

Michigan Medicine - PKUHSC

北京大学医学部 · 密西根大学医学院

临床与转化医学联合研究所

JOINT INSTITUTE

for Translational and Clinical Research



Progress
Report
2019-20

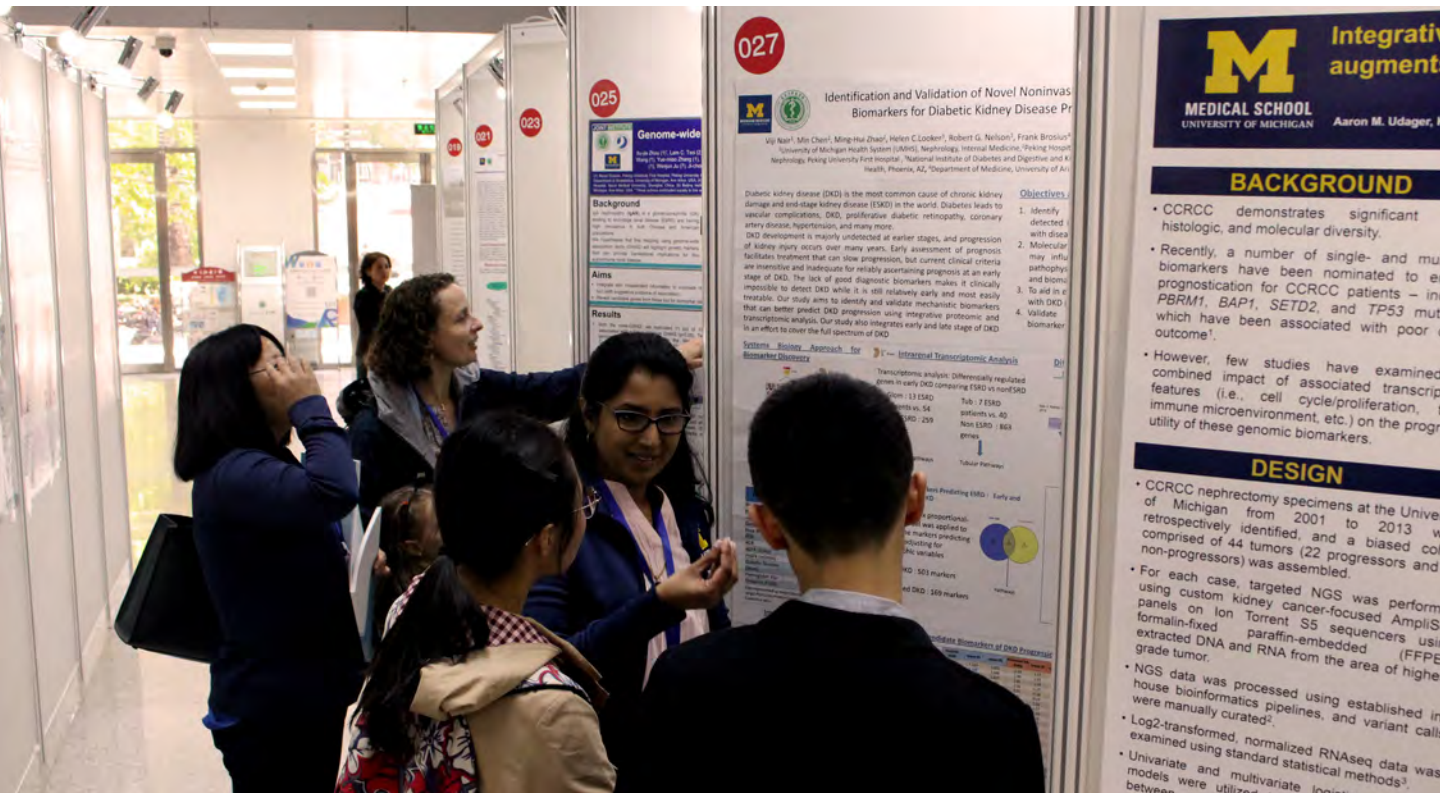
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Letter from the Co-Directors

Colleagues,

We are pleased to present the latest progress update for the Joint Institute. This report comes at a most unusual time – not just in our partnership, but more broadly global health – as the world continues to struggle with COVID-19. The timeframe covered in this document has been extended from one to two years so as to include the JI response to the pandemic.

Prior to the onset of COVID-19, our collaboration was thriving. We were coming off from yet another successful symposium at the Peking University Health Science Center campus in Beijing. An impressive crop of new projects marked the growth of our collaboration into new areas, including precision medicine and cancer research, as we prepared to mark the 10-year anniversary of our partnership.

In short, we were flourishing when a never-before-seen respiratory illness changed everything. At each of our institutions, the pandemic demanded an all-hands-on-deck approach to save lives, protect our healthcare workers, and accelerate discovery as we struggled to learn all we could about the virus that would soon be known as SARS-CoV-2.

Still, even amidst the initial response, our two institutions remained in contact. We exchanged critical clinical best practices and insights in the pandemic's early stages, followed by research ideas across different disciplines impacted by the illness. One COVID-19 JI project is already underway with others anticipated in the near future.

In Mandarin, the word crisis is represented by two distinct characters: 危机. The first, unsurprisingly, means *danger*. But the second is the character for *opportunity*. In the context of a pandemic that (as of this writing) has killed nearly two million and sickened tens of millions around the world, we believe it is important to keep these words in mind. The danger is profound, yet so is the opportunity for this and other international partnerships to address this challenge.

Thanks to our long-standing collaboration, the friendships we've forged, and the trust we've developed, our JI is well positioned to do just that. In the process, we look forward to continuing to demonstrate not just the viability of our partnership, but more importantly, its value to medical discovery for the world.

Xièxiè. 谢谢.



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Leadership



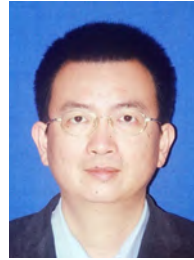
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About the JI

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 each contributed an initial \$7 million and both renewed their financial commitment with repeat \$7 million investments in 2015.

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 successfully compete for extramural funding.

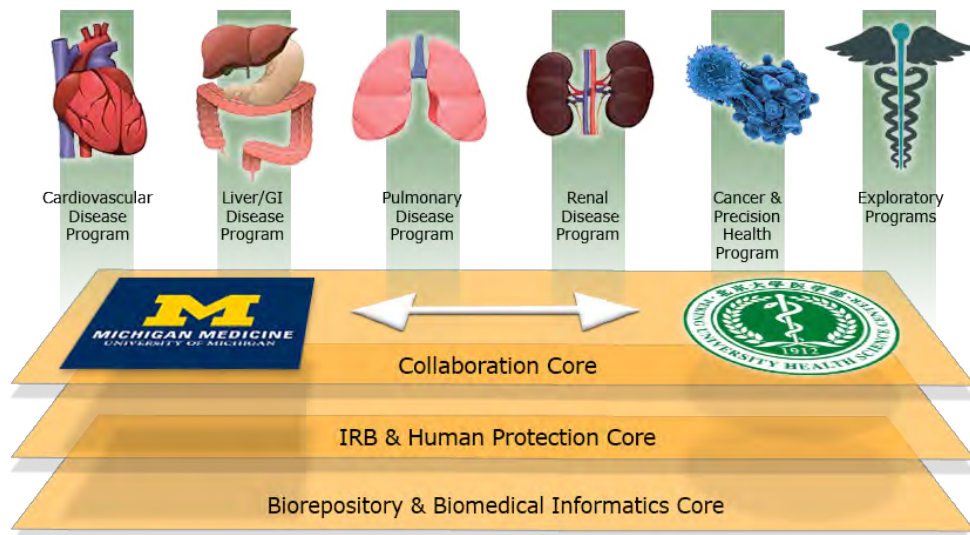
The JI allows faculty at both institutions to partner on research that neither side could conduct alone, advancing health for populations across both the US and China, and beyond.



PKU Third Hospital faculty and administrators on a UM campus tour as part of their Global Executive Education Program experience.

Programs & Cores

Much of the research focuses on four key Program areas of interest to both institutions: cardiovascular, liver, pulmonary, and renal diseases. At the same time, Infrastructure Cores – Biorepository and Biomedical Informatics; IRB and Human Protection; Collaboration – help the partners overcome specific challenges or concerns associated with global collaboration. In 2017, leaders designated two new areas for future project investment and focus: cancer research and precision health.



The JI's collaborative model of mutually agreed-upon organ-based programs supported by administrative cores makes the JI a unique partnership platform between the two institutions.

Vital Statistics

Vital Statistics To Date



JI Awards



Completed Projects



Patients Enrolled in Studies



Publications

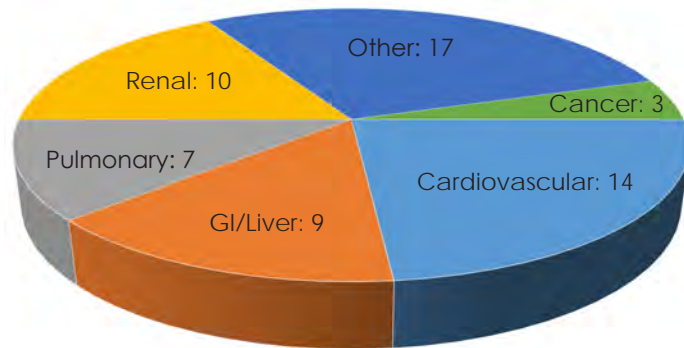


Extramural Funding

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. Most recently, JI leaders decided to prioritize research in the areas of cancer treatment and precision health. To date, 59 projects have received funding from nearly 200 submitted proposals.

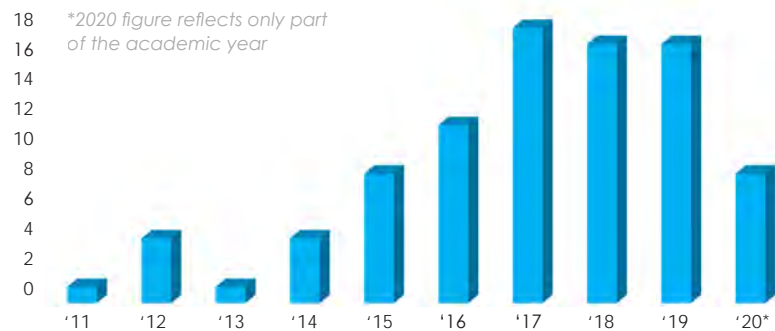
Awards by Program Area (2011-2019)



Publications

JI research has produced 86 publications to date, 60 of which are co-authored by the respective PIs from each institution. JI research has appeared in leading academic medical journals including *Science*, *Academic Medicine*, *PLoS ONE*, *Gastroenterology*, and others.

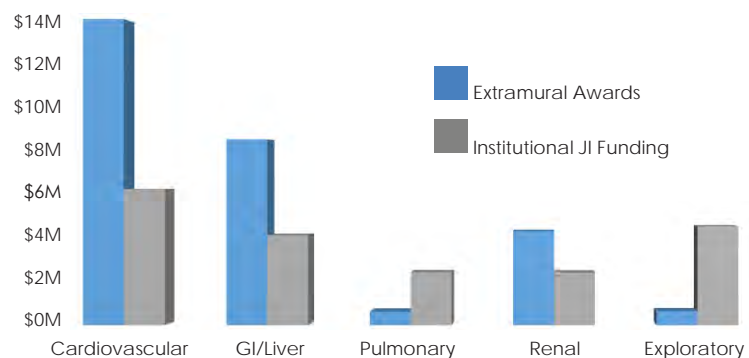
JI Publications (2011-2020)



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 \$28 million in extramural funding for research as a result of their collaborations. Cardiovascular medicine research alone has resulted in \$14 million in extramural funding. Teams in GI/Liver, Renal, and Pulmonary medicine programs have garnered extramural funding as well.

Institutional & Extramural Funding (2011-2020)



New Projects for 2019

A dozen 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, from exploring the genetic causes of intellectual disabilities to studying whether and how risk complications from diabetes differ between the U.S. and Chinese patient populations.



Determining genetic and microbiome effects on non-alcoholic fatty liver disease and its medical complications in a Chinese population

Nonalcoholic fatty liver disease has increased with the rise of obesity and can contribute to liver and cardiometabolic disease. We identified genetic subtypes of NAFLD and environmental causes of NAFLD in genetically predisposed individuals. This work was mostly performed in individuals of European ancestry. Individuals of Asian ancestry have higher rates of metabolic disease including NAFLD controlling for obesity than individuals of European ancestry. Whether this is genetically or environmentally mediated is not known. Further, microbiota have been shown to influence obesity and NAFLD in small populations but their effect in large populations is not known. Here we collected a large well characterized population based cohort from Pinggu China where there is an explosion of metabolic disease. We have excellent measures of NAFLD, DNA, stool and a wealth of covariates. We now aim to genotype the cohort, carry out metagenomic analyses from stool, and collect follow up data on incident liver and cardiometabolic disease. We will then carry out analyses to define genetic and microbiome influences on prevalent NAFLD as well as the effect of NAFLD and its precipitants on incident liver and cardiometabolic disease. Results from this work will define genetic and environmental causes of NAFLD to help further refine treatments and precision care of patients with NAFLD.

Co-Investigators



Elizabeth Speliotes, MD, PhD, MPH
UMMS



Linong Ji, MD
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Three-dimensional scaffold with two-stage siRNA delivery to reconstruct periodontal defects

Periodontitis is a chronic infectious disease occurring in periodontal support tissues. Macrophages plays an important role in the initiation and progression of periodontitis. The M1 polarization of macrophages plays a key role in pro-inflammatory response, while M2 polarization of macrophages plays a role in anti-inflammation and tissue regeneration. Studies have shown that selectively silencing PTEN or Akt2 could promote M2 polarization of macrophages. Our study aims to construct a three-dimensional nanofibrous scaffolds with "two-stage" RNA release capacity. The first stage is to controlled release a novel non-viral siRNA transfection vector from PLGA microspheres, and the second stage is to efficiently transfect siRNA into target cells. The "two-stage" siRNA delivery vector on the 3D scaffold is hypothesized to selectively silence both PTEN and Akt2, thereby to regulate macrophages from M1 phenotype to M2 phenotype, modulating local inflammatory microenvironment and promoting the regeneration of periodontal defects.



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LILRA3 as a novel regulator of thromboinflammation in antiphospholipid syndrome (APS)

Few acquired states carry a higher risk of thrombosis than antiphospholipid syndrome (APS), a systemic autoimmune disease that impacts as many as 1-in-1000 individuals worldwide. Neutrophil extracellular traps (NETs)—tangles of chromatin and microbicidal proteins ejected from dying neutrophils—appear to play a key role in the thromboinflammation inherent to APS. Our Michigan Medicine team has characterized the transcriptome of APS neutrophils, where we discovered 4-fold upregulation of leukocyte immunoglobulin-like receptor A3 (LILRA3). LILRA3 belongs to a family of surface receptors expressed especially by myeloidlineage cells, and best known for modulating HLA class I signaling. Interestingly, the LILRA3 gene product is the only soluble receptor within the LILR family. Another unique feature of LILRA3 is a 6.7-kb deletion polymorphism, resulting in a null allele when present. Null-allele frequencies differ among ethnic groups: 0.560.84 (Asians), 0.17 (Europeans), and 0.10 (Africans). Our PKUHSC team's work in Han Asian individuals has found the null allele to be protective against rheumatoid arthritis and lupus. This study will now be the first to characterize LILRA3 in a thromboinflammatory disorder (APS), leveraging unique expertise of Michigan Medicine and PKUHSC to (i) reveal novel APS-relevant biology, (ii) improve APS risk stratification, and (iii) lay the groundwork for future collaboration in pursuit of new APS biomarkers and therapies.



Jason Knight, MD, PhD
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Jianping Guo, MD, PhD
PKUHSC

New Projects for 2019

Molecular signatures underlying the progression of intestinal metaplasia: a multi-omics approach

Gastric cancer (GC) is a major public health concern worldwide. Chronic inflammation is an important causative factor for the development of gastric neoplasia. One hypothesis is that inflammation and mucosal injury alter the normal homeostatic mechanisms of the gastric epithelium leading to the development of metaplasia, dysplasia and, ultimately, to neoplasia. Both Spasmolytic Peptide Expressing Metaplasia (SPEM), which is characterized by the aberrant expression of Trefoil Factor 2 (TFF2) and of mucins that bind the lectin GSII at the base of glands of the oxyntic mucosa, and Intestinal metaplasia (IM), have been recognized as precursor lesions for GC. However, it appears that only some, but not all patients with metaplasia develop GC. Thus, it is conceivable that there could be specific genetic signatures and environmental factors responsible for the expression of different pathological phenotypes. The mechanisms leading to metaplasia and to its progression to neoplasia have been poorly characterized. The bone morphogenetic proteins, (BMPs) have been shown to inhibit gastric inflammation, cell proliferation and the growth of gastric neoplasms. We previously reported that inhibition of BMP signaling in the stomach of mice enhances Helicobacter-induced inflammation, stimulates epithelial cell proliferation and causes metaplasia and dysplasia, suggesting that alterations in BMP signaling might lead to pathological state of the gastric mucosa in humans. In this application, using proteomics, metabolomics, transcriptomics, and genomics we will characterize subjects with metaplastic changes of the gastric mucosa that progress to dysplasia and GC, placing particular emphasis on the expression of BMP-mediated pathways. In order to explore in more details the mechanisms underlying these events, we will use mouse models to define the role of inhibition of BMP signaling and inflammation in the development of metaplasia and dysplasia. These studies will provide new insight into the factors that control the metaplasia progression cascade, improving our ability to achieve early detection and treatment of gastric dysplasia and neoplasia.

Co-Investigators



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Wen-Qing Li, PhD
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Gaining insight into retinal cell death: rational drug development through vitreous proteomic analysis

Retinal cell death causes vision loss in many ophthalmic diseases. Despite improved treatments, a major knowledge gap remains in understanding the etiology, molecular mechanisms, and functional gene pathways leading to cell death. Drs. Zacks and Yang study retinal cell death in a variety of animal models, with the goal of identifying targets for the rational development of therapeutics to prevent retinal cell death and improve outcomes. Drs. Zacks and Yang will be performing proteomic analysis of the vitreous fluid of patients and perform pathway analyses in an effort to identify relevant stress-response pathways activated during retinal disease. Pathways identified will then be validated for their contribution to cell death (or survival) in our established animal and cell culture systems. The work performed in this Discovery Award will lay the foundation for years of fruitful collaboration, with the potential to rapidly and efficiently identify and test molecular points for therapeutic intervention for preserving retinal cell viability and function – ultimately allowing for improved visual outcomes for our patients.



David Zacks, MD, PhD
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Liu Yang, MD, PhD
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Deferoxamine in the Treatment of Aneurysmal Subarachnoid Hemorrhage (DISH)

Subarachnoid hemorrhage (SAH) is one of the most devastating forms of stroke with the highest immediate mortality of all strokes (exceeding 30%) and leading to severe disability for those who survive. This leads to a significant number of potential life years lost, creating a financial and intellectual loss to society. In addition to the initial insult, delayed cerebral ischemia (DCI) secondary to arterial vasospasm and chronic hydrocephalus requiring permanent CSF diversion are other complicating factors of subarachnoid hemorrhage. To date, aside from nimodipine, there are no preventative options for DCI or chronic hydrocephalus in SAH patients. With such strong data involving DFO use in SAH animal models and recent human data with DFO use in intracranial hemorrhage (ICH), a multicenter, randomized Phase I/II trial to determine the safety and futility of deferoxamine treatment in the human SAH population is expected provide data that changes the current treatment methodology of subarachnoid hemorrhage and improves patient functional outcomes. This proposed trial will evaluate the safety and futility of clinical deferoxamine use in SAH and could lead to changes in the current SAH treatment algorithm. If this trial is successful, it will generate crucial preliminary data that will support further clinical trial grant applications for a Phase III trial with a much larger sample size through the NIH/NINDS (USA) and National Science Foundation (China).



Aditya Pandey, MD
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Yining Huang, MD
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New Projects for 2019

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

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are life-threatening diseases in critically ill patients that continue to increase rapidly. Disease incidence is projected to increase to 335,000 cases/year by 2030, with deaths nearly doubling to 147,000 deaths/year. Treatment of patients typically consists of supportive positive pressure ventilation, as no effective targeted therapy currently exists. Severe sepsis is the most common (33-46%) risk factor for ALI/ARDS. To enable discovery of new specific therapeutic targets and to effectively manage sepsis-induced ALI/ARDS (sepsis-ALI/ARDS), a better understanding of injury-causing pathogenic mechanisms is required. An emerging theory of sepsis-induced ALI (sepsis-ALI) and ARDS (sepsis-ARDS) is that lung damage is due to the release of nuclear proteins from cell death such as neutrophil extracellular traps (NETs) and pyroptosis in the host response to infection. We have discovered that citrullinated histone H3 (CitH3), a subtype of histones, is a significant mediator of sepsis pathogenesis, which was previously unrecognized. We recently generated a novel CitH3 mouse monoclonal antibody which reduces ALI and improves survival significantly in mouse sepsis models. Our project is to develop a humanized CitH3 antibody and explore the new intervention for diagnosis/ treatment of patients with sepsis-induced ALI/ARDS. We will evaluate the mechanism and clinical significance of CitH3 in sepsis-ALI/ARDS. Accomplishment of the proposed studies will considerably advance the field by revealing the potentially crucial role that CitH3 plays in sepsis-ALI/ARDS, which may disclose novel therapeutic targets that could lead to new therapies to ameliorate sepsis-ALI/ARDS.

Co-Investigators



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Michigan-Peking Cancer Biomarker Collaborative

As cancer researchers, new technologies present us with exciting opportunities to address challenges in the field on a global scale. For instance, most cancer diagnostics do not undergo comprehensive testing in diverse patient populations, even though genomic studies have found important molecular differences in cancers between ethnicities. For cancer biomarker development, several validation centers exist in individual countries, but global validation centers are lacking. To address this need, we propose to form the Michigan-Peking Cancer Biomarker Collaborative with the objective of developing novel cancer biomarkers across patient populations in China and the United States, the first- and third-most populated countries in the world. We will begin the Collaborative with development of biomarker assays for detection and risk stratification of prostate cancer. Current prostate cancer screening methods, such as prostate-specific antigen (PSA) testing, have several pitfalls that limit their utility, with one of the most pressing issues being that they are not able to identify potentially aggressive disease to guide appropriate treatment. In collaboration with academic and industry partners, our group at Michigan Medicine previously developed the Michigan Prostate Score (MiPS) test that combines urinary transcript levels of TMPRSS2-ERG and the long non-coding RNA (lncRNA) PCA3 with serum levels of PSA to detect clinically significant prostate cancer, providing a more accurate assessment than PSA alone. However, the transcripts included in our current MiPS assay are not specific to aggressive disease. In the time since MiPS was established, we have performed several studies that have led to a vast compendium of novel prostate cancer-associated transcripts, including thousands of lncRNAs and circular RNAs (circRNAs). For the studies in this application, we will leverage these discoveries to generate a novel expanded quantitative PCR-based MiPS assay (MiPS-QPCR) and a next-generation sequencing-based MiPS assay (MiPS-NGS) that can detect high grade prostate cancer non-invasively with urine samples. Development of MiPS-QPCR will allow rapid clinical transition from our existing MiPS test, while establishment of the MiPS-NGS platform will provide more levels of biomarker information (genetic, transcriptional, and epigenetic). We will also leverage the expertise of our team at Peking University Health Science Center (PKUHSC) in machine learning and metabolomics approaches to develop a complementary lipidomics biomarker assay for detection of aggressive prostate cancer with plasma or urine samples. Critically, all assays will be validated and fine-tuned for accuracy in patient populations from both institutions. The aims of the Collaborative are ambitious but will lead to impactful results for cancer patients in both countries, and it is our goal to become a model global biomarker validation center to fill a current void in this vital arena.



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New Projects for 2019

EMERALD-HF: Evaluation of Mineralocorticoid antagonists in Aldehyde dehydrogenase type 2 Deficiency

An estimated 700 million people in East Asia carry a single nucleotide mutation ALDH2*2 (rs671) that impairs aldehyde dehydrogenase type 2 activity in all carriers. These patients have an increased risk of hypertension, heart failure, chronic kidney disease, coronary artery disease, and myocardial infarction. Both the heterozygous and homozygous mutation lead to impaired ALDH2 enzyme activity and increased ROS, which in turn leads to increased reactive aldehyde production. In a small animal model, we have shown that ALDH2 deficiency benefits from treatment with Alda-1, an ALDH2 activator, by decreasing CaMKII activation by both phosphorylation and oxidation. Adoption of mineralocorticoid receptor antagonists would reduce production of reactive oxygen species and ameliorate aldehyde dehydrogenase deficiency by decreasing aldehydic burden particularly in patients with ALDH2 deficiency. Our study will assess clinical response to spironolactone in patients with HFmrEF stratified by ALDH2 deficiency as determined by genotype. If these patients who are at increased risk of ROS and cardiovascular events can be shown to respond more favorably than those without ALDH2*2 mutations, this would allow a precision medicine approach and would justify an intensive clinical approach in these patients to allow for monitoring for hyperkalemia.



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New Strategy to Identify, Validate, and Eliminate Heterogeneity for Personalized Cancer Therapy of Breast Cancer or Liver Cancer

The advent of extensive genomic and epigenetic studies have shown that different cancer cell subpopulations are present in any given patient, each with its own unique response to therapies. Therefore, targeted therapy that only inhibits one subpopulation of cancer cells without eliminating other non-responsive sub-populations are bound to lead to relapse even though patients may show early clinical remission. Focusing on breast and liver cancers, we plan to use novel single-cell analysis and molecular beacon to identify tumor heterogeneity in order to inform patient-specific treatment plans. At the end of this project, we expect to have a positive impact by changing the paradigm for cancer classification and treatment and potentially provide new strategy to attempt to "cure" advanced breast or liver cancer. Specifically, (1) classification of advanced breast cancers or liver cancers with multiple lesions should no longer be based on subtypes or one molecular target, but rather based on the intra-tumoral heterogeneity of each tumor, which requires very different treatment options; (2) the inter-tumoral heterogeneity of primary and metastatic tumors (or multiple lesions) requires different drug combinations; and (3) the inter-tumoral heterogeneity from each individual patient also requires individualized combination of drug therapy. We envision that once we have established the database for this information, it will be feasible to rapidly translate to clinical trials where individualized combinations of therapies can be tailored to eliminate each sub-population of cancer cell heterogeneity and potentially "cure" cancer in the patients with breast or liver cancer.



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Building a Learning Health System for Kidney Disease through Meaningful Use of Electronic Health Record Data in Yinzhou China

One advent of the widespread adoption of Electronic Health Records (EHR) in the US is the secondary use of the information to improve patient safety and quality of care. Learning Health Systems can leverage the power of big data, accelerating the process of translating newly generated knowledge to clinical practice. China is in the process of adopting EHR systems. We plan to utilize a limited data set derived from regional EHR data from Yinzhou to test the feasibility of building a Learning Health System to improve chronic kidney disease (CKD) care, specifically focusing on anemia. A new Anemia-in-CKD Research Database will help us develop several predictive models for outcomes of common anemia treatments, such as changes in hemoglobin from iron therapy or from using erythropoietin-stimulating agents (ESAs). In addition, we plan to represent, in fully computable form, the actionable recommendations published in the current KDIGO guideline recommendations in both English and Chinese. We will use the open-source Knowledge Grid technology from U-M to package, manage and execute the predictive models we develop and the computable KDIGO guideline recommendations we build. Finally, as proof of concept, we will use real-world patient data from Yinzhou to test the potential impact of the predictive models and computable guidelines as the potential logic of a future clinical decision support system for use in Yinzhou.



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Guilan Kong, PhD
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2019-20 Research Publications

Jl collaborations resulted in 19 publications in 2019 and 2020, scholarship that appeared across a variety of disciplines in high-ranking journals such as *Science*, *Autophagy*, *Circulation*, *Molecular Psychiatry*, and more.

Project: Image-Guided Surgery of Hepatocellular Carcinoma (2016)

PIs: Thomas Wang (UMMS) & Jiye Zhu (PKUHSC)

Program: GI & Liver

Feng, S., Zhou, J., Li, Z., Appelman, H. D., Zhao, L., Zhu, J., & Wang, T. D. (2019). Sorafenib encapsulated in nanocarrier functionalized with glypican-3 specific peptide for targeted therapy of hepatocellular carcinoma. *Colloids and Surfaces B: Biointerfaces*, 184, 110498.



Project: Role of Visceral Adiposity in the Pathogenesis of Non-Alcoholic Fatty Liver Disease in Lean versus Obese Patients: A Comparative Study between Patients at UMHS versus PUHSC (2015)

PIs: Anna Lok (UMMS) & Lai Wei (PKUHSC)

Program: GI & Liver

Zhang, W., Huang, R., Wang, Y., Rao, H., Wei, L., Su, G. L., & Lok, A. S. (2019). Fat Accumulation, Liver Fibrosis, and Metabolic Abnormalities in Chinese Patients With Moderate/Severe Versus Mild Hepatic Steatosis. *Hepatology Communications*, 3(12), 1585-1597.



Zhang, W., Chao, S., Chen, S., Rao, H., Huang, R., Wei, L., & Lok, A. S. (2018). Awareness and Knowledge of Nonalcoholic Fatty Liver Disease Among Office Employees in Beijing, China. *Digestive Diseases and Sciences*, 64(3), 708-717.



Chen, S., Chao, S., Konerman, M., Zhang, W., Rao, H., Wu, E., . . . Lok, A. S. (2019). Survey of Nonalcoholic Fatty Liver Disease Knowledge, Nutrition, and Physical Activity Patterns Among the General Public in Beijing, China. *Digestive Diseases and Sciences*, 64(12), 3480-3488.



Project: Shared and Disease-specific Genetic Study among IgA Nephropathy, Henoch-schonlein Purpura Nephritis and Lupus Nephritis (2016)

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

Program: Renal

Ye, X., Zhou, X., & Zhang, H. (2019). Autophagy in Immune-Related Renal Disease. *Journal of Immunology Research*, 2019, 1-10.



Qi, Y., Zhou, X., & Zhang, H. (2019). Autophagy and immunological aberrations in systemic lupus erythematosus. *European Journal of Immunology*, 49(4), 523-533.



Xu-Jie Zhou, Daniel J. Klionsky & Hong Zhang (2019) Podocytes and autophagy: a potential therapeutic target in lupus nephritis, *Autophagy*, 15 (5), 908-912.



2019-20 Research Publications

Project: β -adrenergic Receptor in Cardiac Injury and Atherosclerotic Plaque Stability: Role of NADPH Oxidase 4 (NOX4) (2018)

PIs: Marshall Runge (UMMS) & Youyi Zhang (PKUHSC)

Program: Cardiovascular

Canugovi, C., Stevenson, M. D., Vendrov, A. E., Hayami, T., Robidoux, J., Xiao, H., . . . Madamanchi, N. R. (2019). Increased mitochondrial NADPH oxidase 4 (NOX4) expression in aging is a causative factor in aortic stiffening. *Redox Biology*, 26, 101288.



Project: Targeting Peptidylarginine Deiminase (PAD) for Diagnosis and Treatment of Severe Inflammation (2015)

PIs: Hasan Alam (UMMS) & Baoguo Jiang (PKUHSC)

Program: Cardiovascular

Tian, S., Lei, I., Gao, W., Liu, L., Guo, Y., Creech, J., . . . Wang, Z. (2019). HDAC inhibitor valproic acid protects heart function through Foxm1 pathway after acute myocardial infarction. *EBioMedicine*, 39, 83-94.



Project: Building Collaborations to Address Drug Problems in the US and China (2016)

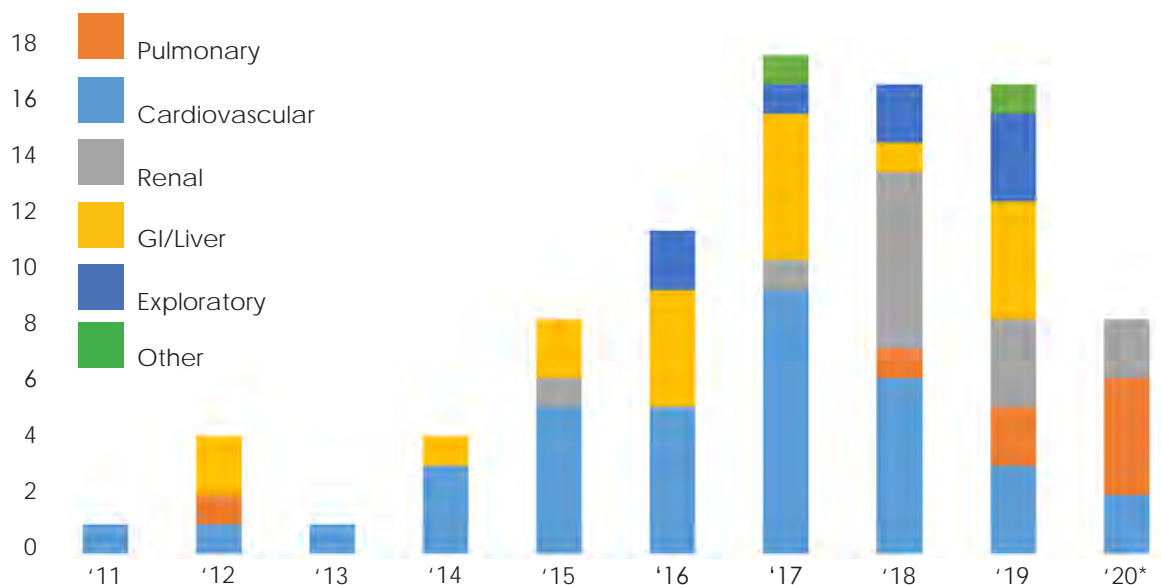
PIs: Frederic Blow (UMMS), Mark Ilgen (UMMS) & Lin Lu (PKUHSC)

Program: Exploratory - Psychiatry

Ma, J., Bao, Y., Wang, R., Su, M., Liu, M., Li, J., . . . Lu, L. (2018). Effects of medication-assisted treatment on mortality among opioids users: A systematic review and meta-analysis. *Molecular Psychiatry*, 24(12), 1868-1883.



JI Publications by Program Area, 2015-2020



*2020 figure reflects only part of the academic year

2019-20 Research Publications

Project: Compartmental Analysis of Metabolite Profiles Associated with Disease Phenotypes in Chinese and US Smokers with and without COPD (2015)

PIs: Theodore Standiford (UMMS) & Bei He (PKUHSC)

Program: Pulmonary

Diao, W., Labaki, W. W., Han, M., Yeomans, L., Sun, Y., Smiley, Z., . . . Stringer, K. A. (2019). Disruption of histidine and energy homeostasis in chronic obstructive pulmonary disease. *International Journal of Chronic Obstructive Pulmonary Disease*, 14, 2015-2025.



Project: Compartmental Analysis of Metabolite Profiles Associated with Disease Phenotypes in Chinese and US Smokers with and without COPD (2015)

PIs: Theodore Standiford (UMMS) & Bei He (PKUHSC)

Program: Pulmonary

Labaki, W. W., Gu, T., Murray, S., Curtis, J. L., Yeomans, L., Bowler, R. P., . . . Han, M. K. (2019). Serum amino acid concentrations and clinical outcomes in smokers: SPIROMICS metabolomics study. *Scientific Reports*, 9(1).



Project: Citrullinated Histone H3: A Mediator and Biomarker of Sepsis-induced Acute Lung Injury (2019)

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

Program: Pulmonary

Zhou, J., Biesterveld, B. E., Li, Y., Wu, Z., Tian, Y., Williams, A. M., . . . Alam, H. B. (2019). Peptidylarginine Deiminase 2 Knockout Improves Survival in Hemorrhagic Shock. *Shock*, Publish Ahead of Print.



Project: Systemic Investigation of the Microbiome-host Interactions in H. pylori-associated Gastric Cancer Patients (2018)

PIs: Jennifer Bragg-Gresham (UMMS) & Luxia Zhang (PKUHSC)

Program: Renal

He, Y., Wang, H., Zheng, J., Beiting, D. P., Masci, A. M., Yu, H., . . . Obeid, J. S. (2019). OHMI: The ontology of host-microbiome interactions. *Journal of Biomedical Semantics*, 10(1).



Project: Multi-ethnic Study of Genetic Risk Factors to Discover Mechanisms of Aortic Aneurysm and Dissection (2016)

PIs: Cristen Willer (UMMS) & Zhe Zhang (PKUHSC)

Program: Cardiovascular

Wolford, B. N., Hornsby, W. E., Guo, D., Zhou, W., Lin, M., Farhat, L., McNamara, J., Driscoll, A., Wu, X., Schmidt, E. M., Norton, E. L., Mathis, M. R., Ganesh, S. K., Douville, N. J., Brummett, C. M., Kitzman, J., Chen, Y. E., Kim, K., Deeb, G. M., Patel, H., . . . Yang, B. (2019). Clinical Implications of Identifying Pathogenic Variants in Individuals With Thoracic Aortic Dissection. *Circulation. Genomic and Precision Medicine*, 12(6), e002476.



Other: UMMS Professor of Family Medicine Michael Fetters completed a Fulbright visiting scholar program at PKUHSC in 2017 and continues to publish with colleagues there.

Lian S, Chen Q, Yao M, Chi C, Fetters MD. (2019) Training Pathways to Working as a General Practitioner in China. *Family Medicine*, 51(3), 262-270.



2019-20 Research Publications

Project: Targeting Peptidylarginine Deiminase (PAD) for Diagnosis and Treatment of Severe Inflammation (2019)

PIs: Yongqing Li (UMMS), Hasan Alam (UMMS) & Tianbing Wang (PKUHSC)

Program: Pulmonary

Wu, Z., Deng, Q., Pan, B., Alam, H. B., Tian, Y., Bhatti, U. F., . . . Li, Y. (2020). Inhibition of PAD2 Improves Survival in a Mouse Model of Lethal LPS-Induced Endotoxic Shock. *Inflammation*, 43(4), 1436-1445.



Wu, Z., Tian, Y., Alam, H. B., Li, P., Duan, X., Williams, A. M., . . . Li, Y. (2020). Peptidylarginine Deiminases 2 Mediates Caspase-1-Associated Lethality in Pseudomonas aeruginosa Pneumonia-Induced Sepsis. *The Journal of Infectious Diseases*.



Magupalli, V. G., Negro, R., Tian, Y., Hauenstein, A. V., Caprio, G. D., Skillern, W., . . . Wu, H. (2020). HDAC6 mediates an aggresome-like mechanism for NLRP3 and pyrin inflammasome activation. *Science*, 369(6510).



Project: Blood Pressure and Hypertension Genetics (2011)

PIs: Santhi Ganesh (UMMS) & Yan Zhang (PKUHSC)

Program: Cardiovascular

Sun, P., Jia, J., Fan, F., Zhao, J., Huo, Y., Ganesh, S. K., & Zhang, Y. (2020). Hemoglobin and erythrocyte count are independently and positively associated with arterial stiffness in a community-based study. *Journal of Human Hypertension*.



Project: Overcoming Racial and Metabolic Heterogeneity in Antiplatelet Therapy (2017)

PIs: Daniel Eitzman (UMMS), Haoming Zhang (UMMS) & Jianping Li (PKUHSC)

Program: Cardiovascular

Sun, Y., Venugopal, J., Guo, C., Fan, Y., Li, J., Gong, Y., . . . Eitzman, D. T. (2020). Clopidogrel Resistance in a Murine Model of Diet-Induced Obesity Is Mediated by the Interleukin-1 Receptor and Overcome With DT-678. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 40(6), 1533-1542.



Global Executive Education



'We all sensed the passion!'

Sixteen physicians and administrators from Peking University Third Hospital became the first to complete a new Global REACH training program for healthcare leaders from overseas.

The group, which included an ophthalmologist, a neurologist, a surgeon, a pediatrician, a gynecologist and others, spent nearly all of May 2019 in Ann Arbor for the inaugural Global Executive Education Program. They met with leaders and chief administrators from various Michigan Medicine units and departments to learn about healthcare administration. Training sessions covered everything from faculty development to Lean Thinking and risk management, in addition to a day-long Leadership Challenge program, and tours of various clinical and research facilities.

"I think everyone in our group was quite impressed with the way the training program was organized. We all sensed the passion of the people at the University of Michigan," said Lixiang Xue, Director of the Peking University Third Hospital Biobank facility. "I feel the passion and the love they bring to their jobs."

Over the course of the three-week program, Xue and other attendees heard from Michigan Medicine leaders in finance, patient safety,

"Everyone in our group was quite impressed with the way the program was organized. We all sensed the passion of the people at the University of Michigan."

- Lixiang Xue, PKU Third Hospital

medical education, clinical research, and more. They got behind-the-scenes tours of many parts of the health system, from Survival Flight and Emergency Medicine to the Medical School's unique simulation training center. About 64 Michigan Medicine faculty and administrators helped deliver the program.

"This training wouldn't be possible without our colleagues across Michigan Medicine who graciously offered their time and talents for the benefit of our guests. I can't thank them enough," said Jiawei Ribudo, PhD, UMMS Global REACH Program Manager, the program's chief organizer. "Because of their willingness to share their expertise, our trainees are returning to China with new tools and ideas to help improve care for their patients."



CLOCKWISE FROM ABOVE: Third Hospital Global Executive Education program participants at the U-M football field; in a U-H Hospital nurse's station; and participating in an outdoor team building exercise.



PKU Third Hospital group kicks off new program for hospital administrators

Trainees were asked on the final day of the program to present before the group about key takeaways and concepts to take back home. Some spoke of faculty development programs, reconfiguring lab space to foster collaboration among research teams, or implementing daily huddle models like those they observed at Michigan Medicine. Nearly every participant singled Lean Thinking as a likely opportunity for future implementation following a two-day Lean course led by physicians Jack Billi, Jennifer Holmes, Cemal Sozener, Benjamin Bassin, and Lean trainers Tom Frederick and Patti Craig.

"For me, Lean Thinking was a powerful concept that I plan to use to empower residents in my ward, creating more opportunities to be active participants in the decision making process," said Pediatrician Tongyan Han, MD, MS.

The group was the first of four from China to visit Ann Arbor in 2019 to participate in the Global Executive Education Program.

"There is really a need for this kind of training," said Orthopedic Surgeon Yuping Yang, MD, PhD, who was the leader of the most recent cohort from Third Hospital. "These concepts can be applied to our daily work, but will take some time because the organization is so large. Step by step we can find some things to reform."



2019 Symposium



Attendees gather for a group picture during the 2019 JI Symposium on the PKUHSC campus.

More than 80 Michigan Medicine leaders, faculty and staff made a recent visit to China to celebrate and advance the Medical School's largest international partnership.

The ninth annual Michigan Medicine-Peking University Health Science Center (PKUHSC) Joint Institute Symposium took place Oct. 30 through Nov. 1 at the PKUHSC campus in Beijing. Themed Molecular Medicine, the meeting included keynote addresses by leaders from both institutions, panel talks on artificial intelligence and technology transfer, presentations by several Joint Institute project PIs, and more.

"There are some challenges between China and America, but I hope the President of the United States and the leaders of our country can come here to see ... the relationship between Peking University and the University of Michigan and the benefits we get from each other," said Qide Han, MD, the past president of PKUHSC and a vice chairman of China's National People's Congress, at the meeting's kick-off session. "This partnership makes me optimistic that our two countries will move in the right direction."

The JI projects touch on many disciplines including cardiovascular, renal, liver, and pulmonary disease, as well as partnerships in emergency medicine, ophthalmology, and women's health.

"I'm often contacted by peers at other institutions asking how we are doing this in China. We've been successful because of the trust, relationships, and unique model we've developed."

- Joseph Kolars, MD

UMMS Senior Associate Dean for Education & Global Initiatives

Among 12 new research projects awarded for 2019 are several areas new to the JI, including dentistry and pharmacy.

"My lab in the School of Pharmacy is already integrated with the U-M Medical School, so this was a good opportunity to enhance multidisciplinary collaboration and at the same time build a broader collaboration with the pharmacy school at PKUHSC," said first-time JI Symposium attendee Duxin Sun, PhD, U-M Professor of Pharmaceutical Sciences. Sun's JI project with PKUHSC Vice President Ning Zhang, PhD explores the possibility of developing personalized cancer therapies through the study of tumor heterogeneity.

"Part of my work involves single-cell tumor heterogeneity in breast cancer. Coincidentally, Ning Zhang studies single-cell heterogeneity in liver cancer, so it was a good match," Sun said. "We have techniques they don't have and vice versa, plus together we have collectively a larger sample size to advance the work more quickly."

As the JI approaches its 10-year anniversary in 2020, leaders from both institutions are looking to advance the partnership in re-defined directions, including exploring connections with – and attracting investments from – the health industry, as well as guiding more collective, multidisciplinary collaboration.

"I'm often contacted by peers at other institutions asking me, 'How are you doing this in China? I know you can't get samples or data out of China.' But we've shown that we can," said Senior Associate Dean for Education and Global Initiatives Joseph Kolars, MD, who serves as co-Director for the JI. "We've been very successful because of the trust, the relationships, and the unique model we've developed."

Features

Joint Institute LDC Provides Insight, Stability

The Joint Institute's Leadership and Development Council, an advisory group interested in helping expand and deepen the JI's reach, continued to meet through the COVID-19 pandemic.

Comprised primarily of philanthropists and healthcare business leaders from across China, the LDC gathered in person in 2019 and hosted a virtual meeting in 2020 to discuss progress, milestones and future strategy with JI leaders.

Co-led by longtime Michigan Medicine supporter Richard Rogel and Lana Hu, Founder and CEO of Amcare Healthcare Group in China, the group's charge is to support the JI collaboration through networking and fund-raising. A primary LDC goal is to connect JI researchers with industry partners for potential research funding.

"We remain grateful to Mr. Rogel, Dr. Hu and all of our LDC board members for their continued support," said JI Co-Director Joseph Kolars. "The pandemic has tested all international collaborations, and particularly US-China partnerships. Thanks to the collective wisdom and insight of the council, we are poised to emerge from these challenges stronger."



JI and UM leaders with members of the Leadership and Development Council at a meeting in Beijing in 2019. The LDC is Co-Chaired Lana Hu (center) and Richard Rogel (center left).

Leaders explore ENT collaborations during PKUHSC visit

Collaborations between Michigan Medicine and Peking University Health Science Center (PKUHSC) continue to expand into new disciplines. The latest is otolaryngology following a visit to PKUHSC Third Hospital by Carol R. Bradford, MD, executive vice dean for academic affairs and professor of otolaryngology-head and neck surgery.

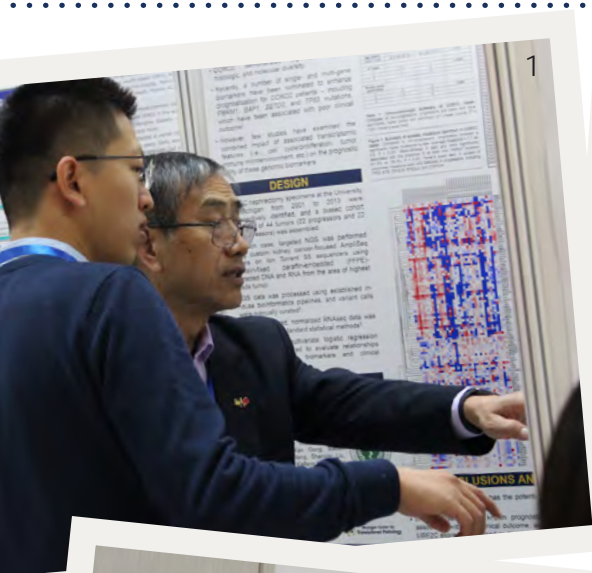
Bradford traveled to China in October 2019 for the annual symposium of the Joint Institute collaboration between the U-M Medical School and PKUHSC. As part of the visit, she met with Li Zhu, MD, chair of the ear, nose, and throat (ENT) department at the PKUHSC-affiliated Third Hospital, and toured the ENT clinical ward. Bradford saw the dedicated ENT inpatient floor as well as outpatient services like audiology, vestibular function examination, and allergy testing. The Third Hospital ENT team sees more than 150,000 patients a year.



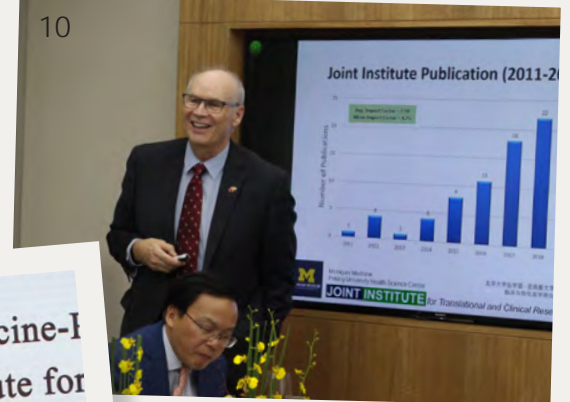
"I enjoyed touring their clinical space and grateful that Dr. Zhu and her team took time from their busy schedule to meet with me," Bradford said. "Their range of services is comprehensive and the way they manage a large volume of patients is impressive."

Third Hospital ENT Chair Dr. Li Zhu tours Dr. Bradford through the otolaryngology outpatient services area of her hospital.

Symposium Scrapbook



2019 Meeting Pictures



1. UMMS Professor of Surgery Yongqing Li views an entry during the poster session.
2. PKUHSC President Qimin Zhan, PhD, welcomes colleagues to the JI leadership meeting and dinner.
3. PKUHSC Professor of Renal Medicine Luxia Zhang gives a presentation to JI colleagues.
4. PKUHSC Vice President Ning Zhang, JI Associate Director, speaks during the leadership dinner.
5. PKUHSC Executive Deputy Dean for Graduate School Dr. Ming Xu poses a question during a presentation.
6. Meeting attendees browse the poster session.
7. UMMS and PKUHSC faculty speak as part of a panel on Artificial Intelligence.
8. UMMS faculty Christopher Bichakjian and Trilokraj Tejasvi talk with PKUHSC researcher Yang Wang.
9. JI administrative directors Qudan Sun (PKUHSC) and Amy Huang (Michigan Medicine) with co-Director Joseph Kolars.
10. JI Co-Director Joseph Kolars addresses colleagues during the annual JI Board of Directors meeting.
11. UMMS faculty Grace Li-Chun Su and Chung Owyang talk during a program break.
12. PKUHSC Past President Qide Han greets UMMS Dean Marschall Runge.

COVID-19 Response

'Our experience will be helpful'

JI colleagues share COVID advice with Michigan Medicine leaders



PKUHSC Leaders including President Qimin Zhan (left) participate in a webinar with Michigan Medicine leaders to discuss COVID-19. PKUHSC sent more than 400 doctors and nurses to Wuhan to help manage COVID-19 patients there.

In the early months of the pandemic, as coronavirus cases began ramping up in the US, physicians in China who had already seen firsthand America's coronavirus future reached out to Michigan Medicine leaders to help.

Doctors from Peking University Health Science Center shared their own experience battling COVID-19 with Michigan Medicine partners on a March 26, 2020 conference call. PKUHSC alone sent more than 400 doctors and nurses to Wuhan to help manage the surge of patients there, said PKUHSC President Qimin Zhan.

"After fighting against this virus for two months, the situation in China is getting better. I think our experience will be helpful to what you are doing right now," Zhan said.

More than 40 people including Michigan Medicine CEO Marshall Runge participated in the teleconference, organized by the Joint Institute.

"We are grateful that you have taken the time to help us this morning and we very much look forward to your guidance regarding what approaches have proven more effective and what has proven less effective," Runge said.

"The level of emotional support has been invaluable. I can't imagine that exchange happening without the Joint Institute."

- Theodore Standiford, MD
Chief of Pulmonary Medicine

"We are turning to you for advice. I know you have wisdom that will be valuable to us."

Participants from PKUHSC included more than a dozen leaders and physicians from pulmonary and emergency medicine who joined the conversation from both Beijing and Wuhan. The 90-minute call

touched on many clinical aspects of COVID-19 as the Michigan Medicine participants asked questions of their Chinese counterparts.

Subsequent meetings between respective specialty groups have allowed for deeper conversations. Michigan Medicine's pulmonary division learned of COVID patients' elevated risk of clotting from Chinese colleagues weeks before the risk was indicated in the scientific literature, said Theodore Standiford, MD, Chief of Pulmonary and Critical Care Medicine.

"We learned of the fairly profound hyper-coagulative state that some of these patients present with. They are treating patients with Heparin, which frankly was off from our radar," he said. "Beyond that, the level of emotional support has been invaluable. Ning Shen and her team are true colleagues in every sense of the word. I can't imagine that exchange happening without the Joint Institute."

COVID-19 Response

Michigan Medicine receives PPE from PKUHSC

One of Michigan Medicine's largest single donations of life-saving personal protective equipment (PPE) early on in the fight against COVID-19 came courtesy of PKUHSC.

The gear – tens of thousands of items including masks, coveralls, and goggles – arrived from several PKUHSC-affiliated hospitals in April, as coronavirus patient volumes in Michigan were beginning to surge and disrupted global supply chains meant PPE shortages for frontline workers. JI Co-Director Joseph Kolars, U-M medical school Senior Associate Dean for Education and Global Initiatives, and Amy Huang, Global REACH Director for Asia Programs and Michigan Medicine JI administrative lead, were on hand to receive the donation at the U-M North Campus Research Complex.

"Our friends at PKUHSC have been there for us when we need it most. It speaks volumes about the value of our collaboration."

- Joseph Kolars, MD, MACP
Sr. Associate Dean for Education
& Global Initiatives

"We are so grateful to our PKUHSC colleagues for their friendship and generosity," said Kolars. "These supplies are badly needed and especially difficult to source. On behalf of all of our front-line workers, I want to thank our collaborators in China. Their donation will help keep our care teams safe in the coming days and weeks."

The bulk of the items, including 60,000 surgical masks and nearly 5,000 N95 masks, came from Peking University Third Hospital. Other gear came from the Peking University First, Second, and Dental hospitals.

PKUHSC Executive Vice President and Third Hospital President Jie Qiao, a Professor of Ob-Gyn and an active JI researcher, reached out to Michigan Medicine leaders to arrange the PPE donation through her hospital's suppliers.

"The Chinese market can be difficult to navigate. Our colleagues at PKUHSC are familiar with the suppliers and know which ones offer top quality. These items are from the same suppliers PKUHSC uses in their hospitals," said Huang.



Drs. Joseph Kolars and Amy Huang receive the PPE from PKUHSC on behalf of Michigan Medicine.

LDC member donations

Michigan Medicine leaders were also grateful for PPE donations from two members of the JI Leadership & Development Council (LDC, see pg. 17). LDC Co-Director Lana Hu procured 10,000 N95 masks as well as ten personal respiratory systems. Isabelle Sun donated 2,800 additional N95 masks. Both are graduates of U-M. Their donations arrived in April 2020, just ahead of Southwest Michigan's spring surge of COVID cases.

"The support we are receiving from those affiliated with our JI during this difficult time is widely appreciated," Kolars wrote to Hu upon receiving the donations. "Just last week, one of my friends on service contacted me to say 'Joe, I am wearing one of the masks from your friends in Beijing.' It brought a smile to my face."

The shipment arrived only weeks after a JI-organized conference call in which PKUHSC physicians with experience battling COVID-19 in Wuhan shared their insights and best practices with Michigan Medicine colleagues.

"It speaks volumes about the value of our international collaboration and the strong relationship we've cultivated through the JI over the past decade," Kolars said. "In first sharing their expertise and now sharing their much-needed supplies, our friends at PKUHSC have been there for us when we need it most."

COVID-19 Project Highlight

Jl project to use bioinformatics in fight against COVID

A new Joint Institute-funded project aims to identify the risk and mechanisms of kidney failure in COVID-19 patients using bioinformatics tools.

University of Michigan Medical School Associate Professor of Microbiology Oliver He, working with Peking University Institute of Nephrology Professor Luxia Zhang, MD, will collaborate to explore the pathogenesis, clinical phenotypes, and risk factors of COVID-related acute kidney injury (AKI). Along with the lungs and heart, COVID-19 has been shown to impact kidney function in some patients.

"We have different backgrounds. Dr. Zhang and her team are clinical experts with extensive experience treating AKI patients. I have been working on kidney disease ontologies. It's a good match and I am very happy to work with them," He said.

He is an international leader in ontology, an emerging field of biomedical informatics that explores how computers can help classify and sort large data sets from different sources for large-scale medical research. Over the past few years, Dr. He has worked extensively with the Michigan Medicine nephrology group on an ontology platform for a national kidney disease precision medicine project. Separately, he developed an ontology platform this summer to begin organizing and categorizing the rapidly growing body of COVID-19 research, a first in the field.

"While I focus now on bioinformatics, my master's training was in viral infectious diseases and my PhD was on bacterial infectious diseases," He said. "After COVID, I thought I needed to do something. It is the intersection of my two passions – infectious disease and computer science – and I wanted to make a difference."

"Each new study and publication is a small piece of the puzzle. Ontology can help us put the pieces together quickly so researchers can best utilize and build a body of work."

- Oliver He
Association Professor of Microbiology



Dr. Oliver He's bioinformatics research at UMMS focuses on ontology, the platforms and language computers use to sort and compare large data sets.

The new project will use He's Coronavirus Infectious Disease Ontology (CIDO) system to begin to standardize, categorize and analyze data from multiple sources – Chinese and American – to define and explore the characteristics of COVID-related kidney injury. In China earlier this year, Zhang helped lead a multi-center study that compared early- versus late-stage kidney injury patients (i.e., how quickly in the progression of the disease did the virus impact the kidneys compared to other organs).

While the team found important differences between the two groups, including distinctly different phenotypes, the reasons aren't well understood. What was clear: those who suffered from AKI were 2-3 times more likely to succumb to the illness before leaving the hospital. The



Partnership to help identify the risks and mechanisms of kidney disease in COVID patients

Dr. He will partner with Dr. Luxia Zhang, from the PKU Institute of Nephrology, who has been involved in multi-center studies focused the progression of kidney injury in COVID patients in Wuhan, China.

"We are demonstrating not just the viability of our collaboration, but more importantly, the value of our partnership to the medical discovery for the benefit of world health."

- Amy Huang

Global REACH Director for Asia Programs

hope is that He's ontology platform will allow the comparison of Zhang's clinical data against other available datasets to accelerate the research and develop a better understanding to save lives.

"We have a lot of data – observational, clinical, pathological, and molecular publication data – but it's difficult to put it all together," He said. "Each new study and each new publication is a small piece of the puzzle. Ontology can help us put the pieces together quickly so researchers can best utilize and build on the collective body of work."

The global coronavirus pandemic and resulting travel restrictions made all international collaborations difficult in 2020, especially those between China and the US. He and Zhang's project was the only project funded through the JI in 2020, although the regular proposal process, which had been postponed in the spring, was re-activated in November and award notices are expected in May, 2021. More COVID-related projects are anticipated as part of those proposals.

"I am grateful to our leaders and faculty at both institutions for their trust and support of Michigan Medicine's important partnership with our Peking University Health Science Center colleagues," said Amy Huang, MD, MHSA, Global REACH Director for Asia Programs. "We are demonstrating not just the viability of our collaboration, but more importantly, the value of our partnership to medical discovery for the benefit of world health."

Celebrating 10 Years of the JI

A decade of friendship.....



A global pandemic changed the venue, but couldn't stop Michigan Medicine and Peking University Health Science Center (PKUHSC) from celebrating their longstanding partnership.

Almost 200 faculty and leaders from both the institutions gathered online in the fall for a webinar marking the 10-year anniversary of their unique collaboration. Established in 2010, the JI has grown over the years to comprise dozens of collaborative research projects spanning numerous disciplines, as well as ongoing education and exchange programs.

COVID-19 forced the cancellation of an annual in-person symposium (typically held each fall) in favor of a virtual event.

"At this moment of extraordinary challenge, holding our JI celebration shows a dedication and willingness to respond to the challenge together," said PKUHSC President and Joint Institute co-director Qimin Zhan, M.D. "The pandemic may have prevented us from meeting face to face, but it will never stop our concerted effort to improve the health and lives of people."

"Our most important collaborations will be with China"

With participants in the US and China, the September 24 event featured U-M President Mark Schlissel, MD, PhD, and Peking University President Ping Hao, PhD, and other institutional leaders. Invited guests Victor Dzau, MD, President of the National Academy of Medicine, and Roger Glass, MD, PhD, Director of the NIH Fogarty International Center, for a panel discussion on the value of scientific collaborations between the US and China.

"I believe our most important collaborations in biomedical research going forward will be with China," Glass said. "This (Joint Institute) has demonstrated the necessary transparency, synergy, and data sharing that are vital to success but also difficult on an international level. You've done it well and deserve congratulations."

The meeting was an opportunity to celebrate the successes of the past decade – 59 joint research projects, 86 publications, more than

JOINT INSTITUTE

CELEBRATING 10 YEARS!

JI leaders gather for 10-year anniversary celebration

\$27 million in extramural funding in the US alone – as well as look ahead to the future of the partnership. UMMS Senior Associate Dean Joseph Kolars, MD, who serves as co-director of JI, outlined the goals for the next decade.

“We’re pleased with what we’ve done in phase one, developing the trust and some of the machinery to partner effectively,” said Kolars. “Going forward into the next phase, it is important for us to look for opportunities that we can’t do alone – things that are beyond what an individual could do alone or two partner scientists could do alone.”

Expanding the scope of partnerships

One such goal is to expand the JI research beyond explorations of individual diseases into theme-based areas – precision medicine, cancer, metabolic diseases – with multidisciplinary teams of investigators tackling larger, more complex projects. Another objective to create opportunities for the JI research teams to partner with private industry in one or both countries.

Professor of Hepatology and UMMS Assistant Dean for Clinical Research Anna Lok, MD has already leveraged some of her hepatitis research through the JI into valuable partnerships in the private sector, securing \$1.5 million from Bristol-Myers Squibb to extend her work on incidence and risk factors for hepatitis C virus related cirrhosis and hepatocellular carcinoma.

“We received that funding largely because we were collaborating with China. The fact that we were studying two parallel cohorts (in the US and in China) and comparing and contrasting was appealing to them,” Lok said. “Either one of us approaching industry alone might not have led to support. The collaboration was what got them interested.”

A JI investigation into the relationship between air pollution and heart disease led not only NIH funding but also engagement with a World Health Organization task force on global air pollution interventions.

Investigations like this that connect physical medicine to environmental health could be an important area of growth for future collaboration between China and the United States, Glass suggested.

“Issues of global health, environmental health, and climate change are critical,” he said. “How do we as two major scientific powerhouses use our science and our health science to improve health going forward?”

Danger and opportunity

In the near term, COVID-19, while it has impeded face-to-face interactions between JI partners, has also provided opportunities for research as teams of researchers have been launching new projects or shifting ongoing collaborations to respond to the pandemic. Ning Zhang, PhD, Vice President of PKUHSC and Associate Director of the JI, noted that ‘crisis’ is represented in Mandarin by writing two characters side by side.

“One word is ‘danger’ but the other is ‘opportunity’. The COVID-19 outbreak has been a test of this partnership,” Zhang said. “We think this challenge provides an opportunity for the next phase of our collaboration.”

U-M President Mark Schlissel echoed the sentiment, noting that the COVID-19 pandemic has paradoxically sharpened the need for international collaboration even as it has made those partnerships more difficult.

“We’re living in a time where it may seem easier to focus on barriers to collaboration rather than to do the work of building bridges,” said U-M President Schlissel. “But we are showing the world what can happen through academic collaboration, shared goals, and strong partnerships. The science we’ve created together has an enormous impact already. It’s inspiring to think of the accomplishments yet to come.”

Project Update

Sepsis project milestones: 'Without JI support, we could not come to this stage'



A Joint Institute project launched in 2015 to identify and stop potentially lethal sepsis could now hold implications for COVID-19.

Assistant Professor of Surgery Yongqing Li's project to develop a new antibody to suppress sepsis – including sepsis-induced acute respiratory distress syndrome (ARDS) – had marked a number of milestones even before the onset of the coronavirus pandemic. Dr. Li and his collaborators, UMMS Professor of Surgery Hasan Alam, PKUHSC Professor of Orthopedics and Traumatology Baoguo Jiang, and PKUHSC Professor of Surgery Tianbing Wang, have produced six publications, most recently in *Science*, documenting their discoveries.

They also have a patent on a novel anti-citrullinated histone H3 (CiH3) antibody, and hold a partnership with a UK-based company to develop a humanized version of the antibody, which is intended to interrupt the same severe immunoresponse processes implicated in the rapid deterioration of some COVID-19 patients.

"Our primary discovery is that CiH3 is a significant driver of sepsis," said Li, MD, PhD. "Since the onset of the pandemic, it's been shown that CiH3 may serve as a biomarker to help diagnose COVID-19. Further, it's possible that the antibody we've developed could potentially be effective in stopping the cytokine storm response and ameliorating ARDS that can be

the cause of COVID-19 deaths."

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.

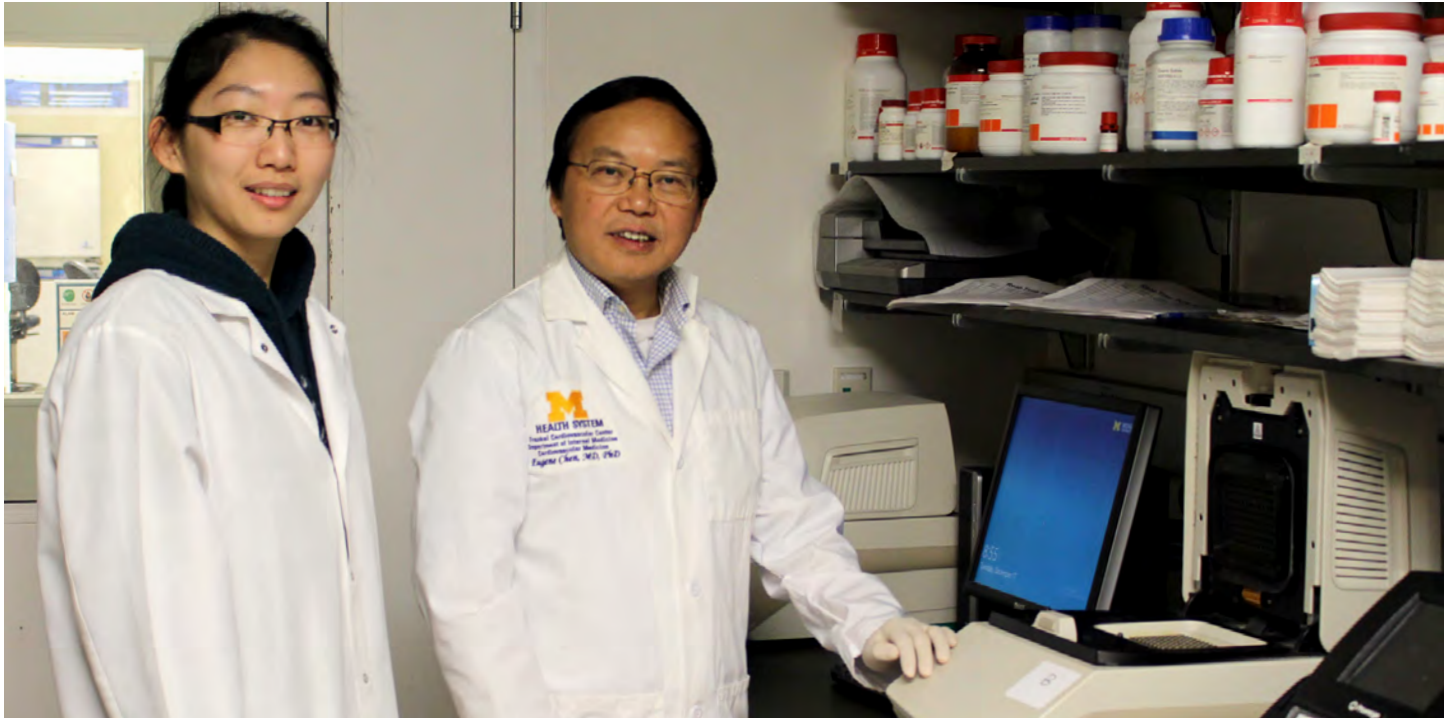
Their first project, launched in 2015 and conducted with Drs. Alam and Jiang as Co-PIs, identified the importance of CiH3. The group's JI award, given in 2019, is to build on that discovery through the creation of the antibody. The JI project brought three PKUHSC scholars to Ann Arbor for extended periods to work in Li's lab.

The culmination of the effort is an NIH R-01 grant that will be potentially funded.

"Without the JI support, we could not come to this stage," Li said. "Like a snowball, once you begin pushing something downhill, it grows larger and larger."

MD-PhD Program Update

Visiting PKUHSC student receives AHA fellowship



Huilun Wang and her UMMS mentor, Dr. Eugene Chen, in the lab.

A visiting student earning her PhD at UMMS has garnered an award from the American Heart Association (AHA) to support her research.

Huilun Wang, from Peking University Health Science Center (PKUHSC), a prominent UMMS partner institution in Beijing, is the recipient of a 2020 AHA Predoctoral Fellowship. Wang is among a handful of MD students from PKUHSC who are spending an extended period at UMMS to earn a PhD, a program that was started in 2014 with backing of U-M alum and philanthropist Richard Rogel, a longtime supporter of Michigan Medicine's partnerships in China.

Since her arrival to Ann Arbor in 2016, she has been a member of Professor of Cardiovascular Medicine Eugene Chen's lab, where her research is focused on learning more about the genetic contributors of abdominal aortic aneurism.

"I'm very grateful to receive the support and eager to continue my training here in Ann Arbor," Wang said. "I think the AHA fellowship elevates our project as a significant project."

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Wang is the third student from PKUHSC student in Chen's lab to receive the award. Haocheng Lu received AHA predoctoral fellowship in 2016 and Wenying Liang did so in 2018. In each case, the support subsidizes their continued research in the final portion of their PhD program.

"These AHA awards are highly competitive and having three PKUHSC students in speaks to the quality of these students and this exchange program," said Chen, MD, PhD. "These are outstanding students and we are privileged to host them as part of our learning community."

The PKUHSC students typically take a five-year break near the end of their their MD training in China to earn their PhD through UMMS before returning to finish their clinical training.

"There is not only the training in the lab, but also the courses in grant writing, experiment design, research ethics and more. We are basically learning how to think as a scientist, training that will help me a lot for my future career," Wang said. "I have always wanted to combine clinical work with research. For me, they cannot be separated."

Project Highlight

Jl partners seek better way to diagnose critical sepsis



Dr. VanEpps with JI colleagues in the newly opened biobank facility at PKUHSC during a visit to Beijing in January 2019.

One Joint Institute research collaboration aims to drastically shorten the diagnostic and treatment window for patients with critical sepsis infections.

Led by UMMS Assistant Professor of Emergency Medicine J. Scott VanEpps and PKUHSC Professor of Emergency Medicine Ya'an Zheng, the project has broad implications not only for getting antibiotics to patients who need treatment quickly, but also for reducing excessive treatment among those who don't.

"When you have severe sepsis, every hour of delay increases mortality. But because symptoms – fever, high heart rate – are non-specific, treatment guidelines typically call for broad-spectrum antibiotics all patients who are symptomatic," said VanEpps MD, PhD. "That helps create more resistance, in addition to unnecessarily exposing patients to these drugs that cause side effects."

Sepsis, which costs US hospitals alone more than \$20 billion each year, is typically confirmed via a blood culture test that takes at least 24 (and sometimes up to 72) hours to complete, often with nonspecific results. VanEpps' lab has devised a new assay using polymerase chain reaction (PCR) technology, boosted by gold nanorods, that could potentially cut the diagnosis window from days to hours, with results focused enough to target specific antibiotics to the respective bacteria discovered.

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- J. Scott VanEpps
Assistant Professor of Emergency Medicine

While the new method has shown promise in the lab, the 2017-awarded JI project aims to begin translating the technology to the clinical setting, testing the PCR assay against traditional culture tests with patients at both Michigan Medicine

and PKUHSC.

"We've demonstrated that this works in the perfect lab environment. The next step involves showing efficacy in the clinical setting using whole blood," VanEpps said.

Teams in both PKUHSC and Michigan Medicine began collecting and preserving samples in late 2018, with the goal of collecting 3,000 total samples in 2019. VanEpps and a researcher from his lab, Erika Martinez-Nieves, MS, traveled to PKUHSC in January to check in on sample collection processes and tour Zheng's lab facilities. Both sites will be running the tests on their respective samples.

"It's one thing to make it work here at Michigan Medicine, but it's another thing to implement something on the other side of the world," VanEpps said. "If we can do that, you get results that are generalizable across the world, something that would be impossible with a US-only study."

"Because antimicrobial resistance is a world-wide problem, both of our teams are motivated to make this work on a global scale," he said.

Other JI News



In January, PKUHSC was designated as a National Center for International Research by the Chinese Ministry of Science and Technology, the first academic medical center in China to receive the distinction. Drs. Joe Kolars, Eugene Chen, Brian Athey, and Amy Huang attended the inauguration ceremony and Dr. Kolars delivered congratulation remarks.

In April, Dr. Gary Smith, UMMS Professor of Ob-Gyn, visited PKUHSC and met with his JI partners, Drs. Jie Qiao and Liying Yan. Drs. Qiao and Smith presented their research funding at the International Federation of Fertility Societies 2019 World Congress in Shanghai.

In May, JI co-Director Joseph Kolars, JI Managing Director Amy Huang, and Dr. Larry Gruppen, Professor of Medical Education visited PKUHSC and provided workshops on Medical Education Reform to medical educators across PKU campus and hospitals. Drs. Kolars and Gruppen also delivered keynotes at the National Center for Health Professional Education Development Anniversary Symposium.

Drs. Carol Bradford, Joe Kolars, Amy Huang attended the JI Leadership Development Council (LDC) meeting in May. The LDC members and JI leaders discussed the strategy to collaborate with industry partners and opportunities to advance the executive training program.

Dr. Qingbian Ma, Professor and Chair of Emergency Medicine at PKU Third Hospital, visited UMMS in May to attend the inaugural EMERGE 2019 Conference.



Sixteen physicians and administrators from Peking University Third Hospital visited Michigan Medicine in May to participate in a new three-week Global Executive Education Training Program.

In June, Dr. Robert Neumar, Professor and Chair of Emergency Medicine at Michigan Medicine, visited PKUHSC and met with Dr. Qingbian Ma. In addition, Dr. Neumar delivered keynotes at the Emergency Medicine Committee of China Medical Education Association annual conference and at the first International Development Forum on China Emergency Medicine Education.

In August, Dr. Luxia Zhang, Professor of Nephrology and Assistant Dean for the National Institute of Health Data Science at Peking University, led a delegation to visit UMMS. They met with faculty members from Learning Health Sciences, Computational Medicine & Bioinformatics, Nephrology Division, and the Kidney Epidemiology and Cost Center to explore Big Data collaborations.

Dr. Han Xiao, Associate Professor of Medicine from the Institute of Vascular Medicine at PKU Third Hospital, visited UMMS for four months beginning in June. Dr. Xiao is collaborating with Drs. Marshall Runge and Nageswara Madamanchi on a JI project on the role of NADPH Oxidase 4 in cardiac injury. She conducted experiments in transgenic mouse models of oxidative stress and delivered a lecture at the Michigan Medicine Executive Education Program.

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