IMMpact Report

FISCAL YEAR 2021
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The courtyard fountains are shown in the foreground of the Brown Foundation Institute of Molecular Medicine for the Prevention of Human Diseases.


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Director’s Message

I am pleased to introduce the latest annual 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. The IMM mission is to deliver translational outcomes from research in molecular medicine that benefit 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 define 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 matched last year, which was a best ever for new funding, capping increases in our extramural grant funding for each of the last 7 years. It is a testament to the outstanding quality and creativity of our scientists that the IMM remains so successful in attracting research funds. Among the many grants our faculty secured this year was a large $6M grant from CPRIT that was awarded to Dr. Jim Liu and his colleagues in the Center for Translational Cancer Research. This CPRIT grant is designed to help cancer researchers from all around Texas take advantage of unique expertise at IMM to progress biological therapeutics through early pharmaceutical evaluation. One example of such biology is antibody-based drugs that are used to treat cancer, which will be the topic of the IMMpact symposium this year.

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 year John Macdonald has stepped down as chair of the council after 3 years of stellar service, and we welcome Alan Baden in his stead.

This brings me to our annual IMM symposium: An illuminating and entertain- ing evening where you can hear exciting research stories directly from our faculty and discuss the implications for the future of medicine and health care. We had to cancel the symposium in 2020 at the start of the COVID pandemic, and for similar reasons did not hold one in 2021, but with vaccinations and boosters now widely available and case numbers dropping fast as I write these introductory comments, we will be going ahead with the 2022 symposium. This will be held at IMM on April 29, and will feature two talks on how antibody-based drugs fight cancer. If you want to hear more about this state-of-the-art technology and how IMM re- searchers are at the forefront of this emerging field of cancer research and treatment, please attend the symposium. 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.

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

Tuesday, April 26, 2022
4:30 pm

Arming antibodies: A new strategy to fight cancer

Drug payloads and designer antibodies: How to build homing anti-cancer missiles
Kyoji Tsuchikama, PhD
Assistant Professor
Texas Therapeutics Institute

Attacking colorectal cancer stem cells with weaponized antibodies
Kendra Carmon, PhD
Assistant Professor
IMM Center for Translational Cancer Research

SAVE THE DATE
Kyoji Tsuchikama, PhD, and his lab have flourished during the pandemic, utilizing new technology to target a variety of diseases.

For many, the last year could be described as challenging, chaotic, and overwhelming. Thanks to a prestigious NIH grant, Kyoji Tsuchikama, PhD, associate professor in the Institute of Molecular Medicine’s Texas Therapeutics Institute, describes the last year as “amazing.”

The R35 grant from the National Institutes of Health provides research support for work within the mission of the National Institutes of General Medical Sciences, allowing an investigator stable funding – up to $750,000 per year for up to 5 years. Such funding allows scientists to focus broadly on their work instead of spending valuable time applying for new grant support.

Tsuchikama’s new R35 grant, “Chemical approaches for generating blood-brain barrier-permeable antibody conjugates” funds research to create a foundation for new antibody agents for brain diseases, including brain cancer, by creating a more efficacious and safer drug-delivery method.

“In the same way we have worked on breast cancer tumors, we are developing novel ADC linker technologies to treat brain diseases, particularly glioblastoma,” he said.

Glioblastoma is the most common occurring malignant primary brain tumor. With about 12,000 cases diagnosed in the United States each year, the average survival time is 12-18 months after diagnosis.

“We are in dire need of improving the drug delivery method,” Tsuchikama said.

The lab is working to take advantage of its technology platform to fight not only cancer but also leverage it for antivirals and other diseases.

“We will try other drug combinations for other non-oncology fields. We have been receiving many requests for collaboration,” Tsuchikama said, adding that they will be developing the ADCs for neurological disorders, such as Alzheimer’s disease, as well as other cancers such as lung and pancreas.

“We are working in animal models now and our next step is to work with experts in each field to see if our molecular platform can work in their models,” he said.

The lab is also funded by the Department of Defense and the Cancer Prevention Research Institute of Texas, a state agency that funds cancer research.

“Glioblastoma is the most common occurring malignant primary brain tumor. With about 12,000 cases diagnosed in the United States each year, the average survival time is 12-18 months after diagnosis.”

Glioblastoma is the most aggressive lethal brain tumor, and poor delivery seems to be the issue for new drugs to treat it. We are in dire need of improving the drug delivery method,” Tsuchikama said.

We need a trick to facilitate reaching the brain. Some drugs are delivered directly to the brain but are invasive – our approach is developing new technologies to facilitate systemic drug delivery of effective antibodies to the brain or brain tumors by intravenous injection.”

— Dr. Kyoji Tsuchikama

Kyoji Tsuchikama, PhD, and his lab have flourished during the pandemic, utilizing new technology to target a variety of diseases.
During the time of the pandemic, there has been a constant disruption. Disruptions in our daily routines, in our interactions with others, and to our sense of time.

Time is central not only to our organized lives but also to our organized bodies. Circadian (i.e. 24-hour) rhythms govern our wake-sleep cycles and responses to light and dark.

Kristin Eckel-Mahan, PhD, associate professor in the IMM’s Center for Metabolic and Degenerative Diseases, focuses her research on circadian rhythms and how their disruptions increase our risk for specific diseases or disorders.

“Historically, circadian rhythms were thought to be primarily controlled by the brain because part of the hypothalamus is directly responsive to light and dark. But the truth is that circadian rhythms occur at a cellular level and in almost all cells of the body. Rhythms occur at the level of gene expression and metabolic pathway activity at the cellular level,” Eckel-Mahan explained.

People with disruption in their circadian clocks – such as those who work night shifts, or stay up too late – move their natural rhythm out of sync. This often involves an eating phase no longer coordinated with the light or active phase. Research shows those out of sync increase their risk of adverse cardiovascular events such as arrhythmias, obesity, and Type 2 diabetes.

Eckel-Mahan and her colleagues seek to understand other connections to disease and circadian disruptions, including connections with obesity and aging, gastric disorders, and cancer.

Working with colleague Mikhail Kolomnin, PhD, Harry E. Bovay, Jr. Distinguished University Chair in Metabolic Disease Research, Eckel-Mahan is looking at the role of the circadian clock in fat tissue and its changes during a 24-hour cycle. “In this study, we are trying to understand how the circadian clock preserves a healthy fat pad throughout the aging of an organism,” she said, adding that they study tissue from gastric bypass surgery patients.

Studying the circadian clock’s role in gastrointestinal function, Eckel-Mahan is partnering with Rick Wetsel, PhD, Hans J. Muller-Eberhard, MD, PhD, and Irma Gigli, MD, Distinguished Chair in Immunology, in an investigation of the complement cascade — part of the body’s immune system. “Epidemiological studies show an increased incidence of irritable bowel disease and other gastrointestinal disorders that we think involves circadian disruptions of the complement cascade,” she said. “Some of these immune response pathways undergo 24-hour changes in activity, and depending on when you apply a toxin, you can get a different immune response.”

Timing treatments (often referred to as “chronotherapy”) also may produce different responses based on our internal circadian rhythms, Eckel-Mahan said. “The time of drug delivery may improve efficacy and reduce toxicity — this is at the forefront of all of our research,” she added.

Cancer is another area Eckel-Mahan and her colleagues are studying for clock connections. Working with scientists at MD Anderson Cancer Center, Eckel-Mahan is evaluating the circadian links associated with the natural flavonoid Nobiletin, a circadian modulating compound extensively investigated by Zheng (Jake) Chen, PhD, associate professor of Biochemistry and Molecular Biology, when applied to acute myeloid leukemia cells.

Her lab is also studying its effects in the context of hepatocellular carcinoma. “We have administered this compound in vivo in mice and have seen accelerated cell death and delayed tumor progression in response,” she explained.

Other ongoing work involves early stage liver disease, including non-alcoholic fatty liver disease, which is a direct result of the obesity epidemic and serves as a risk factor for developing fibrosis and hepatocellular carcinoma. “We think that a high-fat diet decreases the expression of a tumor suppressor in the liver that has circadian activity. The result is circadian activation of proliferation genes that promote tumor formation and progression” she said.

Just one more reason to restore balance in our lives.
After a decade teaching chemical engineering, a new Institute of Molecular Medicine recruit decided to dedicate 100 percent of his effort to a new professional challenge—biomedical research.

Alex Ge, PhD, associate professor with the Texas Therapeutics Institute, joined the IMM in July 2021, serving on the faculty at the University of California, Riverside, where he taught chemical engineering to undergraduate students, in addition to biochemical research.

“Chemical engineering is a well-established discipline,” he admitted. “With biomedical research, there is more freedom, and it has more impact.”

Ge earned his PhD in chemical engineering at McMaster University in Canada and completed postdoctoral training at The University of Texas at Austin.

“During my postdoc training, I worked with biomedical antibodies, and that is what sparked my vision to pursue this direction,” he said, adding that the IMM was the perfect opportunity to develop antibodies in a supportive research environment.

An engineering background gives Ge a unique perspective for research.

“I like challenging targets,” he said. “The engineer in me likes to take things apart to solve problems. Even when I was a boy I would take things apart, and I remember my mom reminding me to put things back together.”

Ge’s research is funded by the National Institutes of Health (NIH) and Department of Defense and focuses on creating antibodies for treatments in areas as various as cancer, pain, stroke, obesity, and snake venom.

His R21 grant from the NIH, considered a “try out” grant on an interesting topic with great need, concerns poisonous snake bites.

According to the NIH, between 7,000-8,000 people in the United States are bitten by a venomous snake each year, with up to 44 percent sustaining long-term injury and five dying. Current antivenom therapy, over a century old, is created by injecting poisonous snake venom into horses and harvesting the resulting antibodies, which are expensive, often ineffective, and may even cause major allergic reactions.

Ge and his colleagues are working on a new method to treat venomous snake bites with new antibodies.

“The action of venom among snakes is similar,” Ge said, “but it contains a spectrum of toxins, so there is a level of complexity. We are starting with the most significant snake in North America, the rattlesnake.”

One major toxic enzyme found in rattlesnake venom interferes with the bloodstream, kicking off a reaction cascade causing severe bleeding. Ge and his colleagues are aiming to specifically block this fatal snake toxin with antibodies developed in the lab.

To get the venom for testing, Ge traveled to the only federally funded Viper Resource Center in the United States. Located in Kingsville, Texas, the National Natural Toxins Research Center is supported by the NIH and Office of Research Infrastructure Programs and houses many snakes.

“When we walked into the room, all of the rattles started making noise— that signals that the rattlesnake wants to strike,” Ge recalled, adding that all of the snakes were in cages.

Although the current research is focused on the rattlesnake, if successful, it could be applied to other poisonous snakes.

“Sometimes you need an engineering mind to consider new ways and new technologies,” he said.
An and his lab decided to create a therapy using IgM antibodies instead of IgG antibodies, which are currently found in emergency-use authorization COVID treatment. The IgM antibodies are 10-valent (10-armed), meaning they can bind up to 10 viral spike proteins at once, versus the IgG antibodies, which are two-armed. More “arms” provides a stronger connection and more possibilities to attach to the virus.

“I knew the virus would mutate, and we needed our antibody to work in the future,” An explained of the IgM choice.

In addition to using the IgM antibodies, An said he and his group carefully chose a nasal delivery to directly target the respiratory tract, thereby using less drug and in a more convenient manner than the current intravenous antibody treatments.

“Respiratory mucosal antibodies are key to clearing SARS-CoV-2 infection and reducing viral transmission, and IgM antibodies are nature’s first line of defense against pathogens such as viruses,” An explained. “The current emergency-use authorization antibodies, which are all IgG antibodies, are administered intravenously at high doses and don’t directly target the main sites of infection.”

Research published in the July 3, 2021 issue of *Nature* found that the team’s IgM antibody nasal spray provided a broad coverage of COVID variants of concern and interest and was 230 times more effective at neutralizing SARS-CoV-2 than the IgG antibody they first tested.

“Our antibody can neutralize the virus,” said An, holder of the Robert A. Welch Distinguished University Chair in Chemistry.

The nasal spray, which has been licensed to IGM Biosciences for drug development, is now being tested in humans in the United States and South Africa.

An said the nasal spray could be an effective alternative to the ubiquitous mask. “Say you were going to a party and wanted to be protected – you could use the nasal spray in advance. Or, if you were at an event and someone was sick, you could use the spray afterwards and be protected for up to two weeks,” An said.

The nasal spray is just one of 10 drugs currently in development from TTI. With a focus on drug discovery and development, the institute’s investigators and collaborators have garnered more than $25 million in research support from NIH, CPRIT, DoD, and the biotechnology/pharmaceutical industry in the last five years.

“TTI is an antibody drug discovery platform,” An said. “Our lab is working on the cutting edge and being responsive – that is what we are here to do. We are here to immediately respond to public health emergencies and create drugs that can help.”
We hold dear our family traditions—from a daily moment at the dinner table to celebrating holidays. The Institute of Molecular Medicine is proud to have been a part of the Runnells’ family tradition of philanthropic support for decades.

Nancy and Clive Runnells created the Nancy and Clive Runnells Foundation in 2000, which is built upon the strong family principles of giving back. Clive’s mother, Mary Withers Runnells, instilled the value of philanthropy in Clive at a young age, recalled his widow, Kathy Smyth. “Clive had a strong belief in philanthropy. He often said, ‘if you don’t do something for others, you ain’t worth a!”’ Smyth said.

Clive Runnells connected to the IMM back in 2004, when he reached out to Rick Wetsel, PhD, director of the IMM’s Hans J. Muller-Eberhard and Irma Gigli Research Center for Immunology, whom he had read about in the Houston Chronicle. “He asked me how much it would take to jump start my research, and I told him $100,000,” recalled Wetsel, holder of the Hans J. Muller-Eberhard, M.D., Ph.D., and Irma Gigli, M.D. Distinguished Chair in Immunology. “I didn’t know if I was asking for too much, or too little. He told me he would have to talk to his wife.” That started Wetsel’s long friendship with the Runnells, who continued to support his stem cell research over the years. “Clive loved getting to know the grant recipients personally and made many lasting friendships,” Smyth said. “His primary interests were medical research and conservation.”

The generous support made a great difference for Wetsel’s research. “Those philanthropic funds have made it possible to develop four of our own stem cell lines – two of which are approved by the National Institutes of Health,” Wetsel said.

The Runnells’ unwavering support of stem cell research was personal. Clive and his wife Nancy’s son, Pierce, suffered a debilitating back injury due to a devastating skiing accident and died before the promise of stem cell therapy could be realized. Clive and Nancy had instilled the value of giving back in Pierce, who, in turn, created the Pierce Runnells Foundation. Pierce died in 2007, Clive died in 2019, and Nancy died in 2016, but their foundations live on in continued support of IMM research.

Today, four trustees work together on these two family foundations to continue the legacy of Nancy and Clive Runnells and their son Pierce Runnells. Smyth leads the Nancy and Clive Runnells Foundation, and Jeff Firestone oversees the Pierce Runnells Foundation.

The foundations continue to support stem cell applications, including preclinical studies of the role of stem cells for correcting cleft palate, headed up by Charles Cox, MD, holder of the George and Cynthia Mitchell Distinguished Chair in Neurosciences; macular degeneration, overseen by Wetsel; and an investigative trial of the use of stem cells in improving stroke outcome, led by Sean Savitz, MD, director, UTHealth Institute for Stroke and Cerebrovascular Diseases and Frank M. Yatsu, M.D., Chair in Neurology.

“Since being introduced to the IMM at an IMMPact Symposium, I have had the pleasure of visiting with some of these dedicated professionals, who have dedicated their lives to their important work,” Smyth said. “I am grateful for what they do, and it is an honor and a privilege to be able to support their work.”
identified new disease-causing genes and have probands and family members. These studies have (ACM). Pathogenic and causal variants are associated with cardiomyopathies, including hypertrophic cardiomyopathies: We have a repository of several hundred cases and their family members. The findings provide the platform for large-scale multi-center efficacy clinical trials. The findings in the model systems are targeted through genetic and pharmacological pathways identified through integrated genomics and epigenetic studies of family members.

III. DNA damage response in human cardiomyopathies: We have detected increased double stranded DNA breaks (DSBs) in human hearts from patients with hereditary cardiomyopathies and in mouse models. Studies are ongoing to define genomic characteristics of DSBs and to define the pathogenic role of DNA damage response pathways in heart failure. 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. A major focus currently is on the canonical WNT and the Hippo signaling pathway.

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. The Center also participates in industry sponsored clinical trials in cardiomyopathies.

Molecular genetics, genomics, pathogenesis, and treatment of hereditary cardiomyopathies

Our long-standing research objectives have been to delineate the molecular genetics, genomics, and pathogenesis of hereditary cardiomyopathies in humans and apply the discoveries to prevent the evolving and reverse the established phenotypes of heart failure and sudden cardiac death. We have active research programs in three common forms of hereditary cardiomyopathies: Hypertrophic Cardiomyopathy (HCM): HCM is the most common form of hereditary cardiomyopathies, affecting ~1 in every 500 individuals in the general population. The affected individuals are hypertrophic, asymptomatic, and sudden cardiac death is often the first manifestation of this disease. HCM is the most common cause of sudden cardiac death in the young. While there are effective therapies to alleviate patient’s symptoms, there is no effective therapy to prevent or reverse the disease process. Dilated Cardiomyopathy (DCM): DCM is genetically the most heterogeneous form of hereditary cardiomyopathies and a major cause of heart failure and heart transplantation in the young. The affected individuals are often present with symptoms of heart failure, cardiac arrhythmias and sometimes, sudden cardiac death. There are a number of effective pharmacological and non pharmacological therapies for DCM, but currently there is no cure for DCM. The overall approach integrates human molecular genetics studies through high-throughput whole exome and genome sequencing to identify the causal genes and the pathogenic variants, followed by genomic studies including transcriptomics and epigenetics to define the molecular remodeling of chromatin in the presence of causal mutations. The aim is to identify the pathogenic pathways and intervention, genetically or pharmacologically, to prevent, attenuate, or reverse the phenotype, initially in mouse models and ultimately in human patients.

Our lab has been a leader in elucidating the interactions between the epigenetic regulators of gene expression and the key regulatory proteins that control cardiac remodeling by ChIP-sequencing. Specific genetic discoveries are then coupled with the genomic studies to identify differentially expressed coding and non-coding transcripts and dysregulated pathways, chromatin remodeling, and DNA methylation in cardiomyopathies. The integrated approach is aimed to identify the key dysregulated pathogenic pathways for preventive and therapeutic genetic and pharmacological interventions. The findings in the model systems are extended to human patients through pilot randomized placebo-control double-blind studies clinical trials. The findings provide the 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, including hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), and arrhythmogenic cardiomyopathy (ACM). 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 predominantly relate to DCM and ACM and include whole transcriptome analysis by RNA-Seq, DNA methylation analysis, and analyzing chromatin remodeling by ChIP-sequencing. Specific genetic regulators of gene expression are identified and targeted in order to delineate their functions in the heart.

IV. Pharmacological suppression of the WNT signaling pathway attenuates age-dependent expression of the phenotype in a mouse model of arrhythmogenic cardiomyopathy (ACM). Pathogenic gene mutations in cardiac adipocytes. There is no effective therapy for ACM.

V. 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. A major focus currently is on the canonical WNT and the Hippo signaling pathway.

VI. 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.

Lab Members:
Research technician: Saman Asghari
Research nurse: Yanli Tan, RN
Research and clinical nurse: Yarih Tan, PhD

Molecular genetics, genomics, pathogenesis, and treatment of hereditary cardiomyopathies

Our long-standing research objectives have been to delineate the molecular genetics, genomics, and pathogenesis of hereditary cardiomyopathies in humans and apply the discoveries to prevent the evolving and reverse the established phenotypes of heart failure and sudden cardiac death. We have active research programs in three common forms of hereditary cardiomyopathies: Hypertrophic Cardiomyopathy (HCM): HCM is the most common form of hereditary cardiomyopathies, affecting ~1 in every 500 individuals in the general population. The affected individuals are hypertrophic, asymptomatic, and sudden cardiac death is often the first manifestation of this disease. HCM is the most common cause of sudden cardiac death in the young. While there are effective therapies to alleviate patient’s symptoms, there is no effective therapy to prevent or reverse the disease process. Dilated Cardiomyopathy (DCM): DCM is genetically the most heterogeneous form of hereditary cardiomyopathies and a major cause of heart failure and heart transplantation in the young. The affected individuals are often present with symptoms of heart failure, cardiac arrhythmias and sometimes, sudden cardiac death. There are a number of effective pharmacological and non pharmacological therapies for DCM, but currently there is no cure for DCM. The overall approach integrates human molecular genetics studies through high-throughput whole exome and genome sequencing to identify the causal genes and the pathogenic variants, followed by genomic studies including transcriptomics and epigenetics to define the molecular remodeling of chromatin in the presence of causal mutations. The aim is to identify the pathogenic pathways and intervention, genetically or pharmacologically, to prevent, attenuate, or reverse the phenotype, initially in mouse models and ultimately in human patients.

RESEARCH PROJECTS

Identification of causal genes for heart failure and sudden cardiac death with a focus on oligogenic nature of the phenotype in small families and sporadic cases.

Validation of the role of the mechanosensing signaling pathways, namely the Hippo and the canonical WNT pathways, in the pathogenesis of hereditary cardiomyopathies.

Defining and characterizing the role of DNA damage response pathway in hereditary cardiomyopathies and the beneficial effects of blocking the DNA damage repair (DSB repair) in attenuating the heart failure phenotype.

Multi-center phase II/III double blind placebo controlled clinical trials to test efficacy of a myosin heavy chain 7 ATPase modulator on improving symptoms, exercise tolerance and left ventricular wall motion obstruction in patients with obstructive hypertrophic cardiomyopathy.

KEY PUBLICATIONS


Priyataksh Gurha, PhD
Assistant Professor

Molecular mechanisms and functions of Non-coding RNAs and epigenetic regulation in heart failure

RESEARCH PROJECTS
• Role of lncRNAs in the pathogenesis of cardiomyopathies and heart failure.
• Identification and characterization of molecular mechanisms and functions of lysine demethylases KDMs in cardiomyopathies and heart failure.

KEY PUBLICATIONS


LAB MEMBER
Post-doctoral fellow: Maniotty Davidpudi

The main objective of my research is to understand the molecular mechanisms that contribute to the regulation of non-coding RNAs in relation to various cardiovascular diseases. Understanding these mechanisms will enable us to develop new therapeutic strategies targeting non-coding RNAs for the treatment of diseases.

Progress in the laboratories of our investigators under the direction of our Center for Human Genetics and Genomics works to generate new understanding about genetic risk for common cardiovascular diseases and to use that information to identify pathways leading to new therapies for these diseases. High blood pressure is an amplifying element that drives cardiovascular disease risk from stroke, heart and kidney disease. These diseases emerge in middle and later life and so 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 re-shape the biological pathways in which disease emerges.

An emerging concept developing in our laboratories is that an important element of chronic disease of the cardiovascular system is that these diseases involve 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 also can create risks of disease even 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 our Center for Human Genetics, 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 disturbances 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. Doris and his group have shown that kidney injury associated with increased blood pressure results from the emergence of auto-antibodies that damage tissues. His work has led to a recognition that we currently cannot assess – the role of complex hypervariable immune genes in disease risk – as we lack an understanding of genome sequencing and assembly methods to overcome this limitation. 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 toward new insights and new opportunities for disease prevention.
High blood pressure is a frequent cause of renal injury, but the risk of renal disease in patients with high blood pressure is best predicted by family history, indicating a genetic predisposition. At present, we have almost no knowledge of why high blood pressure creates kidney disease in some people but not others. To try to fill this knowledge gap, we study a genetic model comprising hypertensive laboratory rats that have high blood pressure. The divergence of hypertension renal risk seen in humans is also present in these rats. Some lines get progressive renal injury, and other lines don’t. Therefore, this model provides a means to investigate what genetic differences can drive kidney disease. We can take what we have learned and conceive of something very similar for one of the cardiovascular disease models we work with. The rightmost plot shows how improved genome assembly with this method uses nanofluidics to identify the relationship between very long strands of DNA from the genome. Going from right to left we see annotation of gene expression.

Improving the structural accuracy of the rat genome. These “circos” plots of show rat chromosomes that have been assembled by optical mapping. This method uses nanofluidics to identify the relationship between very long strands of DNA from the genome. Going from right to left we see that the newer genome alignment shows important differences from an older version that did not rely on optical mapping. The middle plot shows something very similar for one of the cardiovascular disease models we work with. The rightmost plot shows how improved genome assembly with optical mapping results in much better concordance indicating fewer genome errors.

Genetics of cardiovascular end organ injury

Peter A. Doris, PhD
Professor/Center Director
Mary Elizabeth Holdsworth Distinguished University Chair in Metabolic and Inflammatory Disease Research

In rats, we study a genetic model comprising inbred rat models of human cardiovascular disease. This project uses the most recently developed sequencing technologies and will include multi-omics annotation of gene expression. Key questions that are the focus of our current interest are:

1. Do the pathogenic mechanisms active in rats give insight into renal disease in humans? Common genetic variants occur in humans that alter the control of antibody formation and may contribute to disease risk.

2. Do the pathogenic mechanisms active in rats give insight into renal disease in humans? Common genetic variants occur in humans that alter the control of antibody formation and may contribute to disease risk.

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Disorganized electrical signals. VF is usually uncoordinated contraction of cardiac muscles ventricular fibrillation (VF), an irregular and underlying cardiovascular condition. Although cardiovascular diseases. Moreover, in almost of deaths in the United States (~500,000 each year) and accounts for ~15% of all-cause deaths and ~25% from cardiovascular disease. Moreover, in almost half the cases, SCD is the first sign of an underlying cardiac 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 corrected 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 environmentally 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 various diverse forms of heart diseases leading to SCD into one group. Instead, we focus on the electromechanophysical (E-M-P) interval, an intermediate observable characteristic that predisposes to SCD. Electromechanophysiology, also known as E-M-P, measures the electrical activity of heart chambers and the OT interval in an electromechanophysiological corresponding to the time taken by ventricles to depolarize (activated state) and repolarize (resting state) in every heart beat. In the general population OT interval varies across individuals and is a useful clinical marker as both progression and shortening of the OT 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 OT interval variation will potentially impact our understanding of SCD risk and its management. Our study aims to identify the genetic causes for OT interval variation, some of which in turn could serve as potential therapeutic (drug targets or potential biomarkers (genes and protein 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 OT interval variation and that majority of DNA changes leading to OT interval variation do not alter the form of the gene product rather by altering the amount of the gene product made by our heart cells. Starved with known genetic associations between DNA sequence variants and the OT interval in the general population, our work involves pinpointing the causes behind those associations to identify the underlying gene defects and how they impact OT interval.

RESEARCH PROJECTS
Molecular characterization of OT interval genome wide association study (GWAS) signals to identify the underlying causal variants, genes, and their mechanisms.

LAB MEMBERS
Research assistant: Ernesto Sanchez, BS
Undergraduate trainees: Supriya Katiyan, data

Role of non-coding cis-regulatory sequence variation in cardiac arrhythmias and sudden death risk

Kapoor A, Aiyar S, Wang SJ, Mifsud J, Chen Z, Bollinger J, Jan VR, Santos D, Mandel M, Prakash S, Bruns S, Shir driven by homeomorphosis (HOMF), lead to the development of a humanized mouse model to study heart disease. In the humanized mouse model, the entire genome of a human individual is transplanted into a mouse to study the disease. This model allows researchers to observe the effects of human-specific genetic variations on heart disease development. Researchers can use this model to identify potential therapeutic targets and develop new treatments for heart disease.

GT interval associated common noncoding variant rs1171007 at SCN5A acts as a cis-regulatory element with allele-specific in vitro luciferase reporter activity in HEK1 cardio myocytes (left). Representative images of in vitro transient electroporation activity of rs1171007 reference allele at 3 days of subcutaneous transfection (right).

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 transcriptomic (i.e. they focus on measuring mRNA levels and levels of transcription factor binding). While these efforts revealed intricate networks of cooperatively acting transcription factors in shaping complex biological processes, much of the post-transcriptional regulation is left unexplored. It remains unclear whether the process of protein translation is regulated by a network of factors in an extent of complexity similar to transcription regulation. We ask questions such as “Do sequences specific mRNA binding proteins (mRBP) cooperate in controlling translation?” Are there translational regulatory networks that orchestrate critical biological processes? The 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 mRBP binding, to investigate regulatory functions of upstream Open Reading Frames (uORFs), and to integrate these functional genetics 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 studies of a handful of uORFs. We have reported a systematic survey of uORF impact on protein translation and identified genetic variants associated with the impact (Figure 1). We are further expanding this line of research in the context of stress response, where global scale changes in translational are expected. Life-saving binding protein footprint sequencing to investigate translational regulation of protein synthesis. mRBP 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 new tools 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 mammals.

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 is often buffered by the protein level through post-translational processes (Figure 2). In order to evaluate how gene expression can be buffered, we are now expanding our analysis to other tissue types and species.

KEY PUBLICATIONS
Wang SJ and Elgin SDR. The impact of genetic background and cell lineage on the level and pattern of gene expression in position effect variegation. [Genomics & Development. 2017;12(3)]

LAB MEMBERS
Post-doctoral fellow: Sandeep Bansal

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

Ashish Kapoor, PhD
Assistant Professor

Sidney Wang, PhD
Assistant Professor

CENTER FOR HUMAN GENETICS

Role of non-coding cis-regulatory sequence variation in cardiac arrhythmias and sudden death risk

Kapoor A, Aiyar S, Wang SJ, Mifsud J, Chen Z, Bollinger J, Jan VR, Santos D, Mandel M, Prakash S, Bruns S, Shir driven by homeomorphosis (HOMF), lead to the development of a humanized mouse model to study heart disease. In the humanized mouse model, the entire genome of a human individual is transplanted into a mouse to study the disease. This model allows researchers to observe the effects of human-specific genetic variations on heart disease development. Researchers can use this model to identify potential therapeutic targets and develop new treatments for heart disease.

GT interval associated common noncoding variant rs1171007 at SCN5A acts as a cis-regulatory element with allele-specific in vitro luciferase reporter activity in HEK1 cardio myocytes (left). Representative images of in vitro transient electroporation activity of rs1171007 reference allele at 3 days of subcutaneous transfection (right).
The investigators of the Hans J. Müller-Eberhard and Irma Gigli Center for Immunology and Autoimmune Diseases are examining the molecular, cellular, and genetic bases of several different allergic, autoimmune, and infectious diseases. These studies explore the nature, structure, and function of specific cell membrane receptors and their ligands in modulating immune and inflammatory responses.

In concert with the molecular studies, the Center's scientists have engineered mice with specific targeted gene mutations or deletions that are used as models for human disease. These animal studies have facilitated the identification of key gene products that play significant roles in regulating the immune system, as well as for major eye diseases, including macular degeneration and diabetic retinopathy.

Research interests include:
- Asthma and Sinusitis
- Diabetic Retinopathy
- Muosal Immunology & Autoimmunity
- Microbial Infectious Disease
- Acute Lung Injury and COPD
- Lung Surfactant Deficiencies
- Macular Degeneration
- Pulmonary Regenerative Medicine

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. According to our laboratory, the past several years have focused on defining 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 cell surface 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 migration, 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 our ongoing research program, we are investigating the therapeutic use of entryway (H5F) and inducible protein (IP1) 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 are 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 iPSC derived lung cells for surfactant protein deficiencies
- Develop NS-3/4a specific lipid inflammatory cell therapies for treatment of AMD

KEY PUBLICATIONS

LAB MEMBERS
Senior research associate: Aleksey Y. Domoshnin, PhD

Rick Wetsel, PhD
Center Director & Professor
Hans J. Müller-Eberhard, MD, PhD and Irma Gigli, MD Distinguished Chair in Immunology

Innate immunity, inflammation, infectious diseases, and stem cell therapeutics for diseases of the lung and eye

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 entryway (H5F) and inducible protein (IP1) 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.
Adenosine signaling and the regulation of chronic lung disease

- Novel regulation of mPPLA by A2B adenosine receptors in the regulation of pulmonary fibrosis and chronic obstructive pulmonary disease (COPD)
- Examination of the hypoxia as an amplifier of chronic lung diseases
- Understanding new mechanistic roles for IL-6 signaling in pulmonary fibrosis
- Systems biology approaches to understand the progression of chronic lung disease

**KEY PUBLICATIONS**


**LAB MEMBERS**

Assistant professor: Tingting Wang, PhD
Senior research scientist: Kelly Volko, PhD
Research associate: Ning Yuan Chen
Research scientist: Jœuvre Milina, St.
Graduate student: Jinho Kim, PhD

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

**Environmental triggers regulating innate immune responses in chronic airway inflammation**

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

A central hypothesis of my laboratory is that the signaling molecule adenosine is an amplifier of lung inflammation and damage. Adenosine is generated in response to cell damage, and it is our belief that adenosine levels increase in the lung tissue following pathways that damage pulmonary epithelial and inflammatory cells. Most of the projects in my laboratory focus on understanding the mechanisms by which adenosine signaling influences the activities of these cells in the context of lung inflammation and remodeling. We use a combination of genetically modified mice to examine the role of adenosine signaling in chronic lung disease. This includes knockout mice of components of adenosine metabolism and signaling. We make extensive use of genetical mouse models to explore disease-relevant cell types and work extensively with human-embryonic-lung derived organoids following lung transplantation to understand the factor(s) and mechanisms to human disease.

**RESEARCH PROJECTS**

- Examining the role of A2B adenosine receptor expression on pulmonary macrophages during the progression of pulmonary fibrosis
- Investigation of adenosine transport in acute and chronic lung injury

**REFERENCES**

Dvor 40 million Americans suffer from chronic rhinosinusitis (CRS), which causes facial pain and pressure, nasal congestion, and obstruction. These symptoms ultimately drive considerable 18.2 million physician visits yearly with an annual direct healthcare treatment cost of over $3 billion. In addition, patients suffering from CRS often are diagnosed with asthma, specifically those characterized by nasal polyps (NP)-NP. Together, asthma and CRS as chronic respiratory diseases represent some of the most prevalent chronic illnesses in the United States. Despite the 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 studying chronic inflammatory respiratory diseases. CRS patients often undergo surgery providing an opportunity to examine critical tissue and are seen regularly in clinic, which allows periodic evaluation of the patient and disease course.

Our laboratory is interested in the molecular characterization of fungi-mediated signaling responses in chronic airway inflammation and the protocols to evaluate the sinus inflammation.

**RESEARCH PROJECTS**

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

**KEY PUBLICATIONS**


**LAB MEMBERS**

Hua Sun, PhD, Ying Li

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**KEY PUBLICATIONS**


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**KEY PUBLICATIONS**


**LAB MEMBERS**

Hua Sun, PhD, Ying Li
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 investigated 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 age-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 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?
- How do the brain and peripheral clocks control energy balance and metabolism?
- How does the hepatic circadian clock protect against fatty liver disease and liver cancer?
- How does the brain control glucose homeostasis in diabetes?
- What are the functions of the genes mutated in neurodegenerative diseases?
- How does disruption of membrane trafficking and cell homeostasis cause neurodegeneration?
- How does stress accelerate the onset and progression of Alzheimer’s disease?
- How does bearing children contribute to late-life onset of depression, anxiety, and dementia?

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

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

A model of CD36-mediated outside-in and inside-out LCFA transport. Insulin signaling activates extracellular long chain fatty acid (LCFA) uptake mediated by acylated transport CD36 at the cell surface in complex with co-transporters PMB and AM2. Disruption of CD36 enables vascular endothelial and lipid droplet trafficking of LCFA-bound CD36. In lipid-poor conditions, CD36 dissociates, cargo entropies, and lipid uptake trafficking enable CD36 loading with LCFA released from lipid droplets and mobilization from this cell.

My group is interested in the mechanisms underlying aging-related diseases and developing new approaches to target them. We focus on the roles 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. This year, we have published several reports on the mechanisms and role of fatty acid transport in the context of type-2 diabetes and cancer. Another research direction is focused on the role of inflammatory signaling and fat tissue remodeling in metabolic response to anti-diabetes drugs. 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). In obesity, ASCs over-proliferate and undergo replicative senescence, hence, aging-related aging. This was revealed by our studies in mice lacking rat telomerase (TERT) 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 have discovered that chronic disease tissues recruit ASCs, which can halt cancer and chronic 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 have also applied ablation of ASC as a new therapeutic approach to diabetes and muscle dysregulation treatment. Recently, we reported a panel of peptides that can be used for non-invasive detection and imaging of metastatic cancer cells and their conversion to therapeutic blocking cancer progression.
Regulation of muscle nutrient use in type 2 diabetes regeneration

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

**KEY PUBLICATIONS**

**LAB MEMBERS**
Post-doctoral fellow: Antonios Stavrides
Graduate student: Muchen Liu
Research assistant: Elena Dykova, Mark Rosenfeld

**Skeletal muscles of people with diabetes 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 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 identified a hidden route to stimulating efficient nutrient use by skeletal muscle and improving health of people suffering from type 2 diabetes.**

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**Circadian rhythms in health and disease**

The goals of my lab center on the importance of our internal 24-hour biological clock in health and disease prevention. The circadian clock is an exquisite time-keeping system present in all cells of our body that drives daily rhythms in physiology and tissue-specific function. Examples of our internal clock at work include the sleep-wake cycle, variations in internal body temperature, and rhythmic hormone or neurotransmitter secretion. Our 24-hour clock aligns to, and anticipates the rotation of, the earth on its axis. Recent evidence from large epidemiological studies reveals that chronic circadian disruption increases our risk of several diseases. 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 various metabolic diseases. We are trying to understand why circadian disruption produces these effects.

While the ‘central pacemaker’ of our brain, the suprachiasmatic nucleus of the hypothalamus, keeps us entrained to our 24-hour environment via light activation of the retina, other environmental factors can prominently control 24-hour rhythms in several peripheral organs (for example, liver, kidney, adipose tissue, and muscle). Poor quality nutrients as well as food intake at the wrong time not only compromise tissue-specific function, but also promotes body-wide circadian clock ‘disynchrony’. Collectively, these defects in circadian rhythms intimately increase our risk of metabolic disease. This lab is currently trying to understand why environmental factors are most important for tissue-specific clock function and the mechanisms by which tissue-specific clocks protect against metabolic disease. Circadian nutrient excess disrupts 24-hour rhythms in several insulin sensitive tissues that become insulin resistant under condi-
High levels of stress lead to persistent anxiety that can cause and contribute to the development of devastating mental illnesses, most commonly depression, generalised 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. Parkinson’s disease. In addition, high levels of stress promote normal loss in memory that occurs with age. Our 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**

- At the IMM, we have developed many genetic tools that make it possible to perform experiments that test the function of genes involved in diseases. We now manipulate activity of circuits while at the same time monitoring behavior and changes in physiological function in freely behaving animals. Our first discovery in the lab was a new class of hypothalamic neurons that we demonstrated is critical for controlling behavioral, autonomic, and hormonal stress responses. As we have continued our studies of this new class of neurons, we have found they play additional roles by transmitting signals, from Corticotropin Releasing Factor (CRF) neurons to other neurons to influence behavioral and autonomic features of the stress response.

- In our lab at the IMM, 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, uncontrollable 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. We hope to use the information we gain to develop therapeutic strategies to treat debilitating movement-related symptoms caused by neurodegenerative diseases and other diseases that impact the ability to control movement.

- Understanding how the stress response leads to acute and chronic mental illness in mothers. We identified a mechanism by which the stress-released neuropeptide, CRF, directly influences the brain regions, which occurs only in postpartum mothers who have recently given birth. We are currently experimentally testing how the maternal specific CRF signaling to Daytime secretion, which occurs only in postpartum mothers who have recently given birth. We are currently experimentally testing how the maternal specific CRF signaling to Daytime secretion, which occurs only in postpartum mothers who have recently given birth.

The impact of stress on psychiatric and neurodegenerative diseases

Nicholas Justice, PhD
Associate Professor

**The impact of stress on psychiatric and neurodegenerative diseases**

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, uncontrollable 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. We hope to use the information we gain to develop therapeutic strategies to treat debilitating movement-related symptoms caused by neurodegenerative diseases and other diseases that impact the ability to control movement.

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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. PGC-1α). We use a wide-ranging approach, including genetically engineered mouse models, disease models, high throughput gene expression analysis (e.g. RNA-sequencing, CRP-sequencing), pharmacology and signal transduction and in vitro systems in our studies. These tools we are being used to investigate the role of ERRs and PGC-1α in (I) the cellular processes such as gene and RNA expression, mitochondrial biogenesis and angiogenesis; (II) physiological phenomena such as exercise adaptation and whole body metabolism; as well as (III) diseases such as obesity/diabetes, peripheral arterial disease, and muscular dystrophy. Our ongoing work has uncovered the therapeutic role of estrogen-related receptors (ERRs) via metabolic and angiogenic regulation in peripheral arterial disease and skeletal muscle. ERR expression boosts neo-angiogenes is (post-doctoral fellow) Dr. Nus Naran

**LAB MEMBERS**

Research scientist: Shrikanth Rajaman-
silam, PhD

Post-doctoral fellow: Liara Uptapatma,
PhD
Kai Sun, MD, PhD
Associate Professor

Adipose tissue remodeling, metabolic health, and cancer development

RESEARCH PROJECTS
- Hypoxia induced pathological changes in adipose tissue.
- Sympathetic innervation in adipose tissue and energy expenditure.
- Reversibility of adipose tissue fibrosis by novel anti-fibrotic therapies.
- Dynamics of lipid droplets, metabolic regulation and tumor development.

KEY PUBLICATIONS

C3EST levels are correlated with the death rate of cancer by meta-analysis. A. C3EST is enriched in the liver and its levels are significantly increased in the liver tumors. B: C3EST levels are positively correlated with the death rate of cancer.


LAB MEMBERS
Post-doctoral fellows: Xin Li, MD, PhD, Qing Li, PhD
Research assistant II: Shuyue Wang, MS

Qingchong Tong, PhD
Professor
Cullen Chair in Molecular Medicine

Brain control of metabolism

RESEARCH PROJECTS
- Novel neurons and neural pathways for feeding regulation and its relation with emotional states.
- Brain mechanisms mediating blood pressure responses on energy and glucose, and their involvement in obesity and diabetes pathogenesis.
- Chronic stress and obesity development.

The current obesity epidemic and its associated metabolic syndrome has 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, thereby providing conceptual and effective targets for prevention and treatment of eating disorders, obesity, and its associated diabetes.

To toward those goals, we employ various animal models in combination with state-of-the-art techniques, including electrophysiology, optogenetics, chemogenetics, and in vivo live imaging. Crucial to this effort is the identification of novel genes that are enriched in neuron-specific samples from the brain. We are also exploring the use of CRISPR/Cas9 genome editing technology to achieve neuron-specific gene deletion in mouse models and human. These advanced techniques ensure our studies are effective and conclusions are insightful.

One major direction in the lab is to identify and map novel neurons that underlie the emotion and sleep regulation of the brain to control metabolism and stress responses, through manipulation of hypothalamic corticotropin releasing hormone (CRH) neurons. At Genetic approach of CRH loss. Inactivation of conditional AAV-Dio-CRF virus to one side of the hypothalamic of CRH-Dio mice. Cre-mediated DTA (diphtheria toxin) expression killed CRH neurons in the injection side as well as CRH fibers in the median eminence (ME). B) Genetic approach of CRH deletion. Injection of conditional AAV-Cre-GFP to one side of the hypothalamic of Bred CRH mice. Cre-mediated deletion of the CRH gene eliminated CRH expression in the injected side as well as in Cre-GFP positive CRH neurons fibers in ME. doi: 10.1038/s41467-021-22940-4. PMID: 33976218.

The Figure illustrates genetic approaches to alter the HPA axis, the major neuroendocrine pathway for the brain to control metabolism and stress response. Through manipulation of hypothalamic corticotropin releasing hormone (CRH) neurons At Genetic approach of CRH loss. Inactivation of conditional AAV-Dio-CRF virus to one side of the hypothalamic of CRH-Dio mice. Cre-mediated DTA (diphtheria toxin) expression killed CRH neurons in the injection side as well as CRH fibers in the median eminence (ME). B) Genetic approach of CRH deletion. Injection of conditional AAV-Cre-GFP to one side of the hypothalamic of Bred CRH mice. Cre-mediated deletion of the CRH gene eliminated CRH expression in the injected side as well as in Cre-GFP positive CRH neurons fibers in ME. doi: 10.1038/s41467-021-22940-4. PMID: 33976218.


LAB MEMBERS
Assistant professor: Yuancheng Xue
Post-doctoral fellows: Yanyan Jiang, Phiyang Jiang
Graduate students: Jing Cai, Jesse Merrill
Research assistant: Claire Young
Molecular mechanisms of neurodegenerative diseases

As we live longer and enjoy unprecedented longevity, we also become increasingly vulnerable to aging-related neurodegenerative 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 research, 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 the life. To achieve longevity, these long-lived cells and mouse animals, we are studying how these self-maintenance machines become inefficient or nonfunctional, neuronal cell death, 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 degradation as „bedside“ discoveries, “bench to bedside,” and when discoveries are made in the clinic, from “bedside to bench.” A highlight of the CMI is the basic science/scientific translation of inventions and innovations from the laboratory to the clinic, from “bench to bedside” or “bedside to bench.”

An animal model for Parkinson’s disease

The images show the cell bodies of dopamine neurons (top image) in Drosophila brain. Neurotransmitter dopamine (middle image), the messenger for these neurons produce and use to communicate, are enriched in a structure called mushroom bodies (bottom image), the learning and memory center in the brain.

T he Mission of the Center for Molecular Imaging (CMI) is to develop and translate new medical imaging technologies, molecular imaging agents, and companion diagnostics to accelerate discoveries.

The CMI houses a diverse, interdisciplinary team of scientists and engineers who develop and use multi-modality molecular diagnostics and imaging techniques, including nuclear imaging, X-ray computed tomography, bioluminescence, fluorescence, and near-infrared fluorescence (NIRF) to enable new understandings of disease and chronic conditions. Sponsored research projects, the center synergistically drives independent basic science and clinical research projects, the center synergistically drives independent basic science and clinical research. Center Director Eva Sevick-Muraca, PhD

In addition to having an assembly of faculty-driven independent basic science and clinical research projects, the center synergistically operates a “collaboration” where clinicians and researchers partner to effectively apply imaging diagnostics to investigate and translate novel therapeutics and diagnostics.

Eva Sevick-Muraca, PhD
Center Director & Professor
Modulation of immune responses through the lymphatics

Eva Marie Sivick-Muraca, PhD
Professor and Director of the Center for Molecular Imaging
Nancy and Rich Kinder Distinguished Chair in Cardiovascular Disease Research

Over the past two decades, my research program has focused on the development of near-infrared fluorescence imaging agents, instrumentation, and algorithms, as well as the validation against nuclear imaging technologies. Teaming with clinical collaborators and Center faculty, we have translated near-infrared fluorescence imaging technology over 700 infants, children, and adults on the Texas Medical Center. These studies have resulted in discoveries mainly focused upon the lymphatic vasculature, a system involved in cancer and other chronic conditions, but largely neglected medical attention.

One focus of my research program is to harness the lymphatics to attenuate inflammation or effect disease-targeted immune responses. Regional T-cell and B-cell responses are mounted in lymph nodes, which receive antigens and antigen-presenting immune cells through afferent lymphatic responses. Regional T-cell and B-cell re-
mation or elicit disease-targeted immune responses. Regional T-cell and B-cell responses are mounted in lymph nodes, which receive antigens and antigen-presenting immune cells through afferent lymphatic responses. Regional T-cell and B-cell responses are mounted in lymph nodes, which receive antigens and antigen-presenting immune cells through afferent lymphatic responses. Regional T-cell and B-cell responses are mounted in lymph nodes, which receive antigens and antigen-presenting immune cells through afferent lymphatic responses. Regional T-cell and B-cell responses are mounted in lymph nodes, which receive antigens and antigen-presenting immune cells through afferent lymphatic responses. Regional T-cell and B-cell responses are mounted in lymph nodes, which receive antigens and antigen-presenting immune cells through afferent lymphatic responses.

My laboratory focuses on harnessing the lymphatic drainage of tumors to deliver checkpoint blockade immunotherapy for improved anti-tumor responses, Th1/Th17 polarization and pro-inflammatory and cognitive decline in adults. Dr. Bing Zhu and I are collaborating with UofHealth Pediatric Neurosurgery to develop and use imaging that allows us to explore the relationship between checkpoint function and survivals. Our Near-infrared fluorescence lymphatic imaging equipment and a small imaging facility is available to industry and academic partnerships.

I also lead a three-year CPRIT-funded clinical study of reparative microsurgery for LE in a neonatal heart surgery patient, demonstrating that human lymphomas can be detected with near-infrared fluorescence lymphatic imaging (NIRF-LI) at an early stage, allowing early intervention and improved survival rates. This study has shown that, if caught early in development, LE treatment can reverse the disease. In disease states such as LE, NIRF-LI imaging can provide information for early diagnosis and evaluation of treatment efficacy. I lead a five-year prospective and longitudinal study using NIRF-LI surveillance of breast cancer patients to identify early LE development and biomarkers that could suggest pharmacological treatment. This study has shown that NIRF-LI allows very early detection of lymphatic dysfunction, well before obvious arm swelling appears, well before a critical diagnosis of LE is typically delivered. I have presented the first lymphatic-vessel (NIRF-LI) evidence at an international conference showing that, when NIRF-LI detects lymphatic dysfunction and early LE treatment is given, LE is reversible. This study also has shown that certain plasma cytokines are elevated in breast cancer patients destined to develop LE a year later, providing a prognostic tool to enable early identification of at-risk patients for pre-habilitation treatment referral.

I am very active in the LE community, and I was recently appointed to the Scientific and Medical Advisory Board of the Lymphatic Education & Research Network (LE&RN), an international organization of researchers, physicians, therapists, and patients, dedicated to advancing lymphatic health.

I also chaired the committee that established standards and vetted applications for LE&RN’s Centers of Excellence designation, which now enable patients to locate health institutions with lymphatic expertise. To date, over 30 leading institutions, including MD Anderson Cancer Center, Stanford University School of Medicine, and Beth Israel Deaconess/Manuel School of Medicine, and centers in Australia, Europe, Japan, and Taiwan, are part of this program. I have previously participated as a team member imaging treatment responses to head and neck LE, which affects ~95% of head and neck cancer patients. Other past studies include rheumatoid arthritis drug delivery optimization, a case study of chyle in a neonatal heart surgery patient, and imaging of lymphatics in lipedema, a tar disorder that affects ~11% of women.

Evaluating ways to improve treatment outcomes, including decreasing axillary skin that plays a huge role in le patients. I am very active in the LE community, and I was recently appointed to the Scientific and Medical Advisory Board of the Lymphatic Education & Research Network (LE&RN), an international organization of researchers, physicians, therapists, and patients, dedicated to advancing lymphatic health.

I also chaired the committee that established standards and vetted applications for LE&RN’s Centers of Excellence designation, which now enable patients to locate health institutions with lymphatic expertise. To date, over 30 leading institutions, including MD Anderson Cancer Center, Stanford University School of Medicine, and Beth Israel Deaconess/Manuel School of Medicine, and centers in Australia, Europe, Japan, and Taiwan, are part of this program. I have previously participated as a team member imaging treatment responses to head and neck LE, which affects ~95% of head and neck cancer patients. Other past studies include rheumatoid arthritis drug delivery optimization, a case study of chyle in a neonatal heart surgery patient, and imaging of lymphatics in lipedema, a tar disorder that affects ~11% of women.

MALBREERER
Post-doctoral fellows: Carolina Mantilla- Rojas, PhD
Research assistants: Fred Christian Velasquez and Janelle Morton

Tumor draining lymph nodes (MD) receive antigen (Ag) and antigen-presenting cells that cross present to naive T cells to generate tumor-specific, CD8+ T cells in the absence of CD4+ T-cell signaling. T cells leave via lymphatic vessels and can be tolerated against tumor antigens with PD-1 signaling in the lymphat-
ics and in tumor microenvironment (TME)

Imaging lymphatics in Lipedema

Melissa B. Aldrich, MBA, PhD
Associate Professor

Imaging in immunology

Image of lymphatic in Lipedema

Prospective, “see through the skin” near infrared fluorescent lymphatic imaging allows early detection of lymphedema development and early treatment. Catching lymphedema before the appearance of obvious arm swelling, with permanent changes to lymphatic anatomy, results in better outcomes, including lymphedema reversal.

RESEARCH PROJECTS
• Longitudinal study of breast cancer-related LE
• Longitudinal study of reparative microsur-
sgeries for LE
• Imaging of lymphatics in Lipedema
• Imaging of non-traumatic lymphedemas and pediatric lymphedematous anomalies

LAB MEMBERS
• Post-doctoral fellows: Carolina Mantilla-Rojas, PhD
• Graduate student: Anna Vang
• Research assistants: Fred Christian Velasquez and Janelle Morton
• Melissa B. Aldrich, MBA, PhD

IMMPACT REPORT
IMMPACT REPORT
IMMPACT REPORT
A second focus is the relationship between neuroinflammation and lymphatics. Cerebrospinal fluid (CSF) drains into the perihilar lymphatics and the interruption of this drain- age has been implicated in the development of neurological disorders and poor recovery from traumatic brain injury. We recently com- pleted a small study assessing the impact of gravity on the lymphatic drainage in the head and neck region. Under head-down tilt conditions, which mimic the microgravity conditions of space, we observed impaired lymphatic drainage indicating that gravity aids CSF drainage into the lymphatic vessels abnormal, upright positions. This impaired lymphatic drainage, in microgravity, may contribute to fluid shifting from the body to the head in space, resulting in chronically high cerebral pressures that can damage the optical nerves of astronauts. We recently initiated a new study assessing the impact of lymphatic function in patient recovery from traumatic brain injury.

A third focus of our research program en- tails developing new methods for documenting lymphatic dysfunction in longitudinal studies. Current near-infrared imaging systems, provide two-dimensional fluorescence images that are difficult to anatomically relate to the areas of the body being imaged, especially in longitudinal studies seeking to track changes in lymphatic dysfunction with treatment. As part of our continued technology development, we are incorporating novel computer vision technologies, such as depth imaging, into our imaging system to enable the mappings of lymphatics in three-dimensional space. In addition, we seek to further the development of the technology by improving device sensitivity, automating different aspects of the hardware, and developing advanced tools to facilitate lymphatic image processing and analysis, with the ultimate goal of answering new biological and clinical questions not addressed by other technolo- gies.

**RESEARCH PROJECTS**
- Understanding the role of lymphatics in the development of peripheral vascular disease
- Understanding the role of lymphatics in the development and recovery of neurological conditions
- Incorporation of three-dimensional imaging technologies into lymphatic imaging

**KEY PUBLICATIONS**


For over 25 years, advancements in Func- tional Near-Infrared Spectroscopy (fNIRS) optical imaging have shown promise as a valuable brain imaging tool. Imaging from fNIRS allows examination of brain metabolism that is comparable to the BOLD fMRI signal. The fNIRS signal maps total hemoglobin (HbT) as well as oxygenated (HbO) and de-oxygenated (HbR) hemoglobin; this map approximates brain activation and deactivation acting as a proxy for localized glucose metabolism, similar to BOLD fMRI. Diffuse optical tomogra- phy (DOT) is an extension of NIRs that combines the multi-channel data acquisition with imaging reconstruction techniques to provide images of neural related hemody- namic changes. Brain DOT could offer our understanding of dysfunction in the pediatric brain, a critically important step to possibility modifying disabling movement disorders associated with cerebral palsy and devastat- ing cognitive dysfunction associated with childhood-onset epilepsy. Our lab focuses on developing a transcranial NIR optical imaging system, called Cap-based Transcranial Optical Tomography (COTOT) able to image whole brain hemodynamic activity in an awake child. With recent advances to couple fast real-time scientific CMOS (sCMOS) devices and with optical switchable detector Fluor- optics, rapid dynamic COTOT mapping should be possible, which would then enable evalua- tion of functional connectivity in awake infants. In addition, we adapted COTOT imag- ing system called COTOT (fluorescence-based COT) for mapping of cerebrospinal fluid (CSF) dynamics in a closely scaled model of pediatric patients. With 20-second temporal resolution, we dynamically imaged the ICS fluid flow through the lateral, third, and fourth ventricles and into the subarachnoid space before its exit from the central neural system through the lymphatics and subarach- noid granulations. These results demonstrate the feasibility of imaging CSF in the pediatric population using COTOT imaging technique and provide the general surgical management or to improve upon the treatment of post- hemorrhagic hydrocephalus.
Finally, there is increasing evidence for the use of cells or cells/tissues derived from stem cells, present throughout life in various organs such as bone marrow, intestine, and lung, and are involved in active regeneration of cells and tissues lost due to normal cell turnover or injury.

For patients presenting with genetic or inherited disease, Center faculty are utilizing recently developed gene editing technologies to correct the disease-causing mutations in either iPSCs or tissue-resident stem cells. The goal of these studies is development of therapies that can be generated from easily obtained cells from any individual and, in principle, may be employed to replace cells and tissues lost as a consequence of normal aging, injury, or disease.

There are at least two distinct classes of stem cells under active investigation within the Center for such therapeutic applications. The first class of stem cells of significant 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. The second class consists of tissue-resident stem cells; such cells, present throughout life in various organs such as bone marrow, intestine, and lung are involved in active regeneration of cells and tissues lost due to normal cell turnover or injury.

For patients presenting with genetically inherited disease, Center faculty are utilizing recently developed gene editing technologies to correct the disease-causing mutations in either iPSCs or tissue-resident stem cells. The goal of these studies is development of therapies that include correcting the mutations in a patient’s own stem cells, then delivering either the corrected stem cells or cell/tissue derivatives from them back into the same patient.

Finally, there is increasing evidence for the presence within cancers of cells having specific properties typically associated with stem cells. Center faculty are interrogating the role of such cells in the initiation and maintenance of cancers of the blood such as mantle cell lymphoma and multiple myeloma. 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.

My laboratory has as its primary objective the sequence-specific genetic correction of mutations in the chromosomal DNA of primary tissue-resident stem cells and/or induced pluripotent stem (iPS) cells derived from patients with inherited disorders affecting the lung or blood system. This is being pursued with the ultimate goal of developing stem cell-based therapeutic approaches. The ultimate objective is the delivery back to patients of their own lung or blood stem cells, only differing from the original stem cells by the genetic correction of the relevant mutation.

The first major project in the laboratory involves the use of the site-specific correction of gene mutations responsible for inherited blood disorders such as the Wiskott-Aldrich Syndrome (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. In the past year, 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.

We are also presently utilizing the similar gene correction methodologies to correct the CF 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 even more universal in the range of mutations that may be corrected – and to extend the methodology for correction of airway basal cells directly in the airways of CF individuals. We have also utilized DNA sequence-specific nuclease-mediated homology directed repair to correct the most common genetic mutations in iPS cell lines derived from patients with cystic fibrosis – and have demonstrated genetic and functional correction in lung epithelial cells derived from these corrected iPS cells. We have recently reported the ability to specifically derive 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 epithelial cells for testing sensitivity to specific CF drugs – in order to facilitate a personalized therapeutic approach.

My laboratory has as its primary objective the sequence-specific genetic correction of mutations in the chromosomal DNA of primary tissue-resident stem cells and/or induced pluripotent stem (iPS) cells derived from patients with inherited disorders affecting the lung or blood system. This is being pursued with the ultimate goal of developing stem cell-based therapeutic approaches. The ultimate objective is the delivery back to patients of their own lung or blood stem cells, only differing from the original stem cells by the genetic correction of the relevant mutation.

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**LAB MEMBERS**
Post-doctoral fellows: Dr. John M. Avila, Dr. Cristina Barilla
Research instructor: Dr. Shingo Suzuki
Research staff: Dr. Guang Q. Le, Samantha Weilker
Tissue engineering approaches for the treatment of CNS injuries

Laura A. Smith Callahan, PhD
Assistant Professor

Interaction of optimized laminin derived peptides signaling (HAVV and LRE) on extracellular matrix acquires by human induced pluripotent stem cells derived nerve cells (iPSCs). A Fibronectin staining (green arrows) shows higher IHC expression with hippocampal maturation with IFP-HA and without (CTRL-HA) peptide staining. Scale bars=50 μm. (e) Quantification of fibronectin staining intensity. Fibronectin is associated with inflammation and fibrotic scarring, so reduced expression is beneficial to establishing new neural connection during regenerative therapies.

KEY PUBLICATIONS

Porura TH, Kh, R. Howell SM, Kousou YE, Smith Callahan LA. Combination of HAVV, LRE and FTOHS0100 Bioactive Signalizing Peptides Increases Human Induced Pluripotent Stem Cell Derived Neural Stem Cells Extracellular Matrix Remodeling and Neurite Extension. Advanced Biosystems. 2020


RESEARCH PROJECTS

• Optimization of scaffold and matrices to direct human induced pluripotent stem cells to neural progenitor cells to therapeutic tissues using combinational approaches.

• Modification of cellular environment in-vivo to promote cell therapy survival, integration with the host and maturation toward functional mature cell types after central nervous system injury system.

Cellular therapies for neurological injury

Charles Cox, Jr., MD
Professor
George and Cynthia Mitchell Distinguished University Chair

RESEARCH PROJECTS

• Development of Phase 1 and 2 Clinical Trials using non-ESC pluripotent progenitor cells for traumatic brain injury.

• IND-enabling studies using APCs for traumatic brain injury.

• Amniotic Fluid derived MSCs for the treat- ment of neurological injuries associated with congenital heart disease and cardiomyopa- thy/hypertrophic cardiac arrest.

• Novel delivery systems for stem cells in neurological injury.

• Imaging of microglial activation in vivo.

KEY PUBLICATIONS


LAB MEMBERS

Steven Kornach, MD, Ph.D, CCRC-ThE Clinical

Disputing Arrington, MTI, RN-TBI Clinical

Yoshi-Caco Programmer Analyst

Julie Ruiz – Research Coordinator II

Michael Collins Scott, MD-TBI Clinical and Cell Therapy

Jacob Schriner, MD-TBI Clinical and Cell Therapy

Brian Sli, MD-Professor, Research Scott Olson, PhD - Assistant Professor

Christopher Haas, PhD Postdoctoral Research Fellow

James Harper Day-Research Assistant

Jennifer Aranaj, PhD Assistant Professor

Shelby Morton – Research Assistant

Giselle Ortiz – Research Assistant

Julia Ruiz – Research Coordinator II

Yidao Cai-Programmer Analyst

Scott Olson, PhD - Assistant Professor

Assistant Professor

Laura A. Smith Callahan, PhD
Assistant Professor

The research in my laboratory focuses on developing biomaterials to be used in clinical treatments for spinal cord injury, traumatic brain injury (TBI), and stroke. The laboratory uses an interdisciplinary approach involving techniques from cell, molecular, and stem cell biology, chemistry, and material science. Utilizing engineering approaches, the labora- tory seeks to optimize scaffold design for the expansion of clinically relevant cell sources for use in stem cell therapy and to support the cells after implantation into patients. By examining cell-material interactions, we seek to understand which aspects of the native extracellular matrix facilitates tissue repair and integration with the surrounding host tissue. Once optimal composition, architecture (porosity, feature size, fiber alignment, etc.), mechanical properties, and bioactive signaling peptide concentrations have been identified using combinatorial methods, they are integrated into advanced hybrid matrices. These matrices maximize the advantages of both synthetic (tension in fabrication and cellular responsivity and natural (native bioactive signaling) polymers, while mitigating their disadvantages, namely lack of bioactive signaling anchoring to both inconsistency in scaffold properties and cellular response, respectively. When combined with additional bioactive signaling and controlled architecture, these hybrid matrices can begin to emulate the native tissue microenvironment and support tissue development better than traditional matrices. Preliminary studies have focused on formulating matrices to facilitate the expansion of axons from the host across spinal cord lesion cavities in subacute rat models so spinal cord injury. In order to advance biomaterial cell support matrices to wide-spread clinical use, protocols for the expansion and differentiation of clinically relevant cell sources, also, need to be optimized. Human induced pluripo- tent stem cells (iPSCs) offer a potentially autologous cell sources for the treatment of traumatic injuries to the central nervous system. However, the number of viable cells for transplant produced from current differentiation protocols is extremely low. Both biochemical and mechanical properties of the cell culture surfaces have been shown to significantly affect cellular differentiation but have not been studied significantly in respect to NPCT-differentiation. The labora- tory seeks to extend our knowledge of those dimensional culture systems to optimize two-dimensional cell culture surfaces for differentiation of neural stem cells and oligodendrocyte progenitor cells from iPSCs. Preliminary studies have focused on the os- valent tethering of proteins to the surface of Hydrogel containing with a Young’s Modulus gradient to study the effect of mechanical properties on NPSC tissue growth.

RESEARCH PROJECTS

• Optimization of substrates and matrices to support the development of human induced pluripotent stem cells to neural progenitor cells to therapeutic tissues.

• Development of phase 1 and 2 clinical trials using non-ESC pluripotent progenitor cells for traumatic brain injury.

• Development of novel bioreactors for stem cell production.

Our current research program focuses on the use of cellular therapies for neuro- logical injuries, principally traumatic brain injury (TBI). We have been interested in the modulation of the innate immune response to TBI and how cellular therapies have been successful without significant engraftment in the brain long term. Cell-cell interactions in the peripheral reticuloendothelial system have resulted in Treg upregulation and modulation of the microglia/macrophage phenotype in the brain. We use these types of data to help us determine dosing regimens (number of cells, type, and route of delivery, as well as timing), which may be very spec- ific to the pathophysiology in question. We use in-vivo models of injury and in-vitro models.
Skeletal muscle is the largest tissue in hu-
man body and is responsible for maintaining 
body posture, movement, and storage of key 
metabolites such as glycogen. Due to the pres-
ence of muscle stem cells, skeletal muscle 
has tremendous regenerative potential. Nev-
ertheless, there are many disorders that can 
impair this regenerative capacity and affect 
skeletal muscle health. In this context, stem 
cells and regenerative medicine may offer 
prospects for novel treatments for muscle 
failure, or during the aging process. Unfortu-
nately, these disorders often lead to varying 
degrees of muscle dysfunction and lifelong 
disability and without any definitive care. 
Here at the NMMP and Center for Stem 
Cell and Regenerative Medicine (CDRM), we 
utilize human induced pluripotent stem cells 
(iPSCs) for disease modeling, site-specific 
gene correction, and skeletal muscle repair. 
(iPSCs) can be reprogrammed from adult skin 
muscle cells (hDFCs) and can efficiently differenti-
ate into all cell types in the human body. In 
contrast to rodent cells, iPSCs are species-
specific. Therefore, iPSCs are generally consid-
ered as an excellent cell line for personal-
ized stem cell therapy in many degenerative 
diseases.

Our lab is specialized in generation of 
human iPSCs from patients, site-specific gene 
correction, in vitro disease modeling, and 
unique genetic connection, and skeletal muscle 
repair. iPSCs can be reprogrammed from adult skin 
muscle cells (hDFCs) and can efficiently differenti-
ate into all cell types in the human body. In 
contrast to rodent cells, iPSCs are species-
specific. Therefore, iPSCs are generally consid-
ered as an excellent cell line for personal-
ized stem cell therapy in many degenerative 
diseases.

Research Projects

• Disease modeling and site-specific gene correction of 
muscle dystrophies using CRISPR/Cas9 system.
• Therapeutic potential of human iPSCs in 
volumetric muscle loss (VML) injuries
• Therapeutic potential of long non-coding RNAs (lncRNAs) in Duchenne and Becker muscular dystrophies

Key Publications


Wu J, M N, Bhalia S, Darabi R. Evaluation of the Therapeutic Potential of Human iPSCs in a Murine Model of VML. Molecular Dysmorphology.


Lab members

Instructor: Jianbo Wu

Pramod Dash, PhD
Professor and Chair, Department of Neurobiology and Anatomy
Nina and Michael Zilka Distinguished Chair, Neurodegenerative Disease Research

Concussion and stress-related disorders

Concussion (also known as mild traumatic 
brain injury, mTBI) has emerged as a major 
health problem, striking not only athletes participating in contact sports but persons of 
al ages and sexes. According to the Center for Disease Control, approximately 
2.6 million Americans sustain a brain injury each year, of which 87% can be classified as concussive. Recently, due to the increased 
in longevity and the number of falls in our older population, the incidence of concussion is on the rise in older Americans. As a person 
can sustain a concussion without ever losing consciousness, and many of these people never seek medical attention, the above 
statistics may only represent a fraction of actual concussive cases. Currently, there is no objective way to assess if brain injury has 
occurring after a concussion.

It has been recently appreciated that concussion is not a singular event but rather a progressive disease with long-lasting consequences. It remains unknown when, or 
if, the brain returns to its pre-injury state. As the brain remains vulnerable to a second in-
jury, continued research is required to under-
stand the molecular, cellular, and structural 
changes that occur following concussion in 
order to develop treatments, which can offer 
favorable outcomes to patients. For this end, 
we have been examining the influence of repeated 
brain injury in both humans and in animal 
models.

One of the consistent pathologies associ-
ated with both clinical and experimental 
traumatic brain injury is axonal injury, 
especially following concussion. Several 
lines of experimental evidence have dem-
strated a role for NAD+ metabolism in axonal 
regeneration. One of the enzymes that metabolizes NAD+ in axons is Sarm1 (SARM1, also termed TRIF Mott Containing 1), 
and its activity is thought to play a role in axonal 
degeneration. We have been examining the 
role of Sarm1 in axonal injury and cognitive 
outcome after repeated mild closed head 
injury (mTBI). Our results indicate that mTBI elicited white matter damage is

markedly reduced in mice lacking the Sarm1 protein (Sarm1−/− mice). Further, we have found that the activation of Sarm1 in microglia 
and microglia is also altered in the areas with 
white matter damage, suggesting a reduction in inflammation. Associated with these 
alterations, injured Sarm1−/− mice were found to perform significantly better in both motor and cognitive tasks.

Research Projects

• To identify how concussion alters neural 
communication.
• To investigate neurovascular function after 
concussion.
• To investigate the consequences of 
microtubular protein and altered brain 
energy metabolism after concussion.

Key Publications

Ullendorf E, Redell JB, Zhao J, Moore 
AN, Dash PK. A method for assessing 
tissue respiration in anatomically defined brain 

Vadlamani A, Brenner J, Levine HS, 
McCarthy JJ, Dash PK, Redell JB, Yamal JM, Robertson 
CS. Early versus Late Profiles of Inflammatory Cytokines after Mild Traumatic Brain Injury and Their Association with Neuropsychologi-

Maynard ME, Redell JB, Zhao J, 
Hoek KN, Ura SM, Kober N, Dash PK. Sarm1 loss re-

Maynard ME, Redell JB, Kober N, Under-
wood EI, Fischer TD, Hoek KN, Lablache V, 
Warawan MN, Moore AN, Dash PK. Loss of 
PTEN-induced deactivation of PI3K (PTENIP) elicits 
Necroptosis, NAD+ stress, and hippocampal 

Bressoud J, Redell JB, Zhao J, Maynard 
ME, Kober N, Forone A, Hoek KN, Zhang 
XJ, Moore AN, Dash PK. Mild Traumatic 
Brain Injury Increases Inflammation, Spatial Information 
Context and Reduces Place Field Stability of 

Collaborators/Lab Members

Dr. James McCarthy: executive vice pre-
sident and chief physician executive, Memorial 
Hermann. 
Dr. Paul Schulz: associate professor of 
Neurology, director, Dementia and Memory 
Disorders group
Dr. Summer Ott: associate professor of 
Orthopedic Surgery, director, Concussion Pro-
gram at Ironman Sports Medicine Institute 
Dr. Cameron Jackson: associate professor of 
Diagnostics and Biomedical Sciences 
Dr. John Redell: assistant professor-research of
Neurology and Anatomy 
Dr. Jing Zhao: assistant professor-research of 
Neurology and Anatomy 
Dr. Nathalie Kober: assistant professor-research of 
Neurology and Anatomy 

Post-doctoral fellows: Dr. Rebecca West
Research assistant: Dr. Bressoud J, Dr. Kimbley Hood, Me, Anthony Moore, BS

Simplified pathway for NAD metabolism. NAD+ is synthesized from two metabolic pathways: a de novo synthesis pathway (from Na and amino acids) and a recycling pathway. Sarm1 is a NAD+- 
consuming enzyme. Our results indicate that in the absence of Sarm1, axonal injury is reduced suggesting that depletion of NAD+ contributes to axonal damage after repeat concussion.
Human pluripotent stem cells for lung regeneration and disease modeling

My laboratory is interested in applying human pluripotent stem cell (hPSC) models to study the molecular mechanisms of lung development and disease. Examples include influenza virus infection-induced severe infection and acute respiratory distress syndrome, which affects the lower respiratory tract and can result in different responses depending on the subtype.

**RESEARCH PROJECTS**
- Use patient hPSC-differentiated lung and airway epithelial cells to study normal development and pathogenesis
- Understanding the basic mechanisms of lung specification from noradrenaline (NA) or vasoactive intestinal polypeptide (VIP)
- Understanding the molecular and epigenetic regulation of hPSC-derived airway basal stem cell competence

**KEY PUBLICATIONS**


Familial cancer syndromes in a dish

Familial cancer syndromes, including Li-Fraumeni syndrome (LFS) and neurofibromatosis type I (NF1), are caused by genetic alterations in tumor suppressor genes that result in cancer predisposition. In LFS, the inactivation of the tumor suppressor gene TP53 is a hallmark. Several studies have elucidated the mechanisms underlying TP53 inactivation and its role in cancer development.

One way to study these mechanisms is through the use of patient-derived induced pluripotent stem cells (iPSCs). These cells are generated from the patient’s cells and allow for the study of their genetic alterations and cellular behavior in a controlled environment.

Our research focuses on dissecting the natural developmental pathways and the corresponding pathological mechanisms in the context of cancer. Our long-term goal is to identify therapeutic targets for the treatment of cancer diseases.

Our work has demonstrated the potential of iPSCs in modeling human genetic diseases, which can be used to study cancer pathogenesis for drug discovery and development. Furthermore, iPSCs can be used to understand the role of specific genetic alterations in cancer development and to develop personalized treatments.

Specifically, our research team has developed a strategy to generate iPSCs from patients with LFS and NF1. This strategy involves the use of CRISPR-Cas9 gene editing to introduce specific genetic alterations into iPSCs, allowing for the study of their effects on cancer development.

In our latest study, we have shown that the inactivation of TP53 in LFS iPSCs leads to an increase in cellular proliferation and a decrease in cellular differentiation. These findings highlight the importance of TP53 in regulating cell cycle and differentiation in cancer.

In conclusion, the use of iPSCs in cancer research is a powerful tool that allows for the study of cancer pathogenesis and the development of personalized treatments. Our ongoing research aims to further elucidate the role of TP53 in cancer development and to identify novel therapeutic targets for the treatment of cancer diseases.
Investigating and targeting signaling pathways involved in protein homeostasis in cancers and neurodegenerative diseases

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. Chaperones are regulators of protein folding processes and are involved in preventing misfolded proteins from accumulating. Misfolded proteins that escape these control mechanisms must be targeted for degradation, either through the UPS or by autophagic processes. One crucial mechanism that marks the target protein for degradation in both the UPS and autophagy pathways is ubiquitination. UPS-mediated protein degradation is mediated through the recognition of the protein substrates through polyubiquitination. F-box E3 ubiquitin ligases, such as FBXL14, target proteins for ubiquitination and degradation.

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**KEY PUBLICATIONS**


Zhang, H., Chen, Z., Miranda, R. N., Madeira, L., and Magee, N. (2018) Nitrated BACH2 control coordinates mammalian cell senescence and survival through dynamin. Aging 10:783-793, 2017. This article was featured in “This week in Blood” as an Editor's pick.


**LAB MEMBERS**

Post-doctoral fellows: Unyee, PhD, Yuquan Wang, PhD

Research Assistant: Raksha Rao, PhD

**Nami McCarty, PhD**

Professor and Bob Graham Distinguished Chair in Stem Cell Biology

**Pamela Wenzel, PhD**

Associate Professor

Director of Immunology Program, MD Anderson

**Effects of flow on stem cell potential and immune function**

Our lab studies how biomechanical force generated by the flow of blood in the circulatory system impacts cell behavior and health. We have primary research projects addressing how fractional 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 induced pluripotent stem cell lines and generate bioengineered organs.

**KEY PUBLICATIONS**


**LAB MEMBERS**

Graduate student: Paula Horten

Post-doctoral fellow: Sandeep Dunbai

Senior research associate: Miguel Diaz
Gene transcription and regulation of stem cell differentiation and neural injuries

**KEY PUBLICATIONS**


**LAB MEMBERS**

- Post-doctoral fellows: Hsinchao Wai, PhD; Xizi Wu, MD; Mei Research associate Andrew Rohlf
- Resident physician: Michael Montany, MD
- Undergraduate students: Tanuj Prajapati, Neha Taliprapada

**RESEARCH PROJECTS**

- Combines stem cell biology and systems-based approaches involving genomics, bioinformatics, and functional assays to investigate gene expression and regulatory mechanisms during stem cell differentiation, pinpoint key transcription factors and regulatory lncRNAs, and identify key regulators to steer the direction of stem cell differentiation and improve efficiency/safety.
- Characterizes molecular signatures and identifies therapeutic targets for spinal cord injury and neurodegenerative diseases.

**The 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.**
Qingyun (Jim) Liu
Professor
Janice Davis Gordon Chair for Bowel Cancer Research

Investigation of normal and cancer stem cells for the discovery of cancer therapeutics

LEF receptors for the treatment of cancers of the digestive system. We are currently optimizing this approach by protein engineering followed by drug conjugation to increase potency and efficacy in tumor models.

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 role 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
Ts. research associates: Wangsheng Alice Yu, Ling Wu, and Jianhua Yu
Research scientist: Yukimatsu Toh

Forecasting the outcomes of the phenotype and functional analysis of cancer stem cell populations in tumor tissues. We are also investigating the therapeutic potential of targeting cancer stem cells with novel therapeutic agents.

Our research is focused on delineating the function and mechanisms of a group of cell surface receptors called LGRs, RSPOs, and LGR9 in colon cancer. We have discovered that LGR4 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. We are now focused on understanding how RSPOs and LGRs work together to regulate the growth and migration of normal and cancer cells. We found that LGRs and RSPOs work through a different mechanism to control the survival and expansion of intestinal stem cells, which challenges a major current paradigm that LGRs and RSPOs work in an identical way in cell signaling.

We have shown that drug conjugates of anti-LGR4 antibodies showed excellent anticancer efficacy in preclinical models of colon cancer. Recently, we have discovered a novel approach that can target all three LGR receptors for the treatment of cancers of the digestive system. We are currently optimizing this approach by protein engineering followed by drug conjugation to increase potency and efficacy in tumor models.

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KEY PUBLICATIONS

LAB MEMBERS
Ts. research associates: Wangsheng Alice Yu, Ling Wu, and Jianhua Yu
Research scientist: Yukimatsu Toh


Ali Aghadrini, MS, PhD
Associate Professor
John S. Dunn Research Scholar III

Cancer theranostics

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KEY PUBLICATIONS

LAB MEMBERS
Ts. research associates: Wangsheng Alice Yu, Ling Wu, and Jianhua Yu
Research scientist: Yukimatsu Toh

Imaging system

A fluorescent contrast agent that targets neuroendocrine tumors clearly identifies cancerous tissue (solid arrow) using a preclinical imaging system (left; dashed arrow shows kidney). Imaging was then performed using a clinical imager that is part of a surgical robotic system and showed similar detection capabilities. These findings suggest that the selected combination of imaging agent and device can be effectively used in a surgical-oncology setting in patients.
Drug resistance, metastasis, and relapse continue to be leading causes of colorectal cancer-related deaths. In 2017, nearly 140,000 patients in the United States were estimated to have colorectal cancer with 53,800 deaths from colorectal cancer. Despite recent advances in surgical and therapeutic strategies, colorectal cancer remains a major public health burden.

The effective treatment of colorectal cancer requires new therapeutic approaches. One of the main impediments for the effective treatment of colorectal cancer is the subpopulation of tumor cells that become drug resistant. Cancer stem cells (CSCs) or tumor-initiating cells are a subset of tumor cells that resemble normal stem cells and have been shown to mediate drug resistance, metastasis, and relapse. Consequently, numerous strategies have been developed to target CSCs and the CSC-like cell population as a means to evade therapy and induce drug resistance.


cancer stem cells

Therapeutic strategies for targeting colorectal tumors and cancer stem cells

Therefore, recent strategies have been focused on the development of new therapeutic targets that can ultimately lead to the development of new anti-cancer therapeutics for the improved treatment and development of genomic biomarkers and combination therapies to target cells that exhibit phenotypes that are characteristic of CSCs, metastasis, and drug resistance.

In our lab, we are investigating the cellular mechanisms that drive drug resistance in colorectal cancer and correlate with poor patient survival. We have found that LGR5 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 organoids or PDOs. We use the PDOs to study the function of 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 novel therapeutic approaches for the improved treatment and eradication of colorectal cancer.

We are investigating the function of LGR5 and the signaling pathways that drive drug resistance in colorectal cancer using immunoPET. Our lab is focused on understanding the signaling programs underlying cancer progression and development of targeted therapeutic approaches to prevent or treat metastasis.

One of the current research interests of our lab is to discover a more effective treatment for colorectal cancer. We are currently identifying therapeutic strategies that target cancer stem cells, metastasis, and drug resistance.

We have developed a dual- or multi-targeted approach for the eradication of colorectal cancer. We are investigating the function of LGR5 and the signaling pathways that drive drug resistance in colorectal cancer using immunoPET.

In addition to drug resistance, metastasis, and relapse, other major impediments for the effective treatment of colorectal cancer include liver, gastric, and ovarian cancers. The colorectal CSCs, which express LGR5, are capable of directing tumor growth. Interestingly, LGR5-positive CSCs have been shown to have the ability to transition into more drug-resistant LGR5-negative cancer cells, making them a major impediment for the effective treatment of colorectal cancer.

One of the targets that we are investigating is LGR5. LGR5 is expressed in colorectal cancer and correlates with poor patient survival. We have found that LGR5 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 organoids or PDOs. We use the PDOs to study the function of 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 receptor LGR5 in colorectal cancer and generate novel therapeutic approaches for the improved treatment and eradication of colorectal cancer.

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Deciphering proteome alterations associated with diseases

KEY PUBLICATIONS

LAB MEMBERS
Post-doctoral fellow: Lakmeera Savoianerva, PhD
Research scientist: Cheng Miu, PhD
Research coordinator: L-U

RESEARCH PROJECTS
- Mechanistic and biomarker studies of pancreatic ductal adenocarcinoma (PDAC) and its precursors, including pancreatic intraepithelial neoplasia (PanIN) and pancreatic cyst neoplasms (PCN).
- 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.
- Investigation of the proteome and glycoproteome alterations associated with cancer, Alzheimer’s disease, and Gaucher Body Dementia (GBD).
- Innovation of proteomic technologies, including single cell proteomics and glycoproteomics, for basic, translational, and clinical applications.

Proteins are essential functional biomolecules that are involved in all aspects of cellular physiologic activities and have been vital tools in basic, translational and clinical research, providing a unique avenue to investigate diverse associated molecular alterations at a functional level. Proteome alterations that are associated with disease may include changes in protein expression, sequence, post-translational modifications (PTMs), and protein interactions with proteins and 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, neurodegenerative, and other diseases. These studies are carried out with various goals, such as aiming to better understand the molecular mechanisms underlying 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 focius are pancreatic cancer and other GI tract malignances. In addition, through collaborative efforts, our lab also supports proteomic study of neurodegenerative, chronic inflammations, and infectious diseases, as well as therapeutic drug development. Mass spectrometry, systems biology, and chemical biology are important components in our study.

The focus of my lab is to develop targeting agents and smart particles that attack cancer in infectious organisms, such as tuberculosis. Current treatments are often ineffective or create harsh side effects for patients. We use modified DNA joined to drug-like or protein-like attachments (X-aptamers). X-aptamers can be used either as complex particles containing anti-cancer agents to act as a one-two punch. Such particles can be loaded onto larger silicon particles for a sustained release of the disease fighting particles. Aptamer Development - In recent years, we have developed DNA aptamers targeting breast and ovarian cancer. Such DNA can greatly reduce cancer in a dose-dependent manner. However, DNA aptamers are even more effective when used in combination therapy together with chemotherapeutic agents such as SNFRA or drugs like Paclitaxel. When we have shown that our aptamer targeted approach reduces tumor size and, importantly, the spread of metastatic cancer. Furthermore, we have also shown our method is safe in preclinical testing. Our recent aptamer-related research has shown the following results:

**ESFA Multistage particlles directed anti-cancer effect:** SNFRA to the bone marrow, reducing breast cancer metastasis and leading to increased survival rates.

**ESFA** Anti-SNAP4; directed delivery of siRNA to the bone marrow, reducing breast cancer metastasis and leading to increased survival rates.

**ESCA** Aptamer delivery of siRNA improves vascular maturation to enhance anti-tumor effects in ovarian cancer.

**ESCA** X-aptamer directed delivery of siRNA enhances anti-tumor effects in ovarian cancer.

**ESCA** APR, aptamer (Kanlikilicer et al., 2017) can reduce cancer alone and enhances anti-tumor effects in combinational therapy.

**ESCA** Development of X-aptamers targeting cancer with X-aptamers and nanoparticles.


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. Patients’ plasma was incubated with beads-based aptamer library and sorted for aptamer-protein complex by flow cytometry (Figure 1A). 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 with pathological confirmation in patients with cirrhosis. AI has the capacity of converting images into renewable 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 as 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.

Imprinted Multi-Aspects BiomaRk Analysis. By studying differentially expressed miRNAs using data downloaded from TCGA and validating those miRNA-expressed 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 genomic 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


Protein biomarker discovery using bead-based X-aptamer library. (A) Patient and healthy donor plasma were labeled with different fluorophores. (B) Proteins bound to bead-X-aptamer were sorted by flow cytometer.

ONTONIZATION apheresis.

Zhiqiang An, PhD
Professor & Center Director
Robert A. Welch Distinguished University Chair in Chemistry

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, development, and commercialization 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 and Johnson & Johnson, 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, fungal natural products, 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 and natural products that modulate the activity of these targets as potential drug 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 12 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. In response to the COVID-19 pandemic, TTI scientists quickly discovered neutralizing antibodies targeting the SARS-CoV-2 virus. These antibodies are in development as potential therapies for the treatment of COVID-19. 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.
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**
  - Discovery and development of therapeutic antibodies
  - Rescue vaccine using recombinant baculovirus
  - Antibody drug conjugate (ADC) for cancer treatment
  - Vaccination and passive immunization

- **Research of Cyclic AMP (cAMP)**
  - Inhibitors and agonists and in exploring their potential uses in various human diseases including cardiovascular diseases and chronic pain.
  - Prophylactic and neovascularization area at P17.
  - Inhibitors and agonists of second-generation isoform specific EPAC.
  - The down-regulation of anti-angiogenic molecules so that their functions can be understood.
  - The development of small molecule inhibitors and antagonists for immunotherapy in ovarian cancer.

**LAB MEMBERS**

- **Post-doctoral fellows:** Zhiqiang Ku, Jiejun Li
- **Graduate students:** Joshua W. Morse, Mason Ruiz
- **Research technician:** Hannah Boyd
- **Research assistant:** Zhiqiang Ku
- **Research associate:** Wei Lin
- **Instructor:** William Robichaux
- **Research associate:** Wei Lin
- **PhD candidate:** Ningzhou Gu

**KEY PUBLICATIONS**


**EXPERIMENTAL RESULTS**

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, 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 mechanisms of EPAC proteins and to design pathway-specific modulators for those 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 disease 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 cardiovascular diseases and chronic pain.

**KEY 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 chronic pain and proliferative vascular diseases using EPAC knockout mouse models and pharmacological inhibitors.
- Practical development of novel drug candidates targeting EPAC1 for the treatment of diabetic retinopathy.

**LAB MEMBERS**

- Research assistant: Fang Mei
- Instructor: Wei Li
- Research assistant: Wei Lin
- Graduate student: Ningzhou Gu

**EXPERIMENTAL RESULTS**

Cancer 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 shape 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.

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Our research is in the area of protein engineering, focusing on on biopharmaceuticals such as monoclonal antibodies (mAbs), T cell receptors, and therapeutic enzymes. We develop novel technologies to facilitate these biologic discovery, optimization, and production, and further evaluate their therapeutic efficacy in vitro and in vivo.

RESEARCH PROJECTS

- Protease-Inhibiting Therapeutic mAbs (Funded by NIGMS). Proteases are important signaling molecules and represent one of the largest families of pharmaco- logical targets. Our laboratory has been committed to the development of enabling methodologies for the generation of therapeutic mAbs as safe and effective protease inhibitors. Over the past decade, we established a series of novel technologies, including camellia-inspired cassette paratopes, human antibody libraries (PNAS 2016), and inhibition-based rather than binding-based selection/screening methods (PNAS 2019). Current gene expression analysis showed disordered, characterized, and optimized panels of potent and specific mAbs inhibiting numerous proteases of biotechnological importance. Furthermore, our protease-inhibiting mAbs show significant therapeutic efficacy in animal models of cancer, neuropathic pain, obesity, and stroke.

- Efficient Transporation Across Blood-Brain Barrier (Funded by NINDS). 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 payloads as high-efficiency BBB delivery approaches 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 mAbs therapies directly targeting the mechanisms of DPN pathogenesis, and thus with great values in the management of diabetic neuropathy.

- Broad Neutralizing mAbs of Snake Venom Metalloproteinases (Funded by NIAID). Snake venom metalloproteinases (svMPs) are a class of snake venom proteases that cause severe systemic effects after snake bites. Our lab has developed highly specific snake venom metalloproteinase-neutralizing mAbs by targeting svMPs reaction cleft, and further tests their efficacy in vitro and in vivo.

KEY PUBLICATIONS


LAB MEMBERS

Post-doctoral fellow: Hanjuan Chua, Kibaek Loo, Zunang Wang, Xin Wei

Biochemical characterizations of protease inhibitory mAbs. (A) Nanomolar affinity and potency; (B) Exclusive selectivity; (C) Inhibition with physiological substrates; (D) High proteolytic stability; (E) Competitive-mode of inhibition; (F) Epitope overlaps with endogenous inhibitors; (G) Epitope determined by alanine scanning.

Biochemical characteristics of protease inhibitory mAbs. (A) Nanomolar affinity and potency; (B) Exclusive selectivity; (C) Inhibition with physiological substrates; (D) High proteolytic stability; (E) Competitive-mode of inhibition; (F) Epitope overlaps with endogenous inhibitors; (G) Epitope determined by alanine scanning.

My research programs are to obtain critical new knowledge of cancer metastasis and drug resistance of human cancers. This involves new biomarkers and drug targets for the development of better therapeutics for human cancers.

- Cancer metastasis, the spread of tumor to other parts of the body, is responsible for over 90% of cancer deaths. 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, proteomics, and 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 co-option, the anti-leading 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 in the lab is to investigate the mechanisms of cancer cell plasticity and drug resistance. In particular, we study how prostate cancers become resistant to novel 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 the process and target a process called neodermadifferentiation (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 are no effective treatments to prevent or overcome drug resistance related to NED. I 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 Zhiquing An at TTU, we are investigating novel therapeutic antibodies. We are also employing novel combinatory strategies to enhance efficacy of immune therapies, 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 (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 co-option, the anti-leading 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.
- Exploring new combinatory strategies to enhance immune therapy.

key publications


LAB MEMBERS

GSBS graduate students: Samina Nadarizze, Zhid, Irenmey Yung

PhD students: Wei Li, Yihao Gao, Min Zhang, Suyang Li, Xiang Li, Zihao Yu, etc.

OBG inhibits EMT and prostate cancer progression by sequestering and inhibiting AKT activation. (A) Directive kinase B expression is de regulated at prostate cancers progress in patients. (B) OBG silencing promotes colony formation and prostate cancer growth in mice xenografts. (C) OBG physically interacts with inorganic AKT. (D) Modeling on OBG and AKT crystal structures indicates that OBG C-terminal 84aa interacts with AKT7 terminal PH domain, sequesters AKT and blocks its activation, which was confirmed experimentally.
Antibody Drug Conjugate (ADCs) represent a rapidly growing class of anticancer therapeutics. As demonstrated with 12 FDA-approved ADCs 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 ABC-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 linkers. We have developed a glutaric acid-valine-threopropylene linker as a new-generation ADC linker with high transductionability from hands to cell. Our tripeptide linker is highly stable in circulation but immediately degrades once a given ADC gets into the target cell, maximizing ADC stability and therapeutic efficacy. Using this technology, we recently developed ADCs equipped with two distinct payloads (named “dual-drug ADCs,” Figure 1A). Our dual-drug ADC showed improved treatment efficacy in xenograft mouse models representing intratumor HER2 heterogeneity and elevated drug resistance, which are critical issues often seen in breast cancer patient samples. Notably, our dual-drug ADC outperformed single-agent treatment effect and survival benefit than does a co-administration of two single-drug variants (Figure 1B). Our findings suggest that simultaneous delivery of two payloads with distinct drug properties is a promising approach to combating breast cancer heterogeneity and drug resistance. Our next goal is to advance this novel ADC to in-depth preclinical studies and following first-in-human studies within several years.

With our cutting-edge conjugation technology platform in hand, we are currently pursuing next-generation ADCs for treating refractory cancers, including inflammatory breast cancer, glioblastoma multiforme (GBM), pancreatic cancers, and other solid tumors with drug resistance and/or high intratumor heterogeneity. We are also evaluating novel ADC conjugates that can elicit strong anti-tumor immune responses with minimal systemic toxicity. Patients with resistant and heterogeneous cancers often suffer from recurrence of malignancy and exacerbated quality of life because of ineffective chemotherapy. Our lab’s long-term goal is to create new therapeutic options for overcoming such clinical issues. We envision that our novel ADC linker technology platform will help the whole biomedical research community achieve this overarching goal.

**ReseArCH PRoJEcTS**
- Design, synthesis, and evaluation of novel ADC linkers for constructing multi-loading ADCs
- Structural optimization of ADC linkers for high stability, rapid drug release, and enhanced permeability to the brain
- Modulation of the ADC function by chemical modification for organ-specific delivery
- Evaluation of ADCs in refractory cancer models

**KEy PuBlIcAtIOnS**

**LAB MEMBERS**
Instructor: Yasuaki Anami, PhD
Senior research scientists: Chisato Tsu- chikama, PhD
Post-doctoral fellows: Aiko Yamaguchi, PhD, Yin Yue Ha (Summer), PhD

**Kyoji Tsuchikama, PhD** Assistant Professor

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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 therapeutics 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 hallmarks of cancer. Our research has demonstrated the presence of proteolytic impairment of antibody (Ig) in the tumor microenvironment. Tissueautam and peritumoral (anti-HER2) antibody with a single hinge cleavage showed a loss of immune effector function against cancer cells in vitro and reduced antibody efficacy in vivo. Based on our findings and reports by others, we hypothesize that antibodies recognizing tumor-associated antigens (TAA) in the tumor microenvironment is susceptibility to proteolytic impairment through a hinge cleavage by matrix metalloproteinases (MMPs). Such proteolytic hinge cleavage of antibodies not only weakens antibody anti-cancer immunity but also leads to an immune suppressive tumor microenvironment. Our current research programs are centered on better understanding of tumor evasion of antibody immunity and developing therapeutic strategies to modulate antibody-mediated immune response for improvement of cancer treatment. We employ a wide array of experimental approaches including in vitro and 3D cell culture, 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, fluorophore activated cell sorting (FACS), and single cell genomics of antibodies. We have established a monoclonal antibody platform technology to discover and select novel anti-cancer monoclonal antibodies for functional evaluation and preclinical development. The long-term goal of my research is to understand mechanisms of cancer evasion of antibody therapeutics 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**

**LAB MEMBERS**
Senior research associate: Hui Dong, PhD
Senior research scientist: Xuejun Fan, PhD
Research scientist: Liaw Simon Li, PhD
Research associate: Xin Li, MS
Senior research scientist: Wei Xiong, PhD

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Cancer resistance mechanisms to therapeutic antibodies and modulation of anticancer immunity

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**Ningyan Zhang, PhD** Professor

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

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

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**Structural identification of binding epitopes of a functional anti-LILRB1 monoclonal antibody for development of cancer therapeutics.** From H. Chen et al. (2021) Antigen-Mediated Neutralizing Antibodies as a Treatment for Metabolic Syndrome. alif.4e.org/10.7554/eLife.63784.
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-UHM 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 on 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 is 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 time frame 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 UTHHealth 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 UTHHealth 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 cell research.

Nano 3D Printing Service Center
Nano 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

Total Funds Supporting Research

Total Expenses Supporting Research

IMM Extramural Funding Inception to Date

IMM Commercial Outcomes Inception to Date

- U.S. Patents Issued: 57
- License & Option Agreements Executed: 82
- Startup Companies Formed: 21
- Income Generated from Intellectual Property: $19,935,995
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
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Thank you to our donors, who through the establishment of these endowments, enable the IMM to recruit and retain top scientists from around the world.