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**JI Programs & Cores**

- Biorepository and Biomedical Informatics Core
- Collaboration Core
- IRB and Human Protection Core
- Cardiovascular Disease Program
- GI/Liver Disease Program
- Pulmonary Disease Program
- Renal Disease Program

**Key to Commonly-Used JI Abbreviations**

- BRBI: Biorespository and Biomedical Informatics
- COPD: Chronic Obstructive Pulmonary Disease
- CVD: Cardiovascular Disease
- HCV: Hepatitis C Virus
- HDL: High-density Lipoprotein
- IRB: Institutional Review Board
- MI: Myocardial Infarction
- MICHR: Michigan Inst for Clinical & Health Research
- NIH: National Institutes of Health
- NSFC: Natural Science Foundation of China
- PUHSC: Peking University Health Science Center
- UM: University of Michigan
- UMHS: University of Michigan Health System
- UMMS: University of Michigan Medical School

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Dear Colleagues:

The first Joint Institute (JI) newsletter of 2016 finds us all looking forward to escaping the winter’s chill.

In this issue, we are pleased to share with you some of the research and educational exchanges between PUHSC and UMMS that have taken place over the past few months. In addition, we highlight the activities of the myocardial infarction project. We also provide updates on other research programs and the Cores, and an update on the 2016 JI Call for Proposals.

Finally, we remind you of the upcoming 6th Annual Joint Institute Symposium, which will take place in Ann Arbor, Michigan October 12-14, 2016. Details are still emerging, but please put this on your calendars.

We thank you for your continued support and we are looking forward to a strong and innovative 2016. As always, we look forward to working together as we strive for major discoveries that will improve the health and quality of life for people around the world. Please feel free to submit news and suggestions for future issues to Dr. Amy Huang (yanhuang@umich.edu), Director for China Programs at UMMS, or Professor Qiudan Sun (sunqd@bjmu.edu.cn), Director of the Office of International Cooperation at PUHSC.

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Professor of Pathology                        University of Michigan Medical School
Kidney Project Benefits From Collaboration

Fangrui Ding, a fourth-year year PhD student from PUHSC First Hospital, visited Dr. Roger Wiggins’ laboratory at UM in early February 2016. Mr. Ding is the key collaborator on the JI project “Prevention of Kidney Failure in Alport Syndrome by Application of Podometric Technology”. The project integrates a large, well-characterized, database-driven, and genetically-defined Alport Syndrome (AS) cohort developed and managed at PUHSC First Hospital. The project uses novel podometric technology developed by the Wiggins’ laboratory at UM to identify and prevent progression of glomerular diseases.

“The purpose of my visit was to solve some problems that have occurred in the process of establishing podometric technologies at PUSHC,” says Mr. Ding. “The image quality and analysis results we developed in Beijing were not as ideal as the results from Wiggins’ laboratory,” he explains, “and I wanted to find out why there is such difference.” He feels that the two-week visit was very successful and now expects to conduct more accountable and consistent experiments after improving 15 steps in kidney biopsy assay and 16 steps in urine assay.

Mr. Ding expressed his appreciation of the collaboration and communication between the two laboratories.

Jinwei Wang’s Visit at KECC

Dr. Jinwei Wang, a researcher from PUHSC First Hospital, visited the Kidney Epidemiology and Cost Center (KECC) for six weeks toward the end of 2015 to collaborate with the JI project team at KECC as they compared the risk of mortality associated with chronic kidney disease (CKD) among population-based samples from China and the US.

Dr. Wang attended the American Society of Nephrology annual meeting in San Diego in early November, and visited Ann Arbor before he returned to Beijing. During the visit, he was able to see first-hand how research is conducted within the KECC group by attending team meetings for many CKD projects, including the Center for Disease Control CKD Surveillance project and the Veterans Affairs Renal Information System project. He also utilized this time to discuss future collaborative work between the two teams.
and Visits

In December 2015, a delegation from PUHSC visited the Ann Arbor campus. **Drs. Wei Zhang, Rui Huang, Jing Wu, Anqi Li, and Shen Li** accompanied JI GI/liver disease co-leader **Dr. Lai Wei** from Peking University People’s Hospital. Their visit included a tour of the hospital, hepatology clinic shadowing, and meetings with medical school leadership. They also met with the HCV/NAFLD team to review the HCV study, move forward the NAFLD study, and work on the M1 study publication.

On November 11, 2015, **Dr. Weigang Fang** was invited to speak at the 3rd Association of East Asian Research Universities (AEARU) Medical Center Forum. The forum focused on strengthening long-term partnerships among AEARU Universities. Dr. Fang’s presentation was “Collaboration Platforms in China for Translational and Clinical Research: A Case Study Between Peking University Health Science Center and the University of Michigan Medical School”.

**Dr. Ran Liu**, Associate Chief Physician from the Department of Neurology, PUHSC First Hospital, began a one-year laboratory training at UM in February 2016 under the mentorship of **Dr. Guohua Xi**. She is primarily working on the JI project “Quantification of Iron Overload in ICH”, co-led by Drs. Guohua Xi at UMMS and Yining Huang at PUHSC.
Global Collaboration on

Myocardial Infarction (MI) is the leading cause of death in the United States and the 2nd leading cause of death in China. MI is heritable, particularly for those with a family history of early-onset MI.

Despite more than 2,300 Americans and 25,000 Chinese people dying of cardiovascular disease (CVD) every day, little is known about the etiology of MI. Moreover, it is predicted that CVD in China will increase by more than 50% between 2010 and 2030, due to aging and growth of the population.

Genome-wide association studies (GWAS) have proven successful at mapping genomic loci that influence human diseases and traits including MI, CAD, and lipid levels. However, for MI, the vast majority of the heritability remains unexplained. This is because there is no complete understanding of the causal variants and genes at known loci and also because many additional disease genes were likely not found by the GWAS approach.

Although many genetic discoveries have been made in individuals of European ancestry, few investigations into the genetic causes of high cholesterol and heart disease in Chinese have been published. Studying people with a different genetic history provides new insight into which genes and genetic changes are involved in heart disease and how they might be working. In 2011, the Joint Institute (JI) funded a research project “Finding genes for myocardial infarction and blood lipid levels in a Chinese sample from Beijing”, which aims to test whether the same variants and genes identified in Europeans will also be associated in Asian individuals. The project also aims to investigate the evidence for selection at lipid genes.

Project investigators from both institutional partners – the University of Michigan (UM) and Peking University Health Science Center (PUHSC) – met through the JI in 2010. According to Dr. Cristen Willer, co-principal investigator (PI) and scientific lead for the MI project at UM, “the JI provided a great platform for research collaboration. Thanks to the JI, I had the chance to work with collaborators from PUHSC and pioneered the use of the latest in genotyping technologies and resources for discovery genetics.”

Dr. Willer was able to access the samples from another JI project co-led by Dr. Santhi Ganesh (UM) and Dr. Yan Zhang (PUHSC). She explains, “The JI offers new opportunities for research synergies. We used samples collected by Dr. Yan Zhang’s group to confirm our findings, and were able to share the samples for different projects and optimally utilize the resources available for multiple projects.”
Myocardial Infarction Project

In order to validate the findings, the project also involves Hong Kong University (HKU). “When I was studying for a PhD at Oxford University, I built collaborations with scientists at HKU,” Dr. Willer shares. “By performing a meta-analysis with colleagues at HKU, we identified three novel genes associated with blood lipid levels and three novel Asian-specific variants in known genes. The collaborations from the three institutions work extremely well.” By leveraging existing collaborations with a research group in Norway, led by Kristian Hveem, the team was able to quickly compare findings in East Asian and European samples.

Dr. Xu Ming, Co-PI from PUHSC, indicates that this was a very successful collaboration which combines the resources together and sheds light on novel lipid biology and CAD. The project went very smoothly and the two teams work together to design the study, calculate power, and interpret findings using frequent telephone conferences and biannual face-to-face meetings either in Beijing or Michigan.

Through the global collaboration between Michigan, Hong Kong, Beijing, and Norway, scientists have published a manuscript on the discovery of several major new findings regarding blood cholesterol and heart disease:

1. They discovered new genes involved in blood cholesterol levels, one of which has already been shown to increase risk of fatty liver disease;

2. In genes already known to cause heart disease, new genetic variants specific to Chinese individuals have been discovered. This suggests that in the same genes, different genetic changes in Chinese individuals and European individuals developed over time that affected blood cholesterol levels; and

3. Interestingly, all the Chinese-specific lipid variants identified were associated with heart disease, with the exception of HDL-increasing variants in CETP. CETP inhibitors have been developed to increase HDL cholesterol, thought previously to be the good cholesterol, but have not been able to prevent heart disease. This study in Chinese people provides even more evidence that HDL cholesterol might not be the good cholesterol after all, but instead may have no impact on heart disease risk;

Dr. Willer and Dr. Xu were delighted to work together to contribute new scientific findings that may one day result in more effective treatments and prevention for heart disease.
At A Glance

Cardiovascular Program

**Dysfunctional HDL:** IRB application is in progress at PUHSC. IRB has been approved at UM and blood collection has been completed. Samples have not been analyzed for the new proposal pending IRB approval at PUHSC. Two papers are currently being written based on findings of the previous cycle of the grant funding.

**Atrial Fibrillation:** Results were submitted and have been accepted for publication in the Journal of the American College of Cardiology Translational Research. Publication is expected for April 2016.

**Myocardial Infarction:** (see page 4-5).

**Cell Therapy Against Cardiovascular Disease:** The chemical approach for generating induced pluripotent stem cells (ciPSCs) from mouse cells has been successfully completed at UM with guidance from the Deng Laboratory at PUHSC. The proposed experiments to generate human ciPSCs are being carried out.

**Brain Iron Overload:** Dr. Ran Liu, a neurologist at Peking University, has arrived at the University of Michigan for one-year post-doctoral training at Crosby Neurosurgical Laboratories.

**Acute Aortic Dissection:** An average of 1-2 patients are recruited each week. The PUHSC team has collected enough samples for the first experiments of proteinomics. The UM team will identify new target proteins as biomarkers and verify those biomarkers in the patient’s blood samples.

**High Density Lipoprotein Dysfunction:** Both studies at PUHSC and UM have been successfully completed as of February 2016. The teams are in the process of data analyses and will plan to have results available for publication within a few months.

Renal Program

**CKD Comparison:** The team had a face-to-face meeting at the ASN in San Diego. A manuscript for submission to a peer reviewed journal is being developed.

**Alport Syndrome:** The preparation for the biopsy samples will be done in Beijing and the photomicrographs sent to Ann Arbor for processing. Data will be analyzed jointly. IRB approval has been obtained. More than 100 urine samples have been collected from the Peking University First Hospital clinics and from Alport families at the annual Alport family meeting held in Beijing. Approximately 80 archival biopsy samples are available for analysis.

Institutional Review Board Core

Drs. Yali Cong and Haihong Zhang continue to work on obtaining the memoranda of understanding for the individual hospitals; they hope to finish with this in the Spring. These MOUs will serve as IRB-of-Record arrangements, hopefully lessening the burden of dual applications to the IRB at PUHSC and the IRBs at individual hospitals.

Collaboration Core

Collaboration Core is coordinating and facilitating the 2016 grant review process. The review process began in May at both MICH at UM and CRI at PUHSC. The joint MD/PhD program will welcome a student from PUHSC to pursue the PhD degree at PIBS.
GI/Liver Program
IBS: IRB has been approved at both PUHSC and UMMS. Both sites are actively recruiting subjects with IBS and healthy controls. Esophageal Cancer: A new round of data for deeper sequencing in targeted regions has been collected. The team will present a poster in the AACR meeting in mid-April. NAFLD: IRB has been approved at UMMS and is pending at PUHSC.

Pulmonary Program
Pollution and Asthma: In all, 25 out of a targeted enrollment of 50 patients in Beijing with moderate-to-severe asthma have been recruited. DNA from both whole blood and isolated T cells has been collected from these patients at different time points for eventual DNA methylation analysis of targeted genes. Studies of bronchial epithelial cells have shown that genes critical to asthma (TNFalpha, IL-13, ADAM33) are differentially expressed when exposed to particulate matter from Beijing, and DNA methylation changes in these genes are actively being investigated. COPD: IRB has been approved at both PUHSC and UMMS. BAL, sputum and serum samples collected as a component of the multicenter SPIROMICS network have been formally requested and pulled, and shipping is anticipated within the next month. Patient recruitment is ongoing at PUHSC. Wenqi Diao, PhD, will spend at least six months at UMMS working with Dr. Stringer on the metabolomics analysis.

Biorepository and Biomedical Informatics Core
The BRBI Core continues to provide regular IT support for several JI projects on the acquisition, storage, and management of clinical information and bio-specimen. Dr. Kai Zheng visited PUHSC in March 2016. He held meetings with Dr. Yangfeng Wu, director of the Peking University Clinical Research Institute (PUCRI), and the data management team at PUCRI. In these meetings, Dr. Zheng worked with PUHSC colleagues to develop a plan on improving the reliability and stability of the server environment hosting JI’s applications. For example, OpenClinica and REDCap that have served several JI projects will be soon migrated into a centralized computing environment using the virtualization technology, which ensures better performance, easier management, and a higher level of security. He also met with Dr. Yonghua Hu, executive director of PUHSC’s Medical Informatics Center, to discuss the recent development of big data and data science initiatives at PUHSC. Big data and data science remain a key component of JI’s strategic plan in its second five-year funding period.

Other Collaborative Projects
Radiology: IRB has been approved at both PUHSC and UMMS. Patient recruitment is going on smoothly at UM. Epigenetic Effects of Prenatal Environment Exposures: The project has received IRB approval and the reconsenting and recontacting process is ongoing. ER Prediction Tool: IRB has been approved at UM. The UM team is refining the MiChart-based adjustment tool. Dr. Rich Medlin is working diligently to help obtain the existing comorbidity component that adds more predictive power to this tool. Dr. Qingbian Ma is working hard with the IRB on approval details at PUHSC. PAD Severe Inflammation: Both sites have submitted IRB applications.
Update on the 2016 JI Call for Proposals

In each of the past four years, the Joint Institute (JI) put out calls for proposals for pilot funding of projects that would demonstrate an effective team approach to discovery and new findings on diseases relevant to both China and the US, and which could be leveraged for extramural funding opportunities. In addition to the routine RFP, this year the JI is also issued an RFP for clinical trials to move scientific discoveries from the lab to the clinic to enhance treatment options, health outcomes, and clinical values.

The 2016 “Call” yielded fifteen letters of intention including one application for the clinical trial. The new proposed research topics included drug problems, data science platform, hepatocellular carcinoma, peritoneal dialysis, and pediatric epilepsy.

Award announcements are expected to be made in Summer 2016.

SAVE THE DATE! OCTOBER 12-14, 2016
6th Joint Institute Symposium
ANN ARBOR, MICHIGAN

The 6th Annual Symposium of the Joint Institute for Translational and Clinical Research will be held October 12-14, 2016 in Ann Arbor, Michigan. Details are still emerging but we encourage you to mark your calendars now. Two years ago, more than 50 PUHSC community members were in attendance at the 4th JI symposium. We hope to have the same wonderful representation this year. Stay tuned for further updates.
March 2016
Drs. Andrew Admon and Amy Chang, residents from UMMS Internal Medicine, completed a four-week rotation at PUHSC.

March 2016
Pei Li, a student from Xiangya School of Medicine, began her laboratory rotation at UM in Summer 2014. Her project abstract “The b-ZIP Factor E4BP4 Is an Insulin-induced Activator of SREBP1c Stability and Promotes SREBP1c-mediated Lipogenesis” has been selected for an oral abstract presentation at the American Diabetes Association’s 76th Scientific Sessions, which will be held June 10-14, 2016 in New Orleans, Louisiana.

April 2016
UM M4 student Bruce Xu completed a four-week international elective at Shanghai Jiaotong University in April 2016. Another M4 student, Jerry Yan, will return from his four-week international elective at PUHSC in May 2016.

April 2016
Shuai Chen, Xufei Huang, Wanying Zhang, and Yan Zhao from PUMC participated in a four-week clinical elective through the Special Pathway for International Medical Students at UM.

January 2016
A delegation led by Dr. Weigang Fang visited University of Helsinki Medical School in Finland. An MOU between PUHSC and University of Helsinki was signed on January 15, 2016. This was followed by a joint symposium on cancer research and treatment.

March 2016
Dr. Liying Yan, from the Reproductive Medicine Center, Department of Obstetrics and Gynecology, PUHSC Third Hospital, was awarded the Milstein Medical Asian American Partnership Foundation Fellowship for her collaboration with Drs. Gary Smith and Yolanda Smith from OB/GYN at UMMS. They will work together on a project studying the effects of oocyte vitrification on the DNA methylation and gene expression of resulting embryos and early fetuses.

April 2016
On April 13, 2016, Dr. Yingfang Ao, Vice President of Peking University and the Director of Peking University Institute of Sports Medicine, met Richard Rogel in Beijing. They discussed the potential opportunity on collaboration in the field of Sports Medicine and mutual visits in the future.
Executive Officers of the University of Michigan Health System: Marschall S. Runge, MD, PhD, Executive Vice President for Medical Affairs; T. Anthony Denton, JD, MHA, Acting Chief Executive Officer; Kathleen Potempa, PhD, Dean, School of Nursing.

The Regents of the University of Michigan: Michael J. Behm, Mark J. Bernstein, Laurence B. Deitch, Shauna Ryder Diggs, Denise Ilitch, Andrea Fischer Newman, Andrew C. Richner, Katherine E. White, Mark S. Schlissel, (ex officio).

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