FRONTIER MEDICINES

Using chemoproteomics to find new cancer drug targets

by ***Megha Satyanarayana***

Credit: Frontier Medicines

Roberto Zoncu (from left), Chris Varma, and Daniel Nomura, cofounders of Frontier Medicines

Like any good entrepreneur, Chris Varma was looking for the next big thing. In 2018, the life sciences venture capital veteran came upon the work of University of California, Berkeley, chemical biologist Daniel Nomura while scanning research papers. Nomura's lab was making intriguing progress in **drugging the undruggable**.

Most small-molecule drugs work by binding to specific grooves on proteins, often the active site of an enzyme. But Varma says some 90% of the roughly 20,000 proteins in the human body simply don't have a clear pocket—they're too smooth or lack a fixed structure. This lack of a clear binding site is especially true for proteins involved in cancer.

"Undruggable" proteins do feature nooks that form as they move about a cell and encounter different partners. The issue for drug developers is that the pockets quickly disappear after a protein completes its biochemical work.

Varma read about Nomura's success in using a technology called chemoproteomics to find and understand the function of the fleeting nooks (*ACS Chem. Biol.*, 2018DOI: **10.1021/acschembio.8b00381**). By mid-2018, Frontier Medicines was born. The biotech firm, founded by Nomura, his UC Berkeley colleague Roberto Zoncu, and Varma, who is also CEO, is combining machine learning and chemoproteomics to develop cancer treatments.

AT A GLANCE

Launched: 2018

Headquarters: South San Francisco

Focus: Cancer drug discovery

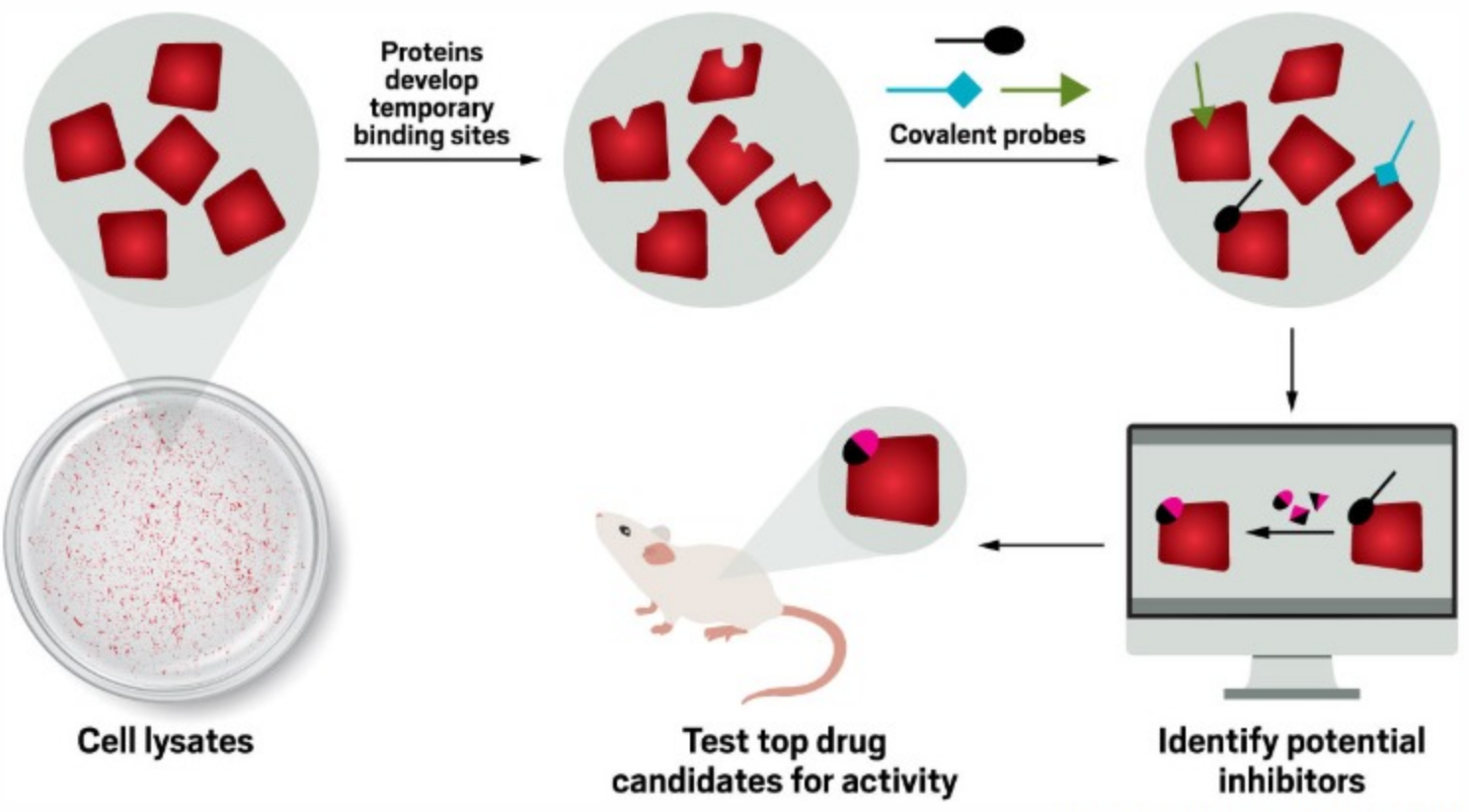
Technology: Chemoproteomics and artificial intelligence–enabled drug design

Founders: Daniel Nomura, Chris Varma, and Roberto Zoncu

Funding or notable partners: $67 million in series A funding, led by Deerfield Management, Droia Oncology Ventures, and MPM Capital

DRUGGING THE UNDRUGGABLE

Frontier Medicines uses a combination of chemoproteomics and artificial intelligence to find small molecules and biologics that can inhibit proteins that have traditionally been difficult drug targets. The company is also developing better protein degraders to aid in the destruction of these difficult drug targets.



Credit: Yang H. Ku/C&EN/Shutterstock

At the company's core is the chemoproteomics platform, which lets scientists bombard proteins with covalent probes as they move about in cells. The probes dock at any spot where a protein might interact with a partner. Frontier's research team has built a long list of these "hot spots" and is using a small-molecule library to understand if engaging a protein at a particular spot alters its function. Varma and Zoncu say they are using machine learning to improve the small-molecule libraries to better the chance of meaningful hits.

"We think we have a unique angle to go after these cancer drug targets," Zoncu says.

Investors agree. In June, the biotech firm announced **$67 million in series A funding**. The team moved into more permanent space in South San Francisco, and Varma says it's been on a hiring spree.

In theory, Varma says, Frontier's technology can design covalent ligands that directly target about half the undruggable proteome. The company hopes to attack the other half using **protein degraders**—bifunctional small molecules that bind a protein of interest to a protein degradation chaperone called E3 ubiquitin ligase to tag it for collection and destruction in the cell's lysosome.

> "We think we have a unique angle to go after these cancer drug targets."
>
> — ***Roberto Zoncu,*** *University of California, Berkeley*

The start-up is one of a handful of players using chemoproteomics to develop drugs against difficult targets. **Vividion Therapeutics**, founded by Nomura's postdoctoral fellowship mentor, Benjamin Cravatt at Scripps Research in California, uses similar technology, and Novartis is working with Nomura and his colleagues at UC Berkeley to build its own **chemoproteomics capacity**.

But Varma and Zoncu argue that Frontier's combination of hot spots, cancer biology, and protein degrader modulation will get it to the front of the pack. They are staring down a list of hundreds of proteins associated with cancer, Zoncu says, and building the knowledge to figure out which can be drugged, what small molecules can drug them, and how to get that molecule into a person with cancer.