2014 Research Grants

Yale University - Jiangbing Zhou MD, PhD

Project Title: Precise delivery of gene therapy

Brainstem gliomas, accounting for 10-20% of childhood brain tumors, are the main cause of death in this young group. The most common type of brainstem glioma is defined as diffuse intrinsic pontine glioma (DIPG). Despite extensive efforts over the past few decades, the overall prognosis for DIPG remains dismal – nearly 90% of children with this disease die within 18 months of diagnosis and the median survival have been about 1 year. The failure of current treatment can be attributed to two major reasons. First, current technologies don't allow for efficient delivery of therapeutics precisely to DIPG tumors in the brain. Secondly, the existing regimen has limited efficacy on this genetically distinct disease. We hypothesize that improved treatment of DIPG can be achieved by adequately addressing these limitations through precise delivery of gene therapy designed for targeting major aberrant genes identified in this tumor. Specifically in this one-year project, we propose to develop a nanotechnology-based platform for image-guided delivery of gene therapy precisely to DIPG tumors in the brain. The success of this project, which we expect based on our existing progress, will result in a new approach for improved treatment of DIPG that can be readily translated into clinical applications to improve the quality of life and the survival rates of children and their families dealing with this lethal disease.

Weill Cornell Medical Center - Hector Peinado Selgas MD, PhD

Project Title: Use of circulating exosomes as surrogate markers of signaling activation and response to therapy in pediatric brain tumors.

Pediatric gliomas and medulloblastomas account for more brain tumors in children than any other. While surgery, chemotherapy and radiation remains the mainstay of upfront treatment, recent advances in molecular interrogation of brain tumors have demonstrated a small number of recurring genetic mutations in these tumors that might be exploited therapeutically. Diagnosis of brain tumors is generally based on imaging features and, when the tumor is biopsied or resected, histopathologic interpretation. Therefore, invasive techniques are normally needed to validate the mutational status and/or determine the activation of specific pathways. Activation of different oncogenic pathways has been found to be crucial for pediatric brain tumor progression. However, there are limited clinical trials for specific inhibitors. Novel therapeutic approaches are urgently needed to improve prognosis and treatment of these patients. We have recently found that small vesicles secreted from the tumor (called exosomes) are shed from cancers and are readily isolated from the peripheral circulation. We have found that exosomes shed from tumor cells contain many molecules representative of the primary tumor (i.e. activated oncoproteins and mutated DNA). Our results demonstrate that exosomal DNA may be used as a surrogate for tumor tissue to determine mutation status in cancer patients. We propose a novel concept in pediatric cancer: that tumor circulating exosomes in the

plasma can be used to monitor oncogene activation and tumor DNA mutations. Our studies will contribute to improve prognosis of pediatric brain cancer progression developing new approaches to monitor response to therapy.

Stanford University – Michelle Monje MD, PhD

Project Title: Neuronal: glioma interactions in the pediatric glioma microenvironment as a novel therapeutic target

Cancer cells grow in the environment of the tissue they are invading, and often take advantage of growth signals present in the normal tissue. This is especially true for cancers of childhood, when normal tissue is naturally in a state of growth and development. High-grade gliomas of childhood, the leading cause of brain tumor death in children, arise from glial precursor cells in the context of the developing brain. Our previous studies of normal childhood brain development indicate that neurons, the electrically active cells in the brain, influence the growth of glial cells such that active neural circuits receive more glial support. We hypothesize that pediatric gliomas may be similarly influenced by the growth-promoting effects of active neurons. Using a revolutionary new technique called "optogenetics", we can control the firing rate of neurons using pulses of light. We find that indeed there is an important interaction between active neurons and pediatric glioma cells. Our preliminary studies indicate that active neurons secrete a molecular factor (or factors) that induces a significant increase in glioma cancer cell growth. In the present proposal, we seek to identify the molecular factor (or factors) responsible for this cancer growth-promoting effect. We hope that this work will result in novel therapeutic strategies for high-grade gliomas of childhood.

University of California, San Francisco – Rintaro Hashizume, MD, PhD

Targeting the Histone H3.3-K27M Mutation for the Treatment of Diffuse Intrinsic Pontine Gliomas

Diffuse intrinsic pontine gliomas (DIPGs) in children continue to carry a very poor prognosis despite the use of intensive multi-modality treatment. No significant advances in the survival of DIPG patients have been made over the last few decades, and new therapeutic approaches are desperately needed. The lack of human DIPG tissue samples and a faithful experimental model system, combined with a limited understanding of the development of childhood brainstem tumors, have hindered the study of this devastating disease, and prevented the identification of effective therapeutic strategies. Recent genetic screenings identified a specific mutation of histone gene H3F3A in DIPGs,

thereby suggesting a role of this mutation in DIPG development. We have recently established tumorigenic DIPG cells from biopsies of pediatric DIPGs, and these have been determined as having the H3F3A mutation in question. These DIPG cells produce tumors in athymic mice, and provide an excellent resource for studying the biological abnormalities of these tumors, as well as for testing experimental therapies for treating

DIPGs. The overall goal of this project is to investigate molecular consequences of the H3F3A mutation, and to evaluate a specific therapeutic for treating these tumors. This project has a high likelihood of influencing DIPG treatment, and for achieving improved outcomes for DIPG patients.

University of Pittsburg – J. Anthony Graves MD, PhD

Therapeutically Targeting OPA1 in Medulloblastoma

Medulloblastoma, the most common malignant pediatric brain tumor, results in significant morbidity and mortality. Specifically, there is one subtype of medulloblastoma that is responsible for the vast majority of tumor-associated morbidity, which is characterized by amplification of the c-Myc oncogene. Among the changes that result from c-Myc overexpression is an increase in mitochondrial fusion. Decreasing the expression of Opa1, a protein essential for mitochondrial fusion, has been shown to kill a variety of cells that overexpress c-Myc. It is proposed to exploit this finding for possible novel treatments of medulloblastoma with high levels of c-Myc.

Yale University – Ranjit Binja MD, PhD

Creation of Isogenic Pediatric Glioma cell lines for High-throughput drug screening campaigns

Pediatric high-grade gliomas (HGGs) are clinically devastating tumors, with associated 5-year overall survival rates of less than 20%. There have been little improvements in survival for this disease over the last 30 years. Most novel therapies for pediatric HGGs are tested in children based on extrapolation from adult HGG studies. However, it is now understood that significant genetic differences exist between gliomas arising in children and adults. In parallel, there is a lack of suitable pediatric glioma cell lines, which can be used for translational research studies. We hypothesize that better cell line models will facilitate drug screening efforts to identify pediatric glioma-specific therapies. In this project, we propose to create a panel of novel glioma cell
lines which harbor mutations in key genes specific to pediatric HGGs. We will characterize these cell lines in a panel of genomics-based studies, and we will provide them to the broader pediatric glioma research community for future research efforts. These cell lines do not currently exist, and they are likely to become indispensable tools for future drug screening efforts.