MCHDI Researchers Awarded $15 Million NIH Grant to Create a Center to Unravel Novel Causes of Food Allergy and Atopic Dermatitis

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MCHDI faculty member Supinda Bunyavanich, MD, MPH, MPhil and colleagues have been awarded $15 million over five years by the National Institutes of Health to create a center to elucidate novel causes of, and contributing factors to, food allergies and atopic dermatitis.

The Systems Biology of Early Atopy (SunBEAm) Analysis and Bioinformatics Center intends to develop a better understanding of allergy development. The center will apply systems biology to identify early-life markers of risk for food allergies and atopic dermatitis (also known as eczema), as well as biological pathways underlying these common conditions, through the profiling and analysis of longitudinal multi-omics data from a multi-center pre-birth cohort of 2,500 children.

Food allergies and atopic dermatitis are complex diseases that affect nearly 8 percent and 20 percent of children, respectively. Food allergies are frequently preceded by atopic dermatitis, suggesting shared risk factors and overlapping pathobiology.

"Individuals with food allergies are at daily risk for potentially life-threatening conditions, including hives, respiratory distress, and/or anaphylaxis following ingestion of a food antigen to which they are sensitized. And for those suffering from atopic dermatitis, they live with chronically inflamed skin that can cover a significant proportion of their bodies," said Dr. Bunyavanich.

"This funding enables us to create a center that will make a significant impact on allergy research. A systems biology approach where the biology of these common conditions is investigated comprehensively at several levels may help identify new knowledge about the development of allergies, ultimately helping us to improve the prevention, diagnosis, and clinical management of food allergies and atopic dermatitis," said Dr. Bunyavanich.

The SunBEAm Analysis and Bioinformatics Center (NIH grant number 1UM1AI173380-01) includes fellow MCHDI member Scott Sicherer, MD and additional investigators from Mount Sinai, Johns Hopkins, the University of North Carolina at Chapel Hill, Northwestern, and National Jewish Health. The SunBEAm birth cohort is a collaborative effort by investigators from 12 sites across the United States who are enrolling families for participation in this cohort study that follows parents and children from before birth through the child’s third birthday. SunBEAm is supported by the National Institutes of Allergy and Infectious Diseases, part of the National Institutes of Health, and spearheaded by the Consortium for Food Allergy Research.

The graphic above illustrates the multi-omic, systems biology approach the new center is pursuing to study allergy development in early life.
Discovering the Causes of Rare Diseases by Statistical Modeling of Genome Sequences

Fewer than half of the approximately 10,000 cataloged rare diseases have a resolved genetic etiology. The generation and statistical analysis of genome sequencing data from large collections of patients with rare diseases provides a route towards resolving the remaining unknown etiologies (1). One major endeavor, the 100,000 Genomes Project (100KGP), has sequenced the genomes and collected clinical phenotype data for 34,523 UK patients and 43,016 unaffected relatives across 29,741 families. Such large genetic datasets are notoriously cumbersome to work with, as the full genotype data are typically stored in unmodifiable files many terabytes in size. Although distributed genotype databases have recently been developed, they depend on specialized computing systems, which hinders deployment. The genotype data are also challenging to integrate analytically with phenotypic data, pedigree relationships, the results of statistical inference and data from external sources. Taken together, these factors hinder etiological discovery substantially.

We noted that the genotypes that correspond to genetic variants with a minor allele frequency (MAF) <0.1% comprise approximately 1% of all genotypes. As the MAFs of pathogenic variants with strong effects on rare disease risk are typically kept <0.1% by negative selection, etiological discovery should be achievable by analyzing only 1% of the genetic data. A reduction in size of this magnitude allows a relational database (RDB) to be used for analysis. RDBs have well-known advantages over ordinary files, including speed, reliability, flexibility, structure and extensibility. We created an RDB (a ‘Rareservoir’), only 5.5 GB in size, of the 100KGP data and applied our Bayesian statistical method BeviMed (2) to identify genetic associations between coding genes and each of the 269 rare disease classes assigned to patients in the 100KGP by clinicians.

We found 260 genetic associations with a posterior probability of association (PPA) >0.95, of which 241 were already known (3). We prioritized three of the 19 previously unidentified associations for validation. Through an international collaboration spanning the USA, Europe, the Middle East and Japan, we validated all three of these associations by searching for pedigrees in other cohorts and using bioinformatic and experimental approaches. Firstly, we showed that loss-of-function variants in the ETS-family transcription factor-encoding gene ERG (4) result in primary lymphoedema. We provided evidence that the variants can lead ERG to become mislocalized outside the nucleus, where it cannot bind to DNA. Secondly, we reported that truncating variants in the last exon of PMEPA1 result in a familial thoracic aneurysm disease that is reminiscent of Loeys-Dietz syndrome (LDS) (5). In accordance with the etiologies of previously known forms of LDS, the variants in PMEPA1 are likely to exert their pathogenic effects by altering TGFβ signaling. Thirdly, we showed that loss-of-function variants in the G-protein-coupled receptor-encoding gene GPR156 give rise to recessive congenital hearing impairment. Given that GPR156 has recently been found to be a critical regulator of stereocilia orientation (6), it is likely that reduced expression of GPR156 in patients disrupts stereocilia formation, leading to the deafness phenotype.

Etiological discovery is an important step in diagnosing, prognosticating and eventually developing treatments for rare diseases. Patients with certain types of unexplained primary lymphoedema, thoracic aneurysm disease or congenital hearing impairment will now be able to receive a genetic diagnosis. The remaining previously unidentified associations contain several plausible candidates that merit following up.

References
Pilot Project: 2023 Awardees

Project Title: Structure-Function Studies of Ara H 2 Specific Antibodies Isolated From Highly Sensitized Children With Peanut Allergy

Principal Investigators: Maria Curotto de Lafaille, PhD (Communicating PI) and Goran Bajic, PhD (Co-PI)

Abstract: High affinity IgE antibodies are essential mediators of food allergy, an important cause of anaphylaxis. While some allergies resolve spontaneously, peanut allergy persists in the majority of affected children. Allergy persistence relies on humoral memory sustained by IgE plasma cells and memory B cells. Using mouse models, we discovered that most IgE cells are plasma cells, and that high affinity IgE is generated by sequential switching of IgG1 memory cells. Human studies support a similar model for the differentiation of pathogenic IgE cells. To understand peanut allergy persistence, our laboratory studies peanut specific memory B cells that have the potential to generate IgE plasma cells. Furthermore, elucidating the molecular recognition of peanut allergens by memory B cell receptors, may teach us on thresholds of reactivity, information that can be used to design inhibitors of IgE-mediated cell activation. To characterize peanut specific memory B cells, we single-cell sorted, from PBMC of peanut allergic children, B cells that bound Ara h 2, the main protein allergen of peanut. Ara h 2 binding B cells were mostly IgG1 and IgM memory cells, but only IgG1 cells carried antibody genes with high level of somatic mutations. Monoclonal antibodies derived from IgG cells, but not from IgM cells, bound Ara h 2 with high affinity. Among Ara h 2 binding cells, we identified convergent clones with similar VH and VL gene sequences in unrelated subjects, suggesting strong selection for specific immunoglobulin sequences in the Ara h 2 response. The goal of this collaborative project between the Lafaille and Bajic labs is to perform structure-function analysis of the binding of Ara h 2 specific IgG-memory derived antibodies to Ara h 2 allergen, and to compare their binding patterns with those of polyclonal peanut-specific IgE from the serum of peanut allergic children. By determining the structures of antibodies bound with the allergen, we wish to identify critical residues involved in high affinity binding to the antigen. This information could then be used to generate candidate inhibitors of IgE-mediated mast cell degranulation.

Project Title: Irritable Bowel Syndrome: An Antigenic Driven Disease?

Principal Investigators: David Dunkin, MD (Communicating PI) and Maria Curotto de Lafaille, PhD (Co-PI)

Abstract: Irritable bowel syndrome (IBS) presents with recurrent abdominal pain and changes in frequency or the form of the stool. IBS is highly prevalent and has a large impact on the quality of life for patients suffering from it, yet the pathogenesis of IBS is not completely understood. It is thought to involve structural, neurological and immune components. The immune pathways involved have not been well characterized except that there is an increased frequency and density of mast cells around the nerve fibers in the intestines. Mast cells have the ability to enhance Th2 polarization and both can induce B cell maturation and class switching. Thus, changes in T and B cell populations and their interaction with mast cells could drive the disease. Our preliminary data show an increase in both Th9 and Th2 cells in the mucosa of IBS patients. This fits with the increased mast cells found in the mucosa and the compelling evidence that food antigens may drive immune activation and thus a lack of tolerance to antigens in IBS. Studies show increased activation of B cell in the peripheral blood, activation of B cells in the jejunal mucosa along with increased IgG+, and colonic IgE activation in IBS.

Our goal is to begin to decipher mucosal immunologic changes in response to food antigens that are occurring in IBS. To achieve this goal, we propose to get pilot data that deeply characterizes T and B cells in the mucosa of the intestines using spectral flow analysis and the T cell changes that occur in response to antigenic stimulation. Ultimately, this will help us understand if there is a loss of tolerance and thus, will lead to better understanding of the role of immune dysregulation in the development of IBS and to the creation of novel immunotherapies for IBS.
**New Extramural Faculty**

### Son Duong, MD

Son Duong, MD, received his medical doctorate at the University of Virginia School of Medicine. He completed his residency training in pediatrics at UPMC Children's Hospital of Pittsburgh and completed a Master of Science in clinical research at the University of Pittsburgh. He then completed his Pediatric Cardiology Fellowship at Lucile Packard Children's Hospital at Stanford, and an advanced noninvasive imaging fellowship at Icahn Mount Sinai and Mount Sinai Kravis Children's Hospital. Dr. Duong's research is focused on application of advanced data analysis techniques to large-scale data sources for better prediction of outcomes in patients with congenital heart disease. He is currently a faculty member of the Artificial Intelligence in Medical Science (AIMS) Lab. As a specialist in cardiac imaging, he is developing artificial intelligence-assisted prediction tools for cardiac structure and function from multimodality data.

**Key Publications:**


### Joan Han, MD

Joan Han, MD, is a Professor of Pediatrics and Chief of the Division of Pediatric Endocrinology and Diabetes in the Jack and Lucy Clark Department of Pediatrics at the Icahn School of Medicine at Mount Sinai and Mount Sinai Kravis Children's Hospital. She earned her undergraduate and medical degrees from Harvard University. She completed her residency in pediatrics at Boston Children's Hospital and Boston Medical Center, and pursued further advanced training in a clinical research fellowship at Nemours Children's Clinic in Jacksonville, Florida, and a pediatric endocrinology fellowship at the National Institutes of Health in Bethesda, Maryland. Prior to joining Mount Sinai, she was Associate Professor of Pediatrics and Director of the Pediatric Obesity Program at the University of Tennessee Health Science Center and Le Bonheur Children's Hospital in Memphis, Tennessee. She is board certified in general pediatrics and pediatric endocrinology and diabetes.

**Key Publications:**

Dirk Hubmacher, PhD

Dirk Hubmacher, PhD is an Assistant Professor in the Department of Orthopaedics, where his team investigates the role of extracellular matrix proteases, ADAMTS-like proteins and fibrillins in the context of developmental short stature syndromes. Dr. Hubmacher received his Ph.D. from the University of Lübeck (Germany) in 2004 where he studied iron uptake in salt-loving Archaea. He entered the field of connective tissue disorders as postdoctoral fellow with Dr. Dieter Reinhardt (McGill University, Montreal) where he studied molecular pathomechanisms underlying Marfan syndrome and homocystinuria. In 2011, Dr. Hubmacher joined the laboratory of Dr. Suneel Apte at the Cleveland Clinic to study the function of ADAMTS proteases and ADAMTS-like proteins in mouse models of rare developmental short stature syndromes. In 2018, he moved to ISMMS where his team continues to investigate pathomechanisms of these syndromes with a focus on geleophysic dysplasia, Weill-Marchesani syndrome, and Marfan syndrome. Dr. Hubmacher has received funding from the NIH/NIAMS, the Marfan Foundation, the Ines Mandl Research Foundation, and the German Academic Exchange Service. His work was recognized by the Harold and Golden Lamport Clinical Research Award (2021), the Mount Sinai Faculty Idea Prize (2019) and the Young Investigator Award from the Marfan Foundation (2005). Dr. Hubmacher served as ad-hoc reviewer on several NIH study sections and DoD review panels and served as an elected council member for the American Society for Matrix Biology (2018-2022).

Key Publications


Behrang Mahjani, PhD

Behrang Mahjani, PhD, has a unique background in analyzing complex biological data using advanced statistical models. He completed his BSc at K.N.Toosi University of Technology in 2004 and his first MSc in complex adaptive systems with a specialization in population genetics at the Chalmers University of Technology, Sweden, in 2008. He continued at the Chalmers University of Technology and received his second MSc in mathematical statistics in 2011. His doctoral dissertation was focused on the development of new analytical methods for the genetic mapping of complex traits. Dr. Mahjani spent one year as a postdoctoral fellow at the Department of Biostatistics and Epidemiology at Karolinska Institutet, where he received training in epidemiology and statistical methods for register-based research. Then, he was a postdoctoral fellow at the Department of Psychiatry at the Icahn School of Medicine at Mount Sinai under the mentorship of Drs. Joseph Buxbaum and Dorothy Grice. Dr. Mahjani's primary interest is to better understand the developmental mechanisms and trajectories of childhood neuropsychiatric disorders, from the prenatal period through adolescence.

Key Publications


Anna-Sophie Rommel, PhD

Anna-Sophie Rommel, PhD is an Assistant Professor in the Department of Psychiatry. Her work as a psychiatric epidemiologist focuses on environmental exposures and their link to the development of adverse health outcomes, including suboptimal pregnancy and birth outcomes, as well as adverse neurodevelopment and longer-term psychopathology. Dr. Rommel is also interested in mental illness related to reproductive events, including pregnancy and menopause. She has been instrumental in setting up two separate birth cohorts and has conducted analyses in several existing birth cohorts to study the outcomes of early life exposure to, for example, maternal mental illness, medication, phthalates, and inflammation. Her lab applies epidemiological,

Key Publications:

Sarah Stanley, PhD
Sarah A. Stanley, PhD, is an Assistant Professor in the Icahn School of Medicine at Mount Sinai in the Diabetes, Obesity and Metabolism Institute, and Neuroscience. Her research focuses on developing and optimizing tools to image and modulate neural circuits and applying these to understand neural control of metabolism.

After receiving her undergraduate and medical degrees from Cambridge University, Dr. Stanley completed her endocrinology training and Ph.D. at Imperial College London. Supported by a Medical Research Council fellowship, Dr. Stanley moved to Rockefeller University for postdoctoral training, focusing on developing novel neuromodulatory tools to study the neural circuits regulating glucose metabolism.

Since joining the Diabetes Obesity and Metabolism Institute at Mount Sinai, Dr. Stanley’s lab has continued to develop and optimize novel imaging and neuromodulatory tools to examine the roles of central and peripheral neural circuits in the regulation of glucose metabolism and determine how these circuits are disrupted in metabolic disease. Ultimately, the aim of these studies is to identify new methods to prevent and treat diseases such as diabetes.

Key Publications:
Facility Grants/Honors

Sharon Baumel-Alterzon, PhD, The American Diabetes Association (ADA) 83th Scientific Sessions, “Nrf2 Regulates Neonatal β-Cell Mass Expansion” oral talk

Dusan Bogunovic, PhD, International Cytokine & Interferon Society, ICIS-Luminex John R. Kettman Award for Excellence in Cytokine & Interferon Research

Behrang Mahjani, PhD, NIH/NIMH, R21, “Risk architecture of postpartum psychosis”

Andrew Sharp, PhD, NIH/NIA, RF1, “A comprehensive study of tandem repeat variation as a cause of Alzheimer’s disease”

Ernest Turro, PhD, NICHHD, R05, “Bayesian genetic association analysis of all rare diseases in the Kids First cohort”

Ernest Turro, PhD, NHLBI, R01, “Integrative analysis of whole genomes and transcriptomes from multiple cell types in rare disease patients”

Trainee Grants/Awards


Lauren Dierdorff, Lausanne Switzerland July 2023, Selected for FENS Chen Institute – NeuroLéman Summer School on Motor control: from thought to action

Tasneem Ebrahim, BA, Weinstein Cardiovascular Development and Regeneration Conference 2023, “Dissecting mechanisms of cardiac specification and differentiation using large-scale CRISPR-based screens” poster presentation

Clifford Liu, MD/PhD candidate, AHA/CHF Predoctoral Fellowship for 2023-2024, “Mechanisms of Cardiac Valve Disease in Noonan Syndrome

Roosheela Patel, PhD, Icahn School of Medicine at Mount Sinai, The Terry Ann Krulwitch Dissertation Award

Faculty Highlights

Publications


Chen X, Elson CO, Dunkin D. Epicutaneous immunotherapy with cb1r alleviates intestinal inflammation. Inflamm Bowel Dis. 2023 Jan 10.

Yu M, Aguirre M, Jia M, Gjonji K, Cordova-Palomera A, Munger C, ... Loos RJF, ... Gennings C. A cross-validation based approach for estimating specific gravity in elementary-school aged children using a nonlinear model. Environ Res. 2023 Jan 15;217:114793.


Gutiérrez-Avila I, Rijoas-Rodríguez H, Colicino E, Rush J, Tamayo-Ortiz M, Borja-Aburto VH, Just AC. Daily exposure to pm (2.5) and 1.5 million deaths: A time-stratified case-crossover analysis in the mexico city metropolitan area. medRxiv. 2023 Jan 17.


