

2011 Research Grants

Reema Habiby, MD , Children's Memorial Hospital, Chicago

Epigenetic Mechanisms of Regulation of Progression in Craniopharyngiomas: Understanding Their Biology and Uncovering New Therapeutic Targets

Craniopharyngiomas are brain tumors that arise from remnants of Rathke's pouch, a structure in the developing embryo arising from the roof of the mouth that becomes part of the anterior pituitary gland (master gland) prior to birth. These tumors, although benign, frequently invade surrounding brain structures leading to hormone dysfunctions and visual problems. Compression of the hypothalamus, the part of the brain just above the pituitary, can lead to severe weight gain, profound fatigue, difficulty regulating body temperature, and cognitive changes. The current treatment for craniopharyngiomas is surgery, with or without radiation therapy. Although surgery can sometimes result in a cure, it can also lead to permanent damage due to the disruption of the Rathke's pouch, we believe that there is abnormal development of Rathke's pouch into the pituitary gland that leads to these tumors. While there is research into other brain tumors examining the cause of the change from a normal cell line to an abnormal cell line, little information of this nature exists on craniopharyngiomas. To obtain this information, we will examine the tissue of patients with craniopharyngiomas to determine the expression of small RNAs, called microRNAs, needed for proper development of the pituitary gland. Evaluating the microRNAs in these patients will help to provide insight into the cause of craniopharyngiomas with the hope of targeting new treatment approaches to minimize the poor long-term outcomes of craniopharyngiomas associated with the current surgical procedures and radiation therapies.

Zhiping Zhou, MD, PhD, Weill Medical College of Cornell University

Targeting Signal Transduction Pathways for the Treatment of Pediatric Pontine Glioma

Brain tumors are one of the most common cancers in children and are the leading cause of cancer death of childhood. Diffuse intrinsic pontine glioma (DIPG), the deadliest of childhood brain cancers, is located in the brain stem, which is the center that controls basic life functions such as breathing, heart beat, blood pressure, swallowing and etc. DIPG has no known cure. Nearly no children with this cancer will survive beyond 1-2 years following diagnosis with current standard therapy. Recently two key signals driving tumor growth in this disease have been identified. Experimental therapies targeting these two overactive signals will be tested in this proposed study. To overcome the

obstacle that drugs do not get into the tumor, we will deliver the drugs directly into the tumor using a technique called convection enhanced delivery (CED). By using combinations of drugs, we expect to slow or even stop growth of the tumor. Additional therapeutic targets will also be screened for using a modern technology called microarray analysis. We expect new therapeutic targets will be found. These efforts will eventually improve the clinical outcomes of patients with DIPG.

Robert A. Johnson, Ph.D, Research Institute at Nationwide Children's Hospital

Determining the impact of EphB2 over expression on radial glia differentiation and transformation endependymoma.

Ependymoma is the third most common pediatric brain tumor and can develop throughout the ventricular lining of the central nervous system. Surgery and irradiation are the preferred forms of treatment; however, more than half of the cases occur in the brains of children under 5 years of age, making irradiation extremely hazardous. Adding to the problem is the fact that ependymomas are largely chemo resistant further limiting treatment options and contributing to the low cure rate of 60%. The lack of model systems in which to study disease development has greatly hindered the identification of new drug targets. Fortunately, a mouse model for ependymoma was recently developed by over expressing the tyrosine kinase receptor EphB2 in the mouse *Ink4a/ARF(-/-)* embryonic neural stem cells (eNSCs) called radial glia (RG). This achievement opens the door for the first studies investigating the abnormal changes leading to ependymoma formation. Analysis of the gene expression profiles of both the human and mouse tumors showed an enrichment of genes involved in neuronal differentiation and maintenance suggesting that these pathways may play a part in disease development. The EphB2 protein consists of a several functional domains known to initiate a number of signaling pathways affecting several neuronal processes. We are interested in determining the role of key EphB2 functional domains on RG cell differentiation and determine their impact on ependymoma formation. In addition, we hope to identify the signaling pathways involved in this process in hopes of identifying novel avenues for chemotherapeutic treatment.