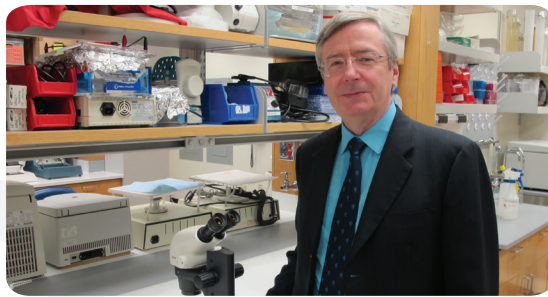


CHILDREN'S MERCY BREAKS NEW GROUND IN CANCER RESEARCH

Rethinking the Approach to Clinical Trial Designs



Under the leadership of Dr. Curran, the Children's Research Institute is focusing on tumor genetics and attempting to create novel therapies.

As researchers learn more about the molecular diversity of tumors, it's becoming clear that cancer therapies must be tailored to molecularly defined subsets of tumors. As such, in many cases clinical trial design is being adapted to the needs of molecular targeted therapies – including at Children's Mercy Kansas City.

At the Children's Research Institute, led by Tom Curran, PhD, FRS, Executive Director, researchers are working to identify hematology and oncology targets, drugs and treatments. Teams are conducting investigator-led research that leads to investigator-led clinical trials. Two of those research projects are described here. Researchers are focused on tumor genetics, working to learn how tumors respond to different drugs and attempting to develop novel therapies.

These projects, each currently in a preclinical phase, share the unique phenomenon that they have focused on pediatric cancer from day one, unlike other projects, in which adult studies are retrofitted for children. This presents a challenge because there are no external corporate partners to support the work due to the small market size. Even so, if researchers can be more precise with the right population and the right therapy, the possibility of more robust data exists early on in the process, despite a small trial size.

DEVELOPING A TARGETED THERAPY FOR GLIOBLASTOMA

Glioblastoma (GBM) is the most common and most aggressive primary malignant brain tumor, with a very poor prognosis in pediatric patients. After the standard surgery and radiation treatment, recurrence with more aggressive tumors is common. To improve outcomes, Taeju Park, PhD, Children's Research Institute, is leading a project funded by the Masonic Cancer Alliance to develop a novel treatment.

Dr. Park's study is focused on two proteins – Crk and CrkL – that are reported to be elevated in some GBM patients and correlated with poor prognosis. Tumor cell migration and invasion contribute to the spread of GBM to healthy brain tissues, leading to high recurrence rates. Dr. Park has demonstrated that Crk and CrkL play important roles in GBM cell migration and invasion. He is working to develop specific inhibitors of these proteins to block GBM cell migration and invasion.

In the lab, he and his team take advantage of genetically engineered mouse models and the gene knockdown technique to study tumorigenic functions of Crk and CrkL. They identified a protein that is activated by elevation of Crk and CrkL and binds to Crk and CrkL. The new malignant connection promotes tumor cell migration and invasion.



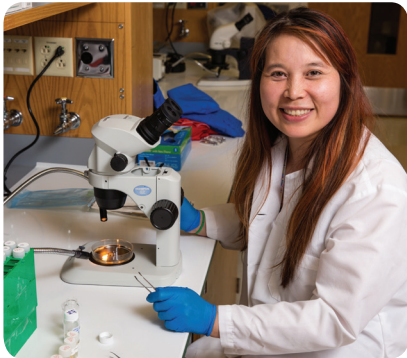
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Dr. Park's goal is to develop drugs that specifically break down the aberrant protein-protein complex between Crk and CrkL and their binding partners.

To test effects of chemical compounds on the binding of these proteins, Dr. Park developed an in vitro assay system and conducted a high-throughput screen. In partnership with The University of Kansas Cancer Center, the team has tested 200,000 chemical compounds and identified more than 600 potential candidate drugs. Today, these compounds are undergoing rigorous post-screening validation using different biochemical experiments.

DEVELOPING A TARGETED THERAPY FOR MEDULLOBLASTOMA AND AT/RT

In another study, Jessica Mei Yin Ng, PhD, Children's Research Institute, is working to develop better treatments for the aggressive brain tumors medulloblastoma (MB) and atypical teratoid rhabdoid tumor (AT/RT). Over the past several years, Dr. Ng and coworkers in Dr. Curran's lab helped develop a new approach to the treatment of MB using Hedgehog (Hh)



In partnership with The University of Kansas Cancer Center, Dr. Ng and her team are focusing on how to target drug-resistant brain tumors.

pathway inhibitors. The lab conducted molecular gene expression studies that identified four major subtypes of MB tumors and developed a mouse model (Ptc1/p53) for high-incidence, early-onset Hh subtype MB. Using this spontaneous central nervous system (CNS) mouse model, they demonstrated that oral delivery of small molecule inhibitors of Smoothed (Smo), called GDC-0449 or vismodegib, eliminated even large spontaneous brain tumors in mice.

They worked with Curis Inc., and later Genentech Inc., to demonstrate proof-of-concept of the use of Hh inhibitors in cancer. This work led to successful Phase I and II clinical trials of Smo inhibitors in pediatric and adult MB that recapitulated all the major findings obtained in mice. Because of these efforts, the first Smo inhibitor (Vismodegib) was approved for treatment of advanced basal cell carcinoma in 2012.

THE ROLE OF PRECISION THERAPEUTICS

With precision therapeutics, researchers are studying biomarkers to learn how a drug works in patients. They are beginning to design trials that treat a specific gene or defective pathway, regardless of the type of cancer. Soon researchers will be seeking patients with specific genetic mutations, rather than a group of patients with the same type of cancer.

Samples from all cancer patients at Children's Mercy are sent to the Center for Genomic Medicine for DNA sequencing. These genomes are stored in a central database. When a trial is opened for specific genetic mutations, patients who qualify can quickly be notified. In addition, researchers continue to evaluate these genomes to see if they can uncover anything today using new technologies. This is the future of research at Children's Mercy.

The next step is to focus on targeting drug-resistant brain tumors. Dr. Ng will use in vitro high-throughput drug screening in partnership with The University of Kansas Cancer Center to identify potentially effective compounds, as well as noninvasive imaging approaches (such as MRI and CT), drug delivery therapies and next-generation sequencing. The ultimate goal of the research is to develop new drugs for clinical trials in pediatric brain cancer.

Dr. Ng's research is also investigating the role of INI1 (integrase interactor 1), also known as SNF5 or SMARCB1. SNF5 is a key component of the SWI/SNF (switch/sucrose nonfermentable) chromatin remodeling tumor suppressor complex, which is an ATP-dependent nucleosome-remodeling complex that regulates gene transcription in CNS development and tumorigenesis, including the pediatric CNS tumor AT/RT. Dr. Ng has generated the first CNS mouse model for AT/RT, which is quite crucial because with this model they can now test potential drugs in vivo and investigate the cell of origin to understand the cancer biology of AT/RT.



LEARN MORE ABOUT THESE TRANSLATIONAL HEMATOLOGY AND ONCOLOGY STUDIES.

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