2021 Grant Recipients

Maya Graham – Memorial Sloan Kettering Cancer Center, NY, NY
Childhood high-grade gliomas are universally fatal brain tumors, with no new treatments in decades. Several mutations in histone H3, a protein that coordinates global changes in gene expression, have recently been identified in these tumors. This finding raises the possibility of developing targeted treatments for these patients, but a better understanding of what these mutant histones do in glioma cells is required. We have developed a new glioma model by putting mutant histones into stem cells grown as cerebral organoids: 3D “mini brains” that mimic human brain development. Using these tumorforming “mini brains”, we will study what types of brain cells can be turned into tumor cells by mutant histones. This will allow us to perform future studies of whether blocking mutant histones after a tumor is formed can kill the tumor, thus enabling better design of treatments for children with high grade gliomas.

Nada Jabado – McGill University Health Center, Montreal, Canada
Cancer often develops when a particular regulator that controls the “reading” of other genes is disrupted by a mutation. This can result in atypical behavior of cells and uncontrolled growth. One example of this type of cancers is childhood brain cancers. In these cancers, genes that control the packaging of DNA, which are called histones, are mutated. My lab and others showed that mutations in the histone H3.3 variant can lead to brain tumors and other types of cancers in bone, soft tissue, and blood. In the present study, we will examine how this mutation induces these tumors using fruit flies as a model system. We have established this tumor model in which we showed candidate genes that are altered and want to expand on identifying additional players that change the fate of these cells in the mutant H3.3K27M oncohistone context. Furthermore, using this powerful in vivo genetic model which previously showed to be effective in therapeutic screening, we will screen for candidates that will mitigate the effects seen by the tumor and identify few potential candidates or combination treatments which will show selectivity and sensitivity to H3.3 K27M bearing childhood tumors.

Jeffrey Rubens – Johns Hopkins, Baltimore, MD
Atypical teratoid/rhabdoid tumors (AT/RT) are the most common malignant brain tumors of infancy. Outcomes are devastating with a median survival of less than one year. We are in dire need of developing novel therapies to improve these dismal outcomes. In this proposal, we develop a unique therapeutic strategy, which precisely targets AT/RT to inhibit tumor progression, therapy resistance, and improve survival. AT/RT have a single recurring genetic mutation in the epigenetic regulator gene, SMARCB1, which disrupts gene expression throughout the AT/RT genome. Our previous studies have shown that this epigenetic abnormality is highly intertwined with AT/RT cellular metabolism. This bi-

directional relationship is a critical driver of AT/RT tumorigenicity because it allows cancer cells to rapidly adapt to changing microenvironments and toxic therapies. In this proposal, we develop a novel therapeutic strategy combining epigenetic modifying therapy with a metabolic antagonist to precisely target this critical mechanism of cellular adaptations and driver of AT/RT tumorigenicity. We prove the efficacy of this novel therapy to prolong survival in AT/RT and work toward rapidly translating our findings into a new clinical trial aimed at improving the lives of our patients suffering from this deadly disease.

Karisa Schreck – Johns Hopkins, Baltimore, MD
Pediatric glioma are a leading cause of cancer-related death in children. Glioma with BRAF mutations can be treated with BRAF inhibitors (BRAFi), but resistance develops over time. Our laboratory has identified some of the mechanisms of resistance to BRAF-targeted therapy in pediatric glioma. In a subset, we could not identify a specific means of resistance, either adaptive or genomic. SHP2 (encoded by the gene PTPN11) is a key part of receptor tyrosine kinase signaling inside cells, and can drive adaptive resistance to MEK inhibitors (MEKi) in some cancers. Our laboratory has shown that SHP2 inhibition (SHP2i) works together with ERK pathway inhibition in NF1-associated malignant peripheral nerve sheath tumors (MPNST). The role of SHP2 in pediatric glioma, however, is unexplored. Herein, we propose a series of experiments to do the following: 1) Evaluate the role of SHP2 activity in regulating treatmentemergent resistance in BRAF-mutant pediatric glioma. 2) Identify drug combinations for prompt clinical translation to children with glioma. We will use our expertise in molecular biology, ERK signaling dysregulation, and adaptive resistance to understand the role of SHP2 and SHP2i in BRAF-mutant glioma, identify novel resistance mechanisms, and evaluate targeted therapy combinations for future clinical trial testing.