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The Matthew Larson Foundation
for Pediatric Brain Tumors

2022 Grant Recipients

Dr. Mariella Filbin

Dana-Farber Cancer Institute Boston, MA

Project Title: Exploring epigenetic dependencies in pediatric diffuse midline glioma

Lay Summary: Histone mutant diffuse midline gliomas are extremely lethal pediatric brain tumors in which most children succumb to the disease within 2 years of diagnosis. Histones are proteins that structurally support DNA and regulate gene expression. In diffuse midline glioma, the histone mutation H3K27M occurs in 80% of cases and drives tumor development. A direct consequence of this mutation is the increase of a chemical modification in histones, termed acetylation, on a specific amino acid, the lysine 27. As EP300 is the enzyme responsible for this acetylation, we seek to investigate its role in glioma. We hypothesize that the histone mutation requires the activity of EP300 to drive tumor progression and that inhibiting EP300 will reverse the oncogenic alterations provoked by H3K27M and impair tumor growth. Indeed, preliminary assays demonstrated that histone mutant tumor cells require EP300 for survival. Therefore, we aim to validate EP300 as a promising target for diffuse midline glioma therapy through loss-of-function assays combined with genome wide sequencing profiling and to preclinically test EP300 targeting agents to identify novel drugs able to impair tumor cell proliferation. The most potent molecules detected will be tested together with a variety of other anti-cancer drugs to identify combinations that potentiate the tumor cell depletion effect. By exploring EP300 as a novel tumor vulnerability and comprehensively testing EP300 targeting agents and drug combinations, we intend to open new avenues for therapeutic exploitation of this target and inform the design of future clinical trials for this universally fatal childhood brain cancer.

Dr. Kelsey Bertrand

St. Jude Children's Research Hospital Memphis, TN

Project Title: FACT complex as a therapeutic vulnerability in ZFTA-RELA ependymoma

Lay Summary: Brain tumors are the leading cause of cancer-related death in children. Despite incredible advancements in pediatric oncology over the last several decades, ependymoma treatment has not changed. Ependymomas are central nervous system tumors, that can be found in the brain and spine. These tumors can be incurable in nearly half of patients. Surgical resection and radiation are standard of care, with no effective targeted therapies identified to

date. Many children develop recurrences, and this comes with a dismal prognosis. Thus, novel molecular targets and pathways are needed to guide future drug development. Ependymoma is not one single entity, but has been shown to have nine different molecular groups, that differ in their biology. One of the most common subgroups is driven by a gene fusion, ZFTA-RELA. Currently, this gene fusion is not druggable, and this proposal seeks to investigate FACT, a protein that interacts with ZFTA-RELA, as a potential driver of this highly lethal brain tumor. Results will offer preclinical insight into FACT as a therapeutic target and establish the efficacy of CBL0137 (a FACT inhibitor), as rationale therapy to inform future clinical trial design for this devastating disease.

Dr. Vijay Ramaswamy

Hospital for Sick Children, Washington

Project Title: Targeting the mTORC1/4E-EBP1 axis in Group 4 medulloblastoma

Lay Summary: Medulloblastoma is the most common childhood cancerous brain tumour. Current treatments consist of aggressive surgery followed by radiation to the whole brain and spinal cord, and non-specific chemotherapy. This aggressive therapy results in 60% survival overall, however almost all survivors are left with life-long side effects of their therapy. At relapse however, medulloblastoma is uniformly fatal and hence there is a huge unmet need to find new treatments. Recently we and others have shown that medulloblastoma actually comprises four very different diseases, specifically four subgroups called WNT, SHH, Group 3 and Group 4, of which Group 4 is the most common group at diagnosis and relapse. Unfortunately, personalized therapies have not been identified for relapsed Group 4 medulloblastoma, due primarily to a lack of mutations and models to work with. In order to address this urgent unmet need in neuro-oncology, we have leveraged a novel platform to look at cell signaling from small amounts of tumour, and we analysed primary and recurrent Group 4 medulloblastoma. Strikingly, we found a very specific pathway that is highly activated in relapse Group 4 medulloblastoma compared to other brain tumour types and normal tissue called the mTORC/PI3K pathway. Our proposal seeks to develop this target further, which we will validate across a panel of Group 4 models. The overall goal of this proposal is to develop mTORC1 inhibition as a rational and promising treatment strategy for recurrent Group 4 medulloblastoma, with the intent of translating our findings into an early phase clinical trial.

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Dr. Nicholas Vitanza

Seattle Children's Hospital Seattle, WA

Project Title: Optimal combination of radiation therapy and CAR T cells for pediatric CNS tumors

Lay Summary: Diffuse midline glioma (DMG), including diffuse intrinsic pontine glioma (DIPG), is a universally fatal brain tumor of childhood. Based on its location, DMG is not resectable and radiation only extends survival to ~11 months. Our team has been developing a new type of personalized immunotherapy: chimeric antigen receptor (CAR) T cells. We use some of a patient's white blood cells and engineer them to target a specific protein on the surface of their tumor and kill the tumor cells. These treatments are very effective against leukemia, where a Seattle Children's trial showed a 93% remission rate. I lead our team optimizing CAR T cells against pediatric central nervous system (CNS) tumors and we now have 3 open clinical trials targeting different proteins on CNS tumors. Almost all children with DMG receive radiation at diagnosis and often at the time of recurrence, but we do not yet know how CAR T cells work in combination with radiation. Here, we will use patient-derived laboratory models of DMG to study the best sequence of radiation and CAR T cells. We will also study how proteins on the surface of tumors treated with radiation change, which will inform the best sequence of our CAR T cells and determine what other CAR T cells we could develop next. Ultimately, this will inform current and future CAR T cell clinical trials and, by best understanding when to give them in relation to radiation, we can hopefully improve outcomes for children with these terrible tumors.

Dr. Thomas De Raedt

Children's Hospital of Philadelphia Philadelphia, PA

Project Title: Interneurons that BiTE: targeting B7-H3 targeting to treat pediatric high glioma

Lay Summary: Pediatric High Grade Glioma (pHGG) is a devastating disease with a median survival of about 12 months. Despite the fact that a substantial number of clinical trials have been conducted over the past few decades, overall survival for pHGG has barely improved. Promising new strategies, like for example CAR-T cell immunotherapy, have shown limited efficacy in the treatment of brain tumors. With CAR-T therapy, one harnesses the strength of the immune system by "teaching" the patient's immune cells to recognize unique tumor antigens like mutated proteins. However, this strategy only works for tumors that display unique and new antigens. Unfortunately, many pediatric high-grade gliomas, have a low mutation count and do not have these unique new antigens, making it more difficult for CAR-T therapy to work. However, the paradigm, where we "teach" cells to hone into a tumor and deliver a cytotoxic response, has revolutionized the way we treat cancer and the way we think about therapeutic development. Any therapy where cells are able to migrate to and kill the tumor is potentially viable. We have developed a highly specific cell based drug delivery system. The cells we use

are essentially young neurons which are unlike their matured counterparts migrate to specific factors. Intriguingly, many brain tumors secrete these same factors! Excitingly, our data shows that, in mice, implanted young neurons indeed find and migrate to brain tumors. In this proposal, we want to evaluate if these neurons can actually deliver cytotoxic agents that shrink tumors in vivo.

Dr. Sameer Farouk Sait

Memorial Sloan Kettering Cancer Center New York, NY

Project Title: Beyond MEK and RAF inhibition: Suppressing nucleotide exchange as a novel therapeutic strategy for pediatric patients with high-risk brain tumors harboring RAS/MAP kinase pathway alterations

Lay Summary:

While many high-grade gliomas (HGGs) are incurable, some HGGs occurring in children/young adults harbor mutations (DNA changes) in genes (BRAF or NF1) that enable cells to constantly “turn on” the mitogen activated protein kinase (MAPK) pathway and obtain unlimited energy. These mutations render HGGs vulnerable to drugs blocking MAPK pathway components (BRAF inhibitors/BRAFi and MEK inhibitors/MEKi). Our laboratory studies demonstrate that while low grade (benign) gliomas shrink with MEKi, HGGs harboring NF1 mutations in mice become resistant to MEKi by increasing the number of energy supply pumps (RTKs/receptor tyrosine kinases). SHP2 and SOS1 are proteins that block several RTKs and can be used in combination with BRAFi/MEKi to more effectively inhibit HGGs. While blocking SHP2 causes many side effects, we hypothesize that SOS1 inhibition (SOSi) will be equally effective but better tolerated (unlike SHP2) because of its partner gene (SOS2). We propose to treat mice transplanted (brain) with human HGG cells with BRAF or NF1 mutations to test the effectiveness and safety of SOS1i together with BRAFi/MEKi. If the combination is unsafe or ineffective, we will study the routes through which cells become resistant using a new method to assess protein function (kinome profiling). This will enable identification of alternative resistance mechanisms and our preliminary studies implicate autophagy, a cellular stress response to starvation is highly activated. We will subsequently evaluate autophagy inhibitors in combination with SOS1 and MEKi/BRAFi. These results will guide optimal drug combinations that merit evaluation in clinical trials to potentially cure BRAF/NF1 mutant HGGs

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Dr. Patrick Pirrotte

Translational Genomics Research Institute Phoenix, AZ

Project Title: Metabolic Targeting of CD114+ Medulloblastoma Cancer Stem Cells

Lay Summary: Medulloblastoma (MB) is the most common malignant brain tumor in children. About one out of three MB patients relapses with extremely poor outcomes. Disease relapse can be attributed to the persistence of chemotherapy-resistant cancer stem cells. We are studying a potential cancer stem cell population in MB that expresses CD114 (“CD114+ MB cells”), the receptor for granulocyte-colony stimulating factor (G-CSF). CD114+ MB cells proliferate in response to G-CSF, a common adjuvant given during chemotherapy, and are more resistant to standard of care chemotherapies. CD114+ cells have been found in all subtypes of MB. Thus, there is a great need for new treatments that block the growth of CD114+ MB cells. Our preliminary analysis showed that CD114+ MB cells have an altered metabolism and identified two metabolic pathways as candidate targets for new therapies: the fatty acid oxidation pathway and the polyamine biosynthesis pathway. This proposed project will test small molecule inhibitors of these pathways to determine how well they inhibit CD114+ MB cell growth and sensitize CD114+ MB cells to standard of care chemotherapies. We will also further investigate the mechanisms by which these metabolic pathways promote CD114+ MB cell growth and chemo-resistance. Our study will lay the foundation for the pre-clinical development of combination therapies that effectively target CD114+ cells and improve treatment outcomes for children with MB.

Dr. Brian Na

UCLA Los Angeles, CA

Project Title: Modeling and Developing New Therapies for Atypical Teratoid/Rhabdoid Tumors

Lay Summary: Atypical teratoid rhabdoid tumor (AT/RT) represents the most common malignant CNS tumor in children below 6 months of age. Unfortunately, despite valiant efforts to develop multiple therapeutic approaches to increase survival rates, many patients pass away or have significant morbidity from treatment. Although the tumor is aggressive, AT/RTs have a very simple genetic mutation that leads to three different subtypes. However, we do not know how each subgroup is formed. Our team has developed a pig AT/RT model utilizing gene editing technology. Through this model, we will be able to better understand how AT/RTs form. By doing so, we will be able to identify new therapies and utilize this large animal platform to rapidly translate our findings into a new clinical trial.

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Dr. Nicholas Whipple

University of Utah School of Medicine Salt Lake City, UT

Application Title: PNOC025: A Phase 1 Study of Magrolimab in Children and Adults with Recurrent or Progressive Malignant Brain Tumors

Lay Summary: Tumors of the Central Nervous System (CNS) are the most common solid tumors in children and the deadliest form of childhood cancer. They are also among the deadliest forms of adult cancer. Children and adults with recurrent or progressive malignant brain tumors have a dismal prognosis. Novel therapeutics are desperately needed. CD47 is a cell surface protein responsible for regulating phagocytosis by the body's immune system. CD47 binds to and activates SIRPα, a receptor which initiates a signal cascade that blocks phagocytosis. CD47 is overexpressed on CNS cancer cells and is a mechanism by which cancer cells evade the immune system. Magrolimab (anti-CD47) is a first-in-class anticancer monoclonal antibody. Binding of magrolimab to CD47 on cancer cells blocks the interaction of CD47 with SIRPα. This blocks the "do not eat me" signal to macrophages, thereby enhancing macrophage-mediated phagocytosis of cancer cells and inhibiting tumor growth and metastasis. Preclinical mice studies have shown that magrolimab treatment leads to reduced tumor volume and prolonged survival in high-grade glioma, atypical teratoid/rhabdoid tumor, diffuse intrinsic pontine glioma, medulloblastoma, and other embryonal tumors. Supported by the Pacific Pediatric Neuro-Oncology Consortium, we are launching a clinical trial of the first-ever use of magrolimab in 12 children and 12 adults with recurrent or progressive malignant brain tumors. We will assess the safety/tolerability of magrolimab and will determine the Recommended Phase 2 Dose for magrolimab in this population. We anticipate that our findings will lead to a multi-institutional Phase 2 efficacy study of magrolimab in children and adults.