2017 Research Grants

Hackensack University Medical Center- Dr. Derek Hanson

Project Title: A Phase I Study of 2- Hydroxyoleic Acid in Pediatric Patients with Advanced Brain Tumors

2- hydroxyoleic acid is a new anti-cancer agent being investigated for the treatment of pediatric brain tumors. The drug has been tested extensively in Europe in adults with highly aggressive brain tumors and demonstrated a number of impressive clinical responses. This clinical trial will be the first time that 2- hydroxyoleic acid is studied in the United States and the first time that it is used in children. The trial will attempt to find the best pediatric dose as well as examine the effectiveness of the drug in children with brain tumors.

The outer membrane of cancer cells contains an abnormal distribution of fats when compared to healthy cells. Researchers have found that various cancer-inducing processes inside the cell are dependent on the presence of these abnormal membrane fats. 2- hydroxyoleic acid acts by returning the various fats in the cell membrane to a normal composition, which leads to cancer cell death.

The drug is a fatty acid, similar in nature to olive oil, and is an oral medication with very few side effects. These factors, along with the clinical efficacy seen in adult brain tumor patients, make 2- hydroxyoleic acid an ideal candidate for investigation in children with a variety of central nervous system tumors.

Memorial Sloan Kettering Cancer Center – Alex Kentsis, MD PhD

Project Title: Synthetic Lethal Targeting of PGBD5 in Rhabdoid Tumors

Atypical teratoid rhabdoid tumors (AT/RT) are aggressive tumors of the brain and spinal cord that tend to occur in infants and young children. They remain difficult to treat in spite of intensive chemotherapy, surgery, and radiation therapy. Rhabdoid tumors are known to be driven by abnormal regulation of gene expression, but its mechanisms remain elusive. Our recent

work revealed an unanticipated requirement of an endogenous DNA transposase for the development of rhabdoid tumors. The current project aims to determine the mechanisms of aberrant cell survival in brain rhabdoid tumors and develop chemical inhibitors with anti-tumor efficacy. This knowledge will be used to identify specific molecular dependencies that may be used for the development of improved targeted therapies of refractory brain tumors, and is expected to lead directly to clinical trials for patients.

Trustees of Columbia University - Dr. Adam Sonabend

Immune editing of glioma genome during progression: Modeling T-cell tumor interplay in mouse gliomas and in human glioma xenografts hosted on mice with patient-derived humanized immune system.

More than 23,700 Americans were diagnosed and 16,000 died from brain tumors in 2016. In the case of children, brain tumors are the most common solid cancers, and their treatment is associated with significant cognitive side effects in the developing brain. Malignant gliomas, and glioblastoma (GBM) in particular, is the most aggressive and most common of all primary malignant brain tumors. These tumors are resilient to current therapies, bear a mixed set of mutations, and evade recognition by the immune system. Recently, immunotherapy has proven efficacious in eradicating other cancers, but its implementation for gliomas has been challenging and unpredictable. The central theme of this proposal is to understand the interplay between anti-tumoral immunity and development of genetic alterations during glioma progression, or in other words, which tumor mutations are selected as a means of avoiding immune recognition. We will use a mouse glioma model in which tumors are induced on neonate mice and develop mutations over time, and investigate this question by comparing the mutations in tumors induced in mice with and without immune system. Given the limitation of a mouse tumor model to study a human cancer, using cutting-edge stem cell based technologies we will also develop a model in which a human glioma will be grown in a mouse with a human immune system. This tool will allow the study of the interplay between immunity and tumor development of a human tumor in vivo, and serve as a model to test novel immunotherapies for these tumors.

Children's Hospital of Philadelphia Dr. Kristina Cole

Targeting ATRX Deficiency in pediatric malignant Glioma

Children and young adults with a high-grade malignant glioma have a very poor outcome and identification of therapeutic vulnerabilities may identify novel treatment approaches. Approximately one-fourth of tumors from these individuals have mutations in the gene ATRX that contributes to their ability to continue to divide and also causes long DNA telomere ends. These changes likely require reliance on other compensatory proteins, most of which are not known. By systematically inhibiting proteins that only halt the growth of malignant glioma cells genetically depleted of ATRX vs. those that have ATRX, we hope to identify the compensatory proteins and, therefore potential inhibitors of high grade glioma. In addition, since there are very few cell line models of ATRX mutated pediatric malignant glioma, we are also creating and characterizing 36 patient derived cell lines to validate any candidate drugs or genes that seem promising.