Through innovative collaborations, physicians, educators and researchers from SKMC are teaming up with medical experts in the People’s Republic of China to answer these and other health questions that transcend borders and time zones. Here are just a few of the many connections SKMC is making halfway around the globe.

**DERMATOLOGY: THE GENETIC ROOTS OF RARE DISEASES**

For one in 50,000 people, the inherited skin disease pseudoxanthoma elasticum (PXE) leads to a buildup of minerals in the skin, eyes and cardiovascular system that can dim vision, boost risk for heart attacks and stroke and scatter yellow bumps at skin folds. There’s no cure, but early research suggests identifying the genetics behind the condition could open the way for cell- and gene-based therapies. The hitch: Mutations vary by ethnic group.

Now, a collaboration between Jouni Uitto, MD, PhD, chair of the Department of Dermatology and Cutaneous Biology at SKMC, and Gang Wang, MD, PhD, chair of the Department of Dermatology at Xijing Hospital at China’s Fourth Military Medical University, has identified 16 mutations among Chinese women and men with PXE. The work, published in 2015 in the *Journal of Investigative Dermatology*, can help with genetic counseling, pregnancy planning in families with PXE and development of future treatments, the researchers say.

“Here in the U.S., we’re testing different allele-specific treatments on a pre-clinical level, looking at gene replacement and cellular therapies to stop PXE,” Uitto says. “It’s important to understand the mutations in different populations, so that one day therapy can be personalized.”

In 2013, the first Center of Excellence on PXE Research and Clinical Care in China opened at Fourth Military Medical University through the efforts of Uitto and Wang, with funding from the patient advocacy group PXE International and the Milstein Medical Asian American Partnership Foundation.

There, joint research using high-throughput sequencing to rapidly identify mutations “has significance beyond PXE,” Uitto says. “It’s a model for collaboration in studying the genetics of a wide variety of rare diseases.
that affect 26 million Americans and up to 150 million Chinese.”

Meanwhile, Uitto and colleagues are also working with partners at Beijing Children's Hospital to uncover the genes driving another group of devastating inherited diseases, called epidermolysis bullosa, that leave skin fragile and blistered.

CARDIOVASCULAR DISEASE RESEARCH: THE TRANSLATIONAL APPROACH

In China, one in five adults has cardiovascular disease. Heart attack, stroke and related conditions are responsible for 20 percent of deaths—a number expected to rise to 30 percent in the next 15 years, according to the World Health Organization. As attention focuses on primary prevention, Xinliang (Xin) Ma, MD, PhD, professor and director of the Cardiovascular Research Program in SKMC’s Department of Emergency Medicine, has expanded his work looking at heart failure and ischemic damage to cardiac muscle tissue across many time zones.

Ma, who received his PhD from Fourth Military Medical University in 1988 and came to Jefferson in 1989, began collaborating with colleagues in China in 1998. “A group from the university came to the U.S. to talk with Chinese researchers. They flew from San Francisco to New York, then took a Greyhound bus to Philadelphia to meet me,” Ma recalls. “I’m an emotional guy and that really moved me.”

More than 20 researchers have trained in his lab and returned to Fourth Military Medical University in China. “They’ve contributed immensely to my research,” he says. “Most are clinicians and have been able to do exciting translational research at home—taking findings from their work with patients and tracing them back to make new discoveries about cardiovascular disease. This is the new direction in translational medicine, rather than working all the time from the test tube up to humans.”

Since 2010, Ma has worked with heart researchers at Capital Medical University in Beijing, including Changsheng Ma, MD, chair of the university’s cardiology department. The relationship went in an unexpected direction. “The head of the university’s hospital is an ear, nose and throat specialist who also wanted to collaborate,” Ma says. “We decided to focus on obstructive sleep apnea (OSA), which greatly increases risk for heart disease. We have seven investigators, 30 PhD students and a whole team looking at the connection in many ways. I’m looking for clinical problems that I can use to generate useful scientific questions, then take them back and do basic science.”

One example: Ma and the team are on the lookout for people with extreme OSA who do not have cardiovascular disease. “We can then look for genetic mutations that are protective,” he explains. “That could lead to new treatments down the road.”

ULTRASOUND

Every day, the ultrasound department at West China Hospital of Sichuan University is remarkably productive: 25 doctors scan more than 1,000 patients. Despite this throughput, there is a backlog. Yan Luo, MD, director of the ultrasound department, is working with Jefferson to create new systems to care for her patients.

“In China, physicians perform almost all ultrasounds. They’re highly trained to do the scanning of every patient, and then read and dictate reports by themselves…But that’s beginning to change,” says Ji-Bin Liu, MD, professor of radiology at SKMC and director of the China-America Ultrasound Scholar Training Program. The Jefferson Ultrasound and Radiology Education Institute (JUREI), its China-America Ultrasound Scholar Training Program and the Department of Radiologic Sciences are collaborating with Sichuan University to hone a new health profession: sonography.

The universities are also working together to create a unique curriculum for Chinese students, with the ultimate goal to certify and credential the new sonographer profession through the American Registry for Diagnostic Medical Sonography. The Chinese sonographer program will also send some of its top students to Jefferson for advanced study.

Education has begun in both countries. In 2014 and 2015, Liu and colleagues Laurence Needleman, MD; Flemming Forsberg, PhD; John Eisenbrey, PhD; and Levon Nazarian, MD, taught at Sichuan University symposia and other sites in China. In summer 2015, Jefferson’s Traci Fox, EdD, attended the international exchange teacher program at West China Medical School to teach immersion courses in the principles and instrumentation of medical ultrasound and hemodynamics. Sonographers and physicians from West China Medical School and Hospital have also come to Jefferson for study.

The relationship between Jefferson Ultrasound and China began in the 1980s. More than 300 Chinese ultrasound physicians have visited Jefferson in the past 20 years. In 2013, supported by Vijay Rao, MD, the David C. Levin Professor and Chair of the Department of Radiology, the China-America Ultrasound Scholar Training Program was established between the Beijing Medical Ultrasound Association and JUREI to promote medical ultrasound career development for clinicians and researchers throughout China. Through JUREI, Jefferson has established ultrasound education centers at Zhongshan Hospital at Fudan University in Shanghai; Peking Union Hospital at Peking Union Medical College in Beijing; Xijing Hospital at Fourth Military Medical University in Xi’an; and Erdos Central Hospital at Erdos, Inner Mongolia. In 2015, SKMC partnered with Third Hospital of Peking University in Beijing to create a Musculoskeletal Ultrasound Collaboration Training Center.

“Many physicians from these centers come to Jefferson for symposia and fellowships and take back what they’ve learned to improve clinical care and research,” notes Liu, a graduate of Bethune Medical College at Jilin University in
Testing TCM

Traditional Chinese medicine (TCM), practiced for thousands of years, includes complex herbal formulas deployed against a wide variety of ailments. Now, researchers from SKMC are teaming up with colleagues at Zhejiang Traditional Chinese Medical Hospital (ZTCMH), affiliated with Zhejiang Chinese Medical University in Hangzhou, China, to take a deep look at TCM’s most potent active ingredients.

“First, ZTCMH will send research fellows, residents and dermatologists to SKMC for training in dermatology research laboratories and/or clinics,” says Qiaoli Li, PhD, research associate professor in SKMC’s Department of Dermatology and Cutaneous Biology. She is leading the project with Jouni Uitto, MD, PhD, chair of the department.

“Second, with many compounds/molecules extracted from complex TCM remedies at ZTCMH, a potential program may be established to test these compounds at Jefferson in skin and vascular derived cells in vitro. Active compounds, once identified, will be tested at Jefferson in pre-clinical animal models for skin diseases in vivo.”

ZTCMH researchers are particularly interested in compounds from formulas used to treat oxidative stress and inflammation in various pathologies. Ultimately, the project could yield new medicines drawn from an ancient tradition.

Rehabilitation Medicine Advances

Important goals of rehabilitation medicine include treating pain, healing or minimizing musculoskeletal injuries and addressing loss of function due to a wide variety of neurologic and musculoskeletal conditions such as stroke, arthritis and osteoporosis. An international program in SKMC’s Department of Rehabilitation Medicine that hosts visitors from the People’s Republic of China and encourages faculty to travel there to teach and train is doing both—and more.

“Rehabilitation medicine has grown rapidly in China since I first visited in 1981,” says John Melvin, MD, department chair and the Jessie B. Michie Professor of Rehabilitation Medicine. “We always have one or two visitors in our department. And professionals we have hosted have gone home to take important leadership roles.”

These include Jianan Li, MD, professor and chair of rehabilitation medicine at Nanjing Medical University and current president of the International Society of Physical and Rehabilitation Medicine. Li spent six months at Jefferson in 2001, noting at the time, “I have visited rehabilitation facilities in more than a dozen countries. There is no doubt that the strength of rehabilitation
Changchun, China, who came to Jefferson as a research fellow in 1987. He also collaborates with Chinese ultrasound researchers. “Jefferson also provides training materials to the centers and many faculty members have visited to give lectures. I don’t think there’s another ultrasound education program like JUREI anywhere in the world. The group has more than 75 affiliates from Afghanistan to Honduras to Nigeria and beyond and is recognized by the World Health Organization as a Collaborating Center for Continuing and General Education in Diagnostic Ultrasound.”

“Improving ultrasound through worldwide collaborations is an important part of JUREI’s mission. Face-to-face education here and in China between faculty and students encourages deeper ties and better education. We are also thrilled to lend our experience to start a new model of clinical ultrasound which incorporates sonographers,” says Nazarian, professor of radiology and JUREI director.

**RADIATION ONCOLOGY: RESEARCH HORIZONS**

Chinese research fellows are exploring important questions in radiation oncology for the treatment of cancer with SKMC investigators. “At any time, we have three to six physicians and researchers from China here through our department’s International Fellowship Program in Radiation Oncology, Molecular Radiation Biology and Medical Physics,” says Adam Dicker, MD, PhD, chair and professor of radiation oncology, pharmacology and experimental therapeutics. “We’ve forged close relationships with institutions across China.”

Recent collaborations include:

- An evaluation of robotic surgery guided by magnetic resonance imaging and of an image-guided brachytherapy system, which implants radioactive “seeds” directly in affected tissues. These are collaborations between Yan Yu, PhD, MBA, vice chair of the Department of Radiation Oncology and director of the Division of Medical Physics at SKMC, and investigators from Tianjin University’s Center for Advanced Robotics.

- An investigation of novel genetic mutations driving radiation-resistant cancers. Work is underway by a researcher from the Shanghai Cancer Center at Fudan University in the lab of Bo Lu, MD, PhD, director of the Division of Molecular Radiation Biology in Jefferson’s Department of Radiation Oncology.

- A comparison of surgery and stereotactic radiotherapy for early non-small cell lung cancer—one of the most common forms of cancer in the world. This multi-center study involves a collaboration between Ying Xiao, PhD, professor of radiation oncology and director of SKMC’s International Fellowship Program, and researchers from five Chinese universities.

- Immunotherapy combinations of checkpoint inhibitors and DNA-damaging agents using preclinical models of lung cancer. The goal is to have data for the development of the next generation of lung cancer clinical trials. This collaboration involves Dicker, Bo Lu and You Lu of West China School of Medicine, Sichuan University.

“Our relationships began as personal contacts as Chinese-born faculty and researchers from SKMC gave lectures and did trainings in China through the years. This has grown into very strong collaborations,” Dicker says. Recently, Jefferson’s Department of Radiation Oncology sponsored the Shanghai Cancer Center at Fudan University—one of China’s largest cancer centers—as an affiliate member of the Radiation Therapy Oncology Group (RTOG), a key clinical research component of the American College of Radiology. The RTOG (now known as NRG Oncology) is part of the National Clinical Trials Network, an international research cooperative funded by the National Cancer Institute that aims to increase survival and improve the quality of life for cancer patients.

In one notable Philadelphia-Shanghai collaboration, physicists from SKMC and Fudan University demonstrated that a semi-automatic review process for personalized radiation treatment plans shortened patient wait times and reduced the risk of human error. “The tools developed from the study will benefit Chinese radiation oncology departments where a large number of patients are being cared for,” said Zhen Zhang, MD, PhD, chairman of radiation oncology at Fudan University Shanghai Cancer Center, when the work was published in the journal *Physics in Medicine and Biology* in 2013.

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**Melvin adds. “They’re developing a national system for measuring outcomes. The reason we all go into rehab medicine is to help people. Good measuring tools will let us see how well our efforts are working and what needs to be changed.”**

**RMBL**

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