Alex's Lemonade Stand
Foundation for Childhood Cancer™

13th Annual Young Investigator Summit

November 4-6, 2025

Philadelphia, PA

Presented by

Northwestern Mutual®

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Dear Attendees,

We at Alex's Lemonade Stand Foundation (ALSF) and Northwestern Mutual are proud to welcome you to the 13th Annual ALSF Young Investigator Summit. It is our honor to bring together researchers with the hope of changing the future of pediatric cancer, encouraging innovation, and cultivating the brightest minds to achieve the greatest possibilities.

Now more than ever, we are committed to funding bold ideas and early career researchers. That's why we're increasing our Young Investigator Grant funding in 2026 – to fund more projects like yours that are fueling the next generation of pediatric cancer breakthroughs. By sharing your novel ideas, forming more working relationships, and learning new ways to apply the latest research advancements to your own projects, you are paving the way to discovering better treatments and cures for kids with cancer. We are so thankful to have you here. Because of your dedication in the lab, there will be more cures.

These next few days will hold fascinating presentations, stimulating conversations and the chance to connect with fellow leaders in your field. From long-time grantees to emerging Young Investigators, the work you do is essential, and we can't wait to see your impact on the future of childhood cancer research.

Thank you!

Liz & Jay Scott
Alex's Parents/Co-Executive Directors
Alex's Lemonade Stand Foundation

Steve Radke
President, Northwestern Mutual Foundation

Northwestern Mutual
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Alex's Lemonade Stand Foundation would like to thank our corporate partner, Northwestern Mutual, for making this amazing opportunity possible.

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Things to Know

Onsite Contact Information:

Amy Levine, Event Planner, ALSF
Phone: (610) 291-9640

The Notary Hotel
21 North Juniper Street, Philadelphia, PA 19107
Phone: (215) 496-3200

Wi-Fi Network: Notary_CONFERENCE
Password: Liberty1

Baggage:

On departure day, please bring your luggage to hotel lobby for storage with the front desk, or to the Juniper Ballroom where there will be space to store your bags in the back of the room.

Lyft Credit:

Lyft credits need to be utilized within a half mile of the airport or hotel in Philadelphia.

How to redeem the credit:

Step 1: Download the Lyft app for iPhone or Android and set up your account.

Step 2: Scan the QR Code below to claim your Lyft pass. Or enter **2025YISUMMIT** in the Lyft Pass section of the 'Payment' tab in the app menu. You must be in "Personal" mode for the code to apply. Select your pick-up location and complete the ride request.

Lyft code: 2025YISUMMIT

SCAN TO GET YOUR LYFT PASS

Summit Agenda

ALL SESSIONS WILL TAKE PLACE AT: THE NOTARY HOTEL, 21 N JUNIPER ST, PHILADELPHIA, PA 19107

Tuesday, November 4, 2025

6:00PM-9:00PM	**Welcome Cocktail Reception**	**Grand Ballroom Foyer (First Floor)**

Wednesday, November 5, 2025

6:00AM-7:00AM	**Group Activity:** Meet for morning run with Conner, walk with ALSF	**Hotel Lobby**
7:30AM-8:30AM	**Registration and Breakfast**	**Salons 3 & 4 (First Floor)**
8:30AM-8:50AM	**Welcome** from ALSF & Northwestern Mutual Foundation	**Juniper Ballroom (Mezzanine Level)**
8:50AM-9:30AM	**Speed Presentations 1:** (6 New Class x 6 min = 36 min)	**Juniper Ballroom**
9:30AM-10:00AM	**Speed Presentations 1:** Q&A	**Juniper Ballroom**
10:00AM-10:20AM	**Break**	**Mezzanine Foyer**
10:20AM-11:00AM	**Speed Presentations 2:** (5 New Class x 6 min = 30 min)	**Juniper Ballroom**
11:00AM-11:30AM	**Speed Presentations 2:** Q&A	**Juniper Ballroom**
11:30AM-12:30PM	**Group Photo and Lunch**	**Salons 3 & 4**
12:30PM-1:00PM	**Speed Presentations 3:** (5 New Class x 6 min = 30 min)	**Juniper Ballroom**
1:00PM-1:30PM	**Speed Presentations 3:** Q&A	**Juniper Ballroom**
1:30PM-1:45PM	**Break**	**Mezzanine Foyer**
1:45PM-2:30PM	**Elliot Stieglitz, MD, UCSF Benioff Children's Hospitals** All in the family: How ALSF has supported my journey from YIA to R Accelerated and many steps in between	**Juniper Ballroom**
2:30PM-3:15PM	**Where Are They Now?**	**Juniper Ballroom**
3:15PM-3:35PM	**Poster Preview 1**: (Current & Alumni) 1 min/1 slide for posters (17)	**Juniper Ballroom**
3:35PM-4:30PM	**Poster Session 1:** (17) - (Current & Alumni)	**Grand Ballroom Foyer**
5:45PM	Meet in Hotel Lobby	**Hotel Lobby**
6:00PM-9:00PM	**Dinner & Event** (Offsite): ~10 min walk from hotel Flight Club, 1417 Walnut St, Philadelphia, PA 19102	**Flight Club Darts**

Summit Agenda

Thursday, November 6, 2025

7:45AM-8:30AM	**Breakfast**	**Salons 3 & 4 (First Floor)**
8:30AM-8:35AM	**Welcome & Ambassador Intro**	**Juniper Ballroom (Mezzanine Level)**
8:35AM-8:45AM	**Childhood Cancer Hero Ambassador:** Megan Roberts	**Juniper Ballroom**
8:45AM-9:00AM	**Resource Sharing Awards:** Audra Brennan, Northwestern Mutual	**Juniper Ballroom**
9:00AM-9:45AM	**Keynote:** Katie Janeway, MD, MMedSc, Dana-Farber Cancer Institute Achieving molecular stratification in sarcoma through collaboration	**Juniper Ballroom**
9:45AM-10:05AM	**Poster Preview 2 (18):** (Current & Alumni) 1 min/1 slide for posters	**Juniper Ballroom**
10:05AM-11:00AM	**Poster Session 2 (18) & Break** (Current & Alumni)	**Grand Ballroom Foyer**
11:00AM-11:45AM	**Career Breakout Session** - PhDs (30) - MD, MD/PhD (34)	**PhDs are in Salons 1 & 2** **MD, MD/PhD are in Juniper Ballroom**
11:45AM-12:30PM	**Lunch**	**Salons 3 & 4**
12:30PM-1:45PM	**Shark Tank Competition & Voting**	**Juniper Ballroom**
1:45PM	**Summit Closing**	**Juniper Ballroom**

Shark Tank Competition

Get ready for another exciting shark tank! Modeled after the TV show, pre-selected researchers will pitch the “sharks” at the 2025 YI Summit on their project’s ingenuity and potential impact for kids fighting cancer. You too will get to weigh in and vote in the People’s Choice award!

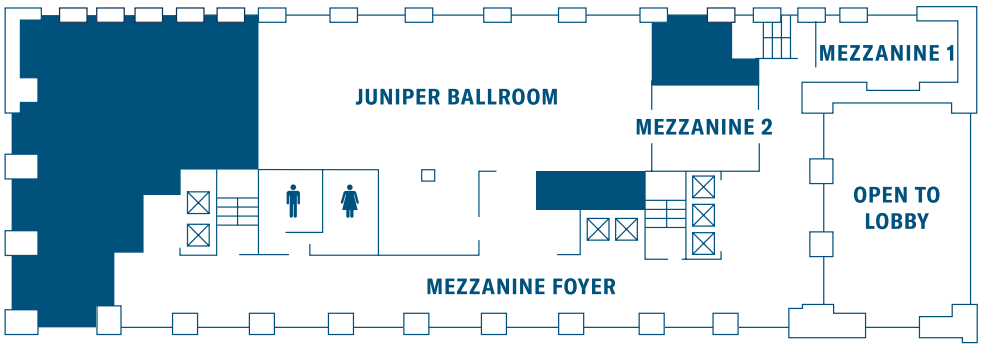
All sessions will take place at:

The Notary Hotel, 21 N Juniper St, Philadelphia, PA 19107

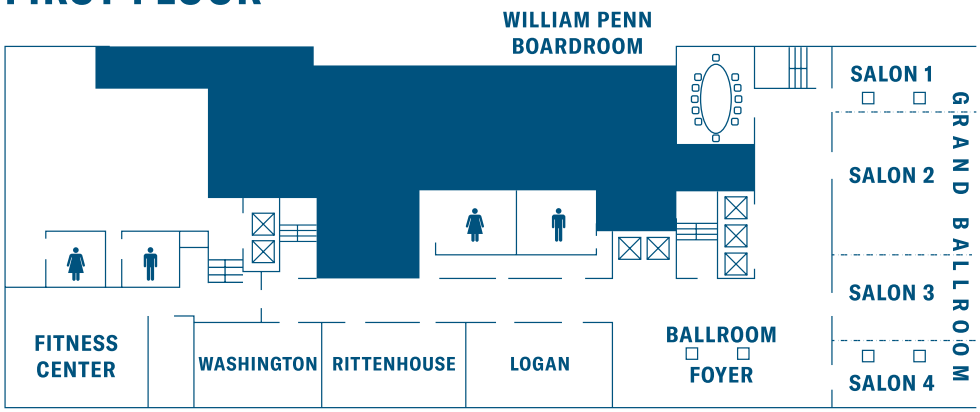
THE NOTARY HOTEL

LOBBY LEVEL

MEZZANINE LEVEL

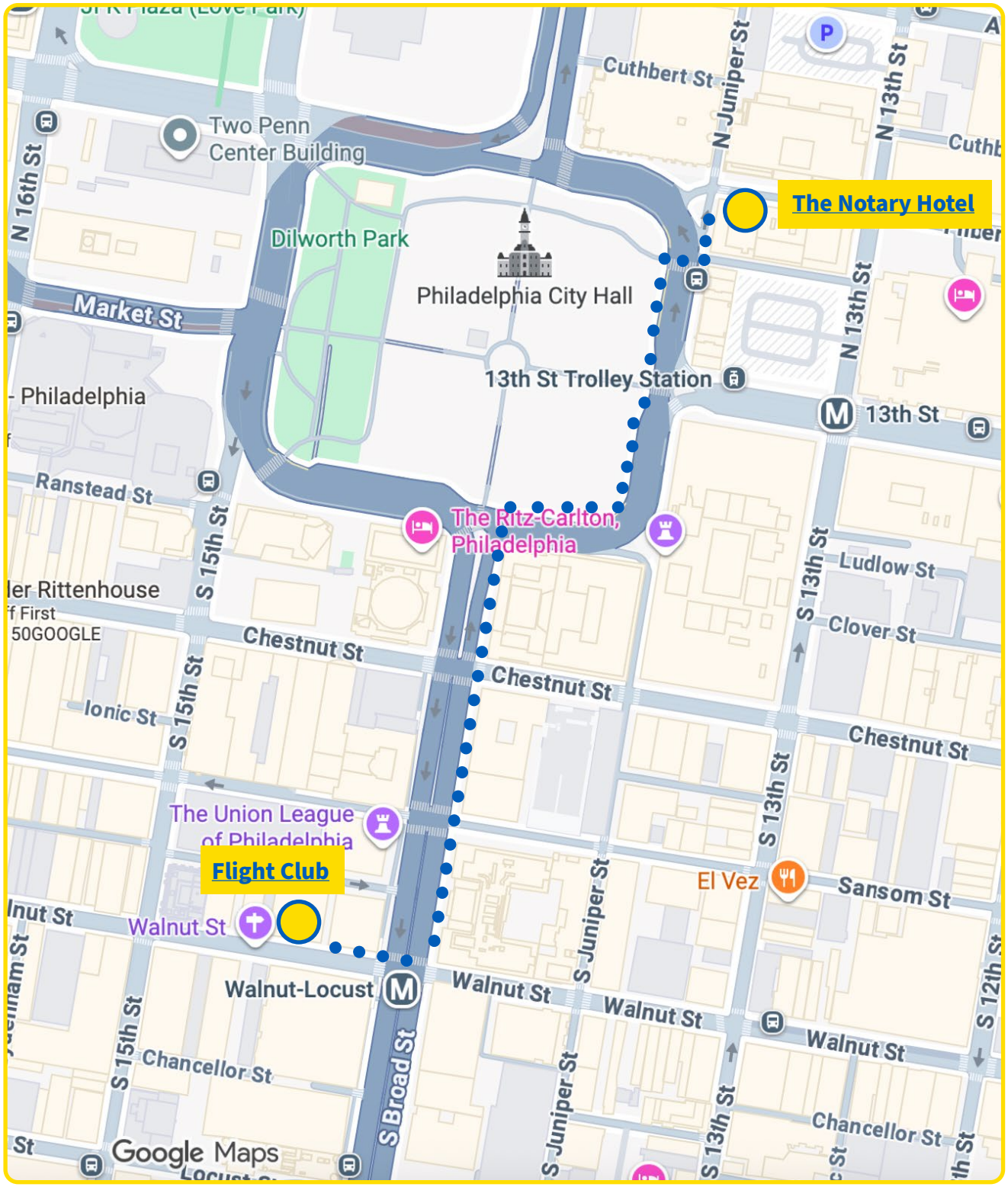


FIRST FLOOR



Directions to off-site activity:

Flight Club, 1417 Walnut St, Philadelphia, PA 19102



About ALSF

Alex's Lemonade Stand Foundation (ALSF) emerged from the front yard lemonade stand of 4-year-old Alexandra "Alex" Scott, who was fighting cancer and wanted to raise money to find cures for all children with cancer. By the time Alex passed away at the age of 8, she had raised $1 million. Since then, the Foundation bearing her name has evolved into a worldwide fundraising movement and the largest independent childhood cancer charity in the U.S. ALSF is a leader in funding pediatric cancer research projects across the globe and providing programs to families affected by childhood cancer. For more information, visit **AlexsLemonade.org**.

Scientific Resources

Childhood Cancer Data Lab

The Childhood Cancer Data Lab (Data Lab) empowers pediatric cancer experts poised for the next big discovery with the knowledge, data, and tools to reach it. They construct tools that make vast amounts of data widely available, easily mineable, and broadly reusable. They train researchers and scientists to better understand their own data and to advance their work more quickly. Read more about the Data Lab on **page 13**.

Childhood Cancer Repository

This repository banks and distributes validated cell lines and patient-derived xenografts (PDXs) established from childhood cancers to investigators seeking to do research on childhood cancer. Learn more at **CCCells.org**.

Childhood Cancer Speaker Series

ALSF's Childhood Cancer Speaker Series features 60-minute webinars which includes a Q&A with esteemed researchers, scientists, physicians and professors who will speak about cutting-edge topics. Prior webinars are available to watch on our website. Learn more at **AlexsLemonade.org/Lectures**.

Join the Conversation with ALSF on Social Media

Tune into our social channels for daily content and updates from the Foundation, including:

- **Childhood cancer facts and research news**
- **Fundraising events throughout the year**
- **Inspirational stories about our childhood cancer heroes and researchers**
- **The global impact of the memory of our Founder Alex Scott**

Follow us on all platforms @AlexsLemonade:

Grant Opportunities

Alex's Lemonade Stand Foundation has funded more than 1,500 research projects at nearly 150 hospitals and institutions working toward the goal of putting an end to childhood cancer. We invest in projects at every stage of the research continuum. As you think about the next phase of funding for your research, keep us in mind!

Below are the grant categories we are offering over the next year.

Early Career Research

'A' Award: Designed for the early career independent scientist who wants to establish a career in pediatric oncology research. The ideal candidate has an original project, can demonstrate outstanding career development support from their institution, and has a strong future commitment to pediatric cancer investigation.

Pediatric Oncology Student Training (POST): The POST program is for undergraduate, graduate, and medical students interested in pursuing a career in pediatric oncology to train with research mentors. Open to mentors who are currently or previously funded by ALSF.

***RUNX1* Early Career Investigator:** Designed to fund research in strategies leading to the development of therapies to prevent the transition from pre-leukemia to leukemia for patients with RUNX1-FPD, while encouraging a new generation of basic and translational scientists to tackle inherited hematologic malignancy predisposition disorders with a focus on RUNX1-familial platelet disorder.

Young Investigator: Designed to fill the critical need for startup funds for less experienced researchers during their fellowship training or early stages of their pediatric oncology research career to pursue promising research ideas.

Research Accelerator

Crazy 8 Initiative Award: Funding research into innovative and rigorous approaches that directly address the most intractable issues in pediatric cancer research today. This award is designed to coalesce cross-disciplinary cores of scientists working collaboratively in order to accelerate the pace of discovering new cures. The 2026 award will be focused on brain tumors.

Innovation: Providing seed funding to experienced investigators to pursue novel, promising, cutting-edge approaches to cure childhood cancers. Nurtures high-risk, high-reward research and "out of the box" thinking.

R Accelerated Award: Research projects should address a testable hypothesis based on strong scientific rationale. Applicants must be recipients of a pediatric cancer research focused NIH R01 award or equivalent (e.g.: ACS etc.) within the last five years.

Reach: Removing the barrier to critical "last mile" testing of therapeutic interventions and propelling cures and treatments from the lab to the clinic.

***RUNX1* RARE Grant:** Designed to fund research that will lead to the development of therapies for patients with *RUNX1*-FPD that will either intercept the transition from a precancer state (clonal hematopoiesis) to MDS/AML or prevention of cancer (before clonal hematopoiesis).

Scan to learn more

Family Services

Alex's Lemonade Stand Foundation offers many programs designed to help families navigate the challenges of having a child with cancer. **Visit ALSFFamilyServices.org** to learn more about all the services we have to offer.

Scan to learn more

Resource Navigator

As families learn of a diagnosis, subsequent treatments and challenges, it can be overwhelming and hard to navigate. ALSF's Resource Navigator will bridge the gap between families in need and available resources, whether it is an ALSF resource or another organization's program. Reach out to Amanda: **FamilyServices@AlexsLemonade.org**.

Travel For Care

ALSF's Travel For Care program ensures families battling childhood cancer have the financial assistance needed to travel to clinical trials, experimental therapeutics, or treatment innovations not currently available at their local institution.

SuperSibs

Childhood cancer affects the whole family, not only the child who receives the diagnosis. SuperSibs is dedicated to comforting, encouraging and empowering siblings of children with cancer, so they can face the future with courage and hope.

Flashes Of Hope

A picture is worth a thousand memories. Flashes of Hope provides childhood cancer families with free photography packages in local hospitals around the country as keepsakes for families to honor the unique life and memory of their hero.

Treatment Journal

This free organizer helps parents keep track of important information during their child's treatment such as appointments, medications, expenses, and more. Journals are available in English and Spanish.

School Support

A childhood cancer diagnosis can be difficult for teachers, administrators and families to manage in a school setting. ALSF is committed to providing support and encouragement for school professionals to address the needs of the school community.

Childhood Cancer Guides

Childhood Cancer Guides are comprehensive books that include explanations of various cancer types, descriptions of treatments, emotional support suggestions, identifying helpful resources, and more. Our books include *Childhood Leukemia, Childhood Brain & Spinal Cord Tumors, Childhood Cancer Solid Tumors, Your Child in the Hospital*, and *Childhood Cancer Survivors.* They are offered for free to families facing a diagnosis.

Lifeline

The Lifeline Fund was created to support the financial needs of families during childhood cancer treatment when other resources are not available or have been exhausted. The types of expenses the Fund will cover are intended to be essential and urgent, covering extenuating circumstances or extraordinary needs.

Flashes of Hope,
Photographer
Scott Knutson

Alex's Lemonade Stand Foundation **Special Events**

The Lemon Ball January 24, 2026 • Springfield Country Club in Springfield, PA

ALSF's "yellow tie" gala celebrates the lasting legacy of Alex Scott and continues to fulfill her dream of funding cures for childhood cancer. Enjoy inspiring talks from childhood cancer heroes and their families as Alex's parents, Liz and Jay Scott, host what is sure to be a fabulous and unforgettable evening.

LemonBall.org

Great Chefs Table: Seattle March 11, 2026 • Seattle, WA

ALSF is coming to Seattle this spring for this inaugural culinary event! Join our guests at the beautiful Lark Seattle for an unforgettable evening with James Beard Award-winning chef John Sundstrom. This multi-course meal prepared by an exceptional chef lineup will allow you to fund childhood cancer research with every delicious dish. **AlexsLemonade.org/Campaign/Great-Chefs-Table-Seattle**

Lemonade Days June 2026 • Nationwide

Lemonade Days commemorates ALSF Founder Alex Scott's tradition of holding her annual summer lemonade stand. Supporters across the country join together to take a stand against childhood cancer during June (or any other time of year) by hosting their own lemonade stands. **LemonadeDays.org**

Alex's "Original" Lemonade Stand June 6, 2026 • Wynnewood, PA

Come to the stand that started it all! Alex's "Original" Lemonade Stand is an uplifting, fun-filled, family-friendly day that continues Alex's yearly summer stand at the elementary school she once attended. This event is complete with food, games, crafts, raffles and, of course, lemonade.

AlexsLemonade.org/Alexs-Original

Great Chefs Event Philadelphia June 13, 2026 • Philadelphia, PA

The original ALSF culinary event, this family-friendly dining experience features chef partner Marc Vetri, his business partner Jeff Benjamin, and more than 30 of their closest chef friends for a tasteful afternoon. Held in the unique venue of Urban Outfitters headquarters, guests can sample the chefs' delicious dishes while making a difference. **GreatChefsPHL.org**

The Million Mile September 2026 • Worldwide

Each September, during Childhood Cancer Awareness Month, participants in this virtual challenge collectively raise millions of dollars and log one million miles by running, walking, or cycling. As an ALSF-funded researcher, when you participate you are eligible to apply for a grant that could potentially match the funds your Million Mile team raises. **TheMillionMile.org**

L.A. Loves Alex's Lemonade October 2026 • Los Angeles, CA

Hosted by Chef Suzanne Goin, business partner Caroline Styne, and Chef David Lentz, this family-friendly cook out features one-of-a-kind food and drink samplings. Mingle with superstar chefs and taste dozens of dishes as you join ALSF in the fight against childhood cancer.

LALovesAlexsLemonade.org

Childhood Cancer Data Lab

The Childhood Cancer Data Lab (Data Lab) empowers pediatric cancer experts poised for the next big discovery with the knowledge, data, and tools to reach it. They construct tools that make vast amounts of data widely available, easily mineable, and broadly reusable. The Data Lab trains researchers and scientists to better understand their own data and to advance their work more quickly. They bring their expertise working with large amounts of data to consult on projects and collaborate with the research community.

The Data Lab is actively contributing to a multi-institutional effort (the Sean Karl cohort) focused on understanding therapeutic vulnerabilities in Ewing sarcoma (EwS). As part of this collaboration, they developed a reproducible workflow called ews-nf, designed to run common analyses across all samples in the EwS single-cell RNA-seq cohort. This pipeline will result in a fully annotated, harmonized dataset that all participating teams can use for consistent downstream analyses. Both the workflow and the generated data will be openly shared with the research community via the Data Lab's Single-cell Pediatric Cancer Atlas (ScPCA) Portal.

Learn about the Data Lab's open source tools, training workshops, and scientific collaborations at CCDataLab.org.

Visit their table to learn more about this project and how the Data Lab can serve your research. Plus, take a few minutes to participate in their study on how researchers are using GenAI tools, and you'll get a free t-shirt!

Speed Presentations

Session 1

Timothy Chang, MD/PhD
Mark Gower, PhD
Grant Grothusen, PhD
Tomasz Grzywa, MD/PhD

Session 2

Clara Libbrecht, MD/PhD
Angela Liou, MD
Siva Kumar Natarajan, PhD
Petri Pölönen, PhD
Jenna Robinson, PhD
Sauradeep Sinha, PhD

Session 3

Daniel Solvie, PhD
Xirui Song, PhD
Helena Yu, MD
Daniel Zheng, MD
Han Zou, MD

Posters

Session 1

Mark Applebaum, MD
Shuhei Asada, MD/PhD
Leidy Diana Caraballo Galva, PhD
Joselyn Cruz Cruz, PhD
Catherine Danis, PhD
Ian Delahunty, PhD
Caroline Diorio, MD
Madelyn Espinosa-Cotton, PhD
Andrea Franson, MD
Rachel Hurley, MD/PhD
Christian Hurtz, PhD
Courtney Jones, PhD
Miriam Kim, MD
Lingzhi Li, PhD
Adrienne Long, MD/PhD
Kyle MacQuarrie, MD/PhD
Sean Misek, PhD

Session 2

Robin Parihar, MD/PhD
Jinseok Park, PhD
Santhosh Kumar Pasupuleti, PhD
Bo Qiu, MD/PhD
Zachary Reitman, MD/PhD
Jezabel Rodriguez Blanco, PhD
Ruby Sims, PhD
Timothy Spear, MD/PhD
Justin Sperlazza, MD/PhD
Christina Turn, MD
Elena Vasileva, PhD
Elvin Wagenblast, PhD
Dong Wang, PhD
Yueyang Wang, PhD
Gregory Way, PhD
Adeline Yang, MD

Speakers

Liz Scott
Audra Brennan
Donald Williams (Will) Parsons, MD/PhD
Maureen M. O'Brien, MD, MS

Elliot Stieglitz, MD
Megan Roberts
Katherine (Katie) A. Janeway, MD, MMSc

Speed Presentations

ALSF

Timothy Chang, MD/PhD

timothyh_chang@dfci.harvard.edu

Dana-Farber Cancer Institute, Boston, MA

2025 Young Investigator Grant

The Role of Senescence in Diffuse Midline Glioma Tumorigenesis and Treatment Resistance

Background: Pediatric diffuse midline gliomas (DMGs) are highly aggressive brain tumors with a universally fatal prognosis, often taking the lives of children within a year of diagnosis. Despite extensive efforts, radiation therapy remains the only treatment that can extend survival, but tumor progression is inevitable. Recent advances in adult cancer research have revealed that a biological process called cellular senescence plays a significant role in how cancers develop, resist treatment, and recur. Senescence is a natural response to stress and plays an important role in normal processes like wound healing and aging. Furthermore, it was once thought to suppress tumors because senescent cells stop dividing. However, new studies reveal that these cells can release proteins — known as the senescence-associated secretory phenotype (SASP) — that can promote tumor growth, invasion, and resistance to therapy in adult cancers. These findings have led me to question whether senescence contributes to the aggressive and treatment-resistant nature of DMGs. By exploring this potential connection, my goal is to uncover new mechanisms that drive this deadly disease and identify innovative strategies to stop its progression.

Project Goal: I am studying whether a process called senescence contributes to the growth, invasion, and treatment resistance of diffuse midline gliomas (DMGs), a highly aggressive and fatal type of brain tumor. By studying individual cells from 16 different DMG tumors before treatment, we discovered some cells showing signs of senescence. In addition, we also found that the senescent cells release proteins that nearby tumor cells can detect and that these proteins are known to help tumors grow and spread in other types of cancers. To explore this further, we plan to study DMG cells in the lab and in a specialized mouse model to see how tumor cells interact with senescent cells and radiation therapy. We will also examine how individual cells respond to these interactions by looking at the genes they activate or deactivate at the single-cell level. By understanding how senescence helps DMGs grow, invade, and resist radiation, we aim to identify new ways to treat this devastating cancer.

Mark Gower, PhD

mark.gower@uhn.ca

University Health Network, Toronto, Ontario, CA

2025 Young Investigator Grant

Elucidating and Targeting the Cell Surface Proteome of Pediatric T Cell Acute Lymphoblastic Leukemia

Background: Acute lymphoblastic leukemia (ALL) is the most common childhood cancer. T cell ALL is an especially aggressive subtype of ALL which affects up to 20% of children with ALL. Up to 25% of children with T-ALL will relapse and succumb to chemotherapy resistant disease. Leukemia survivors experience long-term side effects that permanently affect their quality of life, both physically and mentally. Thus, there is an urgent need to develop targeted therapies to not only improve survival but reduce long-term side effects associated with current treatments. Immunotherapies and small molecule therapeutics, which have seen great success in treating other subtypes of ALL, are currently lacking for children with T-ALL. A major hurdle is the inability to find targets for therapy that spare healthy cells and efficiently eradicate disease. Thus, it is imperative that research works to identify biological characteristics that differ between healthy cells, T-ALL cells from patients who are cured, and T-ALL cells from patients who resist therapy. Recently, we identified inflammation as an underlying biological signature identifying patients at elevated risk of treatment failure. Here, we propose to identify T-ALL proteins associated with inflammation to reveal novel therapeutic targets to improve pediatric patient outcomes.

Project Goal: Here, we propose to identify proteins uniquely expressed on the surface of cells from T cell acute lymphoblastic leukemia (T-ALL) patients. Specifically, we will be comparing the cell surface proteins between patients who show evidence of inflammation at diagnosis versus those who do not as we recently identified inflammation as being associated with poor treatment responses. After identifying proteins unique expression on these inflammatory T-ALL cells, we will utilize genetic editing to delete these proteins from the surface of T-ALL cells to see if they are necessary for survival. When we identify specific proteins that play a role in leukemic cell survival, we will test the ability of antibodies, a type of protein which can bind and block the function of other proteins, to kill leukemic cells. Thus, our project seeks to identify proteins associated with inflammatory T-ALL patient cells that are important for disease survival and progression. Importantly, we will perform preclinical trials to determine if they represent clinically actionable therapeutic targets.

Grant Grothusen, PhD

grothuseng@chop.edu

Children's Hospital of Philadelphia, Philadelphia, PA

2025 Young Investigator Grant

Enhancing GPC2 CAR T Cell Therapy Against Retinoblastoma

Background: Retinoblastoma is the most common childhood cancer of the eye. With early detection and access to current optimal clinical management, retinoblastoma can be controlled in some children, although treatment-related toxicities remain – including potential vision loss and development of secondary cancers. In cases where retinoblastoma has gone untreated or comes back after treatment, removal of the eye is still the only option available to prevent the cancer from spreading to the brain, where it becomes incurable. In recent years, a therapy called chimeric antigen receptor (CAR) T cells, which engineers a patient's own immune cells to fight cancer by enabling them to detect specific cell surface molecules, has achieved great success in the treatment of certain cancers. Our laboratory has developed CAR T cells targeting a cell surface molecule called GPC2 that have progressed to patients with the pediatric solid tumor neuroblastoma. We have also shown that these GPC2 CAR T cells are initially capable of controlling retinoblastoma growth, however our recent studies demonstrate that these eye tumors employ complex defense mechanisms to hide from or disable GPC2 CAR T cells, limiting long-term treatment efficacy. As such, here we propose re-engineering GPC2 CAR T cells with specific enhancements to overcome retinoblastoma immune evasion as a critical next step to achieving sustained antitumor activity.

Project Goal: In this project we will develop next-generation GPC2 CAR T cells enhanced to overcome two different mechanisms that retinoblastoma cells may employ to resist their tumor-killing activity. In our preliminary data, we have shown that some retinoblastomas escape GPC2 CAR T cells by decreasing the amount of GPC2 displayed on their surface, thus enabling them to remain undetected from these potent immune cells. In our first approach, we propose to re-engineer GPC2 CAR T cells with the ability to additionally detect a second retinoblastoma cell surface molecule called GD2, which can also be targeted with CAR T cells and which we have demonstrated to remain at high levels on the retinoblastoma cell surface. Interestingly, not all retinoblastomas appear to down-regulate GPC2 in order to survive therapy, suggesting that other mechanisms may also be employed. We have shown that retinoblastomas secrete high levels of molecules that can inactivate T cells, including one in particular called MIF. Thus, in our second approach, we propose to re-engineer GPC2 CAR T cells with the ability to capture tumor-secreted MIF and convert it into an additional T cell activating signal rather than one that disables them. The preclinical efficacy and safety studies that we propose here will provide proof-of-concept data, propelling the clinical translation of enhanced GPC2 CAR T cells for retinoblastoma and other pediatric tumors such as neuroblastoma that employ similar mechanisms of immune evasion.

Tomasz Grzywa, MD/PhD

grzywat@chop.edu

Children's Hospital of Philadelphia, Philadelphia, PA

2025 Young Investigator Grant

Vaccine-Boosted Tumor Microenvironment-Restricted Multi-Antigen Targeting CAR T for Pediatric High-Grade Gliomas

Background: Brain tumors pose a significant challenge in pediatric oncology and are among the leading causes of cancer-related deaths in children in the United States. Among these, pediatric high-grade gliomas (pHGG) make up about 10% of all brain and central nervous system tumors. These tumors are particularly aggressive and have a very poor prognosis. Patients with pHGG tumors like diffuse intrinsic pontine gliomas (DIPG) typically do not survive more than two years, and there are not many treatment options available for them. Therefore, there is a desperate need for the development of new therapies that can improve the outcomes of these patients. One potential approach is chimeric antigen receptor (CAR) T cell therapy, in which the patient's immune cells are modified to specifically recognize and kill tumor cells. This method of immunotherapy has shown promise in treating blood cancers but has not yet been as successful with solid tumors. In this project, we aim to address this challenge by developing a CAR T therapy that targets multiple antigens. To ensure the safety of the therapy, we will restrict the activity of CAR T cells only to the tumor site. The goal of this project is to improve the treatment's effectiveness while minimizing any unwanted effects on healthy tissues.

Project Goal: The main goal of this project is to develop an effective and safe therapy for patients with a highly aggressive type of brain tumor called pediatric high-grade gliomas. To achieve that we will develop a novel and effective method of immunotherapy in which a patient's immune cells will be engineered to recognize and attack brain tumor cells. Additionally, we plan to create a system that enables us to engineer therapeutic cells to recognize and respond to the specific features of the tumor site in pediatric brain tumors. This therapy will be safe because we will ensure that the engineered immune cells only activate in the tumor site, which is a major concern when developing immunotherapies. To guarantee this safety, we will investigate the mechanisms of the therapy using different preclinical brain tumor models. We will study how the therapy works and find ways to improve it so that it can be used successfully with pediatric brain cancer patients. Our ultimate goal is to provide a targeted and potentially curative option for a disease with limited effective treatments available. This project is a crucial step in the development of therapies that can treat all types of pediatric brain tumors in the future. We hope that our research will pave the way for more effective treatments that can save the lives of pediatric brain cancer patients.

Clara Libbrecht, MD/PhD

clara.libbrecht@seattlechildrens.org

Seattle Children's Hospital, Seattle, WA

2025 Young Investigator Grant

Targeting Chromatin-Remodeling Complexes in ZNF384-rearranged Mixed Phenotype Acute Leukemia

Background: Mixed phenotype acute leukemia (MPAL) is an understudied subtype of leukemia that shares features of acute lymphoblastic leukemia (ALL) and acute myeloblastic leukemia (AML). Unfortunately, patients with MPAL have been left out of clinical trials, leading to a lack of standardized treatment. Instead, they may receive chemotherapies normally used for ALL or AML, and their outcomes remain poor. A better understanding of the disease is essential to design more efficient and targeted therapies. Rearrangements of the ZNF384 gene are a common genetic change in childhood MPAL. These gene changes, which lead to the production of abnormal fusion proteins, are known to drive the development of childhood leukemia. While studies have shown that ZNF384 fusion proteins can turn normal bone marrow cells into leukemia cells, it remains unclear how exactly this occurs. I discovered that the fusion partner protein sequences were full of disordered regions. Most protein domains have a specific shape that helps them perform their function. Instead, disordered regions are flexible and unstructured which makes it easy for them to interact with other molecules. In particular, they have been shown to interact with a protein complex called SWI/SNF, which is essential to regulate the 3D architecture of DNA and gene expression. I hypothesized that ZNF384 fusion proteins are dependent on SWI/SNF to cause leukemia and found that inhibition of SWI/SNF impaired the growth of MPAL cells in vitro.

Project Goal: The long-term goal of this project is to better understand how ZNF384 fusion proteins transform normal bone marrow cells into leukemic cells. This is essential to identify novel therapeutic targets and develop new treatment strategies to improve the outcomes of children with ZNF384-rearranged MPAL. The short-term goals of this proposal are to (1) study the functions of the wild-type ZNF384 protein in blood and bone marrow cells to better understand how it contributes to the oncogenic properties of the ZNF384 fusion proteins and (2) validate SWI/SNF as a novel therapeutic target in ZNF384-rearranged MPAL. Since a drug targeting SWI/SNF is already being tested in clinical trials, the results of the proposed research could quickly lead to novel and improved treatments for children with ZNF384-rearranged MPAL.

Angela Liou, MD

aliou@sbpdiscovery.org

Sanford-Burnham Medical Research Institute, La Jolla, CA

2025 Young Investigator Grant

Targeting H3K27M Pediatric Diffuse Midline Gliomas Through Induced Viral Mimicry

Background: H3.3K27M-altered pediatric diffuse midline glioma (DMG) are fatal brain tumors, accounting for 10% of pediatric brain tumors and affecting young children between the median ages of 5-10 years old. Despite advances in surgical resection, radiation, and chemotherapy, there remains no effective curative option. There is an unmet clinical need to develop new and effective therapies for DMG. The majority of DMGs are driven by mutated histone proteins known as H3.3K27M oncohistones. When H3.3K27M oncohistones are incorporated onto chromatin, they cause genes to be inappropriately transcribed and the production of pro-tumorigenic proteins, but also paradoxically of anti-tumorigenic proteins derived from viral relics in the human genome. My research leverages this susceptibility and explores a novel way to treat DMG using an emerging therapeutic approach called “viral mimicry” to induce virus reactivation. In this process, tumor cells are tricked into thinking they are infected with a virus which prompts the immune system to mount an antiviral response against the tumor, causing tumor cell eradication. Using drugs that promote viral mimicry may therefore constitute a new and effective treatment modality for DMG patients.

Project Goal: My goals are to harness virus reactivation as a form of unexplored treatment avenue for patients with DMG. Specifically, I found that inhibiting specific virus silencing programs such H3K9me3 and DNA methylation to be effective in reactivating antiviral immune programs that can induce tumor cell killing. My proposed project expands on these findings to evaluate powerful drug combinations targeting H3K9me3 and DNA methylation that can enhance antitumor immune effects in DMGs. I hypothesize that our viral mimicry therapeutic approach can be effective in augmenting immunotherapy responses and provide a novel treatment strategy for children with DMG.

Siva Kumar Natarajan, PhD

sivakn@umich.edu

University of Michigan Medical Center, Ann Arbor, MI

2025 Young Investigator Grant

Elucidating the Tumor Promoting Roles of Itaconate in ZFTA-RELA Fusion Driven Ependymomas

Background: Ependymomas are lethal malignancies that bear a dismal prognosis and lack curative treatment strategies despite decades of research. More than 70% of childhood hemispheric ependymomas bear recurrent ZFTA-RELA fusions. Despite these advances, there are no effective treatments, targeted therapies, or clinical trials for ZFTA-RELA ependymomas. Therefore, there is a major knowledge gap and an urgent and unmet need to identify ZFTA-RELA-specific oncogenic mechanisms. Tumor cells alter nutrient uptake and utilization. This is a fundamental hallmark of cancer. Tumor-driving oncogenes, like the ZFTA-RELA fusion, rapidly alter metabolism to promote tumor growth. This proposal aims to target this altered metabolism as a possible treatment strategy. Our proposed research in ZFTA-RELA ependymomas will provide mechanistic advancements by a) defining molecular mechanisms of ZFTA-RELA fusion-driven itaconate metabolism and b) determining the therapeutic potential of inhibiting itaconate production in these tumors.

Project Goal: A majority of hemispheric ependymomas are driven by gene fusions between RELA/p65, part of the fusion activates aberrant NF-kB signaling, while the ZFTA partner causes chromatin remodeling. I intend to show that these tumors rapidly reprogram glucose metabolism to enhance the production of itaconate which is key in driving these tumors. My proposed research will unravel novel ZFTA-RELA-driven mechanisms by which itaconate promotes these aggressive ependymomas and will test if inhibition of itaconate production can be therapeutic. Thus, we expect the outcomes of my proposal to illuminate how ZFTA-RELA fusion-driven ependymomas depend on itaconate and more importantly, aid in the development of new and effective treatment strategies.

Petri Pölönen, PhD

petri.polonen@stjude.org

St. Jude Children's Research Hospital, Memphis, TN

2025 Young Investigator Grant

Uncovering Oncogenic Mechanisms in T-ALL Through Multi-Omics and Advanced Genomic Profiling

Background: Relapsed T-lineage acute lymphoblastic leukemia (T-ALL) is a challenging and life-threatening condition in children, with poor survival rates after relapse. To prevent these relapses, it's crucial to identify which patients are most at risk. In our recent study (soon to be published in Nature), we analyzed the DNA and RNA of 1,309 childhood T-ALL cases to uncover genetic changes that drive the disease and predict poor outcomes. Our study revealed that over 95% of the cases had key genetic drivers, with more than half occurring in non-coding regions of the genome — areas that don't directly code for proteins but still play vital roles in regulating gene activity. We identified 15 distinct subtypes of T-ALL, each with its own set of genetic features, developmental stage, and treatment outcomes. We also showed that these subtypes and genetic changes can predict how patients respond to treatment and their likelihood of survival. However, there are still unanswered questions: 1) around 10% of cases don't show clear genetic drivers or involve complex changes that are difficult to detect; 2) the link between the cell type where the cancer starts, its genetic changes, and how it's regulated remains unclear; 3) We lack accurate tools to predict outcomes based on genetic and epigenetic changes.

Project Goal: The goal of my research is to uncover the genetic and epigenetic factors that drive high-risk types of T-ALL. By understanding these mechanisms, I aim to develop precise tools to classify patients based on their risk and guide them toward more effective, personalized treatments. Over the next three years, I plan to 1) study the hidden, non-coding genetic changes that contribute to T-ALL; 2) investigate how changes in the chromatin landscape influence the disease at diagnosis and relapse; 3) build artificial intelligence (AI) models that can predict a patient's risk of relapse and survival based on these findings. By understanding the genetic and epigenetic landscape of T-ALL, this research will help classify patients more accurately, predict outcomes, and guide better treatment strategies, ultimately improving care for children with this disease.

Jenna Robinson, PhD

jenna_robinson@dfci.harvard.edu

Dana-Farber Cancer Institute, Boston, MA

2025 Young Investigator Grant

Investigation of SMARCAL1 as a Targetable Dependency in BRAF-Mutant Gliomas

Background: Brain cancers are now responsible for more childhood deaths than any other cancer. The most commonly diagnosed childhood brain cancers are known as gliomas. Pediatric gliomas frequently have mutations in the gene BRAF, which causes BRAF to transmit excessive growth signals, leading to uncontrolled cell division. Currently, some drugs are being used to treat pediatric gliomas which inhibit BRAF and switch off the growth signals. Patients generally respond well to these drugs and their tumors stop growing; however, as soon as the therapy is removed, up to 75% of patients' tumors return. Using these drugs for long periods can result in excessive toxicity, and so we need alternative methods to treat these tumors that have longer lasting effects. To discover new therapeutic avenues for the treatment of pediatric brain cancers, our group has created cell models of pediatric gliomas that contain the same BRAF mutations found in patient tumors. We then used gene editing methods to systematically inactivate every gene present in these glioma-like cells, with the goal of finding genes that when removed negatively impact the growth of cancer cells, whilst having limited effects on healthy cells. Our analysis of this screen revealed a hit protein called SMARCAL1 that, when inhibited, selectively stopped the growth of BRAF-mutant cancer cells. I believe that SMARCAL1 has a critical role in the growth of glioma cells and may be a novel therapeutic target.

Project Goal: The goal of my project is to understand why SMARCAL1 is important for the growth of BRAF-mutant cancer cells and to investigate if inhibition of SMARCAL1 may be used to treat pediatric brain cancers. SMARCAL1 has two main roles in the cell. Firstly, it helps cells to replicate DNA quickly without introducing errors; this is very important for fast growing cancer cells that need to replicate and divide their DNA often. I will use microscopy methods to visualize how DNA replication is different in BRAF-mutant cells compared to healthy cells and if SMARCAL1 is needed for fast DNA replication specifically in cancer cells. Secondly, SMARCAL1 helps to control which genes in a cell are switched on or off, including genes that help sustain cancer growth. I will therefore investigate how gene expression changes in cancer cells when SMARCAL1 is inhibited. Finally, there are currently no drugs available that target SMARCAL1; we thus need to design new drugs that can switch off this protein and hopefully stop cancer cells from growing. Towards this aim, I will perform a screen where I mutate different regions of the SMARCAL1 protein to find which mutations most reduce cancer cell growth. This will reveal the "Achilles' heel" of SMARCAL1 which will allow us to rationally design drugs that target the most vulnerable regions. Together, this work will examine the feasibility of targeting SMARCAL1 to stop cancer growth and may give new hope to children suffering with devastating brain tumors.

Sauradeep Sinha, PhD

sauradeep.sinha@stjude.org

St. Jude Children's Research Hospital, Memphis, TN

2025 Young Investigator Grant

A Biophysical Approach to Improve CAR T Cell Efficacy Against Diffuse Midline Gliomas

Background: Diffuse midline glioma (DMG) is an incurable pediatric brain tumor with extremely limited treatment options. The Krenciute Lab at St. Jude is working to develop new types of treatments known as immunotherapy for children with DMGs, in which the patient's own immune system is harnessed to fight the cancer. Specifically, we are interested in developing chimeric antigen receptor (CAR) T cells, a form of immunotherapy where a patient's T cells are re-engineered to better target and attack the cancer cell. Recently, CAR T cell therapies have provided encouraging clinical results against DMGs – motivating us to continue improving CAR T cell strategies. This project will take a unique approach towards achieving this goal. In a DMG tumor, CAR T cells are tasked with a physically taxing job. CAR T cells must get to the tumor site, infiltrate the tumor environment, and engage with the DMG cells. In each step of this process, CAR T cells experience significant physical resistance. In response, CAR T cells must attempt to overcome these physical obstacles and attack the DMG cell; however, they ultimately fail to survive long enough to clear the tumor. Within the field, it remains unknown how these physical obstacles within the tumor cause CAR T cells to fail. This project will seek to address this question and develop new approaches that can help CAR T cells to better function within the physically demanding tumor environment.

Project Goal: The overarching goal of this project is to improve CAR T cell efficacy against diffuse midline gliomas (DMGs) by understanding how CAR T cells are negatively impacted by the physical obstacles they face in the tumor. The first goal is to study how DMG cells physically avoid CAR T cells at the cellular level. CAR T cells need to strongly bind to the target cancer cell to effectively kill it. However, in the presence of CAR T cells, my preliminary data suggests that DMGs form bubble-like bulges along the cell surface called blebs to physically prevent CAR T cells from binding, thereby, avoiding CAR T cell killing. By disrupting DMG cells from blebbing, I hypothesize that CAR T cells will be able to better engage and kill the DMG cells. The second goal is to study how CAR T cells respond when challenged by a mechanical property presented by the entirety of the DMG tumor (the bulk tissue level). This property is known as viscoelasticity, and given my preliminary data, I hypothesize that DMG viscoelasticity is a source of mechanical resistance that impairs CAR T cell function. Completion of both goals will inform the development of new strategies capable of overcoming the physical obstacles CAR T cells face in the DMG tumor at two different levels – the cellular and bulk tumor level. Broadly, findings from this proposal would highlight the importance of considering how to overcome physical obstacles for the design of next-generation immunotherapies.

Daniel Solvie, PhD

daniel_solvie@dfci.harvard.edu

Dana-Farber Cancer Institute, Boston, MA

2025 Young Investigator Grant

Epigenetic Regulation of MYC in Pediatric Cancer: Investigating the Role of Ancestral Repetitive Elements and Nuclear Positioning

Background: Cancer is the leading cause of disease-related death among American children. Despite significant progress in recent decades, which has provided the possibility of a cure for many diagnosed children, we have not succeeded in improving the prognosis for certain cancer subtypes that have seen no advancement in the last 50 years. A key player in many of these aggressive subtypes is a gene called MYC. When MYC becomes overactive, it can cause cells to grow and divide uncontrollably, as well as evade the body's natural anti-cancer mechanisms. Targeting and taming MYC activity has proven challenging, making it one of the holy grails of cancer therapy development. Intriguingly, in some childhood cancers, one copy of the MYC gene is turned off, while the other copy becomes overactive. We don't fully understand why this happens or how it works, but the prospect of identifying a natural mechanism to turn off MYC in cancer cells is very exciting to us.

Project Goal: Our goal is to investigate a so far undescribed, natural mechanism that turns off the MYC gene in several childhood cancers. We believe this mechanism works by physically moving the MYC gene to specific areas within the cell that prevent its activation. Intriguingly, parts of our DNA that do not contain genes and were until recently considered "junk" may serve as literal anchors, guiding MYC to these inactive regions. Using cutting-edge microscopy and sequencing techniques, we aim to unravel this novel mechanism and identify the crucial DNA elements and proteins that control MYC's movement in cancer cells. We believe that these insights will advance our understanding of how cancer-driving genes are not only activated but also inactivated. At the same time, these insights could potentially allow us to hijack this mechanism, artificially repositioning MYC in cancer cells to switch it off. This approach may lead to more effective and less toxic treatments for aggressive childhood cancers, ultimately improving the lives of young patients and their families.

Xirui Song, PhD

xirui.song@stjude.org

St. Jude Children's Research Hospital, Memphis, TN

2025 Young Investigator Grant

Chimeric Cytokine Receptors to Improve CAR T Cell Therapy for Osteosarcoma

Background: The clinical outcome for many patients with solid tumors including bone tumors, called osteosarcoma, remains poor. This is particularly true for patients in whom the cancer has recurred or spread to the lungs. Immunotherapy has the potential to improve outcomes for these patients. We are interested in a form of immunotherapy called chimeric antigen receptor (CAR) T cell therapy, which takes the patient's own immune cells, modifies them in the laboratory to recognize and kill cancer cells, and puts them back into the patients. CAR T cell therapies have been very successful in curing blood cancers, but they have not worked as well for solid tumors. One of the primary challenges is the inability for CAR T cells to persist long enough inside the tumor mass to destroy the cancer completely. Thus, investigators are interested in expressing genes in CAR T cells to increase their killing function within the tumor and make them more effective against solid tumors. Many groups, including us, focus on a specific class of genes that encode cytokine signals, which play essential roles in regulating T cell function and survival. However, T cells can be impacted by many different cytokine signals, and it is not yet understood which signals will have the most profound impact on CAR T cell therapy because they have not been directly compared.

Project Goal: The overarching goal of this project is to improve CAR T cell function against osteosarcoma (OS). This goal will be accomplished by expressing genes responsible for conducting cytokine signals in T cells. I will focus on the two most promising candidate genes, where each of them activates a different cytokine signaling pathway, and make a head-to-head comparison of their functions in murine CAR T cells. I will compare these genetically modified CAR T cells both outside and inside of our animal models using a range of assays. This project focuses on evaluating CAR T cells in mouse models that closely mimic human OS. I will use murine OS cancer cell lines derived from a genetically identical mouse and graft cells into mice with fully intact natural immune systems, which provide better predictions of how CAR T cells behave in humans. This approach is novel as it is standard in the field to test human CAR T cells in mouse models where mice lack full immune systems to enable the establishment of human-derived tumor cells. Our approach not only allows me to evaluate the efficacy of these modified CAR T cells but also offers unique opportunities to gain insights into safety and how they interact with other immune cell populations present within the tumors. If successful, we are planning to develop a clinical study to evaluate our approach in children, adolescents, and young adults with osteosarcoma in the future.

Helena Yu, MD

hyu@rchsd.org

University of California, San Diego, La Jolla, CA

2025 Young Investigator Grant

Establishing Biomarkers of Stem Cell Fitness to Improve HSC Transplants for Pediatric Cancer Patients

Background: Hematopoietic stem cell (HSC) transplant is an essential component of cancer therapy for pediatric patients with aggressive leukemias that have relapsed or are at high risk of relapse. Donor HSCs regenerate blood and immune cells in the patient, and if the function of these donor cells is impaired, the recovery process after HSC transplant is delayed. The number of HSCs received from the donor is traditionally used to predict the success of the HSC transplant, but cell dose is not always the best predictor of transplant success. HSCs require careful regulation of their protein health and disrupting this balance leads to an accumulation of improperly made or misfolded proteins, as well as impairment of HSC fitness and function. Through the proposed project, I aim to determine the biological factors that promote optimal function of HSCs during transplant and will investigate the use of proteostasis as a biomarker for identifying grafts with poor quality HSCs. By identifying HSCs with disrupted proteostasis, we can select and transplant more fit HSCs to significantly improve the recovery process and quality of life for children with leukemias who require HSC transplant.

Project Goal: Through the proposed project, I aim to determine the biological factors that promote optimal function of HSCs during stem cell transplant. I will investigate the use of stem cell protein health as a biomarker for identifying donor stem cells with poor quality HSCs. By identifying HSCs with poor protein health, we could select and transplant more fit HSCs to significantly improve the recovery process and quality of life for children with leukemias who require HSC transplant as part of their treatment.

Daniel Zheng, MD

zhengd1@chop.edu

Children's Hospital of Philadelphia, Philadelphia, PA

2025 Young Investigator Grant

Characterizing the Role of Measurable Residual Disease (MRD) in Pediatric Acute Myeloid Leukemia (AML) Survival Disparities

Background: Acute myeloid leukemia (AML) is a rare but very serious type of blood cancer in children. While treatments for childhood cancer have improved, 20-40% of children of AML still do not survive. Black and Hispanic children are less likely to survive than White children, which may be due to differences in access to care, delays in getting diagnosed, or other barriers that disproportionately affect families from minority communities. Black and Hispanic children are also less likely to be enrolled on clinical trials, but children on clinical trials do better. We don't know why. Doctors use a blood test called measurable residual disease (MRD) to see how well a child is responding to their first round of chemotherapy. MRD looks for tiny amounts of cancer cells left in the body after treatment, and children who don't have any detectable cancer cells are more likely to survive. We don't know if MRD is different across racial and ethnic groups or if it explains why children in clinical trials tend to have better survival rates than those who aren't in trials. One of the things we think may influence MRD is how sick a child is when they are first diagnosed, which may reflect decreased access to health care and a delay in diagnosis. Our prior research showed that Black and Hispanic children are sicker compared to White children when they are first diagnosed and that sicker children seem less likely to enroll on clinical trials.

Project Goal: This project overall aims to better understand why some children with AML do worse than others so that we can improve outcomes for everyone. We will look at whether MRD plays a role in survival differences between racial and ethnic groups and between children who are and aren't enrolled in clinical trials. We'll also explore whether being very sick at diagnosis contributes to these differences. To do this, we're working with 15 different children's hospitals across the country to study a large group of children with AML (around 1,300). We will collect detailed information from their medical record about their AML, how sick they were at diagnosis, their MRD response after chemotherapy, and whether they survived. This research hopes to uncover ways to provide earlier and better care, reduce survival gaps, and ensure that every child with AML has a better chance of beating cancer.

Han Zou, MD/PhD

hanzou@pitt.edu

University of Pittsburgh, Pittsburgh, PA

2025 Young Investigator Grant

Exploring the Functions of SMARCD3-Reeling Signaling in the Metastasis Phenotype and in the Subgroups Transition of Medulloblastoma

Background: Medulloblastoma (MB) arises in the cerebellum. Group 3, one of four MB subgroups (WNT, SHH, Group 3, and Group 4), is the most aggressive and malignant type in children. Group 3 is characterized by frequent metastasis at diagnosis and the worst prognosis. Although surgical resection, radiotherapy, and chemotherapy are effective at eliminating some forms, patients with Group 3 cannot be cured with conventional therapies. Plus, they face a paucity of molecularly targeted therapies. Preliminary studies reveal that SMARCD3/BAF60C (SMARCD3) is associated with poor patient outcomes, MB metastatic phenotype, and is required for cell migration and positioning in cerebellar development.

Project Goal: The central hypothesis of this application is that the SMARCD3 regulates pathways in cell migration and positioning during cerebellar development; however, this neurodevelopmental program is hijacked for MB metastatic dissemination. The central hypothesis will be tested by pursuing two specific aims: 1) investigate the role of SMARCD3 in cell migration and positioning during cerebellar development; and 2) define the mechanism linking SMARCD3-pathway to metastatic phenotype in MB. Under the first aim, a new mouse model will be generated to knock out SMARCD3 in specific cerebellar cells. The role of SMARCD3-pathway in cerebellar development will be investigated using this mouse model. For the second aim, spontaneous mouse MB models will be used to test SMARCD3-pathway-mediated tumor metastatic dissemination. Advanced techniques will be performed to determine how SMARCD3 pathway regulates the Reelin signaling pathway in development and tumor formation. The research proposed in this application is innovative because it focuses on understanding the role of SMARCD3 in both neurodevelopment and medulloblastoma, and the prospect of tumor cells hijacking neurodevelopmental signaling resulting in metastasis. Ultimately, such knowledge has the potential of offering new rationales for the development of innovative therapies for patients with MB.

Posters

Mark Applebaum, MD

mapplebaum@peds.bsd.uchicago.edu

University of Chicago, Chicago, IL

2021 'A' Award

Identification of Immune Landscape Alterations from Cell-Free DNA 5-Hydroxymethylcytosine Profiles from Patients with Newly Diagnosed High-Risk Neuroblastoma

Background: Less than half of children with high-risk neuroblastoma are cured. There is no way to predict response to this highly toxic treatment. Thus, there is a need for new ways to guide treatment choices. We are working to create a robust test using routine blood samples to follow disease and predict which patients will respond to standard treatment. Our team created a new method to find cancer DNA in blood samples. To bring this to the clinic, we are testing samples from patients enrolled on the largest high-risk neuroblastoma clinical trial in North America. To date, we have sequenced approximately 2,200 samples with more ongoing. Although response data from the associated clinical trial is not yet available for analysis, we are optimistic about the ability of our method to detect the amount of circulating neuroblastoma DNA throughout treatment based on our preliminary analysis. We have also developed new ways to track evidence of different kinds of neuroblastoma cells using the same blood samples. We are actively assessing how the amount of resistant neuroblastoma cells change with treatment. Additionally, we have been working to identify and validate immune cell signatures which may reflect the composition of circulating immune cells. We plan to assess if these immune profiles can provide insights for improving the efficacy of immunotherapy approaches. As data analysis continues, we expect this approach will allow more children to receive just the right amount of treatment.

Project Goal: We are evaluating DNA marks in the largest collection of plasma samples from high-risk neuroblastoma patients in North America. Because our methodology can be performed on small amounts of input DNA at low cost, our goal is to optimize the impact of liquid biopsy samples. We are working towards the goal of developing FDA approved biomarkers for predicting response at the time of diagnosis and detecting minimal amounts of otherwise difficult to detect disease and the molecular pathways that are driving poor outcomes and therapeutic response. If we are successful, this approach will provide "real-time" information regarding a patient's response to treatment and more importantly, identify those who are not responding and may benefit from alternative treatments. Thus, this research has the potential to change the treatment paradigm for high-risk neuroblastoma, leading to individualized therapy decisions and, hopefully, improved outcome. Additionally, we will be able to use the information obtained to perform additional experiments to identify novel drivers that we can target to help cure this deadly disease.

Shuhei Asada, MD/PhD

shuhei_asada@dfci.harvard.edu

Dana-Farber Cancer Institute, Boston, MA

2024 Young Investigator Grant

Exploiting a Novel DNA Repair Defect in Ewing Sarcoma

Background: Ewing sarcoma is a group of bone and soft tissue cancers that can occur in children, adolescents, and young adults. The high response rates to DNA-damaging chemotherapy suggest that there may be defects in DNA damage repair pathways that make Ewing sarcoma cells susceptible to chemotherapy-induced DNA damage. However, despite these high response rates, there is still an urgent need for new treatment options for Ewing sarcoma, particularly for patients with relapsed and/or refractory disease. The chromosomal translocation that occurs in Ewing sarcoma cells leads to the generation of the EWS-FLI1 oncoprotein in combination with the loss of an allele of intact EWSR1. However, the mechanism by which EWS-FLI1 expression or loss of EWSR1 affects DNA damage repair pathways is still largely unknown. We discovered that expression of EWS-FLI1 or loss of EWSR1 leads to a unique damage repair defect via aberrant RNA splicing. Due to this unique defect, Ewing sarcoma cells are hypersensitive to radiation and specific chemotherapy as well as targeting DNA repair pathways by the mechanism of synthetic lethality. By exploiting this defect, we have identified a potentially synergistic therapeutic strategy for Ewing sarcoma cells. Therefore, we hypothesize that exploiting this intrinsic DNA damage repair defect of Ewing sarcoma cells will allow us to develop therapeutic advantages by targeting other DNA repair pathways concurrently with the standard treatment used in the clinic.

Project Goal: The goal of this project is to discover new treatment options with novel mechanisms of action for recurrent and/or refractory Ewing sarcoma. To achieve this goal, we have elucidated the precise mechanisms by which EWS-FLI1 expression or loss of EWSR1 causes this unique DNA damage repair defect using biological and biochemical approaches. Second, we have evaluated the consequences of this unique DNA damage repair defect in Ewing sarcoma patients by analyzing genomic data. Third, we have identified a subset of molecules that show a synergistic effect with this DNA damage repair defect in Ewing sarcoma cells. We will confirm the efficacy of our new combination strategy in vivo using a mouse model. If our preclinical studies show promising results, there is great potential for translation to the clinic in an investigator-initiated clinical trial.

Leidy Diana Caraballo Galva, PhD

leidy.caraballogalva@bcm.edu

Baylor College of Medicine, Houston, TX

2023 Young Investigator Grant

Synthetic Gene Expression Regulatory Switches for Improved CAR T Cell Function in Pediatric Solid Tumor

Background: In this project, we introduced mini programs into tumor-redirected white blood cells with the goal of overcoming solid tumors. To achieve this objective, we have designed “Synthetic Gene Expression Regulatory Switches” which will turned ON only when needed and help the white blood cells grow, last long and eliminate tumors. Importantly, we have designed a library containing these mini programs; we screened this library against tumor cell lines and selected the best candidates for further testing in mice. We tested this set of switches in tumor bearing mice, and some of the switches improved the survival and antitumor effect of the engineered immune cells. We are currently running more in vivo testing to select the best one for further development in the clinical setting to help children with solid tumors.

Project Goal: We would like to identify the best candidate for clinical testing. To do so, we plan to optimize the design of the switches after completing the in vivo experiments.

Joselyn Cruz Cruz, PhD

joselyn.cruzcruz@cuanschutz.edu

University of Colorado Denver, AMC and DC, Aurora, CO

2024 Young Investigator Grant

Improving Homing and Activity of CAR T Cells in Pediatric Sarcomas

Background: Pediatric sarcomas are a cancer that affects bones and soft tissues, and despite available treatments, the chances of curing patients remain very low. One promising therapy involves giving patients special immune cells called CAR-T cells. These are T cells that are reprogrammed in the lab to recognize and kill cancer cells. While CAR-T cells have shown efficacy in childhood leukemia, they don't work as well in solid tumors. This is partly because they have trouble reaching the tumor, and even when they get there, the tumor environment can weaken their activity. In this project, soluble factors secreted by sarcoma tumors are being used to guide CAR-T cells move towards them. Another challenge is that sarcomas are full of immune cells called tumor-associated macrophages (TAMs), which help the tumor grow and prevent immunotherapies like CAR-T cells from working. We believe TAMs do this by using a process called efferocytosis. Normally, efferocytosis helps the body clean up dead cells and avoid unwanted immune reactions. But in cancer, tumors may hijack this process to hide from the immune system. In earlier work, I found that blocking efferocytosis helped the immune system fight leukemia more effectively. Now, I am testing whether blocking efferocytosis can also boost CAR-T cell therapy in pediatric sarcomas. This research could lead to better treatments for children with sarcoma by improving how CAR-T cells work and overcoming the tumor's ability to fight back.

Project Goal: This project aims to improve B7H3-CAR T cell therapy for pediatric sarcomas. We've found that adding the IL-8 receptor CXCR2 to B7H3-CAR T cells (known as BC2-CAR T cells) help them better reach IL-8-producing sarcomas in mice. However, not all tumors in mice were cleared after BC2-CAR T cells treatment. We recently discovered that a molecule called TNFa boosts IL-8 levels in sarcoma cells. To take advantage of this, we plan to engineer BC2-CAR T cells to increase TNFa production, increasing IL-8 in the tumor environment and improving CAR-T cell migration to tumors. In addition, we want to reduce the immune-suppressive environment around sarcomas by blocking a protein called MerTK using a drug called MRX-2843. In earlier work, this drug increased CD8+ T cells in the tumor and bone marrow of mice with sarcomas, but we don't know if these T cells are able to recognize cancer cells. We will collect these T cells and test their ability to kill sarcoma cells. Finally, we are looking at combining this MerTK-blocking drug with CAR-T cell therapy. We will test both regular (oral) dosing and targeted delivery of MerTK inhibitor using tiny carriers attached to CAR-T cells. Since MerTK is also active in T cells, we will evaluate CAR-T cell activity after removing MerTK. The goal is to make CAR-T cell therapy stronger and more effective for children with sarcoma.

Catherine Danis, PhD

catherine.danis@cuanschutz.edu

University of Colorado Denver, AMC and DC, Aurora, CO

2023 Young Investigator Grant

A Novel Adjunctive LAT-Activating CAR T (ALA-CART) Cell Platform for the Treatment of Acute Leukemias

Background: Despite decades of progress, multiply-relapsed acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) remain leading causes of childhood cancer deaths. Chimeric Antigen Receptor T cell (CART) therapy has demonstrated remarkable upfront success in children with relapsed ALL, however, CART relapses in ALL patients and the inability to replicate CART success in AML has limited the long term impacts of this therapy. Through the development of a novel CART platform, utilizing an Adjunctive LATActivating CAR (ALA-CART), we have overcome multiple obstacles that limit the efficacy of current CART therapy. We have found that ALA-CART cells last longer in mice, allowing for continued clearance of leukemia. Interestingly, we have found that a particular subtype of cells drives this phenomenon and demonstrate enhanced functionality against leukemias.

Project Goal: Chimeric Antigen Receptor T cell (CART) therapy has demonstrated remarkable upfront success in patients with relapsed B-cell ALL, however, a majority of patients fail to sustain a durable response. To improve CART therapy for this patient population, we have developed a novel CART platform, the Adjunctive LAT-Activating CAR T cell (ALA-CART). These ALA-CART cells have overcome multiple obstacles that limit the effectiveness of current CART therapy. The goal of this project is to further understand why ALACART cells continue to persist to optimize ALA-CART therapy for pediatric leukemias with the hope of translating these strategies to children with relapsed leukemias that no longer respond to conventional therapies.

Ian Delahunty, PhD

ian.delahunty@stjude.org

St. Jude Children's Research Hospital, Memphis, TN

2024 Young Investigator Grant

Capitalizing on Functional Genomics with Targeted Protein Degradation in Neuroblastoma

Background: Children with neuroblastoma (NB) have poor overall survival. Further, the treatments used to manage NB have enormous toxicities, including heart damage, hearing loss, infertility, and a risk of developing new cancers. Despite significant enquiry, children with relapsed NB have limited treatment options. We found a high-confidence compound with potent activity in NB called IDAD1. We initially chose to study IDAD1 because it was very effective in cells with a type of NB that has extra copies of the MYCN gene, but not in those driven by a very similar c-MYC gene. Over the last year, I have found some early evidence that IDAD1 is targeting a protein called GSPT1. GSPT1 is important in many cancer cells, although it's more active and very important in MYCN-amplified cancers. This suggests that compounds targeting GSPT1 may be preferentially effective in MYCN-amplified NB. In addition, I found several other compounds that do not seem to target GSPT1. What their target is in MYCN-amplified NB is unknown. Simultaneously, I am working to understand if targeting GSPT1, or these other potential proteins, will be effective in animal models of NB. To do so, I have developed several other experiments that will be used, including: 1) improving methods to measure the effects of these compounds on NB in animals, 2) selecting the best models to test in animals, and 3) conducting tests to determine whether these compounds can be used in animal models.

Project Goal: I will test the remaining 7 IDADs that do not target GSPT1/2, along with IDAD1 and CC-90009 (GSPT1 degraders) in both Kelly and MHHNB11 (MYCN-amplified NB cells), as well as normal human fibroblasts and 293T cells. This will allow me to determine which compounds display the largest potential therapeutic window. Then, I will perform additional experiments to determine the molecular target of these compounds. I will validate their targets using MG-induced mutational assays in CRISPR-engineered cells, using tools I have developed, including cas9-expressing cells, as well as hypermutable NB cells I have engineered to contain MSH2 knockout. Then, I will determine the effects of IDAD1 and the top nominated non-GSPT1-degrader IDAD2 on the NB malignant phenotype. Finally, I will validate these findings using CRISPR-cas9 deletion of the IDAD target and overexpression-based rescue to blunt IDAD effects. These experiments will establish the targets and dissect the mechanism of action of IDAD1 and 2. Additionally, the in vivo effects of IDAD1 and IDAD2 are unknown. I will first determine the in vivo pharmacokinetic properties and toxicities of IDAD1 and IDAD2 in mice. Next, I will test the effects of these IDADs in three human NB MYCN-amplified patient-derived xenografts, using either inactive stereoisomers or a vehicle alone as controls. Tumors will be profiled for effects on the malignant phenotype by immunohistochemistry (IHC), and target loss confirmed by IHC.

Caroline Diorio, MD

diorioc@chop.edu

Children's Hospital of Philadelphia, Philadelphia, PA

2023 'A' Award

The Role of the Innate Immune System in Immune Dysregulation following CART

Background: The job of the immune system is to fight infection. In healthy people the immune system also prevents cancer. Recently, new cancer treatments using the immune system have been made. These new treatments are called chimeric antigen receptor T-cells (CART). With CART, blood immune cells are collected from a patient. They are reprogrammed in a laboratory to fight cancer. The reprogrammed cells are given back to the patient. CART can cure some cancers. CART is particularly good at curing a type of cancer called B-cell acute lymphoblastic leukemia (B-ALL) in kids. CART work very well but they have side effects. Sometimes they make the immune system overactive. This is called cytokine release syndrome (CRS). CRS can make people very sick. CART can also cause side effects in the brain like seizures and coma. This is called immune effector cell associated neurotoxicity syndrome (ICANS). We do not understand why some people get CRS and ICANS. Understanding CRS and ICANS is important so we can prevent and treat them. Treating CRS and ICANS is essential to making sure CART can be used safely and cure more patients. In the past year, we have looked at individual immune cells between patients who did and did not get CRS. We also look at the RNA that each of these individual cells make. We do this to understand what parts of the cell are "turned on", so we can understand exactly what they're doing to cause CRS. We have also looked at all the patients treated at our hospital who got ICANS.

Project Goal: The first goal of this project is to understand what cells in the immune system contribute to severe side effects caused by life-saving treatments for cancer called CART. The most common side effect is called cytokine release syndrome (CRS). We think that there are cells present in the immune system before patients get treated with CART that make them more likely to have severe CRS. When we have identified what cells are different, we will also look at the genes that are turned on inside those cells. When we know what genes the cells are using to cause CRS, we can identify treatments to stop them. We have identified a specific protein, called MILR1, that is much higher in the blood of patients who develop severe CRS than in patients who don't. We recently discovered that MILR1 is produced by leukemia cells. We have found that leukemia cells in patients with lots of leukemia (high disease burden) make more MILR1 than the leukemia cells in patients with low levels of leukemia (low disease burden). This is important because we know that patients with high disease burden are more likely to get severe CRS. From experiments in the lab, we have shown that MILR1 causes CART cells to make more cytokines when they kill leukemia cells. Another goal is to understand how MILR1 may be helping to cause CRS.

Madelyn Espinosa-Cotton, PhD

espinom1@mskcc.org

Memorial Sloan Kettering Cancer Center, New York, NY

2023 Young Investigator Grant

Pre-Targeted Radioimmunotherapy for Desmoplastic Small Round Cell Tumors

Background: We are using a new type of engineered antibody to deliver potent liquid radiation to desmoplastic small round cell tumors without harming normal tissues and organs. This system is a type of pretargeted radioimmunotherapy that could be used to treat tumors at all stages, even those that have metastasized to different parts of the body.

Project Goal: The goal of this project is to show that one or more of our tumor-targeting antibodies can safely and effectively deliver curative doses of liquid radiation to desmoplastic small round cell tumors in animal models. If we are successful, we plan to move the most promising candidate antibody into clinical trials.

Andrea Franson, MD

atflynn@med.umich.edu

University of Michigan, Ann Arbor, MI

2024 'A' Award

Gene-Mediated Cytotoxic Immunotherapy in Pediatric Patients with Recurrent Malignant Brain Tumors

Background: After recurrence, children with relapsed malignant brain tumors have a low likelihood of long-term survival. Immunotherapy has proved to be a promising approach, with the manipulation of the patient's immune system to recognize tumor cells as foreign and elicit an anti-tumor response. Gene-mediated cytotoxic immunotherapy represents a novel therapeutic approach, using an adenoviral vector encoding the herpes virus 1 thymidine kinase (HSV1-TK) to induce local tumor cell death and neoantigen release when exposed to an antiviral prodrug (valacyclovir) and a second adenoviral vector encoding Flt3L, which stimulates dendritic cell recruitment. The safety of this dual vector approach was demonstrated in 18 adult patients with glioblastoma multiforme (GBM) in a phase 1 trial, and the AdV-HSV1-TK vector was found to persist up to 17 months at the tumor site when patients underwent re-resection. Here, we propose a first-in-pediatrics phase 1 clinical trial of this dual vector gene/immunotherapy injected into the tumor bed at the time of surgical intervention in children with relapsed brain tumors to determine the safety of this approach and conduct biological correlate studies to determine the effects of therapy. The trial is planned to enroll 11 patients, with the final steps of IRB approval underway.

Project Goal: Pediatric brain tumors are the leading cause of cancer-related death in children. Children and adolescents with relapsed or refractory brain tumors have a low likelihood of long-term survival. Modifying or stimulating a patient's immune system has been found to be a strategy to treat certain cancers, with some of these treatments even leading to cures. Unfortunately, the use of immunotherapy for many cancers, including aggressive brain tumors, has proven difficult. One barrier is that most brain tumors have an immune environment that prevents their recognition as "foreign" by the patient's immune system. Here, we propose a two-vector viral-based immunotherapy strategy into a first-in-pediatrics phase 1 clinical trial. The two viral vectors used here encode a cell-killing component (thymidine kinase) and an immune stimulatory component (Flt3L). When these are injected into the area where the tumor was removed during surgery, followed by the taking of the antiviral medication (valacyclovir), cells with the thymidine kinase vector die and cells express Flt3L, stimulating immune cells (dendritic cells). This therapy was tested in a safety (phase 1) study in adults with high-grade glioma and was found to be safe and well-tolerated. Our first goal is to conduct a phase 1 clinical trial for pediatric patients, which is nearly opening at our center. Our second goal is to do immune profiling on the patients' blood and spinal fluid before and after therapy.

Rachel Hurley, MD/PhD

hurleyr@chop.edu

Children's Hospital of Philadelphia, Philadelphia, PA

Centers of Excellence Scholar

Integrating Precision Medicine and Tumor Immunology to Improve Therapeutic Approaches for Sarcoma

Background: My project seeks to identify new therapies for children with non-rhabdomyosarcoma soft tissue sarcomas (NRSTS). I am interested in identifying drugs that change the immune cells in tumors, which I hypothesize will decrease tumor growth and improve sensitivities to current therapies. In brief, I aim to identify small molecules that force monocytes to differentiate to anti-tumor dendritic cells rather than pro-tumor macrophages. I have designed and completed an experiment that screens multiple drugs to see if they force immune cells to become dendritic cells. I have identified a set of the most impressive drugs that support dendritic cell differentiation. I have looked at their impact on human immune cells to confirm that these drugs work similarly on mouse and human immune cells. This allowed me to select a panel of 'top hits' to study in more depth. I will now look at the genes that are changed when I treat immune cells with the drugs. Additionally, I will screen for impact on viability with sarcoma cell lines. Looking forward, I will use sarcoma cells and mouse models to see how these drugs impact the different immune cells in the tumor microenvironment. This will allow me to evaluate a new approach for treating pediatric NRSTS.

Project Goal: Pediatric non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) are a group of tumors that develop in the soft tissues. For children with NRSTS that have disease in multiple locations or disease that comes back after initial treatment, outcomes are very poor. While adults with solid tumors have seen significant improvement in treatment options through the discovery of immunotherapies (a treatment that uses the body's immune system to fight cancer), unfortunately most NRSTS tumors have largely not been responsive to immunotherapy. My overall goal is to change this paradigm. I am working to make NRSTS more sensitive to immunotherapies and extend response times by treating NRSTS with drugs that alter the immune cells. Specifically in this project, my goal is to use a large drug screen to identify two or three drugs that increase the production of anti-tumor dendritic cells in pediatric NRSTS.

Christian Hurtz, PhD

churtz@llu.edu

Loma Linda University, Loma Linda, CA

2022 'A' Award

Targeting Kinase Inhibitor Induced DNA-Damage Response in Ph-Like ALL

Background: We've seen major gains in treating B-cell acute lymphoblastic leukemia (ALL) over the last four decades. Adding ABL-kinase inhibitors to chemotherapy improved remission durability and survival, especially in Philadelphia chromosome–positive (Ph+) ALL. Philadelphia chromosome–like (Ph-like) ALL is another high-risk subtype that looks similar by gene expression but is driven by different mutations. In CRLF2-rearranged Ph-like ALL, signaling through JAK2/STAT5, PI3Kd, and BCR-like pathways is switched on. Targeted drugs such as ruxolitinib, idelalisib, and dasatinib shrink disease in models, but using all three together is unlikely to be tolerated by patients. We therefore turned to chromatin biology and found that Ph-like ALL cells rely on the SWI/SNF ATPase SMARCA4 (BRG1) – a weak spot we can target. Blocking this pathway with FHD-286 works especially well with dexamethasone or vincristine in cell lines, but not with doxorubicin. Why not? Mass-spec metabolomics shows the cells boost reduced glutathione (GSH) after SMARCA4 blockade, an antioxidant that soaks up the reactive oxygen doxorubicin needs, blunting its effect. Taken together, these findings point to SMARCA4-directed therapy paired with dexamethasone and vincristine as our best next step. We will confirm the benefit in mouse models and dissect GSH-linked resistance to design safe, effective combination treatments for patients with Ph-like ALL.

Project Goal: We're tackling a hard-to-treat leukemia called Philadelphia chromosome–like (Ph-like) ALL by aiming at a weak spot: a DNA remodeling protein, SMARCA4 (BRG1). A blocker of this pathway, FHD-286, works especially well with dexamethasone or vincristine in our lab tests, but not with doxorubicin. One likely reason: the cancer cells raise their reduced glutathione (GSH) levels, an antioxidant that soaks up the reactive oxygen species doxorubicin needs to function. Next, we'll move to mouse models built from cell lines and patient samples. We'll test FHD-286 by itself and in combinations: FHD-286+dexamethasone, FHD-286+vincristine, FHD-286+venetoclax (to push cells from growth arrest into death), and FHD-286+doxorubicin plus drugs that lower GSH (for example, BSO) to overcome resistance. To confirm the biology, we'll use gene editing to switch off key glutathione-pathway genes and track simple readouts of drug effects. Not all ALL behave the same. In KMT2A-rearranged (KMT2A-R) ALL, blocking SMARCA4 has little effect; however, our early data show strong killing when we add a menin inhibitor, so we will explore that route in parallel. Deliverables: a short list of practical, well-tolerated combinations ready to move toward early clinical testing, plus easy-to-use biomarkers such as the GSH:GSSG balance to help choose the right patients and schedules.

Courtney Jones, PhD

courtney.jones@cchmc.org

Cincinnati Children's Hospital Medical Center, Cincinnati, OH

2024 'A' Award

Targeting Protein Synthesis in Pediatric Acute Myeloid Leukemia

Background: Our long-term objective is to improve the outcomes for pediatric acute myeloid leukemia (AML) patients by developing strategies to target leukemia stem cells (LSCs) more effectively. Pediatric acute myeloid leukemia is a devasting disease that effects approximately 500 children each year in the United States. The majority of children diagnosed with AML will respond to current therapies, however, 30% of these patients will experience relapse and often succumb to their relapsed disease. A subset of cells called LSCs evade treatment and are the cells responsible for driving disease relapse in a majority of patients. Therefore, there is an urgent need to develop novel therapies to eradicate LSCs in pediatric AML patients. Cellular metabolism represents a key vulnerability of LSCs that can be targeted pharmacologically. Our data shows that pharmacologic perturbing polyamine metabolism can effectively target pediatric AML LSCs. Mechanistically, our data suggests that this occurs through the regulation of the translational elongation factor eIF5A resulting in a reduced level of translation of mRNAs essential for cell cycle regulation.

Project Goal: Our main goal is to improve the health of children with a type of blood cancer called acute myeloid leukemia (AML). We want to do this by finding ways to specifically target the cells that cause AML, known as leukemia stem cells (LSCs). Our initial findings suggest that certain molecules called polyamines play a crucial role in keeping these leukemia stem cells alive in children with AML. Luckily, there are already drugs available that can target polyamines. Importantly, these drugs are already being tested in other types of cancer. We are studying the role of polyamines in samples from pediatric AML patients and working to figure out why leukemia stem cells in children with AML depend on them to survive. Understanding this will help us identify which children with AML could benefit from drugs that target polyamines and if successful could lay the groundwork for a future clinical trial.

Miriam Kim, MD

miriamykim@wustl.edu

Washington University School of Medicine in St. Louis, St Louis, MO

2019 Young Investigator Grant

Investigating How Host Inflammation Impacts Outcomes of CAR T Cell Therapy

Background: T cells can be engineered to target tumor cells by means of a chimeric antigen receptor (CAR), but enforcing T cell recognition of tumor in this manner still has limitations. The normal immune response is dictated not only by T cell stimulation by foreign antigens, but also by inflammatory signals that broadly activate the immune system. While a CAR is designed to provide both T cell receptor and costimulatory signaling, this does not fully capture the multitude of signals that a T cell would be exposed to under physiologic conditions. Notably, CAR T cells can be potent inflammatory stimulators, as evident by the clinical phenomenon termed cytokine release syndrome (CRS). CRS is characterized by acute elevation of inflammatory cytokines after CAR T cell therapy that leads to severe illness in patients. Host myeloid cells have been discovered to be key mediators of CRS, providing direct evidence of crosstalk between CAR T cells and host immune cells, but how this impacts anti-tumor effect is not known. We find that monocytes activated by IFNg produce cytokines and costimulatory receptors that augment CAR T cell proliferation and function. Additionally, tumor-bearing mice genetically deficient for MyD88, a key mediator of inflammatory signaling, have a suboptimal response to CAR T cell therapy. Furthermore, adding LPS or other inflammatory stimuli to CAR T cells in vivo improved both CAR T cell expansion and long-term tumor-free survival.

Project Goal: Our goal is to understand how the host immune environment impacts CAR T cell therapy. While CAR T cells are traditionally studied in the lab outside of the context of the host immune system, in human patients CAR T cells encounter endogenous immune cells that will impact their function. How CAR T cells interact with host immune cells has not been studied in depth and represents a major gap in our knowledge of how they function. The objective of this project is to ascertain how the host inflammatory response triggered by CAR T cells impacts tumor control. We hypothesize that CAR T cell induced host inflammation both directly and indirectly enhances CAR T cell anti-tumor effects. First, IFNg-activated host myeloid cells can directly enhance CAR T cell proliferation and cytotoxicity. Second, IL-1b and/or IL-18 production by host immune cells can mobilize endogenous immune cells against tumor. Finally, we anticipate that intensifying host inflammatory activation can improve outcomes of CAR T cell therapy.

Lingzhi Li, PhD

lingzhi.li@bcm.edu

Baylor College of Medicine, Houston, TX

2024 Young Investigator Grant

MYCN-Induced Molecular Clock Disruption and Metabolic Rewiring Drive Neuroblastoma

Background: MYCN amplification (MNA) is the primary oncogenic driver for neuroblastoma (NB) occurrence, progression, and relapse. As a transcription factor, MYCN is deemed "undruggable," despite advances in treatment. Our lab previously found that MYCN rewires lipid metabolism and disrupts the circadian clock machinery, thereby promoting tumorigenesis. We also found that targeting fatty acid biosynthesis and restoring the core component of the circadian clock, BMAL1, effectively suppresses MYCN-driven lipogenesis and oncogenesis. Collectively, we hypothesize that MYCN reprograms lipid metabolism and induces oncogenesis by repressing BMAL1 signaling. Therefore, targeting MYCN-induced lipogenesis and restoring BMAL1 activity hold promising therapeutic potential. To achieve our ultimate goal of developing innovative treatments for high-risk MNA NB patients, we propose harnessing the circadian regulator BMAL1 to enhance the anti-tumor effects of lipogenic inhibitors. We will identify the specific lipid species regulated by BMAL1, and employ pre-clinical neuroblastoma genetically-engineered mouse (GEM) and patient-derived xenograft (PDX) models to evaluate the BMAL1-dependent lipogenic vulnerabilities.

Project Goal: Our long-term goal is to identify novel and potent therapeutic strategies to block MYCN-driven oncogenesis. We recently found that the ectopic restoration of BMAL1, a core component of the molecular clock, effectively blocks de novo lipid synthesis and storage in MYCN-amplified (MNA) neuroblastoma (NB) cells, and further dramatically suppresses MYCN-driven tumorigenesis both in vitro and in vivo. These findings support our guiding hypothesis that MYCN induces lipid reprogramming and oncogenesis through repressing BMAL1 signaling. Collectively, our project goal is to leverage this circadian regulation for optimizing current lipogenic interventions for high-risk MNA NB patients.

Adrienne Long, MD/PhD

adlong@stanford.edu

Stanford University, Stanford, CA

2024 Young Investigator Grant

Defining How Unique Properties of the Pediatric Immune System Contribute to Poor Efficacy of Checkpoint Blockade in Children

Background: Novel therapies are desperately needed for pediatric solid tumors, where over 30% of patients die from their disease. Immunotherapies offer significant potential to meet this need, but this potential has not yet been realized in children. Immune checkpoint inhibitors (ICIs), a type of immunotherapy, have shown success in many adult cancers but rarely work for children. This is partly because pediatric tumors have fewer mutations than adult tumors. To the immune system, fewer mutations mean pediatric tumors appear more similar to healthy tissue, making it harder for the immune system to attack cancer while sparing healthy cells. In addition to tumor differences, children's immune systems differ from adults, often skewing toward tolerance and reduced activity, which helps prevent autoimmunity but may limit the effectiveness of cancer immunotherapies. How this immune immaturity contributes to poor responses to ICIs remains unknown. To address this, we will use a new cancer organoid model to study how children's immune cells respond differently to cancer and ICI therapy, compared to adults. We will examine how age impacts immune responses to ICIs, how the type of cancer target affects these responses, and uncover molecular reasons why children's immune cells may not respond well to ICIs. Ultimately, this research will define how the immune system recognizes and regulates responses to pediatric cancers to inform development of safer, more effective immunotherapies for children.

Project Goal: The goal of this project is to understand how the unique aspects of pediatric cancers and pediatric immune systems contribute to the poor responses seen with Immune checkpoint inhibitors (ICIs), immunotherapies that have otherwise shown impressive results in adult cancers.

Kyle MacQuarrie, MD/PhD

kmacquarrie@luriechildrens.org

Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL

2023 'A' Award

Genomic and Nuclear Organizational Changes in Chemotherapy-Resistant Rhabdomyosarcoma Cells

Background: Rhabdomyosarcoma (RMS) is a pediatric tumor of skeletal muscle that has used essentially the same treatment for decades. Despite our attempts to improve treatment, patients with disease recurrence – or with widespread disease at diagnosis - still have poor survival. One of the ways that we can improve treatment is to better understand how tumor cells become resistant to chemotherapy drugs. Many studies on chemotherapy resistance in RMS have focused on identifying individual genes that cause resistance, and have compared cells that are very resistant to chemotherapy to those that are not resistant at all. However, there is also reason to believe that tumor cells are affected not just by individual genes, but by the way the parts of the cell nucleus – the control center of the cell – are organized. This suggests that we can gain new understanding of chemotherapy resistance if we understand the changes that occur in that organization. Our results to date demonstrate that when we expose the RMS cells to even very small amounts of chemotherapy, the cells start to change certain aspects of the organization of their nucleus. We have also recently found that analyzing organization in the nucleus shows that certain types of organization associate very strongly with oncogenes - genes that have the potential to drive tumors. In addition, we are currently working on ways to change nuclear organization in RMS cells with the goal of improving the effect of chemotherapy.

Project Goal: This project seeks to understand chemotherapy resistance in rhabdomyosarcoma tumors in two ways: 1) by looking at the organization of their nucleus – the 'control center' of the cell - and 2) as a process that occurs over time. This project will search for differences in various aspects of organization of the nucleus, and connect differences to the ability of tumor cells to resist chemotherapy drugs. This aims to find one - or more - new approaches to making tumor cells more vulnerable to chemotherapy. The nuclear organization of multiple types of rhabdomyosarcoma cells that can be grown in dishes will be studied while they are exposed to slowly increasing amounts of chemotherapy drugs. Among the techniques that will be used to understand their organization is one called PWS (for Partial Wave Spectroscopic) microscopy. This technique utilizes a special microscope that was developed by Dr. MacQuarrie's scientific mentor, and has been used successfully to advance understanding of adult tumors including understanding of their resistance to chemotherapy - but had not previously been used in rhabdomyosarcoma. By using tools like PWS microscopy, and others that specifically look at organization and not just at individual genes, this project aims to both further our understanding of why chemotherapy resistance occurs, and identify a new way to help overcome or prevent it.

Sean Misek, PhD

smisek@broadinstitute.org

Broad Institute, Cambridge, MA

2023 Young Investigator Grant

Mechanisms of BRAF Activation in KIAA1549-BRAF Mutant pLGGs

Background: Most pediatric low-grade brain tumors harbor a specific change in their DNA that promotes tumor growth. This DNA change results in the fusion of two genes. The first gene (called BRAF) is already known to promote tumor growth. The second (KIAA1549) is poorly characterized. Drugs have been developed which block the activity of BRAF, but challenges remain when using these drugs to treat patients with pediatric low-grade gliomas. First, many patients are initially resistant to the drugs, which necessitates alternative treatment strategies. Second, many patients have severe dose-limiting toxicity, which requires cessation of treatment and subsequent tumor rebound in many patients. This highlights a clear need to develop new ways to treat these tumors. A limitation in developing new treatment strategies is that we don't understand how this DNA change activates the BRAF gene. Furthermore, we do not fully understand if there are other targetable genes in these tumors. Gaining a better understanding of these issues may lead to new insights into how to target this fusion gene in pediatric low-grade glioma patients.

Project Goal: There are two main goals behind this project. The first goal is that I want to understand how this DNA change in the BRAF gene activates BRAF. Our experimental observations, as well as observations from other research groups, highlights that our current model of h ow this gene is activated is incomplete. In these studies I will look at how changes in the structure of this gene fusion influences its activity. A second goal of this project is to find new ways to therapeutically target tumors that have this mutation. We have conducted a survey of all genes in the genome with the goal of identifying genes that are necessary for the survival of cells harboring this fusion. Among all genes, the two most essential are POMT1 and POMT2, both members of the heterodimeric POMT complex. In this proposal I will understand why these genes are required for the survival of KIAA1549::BRAF-driven models of pLGG. Furthermore, I will perform experiments to test the potential of POMT as a new drug target in KIAA1549::BRAF-driven pediatric low-grade gliomas.

Robin Parihar, MD/PhD

rxpariha@texaschildrens.org

Baylor College of Medicine, Houston, TX

2021 'A' Award

Turning Killers into THINKers: TME Hostility-Impervious NK Cells for Treating Neuroblastoma and Sarcoma

Background: Children with advanced neuroblastoma or soft-tissue sarcomas continue to die from their disease. New treatments are sorely needed. Treatments that activate the immune system to fight cancer, such as with immune cells called natural killer (NK) cells, have shown promise in the lab. Their ability to cure patients, however, has been limited by a powerful tumor environment that inhibits the immune system. To address this problem, we modified NK cells by genetic engineering technology in two unique ways in order to keep NK cells 'on' within the harsh tumor environment. We added an activating signal and deleted an inhibitory signal specifically within NK cells that should safely maintain their activity. We hypothesize that these double-modified NK cells armed with a tumortargeting protein called a chimeric antigen receptor (CAR) will multiply, survive, and kill cancer cells in the tumor environments of otherwise resistant childhood solid tumors like neuroblastoma and soft-tissue sarcomas. Our findings thus far show that these modifications separately enhance certain aspects of CAR-NK cells. We are now at the final portion of our project where we combine these modifications to generate optimal anti-tumor effect. We expect this project to yield a new type of immune cell therapy with the potential to increase response rates in future clinical trials.

Project Goal: Having completed the goals of Aim 1 and now embarking on last portions of Aim 2, we will test the final co-engineered NK cells deleted of TIGIT and expressing a new TME-inducible version of C7R against human NBL and RMS TME xenografts in mice. We made an inducible version based on results showing detrimental effects from the continuous version of IL-7 signaling seen in our studies.

Jinseok Park, PhD

jinseokp@usc.edu

Children's Hospital Los Angeles, Los Angeles, CA

2024 'A' Award

Cell Cycle Regulation by PAX3-FOXO1 via WEE1 Kinase in Fusion-Positive Rhabdomyosarcoma

Background: Fusion-positive rhabdomyosarcoma is an aggressive form of the most common childhood muscle cancer, rhabdomyosarcoma. We believe its rapid and invasive growth results from teamwork between two types of tumor cells: leaders and followers. The leader cells are at the tumor's edge, creating paths for invasion, while the follower cells behind them grow quickly and push the leaders forward. We found that the follower cells have higher expression levels of a gene called PAX3-FOXO1, a signature gene of fusion-positive rhabdomyosarcoma, which appears to make them grow faster. This gene can abnormally activate other genes that control cell division, leading to uncontrolled tumor growth. One of these target genes is WEE1 kinase, a protein that normally helps regulate when cells divide. However, WEE1 acts more like an accelerator in this cancer, allowing cancer cells to divide without brakes. We study how WEE1 helps follower cells grow rapidly and supports their cooperative invasion. Our discovery helps explain how these cancer cells grow uncontrollably and suggests that drugs blocking WEE1 could offer a new, more precise treatment for children with fusion-positive rhabdomyosarcoma, offering hope for better outcomes.

Project Goal: We use a 3D "mini-tumor" model that mimics how leader and follower cells work together in fusion-positive rhabdomyosarcoma. With this model, we will first test whether the follower cells—found just behind the tumor's outer edge—grow faster than the others. We will also check if this fast-growing region shows higher activity of a protein called WEE1 kinase, which may be helping the cells divide more quickly. Finally, we will examine patient tumor samples to see if this same pattern of high WEE1 activity appears in those regions as well. Second, we will study how WEE1 kinase "breaks the brakes" that normally keep cell growth under control. To do this, we will use special live-cell indicators that allow us to watch the activity of these growth brakes in real time. Lastly, we will test whether drugs that block WEE1 kinase can slow down cell growth and invasion in our mini-tumor models. Together, these studies will help us better understand what drives tumor growth in this aggressive childhood cancer and may pave the way for new, more effective treatments for children with fusion-positive rhabdomyosarcoma.

Santhosh Kumar Pasupuleti, PhD

skpasupu@iu.edu

Indiana University, Indianapolis, IN

2024 'A' Award

Targeting Novel Inflammatory Signaling Pathways in Juvenile Myelomonocytic Leukemia

Background: Juvenile Myelomonocytic Leukemia (JMML) is a rare and aggressive blood cancer mainly affecting young children. It is characterized by the presence of somatic PTPN11 mutations in approximately 35% of cases. Current treatments, like chemotherapy, are not very effective, and stem cell transplants are the only potential cure, but they only work for about half of patients, with relapse being the leading cause of death. Surprisingly, there are currently no FDA-approved medications for treating JMML. Chronic inflammation seems to be involved in JMML development. Certain immune cells called M2-Macrophages, which are elevated in JMML, play a role in immune suppression and cancer cell growth. Our preliminary data from JMML patients and mouse models show elevated PTX3, IL15, and M2-MF levels. We hypothesize that overexpression of PTX3 and IL-15RA in Shp2E76K/+ mutant macrophages induce MCP-1 secretion, increasing M2-MF polarization. This process, along with high Arginase 1 expression, suppresses cytotoxic T-cell activation and proliferation, potentially driving JMML development and leukemia relapse. With funds from this ALSF "A" Grant Award, we will test specific inhibitors such as anti-PTX3 inhibitor and anti-IL-15RA antibody, alongside established inhibitors such as MEK-inhibitor (PD-901) in the PTPN11-mutant JMML mouse model, may rescue T-cell immune suppression and reverse the disease features of JMML.

Project Goal: Over the four-year ALSF "A" Grant Award, our primary goal is to define how the PTX3/IL-15RA signaling axis, in combination with MEK inhibition, influences immune regulation and disease progression in juvenile myelomonocytic leukemia (JMML). We aim to fill key knowledge gaps on how PTX3-driven inflammation promotes leukemic growth and immune evasion. Using single-cell sequencing technology and JMML mouse models, we will correlate with JMML patient sample profiles to delineate how dysregulated PTX3/IL15RA signaling drives abnormal M2-macrophage polarization and suppresses anti-leukemic T-cell responses. Through in vitro and in vivo approaches, we will evaluate the therapeutic potential of targeting PTX3/IL-15RA with MEK inhibition to restore T-cell activity and reduce disease burden. We will also investigate how PTX3/IL-15RA signaling alters macrophage metabolism through the ROS and arginase pathways, promoting the recruitment of regulatory T cells (Tregs) and the suppression of CD8+ T cells. Further, we will assess whether chronic PTX3/IL-15RA-driven inflammation disrupts T-cell receptor (TCR) signaling and thymic development during JMML onset. Finally, we will explore the epigenetic reprogramming of JMML and immune cells under inflammatory conditions. Together, these studies will clarify how inflammation sustains JMML progression and guide the development of novel combination immunotherapies to improve patient outcomes.

Bo Qiu, MD/PhD

bo.qiu@ucsf.edu

University of California, San Francisco, San Francisco, CA

2023 Young Investigator Grant

Targeting Oncogenic N-MYC Complexes in High-Risk Neuroblastoma

Background: Neuroblastoma is a highly heterogeneous disease and a large number of high-risk cases are driven by tumor cell activation of a gene called MYCN. I have shown that MYCN recruits an enzyme named Protein Arginine Methyltransferase 5 (PRMT5) to promote survival of neuroblastoma cancer cells. Using genetic tools and clinically available PRMT5 inhibitors, we have identified how MYCN rewires PRMT5 activity to drive high-risk neuroblastoma. Using a technique that we have developed to directly measure PRMT5 activity, we have identified pathways engaged by PRMT5 inhibitors that drive neuroblastoma cell death. This work provides rationale to develop PRMT5 inhibitor trials for children impacted by MYCN-driven cancer and measures of drug activity that need to be achieved to treat these cancers.

Project Goal: My goal is to perform the key experiments that will provide rationale to test a new class of drugs called PRMT5 inhibitors for MYCNamplified pediatric cancers, including high-risk neuroblastoma.

Zachary Reitman, MD/PhD

zjr@duke.edu

Duke University School of Medicine, Durham, NC

2023 'A' Award

Stimulating the Immune Microenvironment in Diffuse Midline Gliomas

Background: Pediatric diffuse midline gliomas (DMGs) have limited therapeutic options beyond radiation therapy (RT) due to their low mutational burden and lack of targetable neo-antigens, making immunotherapy development challenging. The cGAS-STING pathway, which detects cytoplasmic DNA and initiates immune responses, offers a potential strategy to enhance tumor cell killing, particularly in combination with RT. By using immune-competent animal models and genetic tools to reactivate STING, this research aims to optimize predictive biomarkers and therapeutic combinations for translating STING-modulatory therapies into clinical trials for DMG patients. This will be accomplished in the following three aims:

Aim 1. Characterize the effect of STING activation on DMG pathogenesis using primary immune-competent mouse models.

Aim 2. Examine immune stimulatory and antitumor effects of STING activation in established DMG tumors.

Aim 3. Evaluate the effects of STING activation on the immune stimulatory effects of radiation therapy.

Project Goal: Diffuse midline gliomas are deadly childhood brain tumors and new treatments are needed. Here, we are investigating if therapies that target the stimulator of interferon genes (STING) can affect growth or treatment response for DMGs. In year one, we started generating new models of DMG in which we can express STING and examine the effects of this. We also combined STING expression with different drugs to see if response to different drugs interacts with STING expression to cause DMG treatment response. The ongoing work will determine if future clinical trials should incorporate treatments that affect STING functions to improve outcomes for DMG patients.

Jezabel Rodriguez-Blanco, PhD

rblanco@musc.edu

Medical University of South Carolina, Charleston, SC

2023 'A' Award

Uncovering the Signaling Mechanisms Allowing Medulloblastoma Progenitor Cells to Orchestrate Tumor Relapse

Background: Medulloblastoma is the most common malignant brain tumor in children. While most patients respond to initial treatment, the tumor returns in about 30% of cases, and relapse is uniformly fatal. My research aims to understand why some tumors recur and how we can prevent their recurrence. I focus on a small group of tumor cells that resemble glial progenitor cells found in the central nervous system. We and others have shown that these cells can survive therapy and regenerate the tumor, acting as seeds of relapse. Instead of targeting their specific drivers—since that could also harm normal glial cells in the brain—I aim to uncover the mechanisms that allow these cells to become enriched after therapy, focusing on how the tumor environment supports their resistance. Understanding this process will help us develop safer and more effective treatments to prevent relapse and improve outcomes for children with medulloblastoma.

Project Goal: My goal is to understand how the environment surrounding a medulloblastoma tumor enables certain cells—particularly those resembling healthy brain glia—to survive therapy and drive recurrence. By identifying the key signals and interactions that allow these cells to persist and expand after treatment, I aim to uncover strategies to prevent their enrichment post-therapy. Insights from this work could inform the design of future clinical trials that combine therapies blocking tumor growth with drugs that disrupt the communication of the tumor with its microenvironment. Ultimately, my goal is to prevent relapse, which occurs in about one in three patients and, once diagnosed, carries a median survival of only around 10 months.

Ruby Sims, PhD

rasims@mednet.ucla.edu

University of California, Los Angeles, Los Angeles, CA

2024 Young Investigator Grant

In Vivo Transdermal Generation of CD33 CAR T-Cells Towards Acute Myeloid Leukemia

Background: Acute myeloid leukemia (AML) is the second most common pediatric leukemia, with treatments still based on intense, conventional chemotherapy and overall survival remaining below 70%. Recently, therapeutic research has explored the engineering of a patient's own immune cells to target unique AML cell surface markers. However, to manufacture these therapies immune cells must be collected from patients and re-engineered outside their body. To overcome these challenges, research has been focused on the engineering of a patient's immune cells while inside their body. To deliver these cell engineering therapeutic payloads, a series of nanotechnology tools need to be developed. Our team has designed delivery vehicles known as lipid nanoparticles to transport a set of genetic instructions to immune cells, directing them to target and kill cancer cells. To ensure that these lipid nanoparticles are delivered to immune cells efficiently and safely, we have added immune cell targeting capabilities to the outside of our particles, increasing their delivery efficiency and ability to activate resting immune cells. To deliver these nanoparticles to cells within the body, we have also designed microneedle patches, similar to pimple patches, to access immune cells within the skin. The development of these nanotechnologies will provide the tools required to deliver therapeutic payloads for the re-engineering of immune cells, providing effective treatment options for pediatric patients.

Project Goal: Towards our goal of developing nanotechnologies to advance the targeted delivery of immune cell therapies, we must first ensure that these therapeutic cargos are delivered to the correct immune cells, and not to other types of cells. To achieve this, we have developed methods to decorate the outside of our lipid nanoparticles with immune cell targeting antibodies. We have shown that the addition of these antibodies to the nanoparticles allows us to deliver instructions to, and activate, immune cells in vitro (outside the body), as well as re-engineer their cancer cell targeting capabilities. Going forward, we must now demonstrate the specificity of this delivery to immune cells over other cell types, and the effectiveness of this in mice models. Another key component of our research is focused on exploring ways to painlessly access a patient's immune cells. We are taking a unique approach to this challenge, and have focused our efforts on accessing immune cells located within the body's first line of defense, the skin. To achieve this, we are developing microneedle patches similar to a pimple patch, with the goal to painlessly deliver our nanoparticles directly to immune cells present in the skin. The development of both these nanotechnologies will provide insights into the ability to painlessly re-engineer a patient's own immune cells to target cancers cells within their body, and advance the development of effective treatments for pediatric patients.

Timothy Spear, MD/PhD

speart@chop.edu

Children's Hospital of Philadelphia, Philadelphia, PA

2024 Young Investigator Grant

Vaccine-Boosted CAR T Cell Therapy for High Risk Neuroblastoma

Background: This project is focused on the development of a vaccine to "boost" or enhance the therapeutic efficacy of cell therapies, such as chimeric antigen receptor (CAR) T cell therapy for neuroblastoma, a deadly pediatric cancer. We have developed a mouse model to study the effectiveness of this vaccine boosted CAR-T cell therapy for neuroblastoma. Since the initiation of this proposal we tested the ability of a new type of peptide vaccine that presents a signal for the CAR-T cell to recognize it in mouse dendritic cells (a type of immune cell that vaccines work through). Unfortunately, this approach did not present the CAR target the way we had hoped it would. So, we developed an alternative strategy using mRNA lipid nanoparticles as the vaccine (similar to the way the COVID vaccine works). We found this design was much more effective and activated mouse dendritic cell line cells to "present" the target to mouse CAR-T cells, which in turn activated the mouse CAR-T cells. We genetically engineered a new stain of mouse to isolate primary dendritic cells from the bone marrow of these mice, instead of a cell line to better understand the biology of these responses. We plan to use this mRNA-LNP approach to vaccinate this new strain of mice to understand how vaccine works inside the mouse to complement what we see in a dish.

Project Goal: The goal of this project is to characterize an eptiope-based mRNA-lipid nanoparticle vaccine to enhance the efficacy and persistence of chimeric antigen receptor (CAR) T cell therapy targeting PHOX2B, an essential oncogenic driver of neuroblastoma. We are characterizing ability of the vaccine eptiope to be presented by human and mouse antigen presenting cells, activate human and mouse engineered CAR-T cells, and prolong their persistence in preclinical models of neuroblastoma. Ultimately, this proposal will provide IND-enabling studies for a Phase I clinical trial using this epitope vaccine to enhance efficacy of PHOX2B-targeting CAR -T cells in patients.

Justin Sperlazza, MD/PhD

justin.sperlazza@med.unc.edu

The University of North Carolina at Chapel Hill, Chapel Hill, NC

2024 Young Investigator Grant

Utilizing Chromatin Directed Inhibitors to Regulate Gene Expression in Ewing Sarcoma for Therapeutic Benefit

Background: Ewing sarcoma is the second most common bone cancer in children, and the treatment of Ewing sarcoma continues to rely on traditional chemotherapy, surgery, and radiation. Unfortunately, children who have Ewing sarcoma that returns after initial therapy or whose disease has spread to other places in their body, a process known as metastasis, often do not survive their disease. Immunotherapies are new approaches to treating cancer using the patient's own immune system. One promising immunotherapy option modifies a patient's own T-cells to express a Chimeric Antigen Receptor (CAR), which allows the cells to detect specific tumor cell and eliminate their cancer. CAR T-cell therapy has revolutionized the treatment of blood cancers and holds great promise for treating children with solid tumors, such as Ewing sarcoma. However, pediatric solid tumors lack consistent targets, which reduces the potential therapeutic benefit of CAR-T cells. Gene expression changes in the tumor determine if a cancer cell contains a target or not. Fortunately, recently discovered molecules hold the potential to modify these gene changes. Therefore, this project seeks to identify new medicines to enhance CAR-T cell therapy for pediatric solid tumors.

Project Goal: This project seeks to improve the treatment of Ewing sarcoma by utilizing small molecules to alter how the cancer cells read their DNA, known as gene expression. The first goal of this project will investigate the ability of the molecules tazemetostat and entinostat to force Ewing sarcoma cells to make the cellular target "GD2", which can then allow CAR-T cells to detect and eliminate the cancer cells more efficiently. If successful, this part of the project will lay the groundwork for improving the implementation of GD2-targeted CAR-T cells, which are currently being investigated in multiple clinical trials nationwide. The second goal of this project will investigate the ability of tazemetostat and entinostat to reduce the ability of Ewing sarcoma cells to metastasize, or spread, to other parts of the body. Finally, the third goal of this project is to develop a new way to non-invasively detect tumor GD2 expression utilizing PET imaging.

Christina Turn, MD

turnc@chop.edu

Children's Hospital of Philadelphia, Philadelphia, PA

2023 Young Investigator Grant

Arginine Depletion with DFMO in High-Risk Neuroblastoma

Background: This year, we continued to evaluate the efficacy of treating high-risk neuroblastoma with polyamine deprivation. Polyamines are critical for cancer cell division but also play important roles in immune cell functioning. We have tested the drug difluoromethylornithine (DFMO), which inhibits polyamine production, with a diet lacking proline and arginine, critical polyamine building blocks. This treatment completely cured 1/3 of mice from their tumors without chemotherapy, so we tested whether we could achieve this same success with DFMO and arginine deiminase (ADI-PEG20), a drug that metabolizes arginine. We tested this drug combination in TH-MYCN mice (immunocompetent) and in immunocompromised mice injected with human tumors (xenografts), and we found that this drug combination works almost as well as the diet and DFMO strategy. This is important because these two drugs would be much more likely to be tolerable for children with neuroblastoma to take in the future. We also looked at the tumors from our TH-MYCN mice treated with DFMO with and without the proline/arginine deficient diet. We found that these tumors had increased amounts of macrophages and cancer-associated fibroblasts. Untreated and DFMO-treated tumors have different macrophage-associated gene expression and cytokine profiles, and macrophages grown in culture with tumor cells rescue them from polyamine depletion. We are exploring this macrophage-driven resistance mechanism to polyamine depletion this year.

Project Goal: Our goal for this project is identify and to capitalize upon the macrophage-harnessing effects of polyamine depletion with DFMO and arginine depletion (either through a diet lacking arginine or an enzymatic inhibitor of arginine). In this upcoming year, we aim to identify ways in which tumor-associated macrophages help neuroblastoma to evade the anti-tumor effects of polyamine depletion. Ultimately, these efforts will help us to develop this therapeutic strategy for its eventual translation to treat children with high-risk neuroblastoma.

Elena Vasileva, PhD

evasileva@chla.usc.edu

Children's Hospital Los Angeles, Los Angeles, CA

2023 Young Investigator Grant

Identifying Ewing Sarcoma Developmental Vulnerabilities

Background: Ewing sarcoma (ES) is a malignant bone and soft-tissue tumor that affects children, adolescents, and young adults, with an extremely poor prognosis for patients with metastatic or relapsed disease. Ewing sarcoma occurs when two pieces of different DNA chromosomes abnormally break and fuse together, creating a powerful cancer gene within the cell known as 'EWSR1-FLI1.' We know very little about what type of cell in the body gives rise to Ewing sarcoma, and there have not been effective animal genetic models of the disease to test new treatments for children with that disease. A better understanding of ES's developmental origin(s) can shed light on the lineage-specific dependency of tumor cells on developmental regulators. To understand the disease pathogenesis and to identify cancer cell vulnerabilities, I developed a novel zebrafish model of Ewing sarcoma. This model enables me to observe the behavior of cancer cells labeled with green fluorescent protein during tumor initiation and progression throughout organism growth and development, an approach not currently feasible in mammals. I discovered that the human EWSR1-FLI1 oncogene 'reprograms' initial progenitor cells by inhibiting neuronal differentiation and activating the mesodermal program, resulting in abnormal expression of mesodermal regulators in vivo. Here, I hypothesize that such EWSR1-FLI1-induced activation of mesodermal regulators in 'progenitor' cells lies in the foundation of EWSR1-FLI1-mediated tumorigenesis.

Project Goal: A better understanding of tumor initiation mechanisms will help uncover cancer cell vulnerabilities, leading to the development of new treatment strategies for children with Ewing sarcoma. The goal of the project is to characterize the early events of EWSR1FLI1-induced cell transformation and to target abnormally upregulated mesodermal regulators in Ewing sarcoma cells. The proposed project will help determine sublineages of cells resistant to human EWSR1-FLI1 and identify the mechanisms of cell tolerance to the oncofusion. This will define key regulators of such cell tolerance to EWSR1-FLI1 that could be used to target cancer cells. Using our novel zebrafish model, we have already shown that the EWSR1-FLI1 gene can "reprogram" certain early-stage cells, abnormally turning on genes normally active during the formation of bone, muscle, and cartilage. Additionally, we found that these early reprogrammed cells show a unique pattern of gene activity linked to neural development and signal transduction, which isn't present in healthy cells at this stage. I aim to elucidate how these developmental signaling pathways facilitate EWSR1-FLI1-induced cell transformation and tumor progression. I will leverage my genetic model of Ewing sarcoma to test a novel strategy: targeting the mesodermal program in ES cells to inhibit tumor growth, cancer cell migration, and enhance tumor cells' sensitivity to pharmacological agents.

Elvin Wagenblast, PhD

elvin.wagenblast@mssm.edu

Icahn School of Medicine at Mount Sinai, New York, NY

2022 'A' Award

Characterizing the Developmental Context of Pediatric Leukemia

Background: Leukemia is the most common cancer in children, accounting for almost 1 out of 3 cancers. Acute myeloid leukemia (AML) is a cancer of the myeloid line of blood cells and is the leading cause of childhood leukemic mortality. There is a great need to improve the outcome of children who are diagnosed with AML by developing better-targeted treatment options. Although both children and adults are affected by AML, studies indicate that the specific genetic mutations present in childhood and adult leukemia are different. Because all AMLs originate in stem and progenitor blood cells, we hypothesize that the developmental state of the initiating cell in leukemia could play an essential role in the leukemic transformation. We are interested in investigating why certain mutations are able to initiate leukemia in children but not in adults and for this we are utilizing two childhood leukemia models that we recently developed. First, we will utilize a model of Down syndrome associated leukemia. Children with Down syndrome, who have an extra copy of chromosome 21, have a 150-fold increased risk of developing AML. Secondly, we will utilize a model of leukemia with NUP98-NSD1 gene fusions, which are predominantly seen in childhood cases and is known to be therapy resistant. Using these two models, we aim to characterize the developmental context of leukemia initiation.

Project Goal: The overall vision of the project is to understand the earliest steps of how and why childhood AML initiates and to use this knowledge to innovate new therapeutic options. In order to understand the leukemic development in children, we are proposing to use CRISPR/Cas9 technology in human primary blood stem cells to model the leukemic disease in mice. For this, we are introducing the same mutations observed in leukemic patients, such as in GATA1 and cohesin genes for Down syndrome associated AML and NUP98NSD1 for therapy resistant childhood AML, into human primary blood stem cells and, through this, model the steps of leukemia initiation. By utilizing blood stem cells from either young or adult individuals, we will systematically profile the effect of the developmental state towards leukemic transformation. This will allow us to draw a comprehensive map of which genetic mutations in which cell types are able to induce leukemia in children versus adults. Importantly, with this model in hand, we will be able to characterize the molecular mechanism that is responsible for leukemic susceptibility. We believe that this approach will allow us to identify novel therapeutic targets against Down syndrome associated AML and NUP98-NSD1 induced AML. Our long-term goal is to discover new drug targets in order to directly improve the outcome of children with AML in the clinic.

Dong Wang, PhD

dong.2.wang@cuanschutz.edu

University of Colorado Denver, AMC and DC, Aurora, CO

2024 Young Investigator Grant

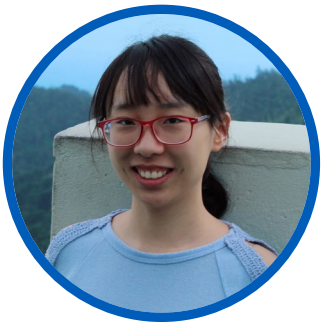
Understanding the Role of CDK8 in Protein Synthesis for Treating MYC-driven Medulloblastoma

Background: Medulloblastoma (MB) is the most common malignant brain tumor in children. This project aims to develop new, more effective treatments for MYC-driven medulloblastoma by identifying and targeting genes that tumor cells rely on to survive. Using a largescale genetic screen of over a thousand druggable genes, we identified CDK8 as essential for tumor growth. Blocking CDK8 with genetic tools or a selective drug greatly slowed tumor growth in both cell and mouse models. We found that CDK8 controls the production of ribosomes, the cell's "protein factories," and that its inhibition reduces overall protein synthesis. We also tested combining CDK8 inhibitors with mTOR inhibitors, which block another protein-synthesis pathway. The combination worked better than either treatment alone, increasing cancer cell death and extending survival without major side effects. These findings reveal a key weakness in MYC-driven medulloblastoma and suggest that dual targeting of CDK8 and mTOR could offer a powerful new therapeutic strategy. Because CDK8 inhibitors are already in early clinical trials, our work may help speed the development of safer, biology-based treatments for children with high-risk brain tumors.

Project Goal: The goal of this project is to discover new treatment option for children with MYC-driven medulloblastoma. Our research focuses on a gene called CDK8, which we identified as a critical vulnerability in MYC-driven medulloblastoma. We found that blocking CDK8, either by genetic methods or with a selective drug called RVU120, slows tumor growth, decreases MYC levels, and reduces the activity of genes that control ribosome biogenesis and mRNA translation. These results suggest that CDK8 plays a key role in keeping the protein-making machinery active in tumor cells. Because MYC-driven tumors also depend on another pathway known as mTOR, which regulates protein synthesis and cell metabolism, we are testing whether combining CDK8 inhibitors with mTOR inhibitors can produce stronger anti-tumor effects. Early results from cell culture and mouse models show that this combination not only slows tumor progression more effectively than either treatment alone but also extends survival without causing major side effects. In the next phase of this project, we will continue to explore how CDK8 and MYC cooperate to sustain tumor growth and identify the exact proteins whose production depends on CDK8. Ultimately, our long-term goal is to translate these discoveries into clinical trials and bring forward new, biology-based treatments for children with medulloblastoma, offering hope for improved survival and a better quality of life.

Yueyang Wang, PhD

ywang133@mgh.harvard.edu



Massachusetts General Hospital, Boston, MA

2024 Young Investigator Grant

The PIK3CA/AKT Pathway Drives Therapy Resistance in Rhabdomyosarcoma

Background: Olaparib and temozolomide (OT) combination therapy is in clinical trial evaluation for rhabdomyosarcoma (RMS). Unfortunately, OT resistance has been reported in other cancers. Using preclinical mouse xenograft experiments, we show that OT effectively suppresses RMS growth, yet over half of RMS tumors develop resistance associated with transcriptomic changes that occur in the absence of recurrent genomic mutation. Importantly, most resistant RMS models upregulate the PIK3CA/AKT pathway, activating NRF2 phosphorylation and subsequent transcriptional expression of multidrug resistance ABC transporters. PIK3CA inhibitor alpelisib re-sensitizes resistant cells to OT by suppressing expression of ABC transporters. The combination of OT + alpelisib also kills RMS cells which are resistant to standard-of-care combination chemotherapy and was effective in preclinical xenograft mouse models at curbing tumor growth. Our work defines a common resistance pathway in RMS and has credentialled PIK3CA/AKT inhibition as a preclinical strategy to kill therapy-resistant RMS.

Project Goal: To elucidate the molecular mechanisms underlying acquired resistance to olaparib-temozolomide (OT) and vincristine-actinomycin D-cyclophosphamide (VAC) therapies in rhabdomyosarcoma (RMS), with the aim of developing a targeted therapeutic strategy to overcome multidrug resistance. Specifically, the project seeks to: i) investigate how long-term OT therapy induces PI3K/AKT pathway activation and NRF2-mediated transcription of ABC transporters in RMS; ii) evaluate the efficacy of PI3Ka inhibition (FDAapproved drug alpelisib) in reversing therapy resistance and re-sensitizing RMS tumors to OT; iii) test the combination therapy (OT + alpelisib) as a novel medicine approach to target therapy-resistant RMS and validate the new combination using preclinical xenograft models. The ultimate objective is to provide a preclinical rationale for clinical trials aimed at improving outcomes for patients with refractory or relapsed RMS.

Gregory Way, PhD

gregory.way@cuanschutz.edu

University of Colorado Denver, AMC and DC, Aurora, CO

2023 'A' Award

A Cell Morphology Landscape of Pediatric Cancer Cell Lines

Background: Science has made impressive leaps in the ability to precisely measure what is unique about each childhood cancer patient, which has improved our ability to treat childhood cancers. However, there remain many patients for which treatments do not work and many more who suffer from life-long toxic side-effects. We therefore need to develop better and less toxic treatments. One strategy that is growing in importance is the concept of high-throughput drug screening. In these experiments, scientists can test cellular responses to many thousands of potential therapeutic agents. However, these responses are most commonly very simple, consisting of only counting how many cells are present before and after drug treatment. This will tell us about the drug's cell killing effect, but will miss more important impacts drugs can have on cells like promoting a healthier phenotype without killing. This category of drug screening research is called "phenotypic drug screening", which uses powerful microscopes and computers to learn details about cancer cells that humans cannot see. We are learning that the information gained from these microscope images provide unique information that may help identify new treatment avenues. With fast, modern computers and smart algorithms we are only just now able to pursue these experiments. We will direct all of this power to curing different types of childhood cancers with microscopy, computers, and phenotypic drug screening.

Project Goal: We will perform drug screening in eight different types of childhood cancers using drugs that have already been approved for many different diseases by the US FDA, which means these drugs have low toxicity. This type of experiment is known as drug repurposing, which is a strategy proven effective in other diseases. Importantly, we will be approaching these drug screens differently than what's been done before. In the past, drug screens have only looked at how effective compounds are at killing cancer cells. Here, we will measure much more detail and learn which drugs make cells look healthier. We will use automated microscopes to take tens of thousands of pictures of thousands of cells and apply advanced computational procedures, like the algorithms in chatGPT, to learn which compounds might be good candidates for followup experiments and clinical trials. We will make all of the data publicly available in an easy to use web application, so that researchers and anyone else can view the microscopy images to see for themselves how these treatments are working. By viewing cells under a microscope, we can also learn subtle differences in the structures within them to ask new questions about how these cancers work to grow, evade treatment, and cause so much suffering in these children and their families. We will build a pediatric cancer drug screening platform, which we will apply to many different cancers in the future, to discover new treatment avenues at a large scale.

Adeline Yang, MD

yanga9@chop.edu

Children's Hospital of Philadelphia, Philadelphia, PA

Centers of Excellence Scholar

Pilot Study of Scaling Busulfan dose to Body Surface Area in Children Undergoing Hematopoietic Stem Cell Transplant Conditioning

Background: Busulfan is highly effective in conditioning the bone marrow for transplant for children with malignant and non-malignant conditions. However, busulfan dosing remains challenging because of its narrow therapeutic window, high variability among how individuals metabolize the drug, and weight-based dosing, which often underdoses younger children. Low drug exposure risks transplant graft failure or disease relapse, while high exposure risks hepatic sinusoidal obstruction syndrome (SOS). SOS occurs in 964% of children, but at 2-5 fold higher rates in younger children, and is fatal in ~11%. Transplant-related deaths have been reduced by therapeutic drug monitoring (TDM), but initial suboptimal exposure remains common. Simulations predict that using body surface area instead of weight for busulfan dosing increases the percentage of children reaching first-day therapeutic goals from 51% to 75%. In this study, up to 38 enrolled children will receive four days of busulfan, with the first dose selected from the BSA-based dosing table, followed by standard TDM; subsequent doses may be adjusted to achieve therapeutic exposure. At least 15 patients will have a BSA < 0.5 m2, capturing children at high risk of underdosing and SOS. Validating if BSA-based busulfan dosing increases rates of attaining first-day therapeutic exposure aims to maximize likelihood of successful engraftment while minimizing risks associated with suboptimal exposure such as graft failure, relapse, and SOS.

Project Goal: The overarching goals of this study are to (1) validate if body surface area (BSA)-based busulfan dosing increases attainment of therapeutic exposure and (2) characterize hepatic sinusoidal obstruction syndrome (SOS) risk factors relative to busulfan exposure, focusing on the high risk group of young children with body surface area (BSA) < 0.5 m2. Moreover, updating busulfan to BSA-banded dosing results in better alignment with recent Children's Oncology Group guidelines for dosing anticancer drugs in infants to reduce toxicity risk. In addition to seeking to improve outcomes in children requiring busulfan transplant conditioning, this study fosters Young Investigator development in conducting clinical trials and building pharmacokinetic models to characterize differences in how children metabolize busulfan and better predict the dose needed to achieve therapeutic exposure. This establishes a strong foundation for my future career leading clinical trials informed by drug exposure/response models with efficacy-based dose determination, rather than maximum tolerability, to improve outcomes and minimize toxicities for children with cancer.

Speakers

Liz Scott

Liz@AlexsLemonade.org

Alex's Mom and Co-Executive Director

Alex's Lemonade Stand Foundation

Liz Scott is the Co-Executive Director of Alex's Lemonade Stand Foundation, but she is most proud of her title of "Mom" to three sons, Patrick, Eddie, and Joey, and daughter Alex. ALSF emerged from the front yard lemonade stand of Liz's daughter, Alexandra "Alex" Scott (1996-2004). In 2000, 4-year-old Alex announced that she wanted to hold a lemonade stand to raise money to help find a cure for other children with cancer. In her lifetime, Alex would raise over $1 million before she passed away in 2004 at the age of 8. Since then, Liz and her husband Jay have worked alongside thousands of supporters across the country to carry on her legacy of hope. To date, ALSF has raised more than $300 million toward fulfilling Alex's dream of finding a cure, funding over 1500 pediatric cancer research projects nationally.

Audra Brennan

Vice-President, Philanthropy

Northwestern Mutual Foundation

Audra Brennan has nearly 25 years of non-profit and public policy experience at the federal, state, and local level. Audra currently serves as the Senior Director of Strategic Philanthropy for the Northwestern Mutual Foundation, which provides more than $20 million annually to strengthen communities and improve outcomes for kids with cancer and their families. In that role, she oversees the team responsible for grantmaking and strategic partnerships across the Foundation's priority areas as well as employee and field community engagement. Brennan's prior experience includes education, health, and tax equity policy roles at the Greater Milwaukee Foundation, State of Wisconsin, City of Milwaukee, Milwaukee Public Schools, and the Congressional Budget Office in Washington D.C. Audra Brennan grew up Peoria, Illinois, the daughter of two public school educators. She graduated from Northwestern University with a degree in Mathematics and Economics. She was selected as a Harris Fellow at the University of Chicago and earned a master's degree in public policy from University of Chicago's Harris School of Public Policy in 1999. Audra Brennan lives with her husband Joel and two teenage children in the Brewers Hill neighborhood of Milwaukee.

Donald Williams (Will) Parsons, MD/PhD

dwparson@texaschildrens.org

Beverly and Daniel C. Arnold Endowed Chair for Precision Medicine, Texas Children's Hospital

Interim Director, Texas Children's Cancer and Hematology Center

Pediatrician-in-Chief, Dan L. Duncan Comprehensive Cancer Center, Baylor College of Medicine

Professor, Department of Pediatrics, Division of Hematology-Oncology, Baylor College of Medicine

ALSF Scientific Advisory Board

ALSF Young Investigator, 'A' Awardee, POST Mentor, Crazy 8 Predisposition Grant

Dr. Donald Williams (Will) Parsons is the Beverly and Daniel C. Arnold Endowed Chair for Precision Medicine at Texas Children's Hospital and Interim Director of Texas Children's Cancer and Hematology Center, Baylor College of Medicine (BCM). He also serves as Pediatrician-in-Chief for Baylor College of Medicine's Dan L. Duncan Comprehensive Cancer Center. He is a board-certified pediatric hematologist-oncologist who also serves as Co-Director of the Cancer Genetics and Genomics Program, and Director of the Center for Precision Oncology within Texas Children's Cancer Center. In addition to conducting innovative translational research in pediatric cancer genomics, Dr. Parsons and his team are making important contributions to the clinical care of childhood cancer patients, including establishment of the Precision Oncology Consultation Service at Texas Children's Cancer Center, which provides recommendations for the use and interpretation of clinical genomic testing for pediatric cancer patients nationwide. He also plays leadership roles within the National Cancer Institute (NCI)-funded Pediatric Brain Tumor Consortium (PBTC) and the Children's Oncology Group (COG).

Maureen M. O'Brien, MD, MS

maureen.obrien@childrenscolorado.org

Professor, Department of Pediatrics, Section of Hematology, Oncology, BMT-Cellular Therapeutics, University of Colorado Anschutz Medical Campus

Leukemia/Lymphoma Program Director, The Robert J. and Kathleen A Clark Endowed Chair for Pediatric Cancer Therapeutics, Children's Hospital Colorado | Center for Cancer and Blood Disorders

ALSF Scientific Advisory Board

Maureen M. O'Brien, MD, MS, focuses on clinical and research related to the development of novel therapies and supportive care for children, adolescents, and young adults with high-risk and relapsed hematologic malignancies, particularly acute leukemias. As the Medical Director of the Leukemia/Lymphoma Program at Cincinnati Children's Hospital Medical Center (CCHMC, 2014-2023) and now at Children's Hospital Colorado (CHCO), she has extensive experience in the development and execution of phase 1 and 2 clinical trials with pharmacokinetic endpoints including investigator-initiated, industry-sponsored, and cooperative group trials, as well as phase 3 trials evaluating novel agents in the frontline setting as an active member of both the Acute Lymphoblastic Leukemia (ALL) and Myeloid Committees in the Children's Oncology Group (COG). She is the COG ALL Committee Vice Chair for Precision Medicine and Novel Agents and leads the investigation of the antibody-drug conjugate inotuzumab ozogamicin (InO) in pediatric ALL in both the relapsed and newly diagnosed settings. In addition, she has an interest in acute and long-term toxicities associated with the treatment of acute leukemias, including pharmacogenomics and pharmacokinetics of conventional and novel agents, and optimizing toxicity surveillance and supportive care for children undergoing acute leukemia therapy.

Elliot Stieglitz, MD

Elliot.Stieglitz@ucsf.edu

Associate Professor, Pediatrics

William Fries II Endowed Professor in Pediatric Oncology

UCSF Benioff Children's Hospitals

ALSF Young Investigator, 'A' Awardee, ALSF Scientific Review Board

Dr. Elliot Stieglitz is a pediatric oncologist at UCSF Benioff Children's Hospitals. He focuses his research on improving outcomes for children with juvenile myelomonocytic leukemia (JMML). During his fellowship and funded by an ALSF YIA grant, he defined the genomic landscape of JMML and demonstrated that virtually all patients have initiating mutations in the RAS pathway and that a higher "mutational burden" is predictive of poor outcome. Later work revealed that DNA methylation profiling can predict the phenomenon of "spontaneous resolution," and this was validated in an international collaboration across three continents and translated into a CLIA-certified assay. As study chair of ADVL1521, Dr. Stieglitz tested trametinib, an oral MEK inhibitor, and demonstrated activity in a population of relapsed and refractory patients. As study chair of the actively enrolling TACL2020-004 trial, newly diagnosed JMML patients are risk-stratified by mutational burden and DNA methylation profiling to receive optimal amounts of therapy. This study also moves trametinib into the front-line setting in combination with azacitidine. Pre-clinically, the Stieglitz laboratory is focused on developing CLL-1 CAR-T cells with or without trametinib in patient-derived xenograft models of JMML with an eye towards a clinical trial. This work is funded by an ALSF R Accelerated grant. Lastly, Dr. Stieglitz hosts an annual JMML Summit supported by ALSF for researchers from across the world to share insights and develop collaborations to help patients with JMML.

Megan Roberts

The Roberts family is a long-time hero family, fundraiser and ambassador for ALSF. In 2011, Megan's son, Declan, was diagnosed with primary CNS rhabdomyosarcoma at 3 years old. Declan passed away just a few months short of his 5th birthday, but his family has continued fighting in his honor ever since. Over the past 13 years, Megan and her family have raised more than $100,000 for childhood cancer research, and they continue to be a voice for hero families by speaking at events like the 2025 Great Chefs Event Philadelphia this past June.

Katherine (Katie) A. Janeway, MD, MMSc

Katherine_Janeway@dfci.harvard.edu

Director of Clinical Genomics, Dana-Farber Cancer Institute

Senior Physician, Dana-Farber/Boston Children's Cancer and Blood Disorders Center

Associate Professor of Pediatrics, Harvard Medical School

Dr. Janeway received her medical degree from Harvard Medical School in 2000. She subsequently completed her residency in Pediatrics at Children's Hospital, Boston. She was a Chief Resident at Children's Hospital, Boston, and then completed her fellowship in Pediatric Hematology-Oncology at Dana-Farber Cancer Institute / Children's Hospital, Boston. In 2007, Dr. Janeway joined the staff of Dana-Farber and Children's Hospital, Boston, where she is a pediatric hematologist-oncologist and investigator with a research focus of pediatric sarcomas.

Brighter breakthrough moments.

Lighting the way to a future without childhood cancer.

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