



Frederick Wilson, MD, PhD

Collateral Damage Creates an Opening Against Cancer

Computational biology and bioinformatics are allowing researchers to explore deep within the genome. Some of their discoveries may become weapons against cancer. One such discovery has recently been translated into a clinical trial at Smilow Cancer Hospital and other locations.

Using computational biology and bioinformatics, a group of researchers that includes Frederick Wilson, MD, PhD, Assistant Professor of Medicine (Medical Oncology), learned that certain cancers sustain their growth by eradicating a tumor suppressor gene called CDKN2A. This assault on CDKN2A often wipes out a nearby innocent bystander, a gene named MTAP that sits next to CDKN2A on the genome.

“MTAP seems to be lost as collateral damage due to its proximity to CDKN2A,” said Dr. Wilson. “Deletion of MTAP is common in many cancers. When MTAP is deleted, cancer cells become dependent on another gene that encodes a protein called PRMT5.”

Dependency means vulnerability, which can be exploited. Dr. Wilson and his colleagues wondered if it was possible to take advantage of this dependency on PRMT5 with a therapeutic strategy. If the answer is yes, the effects could be far-reaching. A phase one clinical trial is now underway at several sites, including Smilow Cancer Hospital, where Dr. Wilson is the principal investigator.

“What’s exciting to us,” said Dr. Wilson “is that MTAP loss is observed in about 15 percent of all cancers. That’s a lot of people. And it’s seen at greatest frequency in certain solid tumors that have historically been very challenging to treat.”

Dr. Wilson did his early research on MTAP at the Broad Institute of MIT and Harvard before coming to Yale in 2017 to start his own lab. Computer biologists at Broad winnowed their discoveries about MTAP and PRMT5 from two large collections of cancer cell lines, the Cancer Cell Line Encyclopedia and Project Achilles. Using these cell lines, the scientists went through the genome one gene at a time, trying to inactivate or turn off the expression of each gene in order to gauge the effect on other genes. That’s how they found subsets of cancer cells that seemed dependent on PRMT5. Next, they looked for a genetic feature that these cells had in common. The answer: cells in which both copies of MTAP were deleted. Dr. Wilson took that insight into the lab and began exploring the mechanistic basis for why the loss of MTAP in cancer cells leads to dependency on PRMT5.

He found that when MTAP is lost, a metabolite called MTA, which is normally broken down by MTAP, builds up in cells that lack MTAP. “It turns out that MTA can inhibit PRMT5,” said Dr. Wilson. “Since PRMT5 activity is essential in most cells, inhibition of PRMT5 by high MTA combined with further reduction of PRMT5 function in cancer cells without MTAP impairs growth.”

Dr. Wilson and his colleagues published these findings in *Science* in 2016. At the same time, two pharmaceutical companies independently made the same discovery, which confirmed Dr. Wilson’s research.

Now, in his Yale lab, Dr. Wilson continues to study how PRMT5 functions in cancer cells where MTAP has been deleted. Additionally, he is working with Agios, one

of the pharmaceutical companies whose research on MTAP mirrored his. Agios has developed a compound that inhibits the PRMT5 pathway. The compound, called AG-270, is designed to deprive MTAP-deleted cancer cells of the PRMT5 activity that they need to survive.

When AG-270 was ready for a phase one trial last fall [2018], Dr. Wilson’s expertise made Smilow Cancer Hospital and Yale Cancer Center a natural choice as one of the locations. The compound has never been used in humans, so the trial’s primary goal is to assess the drug’s safety at various dosages.

Finding the right dosage is crucial. The goal is to deliver just enough of the drug to further reduce the level of PRMT5 activity, which is already lowered in MTAP-deleted cancer cells, to a point where the cancer can no longer grow. But most normal cells also rely on PRMT5, so administering too much drug could cause unwanted side effects.

The potential benefits of finding a way to inhibit PRMT5 in cancers that lack MTAP are striking, especially in solid tumors. MTAP is deleted in about 15 percent of all cancers. But in some cancers that figure is even higher—40 percent of glioblastomas and 25 percent of melanomas, urothelial cancers, and pancreatic cancers.

“If this compound has promising activity in patients,” said Dr. Wilson, “or if we can identify alternative potential targets in this pathway, the results could be relevant to many patients. What’s really exciting is the opportunity to transition from a discovery in the lab to a therapeutic strategy, and to bring that therapy into the clinic for the benefit of our patients.”