

Chemical modulation of chromatin in atypical teratoid rhabdoid tumors.

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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. Its enforced expression is sufficient to induce malignant transformation of normal human cells, and its activity is required for the survival of rhabdoid tumor cells driven by aberrant chromatin remodeling. 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.

Novel methods to detect gene- environment interactions in treatment related brain tumors among childhood cancer survivors.

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Chemotherapy and radiation are cornerstones for most childhood cancers. However, radiation of the brain for childhood cancer can result in the development of new brain tumors (called “second

brain tumors”). The risk of second brain tumors increases with increasing dose of radiation. However, for any given dose of radiation exposure, there exists a significant inter-individual variability in the risk of second brain tumors, suggesting the role of an interaction between genetic susceptibility and radiation in developing second brain tumors. The pathways that lead to the development of second brain tumors are complex and likely to involve the actions and interactions of a large number of genes. However, few studies investigate multiple variants across several genes, partly due to the lack of appropriate statistical methods and detailed information of therapeutic exposures. In this study, we propose novel gene and/or pathway based statistical methods. Using a matched case-control study design, we have enrolled and deep genotyped childhood cancer survivors with second brain tumors (84 cases) and those without second brain tumors (231 controls) using the infrastructure offered by the Children’s Oncology Group (COG). We will comprehensively investigate gene-therapy interaction using the novel statistical methods and the high quality deep genotyped data, along with careful measurement of radiation exposures. Findings from this study will lead to clinical justification for prevention strategies for those at high risk of developing second brain tumors, such as avoidance of radiation or reduction in dose, or, among those already exposed to radiation, instituting aggressive screening for early detection and appropriate management.

B7-H3 Engager T cells for the immunotherapy of high-grade glioma

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The objective of this project is to develop an effective T-cell therapy for pediatric patients with high-grade glioma (HGG).

HGG is a very aggressive brain cancer, and long term survival rates for patients with recurrent HGG are less than 5%. Given these findings novel treatments are needed to improve outcomes for children with this disease. T-cell immunotherapy has the potential to meet this need. T cells are part of the immune system, and normally function to fight off germs. Genetic modification of T cells allows redirecting T-cell capabilities towards killing cancer cells. To avoid side effects from T-cell therapies, targets are identified on cancer cells that do not exist on normal cells. B7-H3 is a recently identified target, which is present on HGG cells, but not on most normal cells. My aim is to improve treatment for pediatric patients with HGG using a highly innovative therapy called Engager T cells. Current T-cell treatment strategies result in T-cells that kill cancer cells directly, without recruiting the body's normal, unmodified T cells to join the fight. Our newly created Engager T cells release a substance that sticks to cancer cells, and this substance acts to signal both the modified and unmodified T cells to attack the cancer. In this scenario, we hypothesize that the anti-cancer effect of Engager T cells is amplified to a significant degree when compared to traditional T-cell therapies. My overall aim is to adapt this method to target B7-H3 and improve outcomes for children affected by HGG.

Anti NRR1 as a Novel Therapeutic Against Human c-Myc Driven Medulloblastoma

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Medulloblastoma is the most common brain tumor in children and young adults. Although the current available treatment has improved survival of children with medulloblastoma, those that

fall under the high-risk category are prone to having the tumor spread to other parts of the brain and spine. Metastasis in such cases is seen in a very high numbers, often requiring more aggressive therapies at the cost of significant life-long mental and physical impairments. In fact most medulloblastoma patients die from inoperable metastasis rather than the primary tumor. Despite this obvious need, very little research has focused on medulloblastoma metastasis. Notch1 is a cell membrane receptor known to play a multi-faceted role in the signaling of cancer cells. We present an animal model of patient-derived medulloblastoma cells that shows the spread of the tumor to the spine, recapitulating the natural progression of medulloblastoma and, therefore, allows us to identify the molecular pathways that play a crucial role in medulloblastoma metastasis. Preliminary studies in our lab have shown increased expression and activity of Notch1 in Medulloblastoma spinal metastasis. We intend to further investigate the effects of blocking Notch1 signaling in prevention of medulloblastoma growth and metastasis through the use of a highly specific and potent blocker of Notch1. Data gathered from these preclinical studies will address our hypothesis that this blocking agent is a safe and effective treatment for medulloblastoma patients, and will be able to replace standard of care treatments in the foreseeable future.

Oncolytic Virus for the Therapy for Children with recurrent medulloblastoma

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Medulloblastoma is the most common malignant brain tumor that occurs in children. While the tumor is found in the part of the brain called the cerebellum, tumor cells often spread into the fluid space around the brain and spinal cord. Tumors that have spread into the

fluid are more difficult to cure. About 40% of children with medulloblastoma die from their tumor. Of the survivors, most suffer debilitating consequences from the treatment for the tumor. Thus, new methods for treatment of this tumor are clearly needed. We have been using an attenuated, modified measles virus as a potential therapy for medulloblastoma. Because medulloblastoma tumors cells express the receptor for the virus at high levels, we are able to kill tumor cells with the virus while sparing normal tissue. We have shown that measles virus can cure animals with human medulloblastoma implants in the brain. In addition, we have shown that measles virus can cure animals with human medulloblastoma cells that have spread throughout the fluid space around the brain and spinal cord. Further, prior safety studies in monkeys have shown that this specific virus is safe to be given into the brain. Herein we are proposing to study the safety and efficacy of measles virus in treating recurrent medulloblastoma. Children who have failed initial therapy will be given measles virus into the recurrent tumor in the brain and/or into the fluid space around the brain and spinal cord, depending on the location of the recurrent tumor.

Molecular Therapeutic of DIPGs using miR129-2

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Pediatric brainstem gliomas (BSGs) account for 15% of all brain tumors in children. Diffuse intrinsic pontine gliomas (DIPGs) are the most aggressive and high-grade tumors among BSGs with the peak age of onset around 6-7 years. Children diagnosed with DIPG have less than 90% chance of survival within two years of diagnosis. Recent advances in DIPG research identified genetic aberrations associated with these tumors. These include mutations in histone 3.3 and p53 genes and activation of tumor

associated signaling pathways. One of the most important of such is PDGFR mediated pathway, which was found to be stabilized by transmembrane protein NG2. In adult gliomas, NG2 expressing cells often co-express PDGFR , where NG2 contributes to the transformation of precursor cells into glioma. Despite the potential role of NG2 in adult gliomas, role of NG2 expression has not been previously studied in pediatric gliomas. In our lab, using postmortem DIPG samples and cultured cells, we observed increased NG2 levels, specifically in tumor samples. In addition, we found that NG2 in DIPG tumor samples and primary tumor cells are negatively regulated by microRNA 129-2 (miR129-2) to decrease NG2 levels. Thus it is valuable to examine if miR129-2 can be used as a therapeutic molecule to target NG2 in DIPGs.