Pediatric brain and spinal tumors are the leading cause of disease-related death in children. There are ~4500 children diagnosed with a brain tumor annually in the United States with slightly more than half of the cases deemed aggressive or malignant. Although advances in clinical care have resulted in nearly 70-80% 5-year survival rates, the majority of survivors who receive therapies including systemic chemotherapy and/or radiation therapy are often left with significant morbidities. These include lower I.Q. scores, endocrine and growth deficiencies, and a risk of secondary malignancies. Furthermore, there are some pediatric brain tumor subtypes such as diffuse midline glioma (DMG) or diffuse intrinsic pontine glioma (DIPG), which have <10% survival at 2 years and <1-2% survival at 5 years.

In response to improving the outcomes for these children, Mount Sinai recently created the Children’s Brain and Spinal Tumor Center following key faculty recruitments in several departments including Pediatrics and Neurology. Two of these physician-scientist recruits include Oren Becher, MD, a pediatric neuro-oncologist with expertise in DMG/DIPG who is Chief of the Jack Martin Fund Division of Pediatric Hematology-Oncology and Praveen Raju, MD, PhD, a pediatric neurologist with expertise in medulloblastoma, the most common malignant pediatric brain tumor. Notably, Dr. Becher and Dr. Raju have pioneered novel genetically-engineered mouse models of DIPG and medulloblastoma, respectively, that have served as the basis for recent studies that provide new insight into the biology of these brain tumors and open up therapeutic avenues.

Dr. Becher has recently published an important paper exploring the pathogenesis of DMG. In a paper published in GLIA in May 2022, Dr. Becher describes a novel model of DMG initiated in neonatal oligodendrocyte progenitor cells, a cell type implicated as the cell of origin for DMG. Surprisingly, they found that the abnormal histone protein, H3K27M, did not promote cell growth in this model. These findings contrast with their prior DMG model initiated in stem cells in the brain. The only consistent effect of the abnormal histone protein across both models was inhibition of immune system activation by the abnormal histone protein. These findings suggest that it will be challenging to successfully treat DMGs with therapies that aim to activate the immune system against the cancer cells without also blocking the abnormal histone protein.

Dr. Raju has developed a novel mouse model of medulloblastoma using sophisticated mosaic mutagenesis approaches that recapitulates the distinct tumor histologies and frequent leptomeningeal metastases seen in patients but rarely found in animal models. Importantly, this medulloblastoma model maintains a tight blood-brain barrier (BBB) that has hindered efforts to deliver high drug concentrations into the brain and partly explains the poor outcomes for these children. In collaboration with chemical biology colleagues, Dr. Raju has recently advanced a novel fucoidan-based nanomedicine platform that allows reformulation of several classes of anti-cancer drugs that can penetrate through a tight BBB specifically at the site of the brain tumor via an active transport mechanism that requires caveolin-1-mediated transcytosis. This work is available as a preprint and has recently been accepted for publication in Nature Materials.

Key References
3. Mount Sinai Children’s Brain and Spinal Tumor Center: https://icahn.mssm.edu/research/cbstc
Hematopoietic stem cells (HSCs) are multipotent stem cells that replenish the entire suite of blood cells needed throughout adult life, and are important for cell replacement therapies and disease modeling studies. However, donor match limitations, and poor in vitro expansion conditions, remain significant bottlenecks to their full translational potential. Thus, our ultimate goal is the transgene-free derivation of HSCs from human (patient-specific) pluripotent stem cells (hPSCs), for “bench and bedside” use. But, this goal remains unrealized, as most differentiation strategies fail to recapitulate the signaling events required for embryonic hematopoietic development.

In the early vertebrate embryo, there are at multiple, successive waves of hematopoietic specification, across anatomically distinct tissues. All of these waves pass through unique progenitor, called “hemogenic endothelium” (HE). The first waves, primitive hematopoiesis and the later-emerging erytho-myeloid progenitor, emerge in the yolk sac, and give rise to a restricted subset of erythroid, myeloid, and unique NK and T cells. Slightly thereafter, a complex, heterogeneous wave of definitive hematopoiesis emerges within both the yolk sac and the embryo proper, yielding a full spectrum of hematopoietic lineages, but not the HSC. These programs culminate in the emergence of the HSC-competent HE, found within the embryo proper, and the specification of this program is dependent on stage-specific retinoic acid (RA) signaling (1).

Aspects of many of these programs have been faithfully recapitulated from hPSC differentiation cultures, with our ability to independently specify either yolk sac-like or intra-embryonic-like HE populations via stage-specific WNT signal manipulation (Figure 1, red and green (2)). However, all of these populations develop from hPSCs in the absence of RA, and studies aimed at treating hPSC-derived HE with RA have not yielded functional improvements. Thus, the identification of RA-dependent HE has remained elusive.

To that end, pioneering work performed by a postdoctoral fellow in the Sturgeon laboratory, Stephanie Luff, utilized scRNAseq to understand the heterogeneity within early-stage differentiation cultures. These analyses unexpectedly revealed that a significant portion of nascent mesoderm uniquely expressed the cell-surface marker CXCR4, and within those cells, was the expression of a key RA-responsive enzyme, ALDH1A2 (Figure 1, blue). Functional analyses revealed that these CXCR4+ cells could not give rise to HE unless RA signaling was provided in a stage-specific manner. This resultant RA-dependent HE was unique – it had high transcriptional similarity to HSC-competent HE found in the human embryo, and when transplanted into mouse models, was able to yield multilineage engraftment. Thus, a major hurdle in hPSC-derived hematopoiesis has been overcome, as we have identified the precise stage and progenitor population that responds to RA during hematopoietic development (3).

Many significant challenges remain. Notably, human chimerism in these mouse models was transient, indicating that HSCs were not specified. Are additional, unappreciated signals required for HSC specification from RA-dependent progenitors? Regardless, the identification of multiple hematopoietic progenitors and their signal requirements open new exciting possibilities to interrogate the functional properties and regenerative medicine potential of blood cell types not available through traditional postnatal donor sources.
For the sixth year, the Mindich Child Health and Development (MCHDI) Trainee Leadership Committee (TLC) continues its dedication in supporting the MCHDI trainees in their professional development and growth. To ensure this support, the TLC mission is to create events that can represent a common ground for trainees with different scientific backgrounds as well as different career stages and aims. The TLC activity highlights are listed below.

The TLC has been hosting the MCHDI Trainee Incubator Series since 2021, offering postdocs, predocs and students the opportunity to lead seminars and get feedback on new project ideas, grant and fellowship applications, job interviews and presentations at major conferences. While considering the Incubator Series for this academic year, the TLC gathered insights from the MCHDI trainees through an online survey, and new initiatives will be employed. A new series of in person meetings will be organized to 1) address career development, grant writing, and data analysis interests; 2) enhance interactions and collaborations amongst trainees from different research areas and educational levels; 3) facilitate networking between faculties and trainees. These are a few examples of how the TLC welcomes and implements suggestions from the trainees in order to enhance their professional skills. Every year, the TLC hosts at least three workshops for the Child Health Research Seminar Series (CHRS) co-chaired by Dr. Rebecca Trachtman and Dr. Shelley Liu. The TLC recruits speakers that study pediatric health at any career level and from different institutes or companies.

In 2019, the TLC launched a trainee pilot grant program in order to support postdoctoral/clinical fellows or PhD/MD-PhD students in pursuing a new independently funded line of research as a critical step towards academic independence. Over the past three years of this unique program, ten trainees have been awarded and successfully completed the program. This year’s recipient is Bhavana Shewale, a PhD candidate, who will host an oral presentation during our MCHDI annual retreat in November and speak at the CHRS in March. Applications for the 2023-2024 academic year will open next Spring, and we encourage all MCHDI trainees with striking proposals to apply!

Finally, we would like to thank all the past and present TLC members for their amazing contributions and work managed and ensured during these six years. During the last academic year, the TLC was led by Carolina Cappi, Xueying Zhang, Adele Mossa, Vahe Khachadourian, and Silvia De Rubeis. We would like to thank Xueying for all her guidance and dedication, and give a warm welcome to our new TLC member, Nefatiti Anderson. We would also like to congratulate Adele Mossa for being elected as the chair of the TLC. Besides the commitment in organizing TLC programs and events, every year one of the TLC members is involved in the organization of our MCHDI fall annual retreat. This year, Vahe has joined the retreat committee as a trainee representative, to provide feedbacks and converge the trainees’ perspectives and interests. We look forward to another fruitful year ahead with MCHDI trainees!
Trainee Highlights

Trainee Pilot Project: 2022 Awardee

Investigating the Role of Rho-Signaling in Cardiac Actin Nucleation During De Novo Sarcomerogenesis

Investigator: Bhavana Shewale, PhD Candidate, Cell, Developmental and Regenerative Biology

Primary Mentor: Nicole Dubois, PhD, Associate Professor, Cell, Developmental and Regenerative Biology, Mindich Child Health and Development Institute

Secondary Mentors: Robert Krauss, PhD, Professor & Program Director, Cell, Developmental and Regenerative Biology; Marek Mlodzik, PhD, Professor & Chair, Cell, Developmental and Regenerative Biology

Abstract: Sarcomeres are highly ordered para-crystalline contractile units present in the cardiac and skeletal muscle. The cardiac sarcomeric cryo-architecture is constantly remodeled during physiologic growth and development. Defects in the sarcomeric structure result in childhood and adult cardiomyopathies. The molecular mechanisms behind the establishment and dynamic reorganization of the cardiac sarcomere during development, remain poorly understood. To address this gap in knowledge, my work in the Dubois laboratory involves studying the earliest steps of cardiac sarcomeric assembly. Through transcriptomic, proteomic and interactome profiling of human pluripotent stem cell-derived cardiomyocytes we show that de novo sarcomeric assembly accompanies key cellular and interatomic changes. We identify sarcomeric precursors called z bodies within early cardiomyocytes poised to form the sarcomeres. We show that these structures are heterogeneous in their composition and distribution. They have a higher diffusion rate of a key protein, alpha-actinin-2, compared to late-stage z discs. Upon depolymerization of microtubules z bodies undergo droplet-like fusion and fission events. In addition to the origins of the z disc we uncovered dynamic regulation of Rho-Rac signaling during de novo sarcomerogenesis. Although actin forms the backbone of the sarcomere, the mechanisms that govern nucleation of the earliest actin filaments is unknown. Our pilot project proposes to elucidate the role of Rho signaling the master regulator of cellular actin and its downstream effector NWASP in de novo sarcomeric actin assembly. The findings from this study will inform on organization of the cardiac sarcomeric actin which is key to understanding its dysregulation in cardiac disease.

New Extramural Faculty

Elvin Wagenblast, PhD
Elvin Wagenblast, PhD, is an Assistant Professor of Oncological Sciences and Pediatrics at the Icahn School of Medicine at Mount Sinai. Dr. Wagenblast earned his PhD in Biological Sciences from Cold Spring Harbor Laboratory. He most recently was a Human Frontier Science Program Fellow and Banting Fellow in the laboratory of John Dick, PhD, FRS, at Princess Margaret Cancer Centre at the University of Toronto. In the summer of 2022, Dr. Wagenblast joined Mount Sinai to study childhood leukemia.

Key Publications:


The central question of his laboratory is to understand how a normal blood stem cell can become leukemic. There, the initiating genetic mutations occur as early as before birth during fetal development. His team applies CRISPR/Cas9 genome editing technologies in human primary blood stem cells to model the leukemic initiation and progression in vivo. His laboratory aims to uncover insights into the genetic, cellular and developmental mechanisms of childhood leukemia and identify novel therapeutic vulnerabilities of the disease. Recently, Dr. Wagenblast developed a model of Down syndrome associated leukemia development to understand why children with Down syndrome have a 150-fold increased risk of developing myeloid leukemia. His team was able to identify receptor tyrosine kinase inhibitors against KIT as a potent mechanism to inhibit the progression of the leukemia.


New Intramural Faculty

Megan Januska, MD

Megan Januska, MD, is an Assistant Professor in the Division of Pediatric Pulmonology in the Jack and Lucy Clark Department of Pediatrics and in the Department of Genetics and Genomic Sciences at the Icahn School of Medicine at Mount Sinai and Mount Sinai Kravis Children’s Hospital. After receiving her undergraduate degree from Grinnell College and her medical degree from the Geisel School of Medicine at Dartmouth, Dr. Januska completed her pediatric residency and pediatric pulmonology fellowship training at the Icahn School of Medicine at Mount Sinai.

Supported by a Cystic Fibrosis Foundation Clinical Fellowship Award, Dr. Januska developed a research project focusing on the cellular and molecular mechanisms that define the pediatric cystic fibrosis airway through the application of single-cell technologies to minimally invasive respiratory specimens obtained during flexible bronchoscopy. Leveraging the developed workflow, Dr. Januska now aims to create a single-cell atlas of the normal pediatric airway along with a corresponding model system through the generation of patient-derived airway organoids with the support of a KL2 Scholars Award. Ultimately, Dr. Januska intends to apply the workflow and generated dataset to develop novel and minimally invasive methods to investigate and diagnose rare and severe pediatric respiratory disorders.

Key Publications:


Faculty Grants/Awards/Honors

Dusan Bogunovic, PhD, NICHD, R01, “Immunologic and Predictive Features of MIS-C”

Lauryn Choleva, MD, MSc, Einstein-Mt. Sinai Diabetes Research Center Pilot and Feasibility Award, “Structure-Function Studies of p57KIP2 in The Human Pancreatic Beta Cell”

Magda Janecka, PhD, Avi Reichenberg, PhD and Avner Schlessinger, PhD (mPIs), NIH/NICHD, R01, “Prenatal Exposure to Medications in Autism, Birth Complications and Developmental Disabilities”

Megan N. Januska, MD, NIH, KL2 (Mentor: Martin J. Walsh, PhD), “Mapping the Pediatric Airway: Learning the “Normal” to Define the Diseased Lung”

Robert Krauss, PhD, NIDCR, R01, “Molecular and Developmental Analysis of Holoproscephaly”

Hirofumi Morishita MD PhD, Simons Foundation Autism Research Initiative Pilot Award, “Role of Autism Risk Genes on Frontal-Sensory Cognitive Control Circuit in Mice”

Hirofumi Morishita MD PhD, NIMH, R01 administrative supplement, “Mechanisms Regulating the Maturation of Prefrontal Top-Down Circuitry in Control of Attentional Behavior”

Dalila Pinto, PhD, NIMH, R21, “Mapping Human Brain Cell Type-Specific Isoform Usage in ASD”

Dalila Pinto, PhD, Chair, Symposium “Autism Spectrum Disorders”, 24rd Biennial Meeting of the International Society for Developmental Neuroscience (ISDN), Vancouver, May 8, 2022

Praveen Raju, MD, PhD, NINDS, R01, “Inducing Neural Maturation in Medulloblastoma by Targeting EZH2”

Praveen Raju, MD, PhD and Oren Becher, MD, ChadTough Defeat DIPG Foundation, Game Changer Grant, “A Clinically Translatable Nanotherapeutic Approach to Enhance BBB Drug Delivery in DIPG”

Andy Stewart, MD, NIDDK, R01, “Phase 1 Translational Diabetes Research Using The DYRK1A Inhibitor, Harmine”

Martin J. Walsh, PhD, NIH, R01, “Effects of Aging and Exercise Training on Intermuscular Adipose Tissue (IMAT) in MoTrPAC Study”

Trainee Grants/Awards/Honors

Yvette Carbajal, BA, NIH-NIDDK Diversity Supplement, “Mannose Metabolism as a Regulator of Hepatic Stellate Cell Activation and Fibrosis”

Charles DeRossi, PhD, Polycystic Kidney Disease (PKD) Foundation, “Glycosylation as a Regulator of Liver Disease in ARPKD”

Charles DeRossi, PhD, PKD Foundation, 2022 Young Investigator Award

Adele Mossa, PhD, Doft Family/FBI Postdoc Innovator Award, “Sex-Specific mRNA Translation in a Mouse Model of Autism Spectrum Disorder”

Adele Mossa, PhD, BBRF, “Sex Differences in Neuronal mRNA Translation in a Mouse Model of Neurodevelopmental Disorder”

Faculty Highlights

Publications


Faculty Highlights

Publications, continued


Lesueur C, Jessel RH, Ohrn S, Ma Y, Li Q, Dekio L, ... Dubois NC. Dissecting mechanisms of chamber-specific cardiac differentiation and its perturbation following retinoic acid exposure. *Development*. 2022 Jul 2;149(13).


Zhang X, Liu SH, Geron M, Mathilda Chiu YH, Gershon R, Ho E, ... Wright RJ. Prenatal exposure to pm(2.5) and childhood cognition: Accounting for between-site heterogeneity in a pooled analysis of echo cohorts in the northeastern united states. *Environ Res*. 2022 Nov;214(Pt 4):114165.

Levy T, Lerman B, Halpern D, Frank Y, Layton C, Zweifach J, Siper PM, Buxbaum JD, Kolevzon A. Champ1 disorder is associated with a complex neurobehavioral phenotype includ-


SAVE THE DATE
10th Annual MCHDI Retreat

Date: November 30, 2022
Time: 8:30AM-6:00PM
Location: Harmonie Club Ballroom, 1st Floor
4 E 60th St, New York, NY 10022