2012 Research Grants

Richard C. E. Anderson, M.D. Assistant Professor of Pediatric Neurosurgery - Columbia University College of Physicians and Surgeons.

Tumor Associated Monocytes/Microglia are a Requisite Target for Immunotherapy in Malignant Gliomas.

The outcome for children with malignant gliomas has not significantly improved over the last 25 years despite technical advances in neurosurgery, radiotherapy, and the development of novel chemotherapeutic agents. Due to limitations of the current standard of card, studies examining the efficacy of immune mediated destruction of malignant gliomas have been pursued for many years. While the majority of immunotherapy research thus far has focused on T cell lymphocytes, we have observed that tumor-associated monocytes/microglia (TAMs), which are immunostimulatory cells with the potential for tumoricidal activity, in fact represent the predominant infiltrating immune cell population in gliomas. We hypothesize that malignant gliomas actively inhibit TAM function and prevent the immune system from mounting an effective immune response against these tumors. We have recently demonstrated using complementary approaches that malignant glioma tumor cells suppress the immunostimulatory function of TAMs. Using a microarray approach we then identified a short list of genes that are strong candidates responsible for the immunosuppressive phenotype in TAMs. We then blocked expression of these candidate genes and were able to identify one gene that when blocked restored significant TAM function. The goal of the present study is to determine if blockage of our identified gene and restoration of TAM function will prolong survival in our murine glioma model. Our collective data, together with the proposed studies, will allow us to identify pharmacologic compounds that could be used in a subsequent clinical phase I study designed to restore TAM function in children and adults with malignant gliomas.

Jeffrey P. Greenfield M.D., Ph.D, Weill Medical College of Cornell University.

Exosome Recruitment of Bone Marrow-Derived Cells Mediates Glioma Transformation.

Many brain tumors in the pediatric and young adult populations initially begin as lower grade tumors with a comparatively better prognosis initially. However, these tumors can transform into malignant high-grade gliomas characterized by profound neovascularization. In our laboratory we investigate the mechanism through which these new blood vessels are stimulated to begin growing and the environment, which supports their growth. We have begun to explore a novel particle called an exosome which is derived from pediatric brain tumor samples - essentially a small piece of the tumor’s genetic material broken off in a small capsule. We are exploring the fundamental mechanisms through which these particles exert malignant phenotypes through the recruitment of blood vessel precursor cells from bone marrow into the tumors. Our hypothesis is that a series of events beginning with these exosome being released by the tumors may initiate the transformation of low-grade tumors into higher-grade gliomas such as glioblastoma multiform through recruitment of cells that live in the bone-marrow.

We have shown that patients with higher grade tumors have more of these exosomes, and by discovering their contents and the genetic messages they are relaying we hope to be able to interrupt the recruitment of the blood vessels these tumors need to grow and invade.

Sabine Mueller, M.D., Ph.D. Assistant Professor, The Regents of the University of California

Targeting Key Cell Cycle Regulatory Kinases for the Treatment of Pediatric Malignant Gliomas.

Pediatric high-grade gliomas continue to have a discouraging prognosis and new treatment approaches are urgently needed. Despite decades of efforts to improve surgery, radiation, and chemotherapy, most children succumb to their disease. A dearth of information regarding molecular events underlying pediatric glioma development and resistance to treatment has hampered efforts to rationally incorporate biologically targeted agents into treatment regimens. Our preliminary studies have shown that the key cell cycle kinases Chk1 and WEE1 are up-regulated in malignant pediatric gliomas and that inhibition of WEE1 with the small molecule inhibitor MK-1775 in combination with radiation improves survival in highly relevant models of pediatric gliomas. This application focuses on expanding on these exciting findings using the specific Chk1 inhibitor AZD7762 for the treatment of malignant gliomas. Furthermore, we aim to assess potential mechanism of resistance to such treatment. We chose inhibitors that have already entered clinical trials for adults and/or children in order to facilitate and hasten transition into the clinic. Results of this proposal will deliver the preclinical rational for clinical trials of these agents for children with malignant gliomas.

Eric Hutton Raabe, M.D., Ph. D, Johns Hopkins University

Targeting Diffuse Intrinsic Pontine Glioma by Blocking the Notch Pathway.

Diffuse Intrinsic Pontine Glioma (DIPG) is a universally fatal pediatric brain tumor. It comprises nearly 15 percent of all pediatric brain tumors. Because of the characteristic MRI appearance and inoperative nature of the tumor, there has traditionally been little tissue available for research. That is now changing due to rapid autopsy programs. Our laboratory now has several DIPG cell lines derived from rapid autopsies, which we will use to test new therapies. One of the more promising molecular signaling systems that we can target is the Notch pathway. Notch regulates cellular growth and maturation as well as resistance to radiation and chemotherapy. This pathway is active in DIPG in general and in our cell lines specifically. Notch is targeted by drugs that have good penetration into the brain, making them good candidates for therapeutics for brain tumors. We will focus on MRK-003, a Notch inhibitor that our lab has shown can decrease the growth of other aggressive brain tumors. Our hypothesis is that MRK-003 will block Notch signaling in DIPG cells, and that blocking Notch will lead to decreased growth of DIPG cancer cells in cell culture and when the tumor cells are transplanted into the brains of mice. We also believe that blocking Notch will enhance the effect of radiation and chemotherapy, which are the traditional treatments for DIPG. Taken together, the experiments we propose in this translational grant application will set the stage for testing of novel treatments for children with this incurable, invasive brain tumor.