Tsinghua University scholars Yang Gao (left) and his roommate, Wei Li, take part in the second annual Pitt-Tsinghua scientific symposium held in April 2013. Gao is investigating the role of inflammatory-related electrophilic fatty acid derivatives in airway dysfunction related to allergic pulmonary diseases. Li is studying potential neuroprotective mechanisms of melatonin in an animal model of ischemic stroke.
"WE ARE FRIENDS."

On his way to a symposium at the University of Pittsburgh in April, Yigong Shi, a PhD, dean of Tsinghua University’s School of Life Sciences, and executive vice dean of its School of Medicine, declined to fly the last leg of his trip from Beijing. Instead he elected to deplane in Chicago, visit colleagues in Illinois, then drive the 460 miles to Pittsburgh, solo.

It felt like coming home, says Shi.

He had first arrived in this country in 1990 to begin a PhD program in molecular biophysics at Johns Hopkins University and remained until 2008, when he gave up a prestigious endowed professorship at Princeton University to return to Tsinghua, his alma mater.

“Twenty-three years ago, I landed in Ames, Iowa, surrounded by cornfields, and drove 22 hours to Baltimore,” Shi recalls. “I’ll never forget the welcoming people of the Midwest or how fascinated I was by the landscape on that long drive.”

And, now, 21 Tsinghua students are making the United States a second home, too.

Shi’s road trip would bring him to the second annual Joint Symposium on Medical Sciences—an unprecedented collaboration between the medical schools at Pitt and Tsinghua.

The students, who arrived at Pitt in August 2012 to begin two years of intensive biomedical research training, have been welcomed by a community eager to provide an unforgettable experience.

As the students came together to formally showcase their work for the first time at the symposium, we had a chance to see how the program was panning out.

Lijia Cui says that she has quickly fallen in love with the unfamiliar, hilly terrain of Pittsburgh, despite the fact that it exhausts her when she bicycles around the city. She was assigned to the lab of Elodie Ghedin, a PhD, MacArthur Fellow, and associate professor of computational and systems biology. Cui was nervous at first about being in an American lab because she still has a lot to learn about conversational English. In Ghedin’s lab, however, she found herself on a team with Americans, Canadians, and an Indian, so the addition of a Chinese med student wasn’t out of the ordinary.

“We are friends,” Cui says now.

Ghedin’s lab studies the genomics of infectious diseases. Working with her new colleagues, Cui developed an experiment using next-generation DNA sequencing to study the fungal microbiome in patients with both HIV and chronic obstructive pulmonary disease (COPD), which tend to co-occur. Her studies yielded 19 fungal genera in these patients that did not show up in healthy controls—only four of which had previously been associated with HIV and COPD in the scientific literature. Next steps for Cui include further research to determine whether fungi are driving COPD symptoms in these patients and how.

Ghedin says that having Cui in the lab has been a boost to the team. Lab staff members are supported by multiple grants, so each member has multiple areas of responsibility. But the Tsinghua students, funded by the collaborative agreement between the partner universities and the Chinese government, are able to focus on one project at a time.

“Because of limited resources, we weren’t even going to do this experiment,” says Ghedin. “But now she is finding really interesting stuff that is going to lead to further research.”

Another student, Luxi Sun, says that the Pitt-Tsinghua program is exactly what she’d hoped it would be. The daughter of two developmental biologists working at the Chinese Academy of Sciences, Sun arrived with a good sense of what interests her. She was thrilled to find that Pitt has a strong and welcoming research program in DNA damage and repair mechanisms. The genome stability group, as it is called, includes multiple investigators from the medical school and the University of Pittsburgh Cancer Institute, including med school dean Arthur S. Levine, who is also senior vice chancellor for the health sciences. Sun is working with mentor Li Lan, an MD/PhD assistant professor of microbiology and molecular genetics. Sun is helping the lab team elucidate DNA-damage-response mechanisms that could have important implications for cancer and aging. Lan and others have figured out a way to induce damage in specific locations in a genome using the fluorescent protein KillerRed; they then observe DNA repair proteins as they migrate to fix the damage in live cells. Sun’s contributions to the lab’s work have already led to coauthorship on a forthcoming publication in The Journal of Cell Biology.

As for life in Pittsburgh, Sun is surprised and delighted by how easy it has been to explore American culture. She has taken in the Pittsburgh Symphony Orchestra performing Beethoven and the national tour of the musical Chicago; both performances were
just a short bus ride from campus. She finds Pittsburgh peaceful and says that the environment has allowed her to relax and commit completely to research.

As a driving force behind the collaboration, Levine has always had high expectations of the Tsinghua students. But after spending much of two days with them at the symposium, he declared himself in awe of the students and their work. Both Levine and Shi said at the event that they hope the Tsinghua students come to think of Pittsburgh as their alma mater.

Further cementing the bonds between these two institutions, the final day of the symposium included a gift from one long-time friend and colleague to another. When he was a grad student at Johns Hopkins, Shi was mentored by Jeremy Berg, a PhD, Pitt’s associate senior vice chancellor for science strategy and planning, health sciences, and director of the Pitt-UPMC Institute for Personalized Medicine. Berg presented Shi with a 3-D model of a protein for which Shi had determined the crystal structure. Berg also announced that Shi had learned that very day that he was among 21 foreign associates elected to the U.S. National Academy of Sciences—a rare honor.

Shi raised his gift in the air and spoke of the personal connections the students and mentors will make in their scientific careers. Some 23 years after first meeting Berg, who is scientific director of the Pitt-Tsinghua program, he is still a valued mentor, Shi said—now for the Tsinghua students.

“You are like the grandsons and granddaughters of Jeremy,” he said.

The next family reunion will be in Beijing in 2014.
As scientists continue to discover promising new methods of treating cancer at the genetic level, one nagging question persists: How to administer them efficiently?

Flordeliza Villanueva, professor of medicine at Pitt and director of Noninvasive Cardiac Imaging at UPMC Presbyterian and of the Center for Ultrasound Molecular Imaging and Therapeutics (CUMIT) at UPMC’s Pittsburgh Heart, Lung, Blood, and Vascular Medicine Institute, has shown that microbubbles—gas-filled globules that are smaller than red blood cells—can transport potent treatments into tumor cells. She is collaborating with Andrew Carson and Jennifer Grandis from CUMIT and the University of Pittsburgh Cancer Institute, respectively.

Microbubbles have many diagnostic applications. As Villanueva has previously shown, these tiny vesicles can be used to image blood flow to the heart. When injected into the body, microbubbles travel everywhere that red blood cells circulate, and when subjected to ultrasound, they light up inside tissue microvessels. Ultrasound causes the microbubbles to expand and contract rapidly. This activity creates a signal that can be detected by an ultrasound transducer, confirming the microbubbles’ location and helping to reveal information about blood flow to the heart.

Microbubbles also have therapeutic applications as a result of their unique vibrations in response to ultrasound—like chiseling through blood clots. Villanueva is hoping they can penetrate cancer’s armor, too.

When microbubbles in the blood vessels are subjected to a particular ultrasound frequency and pressure, they pop, causing temporary leakiness of the outer membranes of blood vessels and nearby cancer cells. The effect is similar to that of a grenade on a fortress; the cancer cell may not crumble, but it will suffer holes and cracks in its protective membrane that leave it vulnerable to entry by drugs. This is where microbubbles can pull double duty.

If an anticancer agent were attached to the exterior of a microbubble and the microbubble were intravenously injected then exposed to ultrasound as it passed through a tumor, Villanueva posited, as the microbubble popped, it might not only poke holes in the cancer cell’s membrane but could also release its payload drug, which could then enter the newly porous cancer cell. Importantly, only areas receiving ultrasound would receive the drug, potentially reducing side effects that typically result from drug delivery to non-tumor sites.

Villanueva’s research team armed the microbubbles with a powerful cancer-inhibiting agent—a small inhibitory RNA (siRNA) directed against epidermal growth factor receptor (EGFR); the siRNA reduces EGFR production. (EGFR is overproduced by cancer cells and plays a major role in tumor growth.) “Therapeutic nucleic acids are, in general, difficult to deliver into a cancer cell,” she says. “They are fragile when injected into the bloodstream, and when injected directly into a tumor, they leak through the injection site or tumor ulcerations or are actively internalized and destroyed by cancer cells. Microbubbles are designed to get around these hurdles.” The team demonstrated the effectiveness of this siRNA-delivery method in a mouse model of head and neck cancer.

EGFR took a hit. Multiple treatments decreased tumor EGFR expression, and tumors took much longer to grow. The work gives credence to the idea of using customized microbubbles as precision delivery systems of siRNA or other gene-targeted molecules for cancer treatment. The therapy, if it aces clinical trials, may be an effective and noninvasive way to kill tumors—one that could be done at the bedside for outpatients and reduce the side effects of other treatments.