Building the Next Platform for Precision Medicine

Faye Rogers, PhD

Faye Rogers, PhD, was puzzled, a fruitful state for a scientist. The Associate Professor of Therapeutic Radiology knew that cells respond to DNA damage by alerting a network of pathways to manage it and thus preserve genomic integrity. "One of the foundational questions of my lab," said Dr. Rogers, "is how do these pathways talk to each other? And, if too much damage occurs, and the DNA can't be repaired efficiently, how do cells determine to activate apoptosis [cell death] to preserve genomic integrity?"

The answers she found to those questions point to new possibilities for cancer treatment. Dr. Rogers and her team have discovered a way to turn on the apoptotic pathway in cancer cells, tricking them into killing themselves while leaving normal cells unscathed. Their research was published in October 2021 in *Nature Biotechnology*.

Working with a model of HER2-positive breast cancer, the scientists had been studying nucleotide excision repair (NER). NER is one of the main pathways for removing damaged strands of DNA and replacing them with healthy strands that restore the normal structure, a double helix. At a specific sequence on the DNA, Dr. Rogers and her team inserted a three-stranded structure using a triplex-forming oligonucleotide (TFO) that binds to the site. Then they watched how the NER pathway responded. Instead of removing and mending the damaged DNA, the pathway signaled for cell death within the tumor.

"We realized that if we created multiple triplex structures, we could induce apoptosis," explained Dr. Rogers. "That gave us a really unique opportunity in cancers that have gene amplification."

Here's why: gene amplification is an abnormality in which multiple copies of a gene appear on a segment of DNA, a disorder that occurs frequently in cancer cells. HER2-positive breast cancers, for instance, are marked by gene amplification. Dr. Rogers realized that those duplicate genes could become targets.

"In HER2 amplified genes, there are multiple TFO binding sites because there are so many copies," she said. "We knew that if we could create enough of these triplex structures at those specific sequences within the cancer, the cell would decide, 'There's too much damage, we can't fix it, so we should just activate apoptosis.' You basically hijack the cell's own mechanisms to make it do what you want it to do."

This ingenious method of attack also spares healthy cells, which carry only two copies of a gene, so NER easily mends damage from the two binding events caused by the TFO.

In animal models of HER2-positive breast cancer, TFOs caused tumors to shrink by about half. That's comparable to the drug trastuzumab (Herceptin), the primary targeted therapy for HER2-positive breast cancer. Trastuzumab inhibits the overexpressed HER2 receptor protein that helps cancer grow.

But TFOs offer a major advantage over drugs that work by inhibiting the overexpressed protein driving the cancer. Gene amplification often allows cancer cells to figure out ways to sidestep the inhibitor and resume growth. This drug resistance has proven to be the Achilles heel of many therapies, including trastuzumab.

"But the gene amplification in the cell remains the same," said Dr. Rogers, "so we can use our strategy to overcome drug resistance in these cancers. We don't need an overexpressed protein to target. In fact, we don't even need the amplified gene to be the driver for our strategy to work against the cancer, because it's not a factor of protein or cellular function, it's a factor of DNA damage response that activates either repair or apoptosis."

The TFO strategy offers another major advantage. Dr. Rogers and her team have designed TFOs that can target and bind to many different sites in the genome. She expects to be able to target genes anywhere within the genome.

That leads to what may be the most exciting vista opened by Dr. Rogers's research. HER2 is just the beginning. More than 460 amplified genes have been implicated in 14 cancer subtypes. All these genes are potentially vulnerable to specific TFOs. Currently, Dr. Rogers and her team are focusing on cancers that lack targeted therapies, such as ovarian cancer. At the top of Dr. Rogers's most-wanted list is c-Myc, an oncogene amplified in up to 70 percent of human cancers, including ovarian.

"Right now, we're designing new TFOs and getting ready to test them to see if we see the same kind of bioactivity we saw when we targeted HER2," said Dr. Rogers. Her lab is also exploring different ways to deliver the TFOs, from nanoparticles to antibodies.

"We're really excited about this work," she added. "I think it has the potential to serve as the foundation for a platform that can be beneficial for the next generation of precision medicine for a wide range of patients who suffer from many different cancers."