



Anna Simos has devoted her career to preventing diabetes and caring for those who have it. **Page 5**

Musician develops drug, changing career in process

By Kim Smuga-Otto

Julie Saiki tried several violins from the Stanford Department of Music's collection until she found one whose sound was just right. But she kept herself from getting too attached. It was on loan — hers for as long as she was enrolled in lessons or performing with her chamber group at Stanford. She assumed returning the instrument would happen after she had earned a PhD in musicology. Instead, it happened because she switched degree programs.

Saiki will always be a musician, but now she is working toward a PhD in Stanford's Chemical and Systems Biology Program.

Saiki's plans for a doctorate in musicology were knocked off course after she was diagnosed with ulcerative colitis, a disabling inflammation of the colon. It wasn't the disease but the cure that sent her in a new academic direction. An herbal remedy put her symptoms into remission, and she went looking for a way to make it available to others. Despite having no science background, she enrolled in a course on drug development; successfully pitched her idea to SPARK, Stanford's drug development training program; and received approval from the U.S. Food and Drug Administration to begin a clinical trial. Each step brought her cure closer to patients, but the experience, and her success, caused her to re-evaluate her career.

"It was a big awakening," she said, upon realizing her curiosity and love of learning could be channeled to directly benefit others.

Saiki is a petite woman with delicate features. Her long, wispy hair falls over her eyes when she nods her head. But the hands that brush back the hair are taut and muscular. They move with precise intent, a consequence of years of violin training.

She doesn't remember a time when she didn't play, and in high school she set her sights on performing professionally. At Colgate University, in New York, her



NORBERT VON DER GROEBEN

Finding an alternative remedy for her ulcerative colitis set Julie Saiki on a new and unexpected career path as a scientist and entrepreneurial drug developer.

focus shifted to scholarship, and after graduating she spent a year as a Fulbright scholar researching Austrian chamber music. The Stanford Department of Music's strengths in Austro-German music made it a logical place to continue her studies. It would have been the perfect fit, if she hadn't gotten sick.

The disease and the cure

Her illness began with diarrhea, then blood in her stools and mild abdominal pains. She was diagnosed with ulcerative colitis her first year of graduate school, in the fall of 2008. The change came as a shock. Saiki, healthy her whole life, was taking up to 12 pills a day and visiting her doctor every

See DRUG, page 6

Karl Deisseroth wins \$3 million for work in creating optogenetics

By Bruce Goldman

Karl Deisseroth, MD, PhD, professor of bio-engineering and of psychiatry and behavioral sciences at Stanford, is the winner of a \$3 million 2016 Breakthrough Prize in life sciences for his contributions to the development of optogenetics, a technique that uses light to control the behavior of cells and has proved especially invaluable in the study of nerve-cell circuits in the brain.

The award was presented Nov. 8 at a private black-tie, red-carpet ceremony in an airplane hangar at Moffett Field in Mountain View, California. Actor and television producer Seth MacFarlane, creator of the animated TV series *Family Guy*, was master of ceremonies for the event; singer and songwriter Pharrell Williams performed. Many Silicon Valley and Hollywood luminaries were in attendance. The Breakthrough Prizes, initiated in 2013, honor prominent individuals in the fields of life sciences, fundamental physics and mathematics. Deisseroth was among three Stanford scientists honored at this year's event.

"The suffering of the mentally ill and the mysteries of the brain are so deep that, to make progress, we need to take big risks and blind leaps," Deisseroth said in his acceptance speech. "The members of my lab have taken a leap: borrowing genes from microbes to control the brain."

In an interview, Deisseroth said, "Optogenetics' biggest impact by

See DEISSEROTH, page 3



STEVE JENNINGS / GETTY IMAGES

Karl Deisseroth speaks Nov. 8. at the 2016 Breakthrough Prize ceremony.

Immune cells' behavior before surgery linked to recovery time

By Kim Smuga-Otto

The behavior of a type of white blood cell can indicate how soon patients will

be back on their feet after hip surgery, according to a study by scientists at the School of Medicine.

The scientists plan to use the findings to develop a diagnostic blood test that patients can undergo before surgery.

U.S. doctors performed more than 50 million surgeries, including some 300,000 hip surgeries, last year. While indicators for negative outcomes — like organ failure, infection and death — have been extensively studied, indicators for

See RECOVERY, page 7



CHANAWIT / SHUTTERSTOCK

Stanford scientists hope to develop a diagnostic blood test that could indicate how soon a patient might recover from surgery.

Study: Drug relieves symptoms of chronic depression in people who have insulin resistance

By Bruce Goldman

A drug that makes the body more sensitive to insulin helped to relieve symptoms of chronic depression in people resistant to the hormone, according to a study by researchers at the School of Medicine.

The 12-week, randomized, placebo-controlled study, published Nov. 18 in *Psychiatry Research*, involved patients whose symptoms of depression had failed to improve substantially, despite treatment, for at least six months leading up to the study's onset.

"This is the first placebo-controlled study to show the antidepressant benefits of treating unremittably depressed patients with an insulin-sensitizing drug," said the study's senior author, Natalie Rasgon, MD, PhD, professor of psychiatry and behavioral sciences.

"The study is important," Rasgon said, "because it bears out a hypothesis we first advanced over a decade ago about the connection between insulin resistance — the body's inability to efficiently process glucose,

See DEPRESSION, page 7



Natalie Rasgon

Drug

continued from page 1

two weeks. The disease took a mental toll, as well.

"I started to care less about my music; it didn't seem as important when my body wasn't functioning properly," Saiki said.

Ulcerative colitis often strikes people in their 20s. In about half the cases, the disease responds to the drug 5-aminosalicylic acid, inflammation recedes and patients live symptom free. In those who don't respond, stronger treatments, such as immunosuppressants, are brought into play. Uncontrolled ulcerative colitis increases the risk for colorectal cancer and, for the 10 percent of patients who do not respond to any treatments, surgical removal of the colon and rectum is required.

Patients and their doctors usually try 5-aminosalicylic acid with corticosteroids before moving on to immunosuppressants, which increase patients' risks for infections and some cancers. In addition to standard medications, Saiki also tried changing her diet by eliminating oily and sugary foods and by taking probiotics. Nothing worked. Months passed, and she wasn't getting better.

When her father mentioned an herbal remedy he'd read about, she decided to give it a try. After tracking down a supplier, she received the herb and mixed it into her tea. It tasted so awful that she couldn't bring herself to drink it. She solved the problem by encapsulating the drug with a manual pill filler and taking it along with her prescribed medication.

"Literally a couple of days after I started taking it, the bleeding stopped," she said. "All my symptoms went away." Things went so well that she tapered off all the other medications and even forgot to take her herbal remedy on vacation. After a couple weeks, her symptoms flared up again. When she went back on her pills, the symptoms receded, convincing her of their effectiveness.

In the age of social media, many of us would have dashed off an enthusiastic Facebook post to a support group to spread the word. But that approach never occurred to Saiki. She wanted doctors to be able to prescribe this as a drug, and for patients to be able to pick it up at their pharmacy. "I wanted to do this the right way," she explained. "I wanted to develop a new treatment for ulcerative colitis patients." (Because she is seeking to have the drug commercially licensed, Saiki asked that the drug's source not be identified in this article.)

A musician among the scientists

Saiki's first inquiries about legitimizing the treatment were to her chamber group's cellist, who — this being Stanford — was also a doctor and professor of hematology. He recommended a literature search. Combing through the scientific publications, she found that no one had performed a clinical trial.

Saiki also typed "drug development" into Stanford's online course catalog. "CSB 240A — A Practical Approach to Drug Discovery and Development" came up. She emailed the instructors — associate professor Kevin Grimes, MD, and professor Daria Mochly-Rosen, PhD, both in the Department of Chemical and Systems Biology — asking to enroll.

They turned her down.

She didn't have the scientific background, they explained. Because the class was group-project-based, if Saiki couldn't keep up, it would hurt her classmates, as well.

But Saiki refused to give up. She believed in her remedy and its usefulness to others. "The class was exactly tailored to what I wanted to learn. It's the only class really available on the topic," she said.

"She kept saying, 'Just give me a chance — I can study, I can learn,'" recalled Mochly-Rosen, who is also the George D. Smith Professor in Translational Medicine. "She's a very unassuming person; you don't expect she'd be so insistent."

In the winter quarter of 2011, Mochly-Rosen let Saiki enroll, despite concern that she wouldn't be able to keep up.

Saiki, Mochly-Rosen observed, was a quiet student, but whenever she was directly questioned about her group's progress or approach, her answers were clear and confident. Saiki admits that initially the science lectures were over her head, but her group's project — a probiotic treatment for *Clostridium difficile* infections — included market research and how to satisfy regulatory requirements, things Saiki found she could contribute to. She set about to master the individual parts of the process, similar to how she would approach a new piece of music. "You pick things up once you start putting the pieces together," she said.

Privately, she'd replicate each assignment for her own drug. When Saiki showed the results to her instructors, they invited her to present her work to the class.

On the final day of class, after the groups had pre-

sented, Saiki pitched the remedy as a potential drug to treat ulcerative colitis. She began with side-by-side medical colonoscopy photographs. The image on the left was puffy, angry-red and inflamed. The one on the right was smooth with faint blood vessels crisscrossing healthy pink tissue. This, Saiki explained, was her colon before and after she began treating herself. From there she carefully laid out the development and regulatory steps needed to bring the drug to clinical trial. After her presentation, Mochly-Rosen, Grimes and the industry guest who was helping to evaluate the students agreed that Saiki should present to the SPARK group.

SPARK was started in 2006 by Mochly-Rosen to support Stanford scientists and doctors in transforming promising compounds into clinical drugs. Every year, a dozen projects, out of nearly 200 considered, are selected for funding and advising support. Successful candidates range from graduate students to professors with full labs. Saiki wasn't aware she was auditioning; she was just excited for the chance to get feedback.

'Like a performance'

On the day of her presentation, Saiki calmly addressed the gathered Stanford faculty and industry professionals. Saiki may have been playing catch-up with many aspects of the world of science, but when it came to taking the stage, she had a long history.

"Most musicians have a journey with nerves," explained Saiki's former violin instructor, Laura Klugherz, a music professor at Colgate University and director of the Colgate Chamber Players. With each recital, each solo performance, more of their nervousness rubs away until the fear is gone. "Julie traveled that journey diligently and successfully," Klugherz said.

"Her presentation was bam!" said Lyn Frumkin, MD, PhD, a SPARK adviser, recalling the first time he heard Saiki present at a meeting about her projects status. "From the time she opened her mouth to the time she finished — clear, articulate, interesting, like a performance."

It wasn't just the delivery. Frumkin was impressed by the originality of Saiki's idea and her deep understanding of the scientific and bureaucratic steps required to establish her drug's efficacy. He was stunned when he learned that Saiki's background was in music.

Other members of the SPARK advisory board were similarly won over. They invited Saiki to join SPARK, and in 2011 awarded her a \$50,000 Spectrum pilot grant, supported through a Clinical and Translational Science Award from the National Institutes of Health, to develop SA100, the working name for her drug. Since then, she's gone on to raise other sources of funding for her project.

Now she had to obtain permission from the FDA through its investigational new drug application. Frumkin, who's worked in the drug industry for more than 20 years, described producing an IND application as "a lengthy process, analogous to a term paper a thousandfold." Beyond making a scientific and medical case for the drug, the IND application must justify drug dosages, manufacturing decisions and clinical study designs, explain how the results will be assessed, and address statistical, regulatory and quality-assurance issues.

"Few, except people in industry, really write them," said Frumkin. He and Saiki pored over her initial first draft and as well as successful IND applications. For each section, Saiki asked detailed questions. "She wanted to know the reason things were one way versus another," said Frumkin.

Outside of SPARK, Saiki was getting up to speed on the science and business of drug development. She earned a master's degree in medicine from Stanford in the spring of 2014, a program that teaches a medical school curriculum without the clinical courses and is designed to prepare science and engineering graduate students for medical research. And in the summer of 2013 she interned at Genentech, a Bay Area drug company.

Drawing on this new knowledge, Saiki and her team wrote their nearly 400 page IND application and sent it off to the FDA. It was accepted in 2014. SA100's effectiveness would be confirmed, or denied,

by a clinical study.

Into the clinic

Unlike large drug companies that can access multiple centers across the United States to run clinical trials, Saiki and the doctor running the trial, Shamita Shah, MD, until recently a Stanford clinical assistant professor of gastroenterology and hepatology, could recruit only patients within driving distance of Stanford. And they were looking for a particular type of patient, one who wasn't responding to the initial 5-aminosalicylic acid treatment but had not yet moved to immunosup-

NORBERT VON DER GROEBEN



Saiki was a graduate student in musicology at Stanford before switching to the PhD program in chemical and systems biology.

pressive drugs — the stage that Saiki was in when she began using her homemade pills.

The similarity wasn't intentional — this was the best group on which to test both the safety and efficacy of SA100 — but Saiki admits to an emotional connection to these patients' predicament.

"We felt the patient group in greatest need was the one that failed 5-aminosalicylic acid treatment," she said. "For that reason, we wanted to go straight to those patients and see if it works."

That type of patient has proved difficult to find. While Shah, who was the clinical director of Stanford's inflammatory bowel disease program, had numerous patients with ulcerative colitis, most had advanced cases and had already switched to immunosuppressants or other treatments. Saiki and Shah reached out to local clinics but found no eligible patients.

Undaunted, they've expanded their search to social media and patient support groups to find patients to enroll. And Shah's recent relocation to the Ochsner Health Center, in New Orleans, means they can look for participants in two locations. Shah is excited to continue her collaboration with Saiki. "She's been the passion behind the study," Shah said. They hope to enroll the 24 patients needed for the trial within the next year.

While Saiki was achieving success with SPARK and her science classes, she was struggling with her musicology PhD. Her interest in medicine drew her away from her research on chamber music. She tried to merge the two by looking for relationships between music and medicine but found that the ways she approached these subjects were too different. She said, "it was very hard to even have an interesting conversation" between them, much less a thesis.

SA100's development was demanding much of her time, and new medical research opportunities were coming her way. She had to make a choice.

"For so many years, I've worked toward this path. Everything — practicing long hours, learning German, spending time abroad — all that was in preparation for an academic career in music," she said. "Withdrawing was truly hard because I felt like I was just giving up."

But medical research, specifically drug development and other interventions to improve patient health, excite her more, she said. She hasn't turned her back on music, but now she more frequently wields a pipette than a violin bow.

"I feel like I am working on something that can potentially help someone," she said. "At the end of the day, that experience is very gratifying."

Those interested in learning more about Saiki and Shah's ulcerative colitis clinical trial can contact clinical research coordinator Ankita Dubey at ankita.dubey@stanford.edu. ISM

Kim Smuga-Otto is a former science-writing intern for the medical school's Office of Communication & Public Affairs.