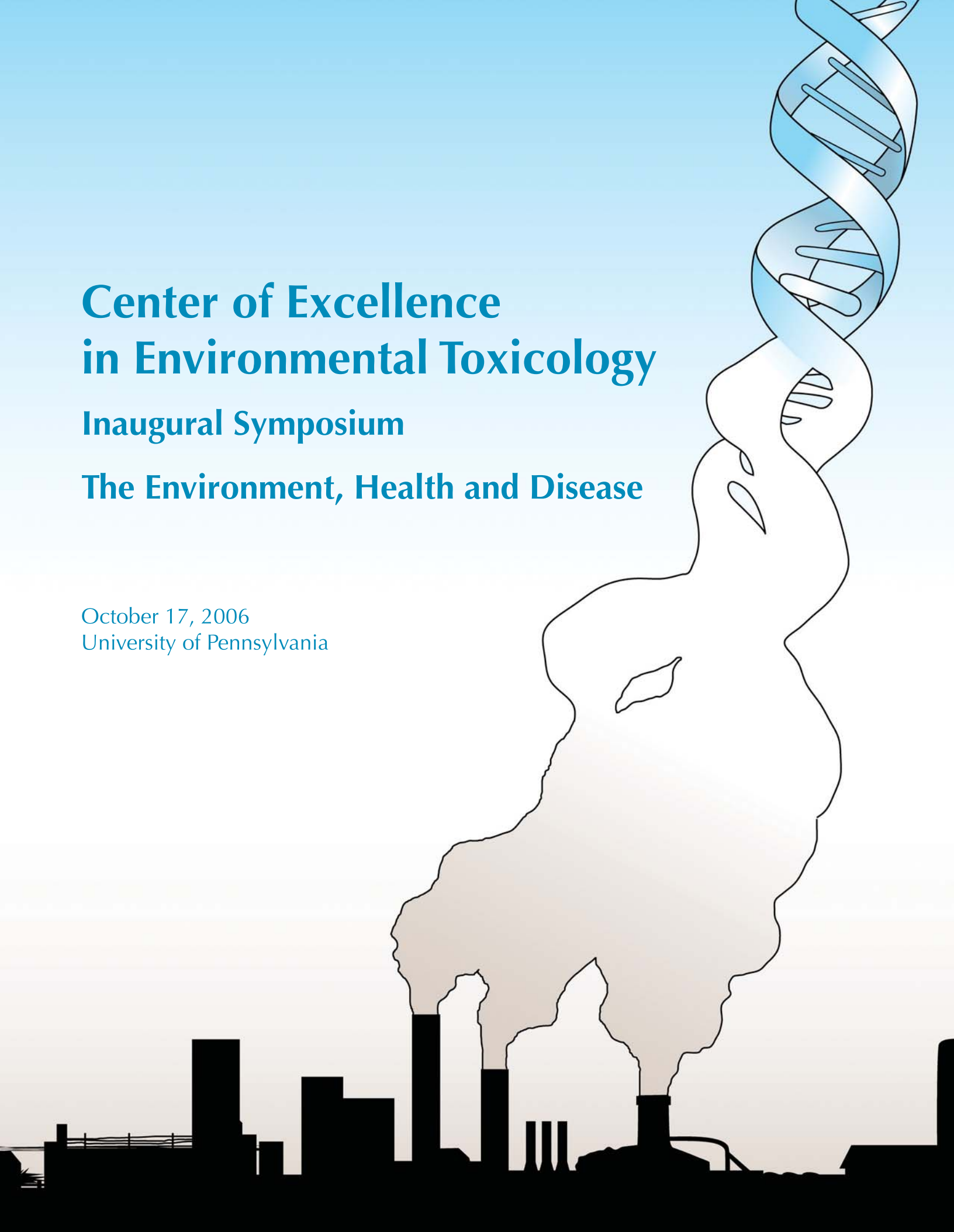


Center of Excellence in Environmental Toxicology

Inaugural Symposium

The Environment, Health and Disease

October 17, 2006
University of Pennsylvania



THE ENVIRONMENT, HEALTH AND DISEASE

INAUGURAL SYMPOSIUM

Presented by

CENTER OF EXCELLENCE IN ENVIRONMENTAL TOXICOLOGY,
UNIVERSITY OF PENNSYLVANIA SCHOOL OF MEDICINE

October 17, 2006
Biomedical Research Building II/III
421 Curie Boulevard
University of Pennsylvania



With support from

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

Mission of the Center of Excellence in Environmental Toxicology

The Center of Excellence in Environmental Toxicology (CEET) was launched in 2005 and receives grant support from the National Institutes of Environmental Health Sciences. It is one of only twenty-two designated Environmental Health Science Centers in the nation.

The CEET mission is to understand the mechanistic link between environmental exposures and diseases of environmental etiology. Understanding these processes can lead to early diagnosis, intervention and prevention strategies. The end result will be to improve environmental health and medicine in our region.

The CEET is a flexible entity that marshals excellence in basic, translational, patient oriented and population based research in the School of Medicine and Children's Hospital of Philadelphia to facilitate an integrative approach to environmental health/medicine. Although primarily housed in the School of Medicine, the 50 CEET Investigators belong to 16 departments and 5 Schools at the University of Pennsylvania.

The CEET marries its relevant research excellence to diseases of environmental etiology that affect our urban region. The CEET includes a research core in Lung and Airway Disease (asthma, lung cancer, mesothelioma, and chronic obstructive pulmonary disease) because of the poor air-quality and air-pollution in our region (ozone, fine particulate matter, allergens, SO₂, NO₂ and CO emissions). The CEET also has a research core in Endocrine and Reproduction Disruption because of the high incidence of adverse pregnancy outcomes that lead to low-weight birth and birth and developmental defects in our region. These organ-based cores are linked to our cores in disease mechanism, which include Oxidative Stress and Oxidative Stress Injury and Genes and the Environment.

The CEET enables its investigators to conduct predictive toxicology by employing Toxicogenomic and Toxicoproteomic approaches to identify the genomic and proteomic fingerprints that can be assigned to toxicant class, and to different stages of diseases of the environment. It is engaged in identifying and validating Biomarkers for these diseases.

The CEET conducts research relevant to the 45 Superfund Sites that permeate the region. Studies elucidate mechanisms of chemical toxicity; exposure levels, risk assessment and health hazard; bioremediation approaches; and effects on ecosystems and biodiversity.

The CEET works with and disseminates research findings to Select Local Communities to empower them with new knowledge so that they are better informed to tackle issues of health disparities and environmental justice. To improve the environmental health of these and similar affected communities, the CEET is actively involved in the education of health care professionals (Residency Program in Occupational and Environmental Health, Nursing concentration in Occupational and Environmental Health, and Masters of Public Health Programs).

The CEET will also disseminate its mission and its research findings to all stakeholders including community organizations, local, state and federal officials and agencies (Pennsylvania Department of Health, Pennsylvania Department of Environmental Protection, Environmental Protection Agency) to affect change in environmental health and public health policies.

Retreat Agenda

7:30 A.M. Continental Breakfast

8:00 A.M. Welcome: Arthur Rubenstein, Dean of the University of Pennsylvania School of Medicine

8:15 A.M. CEET and its Mission: Dr. Trevor M. Penning, Director of CEET

Programmatic Themes:

8:30 A.M. Lung and Airway Disease: *Tackling asthma* – Dr. Reynold Panettieri

9:00 A.M. Endocrine and Reproduction Disruption:
Role of endocrine disruptors on male reproductive tract development – Dr. Jeanne Manson

9:30 A.M. Oxidative Stress and Oxidative Stress Injury:
Oxidative stress-mediated cellular toxicity – Dr. Ian Blair

10:00 A.M. Genes and the Environment: *Susceptibility to melanoma* – Dr. Peter Kanetsky

10:30 A.M. Break

Empowering Investigators:

11:00 A.M. Toxicogenomics: *Gene-environment interactions and preterm birth* - Dr. Sam Parry

11:20 A.M. Toxicoproteomics: *Assembling a sperm tail: You need to know the players* - Dr. Stuart Moss

11:40 A.M. Biomarkers: *Mesothelin as a biomarker for mesothelioma* – Dr. Anil Vachani

12:00 P.M. Lunch

Building Capacity in Environmental Health and Research Training:

1:30 P.M. Collaborative Research with Environmental Health Science Centers
– Dr. Fred Guengerich

2:00 P.M. Translational Research and Environmental Medicine
– Dr. William Martin, Associate Director for Translational Biomedical Research, NIEHS

2:30 P.M. Grants and Initiatives in Environmental Health Sciences
– Dr. Anne Sassaman, Director of Extramural Research, NIEHS

3:00 P.M. Break

Translational and Clinical Research in Environmental Health:

3:30 P.M. Building Ties with the Institute of Translational Medicine and Therapeutics and CTSA
– Dr. Muredach Reilly

4:00 P.M. Integrative Health Facility Service Core – Dr. Michael Feldman

Community Outreach and Education Core:

4:30 P.M. Training Health Care Professionals – Dr. Edward Emmett

5:00 P.M. Community Based Participation in CEET – Richard Pepino

5:30 P.M. Reception

CENTER OF EXCELLENCE IN ENVIRONMENTAL TOXICOLOGY

University of Pennsylvania School of Medicine

ADMINISTRATIVE CORE:

Director: Trevor Penning, Ph.D.

Deputy Director: Ted (Edward) Emmett, M.D, M.S.

RESEARCH CORE I

Oxidative Stress and Oxidative Stress Injury

Co-Director: Ian Blair, Ph.D.

Co-Director: Harry Ischiropoulos, Ph.D.

Benoit Giasson, Ph.D.

Aron Fisher, M.D.

Garret FitzGerald, M.D.

Toshinori Hoshi, Ph.D.

Virginia Lee, Ph.D.

Linda McCauley, M.N., Ph.D.

Vladimir Muzykantov, M.D., Ph.D.

Trevor Penning, Ph.D.

Rebecca Simmons, M.D.

Stephen Thom, M.D., Ph.D.

RESEARCH CORE II

Endocrine/Reproduction Disruption

Co-Director: Jeanne Manson, Ph.D., M.S.C.E.

Co-Director: George Gerton, Ph.D.

Kurt Barnhart, M.D., M.S.C.E.

Phyllis Dennery, M.D.

Ina Dobrinski, M.V.Sc., Ph.D.

Ted Emmett, M.D, M.S.

Norman Hecht, Ph.D.

Mitch Lazar, Ph.D.

Stuart Moss, Ph.D.

Mary Mullins, Ph.D.

Katherine Nathanson, M.D.

Samuel Parry, M.D.

Trevor Penning, Ph.D.

Tim Rebbeck, Ph.D.

Richard Schultz, Ph.D.

Rebecca Simmons, M.D.

Wenchao Song, Ph.D.

Carmen Williams, M.D., Ph.D.

RESEARCH CORE III

Lung and Airway Disease

Director: Rey Panettieri, M.D.

Steve Albelda, M.D.

Yassine Amrani, Ph.D.

Andrea Apter, M.D., M.Sc.

Michael Beers, M.D.

Tyra Bryant-Stephens, M.D.

Melpo Christofidou-Solomidou, Ph.D.

Angela Haczku, M.D., Ph.D.

Vera Krymskaya, Ph.D.

Milton Rossman, M.D.

Anil Vachini, M.D.

RESEARCH CORE IV

Genes and the Environment

Co-Director: Tim Rebbeck, Ph.D.

Co-Dir: Alexander S. Whitehead, D.Phil.

Ian Blair, Ph.D.

Jason Christie, M.D., M.S.C.E.

Peter Kanetsky, Ph.D., M.P.H.

Caryn Lerman, Ph.D.

Jeanne Manson, Ph.D., M.S.C.E

Linda McCauley, M.N., Ph.D.

Katherine Nathanson, M.D.

Trevor Penning, Ph.D.

Dan Rader, M.D.

FACILITY CORE I:

Toxicogenomics

Co-Director: Don Baldwin, Ph.D.

Co-Director: John Tobias, Ph.D.

FACILITY CORE II

Toxicoproteomics

Director: Chao-Xing Yuan, Ph.D.

FACILITY CORE III

Biomarker

Director: Seon Hwa Lee, Ph.D.

COMMUNITY OUTREACH

Director: Ted Emmett, M.D, M.S.

Deputy Director: Richard Pepino

Andrea Apter, M.D., M.Sc

Pamela Dalton, Ph.D.

Ira Harkavy, Ph.D.

Mary Hufford, Ph.D.

Howard Kunreuther, Ph.D.

Directors of CEET



Trevor M. Penning
Director, CEET

Trevor M. Penning, Ph.D.

Professor of Pharmacology, Biochemistry and Biophysics, and OB/GYN

Dr. Penning was interim-chair of Pharmacology from 1994-1996, and was Director of the Office of Postdoctoral Programs, and Associate Dean for Postdoctoral Research Training, School of Medicine from 1997-2001, and was Director of Biomedical Postdoctoral Programs (BPP) from 2001-2005. As Director of BPP, he oversaw the appointments, training and education of 850 postdoctoral fellows across the Schools of Medicine, Veterinary Medicine, and Dental Medicine. He is internationally recognized for his research on steroid hormone enzymology and mechanisms by which polycyclic aromatic hydrocarbons cause cancer. His research is now focused on the emerging role of Aldo-Keto Reductases (AKRs) in hormonal and chemical carcinogenesis. He is Principal Investigator on a P01 entitled: "Molecular Mechanisms of Multi-stage Carcinogenesis", the focus of which is to establish the major pathway of activation of polycyclic aromatic hydrocarbons as it relates to human lung carcinogenesis. He has published over 140 peer-review articles and is the recipient of five U.S. patent applications. He has served on the Editorial Boards of the Journal of Biological Chemistry, Chemical Research in Toxicology, and Steroids. He is a consultant to the WHO International Agency for Research on Cancer. He is Program Chair for the Division of Chemical Toxicology of the American Chemical Society and was elected to the Johns Hopkins Society of Scholars in 1998.



Edward A. Emmett
Deputy Director, CEET

Edward A. Emmett, M.D., M.S.

Dr. Emmett, Professor and Director of Academic Programs in Occupational Medicine, is active in clinical practice, research and education in Occupational and Environmental Medicine. His past experience includes Founding Director of the Divisions of Occupational Medicine in the Schools of Public Health and Medicine and of the Center for Occupational and Environmental Health at Johns Hopkins University from 1978 to 1988, and Chief Executive of the National Occupational Health and Safety Commission for Australia from 1988 to 1996. Dr. Emmett's research contributions include studies of occupational and environmental skin diseases, ultraviolet radiation effects on skin and eyes, the toxicity of polycyclic aromatic hydrocarbons, PCBs, organometals, monomers used in plastics and resins, and other substances. He is currently studying the effects of community pollution by perfluorooctanoates.

Dr. Emmett is a recipient of the Fight for Sight Citation for Clinical Research, and of the Kehoe Award of Merit from the American College of Occupational and Environmental Medicine. He is on several editorial boards and has been a member of many national and international committees. He is certified by the American Board of Toxicology and the American Board of Preventive Medicine in Occupational Medicine. Current activities include Chair of the Human Health and Environment program of the Pennsylvania Consortium for Interdisciplinary Environmental Policy and working with the United Auto Workers Union (UAW) and General Motors Corporation as their "Risk Communicator" to better translate research results into preventive actions at the workplace.

Research Core I: Oxidative Stress and Oxidative Stress Injury



Ian A. Blair

Co-Director: Ian A. Blair, Ph.D.

(Oxidative Stress and Environmental Carcinogenesis)

Dr. Blair received his Ph.D. in Organic Chemistry from Imperial College of Science and Technology, London, where he worked under the direction of the Nobel Laureate Sir Derek H.R. Barton. He was recruited to the University of Pennsylvania in January 1997 to an endowed chair as the A.N. Richards Professor of Pharmacology in order to set up a new Center for Cancer Pharmacology. The Center was officially established in June of 1997 with Dr. Blair as its first Director. He has substantial administrative experience as Director of this Center, as Vice-Chair of the Department of Pharmacology, and as acting Chair of Pharmacology during the sabbatical year of Dr. Garret FitzGerald (2002-2003). Dr. Blair has designed and implemented a new University-wide Proteomics Facility that required the participation of four different schools within the University (Medicine, Arts and Sciences, Engineering and Applied Sciences, Veterinary Medicine). He has organized and chaired symposia on Pharmacology and Toxicology, Oxidative Stress and Lipids, Eicosanoids and Other Bioactive Lipids in Cancer and Inflammation, as well as, Proteomics and Toxicology and recent advances in Metabonomics and Lipidomics, Proteome profiling in cancer detection and therapeutics. Research in Dr. Blair's laboratory has focused on cellular models of oxidative stress. His studies have revealed that antioxidants can in fact also induce damage to cellular macromolecules. This has led to a re-appraisal of exactly how antioxidants function. Dr. Blair is a leader in the application and development of highly novel MS/MS methods for the detection of DNA, lipid, and protein modifications that result from oxidative stress. Dr. Blair has published 193 research articles in leading journals. He is on the Editorial Boards of *Chemical Research in Toxicology*, *Journal of Mass Spectrometry*, and *Current Drug Metabolism* and regularly serves on NIH Study Sections including as an *ad hoc* member of the BET Study Section in February 2005.



Harry Ischiropoulos

Co-Director: Harry Ischiropoulos, Ph.D.

(Oxidative Stress and Protein Modifications during Cardiovascular Disease and Neurodegeneration)

Dr. Ischiropoulos received his Ph.D. in Pathology from New York Medical College in 1989. He was then a postdoctoral fellow with Joe Beckman in the Department of Anesthesiology, University of Alabama at Birmingham. During this time, he made the seminal observations that peroxynitrite was formed from macrophage-derived nitric oxide and that peroxynitrite is a biological source for the nitration of tyrosine residues in proteins. Dr. Ischiropoulos moved to the University of Pennsylvania as a Research Associate in 1992 and has moved up through the ranks to become a Research Professor of Pediatrics and Pharmacology. He held the Parker B. Francis Fellowship in Pulmonary Research from 1993-1996 and was an Established Investigator of the American Heart Association from 1996 to 2001. He received the Young Investigator Award, International Society for Free Radical Research (1994) and Young Investigator Award, Oxygen Society (1995). In 1998, he was appointed as a Stokes Investigator in the Joseph Stokes Jr. Research Institute at the Children's Hospital of Philadelphia. Dr. Ischiropoulos serves on the Editorial Boards of *American Journal of Physiology: Lung Cellular and Molecular Physiology*, *Journal of Pharmacology* and *Experimental Therapeutics and Free Radical Biology and Medicine* where he is an Associate Editor. He was a co-Chair of the 2004 Gordon Conference on "Oxygen Radicals In Biology". He was a reviewer for the NIH Study Section on Brain Disorders and Clinical Neuroscience-3 and the Udall National Parkinson's Centers.

Research Core I: Oxidative Stress and Oxidative Stress Injury

Aron B. Fisher

Aron B. Fisher, M.D.

(Mechanisms of Lung Damage Induced by Reactive Oxygen Species)

Lipid peroxidation and protein oxidation induced by environmental chemicals under varying conditions of oxygenation are correlated with alterations of lung function and with anti-oxidant capacity of the target organ. Dr. Fisher's research involves a study of mechanisms for lung injury associated with decreased organ blood flow. Ischemia/reperfusion injury is evaluated using *in vivo* and isolated perfused rat lung models. This program conducted in collaboration with Drs. Ischiropoulos and Muzykantov investigates mechanisms for initiation of oxygen-derived radical production, the roles of Fe^{2+} and peroxynitrite as oxidants, the pathways for protein oxidation, and novel methods for treatment with anti-oxidants. A goal of these studies is to develop methods for prevention and treatment of ischemia-mediated lung injury. A second area of study is directed towards understanding regulation of the cellular processing of lung surfactant. Current projects include evaluation of granular pneumocyte receptors for surfactant-associated proteins; mechanisms for endocytosis of lung surfactant; coupling of endocytosis to secretion; and pathways for intracellular trafficking and degradation of internalized surfactant components. Major emphasis is directed toward study of the role and properties of a novel Ca^{2+} -independent phospholipase A2 that Dr. Fisher's laboratory has isolated from lung epithelium. Delineation of the pathways of surfactant metabolism will provide important information for understanding the respiratory distress syndrome including its treatment by the administration of exogenous surfactant.



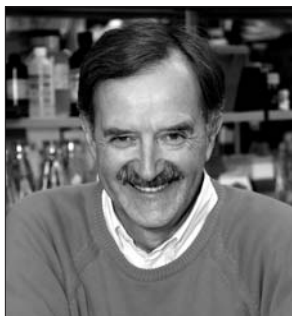
Benoit Giasson

Benoit Giasson, Ph.D.

(Oxidative Stress and Neurodegeneration)

Dr. Giasson's research focuses on how brains of patients with Parkinson's disease (PD) and Alzheimer's disease (AD) accumulate fibrillar pathological inclusions and cause a neurodegenerative disease. One of the pertinacious materials that accumulate in AD brains are neurofibrillary tangles comprised of the microtubule associate protein, Tau whereas Lewy bodies (LBs) composed of the presynaptic protein α -synuclein are the major neuropathology found in PD. Dr. Giasson showed recently that Tau and α -synuclein can mechanistically interact to enhance each other's propensity to form inclusions. Furthermore, Dr. Giasson was the first to demonstrate, in collaboration with Drs. Lee and Ischiropoulos, that α -synuclein in LBs are nitrated suggesting that nitrative/oxidative stress is part of the pathogenic pathways in PD. Indeed, exposure to environmental factors has been directly linked to the incidence of PD, and Dr. Giasson is currently using animal models of synucleinopathies to study the oxidative effects of environmental toxins such as pesticides or arsenic in promoting PD. Thus, his continuing research effort is to better understand the interaction between environmental factors, oxidative and nitrative stress, and the formation of pathological inclusions and neuron death that underlie many neurodegenerative diseases.

Research Core I: Oxidative Stress and Oxidative Stress Injury



Garret FitzGerald

Garret A. FitzGerald, M.D.

(Oxidative Stress and Atherogenesis)

Environmental oxidative stress results in lipid peroxidation and the formation of a series of isoprostanes derived from arachidonic acid. Dr. FitzGerald has pioneered the development of mass spectrometric assays for individual isoprostanes and validated their utility as quantitative markers of oxidant stress in cardiovascular and neurodegenerative disease. Isoprostanes, e.g. iPF2a, cause thromboxane receptor mediated vaso- and broncho-constriction and may be involved in the pathological process. More recently, his laboratory has pursued a more integrated approach in collaboration with Drs. Blair and Ischiropoulos to study the pro-oxidative effects of nicotine in vascular smooth muscle cells *in vitro* and in rodent models of atherogenesis and in humans *in vivo*. These studies utilize mass spectrometric indices of oxidative damage to DNA, modification of protein and lipid in assessing the genomic and proteomic response to this pro-oxidant. These studies are integrated with others, using distinct pro- and anti-oxidative strategies but common analytical platforms in a Specialized Center Of Research (SCOR) in Atherosclerosis.



Toshinori Hoshi

Toshinori Hoshi, Ph.D.

(Protein Oxidation During Oxidative Stress and Aging)

Dr. Hoshi's laboratory has two projects examining protein oxidation that results from environmentally induced oxidative stress - ion channel function and in aging. In particular, he studies the oxidation of the two sulfur containing amino acids, cysteine and methionine, both of which are very readily oxidized, often causing profound changes in protein function. In the first project, his laboratory examines how oxidation of specific cysteine and methionine residues on large-conductance calcium-dependent (Slo1 BK) potassium channels alter their gating behavior using electrophysiological, molecular biological and biochemical methods. These ion channel proteins are important in many physiological phenomena, including synaptic transmission and blood pressure regulation. Impaired vascular relaxation observed with normal aging as well as some cardiovascular diseases involving oxidative stress is likely associated with changes the Slo1 BK channel function. Until now, no clear biophysical and molecular map of the oxidative regulation of the Slo1 BK channel existed. Dr. Hoshi's group is now providing the detailed information. In the second project, Dr. Hoshi examines the roles of reversible oxidation of methionine in aging and senescence-related neurodegenerative diseases, such as Parkinson's diseases. His group hypothesizes that reversible oxidation of methionine residues in proteins involving the peptide methionine sulfoxide reductase (MSR) is a limiting factor in lifespan determination. They postulate that the MSR system protects the cell against a variety of oxidative stress events. These ideas are being tested using *Drosophila* genetics and cultured cells.

Research Core I: Oxidative Stress and Oxidative Stress Injury



Virginia Lee

Virginia Lee, Ph.D.
(Oxidative Stress and Neurodegenerative Disease)

Dr. Lee is presently John H. Ware III Professor of Alzheimer's Research and the Director of the Center for Neurodegenerative Research at the University of Pennsylvania Medical Center, which is committed to research on human neurodegenerative diseases. Dr. Lee is the PI of two program project grants (P01-AG11542-08 "*In vitro* and *In vivo* Models of Alzheimer's Disease"; P01-AG17586-5 "Tauopathies: Genotype and Phenotype") she is also Co-PI of a program project grant on Alzheimer's disease (AD) and Parkinson's disease (PD) (P01 AG-09215-12, "Molecular Substrates of Aging and Neuron Death"). Recently, she and colleagues were recipients of a major donation of \$4 m to develop an AD Drug Discovery Program at the University of Pennsylvania. Dr. Lee's major research interest focuses on the neuronal cytoskeleton and its role in the pathobiology of neurodegenerative diseases such as AD. Dr. Lee's research interests focus on how proteins such as the neuronal microtubule associated protein tau, Ab and a synaptic protein known as a-synuclein aggregate in brains of patients with neurodegenerative diseases such as AD, PD and frontotemporal dementia to form major neuropathologic lesions. It is hypothesized that these abnormal protein aggregates eventually cause the demise of nerve cells and lead to neurodegeneration. Dr. Lee has used a multidisciplinary approach (including *in vitro* aggregation studies, biochemical and molecular studies of neuronal culture systems, animal models and human tissues obtained at autopsy) to model and study the disease phenotypes and to develop an understanding of how these proteins interact with themselves and with each other to form highly insoluble protein aggregates. Environmental factors and toxins (e.g., pesticides such as rotenone, and neurotoxins such as MPTP) which cause oxidative stress have been found to play a prominent role in the pathogenesis of these neurodegenerative diseases, particularly PD. Dr. Lee has conducted many studies to demonstrate the consequences of nitrate/oxidative stress in *in vitro* and *in vivo* models of these disorders as well as in patients with these diseases. Studies in collaboration with Drs. Giasson and Ischiropoulos are currently directed at understanding the role of oxidative stress in the formation of these misfolded protein aggregates.



Linda McCauley

Linda McCauley, M.N., Ph.D.
(Oxidative Stress Induced by Organophosphate Pesticides)

There is compelling evidence from whole animal and tissue culture studies that pesticides, especially organophosphate pesticides (OPs), induce oxidative stress. OPs have also been reported to reduce antioxidant enzyme activity, enhance the production of lipid peroxide, reduce the level of cellular antioxidants, reduce glutathione levels and decrease glutathione peroxidase activity. Increased serum and urinary levels of lipid peroxides and altered blood levels of glutathione (GSH) and antioxidant enzymes have been detected in several cases of pesticide poisoning. Dr. McCauley has conducted investigations of OP exposure and multiple measures of oxidative stress in pesticide applicators and farm workers. Her methods include epidemiological surveys of work practices, dietary intake and lifestyle behaviors. No clear correlation emerged between levels of urinary OP metabolites and any of the biomarkers of oxidative stress but correlations involving APE and the OP metabolites were strongest in the pesticide applicator group. These results provided preliminary evidence of the usefulness of biomarkers of DNA damage and oxidative stress in agricultural workers potentially exposed to pesticides. The possible health implication of the variations in these markers of oxidative stress is undetermined. Dr. McCauley is currently conducting a larger study of 300 farmworkers (adults and adolescents) exposed to OPs during work activities. This work will also include measuring markers of DNA damage (comet assays) in buccal cell samples.

Research Core I: Oxidative Stress and Oxidative Stress Injury

Vladimir R. Muzykantov, M.D., Ph.D.

Vladimir R. Muzykantov (Oxidative Stress in Lung Injury and Cardiovascular Disease)

Dr. Muzykantov's research, which involves substantial collaborations with Drs. Fisher and Ischiropoulos, is focused on three projects. The first project involves the design and testing of novel drug delivery systems for targeted delivery of antioxidant drugs (catalase, SOD, other antioxidant enzymes) to endothelial cells. Major strategies include immunotargeting of these drugs to endothelial cell adhesion molecules and design of polymer nanocarriers that can be loaded with catalase for intracellular delivery. Potential applications of these advanced delivery systems include containment of an acute (eg, hyperoxia, ischemia/reperfusion and acute lung injury) and chronic (e.g., hypertension, diabetes) vascular oxidant stress. The second project is focused on the development of novel animal models of pulmonary and vascular oxidant stress, including targeted delivery of oxidant-generating enzymes to endothelium and effects of abnormal levels of oxygen. The goals are to establish models useful for the testing of drug delivery systems to counter oxidative stress and to better understand mechanisms of vascular oxidant stress. The third project involves investigations of specific mechanisms of vascular oxidant stress associated with ischemia/reperfusion.



Rebecca A. Simmons

Rebecca A. Simmons, M.D.

(Oxidative Stress and Diabetes)

The principal goal of Dr. Simmons' research program is to elucidate the underlying molecular mechanisms that link fetal growth retardation to the later development of type 2 diabetes in adulthood. She currently has three major projects and several smaller projects. The first project focuses on the relationship between oxidative stress and β -cell dysfunction and insulin resistance. Her group has developed a model of fetal growth retardation in the rodent (mice and rats), which leads to the later development of diabetes in adult animals. She has established that fetal growth retardation induces progressive mitochondrial dysfunction, oxidative stress, mtDNA mutations, and electron transport defects. These defects cause abnormal β -cell function and development, hepatic and muscle insulin resistance. Oxidative stress decreases transcription of key genes related to β -cell development, induces modifications of proteins of the Krebs cycle in the liver, and muscle. The goals of the second project are to determine the molecular mechanisms underlying the protective effect of Exendin-4, a glucagon-like peptide-1 homolog. Dr. Simmons has shown that exendin-4 treatment of newborn growth-retarded rats prevents the development of diabetes. Furthermore, Exendin-4 prevents the decline in β -cell mass normally observed in growth-retarded rats, by inducing Pdx-1 (a homeobox gene critical for pancreas development) transcription, which, in turn, enhances β -cell neogenesis and proliferation. The third project is defining the epigenetic mechanisms underlying the permanent changes in gene expression observed in our animal model. Her group is also investigating the possibility that oxidative stress induces chromatin remodeling.

Research Core I: Oxidative Stress and Oxidative Stress Injury

Stephen R. Thom

Stephen R. Thom, MD, Ph.D.

(Oxidative Stress and Myelin Modifications)

The focus of Dr. Thom's work is to identify the pathophysiology of brain injury due to carbon monoxide (CO) poisoning. The mechanism for neuropathology is unclear and cannot be explained simply by hypoxic stress. Over the past 18 years, his laboratory has found a rather intricate cascade of events leading to injuries using rodent (rat and knock-out mouse) models. Intravascular neutrophil activation, an early event closely linked to neuropathology, was recently shown to occur in patients suffering severe CO poisoning. CO interactions with heme-containing proteins contribute to progression of brain injury by causing a transient compromise in cerebral blood flow. In studies conducted with Drs. Ischiropoulos and Fisher, CO-mediated changes in endothelium and platelets were shown to include liberation of reactive species such as nitric oxide and peroxynitrite. Stimulation of N-methyl-D-aspartate (NMDA) receptors and activation of neuronal nitric oxide synthase, in particular, caused perivascular changes that lead to neutrophil sequestration. Neutrophil sequestration-activation and protease-mediated conversion of endothelial cell xanthine dehydrogenase (XD) to xanthine oxidase (XO) are key early events while XO activity drives brain lipid peroxidation. If NMDA receptors are blocked, or neuronal nitric oxide synthase activity is inhibited before CO poisoning, the impairment of learning normally observed with CO poisoning does not occur. Biochemical and immunological studies indicate that myelin basic protein undergoes charge and antigenic alterations in response to CO poisoning. An immune response to the altered protein is the most proximal event leading to development of impaired learning over a three-week period of time.

Research Core II: Endocrine and Reproduction Disruption



Jeanne M. Manson

Co-Director, Jeanne M. Manson, Ph.D., M.S.C.E

(Gene-Environment Interactions and Male Reproductive Tract Anomalies)

Dr. Manson is a molecular epidemiologist with interest in gene-environment interactions causing structural birth defects. Current studies in her laboratory focus on gene-environment interactions that cause male reproductive tract anomalies, including hypospadias and undescended testes. Through collaborations with clinical investigators at CHOP, patients coming in to Pediatric Urology for evaluation/surgical repair of hypospadias are recruited. Questionnaires are administered to parents to obtain information on demographic, clinical and environmental risk factors, and cheek swabs collected to obtain a source of DNA from the mother, father and infant. Candidate genes involved in androgen action and metabolism are examined for polymorphisms, and clinical as well as environmental risk factors evaluated from the questionnaire data. Findings to date in approximately 450 families are that low birth weight is a clinical risk factor for hypospadias, and that maternal as well as paternal pesticide exposure at home is an environmental risk factor. Family history of male reproductive tract anomalies is a genetic risk factor for hypospadias, as well as the occurrence of a V89L polymorphism in the steroid 5- α reductase type II gene. The mother appears to be the major carrier of this polymorphism, which is preferentially passed on from the mother to case infants compared to control infants. This research will elucidate the relative contribution of genetic and environmental risk factors that cause urogenital anomalies.



George L. Gerton

Co-Director, George L. Gerton, Ph.D.

(Spermatogenesis, Fertilization, Pre-implantation and Ectopic Pregnancy: Targets and Consequences of Reproduction Disruption)

Reproduction can be disrupted on several levels. Hormone action is critical for sperm formation, the acquisition of competence for fertilization by gametes, and early events of mammalian embryo development, including the implantation process. Some environmental factors such as smoking and oxidative damage are known to be disruptors of these processes. A major project in the Gerton laboratory is to understand what molecular pathways regulate the construction and functioning of a spermatozoa. One area has focused upon the proteins that comprise the sperm tail with the objective of understanding how these proteins interact to drive sperm motility. A second goal of the Gerton group is to understand the events taking place between sperm and the extracellular matrix of the ovum, the zona pellucida. A third major project focuses on the role of progranulin (also known as acrogranin or the granulin/epithelin precursor) in preimplantation embryo development. Hormones and factors secreted in the female reproductive tract endow the gametes with the competence for fertilization and the researchers in the laboratory are concentrating on how these events take place and what compounds may interfere or promote these interactions. The Gerton laboratory has demonstrated that progranulin, a growth factor, is essential for reproduction and is regulated by steroid hormones. Blocking of the action of progranulin disrupts the ability of the blastocyst to develop and implant in the uterus. A fourth major thrust of the Gerton team is the diagnosis of ectopic pregnancies in the human using proteomic and genomic approaches. A risk factor for ectopic pregnancy is maternal smoking; how this environmental factor may increase the predisposition for this condition is unknown but is an interest in the laboratory.

Research Core II: Endocrine and Reproduction Disruption

Kurt Barnhart

Kurt Barnhart, M.D., M.S.C.E.

Dr. Barnhart is an Associate Professor in the Department of Obstetrics and Gynecology, the Department Epidemiology, and a Senior Scholar in the Center for Clinical Epidemiology and Biostatistics. Dr. Barnhart directs the Reproductive Research Unit of Center for Reproductive Medicine and Surgery at the University of Pennsylvania. He is board certified in Obstetrics and Gynecology and Reproductive Endocrinology and Infertility. Dr. Barnhart's research activities include a NIH funded investigation into the diagnosis and treatment of ectopic pregnancy (RO1). He is also part of a NIH program project evaluating the activity and distribution of novel vaginal contraceptives/microbicides (P01). Specifically he is using MRI to objectively measure the vaginal distribution of topical medications. Dr Barnhart has completed a NIH contract for the conduct of a phase I trial evaluating a novel spermicide/microbicide and has participated in numerous multi-center trials including a trial evaluating the efficacy of spermicides contracted by NICHD to Family Health International (FHI). His interest also includes the accuracy of tests to evaluate fertility potential and the evaluation of new therapeutic modalities in the treatment of the infertile women. He has also evaluated novel methods of hormone replacement such as the combination of androgens and estrogens and the effect of DHEA supplementation as an adjunct to hormone replacement therapy.



Phyllis Dennery

Phyllis Dennery, M.D.

(Role of Heme Oxygenase in Neonatal Hyperoxic Injury)

The heme oxygenase isoenzymes HO-1 (the inducible form) and HO-2 (the constitutive form) catalyze the degradation of heme to yield CO, biliverdin and ferrous ion. The reaction is important in neonatal development because biliverdin is the sole precursor of bilirubin. Both biliverdin and bilirubin are potent anti-oxidants and can protect from pro-oxidant injury. Dr. Dennery has shown that altered expression of HO-1 and HO-2 modifies reactive iron content in cells and tissues. More recent evidence suggests that HO proteins can alter HO-1 promoter activation and that HO-1 can migrate to the nucleus. She has hypothesized that: 1) increased protein expression of HO-1 or HO-2 modifies the transcription of HO-1 mRNA and protein and thereby is a feedback mechanism for the regulation of HO-1 expression; 2) nuclear migration of HO-1 is an important signaling event that impacts cell proliferation and apoptosis; 3) increased nuclear migration of HO-1 in the lungs of neonatal mice is a protective mechanism against oxidative injury. The aims of her research are: 1) to characterize the effects of HO protein on HO-1 transcriptional activation; 2) to document HO-1 nuclear migration and evaluate the resultant effects on cell proliferation and apoptosis; and 3) to determine whether there are maturational differences in the nuclear localization of HO-1 *in vivo* and whether this promotes tolerance to hyperoxia. A better understanding of the mechanism by which HO mediates its actions may help dictate therapeutic strategies to enhance or suppress HO effects. Importantly, CO formed during heme oxygenase catalyzed oxidation of heme has been proposed to play a complementary role with nitric oxide in the regulation of placental hemodynamics and a role in limiting preeclampsia. Others have shown that HOs play a crucial role in pregnancy and low expression of HO-2, as observed in pathologic pregnancies, may lead to enhanced levels of free heme at the fetomaternal interface. Both these effects may be influenced by polymorphisms in HO. The laboratory is interested in environmental triggers that alter HO expression/activity since these may affect pregnancy outcome.

Research Core II: Endocrine and Reproduction Disruption



Ina Dobrinski

Ina Dobrinski, M.V.Sc., Ph.D.

Research in Dr. Dobrinski's laboratory is focused on male germ cell biology in domestic animals and non-human primates. As experimentation in non-rodent target species is inherently difficult, time consuming and expensive, they developed the technique of testis tissue xenografting into mouse hosts as model system for the study and manipulation of spermatogenesis that is applicable to a variety of mammalian species including primates, they developed. This approach allowed for the first time complete spermatogenesis and production of functional sperm from immature testis tissue obtained from different domestic animal species and non-human primates in a mouse host. They employ this strategy not only as a basic science tool for the study of spermatogenesis in different species, but also for preservation of male genetics from immature individuals like endangered animals, valuable laboratory strains or farm animals, and potentially even human childhood cancer patients. They are now utilizing the accessible xenografting system for controlled investigations of male reproductive toxicity in primates. This will allow us to screen for effects of different dosages and exposure times on the primate testis in a controlled fashion without the necessity of experimentation in the target species. Once an effect has been detected, experiments in primates utilizing much smaller numbers of animals than would be required for screening experiments can be targeted at confirming the toxic effects under investigation.

Norman B. Hecht

Norman B. Hecht, Ph.D.

(Molecular Basis of Male and Female Germ Cell Development and Function)

Dr. Hecht's research focuses on mechanisms that regulate the differentiation of mammalian male and female germ cells. Emphasis currently is centered on DNA- and RNA-binding proteins of gametes that regulate gene expression at post-transcriptional levels. One protein, MSY2 functions as a DNA-binding transcription factor and also as a sequence independent RNA-binding protein that facilitates the storage of maternal mRNAs during oogenesis. A second multifunctional protein, TB-RBP, represses translation of stored mRNAs, transports mRNAs to specific subcellular sites in gametes, and binds to chromosomal translocation breakpoints in the nuclei of meiotic germ cells. These systems provide a sensitive molecular assay system to detect reproductive disruption and environmental toxicity to both the male and female reproductive systems leading to human subfertility and infertility. Overall, these systems provide highly sensitive assays to assess whether environmental agents will be toxic to the male and/or female reproductive systems leading to human subfertility and infertility.

Research Core II: Endocrine and Reproduction Disruption

Mitchell Lazar

Mitchell Lazar, Ph.D.

(Regulation of Transcription and Metabolism by Nuclear Receptors)

The large family of nuclear receptors regulates gene expression in response to small lipophilic molecules derived from the environment, nutrition, and metabolism. Nuclear receptor ligands include hormones (both endogenous and environmental), vitamin metabolites, metabolites related to lipid synthesis and processing, and xenobiotics. Dr. Lazar's laboratory is studying the mechanisms by which these receptors regulate gene transcription. He is especially interested in mechanisms by which unliganded receptors repress transcription, but it should be noted that antagonist bound receptors (e.g., tamoxifen-bound estrogen receptor) have similar functions. These studies are particularly relevant to endocrine disruptors that alter nuclear receptor signaling. In the past 5 years, Lazar discovered the CoRNR box regulating corepressor interaction with nuclear receptors, identified Class II histone deacetylases (HDACs) as partners for corepressors N-CoR and SMRT, and purified an endogenous SMRT, thereby identifying HDAC3 and TBL1 as key components of a core SMRT complex. These interactions can in part explain the tissue-specific effects of nuclear receptor ligands, which may also be mimicked by environmental ligands. Dr. Lazar is also studying PPAR γ , a nuclear receptor that is necessary for adipocyte differentiation. He has also shown that MAP kinase-dependent phosphorylation of PPAR γ alters its transcriptional activity, and generated mice with mutations in their PPAR γ alleles that mimic the phosphorylated and non-phosphorylated PPAR γ . Phenotyping of these mice will be critical to understanding the physiological role of PPAR γ phosphorylation, and will shed light on the normal role of PPAR γ in normal metabolism. PPARs may play a more general role in determining cellular differentiation patterns and interest exists in determining whether there are environmental ligands for these orphan receptors.



Stuart B. Moss

Stuart B. Moss, Ph.D.

Dr. Moss' research program in the Center for Research on Reproduction and Women's Health (CRRWH) at Penn has emphasized cell signaling during mammalian spermatogenesis and sperm function. The mature sperm cell is a highly compartmentalized and polarized cell whose only function is to fertilize an egg. This cell contains several structures, many of them unique, with each one functioning in an independent, yet coordinated manner. Relatively little is known about the assembly and function of sperm signaling pathways in different cellular domains. He and George Gerton were the first to identify and characterize a protein, AKAP4, which acts as a scaffold for signaling proteins in mammalian male germ cells and sperm. They identified AKAP4, the major protein of the fibrous sheath of the sperm's flagellum, by its ability to tether the regulatory subunit of the cAMP-dependent protein kinase A. Because sperm motility is regulated by a series of protein phosphorylation/dephosphorylation events, the tethering of protein kinase A to a specific subdomain of the flagellum suggests that AKAP4 is involved in the cAMP-regulation of motility. The identification of scaffolding proteins such as AKAPs has caused a reassessment of the previous conceptions of multi-component signal transduction systems. The assembly of signaling molecules into macromolecular complexes, a.k.a. "transducisomes" or "signalosomes" provides specificity, sensitivity and speed in intracellular signaling pathways.

Recent work has included a proteomic analysis of the accessory structures of the mouse sperm tail. The accessory structures – the fibrous sheath, outer dense fibers, and mitochondrial sheath – are unique to the sperm flagellum and are not found in cilia of other cells. Proteins identified by this analysis have roles in signaling, metabolism, and oxidative stress, indicating that the accessory structures are dynamic entities. Of interest, many of the proteins from the SDS-insoluble tail structures are involved in the generation and utilization of ATP. His laboratory also is investigating the role of the soluble adenylyl cyclase (sAC) in events related to sperm capacitation; the generation of cAMP by sAC regulates a number of proteins including protein kinase A. Our results, using both sperm from sAC-null mice and wild-type sperm incubated with a pharmacological inhibitor of sAC, indicate that capacitation is defined by separable events, e.g., induction of protein tyrosine phosphorylation and sperm motility is sAC-dependent while acrosomal exocytosis is not.

Research Core II: Endocrine and Reproduction Disruption

Mary Mullins

Mary Mullins, Ph.D.

(Genetic Analysis of Maternal Factors in Embryonic Development)

Vertebrate embryos depend upon maternal factors for primordial germ cell development, mesoderm formation, establishment of the dorsal-ventral and animal-vegetal axes, and general cellular processes prior to the onset of zygotic transcription. Little is known about the molecular nature of these maternal factors and the extent of their involvement in normal mammalian embryonic development. Dr. Mullins is exploiting the ability to perform large-scale genetic screens in the zebrafish, *Danio rerio*, to identify and characterize mutants of key genes specifically required in the mother for egg activation, fertilization, development of the germ line, and establishment of the body plan of the vertebrate embryo. The following studies are proposed; 1.) to perform a maternal-effect mutant screen of 2000 ENU mutagenized genomes for defects in primordial germ cell and embryonic body plan formation; 2.) to characterize mutant embryos or oocytes through fine morphological analysis, whole mount antibody stainings, *in situ* hybridizations, and other staining methods to determine if the mutants are defective in egg activation, fertilization, early cellular cleavages, DNA segregation, cell survival, or in cell fate specification of differentiation. This analysis will provide important information regarding the precise defects associated with loss of a particular maternal factor and possible molecular pathways that are defective in the mutants; and 3.) to map a subset of maternal-effect mutations to chromosomal positions to facilitate propagation of the mutant strain and to identify the molecular nature of the maternal-effect gene by examining cloned genes mapping to the same genetic interval. Mutations are expected in genes involved in germ layer development, embryonic axis formation, anterior-posterior pattern formation, morphogenesis of the embryo, egg activation, fertilization, primordial germ cell development, and other critical developmental processes. These studies will be relevant to the nature of human sterilities, birth defects, and human inherited disorders and the effects of environmental mutagens.

Katharine Nathanson

Katharine Nathanson, M.D.

(Mechanisms Underlying Testicular Germ Cell Tumors, TGCT)

Dr. Nathanson's laboratory is conducting a case-control study in testicular cancer examining genetic variants and risk factors in relationship to TGCT susceptibility. Her specific interest is in genetic variants and risk factors that influence testosterone exposure in men and how they correlate with TGCT risk. Infertility and abnormal spermatogenesis are closely linked with testicular cancer, and it is hypothesized that the increase of endocrine disruptors in the environment are associated with the increasing rates of both infertility and testicular cancer. There is a significant genetic component to testicular cancer risk, so Dr. Nathanson is particularly interested in how variants in the genetics that modulate testosterone exposure interact with endocrine disruptors in the environment to influence risk. She has collected 184 cases and 259 controls and has preliminary data suggesting that genetic variants that increase testosterone exposure are underrepresented in testicular cancer cases. In addition, Dr. Nathanson is leader of an international study that has identified the Y deletion *gr/gr*, initially identified as risk factor for spermatogenic failure, as a low penetrance allele conferring risk for TGCT. The frequency of Y deletion *gr/gr* in probands from 432 families with multiple cases of TGCT, 1392 TGCT cases without a family history and 2599 controls from Europe and North America. The *gr/gr* deletion was present in 1.3% of control males, 2.2% of sporadic TGCT patients and 3.0% of TGCT familial patients. Carriage of the *gr/gr* deletion was associated with a two-fold increased risk of sporadic TGCT (adjusted odds ratio [aOR] 2.2, 95% confidence interval [CI] 1.3, 3.6) and three-fold increased risk of familial TGCT (aOR 3.2, (95% CI 1.5, 6.7). Her group has identified the Y deletion *gr/gr* as the first genetic risk factor to link infertility and TGCT.

Research Core II: Endocrine and Reproduction Disruption

Samuel Parry

Samuel Parry, M.D.

(Placental Viral Infections as Risk Factors for Preeclampsis)

Dr. Parry is studying the pathologic effects of placental viral infection. He is testing the hypothesis that viral infection of extravillous trophoblast cells induces pathologic changes that interfere with placental invasion into the uterine wall, resulting in reduced placental perfusion, placental dysfunction and adverse obstetric outcomes that are associated with placental dysfunction. He has formulated a two-pronged approach to test this hypothesis, using *in vivo* and *in vitro* models to correlate viral infection with trophoblast cell death, placental dysfunction, and adverse clinical outcomes. Thus far, Dr. Parry has determined that extravillous trophoblast cells are susceptible to infection by adeno-associated virus-2 (AAV-2), human papillomavirus (HPV) and cytomegalovirus (CMV), and that infection with these viruses induces apoptosis and reduces the invasive activity of extravillous trophoblast cells. Additionally, in case-control studies, placentas from cases of severe preeclampsia were commonly infected with AAV-2, while placentas from spontaneous preterm deliveries were more commonly infected with HPV and CMV than controls. In the future, Dr. Parry intends to study the molecular mechanisms by which viral infections reduce the invasion activity of extravillous trophoblast cells. These experiments will provide new insights into the role of viral infection in the pathogenesis of impaired placental function leading to adverse pregnancy outcomes. Dr. Parry is also studying *Chlamydia pneumoniae* infection of the placenta. *Chlamydia pneumoniae* has been identified in atherosclerotic plaques and has been associated with numerous vascular diseases. However, *Chlamydia pneumoniae* infection of the placenta and its association with adverse obstetric outcomes has not been investigated. In recent preliminary studies, he found that *Chlamydia pneumoniae* efficiently infects placental trophoblast cells, causes apoptosis of extravillous trophoblast cells, and reduces invasion by these cells through an extracellular matrix. He conducted PCR-based studies to detect *Chlamydia pneumoniae* DNA in trophoblast cells from cases of preeclampsia and controls. Thus far, they have detected *C. pneumoniae* DNA in 15/48 (31%) placentas from women with preeclampsia and 3/30 (10%) placentas from controls (P=0.02 [Fisher exact test], OR=4.1, 95% CI 1.1, 15.6). Approximately 50% of reproductive-aged women have been exposed to *Chlamydia pneumoniae* (IgG seropositivity), and documentation of acute infection in these women requires the demonstration of rising IgG titers (reinfection) or IgM seropositivity. Therefore, they plan to obtain paired serum samples at initial prenatal visits (discarded rubella immunology samples) and at 15-20 weeks' gestation (discarded multiple marker screen samples) and will measure paired IgM and IgG antibody titers using commercially available ELISA kits (Bio-Quant, Inc., San Diego, CA). In addition, they will correlate serologic status with the presence of *C. pneumoniae* in maternal PBMCs by performing rtPCR using primers to detect *C. pneumoniae* 16S rRNA.

Richard M. Schultz

Richard M. Schultz, Ph.D.

Dr. Schultz is interested in (1) the role of calcium oscillations during egg activation; (2) RNAi in mouse oocytes and preimplantation embryos; (3) gene expression during oogenesis and preimplantation development; and (4) the effect of culture on gene expression and behavior. With respect to egg activation, his laboratory is pursuing (a) the molecular mechanisms underlying the acquisition during oocyte maturation of the Ca²⁺ oscillatory behavior observed following fertilization, (b) the linkage between these Ca²⁺ oscillations in the 1-cell embryo and changes in gene expression that occur during preimplantation development, and (c) the linkage between these changes in gene expression and post-implantation development. Dr. Schultz developed a transgenic RNAi approach that is suitable to study the function of any gene during mouse oocyte development and early embryogenesis, and is using this method to study the function of several genes that regulate chromatin structure in oocyte development. In addition, he is studying the role of RNAi in constraining retrotransposition in the preimplantation embryo. Using Affymetrix chips he has analyzed temporal patterns of gene expression during preimplantation development and the database generated from these studies is furnishing a trove of information regarding how oocytes and embryos develop. The function of interesting candidate genes is then assessed by their transgenic RNAi approach. The Schultz lab noted that culture conditions can perturb global patterns of gene expression in preimplantation mouse embryos, in particular that of the imprinted *H19* gene. Moreover, they find that mice derived from cultured embryos exhibit specific behavioral alterations in anxiety and spatial memory. He is pursuing these studies by (a) examining the effect of different culture conditions on the expression of a battery of imprinted genes, as well as on global patterns of gene expression as determined by microarray analysis, (b) altering the culture conditions to minimize or eliminate the behavioral consequences of culture, and (c) mimicking clinical procedures known to produce low quality eggs used in ART. The impact of environmental exposures on the quality of eggs and pre-implantation embryos is a major interest of the laboratory.

Research Core II: Endocrine and Reproduction Disruption



Wenchao Song

Wenchao Song, Ph.D.

(Estrogen Sulfotransferase as a Target for Endocrine Disruption)

Dr. Song has been studying an estrogen-specific sulfotransferase (EST) that is expressed in the male reproductive tract and the placenta and is also differentially regulated in breast carcinomas. By creating and characterizing an EST gene knockout mouse, he has revealed that EST plays a critical role in modulating tissue estrogen sensitivity in the placenta and in the male reproductive tract. Thus, absence of EST led to estrogen-induced placental thrombosis and fetal wastage in pregnant mice and to age-dependent pathological changes in the male reproductive system. Recently, human EST has been found to be potently inhibited by hydroxylated PCB and PAH metabolites. This observation and Dr. Song's findings with EST knockout mice suggest that environmental agents may cause endocrine disruption not by directly acting as receptor-active hormones, but rather by inhibiting steroid hormone transforming enzymes such as EST, thereby potentiating endogenous estrogen toxicity.



Carmen J. Williams

Carmen J. Williams, M.D., Ph.D.

(Signaling in Germ Cells; Human Infertility)

The Williams' laboratory has research interests in signal transduction mechanisms important during mammalian oocyte maturation, fertilization, preimplantation development, and implantation. The mouse is used as a model system as it closely approximates early reproductive processes in the human, although some ongoing work involves the use of human tissues. One major focus of the laboratory is the regulation of cAMP-dependent protein kinase (PKA). "A kinase anchor proteins", or AKAPs, serve as scaffolding proteins that tether PKA at specific locations within the cell in order to regulate its function. Dr. Williams identified and is currently characterizing AKAPs in oocytes and preimplantation embryos that likely serve to regulate PKA function in these cells. A second area of interest is cell-cell communication critical for sperm-egg interactions at fertilization and for embryo-uterus interactions at implantation. She is currently examining roles for a tetraspan protein called epithelial membrane protein 2 in these interactions that are critical for the success of early reproductive events. Finally, she is examining the activity of specific human sperm proteins in male fertility. The impact of environmental toxins on oocyte maturation, fertilization, granulosa cell function, and other aspects of fertility is highly relevant to the research themes of the laboratory.

Research Core III: Lung and Airway Disease

Reynold A. Panettieri

Co-Director: Reynold A. Panettieri, Jr., M.D.

(Epithelial/Mesenchymal Cell Function and Human Studies Research Groups).

Dr. Panettieri's research focuses on understanding basic cellular and molecular signaling pathways that modulate airway smooth muscle (ASM) cell function in chronic severe asthma and COPD. ASM serves as the primary cell regulating bronchomotor tone and also plays a critical role in orchestrating and perpetuating airway inflammation. Dr. Panettieri's laboratory focuses on two themes: defining the molecular processes that promote or inhibit ASM cell growth, a common finding in the airways of subjects with chronic severe asthma, and characterizing the mechanisms by which ASM secretes chemokines and cytokines that alter immunocyte function. Importantly, Dr. Panettieri has recently shown that TNF α -mediated effects on mitogen-induced ASM growth and on chemokine/cytokine secretion are due in part to the autocrine secretion of interferon β . These observations have led him to postulate that genetic aberrations in interferon beta and/or other autocrine-secreted "repair" genes may promote airway remodeling and irreversible airway obstruction.

In addition to his basic science research, Dr. Panettieri directs the Airways Biology Initiative (ABI), an interdisciplinary program combining expertise in cellular, molecular, genetic and clinical science devoted to understanding the pathogenesis and to curing airway diseases that include asthma, chronic bronchitis, emphysema and bronchiectasis. The ABI has an outpatient bronchoscopy suite and pulmonary function laboratory dedicated to lung research. The research bronchoscopy suite and pulmonary function laboratory perform transbronchial biopsies, bronchoalveolar lavage and endobronchial ultrasound as well as full pulmonary function testing, exhaled nitric oxide and forced oscillation measurements. These facilities accommodate approximately 200 research bronchoscopies and 500 pulmonary function measurements per year. Current support for this initiative is derived from Dr. Panettieri's SCOR award and industry-sponsored research. ABI membership includes 30 full-time faculty, postdoctoral fellows and students who have primary appointments in the several Schools and myriad Departments. Additionally, faculty from the Wistar Institute, Children's Hospital of Philadelphia (CHOP) and the Schools of Nursing and Dental Medicine are represented.



Steven M. Albelda

Co-Director: Steven M. Albelda, M.D.

(Human Studies Research Group)

Dr. Steven Albelda is the William Maul Measey Professor of Medicine, Department of Medicine, Pulmonary, Allergy and Critical Care Division. He also serves as the Director of Lung Research in the Pulmonary Division, Co-Director of the Thoracic Oncology Laboratories, and is a Member of the Cell and Molecular Graduate Group and the Institute for Environmental Medicine. He is an Adjunct Professor at the Wistar Institute and serves as the Chairman of the Wistar Institutional Review Board.

Dr. Albelda has published more than 175 papers and is a nationally recognized investigator in the fields of cell adhesion, endothelial cell biology, thoracic oncology and gene therapy. He served as an Associate Editor on the *American Journal of Respiratory Cell and Molecular Biology* until 2003 and remains on the Editorial Board. He is on the Editorial Boards of the *American Journal of Physiology*, *Lung Cellular and Molecular Physiology* and *Cancer Gene Therapy*. He has been continuously funded by the NIH since his fellowship and is currently the Principal Investigator of an NCI-funded Program Project on "Gene Therapy for Malignant Mesothelioma," the PI. of an RO1 grant, and the Co-PI. on an RO1, Department of Defense grant, and a Pennsylvania Department of Health Tobacco-Funded Center of Excellence. He serves on the NIH's DNA Recombinant Advisory Committee. He is a former Established Investigator of the American Heart Association and also serves regularly on an ad-hoc basis on numerous NIH/NCI Study Sections.

Dr. Albelda has been active in research training for the past twenty years and has trained over 45 medical students, residents, fellows, and visiting scientists in his laboratory since 1985. He has conducted and has been funded for both basic research and translational studies (including analysis of patient samples and gene therapy clinical trials) allowing him to effectively supervise both the basic and translational research programs of this Core. He continues to serve as an attending physician in the Medical ICU and the Pulmonary Consultation Service.

Research Core III: Lung and Airway Disease



Yassine Amrani

Yassine Amrani, Ph.D.

Despite considerable research effort, the molecular mechanisms inducing asthma remain elusive. Dr. Amrani focuses on the signaling pathways by which inflammatory cytokines engender a "pro-asthmatic" phenotype in airway smooth muscle and potentially promote disease progression. Dr. Amrani provided the first evidence that cytokines augment agonist-induced G-protein coupled receptor-associated calcium signaling pathways in airway smooth muscle and enhance agonist-mediated airway hyperresponsiveness, a hallmark of asthma. Dr. Amrani also characterizes signal transduction pathways, i.e., receptors, transducers, and transcription factors that regulate expression of "pro-asthmatic" genes in airway smooth muscle. Dr. Amrani is an expert in the use of cellular and molecular techniques including whole cell calcium video-imaging, pharmacodynamic studies in murine tracheal rings, cell-based transfection, reporter plasmid studies, electromotility shift assays, *in vitro* kinase assays. Dr. Amrani's central hypothesis states that the airway smooth muscle is no longer a passive contractile unit that solely regulates the degree of bronchomotor tone but also serves an immunomodulatory role influencing the onset and the progression of asthma and COPD.

Andrea Apter

Andrea Apter, M.D., M.Sc.

Dr. Apter is an asthma expert, allergist-immunologist, and epidemiologist. She is chief of the Allergy and Immunology Section at Presbyterian Medical Center. She evaluates patients at the Hospital of the University of Pennsylvania and Presbyterian Medical Center for all allergy-immunology related problems including asthma, allergic rhinitis, sinusitis, adverse drug reactions, immunodeficiencies, urticaria, and anaphylaxis. Her research focuses on asthma, the social factors that influence disease, and on reducing health disparities. She is Associate Editor of the *Journal of Allergy and Clinical Immunology*, a Director of the American Board of Allergy and Immunology, and she served on the FDA Pulmonary Allergy Drug Advisory Committee.

Research Core III: Lung and Airway Disease

Michael F. Beers

Michael F. Beers, M.D.

(Epithelial/Mesenchymal Cell Function Research Group)

Dr. Beers is an Associate Professor of Medicine; Department of Medicine, Pulmonary, Allergy and Critical Care Division (School of Medicine). By virtue of its anatomic position, the pulmonary epithelium sits at the interface between the lung and the environment, and thus represents an important site for host defense and modulation of inflammation. Pulmonary epithelial cells synthesize and secrete a surface-active film of biochemically heterogeneous lipoprotein mixture (lung surfactant) that reduces surface tension at air-liquid interfaces and allows for maintenance of alveolar stability at low lung volumes. More recently and directly relevant to this proposal, several protein components of the surfactant system (Surfactant protein (SP) -A, and -D) are now recognized as part of an emerging family of proteins important for innate host defense and modulation of inflammation, the collectins. The term collectin (collagen-like lectin) has been used to describe this family, which in addition to SP-A and SP-D, includes non-lung protein members mannose-binding protein, bovine conglutinin, and CL-43. Both SP-A and SP-D interact with a variety of pathogens and modulate part of the increasingly complex interplay between host inflammatory cell responses and inhaled stimuli. Furthermore, in humans it is now well established that variations in expression of alleles for both SP-A and SP-D are associated with varied host responses (susceptibility or protection) to a variety of pulmonary injuries including tobacco smoke (COPD), allergens, and viruses. In addition, variations in SP-A and/or SP-D allele frequencies have also been linked to lung diseases including RDS of the newborn and bronchopulmonary dysplasia. Dr. Beers laboratory is engaged in understanding the interplay between the collectin expression and the pulmonary injury response. Current projects include the characterization of collectin expression and function in asthma, in bleomycin induced lung injury, in hyperoxia, and in response to *Pneumocystis carinii* lung infection. Utilizing a variety of collectin knockout, constitutively over expressing, and inducible transgenic mouse models, he has been dissecting the molecular mechanisms underlying the complex role of SP-A and SP-D in pulmonary homeostasis during environmental and infectious insults. In addition to these *in vivo* models, Dr. Beers group has extensive expertise in alveolar epithelial cell biology. A longstanding program has been developed to investigate the life-cycle of the surfactant proteins with emphasis at understanding synthesis, intracellular trafficking, and secretion of surfactant components into the alveolar space. A major focus of this program is directed at characterizing the molecular mechanisms underlying the consequences of mutant SP-C expression in the pathophysiology of interstitial lung disease. Dr. Beers has shown that mutations in the SP-C gene induce the development of interstitial lung disease by a pathway in which the aberrant protein products adopt non-native conformations that lead to endoplasmic reticular stress, protein aggregation, generation of dominant negative effects and production of a toxic gain of function.

Tyra Bryant-Stephens

Tyra Bryant-Stephens, M.D.

(Human Studies Research Group)

Dr. Bryant-Stephens' research and clinical interests focus on education and demonstration projects aimed at improving health care delivery to inner city, low socioeconomic children with asthma. Dr. Bryant-Stephens, a pediatrician, is an expert in community outreach programs and has worked closely with Dr. Panettieri on the Allies Against Asthma, a Robert Wood Johnson sponsored research program. She directs an interdisciplinary program, the Community Asthma Prevention Program (CAPP) of The Children's Hospital of Philadelphia established in 1997 through a cooperative agreement with the Department of Health and Human Services Office of Minority Health. The major objective of CAPP is to provide a comprehensive, community-based program, which through the elimination of many barriers promotes an optimal learning environment for asthma education. The goals of CAPP are: 1) to increase asthma knowledge and improve self-management behavior; 2) to improve quality of life for children with asthma; and 3) to train members of the community to teach their peers about asthma. The program is conducted in the West and Southwest areas of Philadelphia, an urban, poor, and predominately African American community. CAPP's comprehensive program has four components: community classes, a train-the-trainer program, a home visitor program, and an educational program for health care providers for asthmatic children. A major focus of CAPP is to address environmental exposure identification and remediation in the management of pediatric asthma. CAPP has earned recognition for its success in community asthma education and prevention from national organizations. Administrator Christie Whitman, of the US Environmental Protection Agency, visited Children's Hospital of Philadelphia in April 2002 for the purpose of recognizing CAPP. In addition, the Environmental Protection Agency has published the home visitor program as a case study in community-based interventions.

Research Core III: Lung and Airway Disease

Melpo Christofidou-Solomidou

Melpo Christofidou-Solomidou, Ph.D. (Animal Model Research Group)

Dr. Christofidou-Solomidou is interested in evaluating antioxidant radioprotectors in the context of pulmonary fibrosis. Radiation is one of many environmental risk factors of lung disease such as smoking, air pollution, asbestos, indoor allergens, herbicides/pesticides and many others. Radiation may result from occupationally received exposure whether as cosmic radiation during space flights, radon as a miner or exposure while working at nuclear facilities, from toxic waste accidents, nuclear bioterrorism, natural background radiation, or from medical use in nuclear medicine or radiation therapy. Studies of radiation-induced cellular/tissue damage using animal models have been possible for several decades and several potential radioprotecting substances have since been evaluated. The therapeutic potential of radioprotecting substances however is governed by limitations in their half-life, delivery, toxicity, specificity etc. Although she is currently investigating radioprotective effects of Vitamin E and Selenium, PEGylated antioxidant enzymes such as catalase and superoxide dismutase (SOD), she has also focused on the radioprotective efficacy of naturally occurring antioxidants, i.e. antioxidant nutrients and phytochemicals such as curcumin and flaxseed (lignans). She is actively investigating the mechanisms by which they might reduce endpoints of radiation damage such as DNA damage, apoptosis and oxidative modifications of lipids/proteins in lung tissue. Such naturally occurring substances have the advantage of low toxicity when administered at pharmacologic doses. She is currently exploring a novel therapeutic approach for the treatment of inflammatory and chronic fibrotic lung disease, namely the coordinate induction of cytoprotective and antioxidant genes through Nrf2/antioxidant response element (ARE) pathway. Her long-term goal is to design clinical trials where curcumin and lignans can be used preventatively (prior to thoracic radiation of lung cancer patients) for amelioration or abrogation of clinical symptoms of lung injury.



Angela Haczku

Angela Haczku, M.D., Ph.D. (Animal Model Research Group)

Inflammatory airway obstruction is a characteristic pathological feature of chronic obstructive pulmonary diseases and asthma, affecting millions of Americans. Using animal models, Dr. Haczku showed that airway obstruction occurs upon inhaling irritants such as ozone and cigarette smoke or upon inhaling allergens in sensitized mice. Following such exposure, a characteristic inflammation develops that resolves within days of exposure. Both the onset and resolution of the inflammatory changes are mediated by reparative mechanisms that are aimed to protect the lung tissue from damage. In chronic inflammatory diseases of the lung such as asthma and COPD these protective mechanisms are impaired. She has previously identified a class of molecules, termed lung collectins, that regulate the development as well as the resolution of inflammation in the lung. These proteins may play a cardinal immunomodulatory and host defense role by promoting clearance of inhaled pathogenic, toxic and allergenic material by alveolar macrophages and by enhancing dendritic cell migration. The investigation of models of airway inflammation elicited by allergic sensitization, ozone exposure, or cigarette smoke exposure will extend our understanding of the implications of novel pattern-recognition molecules in the pathogenesis of allergen and environmental toxin-induced airway hyperresponsiveness, and will define a novel connection between the innate and adaptive immune system.

Research Core III: Lung and Airway Disease

Vera P. Krymskaya

Vera P. Krymskaya, Ph.D.

(Epithelial/Mesenchymal Cell Function Research Group)

Dr. Krymskaya's laboratory investigates the signaling mechanisms of smooth muscle cell proliferation and migration as it relates to the pathobiology of lymphangioleiomyomatosis (LAM), pulmonary arterial hypertension and asthma. Early studies in collaboration with Dr. Panettieri showed that phosphatidylinositol 3-kinase (PI3K) signaling pathway is critical for human airway smooth muscle (ASM) cell proliferation. In human ASM cells p70S6 kinase (S6K1), downstream effector of PI3K with well established role in protein translational regulation and cell growth, integrates mitogenic signaling from contractile agonists through activated G protein-coupled receptors and growth factors through activated receptor protein-tyrosine kinases (RTKs). Dr. Krymskaya's group identified the function of the tumor suppressor gene tuberous sclerosis complex 2 (TSC2), a susceptibility factor for LAM. In primary human LAM-derived (LAMD) cells mutations of TSC2 leads to constitutive activation of S6K1 and abnormal LAMD cell proliferation. Importantly, a microlide antibiotic rapamycin, a specific inhibitor of mammalian target of rapamycin (mTOR)/S6K1 pathway, abrogates abnormal LAMD cell growth. Currently, the rapamycin clinical trial for the treatment of kidney and lung manifestations of LAM and TSC has been initiated. Dr. Krymskaya's research also includes the elucidation of molecular mechanism of metastatic LAM cell growth and its link to the novel function of TSC1 and TSC2 as regulators of cell motility and adhesion. Dr. Krymskaya's second avenue of research investigates the effect of hypoxia on the PI3K/mTOR signaling cascade in regulating human vascular and airway smooth muscle cell growth and motility as its relates to pulmonary arterial hypertension, COPD and asthma. This direction of Dr. Krymskaya's research is an integral part of the Airway Biology Initiative at the Department of Medicine.

Milton Rossman

Milton Rossman, M.D.

(Human Studies Research Group)

Dr. Rossman is recognized as a world leader in both sarcoidosis and chronic beryllium disease. His laboratory has been involved in understanding the trimolecular complexes involved in sarcoidosis and chronic beryllium disease. Current projects underway in his laboratory involve identifying the HLA class II molecules involved in sarcoidosis and chronic beryllium disease. Dr. Rossman in collaboration with Dr. Rosenman at Michigan State has completed an evaluation of two beryllium processing facilities in Pennsylvania. All former workers have been evaluated and classified as having no evidence of beryllium sensitivity, having beryllium sensitivity without disease or having chronic beryllium disease. Using cases and controls that have been matched for extent of exposure, an analysis of the HLA class II molecules is underway. Early studies suggest that the HLA class II molecule DPbE69 is a marker for hypersensitivity but not disease. In addition, using transformed B cells from subjects with beryllium hypersensitivity, Dr. Rossman hopes to identify the 10-20 amino acid peptide that is involved in the trimolecular complex. How beryllium interacts with this peptide will be critical to understanding chronic beryllium disease and developing better therapeutics. In addition, in collaboration with T. Mark McCleskey at Los Alamos laboratories, a variety of species that bind beryllium very tightly will be tested for their ability to induce beryllium induced proliferation. Molecules that bind beryllium tightly and do not induce beryllium induced proliferation might be useful as agents to remove beryllium from tissues of beryllium exposed individuals. In addition, since it is known that beryllium can stimulate the innate immune system and act as an adjuvant for other antigens, the adjuvant properties of beryllium will be investigated by determining the array of cytokines that are produced and the surface receptors that are up regulated by macrophages and antigen presenting cells after exposure to beryllium.

Research Core III: Lung and Airway Disease

Anil Vachani

Anil Vachani, M.D.

Dr. Vachani is an Assistant Professor in the Pulmonary, Allergy, and Critical Care Division at the University of Pennsylvania and a faculty-fellow in the Department of Biostatistics and Epidemiology. His interest is in the study of biomarkers for early detection and prognosis in thoracic oncology. He received his medical degree from the University of California, San Francisco, followed by clinical training at Penn. He is completing thesis work towards an M.S. in Epidemiology.

In 2005, Dr. Vachani joined the faculty of the University of Pennsylvania and the Philadelphia VA Medical Center. He works as a member of the Penn Thoracic Oncology Program, a multidisciplinary group interested in the development of novel diagnostics and therapeutics for both lung cancer and mesothelioma. He is currently the P.I. of NCI funded project evaluating the role of immune biomarkers on prognosis in early stage lung cancer. Other projects include the development of new biomarkers using novel genomic and proteomic technologies, and the clinical application of biomarkers in mesothelioma.

Research Core IV: Genes and the Environment



Timothy Rebbeck

Co-Director: Timothy Rebbeck, Ph.D.

(Cancer Susceptibility Genes and the Environment)

Dr. Rebbeck's research program is to understand the complex causes and prevention of human cancer. The unifying theme is that both genes and environmental exposures act together to cause the development of a tumor. Dr. Rebbeck uses a multidisciplinary approach to identify and characterize genes that may cause cancer, and to determine how these genes interact with environmental exposures in the development of cancers. He is interested in the development and application of methodological approaches that can be used to capture the complex interactions of these risk factors. These approaches include the efficient use of novel study design and analysis methods in molecular epidemiological research. These studies are being applied to understand the causes of breast, endometrial, prostate, and skin cancers.

Dr. Rebbeck's research has provided improved understanding about the genetic basis of a variety of cancers, and has translated this information into clinically relevant information that has changed clinical practice, including knowledge about surgical risk reduction in women at high risk for breast and ovarian cancer, and prediction of clinical outcomes using genetic data. Specific research includes: (1) developing knowledge about the role of hormones and hormone metabolism in the etiology and prevention of breast, ovarian, and endometrial cancer (P01-CA77596) with emphasis on identifying gene-interactions that may modulate response to estrogens; (2) understanding the role of prophylactic surgery in reducing the incidence and mortality from breast and ovarian cancer in BRCA1 and BRCA2 mutation carriers (R01-CA83855); (3) two case-control studies that directly address the complex, multifactorial etiology of melanoma that involves the interaction of genotypes involved in melanogenesis (melanocortin 1 receptor (MC1R) and tyrosinase (TYR)) with environmental exposures (e.g., UV-sun-light) (R01-CA092428 U01-CA83180); (4) examination of the role of genes involved in inherited susceptibility to prostate cancer, including those that regulate the metabolism of environmental carcinogens (CYP3A4) and steroid hormones [CYP19, 5 α -reductase type II (SRD5A2) and type 2 3 β -HSD (HSD3 β 2)] in prostate cancer etiology (R01-CA85074); evaluation of the multiple sources of prostate outcomes disparity by race (P50-ES012371); and a collaborative study with the Hôpital Gènèrale de Grand Yoff and the Université Cheikh Anda Diop in Dakar, Senegal to compare the etiology and characteristics of prostate cancer across ethnic groups in the U.S. and Senegal.

Alexander Whitehead

Co-Director: Alexander S. Whitehead, D.Phil.

(Genetics of Folic Acid Biosynthesis and Birth Defects)

Over the past 10 years, Dr. Whitehead has defined many of the relationships between common variants of folate/homocysteine pathway enzymes, particularly the 5,10-methylenetetrahydrofolate reductase gene (*MTHFR*), and hyperhomocysteinemia (a risk factor for many pathologies) coronary heart disease, stroke and inflammatory bowel disease. His laboratory was one of two that identified *MTHFR* as the first genetic risk factor for neural tube defects (spina bifida); subsequently he has identified, or generated evidence in support of, four more spina bifida genetic risk factors. It is now recommended that women increase folic acid intake during the periconceptual period to avoid this common birth defect. Environmental exposures linked to spina bifida include organic solvents; agricultural chemicals, including pesticides; water nitrates; heavy metals such as mercury; ionizing radiation; and water disinfection by-products. Whether there is a direct interaction between any of these exposures and *MTHFR* and/or other genes in the folate/homocysteine pathway remains to be explored. As Research Core Co-Director and investigator, he brings substantial expertise in relating "genotype" to "phenotype" which is beneficial to all other members of the Core who wish to model gene-environment interactions with respect to phenotypic outcome.

Research Core IV: Genes and the Environment

Jason D. Christie

Jason D. Christie, M.D., M.S.C.E. (Molecular Epidemiology of Lung Injury)

Research in Dr. Christie's laboratory focuses on clinical epidemiological and translational studies of the etiology, pathogenesis, treatment, and outcomes of lung injury from a variety of causes including environmental exposures. Specific diseases include idiopathic pulmonary fibrosis, asthma, and acute respiratory distress syndrome (ARDS). Dr. Christie has an ongoing collaboration with Dr. Steven Kleeberger (at The Pulmonary Branch NIEHS, Triangle Park) who is studying the effects of diesel-exhaust particles on the expression of Fra-1 a heterodimeric partner of AP-1 to alter the expression of matrix-metalloproteinase in murine lung epithelial cells as a model for alveolar cell injury. They found that Nrf-2 a nuclear transcription factor enhanced AP-1 and (anti-oxidant-response element) mediated gene transcription in lung cells exposed to a variety of environmental insults that lead to oxidant stress. He has an interest in investigating the interaction of single nucleotide polymorphisms in tissue repair genes with environmental and occupational exposures in determining the etiology of idiopathic pulmonary fibrosis.



Peter A. Kanetsky

Peter A. Kanetsky, Ph.D., M.P.H. (Cancer Susceptibility Genes and Environmental Exposures)

Dr. Kanetsky is a molecular epidemiologist with a broad interest in cancer etiology. His research focus is candidate susceptibility genes for cancer and the interaction of genetics with endogenous and exogenous environmental factors. He is an integral investigator in ongoing studies of melanoma that employ various methodological designs, including case-case, case-control, and family-based studies, to explore gene-environment interactions in melanoma etiology. Candidate gene pathways currently under investigation include those involved in pigmentation (e.g. /MC1R/, /ASIP/), DNA repair (e.g. /XPD/, /XPC/, /ERCC1/), immune surveillance (e.g., /IL-6/, /TNF /), and oxidative stress reduction (e.g. /GSTT1/, /GSTM1/). Sun exposure is the major environmental insult associated with melanoma risk. Importantly, sun exposure can result in specific types of DNA damage (e.g. UV-induced cyclobutane pyrimidine dimers (CPD's), local modulation of immune response, and altered expression of components in the pigmentation pathway. Individuals with defects in the nucleotide excision repair proteins XPD and XPC have a greater propensity to develop Xeroderma pigmentosa, and skin cancer. One interest is the association of a candidate susceptibility gene (/MC1R/) and the development of melanoma. Mutations in the candidate gene of interest, the melanocortin-1 receptor (/MC1R/), may affect melanin synthesis, resulting in an increased potential for cellular DNA damage that may lead to melanocytic carcinogenesis. The goals of the study are i) to determine the number and types of gene variants among persons with primary melanoma (MPM) and single cutaneous melanoma (SCM), and ii) to test whether these mutations play a role in the subsequent development of MPM. The results will contribute greatly to the epidemiology of candidate susceptibility genes associated with melanoma and will help focus primary and secondary prevention for persons at increased risk for secondary and primary melanomas. In addition he is investigating whether allelic variants in the /MC1R/ gene explain the pattern of melanoma in families prone to melanoma. Results from this project may provide valuable insight into the genetic predisposition to melanoma seen in some families, and may lead to more efficient mechanisms of primary prevention and clinical follow-up within these families.

Research Core IV: Genes and the Environment

Caryn Lerman

Caryn Lerman, Ph.D.

Dr. Lerman is Mary W. Calkins Professor in the Department of Psychiatry and the Annenberg Public Policy Center at the University of Pennsylvania. She is also Deputy Director of the Abramson Cancer Center. As the Principal Investigator of an NIH-funded Transdisciplinary Tobacco Use Research Center (P50) Grant, her work translates basic research in neuroscience, pharmacology, and genetics to improve the development and delivery of pharmacotherapy for nicotine dependence. Dr. Lerman is also the Principal Investigator of a Center of Excellence in Tobacco Dependence Treatment Research funded by the Commonwealth of Pennsylvania, and holds additional NIH grants focused on pharmacogenetic approaches to nicotine dependence treatment. She has published over 215 peer-reviewed articles and has been a recipient of the Society of Behavioral Medicine New Investigator Award, the American Psychological Association Award for Outstanding Contributions to Health Psychology, and the Cullen Award for Tobacco Research from the American Society of Preventive Oncology. She has served on the National Cancer Institute Board of Scientific Advisors (1998-2003) and the National Human Genome Research (ELSI) Evaluation and Planning Review Board (1997-2000).

Daniel Rader

Daniel Rader, M.D.

(Genetic Determinants of Artherosclerosis and Environmental Exposures)

Dr. Rader's laboratory is interested in the genetic factors that regulate the metabolism and function of plasma lipoproteins and their interaction with the vessel wall in promoting and inhibiting atherogenesis. Understanding these processes will identify candidate genes susceptible to environmental exposures including those that may be regulated by oxidative stress. A variety of basic cell and molecular laboratory techniques, mouse models, and clinical research approaches are used. One project is to examine the dietary and genetic regulation of hepatic lipoprotein production. Gene transfer, transgenic, and cell culture approaches are used to study the interaction between specific genes, such as the microsomal transfer protein and diacylglycerol acyltransferase, and dietary manipulation in the regulation of hepatic apoB production in mice. Lipoprotein kinetic studies are also performed in humans using endogenous labeling of apolipoproteins with stable isotopically labeled leucine. In another project genetic factors associated with premature atherosclerotic disease and high or low levels of HDL cholesterol are being identified. Such genetic factors may be influenced by environmental exposures. Subjects with family history of premature coronary disease or with extremes of HDL cholesterol are recruited and phenotyped for cardiovascular risk factors and clinical and subclinical atherosclerosis. Candidate genes are investigated for their association with subclinical atherosclerosis or variation in HDL cholesterol levels and linkage analysis of sibling pairs and large pedigrees will be performed. The overall focus of his research effort is basic cell and molecular laboratory science with translation into animal experiments and ultimately into patient-oriented research in the areas of lipoprotein metabolism and premature atherosclerosis and their environmental influences.

Facilty Core I: Toxicogenomics



Don Baldwin

Co-Director: Don Baldwin, Ph.D.

Dr. Baldwin is the founding Director of the Penn Microarray Facility, a service resource that provides Affymetrix and printed glass slide assays for clients worldwide. His graduate work at the University of Florida in plant molecular biology was followed by genomics research in the ag biotech industry at Pioneer Hi-Bred to study the maize disease defense response and its modulation by chromatin remodeling. Dr. Baldwin's current research interests at the University of Pennsylvania continue in chromatin regulation of transcription, and development of new microarray technologies including microRNA detection, rapid hybridization and new probe design strategies.



John Tobias

Co-Director: John Tobias, Ph.D.

Dr. Tobias is the Interim Director of the Penn Bioinformatics Core, a service resource that provides experimental design consultation and analytical services to the greater Penn community. He did his graduate work at the Massachusetts Institute of Technology in microbiology, and his post-doctoral research at Harvard Medical School in microbial pathogenesis. He then worked at CuraGen, a biotechnology company, leading a bioinformatics group developing gene expression analysis software. Since joining the Penn Bioinformatics Core, Dr. Tobias has monitored the growing set of analytical tools available and provided guidance and analytical support to Penn investigators utilizing the latest genomics technologies including expression, genotyping, tiling and CGH microarrays.

Facility Core II: Toxicoproteomics

Chao-Xing Yuan

Director: Chao-Xing Yuan, Ph.D.

Dr. Yuan obtained his Master's Degree from the Chinese Academy of Sciences, where he worked on plant hormone regulation and agrobacteria-mediated gene transfer. He received his Ph.D. at the University of Florida where he characterized plant, yeast and human heat shock transcription factors. In the Roeder Lab at Rockefeller University, his postdoctoral research was the isolation and characterization of coactivator protein complex in transcriptional activation, especially, nuclear hormone receptor mediated activation. At DuPont Pharmaceuticals (later Bristol-Myers-Squibb Company) as Sr. Research Scientist, his research interests switched to three areas: 1) Her-2 receptor and its sheddase in breast cancer cell lines. 2) Mass spectrometry-based high-throughput quantitation of Abeta peptides in cell culture and animal models. 3) Biomarker identification for thrombosis. Current research interests as Technical Director of Proteomics Core Facility at University of Pennsylvania continue in mass spectrometry and 2D gel based proteomics analysis, services, and development of new proteomics technologies including protein biomarker discovery and validation for diseases and environmental exposure.

Facility Core III: Biomarker



Seon Hwa Lee

Director: Seon Hwa Lee, Ph.D.

Dr. Lee, a Research Assistant Professor in Pharmacology, received her B.S. (1987-1990), M.S. (1990-1992) and Ph.D. (1994-1999) in Chemistry at Sungshin Women's University, Seoul, Korea. From 1992 to 1999 she worked at the Korea Institute Science & Technology (KIST) as a research scientist. Her research was focused on the altered metabolic profiles of polyamines, estrogens and androgens in leukemia and breast cancer by gas chromatography-mass spectrometry. She joined Dr. Blair's lab in 1999 as a post-doc research fellow. After two-years of post-doctoral training, she promoted to Research Associate (2001-2004). In 2004 she was appointed as a Research Assistant Professor in Pharmacology. She has been interested in understanding the mechanisms by which bifunctional electrophiles are formed from lipid hydroperoxides. She has characterized a novel etheno-DNA-adducts that arises from the reaction of lipid hydroperoxide-derived bifunctional electrophiles and developed LC/MS methodology for their analysis. She was lead author on a paper in *Science*, which described Vitamin C-induced decomposition of lipid hydroperoxides to yield DNA-reactive bifunctional electrophiles. She has also developed targeted lipidomics profile method from cell system using electron capture atmospheric pressure chemical ionization mass spectrometry. Her current research has been focused on cyclooxygenase-2 (COX-2)-mediated DNA damage, lipidomics profile in various cell system and biomarkers of oxidative stress. COXs have been implicated as mediators of carcinogenesis. COX-mediated formation of PGs has long been assumed to play a role in tumorigenesis. However, little attention has been given to the potential for the formation of genotoxic bifunctional electrophiles that result from COX-mediated lipid hydroperoxide formation. Her recent studies have shown that cells permanently expressing the COX-2 gene (RIES cells) form heptanone-etheno-adducts and there is dose-dependent increase in adduct formation in the presence of vitamin C. A targeted lipidomics approach showed that 15(S)-hydroxyeicosatetraenoic acid (15(S)-HETE) was the major hydroxylated non-esterified lipid formed in RIES cells. The corresponding hydroperoxide undergoes homolytic decomposition to the DNA-reactive bifunctional electrophile 4-oxo-2(E)-nonenal, a precursor of heptanone-etheno-2'-deoxyguanosine. She has also detected the endogenous etheno adducts for the first time in a mouse model. She's currently working on developing the analytical method for urinary DNA-adducts to use them as biomarkers of endogenous lipid hydroperoxide-mediated DNA damage.

COMMUNITY OUTREACH AND EDUCATION CORE OF THE CENTER OF EXCELLENCE IN ENVIRONMENTAL TOXICOLOGY

The mission of the Community Outreach and Education Core of the Center is to translate research information from the Center's research and its team of interdisciplinary scientists, into tools and resources for community, professional, and Public Health decision-making constituencies, in order to improve clinical and public health. The Center and the COEC are especially focused on the urban environment and particularly on communities with an aging industrial infrastructure such as Philadelphia and many surrounding communities. We are particularly concerned with the effects on vulnerable populations including children, the elderly, and underserved populations.

Community Outreach and Education Core



Edward A. Emmett

Director: Edward A. Emmett M.D., M.S.

Dr. Emmett has been involved in numerous community environmental health issues. Appointments and activities have included: Chair, Governor's Council on Toxic Substances of the State of Maryland; Chair, State of Maryland Hazardous Toxic Substances Study Commission; Member, Board of Directors, Farmsafe Australia; Chair, Ministerial Advisory Group on Farm Safety, Commonwealth of Australia; Member, Advisory Committee, Baltimore City Cancer Control Program; Vice-Chairman, City of Cincinnati Environmental Advisory Council; Member, City of Cincinnati Air Pollution Advisory and Appeals Board; Member, City of Cincinnati Environmental Advisory Council, Water Committee; and Vice-Chair City of Cincinnati Citizen-Scientist Committee on Drinking Water Quality. Dr Emmett is currently on the Board of Directors of the American College of Occupational and Environmental Medicine, the Board of Trustees of the Occupational Medicine Scholarship Fund and is a past Director of the American Board of Toxicology. He is a member of the Editorial Boards of the Journal of Occupational and Environmental Medicine, Journal of Occupational Health (Japan), and the International Journal of Occupational Medicine and Environmental Health. He is a member of Advisory Committee for the Wharton Risk Management and Decision Sciences Center and of the Scientific Advisory Board, Occupational and Environmental Olfactory Effects Program of the Monell Chemical Senses Center. He is currently Chair, Program Health and Environment Program, PCIEP for the Pennsylvania Departments of Environmental Protection and Conservation and Natural Resources. He developed and directs the Occupational Medicine Residency Program at the University of Pennsylvania, a unique external training program where physicians with full-time employment in Occupational and Environmental Medicine can train in their own communities. Dr. Emmett was listed as one of the Philadelphia region's Top Doctors in 2004, as well as one of America's Top Doctors. He serves as a Principal Investigator for a grant from the NIEHS Environmental Justice Program on Community Exposure to Perfluorooctanate. Dr. Emmett is active in risk communication and since 2001 has been working with the United Auto Workers Union (UAW), General Motors Corporation and Delphi Corporation in a new role as their "Risk Communicator." The object of creating this position is to better translate research results into preventive actions by management and employees.



Richard Pepino

Deputy Director: Richard Pepino

Mr. Pepino is currently teaching at the University of Pennsylvania School of Public Health and the Goodwin College at Drexel University. He is also an Assistant Professor in the Earth & Environment Department at Franklin & Marshall College in Lancaster, PA. where he also serves as the Chair of the Public Policy Committee for the College. Mr. Pepino has twenty-eight years of federal service with the U.S. Environmental Protection Agency holding management positions as Chief of Environmental Impact Analysis, Associate Director of Office of Watersheds, and Chief of Strategic Planning. Areas of Policy interest include non-regulatory approaches to wetlands and watershed restoration, and regulatory applications of the National Environmental Policy Act.

Pamela Dalton

Pamela Dalton, Ph.D.

Dr. Dalton is principal liaison with the Monell Center for the Chemical Senses. Her research explores and characterizes the sensory, cognitive and emotional impact on health following exposure to odorous chemicals in the environment. She focuses on the sensory and health consequences for two groups of susceptible individuals: workers exposed to chemicals on the job and individuals who are exposed to industrial or agricultural odors in their communities. Dr Dalton collaborates with Dr. Emmett and others in a study, as part of the Mt. Sinai World Trade Center Worker/Volunteer Screening Program, to examine the sensory consequences of exposure to pollutants at the World Trade Center site in the period following 9/11. Dr. Dalton represents Monell at area health fairs, provides demonstrations on the chemical senses for Science Days at area schools hosts laboratory tours/demonstrations for selected school groups and is an active participant in the Monell Research Apprentice Program, employing a total of nine high school students, four undergraduates and two graduate students over the five years. She frequently gives presentations to community groups impacted by odours from factories, landfills or confined animal operations, and to regulatory bodies attempting to legislate odour issues. Dr Dalton assists the COEC to address community concerns of odour and sensory irritation.

Community Outreach and Education Core



Ira Harkavy

Ira Harkavy, Ph.D.

Dr. Harkavy is Associate Vice President and founding Director of the Center for Community Partnerships (CCP), University of Pennsylvania. An historian with extensive experience building university-community-school partnerships, Harkavy teaches in the departments of history, urban studies, Africana studies, and city and regional planning. As Director of the Center for Community Partnerships since 1992, Harkavy has helped to develop service learning and academically-based community service courses as well as participatory action research projects that involve faculty and students from across the university. He has been actively involved in working to involve colleges and universities in democratic partnerships with local public schools and their communities.

He served as consultant to the U.S. Department of Housing and Urban Development to help create its Office of University Partnerships and is a Senior Fellow of the Leonard Davis Institute of Health Economics. He is the recipient of Campus Compact's Thomas Ehrlich Faculty Award for Service Learning (2002), the University of Pennsylvania's Alumni Award of Merit (2004), a Fulbright Senior Specialists Grant (2005) and the Historical Society of Pennsylvania's Heritage Award (2006); and, under his directorship, the Center for Community Partnerships received the inaugural William T. Grant Foundation Youth Development Prize sponsored in collaboration with the National Academy of Sciences' Board on Children, Youth and Families (2003) and a Best Practices/Outstanding Achievement Award from HUD's Office of Policy Development and Research (2000).

Mary Hufford

Mary Hufford, Ph.D.

Dr. Hufford is the principal liaison with the Center for Folklore and Ethnography which she directs. As a folklorist for 20 years with the American Folk Life Center, Library of Congress, she directed regional field research and national programs including issues of cultural conservation and environmental health in the Pine Barrens of Southern New Jersey and the coalfields of Southern West Virginia. She has published numerous articles on the cultural dimensions of ecological crisis. In 1997, she received a John Simon Guggenheim fellowship for a study of contending social imaginaries and ecological crisis in the coalfields of southern West Virginia. Her work with coalfield communities centers on integrating cultural conservation, sustainable livelihoods, and natural resource stewardship. She has also worked with community developers and activists to combat culturally destructive effects of mountaintop removal and valley fill coal mining on central Appalachian plateaus. Similar culturally-based issues arise in our target communities including Eastwick, and Pottstown. Dr. Hufford is the social scientist responsible for evaluation on Dr Emmett's Environmental Justice Grant "Community Exposure to Perfluorooctanate". She assists in understanding and addressing the cultural parameters of environmental health in our target communities.

Howard Kunreuther

Howard Kunreuther, Ph.D.

Dr. Kunreuther is principal liaison with the Wharton School Risk Management and Decision Processes Center, the Cecilia Yen Koo Professor of Decision Sciences and Public Policy at the Wharton School, and Co-Director of the Risk Management and Decision Processes Center. He is an authority on risk communication and ways that society can better manage low probability-high consequence events related to technological and natural hazards. Dr. Kunreuther was a member of the National Research Council Board on Natural Disasters and chaired the H. John Heinz III Center Panel on Risk, Vulnerability and True Costs of Coastal Hazards. He is a recipient of the Elizur Wright Award for the most significant contribution to the literature of insurance and is a Distinguished Fellow of the Society for Risk Analysis and a Fellow of the American Association for the Advancement of Science. He is the author with Paul Freeman of *Managing Environmental Risk through Insurance* (1997), co-editor of *Paying the Price: The Status of Role of Insurance Against Natural Disasters in the United States* (1998) and co-editor of *Wharton on Making Decisions* (2001). Dr. Kunreuther assists the COEC in risk communication and in training health professionals about risk.

Community Outreach and Education Core

Target Communities:

We have selected five target communities that are located in Southeastern Pennsylvania and are faced with health issues arising from living in an aging urban environment.

West Philadelphia:

West Philadelphia is a widely divergent community that extends West and South of "University Center" where the University of Pennsylvania is located. About 220,000 people (or about 14% of the City's population) live, shop, and in many cases work in West Philadelphia, approximately three-quarters of the population is African-American. The Philadelphia Planning Commission's Plan for West Philadelphia states, "some West Philadelphia neighborhoods suffer the same ills that affect other older urban areas. Over the last several decades, there has been a substantial loss of middle-class population, widespread poverty, property deterioration and abandonment, main streets that have declined and don't present the best face of the community, deteriorating infrastructure, and too many incidents of crime against people and property that have had devastating impacts in certain neighborhoods. These trends, although not pervasive, are persistent and have affected the quality and the perception of life in the larger West Philadelphia community. The trends that contribute to these negative perceptions must be halted and reversed if West Philadelphia is to sustain itself as a viable urban community." Environmental problems in West Philadelphia include lead exposure from aged housing stock, asthma in children and exposures from abandoned former small industrial sites.

Eastwick:

The Eastwick area of Southwest Philadelphia adjoins West Philadelphia. Environmental concerns include emissions from a petroleum refinery, traffic emissions associated with a major postal distribution Center and a freeway running through the neighborhood, and emissions from the neighboring Philadelphia Airport. In the last three years, two major "100 year floods" of Darby Creek, have inundated a substantial portion of the community, potentially mobilizing toxic substances from a National Priority List ("Superfund") site that is located just upstream in an adjacent county. There is also concern over the environmental health impacts of numerous small businesses including dry cleaning and auto-body shops.

City of Chester:

Chester, 15 miles south of Philadelphia along the Delaware River, has approximately 42,000 people in a 4.8 square mile area. Chester has amongst the highest concentrations of industrial facilities in Pennsylvania; a number of waste-processing plants, a large infectious medical waste facility, and two oil refineries. All solid waste for Delaware County (population 554,000) is incinerated in Chester, and at least 85% of the raw sewage and associated sludge is treated in Chester. Residents perceive that Chester has more than its fair share of environmental insults, including noise, air pollution, and excessive truck traffic. They express concerns about the health effects of living and working amid toxic substances, and they complain about frequent illness. Chester has approximately 75% minority population, the highest unemployment in the county, a large proportion of pre-1950s housing, and a shortage of medical care providers. Chester has the highest infant mortality rate. It also is among the highest for age-adjusted mortality and cancer incidence rates for leukemia, all causes combined, and cancers of the prostate, lung, and trachea of any municipality in the state (Chester Risk Assessment, EPA Region III). Despite substantial environmental health challenges, there is a widespread perception that Chester is turning the corner. Programs have been initiated to address lead and waste hazards, new truck routes have been sited. A new city hall has state-of-the-art computer facilities available to all citizens.

Pottstown:

Pottstown, population of 22,000, is situated approximately 25 miles northwest of Philadelphia. Residents describe living in a "toxic triangle" with a large landfill with substantial odorous off-gassing, an oil refinery (a superfund site) and a nuclear power plant, all located just outside the Borough boundaries. State of Pennsylvania data shows an extremely high prevalence of childhood asthma and elevated rates of certain cancers. Pottstown is undergoing accelerating revitalization. Among the community assets is the well-resourced Pottstown Community Health and Wellness Foundation with a mandate to improve health, and the Montgomery Community College West Campus a potential partner for COEC activities. The State of Pennsylvania has strongly encouraged the COEC to make Pottstown a target community. Don Read, Chair of the Environmental Advisory Board for the Borough of Pottstown will be the representative on the COEC Advisory Committee.

Palmerton:

Palmerton (population of approximately 5,500) is notable as the site of two separate primary zinc smelting operations from 1898-1980. SO₂ and metal pollution from the sites denuded surrounding mountains. That area has some of the highest known soil lead levels with significant cadmium, arsenic, and zinc contamination. In 1980, the West Plant closed and the East Plant transitioned to a secondary metal refining and processing operation. The site was placed on the National Priorities ("superfund") List in 1982, and has been the subject of health assessments by ATSDR (1993) and more recently the Pennsylvania Department of Health. Continuing environmental health issues at Palmerton include permit issues for operation of the sites and recent observations of elevated lead levels in children. PENN has a long history of involvement in Palmerton. Several MS students working with Dr. Robert Giegengack wrote graduate theses around contamination by lead and other metals. More recently, Dr Sulagna De (a resident in the Occupational and Environmental Medicine at PENN working with Dr Edward Emmett) has reviewed various environmental health assessments and made recommendations for further action. Louise Calvin, President of Palmerton Citizens for a Clean Environment, is a member of the COEC Advisory Committee.

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