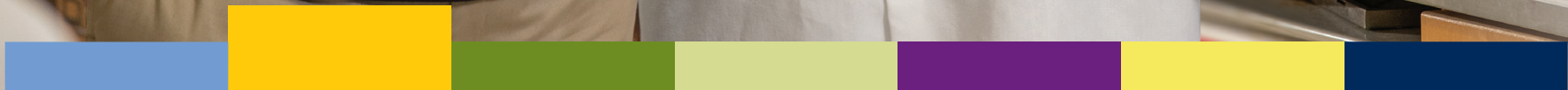


Peter Glazer, MD, PhD

Parker Sulkowski, PhD

# The Race to the Next Target



**To Parker Sulkowski**, the next step was obvious, but he also knew that others would be racing to get there first. A PhD student in the lab of Peter Glazer, MD, PhD, Robert E. Hunter Professor of Therapeutic Radiology and Professor of Genetics, and Chair of the Department of Therapeutic Radiology, Dr. Sulkowski was about to take what he learned from their groundbreaking study of glioma and look for other targets.

In 2016, he joined a Yale project that originated in the lab of Ranjit Bindra, MD, PhD, Associate Professor of Therapeutic Radiology and Pathology. Working collaboratively, the Glazer and Bindra labs discovered a new, counterintuitive tactic for fighting cancer. Instead of trying to stop certain mutations, said the scientists, let's exploit them.

They reached this conclusion by studying the biology of gliomas. Research had shown that many gliomas are driven by mutations of the gene IDH and its mutant metabolite 2HG. Yet a new drug designed to block these mutations was proving curiously ineffective on glioma patients who were also receiving chemoradiotherapy.

Dr. Bindra wondered if IDH mutations somehow made patients more sensitive to chemoradiotherapy. He took this hunch to Dr. Glazer, which is how Dr. Sulkowski entered the picture. Using basic biology, the team learned that IDH mutations drive glioma partly by hindering the tumor's ability to repair damaged DNA, thereby causing more mutations. But the damaged DNA also leaves the cancer cells vulnerable to attack, like a fortress with an unlocked back door.

The Yale researchers knew that if a cell's broken DNA isn't fixed or removed, it eventually will die. They also

knew that repair of damaged DNA in many cases fell largely to a group of proteins called PARP—poly (ADP-ribose) polymerase. And they knew that drugs called PARP inhibitors have successfully targeted BRCA1 and BRCA2, proteins involved with DNA repair that, when mutated, can cause breast, ovarian, prostate, and pancreatic cancers. The scientists discovered that IDH mutations (via excess 2HG metabolite levels) suppress the same DNA repair pathway as is impacted by BRCA mutations, and so they reasoned that a PARP inhibitor might make IDH-mutant cancer destroy itself. They tested an inhibitor called olaparib on brain cancer cells. It worked spectacularly.

IDH mutations are found in many other cancers, including acute myeloid leukemia, gastric cancer, colorectal cancer, melanoma, and cholangiocarcinoma. Based on the Yale team's work, seven clinical trials have started or are about to launch, at Yale and across the United States.

The team's discovery had never been described before, so Dr. Sulkowski knew it would start a scramble to find similar mechanisms and related cancers. "The second I knew our IDH/2HG finding was real," he said, "the race was on."

Dr. Sulkowski had a head start and knew just where to look first. Like other scientists in cancer metabolism, he was familiar with two rare inherited cancer syndromes, Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC) and Succinate Dehydrogenase-related Hereditary Paranglioma-Pheochromocytoma (SDH PGL/PCC). He also knew that they overproduce metabolites, succinate and fumarate, whose molecular structures and functions are very similar to that of 2HG.

"Even for someone in this field," said Dr. Sulkowski, "it's almost impossible to tell the difference between 2HG, succinate, and fumarate. So we hypothesized that there would be converging DNA repair defects there, and I immediately tested them."

The time from his hypothesis to his lab work to a major paper in *Nature Genetics* took only a year, and in late 2019 a clinical trial opened at Yale and at UCLA to test PARP inhibitors against these two rare cancer syndromes. "That's a lot faster than most projects tend to go," said Dr. Sulkowski.

It's easier to win the second leg of a race when you're far ahead after the first leg. But another reason Yale won the race, said Dr. Sulkowski, is that it cultivates amazing science. He pointed to the great relationship and collaboration between the Bindra and Glazer labs, and to the fruitful relationship of both labs with Brian Shuch, MD, a renal cell surgeon and genetics expert who was formerly at Yale and continues to collaborate while at UCLA.

"I don't think we could have done this anywhere else," said Dr. Sulkowski. Obviously it's not luck, it's that Yale puts the top scientists and clinicians all under one roof."

Dr. Sulkowski graduated in early 2020. He says he's most proud of two things from his work at Yale: "Number one is understanding the molecular mechanisms that drive these cancers, and number two is exploiting those mechanisms for therapeutic gain. When you hear gratitude from people with IDH mutations who had been failing other trials and succeeded on ours, that's pretty incredible. It's a reminder of the tremendous responsibility we have as scientists to do high quality work, because it can have really amazing effects."