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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



Research Momentum in ADNP Syndrome CONTINUED

Journal 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 epigenotypes 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 Seaver Team Supports Sinai Postdoctoral Trainees

Given the severe hardships for many members in the postdoctoral community due to the COVID-19 pandemic, an Emergency Postdoctoral Trainee Support Fund was established by the Icahn School of Medicine at Mount Sinai.

It remains an all too real risk that individuals will have no choice but to leave the fields of science and medicine in the coming years, due to the increased strain. These losses will disproportionately occur across racial, gender, and socioeconomic divides, undoing years of efforts to improve the much-needed diversity on all fronts.

We are proud of our Seaver Team Members who not only recognized the importance of this effort, but also personally contributed \$8,100. The Seaver Center was able to match these personal donations, for a total of \$16,200.

We must ensure both the success and the diversity of the next generation of scientists by providing opportunities to thrive.

Please consider supporting our team by making a tax-deductible donation to champion their work to advance autism research and treatments.
giving.mountsinai.org/seaver

Celebrating Our Faculty's Grant Successes!

Congratulations to Assistant Professor, Hala Harony-Nicolas, PhD, and her collaborator, Shlomo Wagner, PhD (University of Haifa Israel), for being awarded a USA-Israel Binational Science Foundation (BSF) Grant. The investigators will use the funding to study the relationship between socio-emotional valence, oxytocin and social brain activity in health and disease.

The USA-BSF Research Grants program funds the highest quality research programs of US and Israeli scientists with evident synergies who wish to work together.

More congratulations are in order for another Assistant Professor, Michael Breen, PhD,

for his Alkermes Pathways Research Award. His project will investigate cell-specific RNA editing and its functional impact on schizophrenia in order to build the foundation for evaluating the therapeutic potential of targeting RNA editing sites and related-pathways as a novel therapeutic approach.

RNA editing is a common molecular mechanism in the brain that introduces base-specific variations in RNA sequences and expands the functional output of many important neuronal genes, which is vital for healthy neuronal development.

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.

NEW SEAVER STAFF



SARAH BANKER

Sarah Banker is a second year Neuroscience PhD student at Mount Sinai. She joined the Seaver Center in the spring of 2020 as a member of Jennifer Foss-Feig's lab, along with co-mentorship from Xiaosi Gu and Daniela Schiller. She is interested in combining computational modeling, human imaging, and clinical assessment to understand the neural mechanisms underlying aberrant social behavior in autism.



GIZEM INAK-GIRRBACH, PHD

Gizem joined the Seaver Center as a postdoctoral fellow in the field of neuroscience and stem cell research in Dr. Nan Yang's lab. In 2009 she received a BSc in Biology and Bioengineering from Sabanci University of Istanbul, followed by a MSc in Molecular and Cellular Neuroscience from Eberhard-Karls-University in Germany, and a PhD from Freie University Berlin. Her research focuses on elucidating the role of ADNP as a chromatin modifier in human iPSC-derived neurons.



MARIE BARBIER, PHD

Marie joined the Seaver Center in January as a Postdoctoral Research Fellow, with Dr. Harony-Nicolas. She has a background in neuroanatomy and behavior. Her work at the Center will focus on studying the impact of Shank3-deficiency on neural circuits of social reward.



VAHE KHACHADOURIAN, PHD

Vahe joined the Seaver Center in April as a Postdoctoral Fellow with Dr. Janecka. He received his MD from Yerevan State Medical University and his PhD in Epidemiology from UCLA. His work at the Center will primarily focus on investigating associations between parental health conditions and risk of autism.



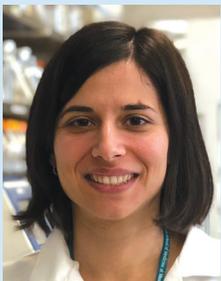
RACHEL COHEN

Rachel joined the Seaver Center in December 2019 as a Program Coordinator. She graduated from Cornell University and previously worked in the Division of Pulmonary at Mount Sinai. In her current role, she supports the Drug Discovery and Development program, and provides operational and programmatic support to the Center.



ENRICO MOSSOTTO, PHD

Enrico Mossotto joined the Seaver Center in January 2020 as Postdoctoral Fellow in the Breen Lab. He received his PhD in Genomics and Bioinformatics from the University of Southampton in 2018 (Southampton, UK). Enrico is currently analyzing RNA editing in transcriptomic data as well as developing pipelines to integrate large-scale genotypic, RNA editing, splicing, gene expression and proteomic data in health and disease.



MARTA GARCIA-FORN, PHD

Marta Garcia-Forn joined the Seaver Center in January 2020 as a postdoctoral fellow in De Rubeis lab after obtaining her PhD in Biomedicine at the University of Barcelona. She will study the development and connectivity of glutamatergic projection neurons in the cortex of mice modeling DDX3X syndrome, and their relationship to behavioral deficits.



LAURA SLOOFMAN, PHD

Laura Sloofman joined the Seaver Center in April 2020 as a bioinformatician. She uses computational techniques to analyze genetic data in autism and other neurodevelopmental disorders. She has a Master's of Science in biophysics and computational biology from the University of Illinois at Urbana Champaign, and previously worked as a bioinformatician in the Pamela Sklar Division of Psychiatric Genomics here at the Icahn School of Medicine.

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.



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- THE SEAVER AUTISM CENTER NEWSLETTER brings you timely updates about new developments related to research and treatment of autism spectrum disorders, as well as activities at the Seaver Autism Center. To be placed on our mailing list, please contact SeaverCenterEditor@mssm.edu or Seaver Autism Center, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1668, New York, NY 10029. Our phone number is 212.241.0961 and our website is www.SeaverAutismCenter.org.
- SEAVER IS CONTINUING TO GO GREEN! Please send your email address to seavercentereditor@mssm.edu to receive this newsletter electronically.

**YOU ARE INVITED TO THE
SEAVER AUTISM CENTER'S
VIRTUAL WINE TASTING**

SIPPING FOR SEAVER

**THURSDAY, OCTOBER 15 | 6-7:30 PM
WITH MACARI VINEYARDS**

Purchase your tasting package(s)/sponsorship:
giving.mountsinai.org/SeaverCelebration



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COVID-19: Autism and Social Distancing

The Seaver team 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.