2018 Medical Grants

Children's Hospital of Philadelphia, PA - Kristopher Bosse, MD

GPC2 as an immunotherapeutic target in medulloblastoma and other pediatric tumors

Medulloblastoma is a cancer that occurs in young children and is often lethal. Recent immunotherapy advances have resulted in enthusiasm for the use of this type of treatment in children with medulloblastoma and other incurable pediatric brain tumors. However, we desperately need new cell surface molecule drug attractants to safely and specifically target with immune-based therapeutic approaches. We have recently discovered that a protein called glypican-2 (GPC2) is abundant on medulloblastoma cells and potentially other brain tumors, but not found on normal cells. Thus, GPC2 may be an ideal cell surface drug attractant for immune-based therapies. We have engineered an antibody-drug conjugate that selectively targets GPC2 on tumors and safely delivers a potent drug payload only to these tumor tissues. Our ultimate goal is the clinical translation of this GPC2-directed antibody-drug conjugate for children with medulloblastoma and other brain tumors. By combing the selectivity of GPC2 specific antibodies with a potent drug payload, this immunotherapeutic offers a potentially more targeted and safer alternative than the highly intensive chemoradiotherapies that currently make up the backbone of standard pediatric brain tumor treatments. Thus, this strategy offers the potential to limit the acute and long-term comorbidities of cancer treatment for these children. Finally, this work will help establish a robust pipeline for the identification of additional tumor specific cell surface molecule drug attractants for immunotherapeutic targeting in pediatric brain malignancies with an aim to make prompt and meaningful differences in the clinical care of children with brain tumors

Weill Medical College of Cornell University, NY - Praveen Raju MD, PhD

Radiosensitization of Medulloblastoma via ATF5 Inhibition

Pediatric brain tumors are the leading cause of cancer-related death in children. Medulloblastoma is the most common malignant brain tumor, however, nearly one-third of afflicted children die within five years of diagnosis despite aggressive treatment that commonly includes surgical resection, whole brain and spinal cord radiation therapy, and chemotherapy. Unfortunately, the vast majority of surviving children have poor outcomes and significant neurological deficits due to the toxicity of these therapies. Despite recent advances in the genomic characterization of medulloblastoma, the vast molecular heterogeneity of these tumors as well as the evolution of the cancer to standard therapy have been limiting to novel targeted treatment strategies and suggest that alternative approaches that enhance upfront therapies including radiation therapy may have utility. Our group has developed a novel animal model of medulloblastoma that recapitulates many aspects of the human disease including diverse histology and frequent leptomeningeal metastases that are rarely seen in current preclinical models. Our

preliminary studies demonstrate that the ATF5 transcription factor is highly overexpressed in medulloblastoma and that pharmacologic interference with ATF5 function can block cell growth. We propose to test whether ATF5 blockade can enhance the effects of radiation therapy in our unique animal model of medulloblastoma in order to achieve increased tumor cell killing and potentially reduce associated toxicity through radiation dose reduction strategies. The results of this preclinical project will lay the foundation and expedite prospective clinical studies to assess whether ATF5 inhibitors may have clinical utility for children afflicted with these devastating diseases.

Columbia University Medical Center, New York, NY - Chao Lu, PhD

Targeting the Epigenome of Pediatric Ependymoma

Ependymoma is a malignancy that arises from the ependyma. While ependymomas occur throughout the neuraxis, hindbrain (also known as posterior fossa or PF) ependymomas predominantly affect children. Compared to other pediatric tumors, treatments for ependymomas remain stagnant and outcomes to therapy are variable with frequent tumor recurrence. This is, in part, due to a poor understanding of the molecular pathway(s) underlying the pathogenesis of this disease. Unlike the vast majority of human tumors, we and others have found that PF ependymomas harbor no recurrent genetic mutations that may underline its pathogenesis. Instead, we observed that PF ependymomas exhibited widespread abnormalities in pathways by which genes are packaged, organized and accessed. These mechanisms are commonly referred to as 'epigenetics' and have been increasingly associated with the development of many pediatric cancers. Importantly, abnormalities in epigenetic pathways are potentially reversible and compounds targeting epigenetic regulators have been approved by FDA or are in clinical trials to treat cancer patients. We propose to further investigate the cause of these epigenetic abnormalities in PF ependymomas, and to test the efficacy of small-molecule epigenetic inhibitors in halting tumor growth using pre-clinical models. Expected results will advance our current knowledge of ependymoma etiology, and may lead to rapid translation to clinical trials involving epigenetic-based therapies.
In addition, proposed studies will generate novel pre-clinical models that will be valuable to basic and translational research of PF ependymoma.

St. Jude Children's Hospital Memphis, TN - Giedre Krenciute, PhD

Genetic modifications to improve CAR T-cell Therapy for Pediatric Gliomas

The intent of this project is to develop antigen-specific T cells as an effective immunotherapy for high-grade glioma, a type of brain tumor that is largely resistant to conventional therapies resulting in poor outcome. Using the patient's own immune system to fight cancers is one promising approach to improve outcomes for adult and pediatric cancer patients who do not benefit from current therapies. Additionally, the body's immune defenses against cancer often fails because the cancer does not induce or actively inhibit immunity. Cancer treatments consisting of the infusion of T cells that recognize tumor antigens, molecule present on many cancers, have shown

promise in early clinical studies. We have now developed such an approach for pediatric patients with high grade glioma. In our method, we target a molecule called IL13Rα2, which is present on glioma cells. We have generated IL13Rα2-specific T cells using a genetic modification and have shown that these cells have antiglioma activity in pre-clinical models. In this project, we now propose to optimize our IL13Rα2-targeted T cell based therapy for high-grade glioma. Now, we wish to explore if additional genetic modifications can improve anti-tumor activity of IL13Rα2- specific T cells. The major goal of the project is to evaluate if elimination of molecules that negatively affect T cell function can enhance IL13Rα2-specific T cell anti-glioma activity. If our pre-clinical approach is successful and a clinical study is justified, we have the resources to develop such a study at our institution.

Children's Hospital of Pittsburgh, PA – Baoli Hu, PhD

Identifying Epigenetic Drivers Associated with Invasion and Metastatsis in Group 3 Medullablastoma

Medulloblastoma (MB) is the most common malignant brain tumor in children. Although surgery, radiation, and chemotherapy are effective at eliminating some forms of MB, they cannot cure patients with aggressive tumors. A form currently known as Group 3 MB is the most aggressive and deadly medulloblastoma. When children are diagnosed with Group 3 MB, they face the worst prognosis, and their cancer frequently spreads (metastasis). Group 3 MB accounts for about 25%-30% of all medulloblastomas. The work of Dr. Hu's project is to find new ways to attack Group 3 MB. Each MB group has distinct abnormalities; for example, Group 3 MB overexpresses a gene called MYC that is linked to many types of cancer. Changes in gene behavior, like overexpression or underexpression, are controlled by what is called epigenetics. Fortunately, manipulating epigenetics is possible. Dr. Hu's research will combine computer-based analysis of MB patients' tumor gene expression data with biology-based validation to identify the unique epigenetic actors that may be working together with the MYC gene to make this cancer able to invade healthy cells. They will use animal models to test whether adding or deleting a suspected epigenetic actor can keep cancer from spreading. Because epigenetic factors are very promising drug targets, if this hypothesis is proven, it may be possible to use existing drugs or develop customized drugs to treat this devastating childhood cancer.

John Wayne Cancer Institute, Santa Monica, CA - Ivan Babic, PhD

Immunosuppression from NAD+ metabolic reprogramming in pediatric medulloblastoma

About 20% of all childhood brain cancers are medulloblastoma, and almost half will have a deletion of chromosome arm 17p. The mitochondrial protein p32 (gene C1qBP on

chromosome17p) may be lost in these tumors. Absence of p32 is known to alter tumor metabolism. This project proposes a novel paradigm that medulloblastoma harboring genetic lesion of the gene for mitochondrial protein p32 on chromosome arm 17p are metabolically reprogrammed. This rewiring of metabolism will significantly impact the tumor microenvironment towards immunosuppression. The goal of this project is to elucidate the role of p32 in this reprogramming and identify metabolic vulnerabilities that can be therapeutically targeted. Chromosome deletion represents an absolute vulnerability of these cancers, and this proposal will test several inhibitors targeting this vulnerability that could quickly move to the clinic to benefit pediatric brain cancer patients.

Children's Cancer Therapy Development Institute, Beaverton, OR – Noah Berlow, PhD

The IL13RA2-HAS2 axis as therapeutic co-targets in DIPG.

Diffuse intrinsic pontine glioma (DIPG) is a fatal childhood brain cancer afflicting approximately 350 new patients in the US per year. Most DIPG patients survive less than 1 year. Chemotherapy, radiation, and many newly explored drugs are nearly ineffective. Our research group started a clinical trial for a drug called panobinostat as a promising treatment for DIPG. However, while panobinostat will likely help extend life, cures for DIPG are needed. We looked at gene activity in 28 DIPG samples and found two genes highly active in DIPG tumor cells and absent in normal cells: IL13RA2 and HAS2. IL13RA2 and HAS2 have both been shown to cause tumor cell growth in brain cancer. HAS2 also modifies the environment around cancer cells, making cancer cells have an easier time growing and thus the tumor grows faster. Recently, published studies have suggested that HAS2 and IL13RA2 being highly expressed at the same time can control a process that turns normal cells into "stem-like" cells. "Stem-like" cells replicate quickly and can move around easily, and are thought to be a cause of extremely dangerous cancers, such as DIPG. We hypothesize that HAS2 and IL13RA2 turn DIPG cells into "stem-like" cells that grow quickly and invade into the cancer promoting environment caused by HAS2. We will perform experiments in petri dishes to confirm our hypothesis. We will also test a HAS2 + IL13RA2 targeting combination treatment in mice with human DIPG to determine if HAS2 and IL13RA2
treatment can be an effective cure for DIPG.