Icahn School of Medicine at Mount Sinai
The Mindich Child Health and Development Institute

MCHDI Developmental Outcomes

Fall 2021

Research Advancements: Food Allergies

Peanut Allergy- Insights on Prediction, Prevention, Diagnosis and Therapeutic Opportunities

Peanut allergy affects up to 2% of children and recent studies suggest that nearly 2% of adults are also affected. As the leader of an observational study in the NIH-sponsored Consortium for Food Allergy Research, we observed that 40% of 511 atopic infants- those with atopic dermatitis or another food allergy at enrollment at age 12 months- developed peanut allergy by age 7. We found that the strongest baseline predictor of peanut allergy was an immunoglobulin E (IgE) response to a specific peanut protein, Ara h 2.

However, the infants recruited into this study were following now outdated advice to avoid early ingestion of peanut. Our observational study revealed that increased environmental peanut found in house dust, and having more severe eczema, were peanut allergy risk factors. These observations build the story, supported by a trial conducted in England, that early ingestion of peanut by infants promotes oral tolerance. Without ingestion, environmental skin exposure, especially on inflamed skin, triggers unopposed allergic sensitization. New guidelines that we co-authored promote introduction of peanut around 6 months of age, and earlier in high-risk infants.

The translation of early peanut introduction to practice has potential barriers and our studies have addressed these as well. Our follow up studies suggest that early peanut introduction can be accomplished with education of parents and pediatricians, as they are receptive of the approach. In some higher risk infants, allergist-supervised peanut introduction (oral food challenge, OFC) is needed and we showed that this can be done safely, with over 80% being able to tolerate peanut. We observed primarily mild reactions among those who were already allergic. Interestingly, we reported that an increase in early peanut introduction may be driving an increase in a non-IgE mediated peanut allergic response, enterocolitis syndrome, which raises interesting questions about the developmental biology of tolerance.

Scott Sicherer, MD
Director, Elliot and Rosyln Jaffe Food Allergy Institute
Professor, Pediatrics

One holy grail in food allergy is to develop diagnostics that would avoid OFCs, and potentially inform prognosis, threshold and severity. Hugh Sampson's lab has developed assays showing that IgE binding to specific segments (epitopes) on peanut proteins can provide diagnostic accuracy superior to commonly available tests and this has recently been commercialized. Supinda Bunyavanich, MD, MPH has been leading integrated transcriptomic and epigenomic studies, and studies of the microbiome, revealing that these modalities may identify severity or provide insights on allergy outcomes. M. Cecilia Berin, PhD is leading studies recently showing how specific T cell responses are related to threshold of peanut reactivity.

In January 2020, the FDA approved the first-ever treatment of food allergy, a commercial peanut oral immunotherapy that was studied here in a trial led by Julie Wang, MD. Our team has ongoing trials of oral, epicutaneous, and injection immunotherapies, as well as various biologics under study for peanut and other foods. Drs. Sampson, Berin, Bunyavanich and Lafaille have integrated laboratory studies in therapeutic trials to identify predictors of success and to understand the underlying immunopathophysiology of the food allergic disorders. We look forward to additional progress in these areas.

Key Select References:

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The KLF1/EKLF Transcription Factor and Congenital Anemia

Anemia is a common scourge around the world, with many cases involving children (Sankaran and Weiss, 2015). Anemia is clinically verified by direct measurement of biophysical blood parameters coupled to morphological examination of peripheral blood smears. Although mutation within individual erythroid proteins (e.g., hemoglobin subunits, red cell membrane, iron transport) gives rise to specific problematic issues, multiparametric deficiencies tend to be caused by mutation or altered activity of erythroid transcription factors. One critical factor that plays a global role in erythropoiesis is KLF1 (aka EKLF), a C2H2 zinc finger protein we originally discovered a number of years ago, and that has recently been the focus of mutational discovery and analysis (Perkins et al., 2016).

Even in the heterozygous state, the KLF1-E325K mutation leads to congenital dyserythropoietic anemia type IV, where newborn patients are transfusion dependent and exhibit morphological defects in their erythroid compartment.

Many of these mutations are benign, and even those that lead to KLF1 haploinsufficiency are phenotypically unremarkable. However, compound heterozygous inheritance of two defective alleles can lead to anemia, with pyruvate kinase deficiency and nonspherocytic hemolytic anemia being two specific examples.

But one rare mutation remains unique in its effect: E325K is located within the second of the three zinc fingers, at a universally conserved amino acid that is critical for proper recognition of the KLF1 cognate binding site. Even in the heterozygous state, this mutation leads to congenital dyserythropoietic anemia (CDA) type IV (OMIM 613673), and newborn pediatric patients are transfusion dependent and exhibit a number of morphological defects in their erythroid compartment (Jaffray et al., 2013). One of the most dramatic is the presence of nucleated red blood cells in circulation, a result consistent with the known role of KLF1 in late stages of erythropoiesis (Gnanapragasam and Bieker, 2017).

Our recent studies have analyzed the molecular basis of the altered phenotype (Varricchio et al., 2019), and the results show an extensive dysregulation of normal levels of many KLF1 targets, including membrane, transport, iron metabolism, and cell cycle proteins that account for much of the defective phenotype of the CDA red cell. The mechanism by which the heterozygous presence of the KLF1/E325K variant prevents the normal function of the WT allele remains perplexing. However, an additional effect is that a novel DNA recognition element is recognized by the E325K variant, leading to ectopic mis-expression of genes that are normally not expressed in the red cell, some of which likely have systemic effects on pre- and post-natal development of other organs (Kulczynska-Figurny et al., 2020).

We are continuing our molecular and cellular analysis of these rare patient red cells, and will utilize derived iPSCs for biochemical and epigenetic testing of models to explain the striking dominant effect of KLF1/E325K on normal erythroid cell function.

James J. Bieker, PhD
Professor, Cell, Developmental, and Regenerative Biology

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Sankaran VG, Weiss MJ. Anemia: progress in molecular mechanisms and therapies. *Nat Med.* 2015 Mar;21(3):221-30.

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Trainee Pilot Projects: 2021 Awardees

Project Title: Oxytocin Modulation of the Supramammillary Nucleus, a Social Novelty Associated Brain Region and Its Role in Autism Spectrum Disorder

Investigator: Keerthi Thirtamara Rajamani, PhD, Postdoctoral Fellow, Psychiatry, Seaver Center for Autism Research and Treatment

Primary Mentor: Hala Harony-Nicolas, PhD, Assistant Professor, Psychiatry, Neuroscience, Seaver Center for Autism Research and Treatment, Mindich Child Health & Development Institute

Secondary Mentor: Hirofumi Morishita, MD, PhD, Associate Professor, Psychiatry, Neuroscience, Ophthalmology, Friedman Brain Institute, Mindich Child Health & Development Institute

Abstract: Social recognition memory (SRM), involves a multitude of cognitive and behavioral processes, and deficits in SRM have been implicated in several psychiatric disorders, including autism spectrum disorder (ASD). However, the neural circuitry underlying this form of behavior is not fully deciphered. Oxytocin (OXT) has been identified as a critical modulator of SRM. OXT projections have been found in lateral septum, medial amygdala and the nucleus accumbens and cumulatively identified as being part of the "social recognition" brain circuit. Through my work in Dr. Hala Harony-Nicolas' lab, I identified a novel posterior hypothalamic region called the supramammillary nucleus (SuM) to receive projections from OXT neurons. These OXT projections originate from a specific nuclei called the paraventricular nucleus and make local synaptic contacts in SuM. The SuM is located rostral to the mammillary body and acts as a major relay area between the brainstem and the hippocampus. It is majorly involved in synchronizing hippocampal theta rhythms through direct innervation of hippocampal CA2 region. Thus, the SuM is a critical nodal point for regulating hippocampal dependent learning and memory processes. Through the Mindich trainee pilot grant, I propose to study the implications of OXT activity within the SuM by examining the impact of PVN-OXT to SuM pathway on SRM. Additionally, I will employ a rodent model of ASD, Shank3-deficient rat, to examine if activation of the PVN-OXT can reverse the long-term SRM deficits that were previously reported in this model, and thus enable the understanding of the role of OXT neurons in SRM.

Keerthi Thirtamara Rajamani, PhD
Postdoctoral Fellow, Psychiatry

Project Title: Aberrant JAK/STAT Signaling in Nephrotic Syndrome

Investigator: Carol L. Shen, MD, Clinical Fellow, Pediatric Nephrology and Hypertension

Primary Mentor: Dusan Bogunovic, PhD, Associate Professor of Microbiology, Oncological Sciences, Pediatrics, Mindich Child Health and Development Institute

Secondary Mentor: Jeffrey Saland, MD, MSCR, Professor of Pediatrics, Division of Pediatric Nephrology and Hypertension, Mindich Child Health and Development Institute

Abstract: Nephrotic syndrome is one of the most common childhood kidney diseases worldwide; however, detailed understanding of the pathogenesis remains elusive. Current treatment involves steroids and long-term immunosuppression, which carry significant risk of morbidity and mortality. Depending on response to treatment and certain histologic features on biopsy, some patients face worse outcomes than others. However, the immunogenetic causes for these differences remain unknown. We recently identified JAK1 gain of function mutation in a patient with nephrotic syndrome and multisystem immune dysregulation, which was successfully treated with a JAK inhibitor. We hypothesize that differential genomic and cellular derangements in JAK/STAT pathway cause different disease entities and treatment response in nephrotic syndrome. In addition, differential dysregulation in the JAK/STAT pathway may lead to different local, infiltrative, inflammatory processes in the kidney. Our proposal includes patients with varying etiologies and clinical severity of nephrotic syndrome. We aim to perform whole exome sequencing, transcriptional analysis of variants, and robust CyTOF analysis for JAK/STAT activity, followed by immunostaining for kidney-intrinsic JAK/STAT hyperactivity in kidney biopsy samples. By studying genomic, transcriptional, cellular and tissue-level JAK/STAT dysregulation in nephrotic syndrome, we will elucidate key determinants in the disease pathogenesis, disease stage and treatment response of nephrotic syndrome. Findings from this investigation could inform targeted-therapy of nephrotic syndrome with increasingly available JAK-inhibitors.

Carol L. Shen, MD
Clinical Fellow, Division of Pediatric Nephrology and Hypertension

The Trainee Leadership Committee (TLC) Annual Report

The Trainee Leadership Committee (TLC) is in its fifth year of bringing together trainees across multiple disciplines and research areas represented in the Mindich Health and Development Institute (MCHDI). Since its start, the TLC has hosted socials, workshops, incubator series, and continued the MCHDI pilot grant. Those activities provided opportunities for MCHDI trainees to develop research skills and to network with other MCHDI trainees and alumni. The past year was a tough year for everyone because of the COVID-19 pandemic. Nevertheless, the TLC still successfully hosted many events in virtual form.

The TLC workshops are part of the Child Health Research Seminar (CHRS) series organized by Dr. Shelley Liu and Dr. Rebecca Trachtman. The TLC will be hosting three seminars this academic year, on 10/26, 12/7, and 1/18.

The flagship TLC initiative is the trainee pilot grant program, now in its third year. This unique program supports the trainee in developing a new independent line of research, a critical step towards establishing an independent academic career. Previous winners include the TLC's own Oscar Rodriguez, Michael Breen, Milo Smith, Hsi-en Ho, Conor Gruber, Carolina Cappi, Sharon Alterzon and Daniel Lorenzo-Ojalvo. This year's recipients are Keerthi Thirtamara Rajamani and Carol Liu Shen. Applications for the 2022-2023 academic year will open next Spring, and we encourage all MCHDI trainees with exciting new ideas to apply!

The MCHDI trainee's incubator series kicked off in the spring of 2021 and will continue this semester. Last semester, our speakers Adela Mossa, David Gonzalez, and Bhavana Shewale presented grant proposals and thesis proposals, and received feedback from other trainees and junior MCHDI faculty. Now we are calling for a new round of speakers for the incubator series. We are excited to meet you and hear about your work!

As a trainee committee, we would also appreciate any suggestion from the trainees about initiatives that can enhance their professional development and that can be implemented with the TLC's support.

Lastly, the TLC would like to thank its members from last year for all their hard work and dedication, Carolina Cappi, Adele Mossa, Xueying Zhang, David Gonzalez, and Silvia De Rubeis. We would like to wish best of luck to David for his future endeavors and give a warm welcome to a new TLC member, Vahe Khachadourian.

Carolina Cappi, PhD
Postdoctoral Fellow, Psychiatry

Vahe Khachadourian, MD, MPH, PhD
Postdoctoral Fellow, Psychiatry

Adele Mossa, PhD
Postdoctoral Fellow, Psychiatry

Xueying Zhang, PhD
Postdoctoral Fellow, Environmental Medicine and Public Health

Silvia De Rubeis, PhD
Assistant Professor, Psychiatry

> *TLC would like to thank its members from last year for all their hard work and dedication, Carolina Cappi, Adele Mossa, Xueying Zhang, David Gonzalez, and Silvia De Rubeis. We would like to wish best of luck to David for his future endeavors and give a warm welcome to a new TLC member, Vahe Khachadourian.*

Jennifer Bragg, MD

Jennifer Bragg, MD is a Neonatologist and Associate Professor of Pediatrics at the Icahn School of Medicine at Mount Sinai. She is the Director of the NICU Follow-up Program and a member of the Cardiac Neurodevelopmental Outcomes Collaborative (CNOC). Dr. Bragg is the Site director for Vermont Oxford Network Critical Transitions Collaborative.

Dr. Bragg received her MD in 2007 from New York University School of Medicine. She completed her Pediatric Residency and Perinatal-Neonatal Fellowship at the Kravis Children's Hospital at Mount Sinai before an additional year as a Research Fellow with a neurodevelopmental focus.

At Mount Sinai Kravis Children's Hospital, Dr. Bragg provides inpatient intensive care and outpatient follow-up. She implemented and runs the Mount Sinai NICU Follow-up Program, a multidisciplinary program that provides neurodevelopmental care to high risk NICU graduates such as those born preterm, with congenital heart disease, seizures, hypoxic ischemic injury, and neurologic disorders.

Dr. Bragg's research focus is on identifying modifiable outcomes with a focus on sensory processing disorders, parental stress and developmental programming. Current projects include implementation of programs including the SENSE Program (positive sensory interactions in the NICU), Reach Out and Reach and Developmental classes for families. Dr. Bragg has several Quality Improvement Initiatives such as Safe Sleep in the NICU and VON Critical Transitions. Finally, she is working with Dr. Bruce Gelb on GEMINI, a multi-center study that assesses how rapid whole genome sequencing improves time to diagnosis, delivery of care and the economic impact of infants with rare diseases.

Jennifer Bragg, MD
Associate Professor, Pediatrics

Key Publications:

Zhang Z, Spear E, Gennings C, Curtin PC, Justa AL, **Bragg JB**, Stroustrup A. The association of prenatal exposure to intensive traffic with early preterm infant neurobehavioral development as reflected by the NICU Network Neurobehavioral Scale (NNNS). *Environ Res.* 2020 Apr;183:109204.

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Bragg JJ, Green R, Holzman I.R. Does early enteral feeding prevent hypoglycemia in small for gestational age (SGA) neonates? *J Neonatal Perinatal Med.* 2013;6(2):131-5.

Geming Lu, MD

Geming Lu, MD, MS is an instructor in Dr. Adolfo Garcia-Ocana's lab of the Diabetes, Obesity, and Metabolism institute and the Mindich Child Health and Development Institute at Icahn School of Medicine.

Dr. Lu completed his Doctor of Medicine in Harbin Medical University and finished Master of Science in the Capital University of Medical Sciences in China. After being a physician working on neuro-autoimmune disorders for 6 years, he started his scientific research career in the Immunology Institute at Mount Sinai in 2011. He focused on the molecular mechanisms of Th17 differentiation and Macrophage polarization in autoimmune animal models. He became a faculty member in his current lab after publications in Immunity, Nature communications, PNAS, and JEM et al. His recent research interests are to develop peptides and compounds treating diabetes by boosting beta cell regenerations and inhibiting auto-reactive T cells. He is using NGS techniques to build up single-nucleus RNA seq references of human islets and target candidate genes using mass cytometry and gene editing technology. He finds HGF-cMET signaling increases MDSC populations, which can significantly inhibit auto-reactive T cells proliferation and delay T1D development; as well, he is exploring the feasibilities of the adaptive Treg transfer and beta cell regeneration with the patent compounds in several T1D mice models.

Dr. Lu received NIH F32 fellowships from 2015-2017. His current research is supported by the Pilot & Feasibility grant and Immuno-Technology Core micro grant of the Einstein-Sinai Diabetes Research Center.

Geming Lu, MD
Instructor, Medicine

Key Publications:

Kang R, Zhang T, Santos L, Rajbhandari P , Garcia-Ocaña A, **Lu G.** Single nuclei RNA Sequencing reveals human islets heterogeneity in vitro and in vivo. [In press]

Lu G, Rausell-Palamos F, Zhang J, Zheng Z, Zhang T, Valle S, Rosselot C, Berrrouet C, Conde P, Spindler M, Graham J, Homman D, and Garcia-Ocaña A. Dextran sulfate protects pancreatic beta cells, reduces autoimmunity, and ameliorates Type 1 diabetes. *Diabetes.* 2020 Aug; 69(8): 1692-1707.

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Zhang R, Qi CF, Hu Y, Shan Y, Hsieh YP, Feihong Xu, **Lu G,** Dai J, Gupta M, Cui M, Peng L, Yang J, Xue q, Chen-Liang R, Chen k, Zhang y, Fung-Leung WP, Mora JR, Li L, Morse HC, Ozato K, Heeger PS, Xiong H. T follicular helper cells restricted by IRF8 contribute to T cell-mediated inflammation. *Journal of Autoimmunity.* 2019.

Li Q, Zhao F, Zhang J, Yang Q, **Lu G,** Xia R, Zhu Z. NLRP3 Inflammasome Activation Regulates Aged RBC Clearance. *Inflammation.* 2018.

New Extramural Faculty

Lauryn Choleva, MD

Lauryn Choleva, MD, MSc is an Instructor in the Division of Pediatric Endocrinology and Diabetes at Mount Sinai Kravis Children's Hospital. Dr. Choleva's research is conducted out of the Diabetes, Obesity and Metabolism Institute at the Icahn School of Medicine at Mount Sinai in the lab of Dr. Andrew Stewart, MD. Her research is focused on the development of novel methods for inducing the replication and differentiation of insulin-producing beta cells for future use as regenerative pharmacotherapy for patients with Diabetes Mellitus. She is also exploring novel roles of the known cell cycle inhibitor p57KIP2 in human beta cells to understand the pathogenesis of childhood hypoglycemic syndromes.
Dr. Choleva graduated with a BSc in Anatomy and Cell Biology from McGill University and with an MSc in Clinical Nutrition from the University of Toronto. She received her medical degree from the Sackler School of Medicine at Tel Aviv University. Dr. Choleva completed her residency in Pediatrics and her fellowship in Pediatric Endocrinology at the Icahn School of Medicine at Mount Sinai. She was a recipient of the 2020 Pediatric Scholars Award from The Icahn School of Medicine at Mount Sinai Department of Pediatrics.

Lauryn J. Choleva, MD
Instructor, Pediatrics

Key Publications:

Wang P, Karakose E, **Choleva L,** Kumar K, DeVita RJ, Garcia-Ocana A, Stewart AF. Human beta cell regenerative drug therapy for diabetes: past achievements and future challenges. *Front Endocrinol (Lausanne).* 2021 Jul 16;12:671946.

Wilkes M, Murphy T, Aluf A, Sperber D, Sherry A, Sethuram S, **Choleva L,** Rapaport R. Shared Education Visits for Adolescents with Type 1 Diabetes. *Diabetes.* June 2020. 69(S1) 2247.

Choleva L, Rapaport R, Romero C, Yau M, Sethuram S, Gujral J, Wallach E, Wilkes M. Papillary Thyroid Carcinoma in a Pediatric Patient with Beta Thalassemia. *Journal of the Endocrine Society,* Volume 3, Issue Supplement_1, May 2019, SUN–613.

Faculty Highlights

Faculty Grants/Awards/Honors

James J. Bieker, PhD, NIDDK, R01, "Function of a Putative Determinant in Hematopoiesis"

Maria Curotto de Lafaille, PhD, NIH/NIAID, R01, "B Cell Memory in Human Food Allergy"

Silvia De Rubeis, PhD, NINDS, R21, "The Development of Cortico-cerebellar Circuits in a Genetic Form of Intellectual Disability"

Silvia De Rubeis, PhD, Alexander von Humboldt Foundation, Wilhelm Bessel Research Award

Lisa Eiland, MD, Subaward Site PI Mount Sinai West, NICHD R01, "NY ScreenPlus: A Comprehensive Flexible, Multi-disorder Newborn Screening Program"

Amy Kontorovich, MD, 2021 Cullman Family Award for Excellence in Physician Communication

Praveen Raju, MD, PhD, NIH/NINDS, R56, "Inducing Neural Maturation in Medulloblastoma by Targeting EZH2"

SAVE THE DATES

9th Annual MCHDI Retreat

Dates: November 30, 2021
Time:TBA
Location: Harmonie Club
Ballroom, 1st Floor
4 E 60th St, New York, NY 10022

Publications

Berin MC, Lozano-Ojalvo D, Agashe C, Baker MG, Bird JA, Nowak-Wegrzyn A. Acute fpies reactions are associated with an il-17 inflammatory signature. *J Allergy Clin Immunol.* 2021 Sep;148(3):895-901.e6.

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Chun Y, Do A, Grishina G, Arditi Z, Ribeiro V, Grishin A, ... **Bunyavanich S.** The nasal microbiome, nasal transcriptome, and pet sensitization. *J Allergy Clin Immunol.* 2021 Jul;148(1):244-9.e4.

Mahjani B, **De Rubeis S,** Gustavsson Mahjani C, Mulhern M, Xu X, Klei L, Satterstrom FK, Fu J, Talkowski ME, **Reichenberg A,** Sandin S, Hultman CM, **Grice DE,** Roeder K, Devlin B, **Buxbaum JD.** Prevalence and phenotypic impact of rare potentially damaging variants in autism spectrum disorder. *Mol Autism.* 2021 Oct 6;12(1):65.

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Icahn School of Medicine at Mount Sinai

The Mindich Child Health and Development Institute

Website: **www.mountsinai.org/mchdi**
Email: **mchdi@mssm.edu**
Facebook: **www.facebook.com/mindichchdi**
Twitter: **@MindichCHDI**
Contact: **Tel: (212) 824-8938 Fax: (212) 241-3310**
Address: **1470 Madison Avenue, 8th Floor**
Hess Center for Science and Medicine at Mount Sinai
New York, NY 10029-6542