2023 PEDAL THE CAUSE IMPACT REPORT

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ST. LOUIS Children's HOSPITAL
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Pedal the Cause Impact Report 2023

Siteman Kids at St. Louis Children's Hospital seeks to advance pediatric cancer research and improve outcomes for kids and families stricken by pediatric cancer. Funding from vital partners like Pedal the Cause, St. Louis Children's Hospital Foundation and the Children's Discovery Institute (CDI) is enabling researchers to discover lifesaving treatments and cures for pediatric cancers.

The research and care taking place at St. Louis Children's Hospital ensure access to the most advanced treatments for children in need in St. Louis, the surrounding region and beyond. Together we make a positive difference for our communities by ensuring healthcare equity for children, to improve their wellness and quality of life.

Your Impact

The breakthroughs enabled through your ongoing support are providing answers for children and families living with cancer and fueling hope that earlier, more accurate diagnoses will lead to improved outcomes. These investments allow our researchers to develop their proof of concept and critical data that they can use in their application to receive a greater share of the federal funds allocated to pediatric cancer research each year. We are profoundly grateful for your support and delighted to report on your extraordinary impact of more than $1.5 million in 2023.

Impact of Human iNKT Cell Expansion with Different Glycolipid Antigens on Malignant Cell Killing

Melissa Mavers, MD, PhD, Assistant Professor, Department of Pediatrics, Hematology and Oncology, Washington University School of Medicine

Project Goal

The goal is to improve existing cellular therapies as well as develop novel cellular therapies for malignant diseases by supporting the development of novel invariant natural killer T (iNKT) cell-based cancer-targeting therapies with enhanced safety and efficacy.

Project Summary

Chimeric antigen receptor (CAR)-based cellular therapies represent an important treatment option for patients with certain blood disorders and diseases including cancer. Robust research is underway to identify new targets to expand their utility. However, CAR-T cell therapy success remains limited when the patient does not have enough of their own cells, and important concerns remain regarding the potential for inducing graft-versus-host disease (GVHD) due to donor cells. Invariant natural killer T (iNKT) cells are part of the immune system that can overcome these limitations. These iNKT cells are incapable of creating responses that trigger GVHD, making iNKT cells an innovative platform for off-the-shelf universal donor cellular therapies.

However, a recent study shows that only a certain subset of these cells are effective at killing malignant cells. Further, iNKT cells require growth outside the human body, known as ex vivo expansion, to facilitate engineering and obtain sufficient numbers for cellular therapy products. However, understanding which glycolipid antigen promotes optimal expansion of iNKT cells towards cytotoxic capacity remains a critical unmet need and is the major question that will be addressed by this project.

The project seeks to determine the expansion conditions that promote maximal iNKT-mediated success by killing off viruses, bacteria and cancer cells, known as cytotoxicity. We plan to compare iNKT cell expansion with different glycolipid antigens and measure the cytotoxic capacity of expanded iNKT cells in vitro and in vivo. The rationale for the proposed research is that skewing iNKT cell populations towards those with enhanced cytotoxic capacity when expanding for engineering to target malignancies is vital to improving the safety and efficacy of this innovative cellular therapy approach.

This work will have a positive impact on advancing the field by informing the development of innovative iNKT-based cellular therapies tailored to enhance safety and efficacy, which will lead to new novel therapies and improve survival rates for cancer patients, aligning strongly with the Pedal the Cause mission. Additionally, our lab is working to determine surface proteins that will enable us to identify functionally distinct subsets of human iNKT cells, which will further support the proposed experiments.

Developing Novel Chatbots Powered by Large Language Models for Pediatric Cancer and Vascular Anomalies

Principal Investigator: Bryan Sisk, MD, MSCI, Assistant Professor, Department of Pediatrics, Pathology and Immunology, Washington University School of Medicine

Co-Investigator: Albert Lai, PhD, Chief Research Information Office, Washington University School of Medicine

Project Goal

The goal is to develop cancer-specific and vascular anomaly-specific chatbots using a retrieval-augmented generation approach and assess the usefulness, quality and acceptability of these tools.

Project Summary

Pediatric oncologists are central to the care of patients with pediatric cancer and vascular anomalies (VAs), which are both rare diseases driven by genetic variants that present in childhood and have a significant impact on mental and physical health. We previously identified unmet communication needs in both populations that can lead to parental distress, loss of trust, financial insult and medical harm. Despite these similarities, parents of children with cancer and VAs have different information needs, available resources, ease of referral to expert centers and medical needs. It is imperative that each group of parents has access to accurate, understandable and accessible information through a scalable communication tool specific to their child's disorder. Chatbots powered by large language models (LLMs), such as ChatGPT, represent a novel technology that could address communication needs in both populations. ChatGPT is an artificial

In 2023, Pedal the Cause donated **$1,501,174** to St. Louis Children's Hospital Foundation.

intelligence (AI)-driven communication tool that uses LLMs to provide human-like communication through a chatbot interface. However, ChatGPT is not trained in medical data and performs poorly for rare diseases such as pediatric cancer and VAs. Developing disease-specific LLM chatbots for pediatric cancer and VAs can provide scalable solutions to the major deficiencies in communication experienced by these parents. Studying parental use of this chatbot will also provide insights into the types of information that parents desire.

We will retrain two separate versions of ChatGPT LLMs with cancer-specific and VA-specific knowledge using a technique called retrieval-augmented generation. Using this methodology, we will provide the LLM with curated information from an external knowledge database that will lead to more accurate answers. We will generate this knowledge database by performing a literature review and by collaborating with professional and patient advocacy groups to collect educational materials. Two committees of clinical experts for cancer and VAs will prioritize literature and evaluate the quality of chatbot output through iterative refinements. After each iteration, the committees will vote to determine whether the chatbots require further training. Once finalized, we will develop a web-based user-interface and perform usability testing to further improve user experience.

We will then provide chatbot access to parents of children with cancer or VAs and collect multiple types of data. Surveys given to the parents will assess for potential outcomes related to knowledge, communication, caregiver burden and psychological distress. Usage data will track the frequency of parental chatbot usage. Evaluating parental questions and chatbot responses will allow us to understand parental information needs and assess quality of chatbot responses.

This project is significant because parents of children with cancer and VAs have unmet information needs that contribute to distress, misunderstandings and caregiver burden. No prior studies have leveraged LLMs for use in rare pediatric diseases, however, families currently have access to generic ChatGPT, which provides inaccurate answers to questions about rare pediatric diseases. This study, with collaboration from Anna Kerr, PhD, will provide generalizable knowledge about how to leverage LLMs to improve communication and care for these and other rare diseases as well as inform future grant proposals for National Institutes of Health (NIH) and Patient-Centered Outcomes Research Institute (PCORI).

Germline Mutations in ETV6 and Cancer Predisposition

Jorge Di Paola, MD, Professor, Department of Pediatrics, Hematology and Oncology, Washington University School of Medicine

Project Goal

The goal is to understand the biological significance of these genetic defects, and their potential impact on human disease.

Project Summary

Recently, we found that mutations in the ETV6 gene lead to mild thrombocytopenia, which is a condition in which the patient has low blood platelets, a tendency to bleed or bruise easily, red cell macrocytosis and predisposition to lymphoblastic leukemia. Among the 96 cases that have been reported and confirmed to carry an ETV6 mutation, 29 (30.2%) were diagnosed with hematological malignancies (HMs). B-cell acute lymphoblastic leukemia (B-ALL) is the most common malignancy, accounting for approximately two thirds of cases. Furthermore, in a study of 4,000 children with ALL, germline ETV6 variants were identified in almost 1%. Individuals with germ line ETV6 variants were more likely to have hyper diploid leukemia, similar to recent findings with germ line IKZF1 variants, and were significantly older at diagnosis than those without.

1 in 285 children in the United States will be diagnosed with cancer before their 20th birthday.

Others reported HMs in mutation carriers include myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), mixed-phenotype acute leukemia, diffuse large B-cell lymphoma, polycythemia vera and multiple myeloma. The mechanisms responsible for the thrombocytopenia, propensity for bleeding and cancer predisposition in patients with ETV6 mutations are unknown. Deep sequencing of the platelet transcriptome revealed significant differences in mRNA expression levels between patients with the ETV6 mutation and non-affected family members, indicating that ETV6 is critically involved in defining the molecular phenotype and function of platelets. In order to study the role of ETV6 mutations in transcriptional regulation we recently generated a transgenic mouse with an ETV6 mutation. Preliminary data show that these mice exhibit decreased platelet counts, small megakaryocytes and decreased platelet activation responses.

The project will test the hypothesis that genetic disruption of ETV6 will result in deregulation of IFN response genes, generating a proinflammatory bone marrow environment that will affect megakaryopoiesis, overall hematopoiesis and predispose individuals to hematological malignancies. Successful completion will identify novel targets of ETV6, providing a platform for potential genetic manipulation for therapies in patients with platelet count disorders.

In addition, the project will determine the consequences of ETV6 disruption in bone marrow homeostasis. We will identify the molecular mechanisms that trigger ETV6 dependent gene deregulation and measure inflammatory markers in the bone marrow environment that may predispose to myelodysplasia and malignancies.

Role of Retinoids in Acute Myeloid Leukemia Treatment

Margaret Ferris, MD, PhD, Instructor, Department of Pediatrics, Hematology and Oncology, Washington University School of Medicine

Project Goal

The goal is to further understand the molecular mechanism of the retinoid receptor/COMPASS-like complex interaction as well as to develop pre-clinical data for a clinical trial of combination menin inhibitor and retinoids.

Project Summary

Mixed lineage leukemia represents a great clinical need as they are less likely to respond to current standard treatment and have a high relapse rate. Revumenib is a novel drug in phase I clinical trials that directly inhibit activity of the MLL-fusion protein (MLL-FP) by inhibiting binding with one of the COMPASS-like complex members, menin. While there is a high initial response rate, development of resistance is common. Multimodal therapies including Revumenib will be necessary for long-lasting remissions. I recently published that MLL-AF9 mouse leukemia is highly sensitive to combination therapy of retinoids. Retinoids target the retinoid receptor, which plays a role in self-renewal and myeloid development. We hypothesized that retinoid receptors recruit KMT2C/D-anchored COMPASS-like complexes to enhancers of retinoid target genes leading to myeloid differentiation and killing off the leukemia cells. We generated a series of knock out (KO) MLL-AF9 cells to determine whether the COMPASS-like complexes are necessary for the anti-leukemic effect of retinoids.

Preliminary experiments show cancelation of the retinoid response in the KO lines. Further, we hypothesized that by combining the KMT2A-directed menin-inhibitors with KMT2C/D-directed retinoids, we will have a synergistic anti-leukemic effect. Preliminary studies with the mouse MLL-AF9 cells as well as human MLLr cell line, MOLM-13, showed strong synergistic killing with the 3-drug combination. This project will allow us to gather much-needed data as we prepare for an upcoming clinical trial. We hope that this will give more options to patients with mixed lineage leukemia in the future and lower the relapse rate.

Only 4% of total National Institutes of Health funding goes to pediatric research.

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Thank You!

Your donation to St. Louis Children's Hospital is more than a gift. It's an opportunity to give kids the chance to just be kids. Your support allows our physicians, nurses and hospital staff to continue providing world class, family-centered care for kids in St. Louis, across the United States and around the globe. Thank you for joining us in our mission to *do what's right for kids*!