TARGETing High-Risk Childhood Cancers

An NCI-led genomics effort identifies drug targets

Standard chemotherapy doesn’t work for 15% to 20% of children diagnosed with acute lymphoblastic leukemia (ALL), and clinicians simply didn’t know why. To find out, Stephen Hunger, MD, chief of pediatric oncology at Children’s Hospital Colorado in Aurora, and colleagues analyzed the genomes of 221 children with high-risk ALL. In 2009, they reported the identification of mutations in a family of proteins called JAK proteins, kinases that help cancer cells spread when activated (Proc Natl Acad Sci U S A 2009;106:9414–8).

The National Cancer Institute (NCI) wasted no time bringing these findings to the clinic. In September 2010, they began a phase I clinical trial testing a drug called ruxolitinib that inhibits JAK proteins. The study demonstrated the drug’s safety, and a clinical trial will soon combine ruxolitinib with chemotherapy for children with ALL.

The ruxolitinib trial is one of the first tangible results from NCI’s Therapeutically Applicable Research to Generate Effective Treatments (TARGET) Initiative, an effort begun in 2006 to use sequencing technologies to identify new drug targets in high-risk childhood cancers. “The big-picture goal is to find out what is driving the cancer in these high-risk cases and identify drugs that are more effective that the nonspecific, toxic chemotherapy that we’ve relied on for decades,” says Hunger, head of the ALL branch of the TARGET initiative.

ALL is just 1 of 5 cancers being studied by TARGET teams. To date, the initiative has spawned 2 clinical trials for new drugs against childhood tumors and identified numerous new mutations and surprising chromosomal abnormalities associated with pediatric tumors. Large portions of those data will be published by the end of the year.

The initiative’s goal is to completely characterize the genome, transcriptome, and epigenome of 100 to 200 cancer specimens from patients with the 5 cancers. “Within a couple years, we will have a much greater understanding of all of the molecular alterations of most of the different types of childhood cancers,” says Malcolm Smith, MD, PhD, founder of the TARGET initiative and associate branch chief for pediatrics in NCI’s Cancer Therapy Evaluation Program.

“It’s inappropriate to assume that the biology of adult cancers, including mutations, can be extrapolated directly to pediatric cancers, because the tissues in which these tumors are developing are very, very different,” adds Richard J. Gilbertson, MD, PhD, director of the Comprehensive Cancer Center at St. Jude Children’s Research Hospital in Memphis, TN.

ADDING TARGETs

The ALL pilot project, led by Hunger, was the first TARGET program initiated, followed shortly by a program in neuroblastoma.

Two-year-old Mya has been treated for neuroblastoma with the drug crizotinib, which blocks the activity of ALK, in a phase I clinical trial with positive results.

The neuroblastoma team has now analyzed over 600 high-risk neuroblastoma specimens using single-nucleotide polymorphisms and gene expression arrays and identified large chromosomal abnormalities in these tumors, says John Maris, MD, chief of oncology at Children’s Hospital of Philadelphia and head of the neuroblastoma group with Javed Khan, MD, of the NCI and Robert Seeger, MD, at Children’s Hospital of Los Angeles.

In addition, the team confirmed the presence of a mutation in anaplastic lymphoma kinase (ALK) in high-risk neuroblastoma tumors. In May, the NCI-supported Children’s Oncology Group (COG), which works closely with the TARGET projects and runs the ruxolitinib trial, announced positive results from a phase I trial in neuroblastoma treated with crizotinib, which blocks the activity of ALK. Of 27 neuroblastoma patients tested with the drug, 3 experienced complete regression of their tumor, and 7 had no disease progression.

In 2009, thanks to the addition of funds from the American Recovery and Reinvestment Act, 3 more types of childhood cancer were added to the TARGET initiative: osteosarcoma, the most common childhood bone cancer, with a 5-year survival rate of less than 70%; Wilms tumor, a type of kidney cancer that occurs primarily in children under the age of 5 years; and acute myeloid leukemia (AML), the second most common leukemia in children.

Preliminary results from the osteosarcoma TARGET group, led by Ching Lau, MD, PhD, of Baylor College of Medicine’s Texas Children’s Hospital, revealed that the genomes of these patients are highly rearranged.

The Wilms tumor research group is about two thirds of the way through analyzing gene expression, copy number, and methylation patterns of patient samples, according to lead investigator Elizabeth Perlman, MD, of Children’s Memorial Hospital of Chicago.

More than 250 samples have been sequenced by the AML research team, says team leader Robert Arceci, MD, PhD, professor of pediatric oncology at the Kimmel Comprehensive Cancer Center at Johns Hopkins University in Baltimore, MD. So far, the results point to several commonly mutated pathways—some of which are similar in adult AML, but not all—and the team is now validating those pathways and determining if they are druggable. “Without the TARGET initiative, none of this would have happened at this pace,” says Arceci. —Megan Scudellari