

# following the biology

*to Develop New Clinical Trials for Young Adults*

**T**wo physicians from Yale are the engines behind a new nationwide clinical trial that might become a model for the future. The trial exemplifies innovation at every stage on the long journey, beginning with a breakthrough in the lab to an application in the clinic, with stops to pick up collaborators, funders, and institutional partners. The trial is also significant for its focus on a group usually overlooked by cancer research—adolescent and young adult (AYA) patients. In this case, the patients are aged 13 to 25.

Ranjit S. Bindra, MD, PhD, Associate Professor of Therapeutic Radiology, and Asher Marks, MD, Assistant Professor of Pediatrics and Director of Pediatric Neuro-Oncology, merged their strengths to create the clinical trial. “AYA cancer patients are kind of stuck in the middle,” said Dr. Marks. “Here at Smilow Cancer Hospital we have a lovely pediatric cancer clinic with clowns and toys, and then we have the adult clinic that serves mostly older patients. AYAs don’t fit into either on the psychosocial side, and they also can be different on the biological side.”

Dr. Marks points out that the National Cancer Institute devotes relatively little money to pediatric trials, and most of that goes to study young children. Pediatric trials also tend to be large phase 3 investigations at centers in major cities with access to a huge volume of patients. Further, big pharmaceutical companies are usually reluctant to fund pediatric trials because the potential market is smaller and less profitable, and the trial regulations more stringent, especially for children under 13.

“The result is that, for most drugs, the pharmacokinetics has only been studied in adults,” said Dr. Bindra.

“Exactly,” said Dr. Marks. “We typically take what’s being done on the adult side and try to apply it to pediatrics. But the more we learn about the biology, the more we see that pediatric cancers have different drivers than adult cancers.”

Their new clinical trial is rooted in biological processes. Two years ago, Dr. Bindra and the scientists in his lab discovered that tumors with IDH1/2 mutations were poor at repairing damaged DNA, especially after being dosed with chemotherapy. Cells, including cancer cells, must constantly repair DNA to stay healthy. Dr. Bindra had the counter-intuitive idea of exploiting an Achilles heel associated with IDH1/2 mutations instead of blocking their

deviant function. Maybe preventing cancer cells from repairing DNA would eventually destroy the tumor.

His lab worked in close collaboration with the lab of Peter M. Glazer, MD, PhD, Robert E. Hunter Professor of Therapeutic Radiology and Professor of Genetics, to test this hunch. DNA repair relies on PARP genes. When the scientists used a PARP inhibitor called olaparib to block the IDH1/2-mutant cells from fixing their damaged DNA, the results were spectacular—brain cancer cells died at 50 times the usual rate.

Dr. Bindra began looking into other PARP inhibitors that might affect IDH1/2-mutant cancers, including a newer one called BGB-290 (pamiparib), made by a Chinese company called BeiGene. BGB-290 had not been tested against brain cancer at the time of their initial discovery, but after multiple phone calls and meetings, BeiGene agreed to give Dr. Bindra the drug for adult trials. The results were impressive. “It’s the inhibitor with the greatest chance of getting into the brain of patients with cancer,” explained Dr. Bindra.

Along the way, Dr. Bindra learned that IDH1/2 mutations had been found in adolescent gliomas. He walked down the hall and asked if Dr. Marks would be interested in testing a new therapy for his AYA patients with brain cancer. That’s when the current trial was conceived, but much needed to be done.

“People think a clinical trial is the beginning,” said Dr. Bindra, “but it’s an enormous, complicated obstacle course to get there. There was no template for getting a rare pediatric cancer into a trial. First, we needed to show that BGB-290 was active against IDH1/2-mutant gliomas in pediatric cancer specimens. Second, we had to convince the pediatric community that these mutations were present in kids, not just adults.” Using gene sequencing data, they demonstrated that IDH1/2 mutations were indeed present in 30 to 40 percent of adolescents with gliomas. They took this data to BeiGene and asked it to support an AYA trial. BeiGene came on board.

Because AYA gliomas are rare, and those with IDH1/2 mutations even rarer, Yale couldn’t possibly recruit enough patients for a meaningful trial as a single center. Drs. Bindra and Marks needed a collaborating partner with lots of reach. They found one in the Pacific Pediatric Neuro-Oncology Consortium (PNOC), a network of 22 pediatric neuro-oncology centers that run clinical trials using



Ranjit S. Bindra, MD, PhD

Asher Marks, MD

new therapies on children and young adults with brain cancer.

The final element they needed was funding. They submitted an NIH grant, but the process can take several years. Meanwhile young patients with gliomas need help now. Drs. Bindra and Marks applied for rapid funding from CureSearch for Children’s Cancer, which supports innovative research likely to be clinically successful. CureSearch was so impressed by Dr. Bindra’s findings that it awarded him its inaugural Catapult Award of \$1 million.

Putting all these pieces together took about 10 months. The trial officially launched in April when PNOC enrolled the first patient at the University of California, San Francisco. Seventeen other institutions in PNOC’s network also are recruiting patients.

Drs. Bindra and Marks, co-principal investigators, expect to enroll their first patient at Smilow this fall. The initial goal is 48 patients, with an eventual total of 68. All will be treated with a combination of BGB-290 and temozolomide, a chemotherapy. The scientists expect the trial to run for three years.

“One of the most exciting things about this, and what makes it different,” said Dr. Bindra, “is that it’s a direct translation from the bench to the clinic for pediatric patients. We’re targeting a very specific brain tumor, it is biomarker driven, and the biology suggests a novel opportunity. Regardless of what we find, we just follow the biology, and this path paves the way for many more innovative, biomarker-driven trials in pediatric cancer.” 