



MCHDI Developmental Outcomes

Research Advancements: Cardiovascular Disease

Regenerative Medicine: c-kit Expression Does Not Label Cardiac Stem Cells

Myocardial loss or dysfunction from ischemic heart disease is the leading cause of mortality worldwide. Transplantation of stem cells may be an effective intervention for patients with heart failure. As such, significant efforts have been made to identify the stem cells for heart repair in cardiac regenerative medicine.

c-kit, a receptor tyrosine kinase expressed on the surface of hematopoietic stem cells (HSCs), has been recognized as a marker for isolating cardiac stem cells (CSCs) for over a decade. In 2003, c-kit-positive (c-kit⁺) cells were first identified as the putative CSCs in the adult rat heart, with self-renewing, clonogenic and multipotent characteristics. Subsequent studies with animal models further showed that cardiac resident c-kit⁺ cells were necessary and sufficient for myocardial regeneration upon injury. While these findings are encouraging, studies have continually drawn divergent observations about the myogenic potential of cardiac c-kit⁺ cells. In 2014, Dr. Jeffery Molkentin's group at Cincinnati Children's Hospital found that c-kit⁺ cells in the mouse heart have minimal potential to differentiate into cardiomyocytes during aging and after injury. However, doubts were immediately cast on this observation, questioning the potential unreliability of the mouse models employed in the study.

As of today, fundamental questions regarding cardiac c-kit⁺ cells remain largely unresolved. Specifically, the true nature or cell type of cardiac resident c-kit⁺ cells is uncertain. It is also unclear if the c-kit⁺ cells can really give rise to multiple cardiac lineages during development and after heart injury, and if the benefits of c-kit⁺ cell-based therapies arise from their ability to differentiate into cardiomyocytes, or due to their paracrine effects upon transplantation.

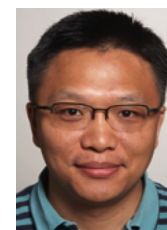


As c-kit⁺ cells are now being clinically tested on human patients with ischemic cardiomyopathy, fully addressing these questions is critical.

Chen-Leng Cai, PhD, Associate Professor in the Department of Developmental and Regenerative Biology, is leading his research group at Mount Sinai to uncover the identity of c-kit⁺ cells. To overcome limitations of antibody-based immunostaining or transgenic mouse lines that may not faithfully recapitulate the endogenous c-kit expression, his team generated a series of knock-in mouse models based on c-kit start codon (*c-kit*^{H2B-tdTomato}, *c-kit*^{nlacZ-H2B-GFP} and *c-kit*^{MerCreMer}) and that ultimately enabled them to characterize the identity of c-kit⁺ cells for the first time. Using these state-of-the-art genetic tools, they unexpectedly discovered that c-kit-expressing cells are in fact a subpopulation of endothelial cells in the mouse heart. They further found that c-kit⁺ cells rarely express the cardiac progenitor marker Nkx2.5 or the

differentiated cardiomyocyte marker cTnT, nor do they turn into cardiomyocytes during development or after injury.

Active c-kit expression in the committed endothelial cells of the heart explicitly demonstrates that c-kit is not a proper marker of resident CSCs. Studies with myocardial infarction mouse models from Dr. Cai's group also revealed that c-kit⁺ endothelial cells rarely de-differentiate into CSCs to contribute to myocardial repair. Future studies are warranted to determine the mechanisms by which c-kit⁺ cells contribute to heart repair (if any) based on their endothelial identity.



Chen-Leng Cai, PhD
Associate Professor,
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The Neurobiological Basis of Avoidant Restrictive Eating: A Novel Study

Avoidant and restrictive food intake disorder (ARFID) is a newly defined disorder, introduced in the Diagnostic and Statistical Manual of Mental Disorders version 5 (DSM-5). ARFID is defined as an eating or feeding disturbance, characterised by avoidant and restrictive eating manifested by persistent failure to meet appropriate nutritional and/or energy needs leading to one or more of: significant weight loss (or failure to achieve expected weight gain or faltering growth in children); significant nutritional deficiency; dependence on enteral feeding or oral nutritional supplements; marked interference with psychosocial functioning. The diagnostic definition also requires that the presentation should not be better explained by lack of available food or by associated culturally sanctioned practice; that no disturbance is present in the way in which one's body weight or shape is experienced. The disturbance seen should not be attributable to a co-occurring medical condition or not better explained by another mental disorder. However, ARFID is often seen in the context of other medical and psychiatric disorders. Therefore, diagnostic criteria require that when the eating disturbance occurs in the context of another disorder, the severity of the eating problem exceeds that which is routinely associated with the condition or disorder and warrants additional clinical attention.

Data on the prevalence of ARFID are scant. A study on 1,444 Swiss 8- to 13-year old children identified 3.2% with likely ARFID. A retrospective chart review of pediatric gastroenterology clinics in the Boston area found a 1.5% prevalence with an additional 2.4% likely to also meet diagnostic criteria. The prevalence of ARFID in specialist child and adolescent eating disorder treatment setting is much higher, estimated to be as high as 22.4%.

ARFID can occur across ages and differs from more common picky or fussy eating, in that the diagnosis of ARFID requires the eating problem to result in persistent failure to meet nutritional and/or energy needs.

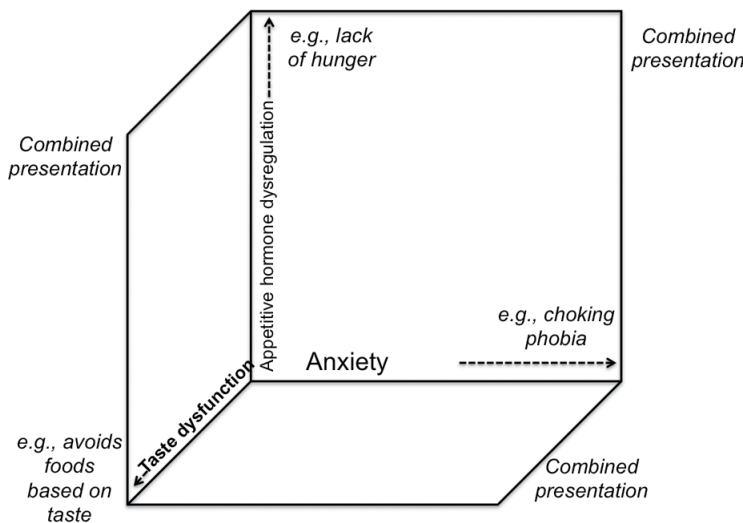
Moreover, patients with ARFID have heterogeneous presentations, with food avoidance due to: fears or anxieties about choking or vomiting; sensory features of the food avoided (e.g. colour, texture); or lack of appetite. They often have comorbid/past medical disorders, e.g. early reflux, early tube feeding dependence amongst others; and psychiatric disorders, e.g. autistic spectrum disorders, anxiety disorders. These patients' first point of contact is often a family physician or general pediatrician, rather than a child psychiatrist.

Nadia Micali, MD, MRCPsych, PhD, FAED and her colleagues at Massachusetts General Hospital are using a dimensional

approach to avoidant and restrictive eating to study children and adolescents with ARFID, aiming to understand whether their difficulties are based on a heightened anxiety response, dysregulation of appetitive hormones affecting brain-gut homeostatic processes, or based on taste (perception) abnormalities. We hypothesize that dysfunction across these three areas might co-occur in children and adolescents with ARFID and be predictive of negative psychiatric and physical outcomes. Preliminary data show overlapping dysfunctions in the majority (56%) of children and adolescents with avoidant and restrictive eating. This is the first NIMH funded study on ARFID and will likely influence our understanding of the pathophysiology and nosology of the disorder, as well as inform appropriate assessment and treatment of this pathology amongst children and adolescents.



Nadia Micali, MD, MRCPsych, PhD, FAED
Associate Professor, Psychiatry



Hypothesized model of avoidant and restrictive eating in childhood/adolescence, dimensional overlap of dysfunction across three neurobiological domains

Faculty Highlights

Mount Sinai Researchers Receive Major NIH Award for Environmental Child Health Research

Researchers from the Icahn School of Medicine at Mount Sinai (ISMMS) have been awarded more than \$9 million by the National Institutes of Health (NIH) under a seven-year initiative called Environmental Influences on Child Health Outcomes (ECHO).

Rosalind Wright, MD, MPH, Horace W. Goldsmith Professor of Pediatrics and Dean for Translational Biomedical Sciences, and Robert Wright, MD, MPH, Professor and Ethel H. Wise Chair of the Department of Environmental Medicine and Public Health, are leading Mount Sinai's consortium studying the influence of chemical, nutritional, and social factors on child neurodevelopment. Susan Teitelbaum, PhD, Professor of Environmental Medicine and Public Health and Annemarie Stroustrup, MD, MPH, Associate Professor of Pediatrics and Environmental Medicine and Public Health and Interim Chief of the Division of Newborn Medicine at ISMMS, and Judy Aschner, MD, Professor of Pediatrics and University Chair of the Albert Einstein College of Medicine, will collaborate on another ECHO study focusing on exposure to chemicals in neonatal intensive care units.

ECHO researchers around the country will collaborate to analyze existing data and collect standardized data on pregnancy outcomes, obesity, asthma, and neurodevelopment. More than 50,000 children from diverse racial, geographic, and socioeconomic backgrounds will become part of the ECHO consortium.

Additionally, ISMMS was awarded further funding for its existing Laboratory Hub, led by Dr. Robert Wright, and Data Repository, Analysis, and Science Center, led by Dr. Teitelbaum, under the NIH's Children's Health Exposure Analysis Resource (CHEAR), which provides resources and infrastructure to analyze samples and data collected through ECHO. Mount Sinai is one of only two institutions in the nation to be both an ECHO and a CHEAR site.



Rosalind J. Wright, MD, MPH

Dean, Translational Biomedical Sciences
Director, Conduits
Horace W. Goldsmith Professor,
Children's Health Research
Professor, Pediatrics and Environmental
Medicine & Public Health



Robert O. Wright, MD, MPH

Professor and Ethel H. Wise Chair,
Environmental Medicine & Public Health
Professor, Pediatrics
Director, Lautenberg Laboratory



Susan Teitelbaum, PhD

Professor, Environmental Medicine &
Public Health



Annemarie Stroustrup, MD, MPH

Associate Professor, Pediatrics and
Environmental Medicine & Public Health

New Extramural Faculty



Karen M. Wilson, MD, MPH

Karen M. Wilson, MD, MPH is the Debra and Leon Black Division Chief of General Pediatrics, and the Vice-Chair for Clinical and Translational Research for the Department of Pediatrics at the Icahn School of Medicine at Mount Sinai. She received her undergraduate degree in psychology from St. Lawrence University, and a Master's in Public Health, and MD with Distinction in Research from the University of Rochester. She completed her Pediatric Residency and Academic General

Pediatric fellowship also at the University of Rochester. Her primary research interests are in understanding the relationship between secondhand tobacco smoke exposure and severity of illness in children hospitalized for respiratory illness, and how to improve outcomes in hospitalized children. Dr. Wilson has an R01 from NCI to study an inpatient parent smoking cessation intervention, and she is one of the Principal Investigators and on the Speaker's Bureau of the AAP/Julius B. Richmond Center of Excellence, which is dedicated to eliminating children's exposure to tobacco and secondhand smoke. In addition, she is the Chair of the Academic Pediatric Association's Research Committee, and sits on their Board of Directors. Dr. Wilson is also the Chair of Pediatric Research in Inpatient Settings Network Executive Council, and Deputy Editor of *Hospital Pediatrics*.

Recent Publications

Wilson KM, Klein JD, Blumkin AK, Gottlieb M, Winickoff JP. Tobacco smoke exposure of children living in multi-unit housing. *Pediatrics*. 2011. 127:85-92.

Wilson KM, Wesgate SC, Pier JC, Weis E, Love T, Evans K, Chhibber A. Secondhand smoke exposure and serum cytokine levels in healthy children. *Cytokine*. 2012 60(1):34-7.

Wilson KM, Pier JC, Wesgate SC, Cohen J, Blumkin AK. Secondhand tobacco smoke exposure and severity of influenza in hospitalized children. *J Peds*. 2013. 162(1):16-21.

Wilson KM, Torok M, McMillen R, Tanski S, Klein JD, Winickoff JP. Tobacco smoke incursions in multi-unit housing. *Am J Public Health*. 2014 Aug;104(8):1445-53.

Wilson KM, Torok MR, Localio R, McLeod L, Srivastava R, Luan X, Mohamad Z, Shah SS; Pediatric Research in Inpatient Settings (PRIS) Network. Hospitalization for community-acquired pneumonia in children: effect of an asthma codiagnosis. *Hosp Pediatr*. 2015 Aug;5(8):415-22.



Marek Mlodzik, PhD

Marek Mlodzik, PhD

Marek Mlodzik, PhD is the Chair and Professor of Developmental and Regenerative Biology (DRB), and Professor of Oncological Sciences and Ophthalmology. He received his undergraduate degree in Biology II: Molecular and Cell Biology, Genetics, Biochemistry and Biophysics and PhD from the University of Basel, Switzerland. He completed his PhD thesis in 1987 in the lab of Walter Gehring, where he identified and analyzed the first maternal homeobox gene, Caudal. He then joined Gerald M Rubin, at the University of California in Berkeley, for his postdoctoral studies with focus on retinal cell type specification mechanisms in the *Drosophila* eye, including the identification of the first *Drosophila* nuclear hormone receptor gene. In 1991, he joined as faculty the European Molecular Biology Laboratory/EMBL in Heidelberg, Germany, with a research focus on developmental signaling pathways using the *Drosophila* eye as a model system. In 2000, he joined the Icahn School of Medicine at Mount Sinai (formerly known as the Mount Sinai School of Medicine) as a Professor. In 2007, he became the Founding Chair of the Department of DRB. His laboratory studies the establishment of epithelial planar cell polarity (PCP) regulated by Wnt/Frizzled-PCP signaling and regulatory mechanisms of Wnt-signaling specificity between the PCP and canonical beta-catenin pathways, and their cross-talk with Notch and RTK/EGF-Receptor signaling. To achieve this they are using a combination of *Drosophila* genetics and *in vivo* studies, cell culture experiments, and biochemistry, which is further enhanced through collaborations in vertebrate models such as zebrafish or mouse.



Lisa Eiland, MD

Lisa Eiland, MD

Lisa Eiland, MD is an Assistant Professor in the Division of Newborn Medicine within the Department of Pediatrics. As a neonatologist, she is intrigued by the potential of neonatal intensive care unit (NICU) stressors to alter neurodevelopment and contribute to the increased prevalence of adverse neurodevelopmental outcome in preterm infants. Using the rodent early life stress model of maternal separation, she has researched the effects of early life stress on the anatomy and function of the limbic system. Specifically, her research demonstrated stress related alterations of pyramidal neurons in the hippocampus, amygdala and prefrontal cortex, that paralleled increased depressive and anxiety like behaviors and impaired spatial memory. Currently, with funding provided by the Nurture Science Program, she will serve as site principal investigator for a multisite randomized controlled trial that explores whether fostering early maternal-infant connectedness in preterm infants impacts neurodevelopment.

Beyond her research interests, Dr. Eiland serves as the site director for the division of Newborn Medicine at Mount Sinai West. She has developed parental education curriculum to help families better understand the illnesses faced by their infants and is working to establish a NICU family advisory council to offer further support to families during their NICU stay.



Dusan Bogunovic, PhD

Dusan Bogunovic, PhD

Dusan Bogunovic, PhD is a tenure-track Assistant Professor in the Microbiology and Pediatrics Departments of the Icahn School of Medicine at Mount Sinai. He completed his PhD thesis at NYU Medical School on the role of immunity in late stage melanoma. Dr. Bogunovic identified an algorithm which uses immune and mitotic parameters to predict survival in metastatic melanoma. He also studied the innate immune signaling in dendritic cells as a function of their ability to mount an adaptive immune defense against melanoma. Subsequently, during his postdoctoral fellowship at The Rockefeller University he discovered genetic errors in ISG15 in otherwise healthy children who suffered from environmental mycobacterial disease. Since starting his laboratory, his team has defined an essential role for free intracellular ISG15 and USP18 in regulation of Type I Interferon induced inflammation. Recently they discovered that ISG15 deficient children have augmented anti-viral responses. Finally, they identified USP18 deficient children and detailed the molecular mechanisms behind the Type I IFN inflammation. The hypothesis of the lab is that inter-individual variability in susceptibility to infectious agents and/or ability to control inflammation can also be explained by the immune genetic composition of the host. To dissect these phenotypes his laboratory uses genomic, genetic, molecular biology, cellular biology, immunology and clinical tools.

Faculty Highlights

Awards/Honors

Jaime Chu, MD, Gilead Sciences, Research Scholars Program in Liver Disease Award

Bruce D. Gelb, MD, Elected to the American Society of Human Genetics Board of Directors

Nadia Micali, MD, PhD, MRCPsych, FAED, Brain and behavior Research Foundation, Independent Investigator Award,

Annemarie Stroustrup, MD, MPH, appointed Interim Chief, Division of Newborn Medicine, Kravis Children's Hospital at Mount Sinai and Interim Director, Newborn Services for the Mount Sinai Health System

Grants

Manish Arora, BDS, MPH, PhD, NIEHS, R01, "Novel Biomarker To Identify Critical Windows Of Susceptibility To Metal Mixture"

Coro Paisan-Ruiz, PhD, American Parkinson Disease Association (APDA), "Elucidating novel genetic mechanisms underlying autosomal recessive Parkinsonism"

Coro Paisan-Ruiz, PhD, Hirschl/Weill-Caulier Trust, "Elucidating and understanding the genetic etiology of movement disorders"

Dalila Pinto, PhD, NIMH, R01, "Integrative genomics to map risk genes and pathways in autism and epilepsy"

Michael Rendl, MD, NIAMS, R01, "Specification and Molecular Control of the Hair Follicle Inductive Mesenchyme"

Andrew Sharp, PhD, NHGRI, R25, "Supplement to Community Research Education and Engagement for Data Science (CREEDS)"

Eyal Shemesh, MD, NIDDK, U34, "Improving Medication Adherence in Children who had a Liver Transplant: IMALT"

Eyal Shemesh, MD, NIAID, U01 Supplement, "CTOT-C-PTSD"

Susan Teitelbaum, PhD and Annemarie Stroustrup, MD, NIH, ECHO, "Developmental Impact of NICU Exposure (DINE)"

Rosalind J. Wright, MD, MPH and Robert O. Wright, MD, MPH, NIH, ECHO, "Consortium on Perinatal Programming of Neurodevelopment"

Trainee Highlights

New MCHDI Trainee Leadership Committee Aims to Enhance Training Environment

The Trainee Leadership Committee (TLC) was established this year to build the MCHDI community of young scientists and improve availability of resources for trainees. The TLC's mission is to create career development workshops, training resources, and social events that promote scientific interaction. Comprised of pre- and post-doctoral representatives from departments across the broad scope of MCHDI, the TLC is off to a great start!

As a first order of business, the TLC established a trainee mailing list, which has recently crossed the 100-trainee mark! This list will be used to announce upcoming trainee social events,

workshops, and other MCHDI news.

The TLC hosted its first MCHDI trainee social on October 6th with great success – over 30 trainees attended – and aims to double attendance at the next event: Science Speed Networking (anticipated February 2017). Attendees at the social were polled to determine interest areas for upcoming Trainee Career Workshops. Based on feedback, the first workshop on December 20th will focus on career negotiation skills, and these surveys will continue to determine the content of future workshops. The TLC is greatly looking forward to this series, and hope the MCHDI trainee community will take advantage of this new resource.

Next, the TLC plans to rollout new programs in early 2017, including a "grant bank" wherein trainees can deposit their successfully funded grant submissions. The grant bank will be accessible to all MCHDI trainees as a model framework for new grant applications and will be an extremely helpful resource for those new to the grant writing process.

Lastly, a **survey** will be sent to gauge interest in the upcoming events and workshops. As always, the TLC is open to more suggestions on how to further improve the training experience!



Charles DeRossi, PhD

Postdoctoral Fellow,
Department of Pediatrics



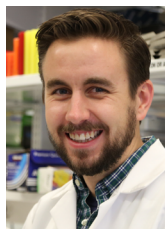
Alison Sanders, PhD

Postdoctoral Fellow,
Department of
Environmental Medicine and
Public Health



**Jeanette Stingone, PhD,
MPH**

Postdoctoral Fellow,
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Public Health



Evan Bardot

PhD Candidate, Department
of Developmental and
Regenerative Biology



Felix Richter

MD/PhD Candidate,
Department of Pediatrics

Publications

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- Tordesillas L, Rahman AH, Hartmann BM, Sampson HA, Berin MC. **Mass cytometry profiling the response of basophils and the complete peripheral blood compartment to peanut.** *J Allergy Clin Immunol*. 2016 Aug 13.
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