Children's Mercy KANSAS CITY

TRANSLATIONAL HEMATOLOGY AND ONCOLOGY RESEARCH

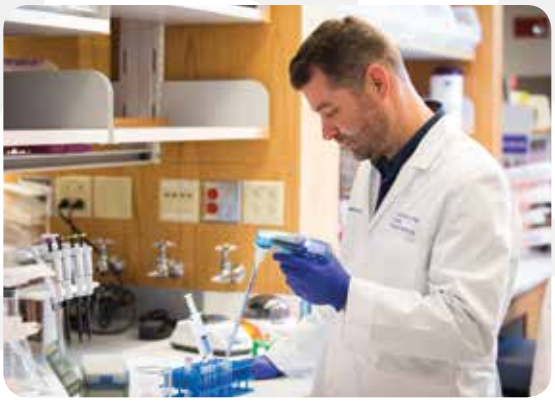
Using Drugs to Ignite the Immune System

SEEKING NOVEL THERAPIES TO ATTACK CANCER CELLS

One of the most important breakthroughs in cancer research has been the realization that the immune system can be ignited to fight cancer. Children's Mercy Kansas City is at the forefront of translational research, seeking novel therapies using existing drugs to jump-start the immune system and attack cancer cells while leaving normal tissue intact, as illustrated by two studies described below. These investigator-led studies have been focused solely on pediatric cancer from the outset.

REPURPOSING DOXORUBICIN AS TARGETED LEUKEMIA THERAPY

With certain types of pediatric leukemia, relapse rates can be as high as 50 percent. And with relapse, the cure rate drops to less than 50 percent. To successfully treat relapsed patients, the toxicity of the treatment is escalated, leading to long-term health consequences for these patients, including higher rates of heart failure later in life. John M. Perry, PhD, researcher with the Children's Research Institute (CRI) at Children's Mercy, is leading a study to identify a solution that offers these patients a cure while preserving their long-term quality of life.



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Through his study, funded by Braden's Hope for Childhood Cancer, Dr. Perry is learning how leukemia stem cells resist current treatments. Working with Dr. Linheng Li at the Stowers Institute for Medical Research, Dr. Perry and his team determined the regulators of normal growth of stem cells and progenitor cells. They identified two genetic signaling pathways that cooperatively drove stem cell renewal. Next, they developed a mouse model with genetic alterations in these pathways that caused excessive stem cell production. Instead of simply expanding stem cells, the mouse model showed permanent genetic alterations in these pathways, causing the mice to develop leukemia.

Dr. Perry then focused on inhibiting these pathways to specifically target the leukemia stem cells. Although they were resistant to many drugs tested, he determined that doxorubicin, a long-used chemotherapy drug, could inhibit the interaction between the two pathways to eliminate resistant stem cells. Most importantly, it was effective at a very low dose at a sustained level.

This approach allowed for a recovery of normal stem cells, stimulating the body's natural immune system.

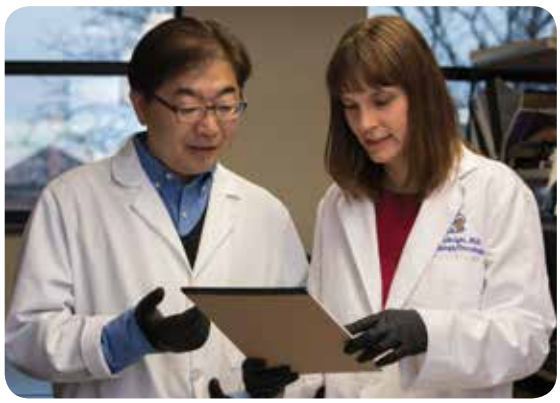
Study findings have been presented at several international conferences, such as the American Association for Cancer Research, the American Society of Hematology and the International Society for Stem Cell Research. An article is currently under revision for possible publication in *Nature*.

At Children's Mercy, Dr. Perry is conducting further research to understand ways to repurpose other drugs to kill resistant cells while reactivating anti-cancer immunity in pediatric patients.

IDENTIFYING NOVEL DRUG TREATMENT OPTIONS FOR OSTEOSARCOMA

Osteosarcoma is a highly metastatic and drug-resistant cancer. For the past 40 years, survival rates for metastatic osteosarcoma have been less than 20 percent, with no new treatments in several decades. Tomoo Iwakuma, MD, PhD, Director, Translational Laboratory Oncology Research Program at the CRI at Children's Mercy, is studying the underlying mechanism of progression in osteosarcoma, and his goal is the discovery of a targeted treatment. With funding support from Braden's Hope for Childhood Cancer, Dr. Iwakuma helped formed a "dream team" in partnership with The University of Kansas Cancer Center. The team is searching for a drug that will target cancer-specific events without damaging non-tumor cells.

Several years ago, using a high-throughput compound library screen, the team screened more than 15,000 compounds and identified one that specifically killed canine and human osteosarcoma cells lacking the tumor suppressor gene p53, with minimal impact on normal cells. Because it was discovered in the lab at the cancer center, the compound was named KU0171032.



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The current phase of study is focused on determining the clinical usefulness of KU0171032. At the present time, the compound is unstable in the human body, so Dr. Iwakuma's team is modifying the chemical structure to find a more stable version of KU0171032 that maintains its cancer-killing property. To meet this challenge, the team developed a mouse model and is continuing to test new versions of the compound. In some cases, tumor growth has been low, offering direction for further research.

Study findings initially were presented at the 2017 American Association for Cancer Research Annual Meeting. The first paper related to this project, focused on dissecting the mechanism of action of this uncharacterized compound, is in development.

CHILDREN'S RESEARCH INSTITUTE

The CRI at Children's Mercy is an integrated research environment where no boundaries exist between science and medicine. Here physicians, scientists, academic colleagues and philanthropic partners are collaborating to change the future for children. Research areas include genomics, precision therapeutics, immunotherapy and health outcomes, among many others. To enhance its research endeavors, a new building, future home to the CRI, is under construction. This building has been carefully designed so research and clinical care work as cross-functional teams, aligned together, to find answers to pediatric medicine's most challenging questions.

Children's Mercy KANSAS CITY

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NCI Cancer Center
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LEARN MORE ABOUT TRANSLATIONAL HEMATOLOGY AND ONCOLOGY RESEARCH.
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