C&E News
10 Startups to Watch
November 10, 2023

HALDA THERAPEUTICS

Using bifunctional small molecules to say RIP to cancer cells

By Gina Vitale

From left: founder Craig Crews, Chief Scientific Officer Kat Kayser-Bricker, and Executive Chair Tim Shannon of Halda Therapeutics

Credit: Halda Therapeutics

AT A GLANCE

Launched: 2023

Headquarters: New Haven, Connecticut

Focus: Small-molecule drug development

Technology: Bifunctional molecules that hold proteins together to kill cancer cells

Founder: Craig Crews

Funding or notable partners:
$76 million from Access Biotechnology, Canaan Partners, Connecticut Innovations, Elm Street Ventures, 6 Dimensions Capital, and other investors

Craig Crews is no stranger to the challenge of devising a punchy name for a new class of drug. The chemical biologist was involved in both the discovery and the naming of proteolysis-targeting chimeras, or PROTACs, which are double-ended molecules that degrade proteins.

When Crews founded Halda Therapeutics to develop another new class of drug, he and the leadership team—including Executive Chair Tim Shannon and Chief Scientific Officer Kat Kayser-Bricker—wanted to give these molecules a moniker that's a little graver.

"We wanted to kill cells," Crews says. "We had to figure out a way to make sure that RIP found its way into the name."

And so regulated induced proximity targeting chimeras, or RIPTACs, were christened. As the moniker suggests, a double-ended RIPTAC brings two proteins together. With one end, it binds a protein that is overexpressed in a tumor, which helps the RIPTAC get to, and stay inside, the cancer cell it needs to kill. With the other end, it binds a protein that the tumor cell needs to survive. The RIPTAC holds these two proteins together, preventing the essential one from functioning, until the tumor cell perishes. The team calls this mechanism "hold and kill."

Many oncology drugs target cancer drivers, which are proteins or other biological entities that contribute to the growth of cancers. But cancer cells can become resistant to these drugs, whereas it's harder for them to become resistant to a drug targeting an essential protein, according to Kayser-Bricker.

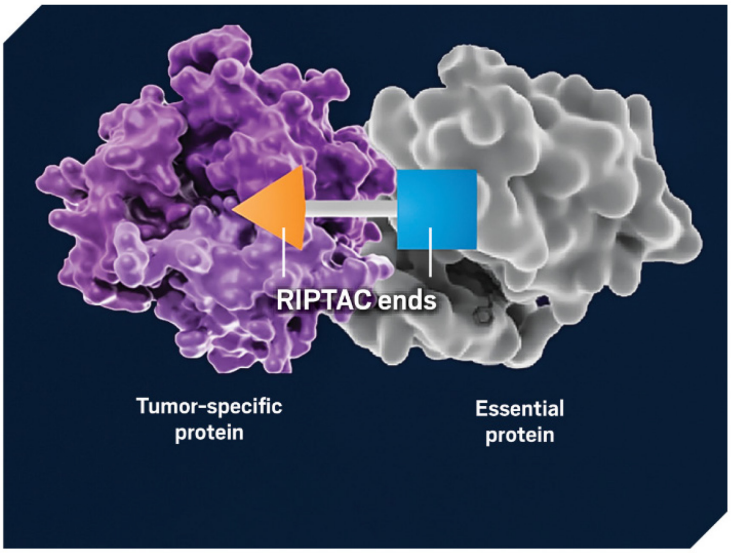
At the American Association for Cancer Research (AACR) annual meeting in April, Halda unveiled data comparing two RIPTACs with Pfizer's enzalutamide, which inhibits the androgen receptor. The androgen receptor, a protein, is a significant driver of prostate cancer. But cancer cells can evolve to sidestep the drug in a few ways: for example, they can use signaling pathways that don't involve the androgen receptor, or the androgen receptor can mutate so that the inhibitor can no longer bind to it enough to block its function.

"Right now, way too many patients unfortunately are succumbing to the disease when their current very powerful oncology drugs start to fail."

Craig Crews, founder, Halda Therapeutics

The RIPTACs that Halda presented at the AACR meeting anchor themselves to a tumor cell using the androgen receptor. To kill the cell, they simultaneously bind a different protein that's critical for its survival.

At the AACR meeting, Halda showed that one of the RIPTACs was able to bind both intended proteins even when the androgen receptor had mutated. And at a different conference earlier this year, Halda presented data showing that after cancer in mouse models became resistant to enzalutamide, it was susceptible to one of the RIPTACs.



Halda Therapeutics' regulated induced proximity targeting chimeras (RIPTACs) are double-ended molecules. One end binds a tumor-specific protein, and the other end binds a protein that the cancer cell needs to survive. The RIPTAC holds these proteins together until the cancer cell dies.

Credit: Adapted from Halda Therapeutics

"What we're trying to do is to give patients options," Crews says. "Right now, way too many patients unfortunately are succumbing to the disease when their current very powerful oncology drugs start to fail."

Notably, Halda also reported at the AACR meeting that both RIPTACs were effective when administered to mice orally. It can be a challenge for drugmakers to make bifunctional compounds—which have two functional ends—that are orally bioavailable. To be taken by mouth, they need to be small enough to be absorbed through parts of the digestive tract, like the intestinal wall, after which they enter the bloodstream.

Oral drugs come with several advantages. They're more convenient for patients to take and less expensive to produce. They can also be small enough to slip through the cell membrane, getting at proteins inside the cell.

Kayser-Bricker notes that larger medicines, like antibody-drug conjugates and bispecific antibodies, depend on a limited lineup of extracellular proteins. Halda is targeting intracellular proteins, which "opens up a lot of uncharted territory for us" to use RIPTACs to go after proteins that may have never been targeted before because they aren't cancer drivers, she says.

Halda joins an ever-growing roster of companies developing bifunctional small molecules that draw two proteins together. That includes **Vicinitas Therapeutics**, a spin-off of the University of California, Berkeley, and Novartis that uses deubiquitinase-targeting chimeras, or DUBTACs, to rescue proteins that are erroneously tagged for destruction. It also includes **Arvinas**, a start-up that Crews founded in 2013 that uses PROTACs to **degrade proteins**.

"We've now seen with Arvinas's products in humans how big a difference that can make to people who need help," Shannon says. "That's what we live for."

Both Halda and Arvinas are nestled in New Haven, Connecticut, a short walk from Crews's office at Yale University. There's no shortage of talent in that pocket of New England, according to the Halda team.

"I would put our 30 people up against anyone," Shannon says. "Not all the smart people are in Boston or San Francisco."