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Biochemistry & Molecular Biology

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From the Chairman's Desk, Dr. Rodney E. Kellems

As a basic science department in a research-intensive medical school, the major mission of the Department of Biochemistry and Molecular Biology (BMB) is to conduct innovative and important multidisciplinary biomedical research. The research activities of the BMB faculty are built on the premise that Biochemistry is the study of the molecular basis of life. This premise is evident in the research programs of each of our faculty members who share a common goal of understanding the molecular structure and mechanisms responsible for biological function. BMB is host to a diverse array of research programs ranging from atomic resolution studies of molecular machines, mouse models of human disease, and translational studies with our clinical colleagues. Basic biomedical research is conducted in cell biology, structural biology, genetics, immunology, microbiology, neurobiology, and circadian biology. Preclinical and translational research is carried out in areas of pulmonary disease, cardiovascular disease, hematology, hypertension, diabetes, obesity, metabolic syndrome, burn injury, pain, sickle cell disease, bioinformatics, and cancer. BMB faculty members are involved in productive collaborations with many faculty members from other departments at the medical school, and in this way, enhance its overall research environment. Particularly active collaborations take place with the Departments of Internal Medicine (Pulmonary and Hematology Divisions), Obstetrics, Gynecology and Reproductive Sciences, Neurosurgery, and Surgery (Center for Translational Injury Research). We also have ongoing collaborations with faculty members from other basic science departments. The fundamental mechanistic approaches taken by our faculty provide meaning to the term "molecular medicine."

Research in the Department

BMB is home to three research centers and a NIH-supported program project grant that represent areas of research excellence within the department. Faculty members associated with the **Structural Biology Imaging Center** (Irina Serysheva, Director) use their investigative tools to determine the structures of cellular machinery at the molecular and atomic level of resolution. Their experimental approaches include X-ray diffraction, nuclear magnetic resonance spectroscopy, and electron cryomicroscopy. These methods determine the three-dimensional structures of biological molecules and their assemblies, providing key structural information that guides research efforts to elucidate functional mechanisms. Faculty members associated with the **Center for Membrane Biology** (John Spudich, Director) utilize multidisciplinary approaches to elucidate the molecular structure and function of membrane proteins and the effects of membrane lipid composition on membrane protein structure and function. Membrane proteins make up 25-30% of the proteome of organisms from prokaryotes to humans and include channels, transporters, signal transducers and enzymes. Membrane proteins are the targets of a large portion of medicines. Faculty members associated with the **Center for Membrane Biology** utilize multidisciplinary approaches including biophysical and spectroscopic methods to elucidate the molecular structure and function of membrane proteins in normal and diseased conditions. **The Pulmonary Center of Excellence** (Michael Blackburn, Director) includes faculty members focused on understanding the molecular basis of pulmonary diseases, including idiopathic pulmonary fibrosis, asthma, pulmonary hypertension, and ventilator-induced lung injury. Mouse models of lung disease, coupled with genetic and biochemical approaches, are used to identify factors contributing to lung disease, and thereby highlight therapeutic opportunities. Additionally, the Pulmonary Center has an active tissue banking program based on procurement of diseased lungs obtained from patients receiving a lung transplant. The Pulmonary Center benefits considerably from an NIH-funded Program Project titled "The Hypoxic Adenosine Response." This PPG is directed by Michael Blackburn and focuses on the beneficial role of adenosine signaling in acute lung injury and the detrimental role of persistent adenosine signaling in chronic lung disease.

Overall, the research activities of BMB faculty provide an atmosphere of discovery and learning that enriches medical and graduate school educational activities. BMB faculty

members are effective and important contributors to numerous medical and graduate school course offerings. BMB faculty members invest heavily in the education and research training of graduate students and postdoctoral fellows, and teach several well attended courses designed specifically for graduate students. The Department presents a weekly seminar series where students and fellows can listen to, learn from, and meet with prominent scientists from around the world, as well as a weekly research workshop that provides important training opportunities to program students and postdoctoral fellows. During these workshops, trainees can communicate their research findings and receive critical feedback, which helps guide their research activities. The department also sponsors an annual two-day research retreat that is held off-site and offers important opportunities for professional interactions in an informal setting. Students and postdoctoral fellows present their research findings in an oral and poster format and receive feedback from other members of the research community. The weekly research workshop, annual research retreat, and graduate student progress reports that are mandated twice a year provide valuable opportunities to inform the BMB research community of research activities taking place in the department.

"Overall, the research activities of BMB faculty provide an atmosphere of discovery and learning that enriches medical and graduate school educational activities."

The BMB faculty is a well-funded community of curiosity-driven scientists conducting significant and innovative research on many frontiers. The research activities of BMB faculty members have no arbitrary thematic boundaries. Thus, we are not restricted to certain areas of biological research, but instead we are free to take our research activities in new directions when opportunities arise, or when our curiosity drives us there. We enjoy our diversity and thrive on the interdisciplinary research opportunities that our diversity provides. Because we have no thematic boundaries, we are able to recruit faculty members in emerging areas of biomedical research who have promising future potential. While we eagerly embrace the latest technological developments, we resist the temptation to follow the crowd and pursue research considered "hot," "trendy," or "fashionable." Ultimately, we aim to be "innovators" and "trailblazers."

The first part of this handbook provides overviews of our research centers and other areas of research excellence in our department. Next, in alphabetical order, are descriptions of the research activities of each faculty member. BMB Facts and Figures are also included.

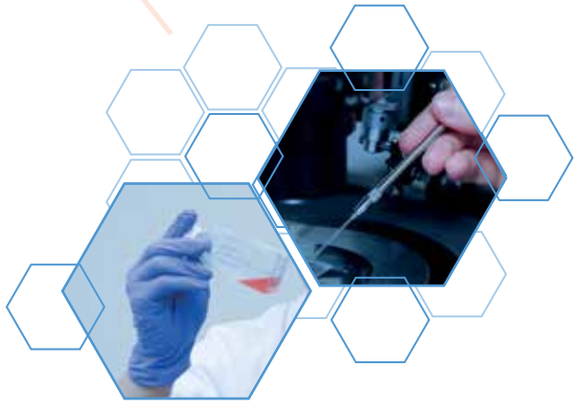
Our McGovern Scholars

Two faculty members from the Department of Biochemistry and Molecular Biology are among the first to be named McGovern Scholars. Yang Xia, M.D., Ph.D., and Vasanthi Jayaraman, Ph.D., both professors, are among the inaugural class of McGovern Scholars – selected as outstanding research nominees at McGovern Medical School.

The other faculty McGovern Scholars include Jun Liu, Ph.D., associate professor of pathology and laboratory medicine; Scott Lane, Ph.D., professor of psychiatry and behavioral sciences; and William Margolin, Ph.D., professor of microbiology and molecular genetics.

"I am delighted to be able to honor some of our outstanding faculty with these new research awards," Dean Barbara J. Stoll said. "This funding is the approximate annual funding from a $1 million endowment, and that is our goal – to be able to work with our Office of Development to fundraise $1 million endowments for our deserving scientists."

Xia is internationally known for research in two areas of cardiovascular research, preeclampsia, and sickle cell disease. She studies how lack of oxygen and inadequate blood supply leads to tissue damage and organ dysfunction and identified markers, which will lead to therapies for sickle cell disease, high blood pressure, chronic pain, pre-eclampsia and chronic kidney disease.



Most recently she has made major discoveries that contribute to understanding human acclimatization to high-altitude hypoxia.

She received her medical degree from Hunan Medical University in China and her doctorate degree from the UTHealth Graduate School of Biomedical Sciences. She completed postgraduate training in biochemistry and molecular biology at the medical school. She joined the medical school faculty in 2001 as a research assistant professor in the Department of Biochemistry and Molecular Biology.

Jayaraman is a leader in the field of structure function investigations of ion channels, working to map changes at the single molecule level. She investigates how signaling occurs in the brain with the aim of understanding physiological processes controlled by these signaling pathways and finding intervention for disease conditions, such as stroke, Parkinson's and Alzheimer's.

"I am honored to be named a McGovern scholar," Jayaraman said. "Being named a McGovern Scholar has allowed me to further my research goals by providing flexibility and allowing us to take up high-risk and high-reward projects. The benefits are already evident with me being able to secure the highly selective National Institutes of Health Maximizing Investigators Research Awards (MIRA) grant."

Jayaraman received her doctorate degree from Princeton University and completed a postdoctoral fellowship at Cornell University.

She joined McGovern Medical School in 2002 as an assistant professor in the Department of Integrative Biology.

All McGovern Medical School chairs were invited to nominate top researchers who were not holders of endowed chairs as McGovern Scholars. An independent committee then reviewed the applicants to select the five winners. Work is under way to fund the five scholars with endowed chairs, which require a $1 million gift. For more information on giving, please see our website.

"I am honored to be named a McGovern scholar."

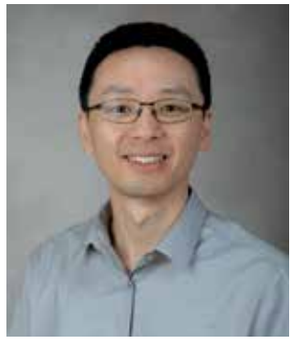
Meet the CPRIT Scholars

With the aid of a program to advance cancer research in the Lone Star State, the Department of Biochemistry and Molecular Biology recently has recruited three researchers who are tackling cancer at the molecular level.

The three new assistant professors, each recruited with a $2 million grant from the Cancer Prevention & Research Institute of Texas (CPRIT) are Leng Han, Ph.D., previously a postdoctoral fellow at MD Anderson Cancer Center; Wenbo Li, Ph.D., formerly a postdoctoral fellow at The University of California, San Diego; and Kuang-Lei Tsai, Ph.D., formerly a postdoctoral fellow at The Scripps Research Institute.

> *“These are the type of young investigators who will develop into our future institutional leaders in this area (...)”*

“The CPRIT program has been tremendously important to help us recruit some of the most outstanding young scientists in cancer research who will help us to continue to build excellence in this and related research areas in the future,” said George Stancel, Ph.D., executive vice president for academic and research affairs and holder of the Roger J. Bulger, M.D., Distinguished Professorship at UTHealth. “These are the type of young investigators who will develop into our future institutional leaders in this area, and the CPRIT support is critically important to help us recruit them to UTHealth".



Dr. Leng Han

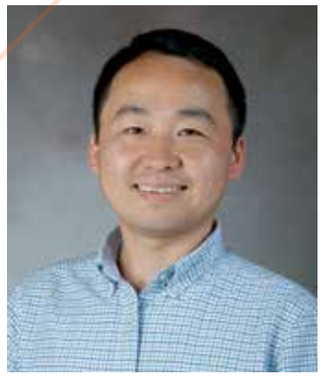
Han is working on the molecular mechanisms shared by 20 different types of cancer, including pancreatic and breast. He said he is particularly interested in identifying differences in RNA expression that distinguish cancer cells from normal cells, which is seen as crucial to the development of targeted therapies.

“We already have huge volumes of data on DNA and RNA sequences from cancer patients,” he said. “The challenge is to interpret this vast amount of sequence information, and I’m developing computational pipelines to address this challenge. When we get a better understanding of the molecular mechanisms of cancer, we can develop better diagnostic and therapeutic strategies.”

“Dr. Han’s extensive experience with next generation sequence data from large cancer data resources has prepared him for this research,” explained Rodney Kellems, Ph.D., chair of the Department of Biochemistry and Molecular Biology.

"CPRIT provides funding through its academic research, prevention and product development research programs."

Beginning operations in 2009, CPRIT has awarded $1.79 billion in grants to Texas researchers, institutions and organizations. CPRIT provides funding through its academic research, prevention and product development research programs.



Dr. Wenbo Li

Whereas most genetic research focuses on the tiny part of the genome housing genes that contain the body's blueprint, Li said the remaining area has information that could play a vital role in the fight against cancer. In his laboratory, Li uses multiple cancer models including estrogen-sensitive breast cancer cells to gauge the impact of dark matter on the activation of critical genes that may influence normal cells to take a route to cancer. His research has provided new insights into the process of genome architecture and gene expression control.

"Cancer has long been linked to mutations in genes that are translated into proteins, the body's building blocks," Li said. "But, I believe that mutations in other areas also contribute to cancer. These are called noncoding regions, or dark matter."

In particular, he has determined how one type of such noncoding regions called enhancers turns thousands of genes off and on.

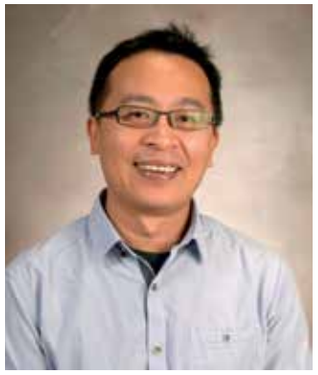
"Enhancers are like the engine of a car and they can make cars drive quickly. But once control is lost, the car just keeps going. This is kind of the same way cancer cells take off," said Li, who emphasized that this once-assumed dark matter is being illuminated by recent advances in genome sequencing technologies.

"These studies suggest a promising therapeutic avenue to target enhancers for cancer intervention," he said."

Dr. Li's postdoctoral research provided the first evidence supporting a functional role for enhancer-derived long noncoding RNAs (eRNAs) in the regulation of gene expression," said Kellems. "His research routinely appears in journals of the highest esteem. He has recently published two authoritative reviews on enhancer RNAs, one in *Nature Reviews Genetics* and another in *Cell Cycle*. Dr. Li adds considerable strength to the RNA biology group within our department."

Li's future studies will attempt to characterize how these noncoding disease mutations take place and how they cause human disease. Because these noncoding mutations are often found to be distinctive among individuals, Li's research has an ultimate goal of achieving personalized medicine for each individual with unprecedented precision.

Li said he is excited to be working in the Texas Medical Center because it gives researchers like him the opportunity to translate their findings from basic biology into new therapies. "I'm grateful for the opportunity to work with Dr. Kellems and the other biochemists," he said.



Dr. Kuang-Lei Tsai

The newest CPRIT recruit is Kuang-Lei Tsai, Ph.D., who joined the faculty as an assistant professor. Tsai received his Ph.D. in bioinformatics and structural biology from National Tsing Hua University in Taiwan and recently completed his postdoctoral training in the structure and dynamics of transcriptional mediator complexes at the Scripps Research Institute in La Jolla, Calif.

Tsai uses cyro-electron microscopy and X-ray cystallography to understand molecular mechanisms and structures involved in gene regulations that cause tumorigenesis.

"Understanding their 3-D structures and molecular mechanisms can help the development of new therapeutic agents to cure cancer," he said. "I am especially interested in understanding the structure and molecular mechanism of macromolecular complexes, such as chromatin remodeling complexes, transcriptional machines, and long non-coding RNA, which are involved in human diseases caused by abnormal gene regulation."

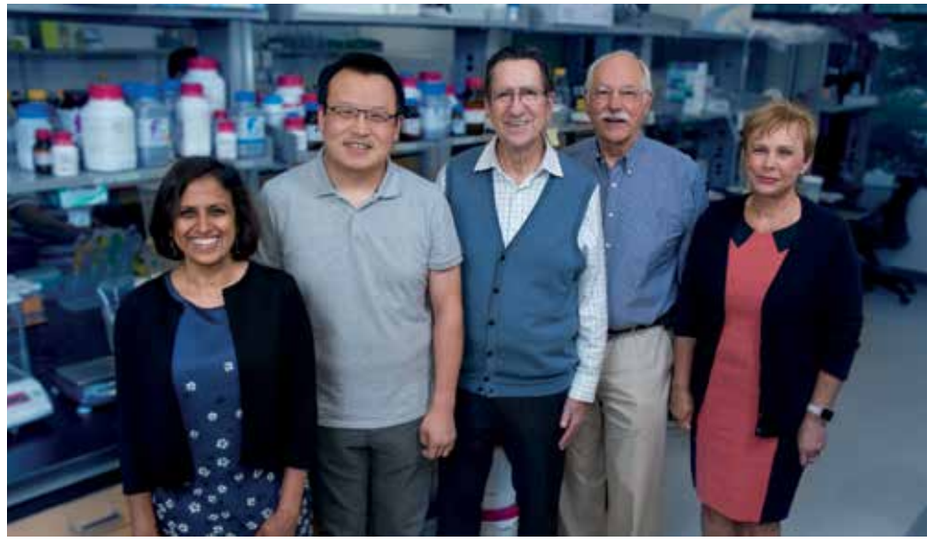
The CPRIT grant will help Tsai purchase high-end equipment and reagents for cell culture, expression and purification of human proteins.

"It will also provide me access to use the cutting-edge cryo-electron microscope and the strongest computational power for structural determination," he added. "This will greatly speed up the structural determination of important biological complexes and help the development of therapeutic agents."

Tsai said he was attracted to the medical school based on its size and potential for collaboration. "The McGovern Medical School is one of the largest medical schools in the United States, and its location is in the biggest medical center on earth," he said. "It provides humongous resources for doing basic science and translational research."

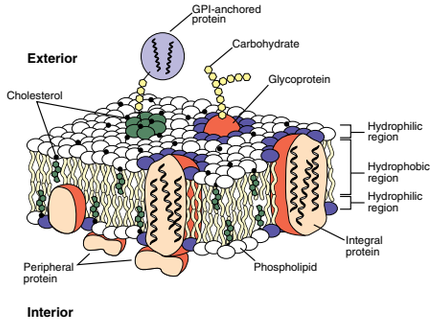
Center for Membrane Biology (CMB)

John L. Spudich, Ph.D., Director



30% of Human Proteins Reside in Membranes

Membranes, films of lipids containing a variety of different types of proteins, surround cells and organelles in all organisms from simple bacteria to humans. Membrane proteins and lipids, often in macromolecular assemblies, are responsible for the transport of materials into and out of cells, cellular energy production, cell sensing and signal transduction, cell-cell contact recognition, cellular recognition of antigens in the immune system, detoxification of reactive compounds, intracellular compartmentalization and communication between cell compartments, and cell-cell communication via hormones, neurotransmitters, chemokines and other signaling molecules. Membrane functions are therefore vital to health and not surprisingly specific defects in membrane proteins and toxic effects of membrane-active substances are associated with numerous known disease states. Membrane proteins are the targets of more than half of all drugs on the market today and are also key components used in the formulation of vaccines against bacterial, viral, and fungal human pathogens.



Generic mammalian cell membrane lipid bilayer with associated proteins and lipids as indicated.

About 30% of the proteomes of all organisms, from bacteria to man, encode membrane proteins. Their diverse and fundamental roles in cellular processes throughout the biological world make them a new focus of biological and biomedical research, which has previously focused more on the soluble components of cells. Because of their non-aqueous environment, membrane protein atomic structures are notoriously difficult to solve, but researchers in our department have been particularly successful in determining their structure and studying their atomic resolution.

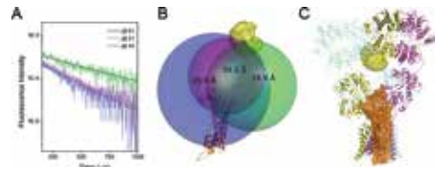
Membrane Biochemistry Research in the CMB

Researchers in the Center for Membrane Biology, housed in the Department of Biochemistry & Molecular Biology, focus on the biogenesis of membranes and cell compartments, lipid-protein interactions, the structure and function of membrane-embedded molecular machines that carry out active transport of ions, metabolic substrates, proteins, and DNA in both prokaryotic and eukaryotic cells as well as the structure, function, and networking of membrane receptors that sense environmental signals and transport information to cytoplasmic signal transduction pathways in microorganisms and human tissues.

A shared objective in CMB research laboratories is to understand at the atomic level how membrane molecular machinery works. A few examples are described below.

Cell to Cell Communication and Ion Channels

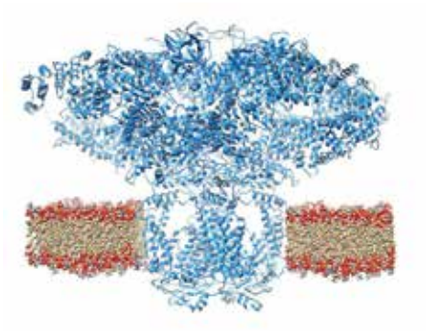
An important example of membrane-mediated cell-cell signaling is the communication between nerve cells, which serves as the basis of all brain activity. A chemical signal, or "ligand," is liberated at the end of one nerve cell and converted into an electrical signal at the second nerve cell. The electrical signal is produced by ion channels that are opened by the ligand, or ligand-gated ion channels.



Stargazin in complex with glutamate (AMPA subtype) receptors.

Dr. Vasanthi Jayaraman's laboratory studies the mechanism underlying this mode of communication in which small molecules that constitute the chemical signals induce large conformational changes in the proteins to which they bind, resulting in the opening of transmembrane ion channels, thus generating the electrical signal in the receiving nerve cell. Dr. Jayaraman focuses on understanding glutamate receptors, or proteins in the central nervous system that form cation-conducting channels upon binding glutamate. Dr. Jayaraman's group is on the forefront of elucidating atomic motions responsible for gating glutamate channels. Her lab is one of the most advanced of its kind in applying a wide range biophysical approaches such as vibrational spectroscopy and fluorescence-based methods, in combination with electrophysiology, to determine structural changes ultimately controlling the electrical currents. One recent innovation developed in Dr. Jayaraman's laboratory is the abili-

ty to resolve single-molecule structural changes; a spectroscopic approach measuring the complete structural and functional landscape that the protein probes, giving a comprehensive understanding of the structure-dynamic control of protein function.

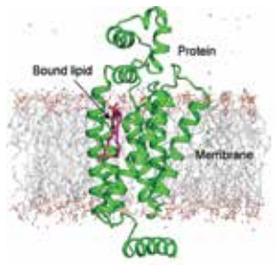


3D structure of inositol-1,4,5-trisphosphate receptor solved by single-particle Cryo-EM to 4.7 Å resolution (Nature 2015).

Dr. Irina Serysheva's research focuses on understanding how molecules, especially ions, are transported across membranes. Ion channels play critical roles in a wide array of cellular and physiological processes; including nerve signaling as discussed above as well as muscle contraction, fertilization, hormone secretion, gene transcription, metabolic regulation, immune responses, and apoptosis. Dr. Serysheva's research emphasizes Ca^{2+} channels, which are implicated in many pathological conditions such as Alzheimer's, Parkinson's disease, Huntington's disease, autoimmune diseases, AIDS, cancer, and stroke. Serysheva's lab has established itself at the forefront of single-particle electron cryomicroscopy (cryo-EM) of ion channels. The group pursues a multidisciplinary approach that includes cryo-EM, biochemical, and biophysical characterization in conjunction with computational methods and bioinformatics. The lab's current efforts are focused on achieving atomic resolution structures of Ca^{2+} channels to explain the physicochemical principles underlying their function. Dr. Serysheva recently determined a near-atomic resolution structure of the inositol 1,4,5-trisphosphate receptor, which is an intracellular Ca^{2+} release channel ubiquitously expressed in eukaryotic cells. These studies are beginning to elucidate how these channels recognize a variety of extracellular stimuli and convert them into Ca^{2+} signals that trigger markedly different cellular actions.

Lipid-Protein Interaction

Interaction of a membrane protein with its lipid environment determines how a protein folds into its functional structure. About 10% of pathogenic mutations in membrane proteins result in their misfolding into a non-functional structure. General aging also results in the accumulation of misfolded proteins. Therefore, a better understanding of the factors that govern membrane folding is important to establish a molecular basis for the wide spectrum of diseases caused by misfolded proteins. A major focus of **Dr. William Dowhan**, a leader in this field, is to understand how lipid-protein interactions determine normal as well as abnormal membrane protein folding. Such information is necessary to guide intervention strategies and preventative measures for many misfolded protein diseases such as cystic fibrosis, Alzheimer's, dementia, Parkinson's, alpha-one antitrypsin deficiency, scabies, and spinocerebellar ataxia. Through combined in vivo mutant analysis in microorganisms and in vitro study of specific lipid-protein interactions, Dr. Dowhan's group has identified direct roles of lipids in topological organization of membrane proteins, initiation of DNA replication, cell division, and energy metabolism.



Crystal structure of a lipid phosphatase PgpB bound with a PE lipid molecule in cell membrane.

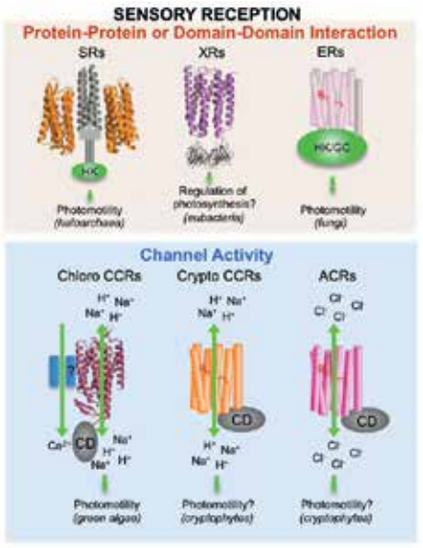
Membrane proteins also act as enzymes that modify lipids, a phenomenon studied by **Dr. Lei Zheng**. Lipids with varied chemical structures of head group and fatty acid chain assemble membrane bilayers for basic cellular compartmentation, and for protecting cellular components from environmental threats. Membrane proteins are either embedded (integral membrane proteins) or anchored (peripheral proteins) in the lipid bilayer, reminiscent of assorted islands in a lipid "ocean." Lipids not only function as solvents for membrane proteins, but also regulate their activity via specific lipid-protein interaction in response to changes either from the environment or in the cells. Recently, Dr. Zheng's group was able to determine the X-ray crystal structure of the bacterial lipid phosphate phosphatase (PgpB) protein in complex with its native lipid inhibitor phosphatidylethanolamine (PE). In the structure shown at left, a PE lipid inserts deeply in a hydrophobic tunnel of the PgpB molecule to prevent lipid substrate access from the bilayer. Dr. Zheng's structure provides a vivid picture revealing how a cell regulates its lipid biosynthesis via specific lipid-protein interaction in the membrane. His group currently focuses on identification of novel lipid enzymes and transporter proteins involved in bacterial infection and metabolic regulation. This ongoing work may help to develop new strategies to enhance antibacterial action of the human innate immune system, as well as elucidate how gut bacteria live in an anaerobic environment.

Transporters and Light-Signal Transduction

Dr. John Spudich studies a family of light-activated, visual pigment-like proteins called microbial rhodopsins, that carry out ion transport and sensory signaling processes. These membrane-embedded proteins offer the experimental advantage in the study of diverse basic membrane functions driven by light, which provides the investigator temporal and spatial resolution not available for similar processes mediated by chemical substances.

> *"Dr. Serysheva recently determined a near-atomic resolution structure of the inositol 1,4,5-trisphosphate receptor, which is an intracellular Ca^{2+} release channel ubiquitously expressed in eukaryotic cells."*

Some of the proteins discovered by Dr. Spudich's laboratory are ion transporters, while others are sensory receptors that use light to gain information about the environment to regulate cell processes (see figure). Recently, the significant contribution of microbial rhodopsins has laid a chemical foundation for the new biotechnology of optogenetics.



Optogenetics, a methodology that uses light to control cell membrane potential in neurons, has revolutionized neuroscience research; especially studies of brain function (see Neurobiochemistry section). Currently Dr. Spudich's group emphasizes basic research on the molecular mechanisms of the light-sensing proteins, especially the new type of light-gated anion channel rhodopsins (ACRs) that his lab discovered this past year. His group also collaborates with neuroscientists to further develop and apply these new tools to understanding neuronal circuitry. Abnormal firing of neurons is either a cause or a major symptom in many pathological conditions such as epilepsy, Parkinson's disease, autism, tinnitus, and neuropathic pain. Furthermore, clinical trials using microbial rhodopsin channels to restore vision to visually impaired patients began in 2016.

Selected Publications:

Govorunova EG, Sineshchekov OA, Janz R., Liu X, and Spudich JL. 2015. Natural light-gated anion channels: A family of microbial rhodopsins for advanced optogenetics. *Science*. 349:647-650.

Fan G, Baker ML, Wang Z, Baker MR, Sinyagovskiy PA, Chiu W, Ludtke SJ, and Serysheva II. 2015. Gating machinery of InsP3R channels revealed by electron cryomicroscopy. *Nature*. 527:336-341.

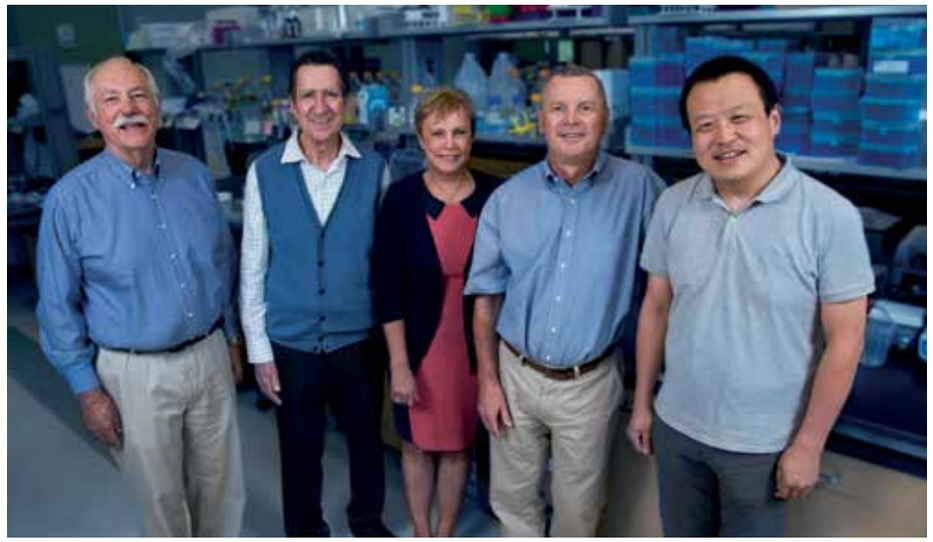
Vitrac H, MacLean DM, Jayaraman V, Bogdanov M, and Dowhan W. 2015. Dynamic membrane protein topological switching upon changes in phospholipid environment. *Proc Natl Acad Sci USA*. 112:13874-13879.

Affiliated Faculty Members:

William Dowhan, Ph.D.; Vasanthi Jayaraman, Ph.D.; Irina Serysheva, Ph.D.; John Spudich, Ph.D.; Lei Zheng, Ph.D.

Structural Biology Imaging Center (SBIC)

Irina Serysheva, Ph.D., Director, Pawel Penczek, Ph.D., Co-Director

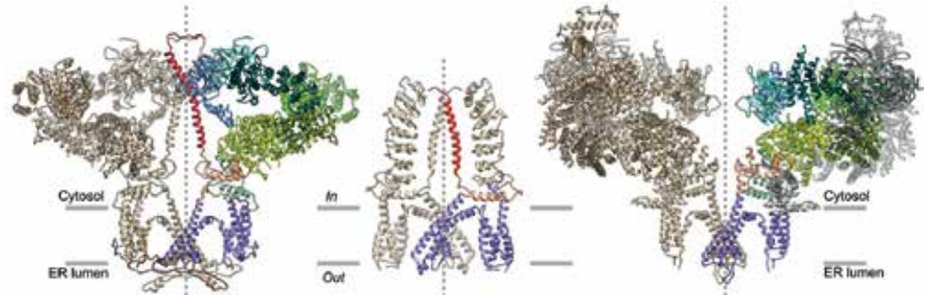


Research Interests of SBIC Faculty

The research activities of faculty associated with the Structural Biology Imaging Center focus on molecular machines involved in the production of cellular energy, ion transport, the interaction of small regulatory molecules with proteins, and development of computational methods for the construction of molecular models of macromolecules. A common goal of the SBIC faculty is to reveal the three-dimensional structure of macromolecules to gain insight into how these machines function and are controlled at the atomic level. Comparing the structure of normal and diseased molecules provides molecular information explaining the underlying cause of diseased states, which is necessary to develop cures. Molecular details of how small molecules interact with proteins provide the information necessary to develop drugs against viral and bacterial pathogens, as well as therapies for treating diseases that are caused by mutated macromolecules.

Dr. Irina Serysheva

The Serysheva laboratory broadly focuses on the area of structure-function of membrane proteins with specific emphasis of structural characterization of Ca^{2+} channels that modulate the continuous flow of Ca^{2+} ions across cellular membranes and are key players in regulation of multiple cell signaling pathways. Understanding how ion channels detect specific signals and convert them into a net of ion transport is an important frontier of structural biology. Dr. Serysheva's laboratory uses the versatility of high-resolution cryo-EM and computer 3D reconstruction to obtain in-depth structural insights into the molecular mechanisms underlying the passage of Ca^{2+}

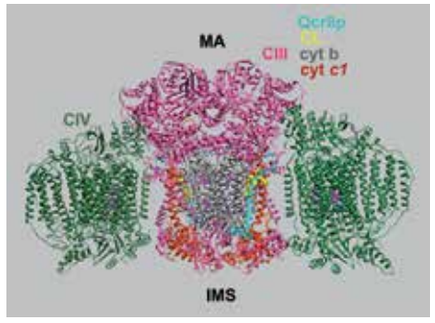


Structural conservation of ion channels

ions via ion channels. Research efforts of the Serysheva laboratory consist of several components: purification of ion channels from natural sources or from high-level expression systems; functional characterization using biochemical and biophysical methods; cryo-EM imaging; image processing and 3D reconstruction; structure annotation using visualization and computational tools; bioinformatics. One important multifunctional family of ion channels is the intracellular Ca^{2+} release channels such as inositol 1,4,5-trisphospate receptor (IP3R) localized in the endoplasmic reticulum membrane of virtually all eukaryotic cells. Utilizing recent technological advances in cryo-EM and advances in image processing algorithms, the Serysheva laboratory has solved the structure of the entire full-length IP3R channel to near-atomic resolution (published in *Nature* 2015).

Dr. William Dowhan

A major focus in the Dowhan laboratory is to understand the role of the phospholipid cardiolipin in modulating energy metabolism in the mitochondria. Deficiencies in normal cardiolipin levels are associated with cardiac muscle dysfunction following ischemia, cardiac and skeletal muscle dysfunction in the male-inherited disease Barth Syndrome and reduced brain function associated with aging. The mitochondrial respirasome that is responsible for the majority of cellular energy production is composed of individual protein complexes that are organized into a supercomplex. Failure to form these higher ordered structures in the absence of cardiolipin is a characteristic of many of the above diseases. The Dowhan lab has determined the structure of one of these supercomplexes using state-of-the-art cryo-EM and has established a direct requirement for cardiolipin in the formation of this supercomplex. Current studies are focused on determining the molecular basis for cellular dysfunction resulting from aberrant cardiolipin levels.



The organization of Complex III (CIII) and Complex IV (CIV) into a supercomplex found in the inner mitochondrial membrane of yeast as derived from single particle analysis of images obtained by cryo-electron microscopy.

Dr. Lei Zheng

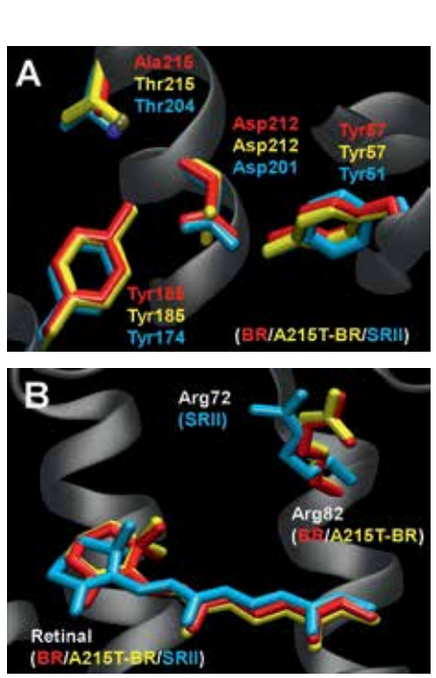
The structural focus of the Zheng laboratory is targeted on two important membrane protein systems using X-ray crystallographic approach. 1) Ca^{2+} transporter NCX protein; The NCX protein promotes Ca^{2+} efflux that is an essential step in a heart contraction-relaxation cycle. Dysfunction of NCX is mediated with ischemia reperfusion and even heart failure. The Ca^{2+} efflux activity of NCX is powered by an inward Na^{+} gradient energy and tightly regulated by the intracellular Ca^{2+} concentration. Dr. Zheng's group has reached several milestones in understanding this complex and dynamic process. First, they have determined the crystal structure of NCX homolog protein to illustrate the structural architecture for specific Ca^{2+} transport in the membrane (see figure), and have also illustrated protein conformational change of its intracellular Ca^{2+} binding domain that is induced by regulatory Ca^{2+} signal. This will help researchers understand these two mechanisms in an integrated setting and help to illuminate the molecular determinants of NCX-mediated cardiovascular diseases. 2) The lab also studies enzymes involved in bacterial phospholipid metabolism to understand lipid-protein interaction (see Membrane Protein section). The novel biological and structural information revealed in this study will help to develop new therapeutic approaches to deal with bacterial infections which continue to pose severe global health problems.

Crystal structure of calcium transporter YfkE protein

Dr. John Spudich

The Spudich lab studies a family of light-activated, visual pigment-like proteins called microbial rhodopsins that carry out ion transport and sensory signaling processes. These membrane-embedded proteins offer the experimental advantage of studying diverse basic membrane functions driven by light, which provides the investigator temporal and spatial resolution not available for similar processes mediated by chemical substances. Several of these light-activated proteins are important to the study of neurological diseases because of their ability to control neuron firing with light, and are of potential use in phototherapeutic treatment of diseases involving neuron hyper- or hypo-activity (see Neurobiochemistry section). Their structure/function study entails atomic-resolution structures of the molecules and their mutated forms. Because of the heterogeneous environment of membrane proteins – partly surrounded by lipid and partly water-exposed - membrane protein atomic structures are notoriously difficult to solve, but Dr. Spudich's laboratory has been notably successful in their structure determination and atomic resolution studies using

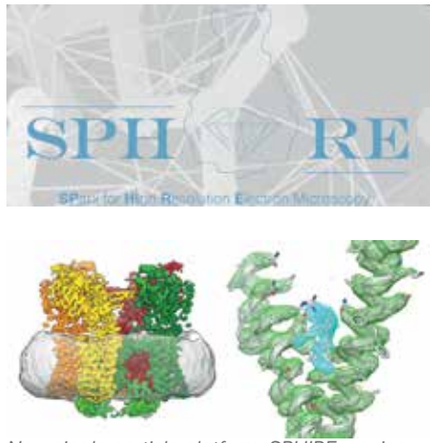
X-ray crystallography. Starting with his group solving the first two light-sensing rhodopsin structures (published in *Science* in 2001 and 2004), crystallographic structures have continued to be an incisive analytical technology in his research program. Dr. Spudich uses the high-energy synchrotron X-ray beamline of the Molecular Biology Consortium, of which McGovern Medical School is a founding member and beamline part owner, at the Lawrence Radiation National Laboratory in Berkeley, California. Currently his focus is on atomic structure determination of anion channel rhodopsins, new types of light-gated ion channels important to neuroscience that his laboratory recently discovered.



Atomic structural differences in the photoactive site of bacteriorhodopsin (red), a sensory signaling mutant of BR (yellow), and sensory rhodopsin II (SRII), showing that subtle changes modify microbial rhodopsin functions (from EN Spudich et al. J Mol Biol 415:455-463, 2012).

Dr. Pawel Penczek

The focus of Dr. Penczek's team is in high-resolution cryo-EM and the development of computational methodologies and efficient and largely automatic tools for cryo-EM structure determination. They primarily focus on single-particle analysis and three-dimensional reconstruction, with additional effort devoted to processing of helical specimen, as well as automation of electron tomography data processing. Their current research interests are focused on the identification of conformational states of macromolecules by single particle EM and validation techniques for cryo-EM. The Penczek laboratory introduced dedicated statistical resampling strategies for EM projection data to obtain information about structural variability in EM maps, and is currently advancing validation techniques for identification of conformers in the sample.



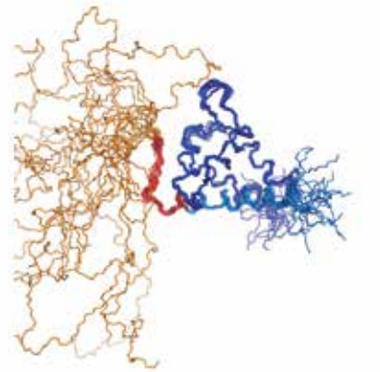
New single particle platform, SPHIRE, paving the way for cryo-EM practitioners.

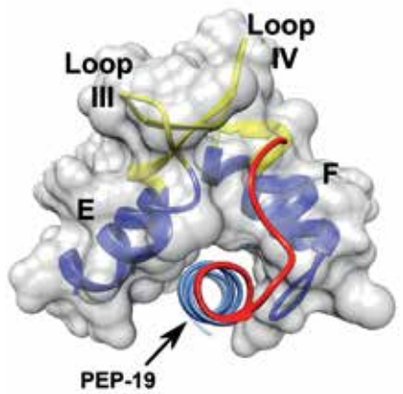
In the last decade, the Penczek team has collaborated with the EMAN2 team (Dr. Ludtke, Baylor College) to develop SPARX, a modern single particle software package. Their current effort is to embed this new software into SPHIRE, a new single particle platform, by providing user-friendly Graphical User Interface that will guide cryo-EM practitioners through the protocol of computational structure determination. This work is done in collaboration with Dr. Raunser's group (Max-Planck Institute) that developed extensive training capabilities of SPARX, including an interactive tutorial, thus facilitating immersion into cryo-EM for new researchers.

Dr. John Putkey

The efforts of structural biologists have provided impressive pictures of biomolecular structures at atomic resolution. But macromolecules, especially proteins, are not the static structures implied by these snapshots. They are instead dynamic molecules with intramolecular conformational changes that occur on the nanosecond to second timeframes. Extreme conformational plasticity is now recognized as the hallmark property of a class of proteins called intrinsically disordered proteins, which have no stable structure, but exist instead as a large ensemble of disordered states. Another hallmark of these proteins is that they can adopt defined structure upon binding to other proteins. It is now recognized that intrinsic disorder is a common property of regulatory proteins, in part because it allows them to adapt to binding sites in multiple target proteins.

NMR is the technique of choice to study intrinsically disordered proteins. The Putkey laboratory uses solution NMR to study the structure and function of calcium binding proteins. Dr. Putkey and his collaborators discovered that the regulatory domain cardiac troponin C remains closed in its calcium bound state, but has sufficient conformational flexibility to assume an open state when bound to calcium sensitizing compounds.



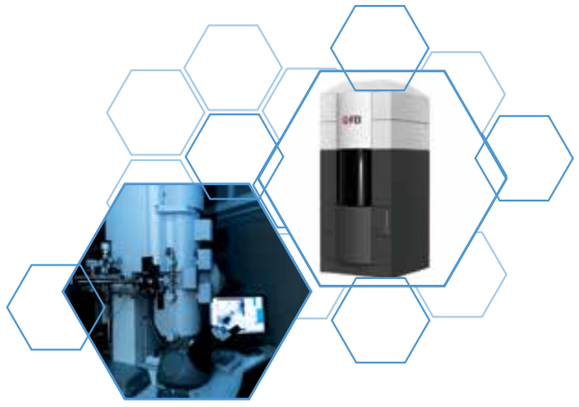


3D NMR solution structure of the PEP-19/apo calmodulin complex. The spaghetti-like strands in the upper panel are regions of disorder. The helix indicated by the arrow in the bottom panel is disordered when PEP-19 is not bound to calmodulin.

They also showed that the dwarfing syndrome called PSACHS is due to mutations in collagen oligomeric matrix protein that render its calcium binding domain disordered. The Putkey laboratory discovered that PEP-19 and neurogranin are intrinsically disordered proteins that act as regulators of calmodulin, which is an essential calcium dependent regulatory protein found in all eukaryotic cells from slime mold to humans. They also showed that PEP-19 and neurogranin adopt a helical conformation upon binding to calmodulin, and that this association profoundly changes or modulates calmodulin's calcium binding properties to tune it to local calcium levels. The Putkey lab used NMR to determine the solution structure of PEP-19 bound to apo calmodulin. This structure revealed that PEP-19 increases the rate of association of calcium to calmodulin by creating a new surface with negative electrostatic potential that "steers" the positively charged calcium to binding sites on calmodulin.

Dr. Kuang-Lei Tsai

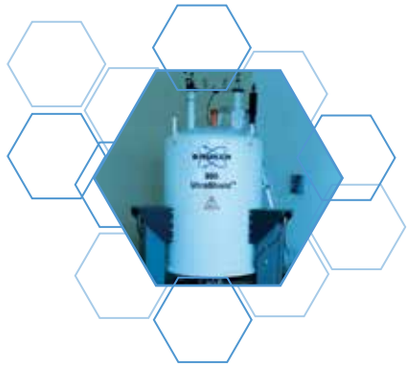
Dr. Tsai's laboratory is interested in understanding the structure and molecular mechanism of macromolecular machines that are involved in human diseases caused by abnormal gene regulation. For structural determination, they use various powerful techniques such as cryo-EM and X-ray crystallography. In the past, they have used single-particle EM to determine the structures of transcriptional Mediator and its complex with RNA polymerase II (RNAPII). These results not only provided detailed information about the Mediator-RNAPII interaction but also improved understanding of how Mediator works in the transcription process. Current projects are focused on structural and functional studies of the eukaryotic transcriptional complexes that regulate gene expression through interaction with long non-coding RNA. By understanding their detailed molecular mechanisms and structures, the long-term goal is to help develop novel therapeutic approaches to combat human diseases.



Technai Polara G2 TEM & Titan Krios

Instrumentation in the SBIC

Visualizing the three-dimensional structures of macromolecules is beyond the ability of standard microscopes. To overcome this, the SBIC at the McGovern Medical School provides state-of-art instrumentation and expertise to determine the three-dimensional structures of objects ranging from individual molecules (proteins, nucleic acids, carbohydrates) and their higher order molecular assemblies (ribosomes, viruses, and entire cells) at the atomic level.



NMR Spectrometer

Electron Microscopy

The center currently houses a Tecnai Polara electron cryomicroscope equipped with a state-of-the-art K2 Summit direct electron detector. In December of 2017, the arrival of the Titan Krios, a cutting-edge electron cryomicroscope, provided new technologies that will accelerate UTHealth studies from cancer biology to drug discovery. Electron cryomicroscopy (cryo-EM) allows visualization of biological specimens in a near-native aqueous environment. Cryo-EM is becoming an increasingly mainstream technology for studying not only the structure of individual molecules and their assemblies at atomic resolution, but also the architecture of entire cells (electron cryotomography, cryo-ET) at molecular resolution. The process of obtaining 3D structures by cryo-EM involves preparation of biological material suitable for EM analysis, vitrification of biological material, and imaging of cryospecimens followed by application of advanced computational image processing techniques. The whole process requires close collaboration between biochemists, biophysicists, electron microscopists, and computational biologists.

Nuclear Magnetic Resonance (NMR) Spectroscopy

SBIC houses a 600 MHz NMR spectrometer capable of atomic level resolution of molecules. NMR spectroscopy is an advanced technique that allows the study of biological material ranging from small molecules to proteins and nucleic acids (DNA and RNA). One advantage of the technique is that molecules can be studied in their natural form in aqueous solution in static conditions as well as dynamic ones where molecules interact with each other. Therefore, detailed information of how small molecules like drugs or individual large molecules interact with each other can be obtained. Such information is important for drug design and understanding complex interactions between molecules.

Xray beamline hutch at the Berkeley ALS Synchrotron

X-Ray Crystallography

SBIC is a member of the Molecular Biology Consortium, which operates the advanced X-ray beamline at the Advanced Light Source synchrotron in Berkeley, Calif. With an annual fee, member researchers have access to and assistance with using the facility to analyze their samples. X-ray crystallography involves rigorous purification of proteins and nucleic acids followed by technically challenging crystallization of the samples. Samples are then subjected to an X-ray beam, which results in a unique defraction pattern. Computational analysis of this pattern provides the highest resolution model of the three techniques available in the center.

Computational Support

Application of advanced computational methods is critical to the conversion of raw data obtained by electron microscopy to a molecular model of the biological sample. Building such models begins with collecting on the order of 50,000 to 100,000 images, which must be individually analyzed for quality, and then merged into a final model. These require application of various software packages developed locally and available online. In addition, local computers are available to utilize these software packages as well as a super computer at UT Austin to construct the final models.

Affiliated Faculty Members:

William Dowhan, Ph.D.; Pawel Penczek, Ph.D.; John Putkey, Ph.D.; Irina Serysheva, Ph.D.; John Spudich, Ph.D.; Kuang-Lei Tsai, Ph.D.; Lei Zheng, Ph.D.

Selected Publications:

Fan G, Baker ML, Wang Z, Baker MR, Sinyagovskiy PA, Chiu W, Ludtke SJ, Serysheva II. 2015. Gating machinery of InsP3R channels revealed by electron cryomicroscopy. *Nature*. 527:336-341.

Mileykovskaya E, Penczek PA, Fang J, Mallampalli VKPS, Sparagna GC, and Dowhan W. 2012. Arrangement of the Respiratory Chain Complexes in Saccharomyces cerevisiae Supercomplex III2IV2 Revealed by Single Particle Cryo-Electron Microscopy (EM). *J Biol Chem.* 287: 23095-23103.

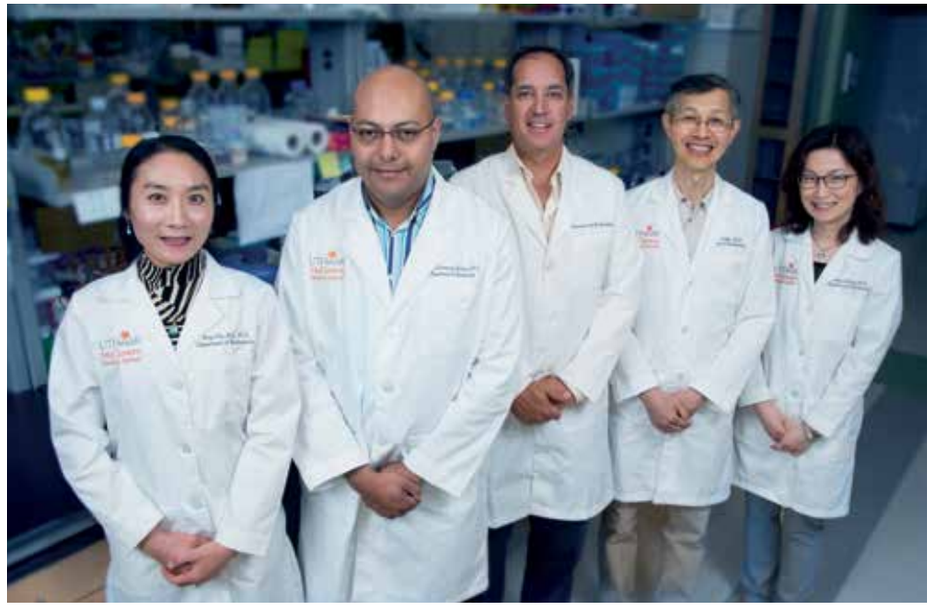
Wu M, Tong S, Dietrich KD, Wang M, and Zheng L. 2013. Crystal structure of H+/Ca^{2+} antiporter YfkE: Structural insight into Ca^{2+} efflux mechanism. *Proc Natl Acad Sci USA*. 110:11367-11372.

Tsai KL, Yu X, Gopalan S, Chao TC, Zhang Y, Florens L, Washburn MP, Murakami K, Conaway RC, Conaway JW, Asturias FJ. 2017. Mediator structure and rearrangements required for holoenzyme Formation. *Nature*. 544:196-203.

Wang X, Putkey JA. 2016. PEP-19 modulates calcium binding to calmodulin by electrostatic steering. *Nat Commun*. 7:13583.

Pulmonary Center of Excellence

Michael R. Blackburn, Ph.D., Director

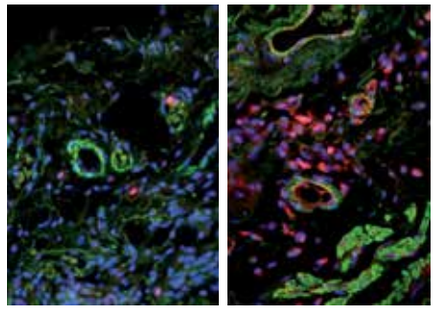


Acute and chronic pulmonary diseases are currently the third-largest killer in the US and fourth-largest worldwide. A recent publication from the *Lancet Respiratory Journal* states that although lung diseases represent a significant worldwide cause of death, funding toward research in pulmonary diseases is significantly below the societal burden of lung disease. Further research into pulmonary diseases is critically needed. Compared to cancer and cardiovascular diseases, the incidence of pulmonary diseases continues to rise in the United States and worldwide. In the United States alone, 35 million Americans suffer from lung disease, accounting for approximately 400,000 deaths per year. Unfortunately, there are limited treatment options for pulmonary diseases such as Acute Respiratory Distress Syndrome (ARDS) and chronic lung diseases such as asthma, lung fibrosis, chronic obstructive pulmonary disease (COPD), or pulmonary hypertension (PH). Current treatments provide symptomatic relief at best, but offer no prospect of cure or disease reversal. Lung transplantation is often the only viable option. This lack of effective treatment options is largely a consequence of our lack of understanding of the mechanisms that lead to the development of these lung diseases. As such, research efforts aimed at understanding the pathophysiology of lung disease are needed to develop new therapies.

The BMB department has made important contributions to pulmonary research. **Dr. Michael Blackburn** made early discoveries that identified

adenosine as major player in acute lung injury, asthma, and lung fibrosis. These discoveries led to several marquee publications in top journals such as the *Journal of Clinical Investigation, The FASEB Journal* and the *American Journal of Respiratory Care and Critical Medicine*. He has been funded continuously by the NIH for the last 15 years. These initial discoveries led to collaborations with pharmaceutical and biotechnology companies in pre-clinical drug testing for several new molecular entities for the treatment of lung fibrosis.

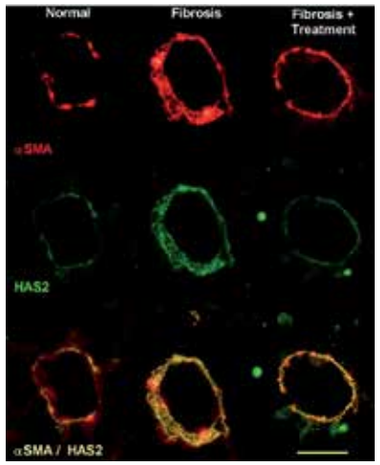
Dr. Harry Karmouty-Quintana, a recent faculty recruit and key contributor to pulmonary disease research who also has been published in the *FASEB Journal*, the *American Journal of Physiology*: *Lung Cellular and Molecular Physiology*, and the *British Journal of Pharmacology*, has made recent discoveries highlighting the role of hyaluronic acid, a component of the lung extra-cellular matrix, in the development of pulmonary hypertension in association with chronic lung injury.



Immunofluorescent staining showing increased signals for hypoxia inducible factor 1 alpha (HIF-1α, red/magenta) in lungs from patients with lung fibrosis (right panel) compared to normal patients (left panel). Blue signals are for DAPI and show nuclei and green is for smooth muscle cells.

He has identified bone morphogenetic protein receptor 2 (BMPR2) as a key mediator in lung fibrosis, and in collaboration with Dr. Blackburn, identified increased signals for hypoxia and adenosine in patients with pulmonary hypertension associated with lung fibrosis. Recently, McGovern Medical School identified pulmonary diseases as a desirable area to expand its research, and established the UTHealth Pulmonary Center of Excellence (PCOE) https://med.uth.edu/pcoe/, spearheaded by Dr. Blackburn. One of the greatest assets of the PCOE is its lung tissue biobank, which is managed by Dr. Karmouty-Quintana. The biobank is one of the largest in the country, providing UTHealth scientists access to highly relevant lung tissue material from the explanted lungs of patients with end-stage lung disease.

As part of this new initiative, PCOE Discovery Awards were created to stimulate high-risk, high-gain pulmonary research initiatives at all UTHealth schools. Several BMB faculty members have been successful in securing PCOE awards that focus on uncovering exciting new research perspectives in lung diseases. Some of these areas of research include post-transcriptional mechanisms that control the inflammatory response of human bronchial epithelial cells in health and in airway disease. This research is being led by **Dr. Ann-Bin Shyu**, a leading RNA biologist with seminal publications in high-profile journals such as *Nature*, the *EMBO journal*, and *RNA*. Dr. Shyu's group recently unraveled a novel mechanism by which microRNA 26 (miR-26) dampens inflammatory responses in human bronchial epithelial cells through down-regulating NF-κB signaling.



Immunofluorescent staining showing the effects of treatment on arterial thickening caused by lung fibrosis. Red signals show muscle (αSMA) and green signals are for HAS2 an enzyme that produces hyaluronic acid. Yellow signals are the merged colors. Note the thick muscle wall in fibrosis that is reduced following treatment, with the drug hymecromone that prevents production of hyaluronic acid.

These findings indicate that miR-26 plays a broader and more critical role in pulmonary disease than previously realized. In collaboration with scientist Dr. Amber Luong, Dr. Shyu is using primary airway epithelial cells from healthy individuals and patients with chronic rhinosinusitis (CRS) to further investigate the role of miR-26 in pulmonary disease. In a separate project, Dr. Shyu is investigating the role of airway inflammation and mRNA N6-methyladenosine (m6A) modification epigenetics in CRS, asthma, and pulmonary fibrosis.

In the study of RNA biology, **Dr. Karmouty-Quintana**; **Dr. Leng Han**, a leading scientist in bioinformatics in the BMB department; and physician scientist **Dr. Bindu Akkanti** received a PCOE grant to study how 3'-untranslated region (3'UTR) length of mRNA, through a process known as alternative polyadenylation, leads to the development of pulmonary hypertension. The relationship between altered mRNA sequences and the development of lung diseases is a largely unexplored area. This line of research is based on initial discoveries made by Drs. Ann-Bin Shyu and Eric Wagner at BMB department. In addition to Dr. Karmouty-Quintana's efforts to understand the role of 3' UTR length in pulmonary hypertension, **Dr. Blackburn** leads research efforts into understanding its role in lung fibrosis.

Another strength of pulmonary research scientists at BMB is our capacity to perform translational research studies. Here **Dr. Yang Xia**, an accomplished scientist with highly-cited publications in *Nature Medicine*, and *Cell Reports*, has identified a unique metabolic signature in patients with Sickle Cell Disease (SCD) where the development of pulmonary hypertension is an important phenomenon that is associated with hypoxic conditions in the lung as a result of sickling of red blood cells. In research funded by a PCOE grant she aims to identify novel metabolic biomarkers for early prediction of pulmonary hypertension in SCD. In a highly translational study, Dr. Xia demonstrated how hypoxic conditions in the lung mediate import-

ant physiological conditions, such as adaptation to high altitude, through red blood cell "memory," as well as understanding the duality of how the hypoxic responses can be both protective in acute settings yet detrimental in chronic disease.

Taken together, pulmonary disease is a highly active and growing area of research in the BMB department that is engaged in basic to translational research. Several other initiatives include understanding aging processes in lung disease (**Tingting Weng, Ph.D.**) and BMB scientists with expertise in areas such as circadian rhythm (**Seung-Hee [Sally] Yoo, Ph.D.**) or lipid biology (**Drs. Askar Akimzhanov** and **Heidi Vitrac**) that are building bridges between their research expertise and lung diseases.

Affiliated Faculty Members:
Michael Blackburn, Ph.D.; Harry Karmouty-Quintana, Ph.D.; Ann-Bin Shyu, Ph.D.; Yang Xia, M.D./Ph.D.; Seung-Hee (Sally) Yoo, Ph.D.

Selected Publications:

Luo F, Le NB, Mills T, Chen NY, Karmouty-Quintana H, Molina JG, Davies J, Philip K, Volcik KA, Liu H, Xia Y, Eltzschig HK, and Blackburn MR. 2016. Extracellular adenosine levels are associated with the progression and exacerbation of pulmonary fibrosis. *FASEB* J. 30(2):874-83.

Liu H, Zhang YJ, Wu H, Yegutkin G., D'Alessandro A, Song AR, Sun KQ, Sun H, Kellems RE, Karmouty-Quintana H, Weng TT, Nemkov T, Hansen KC, Subudhi AW, Julian CG, Lovering AW, Eltzschig HK, Blackburn MR, Roach RC, and Xia Y. 2016. Beneficial role of erythrocyte adenosine A2B receptor-mediated AMPK activation in high altitude hypoxia, *Circulation*. 134(5):405-21.

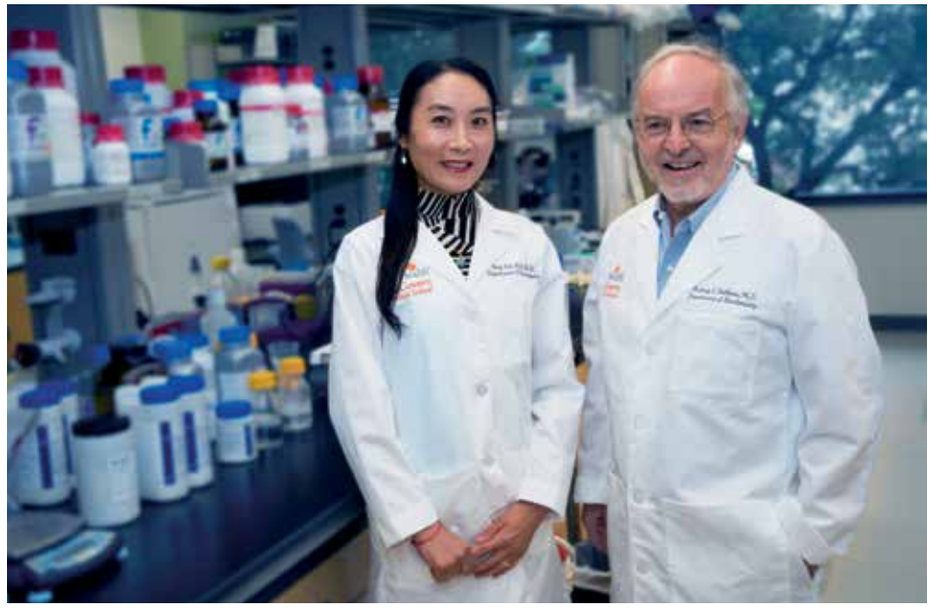
Garcia-Morales LJ, Chen NY, Weng T, Luo F, Davies J, Philip K, Volcik K, Melicoff E, Amione-Guerra J, Bunge RR, Bruckner BA, Loebe M, Eltzschig HK, Pandit LM, Blackburn MR, Karmouty-Quintana H. 2016. Altered Hypoxic-Adenosine Axis and Metabolism in Group III Pulmonary Hypertension. *Am J Respir Cell Mol Biol*. 54(4):574-83.

Le TT, Karmouty-Quintana H, Melicoff E, Le TT, Weng T, Chen NY, Pedroza M, Zhou Y, Davies J, Philip K, Molina J, Luo F, George AT, Garcia-Morales LJ, Bunge RR, Bruckner BA, Loebe M, Seethamraju H, Agarwal SK, Blackburn MR. 2014. Blockade of IL-6 Trans signaling attenuates pulmonary fibrosis. *J Immunol.* 193(7):3755-68.

Weng T, Poth JM, Karmouty-Quintana H, Garcia-Morales LJ, Melicoff E, Luo F, Chen NY, Evans CM, Bunge RR, Bruckner BA, Loebe M, Volcik KA, Eltzschig HK, Blackburn MR. 2014. Hypoxia-induced deoxycytidine kinase contributes to epithelial proliferation in pulmonary fibrosis. *Am J Respir Crit Care Med*. 190(12):1402-12.

The Lancet Respiratory Medicine. Lung disease left out in the cold. *The Lancet Respiratory Medicine*. 2016;4(7):527.

Hypertension: The Silent Killer – Preeclampsia and Beyond



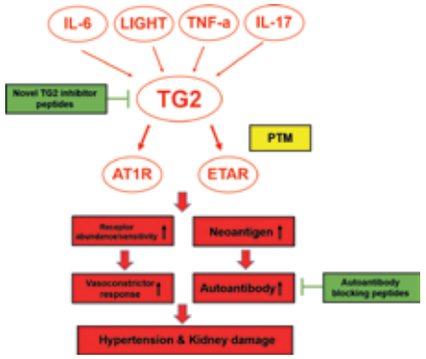
Hypertension is a major risk factor for cardiovascular disease and stroke, two leading causes of death in the United States and the world. Hypertension also causes serious adverse effects on the kidneys and can lead to end-stage renal disease and kidney failure. Hypertension affects approximately 80 million people in the United States and is an enormous health and economic burden on society. Hypertension is often referred to as the "silent killer," as it frequently does not have obvious symptoms; and therefore, most affected individuals are unaware of their condition. One particularly serious form of hypertension, called preeclampsia, occurs in approximately 5% of pregnancies, resulting in a high mortality rate for both the mother and fetus. Preeclampsia is also associated with increased lifelong risk of hypertension and cardiovascular disease. For a number of years, research directed by Drs. Yang Xia and Rodney Kellems has focused on understanding the molecular basis of hypertension, especially pregnancy-induced hypertension, or preeclampsia.

Drs. Xia and Kellems lead research efforts to determine the role of the immune system in the development of hypertension. Data from their research indicates that hypertension is associated with activation of the immune system, elevated levels of inflammatory cytokines, and the presence of autoantibodies capable of activating a major vascular receptor that regulates blood pressure; the angiotensin receptor, AT1R. These pathogenic autoantibodies were initially discovered in women diagnosed with preeclampsia. Research directed by

Xia and Kellems was the first to show that these autoantibodies cause the defining symptoms of preeclampsia, hypertension and proteinuria, when introduced to pregnant mice. These pathogenic autoantibodies also cause hypertension when introduced into non-pregnant mice. The pre-clinical experimental evidence that AT1-AAs contributes to hypertension is extensive and compelling. A substantial body of evidence, recently reviewed by Xia and Kellems, indicates that multiple forms of hypertension, including preeclampsia, malignant hypertension, refractory hypertension, and primary aldosteronism, are associated with the presence of these pathogenic autoantibodies that contribute to hypertension by the activation of AT1 angiotensin receptors (AT1Rs).

Animal models of hypertension developed by Kellems and Xia have provided compelling evidence that angiotensin receptor activating autoantibodies (AT1-AAs) are active contributors to hypertension. For this reason, it is important to understand the circumstances that lead to autoantibody production. Their research has recently shown that the production of these pathogenic autoantibodies is induced by pro-inflammatory cytokines in both pregnant and non-pregnant mice. The molecular mechanisms linking inflammation to hypertension are poorly understood; a knowledge gap being addressed by research conducted by Xia, Kellems, and their colleagues. This research has brought a new understanding of hypertension, one that emphasizes the role of autoimmunity. Animal models that recapitulate the hypertensive consequences of elevated inflammatory cytokines provide a valuable opportunity to determine the mechanism of cytokine-induced hypertension. They have recently shown that cytokine-induced hypertension and the production of AT1-AA require tissue transglutaminase (TG2), the most ubiquitous member of a widely-distributed family of enzymes that modify glutamine residues on proteins. Overall, these results show that TG2 is an essential factor in cytokine-induced hypertension and the production of AT1-AAs. An interesting feature of these autoantibodies is that they uniformly recognize the same epitope (AFHYESQ) located on the second extracellular loop of AT1Rs. It is noteworthy that the epitope peptide contains a glutamine (Q), a potential target of post-translational modification by TG2. These results suggest that TG2 modifies AT1Rs, and that post-translational modification of these receptors by TG2 contributes to the pathogenesis of hypertension. These are important and novel findings that form the foundation of the hypothesis that TG2 is an essential component linking inflammation, autoimmunity, and hypertension.

As a result of these findings, Xia and Kellems hypothesize that some forms of hypertension and most forms of preeclampsia represent an autoimmune condition associated with cytokine-mediated induction of TG2, resulting in the post-translational modification of AT1Rs, leading to the production of hypertensive autoantibodies, or AT1-AAs. They further hypothesize that AT1-AAs are not passive epiphenomena of hypertension, but instead are active contributors to disease. They term this condition "Autoimmune Hypertension," and further hypothesize that it arises from elevated inflammatory cytokines that stimulate increased TG2 production and post-translational modification of angiotensin receptors. Animal models of hypertension, such as those developed by Xia and Kellems, provide an important preclinical opportunity to test therapeutic strategies for blocking the action of these pathogenic autoantibodies, and for preventing their synthesis.



Hypothesis of inflammatory cytokine-induced hypertension. A model of hypertension involving inflammatory cytokines including LIGHT, TNF-a, IL-6, and IL-17-induced tissue transglutaminase (TG2) and its post-translational modification (PTM) of AT1 and ETA receptors resulting in the creation of neoantigens for autoimmune production of receptor agonistic autoantibodies. Innovative and safe therapeutic strategies to neutralize pathogenic autoantibodies and inhibit tissue transglutaminase are being developed for the treatment of hypertensive disorders. (Fron Liu, Kellems, and Xia 2017)

Affiliated Faculty Members:
Yang Xia, M.D., Ph.D.,
and Rodney Kellems, Ph.D.

Selected Publications:

Zhou CC, Zhang Y, Irani RA, Zhang H, Mi T, Popek EJ, Hicks MJ, Ramin SM, Kellems RE, Xia Y. 2008. Angiotensin receptor agonistic autoantibodies induce preeclampsia in pregnant mice. *Nature Medicine*. 14(8):855-862.

Xia Y, Kellems RE. 2013. Angiotensin Receptor Agonistic Autoantibodies and Hypertension: Preeclampsia and Beyond. *Circ Res.* 113(1):78-87.

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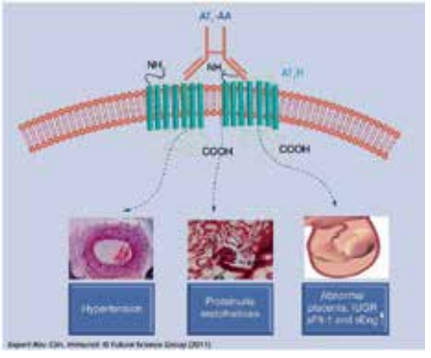
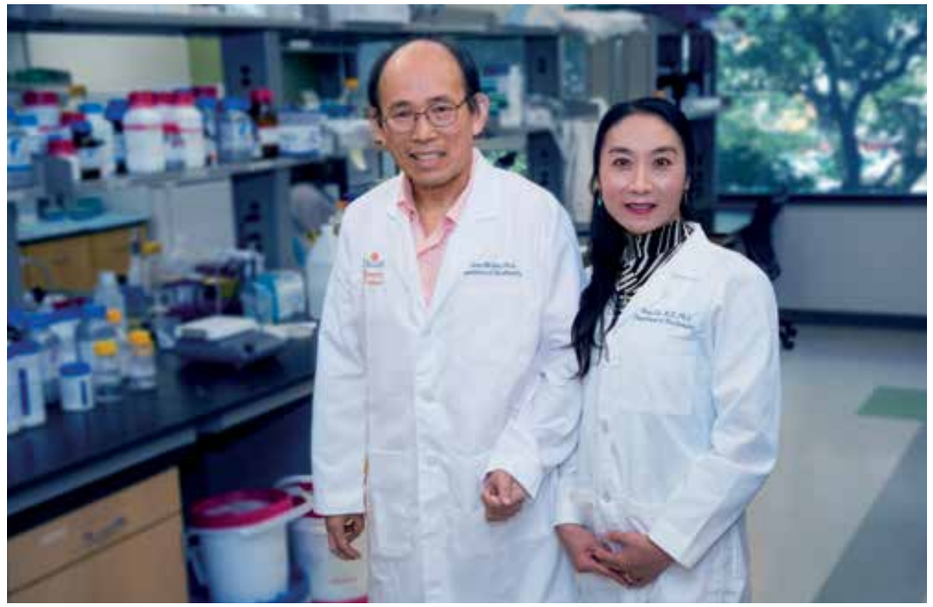


Angiotensin receptor agonistic autoantibodies induce multiple features of preeclampsia in pregnant mice via AT1 receptor activation. This experimental model of autoantibody-induced preeclampsia and IUGR provides important experimental opportunities to test various strategies to prevent autoantibody-induced clinical features associated with preeclampsia. AT1-AA: Angiotensin receptor agonistic autoantibody; AT1R: Angiotensin II receptor; IUGR: Intrauterine growth retardation. (From Xia and Kellems 2011)

Molecular Hematology: Regulating Red Blood Cells



Adult humans have roughly 20 to 30 trillion red blood cells (RBCs) comprising approximately 70% of the total human body cell number. Nearly half of the volume of blood and 95% of blood cells consist of RBCs. RBCs are produced in the bone marrow at a rate of 2 million per second by a process of erythropoiesis. The RBC (also called an erythrocyte) is highly specialized for the uptake, transport, and delivery of oxygen. Oxygen is carried by hemoglobin, a tetrameric protein that carries four molecules of oxygen, and accounts for approximately one-third of the RBC volume and greater than 95% of the protein. Diseases affecting the RBCs are among the most prevalent in the world and include sickle cell disease, thalassemia, and other hemolytic anemias. These diseases occur predominantly in areas of the world where malaria is, or was, endemic. Research activities of two BMB faculty members are focused on erythrocyte biology and physiology, and both groups have used metabolomics to make key discoveries.

Sickle Cell Disease

Dr. Yang Xia's interest in sickle cell disease (SCD) research arose from an unexpected phenotype of priapism observed in adenosine deaminase (ADA) deficient mice. Priapism is a condition of an unwanted and persistent penile erection that is relatively rare in the general population but affects more than half of males with SCD. Xia's research initially illustrated the contribution of excessive adenosine signaling to priapism in ADA deficient mice and then extended these studies to a mouse model of SCD. These original studies were published in The *Journal of Clinical Investigation* (2008) and received extensive coverage in the scientific and lay literature. Subsequently, using high-throughput metabolomic screening, Xia's team discovered that excessive adenosine signaling through the A2B adenosine receptor contributes to the induction of 2,3-biphosphoglycerate (2,3-BPG) in erythrocytes and that excessive 2,3-BPG is detrimental by triggering sickle hemoglobin (HbS) deoxygenation and polymerization, resulting in erythrocyte sickling. This research was published in *Nature Medicine* (2011) and received additional commentary from the journal.

Metabolic screens also uncovered another important metabolite, sphingosine-1-phosphate (S1P) that is elevated in erythrocytes of individuals with SCD. Although S1P is enriched and stored in erythrocytes, its role in erythrocyte physiology had been a mystery prior to the Xia lab discovery that elevated erythrocyte S1P promotes sickling and sickle cell disease progression. This work was published in *The Journal of Clinical Investigation* and *Blood*. Thus, Xia's research has deepened our understanding of molecular mechanisms underlying the pathophysiology of SCD by going beyond the hemoglobin mutation to include adenosine signaling, S1P signaling, and metabolic reprograming. These findings have revealed multiple opportunities for novel therapies for SCD.

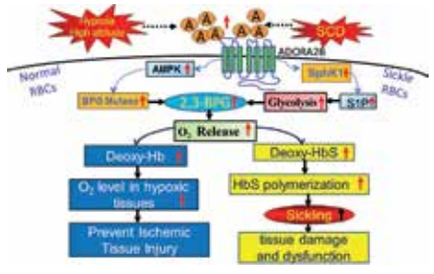


Figure 1. Beneficial role of adenosine and S1P in normal red blood cells (RBCs) becomes detrimental in sickle RBCs. Adenosine and S1P work collaboratively in normal RBCs to induce BPG mutase activity and glycolysis, 2,3-BPG production and more O2 release to counteract tissue hypoxia in normal individuals. However, due to mutation in β-hemoglobin (Hbs) in sickle RBCs, adenosine-S1P mediated O2 release signaling network becomes detrimental to induce more polymerization of HbS, sickling and tissue damage and dysfunction. A: adenosine.

Erythrocyte Metabolism and Function in High Altitude Hypoxia Adaptation

Although the adenosine-activated erythrocyte signaling pathways are detrimental for individuals with SCD, the Xia lab recently showed that these same pathways are activated in healthy individuals at high altitude (5260 meters) and promote enhanced release of oxygen from oxyhemoglobin for individuals facing high altitude hypoxia. In this way, Xia's high altitude research has revealed a previously unrecognized beneficial role of adenosine in the activation of multiple erythrocyte signaling pathways that regulate hemoglobin oxygen affinity. This research solved a decades-old puzzle regarding the molecular mechanisms that regulate hemoglobin oxygen affinity and was published in *Circulation*. Additional research, published in *Nature Communications*, describes the role of sphingosine-1-P signaling in normal erythrocyte physiology in humans adapting to high-altitude hypoxia. Dr. Xia's group published additional studies in *Nature Communications* showing that

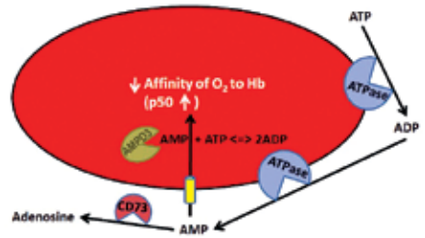
erythrocytes retain "Hypoxic Purinergic Memory" for faster adaptation on re-ascent. Overall, Xia's sickle cell disease research and her high altitude (hypoxia) studies have resulted in fundamentally important discoveries regarding the role of adenosine signaling in the erythrocyte response to physiological hypoxia (Figure 1).

AMP Regulated Oxygen Transport by RBCs

One of nature's many adaptive phenomena is the biological process of deep hypometabolism that takes place in hibernation or torpor in many species of animals. When encountering a prolonged period of metabolic stress, such as a shortage of food supplies or winter, the body temperature of these animals drops to near environmental temperature as they enter hibernation or torpor, allowing them to conserve energy and survive a period of adverse conditions. The underlying molecular basis of torpor remains unclear. A decade ago, Dr. Cheng Chi Lee's laboratory reported a very important discovery in *Nature*. They found that a torpor state can be induced in non-hibernating mammals with a natural metabolite 5'-adenosine monophosphate (AMP) under the appropriate ambient temperature. Dr. Lee's group established a reliable procedure for inducing a torpor state, termed 5'-AMP- induced hypometabolism (AIHM). This procedure is now used by other research groups. Dr. Lee was awarded the prestigious NIH Director's Pioneer Award in 2006, which allowed his group to use mouse genetic tools to investigate the molecular mechanism of AIHM and its potential applications.

Dr. Lee's group examined the molecular changes before, during and after AIHM, applying gene expression profiling and metabolomics approaches. Dr. Lee's studies found that AIHM involves changes in the expression of a relatively small number of genes, and that these changes are largely restored within 48 h post-induction of AIHM, providing molecular evidence that AIHM is a highly reversible process. Interestingly, the gene expression under the control of the circadian clock was found to be largely stalled during AIHM, a feature also observed in natural hibernations. They observed a widespread suppression of energy generating metabolic pathways during AIHM, mainly through the regulation of carbohydrate metabolic pathways. The brain's metabolite flux is minimally affected by AIHM. In addition, their studies revealed that the urea cycle appeared to be functional, thus serving to avoid ammonia toxicity in the animals.

In an effort to understand how AMP induces a hypometabolic state in animals, Dr. Lee's group revealed that the key cellular target of 5'-AMP was the RBC. They found that AMP is directly taken up by RBCs. Using mouse models carrying specific mutations in genes encoding RBC enzymes that regulate extra- and intra-cellular 5'-AMP levels, Lee's group examined how adenine nucleotides (ATP, ADP and 5'-AMP) modulate oxygen transport in RBC. They observed that changes in adenine nucleotide levels in RBCs affect the half-oxygen saturation (p50) value of hemoglobin (Hb), hence its oxygen transport. Studies of Lee's group suggest that AMP levels in the circulation regulate RBC oxygen transport function, thus regulating systemic metabolism.



A working model showing how AMP regulated the oxygen transport function of red blood cells.

There are many exciting potential applications for AIHM, including its use in clinical hypothermia interventions and the maintenance of a torpor state for long-range human space travel. One study from Dr. Lee's group demonstrated that AIHM induces a reversible hypothermia that reduces ischemia/reperfusion damage following a myocardial infarct. Another study demonstrated that whole body cooling increased stability of a temperature-sensitive Cystic Fibrosis (CF) mutant protein, improved its functions, alleviated CF pathological phenotypes and decreased mortality in CF mice. These findings allow the possibility for AIHM-based technologies to be developed into therapeutic hypothermia for clinical applications, and for treating disorders arising from temperature-sensitive protein misfolding defects.

Some of the highlights of these studies from Dr. Lee's group were illustrated in a scientific educational program by National Geographic on the Discovery Channel, as well as in chapter 4 of a published book, Shocked: Adventures in Bringing Back the Recently Dead, by David Casarett (Book Excerpt: http://www.the-scientist.com//?articles.view/articleNo/40663/title/Book-Excerpt-from-Shocked/).

Affiliated Faculty Members:

Yang Xia, M.D., Ph.D.,
Cheng-Chi Lee, Ph.D.

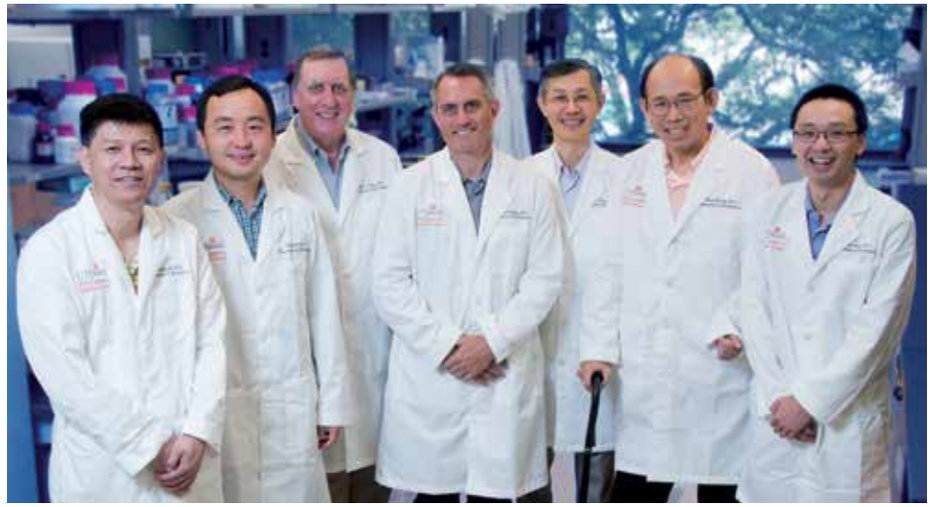
Selected Publications:

Zhang Y, Dai Y, Wen J, Zhang W, Grenz A, Sun H, Tao L, Lu G, Alexander DC, Milburn MV, Carter-Dawson L, Lewis DE. Zhang W. Eltzschig HK, Kellems RE, Blackburn MR, Juneja HS, Xia Y. 2011. Detrimental effects of adenosine signaling in sickle cell disease. *Nature Medicine*. 17(1):79-86.

Zhang Y, Berka V, Song A, Sun K, Wang W, Zhang W, Ning C, Li C, Zhang Q, Bogdanov M, Alexander DC, Milburn MV, Ahmed MH, Lin H, Idowu M, Zhang J, Kato GJ, Abdulmalik OY, Zhang W, Dowhan W, Kellems RE, Zhang P, Jin J, Safo M, Tsai AL, Juneja HS, Xia Y. 2014. Elevated sphingosine-1-phosphate promotes sickling and sickle cell disease progression. *Journal of Clinical Investigation*. 124(6):2750-61.

Sun K, Zhang Y, Bogdanov MV, Wu H, Song A, Li J, Dowhan W, Idowu M, Junega HS, Molina JG,Blackburn MR, Kellems RE, Xia Y. 2015. Elevated adenosine signaling via adenosine A2B receptor induces normal and sickle erythrocyte sphingosine kinase 1 activity. *Blood*. 125(10):1643-52.

Cancer Research: Aiming to Transform Discoveries into Therapeutic Applications



Cancer is a tremendous global health problem. The American Cancer Society has estimated that there will be 1.6 million new cancer diagnoses and almost 600,000 deaths in the United States in 2016. In addition to the emotional toll, the financial burden is tremendous. The estimated cost for the treatment and care of cancer patients in the US is approaching 100 billion dollars per year. Thus, there is an urgent need for new therapeutics to treat this devastating disease. Cancer research using computational, molecular, and cellular approaches is an incredibly powerful approach for identifying new targeted therapeutics. BMB faculty members are using these cutting-edge approaches in cancer research to identify new targeted therapeutics for the treatment of cancer.

Cancer is a disease of the genome. By studying the cancer genome, scientists can discover what genomic changes are causing a cell to become cancerous. Several large-scale initiatives have been established to understand how the genome contributes to cancer development, including the Cancer Genome Atlas (TCGA) and the International Cancer Genome Consortium (ICGC). The research in **Dr. Leng Han's group** applies an integrative approach to study the functional effects of transcriptional and post-transcriptional changes in cancer. Their recent work has focused on characterizing pseudogenes in cancer genomes. In multiple cancer types, they found that the tumor subtypes classified by pseudogene expression showed extensive and strong concordance with the subtypes defined by other molecular data. They also investigated the functional effects of RNA editing in cancer. As an important epigenetic control, RNA editing is a widespread post-transcriptional mechanism that confers specific and reproducible nucleotide changes in selected RNA transcripts. In contrast to somatic mutations, epigenetic mutations at the RNA level caused by RNA editing have received little attention in cancer research. RNA editing events can result in recurrent changes in protein sequences that can function as oncogenic drivers. Thus, the analysis of RNA editing represents a new paradigm with tremendous potential for discovering biomarkers and therapeutic targets.

Recent genome sequencing of cancer patients elucidated that, unexpectedly, most cancer-associated mutations lie in genome regions outside of protein-coding genes. This emphasizes the critical importance to study how these poorly understood noncoding genome regions - the traditionally considered junk DNAs - function in the development of human cancers. **Dr. Wenbo Li's lab** aims to elucidate the basic mechanisms underlying how noncoding regions in dictating gene expression levels in normal cells and how their alteration deregulates critical genes. Li's team will combine cutting-edge genome sequencing technologies, genome editing tools (e.g. CRISPR/Cas9 or C2c2) and increasingly enriched knowledge of human genome mutations in cancer (e.g. TCGA and ICGC databases). His team is eagerly looking for answers for some key questions, for example, do mutations of enhancers (one type of noncoding region) in cancer result in gain or loss of enhancer activity, or alteraction of enhancer-promoter looping events? Could we design novel genome engineering tools to control these disease-associated enhancer mis-behavior? Dr. Wenbo Li also wishes to mine genomes of different species during evolution to gain insights into the functional drifting of regulatory elements such as enhancers. The results of decoding the noncoding genome of cancer will serve as the basis for the next-generation innovative strategies to intervene in human cancer.

Many human diseases, including cancers, are associated with changes in gene expression due to uncontrolled mRNA functions. **Dr. Ann-Bin Shyu's** group studies RNA biology using molecular, biochemical, cellular, and computational biology approaches to investigate how changes in mRNA stability, translation, and localization are regulated in mammalian cells as well as how these processes, when they go awry, contribute to tumorigenesis. The dysregulation of gene expression during tumorigenesis typically involves an increased mRNA expression of oncogenes and a reduced mRNA expression of tumor suppressors. It has become clear that the 3' non-translated regions (3' UTRs) of mRNAs are a reservoir of RNA regulatory elements, and thus a "hotspot" for mutations that lead to many human diseases including cancer. New and compelling evidence demonstrates that alteration of mRNA 3' end formation and length of 3' UTRs, a process termed UTR-APA, provides cancer cells a means of

avoiding or exploiting the repressive nature of 3' UTR regulatory elements such as microRNAs (miRNAs) binding sites and AU-rich RNA destabilizing elements (AREs). This novel example of gene expression plasticity enables cells undergoing cell transformation and tumorigenesis; namely, the ability to drive the expression of oncogenes or dampening the expression of tumor suppressors. Dr. Shyu's group was among the first to show that global 3' UTR shortening elicited by knocking down a core component of the 3' end processing machinery, CFIm25, results in accelerated cell proliferation both in vitro and in vivo. Currently, Dr. Shyu's lab is employing molecular, cell biology, biochemical, and next-generation sequencing-based approaches combined with in-depth bioinformatics analysis to investigate: 1) how APA-elicited global shortening of mRNA 3' UTR influences mRNA stability and translation at the transcriptome-level; 2) how RNA m6A epigenetics, another new theme in regulation of global mRNA turnover, impacts the stability and translation of mRNAs across the transcriptome; and 3) how the changes in these processes may be linked to, or drive, cancer progression.

Genomic and transcriptomic changes lead to altered expression and function of proteins that lead to the uncontrolled cell growth that is characteristic of cancer. Our daily cyclic ritual, including the sleep-wake cycle, is governed by an endogenous molecular clock mechanism. Dysregulation of the circadian clock contributes to many human disorders, including cancer. **Dr. Cheng Chi Lee's group** has led research uncovering the links between the circadian clock and tumor suppression networks. Period 2 (Per2) is one of the essential clock genes. Over a decade ago, Lee's group discovered and characterized Per2's role in tumor suppression, providing the first molecular evidence that a mammalian clock regulator plays a role in cell division cycle regulation. They observed that Per2 deficient mice have abnormal DNA damage response and are prone to tumorigenesis. Several years ago, Lee's laboratory revealed that promyelocytic leukemia protein (PML), a known tumor suppressor, is an important regulator of the circadian clock. More recently, Lee's group discovered that p53 directly controls Per2 expression via a p53-response element in the Per2 promoter. p53 is another well-known human tumor suppressor, mutated or missing in more than 50% of all human tumors. Dr. Lee's group is currently interested in further elucidating how Per2-mediated pathways contribute to the tumor suppression function of p53. They are also interested in how existing p53–targeting drugs may be used by modulating Per2 levels to affect the circadian phase that regulates the sleep-wake pattern, to alleviate sleep disorders often observed among cancer patients and survivors.

Cancer is often associated with the inability of a cell to die in response to damage. This allows genetic mutations to accumulate in the tumor cells contributing to cancer development. **Dr. Darren Boehning's group** is interested in apoptotic cell death, and how this process is altered in cancer. The inositol 1,4,5-trisphosphate receptor (IP3R) is a ligand-gated ion channel which releases calcium from ER stores. The Boehning group has shown that the IP3R plays a critical role in apoptotic calcium release. Boehning's laboratory was first to show that Fas signaling requires the T cell receptor and that this pathway is disrupted in lymphoma. Another project is investigating a role for BRCA1, which is mutated in hereditary breast and ovarian cancer, as a pro-apoptotic protein and modulator of IP3R activity. The Boehning laboratory was the first to show that BRCA1, in addition to its canonical role in DNA repair, also stimulates apoptosis by binding to the IP3R calcium channel in the cytosol. Finally, the Boehning lab investigated how calcium signaling contributes to uterine leiomyoma (fibroid) development. Their laboratory was the first to demonstrate that the cholesterol lowering drugs called statins inhibit fibroid growth in vitro, in vivo, and in human patients by activating apoptotic calcium release. The ultimate goal of research in the Boehning laboratory is to identify new therapeutic targets to inhibit cancer growth.

Cancer cells often have dysregulated signaling pathways leading to uncontrolled cell growth. Protein lipidation is a post-translational modification of cysteine residues with a variety of saturated and unsaturated fatty acid species. This reversible modification has been recognized as a unique regulatory mechanism mediating intracellular localization and trafficking of proteins with direct effects on cell growth. Despite the rapidly growing number of lipidated proteins, the role of post-translational modifications in the pathogenesis of cancer remains largely unexplored. To address this problem, **Dr. Askar Akimzhanov's group** aims to expand the current range of therapeutic strategies for cancer by focusing their studies on two novel classes of enzymes controlling the lipidation state of signaling proteins: protein acyl transferases and serine hydrolases. Their primary research goals are: 1) To uncover the regulatory mechanisms modulating activity of these enzymes, 2) to identify and characterize novel protein targets of these enzymes, and 3) to develop a new generation of anti-cancer agents selectively down-regulating the abnormal activity of these enzymes in tumor cells.

Cancer is often associated with activation of inflammatory pathways. **Dr. Jianping Jin's group** is focused on how cancer signaling is modulated by inflammation. They are specifically interested in the mechanism of constitutive NF-kB activation in basal-like/triple negative breast cancer, and the identification of small molecular inhibitors specifically targeting the ubiquitin and proteasome system (UPS). Dr. Jin's laboratory is also studying how protein ubiquitination controls oncogene function in cancer and in metastasis. Most recently, his laboratory found two potential specific UPS inhibitors from Chinese medical plants. Currently, the Jin laboratory is investigating the exact mechanism of these two UPS inhibitors and their potential applications in cancer therapy.

Once the genomic and cellular perturbations are elucidated, which lead to cancer, the next step is the development of new therapies based on these discoveries. Rational drug design is a cutting-edge, multi-step process that uses 3D structures to identify compounds that are predicted to bind to and alter the activity of target proteins involved in normal or pathological processes, including cancer. The small pluripotent G-protein signaling molecule called K-Ras is a prime target for cancer drugs since somatic mutation in K-Ras occur in about 25% of all human tumors. Compounds that bind to wild type and/or mutant forms of K-Ras would provide a powerful tool in the fight against numerous forms of cancer. Intuitively, an effective drug against K-Ras would be one that binds to its nucleotide binding site. However, such a drug would have a multitude of unwanted side effects since it would also bind to the nucleotide binding site in other G-proteins. It is for this reason that K-Ras has been considered undruggable.

Dr. John Putkey's group, along with UTHealth colleague Dr. Gorfe, have been funded by CPRIT to pursue an alternate approach to the design of drugs that target K-Ras. Computational methods are first used to screen huge libraries of chemical compounds for those predicted to bind not to the nucleotide binding site, but unique pockets on the surface of K-Ras which then exert an allosterically effect to the nucleotide binding site, or interactions between K-Ras and downstream proteins. NMR is then used to determine if these lead compounds bind to the predicted pockets on K-Ras. Biochemistry, biophysics, and cell biology are then used to better characterize the interactions of lead compounds with K-Ras, and to determine their effect on K-Ras signaling pathways. Drs. Putkey and Gorfe have identified several promising lead compounds thus far and are proceeding with pre-clinical development of drugs targeting K-Ras.

BMB faculty span a range of disciplines to comprehensively investigate the genomic, molecular, and cellular changes which contribute to cancer development. They are also on the forefront of therapeutic development using high throughput screening techniques and rational drug design using computational and structural approaches. BMB faculty members are uniquely positioned to discover novel targeted therapeutics to a wide range of cancer subtypes.

Affiliated Faculty Members:
Askar Akimzhanov, Ph.D.; Darren Boehning, Ph.D.; Leng Han, Ph.D.; Jianping Jin, Ph.D.; Cheng Chi Lee, Ph.D.; Wenbo Li, Ph.D.; John Putkey, Ph.D.; Ann-Bin Shyu, Ph.D.

Selected Publications:

Akimzhanov AM, Boehning D. 2015. Rapid and Transient Palmitoylation Of The Tyrosine Kinase Lck Mediates Fas Signaling. *Proc Natl Acad Sci USA*. 112:11876-80.

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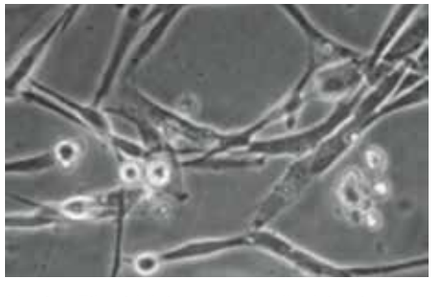
Gong J, Li Y, Liu CJ, Xiang Y, Li C, Ye Y, Zhang Z, Hawke DH, Park PK, Diao L, Putkey JA, Yang L, Guo AY, Lin C, Han L: A pan-cancer analysis of the expresion and clinical relevance of small nucleolar RNA in human cancer. *Cell Reports*, 2017, 21: 1968-1981 (Cover story).

Binding of the tumor suppressor BRCA1 to IP3R in live cells as determined by FRET.



Uterine Fibroid (leiomyoma) cells dying in response to statin treatment.

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Miki T., Matsumoto T., Zhao Z. and Lee C.C. p53 Regulates Period2 Expression and the Circadian Clock. *Nat. Comm*. 4:2444. (2013). PMCID: PMC3798035

Li W, Notani D, Ma Q, Tanasa B, Nunez E, Chen AY, Merkurjev D, Zhang J, Ohgi K, Song X, Oh S, Kim H-S, Glass CK, Rosenfeld, MG Functional roles of enhancer RNAs for oestrogen-dependent transcriptional activation. *Nature* 498 (7455), 516-520

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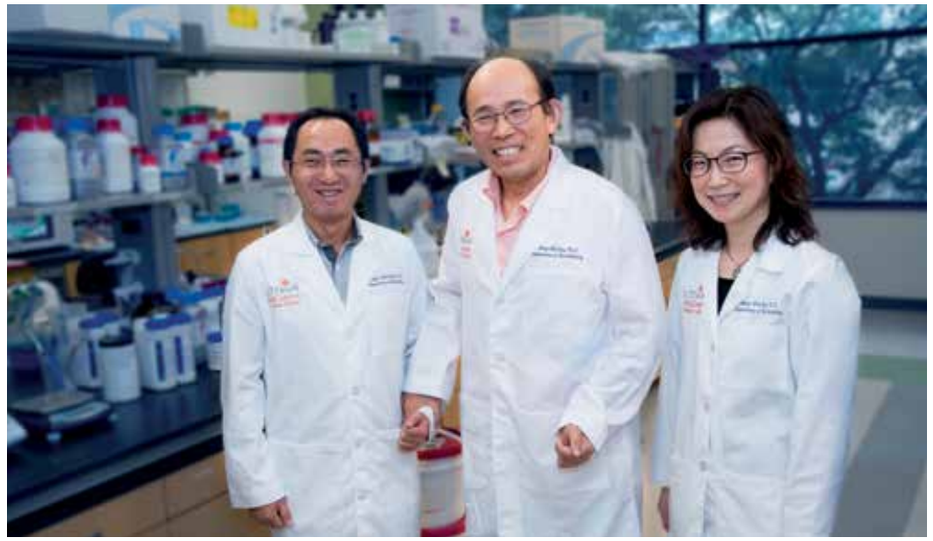
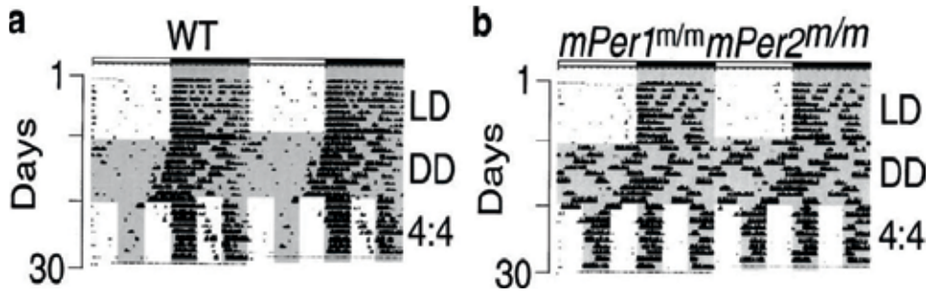
Chronobiology: Timing is Everything



Virtually all life forms on Earth have evolved a biological timer called the circadian clock to translate geophysical cues into biological timing. From lower organisms to mice and humans, proper clock function is pivotal for all essential life processes, including energy balance, sleep/wake cycles, and lifespan. Conversely, abnormal circadian timing is known to compromise fitness and increase risk of disease. Various pathological events have been shown to display strong time-of-day preference (e.g, heart attack in early morning and asthma at night). Furthermore, epidemiological and genetic studies have established an etiological link between dysregulated clocks and various disease conditions, such as sleep disorders, metabolic disorders, cancers, and premature aging. Therefore, it is imperative to understand clock regulation under both physiological and pathological conditions, which will facilitate the development of novel chronotherapeutic strategies to combat diseases and to decelerate aging.

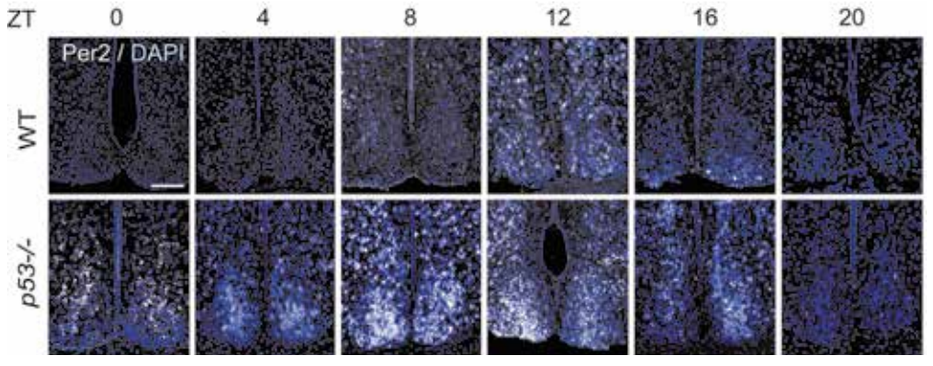
Individually and collectively, three BMB circadian research groups have made fundamental contributions to understanding this biological timing, and on-going efforts promise to advance both scientific knowledge and translational/clinical impact.

Dr. Cheng Chi Lee is an internationally renowned expert in circadian biology. Dr. Lee's laboratory was among the first to identify and characterize key genes of the mammalian circadian clock. The discovery of mammalian clock control gene Per1 by his group was among the studies selected as runner-up for The Break-through-of-the-Year in 1997 by Science. His early work on Per1 and Per2 fundamentally contributed to current understanding of the molecular mechanisms of the circadian clock. Further, Dr. Lee's group pioneered the research initiative demonstrating the interconnectivity between the clock and other cellular networks. Their studies characterizing Per2's role in tumor suppression provided the first molecular evidence that a mammalian clock regulator plays a role in cell division cycle regulation and the DNA damage response. Their recent studies revealed circadian regulatory roles of PML, p53 and MTA1, all known players in human cancers. Currently, Dr. Lee's group is continuing the studies to understand how clock regulators interact with each other; further the investigation on molecular links between the clock network and other important cellular functions; discover and characterize new regulators in the mammalian circadian clock sharing the passion for understanding clock mechanism.



Critical roles of Period genes in intrinsic circadian timing as revealed in mPer double mutant mice. Shown are activity records of wild-type (a) and mPer1, mPer2 double mutant (b) mice that display distinct behavioral responses to light cycles.

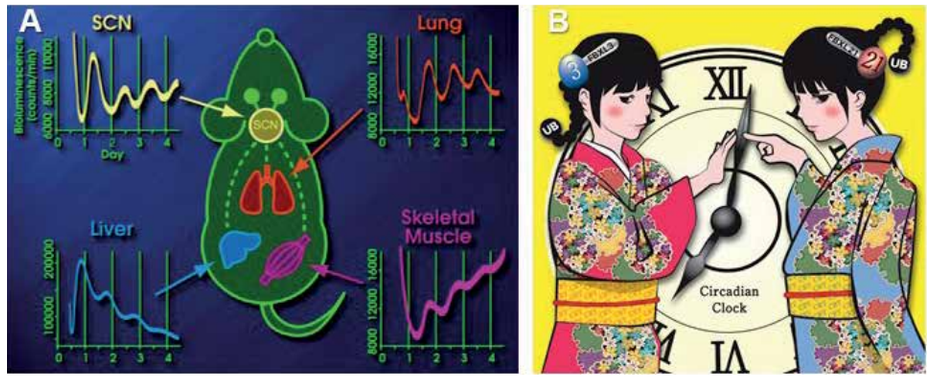
Dr. Seung-Hee (Sally) Yoo uniquely combines forward/reverse mouse genetics with molecular/physiological approaches in her impactful research. She previously developed and utilized



The tumor suppressor p53 oscillates and modulates Per2 expression in the SCN. In situ hybridization detection of Per2 mRNA in SCN of WT and p53-/- mice.

a PER2::Luciferase circadian reporter model to demonstrate the existence of independent peripheral clocks in virtually all mouse tissues. This finding has radically changed the "central dogma" of the mammalian circadian system in which the SCN (Suprachiasmatic Nuclei) in the brain functions as the master clock to drive peripheral slave oscillators. This reporter mouse line has been distributed to over 100 laboratories throughout the world and is among the most widely used and powerful tools in the field of circadian biology. Furthermore, her research on novel ENU-generated circadian mutant mice has led to the discovery of novel clock genes and elegant regulatory mechanisms for mammalian circadian clock, particularly the exquisite check-and-balance impinging upon circadian periodicity. Currently, her laboratory is actively investigating the pathophysiological basis and impact of malfunctioning clocks, specifically in metabolic disease (see below), headache, and lung disease.

Dr. Zheng (Jake) Chen has made seminal contributions to understanding how biological rhythms regulate energy metabolism in budding yeast and mammals. In a novel chemical biological approach, Dr. Chen identified diverse chemical compounds capable of altering or enhancing mammalian circadian clocks. Enhancement of clock amplitude (or robustness) is a particularly intriguing molecular target because disease and aging settings are known to strongly correlate with dampened amplitude. In collaboration with Drs. Lee and Yoo, Dr. Chen's lab identified a natural clock-enhancing compound called Nobiletin, a dietary supplement enriched in citrus peels, which confers strong protection against metabolic disorders including obesity and diabetes by activating key components of the circadian clock. These discoveries together establish an attractive drug candidate targeting the clock machinery to improve energy balance. Currently, Dr. Chen's lab pursues exciting function and mechanism studies of Nobiletin and other clock-enhancing compounds in aging and diseases; furthermore, collaboration is ongoing to exploit the therapeutic potential of improved derivative compounds. These laboratory and translational research activities have laid an excellent foundation for understanding biological timing. Such knowledge is critically required to improve management and treatment of universal health issues, such as sleep disorders and age-related decline. Importantly, each person has a unique chronotype with distinct intrinsic periodicity, as exemplified by early larks and night owls. A major concerted effort is being mounted by our research groups to develop personalized tools and biomarkers; for example, circadian parameters and -omic signatures from skin biopsy constitute excellent predictive biomarkers for human individuals. The ultimate goal is to develop clinically relevant, personalized chronotherapeutics which will effectively improve disease symptoms and prolong healthspan and lifespan.



Circadian clocks are ubiquitous throughout the body, and control integrative physiology of individual peripheral tissues, as evidenced by reporter luminescence recording using tissue explants (A).Circadian clock periodicity is governed by two paralogous F-box proteins FBXL3 and FBXL21 (B).

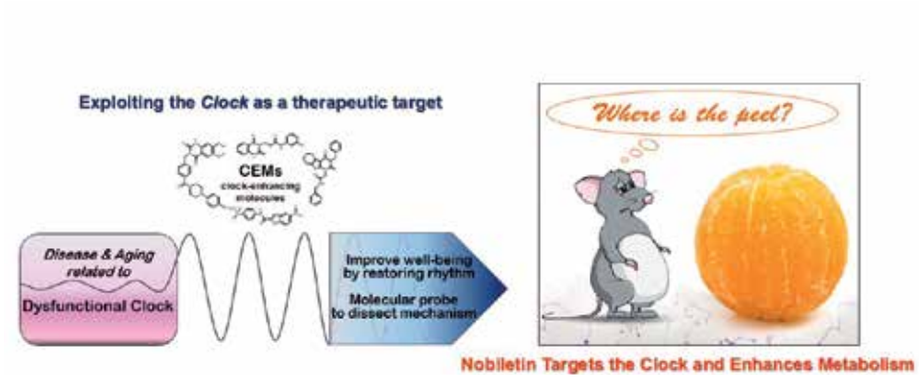
Affiliated Faculty Members:
Zheng (Jake) Chen, Ph.D.; Cheng-Chi Lee, Ph.D.; Seung-Hee (Sally) Yoo, Ph.D.

Selected Publications:

Miki T, Matsumoto T, Zhao Z, and Lee CC. 2013. p53 Regulates Period2 Expression and the Circadian Clock. *Nat. Commun*. 4:2444.

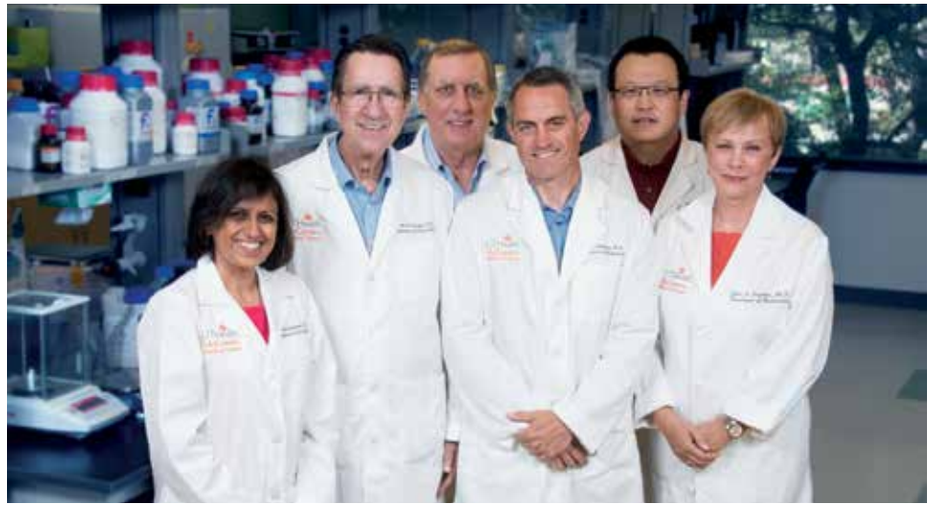
Zhao Z, Van Oort A, Tao Z, and Lee CC. 2014. Metabolite Profiling of 5'-AMP-Induced Hypometabolism. *Metabolomics*. 10(1):63-76.

Yoo SH, Mohawk JA, Siepka SM, Shan Y, Huh SK, Hong HK, Kornblum I, Kumar V, Koike N, Xu M, Nussbaum J, Liu X, Chen Z, Chen ZJ, Green CB, Takahashi JS. 2013. Competing E3 ubiquitin ligases govern circadian periodicity by degradation of CRY in nucleus and cytoplasm. *Cell*. 152(5):1091-1105.* Cover article



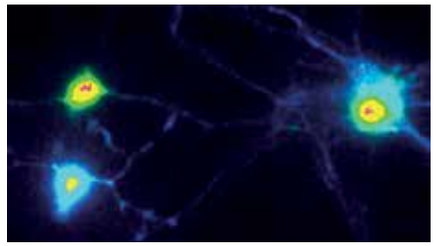
Exploiting the Clock as a therapeutic target

Neurobiochemistry and Calcium Signaling: Unraveling Aspects of Neurodegenerative Diseases



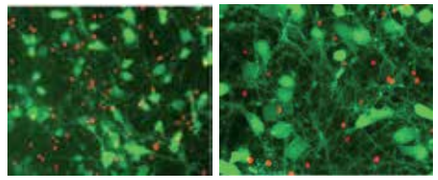
The mammalian central nervous system is composed of a network of specialized cells, such as neurons and glia, which enable action, perception, and cognition. These functions are mediated by a finely tuned interplay of electrical and chemical signals, and the proteins that generate and receive these signals. The research in several BMB laboratories focus on characterizing the biochemical process underlying these signaling pathways and in developing biochemical tools to delineate the neuronal circuity. The overarching goal of the research from these labs is to understand the biochemical basis of neuronal control of physiological process and address changes in these processes under disease conditions.

The Boehning laboratory is interested in understanding the molecular pathogenesis of neurodegeneration. The central focus of his lab is neurodegenerative diseases associated with protein misfolding. These diseases include Alzheimer's disease, Huntington's disease, and more recently amyotrophic lateral sclerosis (ALS). He is particularly interested in a family of proteins called ubiquilins, which are mutated in inherited forms of ALS, and may have altered function in Alzheimer's disease and Huntington's disease. His laboratory discovered that ubiquilin proteins function as molecular chaperones to prevent proteins from misfolding. The work in his laboratory was also the first to demonstrate that ubiquilin proteins are significantly decreased in Alzheimer's patient brains. The current focus in his laboratory is to determine how ubiquilin proteins contribute to neuronal proteostasis, and the functional effects of inherited mutations in these proteins. To perform these studies, he uses techniques spanning the full spectrum from in vitro biochemistry to animal models to human patient samples. Findings from his laboratory have revealed new insights into how neurons are lost in neurodegenerative disease with direct therapeutic relevance.



Glutamate-stimulated calcium release in hippocampal neurons.

The Jayaraman laboratory is interested in understanding the chemical to electrical signaling across neurons with a focus on glutamate receptors, which are the primary mediators of excitatory signaling in the central nervous system. The signaling pathway mediated by this family of receptors underlie learning and memory, and, conversely, over- or under-activation is implicated in a variety of neurological disorders, including Alzheimer's, Parkinson's, ischemic stroke, schizophrenia, and neuropathic pain. Her laboratory uses and develops a wide range of cutting-edge techniques such as vibrational and single molecule spectroscopy methods in combination with rapid electrophysiological methods to map the conformational changes in the protein that controls its ability to convert the binding of glutamate into movement of ions across the membrane. The conformational changes thus identified have provided the first dynamic view of the mechanism of signaling mediated by these receptors at a single molecule level. While these studies have provided a basic understanding of the functional mechanism of the proteins they also have allowed for the development of fluorescence based screening methods to find drugs that modulate this receptors function. Using this assay, her laboratory has identified RNA based ligands that have high specificity to specific subtypes of the receptor and exhibit neuroprotective properties in oxygen deprivation stroke model in cell culture.

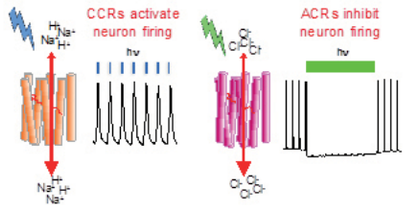


Photographs of neurons to show effect of RNA aptamer neuroprotection neurons after oxygen deprivation.

The Serysheva laboratory broadly focuses on the area of structure-function of ion channels with specific emphasis on characterization of Ca^{2+}-permeable channels. The inositol 1,4,5-trisphosphate receptor (IP3R) as the most ubiquitous intracellular Ca^{2+} channel is a key determinant of cellular Ca^{2+} signaling underlying diverse aspects of neuronal activity such as membrane excitability and synaptic strength, neuronal growth and death, learning and memory. The goal of Dr. Serysheva's research is to obtain in-depth structure-functional insights into the molecular mechanisms of IP3-gated Ca^{2+} channels. In her studies, she combines structural, biochemical and biophysical approaches to reveal the structural basis underlying function of ion channels. Utilizing recent techno-

logical advances in electron cryomicroscopy, the Serysheva laboratory has solved the structure of the neuronal type IP3R channel at near-atomic (4.7 Å) resolution (*Nature*, 2015). Dr. Serysheva's current research efforts are focused on achieving atomic resolution structures of Ca^{2+} channels in different functional states. With this structural information in hand, we can begin to decipher the function of IP3R channels and their relation to multiple neurodegenerative human diseases, such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease (HD), and spinocerebellar ataxias.

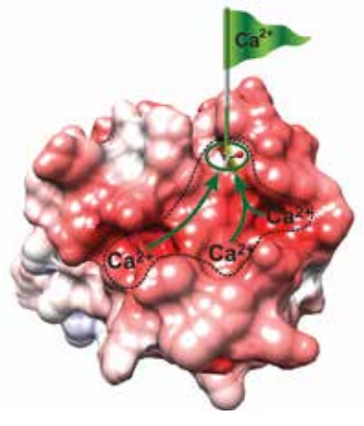
The Spudich laboratory discovered light-gated channels embedded in the membrane in algae that allow positively charged ions ("cation channelrhodopsins", CCRs) or negatively charged ions ("anion channelrhodopsins", ACRs) to flow through the membrane when illuminated. These membrane photocurrents can be used to control membrane electrical potential of neurons with light, an investigator's dream-tool, since light can be delivered and removed with high spatial and temporal precision. Flashes of light absorbed by CCRs induce neurons to fire an action potential and illumination of ACRs silences neuron firing (see figure). The light-gated channels provided the basic tools for a new technique called "optogenetics" that entails targeted expression of the channelrhodopsins to specific types of neurons to allow photocontrol of the neurons' firing patterns. Optogenetics is being used extensively for study of neural circuitry



Light-gated cation channelrhodopsins (CCRs) and anion channelrhodopsins (ACRs) activate and inhibit neuron firing, respectively, providing precise temporal and spatial control of neuronal activity with light (optogenetics).

especially in brains of animal models. The Spudich lab conducts research on the molecular mechanisms of these proteins and also collaborates with brain scientists to further develop and apply these new tools to understand brain circuitry in normal and diseased states. Clinical trials using channelrhodopsins to restore vision to people lacking sight have begun recently, and optogenetic therapy for several neurological diseases, such as epilepsy, Parkinson's disease, autism, tinnitus, and neuropathic pain, is under study in animal models.

The Putkey laboratory has a long-standing interest in the study of calcium (Ca^{2+}) binding proteins that participate in the transmission of Ca^{2+} signals. Calcium is commonly known as a mineral component of bone, but it also plays an essential role in the regulation of numerous cell processes, including muscle contraction, neural transmission and cell division. Recognition and interpretation of changes in intracellular Ca^{2+} levels depends on the structure and biochemical properties of Ca^{2+} binding proteins, such as calmodulin, which is essential for Ca^{2+} signaling in all eukaryotic cells from slime mold to humans. The Putkey lab has made hallmark contributions to the study of calmodulin. The lab currently focuses on two small intrinsically disordered calmodulin binding proteins called PEP-19 and Ng. These proteins, which are abundant in the centrtal nervous system, modulate the biochemical properties of calmoduln and how it senses Ca^{2+} signals. Using a combination of biophysical techniques and NMR, the Putkey lab has shown that PEP-19 modifies the Ca^{2+} binding properties of calmodulin by electrostatically steering this divalent cation to binding sites on calmodulin as illustrated in the figure below. These studies have broad implications since PEP-19 plays a role in learning and memory, as well as cardiac regulation. PEP-19 is also expressed in response to a variety of normal and pathological conditions, including cancer. It is likely that PEP-19 serves to control the activities of calmodulin in the face of abnormal Ca^{2+} levels associated with a variety of disease states.



The figure shows a surface rendering of the PEP-19/apo calmodulin complex derived using NMR. The negative electrostatic surface charge (red) steers Ca^{2+} to binding sites (flag) on calmodulin.

Affiliated Faculty Members:
Darren Boehning, Ph.D.; John Putkey, Ph.D.; Vasanthi Jayaraman, Ph.D.; Irina Serysheva, Ph.D.; John Spudich, Ph.D.

Selected Publications:

Wang, X., Putkey, JA 2016 PEP-19 modulates calcium binding to calmodulin by electrostatic steering *Nature Commun*. 7, 13583 doi: 10.1038/ncomms13583

Govorunova, E.G., Sineshchekov O.A., Li H., Spudich J.L. (2017) Microbial rhodopsins: Diversity, mechanisms, and optogenetic applications. *Annu. Rev. Biochem*. 86:845-872

Fan, G., Baker, M. L., Wang, Z., Baker, M. R., Sinyagovskiy, P. A., Chiu, W., Ludtke, S. J. & Serysheva, I. I. (2015). Gating Machinery of IP3R Channels Revealed by Cryo-EM. *Nature* 527(7578): 336-41.PMID: 26458101.

Stieren ES, El Ayadi A, Xiao Y, Siller E, Landsverk ML, Oberhauser AF, Barral JM, Boehning D. 2011. Ubiquilin-1 is a molecular chaperone for amyloid precursor protein. *J Biol Chem.* 286(41): 35689-35698.

Dolino D.M., Chatterjee S., MacLean, D.M., Flatebo C., Bishop L., Shaikh, S.A., Landes C.F., and Jayaraman V. The structure-energy landscape of NMDA Receptor gating. *Nature Chem. Biol*. 2017 Oct 9. doi: 10.1038/nchembio.2487 (E-pub ahead of print).

Askar Akimzhanov, Ph.D.
Assistant Professor
Biochemistry & Molecular Biology

Dynamic Lipidation of Signaling Proteins

Protein S-acylation is a reversible post-translational modification of cysteine residues by a variety of fatty acid species. Although protein S-acylation was discovered more than 30 years ago and S-acylated proteins have been implicated in pathogenesis of several diseases, including cancer, cardiovascular and immune disorders, it remains one of the most understudied post-translational protein modifications. High lability, one of the key features of protein S-acylation, along with its prominent effect on the protein function, makes it an attractive mechanism for the regulation of intracellular signaling. In particular, rapid changes in the protein palmitoylation (S-acylation with a palmitic acid moiety) status could provide a molecular basis for activation of plasma membrane-localized signaling proteins by targeting them into specific plasma membrane subdomains.

We propose a model in which the engaged T cell receptor (TCR) complex recruits and activates plasma membrane-associated protein acyltransferases (PATs) to increase palmitoylation of key signaling proteins. We aim our studies (a) to analyze the dynamics and regulation of stimulus-dependent palmitoylation of Lck, LAT and other members of TCR signaling pathway and (b) to uncover a previously uncharacterized role of DHHC PATs in the regulation of T cell signaling. We expect that inclusion of a novel class of regulatory enzymes into the canonical TCR signaling pathway would greatly expand the range of potential therapeutic targets for diseases associated with altered T cell homeostasis.

Research Interests:

Protein S-Acylation, Cell Signaling, Calcium Regulation, Cancer, Immunity

Selected Publications:

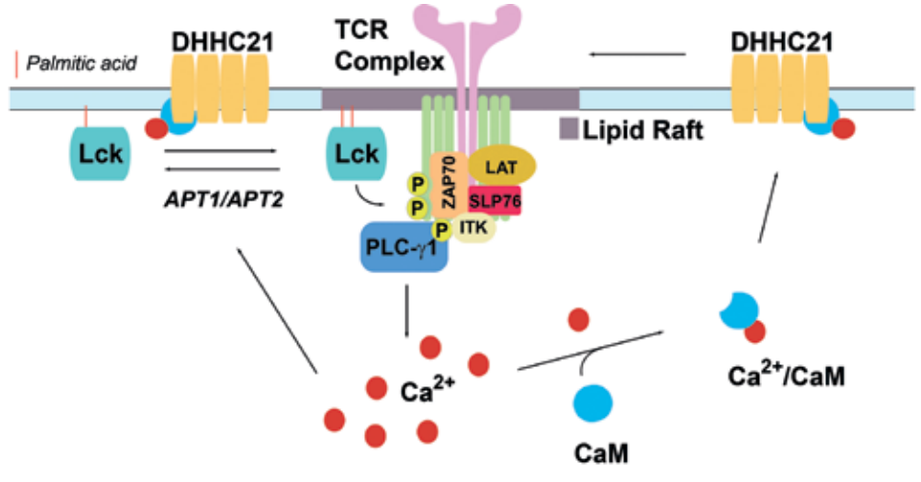
Akimzhanov AM, Boehning D. 2015. Rapid and transient palmitoylation of the tyrosine kinase Lck mediates Fas signaling. *Proc Natl Acad Sci* USA. 112(38):11876-80.

Akimzhanov AM, Barral JM, Boehning D. 2013. Caspase 3 Cleavage of the Inositol 1,4,5-Trisphosphate Receptor Does Not Contribute to Apoptotic Calcium Release. *Cell Calcium*. 53(2):152-8.

Akimzhanov AM, Wang X, Sun J, Boehning D. 2010. T-cell receptor complex is essential for Fas signal transduction. *Proc Natl Acad Sci* USA. 107(34):15105-10.

Akimzhanov A, Krenacs L, Schlegel T, Klein-Hessling S, Bagdi E, Stelkovics E, Kondo E, Chuvpilo S, Wilke P, Avots A, Gattenlöhner S, Müller-Hermelink HK, Palmetshofer A, Serfling E. 2008. Epigenetic changes and suppression of the nuclear factor of activated T cell 1 (NFATC1) promoter in human lymphomas with defects in immunoreceptor signaling. *Am J Pathol*. 172(1):215-24.

Akimzhanov AM, Yang XO, Dong C. 2007. Chromatin remodeling of interleukin-17 (IL-17)-IL-17F cytokine gene locus during inflammatory helper T cell differentiation. J *Biol Chem*. 282(9):5969-72.



The role of DHHC-mediated protein S-acylation in regulation of the T Cell Receptor signaling pathway

Michael Blackburn, Ph.D.

William S. Kilroy, Sr. Chair in Pulmonary Disease
Professor
Biochemistry & Molecular Biology
Director, Pulmonary Center of Excellence
Executive Vice President, Chief Academic Officer
Dean, MD Anderson Cancer Center UTHealth Graduate School of Biomedical Sciences, John P. McGovern Endowed Distinguished Professor

Adenosine Signaling and Chronic Lung Disease

Inflammatory and remodeling responses are prominent features of chronic lung diseases, such as asthma, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, and pulmonary hypertension. Although signaling pathways associated with the genesis of inflammation and the control of tissue remodeling have been described, little is known about signaling pathways that serve to regulate the chronic nature of these diseases. The major goal of my laboratory is to identify pathways that regulate the chronicity of these pulmonary disorders with the intent of developing novel therapeutic strategies.

A central hypothesis of my laboratory is that the signaling nucleoside adenosine is an amplifier of lung inflammation and damage. Adenosine is generated in response to cell damage, and it is our belief that as adenosine levels increase in the lung, they access pathways that serve to promote airway inflammation and remodeling. Adenosine signals by engaging specific adenosine receptors on target cells, such as inflammatory cells, fibroblasts, airway epithelial cells, and smooth muscle cells. Most of the projects in my laboratory focus on understanding the mechanisms by which adenosine receptor signaling influences the activities of these cells in the context of lung inflammation and remodeling.

We make extensive use of genetically modified mice to examine the role of adenosine signaling in chronic lung disease. This includes knockout mice of components of adenosine metabolism and signaling. We also conduct mechanistic experiments in disease-relevant cell types and work extensively with human explanted lungs obtained following lung transplantation here in the Texas Medical Center. These translational approaches help us identify novel strategies for treating chronic lung disease.

Research Interests:

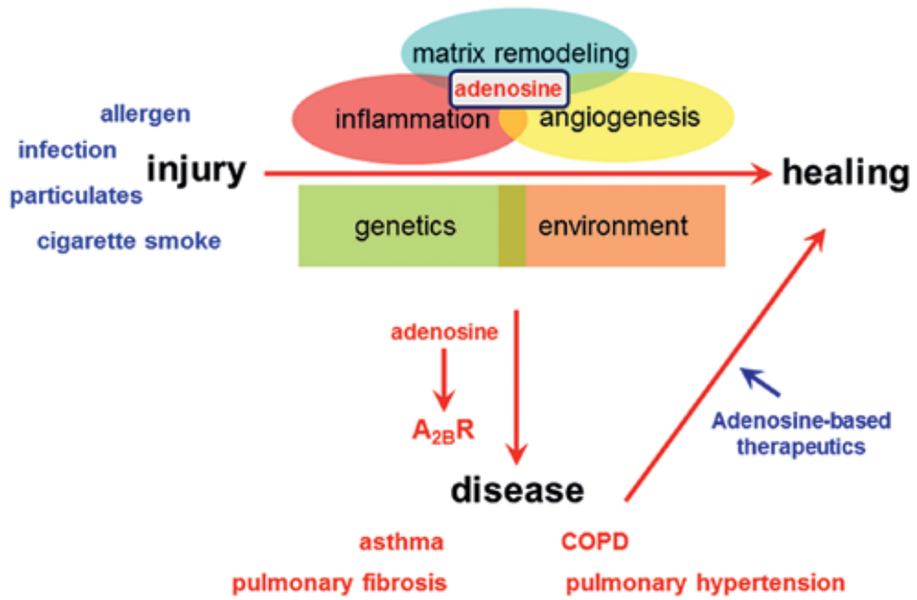
Purinergic signaling; Regulation of lung disease

Selected Publications:

Luo F, Le NB, Mills T, Chen NY, Karmouty-Quintana H, Molina JG, Davies J, Philip K, Volcik KA, Liu H, Xia Y, Eltzschig HK, Blackburn MR. 2016. Extracellular adenosine levels are associated with the progression and exacerbation of pulmonary fibrosis. *FASEB J*. 30(2):874-83.

Weng T, Poth JM, Karmouty-Quintana H, Garcia-Morales LJ, Melicoff E, Luo F, Chen NY, Evans CM, Bunge RR, Bruckner BA, Loebe M, Volcik KA, Eltzschig HK, Blackburn MR. 2014. Hypoxia-induced deoxycytidine kinase contributes to epithelial proliferation in pulmonary fibrosis. *Am J Respir Crit Care Med*. 190(12):1402-12.

Karmouty-Quintana H, Philip K, Acero LF, Chen NY, Weng T, Molina JG, Luo F, Davies J, Le NB, Bunge I, Volcik KA, Le TT, Johnston RA, Xia Y, Eltzschig HK, Blackburn MR. 2015. Deletion of ADORA2B from myeloid cells dampens lung fibrosis and pulmonary hypertension. *FASEB J*. 29(1):50-60.



Working Model: We hypothesize that extracellular adenosine in response to numerous injuries contributes to an abnormal wound healing response by engaging the adenosine A2B receptor (A2BR). We are currently investigating specific mechanisms of heightened adenosine signaling in disease relevant cells and tissues. Our hope is to advance the use of adenosine-based therapeutics for the treatment of chronic lung diseases.

Darren Boehning, Ph.D.
Professor & Director
BCB Graduate Program
Biochemistry & Molecular Biology

Cell Death Signaling in Health and Disease

The death of cells in our body is a normal process that is crucial for maintaining our health. The regulated and organized removal of damaged, aged, or no longer needed cells ensures that our body is functioning optimally. When this organized process goes awry, it can lead to cancer, autoimmune disease, and degenerative disorders. Our laboratory investigates how cells die and the relation of this process to common diseases, with the ultimate goal of discovering new therapeutic targets. We are particularly interested in how calcium ions regulate cell death. Calcium is very tightly regulated within all cells. Increased calcium in a cell activates a cell "suicide" program, which results in cell death. We study how calcium released from a ligand-gated channel called the inositol 1,4,5-trisphosphate receptor (IP3R) leads to cell death. We and others have shown that the IP3R plays a critical role in calcium release during apoptotic cell death. This channel has now been shown to be a central mediator of cell death in a remarkable number of cell death paradigms. Our current efforts investigating how this channel leads to cell death are focused on several related projects.

One project investigates the molecular mechanisms leading to calcium release from the IP3R in response to activation of the Fas death receptor. This is clinically important as mutations in this receptor lead to an autoimmune disease with increased risk of lymphoma called autoimmune lymphoproliferative syndrome (ALPS). Another project is investigating a role for BRCA1, which is mutated in hereditary breast and ovarian cancer, as a pro-cell death protein. We have identified a new role for this tumor suppressor as an activator of calcium release from the IP3R channel, with direct relevance to cancer progression. Our third project on IP3R channels is how this protein contributes to cardiac function and dysfunction in heart failure. In addition to the role of calcium in cell death, we are also interested in how protein misfolding can lead to cell death. Many neurodegenerative disorders, such as Alzheimer's Disease and amyotrophic lateral sclerosis (ALS), are protein folding diseases. We are investigating how the ubiquilin family of proteins contribute to the pathogenesis of Alzheimer's disease and amyotrophic lateral sclerosis. Specifically, we have shown that the ubiquilin proteins function as molecular chaperones in neurons preventing the aggregation of disease-relevant proteins. We are investigating how the activity of these proteins is altered during disease progression to contribute to neuronal cell death.

Research Interests:

The role of protein acylation in Fas-mediated calcium release and cell death in T cells. This project has clinical relevance to the development of autoimmune disease and lymphoma.

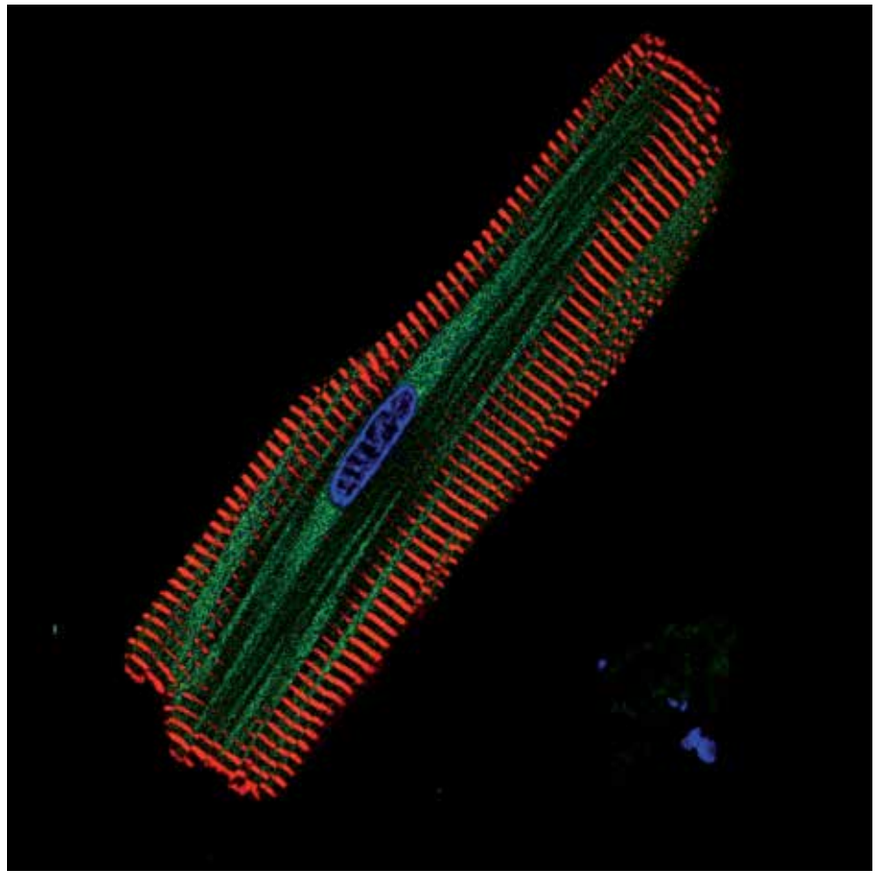
The role of IP3R calcium channels in hypertrophic remodeling of ventricles after heart failure and cardiac stress. This project has clinical relevance to the deleterious changes in heart function after damage.

The function of ubiquilin proteins as molecular chaperones for neuronal proteins. This project has clinical relevance to Alzheimer's disease, Huntington's disease, and ALS.

Selected Publications:

Akimzhanov AM, Boehning D. 2015. Rapid and Transient Palmitoylation Of The Tyrosine Kinase Lck Mediates Fas Signaling. *Proc Natl Acad Sci* USA. 112(38):11876-80.

Hedgepeth SC, Garcia MI, Wagner LE 2nd, Rodriguez AM, Chintapalli SV, Snyder RR, Hankins GD, Henderson BR, Brodie KM, Yule DI, van Rossum DB, and Boehning D. 2015. The BRCA1 Tumor Suppressor Binds to Inositol 1,4,5-Trisphosphate Receptors to Stimulate Apoptotic Calcium Release. *J Biol Chem*. 290:7304-13.



Expression of the alpha-actinin (red) and IP3R (green) in an adult rat cardiomyocyte

Phillip Carpenter, Ph.D.
Associate Professor
Biochemistry & Molecular Biology

Innovate, Lead and Direct: Teaching Graduate and Medical Students

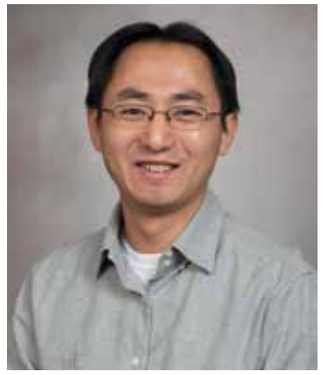
I joined the faculty at UTHealth/McGovern Medical School in 1998 and have been actively teaching graduate and medical students since 1999. I served as the course director for Biochemistry and the co-course director for the MS1 course "Clinical Applications." I have received numerous teaching awards, including the Dean's Excellence in teaching, best biochemistry professor and best course director.

In 2014, I was elected to the Academy of Master Educators. I serve on several committees, including the curriculum and admissions as well as being a member of the McGovern Society. During my tenure as the Course Director of Biochemistry, several important changes were made to the way that Biochemistry was taught to medical students. This was done as a method to discourage the traditional memorization model that plagues biochemistry teaching. One of the biggest flaws in teaching biochemistry concerns the emphasis on memorization of facts (i.e. pathways) rather than the acquisition and application of knowledge. Such a "cram and dump" mentality has eroded student confidence in the relevance of biochemistry in medicine. This is particularly disenchanting as biochemistry is a cornerstone science in medicine. To promote active learning and to dissuade rote memorization of pathways and facts, I led the development of "flipped classroom" conferences where foundational biochemistry topics were studied in the context of disease and health care. For example, rather than memorizing the individual steps of the electron transport chain (ETC), studying clinical cases such as MELAS and Barth syndrome that arise due to dysfunctional ETC provided the foundational framework for understanding not only the etiology of disease, but also to appreciate the symptoms and treatment modalities such as ubiquinone derivatives for MELAS. Such flipped classroom biochemistry sessions were well received, and the biochemistry course that was once the least appreciated class at McGovern Medical School became the most popular class of the students.

In 2016, the pre-clerkship curriculum at McGovern Medical School underwent a major transition. In particular, the traditional, discipline-based classes were changed to an "integrated curriculum" where multiple scientific disciplines are integrated into a cohesive framework. One effect of this is to reduce the walls that exist between traditional disciplines, as well as to more clearly illustrate the links between foundational science and clinical medicine. As a consequence, a two year pre-clerkship period has been reduced to 1.5 years, and students engage earlier in more clinical experiences.

As the co-director of the Foundations of Science module, I have participated in the planning, development, and execution of the MS1 curriculum. This includes global organization, as well as developing new weekly theme cases that integrate fundamental scientific knowledge with clinical principles. In particular, the flipped classroom biochemistry sessions nicely fit into this scheme. As the 2016 curriculum is new, there are still improvements to be made. This includes further integration of the basic sciences with clinical medicine. As an additional goal, I have always dissuaded students from "rote memorization." Clearly, some level of "memorization" must occur in order to gain a broad medical vocabulary, but in the context of biochemistry, for example, too much emphasis has traditionally been placed on the memorization of pathways. In the era of Google and smart phones, many "facts" can be readily looked up. However, the challenge for students is to properly apply them to a given medical scenario. I will continue to examine this topic to determine the correct balance between the acquisition of knowledge and its application.

Dr. Carpenter, on right, is inducted into the Academy of Master Educators.



Zheng (Jake) Chen, Ph.D.
Associate Professor
Biochemistry & Molecular Biology

Small-molecule Probes for Chronobiology and Medicine

The circadian clock is our intrinsic biological timer orchestrating essential cellular and physiological processes. A major research effort in my lab focuses on small molecules capable of enhancing the amplitude, or robustness, of the circadian clock. We hypothesize that such clock-enhancing small molecules (dubbed CEMs) will improve timing and therefore performance of fundamental physiological pathways, which can be exploited for therapeutic gains in aging and chronic diseases, such as metabolic disease known to suffer dampened circadian rhythms.

My lab previously identified CEMs (*PNAS* 2012; *Cell Mol Life Sci* 2013) via high-throughput chemical screening and showed that these compounds can potently enhance peripheral and/or central circadian clocks. In a recent breakthrough study, we showed that a naturally occurring flavonoid enriched in citrus peels, called Nobiletin, is a robust CEM and displays potent clock-dependent protection against metabolic diseases in both diet- and mutation-induced mouse models (*Cell Metabolism* 2016; *Nutr Metab* 2015). More importantly, we identified the nuclear receptors RORs as the direct protein target of Nobiletin (see Figure). These studies laid an excellent foundation for our continuing investigation of circadian regulation of energy homeostasis. Extending beyond metabolic studies, we are also gaining important insights into the roles of Nobiletin and RORs in healthy aging and other clock-related diseases. A long-term goal of this project is to develop novel Nobiletin derivatives for translational and clinical applications.

We also have elucidated novel regulatory mechanisms of metabolic homeostasis. Following a serendipitous finding where a partial clock-deficient mouse mutant surprisingly showed compensatory metabolic enhancement, our in vitro studies uncovered a previously unknown mechanism involving autophagy-dependent turnover of the central clock transcription factor BMAL1 (Jeong et al., *Sci Rep* 2015). Another emerging topic in our lab is the microbial regulatory mechanism for energy balance. Combining microbiome sequencing, metabolomics and fecal microbiota transplantation, we showed that dietary fiber causes transmissible microbial and metabolomic remodeling, leading to improved glucose homeostasis in diabetic mice (He et al., *Sci Rep* 2015). These exciting ongoing projects are expected to synergize with small-molecule studies, and may lead to innovative therapeutic regimens.

Research Interests:

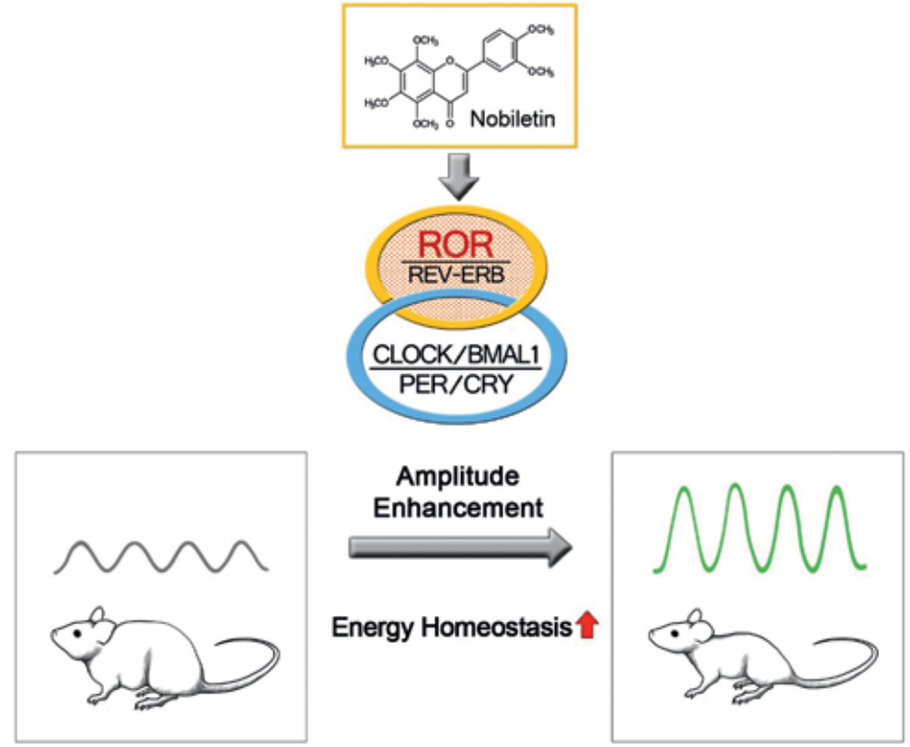
Circadian clocks, small molecule modulators, metabolic disease, aging, nutrition and diets, autophagy, microbiome.

Selected Publications:

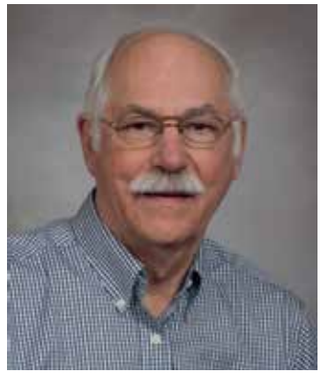
He B, Nohara K, Park N, YS, Guillory B, Zhao Z, Garcia JM, Koike N, Lee CC, Takahashi JS, Yoo SH, Chen Z. 2016. The small molecule Nobiletin targets the molecular oscillator to enhance circadian rhythms and protect against metabolic syndrome. *Cell Metab*. 23: 610-21.

Chen Z, Yoo SH, Park YS, Kim KH, Wei S, Buhr E, Ye ZY, Pan HL, Takahashi JS. 2012. Identification of diverse modulators of central and peripheral circadian clocks by high-throughput chemical screening. *Proc Natl Acad Sci* U S A. 109(1):101-6.

Nohara K, Shin Y, Park N, Jeong K, He B, Koike N, Yoo SH, Chen Z . 2015. Ammonia-lowering activities and carbamoyl phosphate synthetase 1 (Cps1) induction mechanism of a natural flavonoid. *Nutr Metab* (Lond). 12:23. eCollection 2015.



Nobiletin as a clock-enhancing molecule (CEM). Nobiletin directly targets the clock oscillator to enhance circadian amplitude, thereby promoting energy homeostasis and protecting against metabolic syndrome.



William Dowhan, Ph.D.
John S. Dunn Chair and Professor
Biochemistry & Molecular Biology

Structure, Assembly, and Function of Cell Membrane Components

A better understanding of how lipid-protein interactions affect the structure and function of proteins is important for establishing the molecular basis for protein conformational disorders such as cystic fibrosis, Alzheimer's disease, scabies, spinocerebellar ataxia type I, diabetes, sickle-cell anemia, and Nephrotic syndrome. Molecular genetic approaches are being used to construct strains of Escherichia coli in which membrane phospholipid composition can be regulated in a dose-dependent and temporal manner to define the role of specific phospholipids in cell function. Through variation of phospholipid composition, the following roles for phospholipids have been defined: structure, topological organization and function of membrane proteins; function of the cell division and DNA replication machinery; organization of lipid domains in membranes; export of proteins across membranes.

A fundamental objective in membrane biology is to understand and predict how protein sequences determine the number and orientation of transmembrane domains (TMDs). Through the use of strains of E. coli in which the synthesis of the major phospholipid, phosphatidylethanolamine (PE), can be regulated at steady state and temporally during the cell cycle, we have uncovered a central role of membrane phospholipid composition as a determinant of membrane protein topological organization. We have established that initial topological organization, existence of multiple topological conformers, and post-assembly topological re-organization of TMD orientation of membrane proteins are dictated by direct lipid-protein interactions. In more complex eukaryotic cells, changes in local lipid environment temporally or during intracellular vesicular trafficking can change the organization and function of a membrane protein. Current projects focus on defining the molecular mechanism underlying the dynamic properties of membrane proteins in response to their lipid environment using genetic manipulation of proteins and lipid composition and biophysical and biochemical studies in living cells and reconstituted proteoliposomes.

Role of Cardiolipin in Supercomplex Formation

Cardiolipin is a major phospholipid found exclusively in the mitochondria of eukaryotic cells. We established that yeast mutants lacking cardiolipin fail to organize individual respiratory complexes into supercomplexes that make up the mitochondrial respirasome resulting in compromised respiratory function. Using structural (see SBIC Faculty section-Dowhan), genetic and biochemical approaches, our goal is to understand at the molecular level how cardiolipin organizes functional higher order molecular machines. Reduced cardiolipin levels are associated with several diseases as noted in the SBIC section.

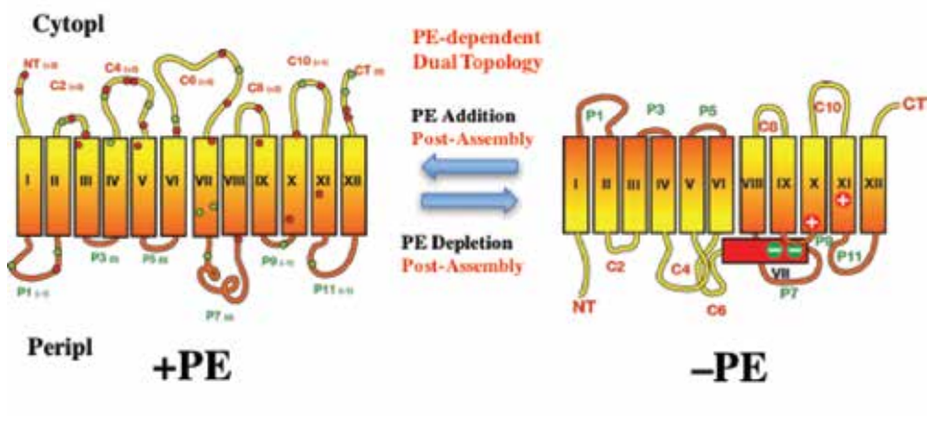
Selected Publications:

Dowhan W. 2013. A retrospective: Use of Escherichia coli as a vehicle to study phospholipid synthesis and function. *Biochim. Biophys. Acta.* 1831: 471-94.

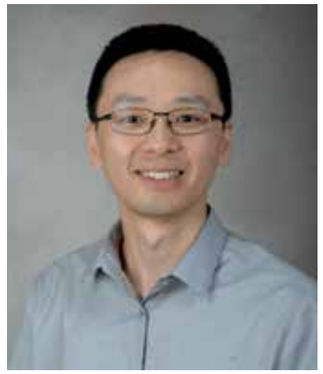
Bogdanov M, Dowhan W, and Vitrac H. 2014. Lipids and topological rules governing membrane protein assembly. *Biochim. Biophys. Acta*. 1843:1475-88.

Vitrac H, MacLean DM, Jayaraman J, Bogdanov M, Dowhan W. 2015. Dynamic membrane protein topological switching upon changes in phospholipid environment. *Proc Natl Acad Sci* USA. 110, 13874-9.

Vitrac H, MacLean DM, Karlstaedt A, Taegtmeyer H, Jayaraman V, Bogdanov M, Dowhan W. 2017. Dynamic lipid-dependent modulation of protein topology by post-translational phosphorylation. J *Biol Chem*. 292:1613-24.



Topological Organization of Lactose Permease as a Function of Membrane Lipid Composition



Leng Han, Ph.D.

Assistant Professor
Biochemistry & Molecular Biology
CPRIT Scholar - Cancer Prevention
Research Institute of Texas

Integrative Analysis of Complex Diseases

Our lab utilizes the high-throughput technologies to dissect the molecular mechanism in complex diseases. We are interested in the following exciting topics but not limited to:

Recent advances in genomic technologies and the ensuing deluge of genomic information related to cancer have accelerated the convergence of discovery science with clinical medicine. Successful translations of genomics into therapeutics and diagnostics reinforce its potential for personalizing medicine. For example, as one of the most important cancer genomic data resources, the Cancer Genome Atlas (TCGA) is a comprehensive and coordinated effort to accelerate our understanding of the molecular basis of cancer through the application of genome analysis technologies (Han et al., *Cancer Cell*, 2015; Han et al., *Nature Communications*, 2014; TCGA, *Nature Genetics*, 2013). We are also interested in other complex diseases, such as stem cells (Wang et al., *Cell Stem Cell*, 2014; Wang et al., *Cell Stem Cell*, 2013), cardiovascular diseases (Dey*, Han* et al., *Circulation Research*, 2013; Lan et al., *Cell Stem Cell*, 2013), psychiatric diseases (Luo*, Huang*, Han* et al., *Schizophrenia Bulletin*, 2014), etc.

High-throughput technologies have greatly improved our ability to evaluate the molecular changes that occur during various biological processes. With the development of next-generation sequencing, our understanding has been advanced through the use of a variety of platforms: methy-seq, ChIP-seq, exome-seq and RNA-seq. The large amount of publicly available next-generation sequencing data, such as datasets from TCGA and ENCODE, has created enormous opportunities for researchers to conduct genomic analysis beyond the traditional sequencing analysis. Transforming genomic information into biomedical and biological knowledge requires creative and innovative computational methods for all aspects of genomics. Therefore, the research in my lab will focus on computational analysis from genomic sequences to other post-genomic data, including both DNA and RNA sequences, protein profiling, and epigenetic profiling, in an ongoing effort to find hidden treasures (Han et al., Briefings in Bioinformatics, 2014; Samuels*, Han* et al., *Trends in Genetics*, 2013).

Research Interests:

Bioinformatics, Next-Generation Sequencing, Cancer Genomics

Selected Publications:

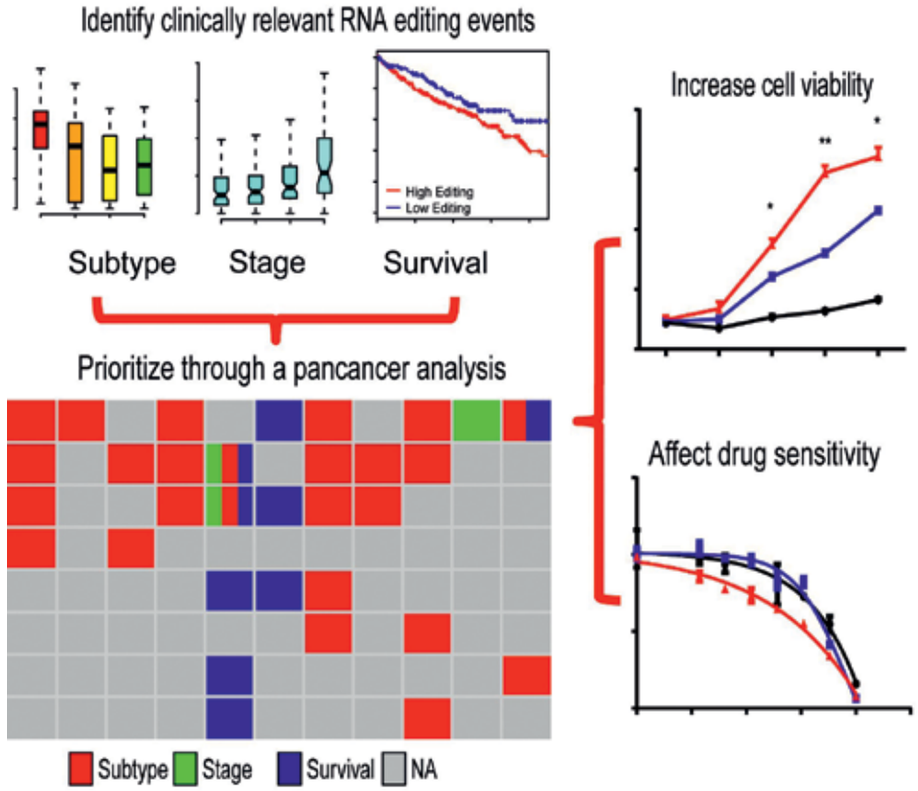
Han L, Diao L, Yu S, Xu X, Li J, Zhang R, Yang Y, Werner HM, Eterovic AK, Yuan Y, Li J, Nair N, Minelli R, Tsang YH, Cheung LW, Jeong KJ, Roszik J, Ju Z, Woodman SE, Lu Y, Scott KL, Li JB, Mills GB, Liang H. 2015. The Genomic Landscape and Clinical Relevance of A-to-I RNA Editing in Human Cancers. *Cancer Cell*. 28(4):515-28.

Li J, Han L, Roebuck P, Diao L, Liu L, Yuan Y, Weinstein J, Liang H. 2015. TANRIC: An Interactive Open Platform to Explore the Function of lncRNAs in Cancer. *Cancer Res*. 75: 3728-37.

Han L, Vickers KC, Samuels DC, Guo Y. 2015. Alternative applications for distinct RNA sequencing strategies. *Brief Bioinform*. 16:629-39.

Han L, Yuan Y, Zheng S, Yang Y, Li J, Edgerton ME, Diao L, Xu Y, Verhaak RG, Liang H. 2014. The Pan-Cancer analysis of pseudogene expression reveals biologically and clinically relevant tumour subtypes. *Nat Comm*. 5: 3963.

Samuels DC, Han L, Li J, Quanghu S, Clark TA, Shyr Y, Guo Y. 2013. Finding the lost treasures in exome sequencing data *Trends in Genetics*. 29: 593-599.



We characterized global A-to-I RNA editing profiles across 17 cancer types and experimentally demonstrated the effects of several cross-tumor nonsynonymous RNA editing events on cell viability and drug sensitivity.

Vasanthi Jayaraman, Ph.D.

Professor
Biochemistry & Molecular Biology
McGovern Scholar
Regents' Outstanding Teaching Award (ROTA)

Structure and Function of Neurotransmitter Receptors

Communication between nerve cells serves as the basis of all brain activity, and one of the fundamental steps involved in signal transmission between the nerve cells, is the conversion of a “chemical” signal liberated at the end of one nerve cell, into an “electrical” signal at the second nerve cell. This step is mediated by a class of membrane-bound proteins known as neurotransmitter receptors. Glutamate receptors belong to this family of proteins and are the main excitatory receptors in the central nervous system.

Our laboratory is interested in gaining an understanding of agonist-mediated activation and desensitization of this receptor by determining the structural changes in the protein induced by agonist binding. This is achieved by using various cutting-edge spectroscopic methods that allow the characterization of the dynamic state structure of the proteins at a significantly higher resolution than X-ray structures. The structural changes thus determined are correlated to the functional consequences as measured by electrophysiological measurements. These investigations provide a detailed understanding of the agonist controlled function of the glutamate receptors, and hence, aid in the rational design of drugs targeting this group of important proteins that are involved in diverse neuropathologies, such as epilepsy and ischemia.

Research Interests:

Structure and function of Membrane proteins; Ligand gated ion channels

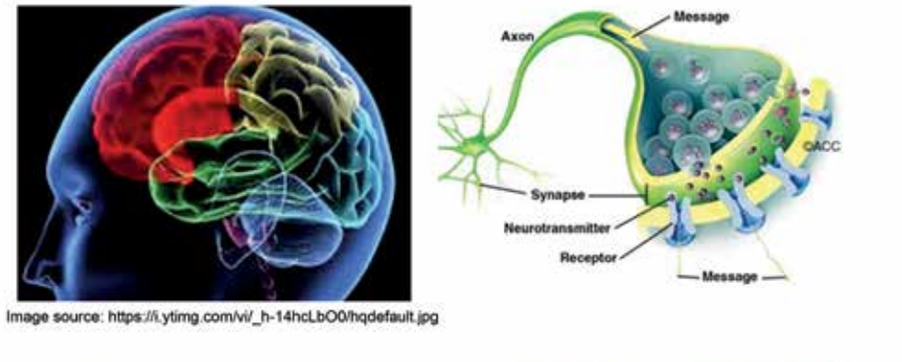
Selected Publications:

Sirrieh RE, MacLean DM, Jayaraman V. 2015. A conserved structural mechanism of NMDA receptor inhibition: A comparison of ifenprodil and zinc. *J Gen Physiol*. 146(2):173-81.

MacLean DM, Ramaswamy SS, Du M, Howe JR, Jayaraman V. 2014. Stargazin promotes closure of the AMPA receptor ligand-binding domain. *J Gen Physiol*. 144(6):503-12.

Sirrieh RE, Maclean DM, Jayaraman V. 2013. Amino-terminal Domain Tetramer Organization and Structural Effects of Zinc Binding in the N-Methyl-D-aspartate (NMDA) Receptor. *J Biol Chem*. 288(31):22555-64.

Landes CF, Rambhadran A, Taylor JN, Salatan F, Jayaraman V. 2011. Structural landscape of isolated agonist-binding domains from single AMPA receptors. *Nat Chem Biol*. 7(3):168-73.



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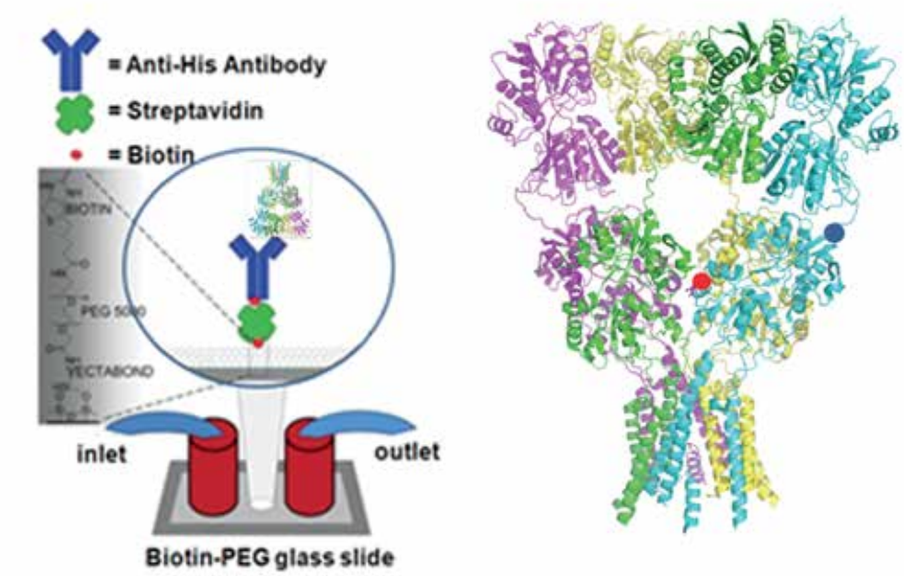
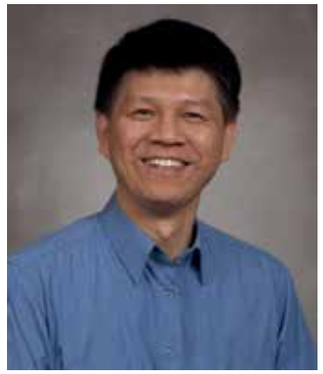


Chemical Interactions, Dynamics and Function



Jianping Jin, Ph.D.
Associate Professor
Biochemistry & Molecular Biology

Ubiquitin Signaling Pathway: From Basic Mechanisms to Human Diseases

Protein ubiquitination is mediated by three enzymes: a ubiquitin activating enzyme (E1), a ubiquitin conjugating enzyme (E2) and a ubiquitin ligase (E3). One of the major consequences of ubiquitination is protein proteolysis through the 26S proteasome, which is the primary pathway that regulates the levels of many short-lived proteins in eukaryotes. The substrate specificity of ubiquitination is governed by the E3s. Mutations in E3s or their cognate substrates result in substrate stabilization, often with deleterious consequences on cellular function. Dysregulation of protein ubiquitination has been associated with numerous human diseases, such as cancer, mental retardation and autoimmune diseases (see Figure 1).

NF-κB Activation, Inflammation, and Cancer

NF-κB is a family of transcription factors, which transcribe many inflammation-related genes. We are currently investigating the roles of p97 and its associated factors in cytokine-induced NF-κB activation. Moreover, we are striving to understand why certain tumor cells, especially those advanced ones, have constitutive NF-κB activation.

Ubiquitination and Genome Instability Control

Cullin-RING ubiquitin ligases (CRLs) is the largest subfamily of multi-subunit E3 complexes. CRLs control ubiquitination of many important oncogenes and tumor suppressors, such as Cdc25A, c-Myc, c-Jun and p27. Emerging evidence indicates that CRLs play indispensable roles in the DNA damage response, cell division, DNA replication and other biological activities. Mutations in components of CRLs have been found to be causative agents in certain cancers and other human diseases. Our laboratory focuses on the regulation of the DNA damage response through ubiquitination by CRLs, particularly, by DCAF proteins that are the receptor subunits in the CRL4 ubiquitin ligases.

Ubiquitin Proteases Inhibitors as Cancer Drugs

Protein ubiquitination is a reversible process (see Figure 2). The deubiquitination step is controlled by ubiquitin proteases (DUBs). There are ~100 DUBs in the human genome. Current studies suggested that certain DUBs are good drug targets. By small molecule screening, we have identified two small molecules from Chinese medical plants that regulate DNA damage response via inhibiting deubiquitination. These two inhibitors could kill cancer cells synthetically with Olaparib, an FDA-approved cancer drug. We are currently investigating their exact roles in inhibiting certain DNA damage response-related DUBs.

Research Interests:

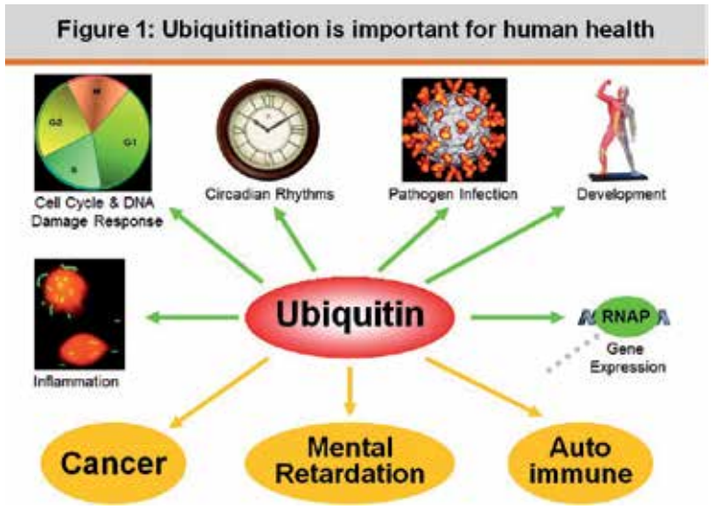
Protein Ubiquitination, Cancer, Inflammation and DNA Damage Response

Selected Publications:

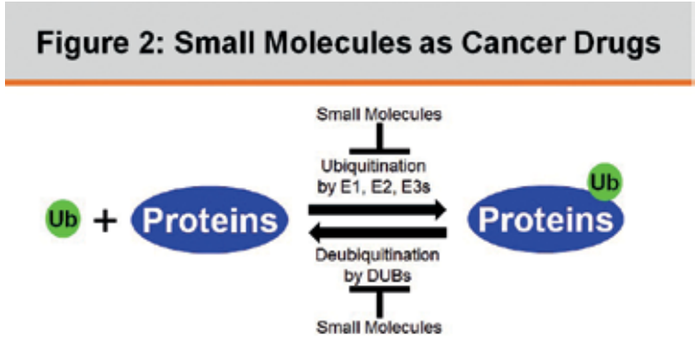
Jin J, Arias EE, Chen J, Harper JW, Walter JC. 2006. A family of diverse Cul4-Ddb1-interacting proteins includes Cdt2, which is required for S phase destruction of the replication factor Cdt1. *Mol Cell*. 23(5):709-21.

Jin J, Li X, Gygi SP, Harper JW. 2007. Dual E1 activation systems for ubiquitin differentially regulate E2 enzyme charging. *Nature* 447(7148):1135-8.

Li JM, Wu H, Zhang W, Blackburn MR, Jin J. 2014. The p97-UFD1L-NPL4 Protein Complex Mediates Cytokine-induced IκBα Proteolysis. *Mol Cell Biol*. 34(3):335-47.



Ubiquitination is important for human health



Small Molecules as Cancer Drugs

Harry Karmouty-Quintana, Ph.D.

Assistant Professor
Biochemistry & Molecular Biology

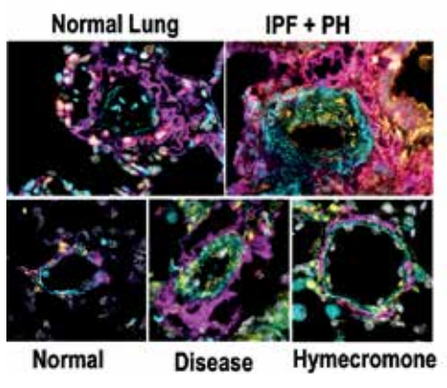
Novel Mechanisms in Chronic Lung Disease

Chronic Lung Diseases (CLDs) such as Idiopathic Pulmonary Fibrosis (IPF), Chronic Obstructive Pulmonary Disease (COPD) and Pulmonary Hypertension (PH) represent the third-leading cause of death in the US. Despite reductions in mortality in cancer and cardiovascular disease, mortality rates for CLD have remained unaffected over the last decade. This a direct result of disparate funding allocated toward research in CLD that in no way reflects the heavy societal burden of the disease, as well as an overwhelming lack of effective therapies capable of targeting the airspace and vascular remodeling that is a pervasive hallmark in many CLDs. Through the use of experimental models of disease and access to the UTHealth Pulmonary Center of Excellence Bio-bank, our research aims to understand the processes that govern disease progression in order to develop new therapies that are desperately needed.

Understanding How Changes in the Lung Extracellular Matrix (ECM) Lead to Vascular Remodeling in PH Associated with IPF

The presence of PH in patients with IPF is the single most significant predictor of mortality, yet there are no cures at present that effectively prevent or treat PH in patients with IPF. In this project we have identified increased levels of hyaluronan, a component of the lung ECM, in the lung of patients with a diagnosis of PH associated with IPF. We next demonstrate that the increase in hyaluronan is mediated by an elevation in hyaluronan synthase 2 (HAS2), an enzyme that makes hyaluronan. Finally, we demonstrate that treatment with hymecromone, a drug that inhibits HAS2, is able to reduce levels of hyaluronan and treats PH associated with IPF.

We are currently examining the mechanisms that lead to HAS2 increases in patients with IPF and examining how selective deletion of HAS2 from smooth muscle cells contributes to the development of PH.



Alpha Smooth muscle actin (cyan), hyaluronan (magenta), hyaluronan binding protein2 (HAPB2, yellow) and DAPI (grey) from human lungs (top panels) or from mice models of chronic lung disease (bottom panels).

Evaluating How Changes in mRNA 3'UTR Length Participates in the Development of COPD

In collaboration with leaders in RNA-biology and with Dr. Leng Han, an expert in bio-informatics at UTHealth, we have identified changes in the 3'UTR length of mRNAs in patients with COPD. These mRNAs encode many proteins associated with the development of disease. In addition, we show that a protein known as cleavage factor 25 (CFIm25) regulates the length of the 3'UTRs and that depletion of this protein results in global shortening of mRNAs. This protein was also found to be depleted in patients with COPD. Our research efforts are aimed at elucidating how 3'UTR shortening contributes to the development of COPD, using tissue samples from the UTHealth Pulmonary Center of Excellence bio-bank and sophisticated experimental models of disease.

Research Interests:

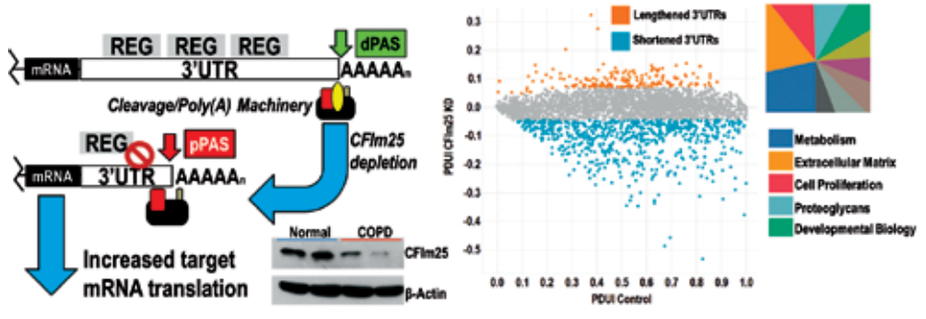
Pulmonary Hypertension, Lung Fibrosis, Chronic Obstructive Pulmonary Disease

Selected Publications:

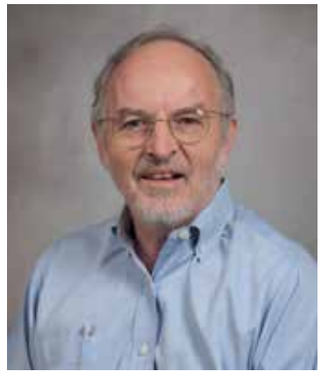
Collum SD, Chen NY, Hernandez AM, Hanmandlu A, Sweeney H, Mertens TCJ, Weng T, Luo F, Molina JG, Davies J, Horan IP, Morrell NW, Amione-Guerra J, Al-Jabbari O, Youker K, Sun W, Rajadas J, Bollyky PL, Akkanti BH, Jyothula S, Sinha N, Guha A, Karmouty-Quintana H. 2017. Inhibition of Hyaluronan Synthesis Attenuates Pulmonary Hypertension Associated with Lung Fibrosis. *Br J Pharmacol*. 174:3284-3301.

Garcia-Morales LJ, Chen NY, Weng T, Luo F, Davies J, Philip K, Volcik K, Melicoff E, Amione-Guerra J, Bunge RR, Bruckner BA, Loebe M, Eltzschig HK, Pandit LM, Blackburn MR, Karmouty-Quintana H. 2016. Altered Hypoxic-Adenosine Axis and Metabolism in Group III Pulmonary Hypertension. *Am J Respir Cell Mol Biol*. 54(4):574-83.

Karmouty-Quintana H, Weng T, Garcia-Morales LJ, Chen NY, Pedroza M, Zhong H, Molina JG, Bunge R, Bruckner BA, Xia Y, Johnston RA, Loebe M, Zeng D, Seethamraju H, Belardinelli L, Blackburn MR. 2013. Adenosine A2B receptor and hyaluronan modulate pulmonary hypertension associated with chronic obstructive pulmonary disease. *Am J Respir Cell Mol Biol*. 49(6):1038-47.



Alternative polyadenylation (APA) and subsequent 3'UTR shortening consistent with reduced CFIm25 in COPD tissue (Left panel). Percentage of distal PAS usage index (PDUI) showing shortened transcripts and pathway analysis (right panel).



Rodney E. Kellems, Ph.D.
Professor and Chair
Biochemistry & Molecular Biology

Autoimmune Hypertension: The Role of Receptor-Activating Autoantibodies in Disease

Numerous forms of hypertension have an underlying autoimmune component associated with elevated levels of inflammatory cytokines and the presence of autoantibodies capable of activating the major angiotensin II receptor, AT1R (Xia and Kellems 2013). Although these autoantibodies were originally observed in women with preeclampsia (a serious hypertensive disease of pregnancy), they have now been observed in numerous other hypertensive conditions, including malignant hypertension, refractory hypertension and aldosteronism. I have collaborated extensively with Dr. Yang Xia to understand the pathological consequences of these autoantibodies. We were the first to report that these autoantibodies, termed AT1-AA, cause features of preeclampsia when introduced into pregnant mice. Evidence that AT1-AAs contribute to hypertension in experimental animals is now extensive and compelling. A fascinating feature of these autoantibodies is that they uniformly recognize the same epitope (AFHYESQ) located on the second extracellular loop of AT1Rs. In view of the wide-ranging pathophysiological consequences of these autoantibodies, it is important to understand the molecular mechanisms and immunological conditions that initiate their production. This goal is best achieved with an animal model in which the production of these autoantibodies can be experimentally induced with convenience and reproducibility. We have recently developed a mouse model of cytokine-induced hypertension that fulfills these criteria. Our research has revealed that tissue transglutaminase (TG2), a widely distributed enzyme that modifies glutamine residues of proteins, to be required for AT1-AA production and cytokine-induced hypertension. These are important and novel findings that form the basis of our hypothesis that many forms of hypertension result from an autoimmune condition in which cytokine-mediated induction of TG2 results in the post translational modification of AT1Rs, leading to the creation of a neoantigen that stimulates autoimmune production of AT1-AAs. The results of our research are expected to identify therapeutic peptides that will block the hypertensive actions of AT1-AA. Additional research is expected to highlight the use of TGase inhibitors to block the cytokine-induced production of AT1-AA and reduce hypertension.

Research Interests:

Receptor activating autoantibodies and disease. Inflammation, autoimmunity and hypertension. The role of tissue transglutaminase (TG2) in hypertension.

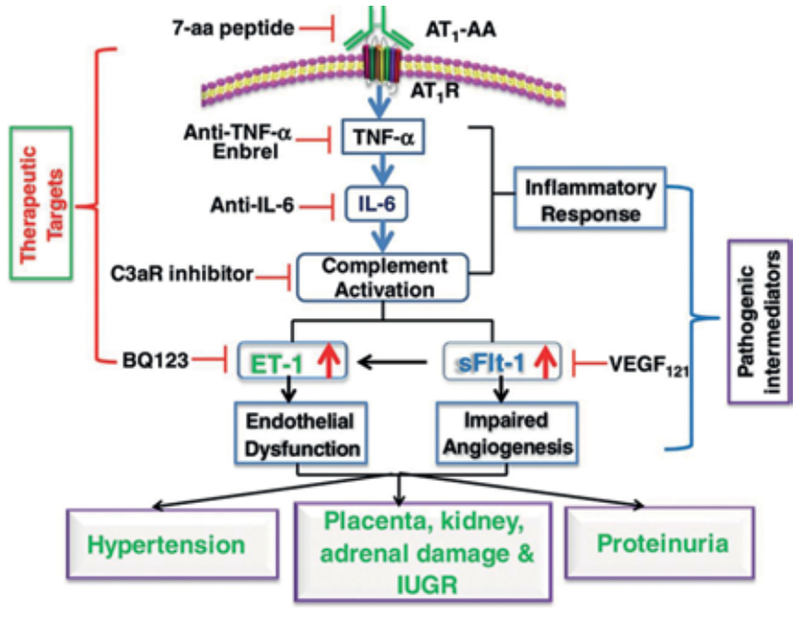
Selected Publications:

Xia Y, Kellems RE. 2013. Angiotensin receptor agonistic autoantibodies and hypertension: preeclampsia and beyond. *Circ Res*. 113(1):78-87.

Liu C, Luo R, Wang W, Parchim NF, Iriyama T, Elliot SE, Daugherty PS, Blackwell SC, Sibai B, Kellems RE, Xia Y. 20115. Elevated transglutaminase activity triggers angiotensin receptor activating autoantibody production and pathophysiology of preeclampsia. *J Am Heart Assoc*. 4:e002323.

Luo R, Liu C, Elliott SE, Wang W, Parchim N, Iriyama T, Daugherty PS, Tao L, Eltzschig HK, Blackwell SC, Sibai BM, Kellems RE and Xia Y. 2016. Transglutaminase is a critical link between inflammation and hypertension. *J Am Heart Assoc*. 5:e003730.

Liu C, Kellems RE, Xia Y. 2017. Inflammation, Autoimmunity, and Hypertension: The Essential Role of Tissue Transglutaminase. *Am J Hypertens*. 30:756-764.



Pathogenic mediators of angiotensin II type I receptor (AT1R) agonistic autoantibodies (AT1-AA)–induced preeclampsia in pregnant mice. (From Xia and Kellems 2013)

Cheng Chi Lee, Ph.D.
Professor
Biochemistry & Molecular Biology

Connectivity of the circadian clock mechanism and other cellular pathways

The daily rhythmic behavioral pattern of many living organisms is ultimately driven by an endogenous molecular clock, the circadian clock. The circadian clock exerts temporal regulation of biological process at the molecular, cellular, and physiological levels. In humans, disruption of circadian function has been associated with disorders of sleep, mood, behavior, metabolic diseases, and cancer. Therefore, deciphering the mammalian clock mechanism will provide insight into many fundamental biological processes, as well as various pathological conditions. My laboratory contributed to the landmark discoveries of identifying the mammalian Period 1 (mPer1) and Period 2 (mPer2) genes. Our genetic studies demonstrated that both mPer1 and mPer2 are key circadian regulators. Mice deficient in mPER1 and mPER2 function have no intrinsic circadian rhythm, and they are completely entrainable to external signals such as very short light-dark cycles.

Over the past decade, my laboratory was among the first groups to investigate the molecular links between clock mechanism and other cellular pathways. Our studies established a role for PER2 in the DNA damage response and tumor suppression. Our more recent studies characterizing circadian regulatory roles of two human tumor suppressors promyelocytic leukemia protein (PML) and p53, provided additional direct links between clock function, tumor suppression and stress response pathways. We are continuing our investigation of the interactions among these proteins and core clock proteins, as well as elucidating the biological implications of these inter-pathway connections.

Energy Metabolism Regulation

The mammalian circadian mechanism has been linked to cellular redox regulation. Our investigations demonstrated that the heme is an important regulator of the circadian clock mechanism in mammals, exhibiting reciprocal control between heme biosynthesis and the circadian rhythm mechanism in vivo. Our studies identified genes in peripheral tissues that were activated by constant darkness, an environment encountered by mammals during hibernation, and revealed that such gene activation was associated with the elevation of circulating 5′-AMP. Mammals given 5′-AMP can enter a deep hypometabolic state that mimics behaviors observed in hibernation and torpor. Our studies implicate a key role for erythrocytes in AMP induced hypometabolism (AIHM). We demonstrated that AIHM is a safe and reversible process. Therefore, our group has explored the potential of AIHM in therapeutic applications of hypometabolism. One of the research goals in my laboratory is to further understand the mechanism underlying the 5′-AMP mediated hypometabolic state in mammals.

Research Interests:

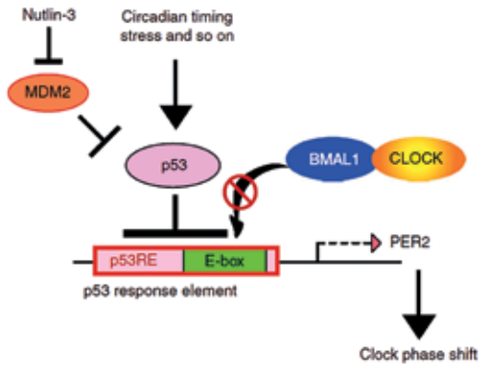
Molecular mechanism of the circadian clock and its connections to other cellular pathways, Molecular mechanism of AMP-induced hypometabolism.

Selected Publications:

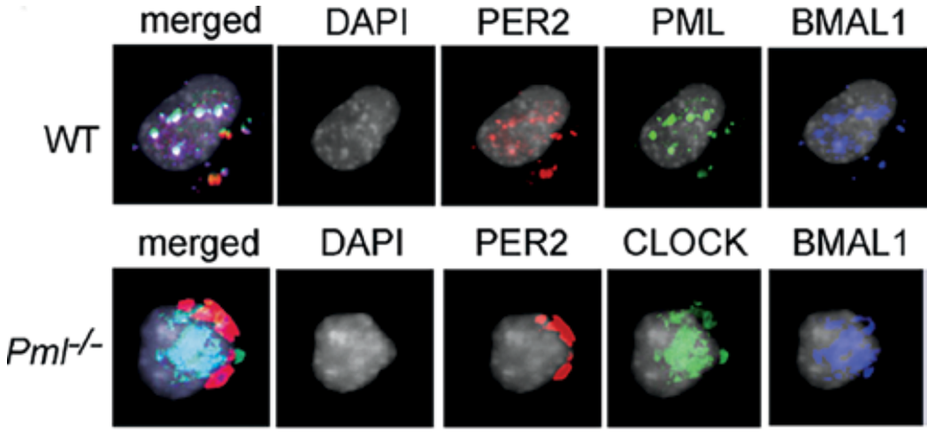
Fu L, Pelicano H, Liu J, Huang P, Lee CC. 2002. The Circadian Gene Period2 Plays an Important Role in Tumor Suppression and DNA-Damage Response In Vivo. *Cell*. 111, 41-50.

Miki T, Matsumoto T, Zhao Z, Lee CC. 2013. p53 Regulates Period2 Expression and the Circadian Clock. *Nat. Commun*. 4:2444.

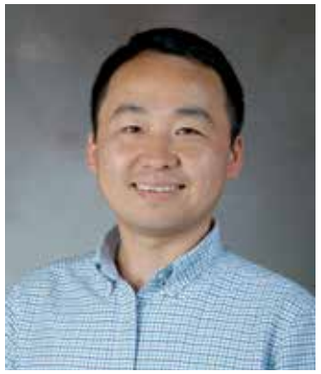
Zhang J, Kaasik K, Blackburn MR, Lee CC. 2006. Constant darkness is a circadian metabolic signal in mammals. *Nature*. 439, 340-343.



A model of p53 repression of Per2 expression and modulation of the circadian clock.



PML mediates the interaction of PER2 with the BMAL1/CLOCK heterodimer in the circadian clock.



Wenbo Li, Ph.D.

Professor
Biochemistry & Molecular Biology
CPRIT Scholar -
Cancer Prevention Research Institute
UT System Rising STAR award recipient

Charting the function and regulation of the noncoding human genome

A decade after the completion of the Human Genome Project, a new challenge now is to decipher the function and regulation, as well as the complex interplay, of millions of regulatory elements in the human genome. These elements together govern almost all basic cellular functions, in particular the gene expression control. Importantly, the mutations of noncoding regulatory elements, such as enhancers and promoters, are associated with various diseases. My laboratory attempts to contribute to solving this challenge by focusing on the following major directions. Highly interdisciplinary approaches will be utilized including those of biochemistry and molecular biology, epigenetics/epigenomics, and bioinformatics.

Elucidating the molecular functions of enhancer-derived noncoding RNAs (eRNAs)

Networks of regulatory enhancers dictate distinct cell identities and cellular responses by instructing precise spatiotemporal patterns of gene expression. However, 36 years after their discovery, enhancer functions and mechanisms remain incompletely understood. Intriguingly, recent evidence suggests that many, if not all, functional enhancers are themselves transcription units, generating eRNAs. This observation provides a fundamental insight into the inter-regulation between enhancers and promoters; it also raises crucial questions regarding the regulation of the enhancer transcription and potential roles of non-coding eRNAs (See Figure).

We will use biochemical and omics approaches such as GRO-seq (global run-on sequencing) and CLIP-seq (cross-linking immunoprecipitation and sequencing) to study the targets of selective eRNAs, their protein partners, and potential RNA chemical modificaitons, which will shed new light on gene regulation, 3D genome organization as well as the development of human disease, such as cancer.

Characterizing the three-dimensional genome architecture in gene regulation and cancer

An amazing feature of eukaryotic nuclei is that as long as 2 meters of DNA in linear length (3 billion base pairs in humans) needs to be packaged into a space of less than 10 μm a diameter, while the information stored in all regions of this stretch of DNA can still be very quickly (in minutes or seconds) and effectively retrieved. To characterize the three-dimensional (3D) genome architecture will offer new insights into the process as to how regulatory elements talk to each other in this highly folded space. Importantly, it is an increasing realization that many human diseases are associated with the disruption of proper chromatin architecture, raising the possibility that by understanding and modulating the genome architecture, there could be innovative ways to interfere with human disease. We focus on important chromatin architecture regulators particularly cohesin and condensin complexes, which were found highly mutated in many human cancers, but the underlying mechanisms are unknown. We will use system-wide genome architecture assays named 4C-seq and HiChIP/PLAC-seq, extensive bioinfommatic analyses and mathematic modeling to understand how these molecules intertwine the 3D genome, and how their mutations lead to cancer.

Selected Publications:

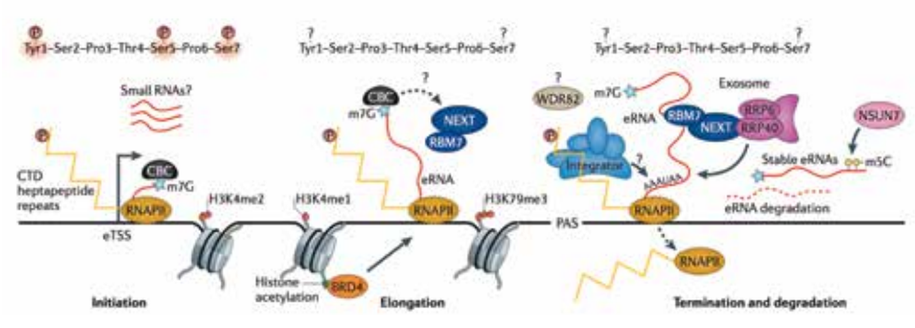
Li W, Hu Y, Oh S, Ma Q, Merkurjev D, Song X, Zhou X, Liu Z, Tanasa B, He X, Chen AY, Ohgi K, Zhang J, Liu W, Rosenfeld MG. 2015. Condensin I and II Complexes License Full Estrogen Receptor α-Dependent Enhancer Activation. *Mol Cell*. 59: 188-202.

Li W, Notani D, Ma Q, Tanasa B, Nunez E, Chen AY, Merkurjev D, Zhang J, Ohgi K, Song X, Oh S, Kim HS, Glass CK, Rosenfeld MG. 2013. Functional roles of enhancer RNAs for oestrogen-dependent transcriptional activation. *Nature*. 498:516-20.

Li W, Notani D, Rosenfeld MG. 2016. Enhancers as non-coding RNA transcription units: recent insights and future perspectives. *Nat Rev Genet*.17:207-23.

Research Interests:

Genomics, epigenomics, bioinformatics, enhancers, enhancer RNAs (eRNAs), long noncoding RNAs, RNA binding proteins, three-dimensional genome architecture, cohesin and condensin, genomic variations/mutations.



The transcription process of enhancers and some recently uncovered regulators.

Pawel Penczek, Ph.D.

Professor and Co-Director
Structural Biology Imaging Center
Biochemistry & Molecular Biology

Structural Determination of Proteins and Molecular Assemblies

We are interested in the determination of three-dimensional structures of large macromolecular complexes with low or non-existing symmetry in single-particle form using stain and cryo-electron microscopy (cryo-EM) and computer image processing techniques.

Unconstrained by crystal packing, the molecule in a single-particle specimen can be thought to exhibit the entire range of native conformations. The ability to find the structure of each conformer is one of the most important potential assets of 3D cryo-EM of single particles. On the other hand, the realization of high resolution for each of these conformers poses daunting problems of data collection and processing, considering the statistical requirements stated before. Therefore, we are also interested in the development of efficient and robust computational methods of structure refinement and structure validation in the presence of multiple conformational or binding states.

We develop, in collaboration with other groups, a single particle software package SPARX/SPHIRE (Hohn, et al). SPARX is provided free of charge as a service to the scientific community and its main features include:

1. SPHIRE is driven by a user friendly GUI supported by a Wiki-based interactive documentation.
2. New generation of 2D and 3D alignment protocols.
3. Ab initio structure determination programs.
4. Advanced code for multivariate statistical analysis (PCA, Varimax).
5. Extensive C++ library of general and EM-specific image operations with Python bindings, thus accessible to Python programmer.
6. All structure determination applications written as user transparent Python scripts

SPARX is available for download at http://sparx-em.org

Research Interests:

Cryo-electron microscopy,
Single particle reconstruction

Selected Publications:

Fu TM, Li Y, Lu A, Li Z, Vajjhala PR, Cruz AC, Srivastava DB, DiMaio F, Penczek PA, Siegel RM, Stacey KJ, Egelman EH, Wu H. 2016. Cryo-EM Structure of Caspase-8 Tandem DED Filament Reveals Assembly and Regulation Mechanisms of the Death-Inducing Signaling Complex. *Mol Cell*. 64:236-250.

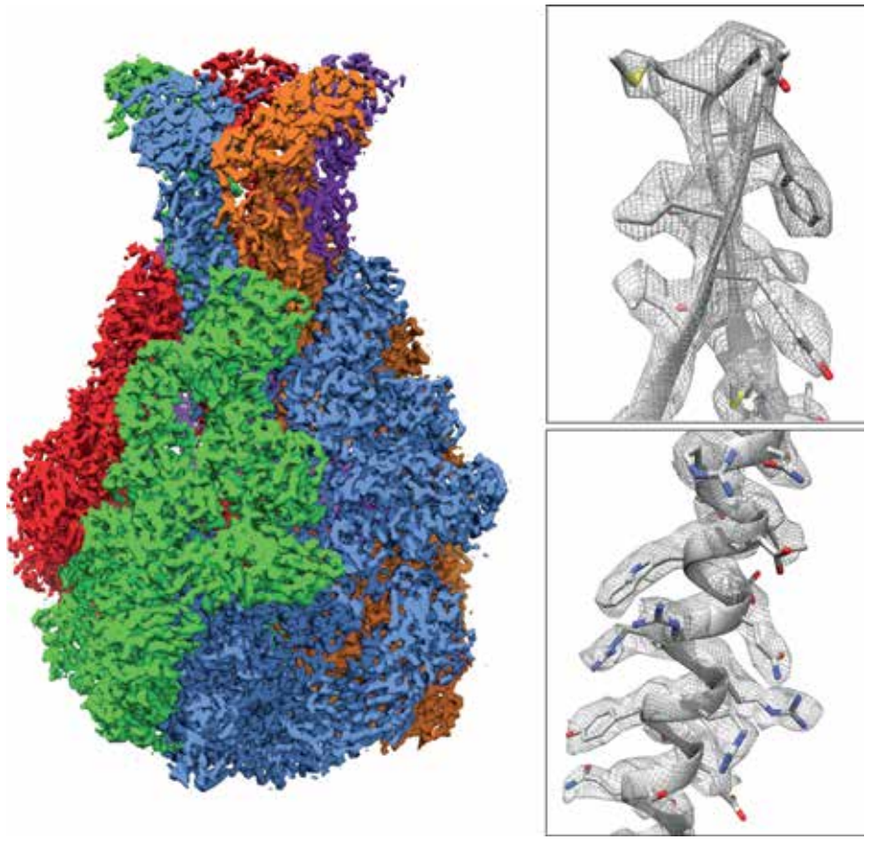
von der Ecken J, Muller M, Lehman W, Manstein DJ, Penczek PA, Raunser S. 2015. Structure of the F-actin-tropomyosin complex. *Nature*. 519:114-117.

Cheng Y, Grigorieff N, Penczek PA, Walz T. 2015. A primer to single-particle cryo-electron microscopy. *Cell*. 161: 438-449.

Behrmann E, Loerke J, Budkevich TV, Yamamoto K, Schmidt A, Penczek PA, Vos MR, Bürger J, Mielke T, Scheerer P, Spahn CM. 2015. Structural snapshots of actively translating human ribosomes. *Cell*. 161:845-857.

Wu B, Peisley A, Tetrault D, Li Z, Egelman EH, Magor KE, Walz T, Penczek PA, Hur S. 2014. Molecular imprinting as a signal-activation mechanism of the viral RNA sensor RIG-I. *Mol Cell*. 55:511-523.

Shukla AK, Westfield GH, Xiao K, Reis RI, Huang LY, Tripathi-Shukla P, Qian J, Li S, Blanc A, Oleskie AN, Dosey AM, Su M, Liang CR, Gu LL, Shan JM, Chen X, Hanna R, Choi M, Yao XJ, Klink BU, Kahsai AW, Sidhu SS, Koide S, Penczek PA, Kossiakoff AA, Jr VLW, Kobilka BK, Skiniotis G, Lefkowitz RJ. 2014. Visualization of arrestin recruitment by a G-protein-coupled receptor. *Nature*. 512:218-222.



Atomic resolution structure of Insecticidal toxic complex protein TcdA1. The structure was determined to a resolution of 2.7 Å from a data set collected and processed at the MPI Dortmund using SPHIRE.

John Putkey, Ph.D.
Professor and Vice Chair
Biochemistry & Molecular Biology

Molecular Mechanisms of Calcium-Dependent Cell Regulation

Calcium is most commonly recognized as a primary mineral component of bone, but it also plays an essential role in the regulation of numerous cell processes. When calcium levels in cells increase in response to a variety of stimuli (see Figure), it binds to calcium regulatory proteins, which then trigger cascades of protein-protein interactions. The most important calcium regulatory protein is called calmodulin. It is highly conserved in all eukaryotic cells from slime mold to humans, and it plays a critical role in regulating essential cellular processes, including muscle contraction, neural transmission and cell division.

The Putkey lab has made hallmark contributions to the study of calmodulin, including isolating the first cDNA clone for vertebrate calmodulin, and the structural and biochemical characterization of recombinant calmodulin. Currently, the Putkey lab focuses on two small, intrinsically disordered proteins called PEP-19 and Ng that bind to calmodulin and modulate how it senses calcium signals. Using a combination of biophysical techniques and NMR solution structure determination, the Putkey lab has shown that PEP-19 modifies the calcium binding properties of calmodulin by electrostatically steering calcium to binding sites on calmodulin (see Figure). These studies have broad implication since PEP-19 expression is induced in response to a variety of normal and pathological conditions, including cancer. It is likely that PEP-19 serves to control the activities of calmodulin in the face of abnormal calcium levels associated with these conditions.

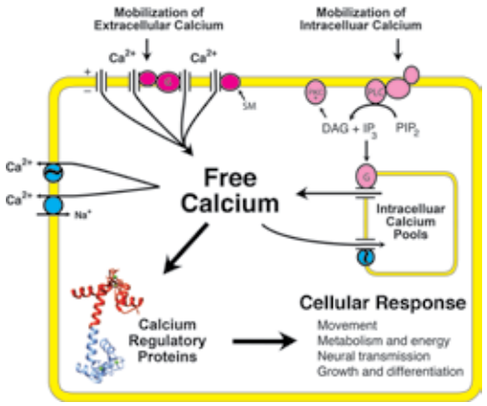
Development of Anti-Cancer Drugs

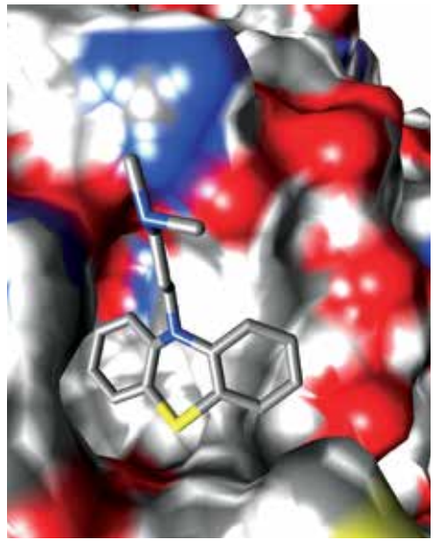
Rational drug design is a cutting-edge multi-step process that uses 3D structures to identify compounds that are predicted to bind to and alter the activity of target proteins involved in normal or pathological processes, including cancer. The small pluripotent G-protein signaling molecule called K-Ras is a prime target for cancer drugs since somatic mutations of K-Ras occur in about 25% of all human tumors. Compounds that bind to wild type and/or mutant forms of K-Ras would provide a powerful tool in the fight against numerous forms of cancer.

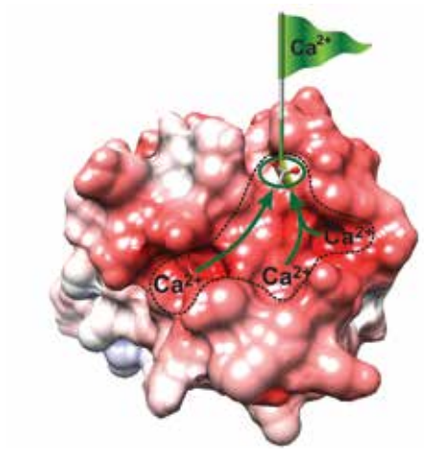
Dr. Putkey's group, along with UTHealth colleague Dr. Gorfe, is pursuing an approach to design drugs that target K-Ras. Computational methods are first used to screen huge libraries of chemical compounds for those predicted to bind to unique pockets on the surface of K-Ras to exert an allosteric effect on the nucleotide binding site, or interactions between K-Ras and downstream proteins. NMR is then used to determine if these lead compounds bind to the predicted pockets on K-Ras. Biochemistry, biophysics, and cell biology are then used to better characterize the interactions of lead compounds with K-Ras, and to determine their effect on K-Ras signaling pathways. Drs. Putkey and Gorfe have identified several promising lead compounds thus far (see Figure) and are proceeding with pre-clinical development of drugs targeting K-Ras.

Research Interests:

Structural and molecular basis of calcium signaling in normal and disease states. Identifying drugs that bind to K-Ras and that have therapeutic benefits.







The upper left Figure shows the various channels and pumps that coordinate to raise or lower intercellular calcium levels. Changes in calcium levels are sensed by calcium regulatory proteins to regulate numerous cellular processes. The upper right shows the surface of the NMR solution structure of a complex between calmodulin and PEP-19 in which negative charges (red) contributed by PEP-19 "steer" the positively charged calcium (Ca^{2+}) to a calcium binding site in calmodulin. The Figure on the left shows a 3-dimensional model in which a small molecule binds to a pocket on the surface of K-Ras.

Selected Publications:

Wang, X and Putkey, JA. 2016. PEP-19 modulates calcium binding to calmodulin by electrostatic steering. *Nat. Commun*. 7, 13583 doi: 10.1038/ncomms13583.

Wang Xu, Xiong LW, El Ayadi A, Boehning D, Putkey JA. 2013 The calmodulin regulator protein, PEP-19, sensitizes ATP-induced Calcium release. *J Biol Chem* 2883: 2040-8.

Wang Xu, Kleerekoper QK, Xiong LW, Putkey JA. 2010 Intrinsically disordered PEP-19 confers unique dynamic properties to apo and calcium calmodulin *Biochemistry*. 49: 10287-97.

Irina Serysheva, Ph.D.

Associate Professor and Director
Structural Biology Imaging Center
Biochemistry & Molecular Biology

Structure and Function of Integral Membrane Proteins

Our research aims to understand molecular mechanisms underlying transport of molecules into and out of the cell across the surface membrane, or between different intracellular compartments through structure-functional studies of integral membrane proteins known as ion channels, and the macromolecular complexes they form. Ion channels regulate many diverse biological functions that include muscle contraction, hormone secretion, gene transcription, metabolic regulation, neurotransmitter release, fertilization and apoptosis. The knowledge about the three dimensional (3D) architecture of ion channels is required to understand molecular basis of ion channel gating (opening/closing process), and how this process is controlled by a wide variety of endogenous molecules and pharmacological modifies. To answer these questions, we use a combination of electron microscopy and computer reconstruction techniques in conjunction with biochemical, electrophysiological and molecular biological approaches. Our structure research efforts include: 1) purification of ion channels from natural sources or from high-level expression systems; 2) electron cryomicroscopy (cryo-EM) of the purified channel assemblies; 3) computer image processing and 3D reconstruction; 4) structure analysis and annotation using combination of visualization and computational tools; and 5) prediction of functional roles of the identified structural domains via bioinformatics.

Recent focus has been on structural analysis of Ca^{2+} channels that mediate ligand-gated release of Ca^{2+} from intracellular stores: the ryanodine-sensitive Ca^{2+} release channel (RyR), the primary Ca^{2+} release channel in muscle cells, and the inositol 1,4,5-trisphosphate-sensitive Ca^{2+} release channel (IP3R), localized in the endoplasmic reticulum. Both channels are large tetrameric protein complexes with a molecular mass of ~2.3 MDa for RyRs and 1.2 MDa for IP3Rs. Defects in these channel proteins cause abnormal regulation of cell Ca^{2+} level underlying numerous human diseases: Malignant Hyperthermia, Central Core disease, cardiac hypertrophy, heart failure, hereditary ataxias, Huntington's disease, Alzheimer's disease, osteoporosis, atherosclerosis, and some migraines.

Research Interests:

Structure and function of integral membrane proteins and macromolecular assemblies.

Selected Publications:

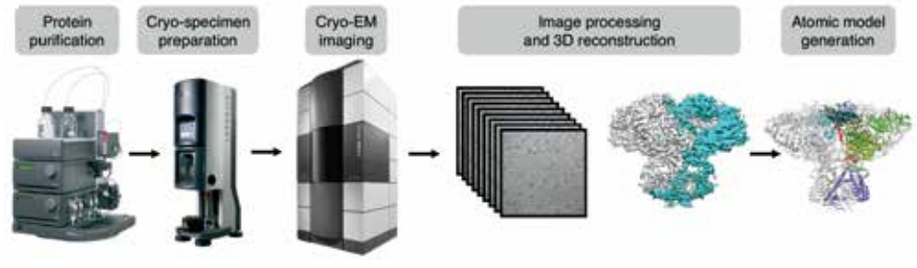
Fan G, Baker ML, Wang Z, Baker MR, Sinyagovskiy PA, Chiu W, Ludtke SJ, Serysheva II. 2015. Gating machinery of InsP3R channels revealed by electron cryomicroscopy. *Nature*. 52:336-441.

Baker MR, Fan G, Serysheva II. 2017. Structure of IP3R channel: high-resolution insights from cryo-EM. *Curr Opin Struct Biol*. 46:38-47.

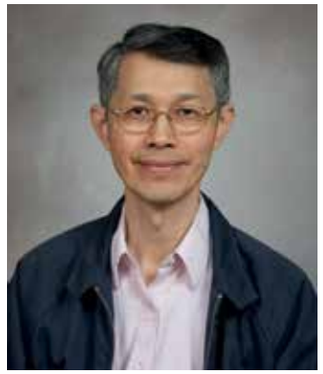
Ludtke SJ, Tran TP, Ngo QT, Moiseenkova-Bell VY, Chiu W, Serysheva II. 2011. Flexible architecture of IP3R1 by Cryo-EM. *Structure*. 19(8):1192-9.

Murray SC, Flanagan J, Popova OB, Chiu W, Ludtke SJ, Serysheva II. 2013. Validation of Cryo-EM Structure of IP3R1 Channel. *Structure*. 21(6):900-9.

Jarius S, Ringelstein M, Haas J, Serysheva II, Komorowski L, Fechner K, Wandinger KP, Albrecht P, Hefter H, Moser A, Neuen-Jacob E, Hartung HP, Wildemann B, Aktas O. 2016. J Inositol 1,4,5-trisphosphate receptor type 1 autoantibodies in paraneoplastic and non-paraneoplastic peripheral neuropathy. *J Neuroinflammation*. 13(1):278.



The cryo-EM structure determination pipeline that allows for solving atomic resolution structures of biological assemblies in different functional states.



Ann-Bin Shyu, Ph.D.

Jesse Jones Chair and Professor
Biochemistry & Molecular Biology

My lab has a long-standing interest in understanding the principles and regulatory mechanisms that govern the cytoplasmic fate of messenger RNA (mRNA) in mammalian cells. These post-transcriptional processes (including mRNA turnover, translation, and localization) play an essential role in modulation and quality control of gene expression, and when they go awry, they can contribute to the pathogenesis of human disease such as cancer and airway inflammation. We have been using molecular, biochemical, cellular, and computational biology approaches, including next-generation sequencing-based methodologies combined with in-depth bioinformatics analysis to study the regulation of these critical processes in mammalian cells. We are applying/developing transcriptome-based metabolic pulse-chase labeling and RNA-IP approaches that allow better characterization of changes in global mRNA turnover caused by specific cellular events. Currently, we focus on investigating 1) how rates of mRNA decay may be coordinated for groups of mRNAs during cell growth and differentiation, and 2) the mechanisms by which global mRNA turnover shapes or reprograms the overall mRNA expression profile or transcriptome in mammalian cells responding to intra- or extra-cellular stimuli.

Post-translational Modifications of General Decay Factors

Deadenylation (i.e., shortening of the mRNA 3' poly(A) tail) begins when mRNAs arrive in the cytoplasm and is a rate-limiting step for mRNA decay and translational silencing. Thus, deadenylation greatly affects the cytoplasmic fate of mRNAs and is a critical point for controlling mRNA functions. We currently focus on studying key mRNA deadenylation factors that contain poly(A)-binding protein (PABP)-interacting PAM2 motif. Reversible phosphorylation within the intrinsically disordered region (IDR) where the PAM2 motif resides modulates the interactions between these proteins and PABP, leading to changes in mRNA fate. This line of research offers a new framework for elucidating dynamic signal dependent regulation of mRNA stability across the transcriptome in mammalian cells.

Mechanisms Regulating Global mRNA Turnover in cis

Shortening of mRNA 3' UTRs via Alternative 3' End Processing and Polyadenylation (APA). More than two-thirds of mammalian mRNA genes express isoforms with distinct 3' untranslated regions (UTRs) due to alternative 3' end processing and polyadenylation (APA) of pre-mRNA. mRNA 3'UTRs harbor many regulatory elements and also bind various RNA-binding proteins, each of which can affect a transcript's cytoplasmic fate. The UTR-APA process introduces a dichotomy between use of distal and proximal polyadenylation sites, allowing production of mRNA isoforms either containing or lacking the full array of cis-regulatory elements in the 3' UTR. As the 3'UTR elements can be activating or repressive, shortening of 3'UTRs via APA may help a particular mRNA escape positive or negative regulation. Currently, we are employing next-generation sequencing-based approaches, such as BrUchase-seq and ribosome-profiling, to investigate how APA-elicited global shortening of mRNA 3'UTR reprograms the mammlian transcriptome and how the changes in mRNA fate may be linked to tumorigenesis.

N6-methyladenosine Epitranscriptomics and mRNA Fate. N6-methyladenosine (m6A) is the most abundant eukaryotic modification of mRNAs and long noncoding RNAs. Recent discoveries of the locations, functions and mechanisms of m6A have shed light on a new layer of gene regulation at the RNA level, giving rise to the field of m6A epitranscriptomics. A major limitation of m6A studies so far is the use of poorly characterized mixtures of m6A modified and un-methylated transcripts. As a result, the impact of m6A modification on mRNA turnover across the transcriptome remains very much an open issue. In this line of research, we use a novel RNA-immunoprecipitation based approach developed in our lab to measure decay rates for un-methylated and methylated pools of newly synthesized transcripts in parallel. The results will give important new insights into the mechanisms by which m6A regulates global RNA turnover. Moreover, they will also lay the foundation for investigating how m6A across the transcriptome may be altered during tumorigenesis and inflammation.

Research Interests:

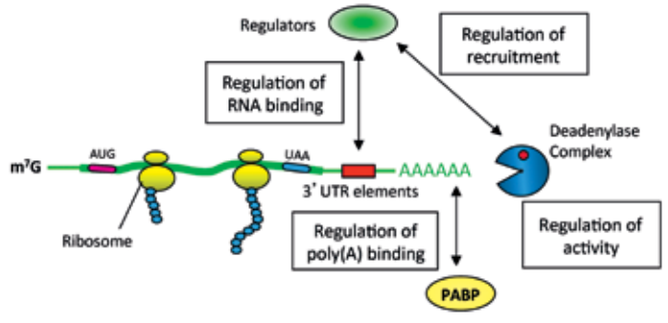
Messenger RNA functions in human disease

Selected Publications:

Chen CYA, Zheng D, Xia Z, Shyu AB. 2009. Ago-TNRC6 complex triggers microRNA-mediated mRNA decay by promoting biphasic deadenylation followed by decapping. *Nat Struct Mol Biol*. 16:1160-6.

Masamha CP, Xia Z, Yang J, Albrecht TR, Li M, Shyu AB, Li W, Wagner EJ. 2014. CFIm25 links Alternative Polyadenylation to Glioblastoma Tumor Suppression. *Nature*. 510:412-6.

Chen CYA, Shyu AB. 2017. Emerging Themes in Regulation of Global mRNA Turnover in cis. *Trends Biochem Sci*. 42:16-27.



Control of mRNA deadenylation involves regulation of interactions among deadenylase complexes, 3' UTR regulatory elements and their cognate binding proteins (Regulators), and poly(A)-binding protein (PABP)

John Lee Spudich, Ph.D.

Robert A. Welch Distinguished Chair in Chemistry
Professor, Biochemistry & Molecular Biology
Director, Center for Membrane Biology

Microbial rhodopsins: diversity, mechanisms, and optogenetic applications in basic and translational research

My primary interest is in microbial sensory rhodopsins: their molecular mechanisms and applications as molecular tools for research and gene therapy. After discovery of the first microbial sensory rhodopsin, a phototaxis receptor in an archaeal prokaryote, our subsequent work revealed homologous photosensors to be widespread among both prokaryotic and eukaryotic microorganisms. In particular, we identified sensory rhodopsin homologs in green algae that mediate phototaxis by light-induced membrane depolarization. The photodepolarization is due to light-gated cation conduction by the photosensors, accordingly named channelrhodopsins. Over the years we have implemented photochemistry, structural biology, and biophysical methods to elucidate atomic structure/function relationships in sensory rhodopsin activation, and developed methods for studying their function in animal cells, including neurons and other excitable cells, and in purified systems. Our current research is focused on the light-gated channel activity of channelrhodopsins. In addition to their interest from a basic biology perspective, channelrhodopsins have been the driving force for the technology of optogenetics.

Optogenetics is based on genetic targeting of microbial rhodopsins to defined populations of neurons, enabling use of light to control the targeted neurons' firing without affecting other neurons in the tissue. Elegant work of neuroscientists has made optogenetics a transformative technology for research on neural circuitry. Because of the temporal and spatial precision provided by using light to activate and silence neuron firing, optogenetics has revolutionized the study of brain circuitry, e.g. learning and memory, the neural determinants of emotions such as pleasure and fear, and the basis of neurological diseases such as epilepsy, Parkinson's disease, autism, anxiety and depression, and chronic pain. Clinical trials are currently underway using neuron-activating channelrhodopsins in gene-therapy to treat human retinal degeneration diseases causing blindness. The combination of inhibitor and activator optogenetic tools would enhance vision restoration gene-therapy since human vision entails an interplay of photoinhibition and photoactivation of neural pathways. However, until recently, only cation-conducting channelrhodopsins (CCRs) were known, and only weak tools were available for neural inhibition. Our recent discovery of potent neuron-inhibiting natural light-gated anion (physiologically chloride) channels (ACRs) provides new opportunities for neural inhibition for research and clinical use.

Clinical optogenetics necessarily began with a neuron-activating rhodopsins because efficient neuron inhibitors were not available. The discovery of natural rhodopsin anion channels by our laboratory group (Govorunova et al Science 2015), which efficiently silence neurons by light-gated chloride conductance, has opened the way for gene therapy for conditions in which excessive neural firing needs to be suppressed. Indeed, neuron hyperactivity is centrally involved either as a cause or as a major symptom in myriad neurological disorders, such as epilepsy, Parkinson's disease, autism, tinnitus, migraine, and chronic and post-operative neuropathic pain. Also ACRs enable optical control of cardiac function for research and potentially therapy. For example, optical shortening of cardiac action potentials may benefit treatment of cardiac disorders such as long QT syndrome. Our laboratory is currently focusing on understanding the molecular mechanisms of anion channel rhodopsins as well as engineering them for use in optogenetic therapeutics.

In addition to pursuing my research interests, I am active as an elected Fellow of the American Academy of Arts and Sciences, one of the country's oldest learned societies and independent policy research centers, and currently serve as President of the International Union of Photobiology, whose mission is to advance research on the roles of light in biology and on photomedicine, including clinical optogenetics, light-therapy for seasonal depression, DNA photo-damage and carcinogenesis, and photodynamic therapy (PDT) for non-surgical cancer treatment.

Research Interests:

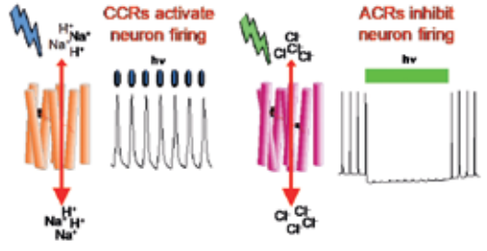
Biological light-sensing, light-sensor photochemistry, optogenetics use in research and clinical applications, photomedicine, non-invasive phototherapeutics

Selected Publications:

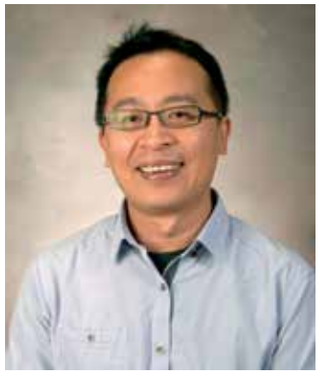
Govorunova EG, Sineshchekov OA, Janz R, Liu X, Spudich JL. 2015.Natural Light-gated Anion Channels: A Family of Microbial Rhodopsins for Advanced Optogenetics. *Science*. 349:647-650.

Sineshchekov OA, Li H, Govorunova EG, Spudich JL. 2016. Photochemical Reaction Cycle Transitions During Anion Channelrhodopsin Gating. *Proc Natl Acad Sci* USA. 113:E1993-2000.

Govorunova EG, Sineshchekov OA, Li H, Spudich JL. 2017. Microbial Rhodopsins: Diversity, Mechanisms, and Optogenetic Applications. *Annu Rev Biochem*. 86:845-872.



Light-gated cation channelrhodopsins (CCRs) and anion channelrhodopsins (ACRs) activate and inhibit neuron firing, respectively, providing precise temporal and spatial control of neuronal activity with light (optogenetics).



Kuang-Lei Tsai, PhD

Assistant Professor
Biochemistry & Molecular Biology
CPRIT Scholar - Cancer Prevention
Research Institute of Texas
UT System Rising STAR award recipient

Many human diseases are often caused by abnormal gene expression. In human cells, gene expression is tightly regulated by many large macromolecular complexes, such as coactivators, chromatin remodeling complexes, and long non-coding RNA molecules (lncRNAs). Studying their structures and molecular mechanisms is necessary for understanding how these complexes work and how gene regulation is controlled. Recent development in cryo-electron microscopy (cryo-EM) has already made it possible to determine the structure of the macromolecular complex at near-atomic resolution. We combine the advanced cryo-EM techniques with various biochemical and biophysical approaches to explore the structures and functions of macromolecular assemblies involved in gene regulation. Currently, we are especially interested in the two directions:

1. Structural and functional studies of the eukaryotic transcription complexes

The human 1.5 MDa transcriptional Mediator complex, consisting of 25 core Mediator proteins and a dissociable CDK8 kinase module, plays an essential role in transcriptional regulation by conveying regulatory signals to the RNA polymerase II (Pol II) transcription machinery. While the molecular mechanism by which Mediator regulates transcription has not been entirely elucidated; its dysfunction and dysregulation have been extensively linked to a variety of human diseases, including cancer. Recently, we successfully determined the core Mediator structure at near-atomic resolution (Figure 1), revealing the molecular interactions between core Mediator and Pol II during transcription initiation (Published in *Cell* 2014 and *Nature* 2017). Our near-term goals are to 1) explore the molecular mechanism underlying Mediator regulation by lncRNA and 2) identify new lncRNAs potentially linked to diseases through interactions with Mediator.

2. Macromolecular complexes involved in regulation of 3D genome architecture

In the cells, the structure of the 3D genome influences gene regulation, evolution, and cell fate decisions. How chromatin is organized within the nucleus and how genome architecture is regulated and maintained are important emerging biological questions. To regulate genome architecture, numerous protein complexes are involved in this process. We will use various structural and molecular approaches to study the structures and molecular mechanisms of the complexes involved in the regulation of genome architecture.

Research Interests:

Mediator, transcription, gene regulation, epigentics, cancer, nucleosome, chromatin remodeling, long noncoding RNA (lncRNA), 3D genome architecture, structure, x-ray crystallography, and cryo-EM.

Selected Publications:

Tsai KL, Yu X, Gopalan S, Chao TC, Zhang Y, Florens L, Washburn MP, Murakami K, Conaway RC, Conaway JW, Asturias FJ. 2017. Mediator structure and rearrangements required for holoenzyme Formation. *Nature*. 544:196-203.

Murakami K, Tsai KL, Kalisman N, Bushnell DA, Asturias FJ, Kornberg RD. 2015. Structure of an RNA polymerase II pre-initiation complex. *Proc Natl Acad Sci* USA. 112:13543-13548.

Tsai KL, Sato S, Tomomori-Sato C, Conaway RC, Conaway JW and Asturias FJ. 2014. Subunit architecture and functional modular rearrangements of the transcriptional Mediator complex. *Cell*. 157: 1430-1444.

Tsai KL, Sato S, Tomomori-Sato C, Conaway RC, Conaway JW and Asturias FJ. 2013. A conserved Mediator–CDK8 kinase module association regulates Mediator–RNA polymerase II interaction. *Nat Struct Mol Biol*. 20: 611-9.

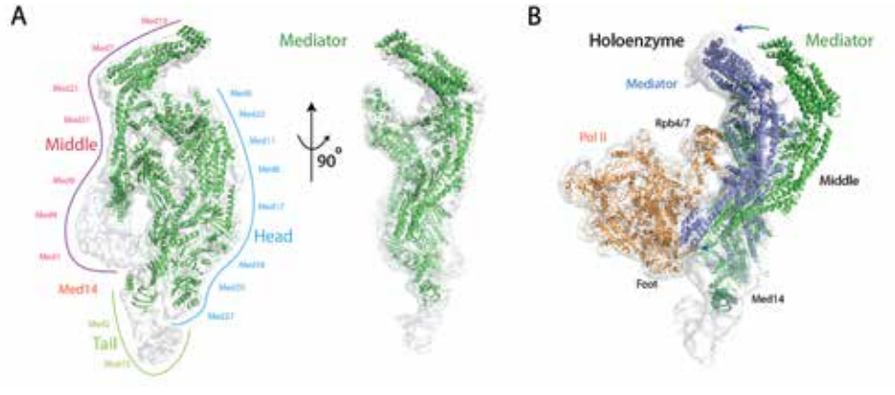


Figure 1. Transcriptional Mediator and its complex with RNA polymerase II (Pol II). (A) Structure of the core Mediator. (B) Structure of Mediator and Pol II complex. Conformational change of Mediator is required for its interaction with Pol II.

Yang Xia, Ph.D.
Professor
Biochemistry & Molecular Biology
McGovern Scholar

Molecular Basis of Hypertension and Blood Diseases and Human Translational Studies

My laboratory focuses on translational research of cardiovascular diseases including hypertension, preeclampsia, chronic kidney disease, blood disorders (sickle cell disease) and high altitude acclimatization. Those projects are united by a common feature of hypoxia. My goal is to translate discovery-driven basic science research smoothly and quickly to the clinic to improve human health. To accomplish this goal, my laboratory has conducted multiple non-biased screening approaches (including metabolomic and gene expression screening) to identify potential pathogenic markers for the diseases. Extending from the initial screens, we have conducted preclinical studies using both pharmacological and genetic approaches to determine the pathophysiological role of these newly identified molecules in animal models of specific diseases. Finally, our laboratory has conducted human translational research to determine whether these newly identified pathogenic biomarkers are diagnostic makers for early detection and therapeutic targets (see Figure 1 summary).

Our laboratory consists of a highly interactive, collaborative, and productive research team, including both basic and clinical research scientists. As a pioneer in adenosine signaling involved in physiological and pathological conditions, my lab has conducted preclinical research with mouse models of human disease and translational research with tissue and blood samples from humans with the relevant medical condition. Our research is driven by multidisciplinary cutting-edge technologies including high throughput unbiased metabolomics, proteomics, isotypically labelled metabolite flux, microarray, and deep confocal imaging. My laboratory has demonstrated the beneficial role of accumulated adenosine in acute hypoxia settings and the detrimental consequences of excessive adenosine signaling in several areas of pathophysiology, including sickle cell disease, preeclampsia, chronic pain, and chronic kidney disease. These findings provide new insight to pathogenesis of these diseases and identify innovative therapies for them and set up a foundation for future clinical trials.

Research Interests:

Preeclampsia, sickle cell disease, chronic kidney disease, hypertension, hypoxia, high altitude, erythrocyte metabolic reprogramming and metabolomic profiling

Selected Publications:

Zhang Y, Dai Y, Wen J, Zhang W, Grenz A, Sun H, Tao L, Lu G, Alexander DC, Milburn MV, Carter-Dawson L, Lewis DE. Zhang W. Eltzschig HK, Kellems RE, Blackburn MR, Juneja HS, Xia Y. 2011. Detrimental effects of adenosine signaling in sickle cell disease. *Nat Med*. 17(1):79-86.

Zhang Y, Berka V, Song A, Sun K, Wang W, Zhang W, Ning C, Li C, Zhang Q, Bogdanov M, Alexander DC, Milburn MV, Ahmed MH, Lin H, Idowu M, Zhang J, Kato GJ, Abdulmalik OY, Zhang W, Dowhan W, Kellems RE, Zhang P, Jin J, Safo M, Tsai AL, Juneja HS, Xia Y. 2014.Elevated sphingosine-1-phosphate promotes sickling and sickle cell disease progression. *J Clin Invest*. 124(6):2750-61.

Sun KQ, Zhang YJ, D'Alessandro A,, Song AR, Wu H, Bogdanov MV, Nemkov T, Hansen KC, Subudhi AW, Van Houten SW, Julian GG, Kellems RE, Dowhan W, Lovering AW, Roach RC, Xia Y. 2016. Sphingosine 1 Phosphate Promotes Erythrocyte Glycolysis and Oxygen Release for Adaptation to High Altitude Hypoxia. *Nat Commun*. 7:12086.

Song AR, Zhang YJ, Han L, Yegutkin GG, Liu H, Sun KQ, D'Alessandro A, Lee J, Karmouty-Quintana H, Iriyama T, Weng TT, Zhao SS, Wang W, Wu HY, Nemkov T, Subudhi AW, Houten SJ, Julian CG, Lovering AT, Hansen KC, Zhang H, Bogdanov M, Dowhan W, Jin JP, Kellems RE, Eltzschig HK, Blackburn MK, Roach RC, Xia Y. 2016. Erythrocytes retain hypoxic adenosine response for faster acclimatization on re-ascent. *Nat Commun*. 8:14108.

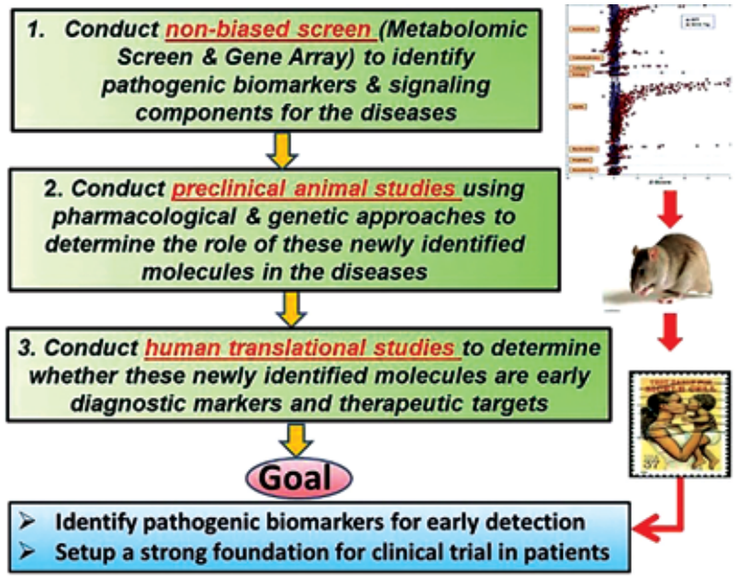
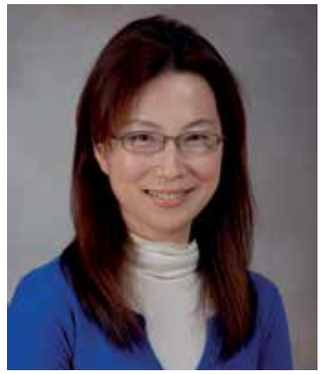


Figure 1. - Dr. Xia's lab conducts translational studies in multiple cardiovascular diseases including hypertension, preeclampsia, chronic kidney diseases, sickle cell disease and high altitude.



Seung-Hee (Sally) Yoo, Ph.D.
Assistant Professor
Biochemistry & Molecular Biology

Regulatory Mechanisms and (Patho) physiological Functions of Mammalian Circadian Clocks

In response to daily environmental changes imposed by Earth's rotation, almost all species, ranging from cyanobacteria to humans, have evolved physiological and behavioral rhythms called circadian rhythms. Circadian rhythms are not passive responses to environmental changes; rather, they are driven by an active clock system, capable of anticipating changes and coordinating tissue-specific function and generating systemic output responses. The harmony between our intrinsic biological timing and the daily environmental oscillation is critical to physiological well-being; conversely, disrupted circadian rhythms have been shown to cause or increase the risk of various chronic diseases. In our lab, we focus on delineating fundamental cellular mechanisms in circadian rhythms and also deciphering physiological and pathological roles of the clock. Our long-term goal is to translate such fundamental mechanistic knowledge into new drug targets and therapeutic strategies for improved prevention and treatment of chronic diseases.

Currently, our labs are pursuing several projects, using an integrative approach combining mouse models with molecular and cellular mechanistic studies. In one project, we investigate the role of miRNAs in circadian clock regulation using a second-generation circadian reporter mouse line Per2::LucSV (see Figure 1), with a particular focus on the mechanistic relationship between clock robustness and metabolic health. In another project, we investigate the differential roles of two circadian E3 ligases (FBXL3 and FBXL21) in skeletal muscle structure and function. Finally, we continue to pursue cloning of novel circadian clock mutants recently identified by a recessive mouse genetic screen.

Research Interests:

Circadian oscillator, miRNAs, F-box proteins, genomics, mouse models.

Selected Publications:

Yoo SH, Yamazaki S, Lowrey PL, Shimomura K, Ko CH, Buhr ED, Siepka SM, Hong HK, Oh WJ, Yoo OJ, Menaker M, Takahashi JS. 2004. PERIOD2::LUCIFERASE real-time reporting of circadian dynamics reveals persistent circadian oscillations in mouse peripheral tissues. *Proc Natl Acad Sci* USA. 101(15):5339-46.

Yoo SH, Mohawk JA, Siepka SM, Shan Y, Huh SK, Hong HK, Kornblum I, Kumar V, Koike N, Xu M, Nussbaum J, Liu X, Chen Z, Chen ZJ, Green CB, Takahashi JS. 2013. Competing E3 ubiquitin ligases govern circadian periodicity by degradation of CRY in nucleus and cytoplasm. *Cell*. 152(5):1091-1105.

He B, Nohara K, Park N, Park YS, Guillory B, Zhao Z, Garcia JM, Koike N, Lee CC, Takahashi JS, Yoo SH, Chen Z. 2016. The small molecule Nobiletin targets the molecular oscillator to enhance circadian rhythms and protect against metabolic syndrome. *Cell Metabolism*. 23: 610-21.

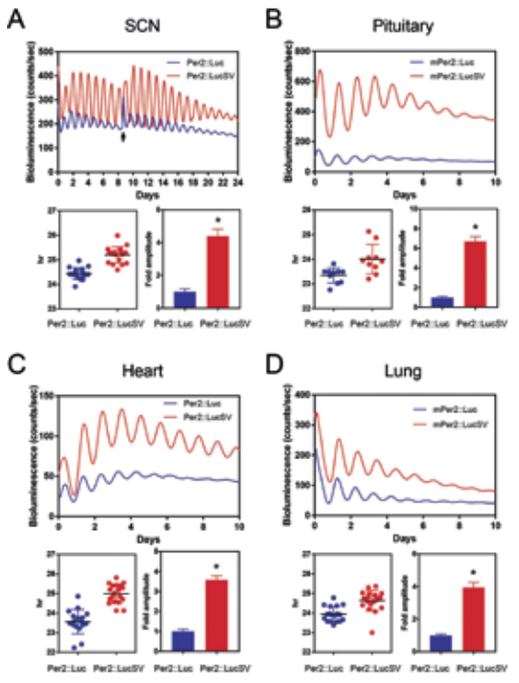


Figure 1. Comparison of real-time bioluminescence analysis of circadian expression of Per2::Luc and Per2::LucSV. Left panels: representative bioluminescence traces. Right panels: periods from individual replicates.

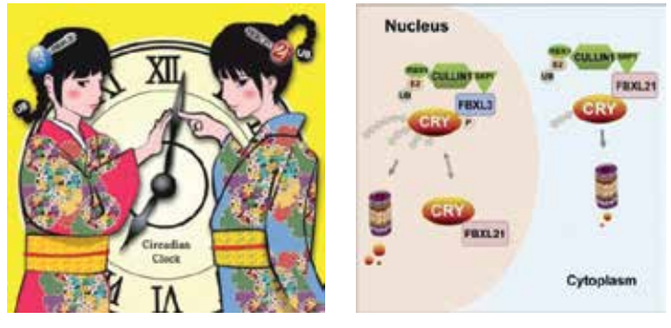
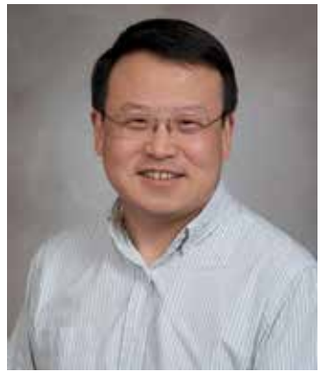


Figure 2. Circadian clock periodicity is governed by two paralogous F-box proteins FBXL3 and FBXL21. These two E3 ligases regulate levels of the circadian components CRY through a balance of protein degradation and stabilization. FBXL21 plays a dual role: protecting CRY from FBXL3 degradation in the nucleus and promoting CRY degradation within the cytoplasm. (Yoo et al., Cell 2013).



Lei Zheng, Ph.D.
Associate Professor
Biochemistry & Molecular Biology

Structural Studies of Membrane Proteins

The research of my laboratory focuses on structural characterization of integral membrane proteins. Membrane proteins are fundamentally important for nearly all aspects of biological activity. These molecules control material and information communications across the cell membranes. However, their working mechanisms are less understood largely due to the notorious difficulties to study them structurally. We are currently focusing on two important membrane protein systems involved in Ca^{2+} homeostasis and phospholipid metabolism. We aim to understand structure, function and regulation of these membrane proteins by using a combination of biochemical and biophysical approaches, primarily X-ray crystallography.

Calcium Cation Antiporter Proteins (CaCAs)

Calcium ion, the most abundant cation in the human body, serves as a universal secondary messenger to modulate a broad array of biological processes. CaCA proteins constitute a large membrane protein family, existing in all kingdoms of life. CaCAs promote Ca^{2+} extrusion out of cells by utilizing an electrochemical gradient of other cations such as H^+ or Na^+, playing an important role in Ca^{2+} homeostasis. The most studied CaCA proteins are Na^+/Ca^{2+} exchangers (NCXs), which are critical in maintaining cardiac contractibility in hearts and in facilitating neuronal transmission in brains. NCX proteins have a conserved structural motif, in which 10 predicted transmembrane helices forming a Na^+/Ca^{2+} exchange pathway and one large intracellular domain between TMs 5 and 6 regulating ion exchange based on the needs of intracellular Ca^{2+} signaling. Our current effort is to help understand two mechanisms of NCXs and CaCAs: 1) The Ca^{2+} transport mechanism: What is the structural basis of Ca^{2+} ion selectivity and how do these proteins catalyze Ca^{2+} exchange across the membrane bilayer using diverse cation driving forces? 2) The Ca^{2+}, Na^+ regulatory mechanism: How the regulatory domain controls NCX activity to facilitate rapid cellular Ca^{2+} homeostasis? Our structural investigations help understand the role of these important proteins in calcium signaling processes.

Phospholipid Metabolism

Phospholipid metabolism is fundamental in cells. It not only generates basic biological membranes, but also plays important roles in cellular signaling processes in nearly all tissues. In addition, many proteins, both globular and membrane bound, require specific phospholipids to fulfill their functions. Cells maintain a complicated and regulated metabolic network to synthesize a great diversity of phospholipids and degrade them in a timely fashion to meet cellular requirements. Many steps of phospholipid metabolism take place on the cell membrane and are catalyzed by membrane-embedded enzymes. Their molecular mechanisms are poorly understood largely due to the paucity of structural information. In particular, how these enzymes select their substrates from the lipid membrane bilayer and carry out catalysis in a hydrophobic membrane environment, is a central question still unanswered for general phospholipid metabolic mechanisms. Our ongoing project is expected to gain structural information to address this question.

Research Interests:

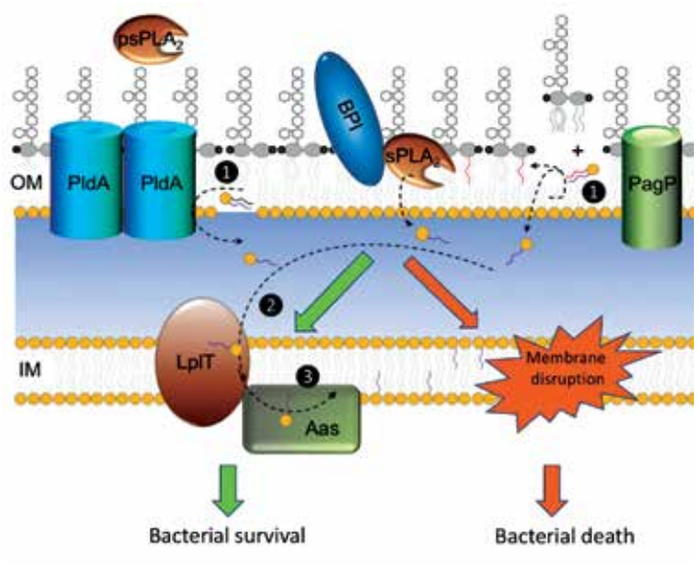
Structural biology of membrane transporters and phospholipid metabolism

Selected Publications:

Zheng L, Kostrewa D, Bernèche S, Winkler FK, Li XD. 2004. The mechanism of ammonia transport based on the crystal structure of AmtB of Escherichia coli. *Proc Natl Acad Sci* USA. 101(49):17090-5.

Wu M, Tong S, Gonzalez J, Jayaraman V, Spudich JL, Zheng L. 2011. Structural basis of the Ca^{2+} inhibitory mechanism of Drosophila Na^+/Ca^{2+} exchanger CALX and its modification by alternative splicing. *Structure*. 19(10):1509-17.

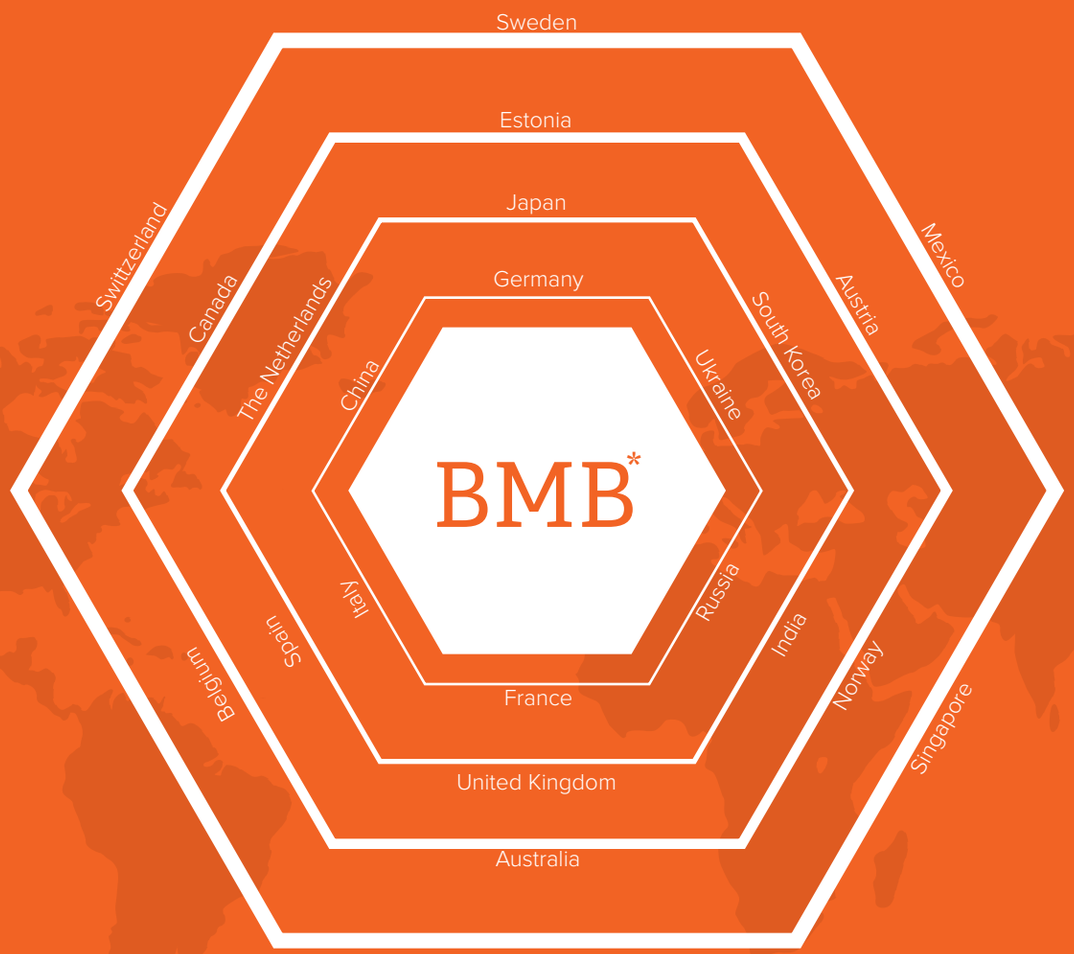
Wu M, Tong S, Waltersperger S, Diederichs K, Wang M, Zheng L. 2013. Crystal structure of Ca^{2+}/H^+ antiporter protein YfkE reveals the mechanisms of Ca^{2+} efflux and its pH regulation. *Proc Natl Acad Sci* USA. 110(28):11367-72.



Lysophospholipid remodeling system LplT/Aas protects Escherichia coli from host sPLA2-induced bacterial killing.

Our Diverse Department

Our Collaborations

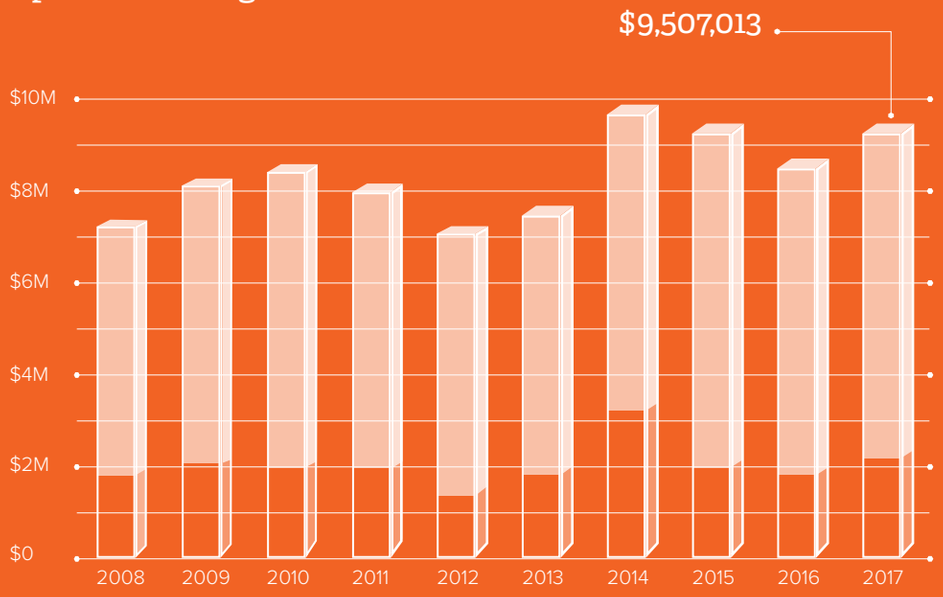


*Department of **B**iochemistry & **M**olecular **B**iology

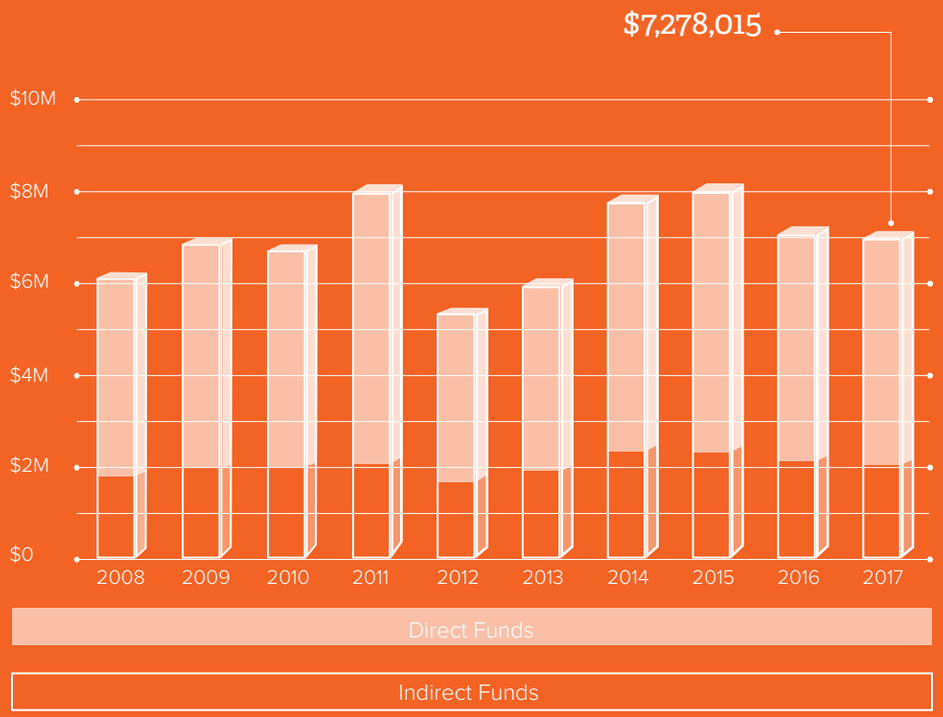
Top-Tier Journals - Where We Publish!

Nature
Nature Biotechnology
Biochemistry
Nature Medicine
Structure
Nature Cell Biology
Journal of Neuroinflammation
Journal of Experimental Medicine
Nature Review Genetics
Nature Chemical Biology
Nature Communications
Nature Methods
Trends in Genetics
Trends in Biochemical Sciences
Science
Cell
Cellular Signalling
Cell Metabolism
Cell Calcium
Cell Molecular Life Science
Molecular Cell
Blood
Proceedings of the National Academy of Sciences of the United States of American (PNAS)
Circulation
Hypertension
The Federation of American Societies for Experimental Biology (FASEB) Journal
Circulation Research
Journal of Clinical Investigation
Journal of Biological Chemistry
Molecular Cell Biology
Computational and Structural Biotechnology Journal
RNA
Cancer Cell
Scientific Reports
Cancer Research
Immunity
Journal of General Physiology
American Journal of Respiratory Cell and Molecular Biology
Journal of the American Heart Association
American Journal of Hypertension
The EMBO Journal
Metabolomics
Journal of Biomedical Science
PLOS ONE
Journal of Neuroscience

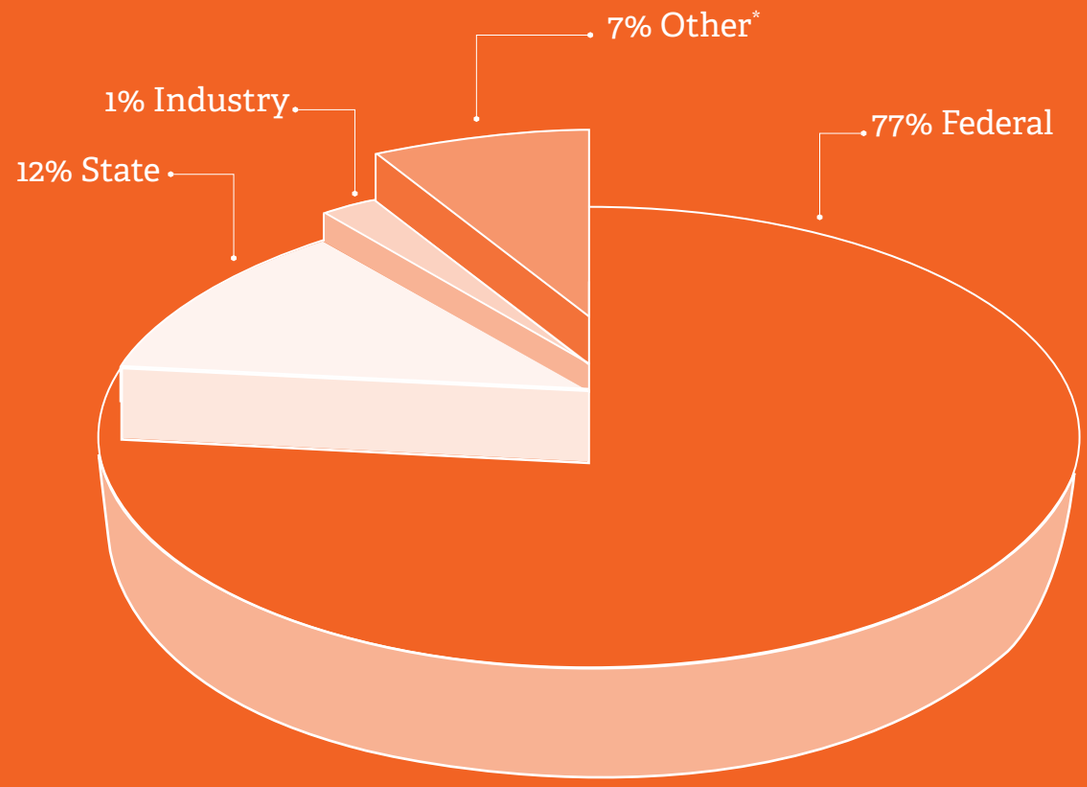
Sponsored Program Awards



National Institutes of Health Awards



Sources of External Funding for the Fiscal Year 2017



*Other includes:
American Heart Association, American Lung Association, Welch Foundation, Muscular Dystrophy Association, UTHealth Pulmonary Center of Excellence Discovery Awards

State & Other Funding Sources 2017

Cancer Prevention Research Institute of Texas

$1,186,658

UTHealth Pulmonary Center of Excellence Discovery Awards

$300,000

Welch Foundation

$290,404

American Heart Association

$244,000

American Lung Association

$40,000

Muscular Dystrophy Association

$46,500

Students 2017-2018

31
Research Graduate Program*

6
Summer Research Program

17
Visiting Students

*As of September 1, 2017, the graduate program was reorganized from Biochemistry & Molecular Biology (BMB) Graduate Program to Biochemistry & Cell Biology Graduate Program (BCB). The BCB program currently consists of 100 program faculty members and 31 graduate students.

BMB Faculty – Graduate Education and Postgraduate Training

Askar Akimzhanov
2005, Ph.D., University of Wurzburg, Wurzburg, Germany; 2005-2007, Postgraduate Training, UT MD Anderson Cancer Center; 2007-2013, UT Medical Branch, Galveston; 2013-2014, UT Health Science Center at Houston

Michael Blackburn
1993, Ph.D., Thomas Jefferson University, Philadelphia, PA; 1993-1997, Postgraduate Training, Baylor College of Medicine

Darren Boehning
2001, Ph.D., Thomas Jefferson University, Philadelphia, PA; 2001-2004, Postgraduate Training, Johns Hopkins University, Baltimore, M.D.

Phillip Carpenter
1994, Ph.D., University of Illinois at Urbana-Champaign
1994-1998, Postgraduate Training, California Institute of Technology

Zheng (Jake) Chen
2003, Ph.D., Columbia University, New York
2003-2008, Postgraduate Training, UT Southwestern Medical Center, Dallas

William Dowhan
1969, Ph.D., University of California, Berkeley
1969-1972, Postgraduate Training, Harvard Medical School

Leng Han
2010, Ph.D., Chinese Academy of Sciences, China; 2010-2012, Postgraduate Training, Stanford University, California;
2012-2015, UT MD Anderson Cancer Center

Vasanthi Jayaraman
1995, Ph.D., Princeton University, New Jersey
1995-1997, Postgraduate Training, Cornell University, New York

Jianping Jin
2000, Ph.D., Texas A&M University at College Station; 2000-2001, Postgraduate Training, Cold Spring Harbor Laboratory
2001-2003, Baylor College of Medicine
2003-2007, Harvard Medical School

Harry Karmouty-Quintana
2006, Ph.D., King's College London, United Kingdom; 2007-2010, Postgraduate Training, McGill University, Canada
2010-2012, UTHealth Science Center at Houston

Rodney Kellems
1974, Ph.D., Princeton University, New Jersey
1974-1978, Postgraduate Training, Stanford University, California

Cheng Chi Lee
1986, Ph.D., University of Otago, Dunedin, New Zealand; 1986-1990, Postgraduate Training, Baylor College of Medicine

Wenbo Li
2009, Ph.D., National University of Singapore
2009-2014, Postgraduate Training, University of California, San Diego

Pawel Penczek
1988, Ph.D., Warsaw University; 1989-1992, Postgraduate Training, Dr. Joachim Frank, Wadsworth Center for Laboratories and Research, Albany, New York

John Putkey
1982, Ph.D., University of California, Riverside
1982-1985, Postgraduate Training, Baylor College of Medicine

Irina Serysheva
1984, Ph.D., Russia Academy of Sciences, Moscow; 1984-1986, Postgraduate Training, Russia Academy of Sciences, Moscow

Ann-Bin Shyu
1986, Ph.D., Indiana University; 1987-1990, Postgraduate Training, Harvard Medical School

John Spudich
1976, Ph.D., University of California, Berkeley
1976-1980, Postgraduate Training, Harvard Medical School; 1978-1980, Postgraduate Training, University of California Medical School, San Francisco

Kuang-Lei Tsai
2009, Ph.D., National Tsing Hua University, Taiwan; 2010-2017, Postgraduate Training, The Scripps Research Institute, La Jolla, CA

Seung-Hee (Sally) Yoo
2004, Ph.D., KAIST, South Korea;
2005-2006, Postgraduate Training, Florida State University; 2006-2008, Northwestern University

Yang Xia
1992, M.D., Hunan Medical University, China
1998, Ph.D., UT Health Science Center at Houston; 1998-2001, Postgraduate Training, UT Health Science Center at Houston

Lei Zheng
2003, Ph.D., University of Bern, Switzerland
2003-2006, Postgraduate Training, Paul Scherrer Institute, Switzerland

Research Track BMB Faculty

Mariah Baker, Ph.D., Assistant Professor
Mikhail Bogdanov, Ph.D., Associate Professor
Chyi-Ying Chen, Ph.D., Associate Professor
Ti-Chun Chao, Ph.D., Assistant Professor
Elena Govorunova, Ph.D., Assistant Professor
Eugenia Mileykovskaya, Ph.D., Associate Professor
Tingting W. Mills, Ph.D., Assistant Professor
Kazunari Nohara, Ph.D., Instructor
Oleg A. Sineshchekov, Ph.D., Professor
Anren Song, Ph.D., Instructor
Heidi Vitrac, Ph.D., Assistant Professor
Xu Wang, Ph.D., Instructor
Zhaoyang Zhao, Ph.D., Associate Professor

Professor Emeritus

John A. DeMoss, Ph.D.
Julia Lever, Ph.D.
Barbara Sanborn, Ph.D.
James K. Stoops, Ph.D.
Henry W. Strobel, Ph.D.

Cross-Appointment Faculty

Joseph Alcorn, Ph.D., Associate Professor, Pediatrics-Neonatology
Holger K. Eltzschig, M.D., Ph.D., Professor and Chair, Anesthesiology
Changqing (Cynthia) Ju, M.D., Ph.D., Professor, Anesthesiology
Richard J. Kulmacz, Ph.D., Professor, Internal Medicine, Hematology
Nancy O. McNiel, Ph.D., Senior Associate Dean, Administrative Affairs at the Medical School
Nami McCarty, Ph.D., Associate Professor, IMM, Stem Cell Research
John O' Brien, Ph.D., Professor, Ophthalmology and Visual Sciences
Eric C. Swindell, Ph.D., Assistant/Associate Dean of Graduate Education
Ah-Lim Tsai, Ph.D., Professor, Internal Medicine, Hematology
Rick A. Wetsel, Ph.D., Professor, IMM, Immunology & Autoimmune Disorders
Wa Xian, Ph.D., Assistant Professor, IMM, Stem Cell Research

BMB Annual Research Retreat

For over 20 years, the Department of Biochemistry & Molecular Biology (BMB) has hosted an annual research retreat at Camp Allen, in the piney woods of Navasota, Texas. Departmental and graduate program faculty, postdoctoral fellows, graduate students, visiting scientists and students gather together in this rustic and forested setting to engage each other in not only rounds of research presentations and discussions but also in various outdoor activities from horseback riding and archery, to skeet shooting, trail hikes and fireside chats.