
Mount Sinai
Seaver Autism Center for Research and Treatment
seaver autism center
for Research & Treatment at Mount Sinai
ANNUAL REPORT
2016

seaver autism center for research & treatment @ mount sinai

The Seaver Autism Center for Research and Treatment was founded in 1993 through the generous support of the Beatrice and Samuel A. Seaver Foundation (Hirschell E. Levine, Esq., and John D. Cohen, Esq., Co-Trustees).

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Cover art by Jessica S. Johnson, MFA

Mission Statement

The Seaver Autism Center for Research and Treatment is a fully integrated and translational center dedicated to discovering the biological causes of autism and developing breakthrough treatments. Our mission is to prevent, treat, and cure autism by bridging the gap between new discoveries at the basic science level and enhanced care, with the parallel translation to the community of new and improved approaches to caring for people with autism.

Message from the Director

In 2016, the Seaver Center continued its groundbreaking work on the causes and treatment of autism spectrum disorder. Seaver researchers have identified additional causes of autism, and we continue to focus on translating scientific discoveries into patient treatment.

This past year, we increased our efforts in the development of biomarkers for autism. A biomarker is a measurable indicator, such as a protein in the blood or a pattern of brain activity, that can help researchers to identify, diagnose and treat patients based on their specific biology. Developing biomarkers will be key in creating effective personalized treatment plans for individuals with autism.

The Seaver Center was awarded support in 2016 from the National Institutes of Health for multiple new studies, including a study to develop biomarkers for autism, a study focused on risk genes in autism and epilepsy, and a study on autism and prenatal endocrine disruptors. The NIH also renewed their support of the Autism Sequencing Consortium with an additional commitment of $7M. This Consortium now includes over 40 groups from all over the world, with over 150 researchers. The current dataset includes DNA data from 29,000 individuals, making it the largest sequencing study in psychiatry. With this additional support, we expect to reach a target of samples from 50,000 individuals by 2021. The Autism Sequencing Consortium was specifically highlighted during the presidential campaign as part Hillary Clinton's autism platform.

The Seaver Center was also awarded important foundation support for pilot projects, including an award from the Autism Science Foundation for the Autism Sisters Project, which aims to understand the female protective effect, and an award from the Phelan-McDermid Syndrome Foundation to explore electrophysiological biomarkers of Phelan-McDermid syndrome.

We continue to be committed to inclusivity of the most severely affected individuals, as well as individuals of all ages and in underrepresented groups. In 2016, Pilar Trelles, MD, was awarded funding from The Klingenstein Third Generation Foundation to improve access to care for minority youth with autism using the Family Peer Advocate model, as well as assess and expand the model. Dr. Trelles saw 15 families in 2016, and plans to expand the program to 70 families over the next two years.

In 2016, we announced an exciting new research initiative called the Study of Psychiatric Disorders to Explore Relationships (SPyDER). SPyDER aims to enhance collaboration between researchers working in psychiatric disorders that are comorbid with autism, including obsessive compulsive traits, anxiety disorders, attention deficits and intellectual disability. The Seaver Center has received pilot funding through the Associates Committee to launch this initiative, and is currently raising additional funds to propel the project forward.

The Center's Outreach Program hosted multiple lectures and events for families and researchers including community lectures, the Seaver Seminar Series, and the Annual Advances in Autism Conference. This year we celebrated the landmark 20th anniversary of this conference.

We welcomed four new Seaver Fellows in 2016, including three Postdoctoral Fellows and one Graduate Fellow. This class of Fellows will explore various research topics, including genetic mutations in mice models, and biological and environmental risk factors for autism.

We are delighted to share our progress from the past year in this Annual Report, and we look forward to what we can accomplish in 2017 to improve the lives of individuals with autism. We welcome your feedback and support.

Joseph D. Buxbaum, PhD
Director

Message from the Clinical Director

This past year has been an exciting one for the Clinical Research Program at the Seaver Autism Center. We were thrilled to have recruited Jennifer Foss-Feig, PhD, as an Assistant Professor. Dr. Foss-Feig joins our important effort to establish biological markers of autism spectrum disorder in order to design better clinical trials and eventually develop more personalized treatments, and she has already made major contributions to our efforts in biomarker discovery. She will be collaborating with our Chief Psychologist, Paige Siper, PhD, and the rest of our team in studying electrophysiological responses to auditory and visual stimuli to better understand sensory deficits in autism and single gene forms of autism, like Phelan-McDermid syndrome.

In 2016, our group completed a trial of insulin-like growth factor-1 in Phelan-McDermid syndrome and is in the midst of analyzing a wealth of data. We continue to collect crucial information about the clinical features and natural history of Phelan-McDermid syndrome through the Rare Disease Clinical Research Network - Developmental Synaptopathies Consortium. We also completed recruitment for the National Autism Center of Excellence Network Study of Oxytocin in Autism to improve Reciprocal Social Behaviors (SOARS-B) and anticipate preliminary results by the summer of 2017. We expect SOARS-B to be the pivotal study that will determine whether oxytocin is effective in autism, and if so, which children and adolescents are most likely to benefit.

A major area of focus in 2016 was the development of biomarkers and objective clinical outcome measures in autism. Among several accomplishments, Dr. Siper has published two important papers on the utility of visual evoked potentials and the Sensory Assessment for Neurodevelopmental Disorders (SAND) to measure sensory reactivity in autism. We believe the key to successful clinical trials in the future will be to establish biomarkers of treatment response and objective tools to measure clinical improvement. There are many promising results emanating from the basic science literature testing a wide array of potential treatments in model systems with animals and neurons derived from human pluripotent stem cells. However, many of these treatments have not been successful in clinical trials in humans and now, more than ever, it is critical to discover new ways to select patients for participation in studies, predict treatment response, and precisely monitor change over time.

The past year has been an especially busy one filled with success and challenges. Our team is filled with optimism about the potential for identifying biomarkers and developing new treatments in autism in the near future. As always, we remain dedicated to improving the lives of people and families affected by autism. We are extremely grateful to the Seaver Foundation, and this year, to the New York Community Trust Edith and Jules Klein Fund for their generous donations, in addition to all the organizations and individuals who sponsor our work.

Alexander Kolevzon, MD
Clinical Director

Research Program

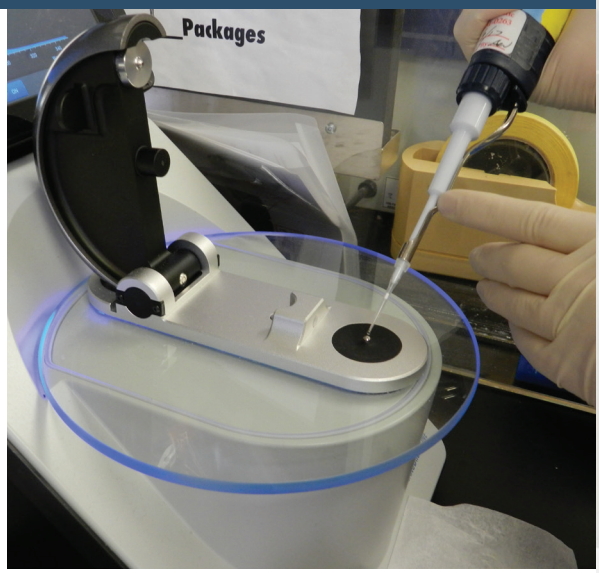
The Seaver Autism Center continues to grow as an integrated preclinical and clinical center for autism.

PRECLINICAL RESEARCH

At the Seaver Autism Center we take advantage of a "genetics-first" approach to tackle the complex biology of autism.

This approach starts with identifying autism genes: we run comprehensive genetic analysis of thousands of individuals with autism and healthy controls recruited from around the world to identify risk factors through DNA sequencing. Genetic findings have important implications for people with autism and their families: they lead to more accurate diagnoses, improved genetic counseling and better support and care for patients. In addition, they shed light on biological pathways in autism.

It is a major goal of the Seaver Center to translate genetic discoveries into novel therapeutics. We use genetic findings to build cell and animal models of disease, and study these models to understand the consequences of gene mutations on biological processes. These models are used to test drugs for therapeutic intervention.



GENETICS

In 2016, Seaver Center investigators completed three major research studies on the genetic causes of autism and associated disorders. These studies stem from our ongoing efforts in the Autism Sequencing Consortium, an international collaboration of over 40 research teams founded and led by the Seaver Autism Center and Dr. Buxbaum. We also continue our efforts on the Population-based Autism Genetics and Environment Study (PAGES). The results from these studies, described below, represent the forefront of autism genetics research.

• De novo mutations

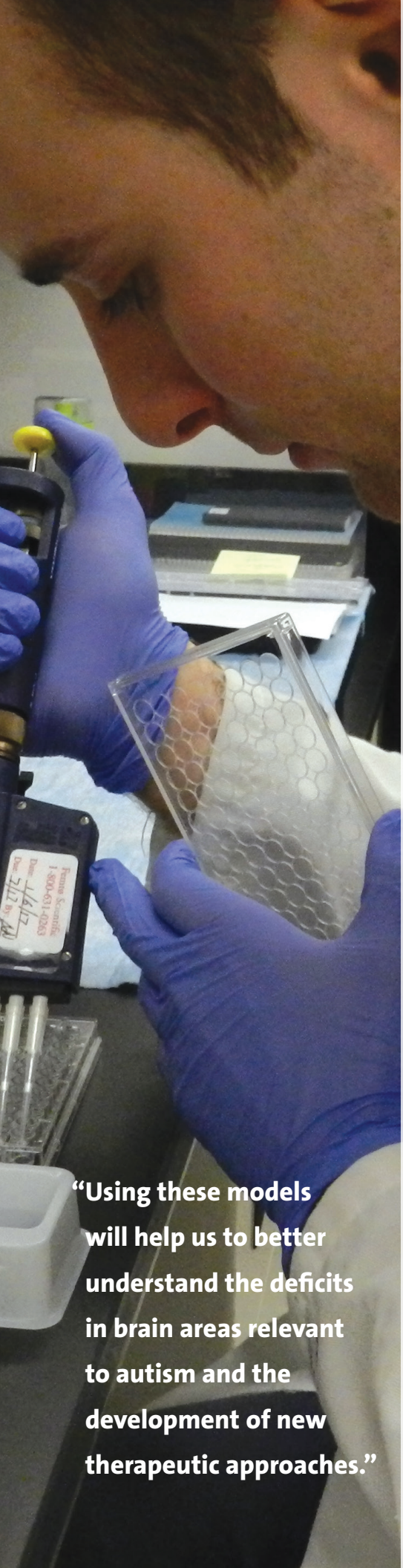
This study explored how rare de novo mutations, which are mutations that are found in the child but not present nor transmitted from their parents, in individuals diagnosed with neurodevelopmental disorders differ from those found in the general population with the goal of discovering novel risk genes. We studied genetic mutations in 9,246 families with individuals affected by autism, intellectual disability, or developmental delay, and compared them with those found in 60,706 controls. We found that one third of the mutations in affected individuals can be also detected in the general population and do not influence risk for neurodevelopmental disorders. We also found that the bulk of risk is associated with mutations in genes that are intolerant to mutations in the general population. Our findings define novel approaches to rigorously pinpoint mutations that contribute to risk and to precisely identify genes associated to neurodevelopmental disorders. A paper on this research, titled "Refining the role of de novo protein truncating variants in neurodevelopmental disorders using population reference samples", was recently published in *Nature Genetics.*

• Recessive mutations

This study was the largest analysis to date of the role of biallelic (recessive) mutations in autism. Mutations are defined as biallelic when they are present in both copies of a gene, with each copy (allele) typically inherited from a healthy parent. By analyzing the sequence data of over 8,000 individuals, we discovered that individuals with autism carry an excess of damaging biallelic mutations. We estimated that biallelic mutations can contribute to up to 3% of autism cases, a figure that rises to 10% when considering girls with autism. We identified dozens of genes that are disrupted by biallelic mutations in individuals with autism. Among them are novel candidate genes including genes required for development of the serotonergic neurons, which modulate key brain functions and affect mood, anxiety, and aggressive behavior. A paper on this research, titled "Biallelic mutations reveal inherited genetic architecture and implicate glutamatergic and serotonergic dysfunction in ASD", is currently under review by *Nature Neuroscience.*

• Postzygotic mosaicisms

This study was the largest study to date on the role of postzygotic mosaicisms in the pathogenesis of autism. Postzygotic mosaicisms are genetic mutations that happen sporadically very early during prenatal life, resulting in a mutation in only a fraction of the cells. As a result, the individual is defined as a mosaic. We developed novel strategies to identify postzygotic mosaic mutations from blood and applied them to over 4,000 families with a child diagnosed with autism. We found that individuals diagnosed with autism have an excess of postzygotic mosaic mutations in genes expressed during prenatal life. In particular, we observed an enrichment of postzygotic mosaic mutations in genes highly expressed in the amygdala, a brain area important for emotional and social responses. We identified two novel genes associated with neurodevelopmental disorders strongly enriched with postzygotic mosaicisms. A paper on this research progress, titled "Distribution, and Implications of Postzygotic Mutations in Autism Spectrum Disorder", is currently under review by *Nature Neuroscience.*



"Using these models will help us to better understand the deficits in brain areas relevant to autism and the development of new therapeutic approaches."

CELL AND ANIMAL MODEL SYSTEMS

Rodent Models

At the Seaver Center, researchers are characterizing mouse and rat models with mutations in several autism risk genes, including *SHANK3* and *FMR1*. These studies provide objective measures of the biological effects of the loss of these genes on nerve cell connectivity, strength of the communication between nerve cells (synaptic plasticity), and cognitive, motor and social behavior. As an example of the strength of such studies, we discovered that treatment of *SHANK3*-deficient mice with Insulin-like Growth-Factor-1 (IGF-1) improves some synaptic plasticity and motor deficits. These findings led to clinical trials testing the effects of IGF-1 in individuals carrying mutations in *SHANK3*, which are ongoing. Researchers at the Seaver Center are also testing translatable biomarkers, which are measures that can be assessed comparably in both human and animal subjects. These biomarkers will serve as tools to examine the efficacy of potential therapeutics in animal models to predict their effect in human subjects, and inform clinical trials.

Our most recent efforts have been focused on rat models for autism. Compared to mice, rats have specific advantages for research, including a more complex and humanlike neural circuitry and behavioral repertoire. Using these models will help us to better understand the deficits in brain areas relevant to autism and the development of new therapeutic approaches. Seaver Center researchers have generated and characterized a novel genetically modified rat model carrying a mutation in the *SHANK3* gene. Similarly to the *SHANK3*-deficient mouse, the rat model displays synaptic plasticity deficits. It also exhibits social behavior and attentional deficits, recapitulating the neuropsychiatric features of Phelan-McDermid syndrome. In this model, researchers demonstrated that the hormone oxytocin significantly improved social memory, attention, and synaptic plasticity deficits. These findings indicate that oxytocin may have therapeutic potential for not only social, but also non-social deficits in Phelan-McDermid syndrome, specifically attention, and support our clinical trials with oxytocin in individuals with this syndrome. A paper discussing these findings, titled "Oxytocin improved behavioral and electrophysiological deficits in a novel *SHANK3*-deficient rat" was recently published in *eLife*.

However, both the recently developed rat model and the existing mouse model only disrupt the full-length *SHANK3* isoform and do not reflect the vast majority of known Phelan-McDermid syndrome cases, which are caused by haploinsufficiency of all isoforms of *SHANK3*. We have therefore developed a novel mouse model of Phelan-McDermid syndrome that is similar to most known human mutations. These mice have a significant reduction in both induction and maintenance of cellular markers of memory, and have electroencephalographic (EEG) deficits similar to those seen in patients with Phelan-McDermid syndrome.

Induced Pluripotent Stem Cells

Seaver Center researchers continue to develop the use of stem cells in autism research. This model system is critical for the study of autism as it allows for the study of human nerve cell function in autism without the need for brain tissue from patients. In addition, stem cells can be used for gene discovery, using systems biology to look at disrupted molecular pathways and to identify novel treatment targets. Stem cells can also form the basis for intermediate- and high-throughput small molecule screening for new autism medicines, as stem cells can be expanded extensively for such experiments. To date, we have collected over 350 samples from 120 families for stem cell research including about 40 families who have children diagnosed with Phelan-McDermid syndrome. From those, over 50 lines of induced pluripotent stem cells have been produced and many are now used to generate live neurons in culture for our studies.

ENVIRONMENTAL RISK IN AUTISM PROGRAM

The Environmental Risk in Autism Program focuses on identifying non-genetic factors that contribute to autism risk and studying how such factors interact with genetic processes to determine individual difference in risk and disease severity. Our work in the past year has shown that environmental factors play an important role in the etiology of autism, yet with environmental exposures, the impact of timing of exposures and confirming levels of individual exposure have been difficult to ascertain. We are conducting two pilot studies: one aimed at reconstructing exposure history using primary baby teeth, and one assessing exposure to persistent organic pollutants and risk for autism. In addition, using the International Collaboration for Autism Registry Epidemiology (ICARE), we are leading projects examining the association between planned vs. emergency cesarean and risk for autism, and the relationship between Apgar score at birth and risk for autism.

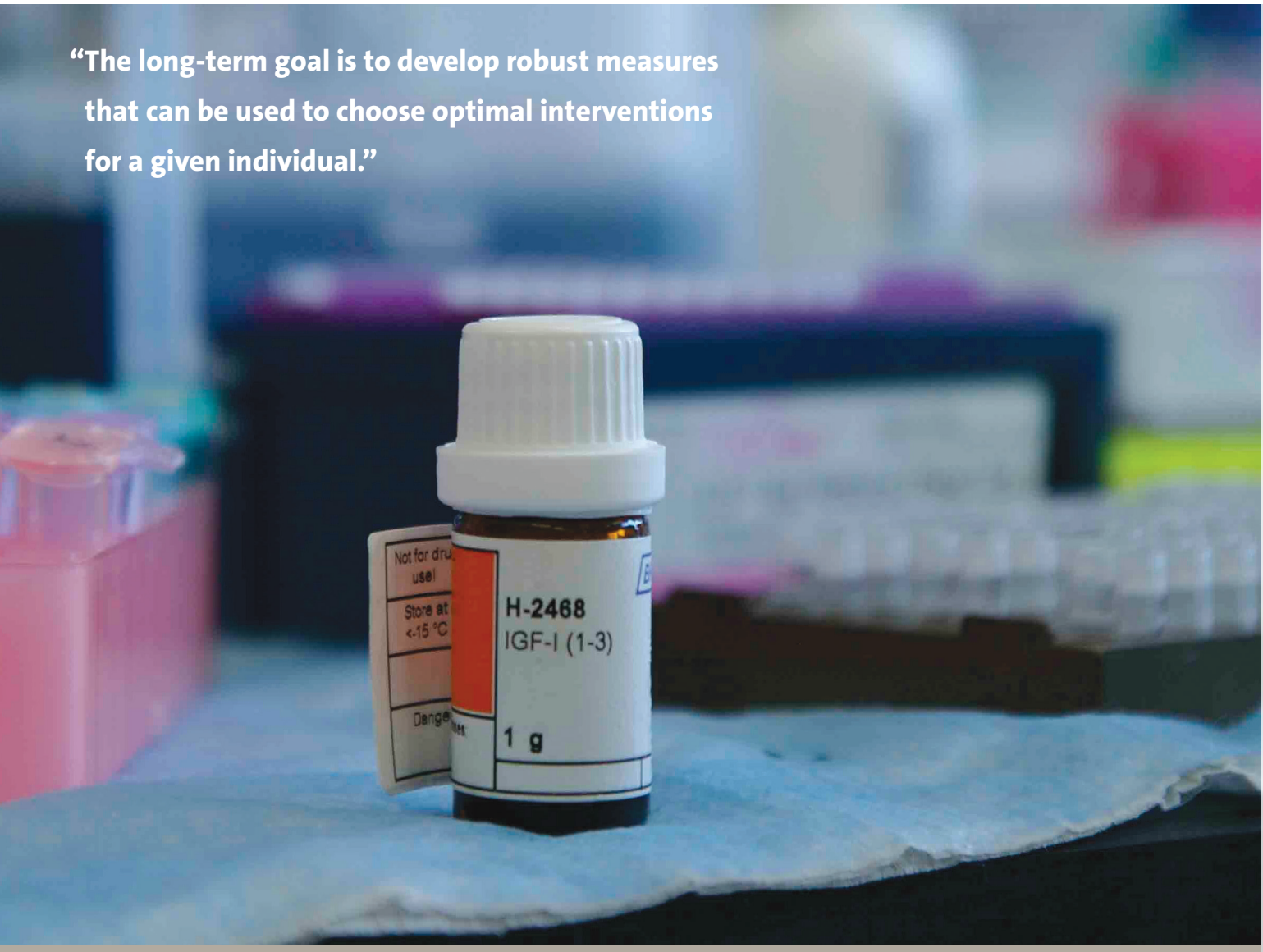
CLINICAL RESEARCH

BIOMARKER DISCOVERY AND EXPERIMENTAL THERAPEUTICS

Researchers at the Seaver Autism Center are using multimodal brain imaging (EEG, MRI), eye tracking, and targeted clinical assessments to identify biomarkers of idiopathic and single-gene forms of autism. The goal of our work is to establish novel, objective measures that can be used to parse out the heterogeneity of autism by identifying subtypes based on neural profiles. We are also interested in using our battery of objective measures to assess treatment response. Our long-term goal is to develop robust measures that can be used to choose optimal interventions for a given individual. In 2016, we incorporated these methods into our core phenotyping battery. We now collect electrophysiological and eye tracking data on all interested research participants. We also obtained grant funding from the NIH to examine the relationship between EEG responses and sensory phenotypes as well as funding from the Phelan-McDermid Syndrome Foundation to support multi-site electrophysiological efforts towards clinical trial readiness.

Our battery of neuroimaging assessments is now integrated into our longstanding experimental therapeutics program. In 2016 we began using our objective measures as exploratory outcomes and in 2017 we will begin looking at these measures as predictive markers of treatment response. The Study of Oxytocin in Autism to Improve Reciprocal Social Behavior (SOARS-B) completed enrollment at the end of 2016. Results from this five year, multi-site, placebo-controlled Phase II clinical trial will provide the autism community with an answer regarding the efficacy of intranasal oxytocin for the treatment of core social deficits in children with autism. In 2016, we began recruitment for a new pilot study examining the efficacy of intranasal oxytocin for the treatment of attention, social memory, socialization, language, and repetitive behaviors in Phelan-McDermid syndrome. We also completed enrollment for the second phase of our study examining the effects of Insulin-like Growth-Factor-1 (IGF-1) in Phelan-McDermid syndrome. Data analysis will be completed in early 2017. Finally, we are continuing enrollment for our IGF-1 in idiopathic autism study. We anticipate 2017 will be an exciting year as we begin to return results from these large endeavors.

"The long-term goal is to develop robust measures that can be used to choose optimal interventions for a given individual."

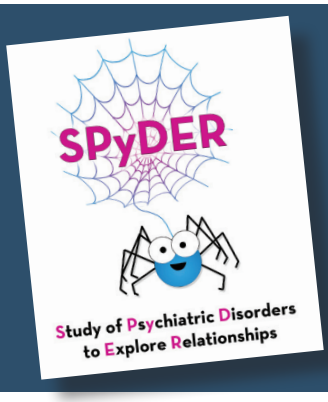


AUTISM SISTERS PROJECT

The Autism Sisters Project is a new initiative established in 2016 through support from the Autism Science Foundation. The Sisters Project seeks to advance our understanding of the male sex bias in autism through an examination of the Female Protective Effect. Here at the Seaver Center, we are carrying out a prospective study to gather both genetic and phenotypic data from individuals with autism and their siblings and parents. A primary aim of the study is to validate web-based assessments that can ultimately be administered remotely. Our long-term goal is to use phenotyping data to better understand the relationship between genetic and phenotypic variables. Results from this study will allow us to make informed decisions about an optimal phenotyping battery for widespread dissemination. In addition, we are collecting genotype data through saliva samples, which reduces the burden of specimen collection. In 2017, the Sisters Project plans to leverage existing datasets such as the Autism Sequencing Consortium to examine the Female Protective Effect within large cohorts.

MAPPING THE GENOTYPE, PHENOTYPE, AND NATURAL HISTORY OF PHELAN-MCDERMID SYNDROME

The Seaver Autism Center is currently leading the first ever natural history study of Phelan-McDermid syndrome. In conjunction with five other institutions across the United States, the NIH-funded Rare Diseases Clinical Research Network (RDCRN), is studying three single-gene forms of autism that share similar signaling pathways. Our Developmental Synaptopathies Consortium is comprehensively characterizing children and adolescents with Phelan-McDermid syndrome, PTEN mutations, and Tuberous Sclerosis. Mount Sinai is the lead site for the Phelan-McDermid syndrome study. Participants are followed over a two-year period and receive thorough medical and neuropsychological testing by a multidisciplinary team of psychiatrists, psychologists, neurologists, and clinical geneticists. The study seeks to enhance our understanding of Phelan-McDermid syndrome across individuals and over time. In 2017 we will begin to include adults with Phelan-McDermid syndrome through additional funding from the Phelan-McDermid Syndrome Foundation.



NEW RESEARCH INITIATIVE

In September, we launched SPyDER (Study of Psychiatric Disorders to Explore Relationships), an initiative to enhance collaboration between scientists working in psychiatric disorders that are comorbid with autism spectrum disorder, including obsessive compulsive traits, anxiety disorders, attention deficits (ADD/ADHD) and intellectual disability. Scientists involved in SPyDER share genetic and behavioral data in order to generate a rich, valuable database of information. This database will allow scientists to work together to investigate possible relationships between different childhood psychiatric conditions to identify causes and treatments. We have received pilot funding to launch this ambitious initiative, and are currently raising additional funds to propel the project forward.

NEW GRANT HIGHLIGHTS

Development of Behavioral and Neural Biomarkers for Autism Spectrum Disorder Using a Genetically Defined Subtype

SPONSOR: NATIONAL INSTITUTES OF MENTAL HEALTH

This study, led by Dr. Buxbaum and Dr. Siper, aims to develop behavioral and neural biomarkers of autism, which are feasible in severely affected individuals (including individuals with Phelan-McDermid syndrome) and can be translated to other genetically defined subtypes and across sensory modalities. Specifically, the research team aims to develop reliable measures of behavioral and neural sensory reactivity within the visual system of children with Phelan-McDermid syndrome and autism more broadly.

Autism Sisters Project: Recruiting families and expanding understanding of the female protective effect

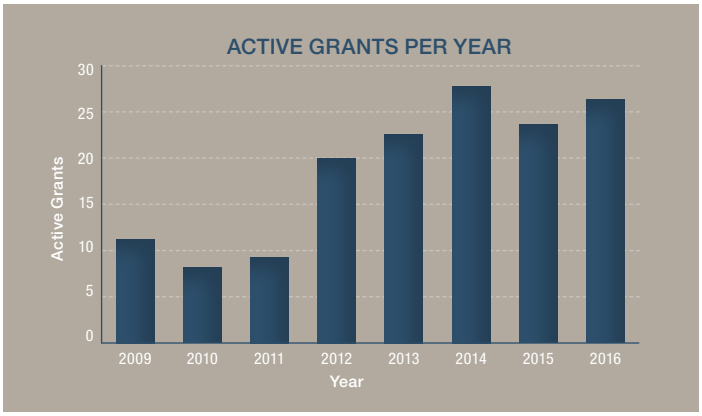
SPONSOR: AUTISM SCIENCE FOUNDATION

The Autism Sisters Project seeks to better understand the relationship between genetic factors and phenotypic variables such as cognitive functioning, autism symptoms, and developmental milestones in siblings of children with autism. This initiative, led by Dr. Siper, involves the development and validation of a web-based battery of assessments that can be distributed remotely and used reliably in siblings and parents of children with autism. The long-term goal is to investigate the Female Protective Effect in autism by adding phenotypying data on family members to large genetic databases.

Electrophysiological biomarkers of Phelan-McDermid Syndrome

SPONSOR: PHELAN-MCDERMID SYNDROME FOUNDATION

Led by Dr. Siper, this pilot research project aims to validate measures of neurophysiological visual and auditory reactivity in individuals with Phelan-McDermid syndrome, which can be used as outcome measures in pharmacological and behavioral intervention studies and aid in predicting treatment response. The central hypothesis is that individuals with Phelan-McDermid syndrome will display significant abnormalities in basic neural responses that can be understood in the context of glutamatergic (excitatory) and GABAergic (inhibitory) activity. The long-term goal of the study is to validate neurophysiological outcome measures, which are feasible across the lifespan for individuals of varying levels of functioning, and are sensitive to change with treatment.



Improving Access to Care for Minority Youth with Autism Spectrum Disorder Using a Family Peer Advocate Model

SPONSOR: THE KLINGENSTEIN THIRD GENERATION FOUNDATION

Led by Pilar Trelles, MD, the objective of this study is to facilitate access to care for children with autism by establishing a Family Peer Advocate model of care. The central hypothesis, based on preliminary data, is that caregiver focused contact with a Family Peer Advocate will reduce caregiver strain and improve quality of life in affected families by increasing treatment utilization, normalizing distress, and promoting positive parent-child interactions. In addition, the research team will evaluate the impact of ADHD symptoms and caregiver strain on treatment response.

Pilot Research Award for Child and Adolescent Psychiatry

SPONSOR: AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY

Led by Dr. Trelles, the overall objective of this study is to characterize attention deficits in autism and to examine the impact of these deficits in autism on overall symptom severity, adaptive functioning, and cognitive performance in a representative community sample. In addition, using eye-tracking paradigms, the research team expects to validate an objective measure of the attention domain in autism that will distinguish between social and non-social attention and may be relevant to future clinical trials.

The Autism Sequencing Consortium: Autism Gene Discovery in >50,000 Exomes

SPONSOR: NATIONAL INSTITUTES OF MENTAL HEALTH

Founded in 2010 by Dr. Buxbaum, the Autism Sequencing Consortium is an international group of scientists who share autism samples and genetic data. This supplement to the original grant was awarded in 2016 in order to continue the work of the Autism Sequencing Consortium, largely by continued production and analysis of sequence data from autism subjects and their families. This supplement includes new avenues of research, such as integrating whole genome sequence (WGS) data and building on ideas that have emerged from the study of common variants to understand the interplay of common and rare variants to impact risk. Through this new research, the team will accelerate its overall objective, which is to identify autism genes in pursuit of novel treatments.

Integrative genomics to map risk genes and pathways in autism and epilepsy

SPONSOR: NATIONAL INSTITUTES OF MENTAL HEALTH

Led by Dalila Pinto, PhD, the goal of this study is to identify risk genes and components of the emerging molecular pathways shared among autism and epilepsy as necessary steps toward more tailored treatments.

Autism and Prenatal Endocrine Disruptors (A-PED)

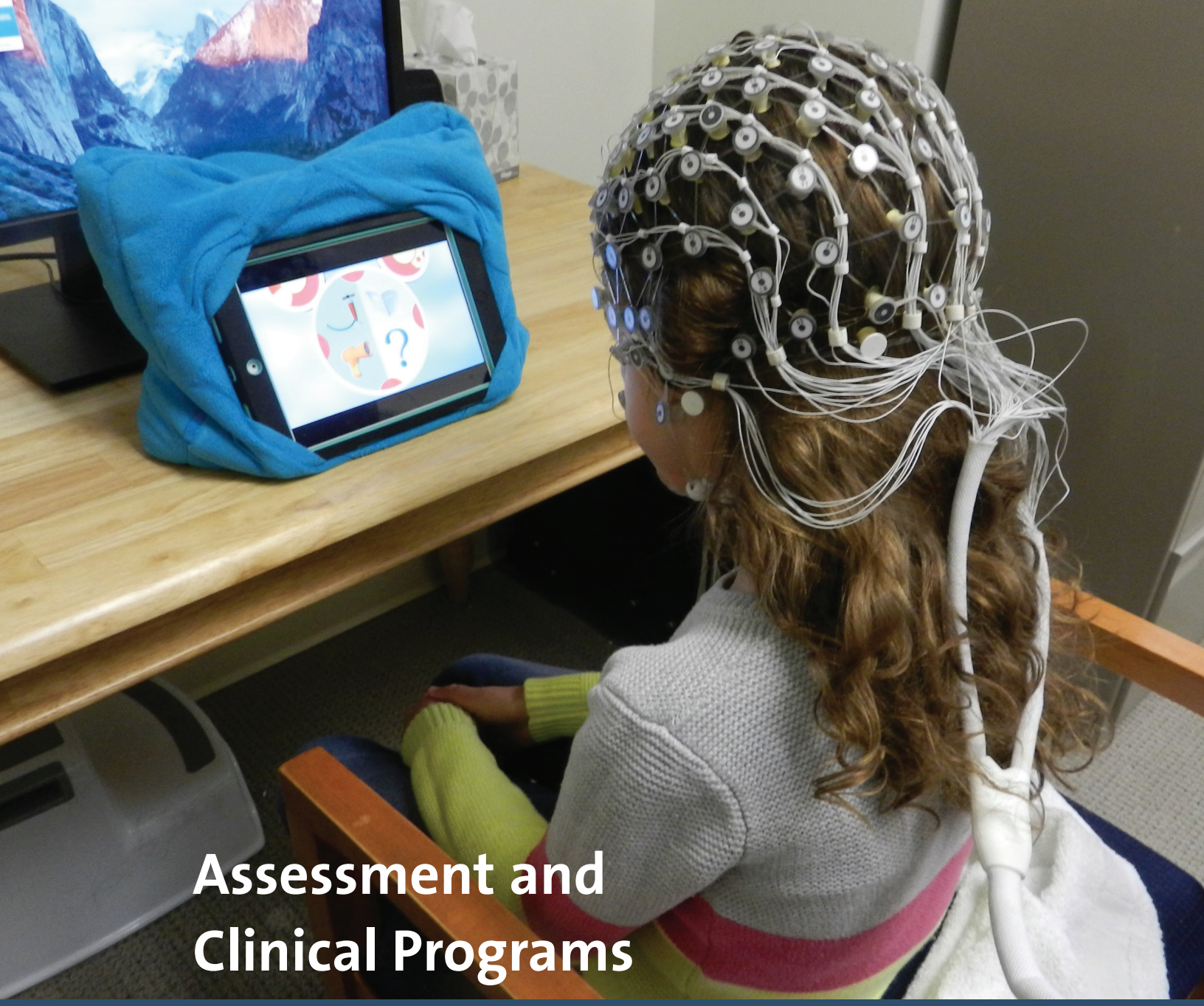
SPONSOR: NATIONAL INSTITUTES OF ENVIRONMENTAL HEALTH SCIENCES

Led by Avi Reichenberg, PhD, the goal of the project is to use existing population-based resources to examine how exposure to endocrine disrupting chemicals in pregnancy contributes to risk of developing autism.

Developing Personalized Approaches to the Treatment of Autism

SPONSOR: THE NEW YORK COMMUNITY TRUST, EDITH AND JULES KLEIN FUND

This project, led by Dr. Kolevzon, aims to investigate how insulin-like growth factor 1 (IGF-1) may be used as a treatment in individuals with idiopathic autism. IGF-1 has proven effective in modifying the symptoms of patients with Phelan-McDermid syndrome. Dr. Kolevzon and his team will use electroencephalographic (EEG) measures of brain activity to characterize a subset of individuals with autism who share biomarkers with individuals with Phelan-McDermid syndrome. This subset will engage in a double-blind, placebo-controlled, crossover clinical trial to evaluate the use of EEG to detect change with IGF-1 treatment, in order to investigate the mechanism of IGF-1 as a treatment for Phelan-McDermid syndrome, and consequently the use of IGF-1 as a possible treatment option in the larger population. *A generous philanthropic gift made this particular research project possible. If you are interested in contributing towards a specific research project or initiative, please contact us at 212-241-0961 or theseavercenter@mssm.edu.*



Assessment and Clinical Programs

The Assessment and Clinical Programs at the Seaver Autism Center work together to enroll individuals in clinical research studies, while providing genetic testing, gold-standard diagnostic evaluations, treatment and medication management.

Message from the Chief Psychologist

The Clinical and Assessment Programs at the Seaver Center witnessed tremendous growth over the past year. In 2016 our investment in new faculty and technology allowed us to expand our focus on biomarker discovery, placing us at the forefront of electroencephalographic (EEG) research in autism. We have now integrated EEGs into our assessment core, making it part of routine phenotyping for individuals participating in research. We are optimistic that our examination of brain activity will improve our ability to objectively assess treatment efficacy and will ultimately pave the way towards more personalized interventions. We are also excited about the Autism Sisters Project, a new initiative supported by the Autism Science Foundation to examine the Female Protective Effect in autism. In the area of training, our Seaver Clinical Fellows had an outstanding first year with successful grants obtained from the American Academy of Child and Adolescent Psychiatry, the Klingenstein Foundation, and the Phelan-McDermid Syndrome Foundation. Finally, our Clinical Program continued to thrive as we evaluated and treated children, adolescents, and adults. In 2016 we were proud to serve families from around the country and abroad, including Australia, Russia and the Middle East.

Paige Siper, PhD
Chief Psychologist

CLINICAL PROGRAM HIGHLIGHTS

- In 2016, the Assessment Program enrolled 180 individuals for participation in treatment and clinical or genetic research protocols.
- All enrolled patients continue to receive comprehensive clinical/diagnostic reports for use with treatment and educational planning, and all families participating in research are seen free of charge.
- The Clinical Program saw approximately 100 patients for evaluations and ongoing treatment in 2016. Treatments offered include psychotherapy, social skills groups, and/or medication management.

CURRENT CLINICAL STUDIES

- *Development of Behavioral and Neural Biomarkers of Autism Spectrum Disorder Using a Genetically Defined Subtype* (NIH)
- *Electrophysiological Biomarkers of Phelan-McDermid Syndrome* (Phelan-McDermid Syndrome Foundation)
- *Autism Sisters Project* (Autism Science Foundation)
- *Improving Access to Care for Minority Youth with Autism Spectrum Disorder Using a Family Peer Advocate Model* (Klingenstein Foundation)
- *Piloting Treatment of Intranasal Oxytocin in Phelan-McDermid Syndrome* (Seaver Foundation)
- *Mapping the Genotype, Phenotype, and Natural History of Individuals with FOXP-1 Mutations* (Private Donations)
- *An Employment Based Social Skills Program (JOBSS) for Adults with Autism Spectrum Disorder: A Pilot Randomized Controlled Trial* (UJA Federation of NY & Seaver Foundation)

If you are interested in participating in a clinical trial, please contact us at theseavercenter@mssm.edu or 212-241-0961.

Training Program

The Seaver Autism Center offers a robust Training Program with training opportunities across disciplines within the Seaver Center, including genetics, model systems, and clinical research.

Message from the Director of Psychology Training

This past year was very exciting for the Psychology Training Program at the Seaver Autism Center. We have been increasingly dedicated to providing a broad and diverse training experience, enhancing knowledge and skills through direct assessment, individual supervision and didactic instruction.

As in previous years, psychology trainees had opportunities to participate in ongoing research and clinical activities at the Seaver Center. Trainee responsibilities include: learning and administering research standard diagnostic instruments; conducting evaluations of cognitive, behavioral and neuropsychological functioning; assisting with social skills therapy groups; participating in weekly clinical and research meetings; and additional research activities. In addition, trainees participate in workshops on the Autism Diagnostic Observation Schedule – Second Edition (ADOS-2) and the Autism Diagnostic Interview – Revised (ADI-R) and attend didactic sessions led by local and nationally renowned clinicians working in the field.

It is extraordinary that a considerable number of Seaver faculty, including the majority of the psychologists at the Seaver Center, were previously educated and mentored as members of our Training Program. For example, 2016 was the fifth consecutive year that a former Clinical Research Coordinator returned to the Center for graduate training. Our didactic program has expanded to include trainees from other programs within the Mount Sinai Health System.

In 2016, we were pleased to welcome four new externs from three different graduate institutions. Our team remains extremely invested in training future clinicians and researchers focused on improving the lives of individuals and families affected by autism.

Danielle Halpern, PsyD
Director of Psychology Training

PSYCHOLOGY TRAINING

The Seaver Autism Center offers training opportunities for advanced psychology doctoral students interested in gaining research and clinical experience through externships, internships, and fellowships. The Center also offers training for medical students, residents, and clinical research coordinators to create a pipeline of scientists and clinicians invested in autism research and treatment.

SEAVER FELLOWSHIP PROGRAM

The Seaver Foundation supports the core programs of the Seaver Autism Center and, in addition, sponsors the Seaver Fellowship and Scholar Program. These research and clinical fellowships and scholar awards are awarded to graduate students, postdoctoral fellows, and junior faculty in various areas such as genetic analysis, development of model systems for autism, neuroimaging studies, and development and assessment of behavioral and pharmacological interventions.

With the early career support provided by the Seaver Foundation, Fellows and Scholars are well positioned to obtain further funding from foundations such as Autism Speaks, Autism Science Foundation, Phelan-McDermid Syndrome Foundation, and Simons Foundation, as well as federal funding from the National Institutes of Health.

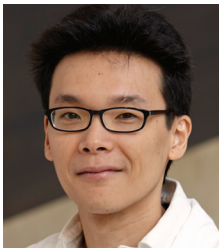
A new round of Seaver Fellows and Seaver Scholars are selected each year, and fellowships range in length from two to three years. In 2016, three postdoctoral fellows and one graduate fellow joined the Seaver Fellowship program.

SEAVER GRADUATE FELLOW

Elisa Nabel is a graduate student in the laboratory of Hirofumi Morishita, MD, PhD. As a Seaver Fellow, her work is focused on attentional circuit maturation in autism.

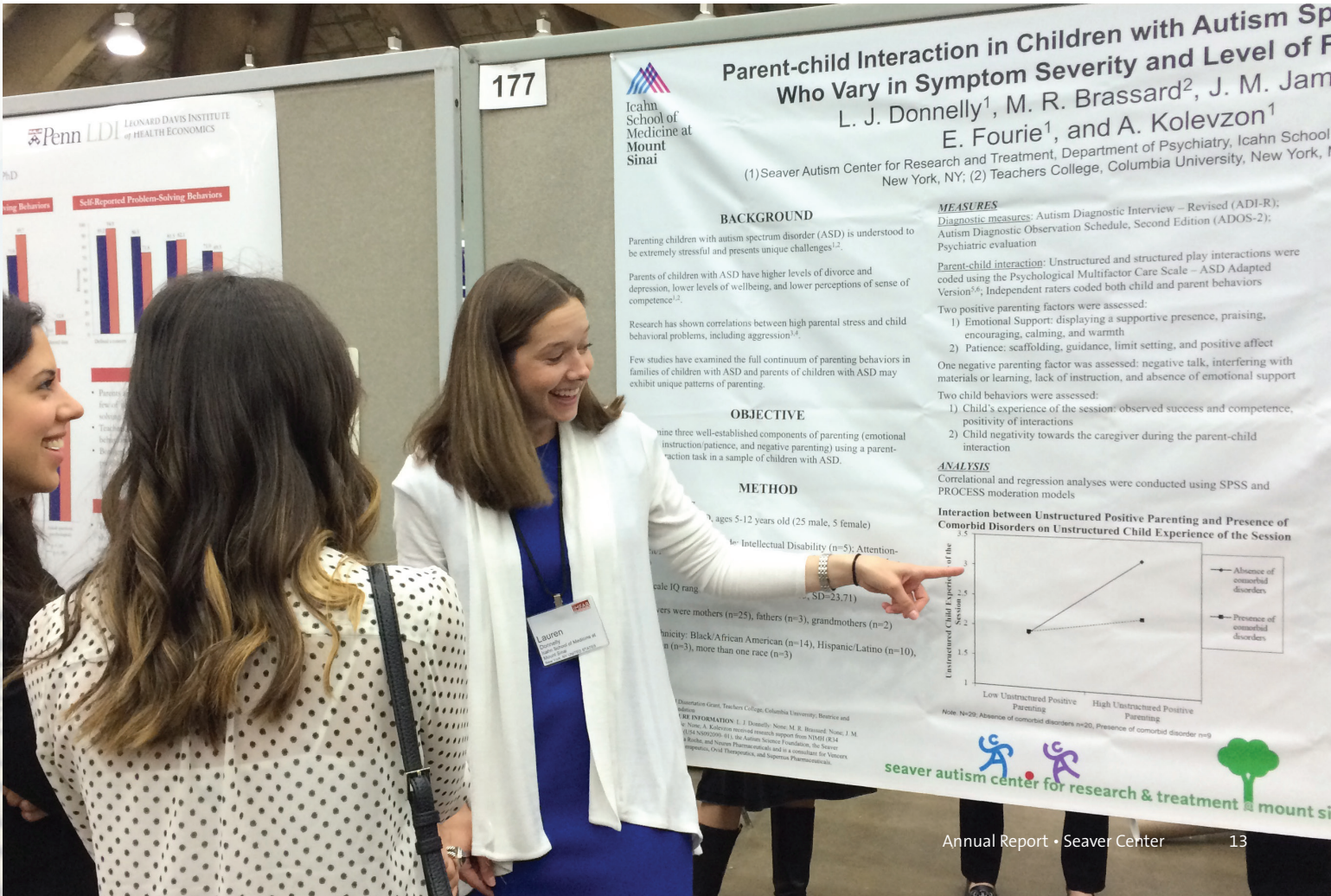
SEAVER POSTDOCTORAL FELLOWS

Magdalena Janecka, PhD, is a postdoctoral fellow in the lab of Avi Reichenberg, PhD. As a Seaver Fellow, Dr. Janecka is working with Dr. Reichenberg to study advanced paternal age and autism risk.



Yuji Kajiwara, PhD, previously a postdoctoral fellow in the lab of Dr. Buxbaum, was promoted to Instructor in the Seaver Autism Center in Spring 2016. Under the mentorship of Elodie Drapeau, PhD, and Dorothy Grice, MD, Dr. Kajiwara is examining a Slitrk1 frame-shift mutation in mice.

Drew Kiraly, MD, PhD, is a Psychiatry Resident on the Physician-Scientist track. Dr. Kiraly works in the laboratory of Eric Nestler, MD, PhD, where he has been studying the role of gut microflora on the development of cocaine addiction in a mouse model. As a Seaver Fellow, he is applying this model to study intestinal microbiota in autism-related behaviors.



Outreach Program

The Outreach Program is committed to disseminating research findings and educating patients, families and the general public on the causes and treatments of autism.

Message from the Director of Community Outreach

2016 was a year of incredible success in terms of building and maintaining community relationships. As in previous years, Seaver Center staff provided lectures to parents across the tri-state area at several community agencies and schools. Seaver Center staff also provided training to other organizations and programs regarding our work and how it can inform their practice. The Seaver Center hosted several distinguished lecturers from across the country on various topics related to autism, and hosted the 20th Annual Advances in Autism Conference, attended by scientists, clinicians, educators, and individuals with autism and their families.

The Seaver Center continues to receive support from UJA Federation of New York to help community centers develop evidence-based social skills programming for individuals with autism. This past year we collaborated with five different community centers on social skills programming for children, adolescents and young adults. In 2016, we developed a new Job Based Social Skills curriculum (JOBSS) focused on social skills needed to obtain and maintain employment. The group launched at the Manhattan Jewish Community Center in February 2016, and we have collected pilot data on the effectiveness of the curriculum and are in the process of analyzing it. We will expand the program to other community centers beginning in Spring 2017. The social skills programs at each community center continue to expand, and every year we are able to serve more children and families.

The Seaver Center continues to focus on helping cultural organizations develop more accessible programs for children and families with autism. The Museum Tour Program, developed in collaboration with the American Museum of Natural History, continues to grow. In Spring 2016, this program introduced additional tours in response to high demand from families. I have also taken on a leadership role in the Museum Access Consortium (MAC) as a member of the Steering Committee. MAC is an organization made up of parents and professionals that focuses on educating and implementing best practices for access and inclusion in cultural facilities across the tri-state area. I now also serve on the advisory board for the Long Island Children's Museum. In this position I am helping them create more accessible programs for children and teens with autism.

We are grateful for all of the support that we receive from our community partners and funding agencies. We look forward to continuing to disseminate the exciting research that is being done at the Seaver Center to the community as well as creating more opportunities for individuals with autism and their families.

Michelle Gorenstein-Holtzman, PsyD
Director of Community Outreach

20TH ANNUAL ADVANCES IN AUTISM CONFERENCE

On September 25, 2016, the Seaver Autism Center hosted the 20th Annual Advances in Autism Conference. To commemorate 20 years of sharing scientific progress, encouraging collaboration, and sparking discussion, this year's conference was held at the beautiful and historic New York Academy of Medicine. The conference had a record attendance from a diverse audience of researchers, healthcare professionals, educators, and individuals with autism and their families. The conference program included several presentations on the state of autism research and future directions in research and care.

We are celebrating the 21st Annual Advances in Autism Conference on September 20, 2017.

For more information and to register, please email annualconference@seaverautismcenter.org.

AUTISM AWARENESS MONTH

In April 2016, the Seaver Center celebrated Autism Awareness Month with the second year of the #SeaverStories social media campaign, featuring stories of families of individuals with autism, and stories of the researchers working with and for these families at the Seaver Center. The Center also hosted Jeremy Veenstra-VanderWeele, MD from Columbia University to give a Seaver Seminar talk titled "Precision Medicine versus Symptomatic Treatment in Autism Spectrum Disorder."

SOCIAL SKILLS PROGRAM

In 2016, we continued our collaborations with community agencies on social skills programming for children, adolescents, and young adults. Our new young adult curriculum focuses on employment based social skills and was piloted in 2016 at the Manhattan Jewish Community Center. Our existing social skills programs for children and adolescents continue to thrive at Westchester Jewish Community Services, Shorefront YM-YWHA of Brighton-Manhattan Beach, Edith and Carl Marks Jewish Community House of Bensonhurst, The Samuel Field Y, and the Manhattan Jewish Community Center.

MUSEUM ACCESS

The Seaver Center continues to work with organizations and institutions to create friendly spaces for individuals with autism and their families. In 2016, Michelle Gorenstein-Holtzman, PsyD was named to the Advisory Board of the Long Island Children's Museum to provide guidance on programs for individuals with autism. Dr. Gorenstein-Holtzman is also on the Steering Committee for the Museum Access Consortium. In 2013, Dr. Gorenstein-Holtzman, along with Danielle Halpern, PsyD, Director of Psychology Training, worked with the American Museum of Natural History to develop The Discovery Squad, a monthly tour program for children with autism, which was expanded in 2016 to accommodate high demand from families.

Seaver Autism Center team at the 2016 Holiday Party

Seaver Autism Center Team

Joseph D. Buxbaum, PhD, Director

Alexander Kolevzon, MD, Clinical Director

Paige M. Siper, PhD, Chief Psychologist

Michelle Gorenstein-Holtzman, PsyD, Director of Community Outreach

Danielle Halpern, PsyD, Director of Psychology Training

Lynn Hendrickson, MBA, Administrative Director

PRECLINICAL RESEARCH TEAM

Michael Breen, PhD
Andrew Browne
Silvia De Rubeis, PhD
Elodie Drapeau, PhD
Carla Golden
Hala Harony-Nicolas, PhD
Yuji Kajiwara, PhD
Drew Kiraly, MD, PhD
Lacin Koro
Elisa Nabel
Dalila Pinto, PhD
Jennifer Reichert
Mohammed Riad
Sankalp Sonar, MS
Ram Srinivasan, MS
Debbie Suarez
Xinyi (Shelly) Xu, MS

CLINICAL RESEARCH AND CLINICAL TEAM

Lauren Donnelly, PhD
Allison Durkin
Elyana Feldman
Jennifer Foss-Feig, PhD
Yitzchak Frank, MD
Emanuel Frowner
Julia George-Jones
Michelle Gorenstein-Holtzman, PsyD
Danielle Halpern, PsyD
Emily Isenstein
Kristin Meyering
Jordana Norry
Paige Siper, PhD
Pilar Trelles, MD
A. Ting Wang, PhD
Jessica Zweifach

EPIDEMIOLOGY TEAM

Avi Reichenberg, PhD
Sven Sandin, PhD
Eva Velthorst, PhD

ADMINISTRATIVE TEAM

Samantha Bright
Lynn Hendrickson, MBA
Savannah Lennertz
Ellen Paley

AWARDS AND HONORS

Seaver researchers are frequently acknowledged for their commitment to enhancing autism research and care.

NATIONAL ACADEMY OF MEDICINE INDUCTION CEREMONY.

Joseph Buxbaum, PhD, was inducted into the National Academy of Medicine at the Induction Ceremony on October 15, 2016.

Dr. Buxbaum was also awarded the Richard Todd Award at the World Congress of Psychiatric Genetics.

Silvia De Rubeis, PhD, an Instructor at the Seaver Center, was awarded the Winter Conference on Brain Research Travel Fellowship.

Carla Golden, a Graduate Student in the Seaver Center, was awarded the 2016 International Meeting for Autism Research (IMFAR) Early Career Workshop Travel Award.

Drew Kiraly, MD, PhD, a Seaver Fellow, was awarded the American College of Neuropsychopharmacology Young Investigator Memorial Travel Award.

Pilar Trelles, MD, a Seaver Clinical Fellow, was awarded the 2016 International Meeting for Autism Research (IMFAR) Diversity Award.

IN THE NEWS

The high-impact research carried out at the Seaver Autism Center is consistently recognized by national and local news outlets and even, in 2016, by a Presidential candidate.

Associated Press

The Associated Press interviewed Evee and Tom Bak, siblings who are enrolled in the Autism Sisters Project. When the Associated Press published the article with an accompanying video in October, the story was picked up by major news outlets, including CBS News, US News & World Report, and international news outlets.

Spectrum News

Spectrum News, the leading source of news and expert opinion in autism research, published an article on Dr. Hirofumi's research, in collaboration with the Seaver Autism Center, into the link between cellular deficits and social behavior in autism in mice.

CUNY Television

Dr. Buxbaum was featured on the CUNY Television show "Science and U!" in a segment on "Science and Genetics." On the show, Dr. Buxbaum discussed the Autism Sequencing Consortium and ongoing genetic research in autism.

Hillary Clinton's Plan to Support Children, Youth, and Adults Living with Autism and their Families

During the Presidential campaign, Hilary Clinton announced her initiative for children and adults with autism, which included her plan to invest heavily in research, and work specifically with the Autism Sequencing Consortium, which was founded and continues to be led by Dr. Buxbaum.

NOTABLE PUBLICATIONS

Researchers from the Seaver Autism Center published over 35 papers in 2016, including many in high impact scientific journals. A few notable publications are highlighted below.

Sensory Reactivity in Children with Phelan-McDermid Syndrome

MIESES, A. M., TAVASSOLI, T., LI, E., SOORYA, L., LURIE, S., WANG, A. T., SIPER, P.M., & KOLEVZON, A.

This study, published in *Journal of Autism and Developmental Disorders*, is the first to demonstrate differences in sensory reactivity between children with Phelan-McDermid syndrome and idiopathic autism, helping to refine the Phelan-McDermid syndrome phenotype.

Neural selectivity for communicative auditory signals in Phelan-McDermid syndrome

WANG, A. T., LIM, T., JAMISON, J., BUSH, L., SOORYA, L. V., TAVASSOLI, T., SIPER, P.M., BUXBAUM, J.D., & KOLEVZON, A.

Also published in *Journal of Neurodevelopmental Disorders*, this study found that children with Phelan-McDermid syndrome responded to communicative vocal sounds, in contrast to children with idiopathic autism, despite both groups possessing similar clinical characteristics, indicating a strength for individuals with Phelan-McDermid syndrome.

Rapid and Objective Assessment of Neural Function in Autism Spectrum Disorder Using Transient Visual Evoked Potentials

SIPER, P.M., ZEMON, V., GORDON, J., GEORGE-JONES, J., LURIE, S., ZWEIFACH, J., TAVASSOLI, T., WANG, A.T., JAMISON, J., BUXBAUM, J.D., & KOLEVZON, A.

In this paper, published in *PLOS ONE*, Seaver researchers describe a rapid electroencephalography (EEG) to successfully identify abnormalities in the brain response of individuals with autism.

Identification of novel genetic causes of Rett syndrome-like phenotypes

LOPES, F., BARBOSA, M., AMEUR, A., SOARES, G., DE SA, J., DIAS, A.I., ... PINTO, D., & MACIEL, P.

This paper, published in *Journal of Medical Genetics*, aimed to identify new genetic causes of Rett-like phenotypes. Researchers found new genes and new protein interactions that have the potential to identify genes that may case Rett syndrome.

Impaired Gas Exchange at Birth and Risk of Intellectual Disability and Autism: A Meta-analysis

MODABBERNIA, A., MOLLON, J., BOFFETTA, P., & REICHENBERG, A.

This meta-analysis of 67 studies, published in *Journal of Autism and Developmental Disorders*, found an increased risk of intellectual disability and autism in children with neonatal hypoxia.

Measuring Sensory Reactivity in Autism Spectrum Disorder: Application and Simplification of a Clinician-Administered Sensory Observation Scale

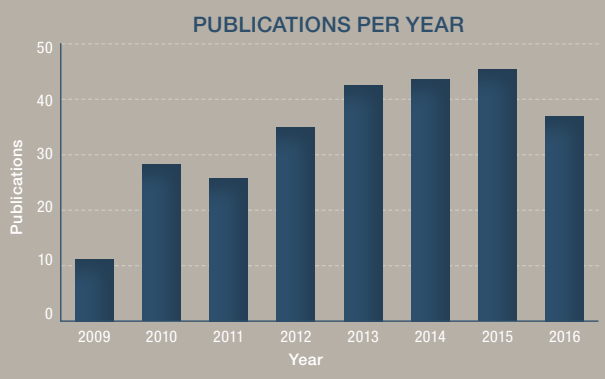
TAVASSOLI, T., BELLESHEIM, K., SIPER, P.M., WANG, A.T., HALPERN, D., GORENSTEIN, M., ... KOLEVZON, A., & BUXBAUM, J. D.

This study, published in *Journal of Autism and Developmental Disorders*, aimed to validate the Sensory Processing Scale Assessment (SPS) to measure sensory reactivity, and found that a combination of parent-report and five specific observational tasks were most effective in identifying sensory processing issues.

A spectral approach integrating functional genomic annotations for coding and noncoding variants.

IONITA-LAZA, I., MCCALLUM, K., XU, B., & BUXBAUM, J.D.

This study, published in *Nature Genetics*, reports a statistical method that Seaver researchers developed to better classify genetic differences using an artificial intelligence approach. The human genome has millions of differences across individuals, and understanding which of these differences may contribute to a disorder is incredibly challenging. This novel method is highly effective in clarifying genetic changes in order to identify those genetic differences that contribute to disease.



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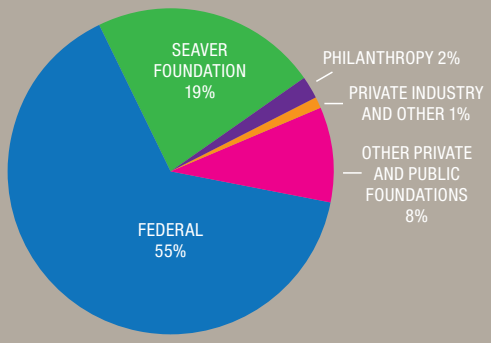

Federal Sponsors

National Institutes of Health
- National Institute on Aging
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Beatrice and Samuel A. Seaver Foundation
Human Frontier Science Program Organization
The Klingenstein Third Generation Foundation
The New York Community Trust, Edith and Jules Klein Fund
Phelan-McDermid Syndrome Foundation
Simons Foundation Autism Research Initiative
UJA-Federation

THANK YOU

Our research is directed by the need to provide better care and service for families affected by autism. Our commitment to research is driven by our compassion and dedication to patient care, as well as to advance the field of autism research. The Seaver Autism Center is a major player in this field at every stage, from laboratory and clinical research, to training and outreach in the community. As a result, the Center is at the forefront of translating research findings into improved community care. Moving forward, we will continue to identify the causes of autism and advance effective treatments in order to reduce disability and improve the lives of families affected by autism.

We would like to give special thanks to the Beatrice and Samuel A. Seaver Foundation. Since the founding of the Seaver Autism Center, the Seaver Foundation has been committed to the philanthropic and strategic support of the Seaver Autism Center.

Hirschell E. Levine, Esq., *Co-Trustee*
John D. Cohen, Esq., *Co-Trustee*
Deanna Levine
Ann Cohen
Stephanie and Richard Goldman
Myles McGinley
Jamie and Marc Roitman
Stephanie Rosenblum
Terri and Marc Rosenblum

We would also like to thank the Seaver Center Associates Committee for their generous support.

Alison Singer, *Chair*
Marilyn and Jerry Blaine
Morgan and Brett Drexelius
Carol and Harvey Eisenberg
The Greenfeld Family
Inna and Joshua Needelman
Alison von Klemperer

The Associates Committee is a group of committed stakeholders that drive the Center's scientific mission forward. Members of the Committee commit to an annual charitable pledge. If you are interested in learning more about the Associates Committee, please contact Savannah Lennertz at savannah.lennertz@mssm.edu or 212-249-0349.

Mount Sinai

Seaver Autism Center for Research and Treatment

The Seaver Autism Center relies on the generosity of our supporters to advance autism research and care.

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seaver autism center for research & treatment @ mount sinai

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theseavercenter@mssm.edu | 212-241-0961

If you would like to learn more about research being conducted at the Seaver Autism Center, please visit us online at **www.seaverautismcenter.org.**

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