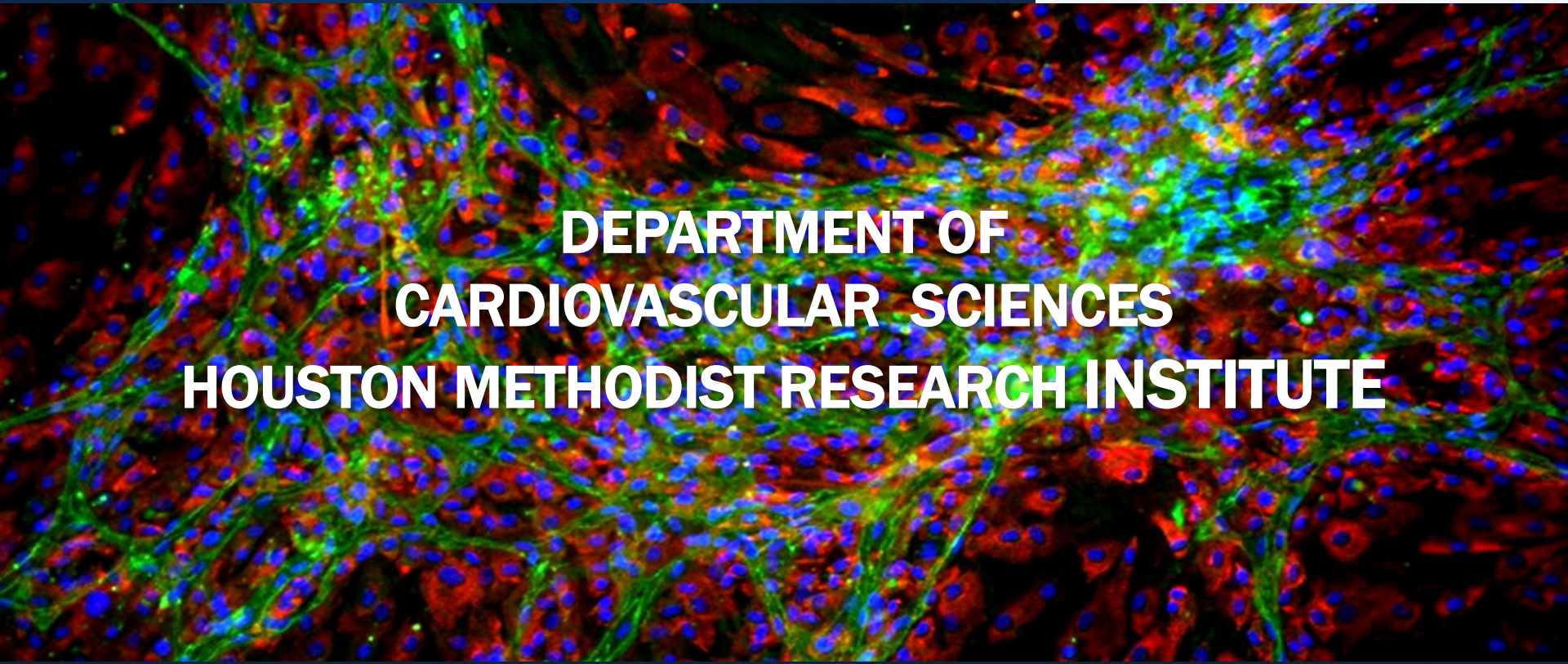
Annual Report 2022

HOUSTON Methodist
LEADING MEDICINE



DEPARTMENT OF CARDIOVASCULAR SCIENCES
HOUSTON METHODIST RESEARCH INSTITUTE

Generating Great Ideas to Transform Cardiovascular Care

Chairman's Message

- The mission of our Department of Cardiovascular Sciences is to generate great ideas that transform cardiovascular care. The Department comprises three basic research centers, as well as administrative support for the clinical research underway in the DeBakey Heart and Vascular Center. Approximately 200 investigator-initiated or industry-sponsored clinical trials are underway in the DeBakey Heart and Vascular Center, which will be the basis of a separate report. This document focuses on our basic research efforts in 2022.

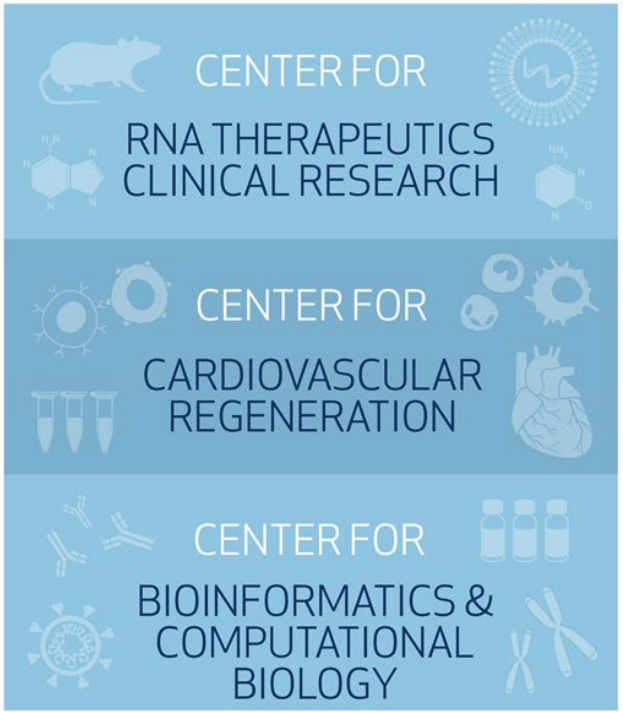
- This year, the work of our faculty and young scientists has led to new insights into the mechanisms of angiogenesis, vascular aging, vascular inflammation, lymphangiogenesis electromechanical coupling, and the determinants of cardiovascular cell identity. Notably, the scientists in our department freely traverse the bounds of our discipline, supported by multimillion-dollar awards from the federal and state governments and NGOs. Our intradisciplinary work includes an RNA vaccine for heart failure, therapeutic transdifferentiation for peripheral arterial disease, and a device to reverse myocardial ischemia. Our dedicated scientists and staff know that one must focus, yet fearlessly adopt new tools, technologies and directions to generate great ideas that transform human health.

Cover: A Web of Cell Interactions**:** Cell to Cell Interactions between Cardiac non-myocytes giving rise to vascular patterns formed mainly by endothelial cells (CD144 in green) surrounded by fibroblast cells (Col1a in red). Yellow staining cells are the dual staining cells that might be transdifferentiating from one cell type to another. Courtesy of Ranka Rajul, PhD

Cardiovascular Research
at Houston Methodist

HOUSTON Methodist LEADING MEDICINE

BASIC RESEARCH



CLINICAL RESEARCH

RESEARCH AFFINITY GROUPS


JOHN COOKE, MD, PHD


ALAN LUMSDEN, MD


WILLIAM ZOGHBI, MD

CARDIOVASCULAR REGENERATION JOHN COOKE, MD, PHD	ELECTROPHYSIOLOGY ARRYTHMIA MIGUEL VALDERRABANO, MD	PREVENTATIVE CARDIOLOGY KHURRAM NASIR, MD
VASCULAR ERIC PEDEN, MD	IMAGING DIPAN SHAH, MD	HEART FAILURE & TRANSPLANT ASHRITH GUHA, MD
CV HEMODYNAMICS IMAGING LAB STEPHEN LITTLE, MD	STRUCTURAL INTERVENTIONAL NEIL KLEINMAN, MD	ENTREPRENEURIAL INSTITUTE STUART CORR, PHD

Cardiovascular Research
at Houston Methodist

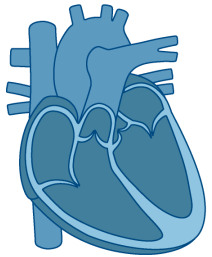
HOUSTON Methodist LEADING MEDICINE

GRANTS

83 grants submitted

17 grants awarded

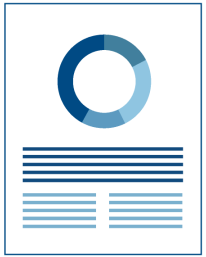
$10.4M grant funding awarded

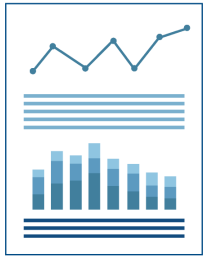


113 research personnel

PAPERS

401 publications





Clinical Research

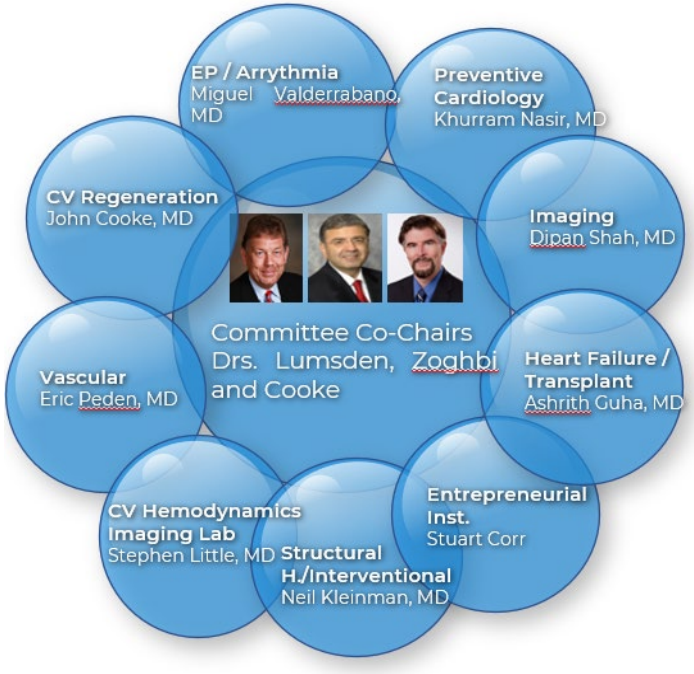
Heart Center
Research Affinity Groups (RAGs):

RAGs are self-assembled clusters of clinical research faculty, with a total of 35 faculty Principal Investigators.

The RAGs also include research fellows, nurses, lab personnel, coordinators, managers and regulatory and financial specialists with common research interests.

RAGs develop research interests, implement research programs, monitor quality and direct resources.

The RAGs currently have approximately 200 ongoing clinical trials or research projects with about half of these investigator-initiated. The others are industry-sponsored trials.



Basic Research
Department of Cardiovascular Science

This annual report focuses on the basic research of the Department of Cardiovascular Sciences.

Center for Cardiovascular Regeneration

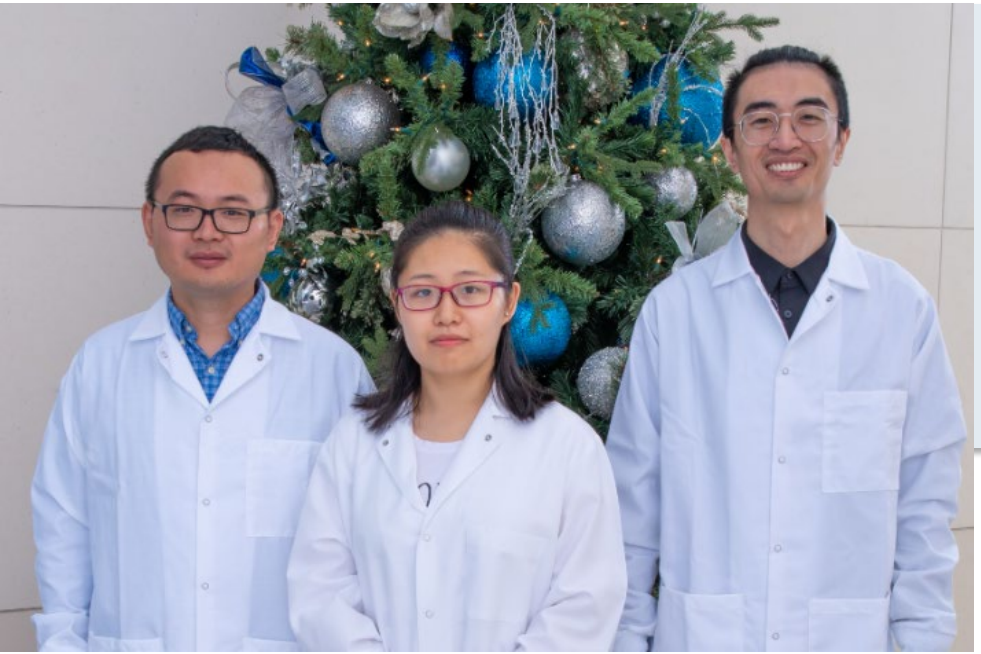
HOUSTON Methodist LEADING MEDICINE

Our mission is to generate great ideas that transform cardiovascular care. Our aims are to restore cardiovascular health, reverse cardiovascular aging and regenerate cardiovascular tissue.

To do so, we use advanced tools and technologies in high throughput genetic, epigenetic, proteomic and metabolomic characterization, combined with human cell and animal models, confirming our observations with human tissues from our biorepository

Center for Bioinformatics and Computational Biology

HOUSTON Methodist LEADING MEDICINE

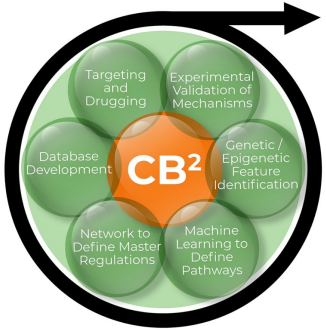


Our Mission

To advance computational modeling of the cells' functions, interactions and regulation in development and diseases.

Our Research

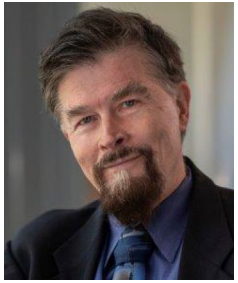
CB^2 develops novel bioinformatics methods (e.g., Science Advances 2022, Genome Biol. 2020), post-transcriptional regulation, and genetic regulation and discovers new molecular processes that generate epigenetic and genetic alterations in disease.



Center for RNA Therapeutics

Our mission is to generate great RNA ideas that lead to transformative therapeutics. The Center is enriched by RNA biologists generating foundational insights, including scientists with skills in RNA construct design, synthesis, purification and validation; a GLP program to generate pre-clinical data for IND submissions; a cGMP team with clean rooms to manufacture clinical-grade RNA therapeutics; a first-in-man clinical trials unit; and faculty collaborators in the Department of Nanomedicine who devise customized solutions for RNA delivery. We are funded by the NIH, DOD, CPRIT, CEPI and industry partners. We intend to be the leading academic group in RNA Therapeutics, focused on improving human health.

Faculty



John P. Cooke MD, PhD

Is Professor and Chair of the Department. His research focuses on mechanisms of vascular cell identity and aging. He discovered the process of transflammation that underlies cell fate transitions. He has also studied the role of telomerase in reversing cellular dysfunction associated with aging. He also directs the Center for RNA Therapeutics.

Rajarajan Amirthalingam PhD

Is an Assistant Research Professor who studies the influence of RNA regulation on the progression of heart failure. In particular, he has discovered a role for alternative polyadenylation of RNA underlying fibrosis in heart failure.

Francisco Altamirano, PhD

Is an Assistant Professor who is elucidating the molecular mechanisms driving cardiac hypertrophy, heart failure, and arrhythmias using multi-disciplinary approaches and technologies. In particular, he and his team focuses on delineating the role of polycystin-1 actions in the activity and growth of atrial and ventricular cardiomyocytes.

Kristopher Brannan, PhD

Is an Assistant Professor whose focus is on finding new therapeutic targets for cancer, cardiovascular and neurodegenerative pathologies caused by aberrant RNA processing, localization and translation. His research into RNA-protein integration integrates innovative experimental and computational approaches to develop new RNA therapeutics.

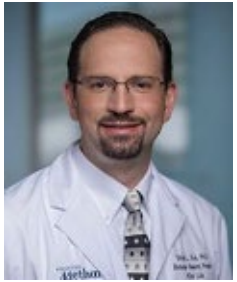
Faculty

Longhou Fang, PhD

Is an Associate Professor in the department who employs zebrafish and mouse models to investigate the role of lipid metabolism in vascular biology, including angiogenesis, lymphangiogenesis, and hematopoiesis. Dr. Fang has discovered a lipid protein that also mediates hematopoiesis and angiogenesis.

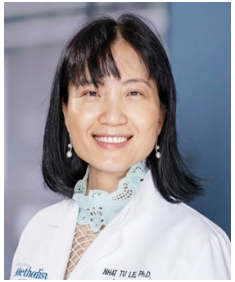
Li Lai, PhD

Is a Research Assistant Professor who studies the metabolic and epigenetic coupling in vascular disease and regeneration. She has discovered metabolites that are critical epigenetic mediators of cell fate transitions.



Daniel Kiss, PhD

Is an Associate Professor who has discovered a new layer of RNA regulation called cytoplasmic recapping. In addition, he is developing circular RNAs therapeutics for cardiovascular disease, cancer, and infectious diseases.



Nhat-Tu Le, PhD

Is an Associate Professor who studies signaling events involved in endothelial cell senescence, apoptosis, and activation. These are all processes that play a critical role in atherosclerosis, the major cause of heart attack and stroke.

Faculty

Anahita Mojiri, PhD

Is a Faculty Fellow and Instructor who studies vascular aging using induced pluripotent stems cells from children with Hutchinson Gilford Progeria Syndrome (HGPS) as well as a mouse model of HGPS. She developed an RNA telomerase therapy for HGPS and discovered non-canonical actions of telomerase to reduce genomic DNA damage.

Keith Youker, PhD

Is an Associate Research Professor whose primary focus is the role of inflammation in the progression of heart failure and fibrosis. He has developed a cannabinoid receptor agonist that ameliorates cardiovascular inflammation and heart failure, as well as a vaccine for heart failure. He works closely with our clinical cardiologists to facilitate bench-to-bedside translational work.

Guangyu Wang, PhD

Is an Assistant Professor whose focus is on developing algorithms to extract insights from high-throughput multi-omics datasets, mostly derived from DNA and RNA sequencing, to develop models that explain how cell state and cell identity are regulated.

Ewan K.S. McRae, PhD

A biochemist and structural biologist whose research focuses on the design and characterization of RNA structures. The McRae lab will work to create novel RNA therapeutics and new modalities for existing mRNA therapeutics.

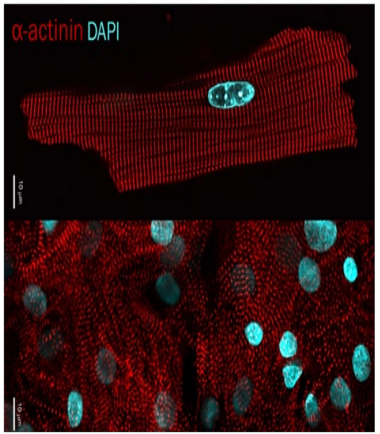
Research:
Altamirano Lab

Mechanisms driving cardiac dysfunction in Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Our lab focuses on Polycystin-1 (PC1) mutations and cardiac disease. We discovered that this protein is essential for normal cardiac function. Its deletion in cardiomyocytes impairs ventricular function and predisposes to atrial fibrillation. Our team uses multiple approaches to study the role of PC1, including transgenic animals, human pluripotent stem cell-derived cardiomyocytes, and engineered tissues. We have discovered that PC1 regulates ion channels and gene expression in cardiomyocytes, which are essential for normal heart function. Our work may provide insights to develop therapeutic strategies against arrhythmias and heart failure.

Cardiac autonomic activation in atrial fibrillation triggers and substrate

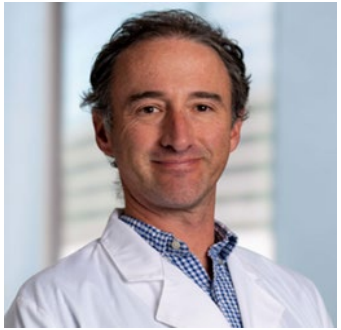
In collaboration with Dr. Miguel Valderrábano, Chief of the Electrophysiology Division, we study how sleep apnea increases atrial fibrillation using our unique clinical and basic science experience. We aim to elucidate how alteration in cardiac nerves increases susceptibility to atrial fibrillation in obstructive sleep apnea. Our integrative approach – includes human data, experiments in large animal models, and state-of-the-art technology to generate engineered tissues from human pluripotent stem cell-derived cardiomyocytes – aims to discover novel molecular mechanisms driving atrial fibrillation



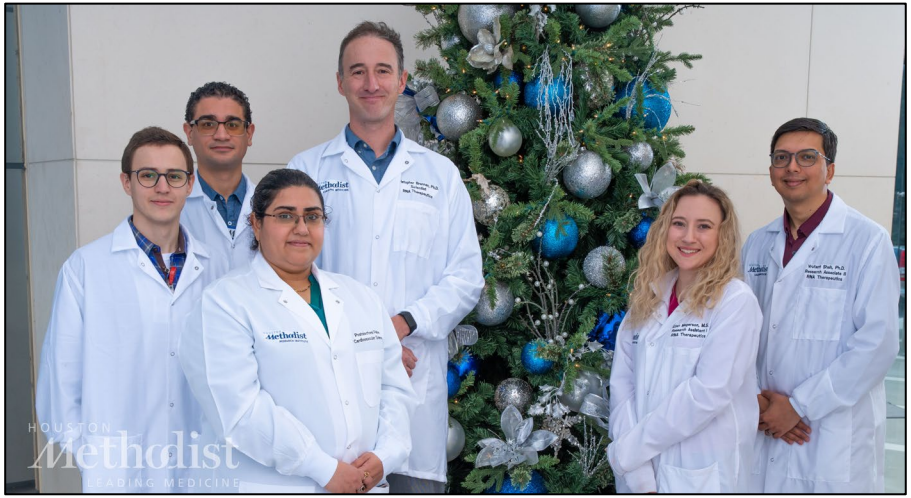
Adult (top) vs hiPSC-CMs (bottom)

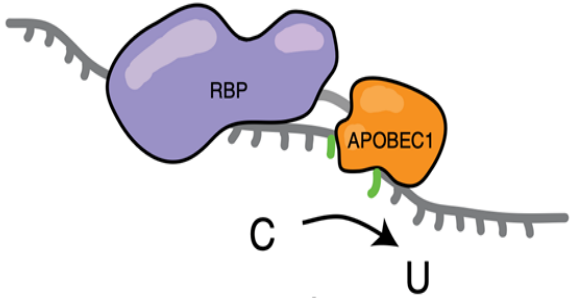
Our Team

Research:
Brannan Lab



We integrate technology-development and systems approaches to study how RNA-protein interactions mechanistically regulate gene expression, and how disruption of these interactions drives cancer and neurological disease. We develop tools to probe RNA-binding and RNA-translation landscapes, to programmably target and modify RNA, and to map RNA binding protein (RBP) networks. We will use biological insights obtained using these tools to design, build and test RNA-based medicine.



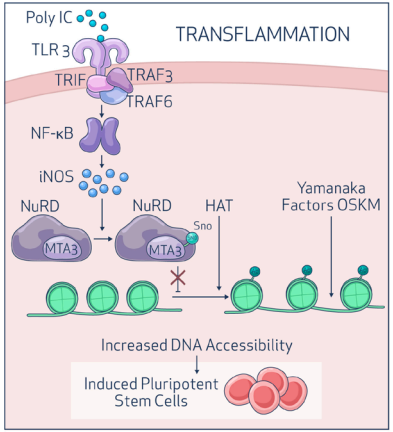


Research:
Cooke Lab

HOUSTON Methodist LEADING MEDICINE

Vascular Identity and Regeneration

We study the determinants of vascular aging. Hutchison-Gilford Progeria (HGPS) syndrome accelerates aging in children, leading to death from heart attack and stroke in the teen years. We find that iPSC-derived vascular cells from these children have severely disturbed function, which explains the accelerated vascular disease in HGPS (Matrone et al, Cell Cycle 2019). Intriguingly, we find that treatment with mRNA encoding human telomerase (hTERT), restores normal vascular function (Mojiri et al, Eur Heart J, 2021). We intend to develop an mRNA therapy for these children, and for other people suffering with syndromes of accelerated aging.



We discovered that Inflammatory signaling increases DNA accessibility to facilitate cell fate transitions, i.e.,“Transflammation” (Lee et al, Cell 2012; Li et al, Circulation 2019; Chanda et al Circulation 2019). This process is activated in defense against pathogens, in tissue regeneration, and in the generation of stem cells (Figure). However, when this process goes awry, it can lead to disease, such as when endothelial cells transition into fibroblasts, which causes scarring in an organ.

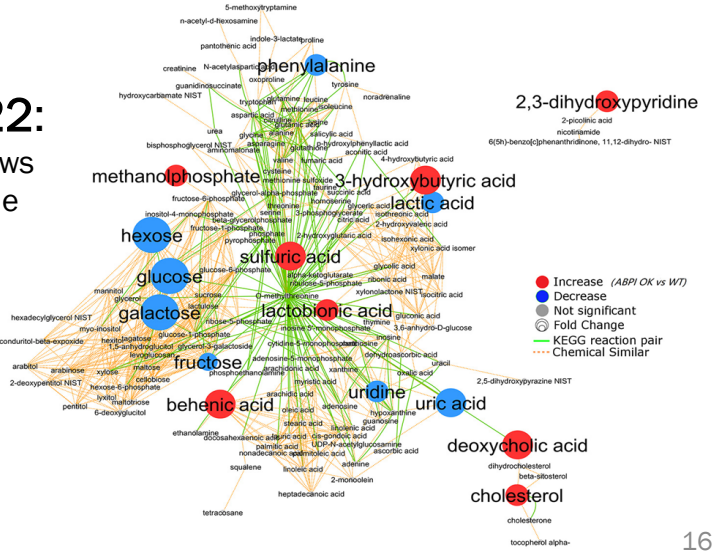
Research:
Fang Lab

HOUSTON Methodist LEADING MEDICINE

With the unrelentless support from Dr. Cooke and the administrative team, the Fang lab has made significant achievements in the year 2022. The Fang lab has a long-term interest in vascular biology, including lymphangiogenesis, angiogenesis, and hematopoiesis. Our manuscript was submitted to *Nature Cell Biology* in 2021 and received a favorable review. The findings are important because lymphatic dysfunction is associated with obesity, inflammation, cardiac regeneration, retinal disease and Alzheimer's disease. As evidenced below, many of our grant submissions are now centered on these arenas.

The graphic summary of our published work in 2022:

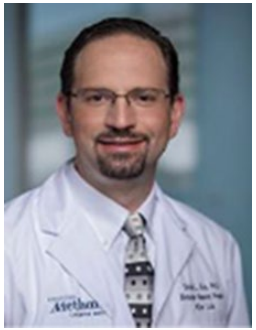
Our unbiased screen of AIBP-regulated metabolites in the cardiac tissue shows that while present in the mitochondria, AIBP has a previously unidentified role in ketone (3-hydroxybutyric acid) and lipid (cholesterol and deoxycholic acid) metabolism but not in the mitochondrial redox function.



Accepted Publication in 2022:
AIBP Regulates Metabolism of Ketone and Lipids but Not Mitochondrial Respiration. Jun-dae Kim [1], Teng Zhou [1,†], Aijun Zhang [2,4], Shumin Li [2], Anisha A. Gupte [2,4], Dale J. Hamilton [2,3,4], and Longhou Fang[1,,3,4] ***Cells*** 2022
PMID: 36429071

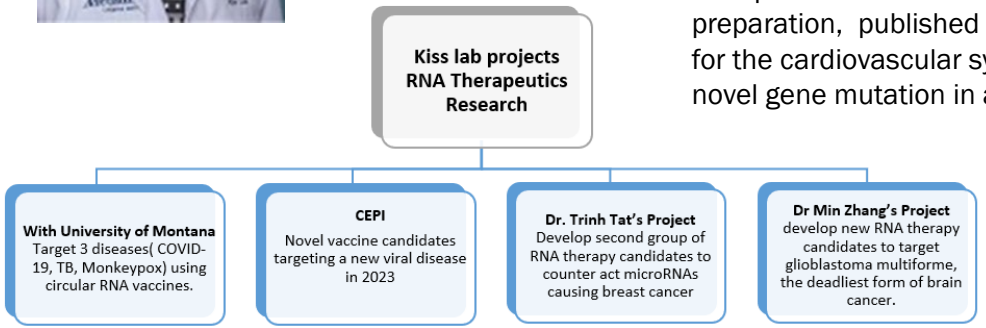
Research:
Kiss Lab

HOUSTON Methodist LEADING MEDICINE



Engineering new RNA therapies and vaccines and understanding fundamental RNA molecular biology

2022 has been another big year for the Kiss RNA Lab. We secured the Center for RNA Therapeutics' first NIH awards directly for RNA therapy research (vaccine candidates for Monkeypox and TB), the lab's circular RNA platform is the centerpiece of a new RNA vaccine grant from CEPI, and Dr. Rachel Kieser secured two years of NIH-funding for her postdoc. Although some key members have taken their next steps, the lab has grown as we welcomed Ms. Tiara Watson (technician), Ms. Suchitra Sridhar (lab manager), Dr. Kathrina Castillo (Research Associate), plus Dr. Shaheerah Khan and Dr. Luisa Orlando as postdoctoral fellows, **and we still have two additional positions open**! Besides presenting our research at multiple national and international scientific meetings, our lab has two review articles in preparation, published a new review article about RNA therapeutics under development for the cardiovascular system and a research article characterizing the functionality of a novel gene mutation in a multi-generational patient family.



RNA Therapeutics Research

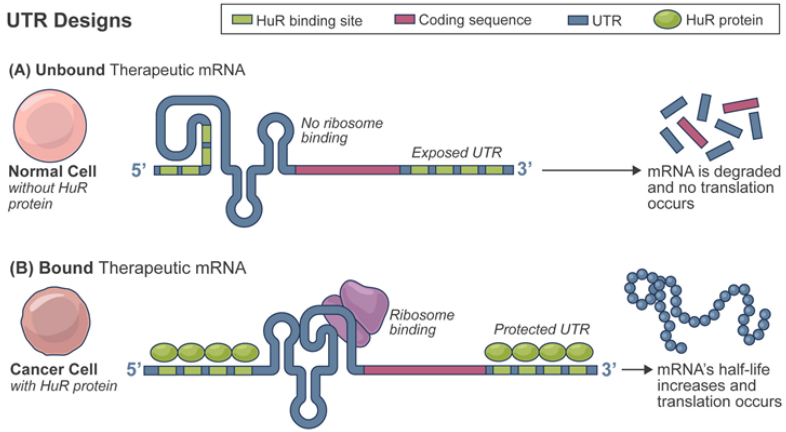
The lab's RNA Therapeutics Program designs and tests novel RNA drug candidates with the hope of treating or preventing human diseases. Dr. Trinh Tat and Dr. Min Zhang are also developing RNA approaches to treat different types of cancer. These therapies hold the potential to be tumor specific with less toxicity than current approaches.

Research:
McRae Lab

HOUSTON Methodist LEADING MEDICINE

Structure based design of RNA therapeutics

The current generation of RNA therapeutics is very much focused on the primary structure of the RNA being delivered. However, many important regulatory and immune stimulatory interactions are mediated by the secondary and tertiary structure of RNA. We aim to improve RNA therapeutics stability, efficacy and specificity by engineering structural elements into RNA therapeutics. Our structural design pipeline uses a combined computational and experimental approach, utilizing the latest RNA structure predication software as well as state of the art cryogenic electron microscopy to study the structure and folding of RNA.



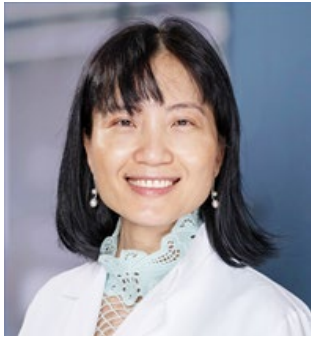
Two projects are currently being prioritized in our lab.

Firstly, we are creating designer untranslated regions for mRNA therapeutics that allow for cell-type specific expression of the mRNA payload. By inserting RNA binding motifs at key regions in these structured domains we create a dynamic structural switch that responds to specific RNA binding cellular proteins.

Secondly, we are designing improved RNA aptamer therapies that incorporate structural elements designed to increase the binding affinity of the aptamers by taking advantage of avidity effects.

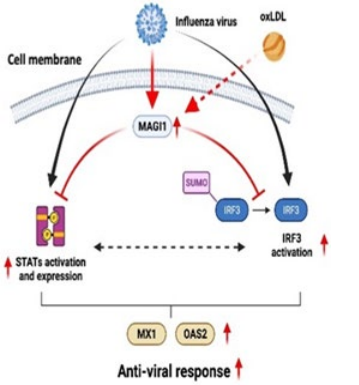
Research:
Le Lab

HOUSTON Methodist LEADING MEDICINE



MAGI1 is a potential therapeutic target for influenza virus infection

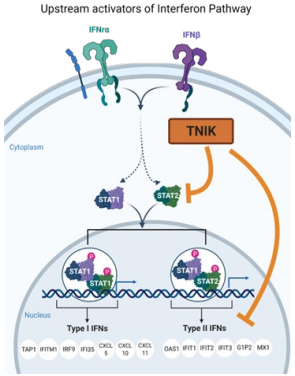
The severity of influenza virus A infection (IAV) depends on the host inflammatory response, in which endothelial cell (EC) activation is crucial. We study MAGI1, an EC scaffold protein, and its role in chronic inflammatory diseases. We reported that MAGI1 depletion inhibits EC activation elicited by proatherogenic type of flow, and that MAGI1 is involved in regulation of EC permeability. This year, we found that IAV increases MAGI1 expression in ECs and MAGI1 depletion suppresses IAV via upregulating MX1, which may induce interferon production. We also discovered that OxLDL increases IAV replication by upregulating MAGI1. *Front Cardiovasc Med. 2022; 9:791143.*



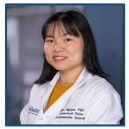
TNIK activates interferon signaling to suppress viral replication in ECs

For the first time, our study shows that TNIK, a Traf2 and Nck interacting kinase, suppresses viral replication in ECs via activating interferon signaling

Front Immunol, in revision



Our Team



Minh Nguyen

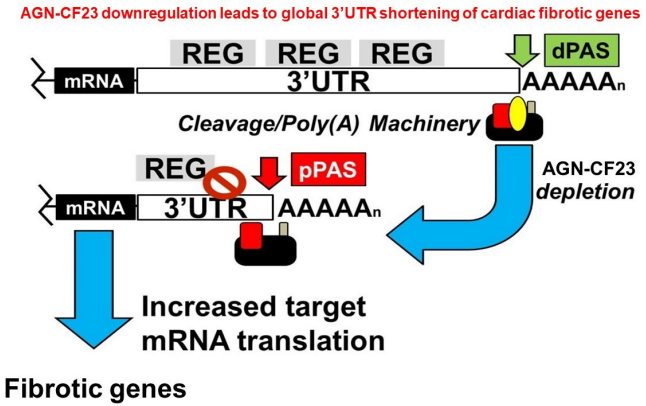
Estefani Berrios Turcios

Khan Chau

Research:
Thandavarayan Lab

Unraveling the RNA mis-regulation in heart failure

Dr. Rajarajan A. Thandavarayan leads a scientific effort, together with clinical collaborator Dr. Ashrith Guha, to investigate pathophysiological mechanisms behind heart failure (left and right ventricular) and pulmonary hypertension.



Alternative cleavage and polyadenylation (APA) in fibrotic mRNAs

In fibrotic environments, there is a switch from distal polyadenylation (dPAS) to proximal polyadenylation (pPAS) due to downregulation of a key component of the cleavage/ polyadenylation machinery, AGN-CF23. This results in mRNAs with shortened 3'UTRs that can no longer be regulated by microRNAs, which leads to enhanced pro-fibrotic gene activation and protein production.

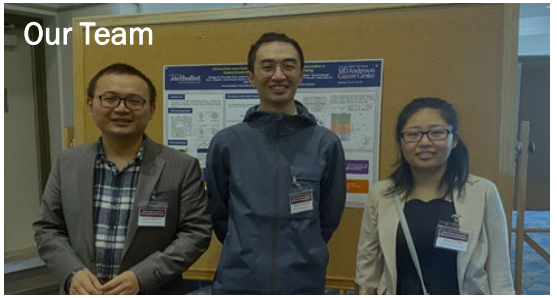
The findings provide insight into a novel pathway by which profibrotic factors are exacerbated in heart failure.

Research:
Wang Lab

HOUSTON Methodist LEADING MEDICINE

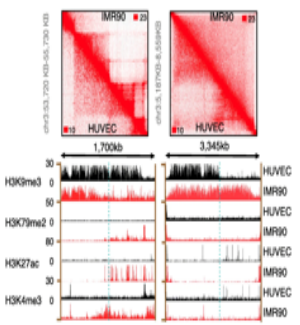
Single-cell dynamics

Single-cell transcriptomics (scRNA-seq) and single-cell epigenomics (scATAC-seq) have revolutionized the field of regulatory genomics. We combine cutting-edge computational approaches with state-of-the-art single-cell profiling to better understand cell state transitions, to decode cis-regulatory programs, and to predict the effect of TF perturbations in single-cell datasets and their effect on cell identity.

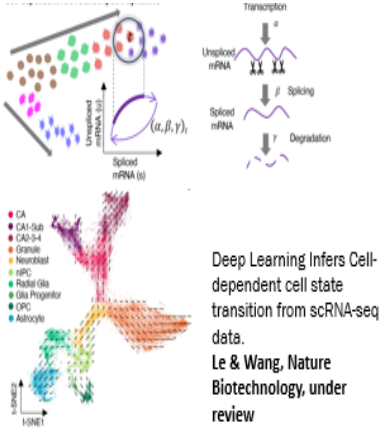


Chromatin structure & histone modification

Epigenetic factors including histone modification, chromatin configuration, and DNA methylation play important roles in transcriptomics and cell differentiation. We investigated new mechanisms for regulation of cell differentiation and disease progression using computational biology innovations. We developed TADsplimer to reveal that cell differentiation is associated with splits and mergers of topological associating domains (**Wang et al, Genome Biology, 2020**); we developed MACMIC to reveal that super enhancers at cell identity genes are regulated by CTCF (**Wang et al, GPB, 2021**); we developed machine learning algorithms to uncover cell identity regulators by histone code (**Xia & Wang et al, Nature Communications 2020**). We continue to apply computational biology techniques to investigate aging by integrated multi-omics and deep learning methods to predict cell differentiation on single cell level.



Topological associating domains splits and mergers are associated with changes in chromosome state.
Wang et al, Genome Biology, 2020



Deep Learning Infers Cell-dependent cell state transition from scRNA-seq data.
Le & Wang, Nature Biotechnology, under review

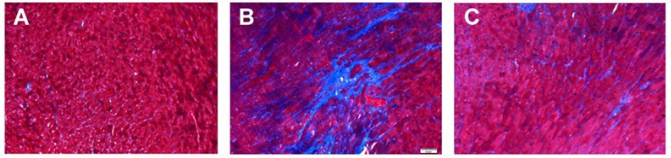
Research:
Youker Lab

HOUSTON Methodist LEADING MEDICINE

Keith Youker, PhD, works together with a clinical collaborator, Arvind Bhimaraj, MD, MPH, to understand Heart Failure and Post-Transplant biology with a focus on clinical translation to benefit our patients. We study the role of the immune system, and cell fate transitions, in the recovery from heart failure. We combine data from human tissues and hypothesis-driven wet-lab research to test our hypotheses. In collaborative work with Dr. Cooke, we assess the role of microvascular regeneration in heart failure recovery, as well as the anti-fibrotic effects of CBD.

A vaccine for heart failure

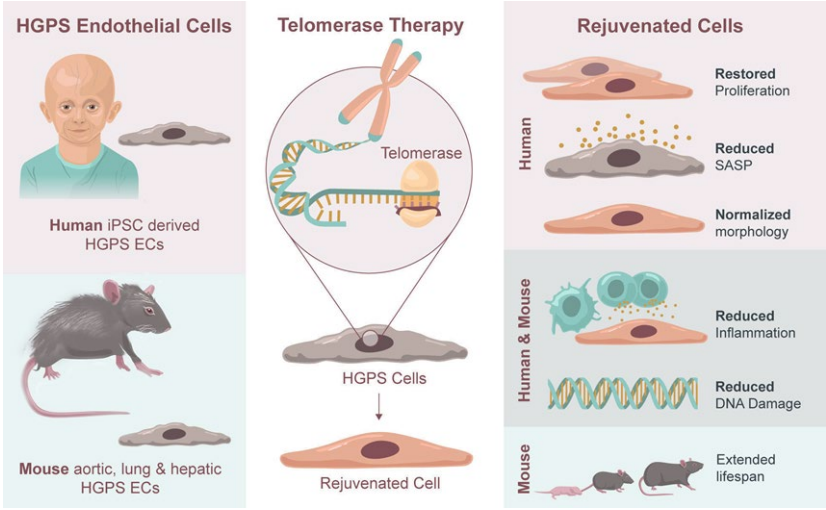
In our studies of the biology of heart failure we have uncovered several molecules which promote injury and may be intimately involved with the continued progression of heart failure. One of those molecules, HSP60, has been known for years as a damage associated protein but it is also known to activate inflammatory and immune responses and induce cell death. This cytoplasmic protein is aberrantly released into the extracellular space in heart failure in humans. We developed a vaccination strategy to neutralize extracellular HSP60. In our animal model of heart failure this strategy decreased cardiomyocyte cell death and greatly diminished the progression of heart failure. We are now in the process of identifying the patient population which may most benefit from a vaccine strategy.



Trichrome staining of myocardial tissues showing fibrosis (blue) in A) control heart, B) heart failure, C) heart failure vaccinated against HSP60.

Rising Stars:
Anahita Mojiri, PhD, Instructor

Hutchinson-Gilford progeria syndrome (HGPS) is an accelerated aging syndrome associated with premature vascular disease and death due to heart attack and stroke. In HGPS, a mutation in lamin A (progerin) alters nuclear morphology and gene expression. Endothelial cells (ECs) derived from HGPS-iPSCs exhibited hallmarks of senescence including replication arrest, DNA damage, short telomeres, and abnormal functions, such as impaired generation of nitric oxide and increased secretion of inflammatory cytokines. We find that treatment with telomerase mRNA (hTERT) reverses these signs of senescence. In conclusion, *vascular* rejuvenation using hTERT is a promising approach for HGPS and perhaps other age-related vascular diseases (Mojiri et al, Eur Heart J, 2021)

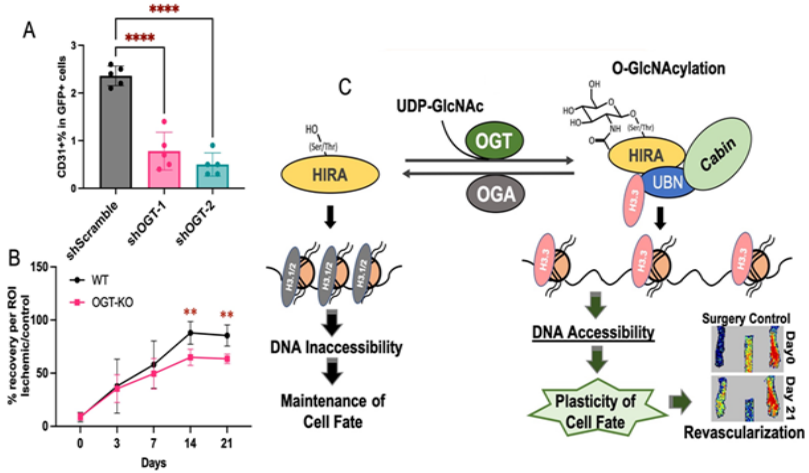


Rising Stars:
Li Lai, PhD, Research Assistant Professor

HOUSTON Methodist LEADING MEDICINE

O-GlcNAcylation Regulate Transdifferentiation and Vascular Regeneration

We have discovered that O-GlcNAcylation (a post-translational modification) regulates cell fate transitions in vascular regeneration. Specifically, we found that UDP-GlcNAc is the most upregulated metabolite during cell fate transition (specifically fibroblast to endothelial cell transdifferentiation). Using lineage tracing and a hindlimb mouse model, we identified a dramatic accumulation of O-GlcNAcylation in the fibroblast progeny cells which transdifferentiate to endothelial cells during vascular recovery. Further, enhancement of O-GlcNAcylation increases transdifferentiation and vascular recovery in vitro and in vivo. Mechanistically, the O-GlcNAcylation of histone variant H3.3 chaperon HIRA is essential for transdifferentiation by depositing H3.3 in the nucleosome to enhances DNA accessibility and facilitates cell fate transition.



A. OGT is the enzyme that induces O-glycnacylation. Knockdown of OGT reduces O-GlcNAcylation in the fibroblasts and impairs transdifferentiation in vitro.
B. Fibroblast-specific OGT knockout mice manifest impaired revascularization of the ischemic hindlimb.
C. O-GlcNAcylation mediated histone variant H3.3 deposition is essential for transdifferentiation.

Center for RNA Therapeutics Affiliate Members

HOUSTON Methodist LEADING MEDICINE

Shu-Hsia Chen, PhD is the Emily Herrmann Chair in Immunology and Director of the Center for Immunotherapy Research. She is also a Professor of Medicine and Oncology and a member of the Cancer Center. Dr. Chen develops cancer vaccines using RNA therapeutics.

Biana Godin, M. Pharm, PhD is an Associate Professor of Nanomedicine and Obstetrics and Gynecology in HMRI and HMH with adjunct faculty appointments at Texas A&M and UTHealth. Dr. Godin is currently collaborating with Dr. Cooke to develop a telomerase mRNA nanotherapeutics for skin and vascular regeneration and traumatic brain injury. She also works on developing RNA-based nanotherapies for cancer.

Malgorzata Kloc, PhD, Dr. Sc. is the Weill Cornell Professor of Cell and Molecular Biology at The Methodist Hospital Research Institute, and Adjunct Professor, at The University of Texas, M. D. Anderson Cancer Center. Dr Kloc focuses on macrophages and molecular mechanisms of chronic rejection of transplanted organs, and structural role of mRNA in the organization of cytoskeleton in oogenesis and development.

Roderic Pettigrew, MD, PhD is CEO of EnHealth and Executive Dean for EnMed at Texas A&M University and Adjunct Professor of Nanomedicine Houston Methodist. Dr. Pettigrew is designing delivery systems for RNA therapeutics

Francesca Taraballi, PhD is an Assistant Professor of Orthopedic Surgery and Center for Musculoskeletal Regeneration. Dr. Taraballi has developed a biomimetic drug delivery system known as leukosomes that possess macrophage surface proteins that facilitate delivery of RNA therapeutic to sites of inflammation.

Yi-Lan Weng, PhD is an Assistant Professor of Neurosurgery and Center for Neuroregeneration. His interests are in m6A RNA methylation in regulating RNA trafficking, localization and translation, as well as how dysfunction of these mechanisms could be linked to brain disorders.

Keith Youker, PhD is an Associate Research Professor of Cardiovascular Sciences and DeBakey Heart & Vascular Center. Dr. Youker is creating an RNA vaccine to protect against heart failure.

Management Team

Saba Arshad Khan, MBBS, CCRP
Clinical Trials Manager, Heart Center Research

Jihad (Jimmy) Yahya, MSA, MBA
Financial Analyst, Clinical Research

Nelcy Ramirez, MBA
Operations Manager
Center for Cardiovascular Regeneration

Tenisha Madkins, MBA
Operations Manager, Clinical Research

Maria Del Pino, MS, CVRN-BC, CCRP
Clinical Trials Manager, Heart Center

Susmitha Gadde, MBBS, MBA, CCRP
Multi-Department Administrative Director

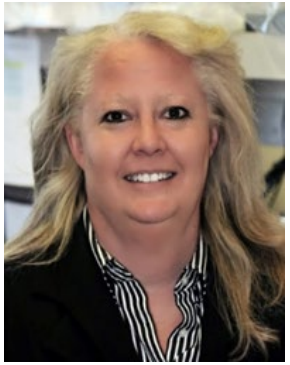
Ray Prakash, MBA
Sr. Operations Manager
Center for RNA Therapeutics

Administrative Team

RNA Core Project Managers
Trinh Tat, PhD
Crystina Kiss.PhD
Hongye Li, PhD
Tulsi Damase, PhD

Lab Operations Lead
Angelica Aguilar, BS

Department Lab Lead
Elisa Morales, MS



Scientific Writer
Elizabeth Davis, PhD

Lab Leads
Suchitra Sridhar, MS
Estefani Berrios turcios, BS
Vrutant Shah, PhD
Kaylee Carter, BS
Jun-dae Kim, PhD

Administration Assistant
Rene Castillo
Dora LeBlanc

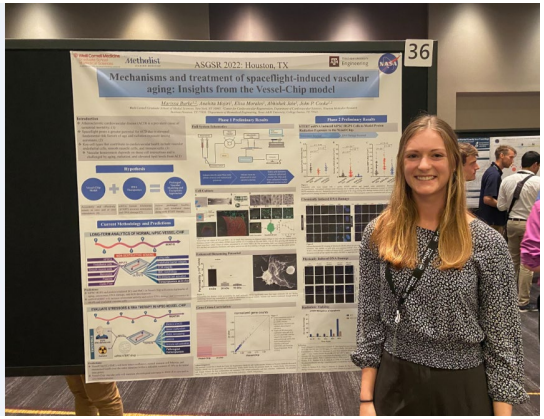
Financial Analyst
Annalise Brisco, MBA
Martin Vu, MHA

Sr. Academic Coordinator
Michelle Sullins, BS

Trainees

Texas Southern University
University

Undergrads, Blake Stevenson and Shaun Melton are pictured with Postdoc Min Zhang and their mentor Dr. Kiss.



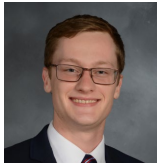
Weill Cornell Medicine
Graduate School
of Medical Sciences
A partnership with the Sloan Kettering Institute

Graduate Student, Marissa Burke represented the Cooke Lab and Weill Cornell at the 38th American Society for Gravitational and Space Research Conference. She placed second for her poster on Mechanisms and treatment of spaceflight-induced vascular aging: Insights from a Vessel-Chip model.

Texas A&M University
University in Texas, USA

Abishai Dominic graduated from the department of Molecular and Cellular Medicine in Dr. Le's lab. He is now beginning his postdoctoral fellowship

Alexander Lu MD, PhD Student
Mentor: Dr. Cooke



Graduate student, Matthew Fiedler works closely with Dr. Mojiri in Dr. Cooke's lab. He is studying mechanisms of transdifferentiation and methods to enhance mesenchyme-to-endothelial transition.

Graduate student Weiqing Chen will start her research training in Dr. Wang's lab.

New Initiatives

Our Response to the Next Global Pandemic

Houston Methodist's Center for RNA Therapeutics has been selected for a $3.5M award by the Coalition for Epidemic Preparedness Initiative (CEPI) in an international competition to develop a novel RNA vaccine platform against infectious diseases with pandemic potential.
CEPI is a global coalition of 32 governments including the United States, with several billion $$ under management, to accelerate the production of vaccines against diseases that posed the greatest threats to public health, and to ensure equitable access to vaccines worldwide. During the COVID-19 pandemic, CEPI provided over 1.3 billion vaccines to low and middle-income countries.

We will develop the next-gen RNA vaccine platform for CEPI, led by John P. Cooke, Director of our Center for RNA Therapeutics (CRT). Dr. Jimmy Gollihar, Head of Antibody Discovery & Accelerated Protein Therapeutics (HMAI) will screen viral antigens for the strongest vaccine targets. Dr. Dan Kiss, Associate Professor (HMAI) and the inventor of a novel circular RNA technology, will use the sequence information generated by Dr. Gollihar to synthesize the circular RNA vaccine. Dr. Francesca Taraballi, Assistant Professor (HMAI) will generate lipid nanoparticles for encapsulating the RNA vaccine; and Dr. Cooke's group in the RNACore will scale up the processes for cGMP production, with Dr. Chris Lincoln, the director of the Office of Translational Production and Quality. Dr. Scott Weaver at the University of Texas, Medical Branch, will test the vaccine in small and large animal models. The initial vaccine is targeted against chikungunya, a mosquito-borne disease that causes high-grade fever and incapacitating joint pain and affects hundreds of thousands of people annually.

Circular RNA technology is superior to traditional linear mRNA vaccines. Circular RNA has greater stability, which allows for a prolonged expression of the vaccine antigen, which is expected to stimulate a more robust and long-lasting immune response. Collaboration with CEPI positions Houston Methodist firmly at the forefront of the response to the next global pandemic. The CEPI relationship will foster connections with other leaders in the field of vaccine development through CEPI's extensive network of academic institutions, biotechnology companies, NGOs, government entities, and philanthropic foundations. With CEPI's goal of producing an effective vaccine against pathogens within the first 100 days of an outbreak, Houston Methodist is poised to lead timely vaccine development efforts for future pandemic responses.

New Grants
Center for Cardiovascular Regeneration

HOUSTON Methodist LEADING MEDICINE

Francisco Altamirano, PhD

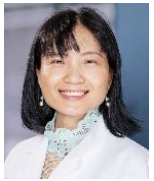
R01HL158703-01A1 – Mechanisms driving cardiac dysfunction in Autosomal Dominant Polycystic Kidney Disease
we propose to elucidate the molecular mechanism driving cardiac dysfunction in ADPKD patients.
R01 with Dr. Miguel Valderrabano, Collaborator, Dr. Wang – Cardiac Autonomic Activation in Atrial Fibrillation Triggers and Substrate
We will elucidate the mechanism whereby cardiac intrinsic nerves causes AF at the molecular, cellular, and physio-logical levels in humans and dogs. We propose that CANS produces a substrate for AF through neural (nerve firing) and humoral effects (secretome), in which SP – released by CANS sensory neurons – plays a major role in increasing susceptibility to AF through direct electrophysiological and genomic effects in atrial cardiomyocytes.

Longhou Fang, PhD

NIH Competitive Award Initiative. This grant will assess the role of flow-regulated lipid metabolism in hematopoiesis.
Collaborative Pilot Grants in Alzheimer's Disease and Related Dementias (HM & BCM)
This grant will investigate the role of AIBP-regulated pathway in the treatment of Alzheimer's Disease.
Kostas Foundation Grant
This grant will determine the effect of nanoparticle-mediated SREBP2 siRNA delivery on adult angiogenesis following hindlimb ischemia.

Guangyu Wang, PhD

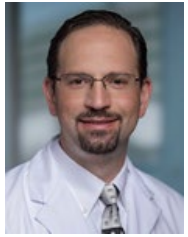
R01/NIH- Premature aging disorders, metabolites, and atherosclerosis
Abe (PI), (Role: Co-investigator)
The goal of this project is to understand the mechanisms by which radiation therapy promotes cardiovascular dysfunction and facilitates the development of new therapeutic approaches for atherosclerosis, especially in the growing population of cancer survivors. I lead the bioinformatics studies in this project.
NASA-Long-term Patient iPSC Vessel ChIP Model to Assess Stressors of Atherosclerosis and mRNA Therapeutics
Jain(PI), (Role: Co-investigator)
The objective is to establish the long-term culture and feasibility of our vessel-on-chip system that helps dissect pathophysiology of atherosclerosis and toxin/drug-tissue interactions with much higher specificity and sensitivity than other models. I lead the bioinformatics studies in this project to improve applications of the organ-on-chip technology in translational research in atherosclerosis and other aging-associated vascular and hematological diseases.
R01/NIH-Cardiac autonomic activation in atrial fibrillation triggers and substrate
Valferrabano(PI),(Role: Collaborator)
The goal of the grant is to study how the autonomous nervous system increases susceptibility to atrial fibrillation. There are some ganglia located in the heart with sensory, sympathetic, and parasympathetic neurons.



Nhat Tu-Le, PhD

1R01HL163857-01A1 NIH *grant supports us to investigate the mechanisms of premature aging-induced atherosclerosis via metabolite changes.*

New Grants



Daniel Kiss, PhD

Grant Title: Administrative supplement to Kiss R35: Understanding the mechanisms that regulate cytoplasmic capping and defining its contributions to post-transcriptional gene regulation", **Dr. Kiss's role:** PI
This NIH grant supplement was awarded to support Dr. Rachel Kieser's research on cytoplasmic capping. She will work to adapt the most advanced sequencing methods to answer questions about the effects of cytoplasmic capping in vivo.

Grant Title: Enhancing the stability of RNA therapeutics via gas-phase encapsulation
Grant Mechanism: Rice University and Houston Methodist 2022 Seed Grant Program in Cardiovascular Bioengineering, **Dr. Kiss's role:** Co-PI
A general limitation of RNA therapeutics is the instability of RNA in aqueous environments. To overcome this limitation, we aim to develop an innovative strategy to store RNA therapeutics in nanoscale gas-filled protein structures and thus insulate them from aqueous environments.

Grant Title: Administrative supplement to help develop a novel RNA vaccine for Tuberculosis
Grant Mechanism: NIH Sub-contract via Univ Montana, **Dr. Kiss's role:** sub-contract Co-Investigator
This grant subaward was given as part of the NIH's attempts to develop novel vaccines to prevent Tuberculosis. Our portion of this award is to develop three circular RNA vaccine candidates for our collaborators to test using their in vivo models.

Grant Title: Administrative supplement for rapid advancement of a safe and effective vaccine targeting Monkeypox
Grant Mechanism: NIH Sub-contract via Univ Montana, **Dr. Kiss's role:** sub-contract Co-Investigator
This grant subaward is in response to the rapidly expanding Monkeypox epidemic. Our portion of this award is to develop two linear and two circular RNA vaccine candidates for our collaborators to test using their in vivo models.

Kristopher Brannan, PhD

Grant Title: CRISPR-Based Genome Editing of Ribosomal Protein L39 (RPL39) for Personalized Metaplastic Breast Cancer therapy.
For this collaborative grant, we will develop a new multimodal targeted cancer therapy combining biomimetic nanoparticle (NP) technology with a multiplexed NP approach involving co-delivery of siRNA, Cas9 mRNA and sgRNA against the metaplastic breast cancer (MpBC) prevalent RPL39 A14V mutation, to facilitate tumor delivery and enhance gene-editing efficacy in vivo.

Rajarajan Amirthalingam, PhD

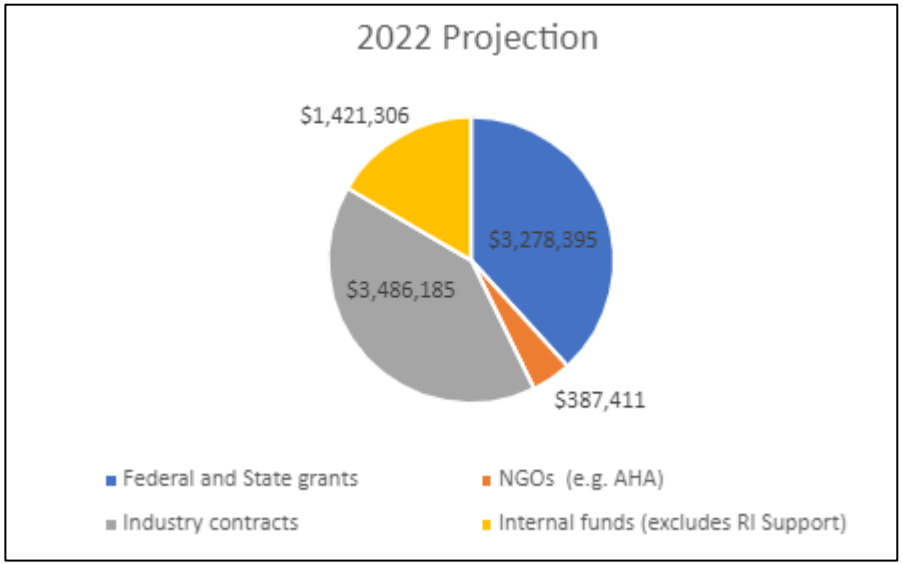
22TPA969556- Role of CstF64 mediated alternative polyadenylation in heart failure.
(PI: Rajarajan Amirthalingam)
Funding Agency: American Heart Association (Transformational Project Award)
This project focuses on evaluating the role of CstF64 in 3'UTR shortening and how it contributes to cardiac fibrosis.

R21 ES033813-01A1- Resolvin D1 resolves inflammation in metabolic stress associated HRpER.
(Co-I Rajarajan Amirthalingam; PI: Suresh Palaniyandi)
Funding Agency: National Institute of Health (R21)
This project focuses on evaluating the role of Resolvin D1 systemic and cardiac inflammation and how it contributes to heart failure with preserved ejection fraction.

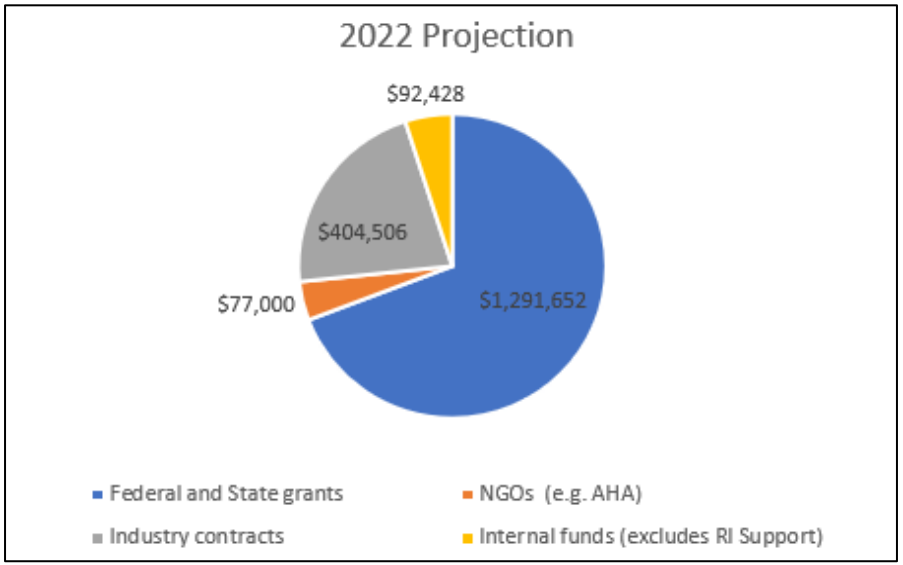
2022 Faculty Funding From Grants & Awards

HOUSTON Methodist LEADING MEDICINE

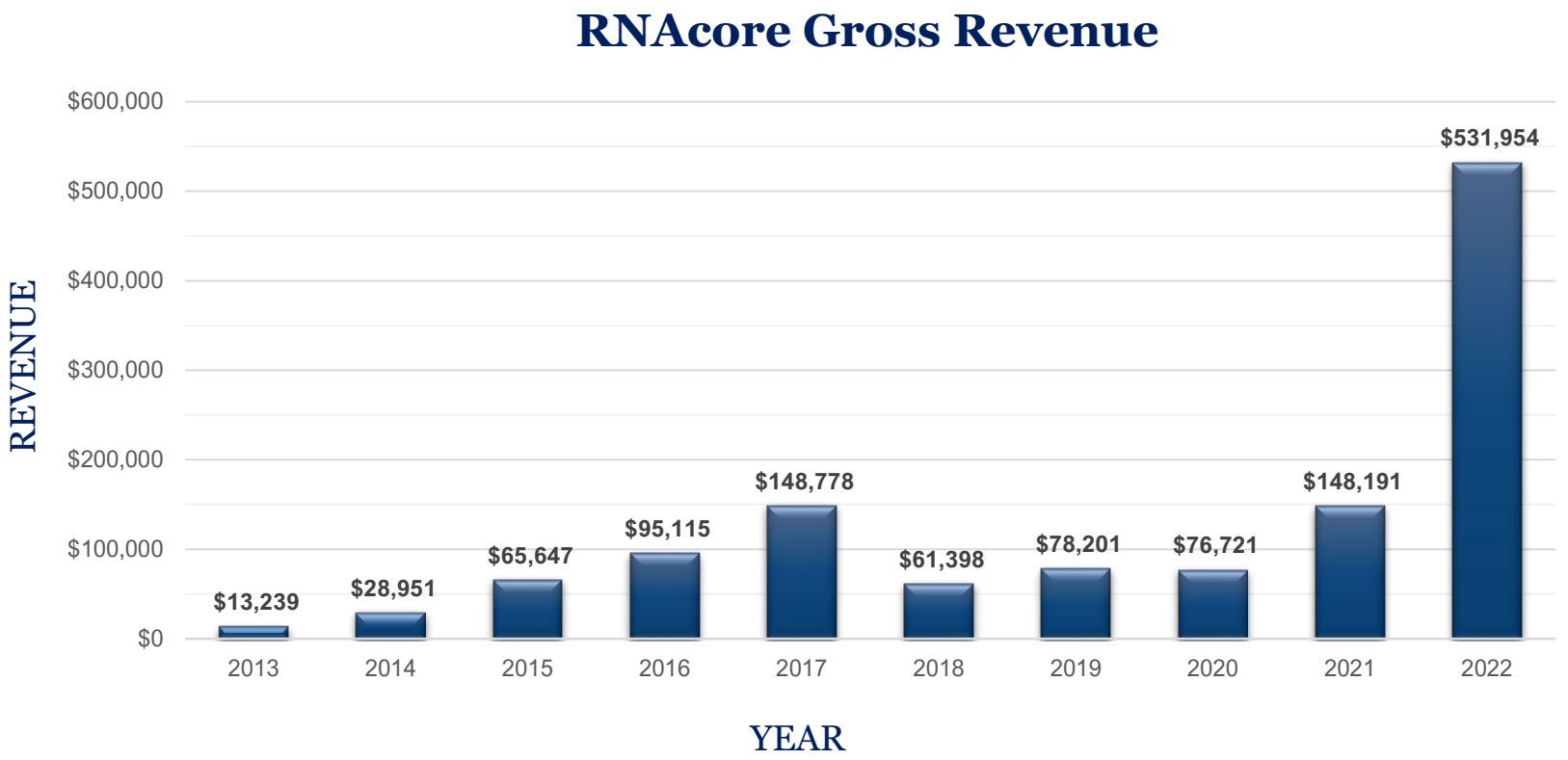
Center for Cardiovascular Regeneration



Center for RNA Therapeutics

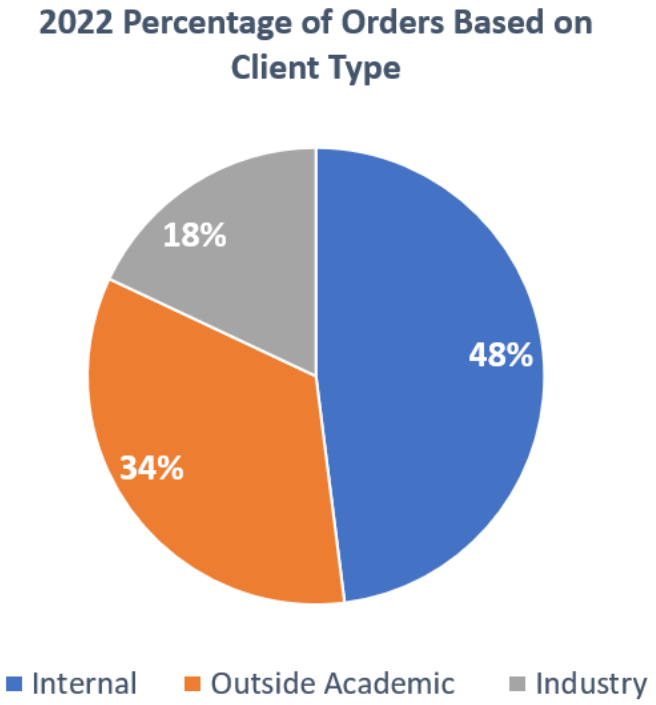


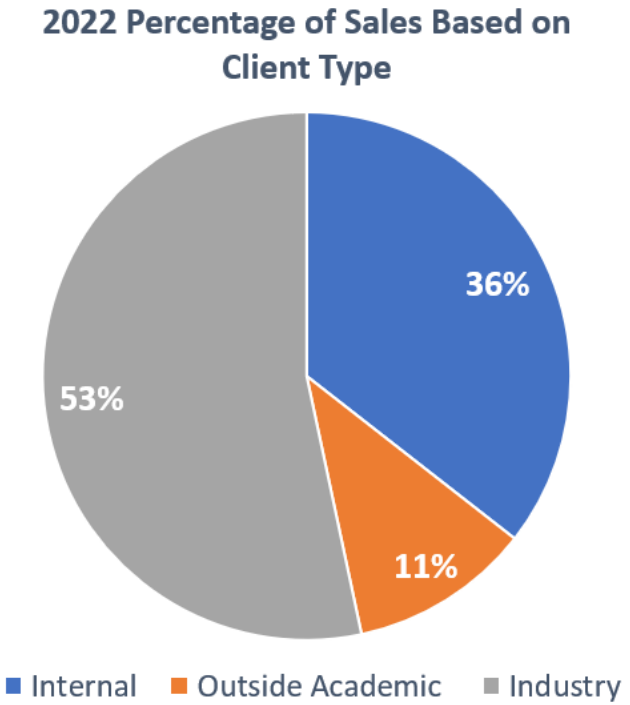
RNACore Revenue



RNACore Revenue

HOUSTON Methodist LEADING MEDICINE





Events and Activities

HOUSTON Methodist LEADING MEDICINE

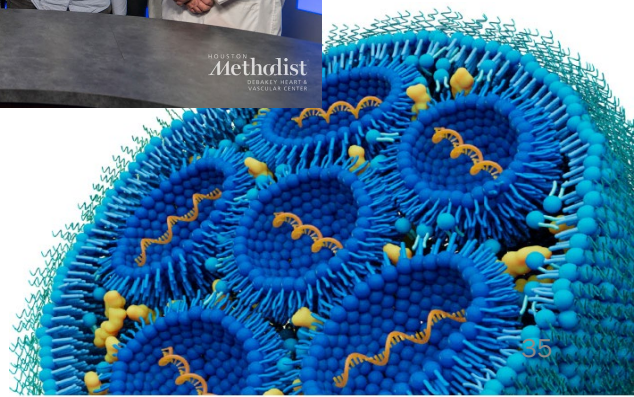
THE NEW FRONTIER OF RNA NANOTHERAPEUTICS

The George and Angelina Kostas Research Center for Cardiovascular Nanomedicine Annual International Meeting

Shark Tank: Competition Cardiovascular Nanomedicine

WINNERS

Dr. Youker and Dr. Rajarajan were awarded 10k, towards development of a Heart Failure Vaccine.

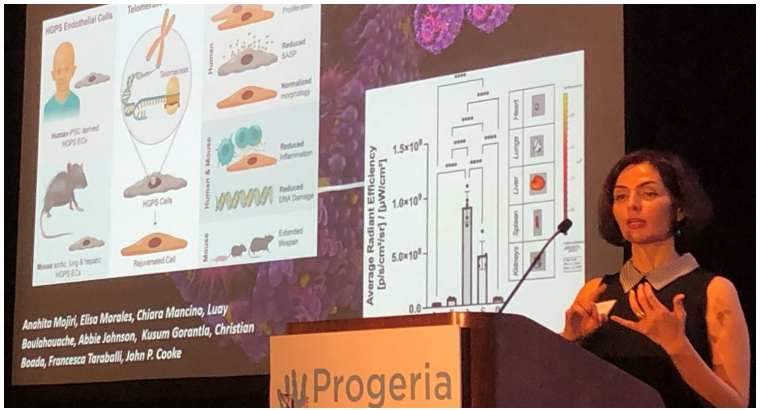


Events and Activities

HOUSTON Methodist LEADING MEDICINE

Progeria Research Foundation Workshop, Boston

Dr. Cooke, Dr. Mojiri and Elisa Morales are pictured with Sammy Basso. Our team was able to share their findings with the Progeria Research Foundation Community.



Dr. Anahita Mojiri presented her work on Telomerase Reversal of Senescence.

Progeria Research Foundation
FOR THE CHILDREN ♥ FOR THE CURE

Events and Activities

Dr. Cooke and Dr. Kriss, hosting the Center for RNA Therapeutics and RNA CORE booth.

Awards & Honors

Dr. Ewan McRae
CPRIT Early Investigator Award ($2M)

Award enabled Dr. McRae's recruitment to our Center for RNA Therapeutics

Dr. Ewan McRae will join us as an Assistant Professor in the Center for RNA Therapeutics. He is focused on RNA folding and the design of stable and functional RNA nano-devices. Dr. McRae received his BS and PhD in Biochemistry, from the University of Manitoba, and is completing his postdoctoral training at I Nano, Aarhus University in Denmark. Dr. McRae's honors and awards include the Distinguished Dissertation Award, University of Manitoba; The Natural Sciences and Engineering Research Council of Canada Award; and the Faculty of Science Award. Dr. McRae will lead our efforts to elucidate RNA structures of physiological significance and potential therapeutic benefit.

Awards & Honors

2022 Fire Awards:
7 Top Health Care and Life Sciences Innovators

Our Center for RNA Therapeutics was recognized by a 2022 Fire Award by the Houston Business Journal.

The award is in recognition of the position that our Center has achieved on the forefront of RNA therapeutics. Our Center has generated over 200 RNA drugs for over 60 clients worldwide, many of them in Texas. We have developed proprietary methods for the synthesis, purification, lyophilization, encapsulation and validation of RNA drugs, and can make them clinical-grade for testing in humans. A Houston corporate manufacturing organization for DNA drugs, VGXI Inc, has licensed our technology for manufacturing linear mRNA, and is currently working with us to scale the manufacturing processes in their RNA manufacturing facility in Conroe at the Deison Industrial Park.

Awards & Honors

Dr. Altamirano received the Cornerstone Award.

Dr. Fang received the HMAI President's Award.

Minh Nguyen from Dr. Le's lab, was selected to present her work at the moderated poster section at the AHA Scientific meeting 2022. Minh Nguyen is investigating the role of the deSUMOylase SENP2 S344 phosphorylation in endothelial activation and atherogenesis.

Dr. Keith Youker received the Kostas Award, awarded by Methodist Hospital Foundation.

Khanh Chau from Dr. Le's lab, was selected to present his work on ATVB Early Career Poster & Networking Reception at the AHA Scientific meeting 2022. Khanh Chau is investigating the role of TERF2IP K240 SUMOylation in endothelial senescence and atherogenesis.

Dr. Rajarajan Amirthalingam received an American Heart Association (AHA), Role of CstF64 Mediated Alternative Polyadenylation in Heart Failure.

Social Events

HOUSTON Methodist LEADING MEDICINE

Department Ping Pong Tournament

Halloween

A Brewing Disaster Pumpkin placed 3rd in the Houston Methodist Pumpkin contest. Congratulations to Elisa Morales, Angelica Aguilar, Grace Abbie & Estefani Berrios Turcios, the department thanks you for your hard work and representation.

WINNER
Michael Graber

HAPPY HOUR

Admin Happy Hour

Social Events

HOUSTON Methodist LEADING MEDICINE

Kiss Lab Welcomes Baby Zhang

Cooke Lab Pizza Party

Thankful for One Another

Onward and Upward

We said farewell to visiting Postdoctoral Fellow Michael Graber, as he moves to Cardiac Surgery Fellowship.

Postdoctoral Min Zhang said goodbye to the Kiss Lab.

Dr. Roman Sukhovershin departed to complete his medical residency.

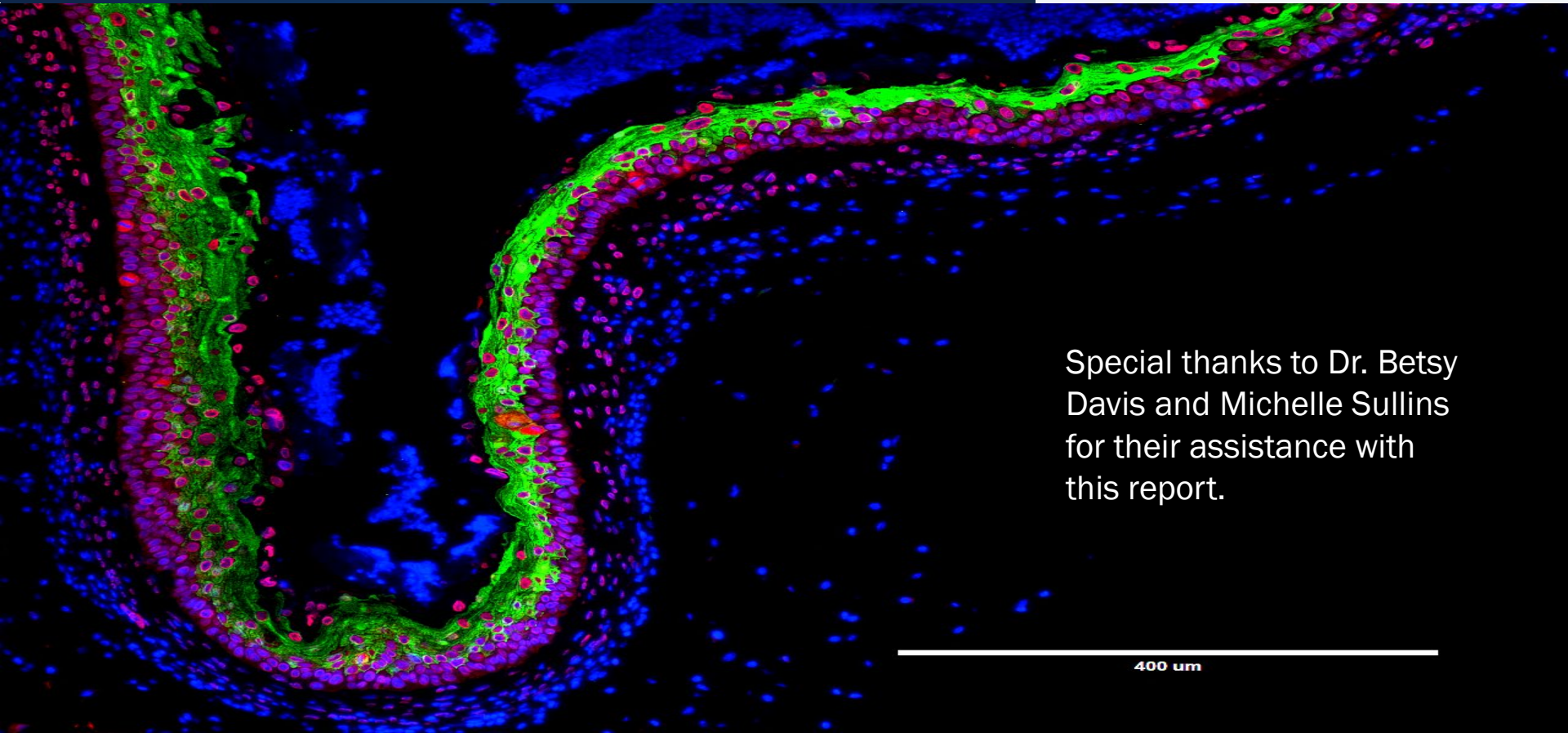
Administrative Departures

Rebekah Sieker
Executive Assistant

Nayeli Rodrigues
Financial Analyst

With gratitude for your support on our path to discovery and health

HOUSTON Methodist
LEADING MEDICINE



Special thanks to Dr. Betsy Davis and Michelle Sullins for their assistance with this report.


HOUSTON
Methodist
LEADING MEDICINE