Taking a Dumbbell to Drug-Resistant Cancers

The partnership of Daniel Petrylak, MD, and Craig Crews, PhD, didn't quite form by accident, but it was spurred by a bit of luck.

Dr. Crews is the John C. Malone Professor of Molecular, Cellular, and Developmental Biology and a Professor of Chemistry, of Pharmacology and of Management, plus the Executive Director of the Yale Center for Molecular Discovery.

Dr. Petrylak is a Professor of Medicine (Medical Oncology) and Urology at Yale Cancer Center and Smilow Cancer Hospital and a pioneer in treatments for prostate, bladder, kidney and testicular cancer.

The pair met at an informal get together hosted by the chemistry department to show their researchers' work. In addition to his roles at Yale, Dr. Crews is also a biotech entrepreneur. He and Dr. Petrylak realized that they might be able to collaborate on a new kind of drug to treat prostate cancer.

The CEO of Proteolix, Dr. Crews' first company, died of the disease, and he "wanted to make sure that if I had the opportunity to develop another oncology company, the first cancer I'd target would be prostate," Dr. Crews said.

When he was talking with potential investors for his new company, Dr. Crews said he "dragged them down to Dan's office, and Dan was kind enough to entertain the two of us and convince the investor that a new class of cancer treating drugs was possible, and needed."

Together, they have done exactly that with ARV-110, a proteolysis-targeting chimaera, or PROTAC, now in clinical trials at Smilow Cancer Hospital. It is designed to get around the "drug resistant" part of drug resistant prostate cancer, with the promise that the same concept can work in other cancers that are currently considered untreatable.

PROTACs work by using elements of the body's natural protein recycling system, and recruiting them towards cancerous proteins. "We're using this biological function and hijacking it to get rid of other proteins," explained Dr. Crews, who is developing this drug through Arvinas, the company he founded in part by introducing those investors to Dr. Petrylak. "It's co-opting a natural process and is a completely different approach from how other cancer drugs work today."

PROTACs do this in dumbbell form. One side binds to a cancer protein with the other latching onto a ubiquitin ligase, which adds a "flag" to mark proteins as ready for recycling. Proteasomes roam around cells looking for those flags so they know what to pick up and shred. Once PROTACs mark a cancer protein with a flag, proteasomes pick it up and recycle it just like any other protein.

Dr. Crews first came at the problem from the opposite direction. Instead allowing the ubiquitin system to break cancer proteins down, he worked on a drug that gummed up the works. As a result, levels of toxic proteins that should have been recycled kept building up until they killed the cell. It worked and became carfilzomib, a treatment for multiple myeloma.

But using the body's own recycling system to eliminate problem proteins made more sense. It's also more efficient. "It only takes one PROTAC to take out about 400 proteins," said Dr. Petrylak. One PROTAC can keep flagging cancer proteins over and over and over again.

ARV-110 specifically targets metastatic castration-resistant prostate cancer (mCRPC), which accounts for most of the 28,000 prostate cancer deaths in the U.S. each year. Hormone sensitive prostate cancer is typically treated with androgen deprivation treatments, which block the natural production of cancer-spurring androgens. While initially effective, most patients become resistant to it, after which the cancer can metastasize.

In a preliminary Phase I clinical trial of 22 patients who had already undergone at least two different unsuccessful treatments, seven were treated with the level of ARV-110 that pre-clinical trials showed should be effective. Of those seven, two patients had a more than 50 percent reduction in prostate-specific antigen (PSA). One patient's tumor shrunk more than 50 percent. "In some patients, the response lasted for more than seven months," said Dr. Petrylak.

The hope is that PROTACs can treat other "undruggable" cancers that don't respond to current treatments, including types of lung, breast, and colorectal cancers that may not have an active site on which a small-molecule drug or monoclonal antibody could bind. PROTACs don't need that specific of a site. "This is not an approach that is prostate-specific. It's not even target-specific. You can have multiple targets that you want to down regulate," said Dr. Petrylak.

The research has been invigorating, and exciting, he added. "I've had so much fun working on this from the standpoint that it's incredibly justifying to see something that Craig has done in the laboratory and then take that into patients and learn a lot about not just this drug but also the biology of diseases."