Icahn School of Medicine at Mount Sinai
The Mindich Child Health and Development Institute

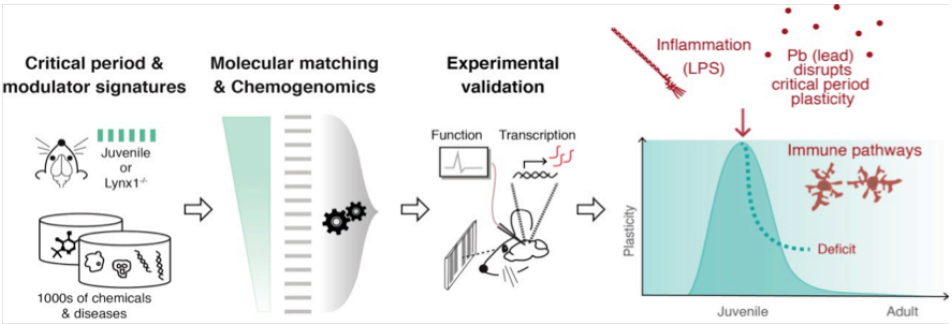
MCHDI Developmental Outcomes

Spring 2019

Research Advancements: Neurodevelopmental Disorders

Discovering Disease and Chemical Modulators that Disrupt Neuroplasticity During Childhood

Neuroplasticity is the ability of a nervous system to reorganize in response to its environment in order to optimize function. Critical periods are childhood windows of temporarily heightened neuroplasticity that enable social and sensory experience to refine brain circuitry toward optimal perception, cognition, and behavior (i.e. the acquisition of spoken language).



Discovering disease and chemical modulators that disrupt critical period plasticity will facilitate optimal brain development. However, discovering modulators of critical period plasticity is a major challenge unable to keep up with the rapidly expanding disease nosology and industrial chemical space: vast, unmapped landscapes of factors that may disrupt brain development. Given the high prevalence of neurodevelopmental disorders such as autism, identifying disruptors of developmental plasticity represents an essential step for developing strategies for prevention and intervention.

In the past few years, supported by the MCHDI pilot award and NIEHS P30ES023515 pilot award at Sinai, we collaborated with the Institute of Next Generation Healthcare led by Dr. Joel Dudley at Mt. Sinai to develop and apply an integrative bioinformatics approach to systematically scan across thousands of potential plasticity modulators to identify hundreds of diseases, disease pathways, neurotoxicants, and environmental chemicals that putatively disrupt critical period plasticity and provide new biological evidence for a handful of them.

In our recent proof-of-concept study, we systematically assessed connections between 436 transcriptional signatures of disease and multiple signatures of neuroplasticity, and identified inflammation as a common pathological process central to a diverse set of diseases expected to dysregulate plasticity signatures. We also experimentally confirmed in a mouse model that inflammation disrupts neuroplasticity during a visual cortex critical period. These findings suggest inflammation may have unrecognized adverse consequences on the postnatal developmental trajectory and indicates that inflammatory pathways as potential therapeutic targets.

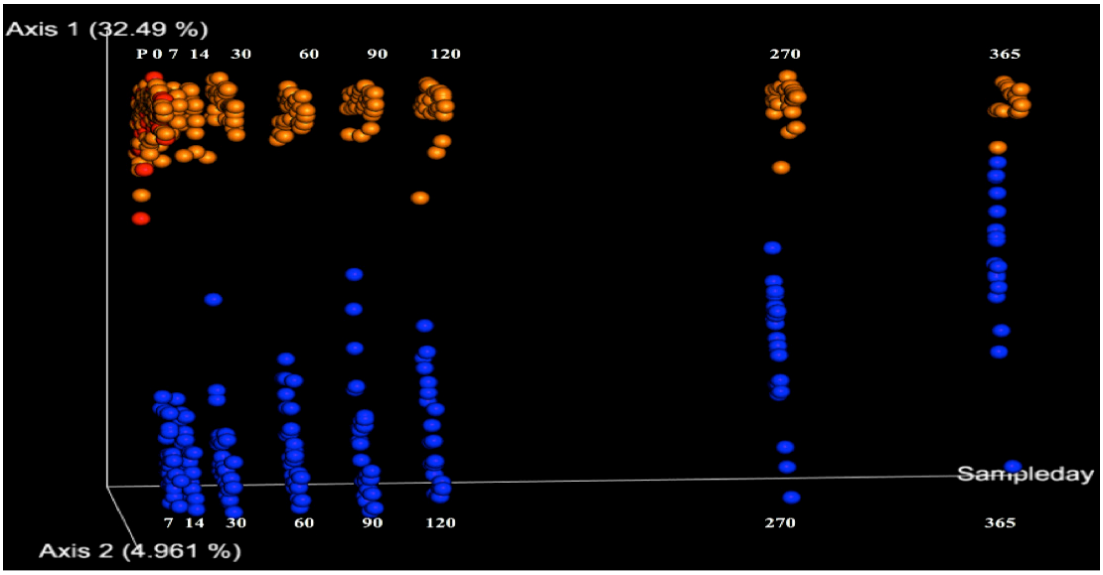
In our next study, we aimed to generalize our approach to environmental chemicals. We focused on a subset of environmental chemicals that have been established as human neurotoxicants. By mapping between a critical period plasticity signature and over a hundred neurotoxicant signatures derived from public data, we identified the metallic element lead (Pb) as a top ranked neurotoxicant and experimentally confirmed that Pb suppressed functional, critical period plasticity using a chronic exposure similar to that seen in children who later develop autism. Most recently, we expanded our analysis to all environmental chemicals with sufficient available public data (2001 chemicals) and identified 50 chemicals including pesticides, automobile pollution, and industrial waste products that dysregulate critical period gene signatures *in silico*. We also revealed inflammatory and immune cell pathways as reliably associated to these chemicals, consistent with our early work showing that inflammation disrupts critical period plasticity.

Together our work demonstrates the validity and utility of an integrative bioinformatics approach to rapidly discover modulators of brain plasticity. Our hope is that these efforts will be built upon to further amplify the rate at which modulators of critical period brain plasticity are discovered, toward optimal brain health for children.

Hirofumi Morishita, MD, PhD
Associate Professor, Psychiatry, Neuroscience, and Ophthalmology

Insights into the Early Life Gut Microbiome

The gut microbiome is tightly linked to human health and this relationship may be established much earlier than previously thought. Some factors thought to affect the development of the postnatal infant gut microbiome have been identified (delivery mode, antibiotic exposure and preterm birth). However, it remains unclear when and how a newborn's first gut microbiome is colonized. Very little is known about the bacteria that first populate the newborn's gut and how the *in utero* environment may be involved.



Three-dimensional unweighted UniFrac beta diversity plot (a measure of how different the gut microbial composition is between individuals). Green=mothers, red=fathers, blue=infants. The study timeline increases from left to right. Adults have similar gut microbiome composition, while composition of the children's gut microbiome shifts toward adult-like signatures by one year.

Historically, newborns' guts were considered sterile, undergoing initial bacterial colonization during delivery and thereafter from exposure to the environment. However, recent studies have detected bacteria in infant's first stool. This indicates that gut colonization may occur prior to birth in utero. Bacteria have been detected in the blood, umbilical cord blood, amniotic fluid and placental tissue of mothers, suggesting that maternal transfer of bacteria to the fetus *in utero* is plausible; a concept supported by findings in animal models. The early gut microbiome is unstable and matures as diet and environmental influences begin to shape a stable "core" microbiome over time. This process is significantly influenced by early feeding practices (breast vs. formula) and the introduction of solid foods. Deviations from this stability are associated with disease risk. Thus, an understanding the origins of the infant gut microbiome and the process of development is essential to understanding the role of the early microbiome in long-term child health.

With funding from an MCHDI Pilot Award, a collaborative team of researchers at Mount Sinai (Ryan Walker, Ruth Loos, Jeremiah Faith, Jose Clemente and Inga Peter), together with doctors at the Hospital Sant Joan de Deu in Barcelona, Spain, has recently completed a longitudinal birth cohort study designed to address these knowledge gaps. We recruited 40 healthy pregnant mothers and followed them, the fathers and their children through birth until one year. Nearly 600 stool samples, from day 0 through year 1, were collected and 16s rRNA regions of bacterial DNA were sequenced to yield prospective measures of gut bacterial diversity, abundance and taxonomy. We collected clinical and detailed nutritional information from adults during pregnancy and tracked infant diet feeding prospectively. Additionally, placenta, amniotic fluid, cord blood, saliva, skin, vaginal and longitudinal breast milk samples were collected for future analyses.

Early results show that infant gut microbiome communities, as a whole, are distinctly different from that of adults. As infants age, their gut microbiota become increasingly similar to adults with changes in both abundance and diversity across the first year of life (Figure). Diet exerts robust influence over the gut microbiome and a current aim is focused on understanding how breast-feeding duration and complimentary feeding contribute to this development. Future analyses aim to elucidate the role of the breastmilk microbiome and its metabolites in infant gut development and to determine whether maternal pregnancy microbiome communities (placenta, amnion, cord blood) contribute to the first fetal gut inoculation *in utero*.

Gaining insights in the origins of the gut microbiome and identifying modifiable factors that contribute to its development are crucial first steps towards developing potential interventions to optimize child health. We welcome collaborations on the project and for questions or to obtain information on the study please feel free to contact ryan.walker@mssm.edu.

Ryan W. Walker, MS, PhD
Postdoctoral Fellow, Environmental Medicine and Public Health

Trainee Pilot Projects: 2019 Awardees

Project Title: Assessing the role of microRNAs in Obsessive-Compulsive Disorder (OCD)

Investigator: *Carolina Cappi, Post-doctoral fellow, Department of Psychiatry, Icahn school of Medicine at Mount Sinai, NY*

Primary Mentor: *Dalila Pinto, PhD, Assistant Professor of Psychiatry, and Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, NY*

Secondary Mentor: *Thomas V. Fernandez, MD, Assistant Professor in the Yale Child Study Center and of Psychiatry, Yale University School of Medicine, New Haven*

Abstract: Obsessive compulsive disorder (OCD) is a developmental neuropsychiatric disorder with a lifetime prevalence of 2.0%. Current available treatments, both pharmacological and psychotherapeutic, can only benefit up to 60% of the OCD cases. Treatment-refractory disease is common and untreated OCD generally persists and becomes chronic. The fundamental challenge in identifying novel therapeutic targets is our limited understanding of the underlying biological mechanisms. Twin and family studies provide strong evidence for a substantial genetic contribution to OCD risk, with estimates of heritability around 40%, but progress in identifying risk genes has been slow. Increasing evidence over the last decade has identified micro-RNAs (miRNAs) as important effectors in psychiatric conditions. Here, we propose to assess the role of miRNAs in OCD by identifying differentially expressed miRNA in brain tissue (middle frontal gyrus) of 10 unrelated OCD cases that underwent deep brain stimulation (DBS) surgery compared to 10 non-OCD controls using small RNA-Seq. We will further identify differentially expressed miRNA in cerebrospinal fluid (CSF) collected from the same OCD cases and compare to miRNA dysregulated in brain. Finally we will investigate if the miRNA targets of OCD-affected miRNAs will be enriched in OCD risk genes mostly implicated through rare de novo and inherited variation from our ongoing whole exome sequencing of OCD families. Identification of dysregulated miRNAs via this study will allow us to further perform integrative analyses of biological pathways and gene networks that underlie OCD etiology.

Carolina Cappi, PhD
Post-doctoral fellow, Department of Psychiatry, Icahn school of Medicine at Mount Sinai, NY

Project Title: Assessing the Role of Monoallelic Expression in Primary Immunodeficiency

Investigator: *Conor Gruber, MD, PhD Candidate in the Department of Microbiology and Precision Immunology Institute at Icahn School of Medicine at Mt. Sinai*

Primary Mentor: *Dusan Bogunovic, PhD, Associate Professor in the Department of Microbiology, Department of Pediatrics at Mt. Sinai School of Medicine and Mindich Child Health and Development Institute.*

Secondary Mentor: *Brad Rosenberg, MD, PhD, Assistant Professor in the Department of Microbiology at Mt. Sinai School of Medicine.*

Abstract: Transcription of an autosomal gene is traditionally thought to occur from both homologous chromosomes, such that both maternal and paternal alleles are expressed. However, it has recently become clear that approximately 2-10% of autosomal genes can be expressed from a single allele in a random fashion across cells from one individual. Termed monoallelic expression (MAE), this phenomenon may have important consequences on the phenotypic manifestations of genetic disease. In particular, MAE may help explain phenotypic variation in monogenic disorders, in which incomplete penetrance and variable disease severity are often observed. However, the impact of MAE on specific genetic disorders has yet to be evaluated. Here, we aim to investigate the role of MAE in primary immunodeficiencies (PIDs). With inborn errors identified in 325 unique genes, PIDs constitute a diverse class of monogenic disease with significant morbidity and mortality in child health. Preliminary analysis of PID genetics has revealed that a subset of these genes may undergo MAE. This proposal will (1) systematically screen all primary immunodeficiency genes for MAE by computational and experimental methodologies and (2) determine the functional impact of MAE on specific PIDs. Taken together, these studies will directly inform the biological underpinnings and clinical genetics of PID, and may provide a new lens from which to study genetic disease.

Conor Gruber, MD, PhD
MD, PhD Candidate in the Department of Microbiology and Precision Immunology Institute at Icahn School of Medicine at Mt. Sinai

"These studies... may provide a new lens from which to study genetic disease."
—Conor Gruber, MD, PhD

Pilot Project: 2018-2019 Awardees

Project Title: Food-Specific T Cells in Eosinophilic Esophagitis

Principal Investigators: M. Cecilia Berin, PhD, MCHDI Investigator and Professor of Pediatrics; David Dunkin, MD, MCHDI Investigator and Assistant Professor of Pediatrics

Abstract: Eosinophilic esophagitis is a food-triggered inflammation and esophageal dysfunction that affects approximately 0.4% of children and adults. Children with EoE typically present with feeding difficulties, vomiting, and abdominal pain, and the esophagus features inflammation, remodeling and fibrosis. Strict elimination of dietary triggers resolves the inflammation, but there are no diagnostic tests that identify food triggers. Current management commonly includes a restrictive 6-food elimination diet (milk, egg, wheat, soy, fish/ shellfish, peanuts/tree nuts), and if inflammation resolves and there is a wish to broaden the diet, one food is added back at a time with re-biopsy to confirm tolerance. This is a time-consuming, restrictive, and invasive management approach. EoE is believed to be mediated by inappropriate T cell responses to food allergens that penetrate a leaky esophageal epithelium. We have developed methods for identifying and profiling foodspecific T cells in the peripheral blood of children with IgE-mediated food allergy. Here, we propose to use a similar approach to identify and phenotype milk-responsive T cells in the peripheral blood and esophagus of patients with EoE. In this pilot proposal, we will profile tissue CD4+ T cells by CyTOF and CITE-Seq, and identify milk-responsive T cells in peripheral blood using activation markers detected by flow cytometry. Once we have (1) identified the phenotype of CD4+ T cells in the inflamed esophagus and (2) identified allergen responsive CD4+ T cells in the peripheral blood, our objective is to use this preliminary data to apply for R01 funding to determine the utility of allergen-specific T cells in peripheral blood in predicting clinical response to dietary elimination in EoE.

M. Cecilia Berin, PhD
Professor, Pediatrics

David Dunkin, MD
Assistant Professor, Pediatrics

"In this pilot proposal, we will profile tissue CD4+ T cells by CyTOF and CITE-Seq, and identify milk-responsive T cells in peripheral blood using activation markers detected by flow cytometry."

Project Title: Neurodevelopmental Basis of Genetic Vulnerability for Cannabis Use Disorder

Principal Investigators: Hirofumi Morishita, MD, PhD, MCHDI Investigator and Associate Professor of Psychiatry, Neuroscience, and Ophthalmology; Yasmin Hurd, PhD, Professor of Neuroscience, Psychiatry, Pharmacological Sciences and Director of Addiction Institute

Abstract: Cannabis use is increasingly pervasive among adolescents today, even more common than cigarette smoking. The evolving policy surrounding the legalization of cannabis reaffirms the need to understand the neurodevelopmental basis of cannabis use disorders. Recent GWAS of cannabis use disorder identified the nicotinic Acetylcholine receptor α2 subunit (CHRNA2) as a single robust genome-wide significant locus in cannabis use disorder. eQTL analysis further showed that the risk loci is associated with reduced expression of CHRNA2 in brain. While cannabis may itself increase drug addiction and psychiatric vulnerability, risk genes are expected to contribute to pre-existing prodromal states (or disease vulnerability) which may initially promote the self-medication and that through repeated use, led to dependence 2. The goal of this pilot study is to identify the neurodevelopmental impact of a newly identified risk gene for cannabis use disorders by examining the neurobiological consequence of reduced CHRNA2 expression at behavior (Aim1), cellular/ circuit (Aim2), and molecular level (Aim3) using rodent model. Given that the loss of control over drug intake that occurs in addiction results from disruption of the prefrontal cortex (PFC), our study will focus on PFC circuitry and its regulation of reward behavior. We are well qualified to conduct the proposed study. Dr. Morishita (co-PI) is an expert of CHRNA2 function for cortical development and plasticity and Dr. Hurd (co-PI) has an extensive expertise on cannabis use disorders, making both PIs highly relevant to conduct the proposed study.

Hirofumi Morishita, MD, PhD
Associate Professor, Psychiatry, Neuroscience, and Ophthalmology

Yasmin Hurd, PhD
Professor, Neuroscience, Psychiatry, Pharmacological Sciences
Director, Addiction Institute

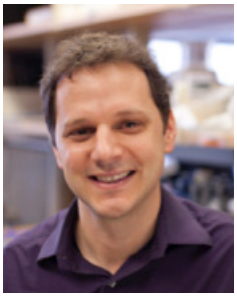
"The goal of this pilot study is to identify the neurodevelopmental impact of a newly identified risk gene for cannabis use disorders"

Pilot Project: 2018-2019 Awardees

Project Title: Association Studies of Multicopy Genes in the Mount Sinai BioMe Exome Sequencing Cohort

Principal Investigators: Andrew Sharp, PhD, MCHDI Investigator and Associate Professor of Genetics and Genomic Sciences; Ruth J.F. Loos, PhD, MCHDI Investigator, Professor of Environmental Medicine and Public Health and Co-Director of the Charles Bronfman Institute for Personalized Medicine

Abstract: The human genome contains hundreds of exons and genes that show extensive copy number variation (CNV), many of which are contained in large tandem repeats (TRs). Although these multicopy genes represent a rich source of functional genomic variation, due to their repetitive and highly polymorphic nature, they are typically ignored by most genomic technologies. While a few targeted studies of multicopy genes have indicated that CNV of these can exert strong effects on disease risk, there are many conflicting reports in the field, which is largely attributable to a historic lack of robust genotyping technologies for high copy number sequences. Here, using ~32,000 individuals from the Mount Sinai BioMe biobank that have undergone whole exome sequencing (WES), we will test the hypothesis that CNV of multicopy genes influences multiple human phenotypes and disease risk. In our preliminary data, we show that we can generate accurate copy number estimates for multicopy genes based on read count data from WES. We will utilize these copy number calls to perform Phenome-Wide Association Study (PheWAS) analyses in the BioMe biobank, considering several hundred multicopy genes and hundreds of traits, including many diseases with childhood onset. As this is an understudied field, we anticipate that our analyses will (i) uncover novel associations between multicopy and multiple human phenotypes that may point to new biology, and (ii) provide key preliminary data that can be used to apply for NIH funding to investigate the role of multicopy genes and large TRs using data produced by the GTEx and TOPMed programs.



Andrew Sharp, PhD
Professor of Genetics and Genomic Sciences

Ruth J.F. Loos, PhD
Professor of Environmental Medicine and Public Health
Co-Director of the Charles Bronfman Institute for Personalized Medicine

"Here, using ~32,000 individuals from the Mount Sinai BioMe biobank that have undergone whole exome sequencing (WES), we will test the hypothesis that CNV of multicopy genes influences multiple human phenotypes and disease risk."

Grants, Awards/Honors, Publications

Faculty Grants

David Dunkin, MD, The Helmsley Charitable Trust, Clinical Trial Grant "Study to Evaluate Safety and Tolerability of Oral BFAHF-2 in Subjects with Mild-to-Moderate Crohn's Disease"

Hala Harony-Nicolas, PhD & **Lior Zangi**, PhD, (mPIs), NIMH, R21, "An RNA-Based Approach to Intranasal Delivery of Neuropeptides to the Brain"

Trainee Grants

Maya Deyssenroth, PhD, PI: **Jia Chen**, 2019 Teratology Society Postdoctoral Fellow Travel Award

Corina Lesseur, MD, PhD, PI: **Jia Chen**, NICHD, K99, "Integrative Analysis of Human Placental Epi/genome in Relation to Fetal Growth"

Faculty Awards/Honors

Jaime Chu, MD, AASLD Foundation, AASLD Foundation Bridge Award

Bruce Gelb, MD, President of the American Pediatric Society

Bruce Gelb, MD, Treasurer of the American Society of Human Genetics

Hala Harony-Nicolas, PhD, Friedman Brain Institute Scholar Award, "Implication of the Hypothalamic Oxytocin System in Autism-Associated Social Deficits"

Robert Krauss, PhD, Mount Sinai Student Body, 2019 Outstanding Teaching by a Faculty Member Award

Publications

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7th Annual MCHDI Retreat

Save the Date
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Date: November 12, 2019
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