

Ranjit Bindra, MD, PhD and Peter M. Glazer, MD, PhD

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A Counterintuitive Breakthrough in Brain Tumor Therapy

Ranjit Bindra, MD, PhD, was puzzled. His patients were not responding as expected to a heralded new drug, enasidenib, for brain tumors, which targeted a mutation in the IDH gene, implicated in gliomas. When combined with chemoradiotherapy,

enasidenib was supposed to improve outcomes for people whose brain tumors carried the mutation. But in the clinic, Dr. Bindra, Assistant Professor of Therapeutic Radiology and Pathology, found that patients with the mutation who didn't receive enasidenib were responding more strongly to chemoradiotherapy than the patients who received the targeted drug. Enasidenib did perform as advertised, blocking IDH mutations. So why the discrepancy in responses between patients who did and did not take the drug?



Dr. Bindra and Jennifer Garbarino, a second year PhD student.

It seemed counterintuitive, but Dr. Bindra wondered if IDH mutations somehow made brain tumors more susceptible to chemoradiotherapy. He explored this hunch in his lab by creating a model cell line and making it IDH-mutant. In the summer of 2015, his lab screened 3,000 cell lines. “We tested whether the mutation induced sensitivity to radiation chemotherapy,” he said, “and that’s exactly what we saw.”

This was the first discovery. To

Dr. Bindra, the next counterintuitive implication was clear: instead of blocking IDH mutations, exploit them. But how?

His lab began testing drugs on the mutated cell lines, looking for something that increased the mutation’s sensitivity. In January 2016, a research fellow in his lab named Nathaniel Robinson, MD, told Dr. Bindra that the drug screen had turned up only one hit, on a drug called olaparib that was

approved against ovarian cancer. The surprise: olaparib was a PARP inhibitor.

“That was the big aha moment,” said Dr. Bindra. “We realized that we were on to something that could be clinically significant.”

PARP—poly (ADP-ribose) polymerase encompasses a group of proteins crucial to the continuous process of repairing damaged DNA. Regardless of whether a cell is normal or cancerous, if its faulty DNA isn’t mended or removed,

it will die. PARP inhibitors block one of the main pathways by which cells fix damaged DNA. Olaparib potently kills cancer cells with BRCA1 and BRCA2 mutations, known to cause ovarian, breast, pancreatic, and prostate cancers, because BRCA proteins are important for a second pathway of DNA repair. The cancer cells cannot survive the effect of olaparib on DNA repair when the BRCA-related DNA repair pathway is also defective.

Dr. Bindra’s discovery excited him because if IDH mutations resemble BRCA mutations and respond similarly to a PARP inhibitor, new possibilities opened for treating brain cancer. The discovery also called into doubt the current standard of care for treating patients with IDH mutated gliomas.

Though Dr. Bindra had established that IDH mutations respond to a PARP inhibitor, he did not know how and why. He turned to colleagues at Yale, beginning with Peter M. Glazer, MD, PhD, Robert E. Hunter Professor of Therapeutic Radiology and Professor of Therapeutic Radiology. A decade earlier, Dr. Bindra had been a PhD student in Dr. Glazer’s lab. More recently, in 2012, Dr. Glazer recruited Dr. Bindra away from Memorial Sloan Kettering to start his own lab at Yale. Dr. Bindra’s former mentor became his partner.

Dr. Glazer immediately saw the importance of Dr. Bindra’s discovery. He assigned a graduate student, Parker Sulkowski, to dig into the biological mechanisms involved. Mr. Sulkowski, along with Chris Corso, MD, PhD, a resident in Dr. Bindra’s lab, did the animal work critical to providing proof of principle. Important additional assistance came from the labs of Stephanie Halene, MD, PhD, Associate Professor of Medicine, Hematology; and Murat Günel, MD, FACS, FAHA, Nixdorff-German Professor of Neurosurgery and Professor of Genetics and of Neuroscience, and Chief of Neuro-

surgery at Yale New Haven Hospital.

Previous research had established that mutated IDH pumped out a mutant metabolite called 2-Hydroxyglutarate (2HG) at abnormally high levels. “If a mutation is making something that it shouldn’t be making,” explained Dr. Bindra, “the first and easiest thing to say is, ‘Let’s make it stop.’ That’s the typical

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pharmaceutical paradigm.” In this case the result was enasidenib, developed by Agios Pharmaceuticals.

But Drs. Bindra and Glazer thought enasidenib solved the wrong problem. “They are correct that 2HG makes a tumor,” said Dr. Bindra. “Where they went wrong was to say, ‘We have to close this door because we know this mutation opened it.’ Think of it like a horse in a barn. That first mutation likely broke the lock on the door, and the horse started running. So by the time they closed the door, the horse was long gone.”

That is, the initial mutation creates a malignant cell, but the real problem comes later, as unrepaired DNA triggers lots of other mutations. “By then, stopping the metabolite doesn’t do much to help you on the malignant phenotype,” said Dr. Glazer. “Instead, let the metabolite be made and then exploit the vulnerability it creates.”

That insight came out of Dr. Glazer’s lab in the summer of 2016. “There are six or seven DNA repair pathways identified in human cells,” he said. “The metabolite 2HG inhibits one of them (the one related to BRCA mutations), so the cell has a deficiency in DNA repair. As with BRCA-deficient cancers, when the PARP inhibitor inhibits another DNA repair pathway, the cancer cell is even worse off.”

Much worse, Dr. Bindra, Dr. Glazer, and their colleagues found that the combination of the IDH mutation and the PARP inhibitor increased the death of brain cancer cells 50-fold.

In February, they published their findings in *Science Translational Medicine*. The paper created a stir among researchers, physicians, and patients. A small phase I trial is underway at Yale Cancer Center. A larger phase II trial has been approved by the National Cancer Institute and is planned to launch at the end of summer, with about 50 patients at 35 cancer centers.

Recent research has found IDH mutations in many cancers, including melanoma, acute myeloid leukemia, gastric cancer, colorectal cancer, liver cancer, cholangiocarcinoma, and others.

“We argue that metabolites in this subset of cancers should not be shut down or blocked, despite the knee-jerk desire to do it, but instead should be exploited,” said Dr. Bindra. “So the implications are profound. We may need to re-evaluate and take a completely different route when the conventional pharmaceutical approach suggests one way but the biology says to go 180 degrees the other way.” Drs. Bindra and Glazer are now researching whether 2HG can function as a biomarker for selecting tumors treatable with PARP inhibitors.

“It’s a testament to following the biology,” said Dr. Bindra. “It’s also a testament to translational science at Yale. I can’t think of another institution where we could have gone so seamlessly from the clinic to the lab and back to the clinic.” ☺