MICHIGAN MEDICINE
UNIVERSITY OF MICHIGAN

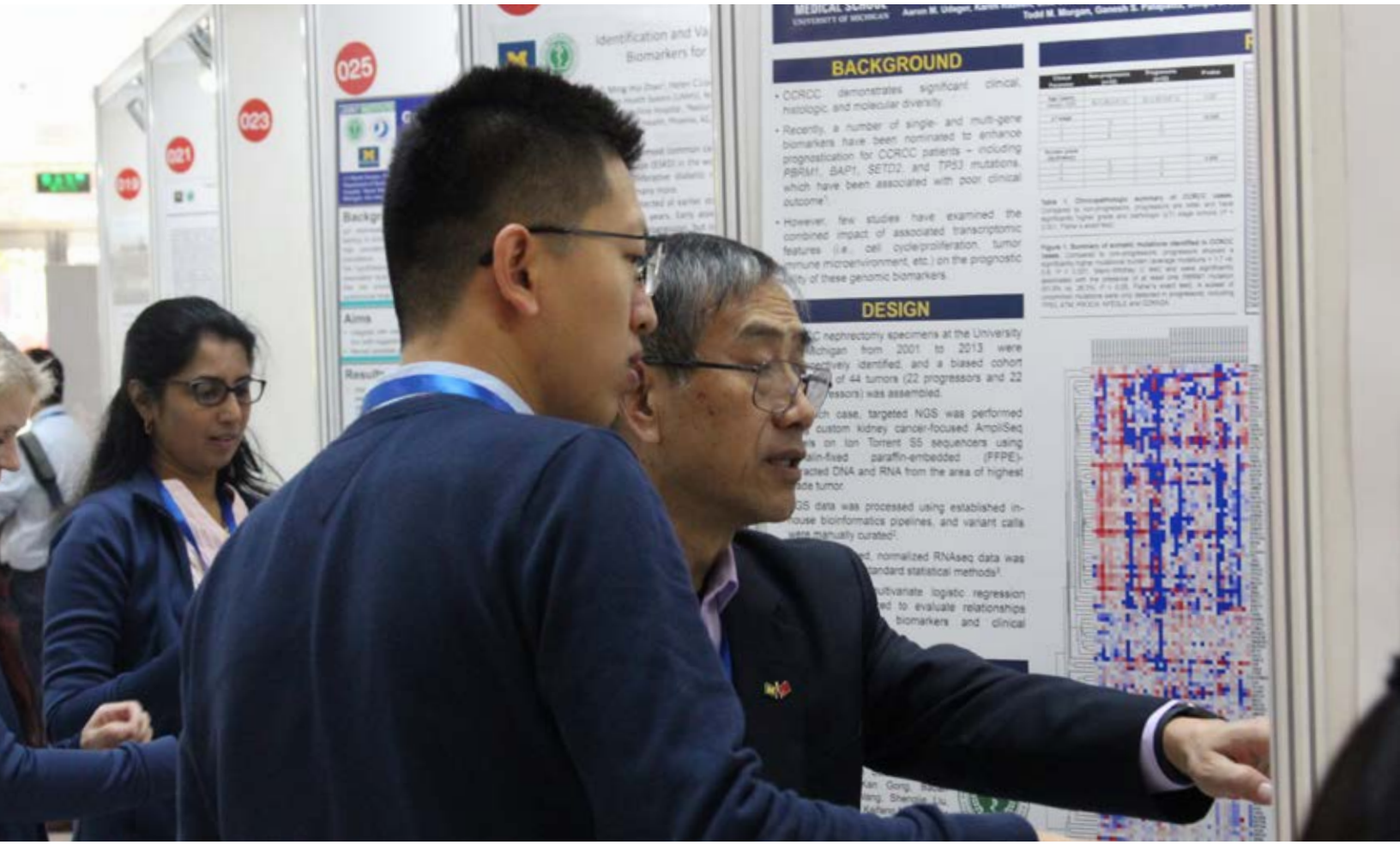
PEKING UNIVERSITY HEALTH SCIENCE CENTER
北京大学医学部
1912

JOINT INSTITUTE
for Translational and Clinical Research

Progress Report
2021-22

GLOBAL REACH
Research, Education, and Collaboration in Health

Table of Contents



Attendees browse the poster session of the 2019 Joint Institute Symposium in Beijing.

Letter from the Co-Directors

Colleagues,

We are pleased to present the latest progress update for the Joint Institute. While the pandemic lingers and travel between China and US remains difficult, our collaboration has adjusted. The Joint Institute is thriving, as you will read in these pages.

Despite the challenges presented by COVID-19, our faculty continue to produce strong research. A record 21 papers resulting from JI research were published in 2021, appearing in some of the top academic journals. This work also continues to yield extramural funding, including a sizeable NIH grant to explore sepsis diagnosis and treatment.

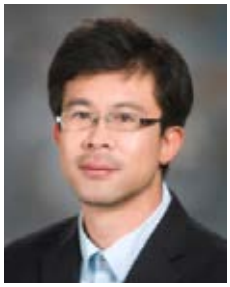
With a recent five-year renewal of our collaboration agreement, including additional funding commitments, we are well positioned to advance our partnership. A shift away from organ-based projects (kidney, lung, circulatory system, etc.) toward areas that cross multiple disciplines (cancer, precision medicine, etc.) has energized our partnership and attracted new researchers from both institutions who are eager to collaborate. Following a one-year funding pause in 2020 because of COVID-19, we resumed regular project awards in 2021, and most of the 10 projects to receive funding align with these new focus areas; one project explores COVID-19 directly.

In addition to new awards, we're enthused about our new Joint Institute Collaboration Scholars program. Set to launch in 2023, this initiative will allow early-career researchers to spend extended periods at the respective partner institution, immersed in JI work. Not only will these scholars advance our ongoing research, they will become strong advocates for collaboration and potential future leaders of the JI once they return to their home institution, helping to ensure sustainability for our partnership over the long term.

In short, although we can't be together in-person, our bond—based on friendship, trust, and a mutual desire to improve the health of our patients—remains as close as ever. This collaboration is an example of the power of international collaboration, and a reminder that we achieve more together than we could ever hope to accomplish alone.

Xièxiè. 谢谢.

Joseph C. Kolars, MD, MACP
Co-Director, Joint Institute
Senior Associate Dean
Josiah Macy, Jr., Professor of Health Professions Education
University of Michigan Medical School



Jiadong Wang, PhD
Co-Director, Joint Institute
President, Peking University Health Science Center
Executive Vice President, Peking University

Leadership

Marschall S. Runge, MD, PhD
Executive Vice President for Medical Affairs
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Vice President, Peking University Health Science Center
Professor, School of Basic Medical Sciences

Rebecca Cunningham, MD
Vice President for Research
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Professor of Emergency Medicine
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About the JI

History

In 2010, Michigan Medicine, the academic medical center of the University of Michigan, and Peking University Health Science Center (PKUHSC) established the Joint Institute for Translational & Clinical Research, commonly known at both institutions as the JI. Michigan Medicine and PKUHSC have each re-invested in the JI partnership through multiple renewal agreements, most recently in 2022.

The JI was established to benefit both partner institutions by:

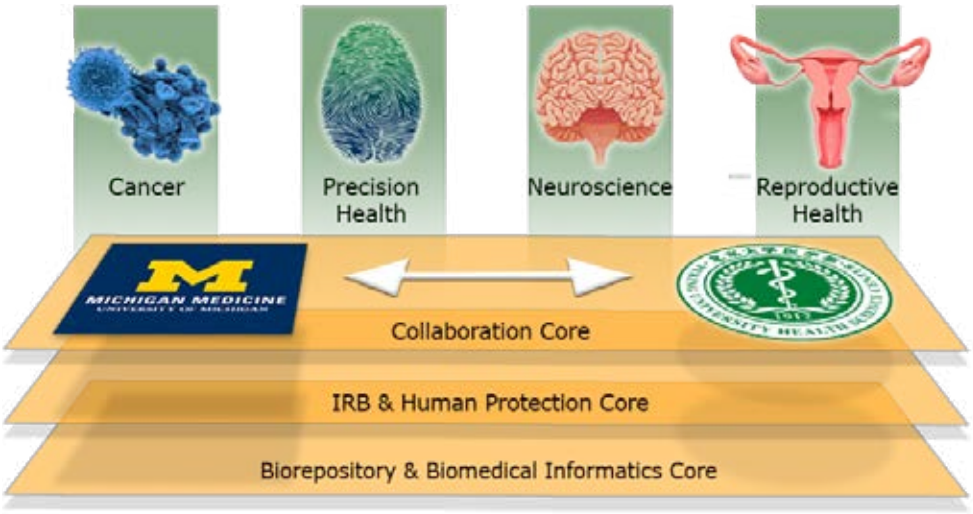
- enhancing translational research capacity;
- bolstering a qualified workforce in both basic science and clinical research;
- promoting student and faculty exchange; and
- helping faculty succesfully compete for extramural funding.

The JI allows faculty at both institutions to partner on research that neither side could conduct alone, advancing health for populations across the US, China and beyond.

UMMS Senior Associate Dean Joseph Kolars speaks at the Joint Institute Symposium in Beijing in 2019..

Joint Institute 2.0

As part of the most recent partnership agreement, JI leaders implemented new research priorities shifting project focus away from individual organs (kidney, heart, lung research, etc.) toward broader areas: neuroscience; precision medicine; cancer; and reproductive health. These four areas were chosen because of their potential for large impact; mutual expertise across the partner institutions; and feasibility to attract investigators across many disciplines. Project proposals beyond these areas are still considered, but those connected to one or more of the new priorities are prioritized.



Our collaborative model of mutually agreed-upon areas of focus supported by administrative cores makes the JI a unique partnership platform between the two institutions.

By the Numbers

Vital Statistics To Date

69 JI Awards

39 Completed Projects

141k Patients Enrolled in Studies

135 Publications

$55M Extramural Funding

Research Areas

The JI fosters scientific research across many disciplines. At the outset, cardiovascular, renal, pulmonary, and gastrointestinal/liver medicine were prioritized. Over the years, other disciplines have been added. Recently, JI leaders prioritized research in the areas of cancer, precision medicine, neuroscience and reproductive health. To date, 70 projects have received funding from some 200 submitted proposals.

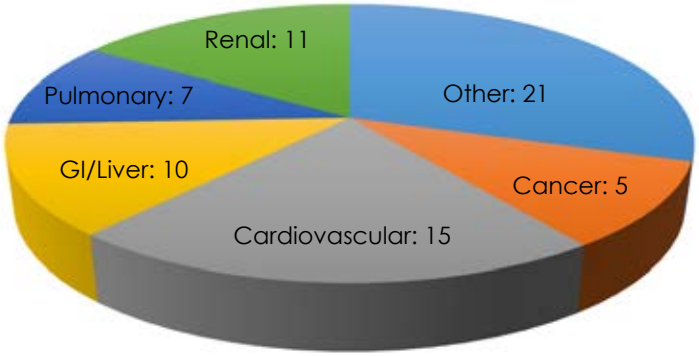
Publications

JI research has produced 135 publications to date, including a record 21 papers in 2021. The majority of these papes are co-authored by the respective PIs from each institution. JI research has appeared in leading academic medical journals including *Science*, *Academic Medicine*, *Blood*, *Gastroenterology*, and others.

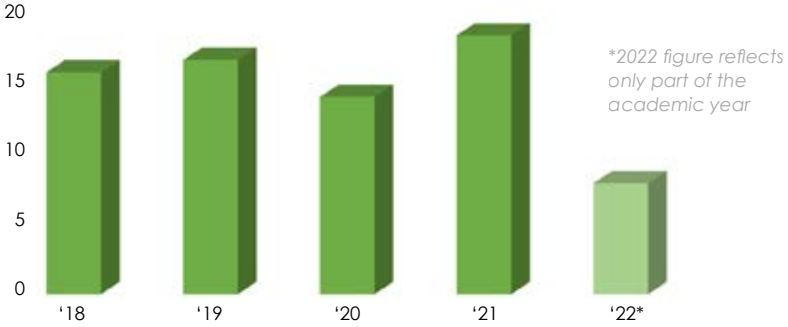
Funding

Institutional investments made through the JI are intended to seed pilot projects that can ultimately garner extramural funding. To date, JI teams have received more than $56.3 million in extramural funding for research as a result of their collaborations. Cardiovascular medicine research alone has resulted in $18.5 million in extramural funding. Teams in GI/Liver, Renal, and Pulmonary medicine programs have garnered extramural funding as well.

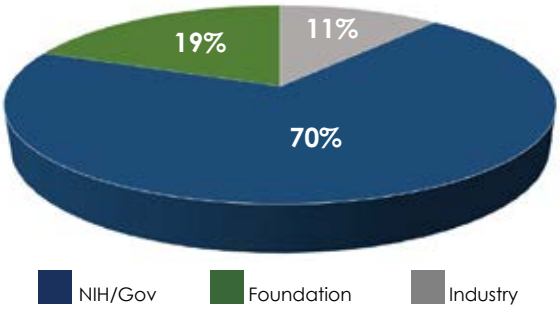
Awards by Discipline (2011-2022)



JI Publications, last five years



$55M Extramural Funding (2011-2022, U-M only)



New Projects for 2021

Ten new research projects have been selected for the most recent round of funding through Michigan Medicine's Joint Institute partnership with Peking University Health Science Center. The projects, each jointly headed by a UMMS faculty member and their PKUHSC partner, span a number of areas, including Biomedical Engineering, Cardiac Surgery, Computational Medicine & Bioinformatics, Internal Medicine, Molecular and Integrative Physiology, Psychiatry, and Radiology.

Single Cell RNA Sequencing to Identify Transcriptional Signatures of Failure to Repair After Acute Kidney Injury in Patients With and Without Covid-19 Disease

Acute Kidney Injury (AKI) is a common complication in those who are hospitalized, and uniformly portends a worse prognosis. Survivors of AKI may develop Chronic Kidney Disease (CKD), which is presumably due to failure to repair of the proximal tubular epithelial cells (PTEC). An AKI event increases the risk of subsequent CKD by 8-fold, and initial data suggests that the problem is even more pronounced among those who survived AKI in the setting of a SARS-CoV2 infection. Animal model data shows that several transcriptional changes occur in PTEC that fail to repair and progress to tubular atrophy, although it is not known which transcriptional changes are shared in episodes of human AKI. This is a critical gap as identification of shared cell-type specific transcriptional changes would be imperative to prioritize non-invasive biomarker development and potential drug targets. The overarching goal of this grant is to leverage the power of single cell RNA sequencing (scRNAseq) to identify shared, cell-specific transcriptional changes between animal models of ischemia-reperfusion injury (IRI) and AKI in human data. Trajectory analysis of the murine data from Dr. Yang's laboratory at Peking University First Hospital (PKUFH) will identify transcriptional changes that portend future tubular atrophy. As we hypothesize that transcriptional changes that portend tubular atrophy will be associated with worse outcomes, these transcriptional changes will be associated with outcomes using publicly available data from the Kidney Precision Medicine Project (KPMP) and local cohorts at the University of Michigan and PKUFH. These data will serve as valuable preliminary data for future grant applications to external funding agencies to identify cell-type specific, non-invasive biomarkers of failure to recover from an AKI event.

Co-Investigators


Matthias Kretzler, MD
UMMS


Li Yang, MD
PKUHSC

Role of Exosome Signaling in Cancer Cell Dedifferentiation and Chemo-Resistance

Intratumor heterogeneity, which favors the selection of drug-resistant tumor cells with cancer stem cell (CSC) properties, constitutes one of the greatest challenges in cancer treatment. Two prevailing models of chemo-resistance arise in tumor cells: the enrichment of pre-existing CSCs and stress-induced dedifferentiation of differentiated bulk cancer cells (DCCs) into CSC-like phenotypes. However, to what extent and how DCC dedifferentiation occurs in response to therapeutic stress remain largely elusive. Exosomes are extracellular vesicles of 50-140 nm in size containing proteins, RNA/DNA, lipids, and metabolites, which mediate juxtracrine/paracrine signaling to promote cancer cell plasticity and metastatic progression. We hypothesize that, exosome communications between CSCs and DCCs are augmented by chemotherapy-induced stress, promoting the dedifferentiation of DCCs into chemo-resistant CSCs. Specific Aims of this pilot grant include: 1) Using CSC epithelial (E) and mesenchymal (M) fluorescent reporters established in different breast cancer cell lines to assess the extent of dedifferentiation from DCCs when treated with or without chemotherapeutics, and determine if exosome secretion from CSCs is enhanced by chemotherapy to promote DCC dedifferentiation; 2) Using zebrafish embryo and mouse xenograft models, we will examine if CSC E/M reporter expression and tumorigenic/metastatic capacity of DCCs are induced when pre-treated with exosomes derived from various CSC states; 3) We will investigate if chemotherapy-induced exosome secretion from breast cancer patient CSCs facilitates the dedifferentiation of DCCs, and define the molecular mechanisms of exosome communications between CSCs and DCCs elicited by therapeutic stress. These studies will result in the development of innovative imaging technologies and animal models to trace tumor cell dedifferentiation at single-cell resolution and provide mechanistic insights to overcome chemo-resistance in advanced breast cancer with the potential to improve patient outcome.


Max Wicha, MD
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Ming Luo, PhD
UMMS


Wei Wei, MD
PKUHSC

New Projects for 2021

The Role of Endoplasmic Reticulum Associated Degradation (ERAD) in Antigen Presentation and Immune Evasion of Multiple Myeloma Cells

Despite the recent development of novel drugs and therapeutic strategies, multiple myeloma (MM) remains an incurable disease, and most patients relapse even after allogeneic hemato-poietic stem cell transplantations (allo-HSCT). Available data showed that immune check-point inhibitors are not as effective in MM as in Hodgkin Lymphoma, and immune evasion of myeloma cells against cellular immunity may be an important factor to explain this refractoriness. However, the mechanism of immune evasion in myeloma cells has not been elucidated. ER associated degradation (ERAD) complexes are important protein quality control systems to ensure the proper processing, folding and assembly of plasma membrane proteins including cell surface antigens and antigen presentation complexes. Our preliminary data showed that the key molecule in Hrd1 ERAD, Sel1L, was expressed in myeloma cell lines and primary MM samples. Furthermore, the cell surface level of peptide-HLA complex (pHLA) on human MM cell lines was significantly altered after Sel1L knockdown. Thus, we hypothesize that Sel1L/Hrd1ERAD may be involved in antigen processing and presentation in myeloma cells, and modulating ERAD might be a new strategy to overcome the immune evasion of MM. The proposed studies will allow us to develop productive collaborations to identify mechanisms of immune evasion in MM, and develop new strategies to enhance response of myeloma cells to immunotherapies.

Co-Investigators

Qing Li, PhD
UMMS

Yujun Dong, MD
PKUHSC

Malic Enzyme Dependence is a Therapeutic Vulnerability in Pancreatic and Gastric Cancers

Gastric cancer (GC) and pancreatic ductal adenocarcinoma (PDA) are a major cause of mortality in China and the United States. A primary reason for this is the lack of effective thera-peutic options. Thus, there is an urgent need to develop new drug targets. Metabolism is rewired in these cancers to support the demands of dysregulated cellular proliferation and tumor growth. Accordingly, tumor metabolism has emerged as a promising therapeutic inroad. Work from the Lyssiotis (University of Michigan) and Ding (Peking University) laboratories has independently demonstrated the potential of Malic Enzyme 1 (ME1) as a novel metabolic drug target in pancre-atic and gastric cancer, respectively. In this collaborative project, our groups will continue our productive international collaboration by further defining the role of ME1 in cancer (mechanism of action), determining the genetic context to target ME1 (precision medicine), and determin-ing the safety profile of ME1 inhibition. Notably, this proposal combines the expertise in cancer metabolism, preliminary data, and a wealth of novel ME1 reagents/tools from the Lyssiotis lab with the expertise in gastrointestinal disease and access to a unique patient cohort and biobank of GC specimens in the Ding lab. We are extremely excited for the opportunity to work together with the PUUMA program and look forward to developing a new metabolism targeted therapy for pancreatic and gastric cancer.

Costas Lyssiotis, PhD
UMMS

Shingang Ding, MD
PKUHSC

Nanobubble Water Combined with Apyrase as Root Canal Irrigant Inhibits Biofilm and Virulence of Enterococcus Faecalis

Estimates suggest that pulpal disease may affect up to 30% of the world's population. Up to 14% of endodontics therapy ends in infections within the root canal system and is difficult to treat. This project aims to establish a novel approach using nanobubble water combined with apyrase during endodontic therapy which focuses on preventing biofilm formation and reducing bacte-rial colonization which consequently minimizes the risk of infections post endodontics therapy. The objectives of this proposal will have a significant impact on public health by providing promising approach for endodontics therapy without changing existing endodontic procedure. We expect to decrease the post endodontics infections to less than 5% by using our novel approach.

Chuanwu Xi, PhD
U-M School of Public Health

Yanmei Dong, DDS, PhD
PKUHSC

New Projects for 2021

Metabolic and Epigenetic Regulation in Cell-based Heart Repair

Myocardial infarction (MI) is the leading cause of death worldwide with severe loss of cardiomyocytes (CMs). Existing treatments for MI do not directly address the fundamental problem of CM loss. Cell transplantation represents a promising therapeutic strategy to restore the damaged myocardial tissue, but is challenged by the low engraftment and integration of the transplanted cells to host heart. MI leads to deprivation of nutrient, oxygen and subsequent histone acetylation decrease in heart. Therefore, we hypothesize that simultaneous restoration of the energy metabolism and histone acetylation would be an effective strategy to protect either endogenous or transplanted cells. Indeed, our studies have identified that energy metabolite octanoate (8C) (UM) as well as nuclear factor erythroid 2-related factor 2 (NRF2) (PUHSC) preserves cardiac function after MI by mediating both histone acetylation and energy metabolism. Moreover, we have developed a novel biodegradable nanofibrous temperature responsive gelling microspheres (NF-GMS), which dramatically improves (10-fold) engraftment of transplanted cells in infarcted hearts (UM). In parallel, we have been able to robustly derive cardiac progenitor cells from human iPSCs (hiPSC-CPCs), which can differentiate further into almost all cardiac lineages (PUHSC).

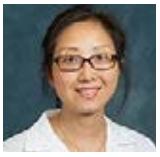
Co-Investigators

Zhong Wang, PhD
UMMS

Ming Cui, MD, PhD
PKUHSC

Decipher Immune Signatures and Therapeutic Response in Chinese and American Multiple Myeloma Patients

Multiple myeloma (MM) is the second most common hematologic malignancy. Recent years of rapid advancement in therapeutic landscape have resulted in deeper remission and longer survival in MM patients. However, many patients still relapse throughout different stages of disease course. This project seeks to investigate the role of comprehensive immune profiling in myeloma microenvironment by applying cutting edge technology CyTOF with a panel of extensive immune markers to identify the immune cell subsets, including cytotoxic and suppressive immune cells. This project is aimed to associate immune signatures with clinical outcomes including deep clinical response such as minimal residual disease (MRD) remission in MM patients at different time points of treatment course and establish a potential immune signature model, including difference between Chinese and American patients. The immune cells distribution and their spatial relationship with myeloma cells in MM bone marrow tumor microenvironment will also be explored using Imaging Mass Cytometry. It is predicted that distinctive immune patterns in bone marrow tumor microenvironment as well as in peripheral blood may help to decipher the biological mechanisms of immune reconstitution in MM patients who responded well to treatments and achieved more favorable clinical outcome including MRD remission.



Christine Ye, MD
UMMS

Xiao-Jun Huang, MD
PKUHSC

New Projects for 2021

Optimization of Limb Salvage Strategy for Critical Limb Ischemia Using Quantitative Vascular Imaging Biomarkers

The goal is to develop and validate an ultrasound-based, non-invasive, portable, quantitative device that measures two critical physiological parameters in patients with critical limb ischemia (CLI): 1) volume of blood delivered to the diseased extremity through its feeding arteries; 2) adequacy of limb oxygen delivery through the difference in the oxygen content of primary feeding artery and its paired vein. Limb perfusion is of paramount importance in the patient with CLI. However, current recommended tests, such as segmental limb pressures and transcutaneous oxygen tension, are imperfect surrogates. This proposal will be the first to use a combined volume blood flow and oxygen extraction estimation system to quantitatively evaluate limb tissue metabolism in patients with CLI. The preliminary data can be used to pursue funding for large-scale trials of this methodology to assess disease level and objectively assist orthopedic and vascular surgeons in optimizing their limb salvage strategies, leading to a profound clinical impact on CLI-related vascular interventions, morbidity and mortality. In the future, this device may become a cost-effective screening tool for peripheral vascular disease and provide accurate vascular assessment prior to, during and after endovascular or surgical procedures.

Co-Investigators


J. Brian Fowlkes, PhD
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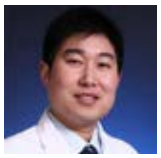
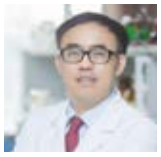

Xiaofeng Yin, MD, PhD
PKUHSC

Clinical Validation of a Patient-specific Pharmacogenomics Assay for Enhanced Treatment Response in Bipolar Disorder-1 (BPD-1) Patients

This discovery proposal is to refine and prepare a detailed plan for a pilot clinical validation study at PKUHSC of a new pharmacogenomic/metabolomic diagnostic assay system for Bipolar Disorder-1 (BPD-1) medication selection. This project is a collaborative effort between a U-M pharmacogenomics innovator (Athey lab) and one of China's leading psychiatric research units (Lu lab). Specific plans include investigating 1) How the UM-provided PhGx test will be further refined using the Michigan Genomics Initiative (MGI) data and biospecimens for delivery to PKUHSC; 2) How a detailed SMART clinical trial will be designed by the PUHSC expert team in collaboration with the U-M team; and 3) How the U-M PhGx testing platform will be extended to analyze the relevant Han Chinese Pharmacokinetic (PK) and Pharmacodynamic (PD) genetic biomarkers and plan to test out two components of U-M PhGx test in China.


Brian Athey, PhD
UMMS


Lin Lu, MD, PhD
PKUHSC

Assessing Genomic and Environmental Drivers of Depression in Training Physicians across China and the US

Drs. Lu and Sun have produced a parallel sample of training physicians in China, identifying parallel problems of stress and depression among young physicians there. Here, we propose to recruit a sample of up to 1,000 last year medical students before they enter their first year of residency (as there is no internship year in China), hence at the same time point as US interns. Prior and continuing work in the US of Dr. Sen will continue and be relevant for comparison. Existing work of Drs. Lu and Sen on medical students will be highly relevant, as many of these medical students will now enter residency and are already in contact with the study. The overall objective of our research is to define contributing factors to stress-associated depression. These factors can be personal experience (childhood adversity, previous depression episodes, personal maturation during natural aging), temperamental (neuroticism score, sleep patterns and needs), genetic factors as well as situational environmental (policies governing internship structure, political events). Genetic factors in turn may affect experience and temperament. Comparing the first year of residency in China with the internship year in the US, our objective is to find both individual and internship similarities and differences. Our research will help better understand the interplay of genetic differences with environmental factors governing medical residency. This better understanding can lead to structural changes to ultimately improve the residency experience.


Srijan Sen, MD, PhD
UMMS


Hongqing Sun, MD, PhD
PKUHSC

Bridging Conference Series

JI leaders launch online seminar series to bolster relationships amidst travel restrictions

Vaccine Strategy
January 2021

As the coronavirus pandemic curtailed international travel and opportunities to meet in-person, JI leaders designed programs around virtual meetings and seminars to connect investigators and advance the collaboration.

Topical "Bridging Conference" sessions throughout 2021-22 brought together experts on a variety of subjects and disciplines.

"Right now, it is more important than ever for us to find ways to continue to engage," said Joseph Kolars, JI Director and UMMS Senior Associate Dean. "We wanted to create a venue that is just for us to share best practices because I think we have a lot to learn from each other."

Early sessions focused on aspects of COVID-19, including treatment and vaccination strategies. Later sessions expanded to include cardiovascular medicine, cancer immunology, artificial intelligence, and more. As many as 100 participants logged on to hear experts from each institution share the latest research, insights, and ideas for collaborative projects. Sessions were led by some of the top researchers in their respective fields, including Frankel Cardiovascular Center Director David Pinsky, MD; Peking University Third Hospital Professor and Chair of Cardiology Yida Tang, MD, PhD; UMMS Madeline and Sidney Forbes Professor of Oncology Max Wicha, MD; and Qimin Zhan, MD, Professor and Director of the Peking University International Cancer Institute.

"In our partnership, we have an opportunity to do things together that are really synergistic and would not only advance health, but also show how we can do things together in ways that benefit our two nations," Kolars said. "The world is looking for examples of ways we can co-create together. We have a chance to shine a light on how we can work together in a positive way for the world to see."

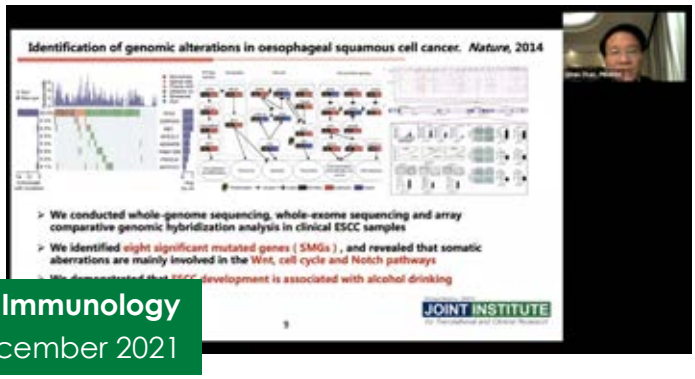
> The world is looking for examples of ways we can co-create together. We have a chance to shine a light on how we can work together in a positive way for the world to see.
>
> *- UMMS Sr. Associate Dean Joseph Kolars*

Michigan Medicine - Peking University Health Science Center

JOINT INSTITUTE

A collaborative bridge to better health

Data Science
April 2021



Cancer Immunology
December 2021

Cardiovascular Medicine
April 2022

Funding renewal reaffirms partnership

A UMMS collaboration with Peking University Health Science Center will continue following a partnership renewal and re-investment.

Signed in June 2022, the new agreement will mean a five-year extension for the Michigan Medicine - Peking University Health Science Center Joint Institute (JI). The extension—the second since the JI was launched—reaffirms U-M Medical School's longest-running partnership in China.

"The Joint Institute is a wonderful example of international research collaboration and a reminder that we can often accomplish so much more when we work together than when we work alone," said UMMS Dean Marschall Runge, MD, PhD.

Since 2010, the JI has funded nearly 70 projects, resulting in 130-plus high-impact publications and some $55 million in extramural funding.

New JI research, including many of the 10 projects awarded in 2021, will target one of four areas of mutual interest that cater to both institutions' strengths: cancer research, reproductive health, precision medicine, and neuroscience.

"I'm particularly grateful to be renewing our agreement with my colleagues at PKUHSC. It's never been more important for us to be cultivating our relationships with colleagues in China," Global REACH Director Joseph Kolars, MD, MACP. "We look forward to deepening our collaborations in the years ahead."

> The JI is a wonderful example of international research collaboration and a reminder that we can accomplish more together than alone.
>
> *- UMMS Dean Marschall Runge*

Collaboration

UMMS insights helped team behind '22 Olympics medevac program in China

Chongli Hospital Associate Dean Yuping Yang (right) toured Survival Flight operations during a three-week visit to Michigan Medicine in 2019. After returning to China, he became part of a team charged with establishing Beijing's first-ever air ambulance ahead of the 2022 Winter Games.

Much of medical support for the Olympics, including standing up Beijing's first-ever air ambulance service, was tasked to Peking University Third Hospital, an affiliate of longtime U-M institutional partner Peking University Health Science Center. When he was assigned to the medevac leadership team, Sports Medicine Physician Yuping Yang recalled his visit to Ann Arbor in 2019, which included a behind-the-scenes look at Survival Flight operations.

Yang, Associate Dean of the new Chongli Hospital, an affiliate of the Third Hospital built near Olympic snowboarding and ski jumping venues, reached out to his Michigan Medicine friends for help. On a videoconference call in March 2021, Survival Flight physicians and administrative leaders offered advice and insights to Yang's team.

"Chongli Hospital was built with a helicopter pad on the roof just for the transfer of patients," Yang, MD, PhD, told his colleagues in the meeting. "We don't have enough experience with that. That's why we asked for this meeting. You have expertise in this area."

> Establishing a new program on such an aggressive timeline is an impressive achievement. We were happy to share our insights and experience.
>
> *- Mark Lowell, MD*
> *Survival FLight Medical Director*

During their one-hour conversation, he and his team were able to ask about training scenarios; communications logistics between the ground, helicopter and hospital teams; patient transport protocols to and from the aircraft, and more.

"We have to be pioneers in helicopter emergency transport. Here, it is an experimental step," Yang said at the call's conclusion. "We thank you for your hospitality and for spending time with us. Thank you so much."

The International Olympic Committee requires helicopter medevac service to transport injured athletes if needed. The new service was put to the test Feb. 7, 2022 when US alpine skier Nina O'Brien required transport from the competition site after a fall on the giant slalom course.

"Establishing a new program on such an aggressive timeline is an impressive achievement. We were happy to share our insights and experience," said Associate Professor of Emergency Medicine and Survival Flight Medical Director Mark Lowell, MD, who participated in last year's call. "Air transport services is a critical aspect of comprehensive emergency care, so any time we have the chance to help others get a new service off the ground, we welcome the opportunity."

Features

New JI program will engage faculty for meaningful exchange, training

The first Joint Institute Collaboration Scholars are expected to arrive at Michigan Medicine in the summer of 2023.

This year saw the introduction of the Joint Institute's Collaboration Scholars Program, an exchange initiative which aims to engage early-career researchers from either institution in extended training experiences in Ann Arbor or Beijing.

Announced in 2022, the program will bring selected scholars into each respective partner institution to work alongside JI faculty mentors on research as well as collaborative initiatives that advance and deepen the partnership between Michigan Medicine and PKUHSC.

The program will support two scholars per year for a minimum 12-month experience with an option to remain for an additional year. The initial cohort from PKUHSC are expected to arrive in Ann Arbor in the summer of 2023. Schalars are to be provided with a stipend and benefits along with some funds for travel and research expenses.

In addition, scholars will receive formal instruction on promoting collaboration as well as career development skills (e.g., administrative, management, communication, grantsmanship skills, etc.).

"We see this as an important step to help ensure the longevity of the Joint Institute," said Amy Huang, MD, MHSA, UMMS Adjunct Clinical Assistant Professor of Cardiovascular Medicine and Administrative Director of the JI. "By engaging scholars early in their career and immersing them in the work of the JI, it is our hope to foster future leaders who can continue to transform and drive collaborations between Michigan Medicine and PKUHSC."

> We see this as an important step to help ensure the longevity of the Joint Institute.
>
> *- Amy Huang, MD, MHSA*
> *UMMS JI Administrative Director*

JOINT INSTITUTE Collaboration Scholars

Research

Another JI project leads to NIH award

The lab team behind the project, including Dr. Yongqing Li (center left), flanked by two long-term visiting scholars from PKUHSC, Panpan Chang and Jing Zhou.

A Joint Institute project to diagnose and combat sepsis, the leading cause of death and readmissions in U.S. hospitals, has garnered funding from the National Institutes of Health (NIH).

Assistant Professor of Surgery Yongqing Li, PhD, is the lead investigator on a recently received NIH R01 award to a study that expands on work begun through a pair of JI grants, the first to study the role of citrullinated histone H3 (CitH3) in sepsis, and more recent project to create a humanized CitH3 antibody and its application in diagnosis of and treatment for sepsis-induced lung injury.

"In many ways, this is a continuation of the JI grant and would not be possible without the support of the JI," said Li of the four-year NIH project. Li is among more than a dozen U-M faculty to receive NIH funding related to JI research with PKUHSC. To date, research seeded by the JI has garnered some $35 million in NIH awards.

Announced in August, Li's project, "PAD2 and CitH3 are involved in pathogenesis of sepsis in humans and animals", has two specific aims: first, dissect the physiological action of PAD2/CitH3 in modulating macrophage functions during sepsis; and second, perform proof-of-concept studies targeting PAD2 and CitH3 as novel therapeutic targets. The latter will use mouse models Li developed as part of his work through the JI.

Li first met his primary PKUHSC collaborator, Dr. Wang, during a personal visit to Beijing in 2013. The two discovered they had a lot in common. Both attended the same medical school in China, Xian Medical University, though at different times, and both shared a common research interest in trauma and sepsis. At the time, Li wasn't aware of Michigan Medicine's then relatively new partnership with PKUHSC.

"I didn't know the JI. It was introduced to me during a meeting and that amazed me, because I had just recently met Dr. Wang at PKU. We started working on a joint proposal right away," Li said. "Without the JI support, we could not come to this stage. Like a snowball, once you begin pushing something downhill, it grows larger and larger."

> Without the JI support, we could not come to this stage. Like a snowball, once you begin pushing something downhill, it grows larger and larger.
>
> *-Yongqing Li, PhD*
> *UMMS Assistant Professor of Surgery*

JI paper explores research ethics in the US and China, implications for collaborations

A JI publication examines research ethics – the similarities and differences in perceptions – among faculty at the two partner institutions, Michigan Medicine and Peking University Health Science Center (PKUHSC).

While the researchers found broad consistencies, comparisons revealed distinct differences on key issues, variations attributable to cultural norms in the workplace and across society more broadly.

"With research partnerships developing between Chinese academic institutions and Western universities and biomedical companies, the comparability of human subject protection standards and bilateral recognition of the importance of research integrity have taken on new importance," the authors write. "Institutions considering collaboration may find assessment of the respective institutional research cultures to be of value in planning their work."

Appearing in *Accountability in Research*, the article was co-written by a number of JI-affiliated faculty including Michigan Medicine Associate Dean for Regulatory Affairs Raymond Hutchinson and PKUHSC Professor and Dean of Medical Ethics Yali Cong, who co-lead the JI's IRB and Human Protection Core. About 100 faculty at each institution answered an anonymous survey, conducted in 2013-14.

Despite these differences, "the survey responses indicate that some aspects of research culture are similar at the collaborating institutions; specifically, perceptions regarding the ethical underpinnings of clinical trials are similar," the authors write. "These may be more aligned than might have been predicted based on recent publications addressing research culture in China."

Given China's increasing footprint in scientific research and development (the country's national expenditures on scientific research are second only to the U.S.) and the rising number of international collaborations between the two countries, exploring and identifying the different perceptions toward research ethics is important. Such knowledge can help set proper expectations, prompt important dialogue and ultimately improve collaboration.

UMMS Director of Regulatory Affairs Patricia Ward leads a session on research ethics for visitors from the Shenzhen Medical Association.

Key study findings

1. *Physicians from both institutions well understood the need to obtain consent from research participants and the voluntary nature of research participation.*

2. *Chinese physicians are more likely to consider input from a patient's family when determining whether to continue participation in a trial in the face of treatment-related discomfort and suffering. This finding aligns with China's culture of including – and at times prioritizing – family members' wishes in medical decision making.*

3. *US physicians indicated a greater willingness to report plagiarism and data falsification, particularly in instances where the suspected offender is a mentor or authority figure, a difference that is likely attributable to an emphasis in Chinese culture on maintaining harmonious relationships.*

4. *The Chinese physicians indicated a greater willingness to attend a hypothetical industry-sponsored drug promotional event in a resort setting. Through conflict of interest education campaigns at the industry and institutional levels, participation in such trips has been widely discouraged in the United States in recent years.*

2020-21 Research Publications

JI collaborations resulted in nearly 30 publications in 2020 and 2021, scholarship that appeared across a variety of disciplines in high-ranking journals such as *Blood, Accountability in Research, JCI Insight,* and more.

Ontological Modeling and Analysis of Experimentally or Clinically Verified Drugs Against Coronavirus Infection

PI: Oliver He (UMMS)

Program: Exploratory-COVID

Liu, Y., Hur, J., Chan, W. K. B., Wang, Z., Xie, J., Sun, D., Handelman, S., Sexton, J., Yu, H., & He, Y. (2021). Ontological modeling and analysis of experimentally or clinically verified drugs against coronavirus infection. *Scientific Data, 8*(1), 16.

Advancing Science and Education Through a Novel Collaboration Platform Between the University of Michigan and Peking University Health Science Center

PIs: Joseph Kolars (UMMS) & Qimin Zhan (PKUHSC)

Kolars, J. C., & Zhan, Q. (2021). Advancing science and education through a novel collaboration platform between the University of Michigan and Peking University Health Science Center. *FASEB BioAdvances, 3*(6), 428–438.

Rapid Single-Molecule Digital Detection of Protein Biomarkers for Continuous Monitoring of Systemic Immune Disorders

PIs: Yongqing Li (UMMS)

Program: Pulmonary

Project: Citrullinated Histone H3: A Mediator and Biomarker of Sepsis-induced Acute Lung Injury

Song, Y., Sandford, E., Tian, Y., Yin, Q., Kozminski, A. G., Su, S.-H., Cai, T., Ye, Y., Chung, M. T., Lindstrom, R., Goicochea, A., Barabas, J., Olesnavich, M., Rozwadowski, M., Li, Y., Alam, H. B., Singer, B. H., Ghosh, M., Choi, S. W., … & Kurabayashi, K. (2021). Rapid single-molecule digital detection of protein biomarkers for continuous monitoring of systemic immune disorders. *Blood, 137*(12), 1591–1602.

Ethical Perspectives of Chinese and United States Physicians at Initiation of a Research Collaborative

PIs: Raymond Hutchinson (UMMS) & Yali Cong (PKUHSC)

Program: IRB and Human Protection Core

Grondin, C., Cong, Y., Keshavarzi, N., Geisser, M. E., Kolars, J. C., & Hutchinson, R. J. (2021). Ethical perspectives of Chinese and United States physicians at initiation of a research collaborative. *Accountability in Research, 29*(5), 294–308.

Disclosure of Clinically Actionable Genetic Variants to Thoracic Aortic Dissection Biobank Participants

PIs: Cristen Willer (UMMS)

Program: Cardiovascular

Project: Multi-ethnic Study of Genetic Risk Factors to Discover Mechanisms of Aortic Aneurysm and Dissection

Beil, A., Hornsby, W., Uhlmann, W. R., Aatre, R., Arscott, P., Wolford, B., Eagle, K. A., Yang, B., McNamara, J., Willer, C., & Roberts, J. S. (2021). Disclosure of clinically actionable genetic variants to thoracic aortic dissection Biobank participants. *BMC Medical Genomics, 14*(1).

2019-20 Research Publications

PINA 3.0: Mining Cancer Interactome

PI: Jianmin Wu (PKUHSC)

Program: GI & Liver

Project: Systemic Investigation of the Microbiome-host Interactions in H. pylori-associated Gastric Cancer Patients

Du, Y., Cai, M., Xing, X., Ji, J., Yang, E., & Wu, J. (2020). Pina 3.0: Mining cancer interactome. *Nucleic Acids Research, 49*(D1).

Reverse Microbiomics: A New Reverse Dysbiosis Analysis Strategy and its Usage in Prediction of Autoantigens and Virulent Factors in Dysbiotic Gut Microbiomes from Rheumatoid Arthritis Patients

PI: Oliver He (UMMS)

Program: GI & Liver

Wang, H., Ong, E., Kao, J. Y., Sun, D., He, Y. (2021). Reverse microbiomics: A new reverse dysbiosis analysis strategy and its usage in prediction of autoantigens and virulent factors in dysbiotic gut microbiomes from rheumatoid arthritis patients. *Frontiers in Microbiology, 12*.

Exome Chip Analyses and Genetic Risk for IgA Nephropathy among Han Chinese

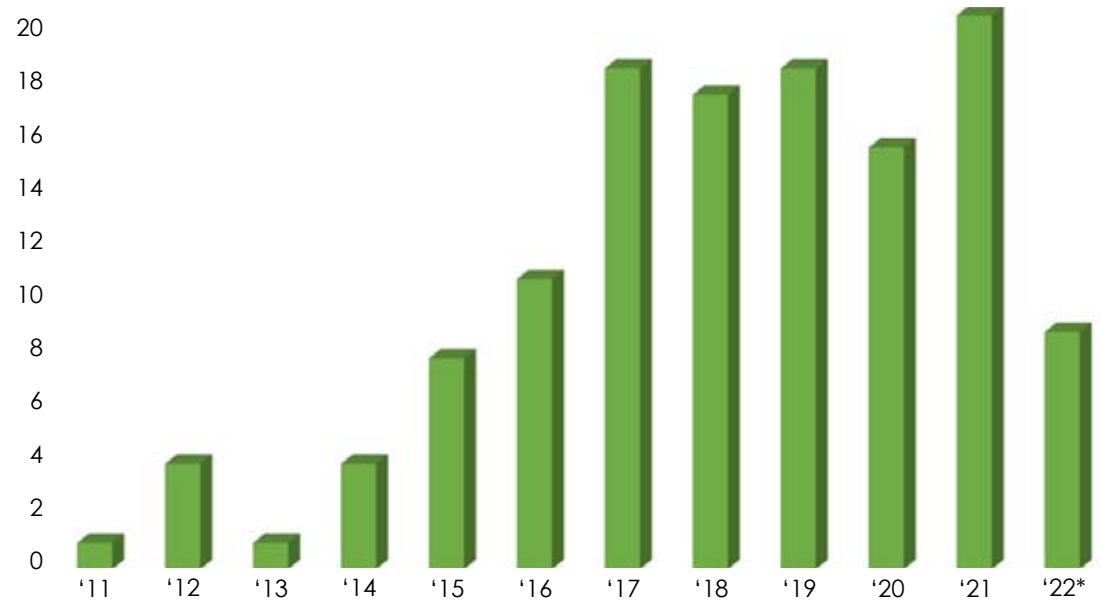
PIs: Celine Berthier (UMMS) & Hong Zhang (PKUHSC)

Program: Renal

Project: Shared and Disease-specific Genetic Study among IgA Nephropathy, Henoch-schonlein Purpura Nephritis and Lupus Nephritis

Zhou, X. J., Tsoi, L. C., Hu, Y., Patrick, M. T., He, K., Berthier, C. C. ... & Zhang, H. (2021). Exome Chip Analyses and Genetic Risk for IgA Nephropathy among Han Chinese. *Clinical Journal of the American Society of Nephrology : CJASN, 16*(2), 213–224.

JI Publications, 2011-2022



**2022 figure reflects only part of the year*

2021-22 Research Publications

Potential Roles of Oral Microbiota in the Pathogenesis of Immunoglobin A Nephropathy

PIs: Hong Zhang (PKUHSC)

Program: Renal

Project: Shared and Disease-specific Genetic Study among IgA Nephropathy, Henoch-schonlein Purpura Nephritis and Lupus Nephritis

He, J. W., Zhou, X. J., Hou, P., Wang, Y. N., Gan, T., Li, Y., Liu, Y., Liu, L. J., Shi, S. F., Zhu, L., Lv, J. C., & Zhang, H. (2021). Potential Roles of Oral Microbiota in the Pathogenesis of Immunoglobin A Nephropathy. *Frontiers in Cellular and Infection Microbiology, 11*, 652837.

Associations of Genetic Variants Contributing to Gut Microbiota Composition in Immunoglobin A Nephropathy

PI: Hong Zhang (PKUHSC)

Program: Renal

Project: Shared and Disease-specific Genetic Study among IgA Nephropathy, Henoch-schonlein Purpura Nephritis and Lupus Nephritis

He, J. W., Zhou, X. J., Li, Y. F., Wang, Y. N., Liu, L. J., Shi, S. F., Xin, X. H., Li, R. S., Falchi, M., Lv, J. C., & Zhang, H. (2021). Associations of Genetic Variants Contributing to Gut Microbiota Composition in Immunoglobin A Nephropathy. *mSystems,* 6(1), e00819-20.

The Prevalence of Diabetic Microvascular Complications in China and the USA

PIs: Rodica Busui (UMMS) & Luxia Zhang (PKUHSC)

Program: Renal

Project: Understanding the Heterogeneity in the Risk for Diabetes Complications in China and U.S.

Lin, Y. K., Gao, B., Liu, L., Ang, L., Mizokami-Stout, K., Pop-Busui, R., & Zhang, L. (2021). The Prevalence of Diabetic Microvascular Complications in China and the USA. *Current Diabetes Reports, 21*(6), 16.

Annexin A1 Alleviates Kidney Injury by Promoting the Resolution of Inflammation in Diabetic Nephropathy

PIs: Wenjun Ju (UMMS); Matthias Kretzler (UMMS); Min Chen (PKUHSC); & Luxia Zhang (PKUHSC)

Program: Renal

Project: Towards Molecular Prognosis of Chronic Kidney Disease (CKD) in UMMS and PUHSC

Wu, L., Liu, C., Chang, D. Y., Zhan, R., Sun, J., Cui, S. H., Eddy, S., Nair, V., Tanner, E., Brosius, F. C., Looker, H. C., Nelson, R. G., Kretzler, M., ... & Zheng, L. (2021). Annexin A1 alleviates kidney injury by promoting the resolution of inflammation in diabetic nephropathy. *Kidney International, 100*(1), 107–121.

Improved Diagnostic Prediction of the Pathogenicity Bloodstream Isolates of Staphylococcus Epidermidis

PIs: J. Scott Van Epps (UMMS)

Program: Exploratory-Emergency Medicine

Project: Rapid Bacterial Identification and Antibiotic Susceptibility Testing in Patients with Sepsis by Chiroplasmonic Nanorod PCR (NR-PCR)

VanAken, S. M., Newton, D., & VanEpps, J. S. (2021). Improved diagnostic prediction of the pathogenicity of bloodstream isolates of Staphylococcus epidermidis. *PloS One, 16*(3), e0241457.

2021-22 Research Publications

Peptidylarginine Deiminase 2 in Host Immunity: Current Insights and Perspectives

PI: Yongqing Li (UMMS)

Program: Pulmonary

Wu, Z., Li, P., Tian, Y., Ouyang, W., Ho, J. W., Alam, H. B., & Li, Y. (2021). Peptidylarginine Deiminase 2 in Host Immunity: Current Insights and Perspectives. *Frontiers in immunology, 12*, 761946.

The Role of HDAC6 in Autophagy and NLRP3 Inflammasome

PIs: Yongqing Li (UMMS) & Tianbing Wang (PKUHSC)

Program: Pulmonary

Project: Citrullinated Histone H3: A Mediator and Biomarker of Sepsis-induced Acute Lung Injury

Chang, P., Li, H., Hu, H., Li, Y., & Wang, T. (2021). The Role of HDAC6 in Autophagy and NLRP3 Inflammasome. *Frontiers in Immunology, 12*, 763831.

Rapid Identification of Pathogens Associated with Ventilator-Associated Pneumonia by Nanopore Sequencing

PIs: Robert Dickson (UMMS) & Ning Shen (PKUHSC)

Program: Pulmonary

Project: Rapid Identification of Pathogens in Ventilator-associated Pneumonia Using Real-time Metagenomics and Real-time PCR

Wu, N., Ranjan, P., Tao, C., Liu, C., Yang, E., He, B., ... & Dickson, R. P., … Shen, N. (2021). Rapid identification of pathogens associated with ventilator-associated pneumonia by Nanopore sequencing. *Respiratory Research, 22*(1), 310.

CD6 is a Target for Cancer Immunotherapy

PI: Venkat Keshamouni (UMMS)

Program: Pulmonary

Ruth, J. H., Gurrea-Rubio, M., Athukorala, K. S., Rasmussen, S. M., Weber, D. P., Randon, P. M., Gedert, R. J., Lind, M. E., Amin, M. A., Campbell, P. L., Tsou, P. S., Mao-Draayer, Y., Wu, Q., Lanigan, T. M., Keshamouni, V. G., Singer, N. G., Lin, F., & Fox, D. A. (2021). CD6 is a target for cancer immunotherapy. *JCI Insight, 6*(5), e145662.

Development of Potent Dimeric Inhibitors of GAS41 YEATS Domain

PI: Venkat Keshamouni (UMMS)

Program: Pulmonary

Listunov, D., Linhares, B. M., Kim, E., Winkler, A., Simes, M. L., Weaver, S., Cho, H. J., Rizo, A., Zolov, S., Keshamouni, V. G., Grembecka, J., & Cierpicki, T. (2021). Development of potent dimeric inhibitors of GAS41 YEATS domain. *Cell Chemical Biology, 28*(12), 1716–1727.e6.

On-Chip Biogenesis of Circulating NK Cell-Derived Exosomes in Non-Small Cell Lung Cancer Exhibits Antitumoral Activity

PI: Venkat Keshamouni (UMMS)

Program: Pulmonary

Kang, Y. T., Niu, Z., Hadlock, T., Purcell, E., Lo, T. W., Zeinali, M., Owen, S., Keshamouni, V. G., Reddy, R., Ramnath, N., & Nagrath, S. (2021). On-Chip Biogenesis of Circulating NK Cell-Derived Exosomes in Non-Small Cell Lung Cancer Exhibits Antitumoral Activity. *Advanced Science* (Weinheim, Baden-Wurttemberg, Germany), 8(6), 2003747.

2021-22 Research Publications

Development of the International Classification of Diseases Ontology (ICDO) and its Application for COVID-19 Diagnostic Data Analysis

PIs: Oliver He (UMMS) & Luxia Zhang (PKUHSC)

Program: Exploratory-COVID

Project: Ontology-based Integrative Modeling and Analysis of AKI-related COVID-19 Data and Underlying Host-Coronavirus Interaction Mechanism

Wan, L., Song, J., He, V., Roman, J., Whah, G., Peng, S., Zhang, L., & He, Y. (2021). Development of the International Classification of Diseases Ontology (ICDO) and its application for COVID-19 diagnostic data analysis. *BMC Bioinformatics, 22*(Suppl 6), 508.

Citrullinated Histone H3 Mediates Sepsis-Induced Lung Injury Through Activating Caspase-1 Dependent Inflammasome Pathway

PI: Yongqing Li (UMMS)

Program: Pulmonary

Project: Citrullinated Histone H3: A Mediator & Biomarker of Sepsis-induced Acute Lung Injury

Tian, Y., Li, P., Wu, Z., Deng, Q., Pan, B., Stringer, K. A., Alam, H. B., Standiford, T. J., & Li, Y. (2021). Citrullinated Histone H3 Mediates Sepsis-Induced Lung Injury Through Activating Caspase-1 Dependent Inflammasome Pathway. *Frontiers in Immunology, 12*, 761345.

Editorial: Targeting Protein Post-Translational Modifications (PTMs) for Diagnosis and Treatment of Sepsis

PIs: Yongqing Li (UMMS) & Panpan Chang (PKUHSC)

Program: Pulmonary

Chang, P., & Li, Y. (2022). Editorial: Targeting Protein Post-Translational Modifications (PTMs) for Diagnosis and Treatment of Sepsis. *Frontiers in Immunology, 13*, 856146.

Soluble LILRA3 is Aberrantly Expressed in Antiphospholipid Syndrome (APS) and is a Potential Marker of Thrombotic APS

PIs: Jason Knight (UMMS) & Jianping Guo (PKUHSC)

Program: Exploratory

Project: LILRA3 as a novel regulator of thrombioinflammation in antiphospholipid syndrome (APS)

Liu, H., Li, C., Shi, H., Guo, Y., Tang, Y., Chen, C., Zhao, Z., Hoy, C. K., Yalavarthi, S., Figueroa-Parra, G., ... & Guo, J. (2022). Soluble LILRA3 is aberrantly expressed in antiphospholipid syndrome (APS) and is a potential marker of thrombotic APS. *Rheumatology* (Oxford, England), 61(12), 4962–4974.

Impact of Histotripsy on Development of Intrahepatic Metastases in a Rodent Liver Tumor Model

PI: Clifford Cho (UMMS)

Program: GI & Liver

Worlikar, T., Zhang, M., Ganguly, A., Hall, T. L., Shi, J., Zhao, L., Lee, F. T., Mendiratta-Lala, M., Cho, C. S., & Xu, Z. (2022). Impact of Histotripsy on Development of Intrahepatic Metastases in a Rodent Liver Tumor Model. *Cancers, 14*(7), 1612.

Prediction of Pathogenic Factors in Dysbiotic Gut Microbiomes of Colorectal Cancer Patients Using Reverse Microbiomics

PI: Oliver He (UMMS)

Program: GI & Liver

Wang, H., Zhang, K., Wu, L., Qin, Q., & He, Y. (2022). Prediction of Pathogenic Factors in Dysbiotic Gut Microbiomes of Colorectal Cancer Patients Using Reverse Microbiomics. *Frontiers in Oncology, 12*, 882874.

2021-22 Research Publications

In-Depth Comparison of Matrigel Dissolving Methods on Proteomic Profiling of Organoids

PI: Jianmin Wu (PKUHSC)

Program: GI & Liver

Project: Systemic Investigation of the Microbiome-host Interactions in H. pylori-associated Gastric Cancer Patients

Wang, M., Yu, H., Zhang, T., Cao, L., Du, Y., Xie, Y., Ji, J., & Wu, J. (2022). In-Depth Comparison of Matrigel Dissolving Methods on Proteomic Profiling of Organoids. *Molecular & Cellular Proteomics: MCP, 21*(1), 100181.

Multi-Scalar Data Integration Links Glomerular Angiopoietin-Tie Signaling Pathway Activation With Progression of Diabetic Kidney Disease

PIs: Wenjun Ju (UMMS) & Min Chen (PKUHSC)

Program: Renal

Project: Identification of Shared and Specific Marker Panels for Diabetic Kidney Disease Progression

Liu, J., Nair, V., Zhao, Y. Y., Chang, D. Y., Limonte, C., Bansal, N., Fermin, D., Eichinger, F., Tanner, E. C., Bellovich, K. A., ... Pennathur, S., Kidney Precision Medicine Project and Michigan Translational Core C-PROBE Investigator Group (2022). Multi-Scalar Data Integration Links Glomerular Angiopoietin-Tie Signaling Pathway Activation With Progression of Diabetic Kidney Disease. *Diabetes, 71*(12), 2664–2676.

Molecular Characterization of Clear Cell Renal Cell Carcinoma Reveals Prognostic Significance of Epithelial-mesenchymal Transition Gene Expression Signature

PI: Ganesh Palapattu (UMMS)

Program: Renal

Project: Comprehensive Molecular Profiling of Renal Cell Carcinoma

Nallandhighal, S., Vince, R., Karim, R., Groves, S., Stangl-Kremser, J., Russell, C., Hu, K., Pham, T., ... & Salami, S. S. (2022). Molecular Characterization of Clear Cell Renal Cell Carcinoma Reveals Prognostic Significance of Epithelial-mesenchymal Transition Gene Expression Signature. *European Urology Oncology, 5*(1), 92–99.

Clinical Outcomes in a Cohort of Patients with Cutaneous T-cell Lymphoma and COVID-19

PI: Trilokraj Tejasvi (UMMS)

Program: Exploratory-COVID

Project: Integrative and Trans-Ethnic Cutaneous T-cell Lymphoma (CTCL) Study to Reveal Clinical and Molecular Determinants for Disease Prognosis

Runge, J. S., Bardhi, R., Xia, Y., Jairath, N. K., Wilcox, R. A., Tsoi, L. C., & Tejasvi, T. (2022). Clinical outcomes in a cohort of patients with cutaneous T-cell lymphoma and COVID-19. *JAAD International, 8*, 52–55.

PEG10 Amplification at 7q21.3 Potentiates Large-cell Transformation in Cutaneous T-cell Lymphoma

PIs: Trilokraj Tejasvi (UMMS); Alex Tsoi (UMMS); & Yang Wang (PKUHSC)

Program: Cancer

Project: Integrative and Trans-Ethnic Cutaneous T-cell Lymphoma (CTCL) Study to Reveal Clinical and Molecular Determinants for Disease Prognosis

Liu, F., Gao, Y., Xu, B., Xiong, S., Yi, S., Sun, J., Chen, Z., Liu, X., Li, Y., Lin, Y., Wen, Y., Qin, Y., Yang, S., Li, H., Tejasvi, T., Tsoi, L., Tu, P., Ren, X., & Wang, Y. (2022). PEG10 amplification at 7q21.3 potentiates large-cell transformation in cutaneous T-cell lymphoma. *Blood, 139*(4), 554–571.

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