



Mount Sinai *The Mindich Child Health and Development Institute*

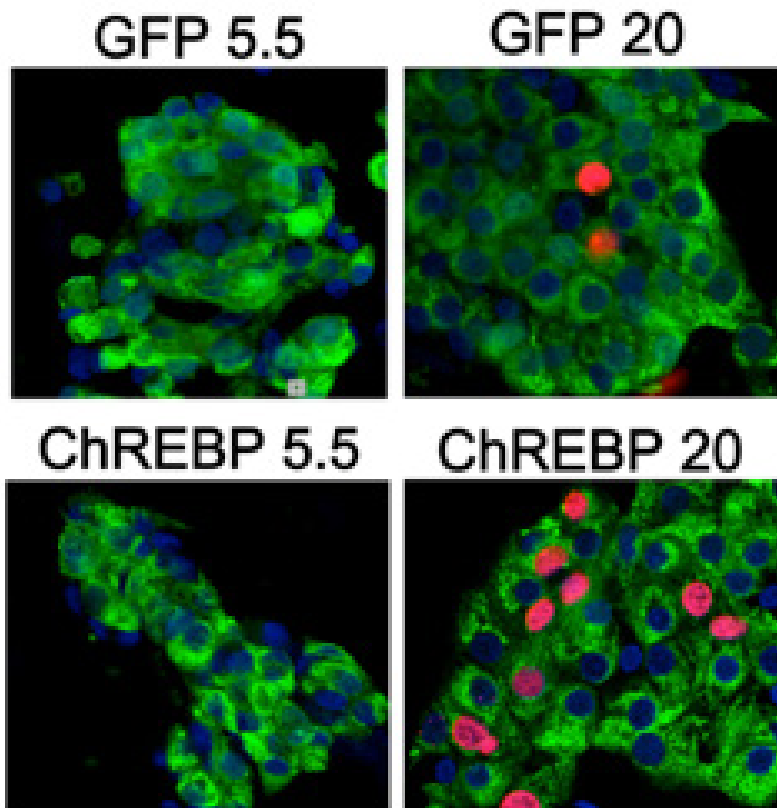
MCHDI Developmental Outcomes

Spring 2015

Research Advancements: Diabetes

Diabetes is a Serious Threat to Children's Health

There are two major forms of diabetes: Type 1 diabetes, which is an autoimmune disease and typically occurs in children, and Type 2 diabetes, which is associated with obesity and is classically thought to be "adult onset." However, alarming increases in obesity-related Type 2 diabetes are occurring in children, and Type 1 diabetes is also trending upwards. Both major forms of diabetes are due to a loss of functional pancreatic beta cell mass—in Type 1 diabetes there are very few remaining cells and almost no insulin—in Type 2 diabetes the beta cells are defective and cannot produce sufficient insulin to maintain normal glucose levels. In young animals, beta cells have a natural ability to increase their functional beta cell mass by dividing, or proliferating, as an adaptation to increased insulin demands, which may occur on a high fat diet for example. Donald Scott, PhD, Professor of Medicine, and his laboratory tries to understand basic pathways naturally used by beta cells to promote beta cell mass expansion and increased insulin production. One natural stimulator of beta cell proliferation is glucose. Beta cells naturally sense if there is too much glucose in the blood and secrete a sufficient amount of insulin to decrease glucose back to baseline levels, establishing glucose homeostasis. The glucose sensing/insulin secreting system is linked to glucose metabolism inside beta cells, and this same metabolic signal stimulates transcription factors that turn on and off genes important for beta cell proliferation. The Scott laboratory showed that a particular glucose sensitive transcription factor, carbohydrate response element binding protein (ChREBP), is required for glucose-stimulated beta cell proliferation in mice, rats and human beta cells. ChREBP is also required for the changes in gene expression required for proliferation



in beta cells. Therefore when we remove the ChREBP gene, glucose no longer can stimulate proliferation, and interestingly, when we overexpress this factor, the glucose-stimulation is amplified. Current projects either submitted for publication or being prepared for publication include understanding the signaling pathways by which overexpression of ChREBP amplifies glucose stimulated proliferation, and understanding in more detail the molecular mechanisms by which ChREBP works. The hope is that understanding these pathways and mechanisms will lead to therapies that grow functional, insulin-producing beta cells to alleviate complications of diabetes.

ChREBP increases beta cell proliferation. Isolated rat beta cells (green) are stained for BrdU (orange) indicating proliferation. When ChREBP is added with a gene therapy technique (an adenovirus), the cells replicate in response to increasing glucose metabolism. GFP is a negative control.



Donald Scott, PhD
Professor of Medicine

Research Advancements: Allergies

Skin-Gut Communication in Food Allergy: Implications for Prevention and Treatment

Food allergy is a prevalent disease that develops in early childhood and for which there is no current treatment. Accidental exposures leading to allergic reactions are fairly common among children with food allergy. Reactions can range from mild hives to severe systemic anaphylaxis and factors that can predict the severity of these reactions have yet to be identified. There is a need for new approaches to prevent, manage, and treat food allergy.

It has been appreciated for many years that there is a link between the gastrointestinal tract and the skin in food allergy. The most common reactions to foods that affect the skin are hives or worsening of eczema, and conversely having eczema is a risk for developing food allergy. In recent NIH-funded studies led by M. Cecilia Berin, PhD, Associate Professor in the Department of Pediatrics, investigators showed that exposure to peanut on the skin led to peanut allergy in mice and furthermore, re-exposure led to systemic anaphylaxis. An immune response in the skin was observed with some potent food allergens, such as peanut and cashew nuts, and was not seen with

other foods such as soy or milk. Peanut caused the upregulation of the cytokine IL-33 in the skin, which is an alarmin or endogenous danger signal. The receptor for IL-33, also known as ST-2, was involved in changing the way that antigen presenting cells in the skin interacted with T helper cells and caused these T cells to become pro-allergic Th2 cells. This work helps to explain why peanuts and tree nuts are such potent food allergens and has implications for the prevention of peanut allergy. Peanut proteins are ubiquitous in the home environment and exposure is therefore hard to avoid, but skin care that could keep these allergens from being easily absorbed by the skin may help to prevent peanut allergy.

The link between the skin and the gastrointestinal tract in food allergy also provides opportunity for therapy. In a collaborative study with DBV Technologies, which has developed a skin patch called Viaskin™ for allergen immunotherapy, investigators in the Berin laboratory are studying immune regulatory pathways that are triggered in the skin and shut down allergic responses

to food allergens in mice. The Viaskin™ patch is currently being studied for the treatment of peanut allergy in a multi-center clinical trial conducted by the Consortium of Food Allergy Research (CoFAR). CoFAR is an NIH-funded consortium led by Hugh Sampson, MD, the Kurt Hirschhorn Professor of Pediatrics, and Dean of Translational Biomedical Sciences at the Icahn School of Medicine at Mount Sinai. Scientists in the Berin and Sampson laboratories are investigating how treatment with the Viaskin™ patch alters the immune responses to peanut at the cellular and molecular level. The aim of this work is to understand how to train the immune system to generate permanent immune tolerance to foods.



M. Cecilia Berin, PhD
Associate Professor of Pediatrics

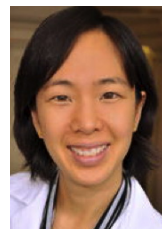
Pilot Projects: 2013–2014 Awardees

Gene Expression and Epigenetic Modifications in Childhood Food Allergy: Parsing the Food Allergic Response

Food allergy is a growing clinical and public health problem that affects 5% of the US population. It disproportionately affects children, impairing their health, growth, and lifestyle. Unfortunately, severe reactions can lead to death, and there is no cure for food allergy. Food allergy manifests when a genetically predisposed child is exposed to a particular food, suggesting that dynamic alterations in DNA interpretation (such as epigenetic and gene expression changes) induced by food may be key to this disease. The goal of the MCHDI Pilot Award-funded project was to examine the epigenome and transcriptome (reflecting gene expression) of 10 well-characterized food allergic patients. During the pilot period, Supinda Bunyavanich, MD, MPH, Assistant Professor of Pediatrics and Genetics and Genomics Sciences, and her team exceeded expectations by recruiting 21 subjects suspected of peanut allergy, each of whom underwent double-blinded, placebo-controlled peanut challenges in the clinical research unit. Subjects received peanut

protein in gradually incremental amounts under close medical observation until they reacted (confirming peanut allergy) or the cumulative dose of 5g peanut protein (confirming no peanut allergy) was reached. Each subject also underwent a placebo challenge. Peripheral blood samples were collected before, during, and after the peanut and placebo challenges for all 21 subjects for transcriptome and methylome profiling. During the oral food challenges, 90% of the subjects (mean age 11.8 years) reacted to peanut, with a mean triggering dose of 25mg of peanut protein. The most prevalent symptoms were throat tightness (43%), angioedema (19%), and urticaria (14%). Epinephrine injection and antihistamines were required in 52.4% and 90.5% of subjects, respectively. High quality RNA sequencing results were obtained, with >98% of bases in mapped reads corresponding to mRNA. Transcriptome analysis for differential gene expression before and after peanut challenge showed 7.8-fold enrichment for gene ontology clusters related to immune response. Methylation profiling of peripheral blood lymphocytes from

the challenges was recently completed. Analytic models are currently in progress and should inform on mechanistic pathways underlying peanut allergy. Results from this pilot grant have helped junior faculty member Dr. Bunyavanich apply for external funding from the American Academy of Allergy, Asthma, and Immunology, where she was a finalist for a faculty development award.



Supinda Bunyavanich, MD, MPH
Assistant Professor of Pediatrics and Genetics and Genomics Sciences

Pilot Co-PIs: Eric Schadt, PhD, Chair of Genetics and Genomics Sciences, Director of Icahn Institute for Genomics and Multiscale Biology, Jean C. and James W. Crystal Professor of Genomics; Hugh Sampson, MD, Dean of Translational Biomedical Sciences, Director of Conduits, Director of Jaffe Food Allergy Institute, Professor of Pediatrics

Epigenomics of Neural Tube Defects

Neural tube defects (NTDs) are among the most common birth defects in newborns. When the neural tube does not close completely during fetal development, severe malformations of the brain or spinal cord occur, most commonly manifesting as spina bifida. Levels of folic acid in a mother's diet during pregnancy have been recognized as playing a key role in determining the risk of NTDs - low folate levels during pregnancy increase a mother's risk of having a fetus with NTDs, while giving mothers folate supplementation reduces their incidence. As a result, many countries now mandate supplementation of folic acid in wheat flour, which has helped to reduce the incidence of NTDs by up to 70% in some parts of the world. However, the mechanism by which folate operates to help prevent NTDs remains unknown, and Andrew Sharp, PhD, Associate Professor of Genetics and Genomic Sciences, and his collaborators, Etylin Jabs, MD, Professor and Vice Chair of Genetics and Genomic Sciences, Professor of Pediatrics and Professor of Developmental and Regenerative Biology, and Gregory Holmes, PhD, Assistant Professor of

Genetics and Genomic Sciences set out to investigate this mechanism.

One of the major biochemical functions of folate is gene regulation, as folate provides the raw materials required for a modification to DNA termed methylation. Having the correct methylation patterns on DNA is critical during development in order to correctly switch genes on and off as the embryo grows. To identify genes that are dysregulated in embryos with NTDs, the Sharp laboratory studied a mutant mouse line that carries a knock-out of the folate receptor gene *Folr1*. As *Folr1* is required to carry folate into cells, these mice have severely reduced levels of folate and suffer from NTDs at a very high frequency. By careful dissection of these mouse embryos Dr. Holmes was able to isolate cells from the neural tube at the precise developmental stage that NTDs occur, enabling studies to be performed that would be impossible in humans. In order to identify genes contributing to NTDs that are dysregulated in the neural tube in the absence of folate, genome-wide profiling of DNA methylation and gene expression in embryos with and without NTDs were performed. Comparison of

these two groups identified ~1,000 regions of the genome where DNA methylation changed, and ~1,500 genes that showed significantly altered expression in mice with NTDs. Thus, folate deficiency leads to widespread changes in gene expression that result in NTDs. Consistent with a role in closure of the neural tube, the set of affected genes identified have roles in cell migration and adhesion, including a number of genes previously implicated in NTDs. Further studies are ongoing to try and home in on key genes within the network that are linked with the development of NTDs in the absence of folate.



Andrew Sharp, PhD

Associate Professor of Genetics and Genomic Sciences

Pilot Co-PIs: Etylin Jabs, MD, Professor and Vice Chair of Genetics and Genomic Sciences, Professor of Pediatrics, Professor of Developmental and Regenerative Biology; Greg Holmes, PhD, Assistant Professor of Genetics and Genomic Sciences



+/+
WT



-/-
KO

Images of wild-type mice embryos with normal neural tubes, and Folr1 knock-out mice with a neural tube defect.

Drug Repositioning for Brain Plasticity Modulators to Reverse Neurodevelopmental Disorders

It is common knowledge that it is easier to learn a new language or musical instrument as a child rather than as an adult. At no other time in life does the surrounding environment so potently shape brain function—from basic motor skills and sensation to higher cognitive processes like language—than it does during childhood. This experience-dependent process occurs at distinct time windows called “critical periods,” which are times of great opportunity but also of great vulnerability for the developing brain. Early disruption of proper sensory or social experiences will result in mis-wired circuits that will respond sub-optimally to normal experiences in the future. For example, if a child’s binocular vision is compromised and not corrected before the age of eight, amblyopia (“lazy eye”) is permanent and irreversible.

One of the most exciting developments in neuroscience in the last decade has been insights into the biology of neuroplasticity, which refers to the brain’s ability to learn, adapt, and rewire itself. Until recently it was thought that neuroplasticity was limited to a critical period in childhood, and that the window was largely closed by adulthood. This meant that neurodevelopmental disorders like amblyopia were mostly untreatable

in adults. However, neuroscientists have come to understand that it is possible to reopen that critical period later in life.

Hirofumi Morishita, MD, PhD, Assistant Professor of Psychiatry, Neuroscience, and Ophthalmology and member of the Mindich Child Health and Development Institute, and his laboratory uses the visual system to identify the molecular mechanisms that govern neuroplasticity and explores how those mechanisms can be applied to the adult brain for therapeutic intervention. This approach led to the discovery that a “brake” of neuroplasticity, Lynx1, can be removed to allow adult neuroplasticity and recovery from amblyopia. Moreover, Dr. Morishita’s team also found that an existing drug used to treat Alzheimer’s disease has an opposite action to Lynx1 and could have possible therapeutic value for amblyopia; this finding is now being tested in an early clinical trial.

Building on these mechanisms of neuroplasticity, the pilot grant aimed to build a pipeline to systematically identify new classes of drugs to enhance neuroplasticity. Graduate student Milo Smith bridged the gap between mechanism and clinic by partnering with Joel Dudley, PhD, Assistant Professor of Genetics and Genomic Sciences and Health Evidence

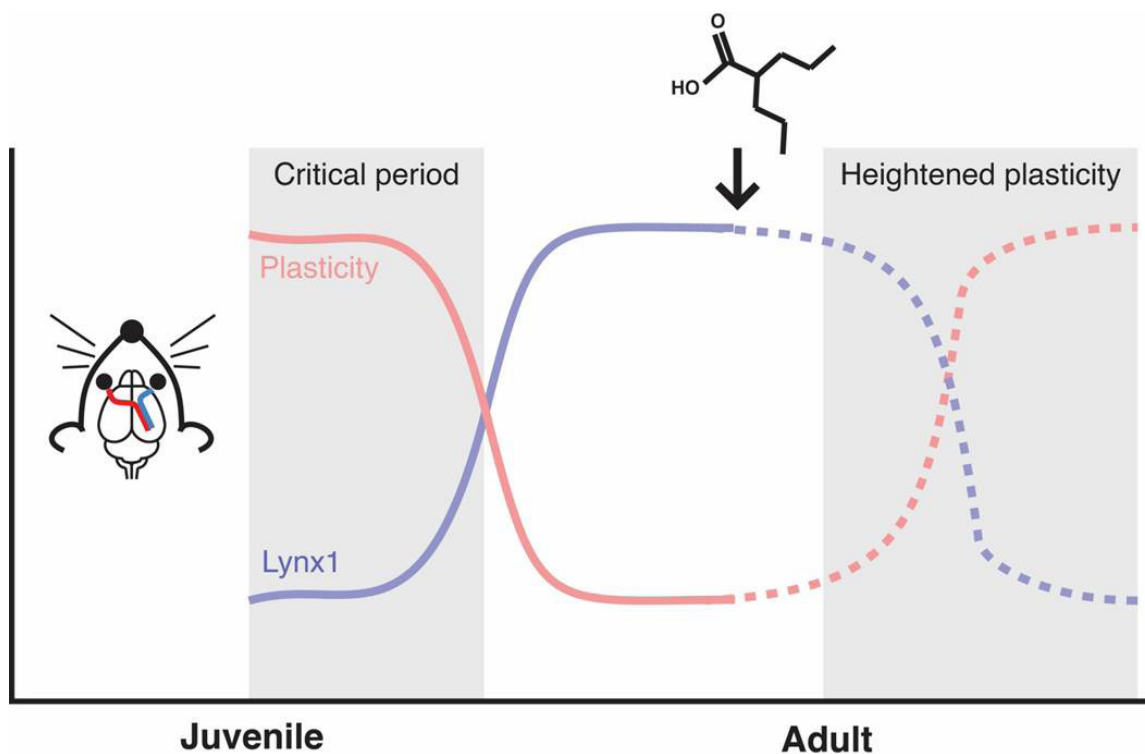
and Policy and member of the Icahn Institute of Genomics and Multiscale Biology, who pioneered a transcriptome-based computational approach to repurpose drugs for other disorders such as inflammatory bowel disease and lung cancer. The group accomplished significant progress by predicting novel and known neuroplasticity-enhancing small molecule compounds. The novel neuroplasticity-enhancing predictions are now being tested for their *in vivo* transcriptional and functional effect on neuroplasticity. The successful computational identification and preclinical validation of a neuroplasticity-enhancing drug will provide an immediate solution for disorders and conditions that could benefit from elevation of neuroplasticity.



Hirofumi Morishita, MD, PhD

Assistant Professor of Psychiatry, Neuroscience, and Ophthalmology

Pilot Co-PI: Joel Dudley, PhD, Assistant Professor of Genetics and Genomic Sciences and Health Evidence and Policy



Pilot Projects: 2014–2015 Awardees

Title: Investigating cardiac dysfunction in Duchenne Muscular Dystrophy using compound screening

Investigators: *Nicole Dubois, PhD, MCHDI Investigator and Assistant Professor of Developmental and Regenerative Biology; Eric Sobie, PhD, Associate Professor of Pharmacology and Systems Therapeutics; Dan Felsenfeld, PhD, Associate Professor of Developmental and Regenerative Biology*

Abstract: Duchenne Muscular Dystrophy (DMD) is a genetic lethal disorder and the most common muscular dystrophy, affecting 1 out of 2400 male infants worldwide. For a long time, DMD was considered predominantly a skeletal muscle disease and cardiac complications in DMD became more prominent only recently as the life of DMD patients could be prolonged with improved therapy for the skeletal and respiratory systems. Cardiac abnormalities in DMD patients consist of arrhythmias and dilated ventricular cardiomyopathy with extensive fibrosis. About 95% of DMD patients develop cardiac complications by 20 years of age and for 20% of these patients the cardiac impairment is lethal. However, the specific mechanisms of the cardiac abnormalities are still substantially understudied. As a consequence, current treatment of the cardiac defects is limited to general cardioprotective or symptom-reducing drugs.

The underlying molecular defect in DMD is the lack of the protein dystrophin. Dystrophin links the sarcomeric cytoskeleton to a complex of transmembrane proteins, which interact with extracellular matrix. Lack of dystrophin results in an increased cellular vulnerability to mechanical stress associated with muscular contraction. Nicole Dubois, PhD, Assistant Professor of Developmental and Regenerative Biology, and her laboratory are using the human induced pluripotent stem cell (hiPSC) model to address some of the pressing questions in DMD. hiPSC lines have been generated from several DMD patients and control subjects and have been differentiated to cardiomyocytes. Using calcium signaling assays differences in the recovery after osmotic shock were observed in hiPSC-derived cardiomyocytes from DMD patients compared to cells from control subjects. The team proposes to apply their established hiPSC disease model to a therapeutically relevant

approach, by screening compound libraries for candidates that will reestablish cardiac function of DMD myocytes based on recovery from osmotic shock. This strategy will allow, for the first time, the discovery and evaluation of potential drugs for the cardiac defects in DMD using human, patient-specific cardiomyocytes.

Title: The origins of fetal gut microbiome: role of the maternal environment during pregnancy and delivery

Investigators: *Ruth Loos, PhD, MCHDI Investigator and Professor of Preventive Medicine; Jeremiah Faith, PhD, Assistant Professor of Genetics and Genomic Sciences and Medicine; Jose C. Clemente, PhD, Assistant Professor of Genetics and Genomic Sciences and Medicine; Inga Peter, PhD, MSc, Associate Professor of Genetics and Genomic Sciences*

Abstract: The common belief that infants are born with a sterile gut is being questioned by a growing number of studies that have identified microbes in newborns' first stool, which is representative of prenatal conditions. This observation has led to the speculation that colonization of the intestine may occur before birth, *in utero*. However, little is known about how and when the fetal gut is first inoculated with bacteria and how the early colonizers influence the developing microbiome during the first months of life. For the Mindich Pilot project, Ruth Loos, PhD, Professor of Preventive Medicine, and her team's aim is to determine the origins of the fetal gut microbiome by assessing the role of the maternal environment during pregnancy, at delivery and the first two weeks of life. [This is the first aim of a larger pilot project in which the aim is also to identify the factors that contribute to the development of the infant's gut microbiome during the first three years of life.] The team will prospectively follow 40 mother-father-child trios from the third trimester of pregnancy, through birth and the first two weeks of life. Maternal and paternal stool samples will be collected before birth and samples of the oral, vaginal, placental, cord blood and amniotic fluid microbiome at birth. The newborn's first stool (called meconium) as well as



2014–2015 Pilot Program Recipients (from left to right): Nicole Dubois, PhD; Ruth Loos, PhD; Yong Zhao, MD, PhD

stool samples from days 7 and 14 will also be collected. Bacterial 16S rRNA DNA of all samples will be sequenced in multiplex to determine their microbiome composition. In addition, body composition will be assessed and detailed dietary information collected.

Comparative analyses will be conducted for bacterial abundance, diversity and overall phylogeny to test similarity and differences between parental and infant samples. Determination of potential sources of the newborns' gut microbiome and factors mediating its subsequent development may provide insight into specific (dietary) strategies during pregnancy, at delivery, or soon after birth to modulate child microbiome development and promote future health.

Title: An integrative systems approach to understand developmental control of sinoatrial node

Investigators: *Yong Zhao, MD, PhD, MCHDI Investigator and Assistant Professor of Genetics and Genomic Sciences; Jun Zhu, PhD, Professor of Genetics and Genomic Sciences; Zhidong Tu, PhD, Assistant Professor of Genetics and Genomic Sciences*

Abstract: The overall goal of the proposal is to understand what controls the development of sinoatrial node (SAN). Pacemaker cells in the SAN set the heart rate. A variety of etiology can lead to sick sinus disease (SSD). SSD can be seen in

Pilot Projects: 2014-2015 Awardees (continued)

children with congenital heart defects or in pediatric patients with otherwise normal heart. These children with severe SSD require permanent pacemaker implantation. Cardiac contraction of the embryonic heart relies on coordinated development of cardiac conduction system and working myocardium. However, the molecular control of these dynamic developmental processes remains poorly understood. Yong Zhao, PhD, Assistant Professor of Genetics and Genomic Sciences, and his team recently discovered an epigenetic pathway involving Baf250a and Tbx3 that maintains proper function of the SAN in adult mice. Disruption of this pathway leads to ectopic activation of the

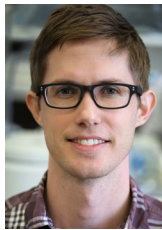
Nkx2-5-directed contractile cardiomyocyte program, causing sinus bradycardia and sinus arrest.

To understand how transcription factors regulate development of the SAN, Dr. Yong's group proposes to integrate systems biology approaches to tackle developmental control of SAN in the following Specific Aims: 1) To identify dynamic co-expression modules in the developing SAN. Single-cell RNA-Seq of pacemaker cells will be performed, and systems biology approaches will be applied to dissect dynamic changes of co-expression modules in developing SAN. Identifying temporal expression

of transcription factors is a key step to understand the complex dynamic processes that drive changes in gene expression 2) To determine how a Baf250-mediated transcriptional hierarchy regulates development of the SAN. Baf250a will be deleted in pacemaker cells at various stages. Single-cell RNA-Seq will be performed after deletion of Baf250a to reveal how Baf250a regulates SAN development. Completion of this project will shed light on the regulatory framework for transcription factors controlling development of the SAN. The data generated in this proposal will facilitate future proposals for NIH grants.

Trainee Highlights

Corey Watson, PhD is currently a postdoctoral fellow in the laboratory of Andrew Sharp, PhD under the department of Genetics and Genomic Sciences. He is the winner of the Young Investigator's Competition in the post-doctoral division. Generally, Dr. Watson's research is focused on exploring the role of genetic and epigenetic variation in disease risk, progression, and treatment outcomes.



While training under Dr. Sharp, he recently helped develop and apply novel methods for characterizing imprinted genes in the human placenta from RNA sequencing data.

Josephine Mollon is a PhD candidate in the Departments of Psychiatry and Preventive Medicine at Mount Sinai and at the Institute of Psychiatry, Psychology and Neuroscience in London. She is the winner of the Young Investigator's Competition in the pre-doctoral division. Her work with mentor Avi Reichenberg, PhD utilizes

longitudinal birth cohort data to characterize the cognitive trajectories of young people at risk for psychosis. In the future she plans to develop and validate models combining clinical and behavioral markers throughout childhood and adolescence to predict transition to psychotic disorder in adulthood.



Faculty Highlights

Grants

Patrizia Casaccia, MD, PhD, BIOGEN, "Investigating indirect mechanism of neuroprotection of Tecfidera in RRMS and Progressive patients"

Patrizia Casaccia, MD, PhD, Department of Defense, Collaborative Team Award, "Mitochondrial dysfunction and disease progression"

Patrizia Casaccia, MD, PhD, Department of Defense, Collaborative Team Award, "A multidisciplinary approach to study the role of the gut microbiome in relapsing and progressive MS"

Patrizia Casaccia, MD, PhD, National Multiple Sclerosis Society, "Understanding the role of gene/environment interaction in oligodendrocytes"

Patrizia Casaccia, MD, PhD, National Multiple Sclerosis Society Collaborative Team "A multidisciplinary approach to study the role of the gut microbiome in relapsing and progressive MS"

David Dunkin, MD, NIH, NIDDK, K award, "Epicutaneous Tolerance Induction for the Treatment of Colitis."

Chris Gennings, PhD, European Commission, "Integrating Epidemiology and Experimental Biology to Improve Risk Assessment of Exposure to Mixtures of Endocrine Disruptive Compounds"

Ruth Loos, PhD, FNIH, "The AMP T2D Initiative - The BioMe Biobank at Mount Sinai: a diverse ancestry biobank to map biomedical traits and elucidate health disparities"

Dalila Pinto, PhD, NIH/NIMH, R21 award, "Long non-coding RNAs in gene regulatory networks underlying Autism"

Annemarie Stroustrup, MD, Mount Sinai Transdisciplinary Center on Health Effects of Early Environmental Exposures Pilot Research Project Grant, "Hospital-Based Chemical Exposure and Neurodevelopmental Outcomes in Preterm Infants"

Shanna Swan, PhD, MS, NIEHS, R01 award, "Phthalate Exposure and Gender-related Development"

Rupangi Vasavada, PhD, NIDDK, R01 award, "Osteoprotegerin and the Pancreatic Beta Cell"

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Save the date: General Faculty Meeting

Save the date: MCHDI 3rd Annual Retreat

SAVE THE DATE
General Faculty Meeting

Date: September 28, 2015
Time: 4:00-5:00PM
Location: Hess Building
Hess Seminar Room B, 2nd Floor
1470 Madison Avenue, New York, NY 10029



Mount Sinai *The Mindich Child Health and Development Institute*

SAVE THE DATE
3rd Annual MCHDI Retreat

Date: November 18, 2015
Time: 8:30AM-4PM
Location: New York Academy of Medicine
Library Reading Room, 3rd Floor
1216 Fifth Avenue, New York, NY 10029



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