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HEALTH CARE

How a UCSF scientist's persistence led to a \$1 million prize and groundbreaking cancer drug

RON LEUTY
Senior Reporter,
San Francisco Business Times

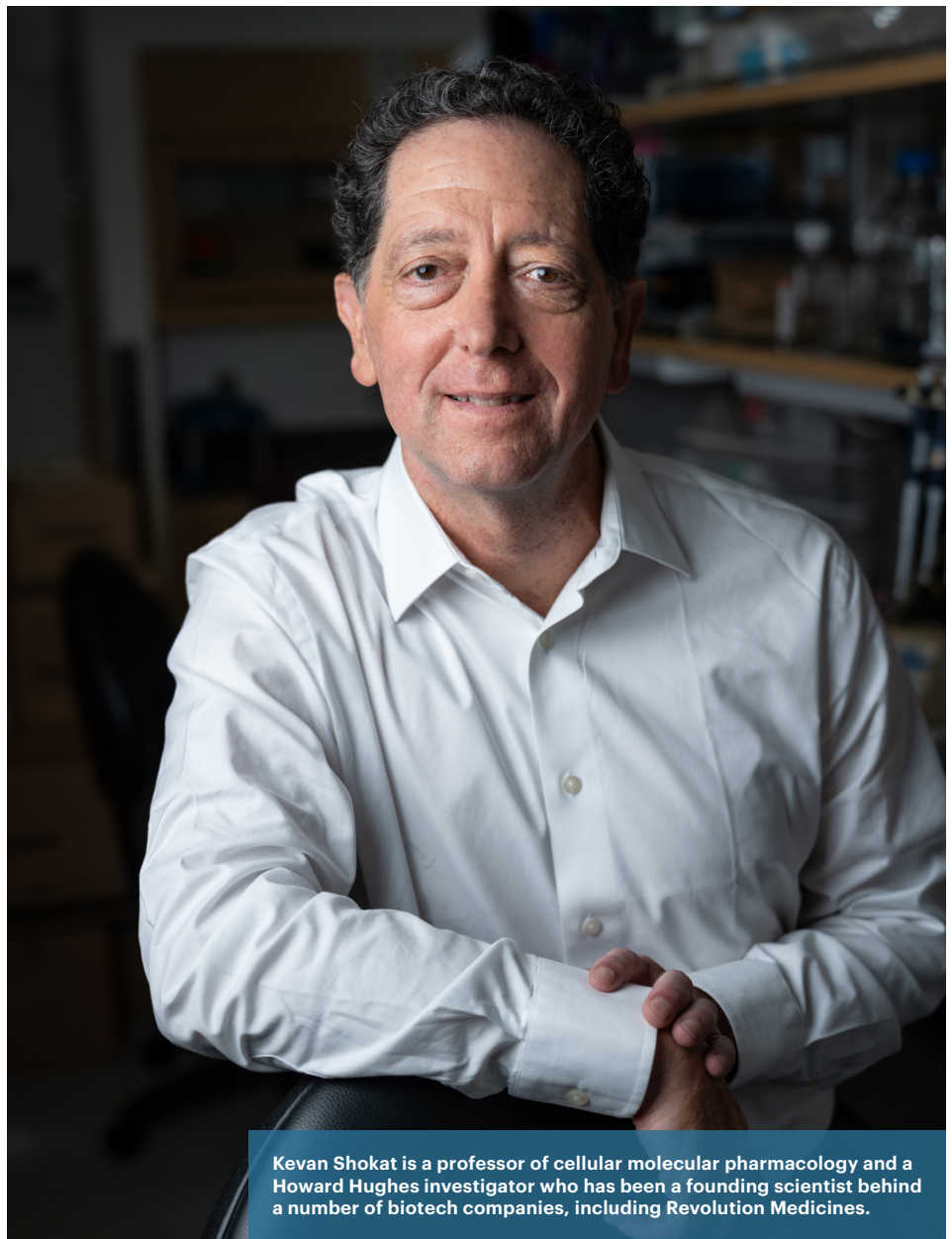
Kevan Shokat's University of California, San Francisco, lab found something in early 2010 while screening several molecules to potentially defeat certain types of cancers. The problem: It wasn't what they expected.

Shokat's lab decided to find out what was happening.

The persistence of that UCSF team led to a seminal 2013 paper and the founding of Revolution Medicines Inc. (Nasdaq: RVMD) by Shokat and fellow scientific founders Michael Fischbach and Martin Burke, with backing from Third Rock Ventures.

On Aug. 26 – the day Shokat turned 62 – the Food and Drug Administration approved Revolution's groundbreaking drug, called daraxonrasib and branded as Rasonque, to treat pancreatic cancer. And on Saturday, Shokat won the \$1 million 2026 Stephenson Global Prize for contributions to pancreatic cancer research.

The prize was awarded at the American Association for Cancer Research's pancreatic cancer conference in San Diego by the Stephenson Global Pancreatic Cancer Research Institute, which is fo-



Kevan Shokat is a professor of cellular molecular pharmacology and a Howard Hughes investigator who has been a founding scientist behind a number of biotech companies, including Revolution Medicines.

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cused on early detection, cutting-edge treatments and research against one of the deadliest cancers.

The switch

The journey for Revolution's drug was unusual in some ways but typical in others, said Shokat, whose research has led to the formation of other companies and other FDA-approved, cancer-fighting drugs.

"The more I think about it, the hardest way to develop a drug is really trying to develop a drug," Shokat told the Business Times. "The best way is to work and see where it fits. ... The inefficiency is kind of the magic of it."

It took 16 years for the lab's work to become an approved drug. But its target – a family of genes called RAS that control how cells grow and divide, specifically a protein called KRAS – gives researchers, companies, doctors and patients hope.

The mutated KRAS gene causes those proteins to be stuck in that position in more than 90% of pancreatic ductal adenocarcinoma cases, the most common and deadly form of pancreatic cancer.

"RAS is a simple binary switch. That's the way it works," said Frank McCormick, the chair of tumor biology and cancer research at UCSF, a leader of the National Institute of Health's RAS Initiative and last year's inaugural winner of the Stephenson Prize.

McCormick recruited Shokat to UCSF to work on RAS.

Redwood City-based Revolution's nearly \$40,000-a-month oral drug, known as a KRAS inhibitor, was approved for a certain set of adults with metastatic pancreatic adenocarcinoma. Those patients have received at least one prior systemic therapy – meaning therapy targets cancer cells throughout the body – or are not candidates for systemic therapies that use multiple agents.

A late-stage study of the drug found that patients with an aggressive form of the disease lived a median of 13.2 months, compared with 6.7 months for those who received chemotherapy.

Pancreatic cancer has the highest mortality rate and lowest survival rate among all major cancers, according to the Pancreatic Cancer Action Network. It is hard to detect because there are no early symptoms, and the relative chances of survival But with no other "on" hits from potential drugs screened by the lab, Shokat and his team took a closer look. "Let's just study this molecule," they thought, he said.

What they found and confirmed after years of work was that their molecule essentially waited out KRAS. As the protein's pocket folded around the molecule, it ultimately flipped to "on," blocking the protein from signaling the expansion of cancer cells.

"It's awesome to see the progress. But it's not like it happened overnight," McCormick said.

'Fascinating biology'

The process of finding something where it originally looked like there was nothing isn't an unusual one in the world of science. "That happens surprisingly often," Shokat said.

At a commercially focused drug company, the initial appearance of a miss – binding in "off" rather than "on," for example – would be the basis to shelve a wannabe drug. "That's why academic drug discovery has a place in the world of drug discovery," Shokat said.

The next wave of RAS drug development, McCormick said, promises more effective, safer and better drugs. And Shokat, who plans to plow his \$1 million Stephenson Prize into his lab's research, will be there to take a look at RAS and other so-called oncogenes that are the mutant command centers for cancer cell growth.

"There's just so much fascinating biology in understanding how cancer develops, how we treat it, which ones get cures," Shokat said, noting the 1989 Nobel Prize-winning work of UCSF's Harold Varmus and the late J. Michael Bishop that showed that drew attention to oncogenes.

"With one mutation, you start a cancer," Shokat said. "How can we develop a drug to wipe that out but not all the tissues?"



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