Research Funded by the Catherine Elizabeth Blair Memorial Foundation

2018-2019

Advancing Breakthroughs in Neuroblastoma Research and Care

November 2018: The Catherine Elizabeth Blair Memorial Foundation is pleased to announce a $25,000 grant to Dr. Anthony Sandler and his team at Children's National Medical Center. Dr. Sandler has established that MCYN, a protein-coding gene that is overexpressed in high-risk neuroblastoma, is associated with immune privilege. The team also showed that PD-L1 checkpoint inhibition, when combined with vaccine therapy and another checkpoint inhibitor, anti-CTLA-4, cures neuroblastoma tumors in mouse models. The next phase of research has five specific aims: 1) Novel vaccine design targeting Myc in tumor cells; 2) Identification of a new gene target to enhance immunotherapy against melanoma; 3) Application of combination vaccine therapy and checkpoint inhibition in different tumor models; 4) characterization of T-cell immunity; 5) determine mechanisms of tumor cell immunogenicity (induced by targeting Myc). These research aims, ongoing in pre-clinical mouse models, will be expanded to human cell lines and tumors. This will allow Dr. Sandler's team to translate the findings in mouse models to human tumors, setting the stage for future clinical trials.

Fully Human Glypican-2 Targeting Bispecifics for the Treatment of Neuroblastoma

December 2018: The Catherine Elizabeth Blair Memorial Foundation made a $25,000 grant to Dr. Colin Correnti, Ph.D. at the Fred Hutchinson Cancer Research Institute in Seattle with key collaborator Julie Park, MD of Seattle Children's Hospital. One of the exciting things about this project is the potential to eliminate the pain associated with many of the immunotherapy treatments available to children. Recently Glypican-2 (GPC2) has emerged as a promising target antigen, with high expression in neuroblastoma and apparently low expression in healthy tissue. The lab has pioneered a new immunotherapeutic approach that allows simultaneous targeting of GD2 and GPC2. This project will accelerate antibody discovery efforts and then express and biophysically characterize the best GPC2 antibodies. This critical first step will create a well-defined palette of clinic-ready antibodies which will be used by the team to build next-generation bispecifics and used by collaborators at Seattle Children's Hospital, Stanford, and Children's Hospital of Philadelphia for use as antibody drug conjugates and CAR-T cells.

Advancing Breakthroughs in Neuroblastoma Research and Care

December 2019: The Catherine Elizabeth Blair Memorial Foundation grants $25,000 to the Anthony Sandler laboratory at Children's National Hospital for continued study of immune-based therapy in

neuroblastoma. The central hypothesis of the team's research proposes that high-risk tumors have immune privilege and in the case of neuroblastoma it is associated with MYC oncogene expression. Targeting MYC in tumor cells seems to induce tumor immunogenicity and exploiting this observation by creating a whole-cell vaccine may enable robust anti-tumor immunity. The next phase of research includes four specific aims: 1) novel vaccine design targeting MYC in tumor cells: whole-cell tumor vaccination has not been used previously in the context of knocking down specific genes to generate immunogenicity, 2) application of combination vaccine therapy and checkpoint inhibition in different tumor models: the proposed model demonstrates the superiority of tumor vaccination combined with two checkpoint inhibitors, anti-CTLA-4 enhances T-cell expansion and anti-PD-L1 diminishes effector T-cell exhaustion and prevents adaptive immune resistance, 3) characterization of T-cell immunity and 4) phenotyping the immune environment in neuroblastoma: we have characterized over 700 genes related to immunity in patient tumors to date.

2016-2017

Clinical Drug Trial

September 2016: The Catherine Elizabeth Blair Memorial Foundation is pleased to announce a $20,000 grant for a Phase I/II Clinical Trial for Neuroblastoma with ALK Mutations. We join a group of charities brought together by Solving Kids' Cancer on a multi-institution clinical trial which will open in early 2017 using a potent new drug for children with neuroblastoma. PF-06463922 is a third-generation inhibitor of a tumor mechanism driven by ALK (anaplastic lymphoma kinase) mutations and aberrations. These aberrations occur in about 15% of children with high-risk neuroblastoma and portend a very poor prognosis. This drug has shown remarkable efficacy in a phase I study of lung cancer patients with this mutation, showing complete responses in some patients even when brain metastases were present. When tested in mice with ALK+ neuroblastoma, the drug shows promising results including complete cure of mice. This study will be open in 15 hospitals in the US and Canada, with plans to open a site in London and in Paris to allow access for children in Europe. Investigators expect that this phase I/II clinical trial will result in rapid FDA and EMA approval for ALK+ neuroblastoma, making the drug widely available for children who are likely to benefit in the near future.

Tumor Vaccine Therapy, year 2

November 2016: The Catherine Elizabeth Blair Memorial Foundation is pleased to announce a $25,000 grant to re-fund the innovative research at Children’s National Hospital that was launched with our support in 2015. This research aims to overcome challenges that have prevented development of an effective tumor vaccine. Dr. Anthony Sandler and his team have explored how tumors behave, how immunity develops, and the long-term effects of vaccine treatment – with the ultimate goal of a clinical trial to test the use of this therapy in children fighting neuroblastoma. Dr. Sandler has reported that our prior funding allowed his team to discover with unprecedented clarity what is happening as the body’s immune system tries to combat tumor cells and, for the first time, to capture images of their vaccine in action that could represent a turning point for researchers as they seek to understand the complex immune

response. They believe that their work has shown the potent effect of creating an immune response by knocking down specific proteins. Our latest funding will allow them to study three proteins (Id1, Id2, and Id3) and the effect of knock down on immunosuppressive molecules. They will also evaluate whether human neuroblastoma tumors have the characteristics that have been identified in mouse neuroblastoma models – a step toward translating their findings to human tumors and bringing vaccine therapy closer to clinical trial.

Tumor Vaccine Therapy, year 3

October 2017: The Catherine Elizabeth Blair Memorial Foundation is pleased to announce a $25,000 grant to continue Dr. Anthony Sandler's research we have funded since 2015. Dr. Sandler's team has made significant advancements in the tumor immuno-biology of neuroblastoma. Combined with immunotherapy called a checkpoint inhibitor, targeting MYCN in tumor cells (as a vaccine) has enabled T cells to attack and effectively destroy neuroblastoma in mice. Further ongoing investigation is providing critical insights on the immunosuppressive behavior of neuroblastoma and the mechanism of their tumor vaccine's effectiveness. Dr. Sandler and the team hypothesize the MYC oncogene regulates immune privilege in tumor cells and targeting MYC in tumor cells induces anti-tumor immunogenicity. The next phase of research includes these aims: 1)novel vaccine design targeting MYC in tumor cells, 2)the application of combination vaccine therapy and checkpoint inhibition in different tumor models, 3)characterization of T cell immunity, and 4)determination of the mechanisms of tumor cell immunogenicity (induced by targeting MYC).

2014-2015

Immunotherapy using Next-Generation T-Cell CARs Against Neuroblastoma

June 2014 - The Catherine Elizabeth Blair Memorial Foundation is pleased to announce a grant of $27,312 in collaboration with our partners at Solving Kids' Cancer for a Phase 1 clinical trial. "Autologous activated T-cells transduced with a 3rd generation GD2 chimeric antigen receptor and icaspase9 safety switch administered to patients with relapsed or refractory neuroblastoma" is currently underway at Texas Children's Cancer Center/Baylor College of Medicine with principal investigator Chrystal Louis, MD. Unprecedented success has been seen with CAR-based immunotherapy using modified T-cells against leukemia. This study seeks to show similar success using the GD2 CAR for neuroblastoma. The trial uses T-cells derived from the patient and engineered to express CARs (chimeric antigen receptors) that target the GD2 antigen on neuroblastoma. The cells are expanded in the laboratory and then returned to the patient as an infusion. Baylor researchers have created a 3rd generation T-cell CAR for neuroblastoma that uses new genes called CD28 and OX40 to stimulate the immune system, as well as a safety switch called iC9, which may result in T-cells that are more effective, persistent and safe cancer killers. This approach has the potential to significantly impact the lives of children with relapsed and refractory neuroblastoma and if proven safe and effective, integrating into frontline therapy in the future.

Tumor Vaccine Therapy

September 2015 - The Catherine Elizabeth Blair Memorial Foundation is pleased to announce a grant of $25,000 in collaboration with the EVAN Foundation for a research study at Children's National Medical Center. The Principal Investigator is Anthony Sandler, MD. Dr. Sandler's laboratory has discovered that by "knocking down" specific members of a family of genes found in tumor cells, the cells become recognizable as foreign to the body and highly capable of creating an immune response. Pre-clinical models demonstrate that the combination of these genetically altered tumor cells vaccinated with immune-stimulating antibodies, also known as checkpoint inhibitors, can cure large, established neuroblastoma in mice. Dr. Sandler's research team is working to develop a vaccine as a method for optimal tumor antigen presentation in combination with targeted checkpoint inhibition. They seek to evaluate the mechanisms of the anti-tumor immune response, the ability of the altered tumor cells to cause an immune response, and the possibility of using this approach with other childhood solid tumors. Their research should translate into a clinical trial to test the potential use of this therapy in pediatric patients fighting neuroblastoma.

2011-2013

Oncolytic Virus Trial

The Catherine Elizabeth Blair Memorial Foundation has made a $10,000 grant to fund a Phase I Clinical Trial of the JX-594 Vaccinia Virus for Relapsed/Refractory Neuroblastoma. JX-594 is an oncolytic virus, a new class of cancer agents that utilizes a different way to kill cancer cells. It is expected to be effective against cancers resistant to conventional surgery, radiotherapy, and chemotherapy. JX-594 is a vaccinia virus that has been genetically engineered to infect, multiply, and kill cancer cells while leaving neighboring healthy cells unharmed. In addition to direct killing of cancer cells by viral replication, JX-594 expresses a transgene GM-CSF which stimulates the immune system to recognize and destroy the cancer cells. The results of several Phase I and Phase II adult trials (multiple cancer types) have recently shown evidence of clinical responses, anti-tumor effect and minimal toxicity. This trial is the first-in-children for this oncolytic virus and will treat advanced/metastatic, unresectable solid tumors refractory to standard therapy. The trial is initiated by Solving Kids' Cancer, who will provide a matching $10,000 for our grant, thus doubling our impact. Principal Investigators: Dr. Timothy Cripe of Cincinnati Children's Hospital and Dr. Chrystal Louis of Texas Children's Hospital/Baylor University.

Highly Active Cell Therapy

The Catherine Elizabeth Blair Memorial Foundation is pleased to announce our second grant of $20,000 to fund the research study "Highly Active Cell Therapy for Neuroblastoma" which will be matched dollar-for-dollar by our partners Solving Kids' Cancer, who initiated this study. The study will take place at Children's Hospital of Philadelphia, the University of Pennsylvania, and Primary Children's Hospital of Salt Lake City. This trial uses immunotherapy, where the immune system is trained to kill the cancer cells. In this study, one type of white blood cells, called T cells, are removed from the body and genetically engineered so that they will target and kill neuroblastoma cells while leaving healthy cells

alone. They are then reinfused into the patient. This model has shown very promising results in two adult studies (different cancer types) and this will be a first-in-children study. The principal investigator from one of the adult studies, Carl June, is one of the investigators on this trial. There are several exciting aspects of this study. 1) The infused "killer" cells will not need to be continually re-infused as with some previous immunotherapy studies. They will continue to live in the body and thus continue to kill neuroblastoma cells. 2) This model of treatment relies on the patient's own cells rather than on drug companies to develop new drugs.

Natural Killer Cell Therapy Trial

The Catherine Elizabeth Blair Memorial Foundation is pleased to announce a new grant of $20,000 in partnership with Solving Kids' Cancer for a Phase 1 clinical trial. This new clinical trial will be the first study to combine Natural Killer Cell Therapy with an immunocytokine and is the first neuroblastoma trial to address the issue of relapsed or refractory patients with bulky tumors. The principal investigators for "Phase 1 Trial of Ex-Vivo Expanded Haploidentical NK Cells and Hu14.18-IL2 for Children with Relapsed/Refractory Neuroblastoma" are Kenneth B. DeSantes and Paul Sondel at the University of Wisconsin-Madison. "We believe this therapy may provide some hope for children with relapsed or refractory neuroblastoma, whose prognosis has historically been extremely poor. The NK cells utilized in this trial have an enhanced ability to kill tumor targets. We anticipate that the administration of these activated NK cells, given in combination with an immunocytokine that specifically recognizes neuroblastoma, will result in significant anti-cancer activity," said Dr. DeSantes.