2019 Research Grants – Lay Summaries

Timothy Phoenix – University of Cincinnati
Targeting immune evasion in diffuse intrinsic pontine glioma

CDK4/6 inhibitors are new therapies developed to target key proteins that promote tumor cell growth. Recent studies have shown that besides their intended target, they also promote an anti-tumor immune response. This is very exciting, as strategies to modulate one's own immune system to attack their cancer has shown great promise. Yet the vast majority of cancer research, especially pediatric neuro-oncology, is performed in mice that lack an immune system. Thus, experiments in these models will not catch the potential synergistic effects ofCDK4/6 inhibitors on cell growth and immune system activation. By applying our expertise in neuro-development and oncology, we have developed new immune-competent mouse models of diffuse intrinsic pontine glioma (DIPG). This unique tool provides us with an exciting opportunity to perform preclinical drug testing in a setting where CDK4/6 inhibitors can impact both tumor cell growth, and immune cell anti-tumor activity. We will perform preclinical tests with CDK4/6 and immune-checkpoint inhibitors, alone and in combination, to determine the therapeutic response in our DIPG mouse model. The proposed research will advance our understanding of CDK4/6 inhibitors, if they increase immune cell infiltration into DIPG, and if combining them with immune-checkpoint inhibitors improves overall response. Our ultimate goal is to provide strong preclinical data that can inform or be directly translated into clinical trials to benefit patients and their families.

Jessica Foster, MD – Children's Hospital of Philadelphia
Development of an mRNA GD-2- directed chimeric antigen receptor (CAR) T cell platform for the treatment of diffuse intrinsic pontine glioma (DIPG)

Chimeric antigen receptor (CAR) T cells are an immune-based cancer treatment that involves taking white blood cells from a patient, reprogramming them to seek out and attack tumor cells, then reintroducing these cells back into the patient. This project will use CAR T cell therapy to treat diffuse intrinsic pontine glioma (DIPG), a universally fatal pediatric brain tumor with a median survival of nine months. The goal of this project is to use CAR T cells to seek out a target called GD2, a sugar molecule that sits on the outside of tumor cells.GD2 was recently found to be on the surface of DIPG at very high levels, which allows the CAR T cells to recognize and attack the DIPG tumor cells. This project is unique because we are using mRNA to create the CAR T cells, which means the CAR T cells will be temporary and can be dosed like a drug, allowing for maximal safety. Our goal is to create optimal dosing strategies of these CAR T cells that will lead directly to clinical trials to help cure these devastating brain tumors.

Sarah Injac – Baylor College of Medicine
Targeting Aurora A in Combination with Radiation

Medulloblastoma is the most common malignant brain tumor of childhood. While a majority of patients with medulloblastoma are cured with current standard therapy which includes surgery, chemotherapy, and radiation, survivors face significant long-term treatment related side effects. In particular, they have difficulty learning which in turn limits their ability to finish school and live independently. Furthermore, for patients whose tumors progress or recur after standard treatments, there are currently no effective second-line curative therapies. The need for new treatments for medulloblastoma, therefore, remains pressing. This is particularly true of sub-groups 3 and 4 of medulloblastoma which have worse outcomes than other medulloblastoma subgroups and because of their molecular variability have not been amenable to rational targeted therapy. Despite major advances in recent years in our understanding of the biology of medulloblastoma, we have yet to significantly change our approach to treating these devastating tumors. This is in part because new drugs require extensive and time consuming testing to determine dosing and side effects and then still frequently fail to show significant benefits when used as single agent therapies in patients. This proposal is designed to address these issues by: 1) Using a compound, the Aurora A inhibitor MLN8237, for which pediatric dosing and side effects are well established 2) Combining MNL8237 with radiation, a mainstay of medulloblastoma therapy. This in turn will allow us to maximize the potential for the rapid and effective translation of any positive findings into a clinical setting.

Tabitha Cooney – University of California, San Francisco

Proof of Mechanism and Phase 1 study of Tumor Necrosis Factor- Alpha(TNF) in combination with Nivolumab for children with Recurrent Medulloblastoma, a Pediatric Neuro-Oncology Consortium (PNOC)

Pediatric brain tumors now contribute to the most cancer-related deaths in children, and little progress has been achieved over several decades. Immunotherapy is emerging as a promising approach to treating cancer. We know checkpoint molecules can be hijacked by cancer cells, switching off the immune response and allowing tumor cells to continue to grow. Checkpoint inhibitors can switch these checkpoints back on, allowing the immune system to be activated and to destroy cancer cells. This strategy has been very successful in a variety of adult tumor types – especially "hot" tumors. However, current data suggest that brain tumors, including pediatric brain tumors, are immunologically "cold"– meaning that they do not trigger a strong immune response.
Our proposed clinical trial builds on exciting preclinical data showing that treatment with low doses of tumor necrosis factor (TNF) can overcome immune evasion in pediatric medulloblastoma and enhance response to immune checkpoint inhibitors – turning these "cold" tumors "hot". We propose to study the immune microenvironment and sensitize these tumors to T cell-based immunotherapies. Ours is the first study to evaluate TNF as a primer for immunotherapy in trial patients, and to test the safety of TNF in combination with checkpoint inhibition.
Results of the proposed project will have a significant impact on the design of the next

generation of immunotherapy trials for children with brain tumors. Within our clinical trial consortium for children with brain tumors – the Pacific Pediatric Neuro-Oncology Consortium – we are poised to test such innovative treatment strategies.

Jain Hu – University of Texas MD Anderson Cancer Center

To investigate the role of histone mutations and their therapeutic implications in pediatric high-grade glioma.

Pediatric brain tumors are the most common solid tumors in children, with approximately 5,000 new cases diagnosed per year in the US. Around 17% of brain tumors in children age 0–14 years are high-grade gliomas (HGGs). Pediatric HGG (pHGG) is the most lethal cancer in children; the median survival duration of this disease is only 12–15 months. Pediatric brain tumors show distinct features from their adult counterparts, and no advanced therapy for the disease has been developed during the last 3 decades. Recently, new driver mutations on an essential gene in pHGG have been identified, which occur in about 50% of the patients. However, the gliomagenic mechanism and the potential targeted therapies related with these mutations are still unclear.

Neural stem cell (NSC) is a type of cell that has the ability to generate all kinds of neural cells in developing brain, and has been considered as the origin of gliomagenesis. We have engineered the first-of-its-kind mouse model by introducing one of these two mutations in NSCs of mouse brain, which generates spontaneous pHGG that mimics human pHGG. By applying multifaceted methods to analyze these tumors, we have identified the two key drivers, which highly express in human gliomas and are greatly associated with poorer patient survival. In this proposal, by taking advantage of the novel mouse models, we plan to illustrate the roles of these newly identified key players in gliomagenesis and try to design new therapeutic approaches by targeting these components to treat pHGGs.

C Xiang – Weill Medical College of Cornell University

Reprogramming pediatric brain cancer cells

Diffuse Intrinsic Pontine Glioma (DIPG), a very aggressive form of brain tumor affecting children has a dismal prognosis of less than a year. This tumor arises in the developing pons, a brain structure involved in the control of functions necessary for life such as breathing. Therefore, surgery is often not an option in the therapy regiment for children developing DIPG. Genetic analyses show that defects in the epigenetic landscape may be driving DIPG tumorigenesis, but how DIPGs arise and grow in the developing pons remains unresolved. Very little is known about the mechanisms that control pons development which when deregulated contribute to DIPG development and progression. We have identified a novel protein that is required for pons development. Our unpublished data show that in mice lacking this factor the pons is underdeveloped. In addition, its expression in DIPG cells changes their epigenetic program. We propose to investigate how this protein maintains cell differentiation in the developing pons and test

whether its reintroduction in DIPG cells may be a therapeutic strategy using different DIPG animal models. This project thus takes both basic and translational approaches to better understand the mechanisms of gene regulation that govern critical cell decisions in the development of cancer from mutant cells arising during normal development. The results of the proposed experiments will contribute in shedding light on key mechanisms underlying DIPG growth and progression, and highlighting possible novel avenues for therapeutic intervention

Ram Kannan – Memorial Sloan Kettering Cancer Center
Modeling and targeting Kiaa1549 – Braf duplication in pediatric brain cancer

Pilocytic astrocytomas (PA) and Diffuse Leptomeningeal Glioneuronal Tumors (DLGT) are brain tumors that occur in young children. Although surgery is a possible treatment option, in operable tumors can lead to premature death especially in the case of DLGT. Recent studies have shown that about 70% of patients with PA or DLGT have alterations in a particular chromosome that results in fusion of two genes in cancer. Currently, there no good models where we can test the effect of this fusion gene and how it promotes PA or DLGT. Generation of this fusion gene in a mouse model should result in a brain tumor that has features similar to patients and will help in identification of new drugs that can be effective in PA or DLGT.I will generate this gene fusion in neural stem cells and inject them into mice to generate a new brain tumor model that has features seen in PA or DLGT. This provides a model where I can testnew drugs in hope to identify the ones that can cure patients with this cancer.