About the cover
The Fayez S. and Susan K. Sarofim Research Building glows at dusk.

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**IMM Director’s Message**

I’m pleased to introduce the latest IMMpact report for The Brown Foundation Institute of Molecular Medicine for the Prevention of Human Diseases (IMM). The IMM is a stand-alone research institute that is embedded within McGovern Medical School. Our mission is to deliver translational outcomes from research in molecular medicine that benefits patients. Inside the report you will find in-depth articles on four of our faculty and highlighted donors, plus an account from each IMM faculty member describing their research programs and recent progress.

There are many metrics that can be used to quantify research and institutional success, including grant funding, scientific publications, spin-off companies, and the capacity to recruit and retain stellar scientists from around the world. By all these metrics the IMM excels; I am especially pleased to report that once again IMM faculty had remarkable success in garnering new grants from the National Institutes of Health, Department of Defense, Cancer Prevention and Research Institute of Texas (CPRIT), and other extramural funding agencies. Over the financial year just ended, our new grants and contracts increased again, capping increases in our extramural grant funding for each of the last eight years. It is a testament to the outstanding quality and creativity of our scientists that the IMM remains so successful in attracting research funds. There also were some major research breakthroughs resulting in high-profile publications from our faculty, including Dr. Kolonin on a new class of anti-diabetes drugs, and Dr. An on novel anti-COVID antibody-based drugs, to cite just two that attracted much press attention.

Nevertheless, full implementation of our mission remains heavily dependent on attracting support from alternative sources, including research charities and foundations, industry collaborations, and, most importantly, the continuing generosity of our friends and donors. Such funding is critical to allow our faculty to start innovative new projects and generate preliminary results that will in turn lead to new grant proposals. In this context, we are as always deeply appreciative of the strong work and dedication of the IMM advisory council, which plays a key role in the continued growth and development of the IMM.

This brings me to our annual IMM symposium. An illuminating and entertaining evening where you can hear exciting research stories directly from our faculty and discuss the implications for the future of medicine and health care. This year the symposium will be held on April 26 and will feature two talks on some very recent new insights into the cellular mechanisms of aging. If you want to hear more about this fascinating science and how IMM researchers are at the forefront of the emerging field of aging research, then please attend the symposium. The work to be presented has important implications for treating degenerative diseases of the nervous system, including Alzheimer’s disease. The talks will be followed, as in years past, with a reception in the Dr. J.T. Willerson Discovery Hall. Full details can be found in this IMMpact report. I look forward to seeing you all there. On a final personal note, I was appointed Executive Dean of McGovern Medical School on September 1, but I will be continuing in my role as Executive Director of IMM.

John Hancock, MA, MB, BChir, PhD, ScD
Executive Director, Institute of Molecular Medicine
John S. Dunn Distinguished University Chair in Physiology and Medicine

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**The IMM has two major objectives:**

1. **Discovery** is the highest priority for the IMM faculty. This is a major challenge, since diabetes, obesity, cancer, Alzheimer’s, and cardiovascular diseases are unsolved medical problems that are not caused by single gene defects. Discoveries lead to new solutions.

2. **New diagnostics and therapies** are derivative of discovery and to the benefit of patients. The IMM focuses on these medical solutions. The IMM has organized talent in the Texas Therapeutics Institute specifically to achieve this goal of patient benefit from discovery.
The Brown Foundation Institute of Molecular Medicine for the Prevention of Human Diseases (IMM) is a research institute that seeks to investigate the causes of human diseases at the cellular and molecular levels, using DNA and protein technologies to elucidate disease mechanisms. This development and progress are of particular interest for future planning in the increasingly important area of clinical research. The institute endeavors to design methods of rational therapy and, wherever possible, strategies for the prevention of human diseases.

Advances in molecular and cell biology have enormous potential for innovative medical research and the future practice of medicine with more novel therapies. These approaches have been most successfully used to determine the causes of infectious disorders and genetic diseases. However, it is clear that molecular and cell biology will play a major role in clarifying the causes of many unsolved problems of modern medicine, such as heart disease, hypertension, vascular disorders, major mental illnesses, and immunologic diseases. The research of the institute’s investigators is inspiring and promises to fulfill the mission of the IMM.

Because the applications of molecular and cell biology to medical practice are of major importance to product development in biotechnology and the pharmaceutical industry, the IMM has the potential and desire to form important links and collaborations between its own research activities and various industries to apply its discoveries and intellectual properties to pharmaceutical opportunities.

As an institute of McGovern Medical School, the Brown Foundation Institute of Molecular Medicine for the Prevention of Human Diseases strives to set the example for research excellence and collaboration locally, nationally, and internationally.
Our Locations

Fayez S. Sarofim Research Building

- Primary home of the IMM’s faculty, administration, and support staff.
- Located adjacent to the The University of Texas Health Science Center at Houston (UTHealth) University Center Tower within the Texas Medical Center.
- Opened in 2006, the building encompasses 255,748 gross square feet.

South Campus Research Building – 3 (SCRB3)

- SCRB3 is a collaboration between The University of Texas MD Anderson Cancer Center and UTHealth, in cooperation with GE Healthcare and the Texas Enterprise Fund.
- Six-stories, 315,000 square-feet located on the South Campus of the Texas Medical Center.
- Opened in 2009, this facility houses Positron Emission Tomography, Magnetic Resonance Imaging, Optical Imaging Tracers, a Cyclotron, wet labs, and support offices.

The Denton A. Cooley Building – Texas Heart Institute at St. Luke’s Episcopal Hospital

- The IMM occupies a 31,000 square-foot high-tech laboratory.
- Located in the Texas Medical Center.
The Brown Foundation Institute of Molecular Medicine for the Prevention of Human Diseases

IMMpact Symposium

Fayez S. Sarofim Research Building
1825 Pressler Street

Wednesday, April 26, 2023
4:30 pm

SAVE THE DATE

Aging: From cells to organs to cognition

Why our cells get old and what we can do about it
Mikhail Kolonin, PhD

Cell housekeeping and brain longevity
Sheng Zhang, PhD

go.uth.edu/IMMpact
Understanding the aging cell

Aging. There is not much we can do about it – or is there?

The causes and effects of cellular aging on the body are a growing research focus for Mikhail Kolonin, PhD, professor and director of the IMM’s Center for Metabolic and Degenerative Diseases. By understanding aging at the cellular level, researchers aim to target therapies to stop disease and degeneration.

“Our lab is working to understand how aging in various cell types contributes to aging of individual organs and the body as a whole,” explained Kolonin, holder of the Harry E. Bovay, Jr. Distinguished University Chair in Metabolic Disease Research.

The main focus is on stromal cells. “Stroma shapes our body’s connective tissue scaffold, which, along with the skeleton, provides support to all of our vital organs,” he explained.

The aging of stromal cells impacts numerous diseases, such as obesity and cancer. “Stromal cells are very important for the proper function of the body,” Kolonin said. “They serve as progenitors of cells storing lipid in fat tissue and support the vasculature. Regenerative capacity of adult stem cells reduces with age and as a result of excessive calorie intake. That’s partly why we lose weight when we get older. It’s essentially a manifestation of cell aging.”

Stromal cells also can differentiate to activate the immune system – responsible for inflammation, secreting cytokines, which is conducive for developing fibrosis, sarcopenia, and other aging-associated conditions.

Cells show their age through senescence – the state at which a cell can no longer divide. Progenitor cells can divide as long as telomeres, the protective ends on the chromosomes, remain sufficiently long. Each time a human progenitor cell divides, telomeres shorten and they continue to do so until they reach the critically small size causing replicative senescence. “Everyone’s telomeres are different lengths at birth. For those who are unlucky being born with shorter telomeres, it will take fewer divisions of their cells until they cannot divide anymore,” he said.

The main factors regulating senescence are lifestyle and environment. “Our cells are subject to constant damage from free radicals. Factors such as sleeping/eating schedule, diet, exercise, and other healthy and unhealthy habits (such as smoking) all contribute to balancing cell stress,” he said.

Those who are obese typically eat more, exposing their cells to higher oxidative damage. “Fat cells overgrowing in obesity become hypoxic, malnourished, and start dying and releasing lipids,” he said. As a result, obesity tends to result in chronic inflammation and type 2 diabetes, which are linked with an increased risk of cancer development.

Kolonin and his lab have long studied the link between cancer and obesity. “If obesity is prevented, the risk of cancer decreases,” he said.

In collaboration with Columbia University, they are investigating the specific role of fat tissue-derived stromal cells in cancer progression. “Normally, if there is tissue damage, the stromal cells will engage in putting a temporary scar on the wound and helping it heal quicker. Cancer is a chronic wound,” Kolonin said. “So, the stromal cells are recruited to keep on fixing that wound as cancer-associated fibroblasts, and that process never stops, which results in cancer progression.”

Collaborating with Askar Akimzhanov, PhD, Department of Biochemistry and Molecular Biology, as well as with Canadian investigators, Kolonin’s lab has been researching how adipose tissue promotes cancer by making fatty acids available as energy sources and building blocks for cancer cells.

The lab is also collaborating with Kristin Mahan, PhD, associate professor, Center for Metabolic and Degenerative Diseases, investigating how circadian rhythm and feeding affect telomere length.

“Normally, progenitor cells in fat tissue divide in a cyclic pattern once a day after an animal eats,” Kolonin said. “But when mice are overfed, this pattern is lost and the cells start dividing more frequently, burning through their telomeres quicker, hence reaching the state of replicative senescence sooner.”

The lab also is looking at late-stage cancer progression and the loss of fat mass. “We are trying to understand the crosstalk between our fat and muscle tissues that is responsible for cancer-associated cachexia,” he said. “Once we identify the molecular triggers, we will be able to suppress body wasting and reduce cancer mortality.”
Mikhail Kolonin, PhD, focuses on the cellular impact of aging and its association with disease.
Jiaqian Wu, PhD, and her lab are investigating neurodegenerative diseases at the cellular level to better understand and treat brain diseases.
Diseases involving the brain and central nervous system, such as stroke, Alzheimer’s, and multiple sclerosis, continue to elude restorative treatment, causing devastating long-term effects for patients and their families.

Jiaqian Wu, PhD, associate professor of neurosurgery, aims to stem the rising prevalence of these brain diseases by understanding pathological processes common to neurotrauma, stroke, and neurodegenerative diseases. Wu and her lab are focused on the activation of astrocytes – a type of glial cell that support neurons, and oligodendrocyte demyelination, which impairs functions in neurodegenerative diseases.

“These pathological processes exist throughout spinal cord injury, brain injury, and neurodegenerative diseases. We use cutting-edge technologies, such as single-cell sequencing and RNA-based therapy, to develop therapeutic approaches to improve the neurological environment and promote neuroregeneration,” she explained.

More than 1 million people in the United States live with multiple sclerosis. More than 795,000 strokes occur in the United States each year, with stroke rates rising among those under 55 years old. And a projected 14 million in the United States are expected to suffer from Alzheimer’s disease by 2060.

“Neurodegenerative diseases, such as multiple sclerosis, Alzheimer’s, and stroke share commonalities at the cellular level. There are a lot of similar pathological processes that we can work on that would benefit these different diseases,” Wu said.

A joint faculty member of both the IMM’s Center for Stem Cell and Regenerative Medicine and the Vivian L. Smith Department of Neurosurgery since 2011, Wu bridges both the research and clinical missions.

“This collaborative environment in the Stem Cell Center is very important for doing research – we form a critical mass of people studying stem cells together,” she explained.

Wu’s research is collaborative among institutions as well. Her research includes four federally funded grants in such areas as spinal cord injury, neural regeneration, and Alzheimer’s disease – with colleagues from Baylor College of Medicine and Tufts University.

“Another specialty of my lab is that we have computational expertise. We are able to analyze big data and then integrate them into bench research,” she said.

The group is working to identify key regulators to modify the pathological environment in neural tissues and facilitate axon regeneration to restore mobility.

The lab is looking to an understudied area – long noncoding RNA – which are essential regulators in the central nervous system. While they do not encode for protein, they can be versatile, forming scaffold to interact with proteins, or RNA or DNA.

“RNA has emerged as a promising therapeutic tool in different diseases – such as the recent COVID vaccine,” she said. “We are taking this one step further by identifying and characterizing essential functions of long noncoding RNA as a therapeutic target for neurological diseases.

“Our goal is to unleash the power of our body to help with regeneration under injury condition, stroke, or other neurodegenerative diseases. Finding the key regulators for this is giving us hope for future potential.”

“...We use cutting-edge technologies, such as single-cell sequencing and RNA-based therapy, to develop therapeutic approaches to improve the neurological environment and promote neuroregeneration.”

— Jiaqian Wu, PhD, associate professor of neurosurgery
More than 100,000 people in the United States will be diagnosed with colorectal cancer this year. While the incidence of this cancer is dropping in the elderly, colon cancer rates are rising among those under 54 years of age.

Qingyun (Jim) Liu, PhD, director, of the IMM’s Center for Translational Cancer Research, and his lab have dedicated years of research to better understand colon cancer and develop potential therapeutics.

“I have been working on colon cancer since I discovered a group of receptors long before I joined UTHealth Houston,” Liu said, adding that this group of receptors has been key to understanding colorectal cancer.

Prior to joining the IMM in 2009, Liu worked 16 years in the drug discovery industry.

Taking a molecular and cellular approach, Liu and his lab are working to discover why colon cancer produces these receptors and how they work within cancer cells.

“We will then be able to develop potential drugs that target these receptors on the cancer cells,” he explained.

Using an approach called antibody drug conjugate (ADC) – whereby the antibody attached with a toxin binds directly to the cancer cell receptor, researchers target points of interest.

“This is like a smart bomb because it targets specific kinds of cells,” he explained, adding that ADC has become successful in treating blood, bladder, breast, and uterine cancers.

The lab has published research on new ADCs for colon cancer and is funded by the National Institutes of Health and the Cancer Prevention and Research Institute of Texas.

“These grants allow us to engineer different antibodies to target these receptors,” Liu said. “We are trying to optimize and broaden our testing, including safety research.”

The lab is also using a ligand-based drug conjugate approach to attack colon cancer cells.

“These receptors bind molecules called the ligand, which is basically the signaling-trigging molecule of these receptors,” Liu explained. “We came up with a clever approach to put a cytotoxin onto the ligand. The trick is, we actually created a ligand that is not active anymore.”

Liu and colleagues modified the ligand so that it becomes inactive but still binds to the receptors very strongly. “It will still target the receptors without doing anything but carrying the drug,” Liu said.

“So far, the results are very promising,” Liu added. “We are working to ensure this approach can be tolerated at a therapeutically effective dose without causing severe side effects.”

Other work of the center includes investigating how cancer cells develop drug resistance and how they metastasize.

“We are also using lighting and imaging to track how drugs enter a tumor and visualize how the tumors develop,” he said.

To further understand cancer, the center takes cancer cells from patients and grows them into a three-dimensional model in a petri dish.

“Since tumors are three-dimensional, this is more like a real tumor,” Liu said. “We can then conduct our experiments in these tumors and see how they will respond to different treatments.”

So far, the results are very promising. We are working to ensure this approach can be tolerated at a therapeutically effective dose without causing severe side effects.

— Qingyun (Jim) Liu, PhD, director, Center for Translational Cancer Research
Qingyun (Jim) Liu, PhD, and his lab are working to better understand colon cancer to develop novel therapies.
Eva Sevick-Muraca, PhD, and her colleagues are shining a light on lymphatics and the role they play to improve health and treatment.
Lighting the lymphatics of the brain

Like a system of bayous, streams, and drains, the lymphatic system transports fluid throughout the body, and in the process, maintains fluid levels, removes waste, and elicits immune responses. As the bayous are essential to Houston during a rainstorm or hurricane, the lymphatic system is key to health and well-being.

For more than two decades, Eva Sevick-Muraca, PhD, director of the IMM’s Center for Molecular Imaging, and her team have literally shone a light on the lymphatics of more than 700 infants, children, and adults in the Texas Medical Center via innovative infrared fluorescent imaging.

“The lymphatics play really important roles in many diseases associated with aging, including peripheral vascular disease,” she said. “When people age, they get venous stasis ulcers, peripheral arterial disease, and diabetic foot ulcers. Through imaging, we’ve been able to show that the lymphatics play a role in the etiology of these conditions and could be an impactful target to treat and possibly even prevent them.”

The group also has used imaging for dosing therapeutics.

“Our work suggests that we can more effectively treat patients with autoimmune disease and cancer through regional lymphatic delivery as opposed to intravenous delivery of these drugs,” she said.

Colleague Melissa Aldrich, PhD, associate professor in the Center for Molecular Imaging, is using the lab’s imaging technology to evaluate breast cancer patients for lymphedema before surgery and every six months after radiation.

Through imaging, Aldrich and her collaborators at MD Anderson Cancer Center were able to see the onset of lymphatic abnormalities 8 to 23 months before the start of irreversible patient symptoms. “If we can treat at the first sign of lymphatic abnormalities, perhaps we can prevent its onset. I hope that with imaging diagnostics, lymphedema will be a disease of the past,” said Sevick, the Nancy and Rich Kinder Distinguished Chair of Cardiovascular Disease Research.

John Rasmussen, PhD, assistant professor in the Center for Molecular Imaging, specializes in engineering optical instrumentation and is currently adapting computer vision techniques to the lymphatic imaging technology that he co-invented. The additional technology will enable clinicians to longitudinally track lymphatic function in cancer survivors, providing an important clinical research tool for future clinical studies to prevent lymphedema.

Sevick and her team are turning their attention to the lymphatics of the brain. In collaboration with Manish Shah, MD, associate professor of pediatric neurosurgery and William J. Devane Distinguished Professor, they are looking at the role of lymphatics in pediatric traumatic brain injury.

“When you have a traumatic brain injury, such as a brain bleed often suffered by premature babies, hemoglobin within brain tissues can cause neuroinflammation. Normally, cerebrospinal fluid (CSF) drains into the lymphatics to remove brain waste. But if the lymphatics are impaired, then brain waste products cannot leave the brain, and the acute neuroinflammation becomes chronic,” Sevick explained.

Via an investigational drug study under review by the FDA, Sevick and her team will trace fluid flow in hydrocephalus patients by adding a safe, fluorescent dye to the infants’ CSF.

“We want to see where that CSF goes, or doesn’t go, and then devise more efficient strategies to reduce fluid and prevent neurological deficits,” Sevick said.

Banghe Zhu, PhD, assistant professor, Center for Molecular Imaging, engineered the specialized cap and optical imaging system, which generates 3D images.

While the team is currently focused on the pediatric population, studies to evaluate the lymphatic contribution are underway and planned in other neurodegenerative conditions.
The Harry E. Bovay, Jr. Foundation, and its leadership, Edward R. Naumes, Peggy Larkin Kelly, C. Ronald Dorchester, Michael L. Patrick, and Carl F. Jaedicke, (not pictured Frances Escriva), continue to bridge gaps in health care, education, and community development, with its commitment to Mikhail Kolomin, PhD, Harry E. Bovay, Jr. Distinguished University Chair in Metabolic Disease Research, and the Center for Metabolic and Degenerative Diseases.
Building bridges to better health

Towering over vast rivers and winding chasms, bridges connect distant people and places, linking entire communities through architectural marvels. For Harry E. Bovay, Jr., an engineer who grew up witnessing how the bridges his father built impacted local communities, these structures came to take on a different meaning.

Through philanthropy, he worked to bridge gaps in health care, education, and community development to create a path forward for future generations—a mission that the Harry E. Bovay, Jr. Foundation continues today.

Bovay earned an engineering degree at Cornell University and pursued a fruitful career in the energy and telecommunications sectors. In 2004, he made his first philanthropic commitment to UTHealth Houston, launching an enduring partnership dedicated to improving health.

He established the Harry E. Bovay, Jr. Distinguished University Chair in Metabolic Disease Research at McGovern Medical School at UTHealth Houston, which is now held by Mikhail Kolonin, PhD, professor in The Brown Foundation Institute of Molecular Medicine for the Prevention of Human Diseases. This initial commitment also laid the groundwork for the Center for Metabolic and Degenerative Diseases at the Institute of Molecular Medicine.

Throughout the Many Faces. One Mission. philanthropic campaign, the foundation has built on this initial commitment and expanded Bovay’s legacy through contributions to initiate new studies on metabolic diseases while advancing the careers of young scientists in the field.

“The Bovay Foundation’s generosity to the Center for Metabolic and Degenerative Diseases has enabled us to kickstart innovative and impactful metabolism research as well as pursue collaborations with other leaders in the field,” said Kolonin, director of the center.

With the foundation’s support, Kolonin and his team are shedding light on cellular aging and the development of diseases associated with obesity. In particular, Kolonin has made critical discoveries linking different types of adipose cells—fatty, connective tissue cells found throughout the body—to common health conditions ranging from cancer to type 2 diabetes.

“Mr. Bovay would be very pleased with the research Dr. Kolonin and his team are doing,” said Michael (Mike) Patrick, president of the Harry E. Bovay, Jr. Foundation. “He would be sitting in meetings with the scientists and asking hundreds of questions about their discoveries. I think he would be tickled by all the wonderful things they are doing.”

The Bovay Foundation also established the annual Harry E. Bovay Lecture Series in Molecular Medicine in 2005, which hosts world-renowned experts who share their latest research findings with students, residents, and faculty. The series honors Bovay as a philanthropist focused on building bridges between the laboratory bench and patient bedside.

In 2022, the Bovay Foundation partnered again with UTHealth Houston by providing vital resources for Kolonin and his team to continue their research in metabolic medicine. The foundation’s support also will help launch research on types of breast cancer resistant to traditional therapies.

“Throughout my career working for Mr. Bovay, he always wanted to find the best possible people and organizations to collaborate with in order to accomplish a goal,” Patrick said. “I think that is what we have found at UTHealth Houston. People like Dr. Kolonin, who have the dedication, desire, and ability to help others, are truly wonderful.”
The IMM Center for Cardiovascular Genetics, established in 2006, focuses on the elucidation of molecular genetics, genomics, and pathogenesis of cardiovascular diseases to utilize the discoveries to prevent and treat cardiovascular diseases in humans. The Center provides specialized clinical services to patients with genetic cardiovascular disorders at the Cardiovascular Genetic Clinic. The Center is involved with clinical research programs, including NIH- and industry-sponsored clinical trials.

Mission: To prevent and treat cardiovascular diseases in humans through the identification and targeting of pathogenic genes and pathways.

The general theme of the research programs:
The research programs at the Center start with the identification of the causal genes and mutations for human cardiovascular diseases, particularly hereditary cardiomyopathies, which are important causes of sudden cardiac death and heart failure. Genetic discoveries are then followed by genomic studies to identify the differentially expressed gene and the epigenetic changes. The integrated approach is used to identify the key dysregulated pathogenic pathways, which are then targeted to prevent and reverse the disease, initially in the model organisms and subsequently in human patients through pilot randomized placebo-control, double-blind clinical trials. The findings are used as a platform for large-scale multi-center efficacy clinical trials.

Research Programs:
The research programs are as follows:
I. Human molecular genetic studies of cardiomyopathies: We have a repository of several hundred cases and their family members with cardiomyopathies. Pathogenic and causal variants are identified by whole exome sequencing in the probands and family members. These studies have identified new disease-causing genes and have advanced the genetic causes of heart failure. We are actively recruiting additional probands and family members.
II. Genomics and epigenetic studies of human heart failure and mouse models of cardiomyopathies: The studies include whole transcriptome analysis by RNA-sequencing, single cell RNA-sequencing, DNA methylation analysis, and analyzing chromatin remodeling by ChIP-sequencing. Specific epigenetic regulators of gene expression are identified and targeted to delineate their functions in the heart. A notable research program is to delineate the role of lysine demethylases KDM5A and KDM5B in the pathogenesis of heart failure, which is led by Dr. Priyatansh Gurha.
III. Genomic instability and activation of the DNA damage response in hereditary cardiomyopathies: We have detected evidence of increased double-stranded DNA breaks (DSBs) in human hearts from patients with hereditary cardiomyopathies and have identified several hundred DSBs in cardiac myocyte genomes in mouse models of hereditary cardiomyopathies. The studies are ongoing to characterize the genomic features of the DSBs and define their pathogenic roles in heart failure. A noteworthy ongoing project is to delineate the role of the DNA damage response pathway in cardiac fibroblasts in nuclear envelopathies involving the heart (led by Dr. Leila Rouhi).
IV. Therapeutic targeting of dysregulated pathways in cardiomyopathies: Dysregulated pathways, identified through integrated genomics, are targeted through genetic and pharmacological interventions in model organisms and their effects on survival, cardiac function, and clinical outcomes are analyzed. Two notable programs include genetic targeting of the canonical WNT pathway in ACM and the cytosolic DNA sensor protein CGAS in cardiac laminopathies.
V. Clinical Studies: The Center participates in investigator-initiated, single-center pilot clinical trials as well as industry-sponsored, multi-center clinical trials in hereditary cardiomyopathy. An NIH-sponsored double-blind randomized pilot study (HALT-HCM) in patients with HCM was recently completed.

AJ Marian, MD
Center Director & Professor
Molecular genetics, genomics, pathogenesis of hereditary cardiomyopathies

RESEARCH PROJECTS
• Identification and characterization of DNA damage, specifically double stranded DNA breaks (DSBs) in common forms of hereditary cardiomyopathies and delineating their role in the pathogenesis of heart failure
• Delineating the molecular mechanisms of cell death programs in hereditary cardiomyopathies
• Phenotypic consequences of genetic blockade of the cytosolic DNA sensing proteins in cardiomyopathies
• Determination of the role of the canonical WNT pathway in the pathogenesis of arrhythmogenic cardiomyopathy

We are also involved in industry-sponsored clinical trials in cardiomyopathies.

KEY PUBLICATIONS


LAB MEMBERS
Research instructor: Leila Rouhigharabaei, PhD
Post-doctoral fellows: Melis Olcum, Benjamin Cathcart
Research assistants: Angelica S. Rodriguez, Maya M. Gonzales, Rebecca Polasek
Research and clinical nurse: Yanli Tan, RN
The main objective of my research is to understand the molecular mechanisms that coordinately regulate gene expression and contribute to the pathogenesis of heart failure. Within this theme, we are studying the function of epigenetics and non-coding RNAs in proliferation, differentiation, and maturation of myocytes and how alteration of these interlinked processes eventually leads to cardiac dysfunction and failure. My previous studies have identified epigenetic dysregulation of miR-184 and its role in the pathogenesis of ACM. We have now begun to investigate how reprogramming of epigenetic code governs gene transcription and ensuing cardiac phenotype in heart failure (HF). Recently, we uncovered the role of DNA methylation and Lamin Associated Domain in Human HF. These studies led us to identify a novel epigenetic regulator KDM5, in the phenotypic manifestation of HF and provided the basis for deciphering the role of KDM5A in the heart. We recently published studies that implicate lysine-specific demethylase 5 (KDM5) as epigenetic regulators of the dysregulated genes in HF induced by LMNA Loss of Function.

The role of KDM5A and B in the heart is unknown. We are using induced pluripotent stem cells (iPSCs) and several mouse models to investigate the tissue and cell type-specific contribution of these regulators in cardiac physiology. We found that KDM5A and B has a direct role in the maturation of iPSC-CMs. The reprogramming toward a maturation state of iPSC-CM is in part regulated through epigenetic control of genes involved in OXPHOS and sarcomere formation by KDM5A and B.

**RESEARCH PROJECTS**

- Role of lncRNAs in the pathogenesis of cardiomyopathies and heart failure
- Identification and characterization of molecular mechanisms and functions of lysine demethylase KDM5 in cardiomyopathies and heart failure.

**KEY PUBLICATIONS**

M Deogharia, P Gurha. The “guiding” principles of noncoding RNA function, Wiley Interdisciplinary Reviews: RNA, 2022, 13 (4), e1704.


**LAB MEMBER**

Post-doctoral fellow: Manisha Deogharia
Research assistant: Michelle Hua

Suppression of KDM5 by small molecule inhibitor KDM-C70 leads to induction of Oxidative phosphorylation genes (Panle A and B) and Oxygen consumption rate of the iPSC derived cardiac myocytes (Panel C and D).
Our work in the Center for Human Genetics seeks to advance understanding of genetic risk for common cardiovascular diseases and to use that information to identify disease pathways leading to new therapies for these diseases. High blood pressure is the single biggest driver of chronic disease in our society and acts to amplify cardiovascular disease risk from stroke, heart, and kidney disease. These diseases emerge in middle and later life and are interlinked with the normal processes of aging. The genetic variation that makes us unique individuals, and that has been passed to us from our parents, impacts our risk of these diseases. Our work targets the identification of genes that contribute to cardiovascular diseases and the mechanisms by which variation in these genes reshape the biological pathways in which disease emerges.

An important element of chronic disease of the cardiovascular system is the involvement of a persistent state of inflammation. For example, in atherosclerosis, the blood vessel wall is invaded by immune cells and the danger posed in atherosclerotic plaques may reflect the ongoing level of inflammation in them. We need a better understanding of these processes of “sterile inflammation” in which our immune systems become activated in response to the emergence of damage to our tissues. We need greater understanding of the genetic variants that determine whether these inflammatory responses subside or remain active or even advance. In order to adapt to the continuous and rapid mutation of pathogens like viruses and bacteria, our immune systems harbor extensive genetic variation. Such variation can provide us a head-start in responding to new or evolving pathogens. But it can also create risk of disease later in life. As our living standards have increased and our lives have lengthened, the advantages provided earlier in life can turn into threats to our health by increasing our risk of chronic cardiovascular and cerebrovascular disease.

Progress in the laboratories of our investigators continues to yield exciting and important insights. Our human population geneticists, working under the direction of Dr. Myriam Fornage, are global leaders in their field, and are making notable progress in the study of susceptibility to stroke and age-related decline in cognitive function. A significant fraction of sudden cardiac death results from rhythm disruptions that arise in genetic variation in the proteins processing the electrical activity within the heart. Our colleague Dr. Ashish Kapoor is an emerging leader in this field. Dr. Peter Doris and his group have shown that kidney injury associated with increased blood pressure results from the emergence of auto-antibodies that damage tissues. He is using cutting-edge genome assembly methods to reveal genetic variation in the hyper-complex genomic regions that encode immune system genes. Our understanding of the complexity of information storage and retrieval in the genome continues to expand. Our colleague Dr. Sidney Wang is addressing approaches to assess, extract, and exploit new levels of genomic complexity that will inform work in this field.

Common cardiovascular disease will eventually impact us or someone close to us. In the Center for Human Genetics, we have the opportunity to work for change, pushing forward the knowledge and moving towards new insights and new opportunities for disease prevention.

Peter A. Doris, PhD
Center Director & Professor
Mary Elizabeth Holdsworth Distinguished University Chair in Metabolic and Inflammatory Disease Research
The risk of kidney disease in patients with high blood pressure is best predicted by family history. This indicates a genetic predisposition. At present, we have almost no knowledge of why high blood pressure creates kidney disease in some people but not others. If we knew which genes are involved, we could infer the disease mechanism and seek treatments that act on the involved, we could infer the disease mechanism and seek treatments that act on the involved.

Do the pathogenic mechanisms active in rats give insight into renal disease in humans? Genetic variation in antibody genes occurs in humans that may contribute to disease risk. However, these genes are the most complex in the genome, and we have not yet even begun to create an inventory of all the genetic variation that exists within them. New methods are emerging that will allow us to study this question in humans, which has not previously been possible.

KEY PUBLICATIONS

LAB MEMBERS
Co-investigators in genome assembly: Ted Kalbfleisch, PhD, University of Kentucky; Melissa Smith, PhD, University of Louisville Research assistants in Doris Lab: Yaming Zhu, MD; Aniket Joshi, BS

Genome assembly permits differences that contribute to genetic risk of disease to be located in the genome with certainty. New sequencing technology employing “long reads” allows assembly that is more contiguous, more complete, and more correct. These “long reads” provide the building block of assembly from which whole chromosomes are ultimately recovered. Typically, we can weave these reads together to chunks about 50 million bases in length, a typical chromosome is about 100 million bases. To correctly tie these chunks together and order them in the correct orientation, additional “scaffolding” methods are used. Finally, we curate the assemblies using a visualization method to search for errors or gaps in the assembly and to identify the missing small pieces that complete the puzzle. The result is a contact map from which the individual complete and correct chromosomes (highlighted as colored boxes) can be recovered.
Molecular epidemiology of the aging brain in diverse human populations

Myriam Fornage, PhD
Professor
The Laurence and Johanna Favrot Distinguished Professorship in Cardiology

Throughout our lifetime, our brain changes more than any other part of our body. Beginning in midlife, aging brings about subtle changes in brain structure, chemistry, and function. These changes are detectable by neuroimaging techniques such as magnetic resonance imaging (MRI) and are associated with a greater risk of future stroke, cognitive and functional impairment, dementia, and death. Current “omics” technologies provide us with high-dimensional information about the sets of biological molecules that make up cells, tissues, and organisms on a population scale. These include, for example, the entire genome sequence of a person; the epigenetic marks or chemical modifications on their DNA that regulate the activation or silencing of genes; and the circulating metabolites and proteins in their blood. Our laboratory uses advanced computational techniques to make sense of this information with the goals to discover novel biomarkers for disease-risk prediction and to enable informed preventive and therapeutic interventions that slow or reverse brain aging and brain vascular disease. Our work has impact on our understanding of brain vascular disease mechanisms and on its application toward precision medicine and public health policies (such as motivating healthy lifestyle). One of the most challenging aspects in the application of genetic information to precision medicine is ensuring that it is equally applicable to all so as to limit exacerbating health disparities. Our group is committed to working on diverse populations.

In collaboration with researchers in the United States and Europe, we seek to identify genes and gene variants that influence risk for stroke, Alzheimer’s disease, brain MRI abnormalities, and their cardiovascular risk factors. These complex traits are determined by DNA sequence variations occurring in many genes that have small effect sizes and act over long periods of time. With this genetic information, we can estimate a person’s “polygenic risk score (PRS)” for a particular trait or disease, which represents the total number of genetic variants influencing the particular trait or disease that a person has inherited. A person’s PRS provides a measure of disease risk due to their genes. Combining PRS with lifestyle and clinical risk factors can give a better idea of how likely a person is to develop the disease during their lifetime than considering either alone.

Using this approach, we have derived a PRS for stroke and estimated the lifetime risk of a first stroke event according to level of genetic risk. We also investigated whether maintaining a good cardiovascular health could offset a high genetic risk of developing a stroke in one’s lifetime. We found that at age 45, persons with the lowest PRS had a 1 in 10 chance of developing a stroke in their lifetime, while those with the highest PRS had a 1 in 5 chance of developing a stroke in their lifetime. For those with a high PRS and a poor cardiovascular health, this risk rose to 1 in 4. Regardless of genetic risk, persons with optimal cardiovascular health had the most significant reduction in their lifetime risk of stroke. Those who had a high polygenic risk and optimal cardiovascular health were observed to mitigate their lifetime risk of stroke by up to 43%, compared to those with inadequate cardiovascular health. This translated into about six additional years lived without a stroke. This research shows us how we can use genetic information to determine who is at higher risk and encourage them to adopt a healthy cardiovascular lifestyle to lower that risk and live a longer, healthier life.

RESEARCH PROJECTS

• Discovering novel genes influencing risk for Alzheimer’s disease, stroke, and neuroimaging abnormalities of brain aging.
• Discovering genes for high blood pressure using gene-lifestyle interactions and pathway analysis. In particular, discovering how depression affects genetic risk of hypertension.
• Investigating the genetic and epigenetic determinants of cognitive function in diverse Hispanics/Latinos.

KEY PUBLICATIONS


LAB MEMBERS

Post-doctoral fellow: Junyu Yang, PhD
Graduate Students: Songmi Lee (PhD program); Xia (PhD program)
Biostatisticians: William Dartora, PhD; Rui Xia, PhD
Research associate: Ping Wang, PhD

Polygenic risk scores can identify groups of individuals in the populations who could benefit from the knowledge of their lifetime risk of stroke to motivate a healthy lifestyle.
Despite the progress in the prevention and treatment of cardiovascular diseases in general, sudden cardiac death (SCD) remains a major public health problem. SCD, defined as a sudden and an unexpected pulseless condition due to a cardiac arrhythmia (when heart beats out of rhythm) without evidence of a non-cardiac cause, is the leading cause of deaths in the United States (~500,000 each year) and accounts for ~15% of all-cause deaths and ~50% of deaths from cardiovascular diseases. Moreover, in almost half the cases, SCD is the first sign of an underlying cardiovascular condition. Although many forms of heart disease can lead to SCD, the most common process underlying SCD is ventricular fibrillation (VF), an irregular and uncoordinated contraction of cardiac muscles of ventricles (lower chambers of heart) due to disorganized electrical signals. VF is usually fatal if not reversed by defibrillation immediately. Most of the existing cardiovascular risk factors are poor at predicting SCD, even in those individuals with a history of heart disease, clearly showing that other environmental and/or genetic factors are likely to play a role in developing VF and SCD. Indeed, from population- and family-level studies there is evidence for genetic susceptibility to SCD. However, studies to identify genetic factors underlying susceptibility to SCD directly have had limited success due to pooling of the very diverse forms of heart diseases leading to SCD into one group. Instead, we focus on the electrocardiographic QT interval, an intermediate observable characteristic/trait (phenotype) that predisposes to SCD. Electrocardiography, also known as ECG, measures the electrical activity of heart chambers and the QT interval in an electrocardiogram corresponds to the time taken by ventricles to depolarize (activated state) and repolarize (resting state) in every heart beat. In the general population QT interval varies across individuals and is a useful clinical marker as both prolongations and shortenings of the QT interval have been known to be associated with increased risk of cardiac arrhythmias and SCD. We are interested in identifying the genes that underlie this variation with the aim that understanding the genetic factors for QT interval variation will potentially impact our understanding of SCD risk and its treatment. Our studies have the prospect to identify the genetic causes for QT interval variation, some of which in turn could serve as potential therapeutic (drug) targets or potential biomarkers (genes and gene products) to identify individuals at high risk for SCD. What we as a community have learned so far is that many genes together contribute to QT interval variation and that the majority of DNA changes leading to QT interval variation do so not by altering the form of the gene product rather by altering the amount of the gene product made by our heart cells. Starting with known genetic associations between DNA sequence variants and the QT interval in the general population, our work involves pinpointing the causes behind these associations to identify the underlying gene defects and how they impact QT interval.

RESEARCH PROJECTS
- Molecular characterization of QT interval genome wide association study (GWAS) signals to identify the underlying causal variants, genes and their mechanisms.
- Evaluation of constitutive, cardiac- and nervous-system restricted Nos1ap null mice to understand its role in cardiac electrophysiology.
- Functional genomic approaches to understand cardiac gene expression regulation.

KEY PUBLICATIONS

LAB MEMBERS
Post-doctoral fellow: Lavanya Gunamalai, PhD
Research assistants: Ernesto Sanchez, BS; Kyla Vickery, BS
Undergraduate trainee: Supraja Kadagandala

Massively parallel reporter assays (MPRA) of all QT interval GWAS loci variants in HL1 mouse cardiomyocytes showing reporter expression and allelic skew at ~700 candidate variants.
Regulation of gene expression is fundamental to a wide range of biological processes. From cell fate determination during development to malignant transformation during tumorigenesis, precise control of gene expression forms the basis of these processes. Our current understanding of gene regulation is, however, far from complete. Most published studies that profile gene expression are transcript-centric (i.e. they focus on measuring mRNA levels and levels of transcription factor binding). While these efforts revealed intricate networks of cooperativity amongst transcription factors in shaping complex biological processes, much of the post-transcriptional regulation are left unexplored. It remains unclear whether the process of protein translation is regulated by a network of factors to an extent of complexity similar to transcription regulation. We ask questions such as "Do sequence specific RNA binding proteins (RBP) cooperate in controlling translation?", "Are there translational regulatory networks that orchestrate critical biological processes?" Our research program focuses on addressing these questions in biological contexts that are relevant to human health. Our immediate goals are to develop novel tools to systemically study RBP binding; to investigate regulatory functions of upstream Open Reading Frames (uORFs); and to integrate these functional genomics annotations with results from genetic studies, in order to fine map the regulatory variants and to provide mechanistic understanding for disease associated variants.

**RESEARCH PROJECTS**

- **Regulation of protein translation by uORF in stress response.** Translation regulation by uORF has long been hypothesized based on supports from studies of a handful of uORFs. We have reported a systemic survey of uORF impact on protein translation and identified genetic variants associated with this impact. We are further expanding this line of research in the context of stress response, where global scale changes in translational regulation are expected.
  - **Using RNA binding protein footprint sequencing to investigate translational regulation of protein synthesis.** RNA binding proteins are known to regulate protein translation. We aim to develop a general and effective tool to facilitate research in this area.
  - **Identification of functional novel coding regions across multiple tissues.** We have previously identified 7,273 novel coding regions from a single cell type using ribosome profiling data. While we provided evidence of active translation at these loci, the biological function and importance of these loci remains unknown. We are following up on this line of research by designing knockout screens to identify loci that are essential for cell survival. We are also expanding our efforts in identifying novel coding regions through performing ribosome profiling experiments in additional cell types and tissues.
  - **Gene expression buffering at the post-translational level.** Gene expression at the transcript level are often assumed to propagate to the protein level. In a series of studies, we have demonstrated that, in our cell line model system, the variations observed at the transcript level are often buffered at the protein level through post-translational processes. In order to evaluate how general this observation is, we are now expanding our analysis to other tissue types and species.

**KEY PUBLICATIONS**


**LAB MEMBERS**

Post-doctoral fellow: Sandeep Bansal

Sidney Wang, PhD
Assistant Professor

Deciphering the regulatory code: A functional genomics approach to protein translation

Genotype of a genetic variant is associated with uORF regulation of protein translation at HMSD locus in HapMap LCL. Negative correlation in the levels of protein translation between the two Open Reading Frames at HMSD locus is clearly shown through stratifying ribosome profiling data by genotype.
Chronic diseases of the lung and eye are often the result of dysregulation of the immune and inflammatory response to pathogenic or toxic substances, resulting in the destruction of healthy tissue, establishment of debilitating pathologies due to fibrosis, and impairment of normal tissue repair mechanisms. However, the paucity of cellular and molecular knowledge regarding lung and eye immunity, inflammation, and repair processes has slowed the development of novel therapeutics that could be used for the effective treatment of chronic diseases of the lung and eye. Accordingly, our laboratory has, for the past several years, focused on delineating the key molecules that mediate the inflammatory and immune responses in the lung and eye during both normal and pathological conditions. Much of this research has involved studies of the complement system. The complement system is a major arm of the innate immune system and is well known for being the first line of defense against bacterial and viral pathogens. It is comprised of over 30 plasma proteins and cellular receptors. It has become evident in the past decade that the complement system is very important in biological functions other than killing bacteria and viruses. These other functions include tissue regeneration, polarization of immune cells, including T-cells and normal development of the central nervous system. In addition to these novel complement biological functions, dysregulation of the complement system has been discovered as a major cause of AMD and a major contributor to lung diseases, such as asthma and COPD. To determine the overall importance and biological functions of complement, we have generated numerous “knock-out” mice in which the genes encoding specific complement proteins, regulators, and cell receptors have been selectively ablated by gene targeting and homologous recombination using mouse embryonic stem cells. The generation of these mice has facilitated the discovery of numerous biological roles of complement in the pathogenesis of various disease pathologies. For example, in studies using mice in which the C3a receptor was deleted, we discovered that the complement anaphylatoxin peptide C3a is an important mediator of key hallmarks of asthma, including airway hyperresponsiveness, and therefore may prove to be an excellent therapeutic target for the treatment of asthma. As part of this overall research program, we are investigating the therapeutic use of embryonic (hES) and induced pluripotent (iPS) stem cell derived cells for repair of damaged retina in AMD, for regeneration of the damaged lung epithelium in acute lung injury, and for cell based gene therapy for newborns born with genetic deficiency of surfactant protein B.

RESEARCH PROJECTS

- Determine how the function of vascular and lymphatic endothelial cells is impacted by complement during the immune response
- Generate “universal donor” embryonic stem cell lines that can be differentiated into transplantable cells that will not be rejected after transplantation
- Evaluate the therapeutic potential of gene corrected iPS cell-derived lung cells for surfactant protein deficiencies
- Develop hES-retinal pigment epithelial cells therapeutics for treatment of AMD

KEY PUBLICATIONS


LAB MEMBERS

Senior research scientist: Stacey Mueller-Ortiz, PhD
Senior research associate: Aleksey Y. Domoshirov, MS
Environmental triggers regulating innate immune responses in chronic airway inflammation

Amber Luong, MD, PhD
Professor, Center for Immunology and Autoimmune Diseases and Department of Otorhinolaryngology – Head and Neck Surgery, Vice Chair for Research, Department of Otorhinolaryngology – Head and Neck Surgery

Over 40 million Americans suffer from chronic rhinosinusitis (CRS), which causes facial pain and pressure, nasal congestion and obstruction. These symptoms ultimately drive conservatively 18-22 million physician visits yearly with an annual direct healthcare treatment cost of over 3 billion dollars. In addition, patients suffering from CRS often are diagnosed with asthma, specifically those characterized by nasal polyps (CRSwNP). Together, CRS and asthma as chronic respiratory diseases represent some of the most prevalent chronic illnesses in the United States. Despite this healthcare burden, much remains unknown about its pathophysiology, and current treatment options, which typically involve recurrent surgeries and anti-inflammatory agents, are not curative. CRS represents an ideal human research model for studies in chronic inflammatory respiratory diseases. CRS patients often undergo surgery providing an opportunity to harvest critical diseased tissue and are seen regularly in clinic which allows periodic evaluation of the patient and diseased mucosa.

Allergic fungal rhinosinusitis (AFRS) represents a unique CRSwNP phenotype typically presenting in patients in their twenties with nasal polyps and inflamed, often expanded sinuses impacted with thick mucin laden with fungal hyphae and eosinophils, that result in dramatic CT sinus findings. AFRS is a severe subtype of CRSwNP that uniquely can present with vision changes and intracranial complications with disease severity associated with lower socioeconomic status.

AFRS represents an excellent disease model for understanding the role of fungi in the pathophysiology of sinonasal inflammation characterized by eosinophils and elevated Type 2 cytokines (e.g. IL-4, -5, and -13). One key characteristic of AFRS is the accumulation of eosinophilic mucin and filamentous fungi within inflamed sinuses. Based on our microarray data, one of the most differentially downregulated genes in AFRS as compared to other CRSwNP phenotypes is histatin 1 (HTN1). We confirmed these results in independent inflamed sinus mucosa and found that the other family member, histatin 3, was also significantly downregulated in AFRS. Given AFRS is characterized by an accumulation of fungal hyphae within eosinophilic mucin, a lack of antimicrobial peptides in AFRS potentially contributes to this phenotype.

We have shown that non-diseased sinonasal epithelial cells (SNECs) are capable of expressing antimicrobial peptides (AMPs), such as histatins, but that regulatory pathways governing AMP expression are impaired in AFRS. Our lab is currently focused on evaluating the role of key regulatory mechanisms of antimicrobial peptide expression in AFRS, IL-22 signaling, and therapeutic options for upregulating AMP expression or activity in treatment of CRS.

Respiratory epithelial cells represent the first line of defense against the environment for sinonasal mucosa. Recent studies have shown that epithelial cells serve an active role through regulation of cytokines and release of anti-microbials. Three identified epithelial cell-derived cytokines, thymic stromal lymphopoietin, interleukin (IL)-25 and IL-33, have been linked to the type 2 immune response.

Our lab has focused on the role of IL-33 in orchestrating the type 2 immune response characteristic of CRS with nasal polyps. We confirmed that the receptor of IL-33 is upregulated in the diseased sinonasal mucosa of CRSwNP. We demonstrated an increased presence of innate lymphoid type 2 cells (ILC2) preferentially in CRSwNP patients relative to health controls. These ILC2 express ST2, the receptor for IL-33, and represent the major cell type producing IL-13 in response to IL-33 (see image 3). Interestingly, we found that fungal antigens, specifically Aspergillus, can stimulate respiratory epithelial cells to release IL-33.

Given the appreciation of the innate immunity and known data of the role of the adaptive immune response in CRS, we are currently interested in the development, and ultimately, in the function of innate lymphoid cells and T helper cells in various CRS subtypes. In addition to antimicrobial peptides, my lab is interested in the molecular characterization of fungi-mediated signaling pathways and the fungal component responsible for signaling in the inflammatory response in some CRS subtypes. This has led us to our recent interest of establishing a mouse model of eosinophilic upper and lower airway inflammation and the protocols to evaluate the sinus inflammation.

RESEARCH PROJECTS

- Characterization of immunologic and molecular defects contributing to pathophysiology of allergic fungal rhinosinusitis.
- Molecular signaling through respiratory epithelial cells of fungi alone and with other environmental triggers responsible for initiating and/or maintaining the characteristic Th2 immune response.
- Clinical characterization and identification of biomarkers for CRS subtypes.

KEY PUBLICATIONS


LAB MEMBERS

Hua Sun, PhD; Yi-Dong Li

Bony erosion of skull base from accumulated eosinophilic mucin laden with fungal hyphae.
The Center for Metabolic and Degenerative Diseases unites eight laboratories that collaborate to investigate aging- and obesity-associated diseases, including cancer. Mechanistic changes in brain activity, energy metabolism, vascular function, cell signaling, protein homeostasis, and cell fate determination that lead to pathophysiology are being interrogated in animal models and studies of clinical specimens. The primary interests include the crosstalk between brain and adipose tissue, as well as integrative physiology changes leading to dysfunction of organs, such as liver and skeletal muscle. Questions pursued by the Center’s faculty include the following:

- Which cells stop dividing with age, leading to aging-associated disease?
- What are the mechanisms underlying circadian rhythms in adipocyte progenitor proliferation?
- Which cells of adipose and muscle tissue can be targeted for therapeutic purposes and how?
- How does lipid metabolism change during cancer progression and cachexia development?
- How does transient inflammation activate heat production by fat tissue?
- What are the mechanisms driving adipocyte mitochondrial dysfunction and promoting obesity?
- What factors mediate the communication between different fat pads or between adipocytes and other metabolic organs under a mitochondrial distress condition?
- What are the mechanisms linking blood vessel formation with the nervous system?
- How do stress hormones regulate sugar and fat utilization in diabetes?
- What is the molecular basis of exercise benefits in metabolic and cardiovascular disease?

Collaboration among the Center’s laboratories promotes research synergy, thereby increasing productivity and innovation. The Center’s members collaborate with clinicians and epidemiologists to translate their discoveries for the benefit of patients with metabolic and degenerative diseases.

Mikhail Kolonin, PhD
Center Director & Professor
Harry E. Bovay, Jr. Distinguished University Chair in Metabolic Disease Research
My laboratory studies mechanisms underlying aging-related diseases and developing new approaches to target them. The focus is on the role of pathogenic fibroblasts, which can be recruited from fat (adipose) tissue in the context of obesity, type-2 diabetes, muscle degeneration, and cancer. While white adipocytes store lipids to release them in times of energy scarcity, brown adipocytes burn lipids off to keep the body warm. In obesity, overgrown white fat becomes inefficient in holding lipids, hence causing diabetes, cardiovascular disease, and cancer. In contrast, active brown fat can prevent the onset of metabolic disease. The past year, we have published several reports on the mechanisms and role of fatty acid transport in the context of type-2 diabetes and cancer. Specifically, we demonstrated the role of prohibitin-1 in mediating bi-directional long chain fatty acid transport in white and brown adipose tissues. Another research direction is focused on the role of inflammatory signaling, mediated by cytokine CXCL12, and fat tissue remodeling in cancer progression to chemoresistance and metastasis. Both white and brown adipocytes are continuously replaced as they undergo senescence, and their pools in fat tissue are maintained by adipose stem cells (ASCs). We have discovered that in chronic disease, tissues recruit ASCs, which can fuel cancer and fibrosis progression. Taking advantage of our expertise in targeted therapeutics, we have developed the first experimental drug (D-CAN) targeting ASCs. Our publications demonstrate that D-CAN prevents obesity and suppresses cancer progression in mice. We also have applied ablation of ASC as a new therapeutic approach to muscular dystrophy treatment. In obesity, ASCs over-proliferate and undergo replicative senescence, hence, aggravating aging. This was revealed by our studies in mice lacking telomerase in ASCs. Currently, we are testing the role of replicative senescence in other types of stem cells and the effects on aging-associated neurological and muscular dysfunction. We also identified peptides that home to metastatic cancer cells and are currently working on identifying their receptors that can be used for targeting.

**RESEARCH PROJECTS**
- Adipose stromal cells: heterogeneity, function in health, and targeting in disease
- Replicative senescence of progenitor cells and its role in aging-associated diseases
- Molecules mediating intercellular interactions and signaling in obesity and cancer
- Identification of tissue-specific drug targets

**KEY PUBLICATIONS**


**LAB MEMBERS**
Research assistant professor: Alexis Daquinag
Post-doctoral fellow: Joseph Rupert
Sr. research scientist: Zhanqguo Gao
Research assistant III: Yongmei Yu
Rebecca Berdeaux, PhD
Associate Professor

Regulation of muscle nutrient use in type 2 diabetes regeneration

RESEARCH PROJECTS
• Regulation of mitochondrial energetics by SIK1
• SIK1 activation of stress-induced mitochondrial fission
• Targeting hormone-activated pathways to boost muscle stem cell activity

KEY PUBLICATIONS

LAB MEMBERS
Post-doctoral fellow: Antonio Soares
Graduate student: Muchen Liu
Research assistants: Elena Dyukova, Mark Rosenfeld

Skeletal muscles of people with prediabetes and type 2 diabetes lose efficiency of burning off dietary sugars and fats. This inefficiency leads to damage of the central cellular ‘power plants’ (mitochondria) and to higher blood sugar and fat deposits in liver. Our program is aimed at identifying new ways that this efficiency can be improved by targeting a specific family of enzymes known as kinases. Using genome editing, we are testing how a stress-induced kinase affects muscle mitochondrial function in type 2 diabetes. Our results indicate that we may have stumbled on a hidden route to stimulating efficient nutrient use by skeletal muscle and improving health of people suffering from type 2 diabetes.

A) Mitochondrial structure in resting muscle cells becomes fragmented when mitochondrial activity is inhibited. We have discovered a potential new way that this process is regulated that has implications for type 2 diabetes. B) Visualization of a gene signature in mice lacking SIK1. By studying gene, protein, and metabolite patterns in muscles, livers, and brains of these mice, a new paradigm is emerging that explains how this enzyme coordinates energy use and storage.
The research in my laboratory centers on the importance of our internal circadian (i.e. 24-hour) clock in health and in the context of disease prevention. The circadian clock is a sophisticated time-keeping system present in all cells of our body that drives daily rhythms in cell metabolism and tissue function. Examples of our internal clock at work include the rhythms in the sleep/wake cycle, body temperature, melatonin and cortisol, and even cognitive function. The internal circadian clock aligns with and anticipates the rotation of the earth on its axis.

Large epidemiological studies reveal that chronic circadian disruption increases the risk of acquiring metabolic disease and even some forms of cancer. Examples of circadian disruption include travel across time zones ("jet lag"), working a night shift or rotating shifts ("social jet lag"), and light contamination by white and blue light sources. In addition, some clock gene mutations lead to sleep disorders. Disruption of the circadian clock, genetically or environmentally, increases the risk for several diseases, including cancer and several types of metabolic disease. We are trying to understand why circadian disruption produces these effects.

While the "central pacemaker" of our brain, located in the hypothalamus, aligns us with the 24-hour environment via light activation of the retina, other environmental factors can drive 24-hour rhythms in several peripheral organs (for example, liver, kidney, adipose tissue, and muscle). A poor nutrient diet as well as food intake at the wrong time compromises tissue-specific function, but also promotes body-wide circadian clock misalignment across tissues that is thought to increase the risk of metabolic disease over time. My laboratory is currently trying to understand the environmental factors that are most important for tissue-specific clock function and the mechanisms by which tissue-specific clocks protect against metabolic disease.

Chronic nutrient excess disrupts 24-hour rhythms in several insulin sensitive tissues that become insulin resistant under conditions of prolonged lipid overload. Our studies point to tight regulation of circadian lipid metabolism in the liver as well as diurnal proliferation of adipocyte precursor cells in the context of adipose tissue. These 24-hour activities are disrupted under conditions of nutrient challenge, predisposing an organism to metabolic disease, such as obesity and type II diabetes. We have also discovered that circadian proteins in the hypothalamus of the brain have specific genomic regulation that helps organisms engage in rhythmic behavior and maintain energy balance. Collectively, these studies demonstrate the importance of the 24-hour biological clock in health throughout aging.

RESEARCH PROJECTS
- Mechanisms by which circadian disruption leads to insulin resistance and metabolic disease
- Mechanisms linking the clock in the hypothalamus to body weight maintenance
- Circadian mechanisms involved in healthy adipose tissue expansion and function

KEY PUBLICATIONS
Expression of p-STAT3 and c-Myc correlates with P2-HNF4α expression in nonalcoholic fatty liver disease (NAFLD).

Hepatic circadian and differentiation factors control liver susceptibility for fatty liver disease and tumorigenesis.

Cellular and physiological circadian mechanisms drive diurnal cell proliferation and expansion of white adipose tissue.

LAB MEMBERS
Research assistant professor: Dr. Baharan Fekry
Post-doctoral fellow: Dr. Rafael Bravo Santos
Graduate student: Rachel Van Drunen
High levels of stress lead to persistent anxiety that can cause and contribute to the development of devastating mental illnesses, most commonly depression, generalized anxiety disorder, and addiction. Being constantly stressed also can dramatically impact the progression of diseases not directly caused by stress, in part due to elevated levels of cortisol, the hormone released by the body in response to stress. Diseases that are particularly sensitive to stress include metabolic diseases like diabetes, high blood pressure and cardiovascular disease, and neurodegenerative diseases, such as Alzheimer’s disease and Parkinson’s disease. In addition, high levels of stress promote normal loss in memory that occurs with age. My lab is focused on how our bodies perceive stress, react to stress acutely, and are impacted by stress exposure. We seek to understand how the responses of the body to stress change our physiology to negatively impact mental and physical health, and accelerate the progression of age-related neurodegenerative diseases, such as Alzheimer’s disease.

**RESEARCH PROJECTS**

- **How the stresses of reproduction lead to acute and chronic mental illness in mothers.**

We identified a new mechanism that causes stress sensitivity in mothers. We found that the stress-released neuropeptide, CRF, can directly signal to oxytocin neurons, only in mother (mice) after they have given birth. Oxytocin, often referred to as “the love hormone” is required to initiate labor and parturition. Oxytocin is also critical during lactation, a time when the unique bond is established between mothers and their children. We are currently investigating how establishing CRF signaling to oxytocin neurons in post-partum mothers causes stress sensitivity. Interestingly, direct signaling between CRF and oxytocin neurons does not cease after newborns leave the nest, but is maintained long after parturition, possibly causing stress sensitivity in mothers later in life.

- **Stress activated neurons project to key motor circuits to influence movement**

We discovered unprecedented neural connections from CRF neurons in the hypothalamus to key neural circuits in the basal ganglia, a brain region that controls movement. The most common neurodegenerative disease associated with dysfunction of basal ganglia circuits is Parkinson’s disease, in which patients experience tremors, uncontrolled movements, and the inability to initiate movement. Interestingly, many Parkinsonian patients report that their symptoms increase when they are stressed. We are currently performing experiments to test how stress responsive circuits transmit this information to basal ganglia circuits to alter dynamics of movement. This direct pathway connecting stress and movement could provide answers to questions involving why we run away when faced with certain stressors and hide in different stressful situations. We hope to use the information we gain to develop therapeutic strategies to treat debilitating movement-related symptoms caused by neurodegenerative diseases, depression, and post-traumatic stress disorder (PTSD).

- **How stress influences Alzheimer’s disease progression**

We have shown that stress can drive the progression of Alzheimer’s disease in rodent models. In addition, we have found that these rodent models have an activated stress system, leading to altered behavior and endocrine function. We are currently performing experiments to test whether Abeta, the toxic aggregating protein that is implicated in Alzheimer’s disease pathogenesis, directly perturbs stress-responsive neurons to elevate stress levels. These experiments aim to identify new molecular mechanisms that cause Alzheimer’s disease patients to suffer from many neuropsychiatric symptoms in addition to loss of memory.

**KEY PUBLICATIONS**


**LAB MEMBERS**

- Post-doctoral fellow: Lierni Ugartemendia, PhD

Oxytocin neurons (green) in a bred female mouse that express the stress receptor CRFR1 (red) cause post-partum mothers to be sensitive to stress.
Vihang Narkar, PhD
Associate Professor
George and Mary Josephine Hamman Foundation Distinguished Professorship in Cardiovascular Research

Gene regulation in muscle and vascular diseases

- Nuclear receptor target discovery for muscle recovery in peripheral arterial disease, Duchenne muscular dystrophy, obesity, and diabetes.
- Role of nuclear receptors in blood vessel growth and diabetic retinopathy.

KEY PUBLICATIONS


LAB MEMBERS

Post-doctoral fellows: Dr. Danesh Sopariwala, Dr. Hao Nguyen
Research assistant: Andrea Rios
Undergraduate trainees: Kondker Salim, Adison Saley

Our laboratory broadly studies transcriptional regulation of metabolic and vascular homeostasis using nuclear receptors as model signaling molecules. Currently, we are investigating the cellular and physiological functions of orphan nuclear receptors (e.g. estrogen-related receptors) and their co-regulators (e.g. PGC1’s). We use a wide-ranging approach, including genetically engineered mice, murine disease models, high-throughput gene expression analysis (e.g. RNA-sequencing, ChIP-sequencing), pharmacology, cell signal, and in vitro systems in our studies. These tools are being used to investigate the role of ERR’s and PGC1’s in (I) cellular processes, such as genome-wide gene orchestration, mitochondrial biogenesis and angiogenesis; (II) physiological phenomenon, such as exercise adaptation and whole-body metabolism; as well as (III) diseases such as obesity/diabetes, peripheral arterial disease, and muscular dystrophies. Our ongoing work has uncovered the therapeutic role of estrogen-related receptors (ERR’s) via metabolic and angiogenic regulation in peripheral arterial disease (PAD), and in Duchenne muscular dystrophy (DMD). Similarly, our studies on peroxisome proliferator activator receptor delta (PPAR-delta) have yielded insights in to exercise mimicking cellular mechanisms that can be harnessed to boost metabolism, protect against obesity, and prevent diabetes. On the other hand, we have also uncovered the detrimental role of nuclear receptor co-activator PGC1-beta in PAD and muscle degeneration via regulation of anti-angiogenic, apoptotic, and autophagic pathways. Our work, spanning the area of metabolic vascular syndromes that include obesity, diabetes, and its cardiovascular complications, has been published in journals including *Cell,* *Cell Metabolism,* *Cell Reports,* *Circulation Research,* *eLife,* *FASEB Journal,* *Nature Communications* and *Science.*

RESEARCH PROJECTS

- Transcriptional regulation of muscle metabolism, vascularization, mass, and fitness by nuclear receptors.
My laboratory discovers and investigates novel factors that regulate the dynamics of adipose tissue remodeling during obesity development. The long-term goal of our research is to address the clinical significance of these factors in human obesity, diabetes, cardiovascular diseases, and a certain type of cancer.

In the past years, we have reported that high fat diet-induced obesity shapes a hypoxic microenvironment that initiates the local inflammation and fibrosis in adipose tissue. The obese adipose tissue further causes insulin resistance and cardiovascular dysfunctions. Interestingly, our study reveals that VEGF-A-induced angiogenesis ameliorates the pathological changes by suppressing local hypoxia and stimulating sympathetic innervation in both white and brown adipose tissues. We further found that the hypoxia-induced activation of MT1-MMP facilitates the healthy expansion of adipose tissue by remodeling the structure of ECM, thereby relieving fibrosis in the tissue.

Most recently, we analyzed the dynamics of lipid droplet-associated proteins during adipose tissue remodeling by mass spectrometry. We have successfully identified several novel proteins that translocalize onto lipid droplets and the interface of endoplasmic reticulum (ER)-lipid droplets in response to different stimuli. Particularly, one of the identified proteins named Carboxyl Esterase 1 (CES1) targets lipid droplets upon β-adrenergic-stimulation where it exerts the lipolytic function. Meta-analysis of clinical data reveals that CES1 levels are significantly increased during the development of certain types of cancer and are tightly correlated with the death rates in the patients, suggesting that CES1 might be a novel target to treat the cancer. We further reported that targeting CES1 sensitizes hepatocellular carcinoma (HCC) for chemotherapeutic agents, such as cisplatin. We are applying state-of-the-art tools and techniques to elucidate the mechanisms governing the functions of the novel factors and investigating their potential implication in metabolic health and cancer.

Figure 1.

A: CES1 gene expression by tissue (x10^4) in normal (left) and tumor (right).

B: Hepatocellular carcinoma survival probability in non-alcoholic, non-hepatitis virus infected.

CES1 levels are correlated with the development of liver cancer. A: CES1 is enriched in the liver and its levels are significantly increased in the liver tumors. The clinical data are analyzed by the tool on https://kmplot.com/analysis/. B: There remains a trend toward a correlation between CES1 levels and death rate in non-alcoholic liver cancer patients. The non-alcoholic fatty liver induced cancer data are analyzed by UCSC Xena: https://xena.ucsc.edu/.
Qingchun Tong, PhD
Professor
Cullen Chair in Molecular Medicine

Brain control of metabolism

The current obesity epidemic and its associated metabolic syndrome have imposed unprecedented challenges to society and medicine but with no apparent effective therapeutics. Our research is directed to understand the fundamental mechanistic insights on key driving causes for defective feeding and body weight regulation, therefore providing conceptual and effective targets for prevention and treatment of eating disorders, obesity, and its associated diabetes.

Toward these goals, we employ various animal models in combination with the state-of-the-art techniques, including electrophysiology, optogenetics, chemogenetics and in vivo live imaging. Cre-lox P, Flp-FRT mouse genetics is used to achieve neuron-specific manipulations in the brain. Various adeno-associated viral vectors (AAV) harboring genes that exhibit Cre- or Flp-dependent expression or inactivation will be stereotaxically delivered to specific brain regions of Cre- or Flp-expressing neurons, achieving neuron expression of foreign tool genes, leading to specific manipulations of neuron function. Example foreign genes include specific channels that either activate or inhibit neurons.

In addition, virus-based tracing is used to map specific neural projections and their implications in physiology and behaviors. We are also exploring CRISPR/Cas9 technology to achieve neuron-specific gene deletion in adult mice. These advanced techniques ensure our studies are effective and conclusions are insightful.

One major direction in the lab is to identify and map novel neurocircuits underlying emotion control of feeding. Emerging evidence suggests that feeding abnormalities are associated with defects in control of emotion and clinical drugs that reduce symptoms of psychiatric disorders cause obesity development. Using unique animal models coupled with behavioral analysis and optogenetics, we aim to delineate important neurons and neural pathways that underscore interactive regulation of feeding and emotion. This line of research is highly significant to current clinical treatments for obesity, psychiatric patients, and eating disorders.

RESEARCH PROJECTS

- Novel neurons and neural pathways for feeding regulation and its relation with emotional states
- Brain efferent pathways controlling peripheral metabolism
- Brain mechanisms mediating blood hormone action on energy and glucose, and their involvement in obesity and diabetes pathogenesis
- Chronic stress and obesity development
- Oligodendrocyte myelin and diet-induced obesity

KEY PUBLICATIONS


This figure illustrates the impact of chronic inhibition of PVH-projected LSV neurons on obesity development. A) Diagram depicting anterograde tracing from PVH by injecting AAV1-Cre-GFP viral particles to bilateral PVH and then delivery of conditional AAV-Flex-Kir2.1-dTomato or AAV-hSyn-DIO-mCherry for specific expression of Kir2.1 or control mCherry in PVH-projected LSV neurons. B) Example expression patterns AAV1-Cre-GFP in the PVH (green) and representative expression patterns of AAV-Flex-Kir2.1-dTomato viral particles in LSV neurons mediated by antegrade transported Cre recombinase from PVH (middle and right panels; the right panel is the amplified picture of boxed area in the middle panel). C) Chronic inhibition of PVH-projected LSV neurons with Kir2.1 expression led to severe obesity. PVH: paraventricular hypothalamus; LSV: ventral part of lateral septum; LV: lateral ventricle.

LAB MEMBERS

Assistant professor: Yuanzhong Xu
Instructor: Zhiying Jiang
Post-doctoral fellow: Yanyan Jiang
Graduate students: Jing Cai, Alex Prince
Research assistant: Claire Young
As we live longer and enjoy unprecedented longevity, we also become increasingly vulnerable to aging-related neuronal degenerative disorders, including Alzheimer’s disease (AD), Parkinson’s disease (PD), and Huntington’s disease (HD), among others. These incapacitating brain diseases inflict unbearable emotional and financial tolls to patients and their families, becoming a pressing threat to our society. However, by now there is little effective prevention and treatments against these maladies.

To address these challenges, we are studying how to keep neurons happy and healthy during normal aging. Our senses, reasoning, and responses are realized through neurons and their functional connections inside our body. However, unlike other cells, such as those from skin and blood that are constantly dividing and being replenished, neurons face unique challenges: once they are born and mature into interconnected functional units, they mostly lose the ability to reproduce and no longer can be replaced for the rest of their life. To achieve longevity, these long-lived neurons have their own self-maintenance machineries to stay healthy and ward off internal crisis and external insults for decades to come.

The self-maintenance machines include chaperones that help proteins to stay in shape, and different internal clearance machineries such as proteasomes, autophagy (meaning “self-eating” in Greek) and lysosomal systems to clean up and recycle worn-out or toxic cellular materials. In neurodegenerative diseases, these protective machineries become inefficient or nonfunctional, leading to excessive buildup of toxic wastes (known as aggregates, tangles or plaques) inside the brain, causing eventual neuronal death.

Using genetic, biochemical, and cell biology tools in different model systems from invertebrate Drosophila to cultured human cells and mouse animals, we are studying how these self-maintenance machines recognize and efficiently clear away internal toxins while sparing and protecting normal cellular constituents. Our eventual goal is to be able to command these innate protection machineries to fight against devastating brain degenerative diseases.

Currently we are especially focusing on the following questions:

1. **Chaperone Hsp110 on neuronal function and survival**
   Chaperone Hsp110 is one of the most abundant proteins in the brain. It helps other proteins to fold into proper shapes to function properly. It is also a major component of a potent molecular machinery called disaggregate that dismantles tightly packed protein aggregates.

2. **Biogenesis of autophagosomes and other specialized cellular organelles and their dysfunction in brain diseases**
   Cells produce many specialized cellular organelles, such as the autophagosome, lysosome-related organelles, and synaptic vesicles. Autophagosomes are garbage bags produced by a cell during autophagic process to collect unwanted or harmful cellular components for their eventual disposal and recycling. These specialized organelles control many aspects of neuronal function and survival, while their disruptions are linked to a spectrum of disorders, including AD, PD, HD, and schizophrenia.

3. **Huntington’s disease gene Huntingtin**
   Huntington is important for neuronal survival and is involved in autophagy, but its exact roles in versatile cellular pathways remain to be fully elucidated.

**RESEARCH PROJECTS**
- Mechanisms of protein folding and cellular clearance pathways in brain degenerative disorders
- Normal functions of Huntingtin and its perturbation in Huntington’s disease
- Biogenesis of autophagosomes and lysosome-related organelles

**KEY PUBLICATIONS**


**LAB MEMBERS**

Instructor: Shiyu Xu, PhD
Graduate students: Yue Yu, Amanda Solbach, Stephen M. Farmer, MS
Research assistants: Xin Ye, PhD, Lili Ye
The translational pathway for molecular discoveries involves \textit{in vivo} confirmation and, if the process involves the development of molecular medicines, visualizing the delivery and pharmacological action within \textit{in vivo} systems. In the Center of Molecular Imaging (CMI), an interdisciplinary group of bioengineers and scientists collaborate across the Texas Medical Center to bring \textit{in vivo} molecular imaging approaches to a variety of projects spearheaded by basic scientists and clinical researchers.

CMI faculty and staff provide expertise in nuclear imaging, namely positron emission tomography (PET) and single photon emission computed tomography (SPECT), as well as fluorescence/bioluminescence imaging following the administration of contrast agents in preclinical studies. Computed tomography (CT) provides anatomical information that complements these imaging approaches. The CMI team has been involved in a myriad of collaborative projects with academia and industry as well their own independent pre-clinical and clinical research programs. These programs involve cardiovascular disease, autoimmune disorders, gastrointestinal conditions, cancer metastases and survivorship, as well as neuroinflammation and neurodegenerative diseases. This coming year, the CMI’s imaging facilities will be updated to include a combined CT/PET/SPECT animal scanner capable of imaging mice, rats, and medium-sized animals, such as rabbits and ferrets.

Beyond these conventional imaging modalities, the team’s expertise lies primarily with optical imaging techniques. Faculty have developed sensitive optical instrumentation which allows for imaging following “microdosing,” i.e., the administration of very small amounts of agents (i.e. labeled drug or dye) that provides contrast for molecular imaging and surgical guidance with an enhanced level of patient safety, facilitating clinical translation. Under FDA investigational new drug/new device regulatory authority, the CMI has deployed near-infrared fluorescence instrumentation to clinically image more than 700 study subjects at the Texas Medical Center. These clinical studies have focused primarily on the lymphatics in health and disease, including cancer, lymphedema, venous disease, adipose tissue disease, and others, as well as the lymphatic response to therapeutic intervention. Additionally, the sensitivity of our unique optical instrumentation facilitates the 3D image reconstruction of interior tissues from optical measurements made at tissue surfaces and provides the rationale for the design and development of dual-modality, i.e. nuclear and optical, imaging agents and for deployment of “activatable” agents for \textit{in vivo} reporting of molecular tissue status.

Eva Sevick-Muraca, PhD
Center Director & Professor
Nancy and Rich Kinder Distinguished Chair in Cardiovascular Disease Research
The lymphatics are an integral part of the cardiovascular system that removes waste products and maintains fluid homeostasis between tissues and the blood vascular system. In addition, the clear, colorless “lymph” carried in lymphatic vessels carries immune-modulating cells to lymph nodes where adaptive immune responses are initiated. When regional lymphatics are dysfunctional, the accumulation of fluid and waste products contributes to edema and chronic inflammation. In addition, adaptive immune responses are impaired. Due to the inability to visualize them, the lymphatics have largely escaped medical attention despite being associated with the chronic conditions that comprise the bulk of health care costs.

Over the past two decades, our group has developed near-infrared fluorescence imaging lymphatic imaging and translated it into clinical studies to uncover the role of lymphatics in chronic conditions in adults and children. In preclinical studies, we combine conventional imaging modalities with near-infrared fluorescence to pharmacologically manipulate the lymphatics and assess systemic responses. My current work focuses upon translating the lymphatic imaging technology in two specific projects.

In the first, we are using fluorescence imaging to direct the lymphatic delivery of cancer checkpoint blockade immunotherapy to lymph nodes in order to improve immune responses against cancer while mitigating the off-target, immune-related adverse events (called irAEs) that occur with current intravenous administration. We are using the combination of transcriptomics, vaccines, transgenic animals, lymphatic delivery of drug, and imaging to show that we can generate more tumor-specific T-cells with cytolytic phenotypes simply by controlling the sequestered environment in a single lymph node basin. Our results show that we can create more effective cancer therapies using less drug and lymphatic delivery to induce more potent, tumor-specific immune responses than can be possible with systemic, or intravenous delivery of drug. The work is especially impactful to the majority of cancer patients who do not benefit from checkpoint blockade immunotherapy treatment or experience relapse and irAEs.

In the second set of projects, we focus on first-in-human applications of fluorescence imaging to understand the drainage of cerebrospinal fluid into the lymphatics. Our goal is to understand how cerebrospinal fluid outflow into the peripheral lymphatics can impact neurological function and prevent neuroinflammation. The work is especially important to devise new treatments for traumatic brain injury, understand the mechanisms of tau and amyloid accumulation in the aging brain, and more urgently, devise new treatment strategies for premature infants who experience brain bleeds. We are currently working with the FDA to secure research approval to image cerebrospinal drainage in premature babies in the NICU using near-infrared fluorescence techniques. The goal of the translational research is to show that the lymphatics represent a therapeutic target that can be manipulated to improve cerebrospinal outflow in these infants and prevent the significant and lifelong, neurological consequences. The information gained may allow a paradigm shift in management practices to alleviate neuroinflammation in neurodegenerative conditions in adults.

**RESEARCH PROJECTS**

- Dynamic near-infrared fluorescence imaging of cerebrospinal fluid outflow: a tool to manage pediatric hydrocephalus
- Lymphatic delivery of checkpoint blockade inhibitors for more effective immunotherapy
- Lymphatic delivery of immunotherapy to prevent irAEs
- Lymphatic delivery of checkpoint blockade immunotherapy to lymph nodes to activate tumor-specific T-cells that leave the lymph node to be delivered into the blood stream for systemic anti-tumor immune responses.

**KEY PUBLICATIONS**


**LAB MEMBERS**

- Post-doctoral fellow: Carolina Mantilla-Rojas, PhD
- Research staff: Fred Christian “CJ” Velasquez, BA; David Wiggins, BS
Imagine receiving a cancer diagnosis, enduring surgery, radiation, and chemotherapy, and ringing the celebratory end-of-treatment bell, only to develop a devastating side effect of cancer treatment: lymphedema (LE), which manifests as a permanently swollen arm, leg, neck, or trunk. Now you are sentenced to 24/7 compression garment wear, you will suffer discomfort, depression, and cellulitis bouts, and—there is no cure. Studies have shown that, if caught early in development, LE treatment can significantly improve the condition. Near-infrared fluorescence lymphatic imaging (NIRF-LI) imaging delivers high-resolution, “see-through-the-skin,” low-cost images of lymphatic vessel architecture and pumping. My recently finished five-year prospective and longitudinal study using NIRF-LI surveillance of breast cancer patients found that:

- NIRF-LI detects LE 8-23 months earlier than the standard arm measurement method used clinically,
- inflammatory cytokines, measured in plasma before a patient even undergoes surgery to remove cancer, can predict those who will get LE over a year later,
- you can have LE before tumor resection and axillary lymph nodes dissection, and
- higher body mass index (BMI) does not necessarily increase your odds of getting LE.

I also lead a three-year CPRIT-funded clinical study of reparative lymphatic microsurgeries, which are gaining in popularity for LE patients for whom traditional palliative care fails. Outcomes for these surgeries have not been objectively assessed to determine if and to what extent lymphatic vessel anatomy and pumping improve. This new study uses NIRF-LI to show whether the surgeries actually improve lymphatic drainage in affected limbs, and may suggest ways to improve outcomes, including decreasing cellulitis risk that plagues LE patients.

I am very active in the LE community—I am a member of the Scientific and Medical Advisory Council and the Executive Board of the Lymphatic Education & Research Net-

work (LE&RN), an international organization of researchers, physicians, therapists, and patients dedicated to advancing lymphatic health. I chaired the committee that established standards and vetted applications for LE&RN’s Centers of Excellence designation, which now enable patients to locate over 45 international health institutions with lymphatic expertise.

RESEARCH PROJECTS
- Longitudinal study of breast cancer-related LE
- Longitudinal study of reparative microsurgeries for LE

KEY PUBLICATIONS


LAB MEMBERS
Medical student: Kay Pham
Graduate student: Anna Vang
Research assistant: Meghan McWain

Melissa B. Aldrich, MBA, PhD
Associate Professor

Imaging in immunology
The lymphatic system is a vital, yet poorly understood, component of the circulatory system. As blood flows through the arteries and veins, water leaks from the vessels, entering the small gaps between the tissue cells. As the water moves through the tissues, it picks up cell waste, foreign contaminants, proteins, etc. and the resulting solution is taken up by the lymphatics, processed for immune response, and is ultimately returned to the veins. In addition, the lymphatics provide a pathway for the absorption of nutrients from the gut. However, because the lymphatics are typically small and primarily transport clear fluids, they are difficult to distinguish from the surrounding tissues, either with our eyes or using traditional clinical imaging modalities, such as scintigraphy, X-ray, MRI, and ultrasound. Over the past few years, my research has focused upon the development and translation of near-infrared fluorescence (NIRF) optical imaging as a way to noninvasively image and characterize human lymphatics and quantify their contractile function in health and disease using microdose amounts of a fluorescent contrast agent.

One of our primary focuses is the relationship between the lymphatics and the blood circulatory system. It has been known for many years that patients with advanced chronic venous disease often co-develop lymphedema, a condition of chronic swelling with fibrotic tissue changes and poor immune response. We recently imaged a group of patients with early venous disease, and observed a degradation of lymphatic anatomy as evidenced by the appearance of segmented lymphatic vessels and increased incidence of dermal backflow, or abnormal movement of contrast agent into the dermal tissues, as venous disease progressed. In addition, the lymphatic pumping rate initially increased to compensate for the increased venous load (C3 disease), but then decreased by nearly half as the disease continued to progress to C4 disease. A better understanding of the role of the lymphatics in early vascular disease may enable the development of more efficacious therapeutic approaches.

In our studies to date, it is increasingly evident that the appearance and extent of dermal backflow in the body, as imaged using NIRF fluorescence lymphatic imaging, plays a crucial role in diagnosing cancer-related lymphedema and assessing their response to treatment even before the onset of clinically measurable disease. In a previous study we demonstrated that, without treatment, dermal backflow was persistent over months and years in head and neck cancer (HNC) survivors. In a subsequent study of early lymphedema in HNC survivors, we noted a reduction in the extent of dermal backflow after just two weeks of daily, at home pneumatic compression therapy and even observed the complete resolution of dermal backflow in one subject. Based on this data, we will soon enroll our first subjects in a study to assess whether this reduction of dermal backflow is durable over time and whether early physiotherapy can in fact prevent the onset of lymphedema in HNC survivors.

As part of our continued technology development, we are incorporating novel computer vision technologies, including depth imaging, into our NIRF system to enable the mapping of lymphatics and the accurate quantification of lymphatic backflow in three-dimensional space. In addition, we seek to further the development of the imaging technology by assessing novel imaging and drug delivery technologies, improving device sensitivity, automating different aspects of the hardware, and developing analytical tools to facilitate lymphatic image processing and analysis, all with the ultimate goal of answering new biological and clinical questions not addressed by other technologies.

**RESEARCH PROJECTS**
- Understanding the role of lymphatics in the development of peripheral venous disease
- Assessing impact of physiotherapy on the onset of lymphedema in head and neck cancer survivors
- Incorporation of 3D imaging technologies into the lymphatic imaging device

**KEY PUBLICATIONS**


**LAB MEMBERS**
Graduate student: Sara Bouhali (University of Houston)
Banghe Zhu, PhD
Assistant Professor

Transcranial optical tomography of brain activation and CSF outflow in pediatric population

Although blood oxygenation level dependent (BOLD) functional MRI (fMRI) is widely used to examine brain activation in adults, technical and logistical challenges frequently limit the ability to perform fMRI scans readily and longitudinally in infants, particularly in those at greatest risk for adverse neurodevelopmental outcomes and developmental delays. Our lab focuses on developing a transcranial NIR optical imaging system, called Cap-based Transcranial Optical Tomography (CTOT) able to image whole brain hemodynamic activity in an awake child. The long-term goal of this research is to develop a safe, non-invasive, non-ionizing clinical imaging tool that will provide reliable quantitative prognostics for brain network dysfunction in infants.

In a second collaborative project with Drs. Sevick at CMI and Shah at the Pediatric Neurosurgery Center, we adapted fluorescence measurements to the CTOT imaging system, called fCTOT (fluorescence-based CTOT), to assess cerebrospinal fluid (CSF) ventricular dynamics and extracranial outflow in similarly sized, intact non-human primates (NHP) following microdose of indocyanine green (ICG) administered to the right lateral ventricle. Currently, we are translating fCTOT into the clinic to image ventricular ICG-CSF dynamics in infants with progressing post-hemorrhage hydrocephalus (PHH). This study will be the first to identify CSF-lymphatic outflow as a therapeutic target to devise future strategies to treat or even prevent PHH.

**RESEARCH PROJECTS**

- Develop fast CTOT imaging system for functional brain mapping
- Develop diffuse optical tomographic reconstruction algorithms
- Translate fCTOT into the clinic to image ICG-CSF dynamic in infants with PHH

**KEY PUBLICATIONS**


The example coronal, sagittal, and axial views of ICG-laden lymph from the lateral ventricle through the third and fourth ventricles into the subarachnoid space within the 30 minutes in intact non-human primate.
Stem cells play an essential role in normal development of humans as well as the maintenance of tissues throughout life. For example, cells of the blood, intestine, and skin are regularly replaced via a process involving stem cell proliferation and differentiation. The faculty, research staff, and trainees of the Center for Stem Cell and Regenerative Medicine (CSCRM) are focused on experimental studies of the biological properties of stem cells in both health and disease. One of our hopes is that this fundamental understanding of stem cells may be effectively translated into regenerative medicine therapies in which healthy stem cells, or their derivatives, can be employed to replace cells and tissues lost as a consequence of normal aging, injury, or disease. In the following pages, you will find brief reports from CSCRM faculty, highlighting their basic and translational research on stem cells and regenerative medicine.

There are at least two distinct classes of stem cells under active investigation for such therapeutic applications. The first class of stem cells of significant therapeutic interest to Center investigators is induced pluripotent stem cells (iPSCs). iPSCs are patient-specific stem cells that can be generated from easily obtained cells from any individual and, in principle, may be specifically guided into the various cell types and tissues present within the human body. Faculty within the Center are seeking to develop efficient and robust methodologies to convert iPSCs into various cells/tissues of therapeutic interest including blood, lung, and muscle – as well as how to best deliver and maintain such cells/tissues for therapeutic benefit. Dr. Darabi and his laboratory are recognized leaders in the effort to derive from iPSCs muscle stem cells that may be used therapeutically in muscle disorders, such as muscular dystrophy. Drs. Davis and Huang generate iPSC-derived airway tissue from iPSCs of patients with cystic fibrosis for purposes of personalized and/or regenerative medicine. The second class of stem cells consists of tissue-resident stem cells present throughout life in various organs, such as bone marrow, intestine, and lung. Dr. Yoshimoto and colleagues are examining how a unique class of immune cells are derived from stem cells that give rise to the blood.

There is increasing evidence for the presence within cancers of cells having specific properties typically associated with stem cells. Dr. McCarty is investigating the role of such cells in the initiation and maintenance of cancers of the blood, such as mantle cell lymphoma and multiple myeloma. In addition, Dr. Lee is utilizing iPSCs from patients with Li-Fraumeni syndrome to dissect the development of osteosarcoma, a cancer of the bone.

In the pages following you will find examples of Center faculty exploring the potential therapeutic value of stem cells for repairing tissues such as spinal cord, brain, muscle, lung, and blood, as well as elucidating the role of stem cells in cancer. Importantly, philanthropic funds made available to Center investigators, either in the form of endowed chairs, gifts, or pilot grants, have been and continue to be essential in seeding the early stage advances required for demonstrating proof of principle and eventual external grant funding.

If I may provide any additional information, please do not hesitate to contact me.

Brian R. Davis, PhD
Professor and Director
The C. Harold and Lorine G. Wallace Distinguished University Chair
My laboratory has as its focus the sequence-specific genetic correction of mutations responsible for inherited disorders of the lung or blood systems. This is being pursued with the ultimate goal of developing stem cell-based therapeutic approaches. The objective is the delivery back to patients of their own lung or blood stem cells, differing only from the original stem cells by the genetic correction of the relevant mutation. Our studies of genetic correction in stem cells involve either tissue-resident stem cells and/or induced pluripotent stem (iPS) cells derived from patients carrying the inherited disease-causing mutations responsible for cystic fibrosis (CF) or the Wiskott-Aldrich Syndrome (WAS). Whereas tissue-resident stem cells must be obtained from the relevant organ, iPS cells can be derived from any cell of the body (e.g. blood or skin) and, in principle, can be turned into any cell type of therapeutic interest.

A primary focus this past year has been the development of gene correction methodologies to correct the CF causative mutations in tissue-specific stem cells directly obtained from CF patients. We have demonstrated highly efficient correction of the CF airway basal cells with functional restoration of CFTR channel activity. We are now working to make this approach applicable to all CF patients, irrespective of their mutation – and, importantly, to extend the methodology to correct airway cells directly in the lungs of CF individuals. We have recently reported the ability to derive, from CF patient iPS cells, early lung progenitors and then airway basal stem cells for purposes of molecular and functional characterization as well as transplantation. We are currently employing CF patient-specific iPS cell-derived lung epithelium for testing sensitivity to specific CF drugs -- in order to facilitate a personalized therapeutic approach. Our findings this past year have contributed to the initiation of a new clinical trial in which CF patients carrying a specific mutation, N1303K, will be tested for their response to a triple drug combination previously shown to be highly effective in CF patients with other mutations.

A second project in the laboratory focuses on the site-specific correction of gene mutations responsible for inherited blood disorders such as WAS, a primary immune deficiency. In 2016, we demonstrated proof of principle for a methodology capable of correcting nearly all the mutations responsible for WAS in iPS cells. We are seeking to extend this methodology to patient-specific blood stem/progenitor cells that may be readily obtained from patients. Since our original 2016 report, we have made significant progress in optimizing the efficiency of correction in blood stem/progenitor cells and have demonstrated that this methodology restores WAS protein and WAS protein-dependent function in cells carrying WAS mutations.

RESEARCH PROJECTS
• Correction of airway basal stem cells from cystic fibrosis patients in vitro and in vivo
• Derivation and expansion of airway basal stem cell from cystic fibrosis patient-specific iPS cells.
• Correction of blood stem cells from Wiskott-Aldrich Syndrome patients

KEY PUBLICATIONS

LAB MEMBERS
Post-doctoral fellows: Dr. John M. Avila, Dr. Cristina Barilla
Research instructor: Dr. Shingo Suzuki
Research staff: Dr. Cuong Q. Le, Dr. Renae M. Bertrand, Samantha Winkler

Schematic of the reporter mimicking CFTR2-27 integration into the CFTR gene.
(Upper panel) CFTR exon 1, intron 1 and exon 2; sites of integration are marked with downward pointing arrows. (Middle panel) Integration of reporter construct into CFTR intron 1.
(Lower panel) Integration of reporter construct into CFTR exon 1.
Skeletal muscle is the largest tissue in the human body and is responsible for maintaining the body posture, movement, and storage of key nutrients, such as glycogen. Due to the presence of the muscle stem cells, skeletal muscle has tremendous self-healing potential after minor to moderate injuries. Nevertheless, there are many more severe disorders that can surpass its regenerative capacity and affect the skeletal muscle health. These disorders include muscular dystrophies due to gene defects, volumetric muscle loss (VML) due to accidents or combat injuries, and muscle wasting during chronic disorders, such as after heart or kidney failure or during the aging process. Unfortunately, there is no cure for these disorders and they often lead to varying degrees of muscle dysfunction and long-term disability.

Here at IMM and the Center for Stem Cell & Regenerative Medicine (CSCRM), we developed state-of-the-art technologies using human induced pluripotent stem cells (iPSCs) for disease modeling, gene correction, and skeletal muscle repair. iPSCs can be reprogrammed from adult skin or blood cells and can generate all the cell types and tissues within the human body. In addition, since iPSCs are derived from the same patients, they are immune-compatible and there is a minimal risk of immune rejection. Therefore, iPSCs are generally considered one of the ideal candidates for personalized stem cell therapy in many degenerative disorders.

Our lab is specialized in generating human iPSCs for skeletal muscle disorders and has developed state-of-the-art technologies using human iPSCs for disease modeling, gene correction, and regenerative applications. So far, we have established innovative methods for derivation of engraftable muscle stem cells and endothelial/vascular progenitor cells from human iPSCs and demonstrated their therapeutic application for skeletal muscle repair in different animal models, such as muscular dystrophy or muscle injury. In addition, one of our recent research projects is to use long non-coding RNA (lncRNA) molecules as therapeutic agents to alleviate the severity of Duchenne and Becker muscular dystrophies.

The ultimate goal of our lab is to develop a stepwise and progressive strategy toward clinical application of human iPSCs for skeletal muscle disorders through generation of multi-cellular muscle constructs. Our research program is currently funded by the awards from National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) of the NIH and the Department of Defense Office of the Congressionally Directed Medical Research Programs (DOD/CDMRP).

**Disease modeling, gene correction, and therapeutic potential of human induced pluripotent stem cells (iPSCs) for skeletal muscle disorders**

- Therapeutic potential of human iPSCs in volumetric muscle loss (VML) injuries
- Study the mechanisms of interaction between iPSC-derived endothelial (ECs) and skeletal myogenic progenitor cells (MPCs) in vitro and in vivo

**KEY PUBLICATIONS**


**LAB MEMBERS**

- Graduate student: Muchen Liu

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**RESEARCH PROJECTS**

- Disease modeling and gene correction of muscular dystrophies using CRISPR/Cas9 system
- Therapeutic potential of human iPSCs in volumetric muscle loss (VML) injuries
- Study the mechanisms of interaction between hiPSC-derived endothelial (ECs) and skeletal myogenic progenitor cells (MPCs) in vitro and in vivo

**Derivation of skeletal muscle and vascular progenitor cells from human iPSCs and their in vivo engraftment in the mouse model of muscle injury.**

(A) Image demonstrates the engraftment of human iPSC-derived myogenic cells expressing skeletal muscle myofiber (dystrophin in red) and human cell nucleus markers (hLamin A/C in green) in the injured muscle of the mouse. (B) Image demonstrates the engraftment of human iPSC-derived endothelial cells into the vessels of the mouse skeletal muscle expressing vascular markers (vWF in pink and human CD31 and Lamin A/C in yellow).
Traumatic brain injury (TBI) is a major human health problem in not only the United States but worldwide. According to the Centers for Disease Control, approximately 1.7 million Americans suffer a TBI with young adults (ages 15 to 19 years) and older adults (ages 65 years and older) among the most likely to sustain a TBI. As a large percentage of people who sustain a concussion do not visit the emergency room; this number is likely to be vastly underestimated.

Recent studies have indicated that TBI doubles the risk of developing Alzheimer’s disease and related neurodegenerative disorders (https://www.alz.org/alzheimers-dementia/what-is-alzheimers/causes-and-risk-factors). Although a single concussion may not increase the risk for developing neurodegeneration, repeat concussion markedly increases the risk of developing traumatic encephalopathy syndrome (TES). The symptoms of TES include memory loss, confusion, impaired judgment, impulse control problems, aggression, depression, anxiety, suicidality, parkinsonism (movement symptoms similar to Parkinson’s disease), and progressive dementia. These symptoms may begin years or even decades after the last traumatic brain injury.

Currently, no treatments are available for TBI or TBI-related neurological diseases. TBI activates multiple cellular, molecular, and neurochemical changes that are thought to contribute to the ensuing cognitive, behavioral, and neurological deficits. It remains unknown which of these mechanism(s) underlies the increased risk for developing Alzheimer’s disease and TSE. To this end, we have been examining the cellular and molecular mechanisms that contribute to the pathophysiology of TBI and the risk of developing neurodegenerative diseases.

**RESEARCH PROJECTS**

- To identify how TBI alters neural circuit function
- To investigate the contribution of systemic and neuro inflammation to TBI pathophysiology
- To examine how brain injury alters cellular bioenergetics

**KEY PUBLICATIONS**


**COLLABORATORS/LAB MEMBERS**

- Dr. Charles Cox Jr, professor of pediatric surgery, George and Cynthia Mitchell Distinguished Chair in Neurosciences, Children’s Fund Distinguished Professor, Center for Stem Cell & Regenerative Medicine, IMM
- Dr. Summer Ott, associate professor of orthopedic surgery; director, Concussion Program at Ironman Sports Medicine Institute
- Dr. H. Alex Choi, associate professor of neurosurgery, director of ICU - Memorial Hermann Hospital
- Dr. John Redell, associate professor, Department of Neurobiology and Anatomy
- Dr. John Broussard, assistant professor, Department of Neurobiology and Anatomy
- Dr. Jing Zhao, assistant professor, Department of Neurobiology and Anatomy
- Dr. Nobuhide Kobori, assistant professor, Department of Neurobiology and Anatomy
- Dr. Erica Underwood, assistant professor, Department of Neurobiology and Anatomy
- Dr. Paul Smolen, adjunct associate professor, Department of Neurobiology and Anatomy
- Dr. Ryota Homma, assistant professor, Department of Neurobiology and Anatomy
- Dr. Laura Zima, PGY4, Department of Neurosurgery

Program manager: Anthony Moore Sr. research associate: Kimberly Hood Research assistants: Dustin Robinson; Jennifer Saldana
Human pluripotent stem cells for lung regeneration and disease modeling

The Huang laboratory is interested in applying human pluripotent stem cells to study the molecular mechanisms of lung cell fate specification in the context of both normal and pathological conditions. The long-term goal is translation of the acquired knowledge into prevention and treatment of currently not curable lung diseases. Lung diseases are among the leading causes of death globally. Lower respiratory infections, chronic obstructive pulmonary disease, and lung cancer together account for approximately 9 million deaths annually worldwide. Despite the huge lung disease burden, we still have very limited understanding of the pathogenic mechanisms responsible for these diseases, and consequently there is a lack of successful therapeutic approaches.

Recently, a human pluripotent stem cell (hPSC)-based model has emerged as a novel system for studies of human diseases. The need for such a system stems from the limitations of the existing animal experimental models, which fall short in demonstrating concordance with human studies. In addition, experimental approaches utilizing primary human adult lung cells are inadequate in large part due to the limited availability of lung tissue from healthy subjects. Realization of stem cell therapy in lung diseases relies on the successful generation of clinically applicable cell types. As a first, critical step in this direction, we have previously developed a step-wise differentiation strategy that directs human pluripotent stem cells to become different types of upper (airway) and lower (alveoli) respiratory lung epithelial cells at large quantities (Huang et al. Nat Biotechnol 2014, Nat Protoc 2015). As a proof of principle, the generated cells can be applied for lung development or disease studies by us and other research groups. Currently, we are working on culture conditions that can direct the human pluripotent stem cell-derived early lung progenitors toward an enriched population of either epithelial cells in air-liquid-interface culture or for modeling airway development and diseases. B. Paraffin sections or whole mount of air-liquid-interface culture stained with the markers of cell types as shown (Unpublished).

**RESEARCH PROJECTS**

- Use patient hiPSC differentiated lung and airway epithelial cells to study normal development and pathogen infection
- Understanding the basic mechanisms of lung lineage specification from NKX2.1+SOX2+SOX9+ human lung progenitors using molecular, genetic, and epigenetic approaches
- Understanding the molecular and epigenetic regulation of hPSC-derived airway basal stem cell competence. We recently developed a new strategy to derive airway basal stem cells with robust potentials to generate rare cell types of the airway, including ionocytes and neuroendocrine cells.

**KEY PUBLICATIONS**


**LAB MEMBERS**

Research assistants: Nicole Acosta, Hui Zhou
The hematopoietic stem cells (HSCs) that produce all types of blood cells in the body are first generated in the aortic region of the mouse embryo at embryonic day (E) 10-11. Interestingly though, there are multiple waves of blood cell production prior to the emergence of the first HSC from endothelial cells (referred to as hemogenic endothelial cells: HECs), and these blood cells include erythro-myeloid, T-, and B-lymphoid cells. Using lineage tracing mouse models and transplantation assays, we have recently found that innate-like B-1 lymphocytes, multipotent progenitors, and the first HSCs are produced simultaneously from HECs. Furthermore, we found paradigm-shifting results that fetal-derived B-progenitors persist into adult life much longer than previously expected. These B-progenitors include not only B-1 but also B-2 progenitors, adaptive immune B-cells. We are elucidating 1) what molecular signals determine the divergent point between innate-like B-1a biased progenitors, multipotent progenitors, and multipotent HSCs in HECs, 2) the possible different functions among fetal-derived and adult HSC-derived B-cells, and 3) how HSC-precursors mature into adult-repopulating HSCs in a limited time window of embryonic development.

B-1 cells are unique murine innate immune cells that are distinguished from conventional adaptive B cells (B-2 cells). B-1 cells secrete natural IgM antibodies that prevent microbial invasion and atherosclerosis. We have developed an aged atherosclerosis mouse model and investigate the role of fetal-derived B-1 cells in reducing chronic inflammation or inflamming. Because B-1 cells are mainly produced only in the embryo, it is critically important to understand the biological roles of B-1 cells and their dysfunction with age. We are developing therapeutic options using mouse and human pluripotent stem cells against chronic inflammation and atherosclerosis.

In order to maximize the benefit of our findings, our research combines the basic science of developmental hematology with disease mouse models.

RESEARCH PROJECTS

- Identify important molecules for HSC maturation and B-1 cell specification in the mouse embryo utilizing single-cell RNA-sequencing.
- Examining the contribution of fetal-derived B cells to IgA secreting cells in the lamina propria of intestine.
- Examining the roles of B-1 cells against atherosclerosis and age-related chronic inflammation (inflammaging).
- Producing human B-1 cells from human iPSCs.

KEY PUBLICATIONS


LAB MEMBERS

Assistant professor: Michihiro Kobayashi MD, PhD
Research assistants: David Huynh; Alina Syed
Research student from Rice University: Brian Lee
Dung-Fang Lee, PhD
Assistant Professor
CPIRT Scholar in Cancer Research

Familial cancer syndromes in a dish

After leukemia, osteosarcoma is the second-leading cause of cancer mortality among children. Genetic alterations (e.g., p53 mutation and RB1 deletion) are strongly associated with osteosarcoma development. Patients with Li-Fraumeni syndrome (LFS), a genetically inherited autosomal dominant cancer disorder caused by germline mutations in the p53 tumor suppressor gene, have increased incidence of osteosarcoma development, which provides a perfect model system to study osteosarcoma.

Modeling human genetic disease has recently become feasible with induced pluripotent stem cell (iPSC) methodologies developed by Dr. Shinya Yamanaka in 2006. Characterized by their ability to self-renew indefinitely and differentiate into all cell lineages of an organism like embryonic stem (ES) cells, iPSCs provide a powerful and unlimited source of cells to generate differentiated cells that can be used to elucidate disease pathogenesis, for drug discovery and development, toxicology screening, personalized healthcare, and eventually cell transplantation-based therapies.

Our research is dedicated to understand cancer pathological mechanisms by applying patient-specific iPSCs and/or engineered ESCs. We have established the first human Li-Fraumeni syndrome (LFS) disease model by using LFS patient-specific iPSCs to delineate the pathological mechanisms caused by mutant p53 in osteosarcoma (Lee, et al, Cell 2015; Gingold, et al, Trends Cancer 2016). LFS iPSC-derived osteoblasts recapitulate osteosarcoma features, including defective osteoblastic differentiation and tumorigenic ability, suggesting that our established LFS disease model is a “disease in a dish” platform for elucidating p53 mutation mediated disease pathogenesis. Since these iPSCs were generated from non-transformed fibroblasts, any recapitulated features of osteosarcoma must be due to the single gene alteration. The patient-specific iPSC model therefore provides a powerful system to elucidate unique gene function in tumor etiology. We continue applying patient-specific iPSCs and TALEN/CRISPR genetically engineered hESCs to illuminate cancer pathological mechanisms.

RESEARCH PROJECTS
- Systems-level analyses and characterization of mutant p53 in LFS-associated osteosarcoma.
- Systematic analyses of genome alterations during LFS-associated osteosarcoma development.
- Model familial cancer syndrome with predisposition to osteosarcoma by patient-specific iPSC approaches.

KEY PUBLICATIONS


LAB MEMBERS
Post-doctoral fellows: An Xu, Mo Liu, Dandan Zhu
Graduate student: Mo-Fan Huang
Research assistant: Ying Liu

Mutant p53 gain-of-function driver cancer through cancer hallmarks. Different mutations on p53 protein arm p53 with new weapons (downstream targets indicated in the figure) to drive cancer development and progression. Each color-coded node indicates gain-of-function of specific mutation of TP53, which further drives cancer through various cancer hallmarks.
Protein homeostasis is orchestrated by coordinated protein synthesis, folding, transport, and degradation. Inappropriate protein assembly or modification promotes protein misfolding, which can lead to not only disruptions to protein homeostasis but also to normal cellular functions. Misfolded proteins that escape these control mechanisms must be targeted for degradation, either through the ubiquitin-proteasome system (UPS) or by autophagic processes.

The UPS and autophagy are independent systems that target proteins for degradation in the proteasome and lysosome, respectively. The UPS is predominantly driven by ubiquitin as a degradation tag, which primarily degrades single, unfolded polypeptides able to enter the proteasome’s narrow channel. Yet autophagy primarily deals with larger cytosolic structures such as protein complexes, cellular aggregates, organelles, or pathogens. Autophagy, including general and selective autophagy, is critical for cellular homeostasis with intricate links to cell metabolism, growth control, the balance between cell survival and cell death, and aging.

Selective autophagy requires one or more selective autophagy receptors, which tag the specific cargo for engulfment in an autophagosome and delivery to the lysosome.

However, the identification of the crucial roles of molecular players such as ubiquitin and p62 in both of these pathways, as well as the observation that blocking the UPS affects autophagy flux and vice versa, has generated interest in studying the cross-talk between these pathways. Dysfunction within either of these two proteolytic pathways, the UPS and the autophagic–lysosomal system, which are involved in clearing incompletely folded proteins or aggregates, has been increasingly implicated in neurodegenerative diseases. These two degradation pathways are interconnected rather than independently regulated; therefore, it is critical to understand the mechanisms of the cross-talk between these pathways.

My lab discovered that TRIM44 is a novel link connecting UPS and the autophagy degradation pathway. Suppressing UPS by treating cell models with proteasome inhibitors induced aggregate formation but upregulated TRIM44 remarkably reduced aggregate protein levels and overall aggregate volumes. TRIM44 colocalized with the autophagy adaptor p62 to aggresomes during proteotoxic stress. This phenomenon was observed in several aggregate-prone disease models, such as the cystic fibrosis CFTRΔF508 model, the Alzheimer’s disease TauP301L model, and the Huntington’s disease HttQ94 model. Moreover, TRIM44 promotes p62 oligomerization and targets oligomerized p62 to autophagy-related structures, which could enhance the degradation of p62 substrates.

These TRIM44 functions are critical for homeostasis control in cancer and multiple myeloma (MM). MM cells are derived from an incurable plasma cell malignancy under constitutive ER stress due to its function. Proteasome-associated ubiquitinating/deubiquitinating enzymes play central roles in modulating MM proteotoxic stress. Hence, MM cells are sensitive to compounds targeting proteasome inhibitors. Bortezomib, the 26S proteasome inhibitor, was the first therapeutic proteasome inhibitor used in humans to suppress cell growth by inducing apoptosis in MM cells. However, most patients treated with proteasome inhibitors develop resistance and eventually relapse, indicating that blocking proteasome-mediated protein degradation causes the cells to use alternative degradation pathways. We also reported that TRIM44 expression is critical for MM cell therapy resistant to protein degradation target agents. The signaling networks connecting the UPS and autophagic degradation are growing and will play a crucial role in cancers and neurological diseases.

**KEY PUBLICATIONS**


Zhang, H., Chen, Z., Miranda, R.N., Madeiros, L.J., and McCarty, N. Bifurcated BACH2 control coordinates mantle cell lymphoma survival and dispersal during hypoxia. *Blood* 130:763-778. 2017. This article was featured in “this week in Blood” as an Editor’s pick.


**LAB MEMBERS**

Post-doctoral fellows: Yuquin Wang, PhD; Trung Vu, PhD
Senior research associate: Raksha Rao, PhD

TRIM44 increases FLNA, RAD51, and S3P1P expression by inhibiting p62 nuclear translocation after irradiation. TRIM44 expression inhibits p62 nuclear translocation after irradiation. TRIM44OE-CON and TRIM44OE, TRIM44KD-CON and TRIM44KD HeLa cells were transfected with mCherry-p62. Images were captured at the indicated times.
Our lab studies how biomechanical force generated by the flow of blood in the circulatory system impacts cell fate and behavior. One of our primary research projects addresses how frictional force caused by blood flow promotes emergence of blood stem cells during embryo development. We are interested in how we might use this information in the laboratory to expand improved sources of these stem cells for treatment of hematologic disorders and cancers, such as bone marrow failure syndromes and leukemias.

Complex signaling occurs in response to flow that potentiates stem cell potential, including activation of integrins, mechanosensitive ion channels, and primary cilia. In our prior published work, we have shown that fluid frictional force in biomimetic microfluidics that matches the intensity of blood flow present in the developing embryo can stimulate calcium sparks within the cytoplasm, thus triggering the cell to produce prostaglandin E2. Calcium is a critical modulator of cellular bioenergetics, which we also find is reprogrammed in hematopoietic precursors during a process in which endothelial cells lining the embryonic aorta undergo transition to a hematopoietic fate. We find that the powerhouses of the cell – the mitochondria – adapt during the course of differentiation to meet the changing metabolic needs of nascent hematopoietic stem cells. These organelles undergo changes in ultrastructure that alter their capacity for energy production both as they differentiate toward the hematopoietic lineage and as they experience vascular forces associated with the heartbeat.

Bioenergetics are particularly relevant during fate commitment of hematopoietic stem cells in the embryo but also could be important in the adult. Mitochondria are critical in hematopoietic stem cells and mesenchymal stem cells of the adult bone marrow, the latter of which are known to be capable of promoting repair of damaged tissues by mitochondrial transfer to injured cells when administered as a cellular therapeutic. Ongoing studies are directed at determining how mitochondria contribute to immunomodulatory activity of bone marrow mesenchymal stromal cells, a progenitor cell attractive for its clinical utility for injury, inflammation, and graft-versus-host disease. We are currently pursuing both collaborative and independent studies aimed at better engineering metabolic pathway utilization in these progenitor populations to enhance their ability to suppress unchecked inflammation in animal models of injury.

Lastly, in work spanning various model systems, evidence has begun to emerge that implicate focal adhesion kinase, Src family kinases, Rho A kinase, and the Yap1 co-transcription factor in regulation of cancer cell motility in response to fluid force typical of that within the lymphatic vasculature. We have examined the contribution of these pathways to control of metastatic behavior of prostate and breast cancer cells.

RESEARCH PROJECTS
- Effects of flow on hematopoietic stem cell fate and the bone marrow niche
- Biomechanical force in modulation of mitochondrial dynamics
- Biophysical modifiers of metastatic behavior in cancer

KEY PUBLICATIONS


LAB MEMBERS
Rice undergraduate student: Ridhi Rukumanna Gari
Graduate students: Chaitali Bhadiadra; Paulina Horton
Post-doctoral fellow: Sandeep Dumbali
Senior research associate: Miguel Diaz

(A) Single-cell RNA sequencing reveals that cells in the embryo undergo a developmental trajectory of differentiation from the endothelial to hematopoietic lineage. (B) Sets of genes involved in endothelial to hematopoietic transition (EHT), mitochondrial protein import, and the electron transport chain (ETC) are upregulated during commitment to the hematopoietic fate. (C) Increased TMRE dye indicates increased mitochondrial membrane potential in hematopoietic progenitors, which correlates with increased mitochondrial capacity. eAE, early arterial endothelium; mAE, mature arterial endothelium; HE, hemogenic endothelium; HPC, hematopoietic progenitor cells.
Jiaqian Wu, PhD
Associate Professor

Gene transcription and regulation of stem cell differentiation and neurological disorders

I am an associate professor with tenure in the Vivian L. Smith Department of Neurosurgery and Center for Stem Cell and Regenerative Medicine. I led the NIH Mammalian Gene Collection effort and cloned thousands of mammalian genes, which are publicly available through Dharmacon now. I also was closely involved in the ENCODE project and employed interdisciplinary approaches to study gene expression, transcription factor regulation, and regulatory networks of stem cell self-renewal and differentiation. In my independent laboratory, we carried out unprecedented transcriptome profiling of eight highly purified neuron, glia and vascular cells from brain by RNA-Seq. Our lab identified a large number of novel long non-coding RNAs, and they identified the role of IncRNA in oligodendrocyte precursor cell (OPC) formation for the first time using functional and genetic experiments. One of the neurological diseases that I am focusing on is spinal cord injury (SCI). Our lab has already published studies for acute and chronic SCI phases in mouse and rat contusive injury models. The Wu lab provided valuable data source and a powerful analysis framework for functional investigations of coding and long non-coding RNAs in CNS cell types and SCI. Our work has been recognized with prestigious honors and awards, including the National Institutes of Health Ruth L. Kirschstein National Research Service Award for Individual Postdoctoral Fellows, and the International Society for Stem Cell Research (ISSCR) Annual Meeting Travel Award, the National Institute of Health Pathway to Independence (PI) Award (K99/R00), R01s, R21s and the Senator Lloyd and B.A. Bentsen Investigator Award. A reviewer for the NIH, New York State Department of Health-Spinal Cord Injury Research Board, MRC, ANR, and many journals, I have presented invited talks and lectures at national and international conferences and institutions. I have authored two books, and written many articles that have appeared in Nature, PNAS, the Journal of Neuroscience, Cell Reports, Genome Research, and Nature Neuroscience among others.

KEY PUBLICATIONS


LAB MEMBERS
Instructor: Haichao Wei, PhD
Resident physician: Joseph Withrow, MD
Post-doctoral fellows: Simranjit Singh, PhD; Jyotirmoy Rakshit, PhD
Undergraduate student: Radhika Thakor

Wu Lab uses interdisciplinary approaches including molecular biology, genetics, genomics, proteomics, and bioinformatics to study gene expression and transcriptional regulation in stem cells and the nervous system.
Translational cancer research aims to identify novel drug targets followed by the discovery and development of drug candidates as potential cancer therapeutics. The goal is to translate discoveries made in basic cancer research to potential drugs that could be tested in human patients. It relies on a plethora of information and data on cancer origination, progression, metastasis, drug-resistance, and disease relapse to uncover the driving mechanisms of tumor growth and invasion. Technologies such as next generation sequencing of DNA and RNA in cancer and non-cancer cells of tumor tissues, CRISPR screening, proteomics, imaging, patient-derived tumor models, drug candidate discovery, and bioinformatics are utilized to reveal drug targets and validate potential drug candidates.

The current research in the Center for Translational Cancer Research emphasizes several areas, including the application of cutting-edge bioinformatic and experimental technologies to identify and validate novel drug targets in several major types of solid tumors, the discovery of specific molecules against the targets with a focus on antibody/protein-drug conjugates, the development of targeted contrast agents for disease visualization, and the study of proteome alterations to elucidate disease mechanism and discover biomarkers.

These efforts connect us with collaborators, such as physicians, pathologists, biologists, bioinformaticians, and bioengineers, across UTHHealth Houston, institutions within the Texas Medical Center, and across Texas to enhance basic, translational and clinical research. At the IMM, we have state-of-the-art mass spectrometers that provide in-depth proteomic analysis of cells, tissues or biological fluids, with the goals to discover novel targets and biomarkers to inform the development of therapeutic treatment and early detection of diseases. We combine critical data from cancer genetics, genomics, and proteomics to identify drug targets, create targeted antibodies and peptides, and synthesize drug conjugates that are then evaluated in tumor models. We also have expertise in the development and application of novel antibody-based agents that have imaging implications in cancer as well as infectious diseases. Furthermore, the Center specializes in the development of multifunctional peptides that combine radioactive and fluorescent contrast to enable tumor identification before, during, and after surgery, thus introducing a precision surgery approach. Recently, the center received major funding from the Cancer Prevention and Research Institute of Texas (CPRIT) and the National Institutes of Health (NIH) to discover and develop novel cancer therapeutics and imaging agents.

In addition to the CPRIT-funded Preclinical Development Core for Large Molecule Therapeutics, the center has the Clinical and Translational Proteomics Service Center, to support many research labs through service and collaborative efforts.

Qingyun "Jim" Liu, PhD
Center Director & Professor
Janice Davis Gordon Distinguished Professor for Bowel Cancer Research
Adult stem cells are specialized cells that can self-renew and give rise to all the other types of differentiated cells in the tissue where the stem cells reside. They are essential for the maintenance of tissues with high turnover rate, such as the gut and skin, and for tissue repair after injury. However, these cells are also believed to be the cells-of-origin for many types of cancer as they are programmed to divide indefinitely. Furthermore, tumor tissues are also heterogeneous in which only a subpopulation of cells can self-renew and provide daughter cells that make up the bulk of the tumor. These self-renewing cancer cells, designated cancer stem cells, or tumor-initiating cells, often bear great similarity to normal stem cells in molecular profile and regulatory systems. Understanding of the mechanisms that govern the control of the self-renewal and differentiation of normal and cancer stem cells will provide crucial knowledge to the discovery and development of novel therapeutics for regenerative medicine and cancer treatment.

Our research is focused on delineating the function and mechanisms of a group of cell surface receptors called LGR4, LGR5, and LGR6 (LGR4-6) that play critical roles in the survival of normal stem cells and tumor cells. Previously, we discovered that LGR4-6 function as receptors of a group of stem cell factors called R-spondins (RSPOs) that are essential for the survival and growth of stem cells. LGR4-6 have now been shown to be enriched in cancer stem cells in colorectal cancer. We are now focused on understanding how RSPOs and LGRs work together to regulate the growth and migration of colorectal cancer stem cells. We found that LGR4 and LGR5 work through a different mechanism to control the survival and expansion of intestinal stem cells, which challenges a major current paradigm that LGR4 and LGR5 work in an identical way in cell signaling. Meanwhile, we showed that drug conjugates of anti-LGR antibodies showed excellent anti-tumor efficacy in preclinical models of colon cancer. We are now developing a strategy that can target LGR4-6 simultaneously using drug conjugate for the treatment of colorectal cancer. This approach has the potential of overcoming drug resistance due to tumor cell plasticity and heterogeneity.

**RESEARCH PROJECTS**
- Delineation of signaling mechanisms of stem cell receptors.
- Determination of the function and mechanism of the receptors in the control of normal and cancer cell growth.
- Investigation of the roles of aberrant expression of the RSPOs in the control of tumor metastasis of lung and colon cancer.
- Identification of lead molecules targeting the RSPO-LGR system as novel anticancer therapeutics.
- Optimization of antibody-drug conjugates targeting the RSPO-LGR system for the treatment of colorectal and other cancers with high LGR expression.
- Determination of the function of a common mutation of RNF43 found in colon, stomach, and uterine cancer.

**KEY PUBLICATIONS**

**LAB MEMBERS**
Research assistant professor: Yukimatsu Toh
My laboratory is at the interface of chemistry and biology and is focused on developing molecules for the visualization and treatment of disease. Using novel chemistry platforms, we have the ability to produce molecules with multiple labels and thus, multiple applications. For example, the addition of radioactive and fluorescent labels onto tumor-seeking agents has allowed us to develop new approaches to specifically identify cancer by whole-body and intraoperative imaging, respectively. This could potentially provide surgeons with real-time intraprocedure images that will distinguish cancer from normal tissue, minimize removal of healthy tissues, and identify small tumors which would otherwise be missed by the naked eye. In cases where cancer has spread and surgery is not possible, we aim to use our chemistry platform to specifically deliver toxins to tumors and visualize the effects to personalize treatment protocols. Our expertise in chemistry, imaging, and drug characterization has allowed us to establish diverse collaborations to study the in vivo properties of novel disease-targeted peptides and antibodies, evaluate the potential benefits of modulating biomarker trafficking in cancer cells, and assess the effectiveness of emerging antibody-based cancer treatments. Common to each project is our focus on translation of discoveries and technologies into the clinic to improve human health.

**Research Projects**
- Development of contrast agents for real-time surgical guidance
- Targeted delivery of chemotherapy agents for treatment of cancer
- Application of non-invasive imaging techniques to study cancer biology mechanisms

**Key Publications**
(* denotes corresponding author)


**Lab Members**
- Assistant director, research operations: Sukhen Ghosh
- Post-doctoral fellows: Solmaz AghaAmiri; Majid Momeny
- Graduate student: Servando Hernandez Vargas
- Research assistant: Vahid Khalaj
- Research assistant: Teresa Sullivan

Translating preoperative neuroendocrine tumor imaging into the operating room- a simulation. (A) Schematic showing how nuclear medicine can be used to determine patient eligibility for personalized intraoperative imaging. (B) Representative “patient” selection with the clinical gold standard, 68Ga-DOTA-TOC, in a mouse model showed radioactive signal in the gut region. (C) *In vivo* optical imaging with the novel surgical imaging contrast agent matches nuclear imaging findings and (D) demonstrated complete tumor resection. (E) *Ex vivo* imaging showed fluorescence only in tumor and spleen metastasis (yellow arrow). (F) The pattern of fluorescence signal (NIRF) was similar to the positive controls (IHC and H&E) and confirmed tumor-specific uptake of the contrast agent. White arrows indicate tumor. (From Hernandez Vargas et al., *Mol Pharm*, 2022).
Drug resistance, metastasis, and relapse continue to be leading causes of colorectal cancer-related deaths, demonstrating the need for new therapeutic approaches. Cancer stem cells (CSCs) or tumor-initiating cells are a subpopulation of tumor cells that behave like normal stem cells and have been shown to mediate drug resistance, metastasis, and relapse; making them a major impediment for the effective treatment of colorectal cancer. Therefore, recent strategies have been focused on the development of novel therapies that can ultimately target and destroy CSCs. LGR5 (Leucine-rich repeat-containing, G protein-coupled Receptor 5), is highly upregulated in colorectal tumors and found on the cell surface of colorectal CSCs. LGR5 also has been shown to be significantly elevated in several other major tumor types, including liver, gastric, and ovarian cancers. Colorectal CSCs, which express LGR5, are capable of driving tumor growth. Interestingly, LGR5-positive CSCs have been shown to have the ability to transition to a more drug-resistant LGR5-negative cancer cell type as a means to evade therapy and promote metastasis. Once LGR5-negative cancer cells reach the site of metastasis, they transition back to LGR5-positive CSCs to increase metastatic growth. As a means to eliminate CSCs, we generated LGR5-targeted antibody-drug conjugates (ADCs). ADCs, referred to as target-guided missiles, are innovative therapeutics that destroy tumors, while sparing normal healthy tissues. They are comprised of a highly specific antibody attached to a cytotoxic chemical “warhead” that is only released once the ADC binds and enters tumor cells. We previously showed that LGR5-targeted ADCs were highly effective in eliminating LGR5-positive colorectal tumors without major adverse effects. However, after treatment was terminated, a fraction of tumors eventually relapsed. These findings suggested targeting LGR5-positive CSCs alone may not be sufficient to eliminate colorectal tumors because of their ability to escape treatment by converting to an LGR5-negative state. Instead, to successfully eliminate colorectal cancer, it may require a dual- or multi-targeted approach.

One of the current research interests of my lab focuses on investigating the roles of LGR5 in colorectal tumor growth, metastasis, and drug resistance. Secondly, we are working to discover a more effective treatment for colorectal cancer by taking novel approaches to modify and improve our LGR5-targeting ADCs and evaluating them in combination with other targeted therapies. We are also generating bispecific antibodies, which are aimed at binding two different cancer targets. Thirdly, our lab is identifying and characterizing new cancer targets for ADC development. One of these new targets is a cell receptor called GPR56, which is highly expressed in colorectal cancer and correlates with poor patient survival. We found that GPR56 can promote tumor growth and drug resistance, and we are investigating the cellular mechanisms that drive its function. Our group has acquired colorectal tumor samples from patients and established 3D cultures called patient-derived tumor organoids (PDOs). We utilize PDOs to study the function of our different cancer targets and evaluate the efficacy of our ADCs before testing in animal models. Our work will lead to elucidating the function and mechanism of different receptors in colorectal cancer and generate innovative targeted therapeutics for the improved treatment and eradication of colorectal cancer.

**RESEARCH PROJECTS**

- Investigation of LGR5 function in cancer stem cells, metastasis, and drug resistance
- Identification of novel therapeutic targets and development of antibody-drug conjugates and combination therapies to destroy colorectal tumors and cancer stem cells
- Elucidating the role and signaling pathways of GPR56 in colorectal cancer

**KEY PUBLICATIONS**


**LAB MEMBERS**

Students: Joan Jacob, Shradha Subramanian
Senior research associate: Zhengdong Liang
Research scientist: Yoo-shin Kim

**Therapeutic strategies for targeting colorectal tumors and cancer stem cells**
Jeffrey Chang, PhD
Associate Professor
CPRIT Scholar in Cancer Research

Deciphering the signaling programs underlying cancer metastasis

RESEARCH PROJECTS

- The role of cholesterol trafficking in cancer stem cell differentiation, the epithelial-to-mesenchymal transition, and cancer metastasis.
- Heterogeneity and progression of metastatic cancers.
- Intelligent computational pipelines for bioinformatic analysis.

KEY PUBLICATIONS

Prijic S, and Chang JT. ABCA1-dependent enhancement of cell motility in mesenchymal breast cancer cells is repressed by MYC. Biomedicines, 10(3), 2022.


Our lab is focused on understanding the signaling programs underlying cancer progression and developing therapeutic strategies to prevent or treat metastasis. We wish to understand the events that lead tumor cells to become metastatic, whether through acquired mutations or epigenetic mechanisms. Our ultimate goal is to translate these findings into the clinic through the development of genomic biomarkers and repositioning of drugs. To do this, we use a range of approaches encompassing genomics, cell biology, and biochemistry, and use models, including cell culture, mouse models, and clinical samples.

Our research program encompasses two broad and complementary areas of emphasis:

1. Breast cancer metastasis. It is estimated that up to 90% of cancer deaths are due to metastasis, in part because metastatic cells do not respond to traditional therapies. To address this problem, we have used computational approaches to characterize the metastatic state and to reposition drugs to target cells that exhibit phenotypes that promote metastasis. Through these studies, we have found that metastasis is driven in part by cells that acquire a stem-like state through deregulation of cholesterol metabolism through altered expression of the ABCA1 cholesterol efflux channel. We are currently identifying therapeutic strategies to inhibit this pathway to reprogram breast cancer stem cells so that they become more amenable to therapies.

2. Artificial intelligence for genomic analysis. Many of our projects require the integration with bioinformatics to mine public data sets, develop hypotheses, or analyze results. To amplify our ability to do bioinformatics, we have developed an artificial intelligence, BETSY, that can automatically plan and execute these tasks, presenting us with finished results. It is a backwards-chaining expert system that leverages a knowledge base containing descriptions of common bioinformatics algorithms.

Sensitivity of breast tumors to PARP inhibitors. PARP inhibitors have shown promise in treating hereditary breast cancers, but tumors become resistant to the drug. To understand why that happens, we performed genomic profiling on breast tumors from a PARP inhibitor clinical trial and found markers that can be used to predict sensitivity to PARP inhibitors, offering a personalized approach to select patients for treatment.

Sensitivity of breast tumors to PARP inhibitors. PARP inhibitors have shown promise in treating hereditary breast cancers, but tumors become resistant to the drug. To understand why that happens, we performed genomic profiling on breast tumors from a PARP inhibitor clinical trial and found markers that can be used to predict sensitivity to PARP inhibitors, offering a personalized approach to select patients for treatment.
Radiation therapy is a long-established and effective component of modern cancer therapy for many locally advanced unresectable cancers. However, its ultimate utility is limited by the fact that some cancer cells are resistant to ionizing radiation and/or the adjacent normal tissues are exquisitely sensitive to ionizing radiation. Attempts to improve outcomes of radiation therapy have largely focused on (i) increasing the dose of radiation delivered to the tumor while sparing adjacent normal tissues, (ii) sensitizing the radioresistant fraction of tumor cells to conventional doses of radiation, and (iii) targeting cancer cells specifically while administering radiation therapy. The next generation of cancer therapies requires technologies that combine multiple approaches. Our laboratory focuses on strategies to sensitize tumors to radiation therapy using nanoparticles, chemotherapy, immunotherapy, and novel radiation techniques and to protect normal tissues from radiation injury using novel agents. A major thrust is the use of nanoparticles wherein we design, fabricate, characterize, validate, and explore mechanisms of action of carbon-based, organic, inorganic, hybrid, and multilayered nanostructures for diagnosis and treatment of cancer. Parallel efforts focus on improving their payload delivery capabilities via stimulus-responsiveness, bio-inspired molecular mimicry, Trojan-horse delivery approaches, and phagocytosis evasion strategies. Lastly, the laboratory anchors a Center for Physical Energy Therapeutics where we evaluate new strategies of combining localized physical energy therapies (ionizing and non-ionizing radiation of all flavors, thermal therapies, ultrasound) with targeted therapeutics (custom nanoparticles, antibody-drug conjugates, targeted protein degraders, immunotherapeutics) in a synthetically lethal one-two punch approach.

**RESEARCH PROJECTS**

- Sensitizing tumors to radiation therapy using gold nanoparticles.
- Physical energy therapeutics.

**KEY PUBLICATIONS**


**LAB MEMBERS**

Assistant professors: Yuri Mackeyev, Geraldine Raja
Post-doctoral fellows: Iona Hill, Okan Tezcan, Khadijeh Koushki
Research assistants: Muhammad Shohayeb, Mariam Elsharnoby, Belal Abousaida

Gold nanoparticle therapeutics. (a) Transmission electron microscopy (TEM) image of gold nanorods (GNRs). (b) pH-dependent charge reversal peptide aids hypoxic area accumulation (adapted from Rauta PR, et al. *Sci Adv* 2022, 8(45):eabm9729. (c) Dark field image of cellular internalization aided by protease-cleavable epilayer shedding (adapted from Raghuram S, et al. *Biomaterials* 2022, 291:121887). (d) TEM image of receptor-mediated internalization of antibody conjugated GNR.
Proteins are essential functional biomolecules that are involved in all aspects of cellular physiologic activities, and have been important targets for drug development and disease diagnosis. Proteome alterations that are associated with diseases may include changes in protein expression, sequence, post-translational modifications (PTMs) and protein interactions with proteins or other biomolecules, which may all lead to a malfunction of cellular processes. In our lab, mass spectrometry based proteomic technologies are applied to study cancer, neurodegeneration, and other diseases. These studies are carried out with various goals, such as aiming to better understand the molecular mechanisms underlying key protein networks implicated in tumorigenesis, to investigate changes in PTM status associated with diseases, to identify protein biomarkers or therapeutic targets, or to interrogate microbiome dysbiosis. The samples involved in our studies include a variety of research and clinical specimens, including tumor tissues, blood and other bodily fluids, as well as isolated cells from various clinical specimens. Currently, our main disease focuses are pancreatic cancer and other GI tract malignancies. In addition, through collaborative efforts, our lab also supports proteomic study of neurodegeneration and chronic inflammations, as well as therapeutic drug development. Mass spectrometry, bioinformatics, systems biology, and chemical biology are important components in our study.

RESEARCH PROJECTS
• Mechanistic and biomarker studies of pancreatic ductal adenocarcinoma (PDAC) and its precursors, including pancreatic intraepithelial neoplasia (PanIN) and pancreatic cyst neoplasms (PCNs).
• Investigation of protein glycation and advanced glycation end products (AGEs) in malignancies, aging, diabetes, and chronic inflammation.
• Metaproteomic study of microbiome implicated in GI-tract malignancies and other diseases.

KEY PUBLICATIONS
Pan S and Chen R, “Pathological implication of protein post-translational modifications in cancer”, Molecular Aspects of Medicine, 2022 Apr 7:101097

LAB MEMBERS
Research scientists: Lakmini Senavirathna, PhD; Cheng Ma, PhD
Research coordinator: Li Li, MS
PhD graduate student: Altai Enkhbayar, MS
Integrate multidisciplinary approaches for cancer biomarker discovery

Aptamer-Mediated Biomarker Discovery: Aptamer-mediated biomarker discovery and targeted therapy are attractive approaches for cancer treatment. Aptamers are single-stranded oligonucleotides with high affinity and specificity to the target molecules. DNA aptamers have many significant advantages over monoclonal antibodies in terms of feasibility, low cost, non-immunogenicity, and facile modification for various applications. We created a systems biology approach that combines a bead-based modified aptamer library with flow cytometry sorting and mass spectrometry to identify proteomic biomarkers. Patient’s plasma was incubated with beads-based aptamer library and sorted for aptamer-protein complex by flow cytometry based (Figure 1). Using this approach, we selected a panel of prognostic biomarkers for hepatocellular carcinoma (HCC) patients under Lipiodol-based transarterial chemoembolization (TACE) treatment.

Artificial Intelligence (AI) Image Analysis: Unlike most solid cancers, the diagnosis of HCC is based on multiphasic CT or MRI without histological confirmation in patients with cirrhosis. AI has the capacity of converting images into mineable data by high-throughput extraction of quantitative features. A seamlessly integrated AI component within the imaging workflow would increase efficiency, reduce errors, and improve diagnostic performance with minimal manual input by interpreting radiologists. Most of the current deep learning approaches focus on image segmentation at a single time point rather than a series of images at the different diagnosing stages of the disease. We will develop a Long Short-Term Memory (LSTM) network based time-series model combined with 3D neural networks (3DCNN-LSTM) and domain adaptation to learn the disease transformations from cirrhosis to HCC and make disease trajectory predictions.

Integrated Multi-Aspects Biomarker Analysis: By studying differentially expressed mRNAs using data downloaded from TCGA and validating those mRNA encoded proteins in tissue and blood samples, we have identified a group of genes and proteins that are significantly differentially expressed between HCC and healthy control groups. We seek to shift current clinical surveillance and early diagnosis of HCC into a new platform (AiCat) to integrate multidisciplinary approaches into one setting, including artificial intelligence (AI) image analysis, proteomics, and genomics biomarkers to improve early diagnosis and outcome prediction for liver cirrhosis patients who are at high risk of developing HCC.

RESEARCH PROJECTS
- Identify proteomic biomarkers for outcome prediction of lipiodol TACE treatment
- Artificial intelligence improves liver cancer surveillance and early detection
- Genetic and proteomic biomarker discovery for hepatocellular carcinoma

KEY PUBLICATIONS


LAB MEMBERS
Research associate: Xin Li
The Texas Therapeutics Institute at The Brown Foundation Institute of Molecular Medicine (TTI-IMM) was established in 2010 with funding from the Texas Emerging Technology Fund, The University of Texas System, and The University of Texas Health Science Center at Houston. TTI-IMM was created for the discovery and development of therapeutic agents and diagnostic tools. Research conducted at the center focuses on the establishment of proof-of-principle for therapeutics and the identification and validation of drug targets.

TTI-IMM investigators have brought in significant funding from biopharmaceutical companies, such as Merck, Johnson & Johnson, and Sanofi, and from government organizations, including the National Institutes of Health, the Cancer Prevention and Research Institute of Texas, and the Department of Defense. TTI investigators have made significant scientific discoveries in the areas of cancer biology, Alzheimer’s disease, and antibody drug development.

Current research activities at TTI-IMM include: 1) signaling mechanisms of receptors and enzymes that have critical roles in human diseases; 2) discovery of biologics that modulate the activity of these targets as potential lead molecules for drug discovery; and 3) characterization of antibodies from animals and humans in response to viral infections and experimental vaccines.

In addition to basic and translational research programs, TTI has built a major drug discovery platform for therapeutic monoclonal antibody lead discovery optimization and development.

Over the last 13 years, TTI established a network of collaborators from institutions across Texas and the nation. TTI has more than 30 active drug discovery projects targeting cancer, metabolic diseases, neurodegenerative diseases, spinal cord injury, fibrosis, acute drug induced liver injury, and viral infections. Ten TTI inventions have been licensed to biotech companies for drug development. Five antibody based therapeutics discovered by TTI scientists are currently in human clinical trials. Licensing deals resulted in significant upfront payments, potential milestone payments, and royalties. The Texas Therapeutics Institute is recognized as the drug discovery engine of McGovern Medical School and UTHealth Houston.

Zhiqiang An, PhD
Professor & Center Director
Robert A. Welch Distinguished University Chair in Chemistry
Zhiqiang An, PhD
Professor and Director of the Texas Therapeutics Institute
Robert A. Welch Distinguished University Chair in Chemistry

Discovery and development of therapeutic antibodies

KEY PUBLICATIONS


Ab18 TVD-Ig/αTfR ameliorates amyloid pathology in 5XFAD mice. Representative images of amyloid plaque immunofluorescence staining of brain slices from 5XFAD mice treated with designated Abs (20 mg/kg, 14 weekly intraperitoneal dosages started when mice were five months old). Scale bars, 70 μm (*Science Translational Medicine* 14, eabq0095 7 10.1126/scitranslmed.abq0095).

Our group focuses on the discovery and development of therapeutic antibodies against human diseases. Currently, we have two major research areas.

RESEARCH PROJECTS
- Antibody response to viral infections and vaccination. Identification of highly immunogenic vaccines that induce neutralizing antibodies against a broad range of clinical isolates is one approach to developing effective viral vaccines. We have ongoing projects to aid the design of HCMV and EBV vaccines by profiling antibody response to viral infections in humans, and to develop SARS-CoV-2 targeting antibodies for the potential treatment of COVID-19.
- Therapeutic monoclonal antibody drug discovery. Our group has built a comprehensive antibody drug discovery platform with a focus on antibody lead optimization technologies, such as antibody phage display, deep sequencing of antibody encoding genes from individual antibody expressing B cells, affinity maturation, and humanization. Currently, we have multiple in-house and collaborative antibody drug discovery projects targeting various cancer types, neurodegenerative diseases such as Alzheimer’s disease, and other human diseases.
TExAS THERAPEUTICS INSTITUTE

Xiaodong Cheng, PhD
Professor
Walter and Mary Mischer Distinguished Professor in Molecular Medicine

**cAMP - mediated cell signaling and drug discovery**

Our laboratory studies intracellular signaling associated with second messenger cAMP, a major stress signal implicated in the development of human diseases. We apply multidisciplinary approaches, coupling biochemistry, biophysics, and cell biology with pharmacology and chemical biology, to understand the structure and function of a family of cAMP sensors: exchange proteins directly activated by cAMP (EPAC). Our goals are to unravel the signaling intricacies of EPAC proteins and to design pathway-specific modulators for these important signaling molecules so that their functions can be exploited and controlled pharmacologically for the treatment of human diseases. We have developed first-in-class EPAC selective inhibitors and EPAC knockout mouse models to study the physiological functions and diseases relevance of this family of important signaling molecules. Recently, we have identified a potential use of EPAC inhibitors in the prevention and treatment of proliferative retinopathy. Currently, we are developing second-generation isoform specific EPAC inhibitors and agonists and in exploring their potential uses in various human diseases including chronic pain and diabetic retinopathy.

**RESEARCH PROJECTS**
- Structural and functional analyses of the exchange proteins directly activated by cAMP (EPAC).
- Examine the roles of EPAC proteins in major human diseases, such as hypertension and proliferative vascular diseases using EPAC knockout mouse models and pharmacological inhibitors.
- Preclinical development of novel drug candidates targeting EPAC1 for the treatment of chronic pain and diabetic retinopathy.

**KEY PUBLICATIONS**

**LAB MEMBERS**
Research assistant professor: Fang Mei
Instructor: Wenli Yang
Research associate: Wei Lin

Epac1 in pathological angiogenesis and as a therapeutic target for retinopathy. (A) Epac1 promotes pathological angiogenesis through sensitization of VEGF signaling and suppression of Notch activation via γ-secretase inhibition. (B) Pharmacological inhibition of Epac prevents neovascularization associated with oxygen-induced retinopathy (OIR). Representative retinal vasculature (upper panel) and high magnification images (lower panel) at P17 in OIR mice treated with Epac inhibitor ESI-09 or vehicle (Con). White lines outline the area of vaso-oblitration. (C, D) Graphs represent avascular and neovascularization area at P17.
Xin (Alex) Ge, PhD
Associate Professor
Kay and Ben Fortson Distinguished Chair in Neurodegenerative Disease Research

Bio-pharmaceutical discovery and engineering

The blood-brain barrier (BBB) poses a great challenge for developing effective therapies for neurological disorders such as brain cancer and neurodegenerative diseases. We design protease-activated bi-specific antibody prodrugs as a highly efficient BBB delivery approach for treating neurological diseases.

- Monoclonal Antibody-Based Therapeutics for Diabetic Neuropathy (Funded by DoD) One of the most common complications of diabetes is nerve damage-associated diabetic peripheral neuropathy (DPN), which affects up to 50% of diabetic patients. This research develops, optimizes, and evaluates highly specific mAb therapeutics directly targeting the mechanisms of DPN pathogenesis, and thus with great values in the management of diabetic neuropathy.

- Broad Neutralizing mAbs of Snake Venom Metalloproteases (Funded by NIAID) Snake envenomation is a serious global health concern, and in N.A., the majority of venomous snakes belong to family Viperidae (e.g. rattlesnakes and copperheads), which bites can lead to fatal hemorrhage and coagulopathy caused by snake venom metalloproteinases (svMPs). This research develops humanized broad neutralizing mAbs by targeting svMPs reaction cleft, and further tests their efficacy in vitro and in vivo.

KEY PUBLICATIONS


LAB MEMBERS
Post-doctoral fellows: Kibaek Lee, Pablo Martinez, Zening Wang
Research scientists: Afshin Ebrahimpour, Yuan Zhong

Monoclonal antibodies discovered in Ge Lab showed efficacy in animal studies. (A) MMP-9 inhibitory mAb L13 attenuated paclitaxel (PTX)-induced neuropathic pain (B) MMP-14 inhibitory mAb 3A2 improves metabolic parameters including glucose tolerance and body weight in mouse models of obesity.
My research programs are (1) to obtain critical new knowledge of cancer metastasis and drug resistance of human cancer cells, (2) to identify new biomarkers and drug targets for the development of better therapeutics for human cancers.

Cancer metastasis, the spread of tumor to other parts of patient’s body, is responsible for over 90% of cancer death. However, cancer metastasis is still poorly understood and the current approaches to prevent or treat human metastatic cancers are mostly unsuccessful. Therefore, there is a huge unmet medical need to better understand cancer metastasis and to develop new therapies against cancer metastasis. Through genomics, RNAi and cDNA functional screens, our lab has identified several crucial but previously unknown regulators for cancer metastasis. Some of the novel regulators control epithelial-mesenchymal transition (EMT), while some others are essential for survival and proliferation of highly metastatic cancer cells (i.e. essential genes). EMT, a developmental process, is believed to play a key role in cancer metastasis, drug resistance, organ fibrosis, and stem cell phenotypes. Essential genes for metastatic cancer cells may be the key to understand colonization, the rate-limiting step of cancer metastasis. Signaling pathways and molecular mechanisms of these novel regulators are under investigation with molecular, cellular, biochemical, genomic, proteomic approaches, and mouse models. These studies are yielding critical new insights for cancer metastasis and facilitating the development of new therapeutics and biomarkers.

Another research topic is to investigate the mechanisms of cancer cell plasticity and drug resistance. In particular, I study how prostate cancers become resistant to new generation of androgen receptor pathway inhibitors and how non-small cell lung cancers become resistant to EGFR inhibitors. The common theme is to better understand and to target a process called neuroendocrine differentiation (NED), which is increasingly accepted as a critical process in cellular plasticity and drug resistance in many cancers. NED is still poorly understood and currently there is no effective treatments to prevent or overcome drug resistance related to NED. We investigate the underlying mechanisms of NED, cellular plasticity and drug resistance, especially the roles and mechanisms of action of several novel epigenetic regulators.

Finally, in collaborations with Drs. Ningyan Zhang and Zhiqiang An at TTI, we are identifying novel therapeutic antibodies. We are also exploring new combinatorial strategies to enhance efficacy of immune therapy, such as combining our kinase inhibitors with immune checkpoint blockade, e.g. anti-PD-1 and anti-PD-L1 antibodies.

**RESEARCH PROJECTS**

- Targeting critical regulators of cancer metastasis.
- Defining new pathways and mechanisms of epithelial-mesenchymal transition.
- Investigating lineage plasticity and acquired resistance to cancer therapeutics.
- Identifying novel cancer therapeutic antibodies.
- Exploring new combinatorial strategies to enhance immune therapy.

**KEY PUBLICATIONS**


**LAB MEMBERS**

Research scientist: Juan Bournat
Research assistant: Michael Bakhoum

![Image of Wenliang Li, PhD]

Wenliang Li, PhD
Associate Professor

**Studying and targeting cancer metastasis and drug resistance**

**Figure 1:**

- **A:** GRK3 expression in stomach cancer patients.
- **B:** GRK3 over-expression promotes xenograft tumor growth of MKN45 stomach cancer cells.
- **C:** GRK3 inhibitor LDZ ablated xenograft tumor growth of GA0518 stomach cancer patient derived xenograft (PDX).

GRK3 is a poor prognosis marker and a therapeutic target in advanced stomach cancers. (A) Higher GRK3 level is associated with shorter survival in stomach cancer patients. (B) GRK3 over-expression promoted xenograft tumor growth of MKN45 stomach cancer cells. (C) GRK3 inhibitor LDZ ablated xenograft tumor growth of GA0518 stomach cancer patient derived xenograft (PDX).
Linker and conjugation technologies for generating novel antibody-drug conjugates (ADCs) toward innovative cancer therapeutics

Antibody-Drug Conjugates (ADCs) represent a rapidly growing class of anticancer therapeutics. As demonstrated with 13 FDA-approved ADCs (as of Nov. 16, 2022) and more than 100 promising ADCs in clinical trials, successful clinical outcomes using ADCs have inspired scientists and clinicians to further advance this new molecular format for effective treatment of cancers. ADCs deliver anticancer drugs (payloads) selectively to blood cancer cells or solid tumors while avoiding healthy tissues, enabling the use of highly active payloads that are too toxic to be used alone. The ADC chemical linker connecting the antibody and the payload molecule is a critical component for enabling tumor-specific drug delivery. Thus, the use of properly designed ADC linkers is a key for successful implementation of ADC-based chemotherapy.

My research group is focused on the development of novel chemical ADC linkers by taking advantage of the power of organic chemistry, medicinal chemistry, and chemical biology. We have developed a glutamic acid-glycine-citrulline (EGC) tripeptide linker as a next-generation ADC linker with high translatability from bench to clinic (Figure 1A). Unlike traditional valine-containing peptide linkers, our glycine-based linker is highly stable in circulation as well as against neutrophil protease-mediated degradation leading to neutropenia. While stable, our linker is immediately degraded once a given ADC internalizes into the target cell, effectively releasing toxic payloads. Using this technology, we developed anti-HER2 ADCs and assessed their potential toxicity and efficacy (Figure 1B). Our ADC showed enhanced treatment efficacy in xenograft mouse models representing intratumor HER2 heterogeneity and elevated drug resistance, which are clinical issues often seen in breast cancer patient samples. Notably, our ADC exerts greater treatment effect and survival benefit than the FDA-approved anti-HER2 ADC Enhertu. Furthermore, our ADC did not cause significant blood or liver toxicity even at 80 mg/kg in healthy mice. These findings suggest that our novel linker system provides a promising platform for generating efficacious and safe ADCs with the potential to overcome cancer heterogeneity and drug resistance. Our next goal is to advance this novel ADC to in-depth preclinical evaluation and following IND-enabling studies within several years.

With our cutting-edge conjugation technology platform in hand, we are currently expanding our next-generation ADC portfolio for treating refractory cancers, including triple-negative breast cancer, glioblastoma multiforme (GBM), pancreatic cancers, and other solid tumors with drug resistance and/or high intratumor heterogeneity. Patients with resistant and heterogeneous cancers often suffer from recurrence of malignancy and exacerbated quality of life because of the lack of effective therapy. Our lab’s long-term goal is to offer novel therapeutic options for overcoming such critical clinical issues. We envision that our novel ADC technology platform will help the whole biomedical research community achieve this overarching goal.

RESEARCH PROJECTS
- Design, synthesis, and evaluation of novel chemical linkers for constructing multi-loading ADCs
- Structural optimization of ADC linkers for high plasma stability, rapid drug release, and enhanced permeability to the brain
- Evaluation of ADCs in refractory cancer models

KEY PUBLICATIONS


LAB MEMBERS
Instructor: Yasuaki Anami, PhD
Senior research scientist: Chisato Tsuchikama, PhD
Post-doctoral fellows: Aiko Yamaguchi, PhD, Yin Yuen Ha (Summer), PhD

Novel linker and ADCs with the potential to overcome breast cancer heterogeneity. (A) Structure of our proprietary tripeptide linker. (B) Our ADC provides enhanced therapeutic efficacy in HER2 heterogeneous breast tumor models (dose: 1 mg/kg, n = 5 or 6).
Monoclonal antibody therapies have revolutionized cancer treatment and been successfully used for treatment of many types of cancer in the clinic. However, similar to many targeted cancer therapies, both innate and acquired resistance are widely reported for monoclonal antibodies. Understanding the mechanism of cancer resistance to therapeutic antibodies is of paramount importance for improvement of efficacy of the antibody therapies to benefit more patients.

Cancer immune evasion is being recognized as one of the hallmarks of cancer. Our research has demonstrated the prevalence of proteolytic impairment of antibody IgG in the tumor microenvironment. Trastuzumab and pertuzumab (anti-HER2 antibody) with a single hinge cleavage showed a loss of immune effector function against cancer cells in vitro and reduced antitumor efficacy in vivo. Based on our findings and reports by others, we hypothesize that antibodies recognizing tumor associated antigens (TAA) in the tumor microenvironment are susceptible to proteolytic impairment through a hinge cleavage by matrix metalloproteinases (MMPs). Such proteolytic hinge cleavage of antibodies not only weakens antibody anticancer immunity but also leads to an immune suppressive tumor microenvironment. Our current research programs are centered on better understanding tumor evasion of antibody immunity and develop therapeutic strategies to modulate anticancer immunity for improvement of cancer treatment. We employ a wide array of experimental approaches including in vitro 2D and 3D cell co-cultures, mouse tumor models, and studies with clinical samples from cancer patients to determine factors influencing proteolytic impairment and to identify mechanisms of cancer immune evasion triggered by proteolytic impairment of antibody hinge. State-of-the-art technologies are used in our studies such as high content fluorescence imaging, mass spectrometry, fluorescence activated cell sorting (FACS), and single cell cloning of antibodies. We have established a monoclonal antibody platform technology to discover and select novel anticancer antibodies for functional evaluation and preclinical development.

The longterm goal of my research is to understand mechanisms of cancer evasion of antibody therapies and to identify key molecular targets for development of effective anticancer immunotherapies.

**RESEARCH PROJECTS**

- Understand mechanisms of cancer immune suppression.
- Develop platform technologies for discovery of therapeutic antibodies.

**KEY PUBLICATIONS**


Xuejun Fan, Zihao Yuan, Hao-Ching Hsiao, Yueshui Zhao, Wei Xiong, Rahmawati Pare, Xin Li, Georgina Salazar, Jianmin Ding, Ahmad Almosa, Kai Sun, Songlin Zhang, Robert Jordan, Cheok Song Lee, Zhiqiang An, Ningyan Zhang (2022) Impairment of IgG Fc Engagement of Effector Cells Contributes to an Immune Suppressive Tumor Microeviroment. Communications Biology, doi.org/10.1038/s42003-022-03931-7.

Guojin Wu, Yixiang Xu, Robbie D Schultz, Heyu Chen, Jingjing Xie; Mi Deng; Xiaoye Liu; Xun Gui; Samuel John; Zhigang Lu; Ningyan Zhang; Zhiqiang An; Chengcheng Zhang (2021) LILRB3 supports development of acute myeloid leukemia and regulates NF-κB signaling by recruiting TRAF2 and cFLIP. Nature Cancer, doi.org/10.1038/s43018-021-00262.

**LAB MEMBERS**

Senior research associate: Hui Deng, MS
Senior research scientists: Xuejun Fan, MD, PhD; Wei Xiong, PhD; Marco Velasco Velazquez, PhD
Research associate: Xin Li, MS

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**Cancer resistance mechanisms to therapeutic antibodies and modulation of anticancer immunity**

Ningyan Zhang, PhD
Professor

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**Schematic diagram for generation and screening of monoclonal antibodies (mAbs) using our established technology platform.**

**Structural identification of binding epitopes of a functional anti-LILRB1 monoclonal antibody for development of cancer therapeutics.**

IMM Service Centers

The IMM is focused on studying and preventing disease at the genetic, cellular, and molecular levels using DNA and protein technologies and animal models. Our service center goal is to provide the latest technology and the highest quality services to our colleagues and customers while operating in a cost-effective manner. IMM’s Service Centers are staffed by top research experts in the technologies offered.

To accomplish IMM’s strategic goal of providing high quality and effective support services for our research capacity, we have initiated a systematic process to further improve our infrastructure and to provide to our faculty and customers access to cutting-edge technology. The establishment of key service centers at UTHealth-IMM is a critical component of this commitment.

Antibody Engineering and Expression Service Center

Antibody therapeutics represents a major breakthrough in combating human diseases, including cancer. Even though the pharmaceutical and biotechnology industries are in the center stage of drug discovery and development, academic researchers are increasingly engaged in discovering new antibody drug candidates. However, advancement of some of the promising antibodies in the early stage of discovery from academic research laboratories is often hindered by the lack of access to the expertise and infrastructure required for antibody engineering and other related key technologies. Our antibody engineering and expression service center offers the services to fill the gap of the much-needed expertise in early discovery of monoclonal antibodies and lead optimization for the research and drug discovery communities. The objective of the service center is to provide technical support and services to antibody identification, molecular cloning, antibody expression, and purification. Results generated from the service center will strengthen the collaborators’ ability to attract external funding to continue development of the optimized therapeutic antibodies with the ultimate goal of translating basic research to novel therapies.

Clinical and Translational Proteomics Service Center

Proteins are the essential functional biomolecules that participate in a vast array of physiological cellular activities and are implicated in all aspects of disease mechanisms. Disease-associated proteome alterations may reflect changes in protein expression, structure, localization, polymorphism, as well as post-translational modifications (PTMs) status. Proteomics can deliver dynamic information of a protein profile in a complex system and thereby provide a vibrant picture of cellular function under biological conditions. Furthermore, quantitative proteomics can identify steady or perturbation-induced proteome alterations associated with a disease status or biological state and are highly relevant to translational and clinical applications.

Our center provides state-of-the-art proteomics services to support basic, translational, and clinical research. The main services include protein profiling, label-free or label-based quantitative analysis, therapeutic protein characterization, and essential PTM analysis. We have the capability to analyze a broad range of research or clinical specimens, from purified proteins to complex mixtures, including cell and tissue extracts, plasma/serum, and other biofluids or biological samples.

We also provide more advanced support through collaborative efforts, such as biomarker discovery and verification, glycoproteomics/glycomics analysis, and microbiome profiling. The center contains state-of-the-art instrumentation and well-trained personnel to provide an integrated proteomics service, including sample preparation, mass spectrometric analysis, and bioinformatics data processing.
FLOW CYTOMETRY SERVICE CENTER

Flow cytometry is a single-cell analysis technology used for cell counting and fluorescent marker detection. It allows high-speed identification and even isolation of specific subsets within mixtures of cells. The fluorescence can be measured to determine cellular properties like relative size, complexity, cell type, and response to specific stimuli such as drugs and genetic manipulations.

These specialized multicolor cell analysis instruments allow researchers to evaluate a large number of samples in a short timeframe and gather information on very rare populations of cells and additionally isolate cell populations to be sorted. The current instrumentation allows simultaneous acquisition of more than 10 fluorescent signals from thousands of individual cells per second.

The Flow Cytometry Service Center offers FACS acquisition and analysis, cell sorting, user training, and consultation for experimental design, interpretation, and troubleshooting.

Our instruments are available on a fee-for-service charge to all research investigators from UTHealth Houston and external organizations.

TRANSGENIC AND STEM CELL SERVICE CENTER

Our Immunology and Autoimmune Diseases Center operates a Transgenic and Stem Cells service center, which was established in 1998. It has generated over 800 new transgenic and knock-out mouse animal models for all research investigators from UTHealth Houston and external organizations on a fee-for-service basis.

The stem cell lines that have been derived in the laboratory are highly effective for the generation of knock-out/knock-in mice and for cell differentiation studies. In addition to the production, cryopreservation, and re-derivation of genetically-engineered mice and rats, the services of the facility also include gene targeting, CRISPR/Cas9 genome editing, derivation of new cell lines and intellectual/technical support in different aspects of microsurgery, cell culture, and stem cells research.

3D PRINTING SERVICE CENTER

3D Printing Service Center provides state-of-the-art 3D printing services. We provide 3D printed models of human and laboratory animal organs, novel surgical tools, and custom-made laboratory supplies, in prototype or final production models.

We have both traditional FDM (Fortus 450mc) thermoplastic as well as multi-color, resin-based, high-resolution Stratasys J750 (14 micron) 3D printers with large print beds.

A wide range of materials with varying Shore A values (hardness) is available. STL files, SolidWorks, or medical imaging files can be used to produce the 3D models.

We are located on the 3rd floor of the Fayez S. Sarofim Research Building.
**IMM By the Numbers**

**Number of Faculty**

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**Total Funds Supporting Research**

- **2018**: $22,713,220
- **2019**: $22,330,042
- **2020**: $22,985,200
- **2021**: $20,299,510
- **2022**: $21,331,816

Note: Excludes all ARRA funds. Sponsored Projects based on award received. Service Centers and Endowments/Gifts based on expenses.

**Total Expenses Supporting Research**

- Federal Government: 68%
- State Government: 19%
- Foundations: 4%
- Industry: 1%
- Service Centers: 8%
IMM Extramural Funding Inception to Date

$223,949,209

- Federal Government: 77.1%
- State Government: 12.9%
- Foundations: 6.1%
- Industry: 3.5%
- Other: 0.4%

IMM Commercial Outcomes Inception to Date

- U.S. Patents Issued: 65
- License & Option Agreements Executed: 84
- Startup Companies Formed: 21
- Income Generated from Intellectual Property: $22,258,817
Gift Report
New Gifts and Bequests Fiscal Year 2022

Amy and Edward Knight
Betty and Alan Baden
Deborah and David Gorenstein, PhD, MA
Judy and Dick Perkins
Katy F. Miner
Laura and D. Bradley McWilliams
Marsha and Charles Parker
Mary and Robert Errera
Patricia and John McDonald
Susan Atkins and Steven Gordon
The Ted and Louana Frois Family Foundation

Thank you to all of our supporters!
Institute of Molecular Medicine Endowments

Annie and Bob Graham Distinguished Chair in Stem Cell Biology
Becker Family Foundation Professorship in Diabetes Research
C. Harold and Lorine G. Wallace Distinguished University Chair
Chair in Biomedical Engineering
Cullen Chair in Molecular Medicine
D. Dudley and Judy White Oldham Research Fund
Dr. Edward Randall, Jr. Memorial Fund
George and Cynthia Mitchell Distinguished Chair in Neurosciences
George and Mary Josephine Hamman Foundation Distinguished Professorship in Cardiovascular Research
Hans J. Muller-Eberhard, MD, PhD, and Irma Gigli, MD, Distinguished Chair in Immunology
Harry E. Bovay Lecture Series in Molecular Medicine
Harry E. Bovay, Jr. Distinguished University Chair in Metabolic Disease Research
IMM General Endowment
James T. Willerson Distinguished Chair in Cardiovascular Research in Tribute from the Ewing Halsell Foundation
Janice Davis Gordon Chair for Bowel Cancer Research
Jerold B. Katz Distinguished Professorship in Stem Cell Research
John S. Dunn Research Scholar Fund I
John S. Dunn Research Scholar Fund II
John S. Dunn Research Scholar Fund III
John S. Dunn Research Scholar IV
Kay and Ben Fortson Distinguished Chair in Neurodegenerative Disease Research
Kozmetsky Family Chair in Human Genetics
Linda and Ronny Finger Foundation Distinguished Chair in Neuroimmunologic Disorders
Marjorie B. Poyner and Herbert F. Poyner, Jr. Endowment for Medical Research in the Institute of Molecular Medicine for Prevention of Human Diseases
Mary Elizabeth Holdsworth Distinguished University Chair in Metabolic and Inflammatory Disease Research
Müller-Eberhard Memorial Lecture Series
Nancy and Rich Kinder Distinguished Chair in Cardiovascular Disease Research
Nina and Michael Zilkha Distinguished Chair in Neurodegenerative Disease Research
Pierce Runnells Memorial Research Fund
Robert A. Welch Distinguished University Chair in Chemistry
Rochelle and Max Levit Chair in the Neurosciences
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