Brain Tumors

Research Update 2013



National Leadership

Neuro-Oncology Program director, Dr. Maryam Fouladi, was recently elected chairman of the *Pediatric Brain Tumor Consortium*. The PBTC was formed by the National Cancer Institute to improve the treatment of primary brain tumors in children. Academic centers and children's hospitals across the country, under Dr. Fouladi's leadership, have been working to rapidly conduct novel phase I and II clinical evaluations of new therapeutic drugs, new biological therapies, treatment delivery technologies and radiation treatment strategies for brain and central nervous system tumors.

Dr. Fouladi also serves as chair for the CNS Tumor New Agents/Relapse Committee for the Children's Oncology Group, and is a member of the Steering Committee for the Collaborative Ependymoma Research Network (CERN). She and Cincinnati Children's Hospital faculty serve as local and national study chairs for active open clinical trials that test new approaches to treat children with very poor prognosis tumors such as high-grade gliomas and diffuse intrinsic pontine gliomas.

Drs. Fouladi, Trent Hummel, Rachid Drissi and Lionel Chow are leading both active institutional and national biology and therapeutic studies through the Children's Oncology Group to delineate the biology of high-grade gliomas and to improve the outcome for these diseases with innovative therapies.

CBDI's approach to brain tumors benefits from collaboration between clinical and basic science researchers on molecularly-targeted therapies and chemoprotection medications in high-dose chemotherapy applications. Potential "tailored" therapies are investigated through studies based at Cincinnati Children's and extended to other pediatric centers by virtue of CBDI leadership roles in national consortia.

Cincinnati Children's Oncology faculty Drs. Maryam Fouladi and Trent Hummel, along with other Cancer Program investigators, are also advancing national studies of host drug metabolism.



Thouwa Samake of the CBDI Translational Laboratories bridges the gap between scientific research and treatments for cancers

Research Highlights

Role of basic growth pathways dysregulation in cancer

A key research focus has been on understanding the role of dysregulation of basic growth pathways in cancer and how to translate these insights into novel clinical treatments. The laboratory of Dr. George Thomas is recognized for ground breaking studies in the purification and cloning of the cell-growth signaling molecules S6K1 and S6K2. He elucidated the role of these key molecules in normal and deranged cell growth, in a pathway regulated by a key signaling component called "mTOR." He also identified key related regulatory components that control this pathway, including an important regulator called the tuberous sclerosis TSC1/TSC2 suppressor complex.

Dr. Thomas's basic science investigations have been part of the underpinning of a new generation of therapies to target this pathway in adult and pediatric malignancies. In particular, his work on the causes of cancer-related syndromes such as tuberous sclerosis and neurofibromatosis that result in brain tumors has led to multiple Cincinnati Children's new treatments that target this pathway. His laboratory is integrated into these new treatments and is investigating new tests to help understand the determinants of response to these important new therapies.



Dr. Trent Hummel with patient

Pediatric Brain Tumor Consortium and Collaborative Ependymoma Research Network Studies

Drs. Fouladi, Kathleen Dorris and Rachid Drissi, are developing a Phase II study of Imetelstat in pediatric patients with recurrent or refractory CNS malignancies.

Dr. Mariko DeWire is leading a new Phase I study of an HSV oncolytic virus in children with recurrent high-grade gliomas through the Pediatric Brain Tumor Consortium. She will develop local and national new treatments for infants and children with medulloblastoma and diffuse intrinsic pontine glioma.

The CERN08-01: A Phase II Study of Bevacizumab and Lapatinib in Children with Recurrent or Refractory Ependymoma is being led by Dr. Fouladi. It is designed to extend our existing research efforts in clinical antiangiogenesis and tumor receptor targeting. The study is a Cincinnati Children's investigator-initiated national study through the Collaborative Ependymoma Research Network (CERN).

The International Diffuse Intrinsic Pontine Glioma

(DIPG) Registry is a collaborative effort by physicians and researchers from North America, Canada, Europe, and Australia to centralize and standardize the collection of clinical data and tumor samples from DIPG patients. Cincinnati Children's CBDI is home to the North American operations of the Registry. The goal of this effort is to support innovative research and ultimately find a cure for DIPG. More details about the program can be found at www.DIPGRegistry.org.

Small molecule (antiangiogenic) therapies

CBDI continues to investigate new approaches to increase the effectiveness of chemotherapy in synergy with new small molecule or antiangiogenic therapies. Building on our center's pharmacology and biology experience with temozolomide, Dr. Trent Hummel is leading a national clinical trial (COG- ADVL0819) investigating the efficacy of the combination of temozolomide with the chromatin remodeling agent vorinostat. This work builds upon research in our center regarding chromatin structure, gene expression and cancer. Models suggest this combination may have substantial synergy in tumor therapy.

Mouse models

The lab of Dr. Lionel Chow uses genetically engineered mouse models of high-grade glioma to uncover new potential treatments for this cancer. These models are also being used to test novel molecularly-targeted small molecule inhibitor drugs alone and in combination, with a particular focus on the PI3-Kinase/AKT/MTOR pathway since this is a core signaling pathway involved in the pathogenesis of high-grade glioma. Taking advantage of the extensive expertise in new treatment design at CCHMC, drug combinations found to be effective in the mouse models will be rapidly moved into early stage pediatric clinical trials. Dr. Chow is a St. Baldrick's Foundation Scholar and Sontag Foundation Distinguished Scientist.

Linking patient samples to the laboratory

In all of these studies targeting basic mechanisms of carcinogenesis, we work to incorporate linking patient samples to the laboratory to improve our understanding of the biology of these diseases, and to provide critical information as to whether our novel therapies are "hitting" their targets. An example of this is seen in our clinical trial of the telomerase-targeting small molecule imetelstat, also led by Dr. Fouladi – in addition to extensive pharmacology and monitoring of the response of the brain tumors by imaging, the protocol incorporates novel laboratory studies of telomerase activity in patient samples conducted in the laboratory of Dr. Rachid Drissi.

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