School of Medicine

Department of Pharmacology and Chemical Biology

Annual Report 2009-2010

General Description

During the 2009-2010 academic year, the Department of Pharmacology & Chemical Biology continued to grow its strengths in discovery and education related to the practice of pharmacology. The discovery component of our departmental missions employs basic chemical principles in developing an understanding of cell signaling events, and then applies these insights in the creation of new therapeutic strategies.

This past year, Pharmacology & Chemical Biology has recruited prominent new faculty members in the course of expanding the scope and strength of our research and educational missions. We have made significant new advances in understanding fundamental mechanisms of cell and tissue communication, how these events impact on cell growth and function, the creation of new drugs to control these processes and, from this, the generation of new intellectual property (patents) that allows the commercialization of these discoveries. In recognition of our excellence in these pursuits, departmental members have been recognized with prestigious awards. Also, in spite of challenging times, the concerted effort of both faculty and staff in making and communicating seminal research advancements has been rewarded by a continued growth in extramural research support that now totals $20,369,869 annually.

Prestigious awards have recently been given to departmental faculty in recognition of their excellence in research and teaching. Notable awardees include Marsha Cole, Ph.D. (Research Instructor) Hartwell Foundation Fellow; Joan Lakoski, Ph.D. (Professor) Chancellor's Affirmative Action Award and election to Member, Academy of Master Educators; Robert Sobol, Ph.D. (Assistant Professor) Hillman Fellow for Innovative Cancer Research and Bennett Van Houten, Ph.D. (Professor) Medal of the Slovak Academy of Sciences for Support of Science.

The teaching missions of the department are a high priority, thus they both thrive and continue to evolve. Donald DeFranco, Ph.D., has been highly effective in his position as Vice Chair for Education. We appointed Patrick Pagano, Ph.D., Professor, as Director of our Molecular Pharmacology Graduate Program. We have continued to restructure and revise the Ph.D. Program in Molecular Pharmacology to be more responsive to student needs and the rapidly evolving training requirements for minting a competitive pharmacologist in the contemporary job market. They are using multiple strategies to inculcate in our students new expertise spanning from synthetic organic chemistry to physiology. In this regard, the Molecular Pharmacology Graduate Program has refocused its areas of specialization to provide additional focus on molecular aspects of signal transduction, cell and organ systems pharmacology, cancer pharmacology and drug discovery. We are especially pleased with student reactions regarding our recent integration of combined clinical simulator- and murine-based "hands-on" training in organ physiology and pharmacology into our graduate curricula. Due to the interest of students outside of the Molecular Pharmacology Graduate Program, we are further expanding these organ physiology and pharmacology teaching missions. Important contributions and leadership have also been lent in graduate education by Guillermo Romero, Ph.D., Associate Director of Graduate Education and Daniel Altschuler, Ph.D., Co-Director of the Molecular Pharmacology course, in addition to our overall departmental faculty.

Notably, the department has successfully deployed 11 students as Ph.D. graduates in the past two years. Thus, we welcome the following doctors to the practice of Pharmacology & Chemical Biology: Jonathan Beckel, Pierre Queiroz de Oliveira, Neil Bhola, Theodora Pene-Dumitrescu, Joshua Snyder, Sangeetha Iyer, Austin Dulek, Nicholas Bateman, Allison Groeger, Yan Wang and David Wheeler. By new mechanisms that regularly evaluate both mentors and students, Drs. DeFranco, Pagano and Freeman have succeeded in reducing our average time for graduation of Ph.D. students to four, and sometimes less than four, years for exceptionally productive students. Departmental faculty are particularly proud of our current outstanding Molecular Pharmacology Ph.D. and M.D./Ph.D. students, who are contributing important new insight into fundamental cell signaling processes, drug actions and drug discovery.

Medical education has also thrived under Dr DeFranco's leadership. He is one of the most highly esteemed educators and researchers in the Department of Pharmacology & Chemical Biology and the School of Medicine, and has recently made important changes in our medical student educational missions this past year with

Stephan Tofovic, M.D., Ph.D. They have dramatically improved the integration of pharmacology instruction into the organ-based, modular instructional approach currently given to Pitt medical students. They have also revised and better integrated our Principles of Pharmacology core curriculum that provides our medical students with a foundation of knowledge for their subsequent organ-based modular medical education. We now teach medical students the fundamental principles of pharmacology and drug toxicology early in their first year "Basic Science Block," specifically in the overall "Cell and Pathologic Basis of Disease" course. In this curricula, Edwin Jackson and Don Defranco have been honored as the most highly rated of all teachers. Additionally, all of the Pharmacology & Chemical Biology faculty participate in the execution of multiple small-group and team-based workshops, focusing on clinically relevant case studies in pharmacology. With constant attention to designing course content, optimal teaching strategies and their execution, we strive to continuously evolve and fulfill our mission to educate medical students and physicians in the conceptual basis for drug selection and administration.

Pharmacology & Chemical Biology faculty are also dedicated to inspiring and growing the next generation of young scientists and physicians. Michael Palladino, Ph.D. continues to direct our highly acclaimed summer undergraduate research program, which attracts some of the brightest young, aspiring basic and physician-scientists from around the country. This program is in part funded by the American Society of Pharmacology and Experimental Therapeutics, as well as participating School of Medicine centers and departments. Our undergraduate research program supports the summer living and laboratory expenses of students who are interested in a broad range of research themes. These students are matched with a laboratory that fits their general interests and by pursuing a research project become exposed to challenging new laboratory skills, classroom experiences and an opportunity to interact with our internationally renowned departmental investigators. This represents a significant investment of time and resources that pays untold future dividends.

The stellar research environment that exists in the Department of Pharmacology & Chemical Biology is reflected by the high impact publications and abundant extramural support levels cited in this report. In order to grow and evolve this vibrant environment, new investments are continually being made in the research tools utilized by departmental investigators. Dr. Edward Levitan, our Vice Chair for Research, has assumed leadership of the Department of Pharmacology & Chemical Biology's microscopy resources and is integrating a unique upright confocal-multiphoton microscope into overall departmental and institutional microscopic imaging capabilities. This Olympus Fluoview 1000 features a spectral detector that can simultaneously scan with two lasers, a special asset for photobleaching and photoactivation experiments. The instrument is also equipped with a tunable titanium-sapphire multiphoton laser for imaging deep in tissue and exciting near-UV chromophores.

Dr. Thomas Kensler, who recently was recruited from Johns Hopkins University, and Bruce Freeman have endeavored to expand departmental and institutional mass spectrometry resources. Their well-equipped adjoining laboratories now house two LTQ linear ion trap mass spectrometers, equipped with electron transfer dissociation capabilities and an Orbitrap/Velos detector, two Applied Biosystems triple quadrupole mass spectrometers and multiple nanoflow high-performance liquid chromatographs. This adds exciting new depth and potential to departmental and University of Pittsburgh basic and clinical investigation activities.

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Sruti Shiva, Ph.D.: Dr. Shiva's lab focuses on the mechanisms by which reactive nitrogen species (particularly nitrite and nitric oxide) regulate mitochondrial function during physiological stress, in particular hypoxia and ischemia. Her focus spans from both the study of fundamental biochemical events occurring at specific respiratory chain subunits to more clinically relevant murine models and clinical occurrences in ischemia/reperfusion injury.

Patrick Pagano, Ph.D.: Dr. Pagano's research focuses on the modulatory role of the adventitia in vascular function and structure under both physiological and pathophysiological conditions. His laboratory was among the first to identify non-phagocytic NADPH oxidases (Nox) in the vascular wall, demonstrating a critical role for the essential subunit p67phox in its activity. The Pagano laboratory continues to explore the roles of different Nox isoforms in cell signal transduction and tissue pathogenesis and is pursuing the development of specific Nox inhibitory strategies.

Thomas Kensler, Ph.D.: Research interests in Dr. Kensler's laboratory focus on the biochemical and molecular mechanisms involved in both the induction of cancer and the actions of chemotherapeutic drugs. In particular, the Kensler lab is noted for discoveries related to oxidant and electrophile regulation of gene expression by chemicals that in turn can serve as drug candidates for the prevention, interruption or reversal of these carcinogenic and inflammatory processes in man. The research conducted by Dr. Kensler and colleagues spans from studying molecular events occurring in transcriptional regulation to clinical studies of electrophile-stimulated clearance of toxins and the anti-cancer actions of naturally-occurring electrophiles.

Steffi Oesterreich, Ph.D.: Dr. Oesterreich's lab includes technicians, graduate students and postdoctoral fellows who are trained in a multi-disciplinary research environment to work in basic, translational, and clinical aspects of breast cancer research. Specifically, her research projects focus on the role of co-regulator proteins that are involved in estrogen signaling and tissue responses in breast cancer. Work in Dr Oesterreich's lab spans from molecular to clinical studies.

Adrian Lee, Ph.D.: Dr. Lee is investigating the endocrine regulation of mammary gland development and progression to mammary cancer, with experimental models ranging from cell and rodent studies to clinical investigation. Specifically, he is interested in interaction between steroid hormones (estrogen and progesterone) with the growth hormone (GH)/insulin-like growth factor-I (IGF-I) axis.

Tija Jacob, Ph.D.: Dr. Jacob is investigating inhibitory synapse formation and the mechanisms regulating cellular trafficking of γ-aminobutyric acid receptors ($GABA_A$Rs) in mammalian neurons. Her broad research goal is to understand the impact of dynamically regulated $GABA_A$R neuronal surface levels and distribution in normal development and pathological conditions where GABA system dysfunction occurs, particularly anxiety, insomnia and depression. The Jacob lab is our newest, and is projected to have construction completed by June 2011. There, a range of molecular biology, pharmacologic and live cell/ in vivo organ imaging studies will be pursued.

Career development and strong mentorship for junior faculty are critical elements for nurturing a healthy future for the department. A new faculty mentoring process was instigated in recent years, whereby the Chair and senior faculty regularly meet with non-tenured and associate professor-level faculty to discuss and strategize how best to pursue career progression and key research objectives. Related to this, Alessandro Bisello, Yu Jiang, Lin Zhang and Qiming (Jane) Wang have been promoted to Associate Professor with tenure. This key rank advancement is a testimony to departmental and institutional recognition of their excellence in the key elements of our profession—teaching, service, research and national/international recognition.

In summary, the practice of Pharmacology & Chemical Biology is unique among basic sciences, as it embraces a broad range of expertise in our efforts to understand fundamental cell communication events, drug-target molecule reactions and, finally, the design, synthesis and therapeutic application of new drugs in patients. This latter effort requires strengths or critical collaborations in computational drug design, synthetic organic chemistry, biophysics, structural biology and organ physiology. Thus, Pharmacology & Chemical Biology maintains strong ties with a variety of basic science and clinical disciplines, while maintaining firm roots in fundamental elements of chemistry, cell and molecular biology, drug actions and drug metabolism. These precepts are exemplified by our premier educational and research missions that include the institution of new educational strategies, the creation of new centers of excellence, the recruitment of stellar new faculty, and the scientific and teaching contributions of our dedicated faculty. We thus invite you to explore in more detail our annual report and, if interested, to join us in fulfilling the departmental mission to excel in education, drug discovery and improved patient care.

Research and Other Scholarly Activities

Research Interests

Bruce A. Freeman, Ph.D
Professor and Chair
Ph.D., University of California, Riverside, 1978

The basic and clinical research activities of the Freeman Laboratory focus on the eukaryotic cell production, reactions and signal transduction properties of oxidizing and free radical inflammatory mediators (e.g., superoxide, hydrogen peroxide, nitric oxide (NO), peroxynitrite, nitrogen dioxide, oxidized/nitrated lipids). In particular, we are interested in the action of these species as both redox signaling mediators under basal conditions and as pathogenic agents in inflammatory diseases. Our observations regarding O_2 and NO-derived reactive species have lent new insight into redox-dependent cell signaling and have revealed new therapeutic strategies for treating acute inflammation, metabolic syndrome, respiratory disorders and cardiovascular diseases.

In the late 1980s, his group studied the cellular and subcellular organelle production of superoxide and hydrogen peroxide. Following the landmark description of endothelial-derived relaxing factor (EDRF) as the free radical NO, the Freeman laboratory pioneered the concept that the inflammatory and signal transduction mediator NO displays unique redox signaling actions following reaction with superoxide, oxidizing fatty acids and heme peroxidases. The "oxidative inactivation" of NO is a kinetically fast reaction, yielding "reactive nitrogen species" as products. This array of reactions of O_2-derived species with NO can serve to both impair and transduce NO signaling via non-cGMP dependent mechanisms.

There is now a rapidly expanding appreciation that NO-derived reactive species display distinct chemical reactivities and exert cell signaling actions beyond the activation of guanylate cyclase – e.g., via thiol oxidation, electrophilic addition and receptor-dependent reactions. This aspect of redox-related chemical biology is an area that the Freeman laboratory continues to investigate, with the intent of defining the linkages between reactive oxygen species and NO-dependent cell signaling mechanisms. From a translational research perspective, his group is addressing how these interactions impact cell and organ function, with particular directed towards metabolic, cardiovascular and pulmonary diseases.

Dr. Freeman's laboratory observed that NO reacts with superoxide (O_2-) to yield the potent biological oxidizing and nitrating species peroxynitrite (ONOO-)and its conjugate acid, peroxynitrous acid (ONOOH). Groundbreaking observations were made in this area by Joe Beckman, PhD and Rafael Radi, MD, PhD. Their work showed that peroxynitrite is both a direct oxidant and, after homolytic scission of peroxynitrous acid, yields the potent oxidant hydroxyl radical (OH) and the oxidizing and nitrating species nitrogen dioxide (NO_2) (Fig. 1). Also, they identified thiols and carbon dioxide as the principal biological targets of peroxynitrite. It is now known that peroxynitrite accounts for many of the pathogenic actions previously ascribed to its precursors - superoxide (and its products) and NO. Work from many laboratories continues to affirm that peroxynitrite mediates redox cell signaling actions upon the oxidation or nitration of target molecules such as thiols, aromatic amino acids, nucleotides and unsaturated fatty acids – with downstream cell signaling events and reactions of peroxynitrite now appreciated to be a consequence of its potent and unique reactivities.

Daniel Altschuler, Ph.D
Associate Professor
Ph.D. (Biology), University of Buenos Aires, Argentina, 1989

Dr. Altschuler's laboratory studies mechanisms of signal transduction by the second messenger cAMP in cell proliferation. cAMP-dependent protein kinase (PKA) and Exchange protein activated by cAMP (Epac) represent the main effectors of cAMP action. Both pathways converge at the level of the small GTPase Rap1b,

via its Epac-mediated activation and PKA-mediated phosphorylation. The role of Rap1 activation (Epac) and phosphorylation (PKA) coordinating the early rate-limiting events in cAMP-dependent cell proliferation are studied using a multidisciplinary approach including molecular and cellular biology techniques in vitro, as well as in vivo validation using transgenic/knock in technologies in endocrine tumor models.

Palaniappa Arjunan, Ph.D.
Research Instructor
Ph.D., Indian Institute of Science, Bangalore, India, 1985

Dr. Arjunan determines the structure of macromolecules of biological interest, and then analyses structure-function relationships. He primarily uses X-ray crystallography to accomplish this.

Dr. Arjunan's current research includes the high resolution three-dimensional structure determination of thiamin diphosphate (ThDP)-dependent enzymes, the yeast pyruvate decarboxylase (PDC) and pyruvate dehydrogenase multienzyme complex (PDHc) from Escherichia coli. The refined structure is then used to address long-standing issues regarding the structure and function of thiamin diphosphate-dependent enzymes. The structure determination also includes the structure of PDHc E1 in complex with a covalently bound reaction intermediate analogue. Other interests are: a) the crystal structural analysis of native and mutant ThDP-dependent enzymes, either alone or in complexes with substrates, inhibitors, activators or with other related enzymes and b) development of techniques for the determination and analysis of macromolecular crystal structure.

Paul R. Baker, Ph.D.
Research Assistant Professor
Ph.D., Wake Forest University, Winston-Salem, NC, 2002

Dr. Baker's research interests are focused on understanding how cells communicate with one another during inflammation. Chemical messages called lipid signaling molecules act to initiate, propagate and resolve inflammatory responses. Dr. Baker is particularly interested in a new class of lipid signaling molecules called 'nitrated lipids;' these molecules mediate generally anti-inflammatory effects and may play an important role in the resolution of inflammation.

Dr. Baker's research has centered on a novel class of lipid mediators, nitrated fatty acids, which have distinct bioactivity from their non-nitrated counterparts. We have discovered that these signaling molecules are present clinically in a variety of vascular cells and plasma under basal conditions as well as clinical pathologies. The current hypothesis is that nitrated unsaturated fatty acids are formed by the "interplay" of nitric oxide and lipid oxidation/signaling reactions. In vitro, nitrated linoleic acid has been shown to regulate vessel relaxation by cGMP-dependent mechanisms and to modulate inflammatory responses including inhibiting neutrophil function and platelet activation via a mechanism involving cAMP. His work has involved identifying and quantifying nitrated lipid species in red blood cells and plasma and has found novel signaling actions that, in general, are anti-inflammatory. Specifically, he has found that nitrated linoleic and oleic acids (LNO_2 and $OA\text{-}NO_2$, respectively): a) up-regulate heme-oxygenase 1 protein expression; b) serve as a potent PPARα, δ and γ ligands that rival or exceed fibrates and thiazolidinediones in their ability to mediate PPAR activation; c) are strong electrophiles that covalently bind biological nucleophiles such as glutathione and protein histidine and cysteine residues, which has been shown to regulate protein functions including inhibition of cytokine release in LPS-stimulated inflammatory cells via adduction to the p65 unit of NF-κB; and d) prevent restenosis in animal models of vessel injury. These observations have broad implications in the clinical pathologies of atherosclerosis and diabetes. Furthermore, he has found that nitrated fatty acids can release nitric oxide during degradation, suggesting that allylic nitro derivatives may be a store of releasable nitric oxide.

Recent advances indicate that the diversity of endogenous nitrated lipids extends well beyond LNO2 and OA-NO2 to include nitrated fatty acids of varying chain length, multiple oxidized nitrated fatty acids (nitro-hydroxy and nitro-hydroperoxy adducts), complex lipids (e.g., nitrated cholesterol linoleate) and enzyme Co-A derivatives. His primary interest is to elucidate the endogenous formation of these species to better understand the role(s) they play in inflammation and basal tissue homeostasis. Using mass spectrometry as a tool, He is currently engaged in structural identification of novel nitrated lipid species and studies to determine the mechanism(s) of their formation.

Dr. Alessandro Bisello
Assistant Professor
Laurea (Chemistry), University of Padova, Italy, 1992

G protein-coupled receptors (GPCRs) represent a major class of membrane-bound proteins that mediate a wide variety of biological functions, including sensitivity to light and odorants, endocrine and cardiovascular control, and neurotransmission. Because of their central role in many physiological processes, GPCRs represent one of the major targets for pharmacological intervention in a large number of pathologies.

The goal of our research program is the elucidation of the molecular mechanisms that determine activation, regulation and trafficking of GPCRs and their relevance to the (patho)physiology of peptide hormones.

These studies provide the opportunity to address key issues regarding the mode and specificity of actions of G protein-coupled receptors. Most importantly, these studies may provide the basis for the identification of novel therapeutic targets for the treatment of osteoporosis, diabetes and vasculopathies.

The general scientific theme in the laboratory is to define the role of accessory proteins (such as arrestins, caveolin, EBP50/NHERF1) in determining G protein-coupled receptor function. Our efforts focus on two specific areas:

1.) The signaling, trafficking and regulation of the parathyroid hormone type 1 and type 2 receptors (PTH1R and PTH2R) and their function in vascular smooth muscle cells, with particular emphasis on their role in mitogenesis. The cardiovascular tissue, and in particular vascular smooth muscle cells (VSMC), expresses and be exposed to the whole spectrum of parathyroid hormone ligand-receptor systems. VSMC express both the type 1 and type 2 parathyroid hormone receptors (PTH1R and PTH2R, respectively). Also, in addition to being exposed to circulating parathyroid hormone (PTH), they produce parathyroid hormone-related protein (PTHrP) and tuberoinfundibular peptide of 39 residues (TIP39). This complexity reflects the varied and distinct actions of these ligands and receptors in both pathophysiology and pharmacology of the cardiovascular system. The central hypothesis of this project is that signaling and regulation of the PTH receptors in VSMC, and consequently the tissue-specific responses, are determined by the expression and function of adaptor proteins.

2.) Cellular regulation of the glucagon-like peptide 1 (GLP-1R) receptor and its role in regulating beta cell function, proliferation and survival. One of the most promising therapeutic targets for the treatment of type 2 diabetes is the glucagon-like peptide 1 receptor (GLP-1R). The well documented ability of GLP-1R agonists, either GLP-1 itself or exendin-4, to stimulate glucose-dependent insulin secretion and increase beta cell proliferation and survival led to the approval of exendin-4 for the treatment of type 2 diabetes. Our studies show that the GLP-1R interacts with caveolin1 and this is necessary for the trafficking of the GLP-1R to the cell membrane and directs its localization to lipid rafts. The central hypothesis of this project is that the interaction between GLP-1R and caveolin1 and its localization in lipid rafts is a fundamental mechanism controlling both the insulinotropic and the proliferative actions of GLP-1 and exendin-4.

Alicia M. Celotto, Ph.D.
Research Instructor
Ph.D., University of Connecticut Health Center, CT, 2002

Dr. Celotto is currently involved in three research projects:

1. The link between glycolysis and Mitochondrial energy production and their effect on the Na/K pump and how their dysfunction may lead to seizures.
2. Allotopic ATP6 expression used to rescue the Drosophila MILS model of mitochondrial encephalomyopathy.
3. Drug discovery using Drosophila neurodegenerative models.

Dr. Celotto's interests are focused on studying the connection between energy production and neurological conditions, such as seizures, migraine and neurodegeneration. She has discovered mutations causing degeneration and reduced longevity that markedly reduce glycolysis or mitochondrial oxidative phosphorylation, neither of which results in a bioenergetic crisis. These results demonstrate that energy derived from different sources cannot fully compensate for such impairments suggesting certain essential processes are dependent upon specific sources of energy. It is believed that ATP produced through glycolysis is specifically generated at sites of high need in the neuromuscular system, for example the Na+/K+ pump, an important regulator of cellular ion homeostasis. Thus changes in the source of ATP production due to mutations affecting glycolysis or mitochondrial function may result in neurological disease by altering Na+/K+ activity. To study this, she uses Drosophila mutants affecting the glycolytic enzyme, triose phosphate isomerase (TPI), a component of the mitochondrial ATP synthase (ATP6) and the Na+/K+ pump (ATPalpha).

Eugenia Cifuentes-Pagano, Ph.D.
Research Instructor
Ph.D., State University of New York at Stony Brook, 1994

Dr. Cifuentes-Pagano's research interests focus on the understanding of the molecular mechanisms of action of novel NADPH oxidase isoforms and their regulation in the vasculature. The phagocyte NADPH oxidase (or respiratory burst oxidase) is a well-characterized reactive oxygen species (ROS)-generating system that catalyzes the one-electron reduction of oxygen to O2-, the precursor to a variety of other reactive oxygen species. The NADPH oxidase paradigm is a multi-subunit enzyme complex that includes two membrane-spanning subunits, p22-phox and nox2, and three cytoplasmic subunits, p40-phox, p47-phox and p67-phox. Our laboratory was the first to discover a nox2-based oxidase in the vasculature and to develop specific inhibitors targeting this robust source of ROS. Since that initial discovery, various isoforms of NADPH oxidase have been described which differ from the nox2 system in unique modifications of their nox-subunit amino acid sequence as well as the cytoplasmic components that they require. Besides their structural differences, the various isoforms present differential tissue and cellular distribution. The multi-level complexity of this family of proteins provides an opportunity to develop new tools to dissect the role of each of the isoforms in vascular function and pathology.

Marsha Cole, Ph.D.
Research Instructor
Ph.D., University of Kentucky, 2004

Dr. Cole's research focuses on the endogenous generation of nitrated fatty acids (NO_2-FA) in metabolic diseases, such as diabetes. Hyperglycemic and hyperlipidemic conditions support the presence of a pro-oxidative milieu in type II diabetes which can lead to increased mitochondrial production of reactive oxygen species and nitric oxide synthase activity. In particular, NO_2-FA are generated in heart mitochondria through

•NO-dependent oxidation and nitration and can mediate reactions that may beneficially modify mitochondrial function.

NO_2-FA derivatives are present endogenously and mediate anti-inflammatory effects through predominately cGMP–independent mechanisms that include electrophilic posttranslational protein modification and potent peroxisome proliferator-activated receptor (PPARγ) ligand activity. As a result of robust thiol reactivity, NO_2-FA also activate phase II enzyme expression in vitro and in vivo (e.g., heme oxygenase 1, HO-1), through nuclear factor E2-related factor 2 (Nrf2) activation of antioxidant response element (ARE) dependent gene expression.

Taken together, generation of NO_2-FA can impact mitochondrial respiratory function, myocardial efficiency, and cardiac contractility in diabetes. And although NO_2-FA are endogenously generated as adaptive cell signaling mediators, therapeutic administration (in higher doses than endogenous concentrations) is of interest as to potentially attenuate hyperglycemia and hyperglycemic-induced myocardial injury.

Thomas Conrads, Ph.D.
Visiting Associate Professor
Ph.D., Ohio State University, 1999

Armed with sequence information of the human and mouse genomes, a major aim of biological science is toward unraveling the underlying molecular events that lead to cellular function/dysfunction in disease with the goal of discovering better diagnostic markers and therapeutic targets. Proteomics aims to facilitate this process by applying newly developed methods and advanced analytical tools for the investigation of the protein complement and its repertoire of post-translational modifications en masse. Our efforts are, therefore, focused on development of new technologies that bridge the fields of chemistry and biology toward their application for characterization of proteomic changes associated with pathophysiology, ascribing to the philosophy that effective biomedical investigation mandates creative multidisciplinary approaches. In practice, we utilize advanced mass spectrometry (MS) tools, molecular biology, and bioinformatics to conduct molecular investigations of human disease. In practiced our research has three major focus areas that include: 1) global profiling of protein and metabolite abundance changes, 2) global and targeted characterization of protein post-translational modifications, and 3) high-throughput assay development based on the use of selected reaction monitoring MS.

Donald DeFranco, Ph.D.
Professor & Vice Chair, Education
Ph.D., Yale University, 1981

The general goal of the neurodegeneration project is to understand the cellular changes that occur in nerve cells that are exposed to oxidative stress. In response to acute injury such as stroke or in many chronic neurodegenerative diseases such as Alzheimer's and Parkinson's disease, nerve cells are subjected to oxidative stress. Through a better understanding of the biochemical changes that occur in response to oxidative stress in nerve cells Dr. DeFranco hopes to identify molecules and pathways that could be targets for therapeutic intervention.

The DeFranco laboratory is also interested in prostate cancer and focuses on important components of the tumor microenvironment, (i.e. stromal cells) that provide the support necessary for cancer cells to survive and expand. The group has identified one molecular target in stromal cells that plays an important role in the communication between stromal cells and developing cancer cells in the prostate. The hope is to devise new strategies for limiting the contribution of the tumor microenvironment through detailed molecular studies of prostate stromal factors essential for cancer development and progression.

Finally, Dr. DeFranco examines the cell biology and clinical relevance of glucocorticoid signaling in various models. The basic mechanism of trafficking of the receptor for glucocorticoids (i.e. the glucocorticoid receptor) is examined using state-of-the-art fluorescence microscopy technology coupled with biochemical approaches. In addition, the impact of glucocorticoids on various tissues during development focusing on the brain in model studies in fetal mice and on white blood cells in critically ill children. Since glucocorticoids are a standard course of therapy for premature infants and critically ill children, we hope to provide insights into appropriate treatment strategies when glucocorticoids therapy is indicated.

Extracellular signal-regulated kinases-1/2 (ERK1/2), members of the mitogen-activated protein kinase (MAPK) family, are well-established regulators of cell proliferation and survival particularly in the brain. However, the DeFranco laboratory was one of the first to demonstrate a role for ERK1/2 in promoting toxicity in neurons using in vitro models of oxidative stress (i.e. neuronal cell line and primary neurons). Many examples have since been documented establishing a role for ERK1/2 in promoting cell death in neurons both in vitro and in vivo. Ongoing analysis of the mechanistic basis for ERK1/2 activation in oxidatively stress neurons has also implicated the oxidative inhibition of select protein phosphatases in persistent activation of ERK1/2 and neurotoxicity. Importantly, one of the secondary consequences of oxidative stress in neurons (i.e. increased accumulation of intracellular Zn2+) also contributes significantly to ERK1/2 activation through selective inhibition of protein phosphatases.

The regulation of promoter activity by nuclear receptors requires the assembly of large multi-subunit complexes that either directly impact the basal transcriptional machinery or modify core histones to affect chromatin structure and remodeling. The mechanisms responsible for maintaining the highly ordered dynamics of protein binding to hormonally responsive promoters have not been definitively established. Dr. DeFranco's laboratory recently developed a novel in situ fluorescence recovery after photobleaching assay that led to the identification of molecular chaperones and their associated cochaperones as nuclear mobility factors for the glucocorticoid receptor. They plan to further exploit this assay to provide additional mechanistic insights into the role of chaperones in nuclear dynamics of glucocorticoid receptor and perhaps reveal how stress response proteins could impact epigenetic events that regulate chromatin remodeling.

Communication between the epithelial and stromal compartments of the prostate that is mediated by growth factors and cytokines is crucial for the maintenance of prostate growth and function. However, alterations in the expression and response to these factors can occur during prostate cancer progression and alter signaling between these compartments. The DeFranco laboratory has identified a prostate stromal cell specific transcriptional coactivator, the Hic-5 protein, that functions in both basal and androgen regulated expression of keratinocyte growth factor, a paracrine factor that impacts prostate cancer cell proliferation. Furthermore, Hic-5 expression in prostate stromal cells is induced by an epithelial cell derived factor transforming growth factor–beta 1, which promotes the transdifferentiation of normal stromal fibroblasts to activated "myofibroblasts." Thus, Hic-5 is integral to stromal/epithelial cell communication in the prostate through its impact on endocrine, paracrine and perhaps autocrine signaling networks.

In their role as essential modulators of basal and stress-related homeostasis, glucocorticoids modulate host immune response, intermediary metabolism, and the cardiovascular system. Due to its anti-inflammatory actions, cortisol has been administered to adults and children with septic shock. Cortisol therapy is clearly beneficial in the Waterhouse-Friedrichsen syndrome characterized by adrenal hemorrhage and infarction, which was first described in children with meningococcal meningitis. However, both beneficial and deleterious outcomes of glucocorticoid therapy among critically ill patients have been reported. Despite the lack of objective data, high dose cortisol therapy has been used in the pediatric intensive care setting. Outcome measures to assess efficacy of cortisol therapy such as cortisol concentrations, adrenocorticotrophic hormone (ACTH)-stimulated cortisol concentrations, and blood pressure are indirect. Furthermore, these measurements do not assess the cellular actions of glucocorticoids, which are mediated by the glucocorticoid receptor (GR), a ligand dependent transcription factor. Many GR target genes participate in the immune

response. We will examine the cellular actions of GR in peripheral blood mononuclear cells (PMBCs) of critically ill children using assays that will provide insights into the anti-inflammatory actions of glucocorticoids.

W. Chet de Groat, Ph.D.
Distinguished Professor
Ph.D., University of Pennsylvania Medical School, 1965

Dr. de Groat is interested in the autonomic nervous system and the neural regulation of pelvic visceral functions. Current studies focus on the reflex control of the urogenital tract and the mechanisms underlying transmission at central and peripheral autonomic synapses. These experiments are designed to examine (1) the neurotransmitters in the reflex pathways, (2) neuroplasticity during postnatal development or following neural injury, (3) the neural pathways responsible for the detection of visceral pain, and (4) the actions of drugs used to treat urogenital dysfunction. Experiments are conducted on a variety of preparations ranging from intact animals to isolated tissues, like spinal cord slices and dissociated neurons.

Julie Eiseman, Ph.D.
Research Associate Professor
Ph.D., Cornell University Medical College, 1980

Research in the Eiseman laboratory is directed at the preclinical evaluation of potential anti-cancer agents. Studies include the determination of the maximum tolerated dose, pharmacokinetics, pharmacodynamics and efficacy. The laboratory is also interested in non-invasively measuring compounds with absorbance spectra in the long visible range.

Specific studies include the pharmacokinetics and efficacy of the pyrimidine compounds, fluorodeoxycytidine (FdCyd) and gemcitabine (dFdCyd) in combination with a cytidine deaminase inhibitor, tetrahydrouridine in CD2F1 mice and SCID mice with human pancreatic cancer xenografts.

The pharmacokinetics and efficacy of tubulin interactive agents including docetaxel, paclitaxel and 6-epi-dictyostatin are also under investigation. Studies with docetaxel have examined the interaction with 9-nitrocamptothecin in an ovarian cancer xenograft (SK-OV3) and a physiological based pharmacokinetic model was developed to describe the disposition of docetaxel. This model will be evaluated for its usefulness in predicting patient docetaxel pharmacokinetics.

Dr. Eiseman is interested in understanding the mechanisms involved during photodynamic therapy with Pc 4 and other phototherapeutic agents and use elastic scattering spectrometry to measure changes in drug concentrations and hemoglobin saturation during and following photodynamic therapy. For these studies, we measure the concentrations of the drug and hemoglobin non-invasively as well as through destructive methods such as HPLC and LC/MS-MS.

Other agents investigated include a wide range of potential cancer chemotherapeutics including DB-67, CKD-602, 2,2-dimethylbutyrate, DA-3003-1, Zebularine, 17-allyl aminogeldanamycin and 17-dimethylamino-geldanamycin.

Melanie Flint, Ph.D.
Research Instructor
Ph.D., Imperial College, University of London, England, 1998

Dr. Flint researches hormonal influences on cell cycle regulation, targeted molecular therapies, drug metabolism, drug resistance and cancer. Her primary research project involves the direct interplay between stress hormones (cortisol, NE, and E), cancer and chemotherapy. This is accomplished through a mechanistic study of administration of stress hormones to cancerous cells, and observing these effects both in vitro and in rodent models. The goal is to identify predictive characteristics for molecular response, elucidating the mechanism of action of hormones in cancerous cells, and characterizing the genomic/proteomic profiles encoding cell cycle regulation.

Dr. Flint's primary research project involves the direct interplay between stress hormones (cortisol, NE, and E), cancer and chemotherapy. This is accomplished through a mechanistic study of administration of stress hormones to cancerous cells, and observing these effects both in vitro by proteomics and in rodent models. We are first investigating paclitaxel, a drug used to treat metastatic breast cancer which acts on the cell cycle.

Peter Friedman, Ph.D.
Professor
Ph.D., SUNY Upstate Medical Center, 1975

Studies in the Friedman laboratory focus on the regulation of parathyroid hormone receptor signaling and regulated trafficking. PTH controls extracellular calcium and phosphate homeostasis. Its effects on kidney and bone are mediated by its cognate receptor, the type I PTH receptor (PTH1R). Key advances have been made in understanding cell-specific PTH1R signaling and trafficking, and recent observations indicate that PTH1R activation, desensitization and endocytosis are mediated through distinct structural states that derive from specific interactions between ligand and receptor.

Agonist- or antagonist-occupied receptor states induce discrete conformations with accessibility to intracellular receptor domains. The differential or inducible involvement of these domains in coupling to G proteins may represent a molecular basis for ligand-selective responses not only for the PTH1R, but also for other G protein-coupled receptors. Current work is directed at elucidating the molecular and structural mechanisms of how cytoplasmic scaffold proteins such as NHERF1 and Dishevelled legislate cell-, ligand-and stage-specific receptor trafficking.

William Furey, Ph.D.
Professor
Ph.D., The State University of New Jersey, 1977

Dr. Furey's research involves the structure determination and analysis of large biological molecules and complexes by x-ray crystallography, and correlating the results with known functions. The work currently focuses on thiamin (vitamin B1) dependent enzymes and cell cycle regulating enzymes, as well as crystallographic methods development. Results of these studies could lead to development of therapeutic agents directed against pathogenic organisms, and anti-cancer drugs.

Ferruccio Galbiati, Ph.D.
Associate Professor
Ph.D., University of Milan, 1996

Most cells can not divide indefinitely due to a process termed cellular senescence. Because cancer cells need to escape cellular senescence in order to proliferate and eventually form tumors, it is well accepted that cellular senescence is a powerful tumor suppressive mechanism. In addition, since several molecular changes that are observed in senescent cells occur in somatic cells during the aging process, investigating the molecular mechanisms underlying cellular senescence will also allow us to better understand the more complicated aging process. Thus, molecules that regulate cellular senescence represent potential therapeutic targets for the prevention/treatment of cancer as well as the fight against aging.

Our work is directed at unraveling the role of caveolin-1 as a novel mediator of cellular senescence. Caveolin-1 is the structural protein component of caveolae, invaginations of the plasma membrane involved in signal transduction. Caveolin-1 acts as a scaffolding protein to concentrate, organize, and functionally modulate signaling molecules within caveolar membranes.

Senescent human diploid fibroblasts express higher levels of caveolin-1, as compared to non-senescent cells. We showed that mouse embryonic fibroblasts derived from caveolin-1 overexpressing transgenic mice are arrested in the G0/G1 phase of the cell cycle and display a premature senescent phenotype. In addition, we demonstrated that oxidative stress induces premature senescence by stimulating caveolin-1 gene transcription through p38 MAPK/Sp1-mediated activation of two GC-rich promoter elements in fibroblasts and epithelial cells. Interestingly, oxidative stress-induced premature senescence (SIPS) does not occur in fibroblasts where caveolin-1 expression is reduced using an antisense mRNA-based approach. Moreover, oxidative stress does not induce premature senescence in caveolin-1-negative MCF-7 breast cancer cells and reintroduction of caveolin-1 in these cells restores IPS.

Taken together, these data indicate that caveolin-1 plays a central role in the signaling events that lead to cellular senescence. We are currently investigating, at the molecular level, the signaling pathways that link caveolin-1 function to oxidative stress-induced premature senescence. These investigations will contribute to elucidate the molecular mechanisms underlying aging and cancerous cell transformation.

Pamela Hershberger, Ph.D.
Research Assistant Professor
Ph.D., Case Western Reserve University, 1991

Hormones such as estrogen and 1,25-dihydroxyvitamin D3 play an important role in controlling cell growth; estrogen tends to promote growth, whereas vitamin D tends to inhibit growth. The goal of Dr. Hershberger's research is to understand how such hormone responses are generated and controlled, and how they may be exploited to suppress the development or growth of lung cancer (a disease that claims the lives of more than 160,000 individuals in the United States annually). Molecules which are found to be important in regulating hormone responsiveness in our studies represent potential new targets for therapeutic intervention in lung cancer chemoprevention and treatment.

Dr. Hershberger's research uses molecular and cellular techniques to evaluate the role of nuclear steroid hormone receptors and their signaling pathways as therapeutic targets in solid tumors. Because the hormone vitamin D exerts anti-proliferative activity in a variety of tumor model systems, we initiated studies to explore its potential as a novel lung cancer therapy. She has found that although lung cancer cells express the vitamin D receptor, they were only moderately sensitive to vitamin D-mediated growth inhibition. In exploring the mechanistic basis for this response, we found that primary human lung tumors but not normal lung tissues express CYP24, the enzyme that catabolically inactivates vitamin D. As the only known function for CYP24

is the regulation of vitamin D metabolism, its frequent up-regulation in human lung tumors implies that tumor establishment and/or progression requires escape from the anti-proliferative action of vitamin D. Based on these findings, our lab is now exploring (1) the effect of CYP24 inhibitors on vitamin D pharmacokinetics and anti-tumor activity in lung tumor xenograft models (2) the potential use of CYP24 as a diagnostic or prognostic marker in lung cancer, and (3) the mechanisms contributing to CYP24 over-expression in lung cancer cells. Ultimately, she seeks to suppress CYP24 action in lung cancer cells to restore endogenous growth control by vitamin D.

Jing Hu, Ph.D.
Assistant Professor
Ph.D., Karolinska Institute, Sweden, 1997

Gene regulation is a key event that is essentially involved in all basic cellular processes and pathological process. A thorough understanding of the molecular mechanisms by which gene regulation is controlled is a necessary foundation for attempts to target deregulated gene expression events for cancer intervention. The main focus of Dr. Hu's laboratory is to investigate how posttranslational modifications (sumoylation, phosphorylation and ubiquitination) control gene expression at both transcriptional and translational level in the process of carcinogenesis.

Dr. Hu recently discovered that posttranslational modification of transcription factor NF-κB2/p100 by the small ubiquitin-like modifier (SUMO) is a determining factor for stimuli-induced p100 processing and subsequent activation of alternative NF-κB pathway. Her results indicate that a threshold of basal p100 sumoylation creates a privileged pool of p100 that are competent for stimuli-induced phosphorylation and subsequent recruitment of ubiquitin E3-ligase β-TrCP, polyubiquitination and ultimate NF-κB2/p52 generation and RelB nuclear translocation. Together, these findings not only provide mechanistic information regarding how SUMO modification participates in the regulation of signaling transduction, but also uncover a novel regulation mechanism of activation of alternative NF-κB pathway. In the future, Dr. Hu will continue explore how functional interplays among posttranslational modifications control the activity of transcription factors and translation initiators.

Dysregulation of protein synthesis is beginning to be recognized as a major step in malignant transformation and progression of tumors, therefore another research interest of Dr. Hu's laboratory is to screen and identify dietary or natural agents for targeting deregulated protein synthesis for cancer intervention. We found that dietary agent phenethylisothiocynate (PEITC), are major bioactive components of cruciferous vegetables, inhibit cap-dependent translation by regulating level and phosphorylation of 4E-BP1. In the future, in addition to expand our understanding of PEITC-mediated translation inhibition by exploring the potential upstream signaling and downstream targets of translation inhibition, we will also search for natural compounds that target cap-dependent translation for cancer intervention through modulating SUMO pathway.

Yi Huang, M.D.
Research Assistant Professor
Ph.D., Medical University of South Carolina, Charleston, SC, 2001

Dr. Huang's research interests focus on the investigation of the molecular mechanisms underlying the epigenetic regulation of aberrantly silenced ER alpha and other genes in breast cancer and the development of novel agents to target epigenetic alterations to restore the silenced genes. DNA promoter hypermethylation in concert with other chromatin modifications has been associated with the aberrant silencing of genes important in breast cancer development. CpG islands at the promoter region of these silenced genes may become abnormally methylated through the active DNA methyltransferases (DNMT) and changes in histone acetylation and methylation have emerged as an important mechanism to mediate silencing of gene expression. We have demonstrated that treatment with DNA methyltransferase inhibitors (5-aza-cytidine or 5-

aza-2'-deoxycytidine) and/or HDAC inhibitor (Trichostatin A) may lead to re-expression of silenced ER alpha in ER-negative breast cancer cells. Our work continues to evaluate the ability of novel class of DNMT inhibitors and HDAC inhibitors to re-express aberrantly silenced ER alpha and other genes in breast cancer. In addition, we are interested in defining the changes in gene expression profiles of breast cancer cells treated with the novel agents targeting epigenetic gene silencing and identifying new genes and pathways that are aberrantly silenced in breast cancer.

Histone modifications include acetylation, methylation, ubiquitylation, phosphorylation, sumoylation and ribosylation, each of which can affect the expression of genes. The recent discoveries of novel FAD-dependent histone lysine demethylase 1 (LSD1) and Jumonji C domain-containing histone demethylases suggest that histone methylation is a dynamic process under enzymatic control similar to other post-translational histone modifications. LSD1 specifically catalyzes demethylation of mono- and dimethyl-lysine 4 of histone 3, key positive chromatin marks associated with transcriptional activation. Based on the structural and catalytic similarities of LSD1 and polyamine oxidases, we have identified specific polyamine analogues as potent inhibitors of LSD1 leading to re-expression of aberrantly silenced genes important in tumorigenesis. Recently, a LSD1 homolog, named LSD2, has been identified, suggesting the existence of a more sophisticated FAD-dependent histone demethylase family in chromatin remodeling and transcription regulation. We are currently investigating the functional connection between activity of FAD-dependent histone lysine demethylases and the transcription activity of estrogen-responsive genes and studying the molecular mechanisms underlying the regulation of novel histone lysine demethylases on aberrantly silenced genes in breast cancer cells. Another goal of this project is the preclinical evaluation and identification of agents as effective inhibitors of novel histone demethylases in targeting epigenetic alterations in human breast cancer.

Edwin Jackson, Ph.D.
Professor
Ph.D., University of Texas at Dallas, 1979

Dr. Jackson's research focuses on cardiovascular and renal pharmacology with an emphasis on understanding the function and mechanisms of endogenous autocrine, paracrine and humoral systems that either augment or inhibit the development or progression of cardiovascular/renal diseases. This research is guided by the concept that a better understanding of the endogenous systems that modulate disease onset and progression will result in new approaches to prevent or treat cardiovascular and renal diseases by inhibiting or augmenting these endogenous factors.

Three endogenous systems are under intensive investigation: sex hormones; adenosine; and the renin-angiotensin system.

Sex Hormones: Based on epidemiological data, cardiovascular scientists once thought that estrogen replacement therapy would prevent cardiovascular/renal disease in postmenopausal women. Unfortunately, randomized clinical trials did not support this simple concept. Dr. Jackson has discovered that estradiol, the main endogenous estrogen, is converted to metabolites that exert cardiovascular/renal protection. Because clinical trials were conducted with horse estrogens (Premarin) that are not precursors of these metabolites, it is likely that use of the wrong estrogenic preparation contributed in part to the negative results from clinical trials. We are currently using the knowledge gained by our experimental studies to design improved hormone replacement therapy that would benefit both women and men. Shown is a photograph of the obese ZSF1 rat (left) compared to a normal non-obese rat. The obese ZSF1 rat models the typical American "couch potato" (obesity, high blood pressure, elevated cholesterol, type 2 diabetes). Estradiol metabolites when given to ZSF1 rats cause weight loss, improve metabolic parameters and reduce heart, vascular and renal disease.

Adenosine: Adenosine is a naturally occurring chemical in the body that serves to protect organ systems from injury. We have discovered that adenosine protects the heart from damage induced by a myocardial infarction (heart attack), the brain from damage induced by traumatic head injury and (unfortunately) tumors when attacked by the immune system. For example, shown is a slice through two hearts, both of which suffered a heart attack. The right slice shows a heart not treated with adenosine and the left a heart treated with adenosine. The whitish/grey areas are dead tissue. We are currently investigating how adenosine levels in organ systems are regulated, what adenosine does to cardiovascular/ renal/ brain/ immune cells and how we can better modulate the adenosine system with drugs for clinical benefit in diseases of the heart, kidneys, blood vessels and brain and in cancer.

Renin-Angiotensin System: Angiotensin II causes constriction of small blood vessels in the kidney, leading to kidney disease and high blood pressure. We have found that the renal affects of angiotensin II are intensified in animals with genetically-susceptible kidneys. This effect appears to be attenuated by a renal enzyme called dipeptidyl peptidase IV (DPP IV) which metabolizes (converts) a gut released peptide (PYY1-36) and a nerve-released peptide (NPY1-36) to less active forms that do not activate the so-called Y1R. A new class of antidiabetic drugs inhibits DPP IV. We are investigating whether this new class of antidiabetic drugs may adversely affect the kidneys by preventing the conversion of PYY1-36 and NPY1-36 to less active metabolites.

Yu Jiang, Ph.D.
Associate Professor
Ph.D., Yale University, 1995

Dr. Jiang's laboratory is interested how environmental conditions, such as nutrient and stresses, control cell growth and proliferation. The laboratory focuses on intercellular signal transduction pathways that sense and transmit the environmental cues to cellular machinery governing metabolism and biosynthesis. Understanding how these pathways work in normal and cancer cells would allow us to development drugs for cancer prevention.

Dr. Jiang's laboratory studies the mechanism underlying the action of rapamycin, a macrolide antibiotic that has been used clinically as immunosuppressant for transplantation and anti-neoplastic drug for cancer prevention. The intracellular target of rapamycin is a kinase called TOR (or mTOR in mammalian cells), which lies at the center of a signaling network that controls many growth-related cellular events in response to changes in nutrient, growth factor, oxygen and energy levels. His laboratory is currently trying to answer two key questions concerning the signaling mechanisms of TOR: 1) how is TOR regulated by many distinct upstream signals? 2) what are the mechanisms by which TOR controls many diverse cellular events? Several projects centering on these two questions are ongoing.

The first project concerns the mechanism that controls mTOR. Jiang's laboratory has recently identified FKBP38, a member of the FK506 binding protein family, as an endogenous inhibitor of mTOR. They are trying to determine how nutrient, growth factor and oxygen levels regulate mTOR through FKBP38 in mammalian systems.

The second project aims to the role of FKBP38 in apoptosis. FKBP38 has been shown to interact with the anti-apoptotic proteins, Bcl-2 and Bcl-xL. Jiang's laboratory is investigating whether nutrient, growth factor and oxygen levels control the anti-apoptotic activity of Bcl-2 and Bcl-xL through FKBP38 in mammalian systems.

The third project focuses on the mechanism by which TOR elicits its pleiotropic roles in cell growth. Recent studies in Jiang's laboratory have established protein phosphatase 2A as a major downstream target of the Tor

pathway. His laboratory is currently investigating how Tor mediates PP2A activity and how PP2A relays Tor signaling activity to many cellular processes using yeast Saccharomyces cerevisiae as a model system.

Paul Johnston, Ph.D.
Research Assistant Professor
Ph.D., University of East Anglia, England, 1983

Dr. Johnston's research interests range from macrophage activation, cytokine biology, and immunology to drug discovery and the development of assays for high throughput (HTS) and high content (HCS) screening. In addition to the development and implementation of biochemical assays for HTS, Dr Johnston has been a pioneer in the application of cell based screening, and is a leader in the field of HCS and the application of image-based assays to drug discovery.

Dr. Johnston's early postdoctoral research focused on the changes in gene expression, signal transduction events and functional responses during macrophage activation. He has investigated and published manuscripts on the cloning, expression and functional characterization of proteins involved in calcium mobilization in mononuclear phagocytes: annexins, gCap39 an actin binding/capping protein, and the inositol 1,4,5-trisphosphate receptor. After joining the Pharmaceutical industry in 1990, Dr. Johnston pursued his interests in Immunology and cytokine biology to design and coordinate the in vitro and in vivo evaluation of recombinant cytokines for the prevention and/or therapy of infectious diseases, and as immunoadjuvants for vaccines.

High throughput screening (HTS) has become the dominant tool in the drug discovery process. Completion of the sequencing of the human genome has increased the number of potential drug targets. In parallel with these changes, developments in robotics and combinatorial chemical synthesis have driven the production of very large numbers of compounds with potential for pharmacological activity. The need to screen large libraries of chemical compounds against multiple targets has stimulated improvements in assay technology, instrumentation, and automation that evolved into the field of HTS and has revolutionized the field of drug discovery. The purpose of HTS is the interrogation of large chemical collections in the context of a biological target to accurately identify active chemotypes. To achieve this purpose, assays must be configured to provide a robust, reproducible signal with adequate throughput to screen large compound libraries. Since the activity or inactivity of any given compound in an HTS will typically be determined in a single well at one concentration, the assay signal window (dynamic range) must be sufficiently rugged to provide adequate separation between the maximum and minimum responses, and should enable the response to active compounds to be discriminated from the background variability (noise) associated with the top and bottom of the signal window. The process of assay development encompasses studies designed to validate the kinetics and pharmacology of the assay, together with efforts to optimize the signal window and/or variability of the assay in the context of a number of variables dictated by the automated process; DMSO tolerance, reagent stability, and signal stability. Superimposed upon assay development parameters associated with biochemical HTS formats, the implementation of cell-based screens present additional challenges; generation and/or characterization of an appropriate cell model, production of sufficient cells for HTS, plating cells for the assay, effects of compound exposure, and capture of the assay signal.

In recent years there has been a growing trend in drug discovery towards the implementation of cell based assays where the target is screened in a more physiological context than in biochemical assays of isolated targets. As a drug discovery scientist Dr. Johnston has pioneered the application of cell based assays for lead generation and optimization. Dr. Johnston has led the development and implementation of 50 assays (22 primary & 28 secondary) for HTS and hit assessment campaigns representing 4 therapeutic areas and diverse target classes; kinases, transporters, GPCR's, ion channels and multidrug resistance. To date, these efforts have yielded quality hits for 22 targets that have evolved into 2 programs, 6 leads, ongoing hit-to-lead efforts, and 3 hit assessment efforts. Dr. Johnston also directed the development and implementation of four in vitro ADME/Tox surrogate assays to provide bioavailability information on hits and leads: kinetic turbidimetric

solubility assay; Caco-2 absorption model; human liver microsome metabolism assay; and an L6 rat myoblast acute cytotoxicity assay.

Fluorescence microscopy, whether confocal or wide field, is one of the most powerful tools that cell biologists can use to interrogate bio-molecules and investigate the molecular mechanisms of the cell. What distinguishes High Content Screening (HCS) systems from the many confocal and wide field microscopes is the integration and automation of the entire analytical process. HCS platforms automate the capture and analysis of fluorescent images of millions of individual cells in tens of thousands of samples on a daily basis, and have made fluorescence microscopy and image analysis compatible with the needs of drug discovery and systems cell biology. Through selection of appropriate probes, antibodies, fluorescent protein fusion partners, biosensors, environmentally sensitive probes and stains, fluorescence microscopy can be applied to many drug target classes, may be configured for simultaneous multiple target readouts (multiplexing), and can provide information on sub-population distributions and cell morphology. Image based assays therefore provide multi-parameter quantitative and qualitative information beyond the single parameter target data typical of most other assay formats, and thus are referred to as high "content" assays. Automated imaging platforms are therefore being deployed throughout the drug discovery process.

In the summer of 2005, Dr Johnston joined the University of Pittsburgh School of Medicine Department of Pharmacology to establish and manage a drug discovery center, one of the recipients of the NIH Roadmap Initiative Molecular Library Screening Center Network (MLSCN) grants (principal investigator Dr. John Lazo). Dr Johnston is pursing his interests in drug discovery and assay development for both HTS and HCS.

Thomas Kensler, Ph.D.
Professor
Ph.D., Massachusetts Institute of Technology 1976

Research interests in my laboratory focus on the biochemical and molecular mechanisms involved in the induction of cancer by chemicals to serve as a basis for the prevention, interruption or reversal of these processes in man. One of the major mechanisms of chemical protection against carcinogenesis, mutagenesis and other forms of toxicity mediated by carcinogens is the induction of enzymes involved in their metabolism, particularly enzymes such as glutathione S-transferases, UDP-glucuronosyl transferases and NAD(P)H:quinone reductase that facilitate the detoxication and elimination of carcinogens. Furthermore, animal studies indicate that induction of these cytoprotective enzymes is a sufficient condition for obtaining chemoprevention and can be achieved in many target tissues by administering any of a diverse array of naturally-occurring and synthetic chemical agents. Our work utilizes animal and cell culture models to elucidate mechanisms of inhibition of aflatoxin hepatocarcinogenesis by dithiolethiones such as oltipraz, isothiocyanates such as sulforaphane and triterpenoids such as CDDO-Im. While induction of glutathione S-transferases clearly play an important role in chemoprevention of aflatoxin hepatocarcinogenesis, ongoing studies are seeking to identify additional genes induced by these agents. The Keap1-Nrf2 signaling pathway is activated by these classes of chemopreventive agents and leads to increased expression of genes that attenuate oxidative stress and inflammation among other actions. Their contributions to protection against carcinogenesis are under investigation.

A practical goal of our research has been to develop the tools to test the hypothesis that enzyme induction is a useful strategy for chemoprevention in humans. Hepatocellular carcinoma is the leading cause of cancer death in parts of Asia and Africa and may relate to hepatitis B virus infection and aflatoxin ingestion. Longitudinal surveys and prospective case-control studies in Qidong, P.R. China demonstrate consistent exposure of individuals in this region to aflatoxins and indicate a prime role for aflatoxin in the etiology of liver cancer, respectively. As a consequence, we have conducted clinical chemoprevention trials of oltipraz and other agents in Qidong. The initial randomized, placebo-controlled intervention of oltipraz demonstrated an increased excretion of aflatoxin-mercapturic acid, a derivative of the aflatoxin-glutathione conjugate, in the urine of participants receiving oltipraz. This study highlights the general feasibility of inducing Nrf2-regulated enzymes

in humans. Follow-up trials are evaluating more effective agents and are assessing whether protective alterations in aflatoxin metabolism can be sustained for extended periods of time and whether diminished incidence of liver cancer can be achieved in this high-risk population.

Joan M. Lakoski, Ph.D.
Professor
Ph.D., University of Iowa, 1981

Elucidating the cellular and molecular neuropharmacology of the aging brain is the focus of the Lakoski laboratory. Using multidisciplinary approaches to investigate biogenic amine receptor expression and function, both normal and pathological aging processes are being investigated in young, middle-aged and senescent small animal models. We are investigating the roles of the steroid hormones estrogen and corticosterone on serotonin receptors, their receptor-effector coupling to G-proteins and related signaling transduction cascades, including the 5-HT1A and 5-HT2A receptor subtypes, and the serotonin neurotransporter (SERT) in discrete brain regions including cortical, hippocampal and midbrain regions; radioligand binding techniques, receptor autoradiography and functional neurochemical assays are among the technical approaches used to study the impact of the circulating hormone environment on the aging serotonergic neuronal system. Related ongoing studies are utilizing in vivo microPET image analysis techniques to elucidate SERT expression and function with respect to aging and hormone treatment. In addition, the impact of selective neurotoxic insults to the dopamine-containing neuronal system is being investigated using behavioral, neurochemical and molecular approaches to better understand how this neurotransmitter system responds and recovers from neuronal injury across the lifespan. Our goal is to contribute new information to understand the biology of central nervous system aging, including normal and neurodegenerative processes, in neurotransmitter systems established as key components in cognitive declines, mood disorders, and stress-related disorders common in the elderly. Ultimately, our aim is to improve the quality of life with advancing age by pharmacological interventions to delay the onset of neuronal decline and/or enhance endogenous repair mechanisms of the biogenic amine neurotransmitter systems.

John Lazo, Ph.D.
The Allegheny Foundation Professor
Ph.D., University of Michigan, 1976

The Lazo laboratory is primarily focusing on studying how enzymes that remove high energy phosphates from proteins controlling cell division, migration and survival using both molecular biological and pharmacological approaches. Other major themes include determining the mechanism of action of new anticancer agents and the development of both high through and high content screens of small molecule chemical libraries.

Edwin Levitan, Ph.D.
Professor
Ph.D., Brandeis University, 1986

The Levitan lab studies long-term regulation of electrical activity and the control of neuropeptide release. The former studies are focused on electrical remodeling that contributes to the actions of antipsychotic drugs in the midbrain and promotes arrhythmias in the heart. The latter is aimed at understanding how electrical activity alters release of transmitters that are important for controlling mood, behavior and sensation. These topics are related because channels support the electrical activity that triggers neurosecretion, while motion and fusion of secretory vesicles support transmitter release and delivery of channels to the plasma membrane.

On the channel front, the lab is exploring how antipsychotic drugs increase Kv4.3 K+ channel expression in dopamine neurons known to be important in cognition and reward. In parallel, Kv4.3 downregulation in

cardiac myocytes induced by angiotensin receptors is studied because this effect is thought to promote arrhythmias and sudden death. The lab is also collaborating on studies of other K+ channels. For example, Kv2.1 channel effects on apoptosis and exocytosis have been described with Drs. Aizenman (Neurobiology, University Pittsburgh) and Lotan (Physiology and Pharmacology, Tel Aviv University).

Another project uses in vivo fluorescent imaging of green fluorescent protein (GFP) constructs in transgenic Drosophila nerve terminals to determine how patterned electrical activity controls neuropeptide release. By optically detecting vesicle motion and signal transduction, new mechanisms have been discovered that acutely regulate secretion (e.g. vesicle mobilization) and maintain nerve terminal function (capture of transiting vesicles). Future studies will incorporate photoactivatable proteins and multiphoton microscopy to probe how neurons produce activity-dependent changes in secretory activity.

Patrick J. Pagano, Ph.D.
Professor
Ph.D., New York Medical College, 1991

Dr. Pagano's research focuses on the modulatory role of the adventitia in vascular function and structure under both physiological and pathophysiological conditions. Dr. Pagano's laboratory was among the first to identify a non-phagocytic NADPH oxidase in the vascular wall, demonstrating a critical role for essential subunit p67phox in its activity. He subsequently cloned vascular p67phox and illustrated its potent activation at the mRNA and protein level in response to the potent pro-hypertensive hormone angiotensin II. Stemming from these early discoveries, Dr. Pagano was the first to develop specific cell- and tissue-permeant peptidic and adenoviral inhibitor of NADPH oxidase, which is widely considered the most specific NADPH oxidase inhibitor available. These and his other more recently developed inhibitors of novel isoforms of NADPH oxidase are expected to provide a platform for the development of new therapies aimed at treating hypertension and other cardiovascular diseases. Moreover, Dr. Pagano is broadly recognized for his pioneering work examining the role of adventitia-derived reactive oxygen species (ROS) and, in particular, superoxide anion and hydrogen peroxide in the modulation of vascular tone, inflammation, and remodeling.

Michael Palladino, Ph.D.
Associate Professor
Ph.D., University of Connecticut, 2000

The Palladino lab uses Drosophila, the fruit fly, as a model system to elucidate the cellular and molecular mechanisms of neurodegenerative diseases and discover therapeutic interventions for these diseases.

Our lab has identified a large collection of novel neurodegenerative mutants using a powerful forward genetic approach. Characterization of these mutants will identify key proteins required for neural maintenance with age and a detailed understanding of the role of these gene products in human disease conditions. The Palladino research program is directed toward three main goals: 1) discovering and characterizing novel pathways that cause neurodegenerative diseases, 2) understanding the physiological, cellular and molecular dysfunction that causes neurodegeneration in vivo, and 3) using our animal system in pharmacological screens to identify neuroprotective compounds for the treatment of human neurodegenerative diseases. We are currently focusing on elucidating the mechanism by which mutations affecting Na/K ATPase, triose phosphate isomerase (TPI), and ATP6 function result in RDP (rapid-onset dystonia parkinsonism), glycolytic enzymopathy, and mitochondrial encephalaomyopathy, respectively.

Guillermo Romero, Ph.D.
Associate Professor
Ph.D., University of Virginia, 1980

G-protein coupled receptors (GPCR) are the largest family of cell surface receptors found in mammalian organisms. These receptors are a major target for drug development. Dr. Romero is interested in the dynamics and traffic of GPCR, with special emphasis on the parathyroid hormone receptor type 1 (PTH1R). His approach is based on the use and development of novel optical techniques to study membrane proteins and their interactions with other cellular components in live cells.

Dr. Romero's research focuses on two main areas: a) the role of the PDZ proteins sodium-hydrogen exchange regulatory factor (NHERF1) and Disheveled-2 in the regulation of the dynamics and traffic of GPCR; and b) the role of phospholipase D in the regulation of receptor traffic and function.

Dr. Romero's approach is based primarily on the analysis of the physical properties of molecules of interest in live cells, using advanced optical techniques such as confocal microscopy, fluorescence recovery after photobleaching (FRAP), total internal reflection microscopy (TIRFM), image correlation spectroscopy (ICS), quantum dots, and others. Using these techniques, Dr. Romero has developed novel methods to examine protein-protein interactions in the temporal domain. For example, he has recently demonstrated that the PTH1R is tethered to the cytoskeleton and accumulates in the vicinity of subjacent actin stress fibers, forming bundles that are highly dynamic structures, moving along these bundles much more rapidly than between them.

Because of his interest in traffic, Dr. Romero is actively pursuing new approaches to the study of endocytic processes. To this effect, he recently developed novel methodologies for the purification and preparation of endosomes based on the use of magnetic nanoparticles attached to peptide ligands. In this technique, peptide ligands, such as insulin or epidermal growth factor, are adsorbed to colloidal iron nanoparticles (5-10 nm in diameter) and applied to the external surfaces of cells. These particles are sufficiently small to be internalized via the standard endocytic pathway and, because of the ferromagnetic properties of the colloidal iron, allow for a simple and rapid isolation of the endocytic vesicles containing the particle. He is using this novel technology to study the role of specific proteins in the endocytic pathway in a time-resolved manner. Figure 2 shows electron micrographs of cells treated with insulin-iron complexes at various times, demonstrating endosome maturation.

James Roppolo, Ph.D.
Research Assistant Professor
Ph.D., University of Michigan, 1970

Dr. Roppolo's research is concerned with the autonomic nervous system's control of bladder activity in normal animals and those with central nervous system injuries. A variety of techniques are used to examine, at the level of the lumbosacral spinal cord and brainstem, the various neuronal processes that occur in maintaining normal excretory function. These methods include: (1) anatomical techniques (HRP tracing and immunohisto-chemical techniques) to determine the location of neurons and possible neuropeptides involved in these processes, (2) neurophysiological techniques (evoked potentials, intracellular and extracellular single neuron recordings) to determine the types of neuronal interactions that occur in this system, (3) neuropharmacological techniques (systemic and iontophoretic application of drugs), (4) behavioral techniques and microstimulation of the of the lumbosacral spinal cord.

Francisco Schopfer, Ph.D.
Research Assistant Professor
Ph.D., University of Buenos Aires, Argentina, 2001

Dr. Schopfer's research is focused on the understanding of the biological effects of electrophilic fatty acids. In particular, he studies the mechanism by which nitrated fatty acid activate and signal through peroxisome proliferator-activated receptor gamma (PPARγ). This receptor is the target of currently used antidiabetic drugs (thiazolidinediones). The activation of the receptor regulates fat and glucose metabolism, resulting in an overall decrease of glucose levels to normal values in patients with type II diabetes. The targeting of this receptor by nitrated fatty acids results in a decrease of the glucose levels to normal values like thiazolidinediones, but without the known secondary effects exerted by thiazolidinediones. In addition to the intrinsic therapeutic value of nitrated fatty acid, they will aid in the understanding of the biological mechanism involved in PPARγ activation, leading to improved designs of anti-diabetic drugs targeting the PPARγ receptor.

The role of the PPARγ receptor in diabetes has been well established. Nonetheless, the role of endogenous signaling molecules on the activation of PPARγ is still unclear and under debate. Nitrated fatty acids are endogenously formed and bind to PPARγ with high affinity rivaling Rosiglitazone (thiazolidinediones), resulting in receptor activation. In addition, nitrated fatty acids covalently modify a critical cysteine (cys285) in the ligand binding pocket of PPARγ, promoting a particular conformational change that results in partial receptor activation. This partial activation results in the expression of a particular subset of genes under PPARγ regulation and a biological outcome that differs from the one obtained when activating the receptor with Rosiglitazone. Dr. Schopfer's work focuses on understanding the mechanism of this selective activation and how it avoids the side effect presented upon full activation by agonist like Rosiglitazone.

Electrophilic fatty acids are constantly formed as fatty acid breakdown products during oxidative stress and as signaling messengers by enzymatic or non enzymatic pathways. Dr. Schopfer studies the formation of biologically relevant electrophiles, in particular nitrated fatty acids, and their signaling mechanisms. The study involves the detection and characterization of novel electrophiles formed during inflammation. Once the molecules are characterized, a chemical synthesis approach is used to generate enough quantities for biological experiments.

Electrophiles induce an important cellular response that includes the induction of phase II genes. This will in turn set up a more protective environment against damaging electrophilic molecules. A key player in the initiation of this biological response is the Keap 1/Nrf 2 couple. Keap 1 is usually bound to Nrf 2 in the cytoplasm. Upon formation of electrophiles, Keap 1, which contains several highly reactive cysteine, is targeted, dissociates from Nrf2 and is routed to degradation by the proteosome. These lead to Nrf2 nuclear translocation and activation of phase II genes. In particular, we study the mechanism by which different biologically relevant electrophiles target KEAP 1 and activate Nrf 2 responses. In addition, a more general proteomic approach is use to evaluate and characterize different electrophilic cellular protein targets. Once critical targets are identified using a mass spectrometry approach, a functional study of the modification is performed to determine the relevance and its cellular effects.

Adrian Sculptoreanu, Ph.D.
Research Assistant Professor
Ph.D., Université de Sherbrooke, 1983

We are using patch clamp techniques to study: a) the neurokinin-activated intracellular signaling mechanisms involved in the conversion of small DRG neurons from phasic to tonic firing; b) the neurokinin-activated intracellular mechanism involved in the TRPV1 desensitization in fast blue (FB) labeled bladder DRG neurons; and c) the neurokinin-activated intracellular mechanism involved in modulation of Ca^{2+} currents. In

these studies we will measure TRPV1 currents activated by capsaicin before and after application of neurokinin agonists, inhibition of PKC, phosphatases or a combination of these treatments. To insure that the DRG neurons tested are UB neurons we will use identified FB labeled neurons from L1-S2 DRG. In these experiments we will test the hypothesis that activation of PKC is in part responsible for nociceptive sensitization mediated by neurokinins, which constitutes the central hypothesis of this grant. Preliminary experiments done by us in DRG neurons of normal cats and rats suggest that an NK_2 selective agonist prevents TRPV1 receptor desensitization and the action of this neurokinin agonist is mediated by PKC. The main goal of our present research is to establish which phosphatases and protein kinase C subtypes are involved in the modulation of TRPV1 currents, and K^+-, Na^+- and Ca^{2+}-currents and in what ways these mechanisms are contributing to changes in excitability and synaptic transmission in nociceptive sensitization. For this purpose we will use selective protein kinase activators, peptide inhibitors and phosphatase inhibitors as well as cell dialysis with active PKCe during recording of TRPV1 currents in whole cell configuration.

Dinara Shakiryanova, Ph.D.
Research Instructor
Ph.D., Kazan State Medical University, Russia, 1993

Dr. Shakiryanova's research interests are focused on studying the mechanisms of neuropeptide release and signaling pathways involved in regulation of neuropeptide secretion.

Neuropeptide vesicle dynamics and release can be measured in vivo at nerve terminals by imaging GFP-neuropeptide fluorescence in our Drosophila melanogaster model. Ca^{2+} signaling mechanisms induce long lasting presynaptic dense-core vesicle mobilization and synaptic plasticity. Specifically, voltage-gated Ca^{2+} channels, Ca^{2+}-induced Ca^{2+} release channels and Ca^{2+}/calmodulin-activated kinase II are studied because they are required for sustained mobilization of dense-core vesicles and post-tetanic potentiation of neuropeptide secretion.

Dr. Shakiryanova's study has revealed that DCVs are mobilized by Ca^{2+} in an F-actin independent manner. Persistence of vesicle mobilization for minutes following seconds of activity indicates a role for signaling in the control of vesicle mobility in synaptic boutons. We have demonstrated that ryanodine receptor mediated Ca^{2+} release from endoplasmic reticulum and activation of CamKII are necessary for initiating DCV mobilization and post-tetanic potentiation of neuropeptide release.

CamKII remains an active subject of our study. Currently she is exploring CamKII activation in animals expressing FRET-based CamKII indicator Camui. Electrical activity induces rapid activation of CamKII in synaptic boutons which persists after the return of Ca^{2+} back to baseline. Furthermore, activated presynaptic CamKII translocates from the cytoplasm to clusters, presumably active zones.

It has long been recognized that cyclic nucleotides regulate synaptic transmission. But determining the mechanisms responsible for activating cyclases that regulate synaptic transmission has been difficult because it has not been possible to directly measure cyclic nucleotides in living nerve terminals. Recently, a ratiometric FRET-based cAMP sensor called epac1-camps has been generated that reports activation of adenylyl cylase by forskolin and receptors. Our experiments revealed that activity rapidly induces a Ca2+-dependent epac1-camps response in Drosophila synaptic boutons. Surprisingly, this response cannot be attributed to activation of rutabaga adenylyl cyclase and is unaffected by the dunce cAMP-specific phosphodiesterase. Instead, the activity-dependent presynaptic epac1-camps signal reflects elevation of cGMP in response to nitric oxide-activated guanylyl cyclase. Post-tetanic presynaptic cGMP is long-lived because of limited phosphodiesterase activity. Thus, nerve terminal biochemical signaling induced by brief bouts of activity temporally summates on a time scale orders of magnitude longer than fast transmission.

Elizabeth Sharlow, Ph.D.
Research Instructor
Ph.D., Pennsylvania State University, 1997

Dr. Sharlow's research focuses on the design and implementation of high throughput and high content screening assays that are used to interrogate large compound libraries for small molecule inhibitors of a molecule target (protein) of interest. Compounds identified in these primary screening assay activities are further characterized in secondary hit confirmation assays which assess the compound's activity and function to determine the specificity of the inhibitory response. Dr. Sharlow's primary goal is to identify small molecules that may have long term therapeutic efficacy as well as small molecules that can be used as chemical probes to help delineate the physiological roles of specific molecular targets (proteins).

The disease model systems with which Dr. Sharlow works include Salmonella, Bubonic plague, Malaria, Leishmaniasis and Cancer with the specific molecular targets being predominantly kinases and phosphatases. The majority of her HTS assays utilize recombinant proteins and, therefore, a significant effort is focused on expressing and purifying mammalian, bacterial and difficult to express Plasmodium falciparum proteins. She currently uses E.coli expression systems; however, she is also implementing wheat germ and insect cell expression systems to broader our protein expression and purification repertoire. Within the Leishmaniasis disease model system, we also use whole organisms (i.e. parasites) for the basis of high throughput screening assays. One particular Leishmaniasis project focuses on examining the differences in drug sensitivity of Leishmania major life cycle forms (promastigotes, axenic amastigotes and cell-based amastigotes).

Sruti Shiva, Ph.D.
Assistant Professor
Ph.D., University of Alabama at Birmingham, 2004

Dr. Shiva's lab focuses on the mechanisms by which reactive nitrogen species (particularly nitrite and nitric oxide) regulate mitochondrial function during hypoxia and ischemia, the factors that influence this regulation and the implications of this regulation on pathology such as ischemia/ reperfusion injury.

Active projects in her lab include: The role of heme proteins in regulating nitrite-dependent modulation of mitochondrial respiration. The anion nitrite (NO2-) is an endocrine storage form of nitric oxide (NO) in blood and tissues that can be reduced to bioavailable NO by heme proteins in conditions of low oxygen. In blood, the reduction of nitrite by hemoglobin mediates hypoxic vasodilation. We are interested in understanding how tissue nitrite reductases regulate mitochondrial function. Specifically, myoglobin, when deoxygenated, can efficiently reduce nitrite to NO and this NO subsequently inhibits mitochondrial respiration by binding to complex IV of the mitochondrial respiratory chain. We are interested in other ways that this interaction between nitrite and myoglobin regulates mitochondrial function as well as characterizing the physiological interplay between mitochondria and myoglobin with nitrite/NO acting as a signaling molecule linking the two.

The regulation of mitochondrial function by nitrite during ischemia/reperfusion. Low concentrations of nitrite have been shown to mediate cytoprotection in a number of models of ischemia/reperfusion of the brain, liver, heart and kidney. However, the mechanism of this cytoprotection is not known. The mitochondria play a central role in the progression of ischemia/reperfusion injury. Hence, we are interested in how nitrite regulates mitochondrial function during ischemia/reperfusion.

We have recently demonstrated that nitrite administered to animals before or during ischemia/reperfusion modulates mitochondrial function by S-nitrosating thiols on mitochondrial complex I, which leads to decreased reactive oxygen species generation, less oxidative damage of mitochondrial proteins, and prevention of

cytochrome c release. We think that these modifications of function prevent mitochondrial dysfunction after reperfusion and lead to cytoprotection.

We are currently using isolated mitochondria, the Langendorff isolated and perfused heart, and in vivo ischemia/reperfusion models to further characterize nitrite-dependent cytoprotection, particularly in relation to other cytoprotective programs, such as ischemic preconditioning.

Mechanisms of nitrite generation and metabolism. Another focus of the lab is determining the mechanisms by which nitrite is formed and metabolized physiologically. Conventionally, nitrite is thought to be formed by the oxidation of nitric oxide. However, in vivo, the reaction of nitric oxide with oxygenated hemoglobin (which produces nitrate) is more kinetically favorable than the reaction with oxygen to produce nitrite. We have recently identified a role for the multicopper oxidase, ceruloplasmin, as an "NO oxidase" that can compete with the nitric oxide-hemoglobin reaction to oxidize NO to nitrite. We are currently further characterizing the role of ceruloplasmin in regulating nitrite levels in physiology and pathology, and in plasma and tissue.

Jill Siegfried, Ph.D.
Professor
Ph.D., Yale University, 1981

Dr. Siegfried investigates the role of growth factors and hormones in the development and growth of human lung cancer. The laboratory focuses on the effects of these cytokines on activation of cell signaling pathways and control of tumor growth, as well as their role in risk for cancer. Growth factors and their receptors currently under investigation include estrogen and its receptors and hepatocyte growth factor and its receptor, c-Met. Growth factors and hormones are also being investigated as possible therapeutic targets and diagnostic or prognostic indicators for lung cancer. Hepatocyte growth factor has been found to be a strong negative prognostic indicator for non-small cell lung cancer, and expression of the enzyme aromatase that mediates estrogen production has also been linked to poor outcome in women with lung cancer. Circulating growth factor levels may also correlate with active cancer. These studies are directed toward development of new methods to identify undetected lung cancer and new therapeutic strategies through increased knowledge of growth-regulatory processes in lung cancer cells.

Hepatocyte growth factor (HGF) and its receptor c-Met are a ligand-receptor pair that initiates signaling pathways promoting proliferation, survival, angiogenesis, and invasion. HGF is a mainly paracrine growth factor that is secreted by fibroblasts in the lung and acts upon the c-Met receptor expressed by airway epithelial and endothelial cells. In lung cancer, c-Met is often upregulated and the tumor cells induce elevated HGF production by neighboring stroma. Elevated HGF in lung cancer patients with early stage disease has identified a population of patients who are most likely to recur and die from their disease. As shown in the Kaplan-Meier survival curves, HGF levels above the median of 22 units was associated with a higher proportion of deaths from all causes (A), lung-cancer specific deaths (B), and recurrence events (C). This observation among others has led us to focus on therapeutic targeting of HGF and its receptor c-Met for control of lung cancer.

To test therapeutic strategies, Dr. Siegfried has engineered a transgenic mouse that over-expresses the human HGF gene in the airways by placing the HGF gene under the control of the Clara cell secretory protein (CCSP) promoter. The lungs of these mice produce human HGF mRNA and protein and contain 2-3 times as many clara cells per micron of airway length as wild-type mice. While the mice show some abnormalities in airway branching, they have normal airway function and they do not develop lung tumors spontaneously at a rate above that of wild-type animals. However, the HGF transgenic mouse is more susceptible to the development of lung tumors initiated by the tobacco carcinogen NNK. Lung tumors produced by carcinogen treatment in the HGF transgenic animal are more invasive and contain higher numbers of blood vessels than wild-type tumors. These effects can be inhibited by a neutralizing antibody to HGF that is now in development for clinical use.

The Siegfried laboratory was one of the first to demonstrate the functional significance of estrogen receptors in lung tumors. This figure shows immunohistochemical staining of a non-small cell lung tumor for the estrogen receptor β, which we have found to be expressed to some degree in over 85% of lung tumors. Staining is observed both in the nucleus and cytoplasm, and we have evidence that both nuclear signaling through ERE elements in the promoter regions of estrogen-sensitive genes, as well as non-nuclear signaling through the EGFR and MAPK pathway occur in lung tumor cells.

Dr. Siegfried also has evidence that estrogen is locally produced by the enzyme aromatase within lung tumors, and this suggests an autocrine ligand-receptor exists for estrogen and its receptor in many lung tumors. Clinical trials are currently on-going to test the clinical activity of estrogen antagonists for therapy of lung cancer.

Shivendra Singh, Ph.D.
Professor
Ph.D., Banaras Hindu University, India, 1984

Despite significant advances towards early detection and targeted therapies, prostate and breast cancers continue to claim thousands of lives each year. The Singh laboratory is interested in preclinical and clinical development of novel agents derived from dietary sources (e.g., garlic and broccoli) and traditional oriental and Indian medicinal plants potentially useful for prevention of prostate and breast cancer in humans.

The research interests of the Singh laboratory are thematically aligned with three main areas: (1) preclinical and clinical development of novel cancer chemopreventive agents, (2) rational design of combination chemoprevention regimens, and (3) elucidation of the mechanism of carcinogenesis by environmentally relevant chemicals. Cellular and transgenic animal models are used to screen potential cancer chemopreventive constituents from dietary sources and traditional oriental and Indian medicinal plants. Cutting edge molecular biological (gene manipulation) and imaging techniques (MRI and bioluminescence imaging in live animals) are used by Singh and colleagues to determine the mechanism of action of promising cancer chemopreventive agents and to monitor their effects on cancer progression.

Cancer chemoprevention is a relatively new but rapidly emerging sub-discipline in oncology and refers to the use of natural or synthetic agents to reverse or delay the process of carcinogenesis. Despite considerable advances towards early detection and targeted therapies, prostate and breast cancers continue to be the leading causes of cancer related deaths. The long latency of most epithelial cancers, including prostate and breast cancers, provides a large window of opportunity for intervention to prevent or slow disease progression. Accordingly, identification of agents that are relatively safe but can be used to prevent cancers could have a significant impact on disease-related cost, mortality, and morbidity for a large segment of population.

Epidemiological studies continue to support the premise that dietary intake of certain vegetables (e.g., garlic) may be protective against the risk of different types of cancers. Anticancer effect of garlic is attributed to volatile sulfur compounds (e.g., diallyl trisulfide), which are generated upon processing (e.g., cutting) of these vegetables. Recent work from the Singh laboratory has revealed that garlic constituent diallyl trisulfide (DATS) suppresses growth of prostate cancer cells irrespective of their androgen-responsiveness or p53 status by activating a novel checkpoint kinase 1-dependent prometaphase arrest (schematically illustrated in Figure 1) and complex signaling culminating into apoptotic cell death. The DATS-mediated apoptosis involves reactive oxygen species-dependent activation of c-Jun N-terminal kinase. Oral administration of DATS significantly retards growth of prostate cancer xenografts in athymic mice without causing weight loss or any other side effects. Studies are in progress to determine efficacy of DATS against prostate carcinogenesis and metastasis using transgenic animal models. Positive outcome of these preclinical studies would rationalize clinical investigations to determine prostate cancer prevention by DATS in humans. Similar preclinical efficacy and

mechanistic studies are underway in the Singh laboratory on prostate and breast cancer chemoprevention by phytochemicals derived from cruciferous vegetables (e.g., isothiocyanates) and traditional oriental (honokiol) and Indian medicine (guggulsterone and withanolides). Another research interest of the Singh laboratory entails elucidation of the mechanism of chemical carcinogenesis by polycyclic aromatic hydrocarbon (PAH) family of environmental pollutants. Singh and his collaborators have discovered a novel mechanism involving cell cycle regulator Cdc25B in PAH-induced neoplastic transformation. These studies have shown that chronic exposure of mouse embryonic fibroblasts (MEFs) derived from the wild type mice, but not Cdc25B knockout mice, to a prototypical PAH (BPDE) results in neoplastic transformation characterized by colony formation and tumor production in nude mice. Investigations are planned to determine in vivo relevance of these cellular findings.

Robert Sobol, Ph.D.
Assistant Professor
Ph.D., Temple University, 1991

DNA repair proteins maintain genome stability and cell survival by efficiently removing cytotoxic and genotoxic DNA lesions generated by endogenous sources (cellular metabolites) and exogenous sources (environmental toxins and chemotherapeutic agents). The Sobol laboratory uses genomic and proteomic tools (i) to study regulation of the base excision repair (BER) pathway in normal and disease-derived cells (i.e., cancer stem cells, neurons), (ii) to study how this pathway repairs chemotherapeutic and environmental agent induced DNA damage, (iii) to identify novel DNA repair and DNA damage-response genes/proteins involved in chemotherapeutic response and (iv) to discover the mechanisms that govern the cellular response to DNA damage or failed DNA repair in normal and diseased cells (See Figure 1 on the Scientific Graphics Page - Model for Base excision repair).

Current projects include a study of the role of BER in the repair of DNA damage induced by alkylation, oxidation and radiation, an investigation of NAD+ and poly-ADP-ribose metabolism and catabolism proteins in DNA repair and DNA damage response, BER-mediated repair of oxidative DNA damage in the control of inflammation & neurodegeneration and epigenetic control of DNA repair gene expression in cancer. These studies involve the use of lentiviruses for gene expression and knockdown, human tumor and cancer stem cell culture, genetic and small molecule inhibitors to regulate DNA repair and DNA damage response, protein biochemistry and proteomic approaches, cell biological methods and molecular biological methods including cDNA cloning, recombinant protein expression & purification and single-gene and whole genome expression, SNP and methylation analyses.

BER protein complex formation and overall BER function is influenced by posttranslational modifications (PTMs) that arise from the cellular state or the DNA damage response. For example, Pol ß function is altered by methylation, acetylation and possibly SUMO-modification. How Pol ß and the BER pathway are controlled by PTMs is only beginning to be understood. The next goal is to assess the potential crosstalk between these PTMs, the ability to form productive repair complexes, and the stability and function of these BER proteins, as a single PTM can positively or negatively influence both enzyme function and the signal for a second PTM. In this context, my lab is studying how Pol ß methylation or acetylation can regulate BER complex formation and therefore impact the stability and function of Pol ß by enhancing or inhibiting CHIP-mediated ubiquitylation and the potential for SUMO modification of Pol ß.

PARP-1 as a Base Excision Repair Checkpoint Protein: In this project, the Sobol lab is studying the role of PARP1 and PARP2 in BER to define the cellular signal generated by aborted BER that leads to cell death. We have demonstrated that Pol ß-dependant sensitivity to alkylation damage in human cells requires repair initiation by Mpg and is contingent on a failure to repair the BER intermediate 5'dRP. Further, the group hypothesizes that PARP1/PARP2 acts as a sensor to incomplete BER, leading to rapid poly(ADP)ribosylation (PAR) and functional inhibition of target proteins that include the mitotic checkpoint kinase aurora B (AurB).

Inhibition of AurB initiates a rapid loss of Histone H3 phosphorylation and a complete block to mitosis leading to a strong cell cycle block at the G2/M border. At later time points this translates to AIF-mediated translocation, the onset of cell death and activation of the ATM-mediated DNA damage response.

A second modifier protein critical to the cellular response to DNA damage is the enzyme PARG, which removes the PAR moieties from PARP-modified proteins (See Figure 3). We hypothesize that the BER pathway, via activation of PARP1, triggers a specific signal that mediates a mitotic checkpoint and prevents tumor cells from dividing, leading to necrotic, autophagic and/or apoptotic cell death and this signal is regulated by PARG. Current studies will extend initial findings by using the clinical PARG inhibitor N-bis-(3-phenyl-propyl)9-oxo-fluorene-2,7-diamide as well as RNA interference (RNAi) to specifically down regulate PARG in glioma cells and evaluate the significance of PARG activity in the cellular response to DNA base damage. Finally, Dr. Sobol proposes to explore the significance of and identification of PARP modified proteins in the cellular response to base damage. The goal is to develop a complete human proteome map of PARP modified proteins and PAR binding proteins that respond to and control the cellular response to environmentally- and chemotherapeutically-induced base damage.

Gene expression variations in normal versus diseased cells impact both the control of genome stability and the cellular response to both environmental and chemotherapeutic exposures. However, gene expression is altered both by sequence variations [Single-nucleotide polymorphisms (SNPs) or disease-related gene mutations] and epigenetically, by cytosine methylation or post-translational modification of histones (methylation, acetylation or phosphorylation). In many cases, epigenetic changes can alter response to chemotherapy by deregulation of response genes. Dr. Sobol is interested in studying the role of cytosine methylation and histone modification in cancer, with an emphasis on epigenetic regulation of chemotherapeutic response. For example, in recent studies, hypermethylation of the promoter of the DNA repair gene MGMT has been found to be of progostic value in oropharyngeal cancer patient survival. Further, MGMT expression appears to correlate with outcome in childhood malignant glioma. Finally, Dr. Sobol is using whole genome approaches to identify genetic alterations (SNPs) that may alter chemotherapeutic response to alkylator therapy.

Gyun Jee Song, Ph.D.
Research Instructor
Ph.D., Seoul National University, Seoul, Korea, 2001

Dr. Song's research is focused on the study of G-protein coupled receptor (GPCR) signaling. G protein coupled receptors, a family of membrane signaling proteins, are the targets of half of the drugs on the market today. Her past research shows that some GPCRs function as dimer or oligomers, and that specific binding molecules regulate receptor signaling and trafficking. Dr. Song is currently focusing primarily on two projects: the study of parathyroid hormone (PTH) receptor signaling in vascular cells and the study of the glucagon-like peptide 1 receptor signaling in the pancreatic islets.

During the past few years, Dr. Song has concentrated on determining the molecular mechanism underlying vascular disease, with particular emphasis on the role of PTHrP and the PTH receptor signaling in the development of arterial restenosis. Her research has revealed some of the mechanisms regulating expression and signal transduction of the PTH1R in vascular smooth muscle cells. Indeed, these molecules are endogenously expressed in vascular smooth muscle cells and play a key role in mediating proliferation and migration of vascular smooth muscle cells, events that are critical for the development of restenosis (the process of occlusion of an artery) following angioplasty.

Dr. Song is also interested in the function of EBP50 (Ezin binding protein, NHERF1) a scaffolding protein in the vasculature. She showed that EBP50 contributes to cell-specific signaling by the PTH receptor and contributes to vascular smooth muscle cell proliferation and migration. These observations suggest that

targeting EBP50 represents a completely novel potential approach for treating this important complication of a commonly used surgical procedure.

Dr. Song is also involved in the study on glucagon-like peptide 1 receptor (one of the GPCRs) function in pancreatic islets. In particular, the role of the adaptor protein Caveolin-1 in the regulation of receptor expression and function is under investigation. Furthermore, her research aims to determine the role of Caveolin-1 in determining the efficacy of GLP-1R agonists in stimulating insulin secretion and β cell proliferation *in vivo*.

Harish Srinivas, Ph.D.
Research Instructor
Ph.D., Indian Institute of Science, India, 2000

Dr. Srinivas' laboratory is interested in studying the function of ligand-dependent transcription factors in normal and cancer cells, and to develop effective strategies for blocking these signaling pathways in an effort to prevent and treat cancer. Currently, their work is focused on estrogen receptors (ERs) and their function in lung cancer. Recent reports show that estrogens contribute to the growth of lung cancer cells, suggesting that the ER pathway is a potential target for lung cancer treatment and prevention. Lung adenocarcinoma, which shows weaker association with tobacco smoke than other types of lung cancer, is found predominantly in women, suggesting a possible role for estrogens in the development of the disease.

Estrogens exert their biological effect through two ER subtypes, ERalpha and ERbeta. In the classical 'genomic' mode of action, these receptors regulate gene expression by binding to estrogen response elements (EREs) in the promoter region of their target genes. In some cases, estrogens can also activate signaling through 'non-genomic' mechanisms by binding to membrane associated ERs, resulting in rapid cellular responses such as activation of kinase pathways.

Dr. Srinivas' group has shown that the estrogenic signals in lung cancer cells are mediated through ERbeta, but not ERalpha. Further they have shown that ERbeta is extranuclear in lung cancer cells and promotes lung cancer cell growth through non-genomic functions. Currently, their laboratory is investigating the non-genomic functions of ERbeta in lung cancer cells.

Laura Stabile, Ph.D.
Research Assistant Professor
Ph.D., West Virginia University, 1999

Dr. Stabile is interested in the role of growth factors and hormones in the development of human lung cancer. The hepatocyte growth factor (HGF)/c-Met pathway and the estrogen pathway both play key roles in the development and progression of lung cancer and represent attractive targeted pathways for drug development. Lung cancer kills more Americans every year than any other type of cancer, and the 5-year survival rate is only 16%. Lung cancer patients are typically diagnosed at a late stage and have very few effective therapeutic options. Thus, new targeted strategies are essential to make an impact on this disease.

c-Met is a receptor tyrosine kinase whose activation by HGF can lead to transformation (conversion of a normal cell into a malignant cell) and tumorigenicity (growth of tumors) in a variety of human tissues. Since c-Met and HGF are frequently overexpressed in lung cancer and there is a strong correlation between overexpression and decreased patient survival, the HGF/c-Met signaling pathway is a potential target for tumor control. Primary projects in this area of interest include: 1) studying the development and inhibition of lung carcinogenesis in a novel transgenic mouse model that overexpresses HGF in the airways 2) preclinical development of therapeutic drugs that target this pathway using a variety of techniques such as neutralizing antibodies to HGF, c-Met small molecule inhibitors, c-Met guanidinium-peptide nucleic acid antisense

technology and 3) understanding the mechanism of signaling interactions between c-Met and the epidermal growth factor receptor (EGFR) pathway.

Dr. Stabile has successfully developed a murine model that mimics the overproduction of HGF found in human lung tumors and has shown that a single human HGF neutralizing antibody, L2G7, has profound inhibitory effects on development of lung tumors in this transgenic mouse model. Furthermore, lung tumors with K-ras mutation are resistant to blockage of the HGF pathway using L2G7. In addition, we have recently demonstrated the importance of induction of the cyclooxygenase 2 (COX-2)/prostaglandin E2 (PGE2) pathway and subsequent activation of EGFR by HGF in lung cancer cells. Figure 2 describes the signaling pathway of HGF that we are studying and areas of therapeutic intervention. Another aspect of research involves the estrogen pathway in lung cancer. Lung cancer is becoming increasingly common in women and in the U.S. accounts for more female deaths annually than breast cancer and all other gynecological cancers combined. Epidemiological studies show that male-female differences exist in the presentation of lung cancer. These observations suggest the role of estrogens in lung carcinogenesis. Primary projects in this area of interest include: 1) understanding both genomic and non-genomic effects of estrogen in the lung 2) elucidating cross-talk pathways between estrogen and the EGFR and VEGF pathways in the lung 3) understanding the differences in estrogen signaling in lung cancer patients who actively smoked versus those who never smoked and 4) preclinical development of therapeutic drugs that target this pathway such as estrogen antagonists and aromatase inhibitors.

Dr. Stabile has demonstrated that estrogen receptors are expressed in both normal lung as well as lung tumor cells and that estrogen promotes the growth of lung tumor cells. The growth stimulation is significantly inhibited in vitro and in vivo with the pure estrogen receptor antagonist, ICI 182,780 (Faslodex, fulvestrant). In addition, Dr. Stabile has demonstrated that the estrogen receptor pathway can cross-talk with the EGFR pathway and targeting both pathways simultaneously using clinically relevant agents show enhanced anti-tumor effects compared to targeting either pathway alone. This drug combination is currently being tested in clinical trials. Dr. Stabile is currently interested in elucidating the role of the newly discovered estrogen receptor, GPR30, which is thought to be responsible for some of the non-genomic actions of estrogen.

The overall goal for both areas of interest are to test different mechanisms by which these pathways control other growth-promoting proteins in the lung and test both available and novel drugs as single agent or combination therapies using novel animal models of lung cancer to determine how to inhibit these pathways most effectively. Optimal preclinical drugs will ultimately be translated to patient clinical trials.

Ben Van Houten, Ph.D.
Professor
Ph.D., Oak Ridge Graduate School of Biomedical Sciences, University of Tennessee, 1984

Our laboratory studies the formation and repair of DNA damage in nuclear and mitochondrial genomes. We are particularly interested in the structure and function of proteins that mediate nucleotide excision repair and the role of oxidative stress in human disease.

Faulty DNA repair can promote mutations, aging, cancer and cell death. The process by which protein components of repair detect damaged or modified bases within DNA is an important but poorly understood type of protein-DNA interaction. The cell contains a series of pathways designed to protect its DNA from environmental and endogenous damage. One of the most remarkable aspects of nucleotide excision repair (NER) is that it can remove a wide range of DNA lesions that differ in chemistry and structure. During bacterial NER UvrA, UvrB and UvrC proteins work together to identify and remove DNA damage.

The UvrA and UvrB proteins are believed to recognize damage-induced distortion in the DNA helix rather than the lesion per se. However, detailed studies of the kinetics, thermodynamics and structures of the Uvr

proteins have been limited due to their instability. To overcome this problem, UvrA, UvrB and UvrC from the thermophilic bacteria Bacillus caldotenax and Thermotoga maritima were recently cloned and overexpressed. The proteins maintain optimal activity at 65ºC and are amenable to both structural and biophysical studies. The group is collaborating with Bob London's NMR group at NIEHS for an analysis of the dynamics of UvrB upon ligand binding using NMR techniques. The group is also collaborating with Caroline Kisker, Ph.D. and her group, in Wurtzburg, Germany, on solving protein and protein-DNA structures by X-ray crystallography. We have recently solved a co-crystal structure of UvrB bound to DNA.

These complexes are being visualized on DNA using atomic force microscopy, performed Hong Wang, Ph.D., and single-molecule techniques using quantum dot labeling, performed by Neil Kad, Ph.D. at the University of Essex. These tools, combined with site-directed mutagenesis and biochemical analyses, allow for structure-function studies of the UvrA, UvrB and UvrC proteins, and form a basis for understanding the fundamental molecular processes of NER. The long-term goal is to have a complete understanding of how structural perturbations induced by specific DNA lesions are detected and removed by the NER machinery at the atomic level. Most recently we have begun to extend our studies to similar proteins found in humans.

Mitochondria represent an important target of reactive oxygen and mitochondrial DNA (mtDNA) appears to be an early and sensitive marker of this stress. Many human diseases are associated with reactive oxygen including cancer, heart disease and neurodegenerative diseases. Mitochondria are essential organelles for generating ATP during oxidative phosphorylation. The mtDNA encodes 13 polypeptides, 11 involved in electron transport and two serving as subunits of ATP synthase. Damage to mtDNA is repaired, but prolonged oxidant treatment results in persistent mtDNA damage, loss of mitochondrial function and apoptosis. These observations suggest that mtDNA damage is important in the toxicity induced by reactive oxygen species (ROS) such as superoxide, hydrogen peroxide and the hydroxyl radical. Our group is testing the hypothesis that ROS generated in the mitochondria results in mtDNA damage causing a vicious cycle of damage: mtDNA damage causes a decrease in transcription and loss of essential mitochondrial proteins, causing an inhibition of electron transport and subsequent release in more ROS. This process causes further mitochondrial decline and many degenerative diseases associated with aging. We have developed a very sensitive DNA damage assay based on quantitative PCR that allows us to examine damage to nuclear and mitochondrial DNA from as little as 100 microliters of human blood. We are currently examining the role of mtDNA damage and repair in several human diseases including cancer and Friedreich's ataxia.

Jean-Pierre Vilardaga, Ph.D.
Assistant Professor
Ph.D., Free University of Brussels, Belgium, 1996

The Vilardaga laboratory carries an interdisciplinary research program aimed at elucidating molecular mechanisms of signal transduction mediated by G-protein coupled receptors in renal, skeletal and other cell systems.

Fluorescence (e.g., FRET-, TIRF microscopy) techniques are used to study transmembrane signaling and intracellular trafficking mechanisms in the context of neurotransmitter, peptide hormone/G protein-coupled receptor systems.

Particular areas for development include: role of chemokines and receptors in cell polarization, molecular mechanisms by which the parathyroid hormone receptor regulate activity in bone, and regulatory mechanisms controlling the function of vasopressin receptor in kidney.

Dr. Vilardaga's objective is dissecting signaling mechanisms to discover novel principles in molecular medicine that will serve the medical community.

GPCRs are key initiators of biological signaling in virtually every type of cell. They recognize a wide variety of extracellular stimuli (hormones, neurotransmitters, ions, light, odors) and initiate transmembrane signaling to regulate cell behaviors. Their roles in many human pathological conditions underscore the importance of determining the molecular functioning of such receptors.

Adrenergic and peptide receptors, which transmit signals for respectively small neurotransmitters (such as noradrenaline and dopamine) and larger peptide hormones (vasopressin, parathyroid hormone, parathyroid hormone related peptide), are two well characterized distinct subtypes of GPCRs that serve as useful models for analyzing GPCR mechanisms. The objective is to elucidate the general principles of signal transduction from the extracellular ligand binding event to intracellular signaling cascades, which are involved in systems as diverse as neurotransmitter and hormonal signaling.

Using optical methods to monitor receptor activation, Dr. Vilardaga's research is aimed at gaining a better understanding of molecular mechanisms of receptor function. Since the publication of the original technology to record receptor activation in living cells in Nature Biotechnology (Vilardaga et al., July 2003) he has improved the approach to record and also image receptor activation – published in Nature Methods (Hoffman, March 2005). These technologies allow following many fundamental questions in receptor pharmacology: What is the nature of inverse agonism? How do ligands bind receptors? What is the signal transduction mechanism in receptor heterodimers? These questions were recently answered in Nature Chemical Biology (Vilardaga et al., June 2005, and Feb 2008), and in PNAS (Castro, Vilardaga, et al., Nov. 2005). Because this technology is likely to be a new standard for GPCR research, much more fundamental questions are and will be studied in receptor pharmacology, cell biology and physiology.

Andreas Vogt, Ph.D.
Research Assistant Professor
Ph.D., University of Hamburg, Germany, 1990

Dr. Vogt's major research interest is the discovery of new therapeutic agents for diseases related to cell proliferation and intracellular signaling. Specific targets of interest are the mitogen-activated protein kinase phosphatases (MKPs), cellular enzymes involved in cancer and inflammation that have thus far eluded discovery efforts. An important part of his research is the development of analysis tools to increase information content of biological assays and to enable small molecule drug discovery screening in whole organisms. It is his hope that the combination of high information content assays with whole organism models of disease will result in higher quality candidate compounds for drug development.

Dr. Vogt's target-based discovery efforts center around mitogen-activated protein kinase phosphatases or MKPs. One MKP in particular, termed DUSP-1 or CL100, appears to be a mediator of the malignant phenotype. MKP-1 is overexpressed in many human tumors and can protect cells from apoptosis caused by DNA damaging agents or cellular stress, suggesting that inhibitors of MKP-1 might find applications as novel target-based antineoplastic therapies, either alone or in combination with clinically used antineoplastic agents. The search for small molecule inhibitors of MKP-1 has been challenging due to a lack of structural guidance for inhibitor design, ambiguities associated with in vitro assays for phosphatase activity, and the absence of definitive assays to probe MKP-1 inhibition in the context of the living cell. By developing an image-based, definitive cellular assay for MKPs, which he has termed "chemical complementation," Dr. Vogt has circumvented many of the challenges associated with MKP inhibitor discovery, screened several thousand small molecules for MKP inhibition in intact cells, and identified several cell-active inhibitors of MKP-1 and MKP-3. Future work will encompass discovery of multiple classes of MKP inhibitors, refinement of their structures and biological activities, evaluation of their mode of inhibition, and their credentialing as potential therapeutic agents. Recently, Dr. Vogt has extended the concept of chemical complementation to collaborations with members of the zebrafish community on the discovery of inhibitors of MKP-3.

Dr. Vogt's second focus is the continued development of novel drug discovery tools that enhance the information content of small molecule screens. Over the past five years, he has been involved in the establishment of the University of Pittsburgh Drug Discovery Institute (UPDDI) as one of only a handful of academic centers with high-content analysis (HCA) capabilities. HCA is an analysis tool to acquire, analyze, and manage multi-dimensional information about target activity and spatial distribution from individual cells. Our emphasis on HCA has substantially contributed to the UPDDI becoming one of nine national screening centers funded through the NIH roadmap initiative on Molecular Libraries and Imaging. Dr. Vogt's research has contributed to the center four R03 funded high-content screens (two for MKPs, one for microtubule stabilizing agents, and one for autophagy), which he is currently running on 200,000 small molecules from an NIH compound collection.

A natural extension of Dr Vogt's prior HCA work is the expansion of image-based analysis to whole organisms such as zebrafish. This work is based upon the observation that advances in high-throughput screening and laboratory automation have substantially improved the speed of target-based drug discovery but that these efforts have not resulted in increased research productivity. An increasingly popular sentiment is that better models are needed to improve the quality of new drug candidates, and it has been proposed that whole organisms could provide such models. Currently, however, there is no animal model that is compatible with the contemporary paradigm of drug discovery encompassing rapid screening of large compound collections. The zebrafish is an animal model that might fill this void. The NIH is currently supporting a collaboration with Neil Hukriede and Michael Tsang (Department of Molecular Genetics and Biochemistry) aimed at developing novel image-based methods to analyze fluorescent transgenic zebrafish embryos. Of particular interest is an intelligent image analysis method termed Cognition Network Technology (CNT). CNT is different from other image analysis methods in that it processes image information in an object oriented fashion, thereby emulating human cognitive processes.

With this approach, Dr. Vogt is able to detect zebrafish embryos in multiwell plates regardless of orientation and to detect and quantify structures of interest within specific parts of the zebrafish embryo. An example is the automated detection and quantification of intersegmental blood vessels in the dorsal trunk of the zebrafish as measure of in vivo angiogenesis. Dr. Vogt developed a rule set that successively identified the entire outline of the embryo and defined regions of interest such as aorta (magenta), head (brown), yolk and yolk tube (yellow), and dorsal area (dark green). This context-based segmentation permitted the isolation and quantification of intersegmental blood vessels (red) without interference from surrounding areas. Because CNT can identify complex zebrafish embryonic structures regardless of orientation, the embryo can be arrayed randomly into any position and CNT will identify these distinct structures. Currently Dr. Vogt is working to generate a rule set that will identify the GFP expression in specific parts of the brain of a transgenic animal expressing an Fgf reporter (Tg (Mkp3:d2eGFP).

Daniela Volonte, Ph.D.
Research Instructor
Ph.D., University of Milan, Italy, 1996

Tumor development is initiated by a multiplicity of genetic abnormalities. Tumor cells need to escape barriers that limit uncontrolled cell proliferation. One of these barriers is represented by cellular senescence. Cancer cells need to overcome this obstacle to produce a clinically relevant tumor mass. For these reasons, cellular senescence represents a natural tumor suppressor mechanism. Thus, molecules that regulate cellular senescence are potential therapeutic targets for the treatment of cancer and the fight against aging.

Caveolae are invaginations of the plasma membrane enriched in cholesterol. Caveolin-1, the structural protein component of caveolar membranes, acts as a scaffolding protein to concentrate and functionally regulate signaling molecules.

In recent years, several independent lines of evidence have emerged suggesting that caveolin-1 may function as a "tumor suppressor protein" in mammalian cells. For example, caveolin-1 protein expression has been shown to be absent in several transformed cell lines derived from human mammary carcinomas, including MCF-7. In addition, caveolin-1 mRNA and protein expression are lost or reduced during cell transformation by activated oncogenes, such as v-Abl and H-ras (G12V); caveolae are absent from these cell lines. In addition, the human caveolin-1 gene is localized to a suspected tumor suppressor locus (D7S522; 7q31.1), a known fragile site (FRA7G) that is deleted in many types of cancer.

Oxidative stress is a known inducer of cellular senescence. We have shown that up-regulation of caveolin-1 is required for oxidative stress–induced cellular senescence in fibroblasts. To unravel the molecular mechanisms underlying oxidative stress-induced up-regulation of caveolin-1 in senescent cells, Dr. Volonte has shown that oxidants stimulate the activity of the caveolin-1 promoter reporter gene construct in fibroblasts. She has identified Sp1 binding to two GC-boxes as the core mechanism of oxidative stress–triggered caveolin-1 transactivation. In addition, through signaling studies she has shown p38 mitogen-activated protein kinase (MAPK) as the upstream regulator of Sp1-mediated activation of the caveolin-1 promoter following oxidative stress. For the first time Dr. Volonte has delineated the molecular mechanisms that modulate caveolin-1 gene transcription upon oxidative stress bringing new insights into the redox control of cellular senescence in both normal and cancer cells.

Thus, cellular senescence may represent one of the molecular mechanisms through which caveolin-1 acts as a tumor suppressor protein. Current efforts are aimed at identifying the signaling molecules which link caveolin-1's function to cellular senescence.

Nobunao Wakabayashi, Ph.D.
Research Assistant Professor
Ph.D., Tohoku University Graduate School, 1959

Loss of cellular homeostasis through exposures to endogenous (e.g., inflammation) and exogenous (e.g., carcinogens) stresses contributes to many diseases including carcinogenesis. The Keap1-Nrf2-ARE signaling pathway evokes an adaptive response to these stresses that serves to enhance cell survival. Through gene expression analyses of the signaling cascade linked to Nrf2, using both *Keap1*- and *Nrf2*-disrupted mice, it appears that multiple signaling pathways intersect with Nrf2 signaling. Our research goals are to elucidate novel signaling crosstalk based on genes bearing functional ARE (Nrf2-sMaf recognition enhancer element) in the promoter of target genes and the underlying mechanistic roles of the Keap1-Nrf2 system in protecting against chronic degenerative diseases *in vivo*. Currently, we are focusing on the role of Nrf2 signaling in tissue repair and regeneration.

Bin Wang, Ph.D.
Research Instructor
Ph.D., Anhui Medical University, Hefei, China, 1999

Dr. Wang researches parathyroid hormone receptor trafficking, interaction with the adapter protein EBP50/NHERF1 and other proteins, and their effects on the signaling in kidney and bone cells. The goal of these studies will contribute to our understanding of mineral ion homeostasis under normal conditions, as well as the pathogenesis of diseases that are related to disordered calcium and phosphorus balance in renal failure, hyperparathyroidism, or osteoporosis. The results will provide insights into developing drugs for selective therapeutic applications.

Q. Jane Wang, Ph.D.
Assistant Professor
Ph.D., Creighton University, 1995

Diacylglycerol (DAG) is a key second messenger in cells. It regulates a variety of fundamental cellular processes by binding to a large family of structurally and functionally divergent protein targets, "the DAG receptors". Deregulated DAG and its receptors actively contribute to the pathogenesis of many diseases including cancer and Type II diabetes.

The overall mission of the laboratory is to determine the function and regulation of these DAG receptors in normal cells and diseases. Current research primarily focuses on protein kinase D (PKD) - a novel family of high affinity DAG receptors, in addition to the best characterized protein kinase C (PKC) family. The PKD family that comprises PKD1, 2, 3 modulates vital cellular functions such as growth, survival, and protein transport. The activity of PKD is controlled by DAG through PKC-mediated phosphorylation. This places PKD downstream of PKC as a unique PKC-regulated DAG targets. However, it remains to be determined whether and how PKD involves in PKC-mediated cellular processes. PKD as a DAG target and a PKC effector has important therapeutic values for diseases with deregulated DAG signaling. Four areas of research are on-going in the laboratory:

The C1 domain is responsible for the binding to DAG and phorbol esters (PE), the pharmacological analogues of DAG. It is a 50 a.a. highly conserved structural motif shared among all DAG receptors. Focusing on the PKD and C1 domain interaction, we have characterized the structural requirements for the binding of PKD C1 domains to DAG and phorbol esters. Individual C1 domains of PKD isoforms selectively bind DAG, implying ligand-specific regulation of PKD isoforms. The relevance of this finding to the regulation of endogenous PKD by endogenously generated DAG is now under investigation.

DAG signaling is critically implicated in acquired insulin resistance. Levels of DAG and activities of certain PKC isoforms are up-regulated in insulin resistant states and Type II diabetes. Here, we are probing a potential role of PKD in the pathogenesis of insulin resistance. The effects of PKD in modulating glucose transport at basal state and in response to insulin stimulation are investigated in fat and muscle cells. Live cell imaging will be employed to evaluate the direct role of PKD in GLUT1 or GLUT4 transporter trafficking. Furthermore, crosstalk to insulin signaling pathways is also exploited as a potential mechanism through which PKD regulates insulin sensitivity and glucose metabolism.

DAG signaling has been implicated prostate cancer carcinogenesis and tumor progression. Isoforms of PKC are differentially involved in the process. The oncogenic PKCε contributes to metastatic transformation of prostate cancer, while PKCδ upon activation by phorbol esters induces apoptosis in androgen-sensitive prostate cancer cells. To gain more insights, we seek to investigate the involvement of PKD as a PKC effector in prostate cancer development. Our study has identified PKD3 as a potential downstream target of PKCε in modulating ERK and Akt activities in androgen-insensitive prostate cancer cells. PKD3 may contribute to prostate cancer progression through a constitutively active PKCε/PKD3 pathway. The study is now extended to other members of the PKD family including PKD1 and PKD2.

This study is conducted in collaboration with the University of Pittsburgh Drug Discovery Institute. We seek to identify highly potent and selective small molecule inhibitors of PKD for clinical application and for dissecting the biological functions of PKD.

Dong Xiao, Ph.D.
Research Instructor
Ph.D., Soochou University, China, 1997

Dr. Xiao's laboratory is using a variety of approaches to study the genetic basis of differential sensitivity to anticancer drugs in human cancer cells. We are also trying to identify novel genes that can be used for predicting treatment outcomes, and the genetic alterations that cause resistance to anticancer drugs. Our long-term goal is to develop improved strategies and novel agents for chemotherapy and chemoprevention of human cancer.

Common epithelial malignancies, including cancers of breast, colon, prostate, and lung, are often resistant to standard treatments such as chemotherapy and irradiation. We are investigating how apoptosis regulators, including PUMA, Bax and SMAC/Diablo, mediate apoptosis induced by chemotherapeutic agents or irradiation, and whether deregulation of these genes contributes to acquired resistance to anticancer agents. We identified PUMA as a BH3-only Bcl-2 family protein an essential mediator of DNA damage-induced and p53-dependent apoptosis. We also found that the proapoptotic Bcl-2 family protein Bax and the mitochondrial apoptogenic protein SMAC/Diablo mediate apoptosis induced by anticancer agents. Efforts are currently undertaken to restore apoptosis regulation in human cancer cells by using small molecules that activate PUMA through p53-independent mechanisms, and agents that mimic the functional domains of PUMA or SMAC/Diablo.

Prevention of human cancer through the use of chemical agents such as non-steroidal anti-inflammatory drugs (NSAIDs) has emerged as a promising strategy to reduce morbidity and mortality of cancer. However, the effects of NSAIDs are incomplete and resistance to NSAIDs often develops. The side effects associated with high doses of NSAIDs present a significant obstacle for general use of these agents for cancer prevention. Our studies demonstrated that apoptosis regulators Bax and SMAC/Diablo are both critical mediators of the anticancer effects of NSAIDs in colon cancer cells. We are studying the in vivo functional roles of these genes in chemoprevention using animal models. We are also testing whether manipulation of SMAC or other apoptosis regulators can be used to improve the chemopreventive effects of NSAIDs so that lower doses can be used for chemoprevention.

Lung cancer, the leading cause of cancer-related death in the US, is often detected at late stages and refractory to conventional anticancer therapies. In collaboration with the Lung Cancer Program at the Pittsburgh Cancer Institute, we identified a panel of novel genes that are frequently silenced by promoter hypermethylation in lung cancer. These genes are likely to be useful for early detection of lung cancer.

Jack Yalowich, Ph.D.
Associate Professor
Ph.D., SUNY at Buffalo, 1980

Recent studies are focused on understanding the mechanisms by which the clinically effective anticancer agent etoposide (VP-16), a phenolic compound, and the environmental carcinogen, benzene, cause acute myelogenous leukemia (AML). The central testable hypothesis is that redox cycling of VP-16 and phenolic benzene metabolites initiated by myeloperoxidase (MPO) in bone marrow precursors amplifies the genotoxicity and carcinogenicity of these compounds via enhanced topo II inhibition. Nutritional antioxidants such as vitamin C and vitamin E homologs are under investigation as a mechanism-based chemo-prevention strategy to eliminate VP-16- and benzene-induced AML by reducing production of peroxidase-dependent free radical and electrophilic metabolites. The long-term goal of these studies is to increase the clinical efficacy of VP-16 in the treatment of cancer, and to prevent benzene leukemogenesis.

Etoposide (VP-16)-related secondary myeloid leukemias (t-AML) are most frequently associated with MLL gene translocations at 11q23. Our central hypothesis is that redox cycling of VP-16 initiated by myeloperoxidase (MPO) found prominently in myeloid precursors amplifies the genotoxicity and carcinogenicity of this otherwise clinically effective DNA topoisomerase II (topo II)-targeted anticancer agent. We propose that MPO converts VP-16 to free radical species and oxidized metabolites that induce oxidative DNA damage and initiate recombinogenic events in myeloid precursor stem cells leading to the chromosomal translocations responsible for t-AML. Specifically, it is proposed: 1) that oxidative DNA damage and abasic DNA sites formed as a consequence of peroxidative activation of VP-16 result in loci that increase topo II poisoning; and/or: 2) that electrophilic VP-16-ortho-quinone formed in MPO-rich progenitors will poison topo II by adduction to sulfhydryl groups on the enzyme. We further posit that nutritional antioxidants such as vitamin C and vitamin E homologs will prevent VP-16-induced AML by reducing or preventing production of peroxidase-dependent free radical and electrophilic metabolites. We propose to determine the mechanism(s) by which peroxidative activation of VP-16 to phenoxyl radical and ortho-quinone metabolites enhances its DNA damaging and recombinogenic activities in genomic regions of the MLL gene known to contain breakpoints associated with t-AML.

Benzene-induced acute myeloid leukemia (AML) is a result of exposure to this genotoxicant. Benzene leukemogenesis has been linked to P450-mediated metabolism of benzene to phenolic compounds. In myeloid progenitors, myeloperoxidase (MPO) converts these phenols to redox-reactive and arylating benzene metabolites such as 1,4-hydroquinone and 1,4-benzoquinone. These benzene metabolites are recently demonstrated DNA topoisomerase II (topo II) poisons like the anticancer agent etoposide (VP-16). Etoposide is a phenolic compound known to cause therapy-related AMLs associated with MLL gene translocations. Benzene-induced AML can also display MLL gene translocations. This knowledge serves as the foundation for our central hypothesis that MPO-catalyzed redox cycling of phenolic benzene metabolites in myeloid progenitors yields carcinogenic species linked to poisoning of topo II. Specifically, it is proposed: 1) that oxidative damage and abasic DNA sites formed as a consequence of peroxidative activation of benzene phenols result in loci known to poison topo II; and/or: 2) that benzoquinones formed in MPO-rich progenitors poison topo II by electrophilic adduction to critical sulfhydryl groups. We further posit that nutritional antioxidants such as vitamin C and vitamin E homologs will prevent benzene-induced AML by preventing production or scavenging of MPO-derived free radical and electrophilic metabolites.

Lin Zhang, Ph.D.
Associate Professor
Ph.D., University of Southern California, 1995

We are using a variety of approaches to study the genetic basis of differential sensitivity to anticancer drugs in human cancer cells. We are also trying to identify novel genes that can be used for predicting treatment outcomes, and the genetic alterations that cause resistance to anticancer drugs. Our long-term goal is to develop improved strategies and novel agents for chemotherapy and chemoprevention of human cancer.

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Molecular Cell
Proceedings of the National Academy of Sciences USA
Annals of the New York Academy of Sciences
Cell Death and Differentiation
Grant Reviews:
Motor Neuron Disease Association
United Mitochondrial Disease Foundation

Guillermo Romero, Ph.D.
Associate Professor
Ad Hoc Reviewer:
Journal of Biological Chemistry
Proceedings of the National Academy of Sciences USA
Molecular Pharmacology
Endocrinology
Molecular Endocrinology
Journal of Lipid Research
Biochemistry
American Journal of Physiology
Journal of Pharmacology and Therapeutics
Ad Hoc Grant Reviewer:
NSF
Veterans Administration
NIDDK
American Cancer Society
Israeli Science Foundation
Instituto de Investigaciones Cientificas (Spain)

Adrian Sculptoreanu, Ph.D.
Research Assistant Professor
Ad Hoc Reviewer:
Canadian Journal of Physiology and Pharmacology
Pflügers Archives
American Journal of Physiology
Molecular and Cellular Biochemistry
Journal of Neurophysiology
Experimental Neurology
Journal of Pharmacology and Experimental Therapeutics
Neuroscience Letters

Elizabeth Sharlow, Ph.D.
Research Assistant Professor
Ad Hoc Reviewer:
ChemBioChem: A European Journal of Chemical Biology
Ad Hoc Grant Reviewer:
National Cancer Institute, National Institutes of Health, NCI Career Development Subcommittee

Jill Siegfried, Ph.D.
Professor
Committee Member:
Subcommittee A - Cancer Centers of the National Cancer Institute Initial Review Group
University of Colorado Cancer Center, External Advisory Board
SPORE Investigators' Workshop Planning Committee
National Lung Cancer Partnership Board of Directors
Eastern Cooperative Oncology Group, Lung Cancer Biology Subcommittee
Grants Reviewer:
NIH/DHHS/PHS, RFA CA-06-014 Tumor Microenvironment Network Review Committee

Associate Editor:
Cancer Research
Molecular Pharmacology
Editorial Board:
Clinical Lung Cancer
Respiratory Research
Ad Hoc Reviewer:
Cancer Research
American Journal of Respiratory and Critical Care Medicine
American Journal of Respiratory Cell and Molecular Biology
Journal of the National Cancer Institute
Molecular Pharmacology
Experimental Lung Research
Lung Cancer
Radiation Research
Carcinogenesis
Molecular Carcinogenesis
American Journal of Physiology
British Journal of Cancer

Shivendra Singh, Ph.D.
Professor
Study Section Member:
Chemo/Dietary Prevention Study Section
Special Emphasis Panel, ZRG1 ONC-L
Special Emphasis Panel, ZRG1 ONC-P
Editorial Board:
Journal of Environmental Contamination and Toxicology
Carcinogenesis
Molecular Pharmacology
Oncology
Molecular Cancer Therapeutics
Ad Hoc Reviewer:
Cancer Research
Carcinogenesis
Prostate
Molecular Cancer Therapeutics
Urology
Clinical Cancer Research
Ad Hoc Grant Reviewer:
Linnaeus Grants, Swedish Research Council
Big-C Grants, UK Foundation
Committee:
Data Safety Monitoring Board, PEITC Trial, University of Minnesota, Minneapolis, MN

Robert Sobol, Ph.D.
Assistant Professor
Editorial Board:
DNA Repair
Editorial Advisory Board:
The Open Toxicology Journal

Ad Hoc Reviewer:
- Biochemistry
- Cancer Chemotherapy & Pharmacology
- Cancer Research
- Carcinogenesis
- Cell Biology & Toxicology
- Cell Cycle
- Chemical Research in Toxicology
- Clinical Cancer Research
- DNA & Cell Biology
- EMBO Reports
- FASEB
- FEBS Letters
- Glia
- Journal of Biological Chemistry
- Leukemia Research
- Molecular & Cellular Biology
- Mechanisms of Aging and Development
- Molecular Cell
- Molecular Pharmacology
- Mutation Research
- Nature Structural & Molecular Biology
- Nucleic Acids Research
- Oncogene
- Toxicological Sciences
- Tumor Biology

Ad Hoc Grant Reviewer:
- Cancer Research UK
- Phillip Morris Research Group
- Susan G. Komen for the Cure Research Grant Program
- LYTMOS
- Research Corporation
- American Cancer Society, Genetics Mechanisms of Cancer Peer Review Committee
- American Cancer Society, DNA Mechanisms in Cancer Peer Review Committee

Gyun Jee Song, Ph.D.
Research Instructor
Ad Hoc Reviewer:
- Human Reproduction
- Journal of Andrology
- Asian Journal of Andrology
- Fertliity and Sterility

Harish Srinivas, Ph.D.
Research Instructor
Grant Reviewer:
- NSF

Laura Stabile, Ph.D.
Research Assistant Professor
Ad Hoc Reviewer:
- American Journal of Physiology- Lung Cellular and Molecular Physiology
- Steroids
- Molecular Carcinogenesis
- Cancer Research
- Cancer Biomarkers
- Lung Cancer
- Clinical Cancer Research

Ad Hoc Grant Reviewer:
- Ireland Health Research Board

Ben Van Houten, Ph.D.
Professor
Ad Hoc Reviewer:
- Biochemistry
- Cancer Research
- Chemistry and Biology
- EMBO J
- Journal of Bacteriology
- Molecular and Cell Biology
- Molecular Carcinogenesis
- Molecular Cell
- Molecular Pharmacology
- Nucleic Acids Research
- Oncogene
- PLos Genetics
- Proceedings National Academy of Sciences

Editorial Board:
- DNA Repair
- Mutation Research Reviews
- Journal of Biological Chemistry

Committees:
- NIEHS Technology Transfer Committee
- NIEHS Microarray User Committee
- NINDS, Scientific Advisor for Specialized Neuroscience Research Program

Jean-Pierre Vilardaga, Ph.D.
Assistant Professor
Ad Hoc Reviewer:
- Nature Chemical Biology
- Proceedings of the National Academy of Sciences
- American Journal of Physiology
- Molecular Endocrinology
- EMBO Reports

Andreas Vogt, Ph.D.
Research Assistant Professor
Ad Hoc Reviewer:
- Molecular Pharmacology

Cancer Chemotherapy and Pharmacology
Cancer Research
Molecular Cancer Therapeutics
FASEB Journal
Chemistry & Biology
Biochemical Pharmacology

Ad Hoc Grant Reviewer:
North Carolina Biotechnology Center

Q. Jane Wang, Ph.D.
Assistant Professor
Reviewer:
BMC Developmental Biology
Trends in Biochemical Sciences
Biochemistry
Trends in Molecular Medicine
Experimental Dermatology

Grant Reviewer:
US Army Department of Defense Study Section Prostate Cancer Research Program-END

Jack Yalowich, Ph.D.
Associate Professor
Ad Hoc Reviewer:
Cancer Research
Clinical Cancer Research
Biochemical Pharmacology
Molecular Pharmacology
Journal of Clinical Investigation
Oncology Research
Cancer Chemotherapy and Pharmacology
Head and Neck
Journal of the National Cancer Institute
Molecular and Cellular Biology
Biochimica Biophysica Acta
Cancer Investigation
Journal of Biological Chemistry
Journal of Pharmacology and Experimental Therapeutics
Biochemistry, Toxicology and Applied Pharmacology
Chemico-Biological Interactions
Proceedings of the National Academy of Science
Leukemia

Study Section Member:
NIH, BMCT (Biochemical Mechanisms of Cancer Therapy) Study Section, Chair
DOD Breast Cancer Research Program, CET#4 Study Section

Lin Zhang, Ph.D.
Associate Professor
Ad Hoc Reviewer:
Nutrition and Cancer
Cancer Research
Clinical Cancer Research
Molecular Cancer Therapeutics

Gynecologic Oncology
Cell Research
Carcinogenesis
Molecular Pharmacology
Molecular Carcinogenesis

Ad Hoc Grant Reviewer:

Chinese National Natural Science Foundation, Chengjiang Scholar Reviewing Committee

Consultant:

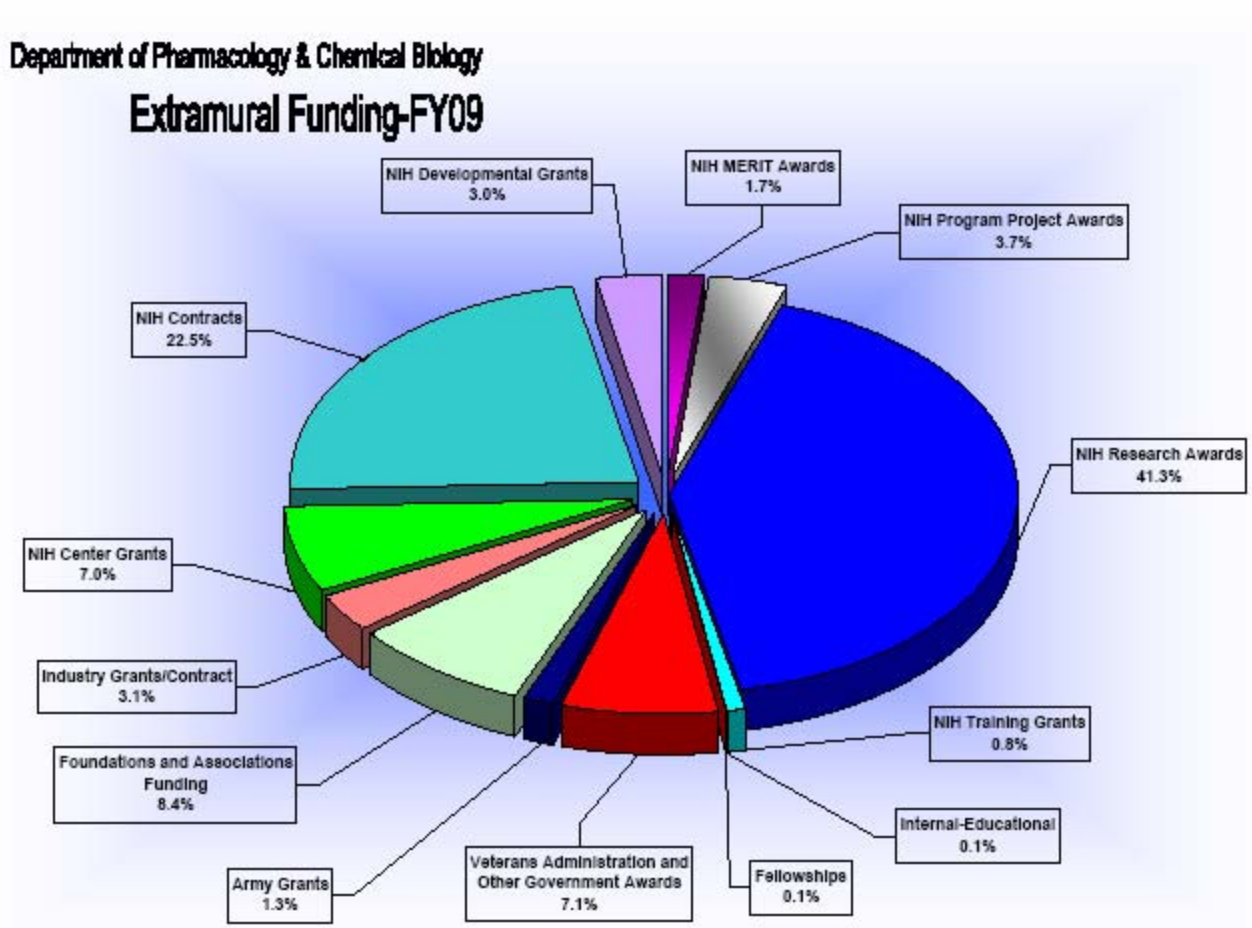
Gerson Lehrman Group, Healthcare Council Member

Research Grant & Contract Activity

Department of Pharmacology & Chemical Biology
FY09 Extramural Sponsored Project Funding

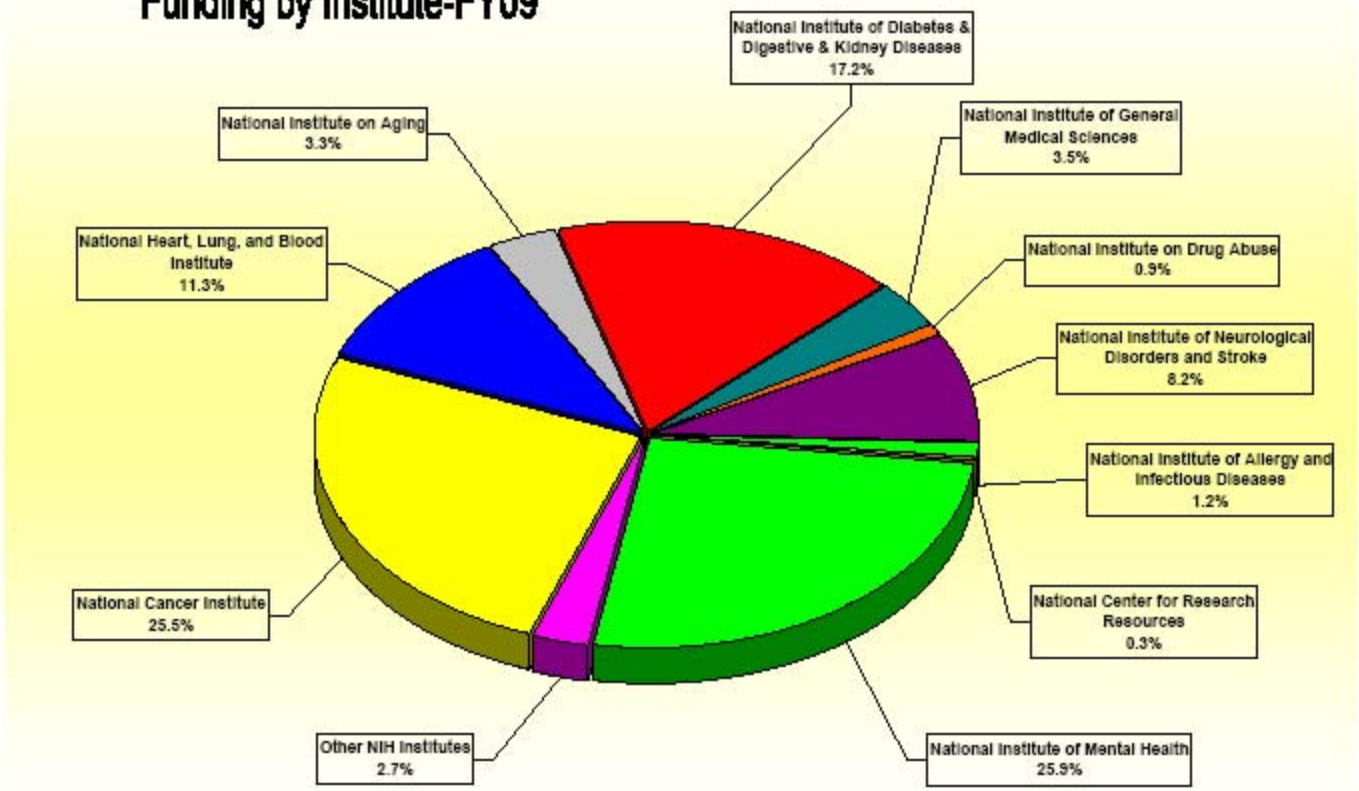
Army Grants	$257,487
Foundations and Associations Funding	$1,696,432
Industry Grants/Contract	$635,055
NIH Center Grants	$1,419,202
NIH Contracts	$4,563,288
NIH Developmental Grants	$611,635
NIH MERIT Awards	$338,743
NIH Program Project Awards	$746,591
NIH Research Awards	$8,373,461
NIH Training Grants	$163,451
Internal-Educational	$23,891
Fellowships	$26,562
Veterans Administration and Other Government Awards	$1,442,082
Total Extramural Funding	**$20,297,879**

National Cancer Institute	$4,141,930
National Heart, Lung, and Blood Institute	$1,828,398
National Institute on Aging	$538,692
National Institute of Diabetes & Digestive & Kidney Diseases	$2,800,290
National Institute of General Medical Sciences	$564,973
National Institute on Drug Abuse	$147,776
National Institute of Neurological Disorders and Stroke	$1,328,514
National Institute of Allergy and Infectious Diseases	$190,682
National Center for Research Resources	$52,655
National Institute of Mental Health	$4,207,942
Other NIH Institutes	$441,080
Total National Institutes of Health Funding	**$16,242,932**


Department of Pharmacology & Chemical Biology
Extramural Funding-FY09
NIH Developmental Grants 3.0%
NIH MERIT Awards 1.7%
NIH Program Project Awards 3.7%
NIH Contracts 22.5%
NIH Research Awards 41.3%
NIH Center Grants 7.0%
Industry Grants/Contract 3.1%
NIH Training Grants 0.8%
Foundations and Associations Funding 8.4%
Internal-Educational 0.1%
Army Grants 1.3%
Veterans Administration and Other Government Awards 7.1%
Fellowships 0.1%

Department of Pharmacology & Chemical Biology

Funding by Institute-FY09



Last Name	Grant Num	Agency Name	Title	Begin Date	End Date	Annual DC	Annual F&A	Annual TC
Altschuler	2 R01 CA071649-06A2	National Institutes of Health	Transduction of the Camp Signal by Rap 1	03/12/04	02/28/10	173,928	79,521	253,449
Altschuler	R21RR021708	National Institutes of Health	A Universal Mouse Line to Access Tumor Clonality	08/03/05	07/31/08	5,647	2,739	8,386
Baker	7-06-JF-06	American Diabetes Association	Characterization of Nitrated Fatty Acids as Partial PPARgamma Agonists	07/01/06	06/30/09	120,000	18,000	138,000
Bisello	2R01 DK054171	National Institutes of Health	PTH Receptor Function Meets Form	05/01/08	04/30/12	14,465	7,377	21,842
Bisello	R01 DK069998	National Institutes of Health	EBP50 Regulation of the PTH Receptor in Bone and Kidney	02/01/09	01/31/11	6,481	3,144	9,625
Bisello	R01DK071158	National Institutes of Health	PTH Receptors in Vascular Smooth Muscle Cells	10/01/06	04/30/10	158,453	69,366	227,819
Bisello	R01DK073039	National Institutes of Health	Modeling Bone Formation and 125 Vitamin D in Humoral Hypercalcemia of Malignancy	04/01/08	06/01/10	11,791	5,719	17,510
Conrads	R21 AI068784	National Institutes of Health	A Quantitative Proteomic Study of myD88 Pathway	03/01/07	02/28/09	1,400	679	2,079
Conrads	P50 CA090440	National Institutes of Health	SPORE in Lung Cancer - Project 3	05/01/08	04/30/11	7,007	3,399	10,406
Conrads	W81XWH-05-2-0066	US Army	Proteomics and Bioinformatics Core Facilities	07/01/05	10/25/08	143,603	9,022	152,625
Conrads	U01 CA117452	National Institutes of Health	Multiplexed Serum Biomarkers for Pancreatic Cancer	8/1/2008	7/31/2009	7,396	3,587	10,983
Conrads	VUMC 31980-R	Vanderbilt University	Molecular Signatures of Lung Cancer	6/1/2008	5/31/2009	13,272	1,991	15,263
Conrads	1R43CA 132081	National Institutes of Health	Quantitative Proteomics of Metastasis	5/1/2008	4/30/2009	25,000	0	25,000
Conrads	W81XWH-08-1-0694	U.S. Army	The Role of Central Metabolism in Prostate Cancer Prevention	9/15/2008	10/14/2011	69,216	35,646	104,862
Conrads	U01 CA114771-04	National Institutes of Health	Molecular Signatures in Lunc Cancer	6/1/2009	5/31/2010	1,170	176	1,346
Conrads	081RA01	DSF Foundation	DSF Clinical Proteomics - Master	2/1/2008	1/31/2010	396,862	0	396,862
Conrads	081RA01	DSF Foundation	DSF Clinical Proteomics - Junior Pilot	2/1/2008	1/31/2010	60,000	0	60,000
Conrads	081RA01	DSF Foundation	DSF Clinical Proteomics - Senior Pilot	2/1/2008	1/31/2010	30,000	0	30,000
Conrads	3401.2919	Magee Womens Research Institute	Biomarker Discovery in Ovarian Cancer	4/1/2008	3/31/2009	21,391	0	21,391
DeFranco	F30 NS053013	National Institutes of Health	Signaling Mechnisms Behind nAChR Clustering at the NMJ	07/01/07	06/30/09	10,758	0	10,758
DeFranco	2R01CA43037	National Institutes of Health	Intracellular Mechanisms of Glucocorticoid Action	07/01/07	06/30/12	184,500	89,125	273,625
DeFranco	3R01DK078394	National Institutes of Health	Intracellular Mechanisms of Glucocorticoid Action -Minority Supplement	07/01/08	06/30/10	53,442	27,523	80,965
DeFranco	GA8851UW	Pfizer	Assessment of Glucocorticoid Receptor Function in PBMCs of Critically Ill Children	09/17/08	06/30/09	13,448	3,362	16,811

Last Name	Grant Num	Agency Name	Title	Begin Date	End Date	Annual DC	Annual F&A	Annual TC
DeFranco	NIH 5T32 GM008424	National Institutes of Health	Predoctoral Training in Pharmacological Sciences	07/01/08	06/30/09	156,004	7,447	163,451
DeFranco	NS049560	National Institutes of Health	The Life History of Mitochondria in Neurons	05/01/05	06/30/09	231,250	110,686	341,936
DeFranco	R01DK078394	National Institutes of Health	Intracellular Mechanisms of glucocorticoid action	07/01/07	06/30/12	184,500	89,125	273,625
deGroat	7032	Helsin	Effect of Netupitant (Netu) in bladder hyperactivity in anaesthetized cat and in the transmission of	10/01/08	12/30/09	73,112	14,623	87,735
deGroat	4R37DK049430	National Institutes of Health	Afferent Mechanisms Underlying Bladder Pain- MERIT AWARD	05/15/05	02/28/10	231,148	107,595	338,743
deGroat	CoLucid	CoLucid Pharmaceuticals, Inc.	Analysis of the effects of LY334370 a 5HT1F agonist on reflex bladder activity in the cat	11/13/08	11/13/09	679	101	780
deGroat	DK067226	National Institutes of Health	Neurophysiology and Biomechanics of Urethera and SUI	04/01/04	03/31/09	11,933	5,787	17,720
deGroat	R01DK057267	National Institutes of Health	Afferent Plasticity Underlying Urethral and Pelvic Pain	03/01/06	11/30/10	6,282	3,046	9,328
deGroat	R01DK071085	National Institutes of Health	Roles of Nitric Oxide and Superoxide in Cystitis	08/01/05	05/31/10	11,489	5,572	17,061
deGroat	R01DK077783	National Institutes of Health	Neuroplasticity of Urinary Tract Disorders after SCI	05/01/07	04/30/11	103,533	49,645	153,178
deGroat	TA2-0701-2	CDRF	Restore continence and micturition after SCI by perigenital electrical stimulation	09/01/08	08/31/09	9,293	929	10,223
Eiseman	U01 CA99168	National Institutes of Health	Phase I Clinical Trails of Novel Anticancer Agents	12/14/09	12/14/09	3,664	1,777	5,441
Eiseman	CHP Acct #H0102	Children's Hospital of Pittsburgh	Evaluation of Molecular Inhibitors of the C MYC Oncoprotein	12/14/09	12/14/09	1,684	816	2,500
Eiseman	5P01 CA078039 07	National Institutes of Health	Combinatoral Approcahes for novel Anticancer Agents	5/15/1998	3/31/2010	137,393	63,050	200,443
Eiseman	1R01 CA121105 01A1	National Institutes of Health	SMAC in Chemoprevention of Colon Cancer	9/1/2007	7/31/2012	2,516	1,220	3,736
Eiseman	N01-CM-52202	National Institutes of Health	Preclinical Pharmacological Studies of Antitumor and Other Therapeutic Agents	12/15/2004	12/14/2009	281,300	91,872	373,172
Eiseman	GC 193460 NGC	Boston University	Optical Spectroscopy For Management Of Cancer Treatment	9/1/2008	8/31/2009	14,099	6,515	20,613
Eiseman	512-085069	VA Maryland Healthcare System	Mechanisms of Drug Resistance in Human Cancers -VA Merit Review	7/1/2008	9/30/2009	29,254	0	29,254
Eiseman	ADDENDUN 2	Endece	In vivo Plasma Pharmacokinetics of NDC E6S	4/20/2007	4/19/2009	12,779	3,194	15,973
Eiseman	GC 193460 NGC	Boston University	Optical Spectroscopy For Management Of Cancer Treatment	9/1/2009	8/31/2009	70,493	32,573	103,066
Freeman	R01 HL058115	National Institutes of Health	Nitric Oxide Regulation of Vascular Oxidant Injury	03/01/06	05/31/13	309,633	147,200	456,832
Freeman	R01 HL064937	National Institutes of Health	Nitric Oxide-Dependent Oxidative Lung Injury	06/21/06	03/31/10	262,719	118,919	381,638
Freeman	R03 TW007431	National Institutes of Health	Anti Inflammatory Properties of Cholesteryl Linoleate Derived Nitrated Lipids	03/17/06	02/28/09	20,081	3,969	24,050
Friedman	R01DK054171	National Institutes of Health	PTH Receptor: Function Meets Form	05/01/08	04/30/12	184,620	94,156	278,776

Last Name	Grant Num	Agency Name	Title	Begin Date	End Date	Annual DC	Annual F&A	Annual TC
Friedman	R01DK069998	National Institutes of Health	EBP50 Regulation of PTH Receptor in Bone and Kidney	02/01/06	01/31/11	195,074	94,611	289,685
Friedman	R21DK075014	National Institutes of Health	Novel Regulatory Mechanisms Controlling Bone Repair and Osteoporosis	07/01/07	06/30/09	125,000	60,625	185,625
Furey	1R56DK080748	University at Buffalo	Mechanism and Molecular Recognition in Human Dehydrogenase Complex	09/01/08	08/31/09	10,368	5,340	15,708
Furey	2R01 GM61791	National Institutes of Health	Pyruvate Dehydrogenase E1: Structure-Function Studies	09/01/04	05/31/09	0	0	0
Furey	2R01GM061791-09A1	National Institutes of Health	Pyruvate Dehydrogenase E1: Structure-Function Studies	06/01/09	05/31/13	16,125	8,304	24,429
Furey	5P01 CA078039	National Institutes of Health	Combinatoral Approaches for Novel Anticancer Agents (Project 3)	07/01/06	06/30/10	7,739	3,753	11,492
Galbiati	1R01 AG022548-01A2	National Institutes of Health	Role of Caveolin-1 in Cellular Senescence and Aging	01/01/05	12/31/09	167,314	77,148	244,462
Galbiati	F31 AG032182	National Institutes of Health	The Role of Caveolin-1 in Stress Induced Premature Senescence (Janine Bartholomew Predoc Indiv NRSA)	08/06/08	02/28/09	15,804	0	15,804
Hershberger	P30 CA047904	National Institutes of Health	CCSG - Pilot Hershberger	06/01/07	07/31/09	12,500	6,063	18,563
Hershberger	Signaling Pathways	Endece LLC	Analysis of the Anti-Proliferative Activity and Signaling Pathways Induced by NDC 1022 in NSCLC Cells	06/01/07	05/31/11	35,802	8,951	44,753
Hershberger	P50 CA90440	National Institutes of Health	SPORE in Lung Cancer-Project 1	7/1/2006	4/30/2012	3,192	1,548	4,740
Hershberger	1R21 CA125514	National Institutes of Health	A Nuclear Biosensor for Identification and Isolation of Nuclear Hormone Receptor Ligands	7/1/2006	6/30/2009	3,894	1,889	5,783
Hershberger	U01 CA099168	National Institutes of Health	Early Clinical Trials of New Anti-Cancer Agent With Phase I Emphasis	3/18/2003	2/28/2012	1,679	855	2,534
Hershberger	U01 CA099168	National Institutes of Health	Phase 1 Clinical Trials of novel Anticancer Agents	3/18/2003	2/28/2012	695	358	1,052
Hershberger	R01 CA132844	National Institutes of Health	Role of CYP23 in Non Small Cell Lung Cancer	5/21/2009	4/30/2014	15,292	7,080	22,372
Hershberger	M2006-0039	Pittsburgh Foundation	CYP24 as a New Diagnostic Prognostic Marker and Therapeutic Target in Lung Cancer	8/1/2006	7/31/2008	3,988	0	3,988
Hershberger	Signaling Pathways	Endece LLC	Analysis of the Anti-Proliferative Activity and Signaling Pathways Induced by NDC 1022 in NSCLC Cells	1/1/2008	4/30/2009	11,898	14,873	26,771
Hu	K22 CA111394	National Institutes of Health	Regulation of NF kB2 by TSA Role of Acetylation	09/01/05	08/31/08	23,971	1,918	25,889
Hu	X Linked Gene Gastrin	The Joan Scarangello Foundation	Targeting the Gastrin releasing peptide receptor and peidermal growth factor receptor in female patitents with non small cell lung cancer	01/01/07	12/31/08	25,000	0	25,000
Hu	R21 CA128681	National Institutes of Health	Effects of Peitc	8/14/2008	7/31/2010	98,346	50,648	148,995
Hu	M2007-0054	Pittsburgh Foundation	Role of Translational Control in Anti Cancer Effects of PEITC	7/1/2007	6/30/2009	73,938	0	73,938
Jackson	R01 NS040125	National Institutes of Health	Mechanisms of Chronic Dysfunction after Brain Trauma	04/01/05	03/31/10	17,222	8,353	25,575
Jackson	1 P30 DK079307-01A1	National Institute of Health	Pittsburgh Center for Kidney Research	9/1/08	7/31/13	126,250	32,188	158,438

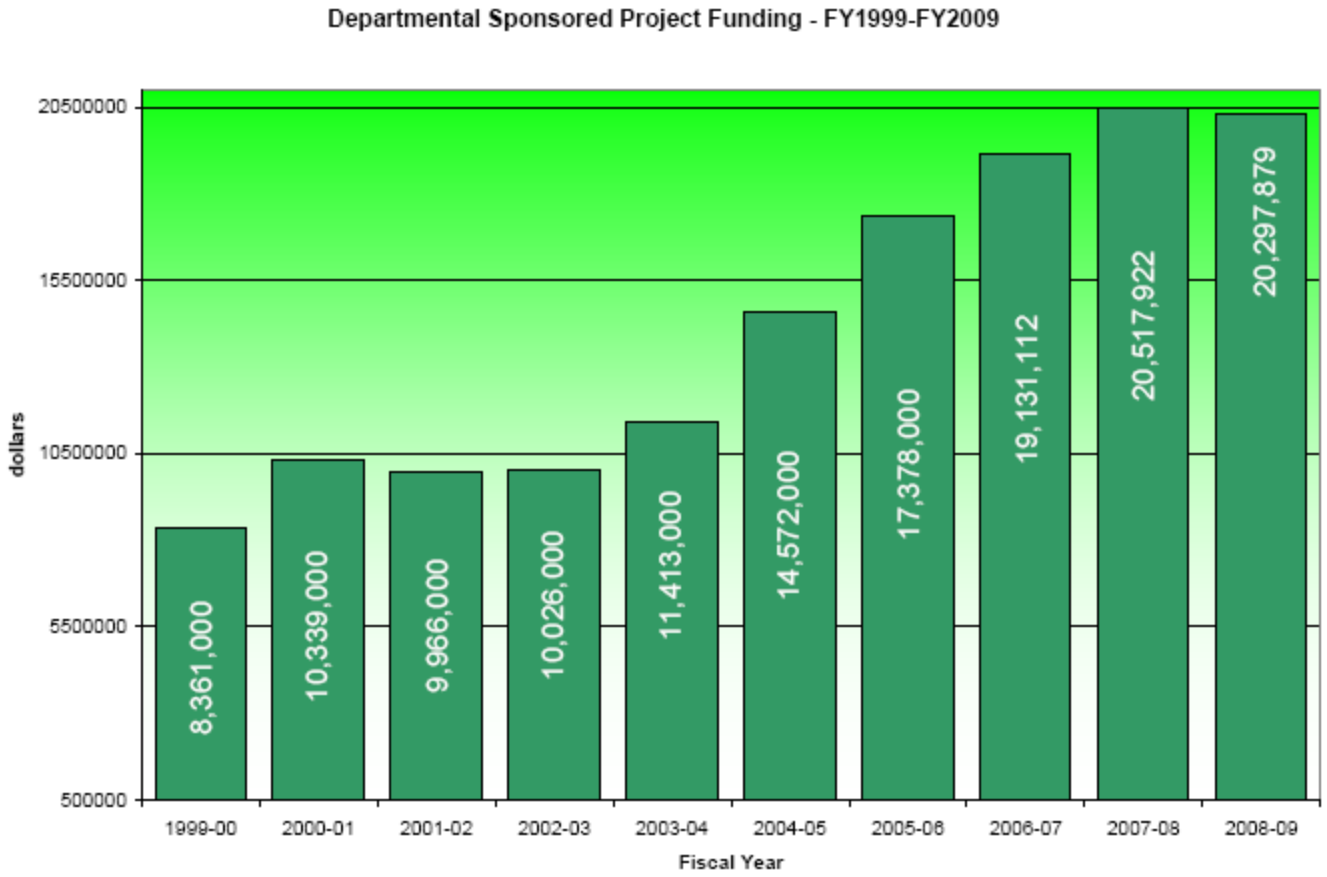
Last Name	Grant Num	Agency Name	Title	Begin Date	End Date	Annual DC	Annual F&A	Annual TC
Jackson	5 R01 DK077777-02	Natl Inst of Diabetes, Digestive, & Kidney Disease	Adenosine Receptor Function in Bladder Uroepithelium	02/15/08	01/31/13	23,958	11,620	35,578
Jackson	5 R01 DK068575-05	Natl Inst of Diabetes, Digestive, & Kidney Disease	Regulation of Renal Cortical Adenosine Levels	03/01/05	02/28/10	197,105	93,598	290,703
Jackson	5 R01 HL069846-07	National Heart, Lung, & Blood Institute	Potentiation of Ang II Induced Vasoconstriction	5/1/07	3/31/12	251,960	119,290	371,250
Jiang	1R01 GM068832-01A2	National Institutes of Health	The Role of PP2A in Yeast Cell Cycle Progression	02/01/05	01/31/10	154,322	70,966	225,288
Jiang	R01CA129821	National Institutes of Health	The Role of FKBP38 in tumorigenesis associated with Tsc deficiency	04/01/08	01/31/13	171,535	87,054	258,589
Jiang	R21 NS058463	National Institutes of Health	Regulation of GTPase Activity of LRRK2 and its implication in Parkinson's Disease	04/01/08	03/31/10	8,800	4,466	13,266
Johnston	1R01DK079806	National Institutes of Health	High Throughput Genetic & Drug Screens for Alph-1 Antitrypsin Deficiency	05/01/08	03/31/12	11,530	5,880	17,410
Johnston	U24AI082673	National Institutes of Health	Novel Modifiers of Toll Like & RIG Like Receptor Signaling	03/15/09	02/28/14	9,223	4,750	13,973
Johnston	U54MH074411	National Institutes of Health	PMLSC-Core 2	07/01/07	06/30/09	913,385	442,992	1,356,377
Kinchington	3P50 CA090440	National Institutes of Health	Transgenic Mouse Model Overexpressing the Gastrin Releasing Peptide Receptor for Novel Therapeutic Evaluation	1/1/2008	12/31/2008	10,574	5,128	15,702
Lakoski	K12RR023267	National Institutes of Health	Mulitidisciplinary Clinical Research Programs (RMI)	02/01/06	07/31/09	11,924	5,783	17,707
Lakoski	R13RR025929	National Institutes of Health	Clinical Research Scholars and Educators Training 2009-2011	03/01/09	02/28/12	10,000	0	10,000
Lazo	SAP 4100026429	PA Department of Health	Small Molecule Protein Disruption Targeting Orphan Diseases	01/01/07	12/31/08	891,081	0	891,081
Lazo		PA Dept of Health	Small Molecule Protein Protein Disruption Targeting Orphan Diseases	01/01/05	12/31/08	345,778	0	345,778
Lazo	2007088	Doris Duke	Doris Duke Clinical Research Fellowship/Nikii Thaker	07/01/08	06/30/09	4,000	0	4,000
Lazo	2P01 NS040923	National Institutes of Health	Novel Strategies for Brain tumor therapy Project I Master	03/01/09	02/28/10	3,899	2,008	5,907
Lazo	2P01CA078039	National Institutes of Health	Combinatorial Approches for Novel Anticancer Agents-Proj 3	04/01/06	06/30/10	233,537	89,015	322,552
Lazo	5 U19 CA052995	National Institutes of Health	Cancer Stress Relevant Protein Phosphatase Targets	05/01/09	04/30/10	17,107	8,810	25,916
Lazo	5U19 AI068021	National Institutes of Health	Mitochondrial Targeting Against Radiation Damage-Core B	09/01/08	08/31/09	52,473	25,448	77,922
Lazo	5U54MH074411	National Institutes of Health	PMLSC-Carryover	09/30/08	06/30/09	375,000	193,125	568,125
Lazo	P01CA07803906	National Institutes of Health	Combinatorial Approches for Novel Anticancer Agents-Core A	04/01/06	06/30/10	43,510	21,102	64,612
Lazo	SAP4100027294	PA Department of Health	Center for Excellence in DDID	06/01/05	05/31/09	146,641	29,328	175,969
Lazo	U19AI068021	National Institutes of Health	Mitochondrial Targeting Against Radiation Damage	09/30/05	08/31/10	54,970	26,660	81,630

Last Name	Grant Num	Agency Name	Title	Begin Date	End Date	Annual DC	Annual F&A	Annual TC
Lazo	U54 MH074411	National Institutes of Health	PMLSC-Supplement	09/30/08	06/30/09	375,000	193,125	568,125
Lazo	U54MH074411	National Institutes of Health	PMLSC-Data Supplement	07/01/07	06/30/09	125,000	35,309	160,309
Lazo	U54MH074411	National Institutes of Health	PMLSC-Core 5	07/01/07	06/30/09	376,999	182,845	559,844
Lazo	U54MH074411	National Institutes of Health	PLMSC-Core 1	07/01/07	06/30/09	70,057	33,978	104,035
Lazo	U54MH074411	National Institutes of Health	PMLSC-Project 1	07/01/07	06/30/09	422,351	198,512	620,863
Lazo	U54RR022241	NIH-Mellon Pitt Corporation	Fluroscent Probes & Imaging for Networks & Pathways	09/30/05	07/31/08	11,153	5,409	16,562
Levitan	1 R01 MH071497-01	National Institutes of Health	Regulation of Dopamine Neuron Excitability	04/01/05	03/31/10	185,806	84,458	270,264
Levitan	1R01NS061097	LSU	Intrinsic currents modulate synaptic integration in dopamine neurons	01/01/09	12/31/13	20,625	10,622	31,246
Levitan	1R21DA025739-01	National Institutes of Health	Multiphoton Monoamine Imaging of Seratonin Neuron Function	09/01/08	08/31/10	83,158	37,537	120,694
Levitan	2R01DK054824-08A1	National Institutes of Health	Nitric Oxide in Bladder Neural-Epithelial Signaling	04/01/07	01/31/12	3,624	1,758	5,382
Levitan	R01HL080632	National Institutes of Health	Long-Term Regulation of Potassium Channels	12/20/05	11/30/09	195,055	94,603	289,658
Levitan	R01NS032385	National Institutes of Health	Channels, Calcium and Peptide Secretion	06/01/08	05/31/12	294,448	126,864	421,312
Levitan	R01NS053050-01	National Institutes of Health	Regulation of Dopamine Neuron Excitability	04/01/05	03/31/10	185,806	84,458	270,264
Makhina	R03 DA026212	National Institutes of Health	High throughput for potassium channel modulators	06/01/08	05/31/09	15,125	7,790	22,915
Nichols	NDC-1022	Endece LLC	Validation of Gene Targets Identified in Microarray Studies and Concomitant Development of an NDC-1022 Signal Trandsuction Pathway in NSCLC Cells	01/01/08	04/30/09	1,534	383	1,918
Nichols	Signaling Pathways	Endece LLC	Analysis of the Anti-Proliferative Activity and Signaling Pathways Induced by NDC 1022 in NSCLC Cells	1/1/2008	4/30/2009	9,203	2,301	11,503
Nichols	RSG 09 054 01 GMC	American Cancer Society	The RNA Fingerprint of Breast Cancer	1/1/2009	12/31/2012	5,455	1,092	6,547
Pagano	0540029N	American Heart Association	NOX in Vascular Neoproliferation	08/01/08	12/31/10	51,042	5,104	56,146
Pagano	R01 HL079207	National Institutes of Health	Reactive Oxygen Species in Vascular Disease	09/19/08	03/31/12	235,973	93,047	329,020
Palladino		ASPET	Summer Undergraduate Research Fellowships	06/01/09	05/31/12	750	0	750
Palladino		ASPET	Summer Undergraduate Research Fellowships	06/01/06	05/31/09	8,250	0	8,250
Palladino	0630344N	American Heart Association	Understanding Mechanisms of Mitochindrial Dysfunction and Progressive Encephalomypathies	01/01/06	12/31/09	59,091	5,909	65,000
Palladino	17319	UMDF	Developing Therapies for Mitochondrial Disease	09/01/06	08/31/08	7,344	816	8,160
Palladino	5R25GM073176	National Institutes of Health	PITT-SPURG Summer Program for Undergrad Research Growth	01/01/08	09/30/09	82,403	6,592	88,995

Last Name	Grant Num	Agency Name	Title	Begin Date	End Date	Annual DC	Annual F&A	Annual TC
Palladino	R01AG25046	National Institutes of Health	Understanding the Mechanisms of Neuropathogenesis	05/01/06	04/30/11	187,492	90,934	278,426
Romero	2R01 DK054171	National Institutes of Health	PTH Receptor Function Meets Form	05/01/08	04/30/12	40,631	20,721	61,352
Roppolo	R01 DK06429	National Institutes of Health	Role of Nitric Oxide in Interstitial Cystitis	08/01/05	06/30/09	10,668	5,174	15,842
Roppolo	5P50 DK064539	UCLA	Women's health and Functional Visceral Disorders Center	09/01/07	08/31/12	9,672	4,769	14,441
Roppolo	5R01NS051671-03	National Institutes of Health	Locomotion Control by Lumbar Spinal Cord Injury	01/01/08	12/31/09	34,120	17,061	51,181
Roppolo	991764754	Ethicon, Inc.	Ethicon Corporate Research Agreement	12/15/07	12/31/11	25,240	6,310	31,550
Roppolo	R01EB007749	National Institutes of Health	Somatosensory feedback for controlling a neuroprosthesis	09/01/07	05/31/11	4,986	2,420	7,406
Roppolo	R56 DK068566	National Institutes of Health	Bladder and Sphincter Control After Spinal Cord Injury	07/01/08	06/30/09	34,633	16,797	51,430
Schopfer	7-08-JF-52	American Diabetes Assoc.	Electrophile-induced PPAR gamma-activation in diabetes	07/01/08	06/30/11	120,000	18,000	138,000
Siegfried	P50 CA090440	National Institutes of Health	SPORE in Lung Cancer - UCLA Supplement	06/01/06	04/30/11	50,364	24,427	74,791
Siegfried	P50 CA090440	National Institutes of Health	SPORE in Lung Cancer - Minority Supplement	06/01/06	04/30/11	79,187	38,010	117,197
Siegfried	P50 CA090440	National Institutes of Health	SPORE in Lung Cancer - Project 1	06/01/06	04/30/11	73,988	35,514	109,503
Siegfried	P50 CA090440	National Institutes of Health	SPORE in Lung Cancer - Administrative Core	06/01/06	04/30/11	245,495	117,837	363,332
Siegfried	P50 CA090440	National Institutes of Health	SPORE in Lung Cancer - Career Development Funds	06/01/06	04/30/11	77,000	37,345	114,345
Siegfried	1P50 CA097190	National Institutes of Health	Specialized Program of Research Excellence in Head and Neck Cancer-Head & Neck SPORE Project #4	07/01/04	06/30/09	98,157	46,124	144,281
Siegfried	2R01 CA079882-10A1	National Institutes of Health	Targeting the HGF/c-Met Pathway in Lung Cancer	03/13/09	01/31/14	65,922	33,950	99,872
Siegfried	2R01 CA098372-06	National Institutes of Health	GPCR Signaling in SCCHN: Integration with EGFR	04/10/09	01/31/14	3,007	1,549	4,556
Siegfried	CA098372	National Institutes of Health	GRPR Signaling in SCCHN: Integration with EGFR	04/01/04	02/28/09	18,001	8,731	26,732
Siegfried	Dulak fellow	PhRMA Foundation	Mechanistic Rationale for Combination Targeting of c-Met and EGFR in NSCLC	01/01/09	12/31/10	10,000	0	10,000
Siegfried	N/A	Abbott Molecular Inc.	MATERIALS AGREEMENT-Bilateral between University of Pittsburgh and Abbott Molecular	01/01/08	12/31/08	3,226	1,774	5,000
Siegfried	P50CA90440	National Institutes of Health	SPORE in Lung Cancer-Project 1 Sub 2	09/13/06	04/30/11	107,034	48,441	155,475
Siegfried	3P50 CA090440 07S1	National Institutes of Health	Function of Micro RNAs	9/1/2007	8/31/2012	79,187	38,802	117,989
Siegfried	VUMC 31980-R	Vanderbilt University	Molecular Signatures of Lung Cancer	6/1/2008	5/31/2009	18,649	2,797	21,445

Last Name	Grant Num	Agency Name	Title	Begin Date	End Date	Annual DC	Annual F&A	Annual TC
Siegfried	VUMC 31980-R	Vanderbilt University	Molecular Signatures in Lunc Cancer	6/1/2009	5/31/2010	1,831	275	2,105
Siegfried	Biomarker Platform	Cemines	Peptide Arrays for the Detection of Lung Cancer Serum Autoantibodies	2/1/2009	1/20/2010	11,116	6,281	17,397
Singh	R01 CA113363	National Institutes of Health	Prostate Cancer Prevention by Diallyl Trisulfide	04/01/05	02/28/10	92,045	44,642	136,687
Singh	R01 CA115498	National Institutes of Health	Prevention of Prostate Cancer by Sulforaphane	07/01/05	04/30/10	93,293	45,247	138,540
Singh	R13 CA132241	National Institutes of Health	Bioactive Food Components Alternative Medicine and Cancer Chemoprevention Recent Advances	09/24/07	08/31/08	2,000	0	2,000
Singh	1R01 CA129347 01	National Institutes of Health	Breast Cancer Prevention by Dietary Phytochemicals	9/7/2007	7/31/2012	15,464	7,542	23,006
Singh	R01 CA101753	National Institutes of Health	Anticarcinogenic Effect of ITCS Agaginst prostate Cancer	12/1/2008	11/30/2013	104,431	53,781	158,212
Singh	R01 CA129127	National Institutes of Health	The Role of PKD3	5/1/2009	2/28/2014	993	512	1,505
Singh	Research Grant	Elsa U. Pardee Foundation	Role of PKD3 in Prostate Cancer Progression	12/1/2008	11/30/2009	1,674	418	2,092
Sobol	R01 NS037704	National Institutes of Health	Molecular Markers as Predictors of Outcomes in Gliomas	02/28/08	02/28/10	38,777	40,237	79,014
Sobol	R01 NS037704	National Institutes of Health	Molecular Markers as Predictors of Outcomes in Gliomas	02/28/09	02/28/10	55,963	22,093	78,055
Sobol	R13 ES016721	National Institutes of Health	Annual Midwest DNA Repair Symposium	04/01/08	03/31/09	1,500	0	1,500
Sobol	119774 / 119772	University of Texas at SA	Base Excision Repair Genetic Integrity and Health Span	09/30/04	07/31/09	63,064	30,586	93,650
Sobol	RSG-05-246-01-GMC	American Cancer Society	The Role of Base Excision Repair in the Anti Tumor Action of Temozolomide	07/01/05	06/30/09	141,220	27,794	169,014
Sobol	P20 CA132385	National Institutes of Health	Environmental Oncology Partnership Between Hampton University and UPCI	9/29/2007	8/31/2010	58,109	27,174	85,283
Sobol	P20 CA132385	National Insitutes of Health	Environmental Oncology Partnership Between Hampton University and UPCI	9/29/2007	8/31/2010	37,914	18,388	56,302
Sobol	R43 GM087798-01	Trevigen, Inc.	DNA Repair deficient human cells for genetic variation analysis	5/1/2009	10/31/2009	24,974	37,836	62,810
Sobol	2007 Research Grant	Brain Tumor Society	PAR regulation of temozolomide Induced mitotic checkpoint activation	9/1/2007	8/30/2009	100,000	0	100,000
Sobol	34-2008-630	Juvenile Diabetes Foundation	Relief of Cell Cycle Inhibition for Human Beta Cell Proliferation	9/1/2008	8/31/2011	28,653	2,865	31,518
Stabile		FAMRI	Targeting the Estrogen Receptor and Epidermal Growth Factor Receptor for Lung Cancer Therapy	07/01/07	06/30/09	100,000	8,500	108,500
Stabile		Pittsburgh Foundation	CYP24 as a new Diagnostic/Prognostic Marker and Therapeutic Target in Lung Cancer	08/01/07	07/31/08	317	0	317
Srinivas	Hillman Y2	Hillman Foundation	Hillman Y2 - Srinivas	01/01/07	11/30/08	28,261	0	28,261
Vogt	5R01 CA120792	National Institutes of Health	Chemical Approaches for Discovery of New Cancer Therapeutic Targets	05/01/08	04/30/10	13,619	6,605	20,224
Vogt	R01HD053287	National Institutes of Health	Utilizing Small Molecule Screens to Delineate Embryonic Signaling Mechanisms	08/03/07	05/31/12	23,111	11,841	34,952

Last Name	Grant Num	Agency Name	Title	Begin Date	End Date	Annual DC	Annual F&A	Annual TC
Wang	1 RO1 DK066168-01	National Institutes of Health	Role of protein kinase D nu in regualted GLUT4 trafficking	03/01/04	02/28/10	145,551	66,953	212,504
Wang	1R03DA024898	National Institutes of Health	IMAP-based fluorescent polarization assay for high throughput screening of protein kinase D inhibito	09/01/07	08/31/08	2,796	1,370	4,167
Wang	705920	Elsa Pardee Foundation	Role of PKD3 in prostate cancer progression	12/01/08	11/30/09	63,434	15,859	79,293
Wang	R01 CA129127-01A2	National Institutes of Health	The role of PKD3 in prostate carcinogenesis	05/01/09	02/28/14	32,464	16,719	49,183
Yalowich	5U19 AI068021	National Institutes of Health	Mitochondrial Targeting Against Radiation Damage	09/01/08	08/31/09	8,614	4,178	12,792
Yalowich	R01CA90787	National Institutes of Health	Mechanisms and Prevention of Etoposide-Induced Leukemia	07/26/07	05/31/12	144,947	70,298	215,245
Yalowich	RSG-05-246	American Cancer Society	The Role of Base Excision Repair in the Anti-Tumor Action of Temozolomide	07/01/05	06/30/09	9,244	1,849	11,093
Yalowich	U19AI068021-03	National Institute of Health	Mitochondrial Targeting Against Radiation Damage (Master PI: Greenberger)	09/01/07	08/31/08	1,535	752	2,287
Zhang	R01 CA121105	National Institute of Health	SMAC in Chemoprevention of Colon Cancer	09/01/07	07/31/08	15,107	7,327	22,433
Zhang	V Scholars	V Foundation	Defects in Apoptotic Machinery and Altered Response to Anticancer Agents in Human Cancer Cells	01/01/04	12/31/08	1,042	0	1,042
Zhang	RSG-07-156-01-CNE	American Cancer Society	Role of SMAC in NSAID mediated chemoprevention	07/01/07	06/30/11	150,000	30,000	180,000
Zhang	RO1 CA106348	National Institutes of Health	Apoptotic Response To DNA Damage Initiated By PUMA	4/1/2004	3/31/2009	129,199	62,822	192,021


Departmental Sponsored Project Funding - FY1999-FY2009
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20,297,879
1999-00
2000-01
2001-02
2002-03
2003-04
2004-05
2005-06
2006-07
2007-08
2008-09
Fiscal Year

Percent of Faculty Support on Research Grants

Altschuler, Daniel	40%	Makhina, Elena	100%
Arjunan, Palaniappa	100%	Nichols, Mark	12%
Baker, Paul	100%	Pagano, Patrick	55%
Bisello, Alessandro	50%	Palladino, Michael	50%
Celotto, Alicia	100%	Romero, Guillermo	30%
Cifuentes-Pagano, Eugenia	100%	Roppolo, James	100%
Cole, Marsha	80%	Schopfer, Francisco	85%
Conrads, Thomas	78%	Sculptoreanu, Adrian	100%
Defranco, Donald	30%	Shakiryanova, Dinara	100%
de Groat, William	65%	Sharlow, Elizabeth	100%
Eiseman, Julie	100%	Shiva, Sruti	100%
Flint, Melanie	25%	Siegfried, Jill	80%
Freeman, Bruce	47%	Singh, Shivendra	90%
Friedman, Peter	90%	Sobol Jr., Robert	80%
Furey, William	25%	Song, Gyun Jee	100%
Galbiati, Ferruccio	27%	Srinivas, Harish	83%
Hershberger, Pamela	56%	Stabile, Laura	90%
Hu, Jing	88%	Van Houten, Ben	80%
Huang, Yi	0%	Vilardaga, Jean-Pierre	0%
Jackson, Edwin	94%	Vogt, Andreas	100%
Jiang, Yu	83%	Volonte-Galbiati, Daniela	100%
Johnston, Paul	100%	Wang, Bin	100%
Kinchington, Edwina	100%	Wang, Qiming	45%
Lakoski, Joan	10%	Xiao, Dong	100%
Lazo, John	89%	Yalowich, Jack	40%
Levitan, Edwin	72%	Zhang, Lin	80%
		Pharmacology Average	**72%**

Training and Project Grants

Last Name	Grant Num	Title	Begin Date	End Date	Annual DC	Annual IDC	Annual TC
EISEMAN	P01 CA078039	Combinatoral Approcahes for novel Anticancer Agents	12/14/09	12/14/09	$137,393	$6,305	$143,698
FUREY	P01 CA078039	Combinatorial Approaches for Novel Anticancer Agents	07/01/06	06/30/10	$7,739	$3,753	$11,492
LAZO	P01 CA078039	Combinatorial Approaches for Novel Anticancer Agents - Project 3	07/01/07	06/30/08	$152,591	$74,007	$226,598
LAZO	P01 CA078039	Combinatorial Approaches for Novel Anticancer Agents - Core A	07/01/07	06/30/08	$32,973	$15,992	$48,965
LAZO	P01 CA078039	Combinatorial Approaches for Novel Anticancer Agents - Core B	07/01/07	06/30/08	$139,139	$67,484	$206,623
SOBOL	P20 CA132385	Environmental Oncology Partnership Between Hampton University and UPCI	09/29/07	08/31/10	$106,754	$50,160	$156,914
CONRADS	P50 CA090440	SPORE in Lung Cancer - Project 3	05/01/08	04/30/11	$7,007	$3,399	$10,406
HERSHBERGER	P50 CA090440	SPORE in Lung Cancer - Project 1	06/01/06	04/30/11	$3,192	$1,548	$4,740
KINCHINGTON	P50 CA090440	Transgenic Mouse Model Overexpressing the Gastrin Releasing Peptide Receptor for Novel Therapeutic Evaluation.	01/01/08	12/31/08	$10,574	$5,128	$15,702
ROPPOLO	P50 DK064539	Women's Health & Functional Visceral Disorders Center	09/01/07	08/31/08	$8,060	$3,974	$12,034
SIEGFRIED	P50 CA097190	Specialized Program of Research Excellence in Head and Neck Cancer- Head and Neck SPORE Project 4	07/01/04	06/30/09	$98,157	$46,124	$144,281
SIEGFRIED	P50 CA090440	SPORE in Lung Cancer/Proj I Sub 2	09/13/06	04/30/11	$101,726	$45,867	$147,593
SIEGFRIED	P50 CA090440	SPORE in Lung Cancer - UCLA Supplement	06/01/06	04/30/11	$50,364	$24,427	$74,791
SIEGFRIED	P50 CA090440	SPORE in Lung Cancer - Minority Supplement	06/01/06	04/30/11	$79,187	$38,010	$117,197
SIEGFRIED	P50 CA090440	SPORE in Lung Cancer - Project 1	06/01/06	04/30/11	$73,988	$35,514	$109,503
SIEGFRIED	P50 CA090440	SPORE in Lung Cancer - Administrative Core	06/01/06	04/30/11	$245,495	$117,837	$363,332
SIEGFRIED	P50 CA090440	SPORE in Lung Cancer - Developmental Funds	06/01/06	04/30/11	$77,000	$37,345	$114,345
SIEGFRIED	P50 CA090440	SPORE in Lung Cancer - Career Development Funds	06/01/06	04/30/11	$77,000	$37,345	$114,345
FREEMAN	P30 DK046204	Nitro-Fatty Acid Modulation Type II Diabetes	08/01/07	03/31/08	$16,875	$8,184	$25,059
HERSHBERGER	P30 CA047904	CCSG - Pilot Hershberger	06/01/07	07/31/09	$12,500	$6,063	$18,563
DEFRANCO	T32 GM008424	Predoctoral Training in Pharmacological Sciences	07/01/05	06/30/10	$156,004	$7,447	$163,451

Participants in research

Graduate Students

Name	Mentor
Nicholas Bateman	Conrads
Neil Bhola	Grandis
Austin Dulak	Siegfried
Amy Furda	Van Houten
Eva Goellner	Sobol
Alison Groeger	Freeman
Melanie Grubisha	Defranco
Rekha Gyanchandani	Grandis
Cassandra Henry	Siegfried
Michael Hezel	Galbiati
Joshua Jamison	Zhang
Carolyn Kitchens	Lazo
Jeffery Koenitzer	Freeman
Courtney LaValle	Wang
Kristen Leslie	Bisello
Anne Lipton	Lazo
Jamie Morocco	Smithgall
Shoghag Panjarian	Smithgall
Kelly Quesnelle	Grandis
Bartholomew Roland	Palladino
Ranmal Samarasinghe	DeFranco
Mitchell Springer	Horn
Hilary Stevenson	Gronenborn
David Svilar	Sobol
Yan Wang	Lazo
David Wheeler	Romero
Man Yan Wong	Levitan
Mark Zimmerman	Homanics/Lazo

Undergraduate Researchers

Name	Lab
Dalya Akyuz	Department
Luiz Araujo	Palladino
Kristen Arena	Palladino
Fortuna Arumemi	Palladino
Kimberly Autore	Yalowich
Jason Banish	Johnson
Alison Bank	Palladino
Matthew Baumgartner	Palladino
Faith Bazley	de Groat
Dacia Beard	Lakoski
Brandy Benoit	Yalowich
Anna Bialostosky	Siegfried

Undergraduate Researchers

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Sarah Boarts	Palladino
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Usma Chatha	Palladino
Zachary Clapp	de Groat
Megan Coldren	Lazo
Vanessa Cole	Palladino
Daniel Contract	de Groat
Emily Cunningham	Palladino
Christina Davis	Siegfried
Alexandra Dixon-Ernst	Laksoki
Charmaine Dogans	Palladino
Alexandra Doyle	Palladino
Katherine Durgin	Palladino
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Joy Ferrell	Department
Steven Fisher	Lakoski
Joshua Gao	Lakoski
Yoana Gendzhova	Palladino
Sonia Gor	Freeman
Lorin Grieve	Palladino Media
Callista Haflett	Yalowich
Anna Hall	Lazo
Matthew Haynes	de Groat
Meagan Haynes	Yalowich
Amelia Hohenadel	de Groat
Marisa Hornbaker	Yalowich
Nicholas Ierovante	Palladino Media
Benjamin Kendall	Palladino
Robert Kiernan	Palladio
Kevin Koronowski	de Groat
Desiree Kosmisky	Palladino
Ibukunoluwa Kusimo	Birder
Megan Lejeune	Lakoski
Maria MacPherson	DeFranco
Laurentiu Maerean	Palladino
Kimberly Maize	Day
Umair Malik	Freeman
Christan Martone	Palladino Media
Sarah McGreal	Freeman
Zane McLain	Palladino Media
Danielle Miller	Lakoski
Uche Motanya	Freeman
Jamie Moroco	Smithgall
Samuel Mula	Palladino
Brandon Nemeth	Lazo

Undergraduate Researchers

Name	
Ijeoma Odigwe	Freeman
Alicia Olson	Palladino
Victoria Oravec	Defranco
Krupa Patel	Palladino
Kellianne Piell	Freeman
Diana Pinchevsky	Lakoski
Jennifer Schaber	Department
Samantha-Jo Schaefer	Baker
Bryan Seelnacht	Palladino
Jacquelyn Seigle	Palladino
Mansi Shah	de Groat
Kristin Silinski	Bisello
Veneta Slavova	Jiang
Hollyann Stevens	Palladino Media
Kimberly Stuchul	Palladino
Dianna Stuckey	Lakoski
Sara Sukenik	Palladino
Arne Ulbrich	Shiva
Regina Ulis	Palladino
Ankit Vartak	DeFranco
Vishash Verma	Lakoski
Jacob Volpe	de Groat
Robert Walker	Furey
Eric Wigton	Singh
Hannah Wills	Palladino
Jacob Winschel	Amara
Megan Wolfe	Palladino
Keith Yatsko	Palladino
Meghan Young	Baker
Wendy Yun	Palladino
Andrew Zheng	Gronenborn
Xiao Zhu	Jackson
Matthew Zurenski	Palladino
Guillermo Barila	Altschuler
Stacey Barrick	Bisello
Joshua Benson	Palladino
Nicole Blackmon	Lazo
Andrew Bodnar	Yalowich
Jennifer Butterfield	DeFranco
Daniel Camarco	Lazo
Samantha Cavolo	Levitan
Keerthi Chadalavada	Vilardaga
John Chaves	Palladino
David Close	Lazo
Catherine Corey	Lazo
Teresa Cox	Altschuler
Stephanie Daugherty	de Groat
Autumn Gaither-Davis	Siegfried

Staff Employees

Name	
Holly Gergely	Administration
Franca Golin Bisello	Freeman
Christopher Gubish	Siegfried
Yun Hua	Lazo
Osita Igwe	Romero
James Kaczynski	Administration
Judith Krigman	Vilardaga
Yumei Lai	Jiang
Stephanie Leimgruber	Lazo
Marcia Lewis	Defranco
Salony Maniar	Lazo
Barbara Martin	Administration
Melanie McClain	Administration
Jeanette McDew	Administration
Lisa McGreal	Administration
Charlotte McKinnon	Administration
Phillip Palmer	Lakoski
Laura Pliske	Lazo
Robyn Reed	Lazo
Virginia Reiner	Administration
James Repko	Palladino
Sarah Richards	Friedman
Mary Rothstein	Siegfried
Roxanne Scarano	Defranco
Richard Serventi	Administration
Sunita Shinde	Lazo
Tongying Shun	Lazo
Patricia Smith	Administration
Richard Smith	Administration
Lynda Sorch	Administration
Gregory Szekeres	Shop
Harold Takyi	Lazo
Brian Taylor	Administration
Rhonda Toth	Lazo
Emily Trostel	Administration
Chandra Vignere	Levitan
Laura Vollmer	Lazo
Shuping Xu	Wang
Yanmei Yang	Friedman

Researchers

Name	Lab
Imad Al Ghouleh	Pagano
Veronica Alonso	Friedman
Juan Ardura	Friedman
Debra Artim	de Groat
Lihua Bai	Eiseman

Researchers

Name	
Michelle Barbi De Moura	Van Houten
Patricia Boley	Kensler
Ajaykumar Bommareddy	Singh
Gustavo Bonacci	Freeman
Monica Buchanan	Zhang
Kumar Chandra Kuntal	Singh
Krishnamoorth Chandrasekhar	Furey
Jun Chen	Wang
Lesley Colgan	Levitan
Gabor Csanyi	Pagano
Davide Del Prete	Altschuler
Crissy Dudgeon	Zhang
Drew Dudgeon	Lazo
Martin Edreira	Altschuler
Loreto Egana	Pagano
Timothy Feinstein	Vilardaga
Chenxi Gao	Hu
Karthik Giridhar	Wang
Jianxia Guo	Zhang
Eun-Ryeong Hahm	Singh
Marjet Heitzer	DeFranco
Yu Ishima	Freeman
Shunqian Jin	Yalowich
Leonel Joannas	Altschuler
Su Hyeong Kim	Singh
Abhai Kumar	Singh
Joomin Lee	Singh
Hua Li	Zhang
Yanqin Li	Jiang
Dongzhu Ma	Jiang
Karina Pena	Vilardaga
Rui Peng	Zhang
Ye Pen	Van Houten
Anna Powolny	Singh
Ilva Putzier	Levitan
Wei Qian	Van Houten
Jin Ren	Jackson
Kozue Sakao	Singh
Sonia Salvatore	Schopfer
Anuradha Sehrawat	Singh
Bing Shen	Roppolo
John Skoko III	Kensler
Silvia Stan	Singh
Pang-Ning Teng	Conrads
Ram Trivedi	Sobol
Jaya Vatsyayan	Singh
Richa Verma	Altschuler
Hong Wang	Van Houten

Researchers

Name	
Peng Wang	Zhang
Tao Wang	Van Houten
Irene Wolf	Defranco
Steven Woodcock	Freeman
Dong Xiao	Singh
Xiang Xu	Hu
Gonghong Yan	Jiang
Li Yang	Kensler
Yongbei Yu	de Groat
Crystal Ann Zellefrow	Lazo
Fang Zhang	Lazo
Xiulin Zhang	de Groat
Qiuhong Zhang	UPCI
Yuxun Zhang	Yalowich
Ting Zhao	Conrads
Huafei Zou	Jiang

Major Collaborations

Bruce Freeman, Ph.D.
Professor and Chair

Fadi Lakkis and Timothy Billiar (University of Pittsburgh): Organ preservation for transplantation
Mitchell Fink and Derek Angus (University of Pittsburgh): Anti-inflammatory strategies for treating sepsis/ARDS
Robert Squires and David Hackam (University of Pittsburgh):Anti-inflammatory strategies for treating GI surgical patients
Kaikobad Irani (University of Pittsburgh): Prevention of cardiac ischemic injury
Mark Gladwin (University of Pittsburgh): Treatment of pulmonary hypertension

Daniel Altschuler, Ph.D.
Associate Professor

Yuri Nikiforov (University of Pittsburgh)
Matthias Buck (Cleveland, OH)
Joanne Ye (University of Pittsburgh)

Alessandro Bisello, Ph.D.
Associate Professor

Nathalie Fiaschi-Taesch (Department of Medicine, University of Pittsburgh): PTHrP actions in the vasculature
Rupangi Vasavada (Department of Medicine, University of Pittsburgh): GLP-1 receptor in beta cells
Andrew Stewart (Department of Medicine, University of Pittsburgh): Bone formation and vitamin D in hypercalcemia of malignancy

Eugenia Cifuentes-Pagano, Ph.D.
Instructor

Dr. Carlos Camacho (Department of Computational Biology, University of Pittsburgh)

Thomas Conrads, Ph.D.
Associate Professor

Dr. Nigel G. J. Richards (Department of Chemistry, University of Florida, Gainesville, FL): Application of quantitative LC-MS/MS for detection of asparagine synthetase in L-asparaginase resistant acute lymphoblastic leukemia patients
Dr. Alan Wayne (Department of Pediatric Oncology, National Cancer Institute): Application of quantitative LC-MS/MS for detection of asparagine synthetase in L-asparaginase resistant acute lymphoblastic leukemia patients
Dr. Deborah Penque (Portuguese National Institutes of Health, Lisbon, Portugal): Involved in a technology and educational transfer program where I co-advise Ph.D. students who spend rotation time in my laboratory learning mass spectrometry-based proteomic techniques
Dr. Michael Lotze (Department of Surgery, University of Pittsburgh): Proteomics of natural killer and dendritic cells in cancer
Dr. Jan Pilch (Department of Urology, University of Pittsburgh): Identification of the CLT1 tumor homing peptide receptor in prostate cancer

Dr. Anna Lokshin (Department of Medicine, University of Pittsburgh): Proteomic biomarkers of breast cancer for early detection
Dr. William Bigbee (Department of Pathology, University of Pittsburgh): Proteomic biomarkers of lung cancer for early detection
Dr. William Bigbee (Department of Pathology, University of Pittsburgh): Serum proteomic biomarkers for colon cancer

Donald DeFranco, Ph.D.
Professor

Dr. Gordon Rintoul (Simon Fraser University Vancouver, Canada)
Dr. Selma Witchel (Division of Pediatric Endocrinology, Children's Hospital of Pittsburgh)
Dr. Elias Aizenman (Department of Neurobiology, University of Pittsburgh)
Dr. Robert Bowser (Department of Pathology, University of Pittsburgh)
Dr. Charlene Chu (Department of Pathology, University of Pittsburgh)
Dr. Wen Xie (Department of Pharmaceutical Sciences, University of Pittsburgh)
Dr. Zhou Wang (Department of Urology, University of Pittsburgh)
Dr. Dean Bacich (Department of Urology, University of Pittsburgh)

W. Chet de Groat, Ph.D.
Professor

Dr. Naoki Yoshimura (Department of Urology, University of Pittsburgh): Collaborative urologic research in spinal cord injury and diabetic bladder afferent neuron function and NGF gene therapy
Dr. Joseph Glorioso (Department of Molecular Genetics and Biochemistry, University of Pittsburgh): Model systems for development of pain gene therapy
Dr. Joseph Glorioso (Department of Molecular Genetics and Biochemistry, University of Pittsburgh): Novel modulators of the vanilloid receptor
Dr. Kacey Marra (Department of Molecular Genetics and Biochemistry, University of Pittsburgh): Development of methods to promote neural regeneration
Dr. Guy Salama (Department of Cell Biology and Physiology): Factors that initiate arrhythmias in long-term QT syndrome
Dr. Lori Birder (Department of Medicine, University of Pittsburgh): Nitric oxide in bladder neural-epithelial signaling.
Dr. Naoki Yoshimura (Department of Urology, University of Pittsburgh): Afferent plasticity underlying urethral and pelvic pain
Dr. Tony Kanai (Department of Medicine, University of Pittsburgh): Role of nitric oxide in bladder cancer
Dr. Changfeng Tai (Department of Urology, University of Pittsburgh): Mechanisms underlying neurogenic bladder disorders
Dr. Seong-Gi Kim (Radiology-Imaging Center, University of Pittsburgh): Neuroplasticity in the spinal cord
Dr. David Vorp (Department of Bioengineering, University of Pittsburgh): Urethral dysfunction
Dr. C. L. Cheng (Department of Urology, Taichung Veterans Hospital): Pharmacology of the lower urinary tract
Dr. Janet Keast (Kolling Institute, University of Sydney, Australia): Estrogen effects on afferent neurons
Dr. Michael Chancellor (Department of Urology, Beaumont Hospital, Michigan): Use of liposomes in drug delivery
Dr. Pradeep Tyagi (Department of Urology, Beaumont Hospital, Michigan): Use of liposomes in drug delivery
Dr. Hamid Chahine (Department of Physiology, University of Laval, Quebec City, Canada): Sodium channel blockade
Dr. Kimio Sugaya (Department of Urology, University of Ryukyus, Okinawa, Japan): Bladder pharmacology

Dr. Cemil Gocmen (Department of Pharmacology, Cukurova University, Adana, Turkey): Bladder pharmacology

Julie Eiseman, Ph.D.
Research Associate Professor

Robert S. Parker, Ph.D. (Department of Chemical and Petroleum Engineering, University of Pittsburgh): Optical pharmacokinetics, modeling and calculations of elastic scattering spectrometer data of Pc4 and motexafin gadolinium; docetaxel pk

Peter Wipf, Ph.D. (Department of Chemistry, University of Pittsburgh): Collaborations on preclinical studies of phosphatase inhibitors and tubulin or motor protein interactive small molecules, Protein kinase D small molecule inhibitors

Dennis Curran, Ph.D. (Department of Chemistry, University of Pittsburgh): Collaborations on preclinical studies tubulin or motor protein interactive small molecules: 6-epi dictyostatin

Billy Day, Ph.D. (School of Pharmacy University of Pittsburgh): Collaborations on preclinical studies of phosphatase inhibitors and tubulin or motor protein interactive small molecules.6-epi dictyostatin

Ed Prochownik, M.D. (Pediatrics, Children's Hospital): Preclinical studies of myc inhibitors

Alex Doemling, Ph.D. (School of Pharmacy, University of Pittsburgh): Tubulycin analogues as anti-cancer agents, MDM2 and MDM4 antagonists

Gabrialla Mustata, Ph.D. (Department of Computation Biology, University of Pittsburgh): Computational biology of c-myc inhibitors

Jerry Collins, Ph.D. (Developmental Therapeutics, NCI): Studies of pyrimidine nucleosides in xenografts animal pharmacology studies

Doug Ross, M.D. (University of Maryland Greenebaum Cancer Center, Baltimore, MD): Mechanisms of drug resistance due to BCRP

Nancy Olienik, Ph.D. (Case Western Reserve University/Ireland Cancer Center, Cleveland, OH): Studies on Pc 4 and other silicon phthalocyanines as photodynamic therapeutics and molecular alterations in xenografts following photodynamic therapy

Ivana Vucenik, Ph.D. (University of Maryland, Baltimore): IP6 pharmacokinetics and inositol

Irving Bigio, Ph.D. (Boston University, Boston, MA): Use of optical pharmacokinetics system (ESS) to measure drugs with absorbance spectra in the long wavelength visible spectra including motexafin gadolineum, motexafin lutetium, PC4, mitoxanthrone

Steve Musser, Ph.D. (FDA, Washington, DC): Characterization of metabolites by LC/MS/MS

David D'Argenio, Ph.D., (School of Engineering, UCLA, Los Angeles CA): Pharmacokinetic and pharmacodynamic modeling of 17-AAG and DMAG, zebularine, FdC

Steven Metallo, Ph.D. (Georgetown University): c-myc inhibitors.

Martin R Austwick, Ph.D. (University College London): Pharmacokinetics of photodynamic therapeutics

Melanie Flint, Ph.D.
Research Instructor

Dr. Blair Jobe (Esophageal Diagnostics and Therapeutic Endoscopy Division of Thoracic and Foregut Surgery, the Heart, Lung, and Esophageal Surgery Institute, University of Pittsburgh Medical Center): Using laser capture micro-dissection to enable identification of protein expression in esophageal cancer patient samples

Dr. Larry Maxwell (Walter Reid Medical Center, Washington, DC): Validating protecomics findings in endometrial cancer using Western blot techniques

Dr. Jennifer Grandis (Department of Otolaryngology, University of Pittsburgh): Head and Neck Spore Cancer Grant

Peter Friedman, Ph.D.
Professor

Dr. Maria Kurnikova (Carnegie-Mellon University)
Drs. Naoki Fujii and Tony Ferreria (St. Jude)
Dr. Greg Clines (VCU)

William Furey, Ph.D.
Professor

Dr. A. Gronenborn (Department of Structural Biology, University of Pittsburgh): X-ray structural studies of cyanovirin-N
Dr. A. Gronenborn (Department of Structural Biology, University of Pittsburgh): X-ray structural studies of sorting nexin 5
Dr. Pei Tang (Department of Anesthesiology, University of Pittsburgh): X-ray structural studies of ketosteroid isomerase
Dr. Mulchand Patel (Department of Biochemistry, State University of New York at Buffalo): Human pyruvate dehydrogenase
Dr. F. Jordan (Department of Chemistry, Rutgers University): *E. coli* pyruvate dehydrogenase multi-enzyme complex component structures
Dr. Guillermo Calero (Department of Structural Biology, University of Pittsburgh): Production of pyruvate dehydrogenase
Dr. Michael Palladino (Department of Pharmacology & Chemical Biology, University of Pittsburgh): Structural studies of trioesphosphate isomerase
Dr. John Lazo (Department of Pharmacology & Chemical Biology, University of Pittsburgh): Structural studies of phosphatase-inhibitor complexes

Ferrucio Galbiati, Ph.D.
Associate Professor

Dr. Peter Di (Department of Environmental and Occupational Health, University of Pittsburgh)
Dr. Steven Shapiro (Department of Medicine, University of Pittsburgh)

Pamela Hershberger, Ph.D.
Research Assistant Professor

Drs. Suresh Ramalingam and Taofeek Owonikoko: Evaluation of novel HDAC inhibitor-based therapeutic combinations in NSCLC cells
Dr. Carol Feghali Bostwick (Department of Medicine, University of Pittsburgh): Role of estrogen signaling in dermal fibrosis
Cytochroma, Inc. (Ontario, Canada): Evaluation of CTAA (CYP24 specific inhibitor) on vitamin D anti-tumor activity in lung cancer
Endece, Inc. (Madison, WI): Determining the structure function relationships of NDC compounds in lung cancer models
Drs. Len Appleman and Lily Shah (Department of Medicine, University of Pittsburgh): Potentiation of gemcitabine/cisplatin activity by ABT-888 in bladder cancer

Jing Hu, Ph.D.
Associate Professor

Dr. Gaozhi Xiao (Department of Medicine, University of Pittsburgh): An *in vivo* study of the role of mTOR signaling in bone formation.
Dr. Billy Day (School of Public Health, University of Pittsburgh): Dissecting the components of TORC1 in yeast
Dr. Yongjian Liu (Department of Neurobiology, University of Pittsburgh): The role of Rheb small GTP in neuronal cell membrane trafficking
Dr. Guoqing Bi (Department of Neurobiology, University of Pittsburgh): mTOR signaling in synaptic plasticity
Dr. Jie Chen (University of Illinois): The role of phosphatidyl acid in regulation of FKBP38 function

Dr. Nahum Sonenberg (McGill University, Montréal, Quebec, Canada).

Edwin Jackson, Ph.D.
Professor

Pat Kochanek, M.D. (Department of Critical Care Medicine, University of Pittsburgh): Adenosine in traumatic brain injury
Ed Dixon, Ph.D. (Department of Critical Care Medicine, University of Pittsburgh): Adenosine in brain dysfunction
Elieser Gorelik, Ph.D. (Department of Pathology, University of Pittsburgh): Role of adenosine in cancer
Gerard Apodaca, Ph.D. (Department of Medicine, University of Pittsburgh): Role of adenosine in bladder function
Derek W. Gilroy, Ph.D. (Division of Medicine, University College London): Role of adenosine in inflammation
Stevan P. Tofovic, M.D., Ph.D.; Center for Clinical Pharmacology, University of Pittsburgh): Estradiol metabolites in renal disease
Raghvendra K. Dubey, Ph.D. (Department of Obstetrics and Gynecology, University Hospital Zurich): Vascular biology of estradiol metabolites
Lisa Satlin, M.D. (Division of Pediatric Nephrology, Mount Sinai School of Medicine): Purine metabolomics
Virginia Miller, Ph.D. (Department of Surgery, Mayo Clinic): Estradiol Metabolomics

Paul Johnston, Ph.D.
Research Associate Professor

Drs. Susan Amara and Spencer Watts (Department of Neurobiology, University of Pittsburgh): Modulators of CNS glutamate transport
Dr. Billy Day (Department of Pharmaceutical Sciences, University of Pittsburgh): High throughput/content Screens for dynein inhibitors
Dr. Gary Silverman (Magee Women's Hospital, Department of Pediatrics, University of Pittsburgh): High throughput genetic and drug screens for alpha-1-antitrypsin deficiency
Dr. Michael Parniak (Department of Molecular Genetics and Biochemistry, University of Pittsburgh): Inhibitors of HIV RT-RNase H – MLSCN screening project & follow up
Dr. Zhou Wang (Department of Urology, University of Pittsburgh Cancer Institute): Androgen nuclear hormone Receptor and prostate cancer
Dr. Tom Smithgall (Department of Molecular Genetics and Biochemistry, University of Pittsburgh): Development and implementation of an HTS assay to identify HIV Nef inhibitors
Drs. Al-Walid Mohsen and Gerry Vockley (Department of Pediatrics, University of Pittsburgh): Inhibitors of Acyl CoA dehydrogneases

Dr. Alan Waggoner (Carnegie Mellon University, Molecular Biosensor and Imaging Center): Driving biology project in the NIH Technology Center for Networks and Pathways Roadmap grant, dedicated to developing novel biosensors for HCS assays
Dr. Ronald Wetzel (Department of Structural Biology, Pittsburgh Institute for Neurodegenerative Diseases): High throughput assay development for Huntington's disease
Dr. Jennifer Grandis (Department of Otolaryngology, University of Pittsburgh): Development of a HCS assay for selective inhibitors of STATs 1 and 3
Dr. David J. Hackam (Department of Pediatric Surgery, University of Pittsburgh): Novel approaches for the treatment of necrotizing enterocolitis - HCS imaging assay for enterocyteTLR4 inhibitors
Dr. David A. Hinkle (Department of Neurology, University of Pittsburgh): Screening for compounds that stimulate astrocyte-mediated neuroprotection against rotenone
Dr. Nabil Seidah, Director of the Laboratory of Biochemical Neuroendocrinology, IRCM, Montreal, Canada): Development and implementation of biochemical and cell based screens to identify inhibitors of Furin
Dr. Junying Yuan (Department of Cell Biology, Harvard Medical School, Boston): Development and implementation of two cell based screens to identify inhibitors of necroptosis

John Lazo, Ph.D.
Allegheny Foundation Professor

Scott Diamond (Department of Chemical and Biomolecular Engineering, Penn Center for Molecular Discovery): New compound screening platforms
Ray Dingledine (Department of Pharmacology, Emory University): New compound screening platforms
Alan Waggoner (Carnegie Mellon University): Probe development
Garth Powis (University of Arizona): New cancer chemotherapy agents targeting cell stress
Marc W. Halterman (Department of Neurology, University of Rochester School of Medicine and Dentistry): Regulation of c/EBP and CHOP-10 influence the pathologic switch in a model of hypoxia-induced neuronal death.
Vojo Deretic (Department of Molecular Genetics and Microbiology, University of New Mexico): HCS for small molecule inducers of autophagy
James Morris (Department of Genetics and Biochemistry, Clemson University): Inhibitors of T. burcei hexokinase 1

Edwin Levitan, Ph.D.
Professor

John Horn (Department of Neurobiology, University of Pittsburgh): Dopamine neuron project
Elias Aizenman (Department of Neurobiology, University of Pittsburgh): Potassium channels and apoptosis
David Deitcher (Cornell) and Randy Hewes (Oklahoma): Neuropeptide release in Drosophila
Glenn Fishman (NYU): Cardiac potassium channel expression

Patrick Pagano, Ph.D.
Visiting Professor

P. Michael Bauer (Department of Surgery, University of Pittsburgh)
Aaron Barchowsky (Department of Environmental and Occupational Health, University of Pittsburgh)
Robin Gandley (Magee Women's Hospital)
Jeffrey Isenberg (Department of Medicine, University of Pittsburgh)
Xiang Gao (Department of Pharmaceutical Sciences, University of Pittsburgh)
Song Li (Department of Pharmaceutical Sciences, University of Pittsburgh)
Carlos Camacho (Department of Computational Biology, University of Pittsburgh)
Guangjie Cheng (Emory University)

Phil Palade (University of Arkansas)
Xiao-Ping Yang (Henry Ford Hospital)
William Beierwaltes (Henry Ford Hospital)

Michael Palladino, Ph.D.
Associate Professor

Greg Beitle (Northwestern University): The study of novel functions of the sodium potassium ATPase alpha protein
Marc Blondel (Faculté de médecine de l'UBO/CHU & CNRS): Collaborate to use yeast and fly models of mitochondrial disease for drug discovery
Carmen Mannella (Wadsworth and New York Department of Health Laboratories): Study of pathogenesis associated with inner mitochondrial membrane alterations
Robert Reenan (Brown University): Studies of RNA editing of Na/K ATPase transcripts and the functional importance of editing to neural excitability and behavior
Wayne VanVoorhies (New Mexico State): Respiration and metabolic studies of Drosophila mutants

Guillermo Romero, Ph.D.
Associate Professor

Meir Aridor (Department of Cell Biology, University of Pittsburgh): Role of PLD in vesicular traffic
Tomas Kirchhausen (Harvard Medical School, Cell Biology): Endocytic transport.

Francisco Schopfer, Ph.D.
Research Assistant Professor

Eugene Chen (University of Michigan): Study of the mechanisms of PPARgamma activation by nitrated fatty acids
Anna Lisa Levonen (University of Kuopio, Finland): Study of the activation of phase 2 genes by nitroalkenes, mainly focusing on KEAP/Nrf2 pathway

Adrian Sculptoreanu, Ph.D.
Research Assistant Professor

M. Chahine (Laval University, Canada)

Elizabeth Sharlow, Ph.D.
Research Assistant Professor

Peter Wipf (Department of Chemistry, University of Pittsburgh)
Jeff Brodsky (Department of Biological Sciences, University of Pittsburgh)
Gabriela Mustata (Department of Computational Biology, University of Pittsburgh)
Ronald Wetzel (Department of Structural Biology, University of Pittsburgh)
Iliya Lefterov (Department of Environmental and Occupational Health, University of Pittsburgh)
Parmjeet Randhawa (Department of Pathology, University of Pittsburgh)
Jeff Aube (Department of Medicinal Chemistry, University of Kansas)
Kip Guy (Department of Chemical Biology and Therapeutics, St. Jude Children's Research Hospital)
Jacob Johnson (Division of Experimental Research, Walter Reed Institute for Research)
James Morris (Department of Parasitology, Biochemistry and Life Sciences, Clemson University)
Kerry Smith (Department of Parasitology, Biochemistry and Life Sciences, Clemson University)
Parag Shah (Penn Center for Molecular Discovery, University of Pennsylvania)

Sruti Shiva, Ph.D.
Assistant Professor

Jeffrey Isenberg (Department of Medicine, University of Pittsburgh)
Mark Gladwin (Department of Medicine, University of Pittsburgh)
Anje Cauwels (University of Ghent, Belgium)
Tienush Rassaf (University Hospital Aachen, Germany)
William Frazier (Washington University, St. Louis, MO)

Jill Siegfried, Ph.D.
Professor

Phoutone Keohavong (Department of Environmental and Occupational Health, University of Pittsburgh): Kras and p53 mutations in airway mucosa
Jennifer Grandis (Department of Otolaryngology, University of Pittsburgh): GPCR-EGFR interactions
Joseph Pilewski (Department of Medicine, University of Pittsburgh): HGF in airway biology
Stephen Shapiro (Department of Medicine, University of Pittsburgh): Inflammation in lung cancer
David Sidransky (Johns Hopkins University): Methylation marker for lung cancer risk

Shivendra Singh, Ph.D.
Professor

Jennifer Grandis (Department of Otolaryngology, University of Pittsburgh): Prevention of head and neck cancer with dietary and CAM agents
Per Basse (Department of Immunology, University of Pittsburgh): Augmentation of NK cell activity by dietary agents
Charles Brown (Department of Surgical Oncology, University of Pittsburgh): Prevention of melanoma by sulforaphane

Robert Sobol, Ph.D.
Assistant Professor

Hideho Okada (Department of Neurological Surgery, University of Pittsburgh): Investigating Dicer in glioma
Patricia Opresko (Department of Environmental and Occupational Health, University of Pittsburgh): Convergent roles of DNA PolB and WRN in genome stability
Barry Gold (Department of Pharmaceutical Science, University of Pittsburgh): Investigations of novel DNA damaging agents
Hussein Tawbi (Department of Medicine, University of Pittsburgh): Temozolomide resistance in melanoma
Robert Ferrel (Department of human genetics): Development of a lymphatic-inclusive tissue system for the study of progression, treatment and unique biomarkers of melanoma
Robert Branch (Department of Medicine, University of Pittsburgh): Mutations of PolB in cancer
Deric Park (Department of Neurological Surgery, University of Pittsburgh): DNA repair status of glioma stem like cells
Andrew Stewart (Department of Medicine, University of Pittsburgh): Potential role of DNA repair genes in diabetes
Emanuela Taioli (SUNY Downstate): Methylation and DNA Repair defects in cancer
Simone Heyliger (Hampton University): Pesticides and genome instability
Bruce Demple (Harvard School of Public Health): Pol B in repair of oxidative lesions
Guy Poirier (Université Laval): Poly-ADP-ribose modified proteins in cancer
Mark Bedford (MD Anderson): Methylation of base excision repair protein.
Michael Wyatt (University of Southern California): Reactive nitrogen modulation of DNA repair proteins

Harish Srinivas, Ph.D.
Research Instructor

Daniel Johnson (Department of Medicine, University of Pittsburgh)
Anil Parwani (Department of Pathology, University of Pittsburgh)
Stephanie Land (Department of Biostatistics, University of Pittsburgh)
Judith Klein-Seetharaman (Department of Structural Biology, University of Pittsburgh)

Laura Stabile, Ph.D.
Research Assistant Professor

Stephanie Land, Diana Lenzer and The Ming Long (Department of Biostatistics, University of Pittsburgh): UPCI SPORE projects
Phouthone Keovahong (Department of Environmental and Occupational Health, University of Pittsburgh): K-ras mutation analysis
Talal El-Hefnawy (Department of Medicine, University of Pittsburgh): CEO project
Joan Schiller and Anne Traynor (University of Wisconsin): Clinical trials
Richard Pietras and Diana Marquez Garban (University of California Los Angeles): Clinical trials
Jin Kim (Galaxy Biotech): L2G7 HGF neutralizing antibody
Pamela Hershberger (Department of Pharmacology & Chemical Biology, University of Pittsburgh): Lung SPORE Project
Jennifer Grandis (Department of Otolaryngology, University of Pittsburgh): Head and Neck SPORE Project
Ann Marie Egloff and Sufi Thomas (Department of Otolaryngology, University of Pittsburgh): Head and Neck and Lung SPORE Projects
Sanja Dacic (Department of Pathology, University of Pittsburgh)

Ben Van Houten, Ph.D.
Professor

Rita Alevriadou (Ohio State University, Columbus, OH): Role of mitochondrial injury in vascular endothelial cells exposed to shear stress
Marcel Bruchez (Carnegie Mellon University): Developing techniques for imaging single-molecules on DNA and inside living cells
Steve Dwretzky (Knopp Neurosciences, Pittsburgh, PA): Analysis of anti-degenerative compounds on mitochondrial function
Marc Greenberg (Johns Hopkins University, Baltimore, MD): Action mechanism of nucleotide excision repair proteins on endogenous DNA damage
Neil Kad (University of Essex, Colchester, UK): Single-molecule dynamics of DNA repair enzymes
Caroline Kisker (University of Wurtzburg, Wurtzburg, Germany): Structure and function of nucleotide excision repair proteins
Steve Kleeberger (NIEHS, Research Triangle Park, NC): Mitochondrial dysfunction in hyperoxia induced injury
Robert London (NIEHS, Research Triangle Park, NC): NMR analysis of UvrB binding to DNA
Mike Resnick (NIEHS, Research Triangle Park, NC): Control of oxidative phosphorylation by p53
Ivet Bahar (Department of Computational Biology, University of Pittsburgh): Protein dynamics in DNA damage recognition
Charleen Chu (Department of Pathology, University of Pittsburgh): Effect of Parkin on mitochondrial oxidative phosphorylation
Simon Watkins (Department of Cell Biology, University of Pittsburgh): Visualization of single-molecules of QDOT labeled DNA repair protein

Mike Lotze (Department of Surgery, University of Pittsburgh): Function of HMG-B1 in mitochondrial autophagy and oxidative phosphorylation in cancer cells
Jean Latimer & Steven Grant (Department of Ob/Gyn and Reproductive Science, University of Pittsburgh): Warburg effect in breast cancer cells
James Gnarra (Department of Urology, University of Pittsburgh): Effects of VDL and Hif1 alpha on oxidative phosphorylation and glycolysis in kidney cells
Laura Niedernhofer (Department of Microbiology and Molecular Genetics, University of Pittsburgh): Role of ERCC1 in mitochondrial function and endogenous DNA damage
Tony Graves and Ed Prochownik (Department of Pediatrics, University of Pittsburgh): Function of Myc expression on oxidative phosphorylation in cancer cells

Jean-Pierre Vilardaga, Ph.D.
Assistant Professor

Harvard University, Endocrine Unit
Harvard University, Center for Systems Biology
University of Wuerzburg (Germany), Institute of Pharmacology
University of Barcelona (Spain), Department of Pathology and Experimental Therapeutics
University of Santiago de Compostela (Spain), Department of Pharmacology

Andreas Vogt, Ph.D.
Research Assistant Professor

Billy Day (Department of Pharmaceutical Sciences, University of Pittsburgh), Scott Nelson and Dennis Curran (Department of Chemistry, University of Pittsburgh): Novel microtubule-perturbing agents
Billy Day (Department of Pharmaceutical Sciences, University of Pittsburgh): Inhibitors of cytoplasmic dynei
Kazonuri Koide (Department of Chemistry, University of Pittsburgh): Chemical approaches for the discovery of new cancer therapeutic targets
Neil Hukriede (Department of Microbiology and Molecular Genetics, University of Pittsburgh): Utilizing small molecule screens to delineate embryonic signaling mechanisms
Michael Tsang (Department of Microbiology and Molecular Genetics, University of Pittsburgh): Small molecule zebrafish screens for regulators of Fgf signaling
Xiao-Ming Yin (Department of Pathology, University of Pittsburgh): Modulators of autophagy
Ruth Perez (Department of Neurology, University of Pittsburgh): Inhibitors of Abeta aggregation
Charleen Chu (Department of Pathology, University of Pittsburgh): Autophagy in dopaminergic cell death
Patrick Moore (Department of Microbiology and Molecular Genetics, University of Pittsburgh): Inhibitors of Merkel cell carcinoma
Garth Powis (MD Anderson): Cancer drugs active against stress signaling pathways
Jana Patton-Vogt (Duquesne University): Inhibitors of the glycerophosphoinositol transporter, GIT1
Keren Hulkower (Platypus LLC, Madison, WI): Development of HTS migration assays
Scott Keefer (Thermo Fisher Cellomics): Development of zebrafish toxicity assay
Tao Zhang (Vanderbilt University): High content screening for zebrafish cardiomyocyte development

Daniela Volonte-Galbiati, Ph.D.
Research Instructor

Y. P. Peter Di (Department of Environmental and Occupational Health, University of Pittsburgh)

Q. Jane Wang, Ph.D.
Assistant Professor

Billy Day (Department of Pharmaceutical Sciences, University of Pittsburgh)
Adam Glick (Penn State University)
J. Frederic Mushinski (National Cancer Institute)
Peter M. Blumberg (National Cancer Institute)

Jack Yalowich, Ph.D.
Associate Professor

Valerian E. Kagan (Department of Environmental and Occupational Health, University of Pittsburgh): Free radical induced activation of VP-16/potentiation of topo II inhibition; mechanisms of phenoxyl radical toxicity and antioxidant protection against toxicity. Role of myeloperoxidase in activating VP-16 to a leukemogenesis species in human myeloid progenitor CD34+ cells.

Billy Day (Department of Pharmaceutical Sciences, University of Pittsburgh): Free radical induced activation of VP-16; sites of adduction of VP-16 (photoaffinity-label) to DNA topoisomerase II. Synthesis of photoaffinity analogs of VP-16. Synthesis/evaluation of VP-16-orthoquinone and VP-16 catechol.

Brian Hasinoff and Lean Chee (Faculty of Pharmacy, University of Manitoba): Mechanisms of action and resistance to bisdioxopiperazine inhibitors of DNA topoisomerase II inhibition by bisdioxopiperazines. Synthesis and evaluation of a photoactivatible form of VP-16; evaluation of bisintercalating bisanthrapyrazole anticancer compounds and bisphenol A as DNA topoisomerase II inhibitors.

Lin Zhang, Ph.D.
Assistant Professor

Xiao-Ming Yin (Department of Pathology, University of Pittsburgh): Studying apoptosis induced by proteasome inhibitor

Cary Wu (Department of Pathology, University of Pittsburgh): Studying apoptosis caused by chance in extracellular matrix

Tao Cheng (Department of Radiation Oncology, University of Pittsburgh): Studies of PUMA-knockout mice

Robert Schoen (Department of Medicine, University of Pittsburgh): Studying chemoprevention of colon cancer by NSAIDs

Wei Zhou (Emory University): Developing molecular markers of lung cancer

Chuanshu Huang (New York University): Studying apoptotis induced by anti-cancer drugs

Jim Herman (Johns Hopkins University): Studying DNA methylation in lung cancer

Gerry Zambetti (St. Jude's Children's Hospital): Studies of PUMA-knockout mice

Chinese Academy of Medical Sciences: Studying esophageal cancer drug response

Entrepreneurial Activities

Ben Van Houten, Ph.D.
Professor
Transgenomics (Omaha, NE 68164) licensed US Patent No. 6,322,984 entitled "Mitochondrial DNA damage as a predictor of coronary atherosclerotic heart disease."

Jean-Pierre Vilardaga, Ph.D.
Assistant Professor
Collaborator with Crinetics Pharmaceutical, San Diego

Awards and Honors

Marsha Cole, Ph.D.
Research Instructor
Hartwell Foundation Fellow, Department of Pharmacology & Chemical Biology, 2009-2011

Joan Lakoski, Ph.D.
Professor
Chancellor's Affirmative Action Award, University of Pittsburgh, 2009

Robert Sobol, Ph.D.
Assistant Professor
Hillman Fellow for Innovative Cancer Research

Bennett Van Houten, Ph.D.
Professor
Medal of the Slovak Academy of Sciences for Support of Science, 2008

Invited Talks

Bruce Freeman, Ph.D.
Professor and Chair

"Transduction of Nitric Oxide and Redox Signaling by Electrophilic Fatty Acids." Mext Symposium, Kumamoto, Japan, July 18, 2009.

"Nitric Oxice: A Molecular 'Switch' in Redox Signaling." New York Academy of Sciences, New York, NY, October 27-29, 2009.

"The Hitchhiker's Guide to Publishing Highly Cited, High Impact Manuscripts." Society for Free Radical Biology and Medicine, San Francisco, CA, November 17-21 2009.

"Fatty Acid Transduction of Redox Signaling Reactions." Vanderbilt University, Molecular Toxicology Program, Nashville, TN, December 11, 2009.

"Transduction of Cardiovascular Redox Signaling by Electrophilic Fatty Acids." Cleveland Clinic, Department of Cell Biology, Cleveland, OH, January 8, 2010.

Palaniappa Arjunan, Ph.D.
Research Instructor

"Structure-Function Effects of Active Site Mutations in the E. coli Pyruvate Dehydrogenase Multienzyme Complex E1 Component." American Crystallographic Association Annual Meeting, Toronto, Canada, July 25-30, 2009.

Alessandro Bisello, Ph.D.
Associate Professor

"Caveolin-1 and Cholesterol Regulate GLP-1 Receptor Function." Mid-Atlantic Diabetes Research Symposium, NIH, Bethesda, MD, September 2009.

Alicia Celotto, Ph.D.
Research Instructor

"The Role of Molecular Chaperones and the UPP in TPI^{sugarkill} Protein Degradation," 50th Annual Drosophila Research Conference, March 4-8, 2009.

Thomas Conrads, Ph.D.
Associate Professor

"Tissue and Proximal Fluid Proteomics for Cancer Biomarker Discovery." Freie Universitat, Berlin, Germany, April 1, 2009.

"Protein Cartography of the Tumor Microenvironment." 57th American Society for Mass Spectrometry Meeting, Philadelphia, PA, June 1, 2009.

"High Resolution Mass Spectrometry for Biomarker Discovery and Validation." Gynecologic Oncology Group, Baltimore, MD, July 17, 2009.

"Proteomic Biomarkers for Prediction of Risk of Progression for Barret's Esophagus." 9th Annual World Human Proteome Congress, Toronto, Canada, Septemer 31, 2009.

"Application of Proteomics for Biomarker Discovery in Gynecologic Malignancies." Villasanti Lecturer, Mid-Atlantic Gynecologic Oncology Society, Homestead, VA, October 9, 2009.

"Proteomic Biomarker Discovery from Tissue." EORTC-NCI-ASCO 2009, Brussells, Belgium, October 15, 2009.

"Biomarkers for Early Detection of Endometrial Cancer." Gynecologic Cancer Foundation, Washington, DC, November 6, 2009.

"Tissue Proteomics for Cancer Biomarker Discovery." Danish Society of Proteomics, University of Southern Denmark, Odense, Denmark, December 2, 2009.

W. Chet de Groat, Ph.D.
Professor

"Pathophysiologic Mechanisms of OAB in Male LUTS." Symposium on Overactive Bladder, Korean Continence Society Annual Meeting. Seoul, Korea, May 28, 2009.

"Neural and Non-Neural Molecular Targets for Drug Therapy of Lower Urinary Tract Dysfunction." State-of-the-Art Lecture, Korean Continence Society Annual Meeting. Seoul, Korea, May 29, 2009.

"Nitro-Fatty Acids, a New Class of Signaling Molecules, Act on TRP Channels and Affect Urinary Bladder Function." Korean Continence Society Annual Meeting. Seoul, Korea, May 27, 2009.

"Afferent Mechanisms in the Regulation of Micturition." Animal and Human Physiology of Continence. Symposium at Meeting of the British Physiological Society. Dublin, Ireland, July 10, 2009.

"The Neurophysiology of the Neuropathic Bladder." Advanced Neurourology: Frontiers of the Neuropathic Bladder. Workshop at the 39th International Continence Society Meeting. San Francisco, California, September 29, 2009.

"Targeting Afferent Modulation for Treatment of Benign Prostatic Hyperplasia/Bladder Outlet Obstruction (Male LUTS). The Role of Afferent Inhibition in the Treatment of Bladder and Prostate Diseases." Workshop at the 39th International Continence Society Meeting. San Francisco, California, September 30, 2009.

"Bladder Reinnervation: Can New Nerves Improve the Function of the Neurogenic Bladder?" State-of-the-Art Lecture at the 39th International Continence Society Meeting. San Francisco, California, October 2, 2009.

"Pathophysiology of Neurogenic Detrusor Overactivity: What Happens in the Bladder Wall?" In "Understanding Neurogenic Detrusor Overactivity in Spinal Cord Injury: a Journey from the Bladder Wall to the Brain." Symposium at the Italian Society for Urodynamics Meeting. Florence, Italy, October 21, 2009.

"Understanding the Neurogenic Bladder." In "Philosophical Counseling and Neurogenic Bladder Management – What's next?" Symposium at The 48th annual meeting of the International Spinal Cord Society. Florence, Italy, October 23, 2009.

"Contributions of Neural-Epithelial Cell Interactions to Sensory Mechanisms in the Lower Urinary Tract." Plenary Lecture at the American Autonomic Society Meeting. St. Thomas, US Virgin Islands, November 12, 2009.

Melanie Flint, Ph.D.
Research Instructor

"Proteomic Analysis of a Combined Psychological Stress and 7,12-Dimethylbenz(a)anthracene (DMBA) Exposure Effects of Liver Drug Metabolizing Enzymes." American Society of Mass Spectrometry, Philadelphia, PA, June 2009.

Peter Friedman, Ph.D.
Professor

10th International PTH-PTHrP Meeting.

UCLA Conference on FGF23 and PTH

William Furey, Ph.D.
Professor

"Structure-Function Effects of Active Site Mutations in the E. coli Pyruvate Dehydrogenase Multienzyme Complex E1 Component." American Crystallographic Association Meeting, Toronto, Canada, July 2009.

"The Phox Domain of Sorting Nexin 5 Lacks Ptdins(3)P Specificity and Preferentially Binds to Ptdins(4,5)P2." American Crystallographic Association Meeting, Toronto, Canada, July 2009.

Ferruccio Galbiata, Ph.D.
Associate Professor

"Istituto di Ricerche Farmacologiche Mario Negri." Laboratory of Molecular Biology, Milan, Italy, 2009.

Department of Experimental Medicine, University of Milan, Monza, Italy, 2009.

Pamela Hershberger, Ph.D.
Research Assisatnt Professor

"Plasma and Tumor Pharmacokinetics of the Anti-Proliferative Agent, 1,25-Dihydroxyvitamin D3 in a Lung Tumor Xenograft Model." Proceedings of the American Association for Cancer Research, 2009.

"The Histone Deacetylase Inhibitor, Vorinostat, Increased Carboplatin and Paclitaxel Activity in Non-Small Cell Lung Cancer Cells." Proceedings of the American Association for Cancer Research, 2009.

Yi Huang, M.D., Ph.D.
Research Assistant Professor

"Histone Lysine-Specific Demethylase (LSD1): An Emerging Epigenetic Target for Polyamine Analogues in Cancer Therapy." Polyamine Gordon Conference, Waterville Valley, NH, June 2009.

"Targeting Histone Lysine Specific Demethylase 1 (LSD1) as a Novel Epigenetic Strategy in Cancer Therapy." Pittsburgh Chromatin Club Symposium, Pittsburgh, PA, December 2009.

Joan M. Lakoski, Ph.D.
Professor

"Shaping Our Research Communities: What Women Do Well and How To Do It Better." 2009 Women in Andrology Conference, Philadelphia, PA, April 5, 2009.

"Managing Your Mentor/Getting the Most out of your Mentor." 2009 National Clinical and Translational Research Education Annual Meeting, Washington, DC, April 14, 2009.

"Training Mentors." 2009 National Clinical and Translational Research Education Annual Meeting, Washington, DC, April 15, 2009.

"Know Your K." University of Pennsylvania, Philadelphia, PA, May 6, 2009.

"NIH Pathway to Independence: K99/R00." University of Pennsylvania, Philadelphia, PA, May 7, 2009.

"Facing New Challenges in Faculty Development." AAMC Group on Faculty Affairs Professional Development Conference, San Francisco, CA, August 8, 2009.

"Know Your K." Memorial Sloan Kettering Cancer Center, New York, NY, September 15, 2009.

"Getting to the Payline: Successful Fellowship Applications." Memorial Sloan Kettering Cancer Center, New York, NY, September 15, 2009.

"Know Your K." Memorial Sloan Kettering Cancer Center, New York, NY, September 16, 2009.

"Building a Successful Research Program." Duke-NIEHS Postdoc Lab Management and Leadership Symposium, Duke University, Durham, NC, September 22-23, 2009.

"Ethics in Clinical Research." 6th Annual Clinical Investigator Workshop for Trainees, The Endocrine Society, Atlanta,GA, October 11, 2009.

"Postdoctoral Leaders Section Orientation." AAMC Postdoctorate Leaders Section Annual Meeting, St. Louis, MO, October 22, 2009.

"Identifying Educational Competencies for Future BSTLs." AAMC Postdoctorate Leaders Section Annual Meeting, St. Louis, MO, October 22, 2009.

"CSML Model of Empowering Postdoc Success: Presentation on the Scientific Management and Leadership." AAMC Postdoctorate Leaders Section Annual Meeting, St. Louis, MO, October 22, 2009.

"Know Your K." Memorial Sloan Kettering Cancer Center, New York, NY, January 12, 2010.

"Strategies for Competitive Applications." Memorial Sloan Kettering Cancer Center, New York, NY, January 12, 2010.

"Know Your NRSA." Memorial Sloan Kettering Cancer Cetner, New York, NY, January 12, 2010.

"Know Your Kangaroo." Memorial Sloan Kettering Cancer Center, New York, NY, January 12, 2010.

"Transitioning from Mentee to Mentor." 2010 Center for Translational Science Activitise (CTSA) Grand Rounds Meeting, Mayo Clinic, Rochester, MN, January 15, 2010.

"Successful Navigation of a Mentoring Relationship: Strategies to Ensure Smooth Sailing for Mentees." 2010 Center for Translational Science Activitise (CTSA) Grand Rounds Meeting, Mayo Clinic, Rochester, MN, January 15, 2010.

"Educating CTSA Leaders and Participants: The Role of Basic Scientists." Association of Anatomy, Cell Biology and Neurobiology Chairpersons (AACBNC), Curacao, Netherlands, January 21, 2010.

"Mentoring and Faculty Development." Association of Anatomy, Cell Biology and Neurobiology Chairpersons (AACBNC), Curacao, Netherlands, January 22, 2010.

"Panel Discussion on Mentoring and Faculty Development." Association of Anatomy, Cell Biology and Neurobiology Chairpersons (AACBNC), Curacao, Netherlands, January 22, 2010.

"K Award Workshop." Pensylvania State University, College of Medicine, Hershey, PA, February 25, 2010.

"Research Advising and Mentoring: Module 1." Pensylvania State University, College of Medicine, Hershey, PA, February 26, 2010.

"Career Transitions for Early, Mid and Late Careers." 18th Annual WISDM Leadership Conference, Virginia Commonwealth University, Richmond, VA, March 5, 2010.

"Assessing Leadership Skill and Talent." 18th Annual WISDM Leadership Conference, Virginia Commonwealth University, Richmond, VA, March 5, 2010.

"Retaining Postdoc Women through Mentoring." National Postdoctorate Association Gender Summit, Philadelphia, PA, March 11, 2010.

"Being a Postdoctoral Advocate." National Postdoctorate Association Gender Summit, Philadelphia, PA, March 12, 2010.

Edwin Levitan, Ph.D.
Professor

Experimental Biology Meeting.

Japan Cell Biology Meeting.

Biophysical Society Meeting.

Jannelia Farm HHMI Insert Neuromodulators Meeting.

Florida State University.

Gunma University.

Tokyo Pharmaceutical University.

Dinara Shakiryanova, Ph.D.
Research Instructor

"CamKII Activation and Translocation to Active Zones in Drosophila Synaptic Boutons." CSHL Neurobiology of Drosophila Meeting, New York, October 2009.

Jill Siegfried, Ph.D.
Professor

"Targeting HGF Pathways in Lung Cancer." Harper Cancer Institute, University of Notre Dame, South Bend, IN, March 26, 2009.

"Basic Mechansms for Gender Influences in Lung Malignancy." American Thoracic Soceity Conference, San Diego, CA, May 18-20, 2009.

"Controversies in Hormones and Lung Cancer." American Society of Clinical Oncology Annual Meeting, Orlando, FL, May 28-31, 2009.

National Lung Cancer Partnership's Seventh Annual Meeting: Advancing Individualized Care in Lung Cancer: New Hope for Screening and Treatment, Orlando, FL, May 29, 2009.

"Estrogen and Progesterone Receptors in Lung Cancer." World Conference on Lung Cancer, San Francisco, CO, July 31-August 3, 2009.

"Targeting the HGF/c-Met Pathway in Lung Cancer." National Cancer Institute Trans-Institute Lung Cancer Program, Washington, DC, September 16, 2009.

NCI Translational Science Meeting, Vienna, VA, November 5-7, 2009.

"Estrogen Receptor Signaling in Lung Cancer." Virginia Commonwealth University, Department of Pharmacology & Toxicology, Richmond, VA, Febraury 24, 2010.

"Aromatase Inhibitors." Annual Targeted Therapies of the Treatment of Lung Cancer, Santa Monica, CA, February 25, 2010.

Shivendra Singh, Ph.D.
Professor

"Cancer Prevention by Bioactive Food Components." Center for Molecular Medicine, University of Conneticut Cancer Center, Farmington, CT, April 1, 2009.

"Mechanism of Cancer Prevention by Sulforaphane." Winship Cancer Institute, Emory University, Atlanta, GA, May 4, 2009.. Title:

"Bioactive Food Components and Cancer Prevention." Department of Pharmacology, Emory University, Atlanta, GA, May 5, 2009.

"Cancer Prevention by Garlic Constituents." Linus Pauling Institute, Oregon State University, Corvallis, OR, June 4, 2009.

"Prevention of Prostate Cancer by Dietary Agents." 2009 Sino-US Forum on Frontiers of Cancer Research: Focus on Prevention, Changsha, People's Republic of China, October 21, 2009.

Robert Sobol, Ph.D.
Research Assistant Professor

"Base Excision Repair and NAD+ Biosynthesis Pathways Modulate DNA Damage-Induced Tumor Cell Death." Department of Biological Sciences, Hampton University, March 19, 2009.

"DNA Polymerase β and BER Regulation of DNA Damage-Induced Energy Failure and Necrosis." NAD Metabolism and Signaling, FASEB Summer Research Conference, June 26, 2009.

"Bioenergetic Metabolites Regulate Base Excision Repair Dependent Cell Death in Response to Chemotherapy-Induced DNA Damage." The University of Arizona, Drug Discovery and Development Seminar Series, Septemer 24, 2009.

"The Intimate Relationship between Base Excision Repair and NAD^+ Biosynthesis in the Response to Chemotherapy-Induced DNA Damage." Environmental Mutagen Society 40^{th} Annual Meeting, St. Louis, MO, October 2009.

Ben Van Houten, Ph.D.
Professor

"Dynamic Damage Searching by Nucleotide Excision Repair Proteins Investigated by Single-Molecule Fluorescnece of Quantum Dot Laeled Proteins." 3^{rd} ASM Conference on DNA Repair and Mutagenesis, Whistler, Canada, May 30-June 4, 2009.

"Reactive Oxygen Species and Genotoxic Stress." Gordon Research Conference on Genetic Toxicology, Colby Sawyer College, New London, NH, August 9-14, 2009.

"Computational Toxicology: From Data to Analyses to Applications." Committee on use of Emerging Science for Environmental Health Decisions, Washington, DC, September 21-22, 2009.

"Watching DNA Repair One Molecule at a Time: Single-Moecule Imaging of Bacterial Nucleotide Excision Repair Proteins." Brazilian Society of Environmental Mutagenesis, Carcinogenesis and Teratogenesis IX Congress, Ouro Preto, Brazil, November 11-14, 2009.

"Mitochondrial DNA Damage and Bioenergetics in Cancer and Neurodegenerative Diseases." IV Fundamental Aspects of DNA and Mutagenesis, Belo Horizonte, Brazil, November 8-10, 2009.

"Mitochondrial DNA Damage, ROS and Human Disease." Mini-Symposium on Mitochondrial Genone Dynamics and Aging, University of Aarhus, Denmark, January 21-22, 2010.

Jean-Pierre Vilardaga, Ph.D.
Assistant Professor

"GPCR Heterodimerization." Mount Sinai School of Medicine.

"GPCR Studies in Live Cells." University of Santiago de Compostela, Spain.

"PTH Receptor Signaling from Endosomes." Harvard Medical School/Massachusetts General Hospital.

"GPCR's: New Signaling Pathways." University of Texas-Houston Medical School.

Andrea Vogt, Ph.D.
Research Assistant Professor

"Quantitation of Fibroblast Growth Factor (FGF) Signaling by High-Content Analysis in Transgenic Zebrafish." Cambridge Healthtech Institute, High-Content Analysis Conference, San Francisco, 2010.

Jack Yalowich, Ph.D.
Associate Professor

"Therapy-Induced AML: Mechanisms and Prevention of Leukemogenesis Caused by the DNA Topoisomerase II Inhibitor Etoposide." Markey Cancer Center, University of Kentucky, May 4, 2009.

Lin Zhang, Ph.D.
Assistant Professor

Mary Babb Cancer Center, West Virginia University, September 16, 2009.

Teaching Activities

UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE
Department of Pharmacology & Chemical Biology
EDUCATIONAL CREDIT UNITS (AY 08-09)
Summary of Faculty ECU's

Faculty Name / Activity	ECURV	Units	ECU's
Daniel Altschuler, Ph.D.			
GS - Lecture	2.0	16.0	32.0
GS - Small group (e.g., PBL, conference, workshop)	2.0	10.5	21.0
GS - Other	2.0	6.0	12.0
GS - Course Director	10.0	2.0	20.0
GS - Member: Comprehensive, Dissertation, Thesis, Preliminary or Reprint Committee	5.0	1.0	5.0
	Total ECU's:		90.0
Alessandro Bisello,			
MS 1, MS 2 - Small group (e.g., PBL, conference, workshop)	2.0	3.3	6.7
GS - Lecture	2.0	2.0	4.0
GS - Small group (e.g., PBL, conference, workshop)	2.0	12.0	24.0
GS - Laboratory supervision (e.g., MSTP, Ph.D. & M.Sc.)	1.0	20.0	20.0
GS - Course Director	10.0	1.0	10.0
GS - Member: Curriculum, Recruiting, Program, or other SOM Committee	2.0	2.0	4.0
GS - Member: Comprehensive, Dissertation, Thesis, Preliminary or Reprint Committee	5.0	4.0	20.0
	Total ECU's:		88.7
Thomas Conrads, Ph.D.			
GS - Chair: Comprehensive, Dissertation, Thesis, Preliminary or Reprint Committee	5.0	1.0	5.0
	Total ECU's:		5.0
Donald DeFranco, Ph.D.			
MS 1, MS 2 - Lecture	2.0	14.7	29.3
MS 1, MS 2 - Small group (e.g., PBL, conference, workshop)	2.0	28.7	57.3
MS 1 and MS 2 - Course Director	100.0	1.0	100.0
MS - Vice-Chair. Curriculum Committee	20.0	1.0	20.0
MS - Applicant Interviewer	1.0	7.0	7.0
MS - Chair, Task Force/Work Group/Subcommittee/or other SOM Committee	5.0	1.0	5.0
MS - Mentoring medical students (e.g., FAST, AOC, or academic advising)	2.0	2.0	4.0
GS - Lecture	2.0	16.5	33.0
GS - Small group (e.g., PBL, conference, workshop)	2.0	5.5	11.0
GS - Laboratory supervision (e.g., MSTP, Ph.D. & M.Sc.)	1.0	14.0	14.0
GS - Program Director	30.0	1.0	30.0
GS - Member: Curriculum, Recruiting, Program, or other SOM Committee	2.0	2.0	4.0
GS - Chair: Comprehensive, Dissertation, Thesis, Preliminary or Reprint Committee	5.0	4.0	20.0
GS - Member: Comprehensive, Dissertation, Thesis, Preliminary or Reprint Committee	5.0	5.0	25.0
	Total ECU's:		359.7
William deGroat, Ph.D.			
MS 1, MS 2 - Small group (e.g., PBL, conference, workshop)	2.0	2.7	5.3
MS - Member, Task Force/Work Group/Subcommittee/or other SOM Committee	5.0	1.0	5.0
GS - Small group (e.g., PBL, conference, workshop)	2.0	3.0	6.0
GS - Member: Comprehensive, Dissertation, Thesis, Preliminary or Reprint Committee	5.0	3.0	15.0
	Total ECU's:		31.3
Julie Eiseman, Ph.D.			
MS 1, MS 2 - Small group (e.g., PBL, conference, workshop)	2.0	3.3	6.7
GS - Small group (e.g., PBL, conference, workshop)	2.0	3.0	6.0
	Total ECU's:		12.7
Melanie Flint, Ph.D.			
MS 1, MS 2 - Small group (e.g., PBL, conference, workshop)	2.0	1.3	2.7
	Total ECU's:		2.7

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Faculty Name / Activity	ECURV	Units	ECU's
Bruce Freeman, Ph.D.			
MS 1, MS 2 - Lecture	2.0	2.7	5.3
MS 1, MS 2 - Small group (e.g., PBL, conference, workshop)	2.0	1.3	2.7
GS - Lecture	2.0	2.0	4.0
GS - Small group (e.g., PBL, conference, workshop)	2.0	4.0	8.0
GS - Laboratory supervision (e.g., MSTP, Ph.D. & M.Sc.)	1.0	6.0	6.0
GS - Ph.D. or M.Sc. Mentor	20.0	1.0	20.0
GS - Chair: Comprehensive, Dissertation, Thesis, Preliminary or Reprint Committee	5.0	2.0	10.0
GS - Member: Comprehensive, Dissertation, Thesis, Preliminary or Reprint Committee	5.0	5.0	25.0
	Total ECU's:		81.0
Peter Friedman, Ph.D.			
MS 1, MS 2 - Small group (e.g., PBL, conference, workshop)	2.0	1.3	2.7
	Total ECU's:		2.7
William Furey, Ph.D.			
GS - Member: Curriculum, Recruiting, Program, or other SOM Committee	2.0	1.0	2.0
	Total ECU's:		2.0
Ferruccio Galbiati, Ph.D.			
MS 1, MS 2 - Lecture	2.0	4.1	8.2
MS 1, MS 2 - Small group (e.g., PBL, conference, workshop)	2.0	2.0	4.0
GS - Small group (e.g., PBL, conference, workshop)	2.0	7.0	14.0
GS - Ph.D. or M.Sc. Mentor	20.0	1.0	20.0
GS - Course Director	10.0	1.0	10.0
GS - Chair: Comprehensive, Dissertation, Thesis, Preliminary or Reprint Committee	5.0	1.0	5.0
GS - Member: Comprehensive, Dissertation, Thesis, Preliminary or Reprint Committee	5.0	1.0	5.0
	Total ECU's:		66.2
Pamela Hershberger, Ph.D.			
GS - Lecture	2.0	1.0	2.0
	Total ECU's:		2.0
Jing Hu, M.D.,Ph.D.			
GS - Member: Comprehensive, Dissertation, Thesis, Preliminary or Reprint Committee	5.0	2.0	10.0
	Total ECU's:		10.0
Edwin Jackson, Ph.D.			
MS 1, MS 2 - Lecture	2.0	9.9	19.8
MS 3, MS 4 - Lecture	2.0	0.8	1.7
	Total ECU's:		21.5
Yu Jiang, Ph.D.			
MS 1, MS 2 - Lecture	2.0	1.0	2.0
MS 1, MS 2 - Small group (e.g., PBL, conference, workshop)	2.0	2.8	5.7
GS - Lecture	2.0	2.0	4.0
GS - Small group (e.g., PBL, conference, workshop)	2.0	11.0	22.0
GS - Course Director	10.0	1.0	10.0
GS - Chair: Comprehensive, Dissertation, Thesis, Preliminary or Reprint Committee	5.0	1.0	5.0
GS - Member: Comprehensive, Dissertation, Thesis, Preliminary or Reprint Committee	5.0	2.0	10.0
	Total ECU's:		58.7
Paul Johnston, Ph.D.			
GS - Small group (e.g., PBL, conference, workshop)	2.0	4.0	8.0
	Total ECU's:		8.0

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Faculty Name / Activity	ECURV	Units	ECU's
Edwina Kinchington, Ph.D.			
MS 1, MS 2 - Small group (e.g., PBL, conference, workshop)	2.0	4.7	9.3
GS - Member: Comprehensive, Dissertation, Thesis, Preliminary or Reprint Committee	5.0	1.0	5.0
		Total ECU's:	14.3
Joan Lakoski, Ph.D.			
MS 1, MS 2 - Lecture	2.0	1.7	3.3
MS 1, MS 2 - Small group (e.g., PBL, conference, workshop)	2.0	1.3	2.7
MS - Applicant Interviewer	1.0	7.0	7.0
MS - Member, Task Force/Work Group/Subcommittee/or other SOM Committee	5.0	1.0	5.0
GS - Small group (e.g., PBL, conference, workshop)	2.0	2.0	4.0
GS - Member: Comprehensive, Dissertation, Thesis, Preliminary or Reprint Committee	5.0	1.0	5.0
		Total ECU's:	27.0
John Lazo, Ph.D.			
MS 1, MS 2 - Lecture	2.0	2.8	5.7
MS 1, MS 2 - Small group (e.g., PBL, conference, workshop)	2.0	1.3	2.7
MS 3, MS 4 - Lecture	2.0	2.0	4.0
GS - Lecture	2.0	2.0	4.0
GS - Small group (e.g., PBL, conference, workshop)	2.0	13.0	26.0
GS - Ph.D. or M.Sc. Mentor	20.0	2.0	40.0
GS - Course Director	10.0	1.0	10.0
		Total ECU's:	92.3
Edwin Levitan, Ph.D.			
MS 1, MS 2 - Lecture	2.0	1.8	3.7
MS 1, MS 2 - Small group (e.g., PBL, conference, workshop)	2.0	5.5	11.0
GS - Lecture	2.0	2.0	4.0
GS - Small group (e.g., PBL, conference, workshop)	2.0	7.5	15.0
GS - Member: Comprehensive, Dissertation, Thesis, Preliminary or Reprint Committee	5.0	1.0	5.0
		Total ECU's:	38.7
Patrick Pagano, Ph.D.			
MS 1, MS 2 - Small group (e.g., PBL, conference, workshop)	2.0	2.0	4.0
GS - Chair: Comprehensive, Dissertation, Thesis, Preliminary or Reprint Committee	5.0	1.0	5.0
GS - Member: Comprehensive, Dissertation, Thesis, Preliminary or Reprint Committee	5.0	2.0	10.0
		Total ECU's:	19.0
Michael Palladino, Ph.D.			
MS 1, MS 2 - Small group (e.g., PBL, conference, workshop)	2.0	3.3	6.7
GS - Lecture	2.0	12.5	25.0
GS - Small group (e.g., PBL, conference, workshop)	2.0	31.0	62.0
GS - Laboratory supervision (e.g., MSTP, Ph.D. & M.Sc.)	1.0	6.0	6.0
GS - Course Director	10.0	1.0	10.0
GS - Member: Curriculum, Recruiting, Program, or other SOM Committee	2.0	1.0	2.0
GS - Chair: Comprehensive, Dissertation, Thesis, Preliminary or Reprint Committee	5.0	1.0	5.0
GS - Member: Comprehensive, Dissertation, Thesis, Preliminary or Reprint Committee	5.0	3.0	15.0
		Total ECU's:	131.7
Guillermo Romero, Ph.D.			
MS 1, MS 2 - Small group (e.g., PBL, conference, workshop)	2.0	4.7	9.3
GS - Lecture	2.0	15.5	31.0
GS - Small group (e.g., PBL, conference, workshop)	2.0	29.5	59.0
GS - Laboratory supervision (e.g., MSTP, Ph.D. & M.Sc.)	1.0	6.0	6.0
GS - Ph.D. or M.Sc. Mentor	20.0	1.0	20.0
GS - Course Director	10.0	1.0	10.0
GS - Member: Comprehensive, Dissertation, Thesis, Preliminary or Reprint Committee	5.0	6.0	30.0
		Total ECU's:	165.3

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Summary of Faculty ECU's

Faculty Name / Activity	ECURV	Units	ECU's
James Roppolo, Ph.D.			
MS 1, MS 2 - Lecture	2.0	0.8	1.7
MS 1, MS 2 - Small group (e.g., PBL, conference, workshop)	2.0	2.0	4.0
	Total ECU's:		5.7
Adrian Sculptoreanu, Ph.D.			
MS 1, MS 2 - Small group (e.g., PBL, conference, workshop)	2.0	1.3	2.7
GS - Member: Comprehensive, Dissertation, Thesis, Preliminary or Reprint Committee	5.0	2.0	10.0
	Total ECU's:		12.7
Elizabeth Sharlow, Ph.D.			
GS - Lecture	2.0	2.0	4.0
	Total ECU's:		4.0
Jill Siegfried, Ph.D.			
MS 1, MS 2 - Lecture	2.0	1.7	3.3
MS 1, MS 2 - Small group (e.g., PBL, conference, workshop)	2.0	1.3	2.7
GS - Lecture	2.0	2.0	4.0
GS - Small group (e.g., PBL, conference, workshop)	2.0	1.5	3.0
GS - Laboratory supervision (e.g., MSTP, Ph.D. & M.Sc.)	1.0	10.0	10.0
GS - Ph.D. or M.Sc. Mentor	20.0	1.0	20.0
GS - Chair: Comprehensive, Dissertation, Thesis, Preliminary or Reprint Committee	5.0	2.0	10.0
GS - Member: Comprehensive, Dissertation, Thesis, Preliminary or Reprint Committee	5.0	1.0	5.0
	Total ECU's:		58.0
Robert Sobol, Ph.D.			
MS 1, MS 2 - Small group (e.g., PBL, conference, workshop)	2.0	1.3	2.7
GS - Lecture	2.0	4.0	8.0
GS - Laboratory supervision (e.g., MSTP, Ph.D. & M.Sc.)	1.0	6.0	6.0
GS - Member: Comprehensive, Dissertation, Thesis, Preliminary or Reprint Committee	5.0	4.0	20.0
	Total ECU's:		36.7
Bennett Van Houten, Ph.D.			
GS - Small group (e.g., PBL, conference, workshop)	2.0	4.0	8.0
GS - Course Director	10.0	1.0	10.0
GS - Chair: Comprehensive, Dissertation, Thesis, Preliminary or Reprint Committee	5.0	1.0	5.0
	Total ECU's:		23.0
Jean Pierre Vilardaga, Ph.D.			
MS 1, MS 2 - Small group (e.g., PBL, conference, workshop)	2.0	1.3	2.7
	Total ECU's:		2.7
Andreas Vogt, Ph.D.			
MS 1, MS 2 - Small group (e.g., PBL, conference, workshop)	2.0	4.7	9.3
GS - Small group (e.g., PBL, conference, workshop)	2.0	5.5	11.0
GS - Member: Comprehensive, Dissertation, Thesis, Preliminary or Reprint Committee	5.0	1.0	5.0
	Total ECU's:		25.3
Qiming Wang, Ph.D.			
MS 1, MS 2 - Lecture	2.0	1.0	2.0
MS 1, MS 2 - Small group (e.g., PBL, conference, workshop)	2.0	4.0	8.0
GS - Lecture	2.0	3.5	7.0
GS - Member: Comprehensive, Dissertation, Thesis, Preliminary or Reprint Committee	5.0	2.0	10.0
	Total ECU's:		27.0

UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE
Department of Pharmacology & Chemical Biology
EDUCATIONAL CREDIT UNITS (AY 08-09)
Summary of Faculty ECU's

Faculty Name / Activity	ECURV	Units	ECU's
Jack Yalowich, Ph.D.			
MS 1, MS 2 - Lecture	2.0	3.0	6.0
MS 1, MS 2 - Small group (e.g., PBL, conference, workshop)	2.0	51.9	103.8
MS 1 and MS 2 - Course Director	100.0	1.0	100.0
MS - Member, Curriculum Committee	20.0	1.0	20.0
MS - Member, Promotions Committee	5.0	1.0	5.0
MS - Coordinator, Undergraduate Medical Education Teaching	5.0	1.0	5.0
MS - Member, Task Force/Work Group/Subcommittee/or other SOM Committee	5.0	3.0	15.0
MS - Member, Evaluation Sub-Committee	20.0	1.0	20.0
GS - Lecture	2.0	5.0	10.0
GS - Small group (e.g., PBL, conference, workshop)	2.0	15.8	31.5
GS - Ph.D. or M.Sc. Mentor	20.0	1.0	20.0
GS - Course Director	10.0	1.0	10.0
GS - Chair: Comprehensive, Dissertation, Thesis, Preliminary or Reprint Committee	5.0	2.0	10.0
GS - Member: Comprehensive, Dissertation, Thesis, Preliminary or Reprint Committee	5.0	4.0	20.0
	Total ECU's:		376.3
Lin Zhang, Ph.D.			
MS 1, MS 2 - Lecture	2.0	0.8	1.7
MS 1, MS 2 - Small group (e.g., PBL, conference, workshop)	2.0	3.3	6.7
GS - Lecture	2.0	5.0	10.0
GS - Small group (e.g., PBL, conference, workshop)	2.0	3.0	6.0
GS - Laboratory supervision (e.g., MSTP, Ph.D. & M.Sc.)	1.0	40.0	40.0
GS - Member: Admissions Committee	5.0	1.0	5.0
GS - Chair: Comprehensive, Dissertation, Thesis, Preliminary or Reprint Committee	5.0	3.0	15.0
GS - Member: Comprehensive, Dissertation, Thesis, Preliminary or Reprint Committee	5.0	2.0	10.0
	Total ECU's:		94.3

Total Faculty reporting: **34** **Faculty ECU Subtotal:** **1996.0**

Total ECU's for Pharmacology & Chemical Biology: 1996.0

Teaching Awards

William Furey, Ph.D.
Professor

Chairman, National Continuing Education Committee, American Crystallographic Association

Joan Lakoski, Ph.D.
Professor

Member, Academy of Master Educators, 2009-2014

Post-doctoral Fellows

Name	Lab
Imad Al Ghouleh	Pagano
Veronica Alonso	Friedman
Juan Ardura	Friedman
Debra Artim	de Groat
Lesley Ashmore	Palladino
Lihua Bai	Eiseman
Michelle Barbi De Moura	Van Houten
Guillermo Barila	Altschuler
Ajaykumar Bommareddy	Singh
Gustavo Bonacci	Freeman
Alan Boruch	de Groat
Jun Chen	Wang
Lesley Colgan	Levitan
Gabor Csanyi	Pagano
Crissy Dudgeon	Zhang
Drew Dudgeon	Lazo
Martin Edreira	Altschuler
Loreto Egana	Pagano
Timothy Feinstein	Vilardaga
Jose Garrido	Romero
Karthik Giridhar	Wang
Jianxia Guo	Zhang
Shuguang Guo	Jiang
Eun-Ryeong Hahm	Singh
Marjet Heitzer	DeFranco
Daniel Hochbaum	Altschuler
Kyoungja Hong	Altschuler
Stacey Hrizo	Palladino
Shunqian Jin	Yalowich
Leonel Joannas	Altschuler
Heini Kansanen	Freeman
Nicholas Khoo	Freeman
Su Hyeong Kim	Singh
Florenta Kullmann	de Groat
Michael Lewen	Lazo

Name	Lab
Hua Li	Zhang
Dongzhu Ma	Jiang
Masanao Nakashima	Lazo
Karina Pena	Vilardaga
Ye Peng	Van Houten
Anna Powolny	Singh
Ilva Putzier	Levitan
Wei Qian	Van Houten
Tanja Rudolph	Freeman
Volker Rudolph	Freeman
Sonia Salvatore	Schopfer
Bing Shen	Roppolo
Karina Soares	Lazo
Silvia Stan	Singh
Pang-Ning Teng	Conrads
Robert Tomko, Jr.	Lazo
Ram Trivedi	Sobol
Jaya Vatsyayan	Singh
Hong Wang	Van Houten
Peng Wang	Zhang
Tao Wang	UPCI
Renaud Warin	Singh
Irene Wolf	DeFranco
Steven Woodcock	Freeman
Xiang Xu	Zhang
Gonghong Yan	Jiang
Hanqing Ye	Altschuler
Yongbei Yu	de Groat
Crystal Ann de la Torre Zellefrow	Lazo
Fang Zhang	Lazo
Xiulin Zhang	de Groat
Huafei Zou	Jiang

Faculty Data

Current Faculty

Primary Faculty

Name	Position
Daniel Altschuler	Associate Professor
Palaniappa Arjunan	Research Instructor
Paul Baker	Research Assistant Professor
Alessandro Bisello	Associate Professor
Alicia Celotto	Research Instructor
Eugenia Cifuentes-Pagano	Research Instructor
Marcie Cole	Research Instructor
Thomas Conrads	Associate Professor
W. Chet de Groat	Distinguished Professor
Donald Defranco	Professor
Julie Eiseman	Research Associate Professor
Melanie Flint	Research Instructor
Bruce Freeman	Professor and Chairman
Peter Friedman	Professor
William Furey	Professor
Ferruccio Galbiati	Associate Professor
Pamela Hershberger	Research Assistant Professor
Jing Hu	Assistant Professor
Yi Huang	Research Assistant Professor
Edwin Jackson	Professor
Yu Jiang	Associate Professor
Paul Johnston	Research Associate Professor
Thomas Kensler	Professor
Nicholas Khoo	Research Instructor
Edwina Kinchington	Research Instructor
Joan Lakoski	Professor
John Lazo	Professor
Edwin Levitan	Professor
Patrick Pagano	Professor
Michael Palladino	Associate Professor
Guillermo Romero	Associate Professor
James Roppolo	Research Assistant Professor
Francisco Schopfer	Research Assistant Professor
Adrian Sculptoreanu	Research Assistant Professor
Dinara Shakiryanova	Research Assistant Professor
Elizabeth Sharlow	Research Assistant Professor
Sruti Shiva	Assistant Professor
Jill Siegfried	Professor
Shivendra Singh	Professor
Robert Sobol, Jr.	Assistant Professor
Gyun Jee Song	Research Instructor
Harish Srinivas	Research Assistant Professor
Laura Stabile	Research Assistant Professor
Ben Van Houten	Professor
Jean-Pierre Vilardaga	Assistant Professor

Name	Position
Andreas Vogt	Research Assistant Professor
Daniela Volonte-Galbiati	Research Assistant Professor
Nobunao Wakabayashi	Research Assistant Professor
Bin Wang	Research Instructor
Qiming Wang	Associate Professor
Dong Xiao	Research Instructor
Jack Yalowich	Associate Professor
Lin Zhang	Associate Professor

Secondary Faculty

Name	Position	Primary Department
Susan Amara	Professor	Neurobiology
Christopher Bakkenist	Assistant Professor	Radiation Oncology
Aaron Barchowsky	Associate Professor	Env. Occup. Health
P. Michael Bauer	Assistant Professor	Surgery
Lori Birder	Associate Professor	Medicine
Robert Branch	Professor	Medicine
Clifton Callaway	Associate Professor	Emergency Medicine
Jun Chen	Professor	Neurology
Merrill Egorin	Professor	Medicine
John Fernstrom	Professor	Psychiatry
Gerald Gebhart	Professor	Anesthesiology
Jennifer Grandis	Professor	Otolaryngology
Gregg Homanics	Professor	Anesthesiology
Kaikobad Irani	Associate Professor	Medicine
Daniel Johnson	Associate Professor	Medicine
Valerian Kagan	Professor	Env. Occup. Health
Anthony Kanai	Associate Professor	Medicine
Thomas Kleyman	Professor	Medicine
Yong Lee	Professor	Surgery
Chester Mathis	Professor	Radiology
Deric Park	Assistant Professor	Neurological Surgery
Jerome Parness	Visiting Professor	Anesthesiology
James Perel	Professor Emeritus	Psychiatry
Ruth Perez	Assistant Professor	Neurology
Bruce Pitt	Professor	Env. Occup. Health
Richard Steinman	Associate Professor	Medicine
Changfeng Tai	Assistant Professor	Urology
Pei Tang	Professor	Anes. & Comp. Biol.
Margaret Tarpey	Professor	Anesthesiology
Gonzalo Torres	Assistant Professor	Neurobiology
Zhao Wang	Professor	Urology
Wen Xie	Associate Professor	Pharm. Sciences
Yan Xu	Professor	Anesthes. & CCM
Naoki Yoshimura	Professor	Urology

New Faculty

Tija Jacob, Ph.D., Assistant Professor
Thomas Kensler, Ph.D., Professor
Adrian Lee, Ph.D., Visiting Professor
Steffi Oesterreich, Ph.D., Visiting Professor
Patrick Pagano, Ph.D., Professor
Sruti Shiva, Ph.D., Assistant Professor

Membership in Professional Societies

Bruce Freeman, Ph.D.
Professor and Chair
American Association for the Advancement of Science
American Chemical Society
American Heart Association
American Physiological Society
American Society for Cell and Molecular Biology
American Thoracic Society
Biochemical Society
Society for Free Radical Biology and Medicine

Daniel Altschuler, Ph.D.
Associate Professor
The Endocrine Society

Palaniappa Arjunan, Ph.D.
Research Instructor
American Crystallographic Association
Pittsburgh Diffraction Society

Paul Baker, Ph.D.
Research Assistant Professor
American Diabetes Association
Society for Free Radical Biology and Medicine

Alessandro Bisello
Assistant Professor
American Society for Bone & Mineral Research
Endocrine Society

Alicia Celotto, Ph.D.
Research Instructor
Genetics Society of America
Society of Neuroscience
ASPET

M. Eugenia Cifuentes-Pagano, Ph.D.
Instructor
American Cancer Society

Marsha Cole, Ph.D.
Research Instructor
American Chemical Society
Society for Free Radical Biology and Medicine

Thomas Conrads, Ph.D.
Visiting Associate Professor
American Society for Mass Spectrometry
American Association for Cancer Research
Human Proteome Organization
American Society of Pharmacology and Experimental Therapeutics

Donald DeFranco, Ph.D.
Professor
American Association for the Advancement of Science (AAAS)
Endocrine Society
Society for Neuroscience

W. Chet de Groat, Ph.D.
Professor
Rho Chi Pharmaceutical Honor Society
Philadelphia Physiological Society
American Association for the Advancement of Science
Sigma Xi
American Society for Pharmacology and Experimental Therapeutics
Society for Neuroscience
Pittsburgh Neuroscience Society
New York Academy of Sciences
Urodynamics Society
International Brain Research Organization
American Gastroenterological Association
International Medical Society of Paraplegia
Society for Basic Urologic Research
Mid-Atlantic Pharmacology Society
American Motility Society
International Continence Society
The American Autonomic Society
The Dana Alliance for Brain Initiatives
International Society for Autonomic Neuroscience
International Spinal Cord Society

Julie Eiseman, Ph.D.
Research Associate Professor
American Association for Cancer Research
FASEB
American Association for the Advancement of Science
Society of Toxicology

Peter Friedman, Ph.D.
Professor
American Physiological Society
American Society for Biochemistry and Molecular Biology
American Society for Bone and Mineral Research
American Society of Nephrology
American Society of Pharmacology & Experimental Therapeutics
Biophysical Society
Endocrine Society
International Society of Nephrology
Salt & Water Club
Society of General Physiologists
British Society for Endocrinology
American Chemical Society

Melanie Flint, Ph.D.
Research Instructor
American Society for Mass Spectrometry
Society of Toxicology
Society of Toxicologists
American Association of Immunologists.

Peter Friedman, Ph.D.
Professor
American Physiological Society
American Society for Biochemistry and Molecular Biology
American Society for Bone and Mineral Research
American Society of Nephrology
American Society of Pharmacology & Experimental Therapeutics
Biophysical Society
Endocrine Society
International Society of Nephrology
Salt & Water Club
Society of General Physiologists
British Society for Endocrinology
American Chemical Society

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Professor
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Pittsburgh Diffraction Society
New York Academy of Sciences
American Association for the Advancement of Science

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Associate Professor
American Society of Pharmacology & Experimental Therapeutics
American Society of Cell Biology
American Physiological Society

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American Association for Cancer Research
National Lung Cancer Partnership

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American Heart Association
American Association for Cancer Research

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American Association for Cancer Research

Yu Jiang, Ph.D.
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American Society for Microbiology
American Society for Pharmacology and Experimental Therapeutics
American Society of Genetics

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Professor
American Heart Association
American Society for Pharmacology and Experimental Therapeutics
Council for High Blood Pressure Research

Yu Jiang, M.D., Ph.D.
Associate Professor
American Society for Microbiology
American Society for Pharmacology & Experimental Therapeutics
American Society of Genetics

Paul Johnston, Ph.D.
Research Associate Professor
Society for Biomolecular Sciences

Thomas Kensler, Ph.D.
Professor
American Association for the Advancement of Science
American Association for Cancer Research
Society of Toxicology
American Society for Pharmacology and Experimental Therapeutics
Oxygen Society
American Chemical Society: Division of Chemical Toxicology

Joan Lakoski, Ph.D.
Professor
American Association for the Advancement of Science
American Society for Pharmacology & Experimental Therapeutics
The Endocrine Society
International Society for Developmental Neuroscience

International Society of Neuroendocrinology
Serotonin Club
Sigma Xi
Society for Neuroscience
American Endocrine Society
Society for Executive Leadership in Medicine
National Postdoctoral Association
Association for Clinical Research Training

John Lazo, Ph.D.
Allegheny Foundation Professor
American Society for Pharmacology and Experimental Therapeutics
American Association for Cancer Research
American Chemical Society
American Society of Biochemistry and Molecular Biology
American Association for the Advancement of Science
New York Academy of Sciences
American Thoracic Society/American Lung Association

Edwin Levitan, Ph.D.
Professor
Society for Neuroscience
Biophysical Society
AHA basic science council
Society of General Physiologists

Patrick Pagano, Ph.D.
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American Physiological Society
American Association for the Advancement of Science
Society for Free Radical Biology and Medicine
International Society for Free Radical Research

Michael Palladino, Ph.D.
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Society for Neuroscience
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American Diabetes Association
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Neuroscience Society
American Physiological Society

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Society of Biomolecular Screening

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Nitric Oxide

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Society for Executive Leadership in Academic Medicine
National Lung Cancer Partnership

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Society of Toxicology
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American Association for Cancer Research

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American Association for Cancer Research
American Society for Microbiology
American Society for Cell Biology

Environmental Mutagen Society
American Cancer Society
International Society for Cell & Gene Therapy of Cancer

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American Heart Association
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American Society for Reproductive Medicine
American Society of Andrology

Laura Stabile, Ph.D.
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Association for Women in Science

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The Molecular Biology Society of Japan
The Japan Biochemical Society
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American Association for Cancer Research
American Association for the Advancement of Science

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American Association for Cancer Research
American Society for Pharmacology and Experimental Therapeutics

Lin Zhang, Ph.D.
Associate Professor
American Association for Cancer Research (AACR)
American Society of Human Genetics (ASHG)
American Association for the Advancement of Science (AAAS)

Three Year Bibliography

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Financial Plan

Executive Summary

I. Mission and Goals

The principal goal of the Department of Pharmacology and Chemical Biology is the creation of an intellectual and physical environment in which teaching and research in Pharmacology and Chemical Biology are pursued as one common enterprise. The major responsibilities of the Department are to: (1) educate medical students and physicians in the rationale for drug selection; (2) train contemporary pharmacologists; (3) develop new knowledge in the biomedical sciences; and (4) provide information about existing and emerging drugs to members of the University of Pittsburgh Medical Center, the University of Pittsburgh and the general community.

The philosophical approach of the Department is guided by the view that the field of Pharmacology exhibits a unique combination of characteristics that distinguish it from other basic medical sciences. Pharmacology encompasses a broad range of interests extending from the abstract domain of the physical chemistry of ligand-receptor interactions to the therapeutic use of drugs in patients. Thus, Pharmacology has stronger clinical ties than most other basic science disciplines. In the current revised medical curriculum, the faculty inculcates both core pharmacological principles and places them in the context of specific organ systems and bodily functions. Collectively, we provide a key educational experience to both medical and graduate students. Our faculty members also maintain vigorous research programs that are interactive and interdisciplinary. We have bridged with the Department of Chemistry in a unique and constructive manner through our activities in Drug Discovery.

The goals of the Department are:

- To be one of the top five NIH funded Departments of Pharmacology in the USA.
- To define pharmacological research for the 21st century.
- To improve the presence of Structural Pharmacology and Drug Discovery at the University of Pittsburgh.
- To educate premier future basic researchers, physician-scientists and teachers.
- To enhance the quality of graduate students matriculating and graduating from our PhD program at the University of Pittsburgh.

II. Departmental History and Status:

Major growth in the Department of Pharmacology and Chemical Biology occurred within the last 18 years after a new Chair was recruited and new funds were directed to the Department. As evidenced by the tremendous growth in research support funds, faculty publications, numbers of postdoctoral fellows and the number of members on the Graduate Faculty, we have evolved to become one of the top departments in the country based on our extramural research support and our impact on postdoctoral training. Last year we were ranked eighth in the nation for NIH funding among the more than 100 medical school departments and this year we were ranked seventh. Our Department now views its primary peer programs to be the following institutions: Yale University, University of Michigan, University of North Carolina, University of Pennsylvania, University of Virginia, Emory University, University of Texas Southwestern, University of Washington, Washington University, Vanderbilt University and the Johns Hopkins University.

III. Strengths:

In January 2006, Dr. Bruce A. Freeman was appointed Chair of the Department of Pharmacology and Chemical Biology to lead our strong cohort of well-funded and nationally recognized pharmacologists, cell and chemical biologists and geneticists. The department has about 50 primary faculty and 35 secondary faculty that contribute to the missions of the department. The members of the Department of Pharmacology and Chemical Biology are highly interactive with frequent co-authorship and co-funding. In spite of challenging times, our faculty members are well-funded, with departmental primary faculty currently receiving $7.4 million in total direct

annual costs and $10.3 million in total annual costs. During the past five years, the Department has emphasized cell signaling as an area of excellence. These interests address primary themes such as cancer, cardiovascular, renal and neurobiology. We are now extending this research focus to include two new areas of excellence: drug discovery and structural pharmacology. To supplement our training in these areas, the Department of Pharmacology has an NIH Predoctoral Training Grant in Pharmacological Sciences. The faculty also is well recognized for both their Medical School and Graduate School teaching. The prominence of our faculty members is recognized by their important leadership positions with Centers and Institutes, such as the UPCI, the PINDS, the Drug Discovery Institute, the School of Medicine and the University.

IV. Initiatives:

The Department will initiate a search for two or three new faculty members. The Department also intends to continue to replace aging equipment, renovate laboratory space and in this context, relocate faculty within thematic areas. We will also continue developing a strong interdisciplinary Drug Discovery Program, The Department will continue to partner with the emerging programs in Computational and Structural Biology as we emphasize Structural Pharmacology in faculty recruiting processes.

SWOT Analysis

Strengths

Since John S. Lazo assumed the Chair, the Department of Pharmacology and Chemical Biology has grown from three tenure-stream faculty to 42 faculty of which 22 are either tenured or in the tenure stream. This growth reflects department-initiated recruitment as well as "opportunistic" recruitments in collaboration with the UPCI that have benefited both the UPCI and the University. Thus, six of our current tenure stream faculty members are physically located within the UPCI as well as 9 nontenure stream faculty. One tenure stream faculty member is physically located in the Center for Clinical Pharmacology. Virtually all faculty are well-funded, with the Department currently receiving more than $6.9 million in total direct annual costs, approximately $2.0 million of which is co-credited to the UPCI or the Center for Clinical Pharmacology because the faculty members have appointments and space there. Our research success reflects strong independent investigator-initiated research support, a key factor for the development of future thematic research projects. We have already begun to define areas for interactive intra-institution research teams. During the past five years, the Department has emphasized cellular signaling and communication as an area of excellence. These interests are spread over three existing disease/organ areas: cancer, cardiovascular/renal and neurobiology. We are now intending to complement this research focus on cellular signaling with two new areas of excellence: drug discovery and structural pharmacology.

The members of the Department of Pharmacology and Chemical Biology have extensive interactions with other Basic Science Programs. In particular, strong collaborative relationships exist with School of Medicine faculty studying cellular communication and signaling, including faculty from the Departments of Cell Biology and Physiology, Molecular Genetics and Biochemistry, Pathology, Neurobiology, and Immunology. Topics of interest range from protein phosphorylation and dephosphorylation, cell cycle checkpoints, G proteins, receptor biology, cell death, pain, combinatorial chemistry, neurotransmitters, channels and redox signalling. Forceful relationships with clinical elements of the Medical Center also exist. These include strong collaborative projects with the Departments of Medicine, Surgery, Anesthesiology, Critical Care Medicine, Pediatrics, Neurology, Urology, Psychiatry and Pathology. The laboratories of members of the Department of Pharmacology house advanced fellows from several clinical units: Pulmonary Medicine, Medical Oncology, Surgery, Anesthesiology and Critical Care Medicine. Interactions also exist with the key Centers and Institutes within the Medical Center and Main Campus including the CNUP, UPCI and the Center for Clinical Pharmacology. These activities reflect the strong commitment of the Department of Pharmacology to engage in translational research and to provide a forum for integrative sciences. The Department considers its role in bridging the basic and clinical sciences of UPMC as a core element of its missions related to fundamental investigation and drug discovery.

Active programs reaching out to the Main Campus have also been instituted. Consequently, there are major collaborations between members of the Department of Pharmacology and the Department of Chemistry. Members of the Department also interact with investigators in the Departments of Environmental and Occupational Health, Biological Sciences and Neuroscience, as well as investigators at Carnegie Mellon University, particularly from the National Science Foundation Center for Fluorescence. Because of this multidisciplinary research activity, the Department took a leadership role in the submission of the multimillion dollar Pittsburgh Molecular Target Laboratory application, which is making Pittsburgh an epicenter for academic drug discovery.

The Department of Pharmacology and Chemical Biology was honored that it was selected to receive an NIH Predoctoral Training Grant in Pharmacological Sciences. This was the only new graduate Training Grant for Pharmaceutical Sciences to be awarded by the NIH in 1994. Moreover, our program was one of only a few recently initiated grants to be renewed for a second cycle. The acquisition of this training grant, which supports four students, was a primary goal of the Department for several years and we are proud to have obtained it.

In addition to their splendid research record, the faculty has displayed outstanding teaching records, both in the Medical School and Graduate School courses. We believe this is due primarily to placing special emphasis on quality teaching and limiting the student interactions of those teachers rated less effective by the students. Our faculty members have also assumed important leadership positions with Centers and Institutes, such as the UPCI, the School of Medicine and the University. To summarize, we have created:

- Strong research activities and NIH grant support
- Interactive faculty
- Interdisciplinary program with the Department of Chemistry
- NCI funded Program Project on Drug Discovery
- Funded NIH Predoctoral Training Grant in Pharmacological Sciences
- NCI funded Specialized Program of Research Excellence in Lung Cancer
- Focus on Cell Communication, Drug Discovery and Structural Pharmacology
- Outstanding teachers of medical and graduate students, e.g. Professor de Groat, who is a five-time winner of the School of Medicine “Golden Apple Award”.

Weaknesses

During the past five years tenured and non-tenured faculty left the Department. We expect that one of our prized lecturers, Professor de Groat, will select retirement within the next three years. Thus, the Department must continue to recruit new faculty to ensure quality teaching to medical school students and retain the critical mass required to be among the top five programs nationally. The curriculum for medical students is routinely being reviewed so that we can develop more blueprints for teaching pharmacology to medical students. We are encouraged by the medical students who realized the importance of strong pharmacological training not only for scoring highly on board examinations but also for treating patients. A basic introductory lecture series on classical pharmacology is currently deemed essential to the current organ system-based training of medical students.

The Department was criticized in the most recent review of its Training Grant that it had too few junior faculty members. To allow the Department to function effectively and to achieve critical mass, additional faculty will be needed.

Currently there are only two program project-type research grants (P01, P50) within the Department of Pharmacology and Chemical Biology; the national emphasis on specific disease areas lends itself to programmatic efforts and the Department should exploit this. The increased awareness of the productive aspects of linking contemporary chemistry with modern biology also should be an area in which Pharmacology plays a key role. Indeed, we organized a response to an NIH Request for Proposals on Molecular Targets Laboratory,

because of the close research links between these two programs. The Department has now focused on Cellular Signaling and Communication as a major theme. We also believe our interest in Drug Discovery and Structural Pharmacology is both timely and institutionally appropriate. In contrast to the Cellular Signaling and Communication, we have not yet reached critical mass in Drug Discovery and Structural Pharmacology. We plan to fortify these areas by recruiting new faculty members in a manner that would complement the academic mission of the University.

There are limited amounts of pharmaceutical research dollars awarded to the Department of Pharmacology and Chemical Biology. The Department has not placed enough emphasis on obtaining funding from pharmaceutical organizations but rather has paid more attention to Federal dollars. We are now placing more focus on the commercial sector to support research, but intellectual property issues and data sharing are still hurdles.

There continues to be a need for capital investment within the Department of Pharmacology and Chemical Biology to replace aging equipment and to advance our depth in new technological capabilities. The rapid advances in new technologies mandate that new investments be made for our faculty and trainees to maintain our national competitive standing. In summary, we need to:

- Maintain critical mass of faculty
- Grow and better integrate space and facilities for research
- Limited financial research support from pharmaceutical and biotechnology firms and budget cuts at the National Institutes of Health

Opportunities

During the past four years there has been a remarkable and unprecedented growth in drug discovery and development in the US. Both large pharmaceutical firms and biotechnology companies have invested heavily to exploit this new knowledge. Consequently, major new therapeutic advances directed against important disease groups are now emerging. The completion of the Human Genome Project has increased the number of potential therapeutic targets by more than one order of magnitude. The future challenge will be to identify the drugs that will interact with these emerging biochemical and molecular targets. Because of the unique attributes at the University of Pittsburgh that place Chemistry physically close to Biology, we posit:

- There is a unique opportunity for a few academic institutions to participate and profit from this changing paradigm in drug discovery. The Bayh-Dole Act now allows resourceful Universities the opportunity to replace the income lost from managed care with income derived from its intellectual property. A strong Department of Pharmacology is a vital component of such an activity.
- There will be a significantly increased industrial and academic need for well-trained graduates from Ph.D. granting programs with a concentration in Pharmacological Sciences and Drug Discovery. A strong Department of Pharmacology and Chemical Biology is a vital component of such an activity.
- Important new knowledge and reagents continue to emerge that are relevant to many biological systems and all aspects of cell communication. A strong Department of Pharmacology and Chemical Biology is a vital component of such an activity.
- Advances in Structural Biology and Bioinformatics should make it possible in the near future to optimize small molecules that are more selective and potent towards their molecular targets. The area of Structural Pharmacology will be grown to be a vital component of the Department of Pharmacology.
- Ph.D., D.M.D. and M.D. students will need to become even more cognizant and thoughtful about the highly selective therapies of the future that may be used based on the genetic profile of each patient. A strong Department of Pharmacology is a vital component of such an activity.

The University of Pittsburgh is uniquely situated to participate in defining future research and graduate education in Pharmacology and in recruiting to its campus some of the best students. The University of Pittsburgh's advantages are:

- A cohort of dedicated faculty members, who are eager to teach graduate students
- The presence of strong existing programs in neuroscience, virology, tumor immunology, cancer biology, developmental biology, structural biology and computational biology
- The presence of strong clinical programs
- A growing drug discovery enterprise

Barriers

One of the greatest threats to the Department of Pharmacology and Chemical Biology would be to lose its vigor and enthusiasm during the current downward trend in NIH funding. Currently the program is nationally identified as a model of growth. This has helped in the recruitment of new faculty. Nonetheless, other institutions have become eager to develop programs in drug discovery and to enhance their pharmacology departments. We believe it is likely that they will seek to recruit our valuable faculty.

Initiative and Implementation Strategies

- To achieve the overall goal of becoming one of the top three Departments of Pharmacology in the next three years, the Department will recruit new faculty members during the next few years. The Department of Pharmacology and Chemical Biology intends to focus on the three defined areas of research interest previously identified: Cellular Communication, Structural Pharmacology and Drug Discovery. In particular, the Department will continue to partner with the new Drug Discovery Institute, providing unique instrumentation, archived chemical libraries and specialized research services and teaching for members of the University and UPMC.

3. Financial Statement

University of Pittsburgh School of Medicine
Statement of Revenues and Expenses – June 30, 2009

	Hard Money	Self Supporting (a)	Discretionary and Restricted	Research	Total
Revenue					
School of Medicine - ECU	487,940				487,940
Indirect Cost Recovery	2,132,170				2,132,170
Direct Grants				5,867,658	5,867,658
Endowment Income			81,400		81,400
Other Revenue	-	17,125	111,883		129,008
Total Revenue	2,620,110	17,125	193,283	5,867,658	8,698,176
Expense					
Medical Faculty Salary	1,564,821	-	69,056	1,814,310	3,448,187
Other Faculty Salary	4,167	-	126,708	873,450	1,004,325
Staff Salary	733.660	12,334	301,615	784,976	1,099,659
Medical Faculty Fringes	397,465	-	17,540	413,800	828,805
Other Faculty Fringes	1,133	-	34,465	215,940	251,538
Staff Fringes	172,517	14	46,168	145,515	364,214
Subtotal Compensation	2,873,763	12,349	596,001	4,247,990	6,996,728
Other Expense	382,658	22,761	1,753,284	1,619,667	3,778,370
Transfers (intra-department)	(5,613)	(7,127)	(79,162)	-	(91,902)
Transfers (inter-department)	-	-	(1,512,875)	-	(1,512,875)
Subtotal Other Operating	377,045	15,634	(1,227,553)	1,619,667	2,173,593
Stepdown	2,548,032	7,127	24,281	0	2,579,440
Total Expense	5,065,914	35,109	(796,964)	5,867,658	11,749,761
Surplus/(Deficit)	(2,742,318)	(17,984)	(587,797)	0	(3,054,585)

June 30, 2008 Fund Balance	6,763,364
Restricted Net Activity Year to Date (from above)	(520,735)
Prior Year Settlement Transfer	5,215
Current Month end Restricted Fund Balance	6,247,844
SOM Quasi Endowment Market value – Dec 2008	1,517,408
Total Available Balances	7,765,252