The regulation of RNA polymerase II-mediated transcription by the Cdk9 kinase and the PP1 and PP4 phosphatases (Parua lab).

Jonathan M. Backer, M.D., Chair

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Michael Aschner, Ph.D.  Roman Perez-Soler, M.D.
Michael D. Brenowitz, Ph.D.  Pabitra K. Parua, Ph.D.
C. Fred Brewer, Ph.D.  Jeffrey E. Pessin, Ph.D.
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Edward Chu, M.D., M.M.S.  Gaetano Santulli, M.D., Ph.D.
Lloyd D. Fricker, Ph.D.  Edward L. Schwartz, Ph.D.
Matthew J. Gamble, Ph.D.  Kosaku Shinoda, Ph.D.
I. David Goldman, M.D.  Kamini Singh, Ph.D.
Susan Band Horwitz, Ph.D.  Allen Spiegel, M.D.
Derek M. Huffman, Ph.D.  Sylvia O. Suadicani, Ph.D.
Young-Hwan Jo, Ph.D.  Ji Ying Sze, Ph.D.
Sridhar Mani, M.D.  Mia M. Thi, Ph.D.
Pharmacology is the study of drugs and the signaling proteins that they target. Research in Molecular Pharmacology at Einstein has a strong emphasis on signal transduction and hormone action at the nuclear, cellular and organismic level; the mechanisms of drug action and the development of new therapeutics; and the disruption of normal physiology by toxicants. Work in our department targets important diseases such as cancer, diabetes and obesity, aging, as well as neurodevelopmental and neurodegenerative disorders. We have strong ties to the Cancer and Diabetes Centers as well as the Institute for Aging Research.

Graduate training in Molecular Pharmacology exposes student to state of the art methodologies that cover a wide range of approaches, including genetic studies in flies, worms and mice, genome-wide studies of chromatin organization, mRNA transcription, splicing and translation, glycobiology, advanced quantitative imaging, and biochemical studies on purified enzymes. Studies with animal models and human-derived specimens insure that our research is at the forefront of translational science.

The Department has 27 primary and secondary faculty members as well as 20 graduate students and postdoctoral fellows. 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.

Graduate students in the Department of Molecular Pharmacology have earned postdoctoral positions in outstanding laboratories and received prestigious fellowships. Our postdoctoral trainees have found positions in academia, biotechnology and pharmaceutical companies, and at the National Institutes of Health and the Food and Drug Administration. We are proud of the accomplishments of our students and postdocs and we welcome new students to join us in this exciting age of scientific advances.
## MOLECULAR PHARMACOLOGY - PRIMARY FACULTY

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## MOLECULAR PHARMACOLOGY - SECONDARY FACULTY

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## MOLECULAR PHARMACOLOGY - ADMINISTRATION

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## MOLECULAR PHARMACOLOGY - RESEARCH TECHNICIANS

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**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.

**Praveen Agrawal, Ph.D.**  The Agrawal lab studies changes in the cellular glycosylation associated with tumor progression, metastasis and resistance to targeted therapy. Our studies utilize cutting edge glycomic techniques, glycogene data mining of clinical samples, in vitro/in vivo functional screens and metastasis models.

**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 Cai lab investigates the roles of the central nervous system, the neuroendocrine system, and the neural-peripheral connections in causing aging, metabolic syndrome and some related diseases (e.g., neurodegenerative diseases, diabetes, stroke, hypertension, and infections). Many important model systems are employed in our research, such as genetic rodent models, drosophila models, neural stem cells and iPSC models. Current highlights of our research include neuroimmunological network, neural stem cells and organoids, exosomes, neural epigenetics, and epigenetic reprogramming.
Edward Chu, M.D. The major focus of my research is to investigate the molecular mechanisms of cellular drug resistance in colorectal cancer that relate to the fluoropyrimidine class of anticancer agents and inhibitors to thymidylate synthase and to develop novel agents that can overcome and/or prevent the development of drug resistance. Our lab has worked on developing novel bifunctional siRNA molecules as well as small molecules and Chinese herbal medicine. In addition, I am actively involved in the early-phase clinical development of novel agents and/or combination regimens for the treatment of colorectal cancer, and my lab has been involved in conducting the key pre-clinical experiments and translational biomarker studies that serve as the rational basis for the first in man clinical studies.

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. My laboratory studies the mechanisms by which folates and antifolates are transported across cell membranes. Current focus is on structure-function of the proton-coupled folate transporter (PCFT, SLC46A1) and the basis for the loss-of-function when PCFT is mutated in the autosomal recessive disorder, hereditary folate malabsorption.

Derek M. Huffman, Ph.D. The Huffman laboratory is focused on four areas: 1) Aging-metabolism interplay, 2) Aging drug synergy, 3) Role of systemic factors in aging, and 4) physiologic resilience and aging.

Young-Hwan Jo, Ph.D. The focus of our laboratory is to examine the roles of the central melanocortin system in the regulation of energy metabolism and glucose homeostasis.
**Sridhar Mani, M.D.**  Our laboratory focuses on the study of host-microbiome relationships as it relates to human and veterinary health and disease (inflammation, metabolism, and cancer).

**Hayley M. McDaid, Ph.D.**  Our laboratory focuses on 1. Senescence biomarker development, 2. defining molecular dependencies of senescent cells for therapeutic targeting, and 3. pre-clinical pharmacology of tubulin ligands for cancer therapy.

**Pabitra K. Parua, Ph.D.**  The research of the Parua lab is focused on dissecting the regulation of the RNA polymerase II (RNAPII) transcription cycle by kinase-phosphatase antagonisms. Our central interest is to uncover novel signaling networks governed by upstream stimuli and converge to regulate gene expression. Intriguingly, the prospective avenues are to explore how the aberrations of that critical molecular circuitry cause neoplasms.

**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.

**Gaetano Santulli, M.D., Ph.D.**  In our laboratory, we study the mechanistic role of intracellular calcium and microRNAs in the pathophysiology of cardiovascular and metabolic disorders, including heart failure, hypertension, and diabetes mellitus.

**Edward L. Schwartz, Ph.D.**  Our lab focuses on the identification of new targets and novel drugs to treat lung and prostate cancer, particularly tumors that have inactivating mutations in the RB1 tumor suppressor gene. This includes determining the critical signaling pathways downstream of RB1 and designing pharmacologic agents that would restore its function and cause tumor regressions.
**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 single-cell genomics and bioinformatics to map cellular lineage and the genetic program of adipocytes in disease states and under normal physiological conditions.

**Kamini Singh, Ph.D.**  My laboratory investigates the gene expression and therapeutic vulnerabilities in cancer through the lens of ribosome. Using bulk and single cell ribosome footprinting approach we study the mechanism of mRNA translation, role of regulatory RNA elements, and the function of aberrant translation products in cancer progression, tumor microenvironment, and immune response.

**Sylvia O. Suadicani, Ph.D.**  Research in our laboratory investigates the involvement of altered ATP and gap junction signaling in mechanisms of disease, with particular focus on urogenital dysfunction and chronic pelvic pain.

**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.

**Mia M. Thi, Ph.D.**  Primary focus of our laboratory is to understand the molecular and cellular mechanisms involved in how cells sense, transduce and signal mechanical stimuli and how cells work in synchrony to propagate locally generated signals throughout the skeletal tissue and others mechanosensitive tissues such as endothelium, urothelium by means of receptor, junctional, cytoskeletal and focal adhesion proteins under healthy and pathological conditions.
Glycans (carbohydrates) can substantially influence and modulate protein structure and function in multiple ways such as protein folding, conformation, stability, activity etc. which directly impact key processes supporting tumor progression and metastasis, including cell adhesion, motility, invasion, signaling activation, cell-matrix interactions, immune evasion. We are specifically interested to study what are the precise mechanisms by which biochemical and structural changes in glycans of a glycoprotein, regulate tumor progression and metastasis and resistance to various therapies.

1. Glycosylation as a regulator of tropism of melanoma metastasis: Malignant melanoma is one of the most aggressive cancers and can disseminate from a relatively small primary tumor and metastasize to multiple sites, including the lung, liver, brain, bone, and lymph nodes. Recently, we identified that a fucosyltransferase FUT8 is a driver of melanoma metastasis (Agrawal et al., 2017). Further, we postulated that adaptation of tumor cells to distinct secondary sites requires specific changes in cell surface glycosylation. To explore this idea and identifying glycans epitopes and glycogenes involved in site specific organ tropism of melanoma, we utilize multiple approaches such as glycomics and glycogenomics of in vivo melanoma metastasis models and clinical patient samples of melanoma. We aim to identify target glycoproteins and their mechanism of action which contributes in site-specificity of melanoma metastasis.

2. Investigation the biological role of L1CAM glycosylation in melanoma brain metastasis: Metastases to the brain are among the most clinically significant, because even a single one is likely to cause serious disability. In our previous study of melanoma, we showed that in vitro L1CAM cleavage is dependent on core fucosylation and a glycosylation site is adjacent to L1CAM cleavage site. L1CAM is known to express by metastatic cells for spreading along brain capillaries and for metastatic outgrowth. Currently, we are testing if modulation of glycosylation site/s affects L1CAM cleavage, protein-protein interactions, and brain metastasis capability using various biochemical approaches and in vivo brain metastasis models.

3. The role of glycosylation alteration in resistance to targeted therapy of Prostate cancer: In the past years, many therapeutic advances have been achieved in castration-resistant prostate cancer (CRPC), with the approval of several new drugs such as AR inhibitors abiraterone and enzalutamide which have shown an improvement in overall survival (OS) however sooner or later acquired drug resistance appears. As glycans are active players throughout cancer development and progression, we are identifying specific changes in glycosylation required for resistance to therapy of PCa. We utilize a multi-step systems biology approach including lectin microarray (Agrawal et al., 2014) and glycan mass spectrometry based glycomics, glycogene data mining of PCa clinical datasets, in vivo high-throughput functional screen with a barcoded glycogene shRNA/sgRNA library and identification of glycoprotein targets using lectin-affinity pulldown and mass spectrometry. These glycoproteins will be further analyzed for role of their glycosylation status and mechanism of action in PCa targeted therapy.

Relevant publications:
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, particularly its role in stromal cells such as macrophages and platelets.

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. S100A4 signaling in macrophages. In collaboration with the Bresnick lab, we are studying the regulation of cellular motility and invasion by the dimeric calcium-binding protein S100A4. S100A4 is prometastatic when expressed in tumor cells. We have recently found that S100A4 also regulates invasion and matrix degradation by both tumor cells and macrophages, and it is required for platelet stimulation of invasion by tumor cells. Using both proteomic and cell biological methods, we are studying how S100A4 regulates vesicular trafficking pathways in both tumor cells and stromal cells that contribute to tumor cell invasion.

Representative Recent 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**


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., Hadjialiirezaei, 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).


Aging and overnutrition are two major etiological conditions for epidemiological diseases such as Alzheimer’s disease, Parkinson’s disease, diabetes, stroke and heart failure. The Cai lab investigates the roles of the central nervous system, the neuroendocrine system, and the neural-peripheral connections in causing aging, metabolic syndrome and some related diseases (e.g., neurodegenerative diseases, diabetes, stroke, hypertension, and infections). Many important model systems are employed in our research, such as genetic rodent models, drosophila models, neural stem cells and iPSC models. Our research has led to a series of paradigm-shifting research breakthroughs, for example, we pioneered discovering the role of the hypothalamus in regulating whole-body aging, identifying hypothalamic neural stem cells (htNSC), and developing htNSC exosomes for anti-aging and various disease treatments. These efforts have resulted in many high-profile publications, some of which are represented below. Current highlights of our research include neuroimmunological network, neural stem cells and organoids, exosomes, epigenetics, and epigenetic reprogramming, each representing an important front of today’s biomedical science.

**Representative Publications**


Colorectal cancer (CRC) is a major public health problem in the U.S. and globally. When metastatic disease is diagnosed, the overall prognosis is poor, with 5-year survival in the 5%-8% range. An enhanced understanding of the key signaling pathways that mediate the growth and survival of CRC may provide the rational basis for developing novel agents to be used either alone or in combination with presently available anticancer drugs to enhance antitumor activity, overcome cellular drug resistance, and prolong overall survival.

Over the past 20+ years, my lab has focused on developing novel agents and/or combination regimens for the treatment of colorectal cancer.

**Translational regulation of gene expression:** My lab was the first to demonstrate that the expression of the folate-dependent enzyme thymidylate synthase was controlled by a translational autoregulatory mechanism whereby the thymidylate synthase protein binds to cis-acting regulatory elements on the cognate TS mRNA and regulates translation. This was a seminal finding as this was the first description of this type of translational autoregulatory mechanism in a eukaryotic organism. My lab then followed up on this observation to demonstrate that the expression of another folate-dependent enzyme dihydrofolate reductase is controlled in an identical translational autoregulatory manner. It has now been well-established that translation autoregulation is a common mechanism by which cellular gene expression can be controlled in a very efficient and rapid manner.

**Development of antisense and siRNAs as novel therapeutic molecules:** The Chu lab has been investigating the potential role of antisense and siRNA’s as novel therapeutic molecules for the treatment of colorectal cancer. The goal of these studies is to identify novel molecules to prevent and/or overcome the development of cellular drug resistance to inhibitor compounds that target thymidylate synthase, a well-established target for cancer chemotherapy. The Chu lab observed that siRNA’s were significantly more potent and specific in their ability to repress TS mRNA translation, resulting in potent inhibition of TS synthesis. Moreover, these molecules were able to completely restore chemosensitivity to anticancer agents that target TS, including the fluoropyrimidines and TS antifolate inhibitors.

**Herbal medicine:** We recently identified bruceantinol (BOL), a natural quassinoid isolated from the plant *Bracea javanica*, as a potent inhibitor of CRC growth. BOL suppressed >90% of tumor growth in both HCT116 xenograft-bearing athymic mice and a syngeneic MC38 tumor model. However, at high doses, BOL treatment was associated with spleen and body weight loss suggesting normal host toxicities. Using multiple biochemical and molecular techniques, we demonstrated that BOL binds to STAT3 resulting in inhibition of STAT3 phosphorylation, and our data suggests that direct targeting of STAT3, by itself, has little to no effect on CRC cell growth. Previous studies have suggested that the mechanism of action of quassinoids may be mediated through inhibition of protein synthesis. A comparison between cycloheximide, a well-established inhibitor of protein synthesis, and BOL revealed similarities as well as significant differences with regard to alterations in protein expression. Newly developed BOL-resistant CRC cells were not cross resistant to cycloheximide suggesting BOL may inhibit protein synthesis in a completely different manner.

The overarching hypothesis of our research is that quassinoids inhibit cancer cell growth through suppression of protein synthesis with subsequent inhibition of cancer-dependent signaling pathways. We believe that they can be developed as novel therapeutic molecules for the treatment of mCRC. Our research has 3 main aims: Aim 1: Investigate the biological activity of BOL and its analogs on protein synthesis; Aim 2: Design and develop novel therapeutic quassinoid analogs. Preliminary data demonstrates that the C15 side chain influences the ability of BOL to inhibit protein synthesis as well as STAT3. We will synthesize novel quassinoid-based analogs to increase in vitro cytotoxicity and in vivo antitumor activity and enhance target selectivities; and Aim 3: Develop novel nanoparticle technologies for BOL delivery. Preliminary data reveal that encapsulation of BOL into nanomicelles reduced BOL toxicities without affecting antitumor activity. The ADME properties of the BOL-nanomicelles will be further characterized.
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 spicing 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), discovered in this laboratory, and shown to be required for the intestinal absorption of folates and antifolates and their transport across the choroid plexus into the cerebrospinal fluid. PCFT also plays a role in the delivery of antifolates, with a high affinity for this transporter, to cancer cells within their acidic microenvironment. This laboratory established that mutations in this gene that result in loss of expression and/or function of the PCFT protein are the molecular basis for the autosomal recessive disorder, hereditary folate malabsorption. Current emphasis is on characterization of PCFT structure/function. This encompasses the identification of residues and domains required for the maintenance of tertiary structure: (i) that make up the external and internal gates of the protein, (ii) that line the aqueous translocation pathway; (iii) that bind folates; (iv) that are involved in proton-coupling and proton-binding; and (v) that determine the rate of oscillation of the carrier among its conformational states. A three-dimensional homology model of PCFT has been developed, simulating the inward- and outward- open conformations of the human carrier that is correlated with functional studies. Very recently, the structure of the chicken PCFT in the outward-open conformation has been obtained that, with extensive data on structure-function and homology modeling from this laboratory, is enabling an ongoing comprehensive analysis of the human PCFT transport mechanism. Concurrently, 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.

**Representative Publications**


1. Aging and metabolism – A major goal of my research are to understand the interplay between aging and metabolism. We have recently published that the IGF-1R is a viable target via IGF-1R mAb treatment to delay aging in female mice, a pattern consistent with several genetic models of low IGF-1 signaling. In related studies, we 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. Studies are further investigating the potential utility of growth factors targeted to the brain via the intranasal route may harbor therapeutic potential for cognitive decline. We have also investigated the role of metabolites in aging, identifying sarcosine, which is a byproduct of glycine-N methyltransferase (GNMT), is upregulated by dietary restriction, and may be a key mediator of its effects. A focus of the lab is to further understanding the role of GNMT in metabolism and aging biology.

2. A geroscience approach to identify aging drug synergy – While single drugs can improve lifespan and healthspan, there is now evidence that combinatorial strategies designed to simultaneously target multiple aging pillars can result in greater efficacy than single agents. However, given the sheer number of potential aging drug combinations, a systems geroscience approach that integrates multi-level data could potentially make powerful, informed predictions regarding probability of synergistic effects between seemingly unrelated compounds. We are currently leveraging this approach in a mouse model of AD to determine the ability to identify aging drug synergy.

3. Role of cell non-autonomous factors in aging – We use several strategies, including heterochronic parabiosis, to understanding the role of systemic factors in tissue and cellular aging. We are currently pursuing studies to identify the systemic factor(s) responsible for driving features of intestinal decline as well as vascular aging.

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, and the gradual loss of resilience with age may underlie the onset of chronic disease, multimorbidity, frailty and death. We are developing a battery of simple, short-term assays to characterize resilience in rodents and are now using these assays in combination with molecular approaches to better understand the molecular mechanisms underlying physiologic resilience in mice and its loss with age.

Representative Publications


Farias-Quipildor G, Mao K, Hu Z, Novaj A, Cui MH, Gulinello M, Branch CA, Gubbi S, Patel K, Moellering DR, Tarantini S, Kiss T, Yabluchanskiy A, Ungvari Z, Sonntag WE, Huffman DM. Central IGF-1 reduces depressive-like behavior and improves cognitive and physical performance with aging preferentially in male mice Geroscience 2019 May 10 PMC6544744

My research program focuses on studying the neurobiology of energy metabolism in general and hypothalamic neural mechanisms associated with metabolic dysregulation and obesity in particular. Accordingly, I seek to understand how distinct hypothalamic neurons differently sense, detect, and respond to circulating hormones, nutrients, and recently hypothalamic temperature. This laboratory has demonstrated that an increase in body temperature during exercise is directly transmitted to ARC POMC neurons that translates it into neuronal signaling through activation of temperature-sensitive TRPV1-like receptors. Using phenotype-specific neuronal mapping and optogenetics, my lab has also showed that cholinergic neurons in the dorsomedial hypothalamus regulate not only energy expenditure via increased brown adipose tissue thermogenesis but also energy intake through activation of ARC POMC neurons. My ongoing study focuses on the role of ARC POMC neurons in modulating hepatic glucose metabolism using neuronal mapping, optogenetics, and \textit{in vivo} fiber photometry. I also had developed a novel noninvasive optogenetic stimulation method permitting direct transcutaneous stimulation of opsin-expressing autonomic efferent nerves. This new technology allows me to study the roles of the autonomic nervous system innervating peripheral organs such as BAT and liver.

In addition, my lab examines 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. We recently found that BAT expresses HCAR1 (or GPR81, lactate receptor). Hence, my lab seeks to determine the role of HCAR1 in the development of hyperglycemia in diet-induced obese mice.

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

\textbf{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**


My lab studies the molecular mechanisms of action and resistance to standard and novel therapeutics for the treatment of malignancy; primarily lung and breast cancer. Our translational studies have contributed to the development of novel tubulin ligands, conceptualizing combinatorial therapies that target molecular dependencies in cancer, and investigating drug-tolerance that manifests as senescence.

Our interests in senescence date back to studies with the tubulin ligand discodermolide (DDM) and the discovery that it is a potent inducer of senescence. We were one of the first groups to propose that **therapy-induced senescence (TIS)** is an underappreciated mechanism of drug resistance and tumor dormancy. Using drug-resistant cancer cells that escaped TIS, we challenged the dogma that senescence was a ‘permanent state,’ at least in cancer. Subsequent and ongoing studies indicate that senescent cells emerge from dormancy with aggressive biological phenotypes, culminating in metastasis. Emerging data from our lab indicate that the proteomic signature of TIS reflects patterns of genomic instability likely selected for in senescence that we hypothesize confer molecular vulnerabilities.

Active laboratory projects include (i) detecting and quantifying TIS in human malignancy (*biomarker development*), and pre-clinical pharmacology directed at (ii) defining molecular dependencies of senescent cells for therapeutic eradication (*senolytics*), and (iii) improving the pharmacologic efficacy of tubulin ligands to attenuate TIS (*chemical-biology*).

**Representative Publications**


Area of Research: Regulation of gene expression; Control of RNA polymerase II transcription cycle; Transcription elongation control; Kinase-phosphatase antagonism in regulating transcription; Unraveling the mechanisms of dependencies of cancer cells on the dysregulated transcription.

Professional Interests
The dysregulation of RNA polymerase II (RNAPII)-dependent transcription can have potentially catastrophic consequences for gene expression and transcription-regulated signaling pathways, leading to the development of diseases including cancer. Therefore, understanding the fundamental molecular mechanisms that control the fidelity and polarity of transcription is of paramount importance. In particular, we seek to decipher the regulation of RNA polymerase II (RNAPII) transcription by the counteraction of kinases and opposing phosphatases in healthy cells and how the aberrations of that critical molecular circuitry cause neoplasms. To examine this, we study in the fission yeast Schizosaccharomyces pombe and human cells. Our research leverages integrated approaches, including biochemistry, cellular and molecular biology, classical genetics, and chemical genetics—a technique to sensitize a kinase to unnatural ATP analogs—in combination with genomics and proteomics.

To obtain mechanistic insights into promoter-proximal pausing – Most of the genes in metazoan (and ~20% genes in fission yeast) are regulated by an early regulatory event, known as promoter-proximal pausing—RNAPII is paused shortly after initiation around 20-80 nucleotides downstream of the transcription start site (TSS). Properly regulated release of stalled RNAPII from the promoter-proximal pause site results in the synthesis of full-length transcripts. Mis-regulation of pausing or its release can result in abnormal gene expression. Given this early regulatory event’s decisive role in tuning RNAPII transcription, dissecting the underlying molecular mechanisms is of utmost importance for understanding transcriptional homeostasis and its disruption in human diseases. Emerging studies suggest that the distinct kinase-phosphatase switch mechanisms control the phosphorylation of effector proteins, modulating the pause establishment, maintenance, and release. These critical kinase-phosphatase networks are mostly unknown, and need to be identified and characterized precisely. We seek to investigate the regulation of promoter-proximal pausing in fission yeast and human cells to understand how the coordination between kinases and phosphatases ensures the pause establishment and synchronized release beneficial for healthy cells.

To investigate the coupling of transcription elongation and co-transcriptional processes – The variations in the rate of RNAPII elongation have been implicated in controlling co-transcriptional processes such as 5’- and 3’-end processing, alternative polyadenylation (APA), and splicing of pre-mRNA. However, much is still unknown, how the elongation rate is controlled, and consequently, the coupled process. The current hypothesis is that normal speeds of RNAPII elongation favor the recruitment of factors necessary to execute a particular step, whereas slower RNAPII promotes aberrant recruitment of factors results in premature outcomes; conversely, faster rates impair the timely execution of exact steps. The primary objective here is to examine unidentified and uncharacterized connections among kinase-phosphatase antagonisms, rate of elongation, post-translational modifications (PTMs) of histones, pre-mRNA splicing, and transcription polarity.

To uncover how spatial and temporal phosphorylation events influence termination – The elongation to termination transition, a crucial step near the end of transcription, prepares RNAPII for efficient and accurate termination following a series of sequential events: (1) deacceleration of RNAPII while crosses the cleavage and polyadenylation signal (CPS), leading to (2) accumulation of Ser2 phosphorylation of RNAPII carboxy-terminal domain (CTD), which in turn facilitates (3) the recruitment of factors involved in pre-mRNA 3’-end formation and termination. A long-standing puzzle was how the transition from elongation to termination is initiated. Recently we identified a novel bistable switch mechanism comprising cyclin-dependent kinase 9 (Cdk9) and protein phosphatase 1 (PP1) that rapidly reverses phosphorylation at the CTD of an essential elongation factor, Spt5 (and possibly other Cdk9 substrates) during the traversal of the elongation machinery through the CPS, leading to RNAPII slowing. The Spt5 CTD phosphorylation is inversely correlated with RNAPII CTD Ser2 and Thr4 phosphorylation at the 3’-end of genes. However, how their reciprocal relations functionally link to influence the termination remains less understood. We will assess the spatial and temporal connections of various phosphorylation events and characterize their molecular roles in transcription termination.
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 mammalians 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 C57BL6/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


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 3 R01, 1 RO0, 1 R56, 1 T32 Grants. The lab is also supported by the American Heart Association. 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 endothelial dysfunction in COVID-19 function.** We have been the first group to propose that COVID-19 is an endothelial disease (Sardu et al. *J Clin Med*. 2020;9:1417) and we are dissecting the functional role of non-coding RNAs and microRNAs in the regulation of endothelial cells in the setting of COVID-19.

- **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):**  
Metabolic flexibility of mitochondria plays a key role in balancing glucose and fatty acid metabolism in the diabetic heart.  
*Diabetes.* (2020);69:2054-2057.

Exosomal microRNA: The revolutionary endogenous Innerspace nanotechnology.  

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.

Impaired mitochondrial calcium uptake caused by tacrolimus underlies beta-cell failure.  
*Cell Commun.* (2017);13;15(1):47.

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

Calcium release channel RyR2 regulates insulin release and glucose homeostasis.  

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 rapid development of chemotherapy resistance, and an overall five-year survival of less than 5%. Dozens of drugs have been tested for clinical activity in SCLC, including more than 40 agents that have failed in phase III trials. The identification of driver mutations and their corresponding targeted drugs have led to significant improvements in the treatment of other 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 clinically reintroduce the wild-type genes into all tumor cells in vivo. 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.

1. **pRb regulates the E3 ubiquitin ligase SCF-Skp2/Cks1 (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 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, SCFSkp2/Cks1, and the knockout of the Skp2 substrate-recruiting subunit of SCFSkp2/Cks1 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. While not as common as in SCLC, prostate cancers can also have mutations that inactivate the RB1 gene, and these are often aggressive, metastatic, and drug-resistant tumors. Using similar strategies as in our lung cancer studies, we are studying Skp2 inhibitors as potential treatments of advanced prostate cancer.

3. 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 (PPIs) that are required for ligase activity. The crystal structure of several PPI surfaces of the SCF-Skp2-p27 complex have been characterized. Using in silico modeling, virtual library screening, and medicinal chemistry syntheses, we are identifying and testing small molecule inhibitors of Skp2 activity for their antitumor effects in mouse and human cancer models.

**Recent Publications**


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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. *The Molecular Mechanisms of Adipose Tissue Aging*. We are studying the molecular mechanism of the decline in brown fat’s mass and function during normal aging and whether preserving brown adipocytes can improve energy balance, insulin sensitivity, and metabolic homeostasis. We have recently found evidence suggesting that mitochondrial fission, also called fragmentation, in brown adipocytes is diminished during aging. It has been hypothesized that mitochondrial fission gives mitochondria better access to energy substrates. This research could lead to strategies to prevent brown fat’s decline with age or even to increase the number of brown fat cells and boost their ability to improve glucose metabolism, burn more calories, and prevent weight gain.

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:**


Activation of mRNA translation is a common feature of cancer cell. However, it is not clear to what extent increased mRNA translation contributes to cancer progression, shaping the tumor microenvironment and immune response. Through the lens of ribosomes, we explore the mechanistic underpinnings of translation reprogramming in MYC and KRAS driven cancer model, the tumor microenvironment, and immune response to cancer.

1. **Differential translation control by different KRAS alleles.** Mutant KRAS is the key driver of pancreatic, lung, and colon cancer. KRAS is frequently mutated at the three missense mutation hotspots (G12, G13 and Q61) and a growing body of evidence suggests that each mutation can have specific structural, biochemical, and biological effects on KRAS function. Intriguingly, different KRAS mutant allele has differential effect on cancer growth, metabolism, and mRNA translation. Our current work focuses on investigating the differential effect of mutant KRAS allele on mRNA expression, translation, and cancer phenotypes.

2. **Explore aberrant translation in pancreatic cancer and microenvironment.** We have identified that RNA helicase eIF4A regulates the translation of key oncogenes such as MYC, KRAS, and this can be readily targeted by using eIF4A inhibitors. KRAS and MYC activation feeds to mRNA translation programs conducive to cancer progression and shaping the tumor microenvironment. My research group investigate the mechanism of mRNA translation and its contribution in the gene expression outputs and functional proteome due to alternate translation start site selection in cancer and microenvironment.

3. **Role of aberrant translation products in cancer immunity.** My work has shown that aberrant translation products are frequently generated upon oncogene activation and alters the protein form of key immune receptors such as CD19. Interestingly, we observed that a significant fraction of translation is activated from upstream open reading frames upon oncogene activation resulting in the generation of “new short peptides of unknown function”. We study the role of these short peptides and aberrant translation products in cancer signaling and cancer immunity.

**Representative Recent Publications**


Cellular communication is essential for proper coordination of organ function. It involves release of signaling molecules, activation of receptors and channels, and direct signaling through gap junctions. Among these key players is ATP and its receptors, pannexin 1 channels and connexin43 (Cx43) gap junction channels. We are interested in determining the role played by ATP (purinergic) and Cx43 signaling in disease conditions. The Suadicani lab works collaboratively with the labs of Dr. Mia Thi, Department of Orthopaedic Surgery, Dr. Kelvin Davies, Department of Urology, and Dr. David Spray, Department of Neuroscience.

1. Urothelial ATP signaling in diabetic bladder dysfunction and in IC/BPS. Urothelial cells line the interior of the urinary bladder and serve both as a protective barrier against urine contents and sensors of bladder distension. Urothelial cells release ATP in response to bladder distension, and ATP signaling from the bladder to the central nervous system regulate micturition. We have shown that the mechanosensitive pannexin 1 (Panx1) channels, which also provide a direct pathway for cellular ATP release, play essential roles in urothelial mechanosensation and ATP signaling. Panx1 has also been shown to mediate inflammatory activation. We are now investigating extent to which dysregulation of Panx1 contributes to development of bladder dysfunction in type 1 diabetes and emergence of pelvic pain and urinary symptoms in Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS).

2. Pannexin 1 and ATP signaling in female sexual dysfunction. The mechanosensitivity of female genital organs and its importance for perception and response to penetrative sexual stimulation are well recognized. However, little is known regarding the molecular mediators and mechanisms involved in vaginal mechanosensory transduction. We show that Panx1 is expressed in the vaginal epithelium and mediates ATP release in response to vaginal stimulation, a response that was altered in animal models of diabetes and menopause, conditions known to be associated with female genital arousal dysfunction. We are now investigating the mechanisms that lead to Panx1 dysregulation in the vaginal epithelium and whether Panx1 channels may provide novel therapeutic targets to manage this condition.

3. Pannexin 1 and Cx43 channels in sensory neuron and glia signaling. Neuronal activity is modulated by glial cells. We have shown that glial communication involves Panx1-mediated ATP signaling and that bidirectional satellite glial cell-neuron signaling in sensory ganglia is altered in animal models of inflammatory pain. We are currently investigating the involvement of altered glial Panx1 and Cx43 signaling in chronic pelvic pain and in mechanisms underlying development of urogenital complications (i.e. erectile dysfunction, bladder overactivity and urinary incontinence) from pelvic surgeries.

4. ATP signaling in the diabetic bone. Diabetes affects the skeletal system, leading to reduced bone density and increase risk for bone fractures. ATP signaling plays a central role in bone homeostasis. We have shown that Panx1 and the purinergic P2X7 receptor form a mechanosignaling complex, and that altered expression of this complex in diabetic bone results in impaired ATP release and response to mechanical loading, which might be implicated in the diabetic skeletal complications. Our studies are now focusing on investigating mechanisms that regulate Panx1-P2X7R expression in the healthy and diabetic bone.

Representative Publications:
This research program investigates the genetic basis for the regulation of neural circuitry by the neurotransmitter serotonin. Dynamics of serotonin signaling underscore long-standing theories of neural circuit plasticity that leads to learning, memory and stress responses. Drugs that target the serotonergic system are the most commonly prescribed therapeutic agents for the treatments 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 a systematic dissection of the genetic pathways and synaptic properties regulated by serotonin signaling and characterizing drugs that might alter them.

**Representative Recent Publications**


Identifying the “mechanosomes”, which is the complex responsible for sensing, transduction and signaling in response to mechanical stimuli, is essential to elucidate molecular and cellular machinery in mechanosensitive tissue. Some of the mechanosome components identified until now includes Panx1 hemichannel, purinergic receptor P2X7R, and integrin αVβ3. We are interested in how the altered mechanosome complex contributes to pathological conditions in mechanosensitive tissues such as bone and bladder. The Thi lab works collaboratively with the labs of Dr. Sylvia Suadicani, Dept. of Urology and Dr. David Spray, Dept. of Neuroscience at Einstein and Dr. Mitchell Schaffler, Dept. of Biomedical Engineering at City College of New York, on projects listed below.

1. **Mechanosomes in sugar coated bone.** We have recently shown that type 1 diabetes (T1D) alters Panx1-P2X7R mechanosignaling complex in osteocytes, key mechanosensing cells in bone, and disrupts proper load-induced bone adaptation and thereby likely contributes to bone loss in T1D. We further hypothesized that load-induced regulation of bone mass occurs not only at the local bone level but remotely involving direct signaling between the bone and the nervous system. Diabetes affects the nervous system, particularly sensory nerves and yet, the extent to which diabetes impairs neural regulation of load-induced bone responses is still unknown. Our studies also indicate that besides its role in osteocytic mechanosignaling, Panx1-P2X7R also participates in bone neuro-mechanosensory signaling and mediates load-induced inflammasome activation. Our current work focuses on this new functions that are also targeted by diabetes.

2. **Structural, molecular and functional specialization of osteocyte mechanosomes.** As the key mechanosensing cells of bone, osteocytes orchestrate a wide range of bone functions including bone modeling, remodeling and loss. However, the precise mechanisms through which they accomplish this sensing task remain unclear. We have discovered that the osteocyte cell processes function as uniquely sensitive mechanosensory elements through specialized mechanosome complex (Panx1, P2X7R, αVβ3 and CaV3.2 T-type calcium channel). We are currently exploring how osteocytes function as mechanosensors in healthy and diseased bone.

3. **Mechanosomes in diabetic bladder dysfunction (DBD).** Along the course of T1D mellitus, the bladder undergoes a progressive transition from a normal to an overactive and then to an underactive state. The factors and mechanisms that regulate these temporal changes in bladder function are still unclear. We have shown that Panx1 plays an essential role in the urothelial mechanosensory, transduction and signaling system. Thus changes in Panx1 expression could alter the bladder sensitivity to distention. We are currently investigating the role of urothelial Panx1 channels in the emergence and temporal progression of DBD.

**Representative Publications**


