



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

Research Advancements: Neurodevelopmental Disorders

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;

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 (2015) 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.

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.



Chris Gennings, PhD

Vice Chair, Research
Design and Methodology
Professor, Preventive
Medicine

Professor, Department of
Health Evidence and Policy

Research Advancements: Allergy and Asthma

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.

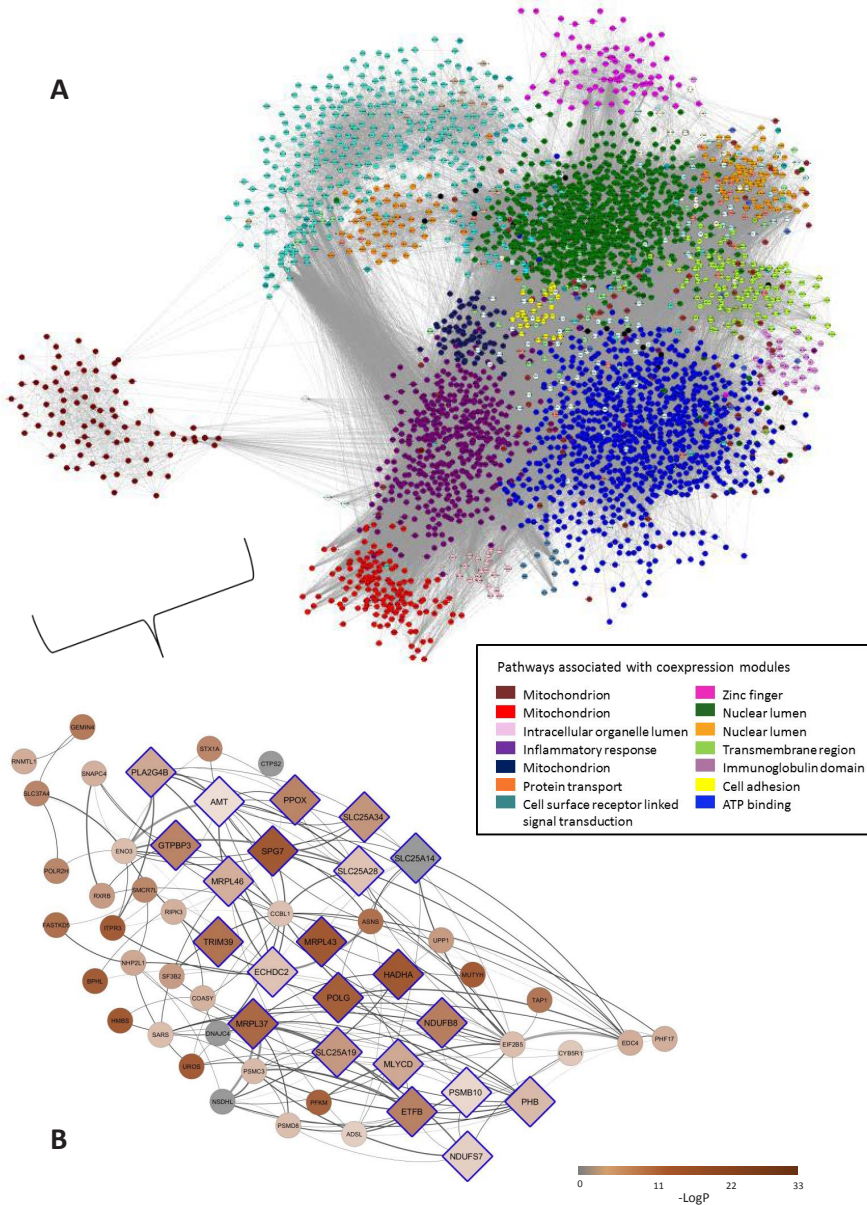
Asthma and allergic disorders affect genetically susceptible individuals exposed to particular environmental conditions. Supinda Bunyavanich, MD, MPH, Assistant Professor of Pediatrics and Genetics and

Genomics 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.

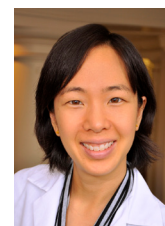
Some of Dr. Bunyavanich's research highlights include:

- 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 hyperresponsiveness 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.



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

“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

Highlights

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

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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.

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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**)

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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, Psychiatry and Neuroscience

Save the date: Retreat

SAVE THE DATE

The 2nd Annual MCHDI Retreat

Date: December 9th, 2014

Time: 8:30am-4pm

Location: New York Academy of Medicine

Library Reading Room, 3rd Floor

1216 Fifth Avenue, New York, NY 10029



The Mindich Child Health and Development Institute



**Mount
Sinai**

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