Bench-to-Bedside Research Changes the Outcome for Relapsed Pediatric Cancers

Almost two-thirds of patients who come to Cincinnati Children's for cancer care are seeking treatment options for disease that has relapsed or is not responding to contemporary therapies. They travel from around the world to see our nationally recognized team of pediatric oncologists and researchers, who offer unique, technically demanding and targeted therapies and an extensive portfolio of advanced clinical trials.

"The mission of the Cancer and Blood Diseases Institute (CBDI) and its integrated clinical and laboratory research divisions is to use disruptive team science to cure relapsed and refractory cancers in children and young adults," says John Perentesis, MD, FAAP, director of the Division of Oncology at Cincinnati Children's. "We achieve this through the integration of scientific discoveries in the CBDI laboratories and bench-to-bedside clinical translational research."

Breakthroughs in NF1 Research Leads to New FDA-Approved Therapy

A recent example is in the area of neurofibromatosis (NF) research. As many as 50% of patients born with NF1 develop one or more plexiform neurofibroma tumors, which are often untreatable and life-threatening. Cincinnati Children's researchers Nancy Ratner, PhD, and Jianqiang Wu, MD, MS, lead an extensive research program that has identified key disordered growth-control pathways in NF1 that lead to tumors. In a pivotal 2013 study, they showed that blocking the MEK protein in the NF1 molecular process could shrink plexiform neurofibromas by more than 70% in mice.

In a bench-to-bedside translation of these discoveries, pediatric oncologist Brian Weiss, MD, and colleagues from the National Cancer Institute (NCI) led clinical trials demonstrating the effectiveness of the MEK inhibitor selumetinib for shrinking life-threatening plexiform neurofibromas in children. Their findings were described in the April 2020 issue *New England Journal of Medicine*. Within 24 hours, the Food and Drug Administration approved the therapy — the first for children with NF1 and inoperable plexiform neurofibromas.

New Therapies Target Relapsed Leukemias and Lymphomas

Cincinnati Children's is a national and international referral center for children with relapsed leukemias and lymphomas. "The program's novel treatment regimens are borne out of our faculty's clinical expertise and fully integrated scientific research programs. This synergy is one reason our team leads the nation in developing new blood cancer therapy regimens targeting the molecular pathways that cause traditional therapies to fail," says Perentesis.

One such therapy involves the use of two chemotherapy drugs — intravenous Vyxeos and oral venetoclax — for pediatric and young adult patients who have refractory or relapsed acute leukemia. Investigators at Cincinnati Children's are testing this therapy in a first-in-the-nation, phase 1 clinical trial that uses new nanotechnology to target the Vyxeos to leukemia cells. Subjects also receive oral venetoclax, which hamstrings the mechanism that the leukemia cells would otherwise use to evade chemotherapy. This study, the first of its kind in the U.S., was developed at Cincinnati Children's and is only available here.

The team also participates in a broad range of clinical trials, including Children's Oncology Group (COG) phase 1 trials, Therapeutic Advances in Childhood Leukemia and Lymphoma (TACL) trials, and industry-sponsored trials.

Our CAR-T (chimeric antigen receptor T cells) program is one of the oldest in the country and has been treating patients for more than five years. CAR Ts can create remissions and cures in many patients who have leukemias that have become resistant to intensive chemotherapies and radiation treatments. The program is led by a team including Christin Phillips, MD, Christa Krupski, DO, MPH, and Stella Davies, MBBS, PhD, MRCP, and offers commercial Kymriah and clinical trials for pediatric lymphomas and

new indications for leukemias. Cincinnati Children's is one of a small number of clinical trial sites in the United States studying CAR-T cell therapy in pediatric lymphomas and as a component of therapy for newly diagnosed B-cell acute lymphoblastic leukemia patients with very high-risk features.

Fresh Perspectives on Targeted Therapies

Basic researchers and physician-researchers are teaming up in several labs at Cincinnati Children's to design and create new targeted therapies. Pediatric oncologist LaQuita Jones, DO, was first author of a preclinical study in the *Journal of Clinical Investigation* (April 1, 2020) showing that the novel inhibitor NCGC1481 was successful in blocking FLT3. FLT3 is one of the most commonly mutated genes in acute myeloid leukemia (AML) and can lead to higher rates of relapse. The study, led by Daniel Starczynowski, PhD, with collaborators from the NCI, described in vitro and in vivo models, and included mutations that can be seen in patients. NCGC1481 is a prototype of a series of new drugs being developed by Cincinnati Children's and the NCI to treat and potentially cure leukemias with FLT3 mutations that are resistant to current targeted therapies.

Basic researchers and physician-researchers are teaming up in several labs at Cincinnati Children's to test new targeted therapies.

"Working in the lab challenged me to think more deeply about the underlying mechanisms that may contribute to relapse or resistant disease, such as genetic mutations that can lead to resistance to targeted therapies," says Jones. "At the same time, my first-hand experiences as a physician helped our basic researchers develop a greater appreciation for the impact that cancer and cancer therapies have on children and their families. It's important to have both perspectives in the lab as we look for more effective and less toxic treatments for children with cancer, including those with relapsed and refractory disease."