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 pharmacologically vulnerable, not by inhibiting their biological function, but by making the problem proteins go away.”

That’s the premise 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...
“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.”

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. Arvinas is working on PROTACs that drag Tau to its death.

Dr. Crews sees the company as the fruit of his lab’s 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.”

IN THE DRIVER’S SEAT

Thanks to Targeted Therapy

In May 2013, Joe Weber had just dropped his son off at Logan International Airport in Boston and was driving back to Connecticut when he decided to stop for a bite to eat. Before continuing his two-hour trip home, he visited the restroom and noticed an exceptional amount of blood in his urine. This came as a surprise to Joe as he had no indication that something was wrong in the weeks or days prior. He immediately made an appointment with his primary care physician.

His physician referred Joe to a urologist, who diagnosed bladder polyps as the cause of the blood, and recommended outpatient surgical removal. Joe went ahead with the surgery, and would continue to be checked every three months for the next year, only to have polyps recur and be removed in two additional surgeries. After his third surgery, Joe questioned whether the polyps could indicate a larger problem and he sought a second opinion.

It was then that Joe received the diagnosis of muscle-invasive bladder cancer. His new urologist recommended he immediately start an aggressive regimen of chemotherapy to precede surgery to remove his bladder and a portion of his small intestine. As testing continued, it was determined the bladder cancer had metastasized to Joe’s lungs, elevating him to a stage IV cancer diagnosis, and surgery was no longer an option. In consultation with his doctor, they decided to proceed with the standard of care for his bladder cancer, and for the next eight months, Joe received chemotherapy once a week. While his treatment did begin to shrink the tumors in his lungs, the side effects were too challenging and Joe decided to end treatment.

Knowing Joe would not be able to tolerate a return to this treatment regimen, his doctor advised he enter a clinical trial, and referred him to Dr. Daniel Petrylak, Professor of Medical Oncology and Urology, at Smilow Cancer Hospital. Dr. Petrylak is a leader in the development of new drugs to fight bladder cancer, and his success with clinical trials has expanded the treatment options for all patients, including many newly FDA-approved drugs.

Joe first met with Dr. Petrylak in July 2015, and for the next two years unsuccessfully participated in two separate clinical trials. In July 2017, Joe became eligible for a third trial touted as “targeted chemotherapy.” This trial combined an antibody targeted at a protein present in bladder cancer cells, with chemotherapy.

After three months, Joe had to again stop the treatment due to side effects, which in this case presented as neuropathy, or weakness and numbness in the feet. Joe paused his treatment for six months, but continued to have scans every eight