STANFORD MEDICINE

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special report

THE FUTURE

HUMAN CENTERED, DISCOVERY LED

sparking drug discoveries

ACADEMIC RESEARCH CATCHES FIRE

BY ROSANNE SPECTOR

ILLUSTRATION BY MARK SMITH

On a spring day last year, Jane Tseng, PhD, was visiting Stanford to make connections to aid her drug development quest. The drug would be based on discoveries made by Tseng and other researchers at National Taiwan University. The compound already looked promising for helping people with schizophrenia and two other neurological conditions, and she wondered if it could help others. But one condition the professor of computer science was definitely not interested in pitting the drug candidate against was autism.

"Because autism is a spectrum, it's going to be hard to test a drug and show it helps. Very hard," she said.

Still, when Kevin Grimes, MD, co-director of Stanford's SPARK drug development program, asked her if she'd like to talk with a Stanford autism expert, she said yes.

"SPARK sparks things. I was at Stanford to get new ideas, so I talked with him," Tseng said.

At home in Taiwan, Tseng is the director of the Drug Research Center of the College of Pharmacy at National Taiwan University. She's known for figuring out how drugs interact with other molecules and how that can enable them to work as treatments. But in Taiwan, as in the United States, most academic researchers know very little about turning a discovery into a drug people can use.

That's where SPARK comes in. The fast-growing program, founded in 2006 at Stanford, has given hundreds of academic researchers around the world training and connections to help get their ideas out of the academic realm and into doctors' and patients' hands. For most, it's a rare chance to see their discoveries helping people in need, and sometimes even saving lives.

The program has also proved to be an engine of discovery, especially for innovative drugs that answer unmet needs. Most of the SPARK projects address child and maternal health, global health and orphan diseases, all sectors neglected by pharmaceutical development.

Of 89 projects Stanford's SPARK program has sponsored in its first decade, 42 have been taken up by companies for further development, with 22 of these making it into clinical trials. SPARK has started 11 other clinical studies, without company involvement, of previously approved drugs for new clinical indications. The result is 37 percent of SPARK projects advancing to clinical testing.

The effectiveness of the approach has been noticed around the globe, with 57 programs based on the SPARK model being launched by academic institutions and governments on every continent except Antarctica. And the program directors have created a network of like-minded scientists in academia ready to address global health challenges when they arise.

"SPARK exemplifies how those of us in academia can go beyond what is expected — which is to teach and write papers," said Daria Mochly-Rosen, PhD, the program's founder and co-director. "It's a very simple and effective way to make sure that the research we publish eventually impacts patients. For us not to harness this potential and not bring it back to society is just irresponsible. This speaks to many of us, who really want to help patients. I think that's why it caught fire."

'this speaks to many of us, who really want to help patients. I think that's why it caught fire.'

The keys to SPARK's success, said Mochly-Rosen, are the outside-the-box ideas provided by university researchers and the mentorship provided by industry experts. She learned how important that mentorship is the hard way.

For her first two decades in academia, Mochly-Rosen was immersed in the lab, typical for a researcher exploring molecular interactions within and among cells. But when one of her discoveries seemed that it could be the basis of a drug to reduce harm from heart disease, she felt compelled to see that drug become reality. And after the university's efforts to interest a company fell flat, she decided she'd form a company of her own. "How hard could it be?" she thought at the time.

Very, she discovered. She took a leave of absence for a year and ultimately succeeded, co-founding KAI Pharmaceuticals Inc. in 2002 (acquired by Amgen in 2011), but it was touch and go at times: "There was no transition in my life that was more dramatic, except maybe the birth of our first child. I knew nothing about drug development, about the rigor and intellectual challenge that drug development entails," she said.

A few years after returning full time to Stanford she started SPARK to help others make the transition — to conduct what's called in academia "translational research." Grimes, at the time KAI's senior director of clinical research, left the company to co-direct SPARK and teach a course about drug discovery with Mochly-Rosen, now the George D. Smith Professor in Translational Medicine.

Another reason for the popularity of SPARK is cost. It can be less expensive than the traditional way universities attempt to spur translational research, which makes the model feasible for institutions with fewer resources, such as the University of Zimbabwe, the site of one of the newest SPARK programs.

"The most common solution for an institution that recognizes the need to do translational research is to create an incubator," said Mochly-Rosen. An incubator is a facility with professional staff to advise the investigators on all aspects of taking an idea and maturing it. Some incubators also provide equipment and help with writing grants.

SPARK at Stanford has no special facility or equipment. What it has is a wealth of volunteer advisers from industry. The program supports about a dozen SPARK inventors, or SPARKees, with up to $50,000 per year for two years to show "proof of concept" for each drug candidate. In other words, they start at the first step of drug development, clinical needs assessment, then move through stages, which include identifying the drug molecule and the molecules

it interacts with; optimizing the drug molecule; assessing toxicity, dosing, and the best way to deliver it, first in lab studies and sometimes even in human trials — all to make the case to industry investors that there's demand for the drug and that it will actually work.

"We de-risk the projects so industry doesn't have to," said Grimes.

At Stanford the mentoring happens every Wednesday evening, when several of the research teams give progress reports to the gathered advisers, Mochly-Rosen, Grimes and other SPARKees. Stanford's program has 200 advisers — pharma scientists and business leaders — and 30 to 40 of them show up on any given Wednesday. If a researcher needs to test an unwieldy molecule for toxicity, one of them has likely tried it before and can share the tricks and pitfalls. They also share little-known facts — for example, did you know that ferrets are useful models for studying how lungs respond to drug candidates?

"They give real-world experience. It's an opportunity to learn not only what succeeded in industry, but what failed — which is really unique," Mochly-Rosen said.

"In each meeting we also have multiple advisers on the same topic. You don't get just a single person's opinion." The industry advisers, who sign nondisclosure agreements, can also meet with the scholars one-on-one and help them connect with potential business partners once the project is ready to leave the academic nest.

Tseng's project, now in clinical trials, is a typical example of how the process works.

She learned about SPARK from the vice president of her university, who heard about her research project and told her she should join. The government of Taiwan supported the first SPARK program outside Stanford, basing programs at National Taiwan University and National Cheng-Kung University in 2013. Now, six universities in Taiwan serve as bases. Tseng liked the idea behind SPARK, applied for funding and was accepted as a SPARK Taiwan scholar. Like Stanford's SPARK, Taiwan's programs have weekly gatherings with advisers from industry and venture capital firms.

Tseng's research focus is molecular modeling. "Basically I design a molecule using algorithms," she said. "We can do fast and robust drug discovery on the computer nowadays. But I was pretty much clueless about commercialization, like most university basic science researchers."

She was leading a huge team — six principal investigators and their labs — working together to see whether a molecular interaction that seemed to control certain symptoms of schizophrenia could be the basis of the drug. The symptoms, known as the negative symptoms of schizophrenia, are decreases or losses of normal functions — for example cognitive abilities, speech production, emotional response and interest in social interaction.

"The people with negative syndrome with schizophrenia are like a stone, no interest in interacting with others. And there's no effective treatment," said Tseng, who is now director of Taiwan SPARK.

The project was spurred in part by findings by others that a common food preservative seemed to comfort patients and alleviate negative symptoms. Tseng considered the molecular structures and interactions while eating lunch, a soothing bowl of instant ramen soup. "I thought, wait a second, I'm pretty sure what I'm drinking right now is a soup containing that same preservative. So are you telling me that everyone who's homesick loves to eat instant noodle just for the preservative? It's a comfort food for nearly everyone. This gave me a clue," she said.

Eventually, she and her collaborators identified a molecule and the key molecular connection that modulates the neurological symptoms. Interestingly, the drug candidate acts on a complicated biological pathway involved in learning, memory and much else — a pathway that hasn't been explored much for antipsychotic drug targets.

The group tested the drug in a small clinical trial of seven patients and it seemed to be working well, but the team didn't know what to do next, Tseng said. Then the project was selected for the 2016 SPARK showcase, an annual event at the Bio Investor Forum, a major international biotech conference. At the showcase, SPARKees from around the world pitch their projects to potential industry partners or funders.

"I had to learn how to do pitching. To be honest, I wasn't even familiar with the term, so I Googled it," she said.

That was another learning experience. "I was very hesitant to say that, 'Guess what, we are starting the company.' I had the idea it was the right thing to do but it was very scary to think down that path.

"It's a different way of thinking," Tseng said. "I had to learn how to pitch my project to VCs and pharma, and at first it didn't really click. You have to get used to thinking from the very end to the very beginning. You have to learn how

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cabinet" is still many years away. The advent of a purposed, customized designer microbiota will have to await the patient collection of dozens or hundreds of "pill bottles" — the discovery and/or manipulation of individual gut microbes, or specific genes in a microbe, that can make a sustainable contribution to human health.

"We're not very far along yet," said Fischbach. "We're making demonstrable progress, though. We've reached the jumping-off point." **SM**

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FEATURE

Sparking drug discoveries

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to ascertain market size and carefully choose an indication for the drug. And think about how VCs and big pharma will view it, and regulatory organizations too. That's all very different from research."

Back at her university, the team completed more research, had more meetings with advisers and Tseng practiced her pitching. "The more you talk with other people in SPARK, the more you understand, the better your project becomes," she said.

The team members' goal is now clear: They are aiming to create a company, and additional research has uncovered more conditions the drug could treat. Initial clinical trials indicate it might also be a treatment for ataxia, a rare, debilitating neurological disease with no treatment, as well as early onset Alzheimer's disease.

One of the participants in the clinical trials was a man with severe dementia. "He couldn't use the phone anymore, he didn't understand what the phone is about," said Tseng. "Then he has six months on the high-dose arm of the trial and he's happily calling his son every day. They were upset after the trial ended.

"You have a heart and scientific ability, but then you have to have the trained skills to bring that into a product. SPARK makes that possible."

At the showcase the next year, she pitched with more confidence. She made progress fundraising and afterward she spent time at Stanford to connect with SPARK's Stanford network of advisers and meet physicians, such as autism expert Antonio Hardan, MD, professor of psychiatry and behavioral sciences.

So about testing her team's compound as an autism treatment? Well, she was eight months pregnant when she met Hardan and she thinks that influenced her decision to take on the challenge. "When you are pregnant and people talk about autism, I think that it gives you courage." The drug candidate is now in clinical trials for autism at Stanford and National Taiwan University Hospital in Taiwan.

"I can relate to those parents," she said. "They would do anything to help those kids, and it made me want to, too." **SM**

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FEATURE

Never give up

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Shefrin has allowed Kwong to take additional skin tissue for research analysis to better understand the disease and possibly develop targeted therapies. Gotlib said he plans to sequence the roughly 23,000 genes in normal and abnormal tissues that encode for proteins, using samples from Shefrin and other patients, in a search for a mutation that might be the source of Schnitzler syndrome.

"We haven't found the gene for this one yet. So it's a fishing expedition," he said.

Although Shefrin's health will never be as good as it was before she developed Schnitzler, not a day goes by that she doesn't think of and thank "my brilliant doctors," Gotlib and Kwong, she said. She is back to sewing and knitting, playing bridge, walking her terrier, and socializing. She will need to inject anakinra every day for the rest of her life; fortunately, she has had few side effects. Without anakinra, the skin rash and severe joint pain return within hours. Because the medication suppresses her immune system, she takes precautions to protect against infection.

She said she decided to share her story in the hope of helping those who may have undiagnosed Schnitzler's. "If just one person recognizes his or her symptoms in my illness and is able to get help, then having told my story will make it worthwhile." **SM**

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