REMEMBERING OUR FOUNDER

James T. Willerson, MD
The Brown Foundation Institute of Molecular Medicine for the Prevention of Human Diseases was the brainchild of founder James T. Willerson, MD, who died Sept. 16, 2020. This issue of the IMMPact Report is a tribute to him.
Contents

2    Director’s Message
3    Mission
20   Center for Cardiovascular Genetics
23   Center for Human Genetics
29   Center for Immunology and Autoimmune Diseases
33   Center for Metabolic and Degenerative Diseases
42   Center for Molecular Imaging
47   Center for Stem Cell and Regenerative Medicine
62   Center for Translation Cancer Research
70   Texas Therapeutics Institute
77   IMM Service Centers
79   By the Numbers
81   Gift Report

Features

4    Dr. Willerson: A vision for excellence
8    Remembering Dr. Willerson
12   Constructing support for the IMM
18   Fayez S. Sarofim Research Building Timeline
I am pleased to introduce the latest annual IMMpact report for The Brown Foundation Institute of Molecular Medicine for the Prevention of Human Diseases (IMM). The IMM is a stand-alone research institute that is embedded within McGovern Medical School. The IMM mission is to deliver translational outcomes from research in molecular medicine that benefit patients. This mission was proposed by Dr. James Willerson, whose passion for molecular medicine was the driving force for the founding of the IMM. It was his single-mindedness coupled with phenomenal fundraising and philanthropy that saw phase one of the project completed in 2006 with the opening of the Fayez Sarofim Research Building that houses the IMM. I say phase one because the opening of this remarkable research building was just the beginning of the outstanding and innovative translational science that continues to define the IMM. Sadly, Dr. Willerson passed on the 16th of September this past year and so to honor him, we are dedicating this year’s report to him by going back to the beginning of IMM, to explore how his vision was received by some of our sister institutions within the TMC. Research operations were scaled back in April while new operating procedures were put in place to ensure safe working in the laboratories and then ramped up again in May, such that by summer all labs were operating pretty much as normal, albeit with all workers masked and social distancing observed. Unfortunately, we had to cancel the IMMpact symposium, which was scheduled in April because of COVID concerns. We have not yet decided on a new date, but if the COVID vaccination program, currently underway in Houston, continues to drive down new cases, then a fall symposium may be possible. In the interim we are in the process of developing an IMM Webinar series as an alternative to the symposium, which will showcase short research presentations from our faculty together with question-and-answer sessions and special video coverage of their respective laboratories. We hope to start releasing these webinars next month.

Despite these challenges I am pleased to report, that once again IMM faculty have nevertheless excelled in NIH, DOD, CPRIT and other extramural grant funding. Over the financial year just ended, our new grants and contracts matched last year, which has a best ever for new funding, capping increases in our extramural grant funding for each of the last seven years. It is a testament to the remarkable quality and creativity of our scientists that the IMM remains so successful in attracting research funds. That said, full implementation of our mission remains heavily dependent on attracting support from alternative sources, including research charities and foundations, industry collaborations, and, most importantly, the continuing generosity of our friends and donors. In this context, we are as always deeply appreciative of the strong work and dedication of the IMM advisory council, which plays a key role in the continued growth and development of the IMM.

In conclusion I want to return to Dr. Willerson, his contributions to teaching, education, medical service and research at UTHealth and the broader TMC are too lengthy to list, but for all of us here paramount is his gift of the IMM, and the enduring legacy of scientific and medical discoveries that have only been possible because of it. In Dr. Willerson’s own words… “Our genes and proteins are the game officials of our lives. They already know if you have a cancer in your future. Or dementia. Or some other devastating disease. We must identify these genes and proteins in our bodies and discover ways in which they might be altered to prevent these diseases from occurring in the first place . . . That research is the role of the IMM.”

We at the IMM are indeed privileged to be realizing Dr. Willerson’s vision for molecular medicine at UTHealth. If you would like to investigate how you also can help us further in this regard, I would be very pleased to talk with you personally.

John Hancock, MA, MB, BChir, PhD, ScD
Executive Director, Institute of Molecular Medicine

John S. Dunn Distinguished University Chair in Physiology and Medicine

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 McGovern Medical School, the Brown Foundation Institute of Molecular Medicine for the Prevention of Human Diseases strives to set the example for research excellence and collaboration locally, nationally, and internationally.
Dr. James Willerson: A vision for excellence

A beautiful burnt orange building in the heart of the Texas Medical Center filled with the world’s best scientists working to cure the greatest diseases of our time in our time.

This was the vision of James T. Willerson, MD, which was realized as the Brown Foundation Institute of Molecular Medicine for the Prevention of Human Diseases rose from a plan to reality with the backing of UTHealth and UT System leadership, colleagues, community members, elected officials, and supporters who believed in the future of science.

Dr. Willerson was a pioneer who embraced a vision of excellence in a quest to create a scientific institute unlike any other. Today that institute is known as the Brown Foundation Institute of Molecular Medicine for the Prevention of Human Diseases (IMM).

Born Nov. 16, 1939, Dr. Willerson grew up in San Antonio with both parents as doctors in private practice. Dr. Willerson had stated his firm intention to follow in their footsteps early in life. His introduction to Dr. Denton Cooley, founder of the Texas Heart Institute, as a teenager, had a profound impact on the direction of his career.

A proud graduate of The University of Texas at Austin, Dr. Willerson earned his medical degree from Baylor College of Medicine and completed postgraduate training at Harvard Medical School and Massachusetts General Hospital. Prior to his work in Houston, he was on the faculty of The University of Texas Southwestern Medical School in Dallas.

As president of UTHealth, a position he held from 2001-2008, Dr. Willerson aimed to build a university foundation poised for greatness. The IMM was integral to that success.

“I am very proud of the fact that we were able, with Beth Robertson and Rodney Margolis and many friends in Houston, Legislature, UT Regents, to build the IMM and continue to recruit some of the world’s best scientists,” he said back in 2008. “As I’ve said about each of our schools, poised for greatness depends on our constant recruitment and retention of the best scientists with a commitment to basic medical science discovery to translate to patients for cure and prevention of their diseases so wonderfully placed in the world’s largest medical center with colleagues. I expect great discoveries that benefit mankind to come from our IMM to uplift scientific discovery and translate to our schools, to develop strong research efforts with collaborative grants and educational programs.”

Throughout his career, Dr. Willerson always stressed the importance of all three areas of the mission – education, patient care, and research, noting no one area was more important than the other. “We need to be outstanding in each area,” he said.

Dr. Willerson always led by example. Not only was he a mentor and teacher, a world-renowned expert pursuing gene therapy and stem cell research, he also was the caring physician for more than 2,000 patients.

The IMM was born in 1989. That was the year Dr. Willerson came to Houston – recruited as chair of the Department of Internal Medicine at The University of Texas Medical School at Houston (now known as McGovern Medical School).

Dr. Willerson imagined the institute as a collaborative environment of scientists not only elucidating the roles of genes in disease but also developing genomic-tailored therapies to combat the most challenging diseases.

“Molecular medicine is a very exciting field, and we must be at the cutting-edge,” he once said. “Genes are the

The vision behind this new building is a vision for understanding the intricate pathways and molecular processes that determine for each individual how human diseases occur.

James T. Willerson, MD, on the dedication of the Fayez S. Research Building, 2006
Our success is dependent on scientific talent, and, most importantly, our will to discover and apply new knowledge in technology to better the human condition.

-James T. Willerson, MD

drugs of the future. Better yet, if you can predict disease or prevent it altogether, then we can reduce human suffering and the difficulties – including cost – that go with it.”

In 1993, Dr. David Low, then-president of the UT Health Science Center, formally announced the university’s support of the institute with the kick-off of a $40 million fundraising initiative headed up by Rodney Margolis.

In 1995, Dr. Willerson recruited the first scientific director of the IMM, Hans Muller-Eberhard, MD, PhD. His wife, Irma Gigli, MD, was recruited to lead the IMM’s Center for Immunology and Autoimmune Diseases. The next decade was spent growing and focusing the IMM as it moved into temporary space in the Texas A&M Institute of Biosciences and Technology, on the outskirts of the Texas Medical Center.

As the human genome sequencing race transfixed the world, Dr. Willerson capitalized on the scientific fervor, winning over the support of generous community members and elected officials with his vision of the IMM. A campaign was initiated – this one chaired by Beth Robertson and Ben Lowe, with a fund-raising goal of $200 million.

More than $236 million later, the seven-story Fayez S. Sarofim Research Building opened as the Institute’s home in 2006, ushering in a new era of research for UTHealth. With scientists in modern labs, pursuing the latest research in a modern environment created to further molecular medicine, the vision became reality.

By 2006, seven research centers had been established at the IMM – each staffed with outstanding faculty pursuing novel work: Cardiovascular Diseases, Cell Signaling, Human Genetics, Immunology and Autoimmune Diseases, Protein Chemistry, Stem Cell Studies, and Nanotechnology. Today’s eight centers are targeted to innovative areas to produce discoveries and translational outcomes.

Dr. Willerson never considered his job work. “It’s not work, it’s opportunity,” he once said. “My goal is to make The University of Texas Health Science Center at Houston what it is supposed to be – a health university with excellence at each of our schools.”

Following the 9/11 attacks on our nation, he sent a university-wide message, reminding “each one of us has an uncertain number of days on this earth in which to do meaningful things. Let us recommit ourselves to using them wisely and work together to create an environment here in which all of us have the opportunity to be the best we can be.”

Dr. Willerson died Sept. 16, 2020, leaving a legacy of excellence – the crown jewel of which was the IMM. At the time of his death, he was the president emeritus, director of cardiology research, and co-director of the Cullen Cardiovascular Research Laboratories at Texas Heart Institute at CHI St. Luke’s Health-Baylor St. Luke’s. On Nov. 19, 2020, the UT System Board of Regents unanimously named him president emeritus of UTHealth.
Remembering Dr. Willerson

Several of our current Institute of Molecular Medicine faculty were founding faculty members, on staff when Dr. James T. Willerson was leading the Institute. We asked them for their remembrances of our founder.

Ali J. Marian, MD
Professor and Director, Center for Cardiovascular Genetic Research,
George and Mary Josephine Hamman Foundation Distinguished Professor in Cardiovascular Research

Dr. Marian published a full paper on the memory of Dr. Willerson in Circulation Research, which may be found at go.uth.edu/willerson. An excerpt is included below.

Leadership was natural to him. It was in his genes. It was coupled with his huge vision, the vision of unifying all forces against cardiovascular diseases. He led at The University of Texas at Southwestern and at The University of Texas Health Science Center at Houston. As the president of the university, he built institutions, established programs, and recruited world-class scientists. He was the founding father of the Institute of Molecular Medicine. He had the strong conviction that from the basic science discoveries will come the knowledge the predict, prevent, and cure cardiovascular diseases.

And he was truly a gracious man. When he was editor of Circulation, I was one of his associate editors, and we were at the annual meeting of the editorial board. He acknowledged several of the associate editors and forgot to mention my name and likely a few others. This is typically not a big deal as no one expects all of the editors to be acknowledged. A day later, he realized he had missed a few names. I received an apology in person, a personal handwritten note, and a beautiful bouquet of flowers. Of course, none of this was expected, and likely the others he forgot received the same treatment.

Ba-Bie Teng, PhD, FAHA
Professor of Molecular Medicine
The Jerry and Maurry Rubenstein Distinguished Professorship in Heart Research
Center for Human Genetics

I joined UTHouston, Institute of Molecular Medicine, in May of 1998 as a young faculty. I remember meeting Dr. Willerson to discuss a proposed collaborative research project. He greeted me and our other collaborators with his famous, fatherly, warm smile and gave us constructive criticism on how to proceed with our project. Dr. Willerson’s enthusiasm for science and medicine was infectious, and it was a motivating force in my career. It was his vision and perseverance that built the Institute of Molecular Medicine and helped it become an icon of research excellence in the Texas Medical Center. I am grateful to have known Dr. Willerson. He will be remembered.

In 1979, I enrolled in the PhD program in physiology at the University of California, Riverside. One of the professors who served on my advisory and examination committees was recently arrived in California from her training at UT Southwestern. She was interested in cardiac glycoside drugs and heart function. As I spent time around her in the lab and in classes, I began to hear of a person who she viewed as a legend in cardiology … a person who bridged excellence in clinical medicine with outstanding innovation in heart research. That person was James T. Willerson, MD. I took note of her impressions and held on to them.

In 1997, I visited Houston in connection with a possible faculty opportunity in the newly created Institute of Molecular Medicine. As I learned about how this new institute had come into creation, I was told that, to attract the legendary James T. Willerson, MD from Dallas to Houston, he was offered the opportunity to bring to reality his vision that contemporary biomedical research needed to move into a new era wherein the tools of molecular biology were harmonized and integrated with the problems of clinical medicine.

I understood whose vision this was, my past recollections about Dr. Willerson as a person committed to advocating for medical research that bridged bench and bedside, created a surge of excitement about the new opportunity I was exploring.

During that visit to Houston, I spent 30 minutes with the legend. Not all legends are larger than life. In my mind, such a person was supposed to be huge both in persona and in stature. But Jim Willerson was a compact person with a quiet, deliberate, and modest demeanor. I was impressed that he wasted no energy: his manner was concise and direct, and he was completely lacking in self-doubt. He knew what he believed, and he believed it because it was obvious to him from his own experience in medicine. This was no follower of the ideas of others. I was certain this was a leader who was completely harmonized with my own aspirations in medical science.

During the early years at IMM, Dr. Willerson was heavily engaged in advancing the nascent institute. He was patient, never hurried, but persevered. I saw his persuasiveness. It surprised me. I learned that leadership and innovation was not about loud or noisy claims regarding his own importance or that of his mission. He reached out to the audience of potential donors who might help build and support his vision in his typical earnest, but restrained manner. Quiet, calm, clear, moderate, and confident.

The combination was utterly persuasive. He generously moved the spotlight from his own aspirations to the actual investigators who were beginning to bring the vision of IMM to reality.

As we moved forward to actually raising and occupying the splendid building that is now our home and filling it with science, I was sometimes surprised to find that Jim Willerson had little interest in taking credit for the new institute that was forming. For him, I think, the accomplishment was not in being recognized for the achievement that was his vision, but in the knowledge that he had helped create something unique and good and valuable. His effort was genuinely for the benefit of the world he lived in and loved.
Dr. Willerson’s legacy in the IMM is a vision of how you can integrate human beings and different components. The IMM is his major contribution, and the opening of the new building of the institute was a very special day for both of us. I think Dr. Willerson loved the IMM, and his devotion to the institute cannot be denied.

I don’t think many people know of how the idea of the institute came about. I was chair of the Department of Dermatology at the University of California San Diego when I was asked to interview a candidate to be the head of cardiology. The candidate was Dr. Willerson. He walked into my office and saw a large poster of a lecture that my husband (Hans Eberhard) had given the year before for an important organization. He sort of fixed looking at it, and said, “I have a great deal of admiration for that man.” And I burst out laughing and said perhaps it’s good to be interested in your own husband. We used different names and had our own careers. Dr. Willerson told me he was not interested in the job for which I was to interview him, but said he was looking for good faculty for when he took a position in Houston. He later met with my husband in Germany and said he had an idea of an institute that studied diseases from many different aspects. He continued to develop this in his mind with Hans as the director and me as the codirector. Finally, he got us to agree, and we then looked for architects and made all of the plans. Before the building was built, we had the top two floors of the A&M building on Holcombe and worked in the labs and recruited people. My husband developed advanced prostate cancer and died after a few years. I worked very hard with the architects to develop the concept that eventually became the building of the IMM. It’s a place that I love.
Constructing support for the IMM

Building and sustaining relationships with generous and supportive friends of the IMM has proven to be one of Dr. James Willerson’s most enduring legacies.

“I am very proud of the fact that we were able, with Beth Robertson and Rodney Margolis and many friends in Houston, the Legislature, the UT Regents, to build the IMM and continue to recruit some of the world’s best scientists,” Dr. Willerson once said.
Houston is a very generous city, and Dr. Willerson was an excellent and caring physician whose scientific knowledge and drive encouraged hundreds to understand, and finance, the power of molecular medicine. “He told me that when he arrived at UTHealth, nothing was singularly more important to him than accelerating and cementing the institution’s research capacity,” recalled Randa Safady, PhD, UT System vice chancellor for external relations, communications, and advancement services. “He knew it was the best way to recruit the best and brightest scientists to UTHealth and the TMC, to draw increased sponsored research support, and to be more competitive on a national and international level. He said he would always be relentless and in a hurry’ with this pursuit. He successfully pushed for more research space to achieve those aspirations.”

Focused on growing research, Dr. Willerson recruited Hans J. Muller-Eberhard, MD, as director and his wife, Irma Gigli, MD, as co-director of the IMM. A team of scientists soon began working in two floors of the Texas Medical Center’s Texas A&M research building. Planning quickly started for an independent IMM building, on which Dr. Gigli worked hand-in-hand with the architects. “I put all of myself in what came to be, and the community was happy in seeing what the money could help to develop,” she said.

“I still remember vividly his vision for the IMM, which he told me about in 1990,” said Ralph Thomas, former chair of the UTHealth development board and senior vice president of Fayez Sarofim & Co. “He impressed me with his vision and dedication. It was inspiring.” In 1995, Dr. Willerson set his sights on realizing a new home for the IMM – a 223,000-square-foot state-of-the-art building, selecting Rodney H. Margolis, Houston community leader, philanthropist, and long-standing friend, to help lead a fundraising initiative to help construct it. “Jim asked me to head up the campaign and thought Dr. Eberhard was brilliant. We

Former UT System Chancellor Mark Yudof with Dr. Willerson

would solicit for philanthropy, and people were so receptive why they would tell their story.

“We would go to a couple of philanthropic groups who had never given money for molecular medicine, and after he spoke they would say, ‘how much money do you want?’” recalled Margolis, who had known Dr. Willerson since their student days at The University of Texas at Austin, where they both were members of the Texas Cowboys. “A brilliant diagnostician and even better caregiver, Dr. Willerson was everybody’s doctor. He had a list of probably 2,500 or 3,000 patients. All ‘grateful patients’, but he knew all of them and found time for all of them,” said Beth Robertson, who in 2001 stepped up as co-chair, with the late Ben Love, of the New Frontiers Campaign, whose goal was to raise $200 million in support of the IMM. Dr. Safady recalled the New Frontiers Campaign’s early days. “Dr. Willerson was thrilled when Beth said she would lead the campaign. I remember she said she couldn’t head up another campaign, and Dr. Willerson said she was the only one he could go to, so she said yes. You can’t say no to Dr. Willerson, and she was so committed to him and the IMM, and the results showed,” Dr. Safady said. “We traveled around Houston and the state where he pitched the idea of the IMM – a world-class institute that would attract world-class researchers/MDs to UT and TMC to make big discoveries that would translate into curing human disease here,” Robertson recalled. “And we had amazing results from these grateful patients. They wanted to support Dr. Willerson and his crusade against human disease. We all believed in Dr. Willerson.”

“We were able to raise a great deal of money,” agreed Dr. Gigli, the Walter and Mary MIScher Distinguished Professor in Molecular Medicine and the Hans J. Muller-Eberhard Chair in Immunology director emeritus. “But the community won’t give money unless it is going to something worthwhile.”

Dr. Gigli also remembered Robertson’s involvement. “Beth Robertson was unbelievable,” she recalled. “She was very involved and expanded our enthusiasm for the institute.” Throughout the life of both campaigns, more than $240 million was raised through 350 gifts. The largest gifts were $25 million from building namesake Fayez S. Sarofim, founder and owner of the investment firm Fayez Sarofim & Co., and $20 million from the Brown Foundation, Inc., for which the IMM is named.

“The Brown Foundation is proud to join UTHealth in celebrating Dr. Willerson’s legacy of excellence and community impact. We are honored to have been an early supporter of his pioneering leadership,” said Will Mathis, on behalf of Foundation Trustees.

The generous support from all donors resulted in the recruitment of world-renowned scientists – through the creation of 27 faculty endowments – and ultimately the 2006 grand opening of the Fayez S. Sarofim Research Building, home of the Brown Foundation Institute of Molecular Medicine for the Prevention of Human Diseases. IMM for short.

“We recently had a good laugh about a meeting we had some 14 years earlier about the long name as it would appear in signage and on buildings. He initially insisted on signage in brightly illuminated orange – in fact, he wanted the whole UTHealth...
“The world-class facility, which we’ve added to the UT System today, was designed to encourage the work of some of the world’s best minds as they advance the cause of better health and health care for Texas and the nation,” Huffines said at the building’s dedication.

“The research done here – every discovery and every advance – will be a testament of generosity that helped to make it happen.”

“Huffines and Yudof were embarking on a comprehensive UT System Competitiveness Initiative, which resulted in more than 6.5 million square feet of lab and research space across the system’s institutions and more than $2.6 billion in new and renovated research and clinical space,” Dr. Safady recalled. “The IMM and Sarofim building were gold-standard examples of how investments from the state, UT System, and philanthropy came together to advance discovery and health research and care for the people of Texas and beyond.”

Support for the IMM and its mission from the community and generous friends continues today. Dr. Gigli, a longtime member of the Development Board and the IMM’s Advisory Council, is unwavering in her passionate promotion of the IMM through gifts of scholarship, the Muller-Eberhard Memorial Lecture Series, and estate gifts.

“I love the IMM, and I think Dr. Willerson loved the IMM. It was put together by three people who loved the idea and loved the place,” Dr. Gigli said. “You don’t get a place like that in one or two years – it takes a commitment to get the right people.”

“My impression of Jim, over time, was that he was the most dedicated, multi-talented person I’ve ever known,” Thomas added. “He led innovative research, was a wonderful physician, and an inspiring leader of the UT Health Science Center, and it was a real privilege for me to be a part of this for over 30 years, seeing the execution of his vision.”

The IMM and Sarofim building were gold-standard examples of how investments from the state, UT System, and philanthropy came together to advance discovery and health research and care for the people of Texas and beyond.”

Dr. Willerson created in the IMM what he envisioned as the standard for medical research, Robertson observed. “He came to UT because he loved the institution. He was a brilliant diagnostician, an incredible leader and had so much energy, doing everything at once. He was prepared to demonstrate that this type of quality and world-class research was what he was thinking for the whole institution, that it would give us a vision of how we would take it from the lab to the bed,” she said.

His supporters and friends still marvel, remembering his unique abilities and talents.

“There won’t be another person like Jim Willerson to cross your path or my path again, for dedication or loyalty again – can’t find anyone stronger again,” Margolis added. “Jim was so dedicated to the concept of molecular medicine there are not words in the dictionary to celebrate his dedication to medicine.”

“How on earth does Jim do that – more blessed to have him as my doctor, but also for his empathic energy/drive and his thoughtful and strategic perspective,” Robertson observed. “He came to UT because he loved the institution. He was a brilliant diagnostician, an incredible leader and had so much energy, doing everything at once. He was prepared to demonstrate that this type of quality and world-class research was what he was thinking for the whole institution, that it would give us a vision of how we would take it from the lab to the bed,” she said.

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“The IMM has done what he hoped, I think,” Robertson said. “A high-quality pinnacle is what he wanted. Jim Willerson was the high-quality pinnacle person. There was never a dull moment raising money with him. He was not going to be denied. A big UT fan and former UT swimming star, he was very competitive. I admired him – not just for his energy/drive and his thoughtful and strategic perspective, but also for his empathic energy/drive and his thoughtful and strategic perspective, but also for his empathic energy/drive and his thoughtful and strategic perspective, but also for his empathic energy/drive and his thoughtful and strategic perspective, but also for his empathic energy/drive and his thoughtful and strategic perspective, but also for his empathic energy/drive and his thoughtful and strategic perspective, but also for his empathic energy/drive and his thoughtful and strategic perspective, but also for his empathic energy/drive and his thoughtful and strategic perspective, but also for his empathic energy/drive and his thoughtful and strategic perspective, but also for his empathic energy/drive and his thoughtful and strategic perspective, but also for his empathic energy/drive and his thoughtful and strategic perspective, but also for his empathic energy/drive and his thoughtful and strategic perspective, but also for his empathic energy/drive and his thoughtful and strategic perspective, but also for his empathic energy/drive and his thoughtful and strategic perspective, but also for his empathic energy/drive and his thoughtful and strategic perspective, but also for his empathic energy/drive and his thoughtful and strategic perspective, but also for his empathic energy/drive and his thoughtful and strategic perspective, but also for his empathic energy/drive and his thoughtful and strategic perspective, but also for his empathic energy/drive and his thoughtful and strategic perspective, but also for his empathic energy/drive and his thoughtful and strategic perspective, but also for his empathic energy/drive and his thoughtful and strategic perspective, but also for his empathic energy/drive and his thoughtful and strategic perspective, but also for his empathic energy/drive and his thoughtful and strategic perspective, but also for his empathic energy/drive and his thoughtful and strategic perspective, but also for his empathic energy/drive and his thoughtful and strategic perspective, but also for his empathic energy/drive and his thoughtful and strategic perspective, but also for his empathic energy/drive and his thoughtful and strategic perspective, but also for his empathic energy/drive and his thoughtful and strategic perspective, but also for his empathic energy/drive and his thoughtful and strategic perspective, but also for his empathic energy/drive and his thoughtful and strategic perspective, but also for his empathic energy/drive and his thoughtful and strategic perspective, but also for his empathic energy/drive and his thoughtful and strategic perspective, but also for his empathic energy/drive and his thoughtful and strategic perspective, but also for his empathic energy/drive and his thoughtful and strategic perspective, but also for his empathic energy/drive and his thoughtful and strategic perspective, but also for his empathic energy/drive and his thoughtful and strategic perspective, but also for his empathic energy/drive. It was blessed to have him as my doctor, but more blessed to have him for my friend.”

Community supporters included Mayor Bill White.
TIMELINE

1989
James T. Willerson, MD joins The University of Texas Health Science Center at Houston and announces his vision to develop an Institute of Molecular Medicine for the Prevention of Human Diseases (IMM) in Houston’s Texas Medical Center. Fundraising begins.

1993
M. David Low, MD, PhD, president of the UT Health Science Center at Houston, formally announces a plan to establish an institute that specifically will target the prediction and prevention of human diseases – The Institute of Molecular Medicine for the Prevention of Human Diseases. He announces the first receipt of gifts totaling $7.2 million to enhance molecular research. A $40 million fundraising initiative also is announced that will later be expanded to the $200 million New Frontiers Campaign to house and support the new institute.

1995
Dr. Gigli becomes the IMM’s first faculty member. Plans to house the IMM in the renovated UT Speech and Hearing Building are revised as space is leased and readied in the Albert Alkek Building of the Texas A&M Institute of Biosciences and Technology.

1995
Müller-Eberhard, MD, PhD, arrives in Houston. Prior to his appointment he was director of the Bernhard Hocht Institute for Tropical Medicine in Hamburg, Germany. He begins development programs in immunology, infectious diseases, cardiovascular diseases, neurobiology, and cancer research at the genetic level. Recruitment of scientists in these specialties begins.

1996
IMM occupies first space in the Albert Alkek Building of the Texas A&M Institute of Biosciences and Technology.

1998
March 3
Dr. Müller-Eberhard dies at MD Anderson Cancer Center.

1998
March 1
Dr. Gigli becomes the IMM’s first faculty member. Plans to house the IMM in the renovated UT Speech and Hearing Building are revised as space is leased and readied in the Albert Alkek Building of the Texas A&M Institute of Biosciences and Technology.

1999
January
1998 Nobel Laureate Ferid Murad, MD, PhD, is named director of the IMM by Low, then-president of the UT Health Science Center. Dr. Murad continues to direct the institute’s Research Center for Cellular Signaling. Dr. Gigli is named associate director of the IMM in addition to her directorship of the Research Center for Immunology and Autoimmune Diseases.

2003
FEBRUARY
The University of Texas System Board of Regents approves plans to move forward with architectural plans and design for a new IMM building. Designed by the Missouri firm of Berkebile Immenschuh Nelson McDowell Architects and Burt Hill Kosar Rittelmann Associates from Pennsylvania, the seven-story building is planned to be adjacent to University Center Tower (UCT).

2003
SEPTEMBER
Groundbreaking event for the IMM’s new building.

2004
January
The Brown Foundation Institute of Molecular Medicine for the Prevention of Human Diseases becomes the official name of the institute, in recognition of a $20 million gift by The Brown Foundation, Inc.

2005
February
UT System Regents approve renaming the new building “The Fayez S. Sarofim Research Building” in recognition of the largest gift ever received by The University of Texas Health Science Center at Houston—$25 million to advance stem cell research.

2006
January
Dr. Willerson announces to the UT Health Science Center Development Board that the New Frontiers development campaign is successfully completed – reaching and surpassing its $200 million goal. Campaign co-chairs, Beth Robertson and the late Ben Love are recognized for their leadership in fundraising.

2006
May
First faculty and staff occupy new Sarofim Research Building.

2006
November
Sarofim Research Building is formally dedicated.

2006
FEBRUARY
Thomas Caskey, MD, is named director—and CEO-elect of the IMM, joining the leadership team of Drs. Murad and Gigli as chief operating officer and executive vice president of molecular medicine and genomics.

2012
John Hancock, MA, MB, BChir, PhD, ScD, is appointed executive director of the IMM.

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FEBRUARY
Thomas Caskey, MD, is named director—and CEO-elect of the IMM, joining the leadership team of Drs. Murad and Gigli as chief operating officer and executive vice president of molecular medicine and genomics.

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We are actively recruiting additional probands and family members.

II. Genomics and epigenetic studies of human heart failure and mouse models of cardiomyopathies: The studies predominantly relate to DCM and ACM and included whole transcriptome analysis by RNA-Seq, DNA methylation analysis, and analyzing chromatin remodeling by ChIP-Seq. Specific epigenetic regulators of gene expression are identified and targeted in order to delineate their functions in the heart.

III. DNA damage response in human hereditary cardiomyopathies: We have detected increased double stranded DNA breaks (DSBs) in human hearts from patients with hereditary cardiomyopathies and in mouse models. Studies are ongoing to define genomic characteristics of the DSBs and to define the pathogenic role of DNA damage response pathways in heart failure.

IV. Therapeutic targeting of dysregulated pathways in cardiomyopathies: Dysregulated pathways identified through integrated genomics are targeted through genetic and pharmacological interventions in model organisms and their effects on survival, cardiac function, and clinical outcomes are analyzed. A major focus currently is on the canonical WNT and the Hippo signaling pathway.

V. Clinical Studies: The Center participates in investigator-initiated single center pilot clinical trials as well as industry-sponsored multi-center clinical trials in hereditary cardiomyopathy. An NIH-sponsored double-blind randomized pilot study (HALT-HCM) in patients with HCM was recently completed. The Center also participates in industry sponsored clinical trials in cardiomyopathies.

AJ Marian, M.D.
Center Director & Professor

Our long-standing research objectives have been to delineate the molecular genetics, genomics, and pathogenesis of hereditary cardiomyopathies in humans and apply the discoveries to prevent the unfolding and reverse the established phenotypes of heart failure and sudden cardiac death. We have active research programs in three common forms of hereditary cardiomyopathies: Arrhythmogenic Right Ventricular Cardiomyopathy (ACM): ACM is an enigmatic form of hereditary cardiomyopathies that clinically presents with cardiac arrhythmias, heart failure, and sudden cardiac death, particularly in the young. A unique feature of this disease is a gradual replacement of cardiac myocytes with fibro-adipocytes. There is no effective therapy for ACM. Hypertrophic Cardiomyopathy (HCM): HCM is the most common form of hereditary cardiomyopathies, affecting ~1 in every 500 individuals in the general population. The affected individuals are typically asymptomatic and sudden cardiac death is often the first manifestation of this disease. HCM is the most common cause of sudden cardiac death in the young. While there are effective therapies to alleviate patient’s symptoms, there is no effective therapy to prevent or reverse the disease process. Dilated Cardiomyopathy (Dcm): DCM is genetically the most heterogeneous form of hereditary cardiomyopathies and a major cause of heart failure and heart transplantation in the young. The affected individuals often present with symptoms of heart failure, cardiac arrhythmias and sometimes, sudden cardiac death. There are a number of effective pharmacological and non-pharmacological therapies for DCM but currently there is no cure for DCM.

The overall approach entails an integrated approach that includes human molecular genetics studies through high throughput whole exome and genome sequencing to identify the causal genes and mutations, followed by genomic studies including transcriptomics and epigenomics to define molecular remodeling of chromosomes in the presence of causal mutations. The aim is to

Activation of DNA Damage Response (DDR) Pathway, induced by increased expression of p53/Parkin, in the heart in a mouse model of arrhythmogenic cardiomyopathy.
Imprint Report

Center for Cardiovascular Genetics

Priyatansh Gurha, PhD
Assistant Professor

Molecular Mechanisms and Functions of Non-coding RNAs and Epigenetic Regulation in Heart Failure

Research Projects
- Role of lincRNAs in the pathogenesis of cardiomyopathies and heart failure.
- Identification and characterization of molecular mechanisms and functions of human disease-associated lincRNAs in cardiomyopathies and heart failure.

Key Publications


Lab Member
Post-doctoral Fellow: Manisha Dragharia

The main objective of my research is to understand the molecular mechanisms that coordinate regulate gene expression and contribute to the pathogenesis of heart failure. Within this theme, we are studying the function of epigenetics and non-coding RNAs in proliferation, differentiation, and maturation of myocytes and how alteration of these interlinked processes eventually leads to cardiac dysfunction and failure. My previous studies have identified epigenetic dysregulation of non-coding RNA (lincRNA) in the phenotypic reprogramming of non-coding RNA (lincRNA) in the phenotypic reprogramming of epigenetics and non-coding RNAs function. A significant body of evidence suggests that epigenetic dysregulation is a key contributor to chronic heart failure.

The main objective of my research is to understand how the molecular mechanisms that coordinate regulate gene expression and contribute to the pathogenesis of heart failure. Within this theme, we are studying the function of epigenetics and non-coding RNAs in proliferation, differentiation, and maturation of myocytes and how alteration of these interlinked processes eventually leads to cardiac dysfunction and failure. My previous studies have identified epigenetic dysregulation of non-coding RNA (lincRNA) in the phenotypic reprogramming of epigenetics and non-coding RNAs function. A significant body of evidence suggests that epigenetic dysregulation is a key contributor to chronic heart failure.

Under the direction of Dr. Myriam Fornage, we are making notable progress in the study of susceptibility to stroke and age-related decline in cognitive function. A significant fraction of sudden cardiac death results from rhythm disturbances that arise in genetic variation in the proteins processing the electrical activity within the heart. Our newest faculty member, Dr. Ashish Kapoor, is an emerging leader in this field. We have shown that kidney injury associated with increased blood pressure results from the emergence of auto-antibodies that damage tissues. This unexpected finding from Dr. Doris’ lab points to a role of immune system genetic variation in creating disease risk. The role of immune responses in chronic heart failure is an emerging area of research. Our lab is exploring the role of non-coding RNA (lincRNA) in the pathogenesis of cardiomyopathies and heart failure.
High blood pressure is a frequent cause of renal injury, but the risk of renal disease in patients with high blood pressure is best predicted by family history, indicating a genetic predisposition. At present we have almost no knowledge of why high blood pressure creates kidney disease in some people, but not others. To try to fill this knowledge gap, we study a genetic model comprising inbred laboratory rats that have high blood pressure. The divergence of hypertensive renal disease risk seen in humans is also present in these rats. Some lines get progressive renal injury, other lines do not. Therefore, this model provides a means to investigate what genetic differences can give kidney disease. We can take what we have learned and concisely of treatment approaches to prevent disease and test them in the model.

What we have learned so far:

- Genes influencing antibody formation affect the emergence of hypertensive renal disease.
- We have identified important genetic variation in the immunoglobulin heavy chain gene, which encodes antibodies. We also have identified genetic deleteries in the gene, Stim1. This is a key gene in immune function and B cell development, and adaptation immunity. The mutations in Stim1 blocks normal B cell function and leads to antibody-mediated autoimmune disease.

**Genetic and pharmacological suppression of antibodies eliminates hypertensive renal disease.**

To prove that antibodies causes hypertensive renal injury in our model system, we deleted the immunoglobulin gene. These animals cannot generate antibodies. They have high levels of blood pressure but have no renal injury. An immunosuppression drug that inhibits B cell function has a similar effect.

Get bacteria activate the hypertensive immune system and create antibodies that cause disease

When hypertensive rats raise to produce antibodies are raised without antibody replacement, they experience blood infection (sepsis). Blood culture indicates that the infecting bacteria are non-pathogenic bacteria that live in the gut. When antibodies are given to hypertensive rats prone to injury, renal injury was markedly reduced. The bacteria induce antibodies to a common bacterial protein. This protein is highly conserved in mammals as well as bacteria. These antibodies may prevent this protein from functioning to protect the kidney from pressure-induced injury.

Key questions that are the focus of our current research:
- Do the protective mechanisms active in rats gain insight into renal disease in humans?
- Common genetic variants occur in humans that alter the control of antibody formation and may contribute to disease risk.

**Key Publications**


**Lab Members**

Post-doctoral fellow: Ishaa S. Dhande, PhD Research Associates: Yaming Zhu, MD; Ankit Joch, BS

**Molecular epidemiology of the aging brain**

Throughout our lifetime our brain changes more than any other part of our body. Beginning in middle age, brings about subtle changes in brain structure, chemicals, and functions. These changes are detectable by neuroimaging techniques such as magnetic resonance imaging (MRI) and are associated with a greater risk of future stroke, cognitive and functional impairment, dementia, and death. Novel ‘omics’ techniques allow us to characterize and quantify the sets of biological molecules that make up cells, tissues, and organisms on a population scale. These technologies have opened new avenues toward biomarker discovery for risk prediction and risk stratification, enabling informed preventive and therapeutic interventions to slow or reverse brain aging.

A decline in cognitive function, such as reasoning, attention, memory, and language, is strongly correlated with brain aging. Our research program investigates the risk factors that influence cognitive aging using genetic data. In collaboration with researchers in the United States and Europe, we apply genome sequencing technologies to identify genes and gene variants that influence risk for cognitive impairment and associated Alzheimer’s disease. We focus on diverse populations, especially those of Hispanic and African ancestry, who disproportionately suffer from these diseases of aging.

We also utilize knowledge about the common genetic variants that control lifestyle exposures, such as high blood pressure, to investigate the causal relations between these modifiable risk factors and health outcomes in large cohorts. This is a technique known as Mendelian randomization. Using this approach, we studied the effect of high blood pressure on cognitive health during middle age, a pivotal period in the life course when cognitive function begins to decline among healthy adults. We showed that high blood pressure, especially high systolic pressure, is causally associated with lower processing speed, verbal memory, and executive function during midlife. By providing support for a causal relationship between blood pressure and cognitive health in middle age, our study underscores the need for further investigations of the mechanisms of blood pressure dysfunction on cognitive health across the lifespan, which may inform on early intervention and timing of treatment of hypertension to maintain brain health. Besides genetic factors, we also study the link between other molecules, such as DNA methylation, proteins, and metabolites with disease of the aging brain. For example, methylation levels measured at defined sites across the genome are correlated with an individual’s chronological age. We showed that accelerated epigenetic aging, which is operationalized as a DNA methylation-based measure of age that is higher than an individual’s chronological age is associated with lower verbal fluency in middle-aged adults.

**Research Projects**

- Discovering novel epigenetic DNA methylation variants that influence risk for brain small vessel disease and its related neurocognitive outcomes.
- Discovering novel genetic variants for high blood pressure using gene-lifestyle interaction and pathway analysis.
- In particular, discovering how depression and anxiety affects genetic risk of hypertension.
- Investigating the genetic determinants of cognitive function in diverse Hispanic/Latino populations.

**Lab Members**

Post-doctoral fellow: Yuning Yang, PhD Graduate Students: Senghe Lee (PhD program); Rui Xia, PhD Biostatisticians: Bin Shi, PhD; Emy Thomas, MS; Pa Xu, PhD Research Associate: Ping Wang, PhD

**Immunglobulin gene in SHR-A3 with duplicated IGHG2 and IGHG3 segments**

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**Immunglobulin gene in SHR-D2 with normal single IGHG2 and IGHG3 segments**

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**Mendelian randomization uses gene variants to interrogate cause and effect in human cohort data. For example, we have examined whether persons genetically predisposed to having high blood pressure are more likely to have cognitive impairment.**

**Key Publications**


**Lab Members**

Post-doctoral fellow: Yuning Yang, PhD Graduate Students: Senghe Lee (PhD program); Rui Xia, PhD

Biostatisticians: Bin Shi, PhD; Emy Thomas, MS; Pa Xu, PhD

Research Associate: Ping Wang, PhD

**Genetics of cardiovascular end organ injury**

Common genetic variants occur in humans that are associated with lower verbal fluency in middle-aged adults. We showed that accelerated epigenetic aging, which is operationalized as a DNA methylation-based measure of age that is higher than an individual’s chronological age is associated with lower verbal fluency in middle-aged adults.

**Research Projects**

- Discovering novel epigenetic DNA methylation variants that influence risk for brain small vessel disease and its related neurocognitive outcomes.
- Investigating the genetic determinants of cognitive function in diverse Hispanic/Latino populations.

**Key Publications**

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

Ashish Kapoor, PhD
Assistant Professor

We have been known to be associated with increased risk of cardiac arrhythmias and SCD. We are interested in identifying the genes that underlie this variation and that understanding the genetic factors for QT interval variation will potentially impact our understanding of SCD risk in its management. Our studies have the prospect to identify the genetic causes for QT interval variation, some of which in turn could serve as potential therapeutic targets (leading to genetic and/or biomarkers (genes and gene products) to identify individuals at high risk for SCD. What we as a community have learned so far is that many genes together converge to QT interval variation and that majority of DNA changes leading to QT interval variation do so not by altering the form of the gene product but rather by altering the amount of the gene product made by our heart cells. Starting with known genetic associations between DNA sequence variants and the QT interval in the general population, our work involves pinpointing the causes behind these associations to identify the underlying genetic defects and how they impact QT interval.

KEY PUBLICATIONS

LAB MEMBERS
Research assistant: Alina Smith, BS
Post-doctoral fellow: Parul Singh, PhD

Enhancer activities (reporter expression) at ~500 QT interval associated variants-centered test elements performed in mouse cardiomyocyte HL1 cells and fitting of Mixture Gaussian to the observed abundance distribution (top). Combined additive effect of five SCN5A causal cis-regulatory elements and their enhancer variants on luciferase reporter activity in HL1 cells (bottom).

Atherosclerosis is an inflammatory disease in the aorta that increases its severity as we age. The disease includes impairment lipid metabolism that leads to hyperlipidemia and maladaptive immune responses that affect the arterial vasculature. Our research focuses on understanding the development of atherosclerosis and to elucidate the cross-regulation between atherosclerosis and immunity. We generated a mouse model that mimics genetic associations with hyperlipidemia by deleting both LDL receptor (LDLR) and ApoA1 (ApoA1) genes (Ldlr−/−Apoa1−/−), these mice develop atherosclerosis as they age. Feeding on a Western high-fat diet accelerates their atherosclerosis development. Moreover, male mice develop atherosclerosis faster and more severe than females. PCSK9 (proprotein convertase subtilisin/kexin type 9) is a causative gene for hyperlipidemia. Patients with elevated PCSK9 levels have increased plasma cholesterol and premature coronary artery disease. We deleted PCSK9 gene from LDL mice, the LDL−/−Apoa1−/−/−Pcsk9 mice show decreased atherosclerosis with improved function of endothelial cell. PCSK9 mediates autophagy signaling pathway, PCSK9 modulates ERK and p38 MAPK (MAPK) pathways in hyperlipidemic mice containing PCSK9.

Using single-cell RNA sequencing analysis to create a comprehensive single-cell atlas of all cells in the aorta. We will delineate the differences in sex and age associated with each signature of cell population. We will identify cell subpopulations that influences vascular disease development.

RESEARCH PROJECTS

Pathogenesis of atherosclerosis and immunity and the development of genetic therapies for the treatment of atherosclerotic vascular diseases

Ashish Kapoor, PhD
Assistant Professor

Post-doctoral fellow: Parul Singh, PhD

Using single-cell RNA sequencing (scRNA-seq) to sequencing aorta to unveil the atlas of cells in the development of atherosclerotic disease.

KEY PUBLICATIONS


Research Associate: Xin Li

Using CRISPR/Cas9 technique, we generated LDL-R knockout mice in the background of LDL mice. We are currently studying its effect on atherosclerosis.

Using genetic therapy such as mRNA for the treatment of atherosclerotic vascular diseases.
Deciphering the regulatory code: A functional genomics approach to protein translation

Regulation of gene expression is fundamental to a wide range of biological processes. From cell fate determination during development to malignant transformation during tumor genesis, precise control of gene expression forms the basis of these processes. Our current understanding of gene regulation is, however, far from complete. Most published studies that profile gene expression are transcript-centric (i.e., they focus on measuring mRNA levels and levels of transcription factor binding). While these efforts revealed intricate networks of cooperativity amongst transcription factors in shaping complex biological processes, much of the post-transcriptional regulation are left unexplored. It remains unclear whether the process of protein translation is regulated by a network of factors in an extent of complexity similar to transcription regulation. We ask questions such as “Do sequence specific RNA binding proteins (RBP) cooperate in controlling translation?” “Are there translational regulatory networks that orchestrate critical biological processes?”

Our research program focuses on addressing this observation is, we are now expanding our analysis to other tissue types and species.

KEY PUBLICATIONS


2. The investigators of the Hans J. Müller-Eberhard and Irma Gigli Center for Immunology and Autoimmune Diseases are examining the molecular, cellular, and genetic bases of several different allergic, autoimmune, and infectious diseases. These studies explore the nature, structure, and function of specific cell membrane receptors and their ligands in modulating immune and inflammatory responses.

In concert with the molecular studies, the Center’s scientists have engineered mice with specific targeted gene mutations or deletions that are used as models for human disease. These animal studies have facilitated the identification of key gene products that play significant roles in regulating the immune system, as well as contributing to the pathogenesis of human disease.

Results from these research efforts have identified several therapeutic targets for the treatment of asthma, septic shock, and lupus erythematosus.

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 as well as for major eye diseases, including macular degeneration and diabetic retinopathy.

Research interests include:

- Asthma and Sinusitis
- Diabetic Retinopathy
- Mucosal Immunology & Autoimmunity
- Microbial Infectious Disease
- Acute Lung Injury and COPD
- Lung Surfactant Deficiencies
- Macular Degeneration
- Pulmonary Regenerative Medicine

Rick Wietel, PhD
Center Director & Professor
Hans J. Müller-Eberhard, MD, PhD and Irma Gigli, MD Distinguished Chair in Immunology
Chronic diseases of the lung and eye are often the result of dysregulation of the immune and inflammatory response to pathogenic or toxic substances, resulting in the destruction of healthy tissue, establishment of debilitating pathologies due to disease, and impairment of normal tissue repair mechanisms. However, the beauty of cellular and molecular knowledge regarding lung and eye immunity, inflammation, and regenerative processes has allowed the development of novel therapeutics that could be used to effectively treat chronic diseases of the lung and eye. Accordingly, our laboratory has for the past several years focused on delineating the key molecules that mediate the inflammatory and immune responses in the lung and eye during both normal and pathological conditions. Much of this research has involved studies of the complement system, the complement system is a major arm of the innate immune system and is well known for being the first line of defense against bacterial and viral pathogens. It is comprised of over 30 plasma proteins and cell surface receptors. It has become evident in the past decade that the complement system is very important in other biological functions other than killing bacteria and viruses. These other functions include tissue regeneration, polarization of immune cells, including T-cells, and normal development of the central nervous system. In addition to these novel complement biological functions, dysregulation of the complement system has been described as a major cause of AMD and a major contributor to lung diseases such as asthma, chronic obstructive pulmonary disease (COPD), 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 serve to regulate the chronic nature of these diseases. The major goal of my laboratory is to identify pathways that regulate the chronicity of these disorders with the aim 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 is far better at modulating levels in the lung they access pathways that serve to promote airway inflammation and remodeling. Adenosine signaling is engaged specific adenosine receptors on target cells, such as inflammatory cells, fibroblasts, airway epithelial cells, smooth muscle cells. Most of the projects in my laboratory focus on understanding the mechanisms by which adenosine signaling influences the activities of these cells in the context of lung inflammation and remodeling. We make extensive use of genetically modified mice to examine the role of adenosine signaling in chronic lung disease. This includes knockout mice of components of adenosine metabolism and signaling. We also conduct mechanistic experiments in disease relevant cell types and work extensively with human explanted lungs obtained following lung transplantation in the Texas Medical Center. These translational approaches help us identify novel strategies for treating chronic lung disease.

**RESEARCH PROJECTS**

- Vascular lumen
- Intercellular tissue

**Model:** Illustrating how the vascular endothelium on stimulation by the complement anaphylatoxin peptides C3a and C5a activates c-800 and polarizes T-cells during an immune response. Endothelial cells shown in brown with abrupt k. T-cells and B-cells shown in green and purple, respectively. The oligodendrocyte cells depicted activated c-800 and polarized T-cells as they transmigrate through the endothelium.

**CENTRAL FOR IMMUNOLOGY AND AUTOIMMUNE DISEASES**

Michael R. Blackburn, PhD
Executive Vice President & Chief Academic Officer, UTHealth
Dean and John P. McGovern Distinguished Professor of Biomedical Sciences,
MD Anderson UTHealth Graduate School
Professor and Vice Chairman, Department of Biochemistry and Molecular Biology
William S. Kelley Sr., Distinguished University Chair in Pulmonary Disease
Dean of Research, UT, McGovern Medical School

Adenosine signaling and the regulation of chronic lung disease

- Novel regulation of sRNA-polyt 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 mechanoic for S6 signaling in pulmonary fibrosis
- Systems Biology approaches to understand the progression of chronic lung disease

**KEY PUBLICATIONS**


Environmental triggers regulating innate immune responses in chronic airway inflammation

The eight laboratories of the Center for Metabolic and Degenerative Diseases investigate age-associated diseases, including type-2 diabetes, muscle wasting, vascular disease, neurodegeneration, and cancer. Mechanisms of aging, stress, and obesity-associated changes in brain activity, energy metabolism, vascular function, cell signaling, protein homeostasis, and cell fate determination that lead to physiological abnormalities are being interrogated in animal models and through studies on clinical specimens. The specific questions being addressed by the center’s faculty include the following:

• How does replicative senescence of adipocyte progenitors underlie diabetes development?
• How do adipocyte-derived fatty acids contribute to diabetes and cancer progression?
• Can cells of adipose tissue be targeted for therapeutic purposes?
• How is angiogenesis, fibrosis, and inflammation implicated in metabolic dysfunction?
• How do stress hormones regulate energy utilization in diabetes?
• What vascular genes can be targeted to treat muscle disease and diabetes?


LAB MEMBERS
Hua Sun, Ph.D.; Dong Li

Nasal polyps

Nasal polyps seen on nasal endoscopy within nasal cavity of CRSwNP patient.
Adipocyte progenitor cells: Dysfunction in disease and aging

Mikhail Kolonin, PhD
Professor & Director, Center for Metabolic and Degenerative Diseases
Harry E. Bowey, Jr. Distinguished University Chair in Metabolic Disease Research

Our group is interested in the mechanisms underlying aging-related diseases and developing new approaches to target them. Specifically, we focus on the role of fat (adipose) tissue in the context of obesity, type 2 diabetes, muscle degeneration, and cancer. While white adipocytes store lipids to insulate them in times of energy scarcity, brown adipocytes burn lipids off to keep the body warm. In obesity, overgrown white fat becomes inefficient in burning fuels, hence causing diabetes, cardiovascular disease, and cancer. In contrast, active brown fat can aid in weight loss, which starts spilling into other organs.

One of the key mechanisms underlying metabolic disease is accelerated adipocyte senescence and shortening of telomeres. Telomeres are the terminal DNA repeats at the ends of chromosomes that allow for DNA replication. As telomeres shorten, they reach a critical length, leading to cellular senescence. In mice lacking telomerase (TERT) in adipose stroma, we used this experimental drug to investigate the mechanism through which ASC promote tumor growth in mice. In more recent work, we have found that D-CAN treatment spares brown fat ASCs.

D-CAN targets human ASCs. Our reports indicate that D-CAN treatment spares brown fat ASCs, leading to generation of brown adipocytes, and enables a short-term metabolic benefit. However, our recent data indicate the importance of maintaining functional ASCs and preventing their replicative senescence in healthy aging. As we age, fat cell numbers decrease and the deficient fat tissue fails to effectively detoxify lipids, which start spilling into other organs. This can cause inflammation and metabolic disorders accounting for cancer and organ failure in the elderly. Our experiments in mice lacking telomerase (TERT) in ASC models suggest that adipocytes run out because ASCs lose replicative potential with age due to telomere shortening and become “exhausted,” which is accelerated by obesity. Understanding the mechanisms and function of fatty acid transport in the context of type 2 diabetes and cancer is one of our most recent pursuits. Another research direction is focused on the role of inflammatory signaling and fat tissue remodeling in metabolic response to anti-diabetes drugs.

RESEARCH PROJECTS
• Adipose tissue dysfunction by adipocyte progenitors and its role in metabolic disease
• Metabolic dysfunction and inflammation in adipose tissue
• Metabolic dysfunction, aging, and cancer

KEY PUBLICATIONS

LAB MEMBERS
Sr. research scientists: Alexis Daquinag, Zhengua Gao
PhD student: Shradha Subramanian
Research assistant: Cale Fussell

Novel pathways regulating type 2 diabetes and muscle regeneration

Rebecca Berdeaux, PhD
Associate Professor
Director, Graduate Program in Biochemistry and Cell Biology

Muscle weakness and compromised muscle metabolism reduce quality of life for aging people or those afflicted with type 2 diabetes. Our lab studies how hormones regulate skeletal muscle function and repair after injury. Our long-term goal is to identify new drug targets to help prevent muscle weakness and loss with aging, to improve insulin and fat burning in people with metabolic disease who may not be able to exercise, and to increase muscle stem activity with aims of improving muscle repair after trauma. Our approach is specifically designed to study proteins and protein complexes that are inherently “drugable” because they are usually turned on and off by hormones such as insulin and adrenaline.

RESEARCH PROJECTS
• Determine how a stress activated kinase tunes target gene expression and regulates insulin and adrenaline signaling
• Identify genes and signaling pathways that drive muscle stem cell replication after injury
• Comprehensive define muscle stem cells and inflammatory cells in human muscle during recovery from traumatically muscle and bone injury

KEY PUBLICATIONS

LAB MEMBERS
Post doctoral fellows: Laura Bahra, Mariane Markmeyer
Research assistant: Elena Dyukova, Chase Hutchinson, Daniel Hancock
Graduate student: Daisy Diaz-Rehena
Medical student: Victor Goncalves
Undergraduate student: Lindsey Kwan

Novel pathways regulating type 2 diabetes and muscle regeneration

Hormones like adrenaline stimulates cAMP. We genetically engineered mice to have high cAMP in muscle stem cells. After injury, high cAMP is sufficient to prolong the activation of these muscle stem cells center photo and graph. We are testing how cAMP activates DNA binding proteins (CREB/ CRTCs) participate in muscle stem cell activity with the goal of identifying new drug targets for muscle healthspan during aging.
Circadian rhythms in health and disease

The regulation of circadian rhythms in health and disease is a complex interplay of genetic, environmental, and behavioral factors. Circadian clocks are present in virtually all parts of the body, controlling a wide range of physiological processes and behaviors. Disruption of circadian rhythms can lead to a variety of health problems, including metabolic diseases, mood disorders, and cancer.

**Mechanisms**

- **Genetic factors**: Variations in circadian rhythm genes can contribute to individual differences in circadian sensitivity and response to environmental cues.
- **Environmental factors**: Light exposure, noise, and temperature can modulate circadian rhythms.
- **Behavioral factors**: Regular sleep patterns, exercise, and meal timing can influence circadian rhythms.

**Consequences**

- **Metabolic diseases**: Circadian disruption has been linked to the development of obesity, diabetes, and various metabolic disorders.
- **Mood disorders**: Circadian disruptions can lead to mood swings, depression, and anxiety.
- **Cancer**: Circadian rhythms play a role in the growth and metastasis of tumors.

**Research Projects**

- **Mechanisms of circadian disruption to metabolic disease**
- **Mechanisms linking circadian disruption to cancer**
- **Mechanisms underlying daily proliferation of adipocyte progenitor cells**
- **Understanding the role of the circadian clock in human adipose tissue**

**Key Publications**

  *Nature Communications* 2018; 9:4469

- “194-h interval four-limbed frog provides a Permissive Environment for Sex-independent Hepatocellular Carcinoma” Bahanan Feby, Alba Ribeiro, Corinne Baungartner, Alaa M.T. Mohamed, Mikhail G. Kaloian, Francesc M. St-Onge, Manuver Yive, Kristin L. Eckel-Mahan
  *Cancer Research* 2012; 72, Issue 22, pp. 5660-5673

**Lab Members**

- Instructor: Baharan Fekry, PhD
- Post-doctoral fellows: Rinaldo Bious Santos, PhD
- Graduate student: Rachel Van Duren, Jamie Tran

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The impact of stress on psychiatric and neurodegenerative diseases

High levels of stress cause anxiety that if continuously present leads to devastating mental illness, most commonly depression, generalized anxiety disorder and PTSD. Stress impacts the progression of other diseases, in part due to elevated levels of the stress hormone cortisol, which is released in response to stress. Diseases that can be exacerbated by stress and high cortisol levels include metabolic disease, cardiovascular disease, and age-dependent neurodegeneration in diseases such as Alzheimer’s disease. Parkinson’s disease, and loss of cognitive ability that occurs naturally with age. We are determined to find the mechanisms used by these neurons to control the stress response to help us avoid diseases that are caused or negatively impacted by stress.

- CRF and other neuropeptide neurons in the PVN project to key motor circuits to influence movement choice.
- We identified another unprecedented neuronal circuit that connects stress hormone release with the central circuits responsible for coordination. This movement circuit, termed “the basal ganglia” is the system that malfunctions in Parkinson’s disease as well as other neurodegenerative disorders and is associated with loss of the ability to move and control movements. We hypothesize that this newly found circuit communicates stress-relevant information to the basal ganglia to influence which movements are made in response to threats in our environment. In this way, stress circuits shape our reaction to a stressful threat, perhaps causing behavior and running away from a threat in certain contexts, and hiding from the threat in other contexts. Given our identification of this new circuit controlling (stress) hormone release and core neural circuits that guide movement, endless possibilities for future discovery lay ahead of which we pursue with passion.

- Oxytocin neurons become responsive to CRF only in mothers who have had offspring. This array of transcriptional animals designed to visualize and manipulate CRF receptor neurons, we found that Oxytocin neurons, which are involved in parturition and lactation, but only see CRFR1 positive Oxytocin neurons in mothers who have had offspring. Using an array of transgenic animals designed to visualize and manipulate CRF receptor neurons. We found that Oxytocin neurons become responsive to CRF during pregnancy and lactation. We hypothesize that this newly found circuit communicates stress-relevant information to the basal ganglia to influence which movements are made in response to threats in our environment. In this way, stress circuits shape our reaction to a stressful threat, perhaps causing behavior and running away from a threat in certain contexts, and hiding from the threat in other contexts. Given our identification of this new circuit connecting (stress) hormone release and core neural circuits that guide movement, endless possibilities for future discovery lay ahead of which we pursue with passion.

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**Key Publications**


**Lab Members**

- Post-doctoral fellow: Shivakumar Rajamanius, PhD
- Research assistant: Jonathan Tao
**Vihang Narkar, PhD**  
Associate Professor  
George and Mary Josephine Hamman Foundation Distinguished Professor in Cardiometabolic Research  
**Gene regulation in metabolic-vascular syndromes**  

**RESEARCH PROJECTS**  
- Transcriptional regulation of muscle metabolism, vascularization, mass, and fitness by nuclear receptors.  
- Nuclear receptor target discovery for muscle recovery in peripheral arterial disease.  
- Duchenne muscular dystrophy, obesity, and diabetes.  
- Role of nuclear receptors in blood vessel growth and diabetic retinopathy.

**KEY PUBLICATIONS**  


**LAB MEMBERS**  
Post-doctoral fellows: Nitya Narayana, Lisa Lin

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**Kai Sun, MD, PhD**  
Assistant Professor  
**Adipose tissue remodeling and metabolic health**  

My laboratory investigates and discovers novel factors that regulate the dynamics of adipose tissue remodeling during obesity development. The long-term goal of our research is to address the clinical significance of these factors in human obesity, diabetes, and cardiovascular diseases. In the past years, we have revealed that high fat diet-induced obesity shapes a hypoxic microenvironment that initiates the local fibrosis and inflammation in adipose tissue. The unhealthy adipose tissue further leads to systemic insulin resistance and cardiovascular dysfunction. Intriguingly, we found that Wnt7a induces angiogenesis and ameliorates the pathological changes by suppressing the local hypoxia and stimulating the sympathetic innervation in both white and brown adipose tissue. Our study further reveals that the hypoxia-induced MT1-MMP facilitates the healthy expansion of adipose tissue by stimulating angiogenesis in combination with VEGF-A and leptin, thus relieving the pathological conditions. Furthermore, we found that MT1-MMP also collages proteins to increase the ECM flexibility in adipose tissue. Most recently, we analyzed the dynamics of lipid droplet-associated proteins during adipose tissue remodeling by mass spectrometry. We have successfully identified several novel proteins that transdifferentiate into lipid droplets and the interface of endoplasmic reticulum (ER) and lipid droplets in response to different stimuli. Particularly, we found that one of the identified proteins named Carbapenem Esterase 3 (Ces3) targets lipid droplets upon β-adrenergic-stimulation where it exerts the lipolytic function on the lipid. We further discovered that another factor called Dystroglycan-Related Protein 1 (Dmp1) transdifferentiates onto ER where it promotes the fusion of the nascent lipid droplets from the ER in response to lipid messengers. We are applying state-of-the-art tools and techniques to investigate the mechanisms governing the functions of the novel factors on the dynamics of lipid droplets.
In addition, virus-based tracing is used to map specific neural projections and their implications in physiology and behaviors. We are also able to stereotaxically deliver to specific brain regions of expressing neurons, achieving neuron-expression or inactivation of foreign tool genes. For example, forebrain genes include specific channels that either activate or inhibit neurons. Thus, virus-based tracing is a crucial technique that is used to map specific neural projections and their implications in physiology and behaviors. We are also exploring the use of CRISPR/Cas9 technology to achieve neuron-specific gene deletion in adult mice. These advanced techniques ensure our studies are effective and conclusions are insightful.

One major direction in the lab is to identify and map novel neuroprotective mechanisms underlying control of feeding. Emerging evidence suggests that feeding anomalies are associated with defects in control of emotion and clinical phenotypes that reduce survival of psychiatric disorders cause obesity development. Using unique animal models coupled with behavioral and genetic approaches, we are able to delineate important neurons and neural pathways that underlie interactive regulation of feeding and emotion. This line of research is highly significant to current clinical treatments for obesity, psychiatric patients, and eating disorders.

**RESEARCH PROJECTS**

- *Hedon neurons and neural pathways for feeding regulation and their relation with emotional states.*
- *Brain efficient pathways controlling peripheral metabolism.*
- *Brain mechanisms mediating blood hormone action on energy and glucose, and their involvement in obesity and diabetes pathogenesis.*
- *Chronic stress and obesity development.*

**KEY PUBLICATIONS**


**LAB MEMBERS**

Instructor: Yang Xiao, MD, PhD

Post doctoral fellows: Ziyi Jiang, PhD; Saniosh Mondal, PhD

Graduate students: Jesse Morritt, Jing Cai, Hong Li (visiting)

Technicians: Claire Young

**Molecular mechanisms of neurodegenerative diseases**

- As we grow older and enjoy unprecedented longer life expectancy, we are also becoming increasingly vulnerable to aging-related neuronal degenerative disorders, including Alzheimer’s disease (AD), Parkinson’s disease (PD) and Huntington’s disease (HD). As these incapacitating brain diseases are resulting in unbearable emotional and financial tolls to patients and their families, they are becoming a pressing threat to our society. However, we know there is little effective prevention and treatments against these maladies.

- We are trying to address these challenges by studying how new neurons can house stability during normal aging. Our sensing, reasoning, and impression are realized through neurons and their functional connections inside our body. However, unlike other organs, such as those from skin and blood that are constantly dividing and regenerating, neurons face unique challenges. In particular, once they are born and mature into interconnected functional units, they are unable to reproduce and no longer can be replaced for the rest of life. To maintain longevity, these long-lived neurons harbor robust self-cleaning machinery to keep healthy and ward off internal crisis, and external insults for decades to come.

- The self-maintenance machinery inside cells include chaperones that help proteins to stay in shape, and proteasomes as well as autophagy (meaning self-eating) in literally and lysosomal systems that act as internal clearance machinery to clean up and recycle worn-out or toxic cellular materials. In neurodegenerative diseases, these protective machineries often become inefficient or non-functional, leading to excessive buildup of toxic wastes (known as aggregates, tangles, or plaques) inside the brain, causing eventual neuronal loss.

- We are focusing on the following studies:

  1. **Chaperone Hypothesis** on neuronal function and survival. Superoxide Hypothesis is one of the most abundant proteins in the brain. It helps other proteins to fold into proper shapes to function properly. It is also a major component of the dis-aggregation machinery that disentangles tightly packed protein aggregates.

  2. **Biogenesis of autophagosomes and other specialized cellular organelles and their dysfunction in brain diseases**

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

- Huntington’s disease gene huntingtin. Huntington is important for neuronal survival. As these incapacitating brain diseases are becoming a pressing threat to our society. However, we know there is little effective prevention and treatments against these maladies.

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**LAB MEMBERS**

Instructor: Sheng Zhang, PhD

Assistant Professor

Becker Family Foundation Professor in Diabetes Research

**Biogenesis of autophagosomes and other specialized cellular organelles and their dysfunction in brain diseases**

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**LAB MEMBERS**

Instructor: Shiyi Xu, PhD

Graduate Students: Yue Yu; Amanda Solbach; Heather Tsong (rotating graduate student)

Research Assistant: Xiu Y; PhD, Mrs. Liu Y
The Mission of the Center for Molecular Imaging (CMI) is to develop and translate new medical imaging technologies, molecular imaging agents, and companion diagnostics to accelerate discoveries.

The CMI houses a diverse, interdisciplinary team of scientists and engineers who develop and use multi-modality molecular diagnostics and imaging techniques, including nuclear imaging, X-ray computed tomography, bioluminescence, fluorescence, and near-infrared fluorescence (NIRF) to enable new understandings of disease and chronic conditions. Sponsored industry, philanthropic, and federal research funding focuses upon autoimmune disorders, neuroinflammation, cancer metastases, hemo- and lymph-vascular diseases, and lymphedema. The team has expertise in instrumentation, imaging agent development, antibody engineering, animal models of human disease, and translational science that effectively moves inventions and discoveries, “bench to bedside,” and when discoveries are made in the clinic, from “bedside back to bench.”

A highlight of the CMI is the basic science/clinical translational team that engages clinicians at UTHealth and at partnering institutions in the Texas Medical Center and in the Houston suburbs. These FDA-approved clinical studies enable visualization of the lymphatic system using photonics technologies for better diagnosis and directed treatments. Conditions such as vascular anomalies, congenital heart disease, peripheral vascular disease, breast cancer, and head and neck cancer are under investigation using our investigational imaging technologies. Earlier, translational activities further explore visualization of brain function in neonates, and in preclinical models of human disease, CSF outflow into the lymphatics, and intraoperative detection of lymph node metastases and tumor margins. Our team focuses upon translating new NIRF molecular imaging agents using validated standards that can be applied across different photonics device platforms.

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

Eva Marie Sevick-Muraca, PhD
Center Director & Professor
Nancy and Rich Kinder Distinguished Chair in Cardiovascular Disease Research
Director, Center in the NCI Network for Translational Research

As higher vertebrates evolved from the sea into land dwellers, terrestrial antigen exposure increased and the adaptive immune system evolved from a centralized lymphatic system to one dependent upon regional draining lymph nodes. The decentralized lymphatic system is organized into watersheds that drain into lymph node basins before emptying into the hemovascular circulatory system. In the regional draining lymph nodes, antigens are presented to activate immune cells that then leave the lymph nodes and disseminate through the body via the blood vasculature.

This organization enables regional processing of immune responses to multiple antigens without overwhelming the immune system and breaking central tolerance, or tolerance to self. Yet despite the watershed organization of lymphatics, drugs that are intended to alter immune responses by targeting key signaling molecules within the lymphatics are administered or dosed systemically. Whether dosed to stimulate the immune system as in cancer checkpoint blockade immunotherapies, or to attenuate immune responses against self as in autoimmune therapies, these pharmacological strategies frequently lead to suboptimal results and, perhaps not surprisingly, adverse immune responses that break central tolerance.

In addition, all tissues drain to at least one lymphatic watershed not only to ensure immunoregulation, but also to collect cellular waste products and excess fluid for return to the hemovascular circulatory system. Lymphatic insufficiencies can result in the buildup of waste products and unprocessed inflammation. For example, in the lower extremities of aging populations, we have found that lymphatic insufficiencies accompany peripheral vascular disease and precede ulcer formation. In the brain, the cerebrospinal fluid (CSF) and interstitial fluid (ISF) drains into the cerebral lymphatic watershed, and in animal models of Alzheimer’s disease, im paired and presumably leads to Aβ aggregation and plaque formation. In our research program, we employ near-infrared fluorescence imaging of the lymphatic vasculature and its function in order to understand chronic conditions that involve the lymphatics and to more effectively deliver therapeutics that can modulate immunity. Specifically, we conduct translational imaging of infants, children, and adults in the Texas Medical Center with chronic conditions and investigate the corresponding animal models of these conditions. Our studies are designed to develop new biological insights that could lead to better prevention and treatment of these conditions. We also engineer new methods of lymphatic imaging to provide better diagnostics of chronic conditions.

RESEARCH PROJECTS
• Lymphatic delivery of immunotherapies for cancer and autoimmune diseases.
• Evaluating the role of CSF outflow in brain health and Alzheimer’s.
• Assessing the role of lymphatics in metabolic disorders.
• Refining measurements of lymphatic anatomy and function.

KEY PUBLICATIONS


LAB MEMBERS

Post-doctoral fellows: Carolina Mandilla-Rejas, PhD
Research assistants/associates: Janelle Morton, BS, Fred Christian “CJ” Velasquez, BA

Professor and Director of the Center for Molecular Imaging
Nancy and Rich Kinder Distinguished Chair in Cardiovascular Disease Research

Understanding how the lymphatic watersheds mediate immune health and chronic disease


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


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Professor and Director of the Center for Molecular Imaging
Nancy and Rich Kinder Distinguished Chair in Cardiovascular Disease Research

Understanding how the lymphatic watersheds mediate immune health and chronic disease


Cancer survivors face the possibility of developing a devastating side effect of cancer treatment: lymphedema (LE), which manifests as a permanently swollen arm, leg, neck, or trunk. LE requires constant compression garment wear; meticulous skin care; and specialized massage. LE patients suffer decreased, depressed, or absent lymphatic vessels, and there is no cure-only palliative treatment. Studies have shown that, if caught early in development, LE treatment can reverse the disease. Near-infrared fluorescence lymphatic imaging (NIRF-LI) imaging delivers high-resolution, low-cost images of lymphatic vessels and pumping. In disease states such as LE, NIRF LI imaging can provide information for early diagnosis and evaluation of treatment efficacy. I lead a five-year prospective and longitudinal study using NIRF-LI surveillance of breast cancer patients to identify early LE development and biomarkers that could suggest pharmacologically targeted treatment. My recent research shows that certain plasma cytokines are raised in breast cancer patients destined to develop LE a year later; providing a predisposition to the development of LE in risk patients for pre-habilitation treatment referral. I have presented the first lymphatic-NIRF-LI evidence at an international conference showing that LE is reversible at early stages. I also lead a three-year CPRIT-funded clinical study of reparative lymphatic microsurgery, which are gaining in popularity for clinical study of reparative lymphatic microsurgery in cancer patients and survivors. Cancers (Basel) 12:2286, 2020.


LAB MEMBERS
Medical student: Kay Pham

Melissa B. Aldrich, MBA, PhD
Assistant Professor

Imaging in immunology

and I was recently appointed to the Scientific and Medical Advisory Council of the Lymphatic Education & Research Network (LE&RN), an international organization of researchers, physicians, therapists, and patients, dedicated to advancing lymphatic health. I also chaired the committee that established standards for LE&RN’s Centers of Excellence designation, which now enable patients to locate health institutions with lymphatic expertise. Delivery of pharmacological therapeutics directly to the site of disease activity could reduce the amount of pharmacologic required, and minimize off-target toxicities. A new model of neuroplasticity, NIRF-LI revealed that delivery of a tumor necrosis factor-alpha (TNF-alpha) blocker directly through lymphatic vessels to lymph nodes resulted in significantly reduced disease activity, as evidenced by improved lymphatic pumping. NIRF-LI studies of patients with lymphoma, a bit disorder that affects ~11% of women, revealed that large lymphatic vessels are dilated and slow pumping, suggesting the disorder is an inflammatory disorder. Compression garment wear to promote lymph flow movement and anti-inflammatory dietary practices have improved outcomes for these patients. I am a member of the Center for Molecular Imaging (CMI) team that participates with a national coalition of researchers to investigate lymphedema. Chylothorax occasionally affects neonatal heart surgery patients. I and my colleagues here at CHRI and Memorial Hermann Hospital have used NIRF-LI to help visualize the source of pleural effusion in babies with chylothorax. We also have imaged numerous pediatric patients with lymphovascular anomalies to help physicians direct optimal care.

UK RESEARCH PROJECTS
• Longitudinal study of breast cancer-related LE
• Longitudinal study of reparative microsurgery for LE
• Imaging of lymphatics in lymphoma
• Imaging of neoplastic chymopapain and lymphovascular anomalies

KEY PUBLICATIONS


LAB MEMBERS
Medical student: Kay Pham

Near-infrared fluorescence lymphatic imaging (NIRF-LI) of lymphatic vessels in a patient with breast cancer-related lymphedema. Green fluorescent dye is visualized through the skin, pumped through vessels (in a healthy arm) or pooling as backflow (in lymphedema). Medical insurers need objective evidence that current prescribed physical therapy actually works. These images are the first visual proof of reversal of lymphedema in response to therapy.

The lymphatic system is a vital, yet poorly understood, component of the circulatory system. As blood flows through the arteries and veins, water leaks from the vessels entering the small gaps between the tissue cells. As the water moves through the tissues it pools into small cell waste, foreign contaminants, proteins, etc., and the resulting solution is taken up by the lymphatics, processed for immune response, and finally returned to the veins. In addition, the lymphatics provide a pathway for the absorption of patients from the gut. However, because the lymphatics are typically small and primarily transport clear fluids, they are difficult to distinguish from the surrounding tissues, either with our eyes or using traditional clinical imaging modalities such as x-ray, MRI, and ultrasound. Over the past five years, my research has focused upon the development and translation of near-infrared fluorescence lymphatic (NIRF) optical imaging as a way to noninvasively image and characterize human lymphatics and quantify their contractile function in health and disease using microscopic amounts of a fluorescent contrast agent. One of our primary focuses is the relationship between the lymphatics and the lymphovascular system. It has been known for many years that patients with advanced chronic venous disease, often co-develop lymphedema, a condition of chronic swelling with fibrotic tissue changes and poor immune response. We recently imaged a group of patients with early venous disease and observed a degradation of lymphatic anatomy as evidenced by the appearance of segmented lymphatic vessels and increased incidence of dermal backflow, or abnormal movement of contrast agent into the dermal tissues, as venous disease progressed. In addition, the lymphatic pumping rate initially decreased to accommodate for the increased venous load (C3 disease) but then decreased by nearly half as the disease continued to progress to C4 disease. A better understanding of the role of the lymphatics in early venous disease may enable the development of more efficacious therapeutic approaches. The drainage of cranial lymphatics have been implicated in the development of neurological disorders, including space-occupying lymphoedema syndrome, where microgravity conditions result in fluid shifts from the body to the head. The resulting chronically high cranial pressures can damage the optical nerves of astronauts. We recently completed a small study assessing the impact of gravity on cranial lymphatic drainage. In this study, subjects were imaged in a head down tilt position to mimic microgravity conditions as well as while laying on their back and sitting up. The images revealed delayed cranial drainage when the subject was in the head down position, indicating that under normal conditions gravity aids cranial lymphatic drainage. We continue the development of this imaging technology, including assessing novel imaging and drug delivery technologies, improving device sensitivity, automating different aspects of the hardware, and developing analytical tools to facilitate lymphatic image processing and analysis, with the ultimate goal of advancing new biological and clinical questions not addressed by other technologies.

RESEARCH PROJECTS
• Understanding the role of lymphatics in the development of peripheral venous disease

• Assessing the development of cancer related lymphedema and its response to intervention

• Understanding the role of lymphatics in the development of neurological conditions

KEY PUBLICATIONS


John Rasmussen, PhD
Assistant Professor
Carolyn Frost Keenan Professor in Cardiovascular Disease Research

Device translation for lymphatic imaging

Banghe Zhu, PhD
Assistant Professor

NIR optical imaging of brain network dysfunction and CSF outflow


LAB MEMBER
Research assistant: Janelle Morton

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

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

In the pages following you will find examples of Center faculty exploring the potential therapeutic value of stem cells for repairing tissues such as spinal cord, brain, muscle, lung, and blood, as well as elucidating the role of stem cells in cancer. If I may provide any additional information, please do not hesitate to contact me.

Brian R. Davis, Ph.D.
Professor and Director
The C. Harold and Lorine G. Wallace Distinguished University Chair
**Genetic correction of stem cells for treatment of inherited lung and blood diseases**

Our laboratory has as its primary objective the sequence-specific genetic correction of mutations in the chromosomal DNA of induced pluripotent stem (iPSC) cells and/or tissue-specific stem cells derived from patients with inherited disorders affecting the lung or blood system. This is being pursued with the ultimate goal of developing stem cell-based therapeutic approaches.

We have utilized DNA sequence-specific nuclease-mediated homology-directed repair to correct the most common genetic mutations in iPSC cell lines derived from patients with cystic fibrosis or Wiskott-Aldrich Syndrome (WAS), a primary immune deficiency. We have demonstrated genetic and functional correction in lung epithelial cells derived from these corrected iPSCs. We have introduced lung-specific fluorescent reporters into iPSCs and utilized to specifically isolate early lung progenitors and then airway basal stem cells for purposes of molecular and functional characterization. Significantly, we have now demonstrated that our iPSC-derived airway basal stem cells (iBSCs) can be used to develop biomaterials for use in clinical treatments for spinal cord injury, traumatic brain injury, and multiple sclerosis.

**RESEARCH PROJECTS**

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

**KEY PUBLICATIONS**


**Future Directions**

- Developing biomaterials to be used in clinical treatments for spinal cord injury, traumatic brain injury, and multiple sclerosis.
- Optimizing substrates and matrices to direct human induced pluripotent stem cells (hiPSCs) to therapeutic progenitor cell lineages.
- Characterizing the molecular and cellular response of hiPSC-derived neural stem cells to therapeutic progenitor cell lineages.

**Tissue Engineering Approaches for the Treatment of CNS Injuries**

**RESEARCH PROJECTS**

- Optimization of substrates and matrices to direct human induced pluripotent stem cells to therapeutic progenitor cell lineages.
- Characterizing the molecular and cellular response of hiPSC-derived neural stem cells to therapeutic progenitor cell lineages.

**KEY PUBLICATIONS**

Stem cells for neurological diseases

Qi Lin Cao, MD
Professor

The development of stem cell therapies for neurological diseases is a promising area of research. Transplantation of neural stem cells (NSCs) is a promising strategy to promote functional recovery after neurodegenerative diseases, including spinal cord injury (SCI) and stroke. However, in situ reprogramming of neuronal precursors derived from integration-free NSCs for SCI therapy. Stem Cell Res. 9:55-64. doi: 10.1016. PMID: 28073086


LAB MEMBERS
Post-doctoral fellow: Yuan Zheng
Graduate student: Chryshee Gallegos
Research associate: Hai Peng Xue
Undergraduate student: Matthew Casey

Astellas scar formation after traumatic spinal cord injury in double transgenic mice of GFP-cmv.AxR.

Currently, we are testing the therapeutic efficacy and long-term safety of NSCs, neural or glial precursors to identify the optimal cell graft for SCI and stroke. Recently, we are testing whether we can directly reprogram the astroglial cells in the injured spinal cord or brain stroke into neurons. Astellas scar is the major inhibitor for axonal regeneration, in situ reprogramming active astrocytes into neuronal precursors will decrease astrocyte inhibition to promote axonal regeneration. The newly reprogrammed neuronal precursors could replace the lost neurons after SCI or stroke. These long-term goals is to develop novel stem cell-based therapies to treat human SCI or stroke.

KEY PUBLICATIONS


Our current research program focuses on the use of cellular therapies for neurological diseases, principally traumatic brain injury (TBI). We have been interested in the modulation of the innate immune response to TBI and how cellular therapies have been successful without significant engagagement in the brain-long term. Cell-cell interactions in the peripheral reticulodendrothelial system have resulted in Treg upregulation and modulation of the microglia/macrophage phenotype in the brain. We use these types of data to help us determine dosing regiments (number of cells, type, and route of delivery, as well as timing), which may be very specific to the pathophysiology in question. We are in vivo models of injury and in vivo cot beds.

Our team directs the Griffin Stem Cell Laboratory and the Hoffberger Stem Cell Laboratory, Our team directs the Griffin Stem Cell Laboratory and the Hoffberger Stem Cell Laboratory, Our team directs the Griffin Stem Cell Laboratory and the Hoffberger Stem Cell Laboratory, Our team directs the Griffin Stem Cell Laboratory and the Hoffberger Stem Cell Laboratory, Our team directs the Griffin Stem Cell Laboratory and the Hoffberger Stem Cell Laboratory, Our team directs the Griffin Stem Cell Laboratory and the Hoffberger Stem Cell Laboratory, Our team directs the Griffin Stem Cell Laboratory and the Hoffberger Stem Cell Laboratory, Our team directs the Griffin Stem Cell Laboratory and the Hoffberger Stem Cell Laboratory, Our team directs the Griffin Stem Cell Laboratory and the Hoffberger Stem Cell Laboratory, Our team directs the Griffin Stem Cell Laboratory and the Hoffberger Stem Cell Laboratory, Our team directs the Griffin Stem Cell Laboratory and the Hoffberger Stem Cell Laboratory, Our team directs the Griffin Stem Cell Laboratory and the Hoffberger Stem Cell Laboratory, Our team directs the Griffin Stem Cell Laboratory and the Hoffberger Stem Cell Laboratory, Our team directs the Griffin Stem Cell Laboratory and the Hoffberger Stem Cell Laboratory, Our team directs the Griffin Stem Cell Laboratory and the Hoffberger Stem Cell Laboratory, Our team directs the Griffin Stem Cell Laboratory and the Hoffberger Stem Cell Laboratory, Our team directs the Griffin Stem Cell Laboratory and the Hoffberger Stem Cell Laboratory, Our team directs the Griffin Stem Cell Laboratory and the Hoffberger Stem Cell Laboratory, Our team directs the Griffin Stem Cell Laboratory and the Hoffberger Stem Cell Laboratory, Our team directs the Griffin Stem Cell Laboratory and the Hoffberger Stem Cell Laboratory, Our team directs the Griffin Stem Cell Laboratory and the Hoffberger Stem Cell Laboratory, Our team directs the Griffin Stem Cell Laboratory and the Hoffberger Stem Cell Laboratory, Our team directs the Griffin Stem Cell Laboratory and the Hoffberger Stem Cell Laboratory, Our team directs the Griffin Stem Cell Laboratory and the Hoffberger Stem Cell Laboratory, Our team directs the Griffin Stem Cell Laboratory and the Hoffberger Stem Cell Laboratory, Our team directs the Griffin Stem Cell Laboratory and the Hoffberger Stem Cell Laboratory, Our team directs the Griffin Stem Cell Laboratory and the Hoffberger Stem Cell Laboratory, Our team directs the Griffin Stem Cell Laboratory and the Hoffberger Stem Cell Laboratory, Our team directs the Griffin Stem Cell Laboratory and the Hoffberger Stem Cell Laboratory, Our team directs the Griffin Stem Cell Laboratory and the Hoffberger Stem Cell Laboratory, Our team directs the Griffin Stem Cell Laboratory and the Hoffberger Stem Cell Laboratory, Our team directs the Griffin Stem Cell Laboratory and the Hoffberger Stem Cell Laboratory, Our team directs the Griffin Stem Cell Laboratory and the Hoffberger Stem Cell Laboratory, Our team directs the Griffin Stem Cell Laboratory and the Hoffberger Stem Cell Laboratory, Our team directs the Griffin Stem Cell Laboratory and the Hoffberger Stem Cell Laboratory, Our team dire
Skeletal muscle disorders consist of a diverse and heterogeneous group of disorders affecting patients’ function and mobility. Common disorders include muscular dystrophies and muscle injuries. Muscle dystrophies are hereditary and genetic disorders of the skeletal muscles. In these groups of disorder due to a mutated gene, a structural protein of the skeletal muscle becomes defective, which leads to progressive muscle weakness, atrophy, and degeneration. Depending on the affected gene, patients may show different degrees of progressive muscle weakness with early or late onset, and in severe cases, such as Duchenne muscular dystrophy (DMD), death may occur in the third or fourth decade. A major group of muscle disorders are muscular emaciation mass loss (MML) injuries and defects, which are very common in traumatic patients, such as car accidents or combat injuries or after tumor resection in cancer patients. These disorders also often lead to a sizable muscle defect and different levels of disabilities. Skeletal muscle disorders are often incurable and are a major cause of disabilities and create a big burden on the health system.

Here at the BMN and stem cell center, we are interested in using induced pluripotent stem cells (iPSCs) for skeletal muscle repair. iPSCs can be easily reprogrammed from adult skin or blood cell and can generate a source of stem cells capable of unlimited differentiation to all cell types in the human body. In addition, since iPSCs are derived from patients, they are fully compatible with the patient with minimal immune rejection risk. Therefore, iPSCs are considered as the top candidate for stem cell therapy in degenerative disorders.

Our lab is using cutting-edge technologies to create iPSCs from muscle disorder patients and use them for generation of large quantities of muscle cells useful for all kinds of applications. To date, we have generated patient iPSCs from over 150 novel types of muscular dystrophy patients (GDOM2D1) due to a defect in a novel gene (POGLUT) and used them to study disease mechanisms and pathophysiology. We also use advanced gene correction methods, such as CRISPR, to design strategies for correction of defective genes in these disorders. In addition, we use different niche models for muscular dystrophies (Sarm1-/- mice which is a model for Duchenne muscular dystrophy and DMD) and muscle loss injury mouse models to model muscle injuries after trauma or combat injury to validate regeneration and reparative potential of human iPSCs. So far, our lab has pioneered new methods for derivation of muscle progenitor cells from human iPSCs and demonstrated their application for skeletal muscle repair in these models. The long-term goal of our lab is to pave the way toward clinical application of human iPSCs to treat skeletal muscle disorders. Our research program is currently funded by two NIH R01 grant awards from National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) to support these exciting and novel projects.

Research Projects:
- Evaluation of the engraftment and functional recovery potential of human iPSCs in the mice models for Duchenne muscular dystrophy (DMD)
- Therapeutic application of human iPSCs for volumetric muscle mass loss injuries (MML) and evaluation of their innovation and functional recovery

Gene correction of muscular dystrophies using CRISPR/Cas9 system

**Key Publications**

Wu J, Hart SD, Matthews N, Senkal-Moffita E, Li J, Abou-Nejel N, Panabad C, Darabi R. Generation of an induced pluripotent stem cell line (CECNRM4-A) from a patient with a new type of lethal muscular dystrophy (LAMD) due to a nonsense mutation in POSGLUT ( Ryu), Stem Cell Research, 2017 Sep 24; 102-105. 2017


**Lab Members**

- Investigator: Jiaruo Wu
- Research assistant: Nasa Xu

**Collaborators/Lab Members**

- Pramod Dash, PhD
- Professor and Chair, Department of Neurobiology and Anatomy
- Nina and Michael Zilkoski Distinguished Chair, Neurogenetic Disease Research

**Concentration and stress-related disorders**

(Sarm1-/- mice) Further, we have found that the activation of atrocytes and microglia is also attenuated in the areas with white matter damage, suggesting a reduction in inflammation. Associated with these improvements, injured Sarm1-/- mice were found to perform significantly better in both motor and cognitive tests.

**Research Projects**

- To identify how stress alters neural communication.
- To investigate the consequences of mtor- cholesterol plasticity and altered brain energy metabolism after concussion.

**Key Publications**


**Conclusive statement**

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Human pluripotent stem cells for lung regeneration and disease modeling

Sarah Xuelian Huang, MBBS, PhD
Assistant Professor

-my laboratory is interested in applying human pluripotent stem cell models to study the molecular mechanisms of lung cell fate specification in the context of both normal and pathological conditions. Our long-term goal is translation of the acquired knowledge into prevention and treatment of currently curable lung diseases. Lung diseases are among the leading causes of death globally. Lower respiratory infections, chronic obstructive pulmonary disease, and lung cancer together account for approximately 9 million deaths annually worldwide. Despite the huge lung disease burden, we still have very limited understanding of the pathogenic mechanisms responsible for these diseases, and consequently there is a lack of successful therapeutic approaches.

Recently, human pluripotent stem cell-based models have emerged as a novel system for studies of human diseases. The need for such a system stems from the limitations of the existing animal experimental models, which fall short in demonstrating concordance with human lung and airway progenitors using molecular, genetic and organotypic approaches.

Researchers are working on culture conditions that can direct lung development or disease studies by us and our colleagues. Examples include in vitro cultures in functional chambers to study airway epithelial cells or distal alveolar lung progenitors toward an enriched population of clinically applicable cell types. As a first step toward large quantities (Huang et al. Nat Biotechnol 2019; 37:1936-1946), we have previously shown that human pluripotent stem cell-derived early lung specification (Development; 2018; 145, doi:10.1242/dev.160776).

Huang is working with Akiyama, Sam M. Hanash, Shioko Kimura, medidas, and colleagues to work on culture conditions that can direct lung development or disease studies by us and our colleagues. Examples include in vitro cultures in functional chambers to study airway epithelial cells or distal alveolar lung progenitors toward an enriched population of clinically applicable cell types. As a first step toward large quantities (Huang et al. Nat Biotechnol 2019; 37:1936-1946), we have previously shown that human pluripotent stem cell-derived early lung specification (Development; 2018; 145, doi:10.1242/dev.160776).

Huang and colleagues have developed a step-wise differentiation strategy that directs human pluripotent stem cells to become different types of upper (airway) and lower (alveoli) respiratory lung epithelial cells of large quantities (Huang et al. Nat Biotechnol 2014; 32:1098; Nat Protoc; 2015). As a proof of principle, the generated cells have been applied for lung development or disease studies by us and other research groups. Currently, we are working on culture conditions that can direct the human pluripotent stem cell-derived early lung progenitors toward an enriched population of either airway epithelial cells or distal alveolar cells. The availability of such enriched airway- and alveolar-fated cells provides a valid platform for studying lung diseases originate in both airway and alveolus. Examples include influenza virus-induced acute lower respiratory syndrome that affects the lower respiratory of the lung and lung cancers that can arise in both the airway and alveolar cells depending on the subtype.

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The hematopoietic stem cells (HSCs) that produce all types of white blood cells in the body are first generated in the aortic region of the mouse embryo at embryonic day (E) 9.10. Interestingly, though, there are multiple waves of blood cell production prior to the emergence of the first HSC from endothelial cells (referred to as hemogenic endothelial cells; HECs), and these blood cells include erythro-myeloid, T-, and B-lymphocyte progenitors. We have recently found that innate-like B-1 lymphocytes and the first HSCs are produced simultaneously from HESCs. As we are elucidating 1) what molecular signals determine the divergent point between innate-like B-1a and multi-potent HSCs, 2) how embryonic B-1 progenitors contribute to postnatal peripheral B-1 cell pool, and 3) how HSC precursors mature into adult-repopulating HESCs in a limited window of embryonic development, B-1 cells are unique murine innate immune cells that are distinguished from conventional adaptive B cells (B-2 cells). B-1 cells localize in the peritoneal and pleural cavities and constitute natural antibodies without T cell help, displaying important roles in the first line of defense against infection, inflammation, and autoimmunity. It has been postulated for decades that B-1 cells are derived from fetal blood cells including erythro-myeloid, T-, and B-lymphocyte precursors. However, recent developments in single-cell RNA-sequencing have demonstrated how fetal-derived B-1 progenitors contribute to the postnatal peritoneal B-1 cell pool, and how HSC-independent B-1 progenitors contribute to the first waves of HSC-independent B-1 cell development from fetal blood cells.

Development of hematopoietic stem cells and innate-like B cells in the mouse embryo

Key Publications


Research Projects

• Lineage tracing for HSC-independent and/or HSC-dependent B-1 cell development from embryos to adults.

• Identifying important molecules for HSC maturation in the mouse embryo utilizing single-cell RNA-sequencing.

• Examining the contribution of fetal-derived B cells to T cell receptor utilization in the adult lymphoid system.

• Producing human B-1 cells from human iPSCs.

Knowledge obtained from above projects will help us to improve the system where HESCs are produced from human iPSCs in vitro, which may be utilized for cell therapy in the patients with hematological disorders or leukemias.

After leukemia, osteosarcoma is the second leading cause of cancer mortality among children. Genetic alterations (e.g., p53 mutation and RB deletion) are strongly associated with osteosarcoma development. Patients with Li-Fraumeni syndrome (LFS) have increased incidence of osteosarcoma development, which provides a perfect model system to study osteosarcoma. Modeling human genetic disease has recently become feasible with induced pluripotent stem cell (iPSC) methodologies developed by Dr. Shinya Yamanaka in 2006. Characterized by their ability to self-renew indefinitely and differentiate into all lineages of an organism, embryonic stem (ES) cells, iPSCs provide a powerful and unlimited source of cells to generate differentiated cells that can be used to elucidate disease pathogenesis, for drug discovery and development, basic cell screen, personalized healthcare and eventually cell transplantation-based therapies. Our research is dedicated to understanding cancer pathological mechanisms by applying patient-specific iPSCs and/or engineered ESCs. We have established the first human Li-Fraumeni syndrome (LFS) disease model by using LFS patient specific iPSCs to delineate the pathological mechanisms caused by mutant p53 in osteosarcoma (Sun et al, Cell 2015; Gingold, et al, Trends Cancer 2016). iPSC-derived osteoblasts recapitulate osteosarcoma features, including defective osteoblastic differentiation and tumorigenic ability, suggesting that our established LFS disease model is a “disease in a dish” platform for elucidating p53 mutation mediated disease pathogenesis. Since these iPSCs were generated from non-transformed family members, any recapitulated features of osteosarcoma must be due to the single gene alteration. The patient-specific iPSC model therefore provides a powerful system to elucidate unique gene functions in tumor etiology. We continue applying patient-specific iPSCs and knowledge obtained from above projects to elucidate disease pathogenesis, for drug discovery and development, basic cell screen, personalized healthcare and eventually cell transplantation-based therapies.

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Ying Liu, MD, PhD
Assistant Professor

Human pluripotent stem cells in cell-based therapy for CNS diseases

Our research focuses on dissecting the neural developmental pathways and the corresponding pathogenesis in CNS injury and neurodegenerative diseases. Our long-term goal is to identify therapeutic targets for the treatment of CNS diseases. Human induced pluripotent stem cells (iPSCs) provide autologous materials for patients, which theoretically obviate the need for immune suppression. We have optimized the more clinically relevant, integration-free CRISPR gene editing protocol and performed directed differentiation of patient-specific iPSCs into neural stem cells, neuronal and glial progenitors, as well as mature cell types for disease modeling, transplantation studies, neural regeneration and repair, and drug screening and testing. The highly efficient CRISPR gene editing tool adapted in the lab allows for quick creation of neural lineage reporters and multigene activation for lineage induction. These neural lineage-specific cells are applied to in-depth study of signal transduction in disease and development.

RESEARCH PROJECTS
• Generation of patient-specific, integration-free iPSCs
• Identification of optimal neural lineage progenitors for cell-based therapy in spinal cord injury
• Down syndrome disease modeling using patient derived iPSCs and neural populations
• Molecular changes in gene expression regulatory networks is glioblastoma.

KEY PUBLICATIONS


LAB MEMBERS
Research scientist: Shengnan Li
Research associate: Hailing Cao

A Neurogenin 2 knockin human iPSC reporter cell line made using the CRISPR/Cas9 system. NEUROG2-mCherry human iPSC clones are induced as embryoid bodies (EBs) which glow red under the fluorescence microscope (A). NEUROG2 antibody staining (green) confirms that mCherry (red, native signal) expression faithfully reflects the endogenous NEUROG2 expression along the differentiation pathway (B, C).

Rapid generation of astrocytes from human iPSCs by endogenous activation of astrocyte lineage specific transcription factors with the piggyBac CRISPR activation system. Human-iPSC cell line was transfected with all-in-one vectors expressing guide RNAs that activate SOX9-NFIA-NFIB-NFIX transcrip-

COMET assay confirms TRIM44 enhances DNA damage repair in MM cells. Cells were treated with ionizing radiation and COMET images were captured using fluorescence microscopy after a couple of hours. Tail moment was calculated as tail length multiplied by tail DNA percentage in at least 100 cells.

Center for Stem Cell and Regenerative Medicine

Deciphering mechanisms of human cancer cell survival within the bone microenvironment

The behavior of cancer cells is not only dependent on their genomic abnormalities but also requires complex relationships between malignant cells and their local bone marrow niche, which provides an environment for multiple myeloma cell growth as well as protection from chemotherapy-induced apoptosis. The bone marrow niche provides a “hiding place” for dormant clones, which are often resistant to chemotherapeutic agents. The major goals of my research program are to decipher molecular pathways that confer selection growth and survival advantages to ma-

RESEARCH PROJECTS
• Survival mechanisms of dormant multiple myeloma cells and their microenvironment in the bone marrow
• Human neural progenitors derived from integration-free iPSCs for SCI therapy
• Generation of patient-specific, integration-free iPSCs
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COMET assay confirms TRIM44 enhances DNA damage repair in MM cells. Cells were treated with ionizing radiation and COMET images were captured using fluorescence microscopy after a couple of hours. Tail moment was calculated as tail length multiplied by tail DNA percentage in at least 100 cells.
Our lab studies how biomechanical force generated by the flow of blood is the circulatory system impacts cell fate and behavior. One of our primary research projects addresses how frictional force caused by blood flow promotes emergence of blood stem cells during embryonic development. We are interested in how we might use this information in the laboratory to expand improved sources of these stem cells for treatment of hematologic disorders and cancer, such as bone marrow failure syndromes and leukemias. Complex signaling occurs in response to flow that potentiates stem cell potential, including activation of integrins, mechanosensitive ion channels, and primary cilia (Fig. 1). In our prior published work, we have shown that frictional force in bioengineered microfluidics that matches the intensity of blood flow present in the developing embryo can stimulate calcium sparks within the cytoplasm, thus triggering the cell to produce prostaglandins. Elevated prostaglandin synthesis is key to forming hematopoietic stem cells that later will supply the body with blood and immune cells into adulthood. We have additionally shown that the force generated by this flow activates classical developmental signaling, including Notch and Wnt. Both of these signal transduction pathways are known regulators of blood development and must be tightly modulated in order to direct differentiation of certain immune cell lineages, including T lymphocytes. Lastly, in work spanning various model systems, evidence has begun to emerge that implicates focal adhesion kinase and the Src family kinases in regulation of transcription factors such as Yap and Taz downstream of fluid force. We are currently pursuing both collaborative and independent studies aimed at better understanding the mechanosensors and intracellular signaling that are central to dictating how blood stem cells respond to biomechanical cues to ensure proper self-renewal and differentiation.

Another related area of research in our lab includes the study of how flow alters biomaterials and, specifically, how the powerhouses of the cell—the mitochondria—adapt to meet the changing metabolic needs of stem cells. We are finding that these organelles change shape and move differently within the cell depending upon the biomechanical cues in the environment. This is particularly relevant during late commitment of hematopoietic stem cells to the embryo, but also could be important in the adult. Mitochon- dria are critical in both hematopoietic stem cells and mononuclear stem cells of the adult bone marrow, the latter of which are known to be capable of repairing damaged tissues by mitochondrial transfer to injured cells when administered as a cellular therapeutic. Ongoing studies are directed at determining how mitochondria contribute to ensuring that hematopoietic stem cells are properly specified in the embryo and how we might modulate mitochondrial behavior to enhance stem cell activity in bone marrow transplantation.

RESEARCH PROJECTS
Effects of flow on hematopoietic stem cell fate and the bone marrow niche
Biomechanical force in modulation of mitochondrial dynamics

KEY PUBLICATIONS


Translational cancer research aims to identify novel drug targets followed by the discovery and development of drug candidates as potential cancer therapeutics. The goal is to translate discoveries made in basic cancer research to potential drugs that could be tested in human patients. It relies on a plethora of information and data on cancer origin, progression, metastasis, drug-resistance, and disease relapse to uncover the driving mechanisms of tumor growth and invasion. Technologies such as next generation sequencing of DNA and RNA in cancer and non-cancer cells of tumor tissues, CRISPR screens, proteomics, imaging, platforms for tumor models, drug candidate discovery, and bioinformatics are utilized to reveal drug targets and validate potential drug candidates.

The current research in the Center for Translational Cancer Research emphasizes several areas, including the application of cutting-edge bioinformatic and experimental technologies to identify and validate novel drug targets in several major types of solid tumors, the discovery of specific molecules against the targets with a focus on antibody/protein-drug conjugates, the development of targeted contrast agents for disease visualization, and the study of proteome alterations to elucidate disease mechanism and disease relapse to uncover the driving mechanisms of tumor growth and invasion. Our center houses several core facilities, including the Nanochemistry Service Center, our center specializes in the development of new models of new surgical tools and instruments or drug conjugates that are then evaluated in tumor models. We also have expertise in the development and application of novel antibody-based agents that have imaging implications in cancer as well as infectious diseases. Furthermore, the Center specializes in the development of multifunctional peptides that combine radioactive and fluorescent contrast to enable tumor identification before, during, and after surgery, thus introducing a precision surgery approach. In addition, we have an active probe development program that includes the development of novel target-specific 3D printers for both fast prototypes and finished production-level models of new surgical tools and instruments or patient-specific organ models.

Our center houses several core facilities, including the Nanochemistry Service Center, and Clinical and Translational Proteomics Service Center, to support many research labs through service and collaborative efforts.

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

Qingyun (Jim) Liu, PhD
Professor
Janice Davis Gordon Chair for Bowel Cancer Research

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

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

Our research is focused on delineating the function and mechanisms of a group of common cancer stem cells called LGR4, LGR5, and LGR6 (LGR4-6) that play critical roles in the survival of normal stem cells and tumor cells. Previously, we discovered that LGR4-6 function as receptors for R-spondins (RSPOs) that are essential for the survival and growth of stem cells. We are now focused on understanding how RSPOs and LGRs work together to regulate the growth and migration of normal and cancer cells. We found that LGR4 and LGR6 work through a different mechanism to control the survival and expansion of intestinal stem cells, which challenges a major current paradigm that LGR4 and LGR6 works in an identical way in cell signaling. Meanwhile, we showed that drug conjugates of anti-LGR antibodies showed excellent anti-tumor efficacy in preclinical models of colon cancer. Recently, we have discovered a novel approach that can target all three LGR receptors for the treatment of cancers of the digestive system.
Molecular imaging probe development


Intraoperative visualization of residual cancer following gross tumor resection under ambient light. While light in situ visualization after tumor resection using direct visual inspection and palpation only (A and C), tumor beds were then surveyed using the Osmole Fluorescence-guided Surgery Imaging system and residual fluorescence was detected (stained white circle) (B and D). A and B are the corresponding NIF images overlaid on A and D, respectively. (From Hernandez Vargas et al. SPMBS. Vol, 12320, 2020.)

Fluorescence imaging (represented by the near-infrared (NIR) signal) in resected tissues shows that HER2 targeted contrast agents are preferentially taken up by tumors (denoted as BT474) compared to normal, mammary fatpad tissue (i.e., normal tissue) (a). Quantitative analysis of the images shows HER2-targeted contrasted agents are preferentially taken up by tumors (denoted as BT474) compared to normal, mammary fatpad tissue (i.e., normal tissue) (b). (From Hernandez Vargas et al., Mol Imaging. 2021; p. 540569.)

Kendra Carmon, MS, PhD
Assistant Professor

Therapeutic strategies for targeting colorectal tumors and cancer stem cells

Emerging evidence has shown that within several different malignant tumor types there exists a subpopulation of cancer cells that behave like normal stem cells. These cells are referred to as cancer stem cells (CSCs) or tumor initiating cells since they have the capacity to fuel tumor growth. CSCs have been implicated in drug resistance, metastasis, and shaping, making them a major impediment for the effective treatment of cancer. Therefore, it is essential to develop new therapies that can ablate target and destroy CSCs. Recent studies have established that LGR5 (Leucine-rich repeat-containing 5, proten-coupled Receptor 5), a receptor expressed on normal adult stem cells, is highly upregulated in primary colorectal tumors. Furthermore, colorectal CSCs which express LGR5 are capable of driving tumor growth and metastasis. In addition, LGR5 expression has been shown to be significantly elevated in several other major tumor types, including liver, gastric, and ovarian cancers. My previous work led to the discovery that LGR5 functions as a receptor of secreted growth factors, called R-spondins, to promote cancer cell adhesive and regulation cell signaling pathways involved in stem cell survival and tumor growth. These findings suggest that LGR5 is a highly specific target for antibody and ADC development. Our lab is currently investigating the GPR56-associated cell signaling mechanisms that drive its function. Our group is also acquiring colorectal tumor samples from patients and establishing 3D culures called patient-derived organoids or PDOs. These PDOs can be used to study the function of our different cancer targets or to evaluate the efficacy of our ADCs before testing in animal models. Our work will lead to the elucidation of the function and mechanism of different receptors in colorectal cancer and generate innovative therapeutic leads to target CSCs for the treatment and eradication of colorectal cancer.

RESEARCH PROJECTS

• Identification of novel therapeutic targets and development of innovative agents to target colorectal tumors and cancer stem cells.

• Investigations of LGR5 function in cancer stem cells, metastasis, and drug resistance.

• Developing novel imaging pathways of GPMS in colorectal cancer

Kendra Carmon, MS, PhD
Assistant Professor

Therapeutic strategies for targeting colorectal tumors and cancer stem cells

Emerging evidence has shown that within several different malignant tumor types there exists a subpopulation of cancer cells that behave like normal stem cells. These cells are referred to as cancer stem cells (CSCs) or tumor initiating cells since they have the capacity to fuel tumor growth. CSCs have been implicated in drug resistance, metastasis, and shaping, making them a major impediment for the effective treatment of cancer. Therefore, it is essential to develop new therapies that can ablate target and destroy CSCs. Recent studies have established that LGR5 (Leucine-rich repeat-containing 5, proten-coupled Receptor 5), a receptor expressed on normal adult stem cells, is highly upregulated in primary colorectal tumors. Furthermore, colorectal CSCs which express LGR5 are capable of driving tumor growth and metastasis. In addition, LGR5 expression has been shown to be significantly elevated in several other major tumor types, including liver, gastric, and ovarian cancers. My previous work led to the discovery that LGR5 functions as a receptor of secreted growth factors, called R-spondins, to promote cancer cell adhesive and regulation cell signaling pathways involved in stem cell survival and tumor growth. These findings suggest that LGR5 is a highly specific target for antibody and ADC development. Our lab is currently investigating the GPR56-associated cell signaling mechanisms that drive its function. Our group is also acquiring colorectal tumor samples from patients and establishing 3D culures called patient-derived organoids or PDOs. These PDOs can be used to study the function of our different cancer targets or to evaluate the efficacy of our ADCs before testing in animal models. Our work will lead to the elucidation of the function and mechanism of different receptors in colorectal cancer and generate innovative therapeutic leads to target CSCs for the treatment and eradication of colorectal cancer.

RESEARCH PROJECTS

• Identification of novel therapeutic targets and development of innovative agents to target colorectal tumors and cancer stem cells.

• Investigations of LGR5 function in cancer stem cells, metastasis, and drug resistance.

• Developing novel imaging pathways of GPMS in colorectal cancer

Kendra Carmon, MS, PhD
Assistant Professor

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• Developing novel imaging pathways of GPMS in colorectal cancer
Deciphering proteome alterations associated with diseases

Proteins are essential functional biomolecules that are involved in all aspects of cellular physiology and have been important targets for drug development and early detection of diseases. Proteomics, especially quantitative proteomics, has been a vital tool in basic, translational, and clinical research, providing a unique avenue to investigate disease-associated molecular alterations at a functional level. Proteome alterations that are associated with diseases may include changes in protein expression, sequence, post-translational modifications (PTMs) and protein interactions with other biomolecules, which may all lead to a malfunction of cellular processes. In our lab, mass spectrometry-based proteomics technologies are applied to study cancer and other diseases. These studies are carried out with various goals, such as aiming to better understand the molecular mechanisms underlying tumorigenesis, to investigate changes in PTM status associated with diseases, to identify disease-associated protein biomarkers or therapeutic targets, or to interrogate microbiome dysbiosis. The samples involved in our studies include a variety of research and clinical specimens, including tumor tissues, blood and other bodily fluids, as well as isolated cells from various clinical specimens. Currently, our main disease foci are pancreatic cancer and other GI-tract malignancies, as well as neurological diseases. In addition, through collaborative efforts, our lab also supports proteomic studies of various diseases, including chronic inflammatory, degenerative diseases, infectious diseases, and therapeutic drug development.

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

1. Breast cancer metastasis. It is estimated that up to 90% of cancer deaths are due to metastasis, in part because metastatic cells do not respond to traditional therapies. To address this problem, we have used computational approaches to characterize the metastatic state and to repurpose drugs to target cells that exhibit phenotypes that promote metastasis. Through these studies, we have found that metastasis is driven by a phenotype of cells that acquire a stem-like state through epigenetic remodeling of the breast tissue following metastatic spread into the bone marrow. These studies have identified potential therapeutic targets and provided new avenues for preclinical drug discovery.

2. Artificial intelligence for genomic analysis. Many of our projects requires the integration with bioinformatics to mine public data sets, develop hypotheses, or analyze results. To amplify our ability to do bioinformatics, we have developed an artificial intelligence, BETSY, that can automatically scan and execute these tasks, presenting us with finished results. It is a backwards-chaining expert system that leverages a knowledge base containing descriptions of common bioinformatics algorithms.©2020 nature research limited. All rights reserved.
Targeting cancer with X-aptamers and nanoparticles

David Volk, PhD
Associate Professor

Aptamer-directed delivery of therapeutic agents and smart particles that attack cancer and infectious organisms, such as tuberculosis. Current treatments are often ineffective or create harsh side effects for patients. We are developing RNA-aptamers to target and destroy breast cancer cells and infectious agents.

Aptamers can be used alone or as complex particles containing anti-cancer agents to act as a one-two punch. Such particles also can be loaded into larger silicon particles for a sustained release of the disease-fighting particles.

Aptamer Discovery: In recent years we have developed DNA aptamers targeting breast and ovarian cancer. Such DNA aptamers can reduce tumor volume and improve survival for cancer patients. However, DNA aptamers are even more effective when used in combination therapy together with chemotherapy agents such as docetaxel or paclitaxel. We have shown that our aptamers targeted approach reduces tumor size and improves survival for cancer patients. Our current research focuses on how to deliver these particles to the desired location.

Development of smart particles to attack cancer and infectious diseases.

• Developing new X-aptamers targeting other diseases.

KEY PUBLICATIONS


LAB MEMBERS
Research associate: Xin Li, MS

Lab members and associates working on various research projects that aim to develop targeted therapies for cancer and infectious diseases.

Targeted cancer therapy with aptamer mediated targeted therapy and targeted imaging offer unique opportunity for selective delivery of therapeutics or RNA and drugs, or imaging agents. Several modified aptamers have been successfully identified in our lab for further targeted studies, such as Annexin A2, (2014) CDC1, PD-L1, Vimentin, and Thy1. Those selected aptamers have great application potential in targeted drug delivery or targeted imaging. By conjugating the specific aptamer with nanoparticles that loaded with drug or siRNA, we demonstrated specific delivery and targeting to ovarian cancer after systemic administration in vivo.

RESEARCH PROJECTS
• Artificial intelligence imaging analysis with blood biomarkers for cancer screening and early diagnosis
• Combined quantitative radiomic features and blood biomarkers for outcome prediction of trans-arterial chemothermolization treatment
• Proteomic biomarker discovery for hepatocellular carcinoma
• Targeted cancer therapy with aptamer mediated nanoparticles drug delivery

Cancer biomarker discovery and targeted therapy

Hongyang Wang, MD, PhD
Assistant Professor

Protein biomarker selections using broad-based X-aptamer library. (A) Patient and healthy donor plasma were labeled with different color of fluorochromes. (B) After incubation, proteins bound to X-aptamer mediated targeted therapy and targeted imaging offer unique opportunity for selective delivery of therapeutics, RNA and drugs, or imaging agents.

KEY PUBLICATIONS


LAB MEMBERS
Research associate: Xin Li

Enhanced delivery of therapeutics to tumors relative to scrambled oligos.
The Texas Therapeutics Institute is recognized as the drug discovery engine of McGovern Medical School and UTHealth.

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

Discovery and development of therapeutic antibodies

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

RESEARCH PROJECTS

- **Antibody response to viral infections and vaccination.** Identification of highly immunogenic vaccines that induce neutralizing antibodies against a broad range of clinical isolates is one approach to developing effective viral vaccines. We have an ongoing project to aid in the design of CMV and SARS-CoV-2 vaccines by profiling antibody response to the experimental vaccines in mice and humans.

- **Cancer antibody drug resistance mechanisms.** Immune suppression is recognized as a hallmark of cancer. Our recent studies have demonstrated a new mechanism of cancer suppressors of immunity. This mechanism involves impairment of antibody effector functions mediated by proto-oncogene enzymes in the tumor microenvironment.

- **Cancer therapeutic monoclonal antibody drug discovery.** Our group has built a comprehensive antibody drug discovery platform with a focus on antibody lead optimization technologies such as antibody phage display, deep sequencing of antibody encoding genes from individual antibodies expressing B cells, affinity maturation, and humanization. Currently, we have multiple collaborative antibody drug discovery projects targeting various cancer types.

KEY PUBLICATIONS


Structural basis for recognition of posttranslational gB by 3-25. (A-C) EM analysis of the posttranslational gB + 3-25 Fab complex. (D-F) The crystal structure of 3-25 Fab bound to gB-p17 peptide. PLOS Pathogens https://doi.org/10.1371/journal.ppat.1008736.

Endotrophin as a viable target for anti-tumor therapy for human breast cancer. Endotrophin (ETP) is abundantly expressed in adipose tissue and a chemokine for macrophages, exerts effects on endothelial cells and through epithelial-mesenchymal transition (EMT), enhances progression of tumor cells. Neutralizing monoclonal antibodies against ETP can tumor growth and enhance chemosensitivity in a nude mouse model carrying human tumor cell lesions. Journal of Clinical Investigation Insight
molecules. We also carry out fundamental discovery of new bioactive natural products that inhibit growth of human pathogens, including Cryptococcus neoformans, a yeast causing Cryptococcus meningitis and cryptococcosis. Extracts of fermented fungi are evaluated for useful biological effects using an ensemble of assay directed at finding molecules that affect human pathogens. After preliminary chromatography, such as flash or column chromatography, active fractions of the extracts are identified through our bioassays against the target pathogens. More refined chromatographic techniques, e.g., preparative HPLC and bioassay-guided, lead us to the activity-causing natural products. These extracts are available through collaborations with other academic and industrial laboratories.

### RESEARCH PROJECTS

- **Biophysics of natural products and pathway engineering for improved antifungals.**
- **Development of methods for reengineering transcription of biosynthetic genes of fungi** to discover or overproduce natural products useful for treating human diseases.
- **Discovery of new antifungal and other therapeutic agents.**

### KEY PUBLICATIONS


### LAB MEMBERS

Post-doctoral fellows: Dr. Nan Lan, Dr. Bruno Perlatti, Dr. Zihan Zhang

Perlatti, B., C.B. Nichols, N. Lan, P. Wiemann, C.J.B. Harvey, J.A. Alspaugh & G.F. Bills. 2020. Chaetoglobosin P is a potent and selective inhibitor of growth of Cryptococcus neoformans. Fig. 1. Structure of chaetoglobosin P. Fig. 2. Visualization of actin polymerization and effects of inhibitors in cells of C. neoformans with TRITC-conjugated phalloidin which binds to F-actin structures. A-B. DMSO, C-D. Chaetoglobosin P, E-F. Actin assembly, positive control. Fig. 3. Graphic representation of genes for encoding the biosynthesis of chaetoglobosin P.
Our research programs are (1) to obtain critical new knowledge of cancer metastasis and drug resistance of human cancer cells, and (2) to identify new biomarkers and drug targets for the development of better therapeutics for human cancers.

Cancer metastasis, the spread of tumor to other parts of the body’s, is responsible for over 95% of cancer deaths. However, cancer metastasis is still poorly understood and the current approaches are to prevent or treat human metastatic cancers are mostly unsuccessful.

Therefore, there is a huge unmet medical need to better understand cancer metastasis and to develop new therapies against cancer metastasis. Through genomics, RNA and DNA functional screens, our lab has identified several crucial but previously unknown regulators for cancer metastasis. Some of the novel regulators control epithelial-mesenchymal transition (EMT), while some others are essential for survival and proliferation of highly metastatic cancer cells (i.e. essential genes). EMT, a developmental process, is believed to play a key role in the acquisition of resistance to ARPIs, some AR-positive prostate adenocarcinoma cancers become highly aggressive neuroendocrine prostate cancers. Similarly, after becoming resistant to EGFRI, some NSCLC demonstrate phenotypes of small cell lung cancer, which is neuroendocrine in nature and very aggressive. NED is still poorly understood, and currently there is no effective treatments to prevent or overcome drug resistance related to NED. We investigate the underlying mechanisms of NED, cellular plasticity and drug resistance, especially the roles and mechanisms of action of a novel set of epigenetic regulators.

Study and targeting cancer metastasis and drug resistance

Yanzhao Yin

Improve your new knowledge of cancer metastasis and drug resistance by allowing students in the field of oncology achieve this long-term goal is to create novel therapeutic options for overcoming such clinical issues. We envision that our novel ADC linker technology platform will help us, other researchers and clinicians in the field of oncology achieve this goal.

Novel linker technologies for generating novel antibody-drug conjugates (ADCs) toward innovative cancer therapeutics

Yin Yuen Ha (Summer), PhD

Novel linker technologies for generating efficacious ADCs for the treatment of acute myeloid leukemia (AML). (a) Construction of anti-LILRB4 ADCs with high plasma stability, rapid drug release, and enhanced permeability to the brain.

Modulation of the ADC function by chemical linker modification for organ-specific delivery of anticancer therapeutics.

Evaluation of ADCs in refractory cancer models

Key Publications

Association for Cancer Research, American Association for Cancer Research (2020) Glioblastoma multiforme (GBM), pancreatic cancers, and other solid tumors with drug resistance and/or intratumor heterogeneity. Patients with these cancers often suffer from recurrence of malignancy and exacerbated quality of life because of ineffective chemotherapy. Our lab’s long-term goal is to create novel therapeutic options for overcoming such clinical issues. We envisioned that our novel ADC linker technology platform will help us, other researchers and clinicians in the field of oncology achieve this goal.

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Cancer resistance mechanisms to therapeutic antibodies and modulation of anticancer immunity

State of the art technologies are used in our studies such as high content fluorescence imaging, mass spectrometry, fluorescence activated cell sorting (FACS), and single cell cloning of antibodies. We have established a monoclonal antibody platform technology to discover and select novel anticancer antibodies for functional evaluation and preclinical development. The long-term goal of my research is to understand mechanisms of cancer evasion of antibody and cellular immunity and to identify key molecular targets for development of effective anticancer immunotherapies.

RESEARCH PROJECTS

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

KEY PUBLICATIONS


LAB MEMBERS

Research associates/scientists: Hui Deng, MS; Peng Gao, PhD; Simon Li, PhD; Peng Gao, PhD; and others.

Schematic diagram for generation and screening of monoclonal antibodies (mAbs) using our established technology platform.
Flow Cytometry Service Center

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

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

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

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

Transgenic and Stem Cell Service Center

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

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

Nano 3D Printing Service Center

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

We have both traditional FDM (Fortus 450mc) thermoplastic as well as multi-color, resin-based, high-resolution Stratasys J750 (14 micron) 3D printers with large print beds. A wide range of materials with varying Shore A values (hardness) is available. STL files, SolidWorks, or medical imaging files can be used to produce the 3D models.

We are located on the 3rd floor of the Fayez S. Sarofim Research Building.
Institute of Molecular Medicine Endowments

Becker Family Foundation Professorship in Diabetes Research
Harry E. Bovay Lecture Series in Molecular Medicine
The Harry E. Bovay, Jr. Distinguished University Chair in Metabolic Disease Research
Cullen Chair in Molecular Medicine
John S. Dunn Research Scholars
The Laurence and Johanna Favrot Distinguished Professorship in Cardiology
Linda and Ronny Finger Foundation Distinguished Chair in Neuroimmunologic Disorders
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Nina and Michael Zilkha Distinguished Chair in Neurodegenerative Disease Research

Thank you to our donors, who through the establishment of these endowments, enable the IMM to recruit and retain top scientists from around the world.

IMM Extramural Funding Inception to Date

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IMM Commercial Outcomes Inception to Date

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