Craig Crews, PhD

Out of the Lab, INTO THE WORLD

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Twenty years ago Craig Crews, PhD, and his colleagues, launched a research project that has generated two biotech companies, hundreds of millions of dollars in investments and partnerships, a host of honors for Dr. Crews, and an FDA-approved drug that has helped more than 80,000 patients so far. The project has also inspired drug candidates now in development against prostate cancer and breast cancer, among other diseases. Dr. Crews is confident that all of this is just the beginning. "It's a platform technology," he said of his discovery, "meaning it could be applied to many different cancers and diseases."

Dr. Crews' story combines groundbreaking science with strong entrepreneurship, a combination that he believes can streamline the arduous process of bringing new drugs to cancer patients. The story began in the late 1990s when he was studying protein degradation, a quality-control mechanism by which worn-out proteins get tagged and removed from cells to make room for new proteins. The mechanism is critical to the health and growth of cells, including cancer cells. "My lab has long been interested in finding molecules that can control this," explained Dr. Crews, the Lewis B. Cullman Professor of Molecular, Cellular, and Developmental Biology and Professor of Chemistry and Pharmacology.

After the initial report of epoxomicin by Bristol-Myers Squibb, a natural product with anti-tumor characteristics, Dr. Crews and his team discovered that it is a potent new proteasome inhibitor that leads to the accumulation of toxic proteins in tumor cells, thus killing them.

Though it was great lab science, Dr. Crews believed that an improved version of this compound from his lab had potential as a drug. In 2003, he started his first company, Proteolix, to develop this novel proteasome inhibitor as a treatment for cancer. Onyx Pharmaceuticals saw potential and bought the company in 2009. Two years later, the FDA gave carfilzomib (trade name Kyprolis) fast-track status, and in 2012 approved it for use against multiple myeloma.

Meanwhile Dr. Crews had been busy designing new molecules called PROTACs (Proteolysis-Targeting Chimeras), a brilliant, pioneering technology that used a different tactic to fight cancer. Instead of blocking protein degradation like the proteasome inhibitor carfilzomib, these PROTACs stimulated it. The advantages were significant. The new PROTACs hunted down cancer-causing proteins, locked onto them, and destroyed them.

"Think of the PROTAC molecule as a dumbbell with two large ends and a connector between them," said Dr. Crews. "One end binds to a part of the intercellular machinery responsible for degrading and eliminating proteins, the other end binds to whatever target protein is causing the disease you want to eliminate. So you are literally dragging this target protein to the quality control machinery and feeding it into the buzz saw. Unlike with inhibitors, this is permanent. And inhibitors only work if you maintain high levels of them in the system; our molecule survives and goes off to seek-and-destroy again, so in theory a patient would need less of the drug."

This approach has another huge advantage over inhibitors. Every cell carries an estimated 20,000 proteins, but only about 25 percent of them can be inhibited by blocking their receptors or enzymatic functions. "That means the vast majority are undruggable because they're scaffolding proteins or transcription factors," said Dr. Crews. "But our PROTAC technology makes all those proteins pharmaceutically vulnerable, not by inhibiting their biological function, but by making the problem proteins go away."

That's the promise behind his second biotech company, Arvinas, which he founded in 2013. It has attracted investments of $113 million as well as licensing partnerships with Merck ($434 million), Genentech ($650 million), and Pfizer ($830 million). The company now employs 85 people in New Haven's Science Park and 100 chemists in China. It has made over 10,000 different PROTACs over the last five years. "That illustrates the amount of effort that goes into drug development," said Dr. Crews.

Two Arvinas projects using PROTAC technology are in advanced stages. One is aimed at prostate cancer, the other at breast cancer. Prostate cancer is driven by the hormone androgen, and the standard of care is androgen depletion therapy using inhibitors. But when the tumor senses this interference, it increases production and mutations, requiring heavier and heavier doses of

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counteractive therapy. "Basically it's chemical castration," said Dr. Crews. Arvinas has designed an oral PROTAC that eliminates the androgen receptor protein from cancer cells, degrades androgen receptor mutations, and slows tumor growth. Dr. Crews expects clinical trials to begin at Yale and elsewhere later this year.

The PROTAC against breast cancer works similarly. An estimated 80 percent of new breast cancer cases are positive for estrogen receptor alpha (ERα), whose proteins encourage tumor growth. Current therapies try to stop growth in ERα breast cancers by inhibiting the receptor, but many breast cancers become resistant, allowing signals from the receptor to break through and stimulate tumor growth. Arvinas' estrogen PROTAC solves that by eradicating ERα proteins. Clinical trials will begin next year.

Another Arvinas project demonstrates how broadly the PROTAC technology can be applied, said Dr. Crews. When the protein called Tau aggregates, it causes neural death that leads to Alzheimer's disease. Arvinas is working on PROTACs that drag Tau to its death.

Dr. Crews sees the company as the fruit of a partnership between academia and private biopharma. Academia develops the idea and demonstrates its feasibility, but it will die if not handed off to the private sector, which can supply money and professional drug developers to mature the concept into a drug. "And now we're on the cusp of clinical trials at Yale with a compound that was a concept here in Kline Biology Tower 17 years ago," said Dr. Crews, "so I'm really very excited by this."

Academics often don't know how to bridge the gap between the lab and private investment. To help them, Dr. Crews started a program called PITCH (Program in Innovative Therapeutics for Connecticut's Health) that he runs through the Yale Center for Molecular Discovery. PITCH is using a $10 million, three-year grant from the state of Connecticut to help scientists from Yale and the University of Connecticut develop promising biotech ideas to the point where they are attractive to venture capital firms. Over the past two years, PITCH has considered more than 90 projects, and 17 have been approved for further development on Yale's West Campus.

"We have been pitching those 17 to venture capitalists over the last year and there's a lot of interest," said Dr. Crews. "We're hoping that some of these proto-companies will soon turn into real companies. Good science is not enough," he added. "It's not an either/or thing. I hope other faculty can see that I've been able to maintain an active academic lab but also play a role through advocacy and consulting to further the development of real-world applications through these biotechs."

He traces his interest in propelling discoveries out of the lab to his father, who worked on materials science at NASA. "He looked at alloys and composite materials for airplane wings, analyzing fatigue and fracture," said Dr. Crews. "He would tell me about plane crashes where engines had failed because the material had been too fatigued due to the pattern of the rivet holes. So it was clear to me early on that my Dad's basic research had practical applications. As a basic researcher driven by my scientific curiosity, I love what I'm doing here, but I'm always asking how we can take what we're learning into the lab and help people."

Right now, Dr. Crews and the 18 members of his lab are investigating leukemia, glioblastomas, lung cancer, and pancreatic cancer. "We're very interested in some of these tough cancers that haven't been easily addressed using the current drug repertoire," he said. "And we're making progress."