


Zhang J, Fletcher JG, Primak A, McCollough CH. Variation in the measurement of object size and attenuation using partial scan reconstruction algorithms in cardiac CT, 2005. Presented at the Sixth International Conference on Cardiac Computed
Tomography Sponsored by Massachusetts General Hospital and Harvard Medical School. Boston, MA, Jul, 2005.


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 (3He) 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 3He 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
PRESENTATIONS AND ABSTRACTS


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.

EARLY DETECTION AND SCREENING OF SMOKING-RELATED CANCERS BY USE OF GREEN FLUORESCENT PROTEIN EXPRESSING HERPES SIMPLEX VIRUS

Yuman Fong, MD; Memorial-Sloan Kettering 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**

**PUBLICATIONS**


**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 concentrations
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 multicomartment homes indicated that the multicomartment 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

BOOK CHAPTERS, ETC.


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 (7micron) 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


**NOVEL MICROVESSEL STRUCTURE IMAGING STRATEGIES FOR EARLY DETECTION OF LUNG CANCER RELATED TO SHS EXPOSURE**

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**


**PRESENTATIONS AND ABSTRACTS**


THE 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


**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**


**PRESENTATIONS AND ABSTRACTS**


**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 CT and genetic analysis of sputum for noninvasive diagnosis of stage I 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**


**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 waterpipe 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**

PRESENTATIONS AND ABSTRACTS


SECONDHAND TOBACCO SMOKE-INDUCED HEART AND BRAIN INJURY

Kevin K. Wang, PhD; 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


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 a model of 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


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


ORGANISIMAL EFFECT OF TOBACCO SMOKE ON TELOMERASE NULL MICE

Kwok-Kin Wong, MD, PhD; Harvard Medical School; 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**


**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**

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**EXPOSURE TO SHS/POPULATION STUDIES**

*Ongoing Research*

**AN INTERVENTION TO PROTECT YOUNG CHILDREN FROM TOBACCO SMOKE EXPOSURE**

Laura Rosen, PhD; Tel Aviv University; YCSA 2008

Dr. Rosen and colleagues are developing and testing a theory-based intervention that will reduce exposure of young children to secondhand tobacco smoke (SHS). A secondary goal is to increase knowledge of measurement of SHS exposure in young children, including parental report, child biochemical measurement, and home environment measurement to explore the relationships among early SHS exposure, illness, and health care utilization. The first stage of the study includes reviews of the literature on child prevention of tobacco smoke exposure, consultation with experts, and a qualitative study to explore parental attitudes towards child tobacco smoke exposure. The team is using a social marketing approach to identify barriers for behavior change and behavior-change recommendations to test the acceptability of program components. The second phase of the research is a pilot study that tested the feasibility and acceptability of the program components, with a sample of 29 families. In the third phase of the research, the team will conduct a randomized controlled trial to test the effectiveness of the intervention on child exposure to tobacco smoke, parental protection of children from tobacco smoke, smoking in the home, and parental perceptions of tobacco smoke exposure. An effective program could serve as a prototype for interventions. (ClinicalTrials.gov Identifier: NCT01335178).

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**


**PRESENTATIONS AND ABSTRACTS**

Rosen L, Ben Noach M. Will parents protect their young children from tobacco smoke exposure? A systematic review and meta-analysis. Presented at the Faculty of Medicine Research Fair, Tel Aviv University. Tel Aviv, Israel, Apr 2012.


Rosen L, Hovell M, Ben Noach M. Will parents quit smoking to protect their kids from secondhand smoke exposure? A systematic review and meta-analysis of intervention trials. Presented to the Faculty of Medicine Fair, Tel Aviv University. Tel Aviv, Israel, Mar 2010.

Rosen L, Myers V, Braun N, Ram A, Rosenblat S, Tzur Y, Zucker D, Guttman N. Biomarker testing of young Israeli children for tobacco smoke exposure: Results from a Pilot Study. Presented at the Tel Aviv University Medical Faculty Research Fair. Tel Aviv, Israel. Apr 2014.

Rosen L, Tillinger E, Braun N. An intervention to reduce child exposure to tobacco smoke. Presented at the Tel Aviv University School of Public Health. Tel Aviv, Israel, Mar 2014.


Rosen L, Tillinger E, Rosenblat S, Guttman N, Zucker D, Rubinstein U, Rosenblum J, Tchernokovski S, Aprimov D, Myers V. Ignorance may be bliss, but knowledge is reassuring: Parental receptivity to child biomarker testing for tobacco smoke exposure. Presented at the Tel Aviv University Medical Faculty Research Fair. Tel Aviv, Israel, Apr 2014.


**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


PRESENTATIONS AND ABSTRACTS


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


REDUCING SECONDHAND TOBACCO SMOKE EXPOSURE AMONG YOUNG CHILDREN

Abu S. Abdullah, MD, PhD, MPH, MFPH; American Academy of Pediatrics; 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


PRESENTATIONS AND ABSTRACTS

Abdullah AS, Hua F, Hurlburt S, Xia X, Bing Q, Qiming F, Siegel M. Predictors of household smoking restrictions in the urban Chinese families with young children. Presented at the 18th Annual Society for Research on Nicotine and Tobacco Meeting. Houston, TX, Mar 12-16, 2012.


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 datasets. 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.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS


A MULTIPLE STAKEHOLDER STUDY REGARDING THE IMPACT OF SECONDHAND 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

PUBLICATIONS


**PRESENTATIONS AND ABSTRACTS**


Hyland AJ. Measuring tobacco smoke pollution in multi-unit housing. Presented at the National Conference on Tobacco or Health Ancillary Meeting on Multi-Unit Housing. Phoenix, AZ, Jun 9, 2009.


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.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS

Alpert HR, Behm I, Connolly GN, Kabir Z. Smoke-free households with children and decreasing rates of paediatric clinical encounters for otitis media in the United States. Tob Control 2011;20(3):207-211.


Alpert HR, Spalletta R, Connolly GN, O’Connor RJ. Recent advances in cigarette ignition propensity research and development. Fire Technol 2010;46(2):275-289.


**PRESENTATIONS AND ABSTRACTS**

Alpert H. Factors associated with youth support of public smoking bans in developing countries worldwide: Results from the Global Youth Tobacco Survey. Presented at 14th World Conference on Tobacco or Health. Mumbai, India, Mar 8-11, 2009.


Alpert H. Youth attitudes and public smoking ban policies in developing countries worldwide: Results from the global youth tobacco survey. Presented at 14th World Conference on Tobacco or Health. Mumbai, India, Mar 8-11, 2009.


Kabir Z, Connolly GN, Alpert HR. Second-hand smoke exposure in the home and neurobehavioral disorders among children in the United States. Presented at the

FETAL AND INFANT EXPOSURE TO SHS AND ITS ROLE IN CHRONIC DISEASE

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

PUBLICATIONS

Bouloukaki I, Tsoumakidou M, Vardavas CI, Mitrouskas I, Koutala E, Siafakas NM, Schiza SE, Tzanakis N. Maintained smoking cessation for 6 months equilibrates the percentage of sputum CD8 lymphocyte cells with that of nonsmokers. Mediators Inflammm 2009;2009:812102.


**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.
FAMRI SUPPORTED RESEARCH

PUBLICATIONS


PRESENTATIONS AND ABSTRACTS


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

PUBLICATIONS


**PRESENTATIONS AND ABSTRACTS**


**RCT OF A FAMILY INTERVENTION TO REDUCE SHS EXPOSURE IN CHILDREN**

Sophia Siu-chee Chan, PhD, MPH, MED, RN, RSCN; 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**


Yau JPL, Chan SSC, Lam TH, Fong DYT. A randomized controlled trial (RCT) of a family intervention to reduce secondhand smoke (SHS) exposure in infants and mothers. Presented at the 13th Research Postgraduate Symposium. Hong Kong, China, Dec 10-11, 2008.

Yau JPL, Chan SSC, Lam TH, Fong DYT. A randomized controlled trial of a family intervention to reduce secondhand smoke (SHS) exposure in babies. Presented at the U21 Doctoral Nursing Research Forum at Health Sciences Meeting, Charlottesville, VA, Sep 15-19, 2008.


Yau JPL, Chan SSC, Lam TH, Fong DYT. Comparing mothers’ saliva cotinine level and infants’ saliva cotinine level in families with smoking fathers. Presented at the Nursing Forum. Hong Kong, China, Jun 5-6, 2009.


Yau JPL, Chan SSC, Leung DYP, Koh D, Ng V, Lam TH. Saliva cotinine levels of babies and mothers living with smoking fathers under different housing types in Hong


SECONDHAND TOBACCO SMOKE GLOBAL RESEARCH NETWORK

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.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS


**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.

**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

PUBLICATIONS


SECONDHAND TOBACCO SMOKE EXPOSURE AMONG BAR AND NIGHTCLUB EMPLOYEES

Ana Navas-Acien, MD, PhD; Johns Hopkins Medical Institutions; 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


**PRESENTATIONS AND ABSTRACTS**


**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


HOOKAH USE AND SECONDHAND TOBACCO SMOKE

Nada Kassem, DrPH, MS, RN, MCHES; 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

PRESENTATIONS AND ABSTRACTS


SECONDHAND SMOKE EXPOSURE AMONG 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**


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 relative risk 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

PUBLICATIONS


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
PUBLICATIONS

Lopipero P, Bero LA. Tobacco interests or the public interest: 20 years of industry strategies to undermine airline smoking restrictions. *Tob Control* 2006;15:323-332.

PRESENTATIONS AND ABSTRACTS


SECONDHAND TOBACCO SMOKE AND HEAD AND NECK CANCER
Edward Peters, DMD, SM, 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
PUBLICATIONS

Peters ES, McClean MD, Liu M, Eisen EA, Mueller N, Kelsey KT. The ADHIC polymorphism modifies the risk of squamous cell carcinoma of the head and neck

**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**

**PUBLICATIONS**


**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


PRESENTATIONS AND ABSTRACTS

OBSTRUCTIVE CHANGES AND CYTOLOGIC ABNORMALITIES: A CROSS-SECTIONAL STUDY OF SHS EXPOSURE

Martin Mahoney, MD, PhD; Roswell Park Alliance Foundation; CIA 2003

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 workplace SHS exposure among hospitality workers.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS


PRESENTATIONS AND ABSTRACTS


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: 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


PRESENTATIONS AND ABSTRACTS

THE EFFECTS OF TOBACCO CONTROL ON SHS HEALTH PROBLEMS: THE USE OF SIMULATION MODELS TO PREDICT AND UNDERSTAND PUBLIC HEALTH PROBLEMS

David Levy, PhD; Pacific Institute for Research and Evaluation and the University of Baltimore; 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


IMPACT OF SECONDHAND TOBACCO SMOKE ON RESPIRATORY HEALTH OF NON-SMOKING ADULTS

Archana Mishra, MD, MS; State University of New York at Buffalo; 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.

SECONDHAND TOBACCO SMOKE EXPOSURE AND HEALTH IN A BLUE-COLLAR POPULATION

Francine Laden, ScD; Harvard Medical School; 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


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


PRESENTATIONS AND ABSTRACTS


BOOK CHAPTERS, ETC.


EDUCATION

Ongoing Research

BAR INTERVENTIONS TO DECREASE YOUNG ADULT SMOKING

Pamela Ling, MD, MPH; Public Health Institute, San Francisco; CIA 2009

Dr. Ling and colleagues are addressing the prevention of diseases caused by mainstream tobacco smoke 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 marketing research on young adults. Because the Master Settlement Agreement restricts marketing to youth, young adults have become an important focus of industry marketing efforts, which often emphasize events at “adult only” venues (bars, nightclubs, and casinos), and which are exempt from these restrictions. Successfully competing with industry promotion in these venues will prevent transitions to regular smoking among young adults, preventing long term morbidity and mortality and preventing them from exposing others, including their future children, to SHS.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS


PRESENTATIONS AND ABSTRACTS


Ling PM. Tobacco marketing strategies targeting youth and young adults. Presented at the Alameda County Tobacco Control Coalition. Oakland, CA, Dec 2, 2014.


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 and colleagues are examining how different characteristics of anti-tobacco smoke pollution (TSP) television advertisements, their focus, and intended target audience interact to affect comprehension, appraisal, recall, advertising engagement, and intention to adopt smoke-free initiatives in households and cars. The findings suggest that ads that use negative visceral images and dramatize the health consequences from TSP exposure, targeting parents specifically, are appraised more highly and more likely to encourage consideration of adoption of smoke-free home and car standards, compared to advertisements that do not share these characteristics. The team also found that parents in localities with stronger comprehensive clean indoor air regulations are more likely to consider instituting these standards in their personal living space compared to parents in localities with weaker initiatives. The team did not find significant differences in the outcomes by survey administration mode, supporting the use of Web-based surveys as a reliable, faster, and less expensive method for ad evaluation compared to in-person sessions.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**


**BOOK CHAPTERS, ETC**


**Completed Research**

**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 smokefree 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**


**PRESENTATIONS AND ABSTRACTS**


**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 smokefree home and car policies, using a pamphlet about the risks of SHS. A question about SHS exposure and a prompt to advise a smokefree 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 smokefree 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 smokefree 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


PRESENTATIONS AND ABSTRACTS


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**


**PRESENTATIONS AND ABSTRACTS**


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.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS


**HEALTH IMPACT STUDY OF SMOKEFREE POLICIES IN LATIN AMERICA**

**Ernesto Sebrió, MD MPH; Roswell Park Alliance Foundation; YCSA 2008**

Dr. Sebrió and colleagues tested whether the 2006 comprehensive smokefree 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 smokefree law implemented in Panama in 2008 is associated with a similar health outcome. The team also determined if the 2006 comprehensive smokefree 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 smokefree 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.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**


Champagne BM, Sebrió EM, Schoj V. The role of organized civil society in tobacco control in Latin America and the Caribbean. *Salud Pública Méx* 2010; Vol. 52 (Sup 2): 330-339.


Cummings KM, Sebrié EM. Latin America: A Laboratory for Tobacco Control Research. *Salud Pública Méx* 2010; Vol. 52 (Sup 2): 91-93.


Thrasher J, Abad-Vivero EN, Sebrie EM, Barrientos-Gutierrez T, Boado M, Yong HH, Arillo-Santillán E, Bianco E. Tobacco smoke exposure in public places and


PRESENTATIONS AND ABSTRACTS


Sebrié E, et al. Barbados cigarette health warning labels study report. Presented at Roswell Park Cancer Institute, InterAmerican Heart Foundation, Heart and Stroke
Foundation of Barbados, University of Waterloo, University of South Carolina, and the Instituto Nacional de Salud Pública de México. 2012.


Sebrié E, et al. Trinidad and Tobago cigarette health warning labels study report. Presented at Roswell Park Cancer Institute, InterAmerican Heart Foundation, Trinidad and Tobago Cancer Society, University of Waterloo, University of South Carolina, and the Instituto Nacional de Salud Pública de México. 2012.


Sebrié EM. Enacting a good law is not the end of the road: the tobacco industry vs. Santa Fe (Argentina). Presented at the 14th World Conference on Tobacco or Health. Mumbai, India, Mar 8-10, 2009.

FAMRI Supported Research


Sebrié EM. Experimental study to evaluate the pre-implementation impact of graphic warning labels in the Caribbean. Presented at the Center for Tobacco Control Research and Education. University of California, San Francisco, Feb 17, 2009.


Sebrié EM. ITC Project. In: ITC Brazil Survey Summary. Presented at the University of Waterloo, Waterloo, Ontario, Canada; and National Cancer Institute of Brazil (INCA) / Ministry of Health. Brazil 2009.


Sebrié EM. Smokefree policies in Argentina: the successful case of the Province of Santa Fe. Presented at the National Conference on Tobacco or Health. Phoenix, AZ, Jun 10-12, 2009.


BOOK CHAPTERS, ETC
Hage, Paul et al. Film: "Warning: Secondhand Smoke is Hazardous to Your Heart" (Spanish version), Roswell Park Cancer Institute (September 9, 2010). http://vimeo.com/14827823.

ITC Project (Feb 2010). ITC Uruguay Survey Summary. University of Waterloo, Waterloo, Ontario, Canada, Universidad de la República, Montevideo, Uruguay; Centro de Investigación para la Epide­mi­da­l de Tabaquismo, Montevideo, Uruguay; University of South Carolina, Columbia, SC, USA; and RPCI, Buffalo, NY, USA. www.itcproject.org/keyfindi/itcuruguay4pagerpdf.


HUMAN SENSORY PERCEPTIONS AND SMOKE MACHINE YIELDS OF CIGARETTES DESIGNED TO HIDE SECONDHAND SMOKE SMELL

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


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**


**SECONDHAND TOBACCO SMOKE COUNSELING FOR PARENTS OF HOSPITALIZED PEDIATRIC PATIENTS**

Alan C. Geller, MPH, RN; Harvard Medical School; 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**


**PRESENTATIONS AND ABSTRACTS**


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).


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


Thomson CC, Hamilton WL, Siegel MB, Biener L, Rigotti NA. Effect of local youth access regulations on progression to established smoking among Massachusetts youth. Tob Control 2007;16(2):119-126.
RESEARCH AND EDUCATION ON SMOKE-FREE AIR FOR PETS AND FAMILIES
Ronald M. Davis, MD (1956-2008); 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

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

PRESENTATIONS AND ABSTRACTS


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, Ling PM, Glantz SA. Implications of the federal court order banning the terms “light” and "mild": what difference could it make? Tob Control 2007;16:275-279.

Anderson SJ, Ling PM. And they told two friends, and so on, and so on: RJ Reynolds’ viral marketing of Eclipse. Tob Control 2008;17(4):222-229.


Ling PM, Glantz SA. Tobacco industry consumer research on socially acceptable cigarettes. *Tob Control* 2005;14:e3


**PRESERVATION OF DOCUMENTS**

**Completed Research**

**TO DEVELOP A DIGITAL LIBRARY CONTAINING KEY TOBACCO EVENTS, STUDIES, DOCUMENTS, AND PROMOTIONS FOR TOBACCO RESEARCH**

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/ashetoashes.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**


**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**

**Ongoing Research**

**FOLLOW-UP SURVEY OF THE 2007 FLIGHT ATTENDANT HEALTH STUDY**

Eileen McNeely, PhD; Harvard School of Public Health; 2013; CIA 2016

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 this exposure.

**FAMRI SUPPORTED RESEARCH**

**PUBLICATIONS**

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 will continue into early 2017.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS


PRESENTATIONS AND ABSTRACTS


BOOK CHAPTERS, ETC.

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 will continue 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


FAMRI Supported Research


PRESENTATIONS AND ABSTRACTS


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.


COMMUNICATIONS AND DISSEMINATION SUPPORT FOR THE FLIGHT ATTENDANT MEDICAL RESEARCH INSTITUTE

Andrew Hyland, PhD and Anthony Brown; Roswell Park Alliance Foundation; 2011

This study will provide educational materials to Flight Attendants about issues related to SHS, and to develop a cohort of Flight Attendants that can be used for specific research studies now and in the future to better understand the relationship between Flight Attendants’ occupational SHS exposure and conditions that may be caused by that exposure.

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; 2016

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 will enroll 380 pre-ban and 190 post-ban flight attendants over 5 years. The investigators will also 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.

REDUCED EXERCISE CAPACITY IN FLIGHT ATTENDANTS EXPOSED TO SECONDHAND SMOKE: PATHOGENESIS AND CONSEQUENCES.

Warren M. Gold, MD and Mehrdad Arjomandi, MD; University of California, San Francisco; 2016

The investigators are examining the hypothesis that reduced exercise capacity in pre-ban Flight Attendants is due to airflow limitation, which may cause dynamic hyperinflation and progressive air trapping resulting in adverse consequences to health-related quality of life.
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**


**PRESENTATIONS AND ABSTRACTS**


**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**


PRESENTATIONS AND ABSTRACTS

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.

FAMRI SUPPORTED RESEARCH
PUBLICATIONS

K. Michael Cummings, PhD; 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. Dr. Cummings’ accomplishments helped educate the public about the harm caused by tobacco smoke pollution, which in turn assists with public health education. In addition, a wide range of media products were created for documentaries on the harmful effects of cigarette tobacco exposure for public outreach on the topic through the media. These efforts were achieved in collaboration with other FAMRI grantees.

FAMRI SUPPORTED RESEARCH
PUBLICATIONS


Borland R, Yong HH, Siahpush M, Hyland A, Campbell S, Hastings G, Cummings KM, Fong GT. Support for and reported compliance with smoke-free restaurants and


**PRESENTATIONS AND ABSTRACTS**


BOOK CHAPTERS, ETC.


Cummings KM. The role of litigation in tobacco control. Johns Hopkins University, Bloomberg School of Public Health, YouTube: https://www.youtube.com/watch?v=Rphl1ZwoEnY. 2014.


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


**PRESENTATIONS AND ABSTRACTS**


**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**


**PRESENTATIONS AND ABSTRACTS**


**BOOK CHAPTERS, ETC.**


**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.
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.

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


Allan M. Brandt, PhD; Harvard Graduate School of Arts and Sciences; 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

BOOK CHAPTERS, ETC.


John F. Banzhaf, III, JD; George Washington University School of Law; 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.

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

Holm AL, Davis RM. Clearing the airways: advocacy and regulation for smoke-free airlines [review]. *Tob Control* 2004;13Suppl1:i30-i36.

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


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**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**

**PUBLICATIONS**


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

PUBLICATIONS


BOOK CHAPTERS, ETC.


Stanton A. Glantz, PhD; University of California, San Francisco; 2002

Dr. Glantz’s work related to secondhand tobacco smoke 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 tobacco industry’s secret efforts to undermine the science that establishes the link between SHS exposure with disease.

FAMRI SUPPORTED RESEARCH

PUBLICATIONS


Ling PM, Glantz SA. Tobacco industry consumer research on socially acceptable cigarettes. Tob Control 2005;14:e3.


BOOK CHAPTERS, ETC.


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 and 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


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.


**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**


Mulcahy M, Repace JL. Passive smoking exposure and risk for Irish bar staff. *Proceedings of the 9th International Conference on Indoor Air Quality and Climate* 2002; Vol II:144-149.


**PRESENTATIONS AND ABSTRACTS**


**BOOK CHAPTERS, ETC.**


**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**

**PUBLICATIONS**


Richmond JB, Burns DM, Cummings KM. public health and the power of individual action [editorial]. *Tob Control* 2004;13(suppl 1):i1-i2.


**BOOK CHAPTERS, ETC.**

Burns D, ed. Those who continue to smoke: is achieving abstinence harder and do we need to change our interventions? Smoking and Tobacco Control No. 15. USDHHS, NIH, NCI, NIH Pub. No. 03-5370, 2003.


BLAND LANE INTERNATIONAL DISTINGUISHED PROFESSOR
Lars Edvinsson, MD, PhD; Lund University; 2007

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 un raveled 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


Dimitrijevic I, Ekelund U, Edvinsson ML, Edvinsson L. Increased expression of endothelin ET(B) and angiotensin AT(1) receptors in peripheral resistance arteries of patients with suspected acute coronary syndrome. Heart Vessels 2009;24(6):393-398.


Lindstedt I, Xu CB, Zhang Y, Edvinsson L. Increased perfusion pressure enhances the expression of endothelin (ETB) and angiotensin II (AT1, AT2) receptors in rat mesenteric artery smooth muscle cells. *Blood Press* 2009;18(1):78-85.


PERSONAL THOUGHTS FROM THE FLIGHT ATTENDANT MEMBERS OF THE BOARD OF TRUSTEES

PATRICIA L. YOUNG

Patty is a Flight Attendant Trustee and former Class Representative (flew for American Airlines for more than 37 years).

My flying career started in mid 1966, and soon after I began my huge, multi-layered fight to have smoking banned on all flights because of what I was seeing and hearing from the non-smoking Flight Attendants. From the start they told me how wonderful the job was because I would be meeting intelligent, interesting people and going to exciting destinations. Some of them also told me that they had the lungs of smokers...and they never smoked. They knew this fact because we had to have a yearly health physical in order to keep our jobs. When I repeatedly asked the medical professionals how a non-smoker could have smokers’ lungs and the diseases of smokers, they had no answers. We know now...people who are forced to breathe secondhand tobacco smoke suffer and die from the same diseases as smokers.

I am very concerned that after half a century in the fight by nonsmokers to ban smoking on all flights and later in all shared airspaces, that the vast majority of the healthcare community is not asking the most basic questions of their patients regarding their secondhand tobacco smoke exposure. We seem to have no faces and no value to medicine. This is unacceptable and must change. The Flight Attendants are and were the canaries in the coalmines and are the major power in the world who forced the no smoking issue into a global movement.

At the completion of the class action with a settlement from the tobacco industry to form a foundation, our attorneys, Stan and Susan Rosenblatt, had the vision to create one with court approval to address the diseases from which non-smoking Flight Attendants suffer because of our exposure to tobacco smoke in our workspace. For this, I am truly grateful.

Our research is breathtakingly comprehensive in finding cures for conditions, diseases and disabilities we, as nonsmoking Flight Attendants, have suffered and continue to suffer from as a result of cigarette smoke in our work place.
Thoughts from FAMRI Flight Attendant Trustees

Investigations through FAMRI funding of stem cells and cell therapies as well as DNA repair are bringing us closer to the cures we seek.  

*FAMRI is the Flight Attendants’ legacy to the world.*

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**LANI BLISSARD**

Lani is a Flight Attendant Trustee and former Class Representative (flew for American Airlines for more than 26 years).

For those non-smoking Flight Attendants who flew before the smoking ban, the cabin conditions were horrific. Indelibly stamped in our minds are images of this intolerable situation...smoke so thick after the no-smoking sign went off that you could not see from the aft jump seat to the front of the cabin, fires started by dropped cigarettes, teeth and light hair discolored by the smoke—and the pungent smell of our uniforms after every flight. Beyond the images, there were burning eyes, bloody noses and frequent respiratory infections, which impacted Flight Attendants down line.

The consequences were denied for decades by airline and medical personnel, misled in part by the faulty tobacco-funded studies. Now the truth is painfully clear—non-smoking Flight Attendants who flew in this toxic environment are paying a very heavy price with cancers, cardiovascular diseases, respiratory diseases and a myriad of other tobacco-generated illnesses. One of our studies, for example, indicate that about half of the participating Flight Attendants are developing COPD/emphysema. When FAMRI incorporated in 2000, we sought to fund research aimed at the earliest detection and cures of these diseases caused from smoke exposure.

*Today we are excited and proud of the excellent science and programs we have funded or established—from a formidable base of relevant cell biology, to stem cell research, DNA repair, state of the art testing centers across the US and other initiatives.*
Leisa is a Flight Attendant Trustee and former Class Member (a currently active flight attendant with American Airlines for 31 years).

I remember the complete dread of waiting for the "No Smoking" sign to go off after takeoff. It was extremely difficult to get a 200 pound beverage cart ready for service with stinging eyes as the entire cabin quickly filled with toxic cigarette smoke. After my trips I would leave my uniform in the garage in order to not pollute my home. Thinking of it now makes the scenario seem ridiculous but the danger of that secondhand tobacco smoke exposure was all too real. FAMRI has been devoted for the past sixteen years towards our mission; to strive for early detection, and cure of diseases caused from this deadly exposure. Examples are the screening centers for early detection provided by two FAMRI funded Centers that are described in this publication. After so many years flying pre-ban, these projects provide opportunity for Flight Attendants to be proactive about their health.

To measure the impact of our funding, we commissioned American Institute of Biological Sciences (AIBS), our grants’ consultant, to perform an H-Index study on the impact of FAMRI-funded publications. The overall impact of FAMRI published research continues to rank among the top academic institutions in both the U.S. and Europe.

We are extremely proud of how far we’ve come and we look forward to making even more of an impact in the future.
KATE JEWELL, ND

Kate is a Flight Attendant Trustee and former Class Member (flew for American Airlines for 37 year). Kate replaces Kathie Cheney, a Flight Attendant Trustee, who died in 2014 due to complications of diseases related to secondhand tobacco smoke exposure.

Today, it’s hard to remember what it was like to fly in a chimney. When I began my career with American Airlines in 1970, I didn’t realize my breathing would be impaired every time the “No Smoking” sign went off. Suddenly I was surrounded by a fog of smoke that permeated the cabin, my hair, my uniform... and my lungs.

Today, it’s hard to remember that we were often forced to breathe in smoke from the table next to us while trying to savor a meal out....choke on the fumes filling the bar while trying to enjoy a drink with friends....be assaulted with smoke from the adjoining cubicle while trying to work.

Today, I travel internationally quite often and realize how I, as an American, take “NO SMOKING” areas for granted. I am grateful for hotels, restaurants, bars, work places that are now smoke-free environments. Much of the credit for this began with Patty Young and other Flight Attendants’ tireless campaign to get smoke off the airplane. A lot has transpired since then: the landmark lawsuit won by the Rosenblatt’s, the formation of FAMRI and the scientific research it has funded, which has deepened our understanding of the hazardous effects of SHS exposure. This research has become a basis for helping many places in the world become SMOKE-FREE!

*Today, I am pleased to serve as a FAMRI Trustee and excited about the possibilities as we continue to strive for discoveries, treatments, and cures that will serve those affected by diseases related to SHS exposure.*

BLAND LANE (1929-2007)

Bland, a former Flight Attendant Trustee and former Class Representative, retired from Pan American World Airways and United Airlines after 48 years of service.

Bland passed away suddenly in San Francisco on February 15, 2007, from complications of COPD that developed due to her years of flying in smoke-filled airline cabins. In spite of limitations from COPD, she worked tirelessly with her
thoughts from famri flight attendant trustees

fellow trustees to advance famri’s mission in order to achieve its position as a world-class scientific research foundation. she was an early advocate of non-smokers rights for flight attendants and passengers, and one of the original representatives in the class action lawsuit filed in 1991 that ultimately created famri. she was an extraordinary and accomplished woman, who led an active and productive life despite the disease that afflicted her due to secondhand smoke exposure in airline cabins.

famri’s wish and goal for the future is for the success of each of our researchers in eradicating diseases suffered by mankind today because of exposure to secondhand tobacco smoke.

kathleen s. cheney (1946-2014)

kathie cheney, a former flight attendant trustee and former member of the class action lawsuit, flew for eastern airlines for twenty years, beginning in 1968 pre-ban; she never got to work on a smoke-free airplane.

in 1987 kathie was diagnosed with a smoker’s throat cancer; having avoided cigarettes all her life but for the smoke-filled skies and other people’s tobacco smoke. after retirement and recovery, kathie worked as an advocate for smoke-free work places and succeeded in having legislation passed in the state of georgia to eliminate smoking from public spaces. kathie became a member of famri’s board of trustees to fill a vacancy due to the death of bland lane and worked ceaselessly with fellow trustees to fund research to build the scientific evidence on the reality of the damage done to never smokers because of exposure to secondhand tobacco smoke. kathie died in august of 2014 due to complications from the diseases she contracted from her exposure to secondhand tobacco smoke as a flight attendant.

famri’s research is used to warn and educate to make change happen faster while searching for the cures that can undo the damage caused by exposure to cigarette smoke.
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