



Icahn School  
of Medicine at  
Mount  
Sinai

*The Mindich  
Child Health and  
Development Institute*

# MCHDI Developmental Outcomes

Fall 2018

## Research Advancements: Diabetes

### MCHDI Researchers Uncover New Agents to Ameliorate Type 1 Diabetes

Type 1 diabetes (sometimes known as juvenile diabetes) affects as many as three million children and adults in the US and the rate of Type 1 diabetes incidence among children is increasing 3% annually. The number of lives and the health care cost associated with treating this disease and its related complications are rising and unacceptable. In Type 1 diabetes, immune self-tolerance is lost leading to the destruction of insulin-producing cells (pancreatic beta cells). Autoreactive T cells target islet-associated antigens and acquire an effector inflammatory phenotype due to co-stimulatory signals leading to tissue invasion and pancreatic beta cell destruction. Therapies focused on preserving functional pancreatic beta cells, gaining immune tolerance, and inducing pancreatic beta cell regeneration are a priority for the treatment of the disease.

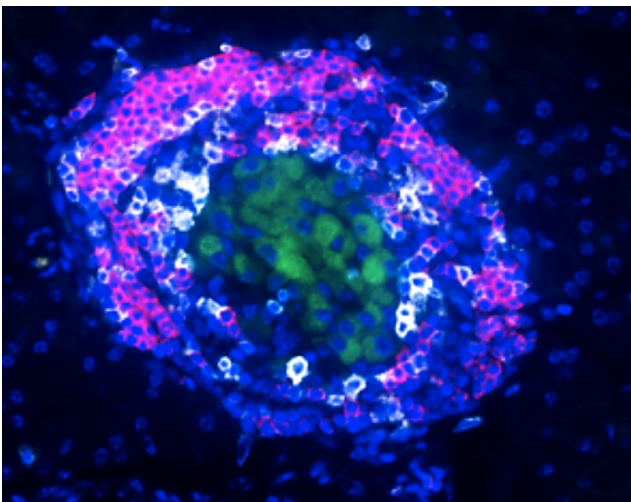
A research team led by MCHDI faculty member Adolfo Garcia-Ocaña, PhD, together with Dirk Homann, MD, faculty member of the Diabetes, Obesity and Metabolism Institute (DOMI), has identified dextran sulfate as a potential candidate for ameliorating type 1 diabetes incidence. Dextran sulfate is a sulfated

semi-synthetic proteoglycan analog with known cytoprotective actions as well as immunomodulatory properties. This research team has found that dextran sulfate has the capacity of reducing inflammation, decreasing pancreatic beta cell death, diminishing activation of effector T cells and increasing the number of regulatory T cells. These significant functions make dextran sulfate a potential candidate for therapy of type 1 diabetes. Indeed, dextran sulfate treatment prevents the development of type 1 diabetes in pre-diabetic mice and, more importantly, reverses diabetes in ~70% of early onset type 1 diabetic mice. These promising studies have recently been funded by the NIH-NIDDK and the Department of Defense and will further analyze in detail the potential future of this drug for early onset type 1 diabetes treatment.

Additionally, patients with established type 1 diabetes would also benefit from treatments that regenerate their decimated pancreatic beta cell population. For that purpose, Dr. Garcia-Ocaña is co-leading collaborative efforts with MCHDI faculty member, Donald K. Scott, PhD, the Director of DOMI, Andrew F. Stewart, MD,

the Director of the Medicinal Chemistry Core of the Drug Discovery Institute, Robert J. DeVita, PhD, and a faculty member of DOMI, Peng Wang, PhD, to develop beta cell regenerative drugs that specifically target pancreatic beta cells. These studies are based on the recent discovery by this group of researchers that harmine, a beta-carboline alkaloid and a potent inhibitor of dual-specificity tyrosine phosphorylation-regulated kinase 1A (Dyrk1A) induces a remarkable increase in human beta replication and regeneration in vivo in mouse models with transplanted human islets. Discovery and optimization of new “harmalogs” with enhanced Dyrk1A inhibitory potency and pancreatic beta cell specificity are being developed and tested in our labs. We envision a future combination therapy in which beta cell protectors and immunomodulators such as dextran sulfate combined with beta cell specific regenerative factors such as “harmalogs” can be of use for the treatment of patients with established type 1 diabetes.

For more information about these studies, please contact [adolfo.garcia-ocana@mssm.edu](mailto:adolfo.garcia-ocana@mssm.edu).



Pancreatic islet from a type 1 diabetic mouse being attacked by immune cells: B cells (red), T cells (white), pancreatic insulin producing cells (green) and cell nuclei (blue).



**Adolfo Garcia-Ocaña, PhD**  
Professor, Medicine

# Pursuing a More Precise Risk Architecture for Obsessive-Compulsive Disorder

About 30% of adolescents are affected by an anxiety disorder. If unrecognized and untreated anxiety disorders can lead to significant difficulties in school function, social life and overall psychosocial development, and can contribute to lifelong impairments. Obsessive-compulsive disorder (OCD) is amongst the more severe anxiety disorders, with a prevalence of about 2-3%. OCD is characterized by intrusive, unwanted thoughts or images (“obsessions”) that provoke high anxiety and emotional distress. In OCD, obsessions typically lead to “compulsions.” Compulsions are ritualized and repetitive behaviors that function to reduce anxiety caused by obsessions, however, in OCD, obsessions and anxiety inevitably return and the cycle continues. Most individuals affected by OCD realize that their fears and behaviors are out of proportion to reality, but, in the moment, the distress engendered by OCD is quite powerful. OCD symptoms often begin during childhood and about half of OCD cases will present before adulthood.

Beyond the clinical complexities of OCD, we do not yet have a thorough understanding of OCD risk architecture. OCD runs in families at significantly higher rates than the population prevalence. Our study in Denmark of over 1.5 million individuals found a very high relative recurrence risk for OCD within nuclear families. Our work confirmed smaller, clinic-based studies that have examined recurrence risk for OCD.

Consistent with elevated family risk for OCD, it has been shown that OCD has important genetic underpinnings, as well as non-genetic or environmental causes of risk. Our lab has taken several approaches to more fully understand the risk architecture for OCD. A pilot grant from MCHDI helped us (Grice PI, Sandin co-PI) conclude that “maternal effects” are an important contributor to OCD risk.

Maternal effects are influences on an offspring’s phenotype that result from the (non-transmitted) maternal genome and the maternal environment. These effects are distinct from the child’s personal genetic makeup. Instead, maternal effects arise from maternal phenotype (which results from her own genetic and environmental influences), which in turn impact the phenotype of the child. Examples of maternal effects could include maternal factors that alter the provision of critical proteins to the developing egg, genetically-driven hormonal effects on in utero environment, or maternal illness that impacts offspring health (e.g. maternal influenza during pregnancy).

Maternal effects have been implicated as significant contributors to IQ and to risk for complex disorders such as multiple sclerosis but they have not been well-studied in psychiatric conditions. Work from Devlin et al (1997) has shown that if maternal effects are not explicitly modeled when studying risk architecture, estimates of heritability (also known as additive genetic effects) for that condition are overestimated. Accurate estimates of heritability and maternal effects are important as they guide the choice of specific genetic analytic approaches.

We recently completed a large population-based study in Sweden to simultaneously model the contribution of maternal effects and heritability for OCD. We showed that maternal effects account for 7-10% of risk for OCD. (Our team also modeled maternal effects in autism and found no evidence that they played a role in risk for autism.) Additionally, we demonstrate that heritability for OCD is over-estimated when maternal effects are not modeled.

Of the total genetic contribution to OCD risk estimated in our study (42% of all risk variance), about 20% resulted from maternal effects. Because maternal effects account for a significant proportion of

risk for OCD, these findings impact the design of future genetic studies of OCD. In addition, we can now begin to identify the specific factors that comprise the maternal effects.

Beyond dissecting specific factors that underlie maternal effects and risk for OCD, our lab also studies the genetics of OCD. Although we know that common genetic variation (and, to a lesser degree, rare genetic variation) contributes to OCD genetic risk, the field has yet to identify the specific genes and loci that underlie this risk. Large-scale genetic collaborations have made significant inroads into understanding genetic risks for autism, depressive disorders, schizophrenia, and bipolar disorder, but OCD has lagged behind. The combined genetic (DNA) samples related to OCD are not yet large enough to provide the statistical power needed to identify OCD-specific genes and loci. To this end, our group has been systematically collecting DNA samples from individuals affected by OCD. In the past year, we collected over 1500 DNA samples and our target is to ascertain 3500 or more. Our contributions, and those from other research groups around the world, to the large-scale OCD genetic consortia will enhance gene discovery and allow a more comprehensive and precise understanding of risks for OCD. As we learn more about risk factors associated with OCD and identify specific risk loci and maternal factors related to risk, we can begin to develop novel therapeutic approaches for OCD and associated conditions.



**Dorothy Grice, MD**  
Professor, Psychiatry

*“Because maternal effects account for a significant proportion of risk for OCD, these findings impact the design of future genetic studies of OCD. In addition, we can now begin to identify the specific factors that comprise the maternal effects”*

*—Dorothy Grice, MD*

## New Extramural Faculty

### Rebecca Trachtman, MD, MS

**Rebecca Trachtman, MD, MS** is an Assistant Professor in the Department of Pediatrics at the Icahn School of Medicine at Mount Sinai. Dr. Trachtman is a pediatric rheumatologist, interested in outcomes and treatment in systemic autoimmune and autoinflammatory disease. She received her undergraduate degree from Barnard College, and her medical degree from Albert Einstein College of Medicine. Dr. Trachtman then completed her pediatric residency training at NYU Langone Medical Center, followed by her pediatric rheumatology fellowship training at Hospital for Special Surgery/Weill Cornell Medicine, where she was the recipient of the Charles L. Christian Award for excellence in musculoskeletal research. During her fellowship training, Rebecca also attained a Masters' degree in Clinical and Translational Investigation through the Weill Cornell Medicine Clinical and Translational Science Center. Dr.

#### Recent Publications:

- Trachtman R, Onel K.** Blau Syndrome. Auto-Inflammatory Syndromes: Pathophysiology, Diagnosis, and Management. [In Press]
- Trachtman R, Sran SS, Trachtman H.** Recurrent Focal Segmental Glomerulosclerosis After Kidney Transplantation. *Pediatr Nephrol.* 2015; 50 (10): 1793-1802.
- O'Donnell HC, **Trachtman R**, Islam S, Racine AD. Factors Associated With Timing of First Outpatient Visit After Newborn Hospital Discharge. *Acad Pediatr.* 2014; 14(1): 77-83.
- O'Donnell HC, Colman G, **Trachtman R**, Velazco N, Racine AD. Impact of Newborn Follow-Up Visit on Subsequent ED Visits and Hospital Readmissions: An Instrumental Variable Analysis. *Acad Pediatr.* 2014;14(1): 84-91.
- Oyeku SO, Driscoll MC, Cohen HW, **Trachtman R**, Pashankar F, Mullen C, ... Green NS. Parental and Other Factors Associated With Hydroxyurea Use for Pediatric Sickle Cell Disease. *Pediatr Blood Cancer.* 2013;60(4): 653-8.

Trachtman's areas of clinical focus include juvenile idiopathic arthritis, systemic lupus erythematosus, vasculitis and periodic fever syndromes. Her research has a clinical and translational focus, specifically evaluating biomarkers and patient-reported outcomes in juvenile idiopathic arthritis, in order to improve treatment. Dr. Trachtman's main area of focus right now is biomarkers for

distinction of disease flare and infection in systemic juvenile idiopathic arthritis.



**Rebecca Trachtman, MD, MS**  
Assistant Professor,  
Pediatrics

## New Intramural Faculty

### Laura Huckins, PhD

**Laura Huckins, PhD** is an Assistant Professor of Genetics and Genomic Sciences at the Icahn School of Medicine at Mount Sinai. Psychiatric disorders are complex, impairing, and highly stigmatized conditions, conferring significant morbidity and mortality, and imposing significant emotional, social, and financial burdens on sufferers and their families. Substantial progress in understanding the genetic basis of these disorders has been made through global collaborative projects, and a number of significantly associated variants have been identified. Despite this, little is known about the biological mechanisms underlying these disorders, and few effective treatments exist. In particular, no effective medications exist for AN, which is understudied and underfunded compared to schizophrenia or bipolar disorder. Similarly, PTSD is underfunded compared to other psychiatric disorders, and existing funding largely focuses on military and combat-based PTSD, rather than interpersonal violence. The Huckins lab will focus on understanding the multi-omic aetiopathology of psychiatric disorders and trajectories, with an

#### Recent Publications:

- Barbeira AN, Dickinson SP, Bonazzola R, Zheng J...**Huckins LM**, Nicolae D, Cox NJ, Im HK. Exploring the phenotypic consequences of tissue specific gene expression variation inferred from GWAS summary statistics. *Nature Communications.* 2018 [In Press]
- Daskalakis NP, Rijal CM, King C, **Huckins LM**, Ressler KJ. Recent Genetics and Epigenetics Approaches to PTSD. *Current Psychiatry Reports.* 2018. [In Press]
- Huckins LM**, Dobbyn A, Ruderfer D, Hoffman G, Wang W, Pardinas AF, ... Stahl EA. Gene expression imputation across multiple brain regions reveals schizophrenia risk throughout development. bioRxiv, 222596. 2017. [Nature Genetics, In Review]
- Huckins LM**, Dobbyn A, McFadden W, Wang W, Ruderfer D, Hoffman G, ... Stahl E. A. Transcriptomic Imputation of Bipolar Disorder and Bipolar subtypes reveals 29 novel associated genes. bioRxiv, 222786. 2017. [Nature Communications, In Review]
- Huckins LM**, Dobbyn A, McFadden W, Ruderfer D, Wang W, Gamazon E, ... Stahl E. A. Identifying tissues implicated in Anorexia Nervosa using Transcriptomic Imputation. bioRxiv, 265017. 2018. [Nature Communications, In Review]

emphasis on understudied disorders and vulnerable groups. They will leverage statistical and analytical expertise to develop and apply machine-learning algorithms, in order to provide novel insights into understudied questions. To this end, her lab will have three synergistic foci (Figure 1): (1) Development of statistical algorithms; (2) generation of new cohorts using clinical recruitment and mining of electronic medical records (EMRs); (3) identification of novel associations. Dr. Huckins intend that these

goals will complement and strengthen existing expertise in the Pamela Sklar Division of Psychiatric Genomics.



**Laura Huckins, PhD**  
Assistant Professor,  
Genetics and Genomic  
Sciences

### Hala Harony-Nicolas, PhD

Dr. Hala Harony-Nicolas is an Assistant Professor at the Department of Psychiatry and a member of the Seaver Autism Center, the Friedman Brain Institute and the Mindich Child Health and Development Institute at the Icahn School of Medicine at Mount Sinai (ISMMS). Dr. Harony-Nicolas is a molecular and behavioral neuroscientist. She received her PhD in Molecular Biology at the Technion Institute, Israel and completed her first postdoctoral training in Molecular Neurobiology at University of Haifa, Israel, where she studied the epigenetic regulation of the mouse oxytocin receptor gene. She joined Dr. Joseph Buxbaum's laboratory and the Seaver Autism Center at the Icahn School of Medicine at Mount Sinai, where she completed her second post-doctoral training and was thereafter promoted to the level of Instructor. During her training she completed the validation and characterization of a new transgenic rat model for autism; the *Shank3*-deficient rat, and demonstrated the ameliorate effect of the oxytocin peptide on synaptic plasticity, social memory, and attentional deficits in this model. Studies in Dr. Harony-Nicolas's

#### Recent Publications:

Golden CEM, Breen MS, Koro L, Sonar S, Niblo K, Browne A, ... De Rubeis S, ... Buxbaum JD\*, **Hala Harony-Nicolas\***. Disruption of the KH1 domain of Fmr2 leads to transcriptional alterations and attentional deficits in rats. *BioRxiv* 338988 [Preprint]. June 9, 2018. \*Co-corresponding

Rajamani KT, Wagner S, Grinevich V, **Harony-Nicolas H\***. Oxytocin as a modulator of Synaptic Plasticity: Implications for Neurodevelopmental Disorders. *Front Synaptic Neurosci*. 2018 Jun 19;10:17. \*Corresponding

**Harony-Nicolas H**, Kay M, Hoffmann JD, Klein ME, Bozdagi-Gunal O, Riad M, ... Buxbaum JD. Oxytocin improves behavioral and electrophysiological deficits in a novel *Shank3*-deficient rat. *eLife*. 2017 Jan 31;6:eLife.18904.

Hsiao K, **Harony-Nicolas H**, Buxbaum JD, Bozdagi-Gunal O, Benson DL. Cyfip1 regulates presynaptic function during development. *J Neurosci*. 2016 Feb 3;36(5):1564-76.

**Harony-Nicolas H\***, Mamrut S\*, Brodsky L, Shahar-Gold H, Gainer H, Barki-Harrington L, Wagner S. Brain region-specific methylation in the promoter of the murine oxytocin receptor gene is involved in its expression regulation. *Psychoneuroendocrinology*. 2014 Jan; 39:121-31. \*Equal contribution

laboratory are focused on understanding the mechanisms by which autism-associated mutations lead to the manifestation of behavioral deficits by asking how do they affect (1) social brain circuits, (2) the oxytocin system, known to modulate social behavior, and (3) the interaction between both in health and disease. Her laboratory applies behavioral and cutting-edge molecular neuroscience approaches, with the ultimate goal to identify molecular

targets for treatment and to uncover altered brain circuits that can be manipulated with circuit-specific non-invasive interventions.



**Hala Harony-Nicolas, PhD**  
Assistant Professor,  
Psychiatry

### Bryn D. Webb, MD

**Bryn D. Webb, MD** is a physician-scientist and Assistant Professor in the Departments of Genetics & Genomic Sciences and Pediatrics with expertise in pediatrics, clinical and molecular genetics, and genomics. She serves as Co-Director of the Mitochondrial Medicine Program in the Division of Medical Genetics at Mount Sinai and Co-Director of the multi-disciplinary Cleft and Craniofacial Program at Mount Sinai. Her research has focused on gene discovery for rare congenital anomalies and patients with undiagnosed disease, and prior research accomplishments has included the following: identification of pathogenic variants in *HOXB1* in a subset of patients with congenital facial paralysis and strabismus (Webb et al, *Am J Hum Genet*, 2012); identification of a novel mitochondrial disorder caused by recessive single nucleotide variants in *MARS2* (Webb et al, *Hum Mutat*, 2015); identification of an additional causative disease gene (*DACT1*) for Townes Brocks syndrome (Webb et al, *Hum Mutat*, 2017); and identification of a novel mitochondrial disorder caused by recessive variants in *MRPS34* (Lake NJ\*, Webb BD\*, et al, *Am J Hum Genet*, 2017; \*=

#### Recent Publications:

**Webb BD**, Shaaban S, Gaspar H, Cunha LF, Schubert CR, Hao K, ... Jabs EW. *HOXB1* founder mutation in humans recapitulates the phenotype of *Hoxb1*<sup>-/-</sup> mice. *Am J Hum Genet*. 2012 Jul 13;91(1):171-9.

**Webb BD**, Wheeler PG, Hagen JJ, Cohen N, Linderman MD, Diaz GA, ... Schadt EE. Novel, Compound Heterozygous, Single-Nucleotide Variants in *MARS2* Associated with Developmental Delay, Poor Growth, and Sensorineural Hearing Loss. *Hum Mutat*. 2015 Jun;36(6):587-92. PubMed PMID: 25754315.

**Webb BD**, Metikala S, Wheeler PG, Sherpa MD, Houten SM, Horb ME, Schadt EE. Heterozygous Pathogenic Variant in *DACT1* Causes an Autosomal-Dominant Syndrome with Features Overlapping Townes-Brocks Syndrome. *Hum Mutat*. 2017 Apr;38(4):373-377.

Lake NJ\*, **Webb BD\***, Stroud DA\*, Richman TR\*, Ruzzenente B, Compton AG, ... Thorburn DR. Biallelic Mutations in *MRPS34* Lead to Instability of the Small Mitochondrial Subunit and Leigh Syndrome. *Am J Hum Genet*. 2017 Aug 3;101(2):239-254. (\*= co-first author).

Bruni F, Di Meo I, Bellacchio E, **Webb BD**, McFarland R, Chrzanowska-Lightowlers ZMA, ... Diodato D. Clinical, biochemical, and genetic features associated with *VARS2*-related mitochondrial disease. *Hum Mutat*. 2018 Apr;39(4):563-578.

co-first author). She currently has an NIH K08 Career Development Award to further study mitochondrial aminoacyl tRNA synthetase disorders, including *MARS2* deficiency, by creating cellular models of these diseases with CRISPR/Cas9 technology and by employing RNA-seq and network analysis. She is also an investigator in the Pediatric Precision Medicine initiative, which aims to diagnose and improve care

for pediatrics patients with undiagnosed disease at Mount Sinai.



**Bryn D. Webb, MD**  
Assistant Professor,  
Genetics & Genomic  
Sciences  
Assistant Professor,  
Pediatrics

## Trainee Highlights

# MCHDI Trainee Leadership Committee Builds on Three Years of Success to Improve Trainee Opportunities

The Trainee Leadership Committee (TLC) is in its third year of bringing together trainees across diverse disciplines and research areas represented in the MCHDI. Since inception, they have hosted 3 socials, led 7 workshops, and started the MCHDI pilot grant. The third social (on September 28th) was as successful as our first two, drawing ~30 pre-docs and postdocs. Attendees voted on workshops for the coming year, and three lucky trainees received MCHDI swag bags (portable charger, umbrella, mug, water bottle) through an RSVP-based raffle.

The TLC workshops are part of the Child Health Research Seminar (CHRS) series, organized by Shelley Liu and Alan Groves. Previous TLC workshops touched on science policy, grant-writing, negotiating, and science communication, and each had 10-30 attendees. This year, the TLC hosted a CHRS workshop on 10/16 focused on communicating research to a lay audience led by Dr. Leora Fox from the Huntington's Disease Society of America. This seminar built on the September seminar on elevator pitches. During the September

seminar, attendees learned that there are a variety of additional techniques they can employ to help pitch their science. Dr. Fox is an expert in removing jargon and decoding research into easy to understand explanations. Dr. Fox's expertise in coaching resulted in a valuable session for all! In addition to this seminar, stay tuned for other TLC-led seminars on peer review (1/15/2019) and Minerva (4/2/2019) through the MCHDI trainee listserv. To join the MCHDI trainee listserv, please email Elena Lum.

The flagship TLC accomplishment is the trainee pilot grant, now in its second year. This unique grant offers trainee support for projects independent of their PIs, a crucial step in any trainee's career. Previous winners were Oscar Rodriguez, and Michael Breen, PhD. This year's new recipients are Milo Smith, PhD and Hsi-en Ho, MD. Applications for the 2019-2020 academic year will open in March, 2019.

Finally, the TLC would like to thank past members Allison Kann and Jeanette Stingone, and welcome Jennie Altman to the team!



**Jennie Altman**  
PhD Candidate,  
Department of Microbiology



**Maya Deyssenroth, PhD**  
Postdoctoral Fellow,  
Department of  
Environmental Medicine  
and Public Health



**Felix Richter**  
MD/PhD Candidate,  
Graduate School of  
Biomedical Sciences

## Faculty Highlights

### Pilot Projects: 2017–2018 Awardees

#### **Project Title: Investigation of germline mutations in PIK3CG in primary immunodeficiency**

**Principal Investigators:** *Minji Byun, PhD, MCHDI Investigator and Assistant Professor of Medicine; Paul J. Maglione, MD, PhD, Assistant Professor of Medicine*

**Abstract:** Common variable immunodeficiency (CVID) is the most common symptomatic primary immunodeficiency, affecting approximately 1 in 25,000. It is characterized by failure of B-cell differentiation and defective immunoglobulin production. Genetic etiologies of CVID are diverse, with monogenic causes most commonly identified in pediatric cases. Patients with CVID are susceptible to sinopulmonary infections. In addition, more than half of patients experience autoimmune or inflammatory manifestations such as inflammatory bowel disease and chronic lung disease for reasons not understood.

In a multiplex family affected by childhood-onset hypogammaglobulinemia and severe inflammatory bowel disease, we identified a novel missense variant in PIK3CG, encoding the phosphatidylinositol-3-OH kinase (PI3K) catalytic subunit p110 $\gamma$ . By screening additional CVID patients, we identified another novel missense variant in PIK3CG in a patient with hypogammaglobulinemia and chronic lung disease. The p110 $\gamma$  subunit is one of the four class I PI3K catalytic isoforms expressed in mammals. Similar to the p110 $\gamma$  subunit, it is enriched in immune cells. Dominant active germline mutations in p110 $\gamma$  were recently identified in patients with immunodeficiency and lymphoid hyperplasia. Germline mutations in p110 $\gamma$  have never been reported in human disease. Based on similar expression and function of p110 $\gamma$  and p110 $\delta$ , and the symptomatic similarities between our patients and the patients with mutations in PIK3CD (encoding p110 $\delta$ ), we hypothesize that

the genetic variants in p110 $\gamma$  underlie immunodeficiency and inflammatory complications observed in our patients. In this collaborative study between a physician scientist, Paul J. Maglione, MD, PhD, and a basic scientist, Minji Byun, PhD, we propose immunophenotyping of the PIK3CG-mutated patients and functional characterization of the mutant p110 $\gamma$  proteins. Findings from this study will provide preliminary data for larger external funding that will enable indepth investigation into the role of p110 $\gamma$  in CVID as well as context for broader functions of p110 $\gamma$  in human immunity.



**Minji Byun, PhD**  
Assistant Professor,  
Medicine

### Pilot Projects: 2017–2018 Awardees, continued

#### Project Title: Generating Cardiac Purkinje Cells from Human Pluripotent Stem Cells

**Principal Investigators:** *Nicole Dubois, PhD, MCHDI Investigator and Assistant Professor of Cell, Development and Regenerative Biology; Andrew Sharp, PhD, MCHDI Investigator and Associate Professor of Genetics and Genomic Sciences*

**Abstract:** Heart defects are the most common birth defects affecting 8 out of every 1,000 births. Abnormalities in the cardiac conduction system (CCS), the cells that initiate and direct the contraction of the heart, are prevalent in the population with congenital heart disease. The majority of these rhythm defects are a result of defective positioning of CCS structures during development, or of the surgical interventions required to treat the congenital defects. A smaller number of the defects are also caused by mutations in genes responsible for the

normal development and function of the CCS. Various animal models have provided insights into the underlying causes of congenital heart defects however, in many cases the defects observed in the human population are not readily recapitulated in animal models. Complementary to these animal models human pluripotent stem cell (PSC) differentiations represent a promising new approach to understand human development and disease, and many of the cell types in the heart can be derived from hPSCs. However, there are currently no available approaches to generate the human ventricular CCS cells in vitro, including the His bundle branches and Purkinje fibers. In this pilot application we propose to generate Purkinje cells from PSC-derived cardiomyocytes via the induction of Notch signaling. In Aim1 we will confirm that Notch signaling converts PSC-derived cardiomyocytes to a Purkinje fiber phenotype, as assessed by morphology,

marker expression and measurement of beat frequency. In Aim 2 we will characterize the underlying mechanisms of Purkinje fiber development. Establishing a differentiation approach for Purkinje fiber myocytes will be relevant to understand inherited disorders of the ventricular CCS, for drug screening assays and for the in depth understanding of human Purkinje cell function.



**Nicole Dubois, PhD**  
Assistant Professor,  
Cell, Development  
and Regenerative  
Biology



**Andrew Sharp, PhD**  
Associate Professor,  
Genetics and  
Genomic Sciences

#### Project Title: Novel biomarkers of intrauterine brain development

**Principal Investigators:** *Shanna H. Swan, PhD, MCHDI Investigator and Professor of Environmental Medicine and Public Health; Allan C. Just, PhD, MCHDI Investigator and Assistant Professor of Environmental Medicine and Public Health; Avi Reichenberg, PhD, MCHDI Investigator and Professor of Environmental Medicine and Public Health*

**Abstract:** Today's highly sensitive ultrasound scans offer an early window into trajectories of fetal brain morphology and growth; correlates of neurodevelopmental processes. We propose to use serial ultrasound measurements, including biparietal diameter, head circumference, and extract validated novel measures of cerebrum and cerebellar size, to describe normative brain development and departures from those norms. Prenatal exposure to environmental pollutants (e.g. phthalate plasticizers) and over-the-counter (OTC) acetaminophen (APAP) have been associated with altered neurodevelopment and behavior in childhood, but their association with in utero brain development has not been studied. Altered trajectories of ultrasound parameters may provide sensitive

early markers of disruption of normal brain growth. We propose to obtain early measures of prenatal exposure to phthalate plasticizers and APAP and examine these in relation to ultrasound trajectories of the fetal brain. We will pilot this study in a pregnancy cohort, enrolling n=250 by gestational week 10, at Maternal Fetal Medicine Associates (MFMA) – a large Upper East Side research-oriented private obstetric practice. We will obtain repeat urine samples and weekly maternal SMS reports on APAP dose and indication. Biospecimens will be banked for future analysis and all anthropometric measures will be abstracted from MFMA's delivery records. This pilot study will demonstrate the feasibility of; 1) recruitment of MFMA moms by pregnancy week 10 and retention through delivery at MSHS; 2) early collection of urinary biomarkers and frequent SMS messaging; 3) longitudinal modeling of fetal brain parameters from repeated ultrasounds at weeks 12, 16, 20 and 24-28 weeks using generalized additive mixed models; 4) epidemiologic analysis of environmental exposures in relation to fetal brain growth trajectories. These pilot results will be used to support an application in response to PA-16-311 (Safety and Outcome Measures of Pain Medications Used in Children and Pregnant Women [R01 from NICHD]).



**Shanna H. Swan, PhD**  
Professor,  
Environmental  
Medicine and Public  
Health



**Allan C. Just, PhD**  
Assistant Professor,  
Environmental  
Medicine and Public  
Health



**Avi Reichenberg, PhD**  
Professor,  
Environmental  
Medicine and Public  
Health

## Publications, Grants, Awards/Honors

### Faculty Grants

**Brian Brown**, PhD, NIH/NCI, R33, “Pro-Codes: A Novel Vector and Cell Barcoding Technology”

**Supinda Bunyavanich**, MD, MPH, NIH, U19 “Biomarkers and Causal Key Drivers of Phenotypic Heterogeneity in Peanut Allergy”

**Jia Chen**, ScD & **Ke Hao**, PhD, (mPIs), NIH, R01, “Placental Functional Networks Linking Developmental Pesticide Exposure and Offspring Neurodevelopment”

**Andrew Sharp**, PhD, NIH/NINDS, R01, “Identification of Novel Pathogenic Tandem Repeat Expansions Using Long Read Sequencing”

**Annemarie Stroustrup**, MD, NIH, UH3, Site PI, “Developmental Impact of NICU Exposure”

**Annemarie Stroustrup**, MD, NIH, U01, Site PI, “Precision Medicine in the Diagnosis of Genetic Disorders in Neonates”

**Martin J. Walsh**, PhD, NIH, R01, “Principles Underlying Chromatin Architecture Define Functionality for CFTR Expression”

**Martin J. Walsh**, PhD & **Donald Scott**, PhD, (mPIs), NIH, R01 “Epigenetic Control of Human Beta Cell Proliferation”

### Faculty Highlights

### Publications

Morris-Schaffer K, Sobolewski M, Allen JL, Marvin E, Yee M, **Arora M**, O'Reilly MA, Cory-Slechta DA. **Effect of neonatal hyperoxia followed by concentrated ambient ultrafine particle exposure on cumulative learning in c57bl/6j mice.** *Neurotoxicology*. 2018 Jul;67:234-44.

**Berin MC**, Grishin A, Masilamani M, Leung DYM, **Sicherer SH**, Jones SM, ... **Sampson HA**. **Egg-specific ige and basophil activation but not egg-specific t-cell counts correlate with phenotypes of clinical egg allergy.** *J Allergy Clin Immunol*. 2018 Jul;142(1):149-58.e8.

Shan M, Carrillo J, Yeste A, Gutzeit C, Segura-Garzon D, Walland AC, ... **Sampson HA**, **Berin MC**, ... Cerutti A. **Secreted igd amplifies humoral t helper 2 cell responses by binding basophils via galectin-9 and cd44.** *Immunity*. 2018 Sep 26.

Gnanapragasam MN, Crispino JD, Ali AM, Weinberg R, Hoffman R, Raza A, and **Bieker JJ**. **Survey and evaluation of mutations in the human KLF1 transcription unit.** *Scientific Reports*. 2018 8:6587.

Barry KC, Hsu J, Broz ML, Cueto FJ, Binnewies M, Combes AJ, ... **Bogunovic D**, ... Krummel MF. **A natural killer-dendritic cell axis defines checkpoint therapy-responsive tumor microenvironments.** *Nat Med*. 2018 Aug;24(8):1178-91.

Feng S, **Bucvalas JC**, Demetris AJ, Burrell BE, Spain KM, Kanaparthi S, ... Sanchez-Fueyo A. **Evidence of chronic allograft injury in liver biopsies from long-term pediatric recipients of liver transplants.** *Gastroenterology*. 2018 Aug 22.

Fazlollahi M, Lee TD, Andrade J, Oguntuyo K, Chun Y, Grishina G, Grishin A, **Bunyavanich S**. **The nasal microbiome in asthma.** *J Allergy Clin Immunol*. 2018 Sep;142(3):834-43.e2.

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### Trainee Grants

**Michael S. Breen**, PhD, PI: Joseph Buxbaum, NARSAD, Brain and Behavior Foundation Young Investigator Grant, “A Trans-generational Transcriptional Map of Maternal Post-traumatic Stress Disorder”

**Maya A. Deysenroth**, DrPH, PI: Jia Chen, NIH-NIEHS, K99, “Intrauterine Metal Exposure, Placental Gene Networks and Fetal Growth”

**Alejandro Martin-Trujillo**, PhD, American Heart Foundation, Postdoctoral Fellowship, “Epigenetic Defect in Congenital Heart Defects”

**Oscar Rodriguez**, PhD candidate, NIH/NINDS, F31, Predoctoral Fellowship, “Identification of Novel Pathogenic Tandem Repeat Expansions Using Long Read Sequencing”

### Trainee Awards

**Felix Richter**, MD/PhD candidate, American Society of Human Genetics, Epstein Trainee Award Semi-Finalist and Oral Presentation

**Gabbay V**, Freed RD, Alonso CM, Senger S, Stadterman J, Davison BA, Klein RG. **A double-blind placebo-controlled trial of omega-3 fatty acids as a monotherapy for adolescent depression.** *J Clin Psychiatry*. 2018 Jun 26;79(4).

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## 6<sup>th</sup> Annual MCHDI Retreat

# Save the Date

## 6<sup>th</sup> Annual MCHDI Retreat

**Date:** November 27, 2018  
**Time:** 8:30 am – 6:15 pm  
**Location:** Harmonie Club  
Ballroom, 1st Floor  
4 E 60th St, New York, NY 10022



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