2016 Research Grants

Sanford Research -- Dr. Haotian Zhao

Proposal titled: Molecular and Cellular Mechanisms of Choroid Plexus Tumors.

Background. Choroid plexus (CP) tumors are rare brain tumors that are predominantly found in childhood and comprise 10-20% of all brain tumors in infants. CP papilloma (CPP) is benign, whereas CP carcinoma (CPC) is malignant. Despite excellent prognosis after surgical removal, incompletely resected CP tumors, recurrence or metastasis, as well as CPCs, can result in high morbidity and mortality rates. Multiple factors such as TP53 mutations, abnormal Notch signaling, and recurrent genomic changes, have been implicated in CP tumor; however, the cell of origin and molecular mechanisms of CP tumors remain incompletely understood. Our long-term objective is to understand the biology of CP tumors and identify targeted therapies for CP tumors that can be developed for use in humans.

Seattle Children's Hospital - Dr. Courtney Crane

Proposal titled: Development of a novel cellular immunotherapy for children with brain tumors.

Therapies for children with brain tumors are highly invasive, non-specific, and often cause devastating side effects. Clinical trials using lentivirally modified T cells indicate that activation of the immune system is sufficient to safely eliminate cancer in patients, without chemotherapy and radiation. For example, a single dose of T cells engineered to express chimeric antigen receptors (CARs) that specifically recognize and kill tumor cells induces remission in children with relapsed leukemia. Unfortunately, similar strategies for patients with solid tumors fail. CAR T cells eliminate tumors that overexpress tumor antigens in xenograft mouse models, which lack many cellular and soluble components of an intact tumor microenvironment. When evaluated in patients, however, these same CAR T cells fail to eliminate tumors, suggesting that a suppressive tumor microenvironment is a significant obstacle to successful immunotherapy. We hypothesize that in patients with brain tumors, local immunosuppression mediated by tumor cells and the cells that they recruit, such as regulatory T cells and myeloid cells, inhibit activation of cytotoxic immune effector cells and allow tumor growth. This proposal will create a novel immune therapy using genetically engineered monocytes (GEMs) that will support Natural Killer (NK) cell functions in the tumor microenvironment

Regents of the University of Michigan -- Dr. Sriram Venneti

Proposal titled: Targeting glutamine metabolism in histone K27M mutant gliomas

One of the fundamental mechanisms that drive cancer is reprogramming of cellular metabolism enabling tumors to take up and metabolize nutrients in vast quantities. Glutamine (Gln) is the most abundant plasma amino acid and is metabolized to _-ketoglutarate (_-KG) by tumors to fuel the tricarboxylic acid (TCA) cycle. Moreover, Gln-derived _-KG is a critical cofactor for the Jumonji C family of histone lysine demethylases that hypomethylates histone residues including H3K27. Therefore Gln is a key nutrient that regulates survival and proliferation of cancer cells by rewiring both cellular metabolism and epigenetics. Gliomas that bear histone H3K27M mutations including pontine gliomas (~80% cases) are lethal pediatric tumors with no effective treatments. Due to H3K27M mutations, there is global reduction in H3K27 trimethylation. However, how these gliomas rewire metabolism, specifically Gln metabolism to regulate the TCA cycle and H3K27 hypo-trimethylation represent a significant gap in our knowledge. Preliminary studies indicate that

glioma cells that bear H3K27M take up large amounts of Gln and are addicted to Gln for their survival and proliferation.

Weill Medical College of Cornell University – Dr. Richard Ting

Proposal titled: Image guided design and delivery of DIPG drugs and nanoparticles.

The current measure for effective drug delivery to a brain tumor requires us to wait for a clinical response (disease-free interval, survival, or a reduction in tumor volume). A failed delivery can miss a tumor or aid in tumor's chemo-resistance. In this scenario, the current metrics are unacceptable, as they would only register after a tumor has progressed significantly. A reliable and noninvasive, image-based assessment of drug delivery is needed to evaluate dosing and route-of-delivery, when early intervention is possible. Phase 0 trials are built on this premise of monitoring tumor response as a correlate of effective drug delivery on an agent-by agent basis. The solution is a theranostic agent, a noninvasive marker of delivery that simultaneously holds therapeutic potential. We propose new technology for quantitatively imaging drug delivery to DIPG. The quantitation of drug delivery could explain why we can be eradicate DIPG in ex vivo studies, but cannot use the same agents, in vivo, to cure patients. Recent preliminary data generated from collaborative efforts support this strategy. In collaboration with the Souweidane lab, we have developed an imaging technology that allows us to monitor Sprycel (Dasatinib)