Micrograph of mouse islets provided by G. Santulli

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Derek M. Huffman, Ph.D.       Rajat Singh, M.D.
Young-Hwan Jo, Ph.D.          Ji Ying Sze, Ph.D.  2019 – 2020
Welcome to Molecular Pharmacology. We study the mechanism of drug action as well as the hormonal and signaling systems that are the targets of most drugs. Molecular Pharmacology at Einstein has a strong emphasis on signal transduction and hormone action at the nuclear, cellular and organismic level; the biosynthesis and processing of hormones; the mechanism of drug action and the development of new therapeutics; and the disruption of normal physiology by toxicants.

Graduate training in Molecular Pharmacology exposes student to state of the art methodologies that cover a wide range of approaches, including genetic studies in worms and mice, genome-wide studies of chromatin and gene expression, advanced quantitative imaging, and biochemical studies on purified enzymes. Our research targets important diseases such as diabetes and obesity, cancer, behavioral disorders, learning and depression, as well as neurodevelopmental and neurodegenerative disorders. Studies with animal models and human-derived specimens insure that our research is at the forefront of translational science.

The Department has 22 primary and secondary faculty members as well as 27 graduate students and postdoctoral. The highly collaborative nature of investigators within the department, and the school as a whole, creates a broad-based and dynamic scientific environment. The Department sponsors a seminar series for visiting scientists from other institutions, as well as journal clubs and weekly work-in-progress research meetings. Monthly afternoon "happy hours" and annual departmental outings promote scientific and social interactions among the students, fellows and faculty.

Graduates of the Department of Molecular Pharmacology have earned postdoctoral positions in outstanding laboratories and received prestigious fellowships. Our graduates have permanent positions in academia, biotechnology / pharmaceutical companies and at the National Institutes of Health and the Food and Drug Administration. We are proud of the accomplishments of our graduates and welcome new students to join us in this exciting age of scientific advances.
# Molecular Pharmacology - Primary Faculty

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# Molecular Pharmacology - Administration

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DEPARTMENT OF MOLECULAR PHARMACOLOGY

Jonathan M. Backer, M.D. – Chair
The Backer Lab studies signaling by phosphoinositide 3-kinases, which regulate cell proliferation, motility, and transformation. Experimental approaches range from biochemical analysis to in vivo studies on metastasis in animals.

Michael Aschner, Ph.D.
The focus of our laboratory is on understanding (1) gene x environment interactions in triggering neurodevelopmental and neurodegenerative disorders, (2) metal uptake and distribution in the brain and their cellular and molecular mechanisms of neurotoxicity.

Michael D. Brenowitz, Ph.D.
Our laboratory seeks answers to questions related to the structure – function relationships that govern macromolecular function by combining quantitative analysis with innovative approaches.

C. Fred Brewer, Ph.D.
Our work is directed at understanding the molecular basis of lectin-glycan and glycan-glycan interactions in cellular homeostasis, pathogenesis and innate immunity.

Dongsheng Cai, M.D., Ph.D.
The interest of our laboratory is to investigate the roles of stress and immunity pathways in the brain for the development of metabolic diseases (obesity, diabetes, and related cardiovascular diseases) and aging-associated disorders.

Lloyd D. Fricker, Ph.D.
The major focus of research in my laboratory is peptides that function in inter- and intracellular signaling, and the peptidases that produce and degrade these peptides.

Matthew J. Gamble, Ph.D.
Through the lens of chromatin biology, we explore the mechanisms which regulate transcription and splicing, and their dysregulation in cancer, using a host of cellular, computational and -omics based approaches.

I. David Goldman, M.D.
Our laboratory studies the molecular pharmacology of antifolate chemotherapeutics; in particular, the mechanisms of their membrane transport and the role of transport in drug selectivity and tumor cell drug resistance.
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<tr>
<th>Name</th>
<th>Description</th>
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<tr>
<td><strong>Susan Band Horwitz, Ph.D.</strong></td>
<td>The focus of our laboratory is on 1) the development of new drugs derived from natural products, such as Taxol, for the treatment of malignancies and 2) the mechanisms by which tumors become resistant to drugs.</td>
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<tr>
<td><strong>Derek M. Huffman, Ph.D.</strong></td>
<td>The Huffman laboratory is focused on four areas: 1) The IGF-1 signaling pathway and aging, 2) Mechanisms of central insulin and IGF-1 signaling on peripheral metabolism, 3) Role of systemic factors on intestinal aging, and 4) The cancer-aging interface.</td>
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<tr>
<td><strong>Young-Hwan Jo, Ph.D.</strong></td>
<td>The focus of our laboratory is to examine the roles of the central melanocortin system in the regulation of energy metabolism and glucose homeostasis.</td>
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<tr>
<td><strong>Sridhar Mani, M.D.</strong></td>
<td>Our laboratory focuses on the study of host-microbiome relationships as it relates to human and veterinary health and disease (inflammation, metabolism, and cancer).</td>
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<tr>
<td><strong>Hayley M. McDaid, Ph.D.</strong></td>
<td>We focus on therapeutics directed at breast, lung and ovarian cancers and defining mechanisms of resistance, in particular those related to tumor cell senescence.</td>
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<tr>
<td><strong>Jeffrey E. Pessin, Ph.D.</strong></td>
<td>Our laboratory examines the molecular, cellular and integrative systems physiology of metabolism and energy expenditure focusing on the insulin signal transduction pathways regulating glucose uptake and lipogenesis.</td>
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<tr>
<td><strong>Charles S. Rubin, Ph.D.</strong></td>
<td>We study protein kinase D, a lipid-activated signaling protein that regulates functions of neurons and intestinal cells. Our work addresses molecular and cellular mechanisms underlying learning and innate immunity.</td>
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<tr>
<td><strong>Gaetano Santulli, M.D., Ph.D.</strong></td>
<td>In our laboratory, we study the mechanistic role of intracellular calcium and microRNAs in the patho-physiology of cardiovascular and metabolic disorders, including heart failure, hypertension, and diabetes mellitus. The experimental approaches range from molecular to <em>in vivo</em> studies.</td>
</tr>
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**Rajat Singh, M.D.** The focus of our laboratory is to examine the organ-specific roles of autophagy in the regulation of energy homeostasis, and the mechanisms of reduction in autophagy that lead to the metabolic syndrome of aging.

**Kosaku Shinoda, Ph.D.** My lab is focused on the biology of adipocytes. Understanding the basic biology of adipocytes is fundamental to the treatment and prevention of type 2 diabetes and obesity. We use cutting-edge high-throughput techniques and bioinformatics to map cellular lineage and the genetic program of adipocytes in disease states and under normal physiological conditions.

**Edward L. Schwartz, PhD.** Our lab focuses on the identification of new targets and novel drugs to treat lung cancer, particularly tumors have inactivating mutations in the RB1 tumor suppressor gene. This includes determining the critical signaling pathways that are downstream of RB1, and designing pharmacologic agents that, by inhibiting those pathway(s), would restore the function of RB1 and cause tumor regressions.

**Ji Ying Sze, Ph.D.** The research in our laboratory investigates the genetic basis of the regulation of synaptic transmission of the neurotransmitter serotonin, using *C. elegans* and mouse as animal models.
Research in our laboratory focuses on the interaction between genetics and the environment in triggering disease both during central nervous system (CNS) development and senescence. We are addressing metal uptake across the blood-brain barrier (BBB) and distribution in the brain (neurons and glia), specifically with methylmercury (MeHg) and manganese (Mn), as well as their cellular and molecular mechanisms of neurotoxicity. Our studies address mechanisms of transport and neurodegeneration in various experimental models (C. elegans, tissue cultures and rodents), as well as follow-up on the sequelae of heavy metal deposition in the brains of human neonates by means of magnetic resonance imaging (MRI).

Hypotheses presently tested include the following: (1) Modulation of C. elegans genes (aat, skn-1, daf-16) that are homologous to mammalian regulators of MeHg uptake and cellular resistance will modify dopaminergic neurodegeneration in response to MeHg exposure. (2) Under conditions of MeHg-induced oxidative stress, Nrf2 (a master regulator of antioxidant responses) coordinates the upregulation of cytoprotective genes that combat MeHg-induced oxidative injury, and that genetic and biochemical changes that negatively impact upon Nrf2 function increase MeHg’s neurotoxicity. (3) PARK2, a strong PD genetic risk factor, alters neuronal vulnerability to modifiers of cellular Mn status, particularly at the level of mitochondrial dysfunction and oxidative stress.

Our studies are ultimately designed to (1) shed novel mechanistic insight into metal-induced neurodegeneration; (2) provide novel targets for genetic or pharmacologic modulation of neurodegenerative disorders; (3) increase knowledge of the pathway involved in oxidative stress, a common etiologic factor in neurodegenerative disorders; (4) develop improved research models for human disease using knowledge of environmental sciences.

**Representative Publications**


Phosphoinositide 3-kinases are lipid kinases that mediate signaling by receptor tyrosine kinases and G-protein coupled receptors (GPCRs). They are important regulators of cellular proliferation, motility, apoptosis, and vesicular trafficking. Mutational activation of PI 3-kinases is commonly found in human cancers. We are interested in how the altered regulation of PI 3-kinase contributes to human cancer. The Backer lab works collaboratively with the lab of Dr. Anne Bresnick, Dept. of Biochemistry, on all of these projects.

1. GPCR-regulated PI 3-kinases in human cancer. The Class IA PI 3-kinase is a heterodimer composed of a catalytic subunit (p110) and a regulatory subunit (p85). Class IA PI 3-kinases are activated when p85 binds to phosphotyrosine residues in receptor tyrosine kinases and their substrates. The PI3Kβ isoform of PI 3-kinase is unique in that it also directly binds to and is activated by Gβγ subunits downstream of activated GPCRs. We have recently identified point mutants that specifically disrupt PI3Kβ binding to Gβγ, and have shown that these mutants block tumor cell invasion in cell culture and animal models of breast cancer metastasis. Our current work focusses on the mechanisms by which PI3Kβ regulates breast cancer invasion.

2. PI 3-kinase regulation by Rab GTPases. The PI3Kβ isoform of PI 3-kinase is also unique in that it specifically binds to the small GTPase Rab5, which regulates vesicular trafficking in the early endosome. We have mapped the Rab5 binding site in PI3Kβ and produced mutants that are specifically defective for Rab5 binding. Cells expressing these mutants show a defect in some endocytic processes, as well as a disruption of autophagy in nutrient-starved cells. We are using knockdown/rescue methods in breast cancer cells, as well as mouse knock-in models, to define the mechanisms by which Rab5-PI3Kβ binding regulates vesicular trafficking and responses to nutrient stress.

3. PI 3-kinase - myosin signaling in macrophages. We are studying the regulation of macrophage motility and invasion. Mutation of PI3Kβ inhibits the ability of macrophages to degrade extracellular matrix and cross endothelial layers. Interestingly, the phenotype of the mutant PI3Kβ macrophages is similar to that caused by disruption of the myosin regulatory protein S100A4, and inhibitors of myosin activity rescue invasion in mutant PI3Kβ macrophages. These data point to an novel interaction between PI3Kβ and the myosin-based contractile apparatus. Using primary bone marrow-derived macrophages from mice expressing PI3Kβ mutants, as well as macrophage cell lines, we are studying the links between PI3K and myosin signaling.

Representative Publications


Biology is a dynamic process. Among the myriad array of reversible association reactions that constitute life, small molecules bind to proteins, proteins self-associate and bind to other proteins and nucleic acids and nucleic acids fold and bind to each other in elaborate processing, signaling and regulatory cascades. What is common to these processes is the physical chemistry that underlies these interactions. For example, electrostatic interactions mediate both the binding of proteins to DNA and the folding of RNA. Proteins that mimic the electrostatic character of DNA may competitively regulate DNA binding by other proteins. Our laboratory seeks answers to questions related to the structure – function relationships that govern macromolecular function by combining quantitative analysis with innovative approaches.

- The longest running programmatic theme of our laboratory is the study of the mechanisms by which proteins recognize and bind specific sequences of DNA. We have turned our attention to proteins involved in epigenetic regulation exploring the biophysics of an epigenetic regulatory methyl-CpG binding protein MeCP2 whose disruption is a cause of the neurological disorder Rett Syndrome.

- Our interest in RNA structure and folding has led us to explore the packaging and delivery of RNA therapeutics. We are using a biophysical method that quantitates the size and density of RNA delivery vehicles in support of their use as novel therapeutics.

- We have developed and utilize a high-throughput method to map protein-protein interactions using amino acid side chain oxidation by the hydroxyl radical to measure solvent accessibility as a tool for mapping the molecular interfaces of regulatory complexes and protein therapeutics.

**Representative Publications**


*Protein Footprinting by Pyrite Shrink-Wrap Laminate, Lab on a Chip* 15(7), 1646 – 50

Cell surface carbohydrates have been demonstrated to be involved in a variety of biological recognition phenomena including cellular recognition and adhesion, regulation of inflammation, control of cell growth and metastasis. Although the structures of many of these carbohydrates have been elucidated, relatively little is known about their molecular recognition properties other than their interactions with glycosylases and lectins. Lectins are carbohydrate-binding proteins that are widely found in nature including plants, animals and pathogenic organisms. Lectins and the cell surface glycans of glycoproteins and glycolipids play important roles in cellular homeostasis and innate and adaptive immunity. Our research includes characterizing the biophysical and biochemical properties of lectins and their interactions with multivalent cellular glycans. We are also investigating the self-binding properties of carbohydrate tumor antigens and have presented evidence for their involvement in oncogenesis. Techniques used to explore these interactions include isothermal titration microcalorimetry, x-ray crystallography, atomic force microscopy and optical tweezers.

Representative Publications


Haugstad, K. E., Hadjialirezaei, S., Stokke, B. T., Brewer, C. F., Gerken, T. A., Burchell, J., Picco, G. and Sletmoen, M., Interactions of mucins including MUC1 that possess the Tn or sialyl Tn cancer antigens are due to GalNAc – GalNAc interactions. Glycobiology 26; 1338 (2016).


Obesity and diabetes represent two important epidemic and public health problems facing the nation which also facilitate aging related disorders. The research in our laboratory is to study how inflammatory pathways mediate the central nervous system dysregulation of systemic physiology to cause obesity- and aging-related disorders such as diabetes, hypertension and neurodegenerative diseases. To address these questions, (1) we aim to study metabolic challenge-induced inflammation in the brain, the connections with glial, neural and neuroendocrine pathways, and the molecular bases for obesity, diabetes and aging-related diseases. (2) We aim to analyze the neural mechanisms of aging and lifespan at both cellular and organism levels and how they are altered under inflammatory environment. (3) We aim to identify the intrinsic molecular systems that counteract metabolic inflammation and to explore why and how these systems are weakened under nutritional oversupply or aging. (4) We aim to translate the mechanistic understandings into developing interventional strategies for preventing neural dysregulation of physiology in order to control the spread of these diseases.

Representative Publications


Purkayastha, S., Zhang, G., Cai, D. Uncoupling the mechanisms of obesity and hypertension by targeting hypothalamic IKKβ and NF-κB. Nat. Med., 17 (7): 883-7, (2011). (Highlighted by Nature Medicine commentary, Cell Metabolism preview; editorial choice of Science Signaling; highlighted as a top-10 article by Faculty 1000)


Peptides play many important physiological roles in most organisms. Neuropeptides and peptide hormones function in cell-cell signaling and are involved with a wide variety of biological functions including feeding and body weight regulation, fear, anxiety, pain, circadian rhythms, memory, reward mechanisms, and many others. We have discovered a number of novel peptides using mass spectrometry-based peptidomic techniques. Some of these are neuropeptides that function in cell-cell signaling that control feeding/body weight. Other novel peptides found in the peptidomic analyses are produced from cytosolic proteins, and some of these peptides are secreted and bind to extracellular receptors; these are termed “non-classical” neuropeptides, a novel class of cell-cell signaling molecule.

In addition to peptides, we are also interested in enzymes that modify peptides/proteins. Our laboratory has discovered a dozen different carboxypeptidases and we are currently working towards determining their functions. One carboxypeptidase, which we named carboxypeptidase E (CPE), is responsible for the biosynthesis of most peptide hormones (such as insulin) and neuropeptides (such as enkephalin). We identified a mouse mutation (originally named fat) that does not produce active CPE due to a point mutation; these mice are obese, sterile, hyperglycemic, and have neurological impairments. Recently, we have developed a conditional knock-out mouse that allows for the elimination of CPE activity in specific cell types. We are currently using this mouse line to determine which cells are involved in abnormal physiology and behaviors of the global Cpe KO mice (e.g. obesity, depression, anxiety). In addition, we are using peptidomic approaches to identify the peptides in these cell types.

Representative Publications


MacroH2As, histone variants with diverse roles in gene expression and DNA damage responses – The macroH2A-type histone variants (which include macroH2A1.1, macroH2A1.2 and macroH2A2) have roles in tumor suppression, cellular senescence, activation and repression of transcription, promotion of DNA repair and suppression of the reprogramming of differentiated cells into stem cells. MacroH2As are typified by a histone H2A-like region fused by a flexible linker to a C-terminal macrodomain, a ligand-binding domains whose functions is modulated by binding to poly(ADP-ribose) produced by a family of poly(ADP-ribose) polymerases. MacroH2A1 regulates the expression of genes found within its large chromatin domains which can span hundreds of kilobases. Through changes in its expression and/or alterations in its genomic localization, disruption of macroH2A1’s tumor suppressive functions are common in cancer; alterations of macroH2A transcription and splicing occur in a variety of cancers including those of lung, breast, colon, ovaries, endometrium, bladder, testicles, and melanocytes. Consistently, macroH2A1 loss in primary cells is sufficient to trigger an oncogenic gene expression profile. We are interested in many aspects of macroH2A biology. 1) How are macroH2As targeted to specific regions of the genome? 2) How does macroH2A1.1 in collaboration with PARPs regulate gene expression? 3) How does macroH2A1 regulate chromatin accessibility at enhancers? 4) How does macroH2A participate in DNA repair? 5) What regulates macroH2A1’s alternative splicing?

Chromatin dynamics during oncogene-induced senescence and cancer – Oncogene-induced senescence (OIS) is an important tumor suppressive mechanism whereby a cell harboring an oncogenic mutation enters a stable proliferative arrest. At the same time the senescent cell secretes a host of inflammatory cytokines, chemokines and metalloprotease called the senescence-associated secretory phenotype (SASP), which serves to recruit immune cells to clear the senescent cells from tissues. The histone variant macroH2A1 plays a critical role in the transcriptional regulation of SASP genes during senescence. We are currently studying the mechanism by which macroH2A regulates the SASP response. We hypothesize that changes in macroH2A1 expression, seen in many cancers, allows these cells to bypass senescence and proceed on the pathway towards transformation.

Interplay between transcriptional elongation rates and alternative splicing – Alternative splicing is a crucial aspect of gene expression, allowing a gene to yield functionally distinct products, the abundance of which are regulated by cellular cues. Splicing dysregulation is central to several cancers and developmental diseases. Alternative splicing can be regulated through the recruitment of splicing factors which promote or repress distinct splicing events. Splicing largely occurs co-transcriptionally, and so, splicing outcomes are also affected by aspects of the transcription process and chromatin environment. The local elongation rate of RNA polymerase II is one aspect of transcription with important consequences on splicing outcomes. A barrier to progress in the field has been the lack of a high-throughput assay to measure splicing rates in mammalian cells. To address this, we have developed SKaTER-seq (Splicing Kinetics and Transcript Elongation Rates through sequencing). With this assay, we are exploring a myriad of factors that regulate splicing, including elongation rate, gene architecture, binding sites for RNA binding factors, chromatin structure and histone modifications. With this powerful approach we will determine the underlying causes of splicing alterations in disease.

Representative Publications


This laboratory has had a long-standing interest in membrane transport processes and their role in the delivery of essential physiological substrates and cancer chemotherapeutics into cells. The current focus is on the proton-coupled folate transporter (PCFT- SLC46A1), recently cloned in this laboratory and required for the intestinal absorption of folates and antifolates and their transport across the choroid plexus into the cerebrospinal fluid. PCFT is also widely expressed in cancer cells and plays an important role in the delivery and anti-cancer activity of new-generation antifolates with a high affinity for this transporter. This laboratory established that mutations in this gene that result in loss-of-function of the PCFT protein are the molecular basis for the autosomal recessive disorder, hereditary folate malabsorption. Current emphasis is on the characterization of PCFT structure/function. This encompasses the identification of residues and domains required for the maintenance of tertiary structure, that make up the external and internal gates of the protein, that line the aqueous translocation pathway, that bind folates, that are involved in proton-coupling and proton-binding, and that determine the rate of oscillation of the carrier between its conformational states. A three-dimensional homology model of PCFT has been developed, simulating the inward- and outward- open conformations of the carrier that is correlated with functional studies. As families are identified world-wide with hereditary folate malabsorption, the functional consequences of causative PCFT mutations are studied along with their relationship to the clinical phenotype. Trainees emerge from this laboratory with a broad understanding of membrane transport physiology, structure- function, and energetics along with the cellular, biochemical and molecular pharmacology of cancer chemotherapeutics with a focus on antifolates.

**Representative Publications**


The research program in this laboratory is focused on: 1) the development of drugs derived from natural products, such as Taxol® and 2) the problem of drug resistance. The mechanism of action of Taxol®, a molecule that enhances the polymerization of tubulin by forming stable microtubules, is being pursued. The novel structure of Taxol®, its unique mechanism of action that was first described in this laboratory, and the positive results that have been observed in ovarian, breast and lung carcinomas have generated extensive interest in this drug. Our laboratory has used photoaffinity analogues of Taxol® to define the binding cavity for the drug within β-tubulin. The goal is to understand at a molecular level the interaction of Taxol® with the microtubule and the mechanisms by which the drug induces growth arrest and cell death in human tumors. Evidence indicates that Taxol® alters specific intracellular signal transduction events essential for drug-induced apoptosis.

Newly discovered potentially important antitumor drugs, such as the epothilones and discodermolide that are currently in clinical trials and whose mechanism of action is similar to that of Taxol®, are being actively investigated. We have searched for differences between these agents that could be exploited in the clinic and have reported that discodermolide is the first microtubule stabilizing agent that includes a powerful induction of accelerated senescence in its repertoire of tumor cell growth inhibitory mechanisms. Quantitative mass spectrometric-based methods to analyze the expression of tubulin isotypes and their posttranslational modifications are being developed. This is crucially important since there is accumulating evidence in human cancer cell lines, tissues and tumors that different isotypes exhibit differential sensitivity to Taxol® and are related to Taxol® resistance. A recent study from our laboratory indicated that compared with other β-tubulin isotypes, βIII-tubulin binds the least amount of Taxol®. Of particular interest is the fact that in several cancers, overexpression of βIII-tubulin is associated with drug resistance. Our laboratory noted that one region of βIII-tubulin contains a unique residue compared with other isotypes. Molecular dynamic simulations indicated that the frequency of Taxol® accommodating conformations decreased in the βIII-tubulin isotype compared with other tubulin isotypes.

This laboratory is committed to using the knowledge gained in research for the development of therapies for the treatment of human cancer.

**Representative Publications**


1) IGF-1 signaling and aging – Mutations that lead to a reduction in IGF-1 signaling are linked to improved lifespan. Pharmaceuticals designed to block IGF-1Rs have already been developed and safely tested in human trials as a cancer therapy, but until now, no study testing the ability of such drugs to delay aging has been performed. Recently, my laboratory led a major study to test whether a drug known as a monoclonal antibody (mAb) designed to block IGF-1Rs, could be repurposed to slow aging. In a study published in *Nature Communications* this year, we report that targeting the IGF-1 pathway with this drug improves health and extends lifespan in female mice, even though it was given relatively later in life. Future goals of the lab are to determine whether this drug can be used to target human aging, as well as the mechanism(s) mediating the well-known sex dimorphism observed in this axis.

2) Role of systemic factors on intestinal aging – Intestinal stem cells and their niche have been well characterized and are responsible for maintaining the integrity of the intestinal epithelium, but we have found that intestinal stem cell function deteriorates with aging, and may perpetuate the overall decline in intestinal and whole organismal aging. Remarkably, utilizing *heterochronic parabiosis*, we have determined that intestinal stem cell homeostasis are markedly impaired in young mice exposed to old blood, suggesting that intestinal aging is modulated by circulating factors in the old systemic milieu. We are currently pursuing studies to identify the systemic factor(s) responsible for driving features of intestinal decline with aging.

3) Studies at the cancer-aging interface – A related area of investigation is the role of aging on cancer risk. Aging is the major underlying risk factor for most cancers, yet tremendous gaps remain in our understanding of why cancer incidence markedly increases with age, in part because pre-clinical cancer studies are almost exclusively conducted in young models. Indeed, prevention strategies proven successful in young animals often prove less effective in older humans. Thus, we are evaluating the efficacy of various dietary and pharmacologic strategies to prevent stem-cell derived intestinal tumorigenesis and improve survival in young versus aged mouse models.

4) Physiologic resilience and aging – Resilience is the ability in which an organism can respond to a physical challenge or stress and return to homeostasis. The gradual loss of resilience with age contributes to, and may underlie the onset of aging-related conditions, including chronic disease, multimorbidity, frailty and death. However, there are no validated measures or methods to evaluate physiologic resilience in mammals. For this reason, we are developing a battery of simple, short-term assays to characterize resilience in rodents and determining if these tests can be prognostic of long-term aging outcomes in mice.

**Representative Publications**


The overall goal of my research project is to define the role of the central melanocortin system in energy metabolism. Proopiomelanocortin (POMC) neurons in the arcuate nucleus of the hypothalamus (ARC) play a major role in regulating energy intake, energy expenditure, and glucose metabolism. We have demonstrated molecular and neurochemical heterogeneity of POMC neurons in the ARC. We have also demonstrated that distinct subpopulations of POMC neurons directly and indirectly interact in a manner that is critical to the net outcome of the melanocortin signaling and hence determine overall energy balance. In addition to this neurochemical heterogeneity, neuroanatomical studies have revealed that distinct sets of POMC neurons project to different target sites. This neurochemical and neuroanatomical heterogeneity of ARC POMC neurons, combined with their broad functional repertoire, strongly support the idea that there is functional heterogeneity of ARC POMC neurons. We examine whether neurochemically and neuroanatomically distinct subpopulations of POMC neurons have distinct target organs and functions.

In addition, we investigate the role of intracellular glycolysis in nonshivering thermogenesis. Interscapular brown adipose tissue (BAT) is the principal site of nonshivering thermogenesis, resulting from the uncoupling of mitochondrial oxidative respiration from ATP production to generate heat. This uncoupling protein 1 (UCP1)-dependent thermogenesis is fueled mainly by fatty acids from intracellular triglycerides. We have shown that glucose uptake and glycolysis play a role in BAT thermogenesis as well. We thus examine whether glucose metabolism in BAT has an impact on overall energy balance.

My laboratory uses multiple cutting-edge techniques such as conditional viral tracing, optogenetics, pharmacogenetics, in vivo calcium imaging, in vivo fiber photometry, CRISPR/Cas-9 gene-knockdown, and electrophysiology.

**Representative publications:**


Pregnane X Receptor (PXR) [a.k.a the Steroid and Xenobiotic Receptor (SXR)] is a master nuclear receptor regulator of host xenobiotic/endobiotic metabolism, detoxification and inflammation. More recently, we have shown that the receptor plays a major role in relaying host microbial signals in the intestines with innate immunity. Specifically, we have shown that microbial metabolites of L-tryptophan, indoles and indole propionates, activate PXR in intestinal epithelial cells to promote intestinal immune homeostasis via a TLR4 specific pathway *. This discovery has led our laboratory into new directions primary focused on molecular mechanisms governing host-microbial and microbial-microbial relationships in the intestines (similar approaches could be used elsewhere or for other physiologic-pathophysiologic conditions).

1. **Discovery of endobiotic PXR ligands and use of microbial metabolite mimicry to design drugs combating intestinal inflammation and cancer.** Here we are investigating how different microbial metabolites bind and activate and/or antagonize PXR function in the intestines with the hopes of establishing a physiologic role for microbial metabolites in mammals. In parallel, we have embarked on chemical biological approaches to discovery of indole propionate analogs as potent PXR ligand agonists, with the eventual hope of designing small molecule drugs combating intestinal inflammation and inflammation-induced cancer. We have also found that PXR has an opposite role in non-inflammation associated colon cancer, and have a longstanding initiative in the lab to develop allosteric PXR antagonists for this condition.

2. **Molecular mechanisms governing role of PXR in innate immunity.** Here we are interested in deciphering the molecular basis for PXR’s effects on innate immunity and inflammation, with a specific emphasis on the inverse relationship between PXR and TLR4 in intestinal epithelial cells. We are using varied approaches to decipher the effect of PXR on TLR4 mRNA and protein expression. Other PXR-related innate immune targets are also being investigated using broader high throughput approaches (e.g., RNAseq).

3. **Discovery of new (novel) microbes and mechanisms governing its regulation of innate immunity.** Here we are interested in deciphering molecular mechanisms of indole metabolites as well as small molecule indole mimics as they interact with the host microbiome (e.g., biofilms, drug resistance etc.) in conditions of homeostasis and intestinal stress. These types of investigations have led to the identification of a novel bacterial strain with a unique community phenotype that alters intestinal inflammation. We have diverted our interests to the study of how and why these novel bacterial strains arise during inflammation. Finally, our goal is to derive probiotic approaches, harnessing our internal microbiome, for the treatment of a variety of health conditions. These projects have led to multidisciplinary approaches of designing probiotic drug delivery systems using physics of bacterial spreading, molecular microbiology and host biology.

**Representative Publications**


Our research is broadly concerned with investigating molecular mechanisms of action and resistance to standard and novel therapeutics; specifically focused on accurately defining the fate of cells within a tumor population following therapy, especially fates that confer drug-tolerance. Drug-tolerant tumor cells often manifest as dormant phenotypes that evade cell death and are a source for re-population of a primary tumor mass and development of metastatic disease that eventually culminates in mortality.

Senescence is a form of growth arrest that can result from anti-cancer therapy. Senescence is largely perceived to be a permanent state in ‘normal’ cells; however recent data now indicate that in the context of cancer, senescence is transient. Persistent senescent tumor cells within the tumor microenvironment are detrimental due to pro-inflammatory secretions that promote migration and disease progression. Moreover, senescent cells often revert to a proliferative state and retain this pro-inflammatory signaling milieu that drives chemoresistance. Certain anti-cancer drugs with reactive moieties can preferentially induce senescence not only in tumor cells, but also in organs such as the heart and lung, resulting in unacceptable toxicity that can be fatal. These often irreversible toxicities also prevent patients with progressive cancer from receiving subsequent therapy.

The study of dormant phenotypes in cancer biology is challenging; however to truly evolve anti-cancer therapeutics to improve long-term survival and quality of life for patients, we need to adopt a more rigorous pre-clinical evaluation program. One important aspect of this research is the design and selection of novel anti-cancer drugs that have potent tumor cell death-inducing capabilities in both asynchronous and dormant-type cells, including senescent and tumor-initiating cancer cells. Coupled with that, new therapeutics must be efficacious in limiting the development of senescence in non-tumor tissue to lessen the risk of therapy-induced toxicity.

Areas of current research focus include:

1. Therapy-mediated senescence in cancer as a cause of intrinsic and acquired resistance associated with residual disease, and/or progressive disease leading to metastasis.
2. Biomarker development to accurately detect senescent cells from solid or liquid biopsies both at diagnosis, and during the course of therapy.
3. Drug-discovery:
   (i) In collaboration with Drs. Susan Horwitz and Amos B. Smith - design, synthesis and testing of novel chemotherapeutics, screening primarily for high tumor cell kill and low senescence induction, and
   (ii) Testing existing and novel drugs for the ability to kill senescent tumor cells, or inhibit the inflammatory secretions of senescent cells.

**Representative Publications**


One major project in our laboratory is to understand the basis for the dysregulation of glucose and lipid metabolisms in the liver. It is well established that in insulin resistant states the regulation of gluconeogenesis is altered such that hepatic glucose production is enhanced in the fasted state with reduced suppression in the fed state. In parallel, hepatic de novo lipogenesis is elevated in fasted state and further increased in the fed state. Numerous studies have examined the regulation of DNA binding transcription factors, transcription factor co-activators and co-repressors in the control of liver lipogenic gene expression. Despite the intensive investigation of these trans-factors, none of these proteins directly interacts with DNA-dependent RNA polymerase II. One critical complex termed the Mediator connects multiple trans-factors to the DNA-dependent RNA polymerase II. In mammals Mediator is composed of at least 30 individual subunits that are assembled from four sub-complexes, head, middle, tail and kinase sub-modules. In yeast, it was originally suggested that the Mediator is a constitutive component of the expression machinery. However, we recently demonstrated that the CDK8/CycC complex a component of the kinase sub-module (CDK8/CycC, Med12 and Med13) undergoes dynamic regulation by insulin and nutritional states. We are currently studying the molecular pathways and functional consequences of the Mediator structural reorganization in both rodent models and in human liver biopsy specimens. In parallel, to these efforts we are also performing comprehensive time-dependent nutritional, developmental/age, circadian cycle, and sex dependent changes in genome-wide chromosomal (Hi-C, Histone/Mediator ChIP-seq, ATAC-seq, DNA methylation) and expression (PRO-seq, RNA-seq) from normal C57BL/6/J mouse livers.

A second major project is based upon our observations that deficiency of a specific SNARE protein responsible for intracellular membrane trafficking (SNAP23) functions to control macroautophagy and cell death in adipocytes. For example, adipocyte-specific SNAP23 knockout mice display a temporal development of severe general lipodystrophy associated with adipose tissue inflammation, insulin resistance, hyperglycemia, liver steatosis and early death. We have found that this loss of adipocytes results from an adipocyte specific apoptosis process resulting from increased levels of the pro-apoptotic protein Bax due to impaired lysosome-mediated degradation. Moreover, SNAP23 deficiency altered the trafficking of ATG9 and knockdown of ATG9 phenocopied the same increase and activation of Bax protein and apoptotic cell death. These events were specific for Bax, as the induction of apoptotic cell death was blocked by BAX knockdown in the context of either SNAP23 or ATG9 deficiency. We are now examining the SNAP23/ATG9 selective versus canonical macroautophagy pathway responsible for Bax activation by using the BAX activation specific antibody 6A7 in combination with shRNA knockdown and/or sgRNA knockout to identify other autophagy family members and SNARE proteins mediating BAX degradation/activation and apoptotic cell death.

Representative Publications


Protein kinase D (PKD) is a protein kinase C (PKC) substrate and effector in diacylglycerol (DAG)-regulated signaling cascades. PKDs are activated by Gq-coupled hormone receptors in cultured cells. However, little is known about physiological functions, upstream regulators and downstream effectors of PKDs in normal differentiated cells in vivo.

We are addressing central problems in DAG signaling by studying C. elegans PKDs named DKF-2A and DKF-2B, which are differentially expressed in intestinal cells and neurons. Strains of DKF-2 deficient (null) C. elegans and transgenic (TG) animals expressing wild type (WT) and mutant DKF-2A or 2B proteins (null background) were created. The hypotheses that (a) C1a and C1b domains are essential for DAG-binding, translocation and activation of DKF-2A/2B in vivo and (b) two P-serines (phosphorylated by PKCs) in the activation loop (A-loop) differentially regulate catalytic activity and degradation of PKDs are being tested. Studies employing fluorescence microscopy and IgGs that bind A-loop P-serines will elucidate relationships among DKF-2A/2B activation, translocation and stability in individual cells in vivo.

Phenotypes of DKF-2 deficient and TG C. elegans are characterized to discover physiological functions of PKDs. Microarray and qRT-PCR analyses indicate that DKF-2A controls expression of ~85 proteins that protect intestinal cells against pathogenic bacteria (inducible innate immunity). Neuronal DKF-2B mediates salt-induced chemotaxis and learning. Measurements of DKF-2 regulated mRNAs and proteins, salt-sensing and learning, and resistance to bacterial infection can quantify and allow visualization of DKF-2A/2B activity in vivo. These assays enable 4 lines of investigation. (1) In vivo activation assays, in combination with genetics, will determine which receptors, heterotrimeric G proteins, PLCs and PKCs are upstream regulators that control PKD activity in intestinal cells and specific neurons. (2) Abilities of DKF-2 isoforms to phosphorylate and regulate (a) a global transcriptional regulator, HDA-4 (a histone deacetylase) and (b) a member of a p38 MAP kinase cascade, NSY-1, will be tested in vivo. (3) Mechanisms by which DKF-2A/2B potently induces accumulation of a large constellation of immune effector proteins will be elucidated. (4) We discovered that signals transmitted by activation of neuronal DKF-2B and intestinal DKF-2A are integrated to generate crucial neurophysiological processes: learning and behavioral plasticity. The molecular basis for gut-nervous system interactions and cooperation in learning and behavior will be elucidated. Overall, studies on the C. elegans model will reveal molecules, mechanisms and pathways that couple external stimuli to PKD-controlled physiological processes in normal differentiated cells and guide examination of these unexplored areas in mammalian systems.

**Representative Publications**


The recently established Santulli Lab studies the functional role of intracellular calcium fluxes and microRNAs in the pathophysiology of cardiovascular and metabolic disorders. The Lab is well funded by the National Institute of Health (NIH): indeed, the PI has been recently awarded a K99/R00 Award and 3 independent R01 Grants. The main current projects are:

- **Intracellular calcium modulates cardiomyocyte function and fibroblast activation in myocardial infarction and heart failure.** We are investigating the functional contribution of intracellular calcium release channels in the regulation of cardiomyocyte fitness and in the phenoconversion of fibroblasts to myofibroblast following cardiac ischemia.

- **Mechanistic role of intracellular calcium in mediating mitochondrial function in pancreatic beta cells.** We are studying the fundamental mechanisms underlying the key role of intracellular calcium release channels in beta cells, both in humans (including human islets) and murine models of diabetes mellitus and obesity.

- **Role of non-coding RNAs in the regulation of blood pressure and myocardial function.** We are dissecting the functional role of non-coding RNAs and microRNAs in the regulation of cell-cell communications between endothelial and vascular smooth muscle cells in the setting of hypertension and between different cardiac cells in response to an ischemic injury.

- **Uncovering the molecular mechanisms underlying sudden cardiac death.** In collaboration with the Children Hospital at Montefiore (CHAM), we are studying the crucial importance of calcium channels in the pathogenesis of sudden cardiac death, using induced Pluripotent Stem Cells that we differentiate in cardiomyocytes.

**Representative Recent Publications (as Corresponding Author):**


Dietary fat is a key determinant in balancing mitochondrial dynamics in heart failure: a novel mechanism underlying the obesity paradox. *Cardiovasc Res.* (2018);114(7):925-927.


Maintenance of normal blood pressure is dependent on IP3R1-mediated regulation of eNOS. *PNAS USA.* (2016);113:8532-8537.


Mitochondrial calcium overload is a key determinant in heart failure. *PNAS USA.* (2015);112:11389-94.
Small cell lung cancer (SCLC) is characterized by aggressive growth, frequent metastases, the development of chemotherapy resistance, and a five-year survival rate of less than 5%. The identification of driver mutations and their corresponding targeted drugs have led to significant improvements in the treatment of many solid tumors; however, similar advances have not been made in the treatment of SCLC. A unique feature of SCLC is the near uniform (>95%) bi-allelic inactivation of tumor suppressor genes RB1 and TP53 to drive tumorigenesis. This defining feature of the disease has not led to a targeted therapy, however, since genetically inactivated RB1 and TP53 cannot be reactivated, nor is it feasible to reintroduce the wild-type genes into all tumor cells clinically. Our lab is interested in identifying key signaling pathways that are activated in RB1-deficient cells, and then to design and test pharmacologic agents that inhibit these pathways, restoring the lost function(s) of RB1, and causing tumor regressions. This work is done in collaboration with the lab of Liang Zhu, Dept. of Molecular and Developmental Biology at Einstein.

1. pRb regulates the E3 ubiquitin ligase SCF<sup>Skp2/Cks1</sup> (Skp2). While the ability of pRB to bind to the E2F transcription factors has been the focus of much research, there are more than 300 cellular proteins that might also interact with the RB1 protein (pRB). pRB has been shown to exert significant cell cycle control that is transcription-independent, and this is due to pRB’s regulation of protein stability by direct effects on the ubiquitin-ligase proteasomal degradation pathway. One repression target of pRB is the SCF E3 ligase, SCF<sup>Skp2/Cks1</sup>, and the knockout of the Skp2 substrate-recruiting subunit of SCF<sup>Skp2/Cks1</sup> effectively blocked pituitary and thyroid tumorigenesis in Rb1-deficient mice. Protein targets of Skp2 include the cyclin-dependent kinase inhibitor p27 (CDKN1b), a key cell cycle regulator which inhibits progression from G1 phase into S phase of the cell cycle. We are using a series of genetically-modified mouse models to determine the role of Skp2, p27, and related proteins in SCLC tumorigenesis. We are also developing conditional mouse models in which expression of critical genes can be turned off after the SCLC tumors have become established and metastasized, as a means of validating those genes as targets for drug therapy.

2. Identify and test small molecule inhibitors of Skp2 activity in SCLC. A challenge in the identification of inhibitors of Skp2 is that the ubiquitin ligases have biochemically distinct active sites, and lack the tight, well-defined pockets of traditional enzymes or receptors. Instead, studies have targeted the coordinated series of protein-protein interactions that are required for ligase activity. The crystal structure of several protein-protein surfaces of the Cks1-Skp2-p27 complex have been characterized. Using computational chemistry, in silico modeling, virtual library screening, and medicinal chemistry syntheses, small molecules that bind to this and other promising regions of the Skp2 complex will be identified and tested for antitumor activity in mouse and human SCLC models.

**Representative Publications**


1. *Single Cell Genomics of Beige Adipose Tissue.* Brown adipose tissue (BAT) is specialized adipose tissue that dissipates energy for thermogenesis through UCP1 (Uncoupling Protein-1), whereas the function white adipose tissue (WAT) is storage of excess energy. Studies suggest that loss of BAT is linked to obesity and insulin resistance in humans. Thus, increasing energy expenditure through regeneration of BAT could be effective to counteract obesity and type 2 diabetes. Certain physiological cues, such as cold exposure, convert WAT into UCP1-positive, mitochondria-rich, energy consuming BAT-like adipocyte. This “browned” adipocyte is referred to as a “beige adipocyte” and recent studies indicate that predetermined progenitor cells exist as a source of beige adipocytes. We are working to determine the marker genes and functional characteristics of beige progenitor cells by single cell RNA sequencing.

2. *Phosphoproteomics to Identify Pharmacological Targets of Adipose Tissue Browning.* Molecular mechanisms for the adipose-selective activation of thermogenesis remain poorly understood. We employed phosphoproteomics to map global and temporal phosphorylation profiles in brown, beige, and white adipocytes under β3-adrenenocceptor activation and found that Casein Kinase2 (CK2) activity is preferentially higher in white adipocytes than brown/beige adipocytes. Pharmacological antagonists of CK2 in white adipocytes activate the thermogenic program in response to cAMP stimuli. Notably, inhibition of CK2 promotes beige adipocyte differentiation and leads to an increase in whole-body energy expenditure and ameliorates diet-induced obesity and insulin resistance. We are working to define the mechanisms by which CK2 regulates browning and thermogenic genes.

3. *Nanopore Sequencing of Human Adipose Tissues.* Sequencing RNA in a biological sample can determine the transcriptional state of cells and tissues. However, current methods have limitations due to short read lengths and PCR amplification biases. We utilize nanopore direct RNA sequencing, a highly parallel, real-time, single-molecule method that circumvents these biases and identifies novel gene isoforms and alternative splicing events specific to developing human adipose tissues.

**Representative Publications:**


Autophagy or “self-eating” is an in-bulk lysosomal degradative pathway that plays a crucial role in cellular homeostasis through protein and organelle turnover. Autophagy occurs at basal levels in all cells and is induced following conditions such as stress or nutrient-deprivation. Briefly, the process of autophagy requires the de novo formation of a double-walled limiting membrane that engulfs cellular cargo destined for degradation and then seals upon itself to form an autophagosome. The delivery of the engulfed cargo to the lysosome occurs by fusion of the autophagosome with the lysosome leading to degradation of the cargo. We demonstrated a novel role of autophagy in the degradation of intracellular lipid stores in liver, thus pointing to a possible function of autophagy in energy homeostasis. We also showed that lipophagy in hypothalamic neurons generates neuron-intrinsic free acids that control neuronal regulation of feeding. More recently, we have elucidated system-wide roles for autophagy in correction of energy balance in a novel twice-a-day feeding model that we developed in the lab. These studies led us to think about autophagy and circadian regulation of metabolism, and from this perspective, we identified that autophagy regulates the circadian clock by degradation the clock repressor cryptochrome 1 (CRY1). Since CRY1 is an inhibitor of gluconeogenesis, we have also shown that autophagy regulates glucose production in liver by degradation CRY1. This is an important mechanism by which autophagy maintains blood glucose levels.

The current focus of the lab is to examine the organ-specific roles of autophagy in the regulation of metabolism and energy homeostasis using biochemical, immunochemical and image-based approaches in conditional knockout mouse models. Since aging associates with reduced autophagy, we are also interested in understanding how age-associated reduction in autophagy contributes to the metabolic syndrome of aging.

**Representative Publications**


This research program investigates the genetic basis of the regulation of synaptic transmission of the neurotransmitter serotonin. Drugs that target the serotonergic system are the most commonly prescribed therapeutic agents for the treatment of a wide spectrum of behavioral and neurological disorders, from depression to eating disorders, autism, schizophrenia and Parkinson’s disease. Using mouse and C. elegans as animal models, our laboratory is undertaking genetic dissection of the genes and biochemical pathways in serotonin signaling and characterizing therapeutics that can alter them.

One project is to identify serotonin deficient mutants in C. elegans. We have isolated a set of neuron-specific serotonin deficient (nss) mutants through unbiased genetic screens. The nss mutants offer us a unique opportunity to elucidate genetic pathways and biochemical mechanisms that regulate the development and function of specific serotonergic neurons.

A second project is to identify and characterize antidepressant-resistant genes. Using chemical mutagenesis and RNA-interference (RNAi) technology, ongoing experiments search genome-wide for mutations that confer resistance or hypersensitivity to selective serotonin reuptake inhibitors (SSRIs) in C. elegans. This screen will broadly explore SSRIs targets distinct from the known serotonin transporter and reveal downstream pathways regulated by serotonin signaling. We will translate genetic leads from C. elegans into functional analysis in mouse models.

**Representative Publications**


