THE UNIVERSITY of TEXAS MEDICAL SCHOOL at HOUSTON’S
BROWN FOUNDATION INSTITUTE of MOLECULAR MEDICINE FOR THE PREVENTION of HUMAN DISEASES

IMMpact Report

FISCAL YEAR 2014
ABOUT THE COVER

The University of Texas Medical School at Houston’s Brown Foundation Institute of Molecular Medicine for the Prevention of Human Diseases was established in 1995 to cure the diseases of our time in our time. The James T. Willerson, M.D., Discovery Hall is shown in this cover photo.

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Director’s Message

I am pleased to provide the latest edition of the IMMPact report for The Brown Foundation Institute of Molecular Medicine for the Prevention of Human Diseases (IMM). The current issue includes in-depth feature articles on recent developments and specific information on every IMM faculty member and the innovative research in which they are engaged. I trust that you will find the report interesting and informative.

The IMM is a stand-alone research institute that is embedded within The University of Texas Health Science Center at Houston, Medical School, which in turn is part of UTHealth. Our unique mission is to deliver translational outcomes from research in molecular medicine that benefits patients. We have teams of outstanding basic and translational scientists who collaborate closely with clinicians in UTHealth. The centers for metabolic and degenerative diseases, molecular imaging, and two of our flagship programs in regenerative medicine and drug development, plus others that are detailed in the report, provide excellent examples of these collaborative teams.

I am pleased to report that despite a persistent, very challenging environment for scientific research funding marked by significant reductions in the NIH budget by Congress over the past few years, IMM faculty have nevertheless been extremely successful. Over the financial year just ended, our new grants and contracts were up some 40% over the preceding year. It is truly a remarkable testament to the quality and creativity of our scientists that the IMM faculty remains so successful in attracting research funds from what is an ever-diminishing pool. That said, full implementation of our mission remains heavily dependent on attracting support from alternative sources, including research charities, industry collaborations, and, most importantly, the continuing generosity of our friends and donors.

In addition to advancing science and medicine, we therefore wish to further develop our relationships with all in our community who value the aspiration of our mission to translate molecular discoveries into new therapies for human disease. In this regard we are deeply appreciative of the strong work and dedication of the IMM advisory council, under the leadership of Mr. Dudley Oldham, which plays a key role in the continued growth and development of the IMM.

If you would like to investigate how you can be involved, we would be delighted to talk with you personally, so please feel free to contact us here at the IMM. Alternatively we would be delighted to see you at the upcoming IMM symposium, which will be held on April 1, 2015. Please mark this date in your calendar because you will hear exciting research stories directly from our faculty and have the opportunity to meet with them and discuss their science and its implications for the future of medicine and health care.

John Hancock, M.A., M.B., B.Chir., Ph.D., Sc.D.
Executive Director, Institute of Molecular Medicine
John S. Dunn Distinguished University Chair in Physiology and Medicine

The IMM has two major objectives:

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

2. New diagnostics and therapies are derivative of discovery and to the benefit of patients. The IMM focuses on these medical solutions. The IMM has organized talent in the Texas Therapeutics Institute to achieve this goal of patient benefit from discovery.

The Brown Foundation Institute of Molecular Medicine for the Prevention of Human Diseases (IMM) is a research institute that seeks to investigate the causes of human diseases at the cellular and molecular levels, using DNA and protein technologies to elucidate disease mechanisms. This development and progress are of particular interest for future planning in the increasingly important area of clinical research. The institute endeavors to design methods of rational therapy and, wherever possible, strategies for the prevention of human diseases.

Advances in molecular and cell biology have enormous potential for innovative medical research and the future practice of medicine with more novel therapies. These approaches have been most successfully used to determine the causes of infectious disorders and genetic diseases.

However, it is clear that molecular and cell biology will play a major role in clarifying the causes of many unsolved problems of modern medicine, such as heart disease, hypertension, vascular disorders, major mental illnesses, and inflammatory and immunologic diseases. The research of the institute’s investigators is inspiring and promises to fulfill the mission of the IMM.

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

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

Fayez S. Sarofim Research Building

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

South Campus Research Building – 3 (SCRB3)

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

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

- The IMM occupies a 31,000 square-foot high-tech laboratory.
- Located in the Texas Medical Center.

Help us cure the diseases of our time within our time

Armed with investigators seeking tomorrow’s cures, the Brown Foundation Institute of Molecular Medicine for the Prevention of Human Diseases is making incredible discoveries for the benefit of those who suffer from such debilitating diseases as diabetes, stroke, obesity, and lung disease. We are able to make a difference in patients’ lives today through the generous support of our donors.
Researchers target
BLOOD CIRCULATION ISSUES

When the body has difficulty pumping blood to legs, arms, and other extremities, bad things can happen.

In the United States, millions have a circulatory problem of the legs called peripheral vascular disease. It can be painful and may even require surgery in serious cases. This disease can lead to severe skeletal muscle wasting and, in turn, limb amputation.

Brown Foundation Institute of Molecular Medicine for the Prevention of Human Diseases scientists tested a non-surgical, preventative treatment in a mouse model of the disease and found it associated with increased blood circulation. Their proof-of-concept study appeared earlier this year in the journal *Cell Reports*.

Unlike previous studies in which other investigators used individual stimulatory factors to grow blood vessels, IMM researchers identified and turned off a genetic switch that stifles blood vessel development, says Vihang Narkar, Ph.D., senior author and assistant professor in the Center for Metabolic and Degenerative Diseases.

“We discovered an inhibitory switch that degrades blood vessels,” Dr. Narkar says. “We were able to genetically turn it off to prevent peripheral vascular disease in a preclinical study.”

Not limited to peripheral vascular disease, this discovery also could aid in the treatment of other conditions affecting blood vessels like diabetic retinopathy, diabetic nephropathy, and atherosclerosis. The prevalence of peripheral arterial disease rises with age, affecting more than 5 percent of individuals between 50 and 60 years of age, and 10 to 20 percent of people more than 70 years of age.

More than 29 million people in the United States have diabetes and its related complications. Approximately eight million of them do not know they have diabetes. Millions have hardening of the arteries – atherosclerosis – that is serious yet asymptomatic.

Dr. Narkar is now testing this genetic switch in mouse models of diabetic vascular complications.

“We found that this inhibitory switch is naturally turned on in a mouse of model of diabetes. We’re doing tests to see what happens when it is turned off,” he says.

The switch is called peroxisome proliferator-activated receptor gamma co-activator 1 beta (PGC1beta).

As for his vision for this research, Dr. Narkar says, “We are trying to identify cellular pathways that we can target with disease-selective drugs to treat vascular complications and build healthy blood vessels.”

“Eighty percent of limb amputations are due to lack of adequate blood flow,” says Kristofer Charlton-Ouw, M.D., assistant professor in the Department of Cardiothoracic and Vascular Surgery.

“The lack of blood flow is primarily due to blockages in the arteries from a build-up of atherosclerotic plaque. Sometimes, clinicians can crush open the plaques using balloons or stents. Other times, we can reroute the blood flow around the blocked arteries using bypass surgery. Unfortunately, many patients have failed treatment or they are not candidates for it and the result is limb loss.”

Dr. Charlton-Ouw adds, “Dr. Narkar and colleagues provide an exciting new potential treatment for these patients by stimulating new blood vessel growth.

“The method is innovative in that they blocked the natural inhibitors and tipped the balance in favor of new growth. This has the potential to treat millions of people with painful and debilitating blood flow problems.”

Dr. Vihang Narkar is working to help those with peripheral vascular disease.
Obesity - is it all in your brain?

Those concerned about their weight know that major lifestyle changes — improving diet and increasing exercise — are the keys to long-term weight-loss success. But one researcher at the Brown Foundation Institute for Molecular Medicine is taking a microscopic approach to controlling weight and preventing obesity.

Qingchun Tong, Ph.D., and his team are working to identify specific neurons and neural pathways in the brain that stimulate or inhibit feeding. The goal is to identify drug therapies to target these brain cells to ultimately regulate weight.

“We are working on neuron-specific manipulation in mice to activate, or inactivate, specific groups of neurons, or key genes in the brain, to delineate neurocircuits important for feeding and energy expenditure.”

Current drugs used to curb obesity are few in number, rife with side effects, and are not very effective. Instead of blindly throwing a dart on a board, hoping to hit a target, Dr. Tong is working on finding very specific targets to create the most effective drug therapies.

“Ultimately, we want to use the brain as the drug target, as the brain is what coordinates the other organs,” he says.

With billions of neurons in the brain, Dr. Tong and his team’s work seems like seeking the proverbial needle in a haystack.

“To achieve our goals, we are using the optogenetic approach, which allows us to activate or inhibit a specific group of neurons with millisecond resolution. This way of using light control of neuron activity provides a direct assessment of inter-neuronal communication,” Dr. Tong says.

An associate professor in the Center for Metabolic and Degenerative Disease, Dr. Tong joined the IMM in 2009. He earned his Ph.D. from SUNY Downstate Medical Center and completed postdoctoral training at Beth Israel Deaconess Medical Center and Harvard Medical School.

His lab’s research on how the brain controls feeding, energy expenditure, and glucose homeostasis recently was published in Cell, Cell Metabolism, and Molecular Metabolism.

“We are generating new mouse tools and combine mouse genetics with optogenetics to identify novel types of neuron in the brain for body weight regulation and feeding,” Dr. Tong explains.

The group also is investigating the underlying actions of the hormone leptin in glucose homeostasis to identify potential drug targets for use in patients with Type 1 diabetes.

Leptin, known as the “fullness” hormone because it increases metabolism, curbs appetite, and maintains body weight homeostasis, is secreted from fat tissues in proportion to fat mass. Recently, it was found that leptin action in the brain fully restores glucose levels to normal in Type 1 diabetes.

In Type 1 diabetes, an autoimmune disease, patients’ blood glucose levels are too high and the body does not make insulin, which is the hormone that regulates glucose use. As many as 3 million Americans have Type 1 diabetes.

“Something goes wrong in Type 1 diabetes — a very low leptin concentration is observed and thus, the leptin action in the brain to control glucose is inactive. We are researching how the brain senses, responds, and transmits the signal for leptin in glucose homeostasis,” Dr. Tong says.

Dr. Tong and his team are studying this pathway in order to identify a new drug target, with a goal of using the target alone, or in concert with insulin, to control the uncontrolled glucose level in Type 1 diabetes.

“We are generating animal models to determine the neurons, transmitters, and pathways involved in Type 1 diabetes,” Dr. Tong says. “The beneficial effect of leptin is that it doesn’t cause hypoglycemia or fat accumulation, the typical side effects associated with insulin treatment.”
Stem cell therapy holds promise for muscular dystrophy

For 45 years, viewers would be glued to the TV as Jerry Lewis would signal the timpani and watch the tote board rise higher and higher as he led the annual Muscular Dystrophy Association (MDA) telethon. Many people first learned of muscular dystrophy through this fundraising show, but what is the status of muscular dystrophy research today?

Thousands of researchers around the globe continue to seek the answers that will one day provide treatment for this debilitating genetic disease. There are still no cures available for patients afflicted with one of the nine types of muscular dystrophy – only palliative measures are offered to improve the quality of life.

Radbod Darabi, M.D., Ph.D., assistant professor at the IMM’s Center for Stem Cell and Regenerative Medicine, has dedicated his research career to developing therapies for Duchenne Muscular Dystrophy (DMD). During the last decade, his research has pioneered use of stem cells for muscle regeneration in mice models of muscular dystrophies. As a recipient of a three-year MDA research award, his goal is to develop a treatment that uses healthy stem cells to replace the muscle cells destroyed by this aggressive disease.

DMD affects about one in 3,500 male births worldwide. Since the disease is caused by a defective gene on the X chromosome, and girls have two copies – one of which can be used as a backup, few girls are affected. Onset of the disease, characterized by muscle weakness, usually starts in early childhood, and by age 12, most patients are confined to a wheelchair. Heart and respiratory muscles are affected by DMD, and few patients live past their 30s.

“In addition to developing stem cell therapies, we want to use patient’s own reprogrammed stem cells for gene correction and therapy,” Dr. Darabi explains.

One of the challenges DMD presents to researchers is that the DMD gene is the largest known human gene, which makes its correction even harder. This gene is responsible for encoding the muscle protein dystrophin. Patients with DMD cannot make the dystrophin protein in their muscles. This deficiency eventually leads to progressive muscle damage and its gradual replacement by fat and fibrotic tissues.

“Stem cells are the one of the best candidates for treatment of degenerative disorders like this, as they can be differentiated to the any needed cell type and be reproduced endlessly,” Dr. Darabi says.

Darabi and his lab currently use a mouse model with DMD to test the human iPS cells – correcting the defective genes, generating muscle progenitor cells from the iPS cells, and then delivering the cells systematically to affected muscle groups. We are also looking to improve vascular circulation in the muscle where the stem cells are transplanted, to provide a healthier environment for them,” he adds.

Therapy must first be validated in mice before it can move to a clinical trial in humans. In order to translate this research to the human patient, a clinical grade safe cell preparation is needed – a very pure myogenic population without any animal product. Due to new advances in this field, especially new gene editing technologies, Dr. Darabi estimates it won’t be very long until we see clinical trials in the United States begin.

Dr. Darabi has been with the IMM for just over a year. He completed his postdoctoral training at UT Southwestern at Dallas and was a research faculty at the University of Minnesota before joining the IMM faculty at the Center for Stem Cell and Regenerative Medicine (CSCRM).
As a medical chemist, Dr. Kyoji Tsuchikama brings a new perspective to the Texas Therapeutics Institute. Medicinal chemists bring knowledge, expertise, and techniques to the translational field of research.

“Medicinal chemists bring knowledge, expertise, and techniques to the translational field of research.” — Dr. Kyoji Tsuchikama

T
he importance of the health care team is ingrained into the students of each of our six health-related schools. It’s not just the doctor, they learn, but a team of health experts who are dedicated to improving the patient’s well-being.

What we do not hear a lot about is the importance of a well-rounded research team. Research doesn’t happen in a silo, there are postdoctoral fellows, lab assistants, and technicians. But what about the researchers themselves — what kind of specialists must they be to move the chains on research?

The Texas Therapeutics Institute (TTI) of the IMM is comprised of investigators mostly from pharmaceutical and biotechnology companies whose goal is to identify and validate drug targets. These researchers have backgrounds rich in biology.

What TTI has lacked is a medicinal chemist who can support the existing research or develop new platforms.

Enter Kyoji Tsuchikama, Ph.D., who was recruited to TTI as an assistant professor in July to provide such chemistry expertise for the institute.

Dr. Tsuchikama hails from Japan, but most recently was at the Scripps Research Institute in La Jolla, Calif., where he completed a postdoctoral training in organic synthesis and chemical biology. He received his doctoral degree in organic chemistry from Waseda University in Japan.

“Chemistry is the basis of drug development, and until now TTI lacked chemists who can support such research,” Dr. Tsuchikama explains.

TTI researchers have identified proteins of interest for drug development. “But without a chemical tool, they suffer from difficulty validating the biochemical process. Such chemical tools are occasionally not commercially available, and a chemist is needed to make compounds and tools,” Dr. Tsuchikama says.

As the only organic chemist in the TTI, Dr. Tsuchikama says he will be expected to have a cooperative program, “filling the gaps” throughout the institute. In addition, he will do his own original research.

He is already in discussions with Gerald Bills, Ph.D., to pursue natural products and chemical agents to suppress microbial infection, and with Xiaodong Cheng, Ph.D., on a kinase inhibitor project that will focus on creating chronic pain and cancer-fighting drugs.

“My goal is to identify promising therapeutics using chemical methods,” Dr. Tsuchikama says.

Dr. Tsuchikama’s areas of research interest include treating and stopping the spread of infectious diseases, like staph and Ebola.

“There are so many proteins involved in cell physiology and diseases. We seek to understand the network of protein function — how the proteins work together to control cell function, or progress or suppress disease,” he says.

Including medicinal chemists on the biomedical research team is catching on with other progressive institutes. The University of Texas MD Anderson Cancer Center has such programs, whereas most traditional universities do not.

“Medicinal chemists bring knowledge, expertise, and techniques to the translational field of research. Our presence will give the TTI more insights to development drug candidates,” he says.

Dr. Tsuchikama says he enjoys being able to bring a new perspective to TTI’s research.

“I really like this environment of having biology experts as colleagues. It’s more important than being with just chemists,” he says. “With our complementary interests and expertise, this place has a lot of chances.”
Sixteen years ago, Steve Gordon and his wife, Janice, lived in a dream world—a world that ended in one day.

“I guess we all think that if you get sick, you go to the doctor, the doctor cures you, and you go home,” he says. “And then one day you’re told there’s no cure.”

At age 54, Janice Gordon’s colonoscopy revealed stage four colon cancer. While the disease can usually be overcome in its early stages, it is almost always fatal if caught later.

She knew from the minute they came out of the room,” Steve Gordon says. Doctors gave Janice Gordon six months to live, but she and Steve Gordon fought the disease for two years before she passed. As her main caregiver, he saw the toll the cancer took.

“The tragic things that happen in your life motivate you to do something,” he says. Since his wife’s passing 14 years ago, Gordon has worked with UTHealth to fight the disease that took her life. He pledged $250,000 in 2004 to establish an endowed faculty position, called the Janice Davis Gordon Distinguished Professorship in Bowel Cancer Research, at the UTHealth Medical School’s Brown Foundation Institute of Molecular Medicine (IMM).

After fulfilling the pledge in 2009, he enhanced the position to an endowed chair with an additional $250,000 commitment.

“The goal in my mind is to find, if not a cure, at least a treatment for advanced colon cancer that would allow people to live sort of like when people are diagnosed with diabetes,” Gordon says.

Dr. Qingyun “Jim” Liu is the current faculty holder of the Janice Davis Gordon Chair in Bowel Cancer Research, and he is exploring treatments that could give new hope to patients. One particular avenue is called “targeted therapy,” which introduces medicine directly into the cancer to kill it without harming surrounding tissue.

“This approach could potentially treat patients much more effectively than we have been able to do so far,” Dr. Liu says.

Gordon knows it’s a tough disease to fight. He remembers his wife undergoing chemotherapies that would work for a few months before the cancer found a way around them. But he is encouraged by Dr. Liu’s work indicating major treatment advances may finally be on the way.

“I don’t want to give up,” Gordon says. “I don’t know any other route than to try to help the research go forward.”

Recently remarried, Gordon is determined that he will not be stricken with colon cancer. He touts his bi-annual colonoscopy appointments like badges of honor and insists that everyone over 50 should have the test done frequently.

“They told me if my wife had gotten a colonoscopy six months or a year before she did, she would probably be alive today,” he says. “It’s that important.”

In addition to giving to support colon cancer research, Gordon dedicates his time to fighting disease by serving on the UTHealth Development Board and the IMM Advisory Council.

“You don’t just stand by as a bystander and hope somebody else is doing something,” he says. “You can feel like you’ve done a little bit in the way of helping mankind toward a cure for a deadly disease.”

It’s a mindset he shares with many others; most of the donors he meets at dinners and meetings have had similar experiences, shaken out of complacency and into action when they or someone they love were struck with a serious illness. They know, as he does, that even if they can’t do it all, they can make a difference.

“In the big picture, what I’m giving is not even a water drop, but you try to do what you can, and maybe in the future at some point there will be a solution to this,” he says. “That’s what we hope for.”

Steve Gordon and Susan Atkins are doing their part to support bowel cancer research.

Loss brings IMM Donor’s Generosity to Life
These studies are designed to delineate the molecular genetic and genomic basis of cardiovascular diseases in humans with a specific focus on three most common forms of hereditary cardiomyopathies: namely Hypertrophic Cardiomyopathy, Dilated Cardiomyopathy, and Arrhythmogenic Cardiomyopathy. The studies entail recruitment and clinical characterization of patients with hereditary cardiovascular diseases, genetic testing through nuclear acid sequencing, and studies to test for the causality of the variants. II. Functional characterization of the generic variants identified in humans with cardiovascular diseases: These studies are conducted in cardiac myocytes through gene transfer studies and in genetically engineered animal models. III. Experimental Therapies: Upon delineation of the molecular mechanisms specific pathways that are responsible for the induction of the phenotype are pharmacologically and genetically targeted in myocytes through in vitro and in vivo studies. IV. Clinical Studies: The discoveries are then confirmed in cell culture systems and animal models in order to delineate the molecular links between the causal variants and the phenotype. Upon elucidation of the molecular links between the physiological mechanisms and the clinical phenotypes, genetic and pharmacological interventions are pursued to block the linking pathways in order to prevent and reverse the phenotype. The initial intervention studies are pursued in cell and animal models and then extended to humans through pilot randomized placebo-controlled trials.

Research Programs: The research programs are categorized into four categories:

1. Human molecular genetics/genomics: These studies are designed to delineate the molecular and genetic basis of cardiovascular diseases in humans with a specific focus on three most common forms of hereditary cardiomyopathies: namely Hypertrophic Cardiomyopathy, Dilated Cardiomyopathy, and Arrhythmogenic Cardiomyopathy. The studies entail recruitment and clinical characterization of patients with hereditary cardiovascular diseases, genetic testing through nuclear acid sequencing, and studies to test for the causality of the variants. II. Functional characterization of the generic variants identified in humans with cardiovascular diseases: These studies are conducted in cardiac myocytes through gene transfer studies and in genetically engineered animal models. III. Experimental Therapies: Upon delineation of the molecular mechanisms specific pathways that are responsible for the induction of the phenotype are pharmacologically and genetically targeted in myocytes through in vitro and in vivo studies. IV. Clinical Studies: The discoveries are then confirmed in cell culture systems and animal models in order to delineate the molecular links between the causal variants and the phenotype. Upon elucidation of the molecular links between the physiological mechanisms and the clinical phenotypes, genetic and pharmacological interventions are pursued to block the linking pathways in order to prevent and reverse the phenotype. The initial intervention studies are pursued in cell and animal models and then extended to humans through pilot randomized placebo-controlled trials.

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Molecular genetics and pathogenesis of hereditary cardiomyopathies

The focus of my research is the delineation of pathogenesis of cardiomyopathies. Cardiomyopathies are genetically transmitted diseases of the heart muscle, associated with high risk of sudden cardiac death and heart failure. Although significant progress has been accomplished over the past two decades in revealing the causal genes, at the present time there is no effective pharmacological or non-pharmacological therapy for these disorders. In fact, even if the current pharmacological approaches provide some benefits for symptom control, they have been unable to fundamentally change the natural history of these diseases.

We study the 3 most common forms of cardiomyopathies, namely hypertrophic cardiomyopathy (HCM), Arrhythmogenic Cardiomyopathy (AC), and Dilated Cardiomyopathy (DCM). Our group has developed cell culture models as well as genetically modified animal models of human cardiomyopathies. The mechanistic findings in the in vitro and in vivo models have led to the identification of key molecular pathways implicated into the pathogenesis of these diseases. More recently, my studies have addressed the pathogenesis of the unique phenotype of MRC characterized by replacement of the cardiac myocytes with fat cells and fibrosis. The main focus of these studies is the identification of the cellular origin of excess adipocytic in AC. Through genetic fate-mapping experiments, I have identified a subset of cardiac progenitor cells from the second heart field (the embryonic source of the right ventricle) as a cell source of fibro-adipogenesis in cardiomyopathies. Gene expression analysis using cDNA microarrays has led to the identification of the fibro-adipogenic pathway for fibro-adipogenesis in cardiomyopathies.

RESEARCH PROJECTS

• Delineation of the signaling pathways involved in the pathogenesis of primary cardiomyopathies.
• Identification and molecular characterization of cellular source of fat-adipogenesis in cardiomyopathies.
• Molecular pathogenesis of cardiac adipogenesis in cardiomyopathies.

KEY PUBLICATIONS


* Authors contributed equally to this work


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Sue Nee Chen, Ph.D., Post-doctoral fellow
Chen, Xiaoran, M.D., Post-doctoral fellow
Karmazin Jennifer, Ph.D., Post-doctoral fellow
Rodriguez Edward, Research Assistant
Grzyna Czernuszewicz, Research Associate

Morphological changes in the HL-1PKP2:shRNA myocytes. Bright field (A) and Phalloidin staining of HL-1PKP2:shRNA myocytes at 3 sets of magnifications (B). The HL-1PKP2:shRNA exhibit altered cellular morphology and cytoskeletal organization.

The efficacy of some of the treatments I tested in animal models has been and is currently being tested in human patients through pilot randomized placebo-control trials. For my studies on cardiomyopathies I was awarded with the “The 2008 Liudas N. and Arnold M. Katz award” from the American Heart Association, which is the most prestigious award given to young investigators in the cardiovascular field.

T he investigators of the Center for Human Genetics work to understand and reduce common cardiovascular diseases. Heart and kidney diseases, high blood pressure, and stroke are linked together and together have a larger impact on the health of our population than any other disease process. Heredity impacts our risk of these diseases. By discovering how variation in our genes produces disease risk, we identify pathways of disease and new avenues for prevention and treatment.

Work in our center targets DNA sequence, gene expression, and gene function using modern genetic and genomic methods. Our work involves large-scale studies of genetic variation and disease in human populations. We also use model organisms to understand how changes in the sequence of the genome affect protein function and how the resulting abnormalities advance to produce disease.

Progress in the laboratories of our investigators has provided important new understanding of susceptibility to atherosclerosis, coronary artery disease, progressive kidney disease, stroke, and high blood pressure. We have begun a major new initiative to identify genetic variation contributing to Alzheimer’s disease and age-related neurodegeneration, extending our studies of the interactions between cardiovascular function and brain disease in this new and critical direction.
Eric Boerwinkle, Ph.D.
Professor and Director of the Center for Human Genetics
Kazemzadeh Family Chair in Human Genetics


genomic sciences to promote human health

**My research interests focus on the genetic basis of common chronic diseases with an emphasis on vascular disease of the brain and brain aging. Patients with acute stroke and dementia represent the easily recognized “tip of the iceberg” but the deleterious effects of vascular and neurodegenerative disease on the brain begin well before clinical symptoms become apparent. Brain abnormalities, readily detectable by magnetic resonance imaging (MRI), are common in asymptomatic populations beginning in middle age. My research program investigates the genetics and genomics of vascular and neurodegenerative disease of the brain in both its clinical and preclinical forms in well-characterized populations from young adulthood to old age. Research strategies combine genetic epidemiology and functional genomic approaches using the latest genome resources and technologies. In recent years, I have used the power of genome-wide association and sequencing studies in collaboration with researchers in the United States and Europe to identify genetic loci influencing the risk of stroke, dementia, and related phenotypes. Current work aims at identifying the specific genes and mutations that underlie these diseases and to understand the function of these genes in brain health and disease.**

**RESEARCH PROJECTS**

- Discovering common and rare genetic variants influencing MR-defined white matter lesions and other MRI traits related to brain vascular disease and dementia using large-scale genotyping and exome sequencing (RO1-AG033193, U01-AG049506, and RO1-NS087544).
- Discovering novel epidemiological variants that influence risk for brain small vessel disease and its related neurocognitive outcomes (RO1-AG038741).
- Discovering common and rare genetic loci influencing risk for ischemic stroke and its etiologic subtypes in well-characterized clinical samples from the MNOS Stroke Genetics Consortium (RO1-A007508).
- Discovering common and rare genetic loci influencing cardiovascular traits (lipid and blood pressure) in diverse ethnic groups as part of the NHGRI Population Architecture and Genomic Epidemiology (PAGE) consortium (U01-HG007316).
- Discovering additional genetic loci for cardiovascular traits using gene-wide interactions, pleiotropy analysis of correlated traits, and pathway analysis (RO1-HL113830).

**KEY PUBLICATIONS**


**LAB MEMBERS**

Xunjie Yan, PhD, Postdoctoral Fellow
Tongbo Chen, PhD, Postdoctoral Fellow
Lei An, BS, PhD Student
Melissa Richards, PhD, Postdoctoral Fellow
Ping Wang, PhD; Research Associate
Li-An Lin, BS; PhD Student
Taebeom Kim; PhD Student
Xueqiu Jian, PhD; Postdoctoral Fellow

**BRAIN MAGNETIC RESONANCE IMAGING SHOWING SUBCORTICAL WHITE MATTER HYPERINTENSITY, ATROPHY OF GRAY MATTER, AND ENLARGED VENTRICLES.**

**CARDIOVASCULAR DISEASE**

Cardiovascular disease is the leading cause of death globally. My laboratory is interested in the discovery of mechanisms contributing to the complex process of atherosclerosis in humans and in animal models. Our laboratory investigates the molecular pathogenesis of atherosclerosis, and we study genes involved in the onset and progression of this disease. Recently, we discovered that PCSK9 (proprotein convertase subtilisin/kexin type 9) is the mediator for the development of atherosclerosis. PCSK9 activates the scavenger receptor LDL-1 (also called scavenger receptor-1) in the vascular endothelial cells, promotes inflammatory responses from monocytes and macrophages, and induces the release of pro-inflammatory cytokines. Furthermore, we explore cell therapies to repair and regenerate atherosclerotic lesions. Our findings provide new therapeutic strategies to manage the progression of atherosclerosis.

We engineer novel human rhomboid zymes as therapeutic agents to inhibit gene expression in vivo. As a result, we have created a novel approach to manipulating gene expression to prevent disease progression. Furthermore, we exploit cell therapies to repair vascular lesions. By better diagnosis of early and progressive disease development, we use new technology and techniques to identify new disease markers. These markers provide valuable information to predict disease events in patients.

**RESEARCH PROJECTS**

- The role of PCSK9 (proprotein convertase subtilisin/kexin type 9) in lipid metabolism and atherosclerosis development.
- Investigating the action of novel fibroblast growth factor in regulating the production of apolipoprotein B and lipoprotein-associated phospholipase A2 (Lp-PLA2) in macrophages.
- The regulation of PCSK9 in atherosclerosis development.
- Identify disease markers by metabolomics and miRNA profiling.
- Development of viral vectors for therapeutics.

**LAB MEMBERS**

Mentor: Pei-Ying Chung, PhD (Assistant professor and Director of NMD-1 Lab)
Research Assistants: Michael Tan
Samantha Lee, Joseph M. Reynolds, Shino Hanabuchi, Huaizhu Wu, Ba-Bie Teng, and Yeonseok Chung.

**Molecular genetics of atherogenesis and the development of genetic and cell therapies for the treatment of atherosclerotic vascular diseases**

**KEY PUBLICATIONS**


Hua Sun, Jere Samantad, Ningyu Zhang, Zemin Yee, Monroe Xang, and Ba-Bie Teng: Proprotein Convertase Subtilisin/Kexin type 9 interacts with apolipoprotein B and prevents its intracellular degradation, irrespective of the low-density lipoprotein receptor. (2012) Arterioscler Thromb Vasc Biol. 32: 1588-1595.


**LAB MEMBERS**

Mentor: Ping Yang Chang, PhD (Assistant professor at School of Nursing)
Research Assistants: Michael Tan
Summer Intern: Jineke Peter Xing, Medical student from University.

**A CROSS-SECTION OF AORTIC AERIALS OF AN LDB MOUSE WITH AVERAGE AORTIC LESIONS. THE SECTION IS STAINED WITH MACROPHAGE MARKER CMU6 (GREEN COLOR), WHICH INDICATES THE LESIONS CONTAIN LARGE AMOUNT OF MACROPHAGES.**
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. In concert with the molecular studies, the Center’s scientists have engineered mice with specific targeted gene mutations or deletions.

As part of its interest in pulmonary immunity, the Center recently established a robust research program focused on the development of stem cell therapeutics for the treatment of acute and chronic lung diseases and for genetic deficiencies that affect normal lung function. The Center’s scientists are also actively pursuing the generation of genetically engineered stem cell lines that will avoid immune mediated graft rejection during transplantation procedures. Research interests include:

- Asthma and Sinusitis
- T-Cells & Cytokine Biology
- Mucoarial Immunology & Autoimmunity
- Microbial Infectious Disease
- Acute Lung Injury and COPD
- Surfactant Deficiencies
- Lung Stem/Progenitor Cells
- Pulmonary Regenerative Medicine

Innate respiratory diseases are a leading cause of mortality and morbidity worldwide. There are over 35 million Americans with lung disease and it is the number three killer (behind heart disease and cancer) in the United States, accounting for approximately 400,000 deaths per year. It is also a major cause of death in babies under 1 year of age, accounting for approximately 30 percent of infant mortality. Current treatments for lung disease at best provide symptomatic relief but offer no prospect of cure or disease reversal. Lung transplantation is the only viable option for patients with severe chronic lung disease. Lung disease is commonly caused by virus and bacterial infections (Pneumonia), environmental toxins (Chronic Obstructive Pulmonary Diseases-emphysema), allergies (asthma), and genetic mutations (Cystic Fibrosis-Surfactant deficiencies). Robust and well regulated immune, inflammatory, and cellular repair responses are critical in controlling the severity of lung disease as well as preventing the development of irreversible chronic lung pathologies. However, the paucity of cellular and molecular knowledge regarding lung immunity and tissue regeneration has slowed the development of novel therapeutics that could be used for the effective treatment of lung disease.

Our laboratory for the past several years has focused on delineating key molecules responsible for mediating the inflammatory and immune responses in the lung during both normal and pathological conditions. Much of this research has involved studies of the complement system, adhesions, and their specific receptors (C3aR and C5aR1). These receptors are seven-transmembrane G protein coupled receptors that mediate numerous biological responses in inflammation and immunity, including smooth muscle contraction, histamine release from mast cells, vasodilation, and directed migration of numerous peripheral blood leukocytes. To examine the requisite role of the anaphylatoxin receptors in lung disease, our laboratory has generated numerous “knock-out” mice in which the genes encoding these receptors, their ligands, and carbohydrates have been selectively ablated by gene targeting and homologous recombination methods. The generation of these mice has facilitated the discovery of numerous biological roles of the anaphylatoxins in the pathogenesis of lung disease. For example, studies using mice in which the C3aR receptor has been deleted have demonstrated that C3aR is a mediator of key hallmarks of asthma, including airway hyperresponsiveness, mucus production, lung cellular inflammation, and the CD4+ TH2 cytokine response. We also are investigating the therapeutic use of embryonic (ES) and induced pluripotent (iPS) stem cell derived progenitor cells. Part of this program has focused on the development of stem cell therapeutics for the regeneration of lung epithelium destroyed by acute lung injury as well as by chronic lung diseases such as COPD. This research has led to the generation of the first pure population of lung alveolar epithelial type II cells from human ES cells. These cells were recently demonstrated to abrogate lung epithelial damage in an acute lung injury model in mice. In addition, we are exploring the therapeutic potential of gene corrected patient specific iPS cells for the treatment of genetic diseases affecting the lung such as surfactant protein B deficiencies.

Research interests include:

- Asthma and Sinusitis
- T-Cells and Cytokine Biology
- Mucoarial Immunology and Autoimmunity
- Microbial Infectious Disease
- Acute Lung Injury and COPD
- Surfactant Deficiencies
- Lung Stem/Progenitor Cells
- Pulmonary Regenerative Medicine

Innate immunity, inflammation, infectious diseases, and pulmonary regenerative medicine

Rick Wetsel, Ph.D.
Professor and Director of the Center for Immunology and Autoimmune Diseases
Hans J. Muller-Eberhard, M.D., Ph.D. and Irma Gigli, M.D. Distinguished Chair in Immunology

Innate immunity, inflammation, infectious diseases, and pulmonary regenerative medicine

Research interests include:

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Innate immunity, inflammation, infectious diseases, and pulmonary regenerative medicine

Rick Wetsel, Ph.D.
Professor and Director of the Center for Immunology and Autoimmune Diseases
Hans J. Muller-Eberhard, M.D., Ph.D. and Irma Gigli, M.D. Distinguished Chair in Immunology

Innate immunity, inflammation, infectious diseases, and pulmonary regenerative medicine
Inflammation and remodeling responses are present features of chronic lung diseases such as asthma, chronic obstructive pulmonary disease (COPD), and pulmonary fibrosis, and pulmonary hypertension. Although signaling pathways associated with the genetics of these diseases have been described, little is known about the signaling pathways that seem to regulate the chronic nature of these diseases. The major goal of our laboratory is to identify pathways that regulate the chronicity of these diseases 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 across pathways that serve to propagate inflammation and remodeling. Adenosine signals by engaging specific adenosine receptors on target cells, such as inflammatory cells, fibroblasts, airway epithelial cells, and smooth muscle cells. Most of the projects in my laboratory focus on understanding the mechanisms by which adenosine signals to control the activities of these cells in the context of lung inflammation and remodeling.

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

**Research Projects**

- Examining the roles of A2B adenosine receptor expression on pulmonary macrophages during the progression of pulmonary fibrosis.
- Investigation of adenosine transport in acute and chronic lung injury.
- Novel regulation of mRNA poly-tails in the regulation of pulmonary fibrosis and Chronic Obstructive Pulmonary Disease.
- Examination of the hypoxia as an amplifier of chronic lung disease.
- Understanding novel mechanistic roles for IL-6 signaling in pulmonary fibrosis.
- Systems Biology approaches to understand the progression of chronic lung disease.

**Key Publications**


**LAB MEMBERS**

Henry Karmouty-Quintana, Ph.D., Assistant Professor
Tingting Wang, Ph.D., Assistant Professor
Keji Vakili, Ph.D., Senior Research Scientist
Jonathan Dawes, M.D., Wounding Scientist
Frank Liu, Ph.D., Postdoctoral Fellow
Kendy Wong, M.D., Ph.D., Student
Ning-Ke Chen, Research Associate
Jose Molina, Sr. Research Scientist
Luis Garcia-Morales, Research Assistant

Primary type I/II alveolar epithelial cells isolated from genetically modified mice.

**Increased expression (brown color) of protein in pulmonary macrophages in mice with pulmonary fibrosis (H&E).**

**Different types of T cell response mediator multiple arms of immune function to efficiently propagate protection immune against infectious disease and malignancy. However, most chronic inflammatory diseases also are associated with aberrant helper T cell responses. Understanding the regulation of helper T cell responses therefore is necessary not only for optimizing protective immunity but also for preventing aberrant inflammatory responses.** In this aspect, we are particularly interested in the regulatory role of IFN-γ and IL-17 producing helper T cells (Th17) in the regulation of helper T cell subsets in disease settings, including allergic asthma, autoimmune disorders, and cancers. Among diverse helper T cell subsets, we are currently focusing on the regulatory function of follicular helper T cells (Tfh) and Th17 producing helper T cells (Th17) as they are associated with many types of immune disorders.

Mucosal areas, including gut and lung, are always exposed to non-self environmental components such as commensals, food, or air-borne infectious agents, allergens, or food. The immune system in these mucosal tissues differs from that of non-mucosal lymphoid tissues. We are currently investigating the cross-talk between mucosal immune components and helper T cell responses by using diverse animal models.

Regulatory T cells are essential for preventing autoimmune disorders but also play a detrimental role in viral and tumor immunity. Our recent study has identified a unique subset of regulatory T cells - termed ‘follicular helper regulatory T cells’ that function to specifically suppress germinal center responses and subsequent antibody production from B cells. Considering many autoimmune diseases are mediated by autoimmune antibody responses, the use of follicular regulatory T cells might be beneficial for the treatment of autoimmune diseases by suppressing the production of the autoreactive antibodies. We are actively investigating the development of this regulatory T cell subset, and whether cellular therapy with follicular regulatory T cells can control autoimmune diseases in animal models. Ultimately we hope to provide a fundamental basis for the use of this novel cell population in a clinical setting.

Another major focus in our group includes understanding the regulation of cell responses by non-immune factors such as obesity, cholesterol, or hormones. The hypothesis here is that the immune system and metabolic pathways mutually regulate the other and contribute to complex disease phenotypes. We are primarily focusing on the changes of cytokine and T cell immunity in animal models of metabolic diseases. Outcomes of this study will allow us to better understand metabolic and immune-mediated disorders with multiple scientific angles.

**Research Projects**

- Understanding helper T cell responses in mucosal area.
- Molecular regulation of follicular regulatory T cells and its application.
- Role of metabolic factors in shaping T cell responses and autoimmunity.
- Developing novel vaccines approaches for cancer and infectious agents.
- Regulation of type 1 innate lymphoid cells in the airway.

**Key Publications**

- Subsets of helper and regulatory T cells
- Inflammation in the spinal cords by autoimmune T cells
- Germinal center reaction

**LAB MEMBERS**

Post Doc: Huyong Lim, Ph.D.
Ph.D. Student: Young Uk Kim

**Assistant Professor**

**PhD Candidate**

**Research Assistant**

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

Respiratory epithelial cells represent the first line of defense against the environment for sinonasal mucosa. Recent studies have shown that epithelial cells serve an active role through regulation of cytokines and release of anti-microbials. Three identified epithelial cell-derived cytokines, rhinoviral strain (interleukin-10, IL-10) and 33, have been linked to the Th2 immune response. Our lab has focused on the role of IL-33 in the Th2 immune response characteristic of CRS with nasal polyps. We recently confirmed that the receptor of IL-33 is upregulated in the diseased sinonasal mucosa of CRSwNP. In a recent publication, we demonstrated that innate lymphoid type-2 cells (ILC2) are preferentially found in CRSwNP patients relative to health controls and patients with CRS without nasal polyps. These ILC2 express ST2, the receptor for IL-33, and represent the major cell type producing IL-13 in response to IL-33. Interestingly, we found that fungal antigens, specifically Aspergillus, can stimulate respiratory epithelial cell release of IL-33. We are currently investigating expanding these initial observations. Ongoing studies focus on clarifying the molecular pathway responsible for the fungal signaling and characterizing innate lymphoid cells in CRS outcomes. In addition, we are investigating translational implications of addressing IL-33 in CRS and asthma.

RESEARCH PROJECTS
• Immune-molecular characterization of important cell types involved in the Th2 immune response.
• Molecular signaling through respiratory epithelial cells of lung alveoli and other environmental triggers responsible for initiating and/or maintaining the characteristic Th2 immune response.
• Clinical characterization and identification of biomarkers for CRS outcomes.

When nasal polyps are seen in nasal endoscopy within nasal cavity of CRSwNP patient.

Bony erosion of skull base from accumulated eosinophilic mucin-laden with fungal hyphae.

Molecular Therapy. 2010; 18: 3,625-634 mar.

Over 40 million Americans suffer from chronic rhinosinusitis (CRS), which causes facial pain and pressure, nasal congestion, and obstruction. These symptoms ultimately cost conservatively 16-22 million physician visits yearly with an annual direct healthcare treatment cost of over 3 billion dollars. In addition, patients suffering from CRS often are diagnosed with asthma. Together, CRS and asthma as chronic respiratory conditions represent some of the most prevalent chronic diseases in the United States. Despite this healthcare burden, much remains unknown about its pathophysiology, and current treatment options, which typically involve recurrent surgeries and anti-inflammatory agents, are not curative. CRS represents an ideal human research model for studies in chronic inflammatory respiratory diseases. CRS patients undergo ongoing surgery, providing an opportunity to harvest critical diseased tissue and are seen regularly in clinic, which allows evaluation of the patient and diseased mucosa. CRS is clinically classified into 2 groups defined by the absence or presence of nasal polyps (see image [1]). This clinical classification has been supported by immunologic profiles of the sinonasal tissue in which CRS without nasal polyps are characterized by predominance of eosinophils and elevated T helper cell type 2 (Th2; cytokines such as IL-4, -5, and -13).

Allergic fungal rhinosinusitis (AFRS) is a subset of CRS characterized by intranasal fungal colonization and accumulation of inflammatory factors or regulatory pathways that control the disease processes for developing a novel strategy for targeted activation of endogenous stem/progenitor cells for lung tissue repair.

Lung stem/progenitor cells are critical for the maintenance of homeostasis of airway and alveolar epithelial cell populations that are constantly exposed to inflammatory stimuli from the environment. There are at least three stem/progenitor cell types responsible for maintaining distal lung epithelial cell populations: 1) alveolar epithelial type II cells; 2) the transient amplifying bronchiolar Clara cells; and 3) a subset of variant Clara cells located at the bronchoalveolar duct junction and the branch point associated with respiratory bronchioles. Loss of normal function of any of these stem/progenitor cell types due to injuries or genetic deficiencies is thought to play an important role in the development of chronic or severe pulmonary diseases, including pulmonary fibrosis, asthma, cystic fibrosis, and eosinophilic respiratory disorders (e.g., HRS). However, little is known regarding the pathogenesis of these pulmonary diseases as well as the corresponding repair mechanisms, since there is no reliable biologic/molecular model available for studying the biological and disease processes both in vivo and in vitro. In addition, currently available treatments for those pulmonary diseases are at best, only symptomatic and improve quality of life within a limited time range, and the long-term outcome is unfortunately not positive. There is an imperative need to develop novel therapies to facilitate the regeneration or repair injured distal lung epithelia. Without doubt, the distal lung stem/progenitor cell represents the key targets for repairing the pathogenesis of lung diseases and the mechanisms of repair from injuries. During the past few years, considerable interest has developed in the potential clinical use of stem cells in the treatment of pulmonary diseases. The embryonic stem (ES) cell lung disease-specific induced pluripotent stem (iPS) cell-derived distal lung stem/progenitor cells are not only promising source of cells that can be therapeutically used to treat distal lung injuries and genetic disorders, but also a good model to study lung disease processes. My research efforts are focused on 1) isolation and A site-specific lung disease-specific iPS-derived distal lung stem/progenitor cells for the treatment of lung diseases.

RESEARCH PROJECTS
• Isolation and characterization of embryonic stem cell-derived distal lung stem/progenitor cell.
• Pathways to regular distal lung stem/progenitor cell fate.
• Therapeutic potential of ES lung disease-specific iPS-derived distal lung stem/progenitor cells for the treatment of lung diseases.
• Generation and characterization of HLA-deficient human ES cell line for tissue regeneration.

Lung stem/progenitor and tissue regeneration

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Lung stem/progenitor and tissue regeneration
The Transgenic and Stem Cells Core Facility was established in 1998 and since that time, it has generated over 700 new transgenic, knock-out and knock-in animal models for investigations from UTHealth, as well as for scientists from numerous other academic institutions. The mouse embryonic stem (ES) cell lines derived in the Core Laboratory are highly effective for the generation of knock-out and knock-in mice and for studies involving cellular differentiation.

In addition to the production, cryopreservation and re-derivation of genetically-engineered mice and rats, the services of the facility also include gene targeting, derivation of new cell lines and technical support in different aspects of animal microsurgery, cell culture, and stem cells research.

RESEARCH SERVICES
- Microinjection of DNA, BAC or YAC clones for the production of transgenic animal models.
- Microinjection of ES cells for the production of knock-out and knock-in mice.
- Re-derivation of mice and rats from fertilized eggs.
- Cryopreservation of fertilized mouse and rat eggs.
- CREP/R/Cold mediated genome editing in mice.
- Gene targeting, selection, expansion, cryopreservation of mouse ES cells.
- Derivation of novel mouse ES cell strains and other cell lines.
- Availability of gemline-competent mouse ES cells and MEF feeder layer cells.

ACCOMPLISHMENTS
- Generation of more than 700 transgenic, knock-out and knock-in animal models.
- Consistently high transgenic rates (average 22%).
- 100% success rate of germline transmission in the production of knock-out mice when using ES cells derived at the facility.
- 100% success rate in re-derivation of mice.
- Derivation of more than 20 mouse and human ES cell lines, including human ES cells approved for NIH-funded research.

KEY PUBLICATIONS


Adipocyte progenitor cells in pathology


Dingjun A., Tong C., Sialamet A., Zhang Y., Tong Q., and Kolonin M.G. Depletion of white adipocyte progenitors induces beige adipocyte differentiation and suppresses obesity development, Cell Death and Differentiation, in press.

LAB MEMBERS

Alexis Depauvillier: Sr. research scientist
Zhanghes Gao: Sr. research scientist
Zhang Yu: Postdoctoral fellow
Chieh Tseng: graduate student
Ali Dadbin: senior research assistant

Adipocytes (green) and blood vessels (red) in mouse adipose tissue. Nuclei are blue.

Research projects

• The lab is interested in how metabolic tissues respond to hormonal cues by activating or repressing genes. We study pathways and proteins regulated by cAMP, a small molecule that mediates intracellular hormone responses, with the overall aim of identifying new targets to promote blood glucose control and skeletal muscle performance in states of diabetes, aging, and muscle injury.

• Type 2 diabetes is an endocrine disease caused by over nutrition, weight gain, and insulin resistance. One of the major problems in type 2 diabetic patients is hypertrophy (increased blood glucose), due in part to excessive activation of cAMP-regulated pathways in the liver. Salt inducible kinase 1 (SIK1) is an enzyme known to inhibit new glucose synthesis in liver cells, and we found that SIK1 protein abundance is very strictly regulated in this cell type. We deleted the SIK1 gene in mice to study its impact on glycemic control in normal and obese states. Through this work, we have identified surprising and complex functions of SIK1 on blood glucose control. Current work is focused on understanding how SIK1 and its partners regulate blood glucose in diabetic animals. Using tissue-specific knockout mice, we will determine which SIK1 functions is most important for regulation of blood glucose in diabetic states.

• Our other major project focuses on skeletal muscle, which comprises 40% of body mass and is responsible for 25% of glucose disposal. Maintenance of skeletal muscle mass is thus critical for both mobility and glycemic control. We aim to uncover how cAMP-activated pathways could be harnessed to promote healthy aging and improve muscle strength and function in individuals with muscle disease or atrophy.

• cAMP-activating hormones act within the body to regulate intracellular transcription and extracellular signaling in skeletal muscle to promote muscle regeneration and suppress obesity development.

• Regeneration of exercise performance by SIK1.

• Regulation of exercise performance by SIK1.

• Chemical genetic methods to stimulate muscle stem-cell proliferation and muscle regeneration to uncover new pathways that promote muscle regeneration and hypertrophy.

• Role of SIK1 in whole-body energy and muscle performance.

KEY PUBLICATIONS


Model of CREB and SIK1 action in type 2 diabetes. SIK1 inhibits CREB activity through phosphorylation of the CREB co-activator CRTC2. At the basal state, CRTC2 is constitutively phosphorylated and CREB activity is inhibited. In conditions of increased glycemic control, CRTC2 kinase activity is reduced and CREB activity is increased. This increased CREB activity promotes muscle growth (hypertrophy) and muscle regeneration, and we showed that the CREB-mediated expression of myostatin is critical for muscle growth.

Signaling pathways regulating glycemic control and muscle performance

Many hormones act within the body to regulate intracellular and extracellular signaling in skeletal muscle to promote muscle regeneration and suppress obesity development. We are currently studying how CREB-stimulated genes, such as SIK1, contribute to muscle regeneration, hypertrophy, and performance. We are carefully examining muscle phenotypes in SIK1 knockdown mice. We are also undertaking an unbiased approach to identify known and unknown proteins that mediate cAMP action in muscle by creating mice that express a "designer" cAMP-activating cell surface receptor that will only respond to a "designer" synthetic drug. We hope that our studies will identify new targets that can be targeted to promote muscle growth and performance in humans.

LAB MEMBERS

Postdoc: Dmitry Akhmedov
Doctoral student: Rondal Stewart
Research assistant: Kavitha Rajendran and Maria Mendes
Medical student (summer): Micah Gibson

The Kolonin Laboratory is investigating the association between obesity and such life-threatening diseases as type 2 diabetes and cancer. We have discovered that white adipocyte progenitor cells serve as the mechanistic link between fat tissue overgrowth and obesity pathogenesis. In clinical studies and in animal models, we have shown that white adipocyte progenitors are mobilized to tumors, and stimulate cancer progression. Studies elucidating the molecular mechanisms of intracellular interactions in fat tissue and of adipocyte progenitor migration are underway. Our group has also taken the lead in the exploitation of pathogenic functions of adipose cells and in developing approaches to their suppression. Based on the expertise in cell population separation and high throughput combinatorial peptide library screening methods, we have identified tissue-specific cell surface receptors and peptide probes for their targeting. Based on them, we are developing a strategy to deplete white adipocyte progenitors for obesity prevention and cancer treatment. A distinct, recently discovered, population of adipocyte progenitors giving rise to metabolically advantageous beige adipocytes is also being explored as a prospective therapy target.

RESEARCH PROJECTS

• Adipose tissue markers and mechanisms of intercellular communication.

• Adipocyte progenitors and dedifferentiated adipocytes in tumor microenvironment.

• Development of therapies targeting white adipocyte progenitors.

• Inhibition of beige adipocyte progenitor recruitment for metabolic reprogramming.

KEY PUBLICATIONS

The role of stress in Alzheimer’s disease pathogenesis

How does stress impact the progression of Alzheimer’s disease?

- How does ongoing Alzheimer’s disease result in changes to the regulation of stress hormones and after anxiety levels.
- How does Post Traumatic Stress Disorder acclimate the acceleration of Alzheimer’s disease.

Targeting amygdala’s circuits to hypothalamic pathways in order to humanize the mitochondria in Alzheimer’s disease.

Local neural circuits that regulate hypothalamic-metabolic axes output.

Modeling Amyotrophic Lateral Sclerosis (ALS) in mouse using a newly discovered expansion c9orf72 locus.


Strategies for treating the direct activation of CRF neurons by two-Ai species.
Obesity and diabetes are imposing a huge burden on our society, while the effective treatment is still lacking. The current obesity epidemic is due to a combination of genetic susceptibility and high fat-high calorie (HF/HD) environment. Thus, we aim to understand the mechanisms underlying HF/HD induced obesity and its interaction with important gene functions.

Specific groups of neurons, especially those in the hypothalamus, receive and integrate nutritional status signals, and thus adjust food intake and energy expenditure accordingly to maintain energy balance. Previous research has identified important functions of a few groups of neurons regulating energy intake and expenditure. However, using novel techniques, including Cre-lox P-based mouse genetics, optogenetics, and pharmacogenetics, we aim to identify novel groups of neurons and neural pathways in the brain that are crucial to regulate feeding, diet-induced obesity and glucoregulation.

To link neuron function with behavior, we specifically activate or inhibit a distinct group of neurons with various channelrhodopsins (ChRs) by light or with designer receptors exclusively activated by designer drugs (DREADDs). These new techniques in conjunction with our novel mouse genetic models will reveal important neurons and circuits in the brain for feeding and glucose homeostasis.

One ongoing project is to understand the neural pathway underlying leptin in restoring glucose to normal levels in type 1 diabetes. Identification of this pathway will offer opportunities to treat type 1 diabetes without insulin, thus avoiding hypoglycemic and lipogenic risks associated with insulin treatments. Ultimately we try to delineate specific neural pathways underlying specific physiological functions, and tries to provide a scientific rationale for effective therapeutic strategies against the current obesity and diabetes epidemic.
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 that advance molecular medicine.

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 (NIR) fluorescence to enable new understandings in several disease states.

The Division of Next Generation Sequencing consists of an interdisciplinary team of scientists and engineers who focus upon multi-modality molecular imaging including nuclear imaging, X-ray computed tomography, bioluminescence, fluorescence, and our specially, near infrared (NIR) fluorescence to enable new understandings in several disease states. In addition to having its own basic science and clinical research projects, the team also operates a “collaboration” center where clinicians and basic scientists from across the Texas Medical Center partner with CMI members to effectively apply diagnostics in preclinical and clinical studies.

The team effectively translates new NIRF molecular imaging technologies literally from “bench-to-bedside and back again,” in efforts that embrace its division and clinical partners in the Texas Medical Center and in the Houston suburbs.

Discoveries made in the process of clinical translation require “back to the bench” studies in the CMI include:

- Biological validation of gene variants found with next generation sequencing using protein studies, cellular functional assays, and transgenic animal models;
- Identification of therapeutic targets to reverse disease phenotypes in cellular and transgenic animal models; and
- Re-engineering of imaging devices and imaging agents to improve clinical utility of diagnostics.

Eva Marie Sevick-Muraca, Ph.D.
Professor and Director of the Center for Molecular Imaging
Nancy and Rich Kinder Distinguished Chair in Cardiovascular Disease Research

The Center for Molecular Imaging (CMI) consists of an interdisciplinary team of scientists and engineers who focus upon multi-modality molecular imaging including nuclear imaging, X-ray computed tomography, bioluminescence, fluorescence, and our specially, near infrared (NIR) fluorescence to enable new understandings in several disease states. In addition to having its own basic science and clinical research projects, the team also operates a “collaboration” center where clinicians and basic scientists from across the Texas Medical Center partner with CMI members to effectively apply diagnostics in preclinical and clinical studies. Our team effectively translates new NIR molecular imaging technologies literally from “bench-to-bedside and back again” in order to make discoveries in translational research. The CMI is one of four Centers in the United States comprising the National Cancer Institute’s Network for Translational Research and has won the 2013 Most Promising Crossover Technology Award from the Rice Alliance.

Discoveries made from the translational near infrared lymphatic imaging studies conducted by the CMI team, include identifying key signaling pathways and regulators associated with aberrant processes of lymphangiogenesis in human diseases and in animal models of human disease. In addition, the team has incorporated new PET gene reporters into novel animal models for small animal imaging and tomography with unique instrumentation that enables visualization of even before-see biological phenomena.

RESEARCH PROJECTS

- Developing, building, and translating NIR fluorescence imaging instrumentation and algorithms for multi-modality molecular imaging and tomography in preclinical and clinical studies.
- Designing, producing, and validating unique NIR and nuclear imaging probes for assessing molecular pathways in preclinical studies and for enhanced diagnostics in Phase I and II combination device/drug clinical studies.
- New molecular imaging agents for non-invasive diagnostic imaging for nodal staging in breast, prostate, melanoma, and other cancers.
- Using molecular imaging to understand the process of lymphangiogenesis involved in cancer metastasis, infection, injury and trauma, vascular diseases, and hereditary disease in unique animal models.
- Evaluating molecular signaling in the process of tissue re-organization in health and disease, including bone fracture, athlosclerosis, and cancer.
- Combining molecular imaging and unique knockout animal models to understand the molecular genetics of disease.

KEY PUBLICATIONS


Lymphatic imaging in case of Parkes Weber Disease (from Butow, et al. 2012)

Eva Marie Sevick-Muraca, Ph.D.
Professor and Director of the Center for Molecular Imaging
Nancy and Rich Kinder Distinguished Chair in Cardiovascular Disease Research

Molecular imaging and diagnostics

Phase I/II combination device/drug clinical studies.
- New molecular imaging agents for non-invasive diagnostic imaging for nodal staging in breast, prostate, melanoma, and other cancers.
- Using molecular imaging to understand the process of lymphangiogenesis involved in cancer metastasis, infection, injury and trauma, vascular diseases, and hereditary disease in unique animal models.
- Evaluating molecular signaling in the process of tissue re-organization in health and disease, including bone fracture, athlosclerosis, and cancer.
- Combining molecular imaging and unique knockout animal models to understand the molecular genetics of disease.

LAB MEMBERS

- Co-Director of Flow Cytometry Service Unit: Amy Hazen
- Chief Histology Technician of Tissue Histology Service Unit: Sarah Aronson
- Research Coordinators: Holly Robitser, Nathan Wilson, Karen Gorin, Grace Wu
- Postdoctoral Fellow: Dr. Chianny Darne (co-advised)
- Graduate Students: Germaine Agollah (co-advised), Cynthia Davido-Viere

Near-infrared fluorescence imaging devices and drug combination
Melissa B. Aldrich, M.B.A., Ph.D.
Assistant Professor

Imaging in immunology

A combination of expertise in translational science and immunology to lead the program of imaging of the lymphatics, the circulatory system, which is critical to immune surveillance and response. Near-infrared fluorescence (NIRF) imaging delivers high-resolution, low-cost images of lymphatic vessel architecture and pumping. In disease states such as lymphoma, manifested by severe lymph swelling, NIRF imaging can provide information for diagnosis and evaluation of treatment efficacy. As part of a translation team, I have conducted clinical measurements that prove the usefulness of NIRF imaging to investigate lymphatic vessel architecture and function in health and disease. This study of NIRF images of breast cancer-related lymphoma arm revealed that the severity of the disease worsens over time not only in the “affected” arms (that received surgical and/or radiological treatment associated with breast cancer treatment), but also in the control arm (unaffected) arms. This work added evidence to other studies, suggesting that lymphoma in a system, not just local disease. Our lab also worked in NIRF imaging studies of prenyl, or genetic, lymphomas and was responsible for the association of genetic disorders with lymphatic abnormalities. “Translation” is a much-used term in research that stresses the importance of research that is relevant to medical practice. Truly crossing the “bench-to-bedside” chasm, however, requires skills that most basic science researchers are not equipped with.

RESEARCH PROJECTS

• Clinical studies of NIRF imaging of lymphatic architecture and function in health and disease.
• Validation in the context of translation.
• Inflammatory cytokine effects on systemic lymphatic function.

KEY PUBLICATIONS


LAB MEMBERS

Grad students: co-advisor Cynthia Davies-Yenn, Via Area Lackachy

Ali Azhdarinia, Ph.D.
Assistant Professor

Molecular imaging probe development

I am the faculty leader of the Radio- and Optical-Pharmaceutical development effort in the Center for Molecular Imaging (CMI). My research interests include the development of targeted agents for the visualization and treatment of cancer. I have served as the leader of the National Cancer Network’s Network for Translational Research (NTR) Chemistry Core and have heavily involved in validation and qualification of preclinical studies prior to translation in both NTR wide and OMI local studies. My work utilizes radiolabeled and near-infrared fluorescent (NIRF) contrast agents, which can be used for whole-body and intraoperative imaging, respectively, and may potentially improve surgical outcome while minimizing morbidities associated with current methods. The combination of both modalities into a single agent in a key area where I have focused my efforts through synthesis of a library of new multimodal chelation (MOC) platforms. My labs uses radionuclid based positron emitters, such as Gallium-68 and Copper-64, for labeling of peptides, proteins, and antibody-based agents and also conducts multi-pharmaceutical characterization of lead compounds to determine suitability for clinical translation. As part of the Center for Molecular Imaging, I have participated in developing a detailed data room for production of probes under the current Good Manufacturing Practices (cGMP) to facilitate translational research. I am actively collaborating with clinical partners to establish creative approaches for translating “labelled” agents.

RESEARCH PROJECTS

• Development of molecular imaging probes with radiolabeled near-infrared fluorophores.
• Synthesis of novel chelation platforms for radiolabelling and drug design.
• Optimization of NIRF labeling methods.
• Pharmacological evaluation of imaging probes targeting tumors and other molecular processes.

Translation “pipeline” for optical imaging modalities


Representative multimodality images in a tumor-bearing mouse at 40 h post-injection of 89Zr-labeled mAb. (A) Tumor signal was visualized by SPECT and NIRF imaging in vivo (circles). Ex vivo imaging on selected tissues showed comparable fluorescence levels in the kidneys and tumor with little signal elsewhere. Quantification of 89Zr uptake to represented in (B) and indicates highest signal in liver, tumors, and kidneys. Arrow indicates excised tumors + kidney. L = lung, H = heart, M = muscle. Scale bar = 1.6 cm. (from Ghosh, S.C. et al., J. Med Chem, 56:406 (2013).


Biodistribution of PEGylated conjugates that NIR fluorescence. (A) HPEL chromatograms of peptide probes. Left: UV detection of PEGylated and NIR-terminating peptide CNGB3MD (containing two Dle protease protecting groups on internal lys residues) at 200 nm. All data refers to absorption units. Right: Fluorescence detection of PEG5-H800 and CNGB3MD-H800. (B) Whole-body NIR fluorescence imaging of cold-acclimated mice 4 and 24 hrs after administration of indicated doses of CNGB3MD-conjugated PEG5 or control PEG5. Arrows: Inter-scapular signal; perirenal signal. Insets show black/white photographs of mice that had skin removed from the back for imaging. Right: Plot of data analysis from r=3 mice per group (mean ± s.e.m., *P<0.05, Student’s t-test). (c) NIR fluorescence imaging of PEG5-H800 and inter-scapular CNGB3MD isolated from cold-acclimated mice injected with increasing doses of CNGB3MD-conjugated PEG5 or a control peptide (PEG5) 1 hr of circulation. Scale shows fluorescence intensity. Black: white photographs of tissues are shown below. Scale bar: 5 mm. Graph plotted quantitative data correspond to NIR images. (adapted from Azhdarinia A. et al., Nat Commun. 4:2412, 2013)
Personalized medicine using bioinformatics and whole genome sequencing for early discovery and diagnosis of human disorders

Manuel L. Gonzalez-Garay, Ph.D.
Assistant Professor

Our laboratory focuses on two main areas:

1. **Identification of genetic markers for Panic disorders**
   - Collaboration of Michael Lorenz, Ph.D. UTHealth.

2. **Transcriptomics in Candida species**
   - Collaboration of Dr. Augusto Rojas-Martinez, Universidad de Monterrey, N. L. Mexico.

**Personalized medicine using next generation sequencing technologies (Next Generation Sequencing, NGS)** in human genome sequencing results in the CLARITY analysis, interpretation and reporting of clinical genome sequence, interpret the information. Your genome sequenced and interpreted will be utilized and customized. Molecular explanation for the disorder. Our findings will enable physicians to detect markers that will allow physicians to identify genetic markers associated with familial panic disorders, Dercum’s disease, Adipositas dolorosa and Madelung’s disease.

**Research Projects**

- **Genome and Bioinformatics Analysis of patients with Lymphedema.**
- **Personalized medicine using next generation sequencing: The CDC Genome Project.**
- **Detection of markers for sudden-death syndrome** in a population from Venezuela. Collaborator of Dr. Rossa Rodrigues, Instituto Venezolano de Investigaciones Científicas.
- **Identification of genetic markers for Panic disorders** in Monterrey, N. L. Mexico. Collaborator of Dr. Augusto Rojas-Martinez, Universidad Autónoma de Nuevo León.
- **Immunohistological Identification of Pathogens.** Collaborator of Peter Doris, Ph.D. U.T. Health.
- **Dermatological and aesthetic dermatology.** Collaborator of Karen L. Herbst, M.D. UC San Diego.

**Key Publications**

- Gonzalez-Garay M.L.*; Gubbiotti G.*, Xie ***,...**

**LAB MEMBERS**

Research Coordinator: Karen Gore

Co-educator: German Aguilah

**Barrett Rowland Harvey, Ph.D.**
Assistant Professor

**Therapeutic and diagnostic antibody development**

Technological achievements in antibody engineering have made antibody drug development one of the fastest growing areas of the pharmaceutical industry. Successful design of antibody based therapeutics or diagnostics requires both the ability to optimize the antibody and a clear understanding of the biology of the target antigen. To this end, our laboratory has two main focuses:

1. To identify and build a functional understanding of novel molecular targets, and
2. To utilize custom antibodies as powerful tools to expedite the research and to develop high throughput strategies and engineering methods to modify the affinity, specificity, epitope site recognition and function of antibodies for therapeutic, diagnostic, and basic research use. Utilizing molecular imaging techniques, antibody agent development can be monitored in vivo to predict efficacy, specificity and to validate targets prior to the clinic. This line of research allows our laboratory to venture into a number of diverse biological fields, with ongoing projects currently focused in oncology and infectious disease.

**Research Projects**

- Generation of surrogate antibodies for metastatic cancer models.
- Molecular imaging for cancer staging.
- Virulence factor regulation governing enterocolitis infection.
- Positive protection from hospital acquired bacterial infections.

**Key Publications**


**Molecularly targeted live animal imaging of bacterial infection.** PET/CT image of enterococcal endocarditis in a live rat imaged 72 h post infection using anti-CaD-DOTA labelling. Labelling and electron microscopy evaluation of major pilin subunit, Ebpg, on surface of enterococcal toothpicks using in-house generated high affinity monomeric antibody.

**IMMPACT REPORT**

Center for Molecular Imaging

Barrett Rowland Harvey, Ph.D.
Assistant Professor

Therapeutic and diagnostic antibody development

Key publications:


Molecularly targeted live animal imaging of bacterial infection. PET/CT image of enterococcal endocarditis in a live rat imaged 72 h post infection using anti-CaD-DOTA labelling. Labelling and electron microscopy evaluation of major pilin subunit, Ebpg, on surface of enterococcal toothpicks using in-house generated high affinity monomeric antibody.

**LAB MEMBERS**

Barrett Rowland Harvey, Ph.D.
Assistant Professor

Therapeutic and diagnostic antibody development

Key publications:

Functional lymphatic imaging in animal models of lymphovascular disorders

**KEY PUBLICATIONS**


**LAB MEMBERS**

Student co-adviser: Germaine Agulhon

Research Coordinators: Grace Wu, Holly Robinson

**CENTER FOR MOLECULAR IMAGING**

Sun Kuk Kwon, Ph.D.
Assistant Professor

The Carolyn Frost Keenan Professorship in Cardiovascular Disease Research

I lead the development and application of small animal imaging techniques to address biological questions in unique animal models of cardiovascular disease with an emerging emphasis of gastrointestinal disease. My main research interest focuses on investigating the microcirculatory movement of fluid and macromolecules, particularly in the lymphatic system using fluorescence optical imaging techniques. The lymphatic system plays an important role in edema prevention, immune surveillance, and cancer metastasis. Although the importance of the lymphatic system in physiological and pathophysiological conditions has been well recognized, non-invasive imaging of lymphatic function has significant difficulties, due to the lack of diagnostic imaging approaches. Recently, we have developed non-invasive, dynamic near-infrared fluorescence (NIRF) imaging methods for imaging and quantifying lymphatic function in health and disease. Therefore, non-invasive NIRF imaging can be used to image changes of lymphatic function and architecture in disease and potentially to provide diagnostics and information in response to therapy. Other directions of our scientific interests involve around multi-modality molecular imaging. The Center for Molecular Imaging is developing and translating imaging agents, which are currently labeled with a PET/SPECT radionuclide and an NIR fluorescent dye. I am currently conducting molecular imaging of cancer and LNM metastasis and inflammation in different animal models of disease.

**RESEARCH PROJECTS**

- Non-invasive characterization of lymphatic function and drainage patterns in mice with lymphedema-like phenotypes, hypertension, cancer, and inflammatory and infectious responses to therapeutic agents.
- Non-invasive imaging of gastrointestinal motility using a fluorescence optical imaging technique.
- Multi-modal molecular imaging.

**RFP gene reporter fluorescence tomography**

The reconstructed IRLP-4 gene reporter distribution in the cross-sections with the maximal reconstructed values (the first, second and third rows). Top 80%, 90%, and 99% reconstructed values are shown, respectively. The bottom row shows the position of the cross-sections. “IR,” “IRF,” and “MS” are Mouse 1, 2, and 3, respectively.

**CENTER FOR MOLECULAR IMAGING**

Yujie Lu, Ph.D.
Assistant Professor

Program for multimodal optical tomography and relevant preclinical applications and clinical translation

**KEY PUBLICATIONS**


**LAB MEMBERS**

Co-advisers: Chinmay Danne (post-doc), Holly Robinson, Nathaniel Wilganowski

Data in text box: White light and fluorescent images in mice prior to and after post-surgery lymph node resection (PLN). Reconstructed IFP1.4 gene reporter distribution for BMP2-based ossification for spinal fusion; and red represents the reconstructed images; yellow represents PET imaging information. The artifacts and limitations of the cross-sections (first, second and third rows). Top 80%, 90%, and 99% reconstructed values are shown, respectively. The fourth row shows the position of the cross-sections. "IR," "IRF," and "MS" are Mouse 1, 2, and 3, respectively.
I am the faculty lead of the instrumentation for translational fluorescence imaging. Clinical translation of lymphatic imaging modalities has been hindered by a lack of clinical-grade imaging systems. Our laboratory focuses on developing and translating NIRF optical imaging technology for lymphatic imaging. We have developed and translated NIRF imaging technology using microdose amounts of fluorescent contrast agents. We studied the abnormal lymphatic contractile function after manual lymphatic drainage in humans with near-infrared fluorescence imaging. We also studied the lymphatic abnormal lymphatics in lymphedema patients. We have also developed and translated NIRF imaging instrumentation and image analysis algorithm in preclinical and Phase I/II clinical studies. We have also studied the lymphatic architecture and function in children with peripheral edema after surgery using NIRF imaging. We have also studied the lymphatic architecture and function before and after cancer treatment in head and neck cancer patients longitudinally using NIRF imaging. We have also evaluated the effects of conventional LE treatments and novel treatment devices using NIRF imaging.

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Successful image-guided surgery based upon fluorescently labeled imaging agents requires numerous fluorescent signals from diseased tissues to be above the noise floor and to have adequate contrast relative to background, or normal tissues. Since surgical resection is most facile with fluorescence imaging concurrent with illumination that preserves the surgeon’s visual acuity, it is critical to eliminate ambient light to enable high imaging contrast. We are developing a modulated, intensified CCD (ICCD) fluorescence imaging system for rapid planar imaging that enables electronic filtering of non-modulated ambient light that can contribute to the noise floor. The technique is rapid because it requires acquisition at only three phase delays between the radio frequency (RF) signal driving the image intensifier and laser diode in order to extract images of AC amplitude. Although fluorescence molecular imaging is rapidly evolving as a new combinational drug/device technology platform for molecularly guided surgery and noninvasive imaging, there remain no performance standards for efficient translation of “first-in-human” fluorescent imaging agents using these devices. We are developing a stable, solid phantom designed to exaggerate the confounding effects of tissue light scattering and to mimic low concentrations (μM glutam) of near-infrared fluorescent dyes expected clinically for molecular imaging.

RESEARCH PROJECTS
• Developing NIRF imaging device having the capability of operating in ambient light with frequency-domain measurement approach.
• Collaborating with NIST to develop performance standard for accelerating the clinical translation of NIRF imaging.
• Validating NIRF imaging device using various area detectors and excitation light sources using the developed fluorescent phantom.

IEY PUBLICATIONS


We have developed novel, next-generation modified DNA oligonucleotide aptamers selected from large combinatorial libraries to target a number of proteins for prostate- and nanomedicine. We have developed both in vitro enzymatic combinatorial selection and split synthesis chemical combinatorial methods to identify phosphorothioate-modified oligonucleotide “X-aptamers” and next-gen “X” aptamers to a number of different protein targets. The X-aptamers also include a large range of chemical (X) modifications to the A-U-G-C base pair and thus represent a hybrid of aptamer backbone, protein amino acid like sidechains, and small molecule leads in a self-folding scaffold that can be easily identified by oligonucleotide sequencing. Compared to conventional aptamers, this approach dramatically expands the chemical diversity that can be incorporated to select X-aptamers with high affinity for diverse molecular biomarkers. Large library-based combinatorial libraries of these aptamers can be rapidly selected. These X-aptamers and thioaptamers are being used as antibody substitutes in nanomedicine therapies. As X-aptamers can be rapidly selected, these aptamers can be used as antibody substitutes in nanomedicine therapies and biomarker identification to target tumor cells and tumor vascularization and in various microfluidic and mass spec chips for proteomics and diagnostics. Examples of applications of the bead-based thioaptamer and X-aptamer selection are demonstrated for targeting cancer tissue and cells expressing CD44, AnnexinA2 and E-Selectin.

David Gorenstein, Ph.D.
Associate Dean for Research Chair, Department of Nanomedicine and Biomedical Engineering Professor and Director of the Center for Proteomics and Systems Biology
James T. Willerson Distinguished Chair in Cardiovascular Research in Tribute from the Ewing Halsell Foundation

**NANOmedicine and Proteomics in Cancer and Cardiovascular Disease**

**RESEARCH PROJECTS**

- Next generation aptamer development for drug development
- Proteomics and molecular diagnostics
- Nanoapomizing in cancer and cardiovascular disease
- Development of novel X-aptamer targeting nanoparticles for imaging and therapeutics

**KEY PUBLICATIONS**


Xiaohong Bi, Ph.D.
Assistant Professor

**Optical spectroscopy and imaging for medicine**

Optical spectroscopy and imaging techniques have demonstrated great potential in providing noninvasive in situ diagnosis. Our research focuses on developing optical tests, especially Raman spectroscopy (RS), for clinical problems such as early disease diagnosis, therapy response evaluation, and guidance of surgery. RS exploits subtle changes in the molecular composition of tissue and is sensitive to disease and age associated biochemical changes in tissue environment. We are currently using RS fiber optic system to test patients with inflammation bowel disease (IBD) in clinics. In vivo RS studies on colon biopsies have shown over 99.7% accuracy in differentiating the two distinct yet often intermediate forms of IBD: ulcerative colitis and Crohn’s colitis. The incorporation of RS into colonoscopy is expected to improve diagnostic accuracy in IBD. Further applications of RS in diagnostic cancer and surgical margin assessment is also being explored in our laboratory.

We have extensive experience in quantity bone mineralization and composition, which are important determinants of bone strength. The effect of genetic variations and disease on bone compositional properties and mechanical function is constantly studied in the lab. In addition, we have developed RS spectral markers that are related to breast and prostate cancers induced bone alterations. These markers can be used to assess bone quality and to evaluate the response of metastatic bone to treatment. A noninvasive method is development to test on animal model and patients based on the above findings.

Another area of research involves developing targeted imaging and biosensing methods using surface enhanced Raman spectroscopy (SERS). By combining RS and nanotechnology, such SERS methods can detect biomarkers in body fluid up to its trace.

**LAB MEMBERS**

Postdoc: Hao Ding
Research Scientist: Zhiyong Wang
Technician: Guijin Lu

**RESEARCH PROJECTS**

- Noninvasive optical diagnosis in situ (IBD, cancer, etc.)
- Development of noninvasive transcutaneous Raman measurement (SERS)
- Assessment of metastasis and disease caused bone quality deterioration
- Biomarkers and circulating tumor cells detection
- Raman imaging for pathogenesis

**KEY PUBLICATIONS**


R. Tataryn, H Ding, S.L. Li, R. Taylor, S.B. Synergistic Synergistic acceleration in the osteoblasts of osteosarcoma (US) and cancer, etc) bone quality deterioration.

**LAB MEMBERS**

Postdoc: Hao Ding
Research Scientist: Zhiyong Wang
Technician: Guijin Lu

The ectodermal picture of normal (N) and cancer cells (C). Raman fiber optic probe was inserted through the accessory channel of the colonoscope. Tip of the probe is shown in the picture.
IMMPACT REPORT

3. Computational tools for genomic analysis. Lastly, we are developing infrastructure to distribute our computational algorithms. Each of our projects contains a computational component, and an important aspect of our work is to make our methods available. We have previously described the GATHER website for analysis of gene sets and are now developing a platform (SIGNATURE) for the analysis of oncogenetic pathways. Access to these investigations, we can genomics to reveal the simple fundamental units that constitute complex biological entities (such as the wiring of a cancer cell). We use human cell culture as a model and leverage a range of techniques, including bioinformatics, molecular biology, and chemical biology.

RESEARCH PROJECTS

1. Cancer metastasis. We are dissecting networks of active limbs during the dynamic exercise that was used to for the successful exercise-induced myofibrillar disruption with cavitation-induced of encapsulated microbubbles. Model of structural & functional barriers for the transport-diffusion dilution of O2.

2. Breast cancer metastasis. It is estimated that up to 50% of cancer deaths are due to metastasis, in part because metastatic cells do not respond to traditional therapies. To address this problem, we have used computational approaches to repurpose drugs to target cells that inhibit phenotypes that promote metastasis. We have identified a selection of natural compounds and small molecules that have shown the ability to inhibit metastasis in preclinical models.

3. Growth signaling networks. We are dissecting the structure of signaling cascades, focusing on the Ras network. Ras controls numerous pathways that have shown the ability to inhibit metastasis in preclinical models.

4. Metastasis to the brain and Glioblastoma. The effects of hypoxia on tumorigenic cells. Our research program can be grouped into three areas of focus:

Three areas of focus:

1. Breast cancer metastasis.
3. Metastasis to the brain and Glioblastoma.

Gene expression signatures predict pathway activities.

Gene expression signatures predict pathway activities.

One of our extraordinary scientific achievements from basic research to innovative human application was the success in hand-made assembly of the International Space Station in 2014. Application was the success in hand-made assembly of the International Space Station in 2014. The complexity of the cell signaling network provides it the capacity to produce organisms like ourselves (a good thing). We use human cell culture as a model and leverage a range of techniques, including bioinformatics, molecular biology, and chemical biology.

RESEARCH PROJECTS

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3. Computational tools for genomic analysis. Lastly, we are developing infrastructure to distribute our computational algorithms. Each of our projects contains a computational component, and an important aspect of our work is to make our methods available. We have previously described the GATHER website for analysis of gene sets and are now developing a platform (SIGNATURE) for the analysis of oncogenetic pathways. Access to these investigations, we can genomics to reveal the simple fundamental units that constitute complex biological entities (such as the wiring of a cancer cell). We use human cell culture as a model and leverage a range of techniques, including bioinformatics, molecular biology, and chemical biology.

RESEARCH PROJECTS

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Three areas of focus:

1. Breast cancer metastasis.
3. Metastasis to the brain and Glioblastoma.
One of my areas of interest in the discovery and validation of biomarkers and novel drug targets is for molecular pathways of disease. This work is performed both as basic research in animal and cell models and as translational research in human biological fluids and tissues. Our group has focused on protein-based biomarkers and molecular targets because proteins are the "workhorses" of cells and tissues—i.e., proteins carry out the majority of the cell signaling and metabolic reactions necessary for normal physiology, and deranged protein networks are responsible for altered cellular signals. In this context, disease is necessary for normal physiology, and deranged protein networks are responsible for altered cellular signals. In this context, disease.


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**Interventional oncology research**

**RESEARCH PROJECTS**

- **Prognostic evaluation of hepatocellular carcinoma genetic and metabolic tumor response to minimally invasive therapies.**
- **An investigation on the therapeutic efficacy of phospholipid-coated tumor cell electroporation with TACE on patients with hepatocellular carcinoma.**
- **Evaluation of safety and efficacy of electroporation in the treatment of pancreatic adenocarcinoma.**
- **Use of magnetic resonance spectroscopy in the radiogenomic evaluation of childhood leukemias.**
- **Formation of diffusion weighted MRI to cellular membrane pore formation after electroporation in pancreatic adenocarcinoma.**
- **Evaluation of effects of electroporation and gemcitabine nanoparticle formulation on tumoral response in a pancreatic adenocarcinoma nude mouse model.**
- **Optimization of catheter directed therapy in rabbit VX2 rabbit animal model using vascular normalization.**

**KEY PUBLICATIONS**


**Atomic force microscopy image of the surface of a pancreas 3 cell after electroporation demonstrating several nanopores in the cell membrane.**
My laboratory has as its primary objective the specific genetic correction of mutations in the CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) system. We have utilized Zinc Finger Nuclease-mediated Homology Directed Repair (HDR) for the correction of mutations in iPSC cell lines derived from patients with inherited blood disorders affecting the ratio of blood cells, with the ultimate goal of developing stem/progenitor cell-based therapeutic approaches. We have utilized Zinc Finger Nuclease-mediated Homology Directed Repair (HDR) for the correction of mutations in iPSC cell lines derived from patients with inherited blood disorders affecting the ratio of blood cells, with the ultimate goal of developing stem/progenitor cell-based therapeutic approaches.
Stem cells for neurological diseases

Qi Lin Cao, M.D.  
Associate Professor

Stem cells can be induced to differentiate into functional neurons. They are being studied as a promising therapeutic approach for neurological disorders. Several types of stem cells have been used in preclinical and clinical studies for the treatment of various neurological injuries, including spinal cord injury (SCI) and stroke.

**Key Publications**

- **In vitro and in vivo models:**

- **In situ reprogramming:**

- **Molecular mechanisms:**

- **Immunosuppression:**

**Lab Members**

- **Postdoctoral Research Associates:**
  - Michelle Wang, Yiyan Zheng

- **Senior Research Assistant:**
  - Jun Li

**Research Projects**

- The long-term therapeutic efficacy and safety of NSCs derived from neural progenitor cells or stem cells for spinal cord was shown to promote functional recovery.

- The molecular mechanisms to regulate NSCs for spinal cord injury and stroke.

- This approach to promote functional recovery after SCI or stroke. Our long-term goal is to develop novel stem cell-based therapies to treat human SCI or stroke.

**Key Questions**

- How can stem cells be induced to differentiate into functional neurons?

- What are the safety and efficacy of stem cell therapies for neurological disorders?

- How can we optimize the delivery of stem cells to the site of injury?
**Skeletal muscle regeneration using pluripotent stem cells/new insights using knock-in reporter ES/iPS cells**

**KEY PUBLICATIONS**

**LAB MEMBERS**
- Postdoctoral Fellow: Jianbo Wu, Nadine Matthaus
- Research Technician: Samuel D. Hunt

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**Mechanisms of memory formation and memory dysfunction**

The research objective of my laboratory is to explore the molecular mechanisms contributing to working memory (fastastic), short-term memory (lasting minutes to hours) and long-term memory (lasting days to a lifetime), and the relationships among those types of memories. To accomplish this, we disrupt or augment specific biochemical events in discrete brain regions, such as the prefrontal cortex and the hippocampus, to determine the aspect of memory altered as a result of the manipulation. Human and animal studies have shown that the prefrontal cortex is required for holding information “online” for a period of seconds (referred to as working memory), which is used to guide goal-directed behavior. Working memory is critical for decision-making and coherent thought processes, and is often impaired as a result of normal aging, and diseases such as Parkinson’s, Alzheimer’s, and schizophrenia. Short- and long-term explicit memories are dependent on the function the hippocampus, a structure within the medial temporal lobe. We utilize a multi-disciplinary approach involving molecular, biochemical, genetic, and behavioral techniques to manipulate molecular processes within the prefrontal cortex and hippocampus to determine their role in memory processes.

Both the prefrontal cortex and hippocampus are highly vulnerable to insults, such as traumatic brain injury. Injury to these structures often results in memory loss and a lack of coherent thought processes. Biochemical and molecular cascades initiated as a result of trauma are thought to alter inter- and intracellular signaling, causing changes in the brain ranging from survival and growth to neuronal dysfunction and death. We use an experimental brain injury model in rodents to explore some of the molecular mechanisms contributing to injury-related memory deficits. The long-term goal of this research is to identify potential targets for therapeutic interventions to alleviate the memory disorders associated with brain injuries and degenerative diseases.
Intracranial aneurysms

I specialize in the following diseases:

- Intracranial and extracranial arterial and venous diseases
- Brain and spinal cord injury
- Neurotrauma research
- Stem cell therapy for spinal cord injury

As director of the Mischer Neuroscience Institute, I have a particular interest in the regenerative potential of tissues and organs through stem cells. Specifically, I am interested in the regeneration of the nervous system, particularly through the use of stem cells. My research focuses on understanding the mechanisms of tissue regeneration in the nervous system, with the goal of developing new treatments for neurological disorders.

One of my key areas of research is the use of stem cells to repair damaged neural tissue. I am particularly interested in the use of neural progenitor cells, which have the ability to differentiate into various types of neurons and glial cells. I am currently working on developing strategies to enhance the differentiation and engraftment of these cells in the central nervous system, with the aim of promoting functional recovery after injury.

Another area of focus is the development of new therapies for neurodegenerative diseases, such as Alzheimer's and Parkinson's disease. I am exploring the use of stem cells, particularly induced pluripotent stem cells, to model these diseases and identify potential therapeutic targets.

I am also interested in the use of stem cells to regenerate peripheral nervous system injuries, such as spinal cord injuries. My lab is investigating the use of stem cells to promote the repair of spinal cord injuries and improve functional outcomes.

In addition to my research on stem cells, I am actively involved in clinical care and education. I see patients with a variety of neurological conditions and am dedicated to providing the best possible care. I also mentor medical students and residents, and teach courses on the nervous system and neurotrauma.

I am an advocate for translational research and am committed to translating basic science discoveries into clinical applications. I believe that a collaborative approach, involving scientists, clinicians, and patients, is essential for advancing the field of neurotrauma and neuroregeneration.

I am a member of several professional organizations, including the American Association of Neurological Surgeons and the Congress of Neurological Surgeons. I have published numerous articles in peer-reviewed journals and have presented my research at national and international meetings.

I am also involved in several clinical trials aimed at developing new treatments for neurological disorders. I am dedicated to bringing new therapies to patients and improving outcomes for those with neurological injuries and diseases.

As a leader in the field of neurotrauma and neuroregeneration, I am committed to pushing the boundaries of what is possible in the treatment of neurological injuries. I believe that by working together, we can make a meaningful impact on the lives of patients with neurological disorders.
Human pluripotent stem cells in cell-based therapy for CNS injury

The major goals of our research program are to decipher molecular pathways that confer selective growth and survival advantages to malignant B cells. We are also interested in understanding how stem like cells contribute to drug resistance in these malignancies. Therefore, I began new lines of studies involving the identification and characterization of stem like cells in MCL (mantle cell lymphoma), normal B cells, B and T lineage cells. I initiated collaborations with clinicians at neighboring MD Anderson Cancer Center (MDACC) to obtain multiple MCL patient samples, which we used to prospectively isolate stem like cells in MCL. DNA microarray analyses led to discovery of a signaling axis comprised of MCL transglutaminase 2 (TG2) signaling, which contribute select survival of MCL cells. These stem like populations are also highly resistant to drugs that are currently used in the clinic, such as R-CHOP, R-CNPO, and Fludarabine. These results emphasize that our findings are clinically relevant and further characterization of MCL-ICs may improve patient survival. Another line of research involves uncovering how transcription factors that determine normal B cell lineage differentiation are involved in malignant B cell initiation. On the other hand, normal bone marrow progenitors for cell based therapy in spinal cord injury and stroke.

Characterization of the role of OLIG genes in Down syndrome using patient derived iPS cells and neuronal progenitors. Directed neural differentiation of human induced pluripotent stem cells (iPSCs).
Naoki Nakayama, Ph.D.  
Associate Professor  
Jeroen B. Kats Distinguished Professorship in Stem Cell Research

Stem cell differentiation and lineage specification

- The cartilage of joints is not spontaneously repaired after injury in humans. There has been considerable interest in the clinical application of stem cells to the repair of damaged cartilage; however, current cell therapies using chondrocytes and mesenchymal stem cells (MSCs) face the problems of low yield of cells and their tendency to yield unstable and/or uncartilaginous after expansion. Joint tissue engineering has been proposed. The hypothesis is that the embryonic cells type responsible for limb and joint formation i.e. joint progenitor, common progenitor of several joint components including articular and meniscal chondrocytes and ligaments, would be the best for the regeneration of adult joint cartilage. Pluripotent stem cells (PSCs), whether derived from an embryo, or induced from adult cells, are expected to differentiate into any somatic cell type in culture through processes that mimic embryogenesis, making human iPSCs a promising source of embryonic cells for regenerative medicine. The major challenges have been to direct their differentiation toward the cell type of interest (i.e. to obtain progeny of the right quality), and to isolate them in large quantities without introducing transgens or mutations. 

Quality cells — human joint progenitors: We have previously developed and purified from iPSC paraxial mesoderm and neural crest progenitors, two of the three embryonic origins of cartilage, with the capability to expand and differentiate into articular and meniscectomy chondroprogenitors, respectively. We have recently established a condition to generate chondrogenic paraxial mesoderm, the third embryonic origin of chondrocytes, from human pluripotent stem cell (hPSC) stem cells. Our approach involves over-expressing transcription factors that are involved in processes that mimic embryonic development in vivo. We have recently developed a way to selectively generate and expand, to a limited extent, joint progenitor-like cells that express syndromal (ligament progeny) markers from the paraxial mesoderm progeny. We are currently focusing on the characterization of such joint progenitor-like cells, aiming to demonstrate their capacity to generate joint type stable cartilage as predicted from animal studies.

- Large quantity — long-term expansion of PIC-derived human cells: We have established culture conditions that maintain and expand the articular and meniscectomy chondroprogenitors for an extended period of time, without loss of their chondrogenic activity. Such stable expansion of chondroprogenitors is currently very hard to achieve with adult MSCs. We are focusing on genome wide molecular search (e.g. transcription, proline, melanoma, epithelial analyses) in these expandable chondroprogenitors, aiming to understand the molecular basis in the expansion culture method of adult MSCs in future.

RESEARCH PROJECTS

- Specification, prospective isolation and expansion of three embryonic chondrogenic progenitors: (cartilage, limb mesenchyme and osteo/chondrocyte) from iPSCs.
- Elucidation of the molecular basis of long-term expansion without loss of chondrogenic activity of the hPSC-derived chondroprogenitors.
- Generation, detection, isolation, and expansion of joint progenitors from iPSCs using specific reporter iPSC lines.
- Defining the process of chondrogenesis from the iPSC-derived chondroprogenitors and joint progenitors to elucidate the molecular basis of joint chondrogenesis.
- Establishment of an orthopaedic xenotransplantation model for cell based articular cartilage repair.

Naoki Nakayama, Ph.D.  
Associate Professor  
Jeroen B. Kats Distinguished Professorship in Stem Cell Research

Key Publications


Lab Members

Senior Research Associate: Qing Yao, PhD  
Animal Specialist: Nadine Matthias, DVM
In my laboratory, we combine stem cell biology and systems-based approaches involving genomics, proteomics, bioinformatics, and functional assays to unravel gene transcription and regulatory mechanisms governing stem cell differentiation. One major focus of our group is investigating stem cell neural differentiation and developing effective and safe treatment for spinal cord injury and neurological diseases. We are studying gene expression and the regulation of transcription factors and regulatory RNAs using next-generation sequencing technologies including RNA-Seq and ChIP-Seq. These studies are crucial in understanding the molecular mechanisms of stem cell-neural differentiation and its clinical implications. Our goal is to identify and modulate key regulators as therapeutic targets to direct the differentiation of stem cell into neural cells more efficiently, and to increase transplantation safety.

The other area of our research interest lies in the studies of the regulatory networks of hematopoietic precursor cell self-renewal and differentiation using multiplex ELISA (phytohemagglutinin, anti-CD3, and anti-CD28) cell as a model system. We are using integrated genomic and proteomic approaches to identify key components that control the switch. We have identified TET1, together with RUNX1, as an important regulator in this process. Further study will generate a global interaction network and a novel and comprehensive view of the regulation of early stages of hematopoietic precursor self-renewal and differentiation. This study can serve as a model for the analysis of cell self-renewal and differentiation in general and provide insight for efficient expanding and manipulating hematopoietic precursor and stem cells, including reprogramming partially differentiated cells to return them to a self-renewing state.

**Research Projects**
- Characterize molecular signatures of spinal cord injury and neurological diseases.
- Investigate gene expression during stem cell neural differentiation.

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**Key Publications**


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**Key Resources**

  LAMBERT Academic Publishing.

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**Institutional Focus**

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 for the discovery, development, and commercialization of therapeutic agents and diagnostic tools. Research conducted at the institute focuses on the characterization and validation of drug targets, and establishment of proof-of-principle for therapeutics. TTI-IMM investigators have quickly brought therapeutic agents and diagnostic tools into clinical trials, and have made significant scientific discoveries in the areas of cancer biology and biologics 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, natural products, and synthetic small molecules that modulate the activity of these targets as potential lead molecules for drug discovery; and 3) characterization of antibodies from animals and humans in response to experimental vaccines. In addition to the basic and translational research programs, TTI is building two major drug discovery platforms: 1) the Therapeutic Monoclonal Antibody Lead Optimization and Development Platform and 2) the Natural Products and Small Molecular Drug Discovery Platform. The drug discovery platforms not only support TTI internal projects, but they are also support collaborative projects with scientists from the IMM, the Texas Medical Center, and other Texas-based institutions.
**IMMPACT REPORT**

**TEXAS THERAPEUTICS INSTITUTE**

**Discovery and development of therapeutic antibodies and antibiotics**

with improved oral availability or broader spectrum of antifungal activities. Therapeutic monoclonal antibody drug discovery platform. Supported by a grant from the Texas Emerging Technology Fund and as part of the Texas Therapeutics Institute, our group has been building a comprehensive antibody drug discovery platform with a focus on antibody lead optimization technologies such as antibody phage display, deep sequencing of antibody encoding genes from individual antibody expressing B cells, affinity maturation and humanization.

**RESEARCH PROJECTS**

• HER3 mediated cell signaling and the development of HER3 targeting monoclonal antibodies for cancer therapy. 
• Evaluation of vaccine induced antibody responses in preclinical animal models and humans. 
• Bicombinatorial chemistry approach for natural products drug discovery. 
• Therapeutic antibody discovery and development.

**KEY PUBLICATIONS**


**LAB MEMBERS**

Post Doc: Alexander S. Sakurkin, Wenwo (Eliza) Meng, Leike (Shine) Li, Shu (Shëna) Zhan and Qun Yue (jointly with Dr. Bills), Yan Li (jointly with Dr. Bills), Li Chen (jointly with Dr. Bills). 

Student: Zey (Monki) Huang

**Release mechanisms of fungal PNS-MRPs to yield tetronic acids (Org Lett 16 (14), pp 3744–3747).**

**Cellular organization of breast cancer cells in 2D cultures, Matrigel, hDAM, and xenografts (Biomaterials 35(18):4940-9).**

**Fung produce many bioactive secondary metabolites useful in medicine, including antibacterials (e.g., epothilones), antifungals (e.g., pneumocandins, griseofulvin, and streptolydigin), immunosuppressants (cyclosporin A, rapamycin), anticancer and steriod hormone agents (located), and mirtaoglin and cystatin pharmacologicals (engt alkalds).**

Our lab employs genomics to interpret and predict genetically encoded chemical diversity of microorganisms using filamentous fungi as model organisms, especially biofungicidal families relevant for pharmaceutical intervention in human diseases. For example, we are currently characterizing the polyketide synthase NRPS/condensation pathway responsible for pneumocandin B8, the starting molecule for the antifungal drug CERS3051. Our goal is to develop methods to reprogram human polyketide biosynthetic pathways in fungi and develop new chemical derivativeral that overcome resistance, or that have improved potency, spectrum and pharmacological profile, while reducing fermentation production costs. Characterization of related lipopeptide biosynthetic pathways will enable us to recombine genes from these pathways to produce hybrid natural products with improved therapeutic properties.

We are developing new genetic and physiological methods for expressing and regulating unencoded lipopeptide pathways using filamentous fungi as model organisms. We are in the early stages of building a microbial chemical library focused on characterization of NRPS pathways appropriate for intervention in cancer biology, modulation of human molecular signaling pathways, and in other human therapies. Texas is the United States’ second most biodiverse state. Therefore, our collection will emphasize the vast microbial resources available from Texas and will be promoted among Texas-based screening centers resulting in new chemicals as probes in cell biology and for intervention in human diseases.

**TEXAS THERAPEUTICS INSTITUTE**

**Gerald Bills, Ph.D.**

Professor

Kay and Ben Fortson Distinguished Chair in Neurodegenerative Disease Research

**Genome mining, biosynthesis and discovery of microbial metabolites for infectious diseases and cancer therapies**

**RESEARCH PROJECTS**

• Biosynthesis and pathway engineering of the pneumocandin lipopeptides for improved antifungals. Biosynthesis and production of the thermophiles, potent nocardioavolkoane- amin acid macrodilites from the thermophilic fungus, Daiminges thermophilus (with Prof. Yun-Nai Niu).

• Development of methods for repurposing transcription of bioactive lipopeptide genes of fungi to discover new natural products useful to treat human diseases.

• Development of a natural product’s chemical resource platform for drug discovery for other investigations within the UT System, Texas and elsewhere.

**KEY PUBLICATIONS**

Bills, G. F., L. Chen, Q. Yue, X. Niu & Z. An. 2014. New insights into the echinocandins on horse dung in Arizona in 1903. Its chemical properties have never been investigated. This specimen not only yielded new antimicrobial chemistry, but the collection represents the first report of this microorganism for the state.


**LAB MEMBERS**

Research Associates: Dr. Qun Yue, Dr. Yan Li, Dr. Li Chen (all visiting from the Institute of Microbiology, Chinese Academy of Sciences).
Our laboratory studies intracellular signaling associated with second messenger cAMP. We apply multidisciplinary approaches, coupling biochemistry, biophysics and cell biology with pharmacology and chemical biology, to understand the structure and function of exchange proteins directly activated by cAMP (EPAC). Our goals are to unravel the signaling intricacies of EPAC proteins and to design pathway-specific probes for these important signaling molecules so that their functions can be pharmacologically exploited and modulated for the treatment of human diseases. Our laboratory has developed first-in-class EPAC selective inhibitors and EPAC knockout mouse models to study the physiological functions and diseases relevance of this family of important signaling molecules. Recently, we have identified a potential use of EPAC inhibitors in the prevention and treatment of fatal rickettsioses. Currently, we are actively engaged in the development of novel drug candidates targeting EPAC for the treatment of microbial infections caused by tick-borne bacteria Rickettsia. Development of next generation of bait specific EPAC modulators, in collaboration with NIH National Institute of General Medical Sciences (NIGMS), is underway. The roles of EPAC proteins in major human diseases, such as cancer, chronic pain, diabetes, and obesity, using EPAC knockoat mice models.

Loss of EPAC1 increases hepatic sensitivity and protects mice from high-fat diet induced obesity (Molecular Cellular Biology: 33:918-926).

**RESEARCH PROJECTS**
- Structural and functional analyses of the exchange proteins directly activated by UTP/ATP (ERCA), funded by NIH.
- Development of in vitro chemical probes targeting EPAC for suppressing pancreatic cancer metastasis, funded by NIH.
- Preclinical development of novel drug candidates targeting EPAC for the treatment of human diseases including cancer, diabetes, and chronic pain.

**LAB MEMBERS**
- Research Scientists: Yinghui Zhu, Pei Dong, Hu Wang, Upasana Banerjee
- Student: Yuexia Hu

**Molecular mechanisms of cancer metastasis**

My research is to study novel molecular mechanisms of cancer metastasis with the goal of identifying new biomarkers and drug targets for the development of better therapeutics for human cancers. Cancer metastasis, the spread of tumor to other parts of patient’s body, is responsible for over 90% of cancer death. However, it is still poorly understood and the current approaches to prevent or treat human metastatic diseases are mostly unsuccessful. Through genomic, proteomic, and cell biological screenings, our lab has identified several critical but previously unknown regulators for cancer metastasis. Signaling pathways and molecular mechanisms of these genes are under investigation with molecular, cellular, biochemical, genetic, proteomic approaches and mouse models. These studies will yield new insights for cancer metastasis and may facilitate the development of new therapeutics and biomarkers. My research will identify novel molecular mechanisms of cancer metastasis with the goal of identifying new biomarkers and drug targets for the development of better therapeutics for human cancer.

**RESEARCH PROJECTS**
- New regulators for cancer metastasis and their mechanisms of actions.
- New regulators for EMT and their involvement in cancer progression.
- Development of precision medicine based on selected kinase requirements.
- Development of precision medicine based on selected kinase requirements for cancer metastasis.

**PUBLICATIONS**
- X. Isoform-specific antagonists of exchange proteins directly activated by cAMP play central roles in many aspects of signaling transduction, cell physiology and diseases. (Molecular Cellular Biology, 29:60 T1, 2014).

**LAB MEMBERS**
- Research Scientists: Yinghui Zhu, Pei Dong, Hu Wang, Upasana Banerjee
- Student: Yuexia Hu

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**RESEARCH PROJECTS**
- New regulators for cancer metastasis and their mechanisms of actions.
- New regulators for EMT and their involvement in cancer progression.
- Development of precision medicine based on selected kinase requirements.
- Development of precision medicine based on selected kinase requirements for cancer metastasis.

**PUBLICATIONS**
- X. Isoform-specific antagonists of exchange proteins directly activated by cAMP play central roles in many aspects of signaling transduction, cell physiology and diseases. (Molecular Cellular Biology, 29:60 T1, 2014).
Adapt stem cells are specialized cells that can self-renew and give rise to all the other types of differentiated cells in the tissue where the stem cells reside. They are essential for the maintenance of tissues with high turnover rates, such as the gut and skin, and for tissue repair after injury. However, these cells also are believed to be the cells of origin for many types of cancer as they are programmed to divide indefinitely. Furthermore, tumor tissues are also heterogeneous in which only a subpopulation of cells can self-renew and provide daughter cells that make up the bulk of the tumor. These self-renewing cancer cells, designated cancer stem cells or tumor-initiating cells, can form a fresh tumor after injury. However, these cells also are believed to be the cells-of-origin for many types of cancer, as they are programmed to divide indefinitely. Furthermore, tumor tissues are also heterogeneous in which only a subpopulation of cells can self-renew and provide daughter cells that make up the bulk of the tumor. These self-renewing cancer cells, designated cancer stem cells or tumor-initiating cells, can form a fresh tumor after injury.

Our research is focused on delineating the mechanisms that govern the control of normal and cancer stem cells and providing crucial knowledge to the discovery and development of novel therapeutics for regenerative medicine and cancer treatment.

Our research is focused on delineating the function and mechanisms of a group of stem cell receptors called LGRs (LGR4-6) that play critical roles in the control of normal stem cells and tumor cells. Previously, we discovered that LGR6 functions as a group of stem cell receptors called R-spondins that are essential for the survival and growth of stem cells. We have now determined how R-spondins and LGR6 work together to regulate cell growth and migration. Most recently, we uncovered that RSPO3-LGR4 has a major role in the aggressiveness of lung adenocarcinomas. Our current efforts are focused on identifying and characterizing drug leads targeting the R-spondin system as potential treatment for acute and lung cancers.

**RESEARCH PROJECTS**

- Determination 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.
- Identification of novel molecules targeting the R-spondin-LGR system as novel anti-tumor therapeutics.

**KEY PUBLICATIONS**


Antibiotics are powerful agents for the treatment of infectious diseases. However, their pharmaceutical effect poses evolutionary pressure on pathogens, resulting in the development of drug resistance. The emergence of drug-resistant bacteria such as methicillin-resistant Staphylococcus aureus (MRSA) and multidrug-resistant Pseudomonas aeruginosa is an increasingly serious problem for human health. According to the report from the Centers for Disease Control and Prevention (CD, April 2011), antibiotic resistance in the United States costs us approximately twenty billion dollars per year in excess health care costs and more than eight million additional days spent in hospital. Therefore, alternative antimicrobial strategies based on novel mechanisms of action have been pursued to overcome this clinical challenge.

With this background in mind, my lab is focused on two research projects: (1) taking advantage of the power of organic chemistry and chemical biology, and (2) conducting proteomic profiling using synthetic chemical probes based on antimicrobial metal complexes. In the past decades, metal complexes have attracted enormous attention as potential drugs for the treatment of cancer, autoimmune diseases, and, more recently, infectious diseases caused by drug-resistant pathogens. However, in general, their molecular targets are still unclear. Chemical probes based on such antimicrobial metal complexes will enable us to identify their protein targets and thus provide novel insights into pharmacological mechanisms and drug design for developing innovative antimicrobial therapeutics. Secondly, we will design, synthesize, and evaluate untraditional antimicrobial agents that could potentially circumvent drug resistance development. Our molecular design stems from the concept of “delivering catastrophic agents only to target pathogens.” We will develop and evaluate various types of molecules consisting of “targeting” and “killing” motifs. Through these projects, we hope to drive our efforts toward innovative medical means to save people suffering from serious diseases.

**RESEARCH PROJECTS**

- Proteinomic profiling using chemical probes based on antimicrobial metal complexes.
- Selective killing of drug-resistant bacteria using untraditional chemical agents.

**KEY PUBLICATIONS**


**LAB MEMBERS**

Dr. Kyoji Tsukamoto is currently seeking postdoctoral fellows with experience in organic chemistry/medicinal chemistry.

Kyoji Tsukamoto, Ph.D.
Assistant Professor

Development of chemical agents, tools, and strategies for combating infectious diseases

**LAB MEMBERS**

Dr. Kyoji Tsukamoto joined TID in July 2014 and is currently seeking postdoctoral fellows with experience in organic chemistry/medicinal chemistry.
Heterogeneity of tumor microenvironment and cancer resistance mechanisms to therapeutic antibody treatment

Ningyang Zhang, Ph.D.
Associate Professor

Monoclonal antibodies are becoming a major drug modality for cancer treatment and have shown clinical success for treatment of various types of cancer. Human epidermal growth factor receptor (EGFR) family consists of four closely related type 1 transmembrane epidermal growth receptor (EGFR/HER1, HER2, HER3 and HER4) and plays important roles in cell growth and signal transduction. Abnormal gene amplification and overexpression of EGFR and HER2 are well documented in many types of cancers and multiple therapeutic monoclonal antibodies such as, trastuzumab, pertuzumab target EGFR and trastuzumab and pertuzumab against HER2, are currently used in the clinic for treatment of different types of cancers. Similar to many other targeted cancer therapies, both innate and acquired resistance to those therapeutic monoclonal antibodies have been widely reported and present significant challenges in the clinic. My research interest is to understand resistance mechanisms to cancer therapeutic antibodies targeting EGFR family members including the HER2 targeting antibody trastuzumab. Multiple mechanisms of action of trastuzumab have been proposed, including inhibition of HER2 signaling, prevention of HER2 oncprotein domain shedding, and triggering immune effector function such as antibody-dependent cellular cytotoxicity (ADCC) through the antibody Fc interaction with activating Fc receptors expressed on immune effector cells. Our current research programs are focused on roles of immune modulation and evasion in cancer resistance to therapeutic antibodies such as, trastuzumab. We have established cancer cell/immune cell co-culture systems and in vivo mouse tumor models to investigate immune modulation in response to cancer therapeutic antibody treatment. We employ a wide array of experimental approaches including in vitro-2D and 3D cell culture, mouse tumor models, and studies with clinical samples from cancer patients. State of the art technologies are used in our studies such as high-content fluorescence imaging, mass spectrometry, multi-color flow analysis, and fluorescence activated cell sorting (FACS). We also are studying the role of matrix metalloproteinases (MMPs) in cancer resistance to therapeutic antibodies. The long-term goal of our research is to identify key molecular markers that govern the dynamic interaction between cancer cells and immune cells in tumor microenvironment and to help design effective antibody therapeutic strategies for activation of immune against cancer.

RESEARCH PROJECTS

• Role of proteolytic hinge cleavage of antibody in cancer immune evasion and trastuzumab resistance.
• Modulation of anti-cancer immunity by antibody therapeutic treatment.

KEY PUBLICATIONS


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 highest technology qualitative 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 service 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 UTH-Health IMM is a critical component of this commitment.

Antibody Engineering and Expression Service Center

Antibody therapeutics represents a major breakthrough in combating human diseases including cancer. Even though the pharmaceutical and biotechnology industries are in the center stage of drug development and discovery, academic researchers are increasingly engaged in discovering new antibody drug candidates. However, advancement of some of the promising antibodies in the early stage of development from academic research laboratories is often hindered by the lack of access to the expertise and infrastructure required for antibody lead optimization. Our antibody engineering and expression service center will fill the gap of the much needed expertise for the advancement of monoclonal antibodies from academic researchers to lead optimization and preclinical development for the research and drug discovery communities. Objective of the service center is to provide technical support and services to advance proof-of-concept antibodies to the stage of preclinical development. Results generated from the core facility 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.

Director: ZHIQUAN GAO, PhD
Co-Director: NINGYAN ZHANG, PhD
Associate Professor, Texas Therapeutics Institute
713-500-3332
IMM Center for Molecular Imaging

The IMM Center for Molecular Imaging is a facility that all researchers at UTHealth who are involved in small animal studies should be acquainted with. The Center is directed by Dr. Eva Sevick and led by eight engineering and basic science faculty members whose research focus on different aspects of molecular imaging including new instrumentation, design, and chemistry of targeted probes, innovative algorithms, and pioneering translation of new imaging technologies into clinical trials. The newly formed Molecular Imaging “collaboration” center utilizes this existing expertise to interact with academic and industry researchers across the nation on small animal imaging projects in areas including cancer, drug discovery, autoimmunity disorders, gastrointestinal disorders, nanotechnology, chronic wound care, peripheral vascular disease, and others. Facilities include a Siemens hybrid PET/CT small animal scanner with custom fluorescence tomography capabilities, a Digi-Rad gamma camera, and an array of custom bioimunescence and fluorescence instrumentation that is paired with unique molecules for diagnosis and therapy. Generalized protocols are available to investigators to maximize benefit from the latest developments in molecular imaging.

Director: EVA M. Sevick, PhD
Professor & Director
Center for Molecular Imaging
713-500-3560
Contact: Holly Robinson
Research Coordinator I
713-500-3606

Flow Cytometry Service Center
The Flow Cytometry Service Center is located on the sixth floor of the Fayez S. Sarofim Research Building and maintains four instruments: BD FACS Calibur, BD FACS Aria II, BCI FC500, and a Luminex 200. These instruments are available on a fee-per-services charge to all research investigators from UTHealth or external organizations. These instruments allow scientists to evaluate a large number of samples in a short time frame and gather information on very rare populations of cells. The service center provides training, instrumentation, and technical expertise for both analysis and cell sorting.

Director: EVA M. Sevick, PhD
Professor & Director
Center for Molecular Imaging
713-500-3560
Contact: AMY HAZEN, PhD
Assistant Director
713-500-3612

Tissue Histopathology Service Center
Our Center for Molecular Imaging is now providing in-house routine histology, special stain, and immunohistochemistry services in support of research projects to all research investigators from UTHealth or external organizations. With the growth of research activities that require histopathology services, the laboratory houses equipment for the preparation of thin sections; both paraffin and fresh frozen-tissue. A full range of histopathology services is provided:
• Routine histology (process, embed, cut and stain)
• Section cut rolled and placed in microcentrifuge tub for DNA, RNA studies
• Multi-tissue embedding & sectioning
• Frozen tissue embedding & sectioning
• Blood smear stain
• Immunohistochemistry and special stain

Director: EVA M. Sevick, PhD
Professor & Director
Center for Molecular Imaging
713-500-3560
Contact: SARAH AMRA, BS, HT (ASCP)
Chief Histology Technician
713-500-3386

Microscopy Service Center
The IMM Microscopy Service Center provides assistance in wide-field fluorescence microscopy, confocal microscopy, and image analysis. The facility is equipped with a Nikon Eclipse TE2000E inverted wide-field microscope, a Leica TSC SP5 upright confocal microscope with conventional and resonant scanner, and a dedicated computer workstation running Amira software for post-acquisition analysis of imaging data.

The Microscopy Service Center will support the research needs of all research investigators from UTHealth or external organizations on a fee-for-service basis by providing microscopy technical support, training, and consultation.

Director: EVA M. Zsigmond, PhD
Assistant Professor, Center for Immunology and Autoimmune Diseases
Director, Microscopy Service Center
713-500-2453
Contact: ZHENGMEI MAO, PhD
Manager
713-500-3389

Molecular Diagnostics Service Center
Our Molecular Diagnostic Laboratory, ProtoPath, provides diagnostic testing in a CLIA certified laboratory to all research investigators from UTHealth or external organizations on a fee-for-service basis. Major testing includes mass spectrometry (based on metabolites and Vitamin D) along with research testing. We serve as a diagnostic technology development site for The Brown Foundation Institute of Molecular Medicine, Clinical Laboratories, physicians, and other external organizations.

Director: KEVIN ROSENBLATT, MD, PhD
Associate Professor, Center for Proteomics and System Biology
713-500-3611
Contact: NATALIYA BULAYEVA, PHD (ASCP)
Lab Manager
713-500-3428

Transgenic and Stem Cells Services
Our Immunology and Autoimmune Diseases Center operates a Transgenic and Stem Cells service center, which was established in 1998. It has generated over 750 new transgenic and knock-out mouse animal models for all research investigators from UTHealth 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, derivation of new cell lines and intellectual/ technical support in different aspects of microsurgery, cell culture, and stem cells research.

Director: EVA M. Zsigmond, PhD
Assistant Professor, Center for Immunology and Autoimmune Diseases
Director, Transgenic and Stem Cells Service Unit
713-500-2453
Contact: ALEKSEY DOMOZHROV
Research Associate | Manager
713-500-2452

Mass Spectrometry Specialist | Service Center Manager
713-500-2332

Research Coordinator I
713-500-3606

Manager
713-500-3428

Lab Manager
713-500-3428

Research Associate | Manager
713-500-2452
Number of Faculty

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Total Funds Supporting Research

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Note: Excludes all ARRA funds, sponsored projects based on award received, service centers and endowments/gifts based on expenses.

Total Expenses Supporting Research

- Endowment/Gifts: 54%
- Service Centers: 19%
- Sponsored Projects: 16%
- Industry: 6%
- Federal Government: 5%
- State Government: 6%
- Foundations: 10%
- Service Centers: 5%

Gift Report

New Gifts and Bequests Fiscal Year 2014

We are deeply grateful to UTHealth benefactors who generously made a gift of $1,000 or greater to the Brown Foundation Institute of Molecular Medicine for the Prevention of Human Diseases during fiscal year 2014, September 1, 2013 – August 31, 2014.

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