Major conformational states of the p85alpha homodimer, derived from small angle X-ray scattering, crosslinking-mass spectrometry and analytical ultracentrifugation.
Welcome to Molecular Pharmacology. Traditionally, pharmacology departments have studied the mechanism of drug action and the hormonal and signaling systems that are the targets of most drugs. Molecular Pharmacology at Einstein continues this tradition, with 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 toxins.

Graduate training in Molecular Pharmacology exposes students 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 biophysical studies on purified enzymes. Our research targets important diseases such as diabetes and obesity, cancer, cardiac disease, behavioral disorders, learning and depression, as well as neurodevelopmental and neurodegenerative disorders. Studies with animal models and human-derived specimens ensure that our research is at the forefront of translational science.

The Department has 21 primary and secondary faculty members as well as 40 graduate students and postdoctoral fellows who participate in all departmental activities. 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 scientific retreats 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 - RESEARCH TRAINEES

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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. We explore the mechanisms by which macrodomain-containing proteins (e.g. macroH2A1) couple transcriptional regulation to NAD+-signaling. We strive to determine how these factors influence cancer progression and senescence.

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.

Richard Gorlick, M.D. Our laboratory is focused upon osteosarcoma. In the context of this malignancy we study drug resistance, potential therapeutic targets and mechanisms of pathogenesis with the aim being the improved treatment of this disease.
**Susan Band Horwitz, Ph.D.** 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.

**Gloria Huang, M.D.** The focus of our research is to understand the tumor-host interactions and genomic alterations that drive gynecologic cancer development and progression, and to translate discoveries into innovative therapies for patients.

**Derek M. Huffman, Ph.D.** 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.

**Young-Hwan Jo, Ph.D.** My long-term research goal is to understand the molecular and cellular mechanisms underlying neuronal excitability, synaptic connectivity and synaptic plasticity of hypothalamic neuronal circuits involved in energy homeostasis.

**Hayley M. McDaid, Ph.D.** We focus on therapeutics directed at breast, lung and ovarian cancers and defining mechanisms of resistance, in particular those related to tumor cell senescence.

**Thomas V. McDonald, M.D.** The McDonald Laboratory studies the biology, genetics, and biophysics of ion channels in health and disease. Among the conditions of interest are sudden infant death syndrome, Long-QT syndrome, and malaria.

**Roman Perez-Soler, M.D.** Our laboratory is designing and testing mechanism-based molecular therapies for lung cancer and other solid tumors. Novel drug delivery systems that combine anatomical and molecular targeting approaches are in development.

**Jeffrey E. Pessin, Ph.D.** 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.
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.

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.

Charles S. Rubin, Ph.D. 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.
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 the 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 p85/p110β 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 p110β binding to Gβγ, and have shown that these mutants block p110β-mediated invasion and metastasis. We are now studying the role of Gβγ-regulated signaling by p110β in cell culture and animal models. We are focusing of p110β signaling in breast cancer metastasis, and in the development of endometrial and prostate cancer. These studies will be important for understanding the role of GPCR-regulated PI 3-kinase signaling in human cancer.

2. PI 3-kinase regulation by Rab GTPases. The p110β 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 p110β 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 and prostate cancer cells, as well as mouse knock-in models, to define the mechanisms by which Rab5-p110β binding regulates vesicular trafficking and responses to nutrient stress.

3. The regulation of Class IA PI 3-kinases by dimerization. Using biochemical and biophysical methods, we are studying the mechanism of PI 3-kinase activation. We have recently defined a structural model of the p85 homodimer, which signals independently from p110 catalytic subunits. We are testing the role of p85 homodimerization in its binding to effectors such as Rac, and the PTEN and BRD7 tumor suppressors. We are also studying whether differential oligomerization of p85/p110α and p85/p110β heterodimers could explain signaling differences in cells.

Representative Publications


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 in plants, animals and pathogenic organisms. Lectins and the cell surface glycans of glycoproteins and glycolipids in metazoans 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 glycans and glycoproteins that are cellular receptors involved in signal transduction processes including cell growth, arrest and apoptosis. Techniques used to explore these interactions include nuclear magnetic resonance spectroscopy, isothermal titration microcalorimetry, x-ray crystallography and atomic force microscopy.

Representative Publications


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**


Liu, T., **Cai, D.** Counterbalance between BAG and URX neurons via guanylate cyclases controls lifespan homeostasis in *C. elegans*. EMBO J., 32: 1529–1542, 2013. (*Highlighted as EMBO J commentary*)


Purkayastha, S., Zhang, G., **Cai, D.** Uncoupling the mechanisms of obesity and hypertension by targeting hypothalamic IKKβ and NF-kB. 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*)


Zhang, X., Zhang, G., Zhang, H., Karin, M., Bai, H., **Cai, D.** Hypothalamic IKKβ/NF-κB and ER stress link overnutrition to energy imbalance and obesity. Cell, 135 (1): 61-73, 2008. (*Highlighted by preview in Cell; highlighted as a top-10 article of 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. Many of the other novel peptides are produced from cytosolic proteins, and not from secretory pathway proteins that are the precursors of classical neuropeptides. Some of the peptides derived from cytosolic proteins are secreted and bind to extracellular receptors; these are putative “non-classical” neuropeptides, a novel class of cell-cell signaling molecule. Further studies are aimed at understanding the mechanisms by which these peptides are produced, secreted, and regulated, with the overall goal to identify the peptides' functions.

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, is responsible for the formation of many peptide hormones (such as insulin) and neuropeptides (such as enkephalin). We identified a strain of mouse (named fat/fat) that does not produce active carboxypeptidase E due to a point mutation; these mice are obese, sterile, hyperglycemic, and have neurological impairments. In addition to neuropeptide processing enzymes, several other cellular peptidases are being studied in the laboratory. Current projects use peptidomics and other techniques to identify the physiological function of the peptidase. Some of the enzymes being studied are the cytosolic carboxypeptidases; these enzymes modify tubulin (and possibly other proteins) by removing amino acids from the C-terminus and/or side-chains, thereby altering the properties of tubulin. Mice lacking cytosolic carboxypeptidase 1 show abnormal movement due to neurodegeneration of cerebellar Purkinje cells. Another enzyme currently being studied is carboxypeptidase A6; humans with mutations in this enzyme develop epilepsy. We are studying the role of carboxypeptidase A6 in animal models, with a focus on understanding how mutations in the protein lead to epilepsy.

Representative Publications


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 are 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. MacroH2A1 also plays a critical role in regulating gene expression during oncogene-induced senescence, an important tumor suppressive mechanisms. We recently discovered that during senescence an endoplasmic reticulum (ER) stress-dependent mechanism requiring the DNA damage signaling kinase ATM leads to genome-wide changes in macroH2A1 genomic distribution which resemble that of cancer cells. 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 use a variety of innovative reverse genetics, pharmacological and genome-wide approaches to achieve our overall goals of elucidating the function of macroH2A1 in the regulation of gene expression in normal and senescent cells and to determine how dysregulation of macroH2A1 function contributes to alterations in gene expression that allow senescence-bypass and oncogenesis. Current areas of emphasis in the lab include (1) determining the mechanisms regulating the genome-wide deposition of macroH2A1 into chromatin, (2) determining the mechanism by which macroH2A1-regulation of H2B acetylation regulates enhancer function and transcription, (3) determining the mechanism of ATM activation and macroH2A1 mobilization in response to ER stress during senescence and (4) determining the mechanism by which RNA Pol II elongation rate regulates macroH2A1 splicing. The knowledge about macroH2A1-mediated regulation of gene expression, genomic localization and macroH2A1 splicing regulation gained from our efforts will aid our understanding of how macroH2A1’s functions become dysregulated during oncogenesis.

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. 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 line the aqueous translocation pathway, that bind folates and protons, and determine the rate of oscillation of the carrier between its conformational state. Studies employ both electrophysiological and substrate transport measurements in Xenopus oocytes and analyses of radiolabeled folate flux determinations in cell lines. Current studies utilize the substituted cysteine accessibility method. A three-dimensional homology model of PCFT is being developed in conjunction with the 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


Our laboratory is focused upon osteosarcoma, which is the most common bone cancer in children and adolescents. In the context of this malignancy we study drug resistance, potential therapeutic targets and mechanisms of pathogenesis with the aim being the improved treatment of this disease.

The longstanding focus of the laboratory has been the mechanisms of antifolate resistance that are observed in osteosarcoma. We have evolved from that area to more broadly identifying new therapies that may be relevant for the treatment of osteosarcoma. We are interested in defining the signal transduction pathways that are relevant to osteosarcoma as these pathways may be amenable to inhibition by targeted therapies enhancing the standard treatment with cytotoxic chemotherapy. We are investigating several immunotherapy approaches. We are interested in understanding the cell of origin of osteosarcoma, which may be a mesenchymal stem cell or a more differentiated osteoblast. We are exploring further, the genetic pathways that drive these cells towards an osteosarcoma phenotype. The laboratory performs preclinical drug studies utilizing osteosarcoma xenografts as a site for the National Cancer Institute funded Pediatric Preclinical Testing Consortium. A wide variety of functional and molecular approaches are used to study the various candidate genes as well as to address the drug resistance questions.

Representative Publications


The research program in this laboratory focuses on small molecules of natural product origin, such as Taxol®, which interact with the microtubule cytoskeleton. One goal is to understand, at a molecular level, the interaction of such drugs with the tubulin/microtubule system and the mechanisms by which these drugs induce growth arrest and cell death. An important part of the program is to study the mechanisms by which tumors become resistant, and drug-resistant cell lines have been developed as model systems. These have diverse mechanisms of resistance that include alterations in tubulin isotype expression, mutations in α- and β-tubulin, and changes in endogenous proteins such as MAPs that modulate drug resistance through their interactions with microtubules. Quantitative mass spectrophotometric-based methods are used to analyze the expression of tubulin isotypes and their posttranslational modifications in model systems and human tumors. In addition, hydrogen/deuterium exchange coupled to liquid-chromatography-electrospray ionization mass spectrometry is being used to study conformational effects induced by drugs on microtubules.

A second theme is focused on the seven β-tubulin isotypes present in distinct quantities in mammalian cells of different origin. The expression of β-tubulin isotypes is altered in drug resistant cell lines and human tumors from different organs. The laboratory is presently measuring the quantity of drug that binds to each isotype with the idea that β-tubulin isotype content could be related to drug response and resistance.

Representative Publications


Chao, S.K., et. al. (2011) Resistance to discodermolide, a microtubule stabilizing agent and senescence inducer, is 4E-BP1 dependent. PNAS, 107, 391-396.
Research Description

Our research encompasses the following areas of investigation:

1. Novel functions of the insulin/IGF and hormonal signaling pathways
   The insulin/IGF signaling pathway is now recognized to influence the risk of cancer development and progression, the response of cancer cells to therapy, and the risk of cancer recurrence and death. Our studies established that IGF2 protein expression in tumor tissue is a prognostic factor for recurrence and survival in patients with aggressive ovarian and uterine cancer. We were the first to identify the novel role of IGF2 in Taxol resistance. In ongoing research, we are investigating the effects of tumor-derived IGF2 on host cells and the tumor microenvironment. These studies have provided new insights that we aim to translate into efficacious targeted treatment strategies that circumvent drug resistance.

2. Reversing the metastatic capacity of uterine carcinosarcoma
   Using Next Generation sequencing, my laboratory identified novel genomic alterations in a highly lethal malignancy of the female reproductive tract, uterine carcinosarcoma (UCS). For example, we found that Rac GTPase activating protein 1 (RACGAP1) is highly overexpressed in UCS and promotes its metastatic phenotype. Targeting RACGAP1 or its downstream signaling effectors reverted UCS cells to a non-invasive phenotype. We have developed primary UCS cell lines and patient-derived xenograft models of UCS to evaluate new therapeutic strategies based on our discovery.

3. Characterization of a novel metabolic function of the tumor suppressor ARID1A
   Using a proteomics approach, my laboratory identified a novel interacting partner of ARID1A, a SWI-SWF complex member that is frequently mutated in endometrial and endometriosis-derived cancers. We are currently investigating the mechanisms by which ARID1A regulates a multifunctional enzyme catalyzing pyrimidine synthesis and evaluating strategies to exploit the metabolic vulnerability of ARID1A-deficiency.

Representative Publications


Derek M. Huffman, Ph.D., Assistant Professor
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1) IGF-1 axis and aging – Our lab is interested in the insulin/insulin-like growth factor-1 (IGF-1) signaling axis and aging. A reduction in signal via this pathway has been consistently linked to lifespan, from model organisms to humans. Interestingly, in humans, high IGF-1 levels are associated with increased cancer risk, but are paradoxically linked with protection from other age-related diseases. Relevant to this paradox, we have uncovered novel, beneficial effects of centrally-acting IGF-1 on peripheral metabolism. This has led us to hypothesize that optimally modulating IGF-1 signaling to promote healthy aging and longevity in humans may require shifting the balance of IGF-1 from the periphery to the brain, in order to maximize the ‘good’ effects of IGF-1, while minimizing its ‘bad’ effects on cancer in the periphery. We are currently testing this hypothesis in animal models using a combination of genetic and pharmacologic approaches, including clinical-grade IGF-1 receptor (IGF-1R) antibodies.

2) Central insulin and IGF-1 signaling – A second area involves understanding the mechanism(s) whereby insulin and IGF-1 signaling in the brain control peripheral metabolism. We utilize the “gold standard” hyperinsulinemic-euglycemic clamp to evaluate insulin sensitivity in normal and genetically-engineered rodents with tandem central infusions of peptides/inhibitors, along with state-of-the-art fMRI techniques. Ongoing studies have uncovered novel mechanisms of insulin and IGF-1 signaling in the brain, with implications for treating age-related metabolic decline and type 2 diabetes.

3) Role of systemic factors on intestinal aging – Functional decline is a hallmark of aging in multiple tissues, a process thought to be driven in part by deterioration in resident stem cell function. 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 and tissue 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, including (i) aberrations in intestinal stem cells and niche cells, and (ii) intestinal barrier dysfunction, inflammation and stress.

4) Studies at the cancer-aging interface – A forth 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 a young versus aged mouse models. Evidence of diminished efficacy in old animals could profoundly influence how future cancer prevention studies are designed and interpreted.

Representative Publications


Obesity is a chronic metabolic disorder characterized by an excess of body fat. Obesity results from prolonged positive energy balance (i.e. energy intake exceeding energy expenditure). Because obesity may develop over many years in humans, only small imbalances in energy intake and expenditure are required. The cause of excessive positive energy balance in obesity has not been clearly defined. Nevertheless, key regulatory components reside in the hypothalamus, specifically in the arcuate nucleus (ARC).

The central melanocortin system within the ARC is made up of two distinct subsets of neurons that express either pro-opiomelanocortin (POMC) or agouti-related peptide (AgRP). These peptides regulate their downstream target sites via modulation of melanocortin receptor type 3 (MC3R) and melanocortin receptor type 4 (MC4R) activity. Although POMC neurons were long considered to be a single homogeneous entity, recent studies, including our own, support considerable heterogeneity among POMC neurons. In particular, there are at least two phenotypically distinct populations of POMC neurons in the ARC. We hypothesize that these phenotypic distinctions reflect important functional differences and that the interplay between the phenotypically distinct populations of POMC neurons is required for integration of peripheral and central signaling molecules, thus controlling the anorexigenic outcome of POMC neurons. Thus we are currently determining how novel interactions between distinct populations of POMC neurons contribute to the control of hypothalamic neurophysiology and the regulation of energy homeostasis. Our laboratory employs optogenetics, electrophysiology and transgenic animal models to explore the physiological functions of these novel interactions at the cellular and whole body levels. Understanding POMC-POMC neuronal interactions will help elucidate the elementary hypothalamic microcircuits controlling feeding and energy expenditure. Hence, this understanding will be crucial as we seek to determine the underlying cellular pathogenesis of the ongoing epidemic of obesity.

Representative Publications

Lee DK, Jeong JH, Oh SH and Jo YH* Apelin-13 enhances arcuate POMC neuron activity via inhibiting M-current. PLOS One, Mar 17;10 (3):e0119457 (2015)


Groessl F, Jeong JH, Talmage DA, Role LW and Jo YH* (2013), Overnight fasting regulates inhibitory tone to cholinergic neurons of the dorsomedial nucleus of the hypothalamus. PLOS One, Vol. 8 (4), e60828

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**


Chao, S.K., et. al. (2011) Resistance to discodermolide, a microtubule stabilizing agent and senescence inducer, is 4E-BP1 dependent. PNAS, 107, 391-396.
The research interests of our lab center on investigating the role of ion channel function in normal and disease processes. Ion channels are involved in cellular excitability and signal transduction processes in every type of cell. Mutations of channel genes that alter their function play a prominent role in a wide variety of genetic diseases. We use a multi-disciplinary approach to investigate the normal function of channels and mechanisms of disease-producing mutations.

Specific projects of the lab include:

1) Mutations in several cardiac ion channel subunits cause sudden death in the inherited disease Long QT Syndrome (LQT) and Sudden Infant Death Syndrome (SIDS). These channels also play important roles in the nervous system, intestine, kidneys and in cancer. We are using a combined approach of cellular electrophysiology, proteomics, protein biochemistry, and structural chemistry to understand how these channels are regulated by protein kinases, and through interactions with other cardiac proteins. Of particular interest is:
   a) How mutations alter channel function.
   b) Structural investigation of channel subunit interaction actions.
   c) Signal transduction pathways that control channel expression and activity.
   d) Epigenetic and extra-coding RNA factors regulating channel expression and function.

2) All cells express evolutionarily conserved ion channels. Channels control permeability of membranes and are essential for normal cell function and viability. We are investigating ion channel candidate genes from human parasites (Malaria, Leshmania, Toxoplasma, Trypanasoma) for their roles as determinants of viability, infectivity and virulence. The long-term goal of this research is to identify essential functional proteins that may serve as pharmacological targets.

Representative Publications:


Sroubek J, Krishnan Y, McDonald TV. Sequence and structure-specific elements of HERG mRNA regulate channel synthesis and trafficking. FASEB J (Epub) 2013 April 22. PMID: 23608144


Recently, we have identified a novel crosstalk between insulin receptor signaling and a member of the Src family of non-receptor tyrosine kinases, called Fyn. Fyn null mice are lean and display markedly enhanced insulin sensitivity, glucose tolerance and improved lipid profiles. This results from increased peripheral tissue (skeletal muscle and adipocyte) fatty acid oxidation due to activation of the AMP-dependent protein kinase. In contrast, over expression of Fyn selectively in skeletal muscle results in reduced AMP-dependent protein kinase activity and surprisingly, marked muscle atrophy. The degeneration of skeletal muscle fibers occurs through defects in both mTORC1 and macroautophagy signals. We are currently investigating the signaling cross talk between metabolism and muscle maintenance that has important implications for both aging induced insulin resistance and muscle wasting (sarcopenia).

A second major laboratory program is identification and characterization of adipose tissue inflammation, adipocyte cell death and fibrosis. We have found that following high fat diet, adipocytes secrete an important pro-fibrotic cytokine (IL-13) that induces the differentiation of local adipose tissue macrophages into a TGF-$\beta_1$ secreting population. In turn, local TGF-$\beta_1$ production induces the secretion of extracellular matrix proteins such as collagens creating a fibrotic state. Current, studies are examining the expression profiles of this unique macrophage subpopulation and determining the cellular interactions by using tissue-specific knockout mice.

**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**


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 have recently demonstrated a novel role of autophagy in the mobilization and degradation of intracellular lipid stores in the liver, thus pointing to a possible function of autophagy in energy homeostasis. We have also recently shown that this lipophagic role of autophagy functions in hypothalamic neurons to generate neuron-intrinsic free acids that, in turn, drive neuronal feeding mechanisms.

The primary focus of the lab is to examine the organ-specific roles of autophagy in the regulation of lipid metabolism and energy homeostasis using biochemical, immunochemical, radiochemical and image-based approaches in vitro and in conditional knockout mouse models. Our efforts are currently focused on the function of autophagy in discrete neurons of the hypothalamus and in the white and brown adipose tissues. We are interested in:

1. Elucidating the role of hypothalamic neuronal autophagy in the regulation of food intake and energy homeostasis.
2. Dissecting the upstream nutrient sensing signal cascades that regulate the induction or shut down of hypothalamic autophagy in response to circulating nutrients.
3. Examining the metabolic and regulatory functions of autophagy in white and brown adipose tissue biology.

Aging is considered to reduce autophagic activity. The second focus of the laboratory is to examine the effect of aging-induced reduction of hypothalamic and adipose autophagy on the development of 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**


