Cells constantly produce new proteins, which wear themselves out doing cellular labor. Some proteins are tagged for removal by a maintenance protein called ubiquitin, and then sent to the proteasome, the body’s equivalent of the glue factory. There, the old proteins are broken down and discarded. This process is called protein degradation.

Craig W. Crews, Ph.D., Lewis B. Cullman Professor of Molecular, Cellular and Developmental Biology, has been studying this process for years, looking for ways to control it with drug-like molecules that target cancer-causing proteins. He led his first foray into this field to lead the drug, Krypyx®, (carfilzomib), approved in 2012 for use against multiple myeloma. Krypyx® is a proteasome inhibitor that prevents the degradation of proteins in cancer cells, causing a toxic build-up that kills them.

Now Dr. Crews and his colleagues have developed a different line of attack. "Instead of blocking protein degradation," said Dr. Crews, "we’re including it. We’ve developed a drug strategy whereby the drug enters the cell, seek out and bind to rogue cancer-causing proteins, and then take them to the proteasome for degradation. It’s a seer and destroy approach." These drug-like molecules, called PROTACs (Proteolysis-Targeting Chimeras), were first reported by Dr. Crews in 2001.

Most targeted cancer drugs are inhibitors that bind to receptors and block the mutant proteins that cause cancer. “But when the drug leaves the system, the protein can start working again,” Dr. Crews explained. “To get the clinical benefit, you need to maintain a high level of the drug in the body. What we’re doing is different. It’s not binding and gating up the process, it’s striking the cell’s own quality control machinery to destroy rogue proteins. It’s also permanent. And the drug survives to eat its way through a protein population. So, in theory, one needs less of our drug. This approach should greatly reduce the side effects that accompany high-dosing in the inhibitory paradigm.”

Another strength is the strategy’s broad reach. Dr. Crews points out that each cell contains an estimated 20,000 different proteins, but only about 25 percent are potentially vulnerable to inhibitors, which work by binding receptors or blocking enzymatic functions. That leaves the great majority of proteins untouched, such as scaffolding proteins and transcription factors. Since Dr. Crews’ approach doesn’t depend on inhibition, it should work against this so-called ‘undruggable’ majority.

The science of tagging and eliminating oncogenic protein is new, and so is the technology that makes it possible: a new class of small-molecule PROTACs designed by Dr. Crews and his team of cell biologists, biochemists, medicinal chemists and pharmacologists. Dr. Crews believes that small-molecule PROTACs open up wide new possibilities for cancer therapies. He has formed a company called DecoyTech to explore them and to develop the technology further.

For now, Dr. Crews and his partners are focused on developing PROTACs for leukemia, lymphoma, ovarian cancer, breast cancer, and lung cancer. “But this approach doesn’t really have any limitations with respect to cancer type,” said Dr. Crews. “It’s a platform technology, so the learning around developing one drug could be applied to address the oncogenic proteins that cause different cancers in different tissues.” He hopes that clinical trials for prostate cancer will begin sometime next year.

The National Institutes of Health (NIH) recently made a breakthrough and Dr. Crews was recently selected to receive the inaugural class of a new program at NIH. The new Outstanding Investigator Award will fund $2 million for each of the next seven years.

“I’m very fortunate that for the last 20 years my lab has worked right at the interface of chemistry and biology. It allows me to recognize the important questions in biology and allows my lab to then go out and tackle those problems using chemical approaches,” said Dr. Crews.