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 Therapeutics. A pioneer in treatments for prostate, bladder, kidney and testicular cancer, 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 cancer.

When he was talking with potential investors for his new company, Dr. Crews’ first company, died the day he founded it. He and Dr. Petrylak realized that they might have a chance to develop another oncology company, the first of the disease, and he “wanted to make sure that if I had the ability to collaborate on a new kind of drug to treat prostate cancer I’d target would be prostate,” Dr. Crews said.

“Cancers that are currently considered untreatable. 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 disease.”

“PROTACs work by using elements of the body’s natural protein recycling system, and recruiting them towards cancerous proteins. “We’re using the 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.”

PROTACs do this in a 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 prevented up the works. As a result, levels of toxic proteins that should be recycled kept building up until they killed the cell. It worked and became carfilzomib, a treatment for multiple myeloma. “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.

“Actually, it’s hoped that PROTACs can treat other ‘undruggable’ cancers that don’t respond to cancer 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.

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