Alex's Lemonade Stand
FOUNDATION FOR CHILDHOOD CANCER™

The 6th Annual

Young Investigator Summit

Presented By
Northwestern Mutual®

OCTOBER 14-16, 2018 | MILWAUKEE, WI
Northwestern Mutual Corporate Headquarters

Lake Michigan

FIGHTING CHILDHOOD CANCER, ONE CUP AT A TIME.

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

Alex's Lemonade Stand
FOUNDATION FOR CHILDHOOD CANCER ™

Dear Attendees,

We at Alex's Lemonade Stand Foundation (ALSF) and Northwestern Mutual are so pleased to have this collection of spectacular researchers gathered for the 6th annual ALSF Young Investigator Summit. The fact that it is hosted at Northwestern Mutual's beautiful new headquarters makes it extra special. When we first partnered with Northwestern Mutual back in 2012, they asked us what projects were on our wish list. The Young Investigator Summit was one of them.

We wanted to give our funded researchers a chance to learn, collaborate and discuss their ideas and findings with each other. We hoped those conversations could spark projects and build relationships to help advance research in new, impactful ways. To think we're already in the sixth year of our vision becoming a reality is incredible.

These next few days are filled with groundbreaking presentations, stimulating discussions and a chance to connect with fellow ALSF-funded scientists. Whether you're an 'A' Award grantee from years ago or a brand-new ALSF Young Investigator, your work is truly meaningful for kids like Hana, whose family will share her inspiring story of overcoming childhood cancer with you this week.

Hana benefited from advancements in treatment that wouldn't have been possible without your diligent work. We hope her story inspires you to continue giving kids like Hana a chance at the childhood they deserve.

Thank you!

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

Eric Christophersen
President, Northwestern Mutual Foundation

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THINGS TO KNOW

ONSITE CONTACT INFORMATION

Judy Oliver, Grants Associate, ALSF – 856-745-8027

Morgan Bandkowski, Enterprise Meetings Specialist, Northwestern Mutual – 414-588-3803

WI-FI ACCESS

Westin Hotel: PW: spg2018

Northwestern Mutual: Network: NM Guest PW: remarkable (Case Sensitive)

TRANSPORTATION

To Airport: You will be responsible for coordinating your own transportation to the airport. Please utilize the $50 Lyft credit we have offered.

BAGGAGE

Please bring your baggage to Northwestern Mutual with you on Tuesday. There will be a separate secure room for you to store your baggage near our meeting space.

LYFT CREDIT

Lyft credits need to be utilized within a half-mile of the airport, hotel, Discovery World Museum or Northwestern Mutual Headquarters.

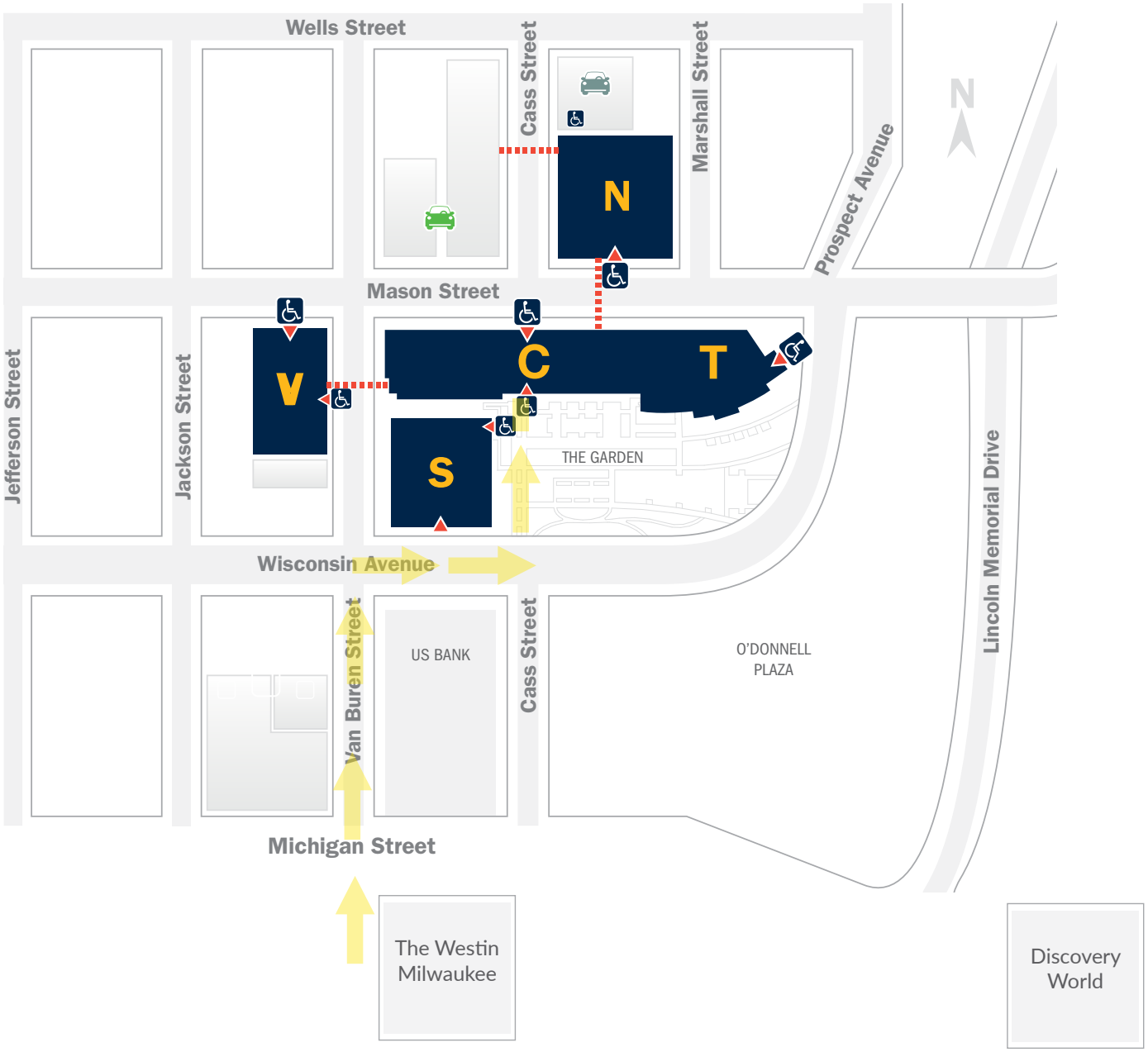
How to redeem the credit:

Step 1: Download the Lyft app for iPhone or Android. Already have the Lyft app? Go straight to step 3!

Step 2: Set up a Lyft account. You'll need to add a credit card, in case your Lyft rides go beyond the event. Any additional tips will be charged to your credit card as well.

Step 3: Select where you are going, click on payment method and add the code YISummit to the "Promo" section of the Lyft app. You must be in "Personal" mode for the code to apply. You will only need to enter this code one time for the entire event. Select your pick up location and complete the ride request.

LAYOUT OF THE CAMPUS



SUMMIT AGENDA

All sessions will take place at **Northwestern Mutual (NM) Headquarters:** 802 Mason Street, Milwaukee, WI. Please enter through the Mason Street Lobby (Building C on the map)
Westin Hotel: 550 N. Van Buren Street, Milwaukee, WI
Discovery World Science and Technology Center: 500 N. Harbor Drive, Milwaukee, WI

Sunday, October 14, 2018

TIME	DESCRIPTION	LOCATION
6:00pm-9:00pm	Welcome Cocktail Reception	Lower Lakes Room Westin Hotel

Monday, October 15, 2018

TIME	DESCRIPTION	LOCATION
6:30am-7:30am	Group Activity: Run/Walk	Westin Lobby
8:00am-8:15am	Walk to Northwestern Mutual Mason Street Lobby Entrance	
8:15am-9:00am	Registration and Breakfast	NM Lobby/Cafeteria
9:00am-9:10am	Welcome – Liz Scott, ALSF & Audra Brennan, Northwestern Mutual	Grand B/C
9:10am-10:30am	**From Research to Resonate: Tell the Story of Your Research to Win Funders and Champions** - How to present your research projects to lay audiences – Shannan Scarseletta, ImproVision	Grand B/C
10:30am-10:40am	Group Photo	Atrium
10:40am-10:55am	Break	Grand B/C
10:55am-11:55am	**Harnessing Natural and Engineered Properties of NKT Cells for Cancer Immunotherapy**: Andras Heczey, MD, Baylor College of Medicine	Grand B/C
11:55am-12:50pm	Lunch	Grand A
12:50pm-1:25pm	Speed Presentations 1	Grand B/C
1:25pm-1:40pm	Speed Presentations 1 Q&A	Grand B/C
1:40pm-2:20pm	Speed Presentations 2	Grand B/C
2:20pm-2:35pm	Speed Presentations 2 Q&A	Grand B/C
2:35pm-2:55pm	Break	Grand B/C
2:55pm-3:55pm	**Precision and Predisposition**-How Next Generation Sequencing is Changing the Face of Childhood Cancer: David Malkin, MD, The Hospital for Sick Children	Grand B/C
3:55pm-4:20pm	Poster Preview 1 – 1 min/1 slide for posters	Grand B/C
4:20pm-5:15pm	Break	
5:00pm-5:15pm	Poster Set Up - For Session 1 Presenters	Discovery World
5:30pm-7:00 pm	Posters (23 ALSF funded researchers) and Cocktail Reception	Discovery World
7:00pm-9:00 pm	Dinner - Discovery World Science and Technology Center	Discovery World

SUMMIT AGENDA CONTINUED

Tuesday, October 16, 2018

TIME	DESCRIPTION	LOCATION
7:45am-8:30am	Breakfast	NM Cafeteria
8:30am-8:35am	Welcome & Ambassador Intro – Liz Scott, ALSF	Grand B/C
8:35am-8:50am	**Hero Ambassador:** Hana Jurgens and Family	Grand B/C
8:50am-9:50am	**ALSF Childhood Cancer Data Lab:** Casey Greene, PhD, University of Pennsylvania & ALSF	Grand B/C
9:50am-10:00am	Break	Grand B/C
10:00am-11:00am	**Professional Development Panel ALSF Scientific Advisory Board:** Todd Druley, Stephen Lessnick, Maureen O'Brien, Will Parsons	Grand B/C
11:00am-11:30am	Poster Preview 2 – 1 min/1 slide for posters	Grand B/C
11:30am-12:30pm	Lunch & Posters (23 ALSF funded researchers)	Grand A & Atrium
12:30pm-2:00pm	Shark Tank Competition	Grand B/C
2:00pm	Summit Closing - Liz Scott	

ABOUT ALSF

CHILDHOOD CANCER DATA LAB

In 2017, Alex's Lemonade Stand Foundation (ALSF) started the Childhood Cancer Data Lab (CCDL), the first lab of its kind dedicated to helping accelerate the pace of pediatric cancer research. After months of work, the CCDL launched the beta version of its data repository, Refine.Bio, in the summer of 2018. Bringing together the over six petabytes of publicly available childhood cancer data, its wealth of information is now getting into the hands of researchers excited for its potential to streamline processing datasets.

This is just the beginning though. Data scientists at the CCDL like Dr. Jaclyn Taroni, the first ALSF staff member with a PhD in genetics, can advise researchers on designing experiments so their data is most beneficial to the research community. The CCDL is also harnessing machine learning to provide researchers greater insight into an individual's specific biology and lead to more targeted treatments.

The CCDL is creating new tools that will pay dividends in the search for cures now and in the future.

CCDL staff will be on site during the summit with a working version of Refine.Bio. Stop by and try it for yourselves!

SHARK TANK COMPETITION

The ALSF Shark Tank Competition is back! Modeled after the TV show, researchers will have a chance to pitch their ideas to an esteemed panel of "sharks." These "sharks" then choose whether they want to invest in the project.

The pre-selected researchers will pitch the "sharks" on their project's ingenuity and potential impact for kids fighting cancer. The pitch should be creative and entertaining, but also understandable to the lay person. This year's "sharks" are a mix of researchers and funders, each with between $15K-20K to invest.

STAY CONNECTED WITH ALSF

Connect, collaborate and network on this LinkedIn page catered to ALSF-funded pediatric cancer researchers (Search for the ALSF Pediatric Cancer Research Connection)

Like ALSF's Facebook page and read stories about promising research projects and the kids and families they are helping every day **@AlexsLemonade**

Follow **@AlexsLemonade** on Twitter for the latest breakthrough research projects, heartwarming stories and Foundation events across the country

Browse stirring hero stories and inspirational photos by following **@AlexsLemonade** on Instagram

GRANT OPPORTUNITIES

Since 2005, Alex's Lemonade Stand Foundation has funded over 800 research projects at 135 hospitals and institutions working towards the goal of putting an end to childhood cancer.

ALSF invests in projects at every stage of the research continuum in the three complementary programs below.

EARLY CAREER RESEARCH

Promising researchers are directed towards long-term careers in pediatric oncology investigation. These grants set the course for a productive research career.

RESEARCH ACCELERATOR

Research is pushed forward by these grants that advance the pace of innovation to find breakthroughs and ultimately new clinical interventions for children with cancer.

QUALITY OF LIFE & CARE

Empowering nurse practitioners and psychologists to make clinically significant discoveries that will improve quality of life or behavioral health outcomes for pediatric cancer patients.

EARLY CAREER RESEARCH

'A' Award: Designed for the early independent career scientist who wants to establish a career in pediatric oncology by supporting research goals, providing necessary equipment and access to ALSF's Scientific Advisory Board.

Young Investigator: Offered to less experienced researchers as a strategic stepping-stone with start-up funds for the most promising scientific minds to be able to commit to the field.

Pediatric Oncology Student Training (POST): POST program is for undergraduate, graduate and medical students to train with pediatric oncology research mentors.

RESEARCH ACCELERATOR

Bio-Therapeutics Impact: Accelerating the development of clinical trials for biological approaches to treating childhood cancer by supporting investigators initiating clinical trials and pre-clinical work necessary before the investigational new drug phase.

Center of Excellence: Intended to create a Center of Excellence to accelerate the development of next-generation therapeutic approaches to childhood cancer. Centers combine pediatric oncology clinical pharmacology/developmental therapeutics training with developing and conducting early phase clinical trials.

Epidemiology: Designed to support investigators who have a specific focus on the epidemiology, early detection or prevention of childhood cancers.

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

Phase I/II Infrastructure: Helping hospitals build the capacity for critical phase I/II clinical trials in order to speed up patient accrual and offer more treatment options for families.

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

RESEARCH ACCELERATOR (CONTINUED)

RUNX1: ALSF and The Babich Family Foundation partnered to accelerate research around familial RUNX1 platelet disorders leading to acute myeloid leukemia (AML) due to germline RUNX1 mutations with the ultimate goal of developing effective therapies to prevent the onset of AML.

QUALITY OF LIFE & CARE

Nurse Researcher: Designed to encourage nurse researchers to investigate topics and issues related to the quality of nursing care and the quality of life for children with cancer.

Psychosocial: Funding studies that aim to explain and/or improve psychosocial and behavioral health outcomes and will have a clinically-significant impact on those affected by childhood cancer.

FAMILY SERVICES

Having a child with cancer is one of the most difficult situations a family can face. ALSF is committed to providing support and resources to families that will make their days a little easier and their challenges more manageable. For more information, please visit ALSFFamilyServices.org.

TRAVEL FOR CARE

Recognizing the financial burden that families often face, the Travel For Care program provides lodging and transportation assistance to families who travel to hospitals in the U.S. and Canada for childhood cancer treatment.

SUPERSIBS

Brothers and sisters of cancer patients often face complex emotions as their family is thrown into the turmoil of managing a child's treatment. SuperSibs is dedicated to comforting, encouraging and empowering siblings.

TREATMENT ORGANIZER

This free organizer helps parents keep track of important information related to their child's care. A Spanish version is available.

HERO AMBASSADOR PROGRAM

Providing families with opportunities to share their stories and raise awareness for the cause.

MY CHILDHOOD CANCER: SURVEY SERIES

A series of surveys that aim to understand the short and long-term impact of childhood cancer on families.

PARENT TO PARENT NETWORK

A forum connecting families with one another for support.

ALEX'S LEMONADE STAND FO

STRIKING OUT CHILDHOOD CANCER • OCTOBER 21, 2018

Petaluma, CA

Whether you can bowl a perfect game or are prone to throwing gutter balls, you will have a fantastic time at this "birthday bowling bash" celebrating the life of childhood cancer hero C.J. Banaszek. This event is held in Petaluma, CA outside of San Francisco. Cocktails, dinner and an auction follow the bowling tournament.

THE GREAT CHEFS EVENT NYC • OCTOBER 23, 2018

New York, NY

Chef Alex Guarnaschelli, star of the Food Network, hosts this culinary event with over 20 all-star chefs under one roof. Signature plates and delicious drinks provide guests a dining experience they won't soon forget.

THE LEMON RUN • NOVEMBER 11, 2018

Philadelphia, PA

Fighting childhood cancer one step at a time, this scenic annual 5K Run/Walk and 100-meter Kids' Dash starts off at Memorial Hall in Philadelphia's historic Fairmount Park. Childhood cancer heroes and families participate too, making the day that much more meaningful for everyone involved.

THE LEMON BALL • JANUARY 19, 2019

Philadelphia, PA

ALSF's annual "yellow tie" gala celebrates the lasting legacy of Alex Scott and continues to fulfill her dream of cures for childhood cancer. Held at the Philadelphia Marriott Downtown, guests can enjoy fabulous food, cocktails, raffles, silent and live auctions and dancing late into the night.

THE LEMON CLIMB HOUSTON • MARCH 30, 2019

Houston, TX

Challenge yourself by climbing the tallest building in Texas! Come to the Chase Tower at 600 Travis in Downtown Houston for this fun-filled day of climbing 35, 60 or 75 flights of stairs at your own pace. Create a team or climb on your own before enjoying food and drink at a joyous after-party.

ALEX'S "ORIGINAL" LEMONADE STAND • JUNE 2019

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 and raffles, and of course lemonade.

OUNDATION SPECIAL EVENTS

ALEX'S LEMONADE DAYS • JUNE 2019

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 this week (or any other time of year).

THE GREAT CHEFS EVENT PHILADELPHIA • JUNE 2019

Philadelphia, PA

The original ALSF culinary event, this family-friendly, daytime event features chef partner Marc Vetri and more than 40 of the country's finest chefs for a tasteful afternoon. Held in the unique venue of Urban Outfitters headquarters at the Philadelphia Navy Yard, guests can sample the chefs' delicious plates and head outdoors for a relaxing drink in the beer garden.

ALEX SCOTT: A STAND FOR HOPE • JUNE 2019

Philadelphia, PA

CBS 3 and The CW Philly host this 14-hour televised fundraiser. CBS television personalities lead the effort, with special segments highlighting Alex Scott's inspirational life and heartwarming interviews with families affected by a childhood cancer diagnosis.

THE GREAT CHEFS EVENT CHICAGO • AUGUST 2019

Chicago, IL

Hosted by chefs Paul Kahan and Tony Mantuano and restaurateur Donnie Madia Gianfrancisco, this exclusive culinary event brings together 30 gourmet chefs from across the country to The Windy City for a scrumptious night of stellar bites, drinks and live music.

THE MILLION MILE - RUN. WALK. RIDE. SEPTEMBER 1-30, 2019

Worldwide

One month, one million miles, one cause. This global, month long challenge brings together supporters to collectively run, walk and ride one million miles to raise money and awareness during September, National Childhood Cancer Awareness Month.

L.A. LOVES ALEX'S LEMONADE • SEPTEMBER 2019

Los Angeles, CA

Chef Suzanne Goin, business partner Caroline Styne and Chef David Lentz gather more than 50 of the country's superstar chefs and over 50 mixologists and vintners to host one of L.A.'s premier culinary events. Guests can taste incredible fare and interact with the chefs behind the dishes.

SPEED PRESENTATIONS

POSTERS

SPEAKERS

SPEED PRESENTATIONS

Serine Avagyan, PhD

Dana-Farber Cancer Institute, Boston, MA • serine_avagyan@dfci.harvard.edu

2018 YOUNG INVESTIGATOR GRANT

Modeling GATA2 Associated MDS/AML Predisposition Syndrome Using Color-Barcoding and Mutagenesis in Zebrafish

BACKGROUND: Children and young adults with inherited mutations in the GATA2 gene have an increased risk of developing blood cancers. These cancers arise from abnormal blood stem cells. The mutant stem cell clone multiplies and expands, acquiring additional mutations that promote leukemia formation. The process is poorly understood, especially in the context of predisposition syndromes to myeloid cancers.

PROJECT GOAL: To study the steps leading to cancer formation, I generated a zebrafish model with GATA2 mutation. My goal is to understand the biology of GATA2 mutant stem cells during development and in young adulthood at a level of individual blood stem cells. I use a special technique of coloring blood stem cell clones, which results in groups of colored blood cells, each representing the progeny originating from a same-colored stem cell clone. In normal hematopoiesis, the contribution from stem cells is balanced, resulting in multicolored blood production. However, in the presence of GATA2 mutation and additional acquired mutations, a precancerous mutant clone expands and a dominant color emerges. I will test the role of specific mutations in GATA2 mutant zebrafish in their ability to promote clonal dominance and eventually leukemia. I will also focus on understanding the effect of GATA2 mutations on stem cells during development in zebrafish embryos, as this may be the key to explaining the risk of cancer later in life. Zebrafish is an excellent model organism for studying blood diseases and presents a unique system to perform chemical screens with a goal of finding new therapeutic modalities for myeloid cancers.

Notes:

Adam Durbin, PhD

Dana-Farber Cancer Institute, Boston, MA • adam_durbin@dfci.harvard.edu

2018 YOUNG INVESTIGATOR GRANT

Interrogation of Neuroblastoma Dependencies and RNAs on the Core-Regulatory Circuitry for Therapeutic Inhibition

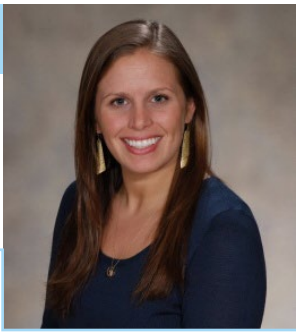
BACKGROUND: Neuroblastoma (NB) is one of the most common solid tumors of childhood. Despite multimodality therapy, nearly half of patients with high-risk neuroblastoma will die of this disease. High-risk neuroblastoma typically has many DNA copies of the MYCN gene. I recently identified a group of six proteins which work together to form a network to drive neuroblastoma. Disrupting any one of these proteins causes all to be lost and the tumor cells to die. Unfortunately, there is no known way to target MYCN or these other proteins right now.

PROJECT GOAL: Here, I will perform experiments to identify new roles for uncharacterized RNAs that are likely to be involved in regulation of the network. Further, I will use chemical inhibitors to disrupt proteins that NB cells require for survival, several of which likely regulate these key factors. These new proteins will also be inhibited in animal models of human neuroblastoma, alone and in combination with drugs similar to those entering clinical trials for NB.

These studies aim to identify new levels of gene regulation and methods to inhibit the genes that establish the cell identity of NB, with minimal side effects.

Notes:

Caitlin Elgarten, MD



Children's Hospital of Philadelphia, Philadelphia, PA • elgartenc@email.chop.edu

2018 YOUNG INVESTIGATOR GRANT

Beyond Febrile Neutropenia: Risks Associated with Antibiotic Choice in Children with Leukemia that Undergo Transplant

BACKGROUND: A subset of children with high-risk leukemia require stem cell transplant in order to cure their disease. Owing to the profound immunosuppression associated with this procedure, children undergoing transplant receive a substantial number of antibiotics. However, the implications of such extensive antibiotic exposures are not well understood.

PROJECT GOAL: This study proposes to evaluate the adverse events associated with antibiotics through complementary aims that specifically strive to understand if there is risk variability across classes of antibiotics that are otherwise considered interchangeable with regards to their anti-infectious properties. This proposal focuses on three common post-transplant complications that lead to significant morbidity: (1) graft-versus-host disease, the major immunologic complication of transplant, (2) clostridium difficile infection, an infection associated with considerable mortality in immunocompromised hosts; and (3) acute kidney injury, an organ toxicity that limits the delivery of other necessary post-transplant medications. Identification of differential risk with regards to one or more of these outcomes will be immediately actionable, factoring into decision-making about antibiotic choice by clinicians at the bedside. Through investigating the adverse outcomes associated with this common exposure, we can immediately influence clinical practice to promote rational and individualized antibiotic selection in children with leukemia and limit the toxicity that is associated with cure.

Notes:

Nick van Gastel, PhD

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2018 YOUNG INVESTIGATOR GRANT

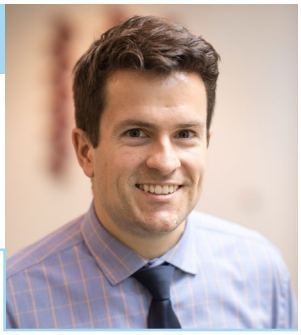
Targeting the Metabolic Drivers of Chemo Resistance in Acute Myeloid Leukemia

BACKGROUND: Acute myeloid leukemia (AML) is one of the most challenging childhood cancers to treat. Induction chemotherapy remains the standard of care, but the incidence of refractory and relapsed AML is high. It remains unclear how certain AML cells manage to survive the extreme stress of chemotherapy. The search for specific genetic mutations that lead to therapy resistance has thus far not been successful. While mutations may certainly play a role, cells have other systems to protect them from stress, such as shifting metabolic programs.

PROJECT GOAL: I hypothesize that chemo resistance in AML arises at the time of maximal selection pressure, with the residual cells manifesting distinctive metabolic features that enable their survival under the extreme stress of chemotherapy. By defining the metabolism of the residual, resistant cells in vivo using a new methodology, I have identified glutamine metabolism as a candidate pathway supporting chemo resistance in AML cells. In the current project, I aim to (i) dissect the mechanism by which activation of glutamine metabolism confers chemo resistance, (ii) develop a therapeutic strategy to eradicate chemo resistant AML cells by targeting glutamine metabolism, and (iii) explore the dynamics of glutamine metabolism during chemotherapy treatment in vivo using intravital microscopy. These studies will offer a new paradigm for how chemo resistance arises and will further deepen our understanding of the link between metabolism and cellular stress. The developed toolset will furthermore be of great value for future studies into cell metabolism in vivo.

Notes:

Colin Godwin, MD



Fred Hutchinson Cancer Research Center, Seattle, WA • colindg@uw.edu

2018 YOUNG INVESTIGATOR GRANT

Novel Antibodies to the C2-set Domain of CD33 for Acute Myeloid Leukemia Immunotherapy

BACKGROUND: Acute myeloid leukemia (AML) is a blood cancer associated with worse outcomes than other leukemias in children and improved treatments are needed. Engineering the immune system to fight AML (i.e. immunotherapy) is promising and the best-studied immunotherapy drug for AML is gemtuzumab ozogamicin (GO). GO acts by binding CD33, a protein found on leukemia cells in most AML patients, and delivering a chemotherapy drug specifically to those cells. Though children with AML treated with GO benefitted on average, half of patients did not benefit, simultaneously proving that CD33-targeted immunotherapy can be effective but also improved. One explanation for the suboptimal efficacy of GO is that CD33 exists in several forms – the full-length form (CD33FL) is recognized by GO, whereas a short form of the protein (CD33dE2) is not. In children with high amounts of CD33dE2, GO was not beneficial.

PROJECT GOAL: Therefore, I hypothesize that immunotherapy drugs recognizing both CD33 forms (CD33dE2+FL-targeting drugs) can improve on current CD33-targeting immunotherapy by attacking more leukemia cells in more patients. In our lab, we have shown that CD33dE2+FL-targeted drugs can be generated. Here, I will test my hypothesis by generating additional CD33dE2+FL-targeted drugs that could be used in humans and then testing these drugs head-to-head against CD33FL-targeted drugs in both a cell culture system and in murine models with humanized immune systems. I believe that my studies can efficiently determine the value of CD33dE2+FL-targeting immunotherapy while producing drugs ready for trials in children with AML, for whom better immunotherapy is required.

Notes:

Christian Hurtz, PhD

University of Pennsylvania, Philadelphia, PA • churtz@pennmedicine.upenn.edu

2018 YOUNG INVESTIGATOR GRANT

Cooperating Signaling Networks Regulate Cell Survival of Pediatric Ph-like ALL

BACKGROUND: B cell acute lymphoblastic leukemia (B-ALL) is the most common cancer in children. Despite significant improvements in chemotherapy combinations, approximately 20% of children with high-risk B-ALL will fail their treatments. It is now clear that there are different subtypes of ALL with different genetic mutations. These mutations activate and disrupt pathways within the leukemia cells that allows the cells to grow out of control. Our laboratory is specifically interested in the Philadelphia chromosome-like (Ph-like) ALL subtype, which is associated with a high risk of relapse and poor overall survival. Based on our preliminary data, we predict that Ph-like ALL cells are driven by three separate pathways that can be inhibited by targeted drugs called kinase inhibitors. Many of these drugs are already approved by the FDA for treatment of other diseases and have known, safe doses in children.

PROJECT GOAL: The goal of our study is to characterize the components of these cellular pathways and identify new treatment strategies that attack multiple pathways at the same time, which may result in better leukemia cell killing and prevention of chemotherapy resistance. We predict that this approach will be far more effective than the currently used chemotherapy regimens alone, and ultimately can improve cure rates for children with Ph-like ALL.

Notes:

Allison Barz Leahy, MD

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2018 YOUNG INVESTIGATOR GRANT

Pedi-PRESTO: Pediatric Patient-Reported Symptom Tracking in Oncology

BACKGROUND: More than 40,000 children undergo cancer treatment in the U.S. annually and all patients experience symptoms and side effects from their therapy. These can range in severity from minor to life-threatening and cause significant distress and suffering. The use of patient-reported outcomes, which are standardized reports of a patient's health condition directly from the patient or caregiver, can make patients and their parents feel more in control of their well-being and help doctors control their symptoms. Indeed, in adults undergoing chemotherapy, the use of patient-reported outcomes for symptom monitoring improves quality of life, decreases hospitalizations and increases survival. Despite the benefits seen in adults, the use of patient-reported outcomes in pediatric oncology is not common.

PROJECT GOAL: This study will investigate the feasibility, benefits and barriers to using patient-reported symptom monitoring for children with cancer, setting the stage for future studies examining the impact of this type of symptom monitoring on quality of life, hospitalization rate and illness severity in childhood cancer. Ultimately, patient-reported outcomes have the potential to help make children feel better, contribute to patient empowerment and assist parents and children in having discussions with their doctors about the things they care about most. When combined with other health data and deployed within the healthcare model, patient-reported symptom information can help tailor medical care, refine healthcare delivery and, potentially, help doctors recognize and avoid serious adverse events. This study is an essential first step in establishing the benefits of these measures for children with cancer.

Notes:

Takaya Moriyama, MD/PhD

St. Jude Children's Research Hospital, Memphis, TN • takaya.moriyama@stjude.org

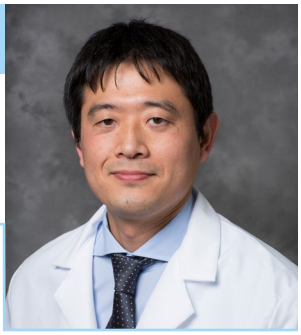
2018 YOUNG INVESTIGATOR GRANT

NUDT15 Polymorphisms and Individualization of Thiopurine Therapy in Children with Acute Lymphoblastic Leukemia

PROJECT GOAL: The major goal of this proposal is to develop pharmacogenetically-guided MP dosing algorithm to optimize thiopurine therapy in children with acute lymphoblastic leukemia (ALL). I hypothesize that we can rationally adjust thiopurine dosage according to variants in the NUDT15 gene and tailor their exposure to thiopurine active metabolites to the most efficient levels regardless of genotypes, similar to the principle of TPMT-guided thiopurine dose modification. I am confident that this research plan is an indispensable step to develop a genotype-guided MP dosing algorithm and eventually improves treatment outcome of pediatric ALL.

Notes:

Satoru Osuka, MD/PhD



Emory University, Atlanta, GA • satoru.osuka@emory.edu

2018 YOUNG INVESTIGATOR GRANT

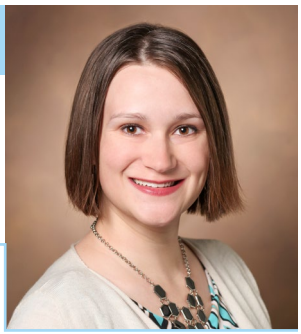
Investigating the role of BAI1 in the Metastasis of Medulloblastoma

BACKGROUND: Medulloblastoma (MB) is the most common pediatric brain tumor. MB cells commonly escape from the primary tumor, spread to the surface of the brain and in the spinal cord where they grow and form metastatic tumors, which cause patient death. Although we know a lot about primary MB, little is known about the mechanisms of metastasis. Currently, there are no effective therapies to inhibit MB metastasis; therefore, their molecular analysis is needed to develop new effective therapies. I found that BAI1, a tumor suppressor, is highly suppressed in MB by epigenetic silencing through EZH2. Low BAI1 is associated with poor prognosis of MB patients and increases MB cell metastasis in a murine model. Furthermore, I showed that BAI1 regulates the activity of TGFβ1 signaling, an important factor controlling metastasis in other cancers.

PROJECT GOAL: In this proposal, I plan to define how BAI1 interrupts TGFβ1 signaling. I will reactivate BAI1 using EZH2 inhibitor, EPZ6438, in MB cells, and evaluate whether it reduces MB metastasis in murine models. The role of BAI1 in MB metastasis has never been examined, making my research novel and innovative. My studies will provide proof-of-principle data to determine whether new epigenetic therapies can prevent or reduce metastasis in the pediatric patients with MB. EPZ6438 is clinically safe and is currently being tested in patients with other cancers in phase II clinical trials; hence, my findings could be rapidly translated in pediatric patients with MB. As a physician-scientist, my goal is to lead my independent research program with a focus on translational pediatric neuro-oncology.

Notes:

Rachael Schulte, MD



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2018 YOUNG INVESTIGATOR GRANT

Effect of SLCO Polymorphisms on High-Dose Methotrexate Clearance in Pediatric Oncology Patients

BACKGROUND: Methotrexate is a chemotherapy agent commonly used in pediatric oncology. 'High-dose' methotrexate is used to treat pediatric cancers such as acute lymphoblastic leukemia, non-Hodgkin lymphoma and osteosarcoma. While high-dose methotrexate is effective in treating these cancers (and others), it has many potential side effects which can be serious. Patients who receive high-dose methotrexate require close monitoring in the hospital until the drug is cleared from their system; the speed at which this happens can be different from one person to the next. If a person's body eliminates the drug too slowly, they may have more side effects, but if they eliminate it too quickly, the drug may not work as well to treat their cancer. We want to understand the role that genes (DNA) play in determining how quickly a person's body clears methotrexate and whether or not these differences influence side effects from this medication. Genes form an 'instruction manual' for the body and some genes tell the body how to eliminate methotrexate.

PROJECT GOAL: We will perform an initial research study at Vanderbilt followed by a larger study involving four academic children's hospitals. We will use the information from this research for personalized care for each patient based on their genetics to maximize the effectiveness of their chemotherapy while minimizing side effects.

Notes:

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2018 YOUNG INVESTIGATOR GRANT

Describing the Biological Impacts of Gain-of-function SAMD9 Mutations

BACKGROUND: Pediatric myelodysplastic syndrome (MDS) is a disorder that causes low blood counts because specialized cells within the bone marrow, or the 'blood factory of the body', do not mature correctly. When this happens, the cells cannot perform their intended job sufficiently. Currently, the only option for a cure for most children with pediatric MDS is a bone marrow transplant. Transplant is a difficult therapy with a less-than-ideal overall prognosis. Recently, our laboratory discovered that inherited mutations in two genes, SAMD9 and SAMD9L, play an important role in a child's risk of developing a specific type of MDS. These children have specifically lost DNA on chromosome 7 and this disease (also referred to as monosomy 7) is especially common in familial MDS. This association was not previously known. Furthermore, we have shown that the mutations in SAMD9 within a MDS patient typically result in a protein that performs its function at an increased level gain of function (GoF). This function decreases cell growth. The cells with a SAMD9 GoF mutation typically lose the copy of chromosome 7 containing the mutation. It is not well understood how, or by what trigger, this specific chromosome loss occurs.

PROJECT GOAL: We hypothesize that an inflammatory stimulus leads to increased SAMD9 production, which slows down cell growth at an increased rate if SAMD9 is mutated, and thus pressures cells without the mutation (cells with monosomy 7) to out-compete the cells with the mutation. We plan to develop a pediatric MDS model system to test this hypothesis. Understanding this process would ultimately help determine which patients would benefit from a bone marrow transplant.

Notes:

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CENTER OF EXCELLENCE SCHOLAR

Precision Medicine in Juvenile Myelomonocytic Leukemia

BACKGROUND: Juvenile myelomonocytic leukemia (JMML) is a malignant hematopoietic disorder of childhood associated with a dismal prognosis. The current standard of care involves hematopoietic stem cell transplantation (HSCT), resulting in many short-and long-term side effects. Despite the intensity of HSCT, outcomes are still poor with event free survival (EFS) at three years of only 50%, indicating the need for novel treatment strategies. Historically, robust biomarkers of favorable and unfavorable prognosis have been lacking in this disease. However, we have recently demonstrated that a hypomethylated DNA signature identified patients most likely to experience spontaneous resolution without HSCT, while the presence of a hypermethylated DNA signature portended a poor outcome even after HSCT. Our earlier work also showed that the presence of more than one somatic mutation was predictive of exceedingly poor outcomes. We thus hypothesize that stratifying patients at diagnosis using an integrated genetic and epigenetic risk stratification model will improve outcomes for patients by reducing toxicity for those in a low-risk category and by delivering novel combinations of targeted compounds for those in a high-risk category.

PROJECT GOAL: Aim 1: To establish a clinical methylation assay using pooled international samples as a validation cohort. Hypothesis: Clinically relevant DNA methylation testing will distinguish patients most likely to experience spontaneous resolution from those with highly aggressive disease.

Aim 2: To test the efficacy of trametinib alone and in combination with azacitidine in mouse models of JMML. Hypothesis: The altered methylome in patients with Ras-driven JMML will be sensitive to the combination of a hypomethylating agent and a MEK inhibitor.

Aim 3: To conduct a risk-stratified trial for patients with newly diagnosed JMML. Hypothesis: Using our published biomarkers will reduce the intensity of therapy for patients in the "low-risk" category and bring up front investigational treatments for patients in the "high- risk" category.

Notes:

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2018 YOUNG INVESTIGATOR GRANT

Accessing Combinatorial Effect of PARP Inhibitor with DNA Damaging Agent in Rhabdomyosarcoma at Single Cell Resolution

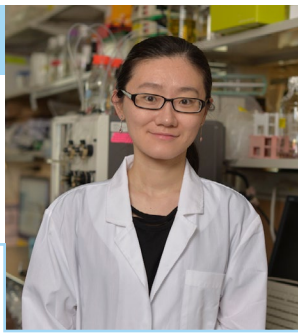
BACKGROUND: Combination therapies using cytotoxic drugs have revolutionized the treatment of pediatric rhabdomyosarcoma (RMS). However, cure rates have largely remained stagnant since their implementation. We recently generated an optically-clear, immune-deficient zebrafish that can engraft human RMS tumors, with growth kinetics and histological features similar to those grown in immune-deficient murine models. However, the zebrafish model has additional powerful attributes including high fecundity, low maintenance cost and the ability to assess growth kinetics at single-cell resolution. PARP inhibitors (PARPi) are now used in the clinic for the treatment of triple-negative breast cancer and ovarian cancer. More recently, it has been demonstrated that the addition of DNA-damaging agents potentiates PARPi cytotoxicity in a variety of cancer types, including Ewing sarcoma. To date, preclinical modeling of PARPi and DNA-damaging agents has yet to be studied in RMS.

PROJECT GOAL: Given that PARPi are now in clinical evaluation in children, are well-known to induce apoptosis in human RMS cell lines and potently synergize with DNA-damaging agents to elevate cancer cell killing in other sarcomas, this project aims to study if the combination of PARPi and DNA-damaging agents will be an effective therapy for pediatric RMS patients.

Aim 1 will elucidate an optimal combination of PARPi and DNA-damaging agents for human RMS cells using xenograft studies into immune-deficient zebrafish. Aim 2 will investigate mechanism(s) of drug action at single cell resolution. Aim 3 will validate the most efficient combination of PARPi and DNA-damaging agents for effects in human PDX models of RMS.

Notes:

Zibo Zhao, PhD



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2018 YOUNG INVESTIGATOR GRANT

Therapeutic Targeting of Childhood Leukemia by Pharmacological Inhibition of Proteolytic Cleavage of MLL1

BACKGROUND: MLL1, which is found in a large number of translocations associated with childhood leukemia, is post transcriptionally processed and cleaved by Threonine aspartase 1 (taspase1). But the biological significance of the cleavage of MLL1 by taspase1 in mammalian cells remains debated due to the different murine models used in previous studies. My preliminary studies in Shilatifard's laboratory demonstrated that taspase1 cleavage destabilized the MLL1 protein and primed the protein to its degradation pathways without affecting its nuclear localization and activation. I have further demonstrated that the phosphorylation on MLL1 flanking the taspase1 cleavage site is a crucial prerequisite for taspase1-mediated cleavage, thus providing us with a molecular means regulating the stability of MLL1. Our lab's recent study published in Cell in 2017 demonstrated that MLL1 stability controls a precise process that determines its activity and occupancy at the target genes.

PROJECT GOAL: The functions of MLL1 in leukemic pathogenesis are substantially affected if the MLL degradation machinery is altered. Therefore, I will take advantage of my findings of the role of taspase1 in the regulation of MLL1 stability through the biological function of MLL1 phosphorylation, coupled with taspase1 cleavage to develop new therapeutic approaches for the treatment of MLL translocation-based leukemia and in tumors with taspase1 overexpression.We propose to extend our data by characterizing AML CRCs in an integrated, unbiased way, in all major subtypes of AML. This will give us a unified understanding of the common and different ways in which AML arises, as well as create an unprecedented way of predicting common and subtype-specific AML vulnerabilities. Our data will create the basis for a new functional classification of AML and identify new targets for drug development.

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2018 YOUNG INVESTIGATOR GRANT

MYC-driven Core Regulatory Circuits in Neuroblastoma

BACKGROUND: Neuroblastoma is a tumor of the developing nervous system that occurs in young children with a median age of 17 months. While neuroblastoma is the diagnosis for just 10% of pediatric cancer patients, it accounts for more than 15% of childhood cancer deaths as many high-risk tumors never achieve a durable response to current therapies. My research efforts are focused on understanding the function of MYC family oncogenes in neuroblastoma tumorigenesis, as well as the genes they synergize with to promote malignancy. Recent advances have fundamentally changed our understanding of how cell identity and disease states are maintained. We have recently discovered that MYC works in concert with a small group of core transcription factors responsible for directing the entire cellular gene expression program. These master regulators bind cooperatively to noncoding regulatory elements known as super-enhancers, which are essential in driving expression of the genes required for cellular identity and in the case of diseases such as cancer, malignancy.

PROJECT GOAL: Using a combination of innovative computational and molecular approaches, I am now dissecting the mechanisms of this core transcriptional unit and determining their specific roles in the establishment and maintenance of tumor cell states. Additionally, I am elucidating the mechanism of action for clinically-used therapeutics targeting transcription to determine how they epigenetically reprogram neuroblastoma cell identity. Ultimately, this research could lead to the development of next-generation circuitry-directed therapeutics targeting the essential factors required for neuroblastoma cell growth and survival.

Notes:

POSTERS

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2016 YOUNG INVESTIGATOR GRANT

Targeting Metabolism as a Therapeutic Approach for High-Risk MYCN-Driven Neuroblastoma

BACKGROUND: In 30% of neuroblastoma cases aberrant activity of the MYCN-gene is present. Current therapies for high-risk MYCN-driven neuroblastoma are ineffective and only 40% of children with the disease can achieve long-term, event-free survival. These realities underscore the urgent need to discover novel therapeutic strategies that are more effective in combating neuroblastoma.

Because cancer cells reprogram their cellular metabolism in order to meet the increased energy and nutrient requirements of uncontrolled cell division, metabolic reprograming represents a fundamental difference between normal and cancer cells. Recent experimental and pre-clinical evidence provide encouraging perspectives to target this metabolic difference in treating cancers driven by c-MYC, a close relative of MYCN. My previous studies on T cell acute lymphoblastic leukemia (ALL) identified a key metabolic enzyme, dihydrolipoamide S-succinyltransferase (DLST), whose partial inactivation significantly inhibits c-MYC-driven leukemia development in zebrafish yet minimally affects fish development. I have since extended this research to include high-risk MYCN-driven neuroblastoma and found DLST is also important for neuroblastoma pathogenesis.

PROJECT GOAL: The goals of this proposed research are a) to test if targeting DLST alone or in combination with another metabolic enzyme (isocitrate dehydrogenase) can suppress neuroblastoma development and b) to understand how DLST contributes to MYCN-driven neuroblastoma. My research will determine viability of targeting DLST and generate information to guide metabolism-based therapy as a new strategy to treat high-risk neuroblastoma.

Notes:

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2016 YOUNG INVESTIGATOR GRANT

CD19 Delta Ex2 Isoform as a Target for Alternative Therapies in Relapsed Pediatric B-ALL

BACKGROUND: In B-cell acute lymphoblastic leukemia, the immune cells responsible for the production of antibodies that protect us from infections (B-cells) are dividing uncontrollably. There are treatment options for kids diagnosed with this type of cancer, however, too often the disease will stop responding to drugs (resistance) leading to further progression (relapse). There has been exciting progress in recent years in treating this resistant form of childhood leukemia. We have learned how to harvest the power of the child's own immune system by instructing it to recognize and destroy the cancer (CD19 immunotherapy). This revolutionary new therapy has been incredibly successful with almost 9 out of 10 patients being completely cured.

PROJECT GOAL: Unfortunately, in 10-20% of treated children the leukemia becomes invisible to the instructed immune system which leads to yet another reoccurrence and progression of the disease. Sadly, there are almost no treatment options left for attacking childhood leukemia that has become invisible to the immunotherapy. We believe that we have found a way to make the leukemia cells visible to the child's own immune system again. If we are successful, we will be able to prevent reoccurrence and increase cure rates for this devastating childhood cancer.

Notes:

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2016 YOUNG INVESTIGATOR GRANT

Developing Targeted Immunotherapy against Pediatric Acute Myeloid Leukemia

BACKGROUND: Despite significant improvements and outcomes for children with acute myeloid leukemia (AML), today's therapies can cause toxic side effects and too many young AML patients still relapse and die from the disease.

One type of therapy that has shown great promise harnesses a patient's immune system to fight their cancer by using gene-modified, cancer-specific T cells. Unfortunately, this approach has not been fully developed in AML, largely because molecules that are targeted by T cells (antigens) and are leukemia-specific have not yet been discovered. T cells can be engineered with one of a huge diversity of natural, antigen-specific T cell receptors (TCRs), each recognizing one antigen. Common AML-specific gene variants can produce abnormal antigens ("neoepitopes") that specific TCRs might recognize.

PROJECT GOAL: To develop new T cell therapy for pediatric AML, we propose to identify AML-specific neoepitopes by merging state-of-the-art gene sequencing of leukemia-specific variants with established HLA-binding prediction algorithms and a high-throughput immune-reactivity screen. We have already identified 166 neoepitopes created by 16 common genetic anomalies and isolated T cell clones recognizing five HLA-restricted neoepitopes from recurrent AML abnormalities. One of these T cells was able to kill AML in vitro. Our method of interrogating AML-specific mutations will reveal T cell targets with which we will develop novel immunotherapies with TCR-engineered T cells that will likely provide an important new therapeutic option for children with high-risk AML.

Notes:

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2017 YOUNG INVESTIGATOR GRANT

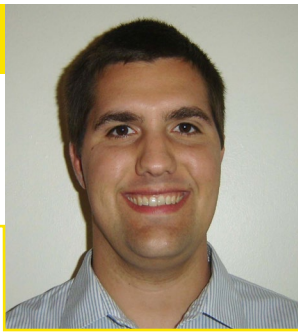
Elucidating the Role of N-Myc in a High-risk Pediatric T Cell Leukemia

BACKGROUND: Although many efficient therapies are available to treat acute lymphoblastic leukemia (ALL), there are subtypes of the disease that do not respond to the drugs or tend to relapse after an initial response. Among these subtypes is the early T cell progenitor acute lymphoblastic leukemia (ETP-ALL), an acute leukemia caused by an alteration of the T-lymphocyte progenitor cells. The mechanism that makes ETP-ALL so difficult to treat is still unknown. While analyzing the blood samples of children with acute leukemia, we observed that those affected by the ETP-ALL subtype had an abnormally high expression of the Mycn gene. This gene encodes for a protein (N-myc) that regulates cell growth and is critical for brain development. An excessive N-myc expression has been observed in brain tumors, therefore we considered that a similar mechanism might drive ETP-ALL too.

PROJECT GOAL: To test this hypothesis, we first generated an ETP-ALL mouse model and we derived cell lines from it. Since this disease model is faithfully overlapping with human ETP-ALL features, we are investigating if the ablation of N-myc (or other targets in this pathway) will make leukemia regress. By sequencing a series of human and mouse ETP-ALL we identified specific genetic and epigenetic elements that may represent viable drug targets to treat this disease. At the same time, we are transplanting patient-derived ETP-ALL cells into recipient mice and performing a drug screening to confirm sensitivity in vivo. This will allow us to see if the inhibition of N-myc is a promising therapy for ETP-ALL patients. In parallel, we are accurately analyzing the molecular changes induced by N-myc aberrant expression to better understand the elements that make this disease difficult to treat.

Notes:

Kristopher Bosse, MD



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2016 YOUNG INVESTIGATOR GRANT

GPC2 as an Oncogene and Immunotherapeutic Target in High-Risk Neuroblastoma

BACKGROUND: Neuroblastoma is an aggressive cancer of the developing nerves that occurs in young children. There has been little improvement in the prognosis of children diagnosed with high-risk neuroblastoma over the last few decades. Recent advances in the field of immunotherapy have resulted in unmatched enthusiasm for the use of this potent treatment to fight against neuroblastoma. However, we desperately need new molecules to safely target on neuroblastoma cells with immunotherapy. We recently discovered that the gene glypican-2 (GPC2) is selectively found on the neuroblastoma cell surface (but not on most normal cells) and that GPC2 helps neuroblastomas grow aggressively. GPC2 may also act as a signal to attract certain types of immunotherapies to the tumor, such as genetically modified immune cells called chimeric antigen receptor (CAR) T cells.

PROJECT GOAL: This work aims to validate a new targeted and potent immunotherapy for children with neuroblastoma. First, the project will focus on understanding why there are high levels of GPC2 on neuroblastomas and how GPC2 helps neuroblastomas grow aggressively. We will also engineer GPC2 redirected CAR T cells to specifically seek out neuroblastoma cells to see if this prevents tumors from growing. In addition, learning how GPC2 helps neuroblastomas proliferate could provide us with critical information that may contribute to improved neuroblastoma treatments.

Notes:

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2015 YOUNG INVESTIGATOR GRANT

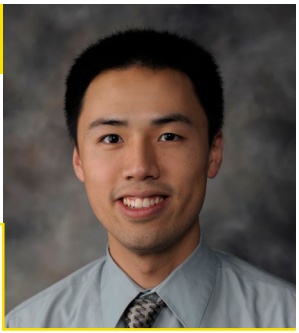
Elucidating the Mechanism of ERK Mediated Pathogenesis of LCH

BACKGROUND: Langerhans cell histiocytosis (LCH) is a rare form of cancer that occurs mostly in children. The incidence of LCH is 3 to 5 cases per million children, similar to that observed in Hodgkin Lymphoma or acute myeloid leukemia. Despite similar incidence and survival, LCH patients have benefited from far less research funding and attention than other childhood hematologic neoplasias, likely due to incomplete understanding of the disease. LCH is caused by abnormal proliferation of cells derived from bone marrow. Recently mutations in the MAPK pathway have been characterized in LCH patients. However, the exact origin of LCH is still not known and the rationale for treatment is therefore largely empiric.

PROJECT GOAL: The Histiocytosis Program at Texas Children's Cancer Center (TXCCC) has the largest Histiocytosis patient population in North America. Using this resource, we have validated BRAF gene mutation and have observed that the presence of the mutation correlated to treatment failure. In addition, we have identified mutations in MAP2K1 gene, which might potentially contribute to the pathogenesis of LCH. Hence, the current proposal aims to identify the underlying disease mechanism of LCH by molecular dissection of the effect of each of the observed mutations in LCH patients. Specifically, we will query how each of the mutations contribute in activating a protein called extracellular regulated kinase (ERK), which we hypothesize is the critical determinant in LCH pathogenesis. The findings from the proposed study will have broad implications for improved diagnostic and therapeutic benefits for LCH patients.

Notes:

Kenneth Chen, MD



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2016 YOUNG INVESTIGATOR GRANT

The Role of MiRNA Impairment in Wilms' Tumor Formation

BACKGROUND: Wilms' tumor is the most common pediatric kidney cancer. While many patients are cured, children with high-risk disease continue to have poor outcomes. No alternative targeted therapies have proven effective for Wilms' tumor. One-fifth of Wilms' tumors harbor mutations in the enzymes that are responsible for producing microRNAs, small RNA molecules that regulate expression of target genes. How these mutations contribute to tumor formation is unknown.

PROJECT GOAL: I will build on these findings by defining precisely how these mutations drive tumor formation. Specifically, the central hypothesis to be tested is that DICER1 and DROSHA mutations cause Wilms' tumor by impairing production of key microRNAs and de-repressing key oncogenes. Understanding exactly how these mutations cause Wilms' tumor will lead to future studies investigating novel strategies to therapeutically target these tumorigenic mechanisms. I have identified one key microRNA target gene, PLAG1, which regulates IGF2.

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CENTER OF EXCELLENCE SCHOLAR

Sensitizing Pediatric Tumors to Immunotherapy by Targeting the Tumor Immune Microenvironment

BACKGROUND: The majority of patients do not respond to immune checkpoint blockade, suggesting the existence of resistance mechanisms that limit the efficacy of current immunotherapeutic approaches. Pediatric tumors, in particular, are refractory to therapy with checkpoint blockade, but the mechanisms that lead to low response rates in children are poorly understood. We hypothesize somatic, cancer-associated mutations account for heterogeneity in spontaneous response to tumors and response to immunotherapy.

PROJECT GOAL: We have shown specific oncogenes can confer resistance to immune attack by modulation of the immune microenvironment. Our preliminary studies have used a pooled in vivo screen of hundreds of tumor-associated mutations in a mouse tumor model to reveal that a mutation in Phosphoinositide-3 Kinase (PI3K), PIK3CA H1047R, confers resistance to checkpoint blockade by causing tumor cells to recruit immunosuppressive MDSCs. Indeed, treatment with a PI3Kinase inhibitor restores sensitivity to anti-PD-1 therapy. We propose a model whereby PI3K activation recruits an immunosuppressive microenvironment that inhibits CD8+ T cells after activation by anti-PD-1. Our data suggest PI3K has, in addition to its well-described oncogenic role, a role in tumor immune evasion mediated by establishment of an inhibitory myeloid microenvironment. As such, activating mutations in PI3K may be useful as a biomarker of poor response to immunotherapy, and these studies provide a rationale for therapeutic combination trials of PI3K inhibition with checkpoint blockade and other myeloid-targeting immunotherapies. Pediatric tumors in general, but specifically osteosarcoma and rhabdomyosarcoma, are particularly dependent on the PI3K pathway and would be expected to benefit from such an approach.

Notes:

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2015 'A' AWARD

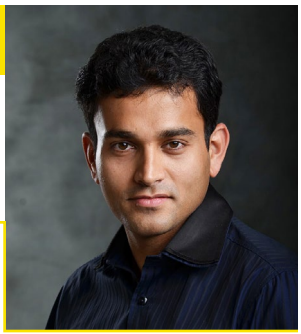
Genetically Modified, Cord Blood Derived Natural Killer Cell Therapy for High Grade Pediatric Brain Tumors

BACKGROUND: Certain brain cancers in children do not respond well to current treatment options. Newer therapies, like immunotherapy—which uses the body's own defenses (the immune system) as a "drug" for diseases—are particularly promising. However, these therapies are not readily applicable in the brain cancer setting. Brain cancers do not have any single identifying mark that the immune system can use to differentiate it from healthy organs and the cancers themselves maintain an environment that is harmful to immune cells. Therefore to be useful, immunotherapies need to reliably differentiate brain cancer from the rest of the body and remain functional in hostile surroundings.

PROJECT GOAL: Among immune cells, a certain group called natural killer cells (NK cells) distinguish "self" from "nonself" as a means of detecting their potential targets. We believe that if we use "nonself" NK cells, we can potentially recognize tumors. We propose using cord blood as a source of NK cells because of the ready availability of multiple cord blood banks around the world, and we further propose to arm these NK cells so that they can withstand the harmful effects of the cancer environment. This work will pave the way for the use of these novel cell therapies for brain cancer in children.

Notes:

Rohan Fernandes, PhD



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2016 'A' AWARD

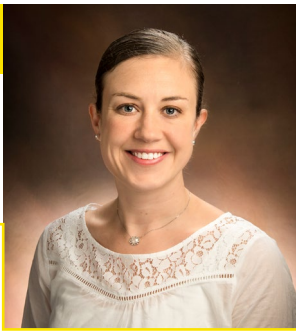
An Engineered Nanoimmunotherapy for Treating Neuroblastoma

BACKGROUND: Neuroblastoma is a common childhood cancer accounting for 15% of cancer-related deaths in children. Patients within this "high-risk" population have overall survival rates ranging between 30% and 40%. We have developed a "nanoimmunotherapy," which combines the advantages of nanoparticles and immunotherapy for treating neuroblastoma. Specifically, we use Prussian blue nanoparticles for photothermal therapy combined with anti-CTLA-4 immune checkpoint inhibition. Photothermal therapy serves as a method to rapidly destroy tumors by heat and, in doing so, breaks up the tumor, which results in a vaccination effect. These effects are complemented by the addition of anti-CTL-4 immune checkpoint inhibition, which elicits robust antitumor responses from the immune system. In earlier studies, we have demonstrated that our nanoimmunotherapy can effectively treat neuroblastoma tumors and confer long-term survival in animal model of the disease. The results are significantly better than those obtained by using the nano- or immunotherapy by itself. Importantly, treated animals are able to reject tumor recurrence indicating that our therapy not only treats neuroblastoma but also confers immunity against recurrence.

PROJECT GOAL: In this project, we seek to elucidate the effects of our nanoimmunotherapy on the immune system and understand how these effects can be harnessed to treat neuroblastoma. Successful completion of this project will facilitate further development of nanoimmunotherapy in an animal model of high-risk neuroblastoma and ultimately clinical testing of this possible treatment regimen.

Notes:

Andrea Flynn, MD



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2017 YOUNG INVESTIGATOR GRANT

Targeting Protein Translation to Antagonize MYC-driven Neuroblastoma

BACKGROUND: Neuroblastoma is a childhood tumor that arises from the developing sympathetic nervous tissue, and often behaves aggressively. Treatment currently includes intensive therapy, yet only about 50% of children with high-risk disease survive. Difluoromethylornithine (DFMO) is an oral agent that is FDA-approved to treat African Sleeping Sickness (Trypanosomiasis). DFMO blocks an enzyme (ODC) needed to synthesize polyamines from the urea cycle, which have been found to be necessary for cell survival. Tumors in which amplification of the MYC oncogene are particularly dependent on polyamines and we aim to exploit this dependence.

PROJECT GOAL: We and others have shown that DFMO has strong activity against neuroblastoma cells (which often have MYCN amplification), so we aim to "re-purpose" DFMO as a novel neuroblastoma drug. We will explore which genetic amplification events make neuroblastoma cells vulnerable to DFMO. We found that a subset of neuroblastomas have ODC1 amplification (which encodes the enzyme that DFMO targets) in addition to MYCN amplification. We aim to uncover which amplification events (if any) lead to differential response to DFMO. Our work to date demonstrates that DFMO inhibits protein translation in neuroblastoma cells, and we aim to understand the mechanism(s) behind this inhibition. With this knowledge, we will be able to better predict which children with neuroblastoma may respond to DFMO and which additional therapies may work in synergy with DFMO.

Notes:

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2017 YOUNG INVESTIGATOR GRANT

Anthracycline-Induced Cardiac Toxicity in Pediatric Acute Myeloid Leukemia

BACKGROUND: Acute myeloid leukemia (AML) is the most life-threatening form of leukemia requiring the most intensive treatment. While advances in its treatment have improved survival, chemotherapy exposure results in significant side effects. One class of drugs, anthracyclines, increases the risk for heart complications. On-treatment cardiotoxicity has been linked to high risk for relapse and poorer overall survival. Efforts to improve the long-term cardiovascular health and mortality among AML survivors should be directed at early detection and prevention of cardiotoxicity. There is little data evaluating the factors that increase the risk for early-onset anthracycline-associated cardiac toxicity or the clinical utility of cardioprotectantion in pediatric AML. The typical measures used to monitor heart function in childhood cancer may not detect injury until a serious amount of irreversible damage to the heart has taken place.

PROJECT GOAL: The proposed project aims to identify demographic and clinical correlates of early cardiotoxicity and to evaluate myocardial strain and strain rate as early markers for later dysfunction in an effort to improve the detection of high-risk patients. We also aim to assess the potential utility of dexrazoxane as a cardioprotective intervention in pediatric AML.

Notes:

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2017 YOUNG INVESTIGATOR GRANT

Epigenomic Mechanisms of Neuroblastoma Tumorigenesis

BACKGROUND: Neuroblastoma is a pediatric cancer of nerves that develop outside of the brain. Commonly, it presents as a tumor mass in the abdomen. Although the five-year survival rate for children in the low- and intermediate-risk groups ranges over 95% children with high-risk disease have only a 40% likelihood of survival. Furthermore, high-dose chemotherapy increases risk of infertility, severe hearing loss, cardiac toxicity, and/or secondary cancers. We urgently need to identify new therapies for children with high-risk disease. In each child's tumor, we detect very few mutations within the portion of genes that codes for functional proteins (exons). The remaining mutations responsible for neuroblastoma likely reside within the non-coding region of the tumor's DNA, either within genes (introns) or between genes. We now know that these non-coding regions play important roles in gene regulation as they help turn genes on or off. We can gauge this regulation based on genome-wide signatures of proteins that package the DNA in our cells (histones). Therefore, mutations within these regions can cause gene dysfunction, which can lead to cancer.

PROJECT GOAL: My project focuses on using sequencing to find mutations within non-coding regions of the neuroblastoma tumor genome that disrupt the normal cell state and test their biological function and clinical relevance. We hope to identify novel genomic regions which are susceptible to therapeutic intervention and can be tested preclinically.

Notes:

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2016 YOUNG INVESTIGATOR GRANT

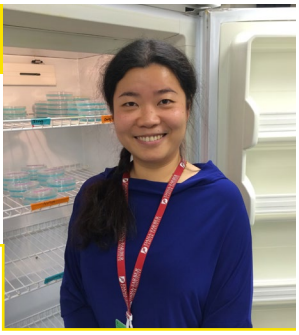
A Role for Non-Canonical Wnt/PCP Signaling in Growth and Self-Renewal of Embryonal Rhabdomyosarcoma

BACKGROUND: Relapse is the major clinical problem facing patients with embryonal rhabdomyosarcoma (ERMS), a pediatric malignancy of the muscle. In ERMS, a small population of cells is responsible for relapse and if these cells could be eliminated, tumors would regress and patients could remain relapse free. In the Langenau lab, we use zebrafish to uncover novel biology underlying ERMS and to help understand tumor propagation in humans. Wnt signaling is an important regulator of muscle development, and in the stem cell compartment a form of non-canonical Wnt signaling called Planar Cell Polarity signaling (Wnt/PCP) is required for stem cell maintenance and self-renewal. In humans, ERMS factors known to regulate Wnt/PCP are expressed and my data suggests that Wnt/PCP signaling plays a role in growth, self-renewal and specification of specific tumor cell types in our zebrafish ERMS model and in human cells. The relationship between Wnt/PCP signaling, ERMS and cancer progression in general remains poorly understood, therefore this project aims to further understand Wnt/PCP signaling during ERMS growth and self-renewal.

PROJECT GOAL: In Aim 1, I will define the role for factors involved in Wnt/PCP signaling as modifiers of tumor propagating cells in zebrafish ERMS. Aim 2 will characterize the therapeutically targetable genetic pathway as a mediator of ERMS biology in vivo using our zebrafish kRASG12D ERMS model and in human ERMS cell lines. Finally, Aim 3 will extend my findings to a pre-clinical mouse xenograft model and define Wnt/PCP signaling as a potential target for patient therapy.

Notes:

Shuning He, PhD



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2015 YOUNG INVESTIGATOR GRANT

A Translational Approach to Identify Drugs with Specific Activity Against EZH2 Mutant High Risk T-ALLs and ETP ALLs that Overexpress the JDP2 bZIP Transcription Factor

BACKGROUND: Outcomes for children with acute lymphoblastic leukemia (ALL), the most common childhood malignancy, have improved dramatically over the last 20 years. However, a subset of patients with ETP-ALL have an extremely poor prognosis. Very recently, it was discovered that many of these high-risk tumors and other high-risk T-ALLs have acquired disruptions of the EZH2 gene. We have shown that the JDP2 gene is upregulated in both ETP-ALL and other high-risk T-ALLs and is required for the growth and survival of these leukemia cells. Thus, JDP2 is a major mediator of aberrant ALL cell survival, drug resistance and the poor prognosis in high-risk ETP- and T-ALL.

PROJECT GOAL: I have established a transgenic zebrafish model that overexpresses JDP2 in thymocytes and develops T-ALL with high penetrance. In this project, I have used these zebrafish to identify small-molecule drugs that will kill the lymphoblasts that express cancer-causing levels of JDP2. After analysis of 1280 FDA-approved drugs in the Prestwick Chemical Library, I have identified a set of approved drugs that can selectively kill JDP2 over-expressing lymphoblasts. In addition, I also analyzed newly developed Phase I/II drugs that have shown activity in adult cancers, and identified two classes of drugs with selective activity against leukemia-initiating thymocytes. Currently, I am working on further validation of these drugs in different leukemia models and human leukemic cell lines.

Notes:

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2016 'A' AWARD

Engineering the CAR T Cells to Overcome Tumor Derived Immune-Inhibition in Glioblastoma

BACKGROUND: Outcome for children with glioblastoma (GBM) is extremely poor. It is highly resistant to conventional methods of treatment and less than 16% of children survive over five years after diagnosis. In addition, aggressive combined therapy causes significant harm. Recent advancements in cancer immunotherapy have enabled us to genetically engineer patients' own T cells to express artificial molecules called chimeric antigen receptors (CARs) that specifically recognize the GBM-associated protein, human epidermal growth factor receptor 2 (HER2).
A phase I trial for HER2 immunotherapy was safe with no treatment-related toxicities and offered clinical benefit to 50% of treated patients. The median survival doubled compared to the other salvage interventions for GBM patients failing front-line therapy. There is still a need to improve the killing activity of these T cells, since tumor-derived immune-inhibitory molecules present at the tumor site can turn off these cells upon encounter. Blocking this immune-checkpoint using monoclonal antibodies has improved outcomes for a subset of resistant cancers, but the best means for overcoming this tumor derived inhibitory mechanism is largely unknown at present.

PROJECT GOAL: Our methodology will enable the T cells to kill GBM cells expressing HER2 and overcome/transform the immune-checkpoint in favor of T cells without organ-system toxicities. This study has the potential to dramatically improve outcomes for GBM patients upon translation into a clinical trial and advance information leading to future standards in pediatric brain tumor immunotherapy.

Notes:

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2015 YOUNG INVESTIGATOR GRANT

Elucidating Mechanisms Driving Renal Medullary Carcinomas to Deliver a Rational Approach to Cancer Directed Therapy

BACKGROUND: Through the natural history of patients with sickle cell trait or disease, we have learned that they are at risk of a rare cancer, renal medullary carcinoma. With a very poor prognosis, it is critical that we understand the molecular underpinnings of this disease in order to devise improved therapeutic options. Unfortunately, there are no models available to study this cancer in the laboratory.

PROJECT GOAL: We have developed several models of renal medullary carcinomas as part of a direct to patient outreach program. These novel model captures the known biology and allowed us to explore additional biology. Furthermore, using high throughput technologies developed in our laboratory and at the Broad Institute of Harvard and MIT, we have identified the ubiquitin-proteasome as being a specific vulnerability for RMC as well as other SMARCB1 cancers.

Funding and support from ALSF has allowed us to 1) identify that these cancers are dependent upon loss of SMARCB1 similar to other cancers like rhabdoid tumor and atypical teratoid rhabdoid tumor, 2) identify the ubiquitin-proteasome pathway as being essential to the survival of SMARCB1 cancers and 3) uncover the mechanism by which this occurs.

Notes:

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2017 YOUNG INVESTIGATOR GRANT

End-of-Life Care of Children with Cancer: Variation and Stakeholder Priorities

BACKGROUND: Two-thirds of children dying of cancer receive intense medical treatments--being hooked up to machines that artificially keep them alive or dying away from their home--despite growing evidence that many do not want such care. In a preliminary study, we found high rates of intense care in patients aged 15-21, those of Hispanic ethnicity and in children with blood cancers. Studies in older adults suggest the rates of intense end-of-life care vary by hospital, but this has not been studied in children. Additionally, intensity of end-of-life care has been shown to be an important marker of quality of end-of-life care in adult oncology patients, but little is known about its appropriateness in pediatric oncology.

PROJECT GOAL: We will first learn the hospital characteristics associated with high-intensity end-of-life care for kids with cancer. We will also ask bereaved family members and pediatric cancer experts for their thoughts on intensity of end-of-life care and other adult end-of-life quality markers and if there are unique quality markers for end-of-life care for children. This study can lead to new end-of-life quality markers for this vulnerable population, which may lead to future studies and treatments. Additionally, learning characteristics of hospitals that have high-intensity end-of-life care can set the stage for in-depth studies of high- and low-intensity hospitals and provide interventions to improve the quality of end-of-life care for this underserved population.

Notes:

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2017 YOUNG INVESTIGATOR GRANT

High-Throughput Gene-Editing via Microfluidic Cell Deformability to Enable Off-the-Shelf Allogeneic Cellular Immunotherapies

BACKGROUND: Chemotherapy, surgery, radiation therapy, and hematopoietic stem cell transplantation strategies are cornerstones in treating pediatric cancers. Unfortunately, there are subsets of patients with relapsed and/or refractory disease that have few options beyond end-of-life supportive care. Immunotherapies that utilize T-cells engineered to recognize and to harness the immune system to attack cancer cells are offering new options for these critically ill children. These approaches have shown promise in pediatric patients with difficult to treat leukemias but are limited to specialized centers in part by how efficiently, cost-effectively, and quickly the immune cells can be engineered into cancer-fighting cells.

PROJECT GOAL: This project focuses on developing and applying engineering solutions that leverage advances in nanoscience and microfluidics to enable the rapid, safe, cost-effective, and efficient generation of cellular immunotherapies. We are designing and testing microfluidic technologies that enable rapid delivery of genome-editing machinery into cells rapidly via temporary pores that form at cellular membranes as cells are squeezed through narrow channels. This strategy is gentler and less toxic than competing approaches which require the use of external electric fields. To avoid clogging the device, we line the microchannels with bio-inspired surface chemistries that prevent cells from becoming stuck via a "slip and slide" effect. Our platform enables rapid and efficient gene-editing of T-cells at scales compatible with mass production to effectively establish assembly lines for these therapeutic cells that overcome obstacles in the clinical translation and deployment of cellular immunotherapies.

Notes:

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2014 YOUNG INVESTIGATOR GRANT

Molecular Mechanism and Development of Therapeutic Strategies Targeting MYCN-induced Calcium Signaling in Advanced Neuroblastoma

BACKGROUND: Neuroblastoma (NB) is a pediatric cancer that forms during the development of the nervous system. The treatment of advanced stage of NB and NB in older children is extremely difficult because children are often diagnosed only after metastases are widespread. Advanced NB has a poor prognosis with a survival rate of only 10-40%. One of the most striking indicators of a poor prognosis is the abundance of the protein MYCN. We have found that tumor cells with high levels of MYCN express increased levels of the calcium channel TRPM7. Calcium is a major regulator of cancer cell growth and migration (e.g., metastasis). MYCN regulates this channel indirectly but through a metabolic enzyme called Ornithine Decarboxylase (ODC), which is known to contribute to NB.

PROJECT GOAL: This study investigates the role of the calcium permeable ion channel, transient receptor potential melastatin family 7 (TRPM7). This protein mediates aberrant calcium signaling that promotes the progression of NB tumors. My first specific aim focuses on revealing how TRPM7 expression and activity is regulated by MYCN/ODC. A second aim focuses on pharmacological inhibitors of TRPM7 to reduce malignancy and will establish TRPM7 as a marker for advanced stage NB. Initial findings show that inhibiting TRPM7 significantly decreases the growth and spread of tumors. In addition, treating NB tumors with FDA-approved FTY720 or a-difluoromethylornithine (DFMO) significantly decreases TRPM7-mediated growth and progression. This may lead to identifying a new biomarker for NB, as well as a potential treatment strategy for advanced stage NB.

Notes:

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2016 YOUNG INVESTIGATOR GRANT

Genetically-Engineered T Cells as Therapy for Pediatric Glioma

BACKGROUND: This project intends to develop antigen-specific T cells as an effective immunotherapy for high grade glioma, a brain tumor that is largely resistant to conventional therapies. Using the patient's own immune system to fight cancers is one promising approach to improve outcomes for pediatric cancer patients who do not benefit from current therapies. However, the body's immune defenses against cancers often fail because the cancers do not induce or actively inhibit immunity. Cancer treatments consisting of the infusion of T cells that recognize tumor antigens, a molecule present on many cancers, have shown promise in early clinical studies. The developed approach for patients with high grade glioma targets a molecule called IL13Ra2, which is present on glioma cells. We have generated IL13Ra2-specific T cells with a genetic approach and have shown that these cells have anti-glioma activity in pre-clinical models.

PROJECT GOAL: We propose to optimize our IL13Ra2-targeted approach for high-grade glioma. In Aim 1, we will evaluate if adding an additional gene to T cells that provides a growth factor called IL-15 can further enhance the anti-glioma activity of our IL13Ra2-specific T cells. In Aim 2, we will then explore if targeting an additional antigen called EphA2 on glioma cells further enhances anti-glioma effects. If our pre-clinical approach is successful and a clinical study is justified, we have the 'set-up in place' to develop such a study at our center.

Notes:

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2017 'A' AWARD

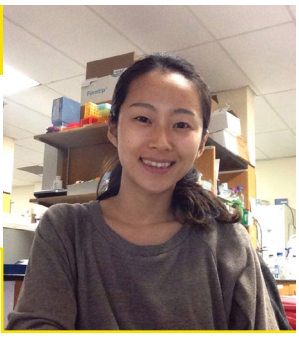
Novel Approaches to AML Differentiation Therapy

BACKGROUND: Children with acute myeloid leukemia (AML) are in desperate need. Survival of kids with AML remains poor because our treatments haven't changed much in 30 years. AML is a disease of DNA – mutations found in leukemia DNA are not seen in normal blood cells. However, we think that the physical structure of DNA itself could also be important in leukemia development. If the DNA in a cell was stretched out, it would be six feet long, yet it has to be tightly packed to fit inside the head of a pin. When we looked at leukemia under the microscope, the DNA was not as tightly wound as it should be. We suspected that AML might result from problems in DNA packing. We found that one protein, often increased in AML cells, directly loosens DNA winding. This especially occurs in kids with Down syndrome or in situations where leukemias have extra copies of chromosomes. When the DNA is "unpacked," the cell loses its ability to develop normally, leading to AML.

PROJECT GOAL: In this project, we propose a new idea in leukemia research: AML may result from unwinding of tightly-packed DNA. Drugs that reverse this process could offer new treatments. We will use cutting-edge techniques to understand how DNA unpacking promotes leukemia and test if drugs that target DNA packing kill leukemia cells. We hope our work will lead to new clinical trials for children with leukemia, using drugs that are more effective and less toxic than our current therapies.

Notes:

Sunhye Lee, PhD



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2016 'A' AWARD

Single-cell RNA-seq Profiling of Transcriptional Transition States during Human Retinoblastoma

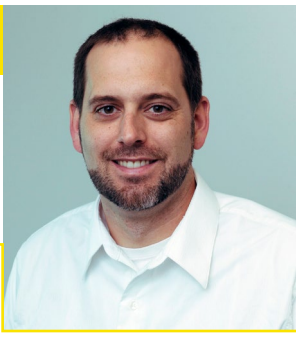
BACKGROUND: Retinoblastoma is a childhood ocular tumor initiated by the inactivation of the RB1 gene and subsequent loss of retinoblastoma protein (pRB). Although pRB loss is the key-initiating event, the molecular mechanisms controlling the transformation of a normal retinal cell into malignancy remain unclear. This project seeks to define the cell state transitions that follow RB1 inactivation in the cone photoreceptor precursor to identify mediators of tumor initiation and transformation that can be targeted to better treat and prevent retinoblastoma.

PROJECT GOAL: Aim 1 will identify human-specific features of the cone precursor gene expression program that collaborate with pRB loss to initiate tumorigenesis, to identify key cancer-predisposing factors. Aim 2 will define the sequential gene expression changes in cone precursors as they begin to proliferate. Individual cells will be analyzed by single-cell RNA sequencing (scRNA-seq) and the tumor initiation states of each cell will be put in order. Aim 3 will define the additional changes that occur after the pRB-depleted retinal cells begin to form tumors in a mouse model. The gene expression changes detected following pRB depletion and in growing tumors will be studied to define their roles in tumorigenesis.

This study seeks to identify novel tumor initiation and transformation-related events that can be pharmacologically targeted to suppress tumorigenesis. It will spark new approaches to treat and prevent retinoblastoma and potentially other cancers in genetically-predisposed children.

Notes:

Jeffrey Magee, MD/PhD



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2016 'A' AWARD

The Role of Inherited MLL3 Single Nucleotide Variants and Fetal Epigenetic Programming in Infant Leukemogenesis

BACKGROUND: My goal is to improve treatments for infant leukemia patients and genetic counseling efforts for their families. To realize this goal, we will develop mouse models to study the interactions between MLL translocations and inherited genetic variants that potentially predispose to infant leukemia – in this case variants in the MLL3 gene. Mice are the optimal model for these studies because they are genetically tractable and mouse blood development closely approximates human blood development.

PROJECT GOAL: Using mouse models, we will learn how genes such as MLL3 regulate blood development and leukemia development. We will use these models to identify druggable pathways that can be targeted to improve survival and reduce toxicity. We will develop a novel method to introduce the genetic variants found in human patients into the mouse genome and test whether they accelerate leukemia development. This will allow us to characterize interactions between many different variants without generating and breeding many different lines of mice. This will be a powerful tool to determine which genetic differences between leukemia patients and healthy children are important for leukemia development and which are inconsequential. We will build a database of functionally proven, leukemia-promoting variants that will inform cancer predisposition counseling and precision medicine. I hope to expand this program to encompass other pediatric malignancies, as inherited genetic variants are becoming increasingly recognized as an underlying cause for pediatric cancer.

Notes:

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2016 'A' AWARD

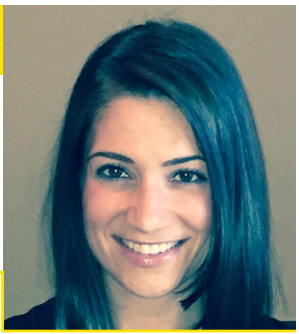
Role of Primary Cilium Signaling and Dynamics in Medulloblastoma Initiation and Progression

BACKGROUND: Medulloblastoma is the most common malignant brain tumor affecting children and comprises ~33% of pediatric brain cancers. Medulloblastoma is a tumor originating in the cerebellum with most tumors arising from unregulated proliferation of cerebellar granule cells. Current treatment strategies are associated with high morbidity and mortality related to recurrence. Thus, there is an urgent need for more effective and targeted therapies that reduce toxicity and prevent recurrence. Cerebellar granule cells proliferate after birth in a developmentally regulated process that depends on the signaling molecule, sonic hedgehog and the primary cilium, a hair-like dynamic signaling antenna for cells, before migrating and maturing as neurons. However, the role of ciliary signaling in granule cell proliferation and ciliary dynamics during migration/maturation in causing medulloblastoma is unknown.

PROJECT GOAL: Using newly developed mice models and studying patient tumor samples, we propose modeling medulloblastomas, particularly sonic hedgehog subtype, as a disease of aberrant cerebellar granule cell development. We determine mechanisms underlying the balance between cilia-regulated proliferative and maturation signals and study these developmental aspects in the context of tumor initiation and progression. Our fundamental discoveries of key factors in the negative regulation of the sonic hedgehog pathway and approaches to study primary cilia dynamics in the context of granule cell cycling and maturation will not only provide unique insights into medulloblastoma initiation and progression, but will also identify key therapeutic targets to treat this devastating pediatric cancer and in preventing recurrence.

Notes:

Joanna Pierro, DO



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2017 YOUNG INVESTIGATOR GRANT

Identification and Characterization of Pathways Dysregulated by MMSET/NSD2 E1099K Mutation in Relapsed Pediatric Acute Lymphoblastic Leukemia and Their Role in Drug Resistance

BACKGROUND: Relapsed acute lymphoblastic leukemia (ALL) remains a major cause of pediatric cancer death. Understanding the underlying biological pathways that promote drug resistance and lead to relapse are therefore paramount to improve patient outcomes. Prior work by our lab and others has identified that two-thirds of mutations seen at relapse occur in epigenetic regulators. The current proposal focuses on mutations in MMSET (NSD2/WHSC1) an epigenetic writer which encodes a histone methyltransferase that catalyzes the conversion of histone 3 lysine 36 into its mono- and demethylated (H3K36me2) forms as well as stereotactic inhibition of EZH2 mediated histone 3 lysine 27 trimethylation (H3K27me3). The activating glutamate to lysine substitution at amino acid 1099 (E1099K) in MMSET has been recognized as one of the most common mutations in relapsed ALL in children, however the effects of this mutation are not well understood.

PROJECT GOAL: As the MMSET E1099K mutation is one of the most frequently observed mutations at relapse, we hypothesize that it is a major driver of disease recurrence. The overarching goals of this proposal are to discover the biological pathways affected by this mutation and to identify potential targets of future therapy. Understanding the mechanism of chemoresistance or the pathways modulated by overactivating MMSET mutations that lead to a clonal advantage are likely to have a significant impact on designing new therapy to improve outcomes.

Notes:

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2014 YOUNG INVESTIGATOR GRANT

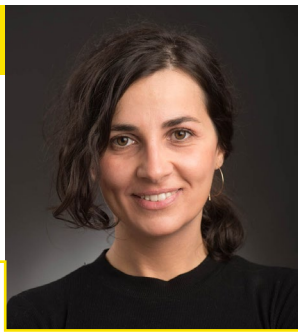
Targeting mitochondrial one carbon folate metabolism for novel T-cell acute lymphoblastic leukemia therapy

BACKGROUND: While cure rates for pediatric acute lymphoblastic leukemia (ALL) have improved dramatically over the last several decades, ALL remains the second leading cause of cancer-related death in children. There continues to be an unmet need for effective therapies for patients with T-cell acute lymphoblastic leukemia (T-ALL), particularly those with relapsed or refractory disease. T-ALL is a disease generally responsive to drugs targeting metabolism, including methotrexate and asparaginase, which form the backbone of T-ALL therapy. Thus, I hypothesize that novel approaches to targeting metabolism may be particularly relevant in T-ALL.

I screened a panel of leukemia cell lines against small-molecule inhibitors of methylene tetrahydrofolate dehydrogenase 2 (MTHFD2) and serine hydroxymethyltransferase 2 (SHMT2), enzymes of the mitochondrial one carbon folate pathway. I discovered that T-ALL cells are highly sensitive to these inhibitors, more so than other leukemia cell lines. This project aims to use the small molecule inhibitors of MTHFD2 and SHMT2, as well as genetic suppression of these enzymes, in vitro and in vivo, to study the mechanistic role of SHMT2 and MTHFD2 in T-ALL pathogenesis. The ultimate goal of the project is to develop novel therapies for patients with T-ALL.

Notes:

Bárbara Rivera, PhD



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2017 YOUNG INVESTIGATOR GRANT

Cancer Susceptibility and Signaling Pathways in Low-Grade Brain Tumors

BACKGROUND: Hereditary cases of benign brain tumors are rare but devastating to affected children. Knowledge gained by studying hereditary tumors can be applied to better understand and treat non-familial cases. Our group discovered that defects in the fibroblast growth factor (FGF) pathway are involved in the development of brain tumors causing epilepsy.

PROJECT GOAL: In this study, we will inventory proteins specifically present in tumors with mutations in the gene FGFR1 to identify proteins or groups of proteins that participate directly in tumor formation. We hope to use this information to explore new treatments as well as anti-epileptic drugs that target these proteins. We will attempt to elucidate specific patterns of mutations responsible for the increased susceptibility to developing epileptic brain tumors in rare hereditary conditions called RASopathies.

In a parallel objective, we will extend our study to Choroid Plexus Tumors that account for up to 20% of brain tumors in children younger than 2 years old. Our first goal is to discover the genetic causes of these tumors to help provide better classification and more accurate diagnoses. If we successfully identify a gene or pathway linked to cancer risk, we will follow the same experimental protocol as described for epileptic tumors above to investigate which proteins participate in tumor development and explore new treatment avenues.

Notes:

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2017 YOUNG INVESTIGATOR GRANT

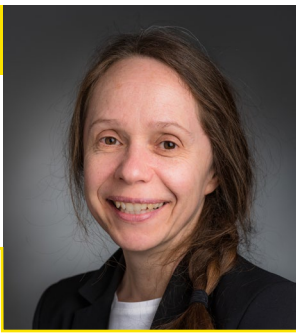
Understanding the Mechanisms of HOX Gene Regulation in Normal and Leukemic Hematopoietic Stem Cells to Identify New Therapies for Pediatric AML

BACKGROUND: Acute myeloid leukemia (AML) arises due to mutations that affect blood stem cells, causing them to proliferate excessively and give rise to immature, leukemic cells. These cells are difficult to eliminate and overall survival rates remain lower than 70%. We do not fully understand the mechanisms regulating proliferation in blood stem cells or what makes them go into overdrive. Using zebrafish, we have generated a model overexpressing the same gene that is often overexpressed in pediatric AML, giving us a unique way to study the molecular mechanisms of this disease. Just like cancer patients, these fish don't develop mature white blood cells which gives us the opportunity to look for ways to rescue this phenotype.

PROJECT GOAL: My first goal is to identify compounds that can promote white blood cell development in this model, which may have therapeutic benefit in pediatric AML. My second goal is to decipher proliferation mechanisms by looking for gene regulators that promote either normal blood stem cell or leukemia cell expansion in zebrafish. This will identify pathways that malfunction in AML and could be targeted therapeutically without harming normal blood cells. It will also reveal new ways to expand HSCs for transplantation.

Notes:

Cecile Rouleau, PhD



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2017 YOUNG INVESTIGATOR GRANT

Identifying Disease Mechanisms and Therapeutic Opportunities in Pediatric Low-grade Gliomas Driven by MYB-QKI Fusions

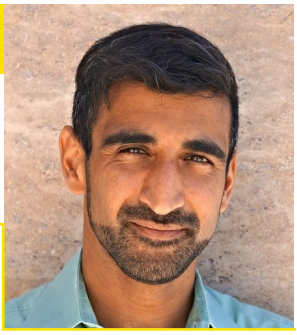
BACKGROUND: Brain tumors are the most common pediatric solid tumors. Low-grade gliomas (LGGs) are the most common pediatric brain tumors. Most become quiescent in early adulthood yet are debilitating during childhood. They can cause elevated intracranial pressure, nausea, vision loss, hormonal deficiency, failure to thrive, seizures and/or behavior changes. Complete surgical resection is often impossible. Unresectable or recurrent tumors require chemotherapy. Severe side effects include hearing loss, infertility, secondary malignancy and/or hematologic disorders. Resistant tumors require radiation, which can irreversibly impair cognition. Safe therapies are needed.

Our laboratories completed a genetic study of pediatric LGGs. We identified a chromosome abnormality as the cause of angiocentric glioma (AG), a subtype of pediatric LGG: two genes, MYB and QKI, are truncated and fused to each other. MYB normally promotes cellular growth and QKI suppresses it. MYB-QKI causes tumors for unknown reasons. Understanding how a disease-causing gene functions is critical to designing therapies that block it.

PROJECT GOAL: We will study how MYB-QKI functions to design new therapies. This proposal emphasizes QKI because it is poorly characterized. QKI genetic alterations are frequent in cancer. Since normal QKI binds to RNA molecules, we will identify the RNAs that bind to MYB-QKI and their roles in AG. Since QKI is controlled by other proteins, we will identify those that control MYB-QKI. Finally, we will search genome-wide for genes that cooperate with MYB-QKI. All findings represent potential therapeutic targets. We previously observed that MYB-QKI activates other genes, including CDK6 and KIT. CDK6 and KIT inhibitors will be tested against MYB-QKI.

Notes:

Amit Sabnis, MD



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CENTER OF EXCELLENCE SCHOLAR

A Synthetic Lethal Relationship between the PAX3-FOXO1 Oncogene and the GATOR2 Complex

BACKGROUND: The presence of the PAX3-FOXO1 fusion gene in rhabdomyosarcoma (RMS) is an independent risk factor for poor survival in patients with non-metastatic disease, and is itself closely associated with the presence of metastases at presentation. The molecular basis for its oncogenic activity remains unclear, and as a consequence, pharmacologic inhibition of PAX3-FOXO1 cannot be currently pursued.

Using a genetic screen, we sought to test whether the presence of the PAX3-FOXO1 oncogene confers novel genetic dependencies on genes that are otherwise dispensable for cell growth and survival. Using the CRISPRi Cas9-KRAB transcriptional silencer and a library of small guide RNAs targeting 2,000 genes, we found that PAX3-FOXO1 positive Rh30 cells are selectively lost in culture upon genetic inactivation of WDR24 or MIOS, two components of the GATOR2 complex that positively regulates mTOR signaling in response to amino acid sufficiency. By contrast, Rh30 cells with shRNA knockdown of PAX3-FOXO1 were able to tolerate inactivation of either WDR24 or MIOS, suggesting a synthetic lethal relationship between expression of PAX3-FOXO1 and loss of GATOR2.

In subsequent work, we have confirmed that loss of either WDR24 or MIOS 1) suppresses both basal and amino-acid stimulated levels of mTOR activity, and 2) is toxic to other PAX3-FOXO1 positive cell lines (RMS13, Rh41). We have also found that strong genetic suppression of PAX3-FOXO1 renders cells resistant to these effects. Loss of GATOR2 complex members is associated with apoptosis, cell cycle changes with G2 arrest, and alterations in autophagic flux.

Surprisingly, while dual inactivation of GATOR2 and the Rag-GTPase activating protein complex GATOR1 is sufficient to restore mTOR signaling in RMS cell lines, it is insufficient to rescue loss of viability. Our data therefore suggests an mTOR-independent function of GATOR2 that is essential for the growth and/or survival of PAX3-FOXO1 expressing RMS cells.

PROJECT GOAL: In ongoing work, we hope both to dissect that novel function of GATOR2 that supports RMS viability, and identify the molecular connection between PAX3-FOXO1 and GATOR2. These aims will permit the rational design of therapies to exploit a newly-discovered synthetic lethal relationship and help cure more RMS patients.

Notes:

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2016 YOUNG INVESTIGATOR GRANT

Role of Kindlin-3 in Natural Killer Cell Mediated Tumor Killing

BACKGROUND: Intensive chemotherapy regimens, radical surgeries and high-dose radiation continue to be used to induce remission, but many cancers remain refractory to conventional treatments. Additionally, for patients that survive their cancer the treatment side effects of these therapies can be devastating and even fatal. Researchers are now studying how to use immunotherapy to fight cancer.

PROJECT GOAL: Our work is focused on an important immune cell in the body known as natural killer (NK) cells. NK cells are unique because they can destroy cancer cells that attempt to escape the immune system by recognizing the absence of specific proteins on cancer cells. The mechanisms used by NK cells to identify and then destroy cancer cells are poorly understood. A rare immune deficiency with dysfunctional NK cells, Leukocyte Adhesion Deficiency Type III, identifies Kindlin-3 as a key protein in NK cells. By determining how NK cells use Kindlin-3, we will better understand how NK cells recognize cancer cells, signal the immune system and ultimately destroy tumors. Using Kindlin-3, we hope to unlock the potential of NK cells to develop a new immunotherapy with fewer side effects and more cures.

Notes:

Hui Shi, PhD

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2016 YOUNG INVESTIGATOR GRANT

The Role of ARID1A in Neuroblastoma Pathogenesis

BACKGROUND: Neuroblastoma is a solid tumor of the peripheral sympathetic nervous system (PSNS) in children. It is difficult to treat in many of the children with high-risk disease and accounts for 15% of childhood cancer deaths. MYCN amplification is present in approximately 20-25% of neuroblastomas and has been the most common genetic aberration that is associated with poor prognosis in neuroblastoma. A tumor suppressor gene called ARID1A is inactivated by mutation and deletion in neuroblastoma tumors from up to one third of children with high-risk neuroblastoma and also in adult tumors, such as ovarian cancer and endometrial tumors.

PROJECT GOAL: I have created the first zebrafish model of ARID1A inactivation and my preliminary data has shown that loss of ARID1A dramatically accelerates the onset and increases the penetrance of MYCN-induced neuroblastoma. Thus, my fish model provides the ideal system to study the mechanism of the loss of ARID1A in tumorigenesis. My novel work is highly likely to result in improved targeted treatments for high-risk neuroblastoma, as well as for other human tumors such as ovarian and endometrial tumors that also exhibit loss of the ARID1A tumor suppressor gene.

Notes:

David Shulman, MD

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CENTER OF EXCELLENCE SCHOLAR

Phase 1 Study of the Dual MDM2/MDMX Inhibitor ALRN-6924 in Pediatric Cancer

BACKGROUND: p53, known as the "guardian of the genome," is a protein found in all of our cells that is responsible for monitoring the integrity of our genes. This protein helps to sense damage to our genes, and when present, pause cell division for DNA repair, or cause the cell to die if the damage is unrepairable. Turning off p53 is a key step in the development of many cancers. While the gene that encodes p53, TP53, is mutated in many adult cancers, it is uncommonly mutated in pediatric cancers. Instead, p53 is suppressed in many pediatric cancers through different mechanisms and sometimes through proteins that inhibit p53. MDM2 and MDMX are proteins found in our cells that can inhibit p53 and are known to be increased in some types of cancer affecting children. ALRN-6924 is novel drug developed in the laboratory of Dr. Loren Walensky at DFCI that inhibits MDM2 and MDMX. This is a new type of drug that is a specially crafted protein, designed to selectively inhibit MDM2 and MDMX, allowing for restoration of p53 activity. We believe that restoring p53 activity in some cancer cells will halt their growth and cause them to die. ALRN-6924 has been tested in two adult clinical trials, and found to be safe, with efficacy in controlling disease for some patients with leukemia and patients with solid tumors.

PROJECT GOAL: We have designed a phase 1 clinical trial to begin evaluation of ALRN-6924 in children with advanced cancers. This trial is designed to determine the correct dose of ALRN-6924 in children with leukemias, lymphomas, solid tumors or brain tumors. Given that single-agent therapy is often not effective at controlling leukemia, and cytarabine is an effective drug that induces DNA damage in leukemia, patients with leukemia will receive ALRN-6924 in combination with cytarabine. This trial aims to evaluate multiple correlative biology aims to improve our understanding of how ALRN-6924 acts in the body and how it affects cancer cells. The results will inform correct dosing of this drug to move forward for further testing and identify patients most likely to benefit from this drug based on specific genetic mutations seen in their tumors.

Notes:

Emily Theisen, PhD

Research Institute at Nationwide Children's Hospital, Columbus, OH

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2016 YOUNG INVESTIGATOR GRANT

Bad Influence: EWS/FLI Alters LSD1 and NuRD Interactions to Enforce Oncogenic Function in Ewing Sarcoma

BACKGROUND: Ewing sarcoma is an aggressive pediatric bone tumor characterized by the EWS/FLI fusion gene. While advances in multimodal therapy have raised disease-free survival rates above 70% for patients with localized disease, survival rates for metastatic and refractory cases remain stuck below 30%.

This project studies the protein complexes assembled by EWS/FLI in the nucleus to activate tumor-promoting genes and silence tumor-suppressing genes. These complexes contain drug-treatable protein subunits, like histone deacetylases (HDACs) and HDAC inhibitors and those actively pursued as novel targets, such as lysine specific demethylase 1 (LSD1). Such "epigenetic" mechanisms are commonly co-opted to enforce tumorigenic gene expression in pediatric tumors with otherwise stable genomes.

While epigenetic therapies hold great promise for pediatric cancers and Ewing sarcoma specifically, our ability to implement effective clinical regimens is limited.

PROJECT GOAL: We propose to define exactly how EWS/FLI alters LSD1 function, specifically looking both upstream at the biochemical mechanisms required by EWS/FLI and downstream at the epigenomic alterations driving disease. Achieving this goal 1) furthers our ability to advance LSD1 inhibitors for Ewing sarcoma patients and 2) establishes a paradigm for linking deep basic science to drug-treatable epigenetic phenomena in mutationally quiet pediatric cancers.

Notes:

Anastasia Tikhonova, PhD

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2017 YOUNG INVESTIGATOR GRANT

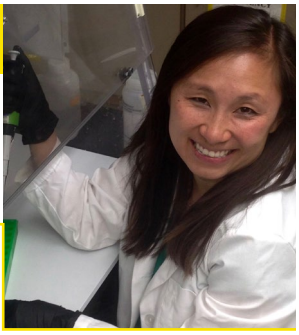
Identification and Targeting of Microenvironmental Factors Controlling Pediatric Leukemia

BACKGROUND: Despite progress in treating T cell acute lymphoblastic leukemia (T-ALL), one quarter of childhood patients relapse within five years and receive a bleak prognosis. The general toxicity associated with recent therapeutic efforts to treat T-ALL stresses the urgent need for novel innovative therapies. Little is understood about how leukemia cells behave within their native milieu, the bone marrow. Several lines of evidence indicate the leukemic cells require a specialized microenvironment to survive, and that disrupting this microenvironment may be a novel, promising therapeutic strategy. Our recent work identified CXCl12, which produces the vascular endothelial cells that constitute the blood vessel networ, as a necessary component of a leukemic niche in the bone marrow. Leukemic cells rely on blood vessels for their supply of CXCl12. We found that interrupting this supply after disease onset dramatically reduced leukemic burden, suggesting a potential new therapeutic paradigm to treat this devastating disease.

PROJECT GOAL: Our proposed studies will: 1) examine which other molecular factors produced by the microenvironment are important for leukemia development, and 2) test the therapeutic potential of CXCl12 blockade. This will be one of the first examples of therapeutic targeting of the cancer microenvironment in leukemia.

Notes:

Melanie Vincent, PhD



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2016 YOUNG INVESTIGATOR GRANT

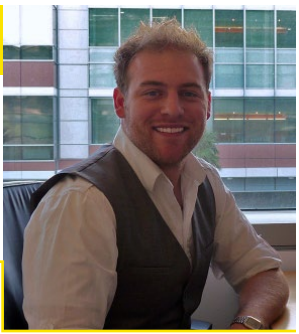
Targeting Eya2 to Inhibit c-Myc driven Medulloblastoma Tumor Progression

BACKGROUND: Medulloblastoma is a deadly pediatric brain cancer. Although there are different types of medulloblastoma, patients are uniformly treated with therapies including surgery, radiation and chemotherapy. To find better treatments with less severe side effects, it is important to understand the different types of medulloblastoma so we can tailor the treatment to each subtype. Group3 medulloblastoma was identified because this subgroup of patients has extremely high levels of a gene called c-Myc in their tumors. c-Myc helps cell growth during development. In cancer, the same developmental processes are turned on and allow the tumor to quickly grow and become more aggressive. Therefore, it is not surprising that patients with Group 3 medulloblastoma have the worst survival rate when compared to other medulloblastoma subgroups.

PROJECT GOAL: To identify novel therapeutics for children with c-Myc-driven medulloblastoma, we will investigate the role of the developmental protein Eya2. It can partner with another developmental protein, Six1, or act by itself to control c-Myc levels. Understanding if and how Eya2 and/or Six1 promotes tumor growth in Group3 medulloblastoma will help us develop and test our novel Six1/Eya2 interaction inhibitors (currently under development in our laboratory) in this devastating disease. We are excited to target the Eya2/Six1 complex with our inhibitors because Eya2 and/or Six1 are excellent therapeutic targets since these genes are only turned on in tumors and not in normal healthy tissues. They provide a novel therapeutic option that avoids the debilitating side effects that occur from current treatments.

Notes:

Kyle Walsh, PhD



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2014 'A' AWARD

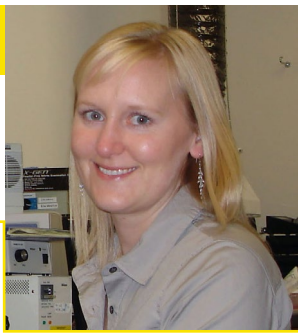
Genetic Susceptibility to Pediatric Osteosarcoma and Interaction with Measures of Childhood Growth

BACKGROUND: Osteosarcoma rates increase with age until puberty when risk declines markedly. Because pediatric osteosarcoma risk is associated with taller stature and male sex, biological pathways related to childhood growth and development likely play a key role in osteosarcoma etiology. This study compares the genomes of 540 children with osteosarcoma to the genomes of 3,545 cancer-free children to identify genetic risk factors underlying this disease. Since this study utilizes biologic specimens collected prior to diagnosis, it enables identification of potential biomarkers of future osteosarcoma risk. We also seek to identify genetic variants and perinatal factors associated with patient prognosis.

PROJECT GOAL: Children who are genetically predisposed to have longer telomeres are at increased risk of developing osteosarcoma. Long telomeres may increase risk of osteosarcoma by allowing a cell to undergo more divisions and accumulate additional tumorigenic mutations prior to senescing. Higher birthweight is associated with more aggressive osteosarcoma as well as tumor location, with smaller newborns likelier to have osteosarcomas in their arms and legs, as opposed to their ribs, pelvis, sternum, or jaw. Children who are born small may experience rapid "catch-up" growth during childhood, increasing their risk of developing tumors in the long bones of their arms and legs. Large-scale genomic analyses are continuing, but results thus far support the idea that telomere length, birthweight, and potentially additional measures of childhood growth are associated with osteosarcoma development and clinical presentation.

Notes:

Anica Wandler, PhD



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2017 YOUNG INVESTIGATOR GRANT

Overcoming Glucocorticoid Resistance in Lymphoid Cancers Leukemia

BACKGROUND: Acute lymphoblastic leukemia (ALL) is the most common childhood cancer, with T lineage ALL (T-ALL) accounting for approximately 15% of cases. Many patients with T-ALL present with "high risk" clinical features and are treated with chemotherapy drugs that kill the leukemia cells, but also damage normal tissues. This causes long-term adverse health effects in some pediatric cancer survivors. Glucocorticoids (also called steroids) are an essential type of chemotherapy drug that has been used to treat pediatric ALL and lymphoma for almost 50 years. ALL cells that respond poorly to glucocorticoids have a much higher chance of causing disease relapse and death. For this reason, drugs that can make glucocorticoids work better would significantly improve the treatment of pediatric ALL and lymphoma patients. We generated T-ALLs in mice, showed that these types of leukemia have many of the same mutations found in pediatric T-ALL patients, and treated them with a glucocorticoid called dexamethasone. This drug was very effective. We also unexpectedly discovered that when T-ALLs relapsed after prolonged treatment they were frequently missing the receptor that glucocorticoids bind. This revealed a novel way that leukemia cells use to become resistant to glucocorticoid treatment, and we showed that this also happens in human T-ALL cells at relapse.

PROJECT GOAL: Our goals are to understand how leukemia cells become resistant by turning off the glucocorticoid receptor and to use this knowledge in order to devise new ways of killing them.

Notes:

Beau Webber, PhD

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2017 YOUNG INVESTIGATOR GRANT

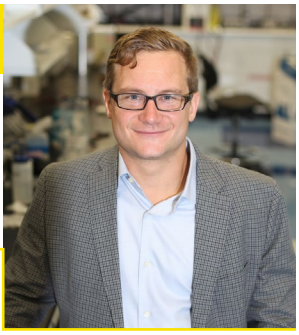
Development and Characterization of Novel Models of Human Osteosarcoma Development and Metastasis

BACKGROUND: Osteosarcoma (OS) is the most common cancer of the bone in children and adolescents, with approximately 900 new cases annually in the United States. Current treatment options for (OS) have not changed over the last four decades, largely because the genes driving OS development and progression are not well understood. Compounding this issue is a lack of models for studying human OS initiation and development. Recently, induced pluripotent stem cells (iPSC) derived from Li-Fraumeni patients have been used to generate osteoblasts (OB) that exhibit properties of OS. Subsequent advances in osteogenic differentiation of iPSC and three-dimensional culture systems allow for more efficient production of bone tissue in vitro. When grafted in vivo, OB derived using these methods are able to produce vascularized neobone structures that we hypothesize could be utilized to create a foundational platform for investigation of human OS initiation, development, and metastasis.

PROJECT GOAL: Our study will implement cutting-edge technologies in the areas of induced pluripotent stem cells (iPSC) and genome engineering to develop a novel and highly impactful platform for functional studies elucidating the mechanisms underlying human osteosarcoma initiation, development, and metastasis. Via tissue engineering, we will use iPSC to produce a developmentally relevant osteogenic platform to replicate human bone tissue in vitro. We will subsequently force genome instability in these systems by using the CRISPR/Cas9 system to disrupt TP53, RB1, and the chromatin remodeling protein ATRX. We will then utilize this platform to alter the function of novel drivers of osteosarcoma via genome engineering and assess their roles in osteosarcoma initiation in vitro and in vivo. This model will be the first of its kind and will facilitate the development of new therapeutic approaches to OS via an unprecedented ability to interrogate OS development, metastasis, and drug resistance.

Notes:

John Wilson, PhD



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2015 'A' AWARD

Inside-Out Immunotherapy: Combating Neuroblastoma via Nanoparticle-Directed Reprogramming of the Tumor Microenvironment Background

BACKGROUND: Despite intensive surgery, chemotherapy and radiation, the survival rate for children with high-risk neuroblastoma is unacceptably low (<40%). The immune system has an intrinsic ability to find and destroy cancer cells. But neuroblastoma tumors have developed mechanisms to protect themselves against this assault by creating a local "microenvironment" that suppresses the tumor killing capacity of the immune system.

PROJECT GOAL: The goal of this project is to develop and evaluate a new class of therapeutic that "retrains" the immune system to eliminate neuroblastoma and prevent its recurrence. We will develop a simple and safe material that can be injected directly into neuroblastoma tumors that cannot be completely removed by surgery. We will engineer this material to sustain the release of a single therapeutic agent that we have designed to target two molecules that regulate immune responses. The first, PD-L1, suppresses the tumor killing ability of immune cells in the tumor, and so we will inhibit PD-L1. The second, RIG-I, helps the immune system kill tumor cells, and so we will activate this pathway. This process will "re-awaken" the immune cells within the tumor, allowing them to kill surrounding cancer cells, while also turning the tumor site "inside-out" by activating immune cells that can search for and destroy neuroblastoma cells throughout the body and "remember" how to kill these cells if they return.

Notes:

Lena Winestone, MD

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2016 YOUNG INVESTIGATOR GRANT

Investigating Racial Disparities in Pediatric Acute Leukemia

BACKGROUND: African-American children with leukemia die more often than children of other races with leukemia. The reasons for this difference between African-American and Caucasian children are unknown. While there are many possible causes of this difference, we have found in previous research that African-American children come to the hospital sicker than Caucasian children prior to the start of chemotherapy.

PROJECT GOAL: We investigated if there are differences in the vital signs and blood tests for African-American children when they come to the hospital and found that while vital signs are similar, African-American children have more laboratory abnormalities at the time of their diagnosis. We know that these children are more likely to have public insurance and lower parental incomes which may make it harder for them to come to the hospital. In other diseases, other aspects of a person's background, such as parents' education level, have also been shown to influence the risk of death and we plan to study the role of these other socioeconomic factors. We also plan to study if there are differences in the leukemia itself that make it grow faster or resist treatment more, causing African-American children to become sicker and die. We can answer these questions with information that is already available from children's hospitals across the United States.

Notes:

Joanna S. Yi, MD

Baylor College of Medicine, Houston, TX • joanna.yi@bcm.edu

CENTER OF EXCELLENCE SCHOLAR

Texas Children's Cancer Center Alex's Lemonade Stand Center of Excellence

BACKGROUND: As a member of Baylor College of Medicine's Center for Drug Discovery (CDD), Dr. Yi seeks to screen driver mutations of pediatric cancers for novel small molecule modulators. Of particular interest is screening a novel kinase in neuroblastoma and sarcoma chimeric fusion proteins against the proprietary DNA-Encoded libraries (DEC-Tec) of the CDD. The DEC-Tec allows synthesis of enormous small molecule libraries (already >1 billion) by appending unique DNA "barcodes" to each compound, which can be screened against targets of interest, and binders can be detected by next-generation sequencing. Bioinformatic analysis will identify the hits and a representative set of diverse hits will be re-synthesized for further testing. Dr. Yi is also developing novel biochemical and cellular assays to characterize and compare hits emerging from the DEC-Tec screens in order to identify lead compounds for in vitro and in vivo testing for both neuroblastoma and Ewing sarcoma. Additionally, the Yi lab is interested in chromatin-modifying small molecules and is studying drug combinations and biomarkers of BET bromodomain inhibitors. Dr. Yi also is developing the first-in-children BET bromodomain clinical trial (ADVL1617) through the Children's Oncology Group.

Notes:

Marielle Yohe, MD/PhD

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2016 YOUNG INVESTIGATOR GRANT

Identification of Mechanisms of Resistance to Trametinib Monotherapy in PAX-fusion Negative Rhabdomyosarcoma

BACKGROUND: PAX-fusion negative rhabdomyosarcoma (RMS) arises from skeletal muscle precursors that have failed to differentiate normally despite the expression of the myogenic master transcription factor, MyoD. The cure rate for relapsed or refractory fusion negative RMS is poor despite aggressive multi-modality treatment. Novel treatment approaches such as targeted therapies that induce differentiation might improve overall survival for patients with fusion negative RMS. Our recent work showed that inhibition of the RAF-MEK-ERK effector pathway with the targeted agent, trametinib, induces G1 arrest and skeletal muscle differentiation in RAS-mutated RMS cell lines. Trametinib slowed tumor growth and prolonged survival in xenograft models of RAS-mutated RMS, but provided no long-term cures in these models. The goal of the current project is to identify mechanisms by which RMS cells acquire resistance to trametinib treatment so that we might design therapies that prevent resistance. We will take three independent approaches toward identifying resistance mechanisms, allowing for the rational design of combination therapies for this pediatric cancer.

Notes:

Shizhen (Jane) Zhu, MD/PhD

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2013 YOUNG INVESTIGATOR GRANT

The Role of PTPRD as a Tumor Suppressor in Neuroblastoma Pathogenesis

BACKGROUND: Neuroblastoma is an embryonal tumor that arises in the peripheral sympathetic nervous system and accounts for ~15% of cancer-related deaths in childhood. Recent research has uncovered two main classes of mutations in high-risk neuroblastoma: those activating ALK (8-10%) and microdeletions involving the PTPRD locus (6-10%). I recently discovered that activated ALK can cooperate with MYCN to induce neuroblastoma in zebrafish by inhibiting cell death (Zhu S et.al., Cancer Cell). I have now found that loss of PTPRD also accelerates the induction of neuroblastoma, but in a different way than does activated ALK. Briefly, loss of PTPRD induces neuroblastoma in both sympathetic ganglia and interrenal gland, an effect I have never observed with activated ALK.

PROJECT GOAL: In this project, I will test the hypothesis that PTPRD functions as a tumor suppressor in neuroblastoma pathogenesis. I intend to uncover the cellular basis and molecular mechanisms underlying the loss of PTPRD signaling in neuroblastoma initiation and maintenance. My studies will provide new insights into previously undefined routes to neuroblastoma development, and will identify novel molecular targets for improved treatment and for establishing robust zebrafish models that I can use to screen for novel therapeutic agents.

Notes:

YI Summit

SPEAKERS

Todd Druley, MD/PhD

Washington University School of Medicine, St. Louis, MO

Druley_t@uwstl.edu

Todd Druley, MD/PhD is a board-certified pediatric hematologist/oncologist and Associate Professor of Pediatrics, Developmental Biology and Genetics at Washington University School of Medicine. He obtained a Bachelor's in Cell and Structural Biology and a minor in Chemistry from the University of Illinois in 1994. He then completed the MD/PhD program at the University of Illinois where he studied mechanisms of chemotherapy resistance. In 2002, Dr. Druley joined Washington University as a pediatric resident and has remained, completing his fellowship in Pediatric Hematology and Oncology and joining the faculty in 2008. He is a member of the Children's Oncology Group (COG) Myeloid Disease Committee and Epidemiology Committee.

Research in the Druley Lab is based on characterizing the link between abnormal human development and early childhood cancer, particularly infant leukemia. The lab has a track record for genomic methodology development and is currently applying that technology to improve molecular diagnostics in pediatric AML. Clinically, Dr. Druley is focused on pediatric cancer predisposition and serves as the co-director of the Pediatric Cancer Predisposition Program at St. Louis Children's Hospital and Pediatric Hematology/Oncology Fellowship Director at Washington University. He is also a member of the ALSF Scientific Advisory Board.

Casey Greene, PhD

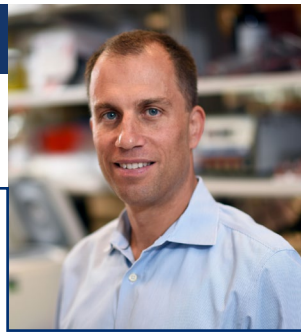
University of Pennsylvania, Philadelphia, PA

Greenescientist@gmail.com

Casey Greene is the Director of the Childhood Cancer Data Lab for Alex's Lemonade Stand Foundation. Before starting the Integrative Genomics Lab at UPenn in 2012, Casey earned his PhD for his study of gene-gene interactions in the field of computational genetics from Dartmouth College in 2009 and moved to the Lewis-Sigler Institute for Integrative Genomics at Princeton University where he worked as a postdoctoral fellow from 2009-2012.

The overarching theme of his work has been the development and evaluation of methods that acknowledge the emergent complexity of biological systems.

Andras Heczey, MD



Baylor College of Medicine, Houston, TX

Axheczey@txch.org

Dr. Andras Heczey is a physician-scientist and full-time faculty in the Department of Pediatrics of Baylor College of Medicine, Section of Pediatric Hematology and Oncology. He is a member of the multidisciplinary solid tumor team and the Center for Cell and Gene Therapy (CAGT).

His research focuses on developing novel treatments for children with solid tumors by redirecting the immune system to attack cancer cells.

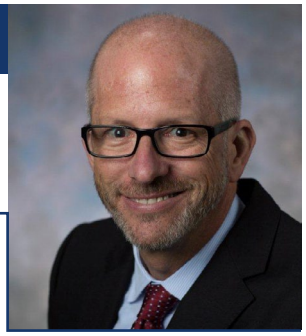
Dr. Heczey has studied and published the first adoptive immunotherapy approach utilizing Natural Killer T cells genetically modified to attack neuroblastoma, he is working on moving this approach from bench-to-bedside in a form of a Phase 1/2a clinical trial.

As the Director of the Liver Tumor Center, Dr. Heczey has developed a strategy to target hepatoblastoma and hepatocellular carcinoma with genetically engineered T lymphocytes and he is currently optimizing this strategy for a smooth transition into the clinic.

Hana Jurgens

Hana is a sweet 6 year old who adores school and playing with her older brother, Aiden. That made it even harder when she was diagnosed with Wilms tumor and couldn't do all the typical activities that she loved. After starting chemotherapy in June 2016 and finishing treatment in November 2017, her latest scans have shown no evidence of disease. Her family supported her as a team throughout this fight and remain amazed by her courage on a daily basis.

Stephen Lessnick, MD/PhD



Nationwide Children's Hospital, Columbus, OH

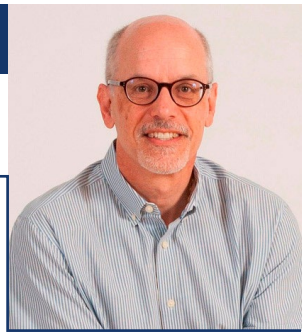
Stephen.Lessnick@nationwidechildrens.org

Stephen Lessnick, MD, PhD, is director of the Center for Childhood Cancer & Blood Diseases for The Research Institute at Nationwide Children's Hospital, a physician for the Division of Hematology and Oncology at Nationwide Children's Hospital and a professor of pediatrics at The Ohio State University College of Medicine.

Dr. Lessnick earned his bachelor's degree from Brandeis University, followed by MD and PhD degrees from the University of California, Los Angeles (UCLA), as part of the Medical Scientist Training Program (MSTP). He trained in pediatrics at Children's Hospital, Boston, and in pediatric hematology/oncology at Dana-Farber Cancer Institute and Children's Hospital, Boston. Dr. Lessnick was on-faculty at the University of Utah for approximately 11 years. In July 2015, Dr. Lessnick joined the faculty at The Research Institute at Nationwide Children's Hospital as the Director of the Center for Childhood Cancer and Blood Diseases and The Ohio State University as a Professor of Pediatrics in the Division of Pediatric Hematology/Oncology/BMT.

Dr. Lessnick is a member of the ALSF Scientific Advisory Board as well as the recipient of an ALSF Innovation Grant for his project, "Molecular diagnostic, prognostic, and therapeutic approaches toward Ewing sarcoma."

David Malkin, MD



The Hospital for Sick Children, Toronto, Ontario, CA

David.Malkin@sickkids.ca

Dr. Malkin received his medical degree from the University of Toronto in 1984 and completed his residency in Paediatrics and Paediatric Hematology/Oncology at The Hospital for Sick Children in Toronto. He completed post-doctoral research training in molecular genetics at Massachusetts General Hospital, Harvard University, where he discovered the link between germline mutations on the p53 tumor suppressor gene and the Li-Fraumeni cancer susceptibility syndrome. Dr. Malkin returned to Canada to accept a faculty position at The Hospital for Sick Children and University of Toronto.

Dr. Malkin is currently a clinician-scientist and paediatric oncologist in the Division of Hematology/Oncology and Director of the Cancer Genetics program at SickKids, as well as a Senior Scientist in the Genetics & Genome Biology Program in the SickKids Research Institute. He is a Professor in the Departments of Paediatrics and Medical Biophysics in the Faculty of Medicine at the University of Toronto. Dr. Malkin has an active clinical oncology practice at the Hospital and both undergraduate and post-graduate teaching responsibilities there as well as at the University.

His research interests are closely integrated with his clinical field of expertise. Focusing primarily on genetic mechanisms of childhood cancer susceptibility, and the genetic basis of childhood sarcomas (cancers of bone, muscle and other soft tissues). His research team was the first to demonstrate that highly variable regions of DNA—termed copy number variations—are found in excess in the blood of some children and adults at very high risk of developing cancer, and may represent the earliest genetic changes that ultimately lead to development of cancer. Recently, his work has focused on application of this genetic/genomic information to develop rational clinical surveillance and treatment guidelines for children and adults deemed at genetic 'high risk' for cancer. In his sarcoma work, Dr. Malkin has studied the molecular and cell biology pathways that are associated with the development and progression of these cancers, and has identified molecules that might represent viable targets for novel drug therapies.

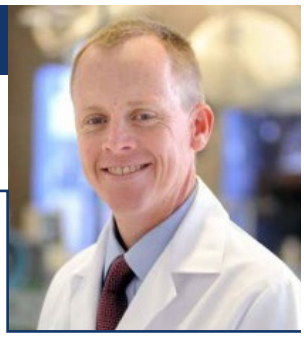
Maureen M. O'Brien, MD/MS

Cincinnati Children's Hospital Medical Center, Cincinnati, OH

Maureen.Obrien@cchmc.org

Dr. O'Brien is an Associate Professor of Clinical Pediatrics and the Medical Director of the Leukemia/Lymphoma program at Cincinnati Children's Hospital. Dr. O'Brien is a clinical researcher with a focus on novel therapies for children and young adults with high-risk and relapsed leukemias. She is an active member of both the ALL and AML committees in the Children's Oncology Group and is currently the COG principal investigator for trials in both relapsed AML (lenalidomide) and relapsed ALL (inotuzumab ozogamicin). She is currently working with the COG ALL task force to develop, and will co-chair, the next COG phase III clinical trial for high-risk pre-B ALL. Specific interests include immunotherapeutic approaches and molecularly targeted therapies for acute leukemias and the translation of laboratory discoveries to clinical trials. She is also a member of the ALSF Scientific Advisory Board.

Donald (Will) Parsons, MD/PhD



Baylor College of Medicine, Houston, TX

DwParson@bcm.edu

Dr. Donald Williams (Will) Parsons has distinguished himself as one of the country's leaders in the genomics of childhood cancer, as well as a leader in pediatric neuro-oncology. Dr. Will Parsons is an Associate Professor of Pediatrics – Hematology/Oncology at Baylor College of Medicine and the Texas Children's Cancer Center. He is board-certified by the American Board of Pediatrics in both general pediatrics and pediatric hematology/oncology. He is a recognized pediatric hematologist-oncologist specializing in the care of children with brain and spinal cord tumors.

After graduating from Princeton University in 1992 with a degree in Chemistry, Dr. Will Parsons obtained his PhD (Pathology) and MD degrees from The Ohio State University College of Medicine. He conducted his residency in pediatrics at Johns Hopkins and a fellowship in pediatric hematology-oncology as part of the combined Johns Hopkins/National Cancer Institute program. He served on the faculty at Johns Hopkins for one year prior to coming to Baylor College of Medicine in 2008.

Dr. Parsons is Co-Director of both the Brain Tumor Program and the Cancer Genetics and Genomics Program where he is also Director of the Pediatric Center for Personal Cancer Genomics and Therapeutics for the Cancer Center at Texas Children's Hospital. Dr. Parsons continues to be a distinguished contributor to the scientific and genomic studies conducted within the Brain Tumor and Liver Tumor Program research laboratories.

Dr. Parsons is a member of the ALSF Scientific Advisory Board and a past recipient of an ALSF Young Investigator grant for studying CNS tumors and an 'A' Award grant for studying pediatric gliomas.

Shannan Scarselletta

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Shannan Scarselletta is on a mission to help tomorrow's innovative leaders turn big ideas into impact and revenue with powerful communication. As a management consultant working with Fortune 500 companies to achieve transformational change, Shannan discovered that her clients' success depended on their ability to inspire, adapt, and innovate. As an improvisational comedian and storyteller performing nationwide with Second City, UCB, and ComedySportz (her "superman job"), she learned the power of storytelling and improvisation to connect and compel audiences. In a world where disruption is the only constant, Shannan believes tomorrow's leading organizations will be those whose leaders can create and communicate through uncertainty, so she founded ImproVision Consulting to bring meaningful improv- and storytelling-inspired learning to the next generation of game changers.

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