Mount Sinai *The Mindich Child Health and Development Institute*

MCHDI Developmental Outcomes

Director's Message

Fall 2014

For the MCHDI, 2014 has so far been a year marked by major growth and development, driven by a vision of encompassing all of children's health research at Mount Sinai. Our expanding group of talented scientists and physician-scientists are subject matter experts in diverse areas of multi-disciplinary research, including Allergy & Asthma, Cardiovascular Disease, Neurodevelopmental Disorders, Obesity & Diabetes, and more. This summer, the MCHDI welcomed 22 new Mount Sinai faculty recruits from the Departments of Pediatrics, Regenerative and Developmental Biology, and Psychiatry, who significantly expand the breadth of our children's health research focus. We are continuing to recruit new faculty to Mount Sinai, most recently Chris Gennings, PhD, and have opened a state-of-the-art environmental chemistry laboratory in collaboration with the Children's Environmental Health Center.

This year, MCHDI faculty have made important scientific discoveries that are critical to advancing child health research, earning them numerous awards and distinctions, such as Thomson Reuters' "World's Most Influential Scientific Minds 2014." The work of these individuals has led to breakthroughs in our understanding of food allergies, toxic environmental chemical exposures leading to neurodevelopmental disorders, as well as promising therapy options for diabetes, cardiovascular disease, and other child health diseases.

In addition to our signature programs such as the Pilot Grant Program, Grant Review Program, and Incubator Lunch Series, we have launched an official MCHDI Facebook page and Twitter, which serve as public portals to share important research updates and news about our institute and faculty. We will also be distributing our newsletter bi-annually to highlight important scientific studies within our institute and continue to promote our progress in advancing child health research through collaborative efforts.

Bruce D. Gelb, MD
Director, Child Health and Development Institute
Professor, Pediatrics and Genetics and Genomic Sciences

The Laboratory for Molecular Environmental Chemistry

Advancing Research on the Environmental Causes of Childhood Diseases

The rates of many childhood diseases are growing globally. Hazardous exposures in the modern environment are also on the rise, and science is beginning to link these two trends to each other. While the discipline of children's environmental health has made substantial gains over the past fifty years, new approaches are needed to advance the field.

The new Laboratory for Molecular Environmental Chemistry opened earlier this summer and is a state-of-the-art facility dedicated to supporting research to discover the environmental causes of diseases in children. The lab is equipped with innovative technologies that not only expand the scope and quality of research conducted at Mount Sinai, but also allow our team to understand how, when, where, and to what degree environmental chemicals enter the body. In addition to measuring exposure biomarkers, the lab utilizes new methods developed by Manish Arora, PhD, BDS, MPH, Director of Exposure Biology Laboratory, that "reconstruct" exposures that occurred years earlier, identify how mixtures of chemicals produce toxicity, and reveal how the chemicals themselves are dispersed throughout the body's tissues.

The Laboratory for Molecular Environmental Chemistry is a collaborative facility shared by the MCHDI and the Children's Environmental Health Center (CEHC). Directed by Robert O. Wright, MD, MPH, a transdisciplinary scientist, member of the MCHDI, and Deputy Director of the CEHC, the lab was established based on the idea that no single field of science can explain the origins of complex diseases. Thus, the work performed in the lab will revolutionize how children's environmental health research is conducted — creating a transdisciplinary scientific enterprise that fosters innovation and encourages the cross-pollination of ideas that span pediatrics, toxicology, environmental health, genetics, epigenetics, and chemistry. For further information or inquiries regarding the lab please contact Rozalyn Paupaw at rozalyn.paupaw@mssm.edu.

Brian Lee, Robert O. Wright, MD, MPH; Jessica Alba; Kenneth L. Davis, MD; Manish Arora, BDS, PHD, MPH; Philip J. Landrigan MD, MSC; Dennis S. Charney, MD; Sean Kane and Christopher Gavigan at the ribbon cutting ceremony for the unveiling of The Honest Company Ultra Clean Room in the new lab on September 10, 2014.

The Laboratory for Molecular Environmental Chemistry
Atran Building, 3rd Floor, Room 002
1428 Madison Avenue New York, NY 10029

Robert O. Wright, MD, MPH
Professor and Vice Chair, Preventive Medicine
Deputy Director, Children's Environmental Health Center
Director, Laboratory for Molecular Environmental Chemistry

Study Reveals Common Genetic Changes Are Significant in Autism

Genetic changes are responsible for roughly 60 percent of the risk for autism, and most of these variants are commonly found in the general population, according to a groundbreaking study led by Joseph D. Buxbaum, PhD, Director of the Seaver Autism Center for Research and Treatment, and Professor of Psychiatry, Neuroscience, and Genetics and Genomic Sciences at the Icahn School of Medicine at Mount Sinai.

The remaining non-genetic factors that account for roughly 40 percent of the risk for autism are not known. However, environmental factors and the interaction between genes and the environment may be a part of these non-genetic factors, says Dr. Buxbaum, the G. Harold and Leila Y. Mathers Research Professor of Geriatrics and Adult Development at Icahn School of Medicine.

Findings from the four-year study—called the Population-Based Autism Genetics and Environment Study (PAGES) Consortium—were published in the July 20, 2014 issue of Nature Genetics.

In the study, the largest of its kind ever undertaken, Mount Sinai researchers worked in collaboration with Swedish scientists, analyzing 500,000 common genetic variants from 3,046 people, 466 of whom had autism. The team then corroborated their results with a longitudinal Swedish study that followed more than 1.6 million families and included more than 14,000 individuals with autism.

"Most of the risk for autism is found in common variants, but we know that in a specific individual, a spontaneous mutation or other rare mutation is often the decider, with the interaction between the common variants and rare mutations leading to the diagnosis," Dr. Buxbaum says. "There was already evidence two years ago that both common and rare genetic variation contributed to autism. Using this unique sample, we were able to make it perfectly clear regarding relative contributions, and showed that common variation is significantly more important than generally appreciated." The study was funded by the National Institutes of Health (NIH) and the Beatrice & Samuel A. Seaver Foundation.

Dr. Buxbaum is currently leading a multinational consortium that is completing a study of 3,800 individuals with autism to identify spontaneous and other rare mutations as well. The consortium is using advanced methods to look at every gene in the genome.

"Together, with support from the NIH and enormous philanthropy from the Seaver Foundation, and others, we are able to be very aggressive in advancing the field, and defining the next generation of diagnostic tools and treatments for autism, both behavioral and pharmacological," says Dr. Buxbaum.

Joseph Buxbaum, PhD

Vice Chair for Research, Department of Psychiatry

Director, Seaver Autism Center for Research and Treatment

Professor, Psychiatry, Neuroscience and Genetics & Genomic Sciences

New Faculty

Chris Gennings, PhD

Dr. Gennings comes from the Virginia Commonwealth University, where she was Professor of Biostatistics and the Director of the Research Incubator for the Center for Clinical and Translational Research. Dr. Gennings received her PhD in Biostatistics from the Medical College of Virginia, Virginia Commonwealth University. Her research interests focus on design and analysis methodologies for studies of chemical mixtures. This has included methods for both toxicology studies and epidemiology/clinical studies. She is the founding director of a T32 training grant from the NIEHS in Environmental Statistics, focused on the integration of mixtures toxicology and statistical methods. Her research has been supported by the National Institute of Environmental Health Sciences, U.S. Environmental Protection Agency, World Health Organization, National Institute of Child Health and Human Development, and the Health Effects Institute.

Recent work includes: a patent for multidrug titration; developing a body burden index with empirically derived weights linked to health outcomes; development of a holistic measure of wellness using biomarkers of effect; development of a holistic nutrition index; development of weighted quantile sum regression – a method that is robust to confounding concerns based on complex correlations among exposure to environmental mixtures; and development of tests for sufficient similarity, a novel approach that complements current cumulative risk assessment methods and does not require the default assumption of additivity.

She is currently serving on the Chronic Hazard Advisory Panel for the U.S. Consumer Product Safety Commission, focusing on mixtures of phthalates, and the Committee for Inorganic Arsenic for the National Research Council.

Recent Publications:

1. Carrico CK, Gennings C, Wheeler DC, Factor-Litvak P. Characterization of Weighted Quantile Sum Regression for Highly Correlated Data in a Risk Analysis Setting. *Journal of Agricultural, Biological and Environmental Statistics.* 2014.
2. Yorita Christensen, KL, Carrico CK, Sanyal AJ, Gennings, C. Multiple classes of environmental chemicals are associated with liver disease: NHANES 2003-04. *International Journal of Hygiene and Environmental Health.* 2013 Nov;216(6):703-9.
3. Marshall, S, Gennings, C, Teuschler, LK, Stork, LG, Tornero-Velez, R, Crofton, KM, Rice, GE (2013) An empirical approach to sufficient similarity: Combining Exposure Data and Mixtures Toxicology Data. *Risk Analysis.* 2013 Sep;33(9):1582-95.
4. Gennings C, Carrico C, Factor-Litvak P, Cirillo PM, Cohn BA (2013) A cohort study evaluation of maternal PCB exposure related to time to pregnancy in daughters. *Environmental Health.* 2013 Aug 20;12(1):66.
5. Carr CK, Watkins AM, Wolf CJ, Abbott BD, Lau C, Gennings C (2013) Testing for departures from additivity in mixtures of perfluoroalkyl acids (PFAAs). *Toxicology* 2013 Apr 5;306:169-75.

Chris Gennings, PhD

Vice Chair, Research Design and Methodology

Professor, Preventive Medicine

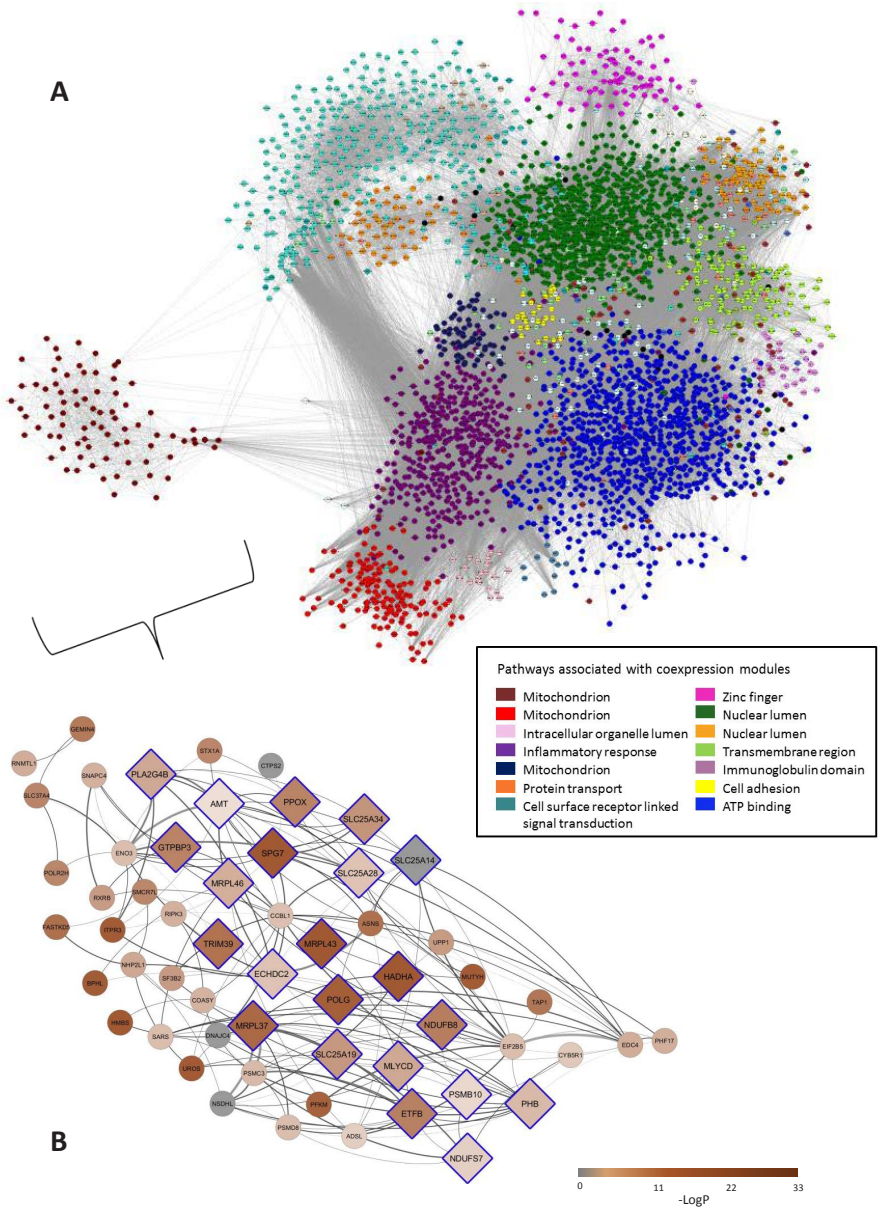
Professor, Department of Health Evidence and Policy

Using epidemiology and genomics to study asthma and allergies in children

Asthma, food allergy, allergic rhinitis (hayfever), and atopic dermatitis (eczema) are common diseases in children that cause significant morbidity and expense. The prevalence of asthma and allergies continues to grow. Approximately 8.4% of the US population has asthma, 10-30% has allergic rhinitis, and 5% has food allergy. 36,000 kids miss school each day due to asthma alone.

Asthma and allergic disorders affect genetically susceptible individuals exposed to particular environmental conditions. Supinda Bunyavanich, MD, MPH, Assistant Professor of Pediatrics and Genetics and Genomic Sciences at the Icahn School of Medicine utilizes a multifaceted approach that combines tools in epidemiology, genetics, genomics, and transcriptomics to study these diseases. Her goal is to better understand and identify risk factors, mechanisms, and potential therapies for asthma and allergies.

Current areas of research include epidemiologic studies in well-characterized cohorts; genome-wide association studies; transcriptional analysis in relevant immune system compartments; gene-by-environment studies; and the integrated analysis of genomic data.

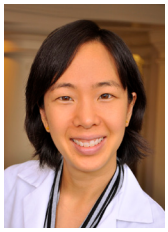


Weighted gene coexpression network that Dr. Bunyavanich and her colleagues constructed for their integrative genomic study of hay fever.

Some of Dr. Bunyavanich's research highlights include:

- An examination of maternal dietary habits during pregnancy in over 1000 mother-child pairs supports that pregnant women should not avoid specific foods during pregnancy to reduce the risk of their children developing asthma and allergies.
- A study of a large epidemiologic cohort showed that peanut allergy is highly prevalent among US school-age children.
- The identification of distinct effects for indoor and outdoor allergens on hay fever.
- The discovery of sex-specific effects for genetic variants associated with innate immune system function in allergic individuals.
- Gene-by-environment studies have shown that exposure to environmental allergens such as dust causes airway hyperreponsiveness only in asthmatics harboring distinct genetic polymorphisms.
- An examination of the relative roles of genes and environment in early childhood asthma through a study of twin children with asthma.
- An integrated genome-wide association study and network analysis of hay fever in over 500 Americans identified genetic susceptibility loci linked to mitochondrial pathways.

"Being part of a community of investigators all interested in child health and development is great for generating ideas, developing collaborations, and receiving constructive feedback. I'm also grateful to the MCHDI for having a pilot grant program, which provides such helpful support for moving new ideas forward."



Supinda Bunyavanich, MD, MPH

Assistant Professor, Pediatrics and Genetics and Genomic Sciences

Awards

Barbara Coffey, MD, The National Tourette Syndrome Association, "Tourette Syndrome Association Center of Excellence in Tics and Tourette Disorder"

Brian Brown, PhD, American Society of Gene and Cell Therapy, "Outstanding New Investigator Award"

Hugh A. Sampson, MD, and **Scott H. Sicherer**, MD, Thomson Reuters, "World's Most Influential Scientific Minds 2014"

Grants

Alex Kolevzon, MD, and **Joseph Buxbaum**, PhD, NIH, "Developmental Synaptopathies Associated with TSC, PTEN, and SHANK3 Mutations"

Brian Brown, PhD, Bayer Pharmaceuticals, "Targeted correction of hemophilia A using CRISPR-mediated editing"

Brian Brown, PhD, Human Frontier Science Program, "Deciphering non-coding RNA regulatory networks and their role in cancer biology"

Joseph Buxbaum, PhD, NIMH, "Population-Based Autism Genetics & Environment Study"

Joseph Buxbaum, PhD, and Patrick Hof, MD, NIMH, "Prefrontal function in the Shank3-deficient rat: A first rat model for ASD"

Vilma Gabbay, MD, NIH, "Neuroinflammation and Positive Valence System (PVS) Deficits in Adolescents"

Publications

Daskalakis NP, Cohen H, Cai G, **Buxbaum JD**, Yehuda R. Expression profiling associates blood and brain glucocorticoid receptor signaling with trauma-related individual differences in both sexes. *Proc Natl Acad Sci U S A.* 2014 Sep 16;111(37):13529-34.

Samocha KE, Robinson EB, Sanders SJ, Stevens C, Sabo A, McGrath LM, ... **Buxbaum JD**, ... Daly MJ. A framework for the interpretation of de novo mutation in human disease. *Nat Genet.* 2014 Sep;46(9):944-950.

García-Ocaña A, Stewart AF. "RAS"ling ß cells to proliferate for diabetes: why do we need MEN? *J Clin Invest.* 2014 Sep 2;124(9):3698-3700.

Stefan M, Wei C, Lombardi A, Li CW, Concepcion ES, Inabnet WB 3rd, ... **Tomer Y**. Genetic-epigenetic dysregulation of thymic TSH receptor gene expression triggers thyroid autoimmunity. *Proc Natl Acad Sci U S A.* 2014 Aug 26;111(34):12562-7.

Kottyan LC, Davis BP, Sherrill JD, Liu K, Rochman M, Kaufman K, ... **Sampson HA**, ... Rothenberg ME. Genome-wide association analysis of eosinophilic esophagitis provides insight into the tissue specificity of this allergic disease. *Nat Genet.* 2014 Aug;46(8):895-900.

Bunyavanich S, Schadt EE, Himes BE, Lasky-Su J, Qiu W, Lazarus R, ... Weiss ST. Integrated Genome-wide Association, Coexpression Network, and Expression Single Nucleotide Polymorphism Analysis Identifies Novel Pathway in Allergic Rhinitis. *BMC Medical Genomics.* 2014 Aug 2;7(1):48.

Gaugler T, Klei L, Sanders SJ, Bodea CA, Goldberg AP, Lee AB, ... **Reichenberg A**, ... **Buxbaum JD**. Most genetic risk for autism resides with common variation. *Nat Genet.* 2014 Aug;46(8):881-5.

Caubet JC, Ford LS, Sickles L, Järvinen KM, **Sicherer SH**, **Sampson HA**, **Nowak-Węgrzyn A**. Clinical features and resolution of food protein-induced enterocolitis syndrome: 10-year experience. *J Allergy Clin Immunol.* 2014 Aug;134(2):382-389.e4.

Boerwinkle E, Chambers JC, Fiorito G, Grallert H, Guarrera S, Homuth G,... **Loos RJ**, Kutalik Z. Novel Approach Identifies SNPs in SLC2A10 and KCNK9 with Evidence for Parent-of-Origin Effect on Body Mass Index. *PLoS Genet.* 2014 Jul 31;10(7):e1004508.

Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. *Nature.* 2014 Jul 24;511(7510):421-7. (**Buxbaum JD** and **Reichenberg A**)

Mehta H, Ramesh M, Feuille E, Groetch M, **Wang J**. Growth Comparison in Children with and without Food Allergies in 2 Different Demographic Populations. *J Pediatr.* 2014 Jul 16. pii: S0022-3476(14)00510-1.

Carrisoza-Gaytan R, Liu Y, Flores D, Else C, Lee HG, Rhodes G, ... **Satlin LM**, Rohatgi R. Effects of biomechanical forces on signaling in the cortical collecting duct (CCD). *Am J Physiol Renal Physiol.* 2014 Jul 15;307(2):F195-204.

Josowitz R, Lu J, Falce C, D'Souza SL, Wu M, Cohen N, **Dubois NC**, **Zhao Y**, ... **Gelb BD**. Identification and purification of human induced pluripotent stem cell-derived atrial-like cardiomyocytes based on sarcolipin expression. *PLoS One.* 2014 Jul 10;9(7):e101316.

Bosquet Enlow M, King L, Schreier HM, Howard JM, Rosenfield D, Ritz T, **Wright RJ**. Maternal sensitivity and infant autonomic and endocrine stress responses. *Early Hum Dev.* 2014 Jul;90(7):377-85.

Brahmachary M, Guilmatre A, Quilez J, Hasson D, Borel C, Warburton P, **Sharp AJ**. Digital genotyping of macrosatellites and multicopy genes reveals novel biological functions associated with copy number variation of large tandem repeats. *PLoS Genet.* 2014 Jun 19;10(6):e1004418.

Zhang L, Nomura-Kitabayashi A, Sultana N, Cai W, Cai X, Moon AM, **Cai CL**, Mesodermal Nkx2.5 is necessary and sufficient for early second heart field development. *Dev Biol.* 2014 Jun 1;390(1):68-79.

Dhandapany PS, Razzaque MA, Muthusami U, Kunnoth S, Edwards JJ, Mulero-Navarro S, ...**Gelb BD**. RAF1 mutations in childhood-onset dilated cardiomyopathy. *Nat Genet.* 2014 Jun;46(6):635-9.

Xue L, Galdass M, Gnanapragasam MN, Manwani D, **Bieker JJ**. Extrinsic and intrinsic control by EKLF (KLF1) within a specialized erythroid niche. *Development.* 2014 Jun;141(11):2245-54.

Taylor-Black SA, Mehta H, Weiderpass E, Boffetta P, **Sicherer SH**, **Wang J**. Prevalence of food allergy in New York City school children. *Ann Allergy Asthma Immunol.* 2014 Jun;112(6):554-556.e1.

Weintraub L, Weiner C, Miloh T, Tomaino J, Joashi U, Benchimol C, ... **Wistinghausen B**. Identifying Predictive Factors for Posttransplant Lymphoproliferative Disease in Pediatric Solid Organ Transplant Recipients With Epstein-Barr Virus Viremia. *J Pediatr Hematol Oncol.* 2014 May 29.

Arora M, Austin C, Sarrafpour B, Hernández-Ávila M, Hu H, **Wright RO**, Tellez-Rojo MM. Determining prenatal, early childhood and cumulative long-term lead exposure using micro-spatial deciduous dentine levels. *PLoS One.* 2014 May 19;9(5):e97805.

Sandin S, Lichtenstein P, Kuja-Halkola R, Larsson H, Hultman CM, **Reichenberg A**. The familial risk of autism. *JAMA.* 2014 May 7;311(17):1770-7.

Pinto D*, Delaby E, Merico D, Barbosa M, Merikangas A, Klei L, ... **Buxbaum JD**, ... Betancur C*, Scherer SW*. Convergence of genes and cellular pathways dysregulated in autism spectrum disorders. *Am J Hum Genet.* 2014 May 1;94(5):677-94. * Equal contribution

Stefan M, Zhang W, Concepcion E, Yi Z, **Tomer Y**. DNA methylation profiles in type 1 diabetes twins point to strong epigenetic effects on etiology. *J Autoimmun.* 2014 May;50:33-7.

Winkler TW, Day FR, Croteau-Chonka DC, Wood AR, Locke AE, Mägi R, Ferreira T, ... **Loos RJ**. Genetic Investigation of Anthropometric Traits (GIANT) Consortium. Quality control and conduct of genome-wide association meta-analyses. *Nat Protoc.* 2014 May;9(5):1192-212.

Bala Tannan N, Brahmachary M, Garg P, Borel C, Alnefaie R, Watson CT, ... **Sharp AJ**. DNA methylation profiling in X;autosome translocations supports a role for L1 repeats in the spread of X chromosome inactivation. *Hum Mol Genet.* 2014 Mar 1;23(5):1224-36.

Wei Y, Peng S, Wu M, Sachidanandam R, Tu Z, Zhang S, ... **Zhao Y**. Multifaceted roles of miR-1s in repressing the fetal gene program in the heart. *Cell research* 2014 Mar;24(3):278-92.

Sicherer SH, Wood RA, Vickery BP, Jones SM, Liu AH, Fleischer DM, ... **Sampson HA**. The natural history of egg allergy in an observational cohort. *J Allergy Clin Immunol.* 2014 Feb;133(2):492-9.

Tsai SY, Sennett R, Rezza A, Clavel C, Grisanti L, Zemla R, ... **Rendl M**. Wnt/ß-catenin signaling in dermal condensates is required for hair follicle formation. *Developmental biology.* 2014 Jan 15;385(2):179-88.

Agudo JA, Ruzo A, Tung N, Salmon H, Leboeuf M, Hashimoto D, ... **Brown BD**. The microRNA-126/VEGFR2 axis controls the innate response to pathogen-associated nucleic acids. *Nature Immunology.* 2014 Jan;15(1):54-62.

Ernst S., Alvarez-Perez J.C., Demerci C., Casinelli G.P., Mellado-Gil J.M.D., **Vasavada R.C.**, **Garcia-Ocana A**. Hepatocyte Growth Factor/c-Met signaling is required for ß-cell regeneration. *Diabetes.* 2014 Jan;63(1):216-23.

Nomura Y*, **Lambertini L***, Rialdi A, Lee MJ, Mystal EY, Grabie M, ... **Chen J**. Global methylation in the placenta and umbilical cord blood from pregnancies with maternal gestational diabetes, preeclampsia, and obesity. *Reprod Sci.* 2014 Jan;21(1):131-7. * Equal contribution

New Internal Faculty

Full Members

Anna Nowak-Wegryzn, MD, Associate Professor, Pediatrics

Avi Reichenberg, PhD, Professor, Psychiatry and Preventive Medicine

Dorothy Grice, MD, Professor, Psychiatry

Jeffrey M. Saland, MD, Associate Professor, Pediatrics

Jia Chen, ScD, Professor, Pediatrics, Preventive Medicine, Medicine, and Oncological Sciences

Lawrence C. Kleinman, MD, MPH, Associate Professor, Health Evidence and Policy and Pediatrics

Lisa M. Satlin, MD, Chair and Professor, Pediatrics and Professor, Medicine

Martin J. Walsh, PhD, Associate Professor, Pediatrics and Structural and Chemical Biology

Mihaela Stefan, PhD, Assistant Professor, Medicine

Patrizia Casaccia, MD, PhD, Professor, Genetics and Genomic Sciences, Neuroscience, and Neurology

Robert S. Krauss, PhD, Professor, Developmental and Regenerative Biology and Oncological Sciences

Shanna H. Swan, MS, PhD, Professor, Preventive Medicine

Valerie Gouon-Evans, PhD, Assistant Professor, Developmental and Regenerative Biology and Medicine

Affiliated Members

Alex Kolevzon, MD, Associate Professor, Psychiatry and Pediatrics

Barbara Coffey, MD, Professor, Psychiatry

Birte Wistinghausen, MD, Assistant Professor, Pediatrics

David Dunkin, MD, Assistant Professor, Pediatrics

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

Julie Wang, MD, Associate Professor, Pediatrics

Madhan Masilamani, PhD, Assistant Professor, Pediatrics

Michael Rendl, MD, Associate Professor, Developmental and Regenerative Biology and Dermatology

Scott H. Sicherer, MD, Professor, Pediatrics

Vilma Gabbay, MD, Associate Professor, Pyschiatry and Neuroscience

Save the date: Retreat

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