Joint Institute Newsletter
April 2015
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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
Dear Colleagues:

The first Joint Institute (JI) newsletter of 2015 finds us all enjoying the return of spring’s welcome.

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 Intracerebral Hemorrhage (ICH) project, which was just awarded a R01 NIH grant. We also provide updates on other research programs and the Cores, and an update on the 2015 JI Call for Proposals.

Finally, we remind you of the upcoming 5th Annual Joint Institute Symposium, which will take place in Beijing, China October 26-28, 2015. Details are still emerging, but please put this on your calendars.

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, Office of International Cooperation at PUHSC.

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Student & Trainee Opportunities

The JI has exciting exchange opportunities available for students, trainees, fellows, and residents from UM and PUHSC. These opportunities are limited in number and are thus highly competitive. If you are interested in more information, please contact Amy Huang (yanhuang@umich.edu) and Qiudan Sun (sunqd@bjmu.edu.cn).

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Education, Training and

The joint MD/PhD program welcomed its first two students from PUHSC in September 2014.

Haocheng Lu began his research experience at Dr. Eugene Chen’s laboratory in August, 2014. He has been working on a project of identifying novel pathway regulating vascular endothelial cells function and novel targets to prevent and treat atherosclerosis. According to Haocheng, the desire to become a physician-scientist motivated him to enroll in program. “Having seen patients with chronic disease which are incurable because of the limited understanding of the human body,” he explains, “I was determined to explore the cellular and biochemical mechanisms underlying physiological processes, especially the mechanisms of metabolic and cardiovascular diseases. The MD/PhD program is a perfect fit. I am impressed by the excellent academic atmosphere, outstanding faculty, and competitive graduate students here.” Haocheng expressed his appreciation for the learning opportunity at Dr. Chen’s laboratory and hoped his project would help to carry out new drug/therapy to treat cardiovascular diseases.

Jiuling Yang, who participated in the 2013 UM summer laboratory rotation, now is a MD/PhD student at Dr. Shaomeng Wang’s laboratory in Department of Pharmacology. “All the previous research experience aroused my strong interest in scientific research,” she points out. “The aspiration of being a research scientist and passion for cancer therapy drove me to apply for the program, and the PhD training will enable me to make breakthroughs beyond the current knowledge.” Jiuling believes she is developing the capability of scientific and critical thinking, as well as a serious and meticulous attitude towards research in the program. Her ultimate goal is to discover effective therapy for breast cancer.

In December 2014, Dr. Joseph Kolars, Senior Associate Dean of Education and Global Initiatives at University of Michigan Medical School (UMMS), visited Beijing to attend the Peking University Healthcare Forum “Innovative Solutions for Future Medicine”, and to participate in the Opening Celebration of Peking University International Hospital, which is the largest non-profit general hospital in China. During his visit in China, he met with several members of PUHSC leadership to discuss challenges and opportunities in the JI collaboration. Dr. Kolars also held a session to introduce the exchange opportunities at UMMS for PUHSC students who are interested in the Joint MD/PhD Program.
Scholarly Exchanges

**Professor Fang Wang**, MD, is Associate Professor from the Renal Department, Peking University First Hospital. In July 2014, she began a one-year International Society of Nephrology (ISN) fellowship at the University of Michigan Kidney Epidemiology and Cost Center (UM-KECC) under the mentorship of Dr. Saran Rajiv. Working on the JI project, “Comparison of Chronic Kidney Disease (CKD) Prevalence, Risk Factors and Outcomes between China and the United States,” she has been learning epidemiology analysis skills and gaining valuable research experience of renal disease, especially CKD.

According to Professor Wang, the purpose of her visit was to learn data mining and analysis skills for doing translational research. “During my first six months here,” she notes, “I learned how to shape research ideas with all of these data and picked up SAS programming, which is an essential tool for our CKD project.” A manuscript on the JI project has been accepted as a poster by the ISN World Congress of Nephrology, 2015.

Professor Wang expressed her appreciation for all of her experience, but especially the ability to learn disease from a public health perspective. “As a physician, my previous focus was on the diagnosis and treatment of renal disease for each individual,” she explains. “I did not realize the importance of the chronic disease prevention until I saw all the research in KECC. By shifting more resources to preventing disease and promoting good health, we can help everyone in our nation live as healthy as possible.”

**Dr. Mengfei Liu**, a PhD student in the Laboratory of Genetics, Peking University School of Oncology visited Ann Arbor from June-December 2014 to collaborate with research investigators in Dr. Jun Li’s laboratory on his JI project “Genomic Evolution and Mutational Signature of Esophageal Cancer in Anyang, China”.

“The main purpose of my visit was to learn Whole Exome Sequencing (WES) and SNP array data analysis skills which are used in the JI project,” Dr. Liu explains. “During my stay in Dr. Li’s laboratory, I learned basic principles and techniques in bioinformatics. Now I am able to do sequencing data analyses on my own.”

“The way Dr. Li treats the students impressed me,” Dr. Liu points out. “He encourages the students to think creatively and work independently. This helps them generate new research ideas.”
Spontaneous intracerebral hemorrhage (ICH) is a common and often form of stroke. Up to 50% of patients die and half of survivors are left with significant disability. Though ICH occurs in about 10-15% of all strokes in the United States, the impact on long-term medical care costs and productivity loss is substantial. ICH costs $6 billion per year in the United States. In China, ICH accounts for up to a third of all strokes, a proportion that is much higher than in Western populations.

If a patient survives the initial bleed, the resulting hematoma within the brain parenchyma triggers a series of events leading to secondary insults and severe neurological deficits. Although the hematoma in humans gradually resolves, the neurological deficits in ICH patients are usually permanent and disabling. Clinical data suggests that iron overload plays a role in brain injury and atrophy following ICH. High levels of serum ferritin, an iron-binding protein, have been associated with poor outcome and severe brain edema in ICH patients; however, deferoxamine, an iron chelator has been found to reduce brain edema, neuronal death, brain atrophy, and neurological deficits in rats and pigs.

To address these challenges, the JI awarded funding to a new project “Quantitative measurements of brain iron overload after intracerebral hemorrhage,” co-investigated by Dr. Guohua Xi and Professor Yining Huang, received JI funding in 2013. In April 2015, the project was awarded a R01 grant of $1.09 million from NIH.

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Top Scientists Collaborate to Challenge

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To address these challenges, the JI awarded funding to a new project “Quantitative measurements of brain iron overload after intracerebral hemorrhage.” According to Dr. Guohua Xi, Richard C Schneider Research Professor of Neurosurgery, UMMS, “brain iron overload is an attractive therapeutic target as it occurs over weeks and it may be amenable to delayed treatment; yet, the natural history of brain iron overload in ICH has not been well studied clinically or in large animal models.” “T2 magnetic resonance imaging (MRI),” he explains, “has been used to examine iron in the brain. However, whether it can be used to quantify brain iron levels in ICH and to examine the effects of iron chelation therapy has not been studied.”

This project aims to validate the utility of T2 imaging mapping in quantifying brain iron after ICH using a porcine model and to use this imaging technique to examine the natural history of brain iron accumulation after ICH and the effects of deferoxamine treatment on that accumulation in pigs and patients. As a biomarker, T2 mapping may provide a method of examining and optimizing iron chelation therapy and establishing a novel endpoint for ICH clinical trials. Dr. Xi adds that the long-term goal of the study is to establish a novel endpoint for ICH clinical trials. T2 mapping may provide a method of examining and optimizing iron chelation therapy as a biomarker.
Spontaneous Intracerebral Hemorrhage

“I have a strong interest in the project since it represents an overlap in my two main research interests, stroke and brain edema” Dr. Xi recalls “I was trained as a blood-CSF barrier neuropathologist during my post-doctoral fellowships and now have over 25-year experience working on blood-brain barriers with over 60 peer-reviewed papers on the subject. On coming to the University of Michigan, I expanded my focus to hemorrhagic stroke and have worked on animal and in vitro models of hemorrhagic stroke for the past 20 years and have over 70 peer-reviewed publications on the subject. There has been a particular focus on delineating brain injury mechanisms in cerebral hemorrhage. I have been continuously funded by NIH to work on brain edema and brain hemorrhage for the past 15 years.”

The co-investigators of this project have a long history of working together. Professor Yining Huang, Chairman and Professor from the Department of Neurology, First Hospital, PUHSC, remarks, “The current work is a part of a long-term collaboration between Dr. Xi and myself looking at brain injury after cerebral hemorrhage (intracerebral, subarachnoid, intraventricular).” Dr. Xi also points out that the rationale to collaborate with the PUSHC team is the strong basic ICH research at UM and a large number of ICH patients at PUHSC.

The experiments at UMMS aim to investigate brain iron quantitative T2 measurements in a pig ICH model, to determine the relationship between T2 values and brain iron concentrations, and to examine effects of deferoxamine on ICH-induced brain iron overload in pigs. Meanwhile, the studies at PUHSC are designed to learn the nature history of brain iron accumulation after ICH, and the effect of deferoxamine on brain iron overload in ICH patients.

Preliminary data at UM show that intracerebral hemorrhage results in a significant increase of brain iron. The dynamic changes of iron accumulation on analyzed MRI scans indicated a tendency for iron accumulation mainly inside the hematoma in the acute stage. It decreased slightly on the second week and gradually increased in the surrounding area of hematoma after that.

In April 2015, a proposal based on the pig MRI data was awarded an NIH Research Project Grant (R01) of $1.09 million, representing the desired goal for all projects that are funded by the JI. Both sides are satisfied with the collaboration and believe their work will ultimately contribute to improved patient care.
At A Glance

**Cardiovascular Program**

**Dysfunctional HDL:** PUHSC has completed transfer of all the samples to UM. Four peer-reviewed publications have been published and one research paper is in review. **Atrial Fibrillation:** UM investigators have completed the initial study aimed at determining the mechanism of the transition from paroxysmal to persistent atrial fibrillation. Using a clinically relevant sheep model of tachypacing induced atrial fibrillation, the results demonstrate a mechanistic involvement of the pro-fibrotic protein Galectin-3 (Gal-3) in the pathophysiology of atrial fibrosis. In addition, it has been demonstrated that therapy with a specific Gal-3 inhibitor, prevents fibrosis and reduces atrial dilatation and AF burden. Study results have been assembled into a manuscript that will be submitted to a high-impact journal. Meanwhile, the first pacemaker implantations at PUHSC were performed. **Dr. Yoshio Takemoto** and **Dr. Rafael Ramirez** from **Dr. Jalife's** lab traveled to Beijing in February 2015 to help establish the sheep model of persistent atrial fibrillation and ensure successful accomplishment of the project. Ten surviving animals have been implanted, and pacing and drug treatment are likely to begin in late April. **Air Pollution and HDL:** The study has received IRB approval from both UM and PUHSC. From September 2014 until the end of April 2015, 106 subjects have been enrolled (PUHSC = 76 subject, UM=30 projects). **Acute Aortic Dissection:** Patient enrollment for Aim 1 has been completed. The UM group finished the analysis of proteomics and identified three proteins as biomarkers and the PUHSC group is conducting the proteomics study on their side to confirm the finding. **Myocardial Infarction:** Genotyping of ~200,000 coding variants in 7,768 samples including 1,764 MI cases have been completed. A paper on initial findings is currently under review. **Blood Pressure Genetics:** The team completed preliminary statistical association testing and generated initial findings. One peer-reviewed paper has been published, and another is in process. **Cardiac Stem Cells:** IRB for collecting patient cells has been submitted at both UM and PUHSC and the UM protocol has been approved. The chemical approach for generating induced pluripotent stem cells (iPSCs) from mouse cells has been successfully completed at UM with guidance from the Deng Laboratory at PUHSC. The proposed experiments to generate human iPSCs are being carried out. **Brain Iron Overload:** Featured on pages 4 and 5.

**Renal Program**

**CKD Prognosis:** The experiments to develop non-invasive molecular markers for progression of glomerular were successful. The result was presented at the 2014 Annual Meeting of American Society of Nephrology. The first manuscript has been completed and will be submitted soon. The team is currently working on the identification of potential causal genes for IgAN. Data from the project is serving as preliminary data for the grant proposal submitted to the Juvenile Diabetes Research Foundation's consortium. **CKD Comparison:** A research poster on comparison of the prevalence and differential impact of risk factors for CKD in China and the USA was presented at the World Congress of Nephrology Conference in March 2015. The team is currently developing a manuscript toward submission to a peer reviewed journal.

**Institutional Review Board Core**

The IRB Core continues to provide support for all the JI collaborations to ensure they meet the human protection standards at both institutions. Both IRB's have recently established standard operating procedures for the review of JI protocols.
At A Glance

GI/Liver Program
HCV: Total enrollment includes over 1,800 patients. Abstracts will be submitted to the 2015 AASLD Liver Meeting. An LOI was submitted for the 2015 JI RFP. Two abstracts from the summer student project were accepted for poster presentation at both the 2015 EASL Meeting and the 2015 DDW Meeting. In June 2015, three M1 students, Jeremy Balch, Mary Guan, and Jiaxin Huang, will begin a summer project in Beijing as part of their global health experience. IBS: Dr. Owyang Chung visited Beijing earlier this year and met with the PUHSC team. IRB has been approved at both PUHSC and UMMS and the project is ready to implement.

Pulmonary Program
COPD: The multi-national project (which included PUHSC and UM) on analysis of the Microbiome in smokers with and without COPD has been successfully completed. Pollution and Asthma: IRB has been approved at both PUHSC and UMMS and the project is ready to implement. The JI Pulmonary group has submitted an LOI for the 2015 JI RFP on compartmental analysis of metabolite profiles associated with disease phenotypes in Chinese and US smokers with and without COPD.

Biorepository and Biomedical Informatics Core
Dr. Kai Zheng and Marisa Conte (Translational Research Informationist at the UM Taubman Health Sciences Library) received a grant of $75,623 from the National Library of Medicine to investigate unique information challenges to the acquisition, integration, and management of research data in collaborative health sciences projects with developing countries such as China. The BRBI Core continues to provide laboratories and IT applications support for the acquisition, storage, and management of bio-specimen and case report forms; solutions that integrate with PUHSC hospital information systems to acquire clinical and administrative data; and assistance in establishing high-throughput computing platforms for clinical phenotyping and analysis. In addition, the BRBI Core is currently identifying support needs for the JI projects awarded in 2014.

Collaboration Core
With the Collaboration Core's coordination and facilitation, 18 joint LOIs were submitted in response to the JI 2015 RFA. Invitations for the full proposal submission have been sent to the PIs. The review process will begin in April at both MICHR at UM and CRI at PUHSC.

Other Collaborative Projects
Radiology: The protocol was approved by the review committee at the University of Michigan Cancer Center. IRB was approved at PUHSC and is under review at UMMS. The MRI protocol optimization has been accomplished in five normal volunteers. The team has also been working on the concurrent retrospective study, collecting and analyzing data from 64 patients. Esophageal Cancer: IRB has been submitted at both UM and PUHSC. SNP genotyping and exome sequencing data for over 130 samples from 13 tumors has been analyzed. The result will be presented at the American Association of Cancer Research meeting in April and the Cold Spring Harbor Laboratory genome meeting in May. Epigenetic Effects of Prenatal Environment Exposures: Dr. Margit Burmeister met with her colleagues at PUHSC. During her stay, she helped organize the samples for the JI project and began the IRB process.
The 5th Annual Symposium of the Joint Institute for Translational and Clinical Research will be held October 26-28, 2015 in Beijing, China. Details are still emerging but we encourage you to mark your calendar now. Two years ago, over 50 UM community members were in attendance at the 3rd JI symposium. We hope to have the same wonderful representation this year. Stay tuned for further updates.
Five medical students from Central South University Xiangya School of Medicine (Pei Li, Xueying Liu, Lunchang Wang, Xiong Wei, and Mi Zhang) arrived on August 1 to spend two years in a research training program at UMMS.

**September 2014 - January 2015**
Dr. Xin Zhang from PUMC spent 18 weeks in the Learning Health Sciences department learning about procedures and principles of educational administration and participating in a research project on “Mental Health in First-year Interns”.

**November 2014 - December 2014**
Four final-year PUHSC students, Chang Wang, Chen Liang, Jianting Gao, and Jiwei Wang, participated in month-long electives at UMHS.

**July 2014 - July 2015**
In July 2014, Professor Hongtao Wu from Central South University began a one-year training program at the Department of Laboratory Animal Medicine under the mentorship of Dr. Evan Keller.

**April 2015 - May 2015**
Three medical students from PUMC (Shu Shi, Zhenlei Liu, and Tao Xixi) arrived in April and will participate in month-long electives at UMHS.

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**News From UMHS**

**News From PUHSC**

December 2014
The Beijing New Journey Cancer Hospital, which was established by New Journey Hospital Group and Peking University Cancer Hospital, held its opening ceremony on December 21, 2014.

**December 2014 - January 2015**
Dr. Margit Burmeister visited several hospitals, including Peking Union Medical College Hospital, to discuss potential collaboration on the topic of “Intern Health Study”.

**March 2015**
PUHSC faculty, Professors Minghui Zhao (JI) and Junbao Du, were recognized as the Most Cited Chinese Researchers by Elsevier.

**March 2015**
The Peking University People’s Hospital was awarded the Strategic Initiative for Developing Capacity in Ethical Review at the Forum for Ethical Review Committees in Asia and the Western Pacific.
Executive Officers of the University of Michigan Health System: Marschall S. Runge, MD, PhD, Executive Vice President for Medical Affairs; James O. Woolliscroft, MD, Dean, U-M Medical School; 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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