IN THIS ISSUE

1  FBI SCHOLARS AWARD
EXCITING RESEARCH MOMENTUM IN ADNP SYNDROME

2  THE SEAVER TEAM SUPPORTS SINAI POSTDOCTORAL TRAINEES
CELEBRATING OUR FACULTY’S GRANT SUCCESSES!

3  NEW FACULTY AND STAFF
AUTISM AWARENESS MONTH GOES VIRTUAL

4  SPRING EVENT: SIPPING FOR SEAVER
COVID-19 – AUTISM AND SOCIAL DISTANCING

FBI Scholars Award

Assistant Professor, Silvia De Rubeis, PhD, was awarded a 2020 Friedman Brain Institute Fascitelli Research Scholar Award. Dr. De Rubeis and her collaborator, Zhuhao Wu, PhD, will take advantage of complementary expertise and innovative tools to understand how the cerebral cortex develops in a mouse model of DDX3X syndrome.

Funded entirely through philanthropy, the goal of the Friedman Brain Institute Scholars Partnership is to encourage innovative brain research and offer young pioneers who are venturing into a new area of investigation the freedom to follow their science.

The investigators will study the way brain cells in the cortex develop and communicate with other brain regions using a technique that allows the visualization of single brain cells in an intact brain, with high resolution. They will also study the molecular signatures of these brain cells.

By comparing typically developing and DDX3X mutant mice, the studies will uncover how brain connections are altered in DDX3X syndrome.

Exciting Research Momentum in ADNP Syndrome

The parents from the ADNP Kids Research Foundation have been working tirelessly to raise money to support research progress for their children. Their enthusiasm and hard work have enabled the Seaver Center to launch the first ever clinical trial for ADNP Syndrome – fully funded by the Foundation.

Seaver researchers have begun to recruit participants for the new drug trial, which will evaluate the safety, tolerability, and efficacy of a low dose of ketamine in children diagnosed with ADNP syndrome (also known as Helsmoortel-VanDerAa syndrome), a rare neurodevelopmental disorder caused by mutations in the activity dependent neuroprotective protein (ADNP) gene.

The ADNP gene affects brain formation, development, and function, and the protein produced from it helps control the expression of other genes. Individuals with the disorder produce roughly half of the proper amount of protein. ADNP mutations are one of the most common single-gene causes of autism.

The potential of ketamine as a treatment modality for ADNP syndrome was identified by mediKanren, an artificial intelligence (AI) tool that scans medical literature and uses AI reasoning. Using that information, two parents of children with ADNP syndrome—Matthew Davis, MD, and Sandra Sermone, founder of the ADNP Kids Research Foundation—began their own analysis by scouring medical literature and processing the results. They found several animal model studies that showed ketamine was able to boost ADNP production in brain cells. The parents presented the evidence and their hypothesis to Joseph Buxbaum, PhD, Director of the Seaver Autism Center, who agreed that this was a potentially viable approach.

The Seaver Autism Center will enroll 10 participants, ages 5 to 12, at The Mount Sinai Hospital. Participants will receive one low-dose infusion of ketamine for 40 minutes and be monitored for four weeks. At each clinic visit, participants will undergo safety monitoring, clinical evaluations, and biomarker studies using electrophysiology and eye tracking.

Another milestone by Seaver researchers is their recent American
Journals of Human Genetics publication. The research findings revealed that DNA methylation changes in ADNP syndrome show little correlation to severity of symptoms.

“DNA methylation is a chemical modification of the DNA molecule, and is one of the epigenetic mechanisms that control the activity of our genes, defining where and when they are expressed. In the past few years, several neurodevelopmental disorders have been associated with specific changes in DNA methylation,” said Silvia De Rubeis, PhD, Assistant Professor at the Seaver Autism Center and co-senior author of the paper.

Researchers at the Seaver Center replicated previously published findings demonstrating that individuals with ADNP syndrome have profound DNA methylation changes in their blood, and these changes depend on the type of ADNP mutation that they carry. Individuals with the disorder segregate into two groups based on the location of their mutations.

The team then used behavioral and neurobiological data from two prospective cohorts of individuals with a genetic diagnosis of ADNP syndrome to examine the relationship between these epigenetic signatures and clinical presentation. Results showed limited differences between the two ADNP groups, and no evidence that individuals with more widespread methylation changes were more severely affected.

“As clinical trials in ADNP syndrome begin, understanding the utility of biomarkers and their relationship to clinical symptoms becomes critical. Our results caution against using DNA methylation episignatures as a biomarker for clinical trials.” Paige Siper, PhD, Chief Psychologist at the Seaver Autism Center and senior co-leading author on the study.

Furthermore, the compelling data that ADNP mutations lead to two, very distinct molecular phenotypes reveals that existing mouse models that do not accurately reflect the human mutation spectrum may be less useful for preclinical work.

To achieve accurate representation of the disorder to expand preclinical testing, the Center proposed a plan to the ADNP Kids Research Foundation to generate two mouse models with clinically relevant mutations identified in individuals with ADNP syndrome.

The Foundation prioritized funding to generate the mice, which is in progress now. Once the animals are available, our Center will initiate in-depth characterization starting with the electrophysiological analyses, as well as epigenetic and transcriptomics, to validate the biomarkers identified in the blood of patients and in human neurons in vitro.

To help progress the field of ADNP research, these mouse models will be available to other researchers through Jackson Laboratory.

The research findings revealed that DNA methylation episignatures as a biomarker for clinical trials. Dr. Breen’s recent work identified strong evidence for widespread differential RNA editing patterns across several hundred cortical samples from individuals with schizophrenia, however the cellular context and physiological consequences of these events remain unknown.

Findings from this project will be useful to inform future studies focused specifically on RNA editing in autism.
Autism Awareness Month Goes Virtual

This year, the Center’s celebration of Autism Awareness Month looked a little different than in years past. Due to the pandemic, we were unable to host our annual Family Appreciation Day event. We were saddened to miss spending quality time with our research families, but we still wanted to do something special. Our team put together care packages for the families who registered to attend the original event and provided a virtual activity package to help families stay engaged with activities. We were also able to host two live virtual Little Maestros music classes, an activity that families typically get to experience at the event.

Throughout the month, we shared a special social media campaign that highlighted the many meanings autism has to each individual and family. This campaign engaged our research families and members of the community to share what autism means to them – its challenges and silver linings.

Mount Sinai Health System also produced a Facebook Live segment that featured our Director of Community Outreach, Michelle Gorenstein, discussing ways to work on social supports while social distancing. Michelle also kicked-off the month by hosting a free webinar to help caregivers structure their families days during social distancing. The virtual event was so well-received that webinars became a regular offering, hosted each week during April and have continued throughout the summer.

While the Center’s plans for Autism Awareness Month had to be changed, come pandemic or high water, we will always celebrate our families and the mission we work on tirelessly year-round.
The Seaver Autism Center has compiled resources for families, including approaches to talk to kids about coronavirus, social stories, behavior management strategies and visual and sensory supports.

To learn more, please visit our Autism and COVID-19 resources webpage: bit.ly/SeaverAutismCOVID19

Follow our social channels for updates and information about our free webinar series that aims to help families affected by autism during this difficult time.