seaver autism center
for Research & Treatment at Mount Sinai

Mount Sinai

Seaver Autism Center for Research and Treatment

ANNUAL REPORT

2015

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).

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.

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Cover art by Jessica S. Johnson, MFA

Seaver Autism Center Leadership

Message from the Director

In 2015, the Seaver Center continued its groundbreaking work on the causes and treatment of autism spectrum disorder (ASD). Researchers have made more etiological discoveries and we continue to have a significant impact on the translation of scientific discoveries into patient treatment. The work on genotyping and phenotyping patients with a SHANK3 mutation and Phelan-McDermid syndrome, and in a clinical trial of insulin-like growth factor-1 in children with Phelan-McDermid syndrome, has been significant. We continue to publish in the highest-level journals, with over 45 publications in 2015 and 120 within the past three years. In addition, we have made over 50 presentations to families and experts in the past year to share our knowledge and to receive feedback from families and from other experts.

In the spring, we hosted the second annual event of the Seaver Autism Center Associates Committee. This event was a "Listening Night," the first of its kind for the Seaver Autism Center, and it was unique in that it involved the attendees providing their perspectives on the field of autism; and instead of presenting, the scientific researchers listened. Seaver Center leadership had the important opportunity to see through the eyes of parents and other relatives of people with autism, and to gain a new perspective, and participants enjoyed and appreciated this opportunity.

We are committed to inclusivity of the most severely affected individuals, and individuals in underrepresented groups. To that end, we have developed the Sensory Assessment for Neurodevelopmental Disorders (SAND), a novel and objective clinician-administered observation and corresponding caregiver interview that captures sensory reactivity symptoms. This assessment is appropriate across a wide range of functioning levels, including with children who are minimally verbal. In addition, we are partnering with YAI to assess the Family Peer Advocate model in families of Hispanic or African-American descent. To date we have seen 42 families. Lastly, we have hired two Spanish-speaking faculty in the past year so we can continue our important work in underserved populations.

Last year the Seaver Center received additional support from the National Institutes of Health (NIH) for both the Autism Sequencing Consortium (ASC) and the Population-Based Autism Genetics & Environment Study (PAGES). Through the Mount Sinai Transdisciplinary Center on Early Environmental Exposures Pilot Projects, Avi Reichenberg, PhD, and his group are moving in a new direction around organic pollutants and risk for autism. We have also received important support from the Human Frontier Science Program to study brain oxytocin circuits that affect social behavior.

The Center's Outreach Program program hosted several lectures on-site for families and researchers in the past year, including community lectures, the Seaver Seminar Series, the Distinguished Lecturer Series, and the Annual Advances in Autism Conference. This year we are celebrating the 20th Anniversary of this Conference.

The Training Program encompasses trainees at all levels, including junior faculty fellows, interns and externs, postdoctoral fellows, graduate students, residents, and medical students. We welcomed multiple new Seaver Fellows this past summer, including two in the newly created Seaver Clinical Fellowships. The Clinical Fellows are Pilar Trelles, MD, a child psychiatrist, and Lauren Donnelly, PhD, a psychologist. These Fellows are receiving training on ASD treatment and evaluation, which will be conducted as part of various research studies within the Seaver Center. They will gain exposure to all aspects of autism diagnosis and treatment, and they will contribute to ongoing research studies.

In addition to Drs. Trelles and Donnelly, last year we also recruited Sven Sandin, PhD, and Reymundo Lozano, MD, as additional faculty in the Center. For more information, see the Training Program section.

We are very excited to be celebrating the 20th year of the Annual Advances in Autism Conference and the 23rd year of the Seaver Autism Center. This is a critical time in preclinical and clinical research in ASD and we welcome your feedback and support.

Joseph D. Buxbaum, PhD
Director

Message from the Clinical Director

This past year has seen enormous growth in the Clinical Research Program at the Seaver Autism Center. We were thrilled to promote Paige Siper, PhD, to the role of Chief Psychologist. We remain extremely committed to an interdisciplinary approach and have recruited two new clinical fellows, Lauren Donnelly, PhD, a psychologist, and Pilar Trelles, MD, a child and adolescent psychiatrist. In addition, Reymundo Lozano, MD, a pediatrician and clinical geneticist, has joined our effort, and together we look forward to many exciting opportunities to better understanding the neurobiology and treatment of ASD.

In 2015, our group was hard at work collecting data for several important federally funded studies, including the Rare Disease Clinical Research Network Developmental Synaptopathies Consortium where we are leading efforts to study the phenotype and natural history of Phelan-McDermid syndrome and testing the first novel therapeutic, insulin-like growth factor-1 (IGF-1), in this syndrome in the United States. We have also been actively recruiting for the National Autism Center of Excellence Network Study of Oxytocin in Autism to improve Reciprocal Social Behaviors (SOARS-B). When SOARS-B is complete, we will be able to determine whether oxytocin is effective in ASD, and how to identify which children and adolescents are most likely to benefit.

Another major area of focus in 2015 was the development of novel and objective clinical outcome measures in ASD and single gene forms of ASD in order to refine the phenotype and explore possible biological markers for use in clinical trials. Dr. Siper's work with visual evoked potentials has been extremely promising and, along with Teresa Tavassoli, PhD, she has developed an objective Sensory Assessment for Neurodevelopmental Disorders (SAND). Ting Wang, PhD, recently published exciting results from her functional neuroimaging work in Phelan-McDermid syndrome where she found evidence that despite severe language impairments, children with Phelan-McDermid syndrome showed selective and preferential activation in language and social cognition centers of the brain in response to communicative sounds, as compared to children with idiopathic ASD. This is an exciting finding and has sparked additional work exploring specific language interventions for these children that we intend to study.

The past year has been filled with success and challenge, and our team remains extremely invested in developing new treatments and improving the lives of people and families affected by ASD. As always, we are extremely grateful to all the families who participate in our studies, to the Seaver Foundation, and to all the organizations who sponsor our work.

Alexander Kolevzon, MD
Clinical Director

Joseph D. Buxbaum, PhD

Alex Kolevzon, MD

2015 Awards and Honors

Joseph D. Buxbaum, PhD, elected to the National Academy of Medicine.

Alex Kolevzon, MD, promoted to full Professor of Psychiatry and Pediatrics.

Paige Siper, PhD, promoted to Chief Psychologist of the Seaver Autism Center.

Paige M. Siper, PhD

Research Program

The Seaver Autism Center continues to grow as an integrated preclinical and clinical center for ASD. With more than 45 publications in the past year and 120 within the past three years, the Seaver Center conducts and publishes research at the forefront of the field in high-level journals, including *Nature, Nature Genetics, The Journal of the American Medical Association, Proceedings of the National Academy of Sciences USA,* the *American Journal of Human Genetics, PLoS Genetics,* and *Molecular Autism.*

An Integrated Genetics – First Approach

Here at the Seaver Autism Center we take advantage of a "genetics-first" approach to tackle the complex biology of ASD.

This approach starts with identifying autism genes: we run comprehensive genetic analyses of thousands of individuals with autism and healthy controls to identify the risk factors rooted in our genome. We enroll families with a child with autism from all over the world, including families seen at the Seaver Center, in genetic research protocols. We then collect the DNA from the family members and analyze it with a method called exome sequencing.

Exome sequencing is a technology that decodes the most meaningful fraction of the DNA of an individual, the exome. The human genome includes about 22,000 protein-coding genes. Each gene contains exons,

functional units that translate the genetic information encrypted in each gene into a protein with specific functions in the cell. The entire gene repertoire of an individual is called the genome, and the collection of all exons is called the exome. Although the exome represents only 2% of the entire genome, it contains the vast majority of the most relevant genetic information. Exome sequencing focuses on that region of our DNA that is most likely the source of genetic risk for disease.

The data obtained with exome sequencing is then used to identify rare and deleterious mutations and thus define genes that, if mutated, increase the risk of developing ASD. 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.

Over the longer term, the identification of ASD risk genes will unveil the biological processes disrupted in autism, and will lead to the design of novel therapeutic approaches in autism. At the Seaver Center, we aim to translate genetic discoveries into novel therapeutics. We use the genetic information to build cell and animal models that can recapitulate the disease. We then study these models to understand the consequences of the gene mutations on biological processes that are relevant for the development of the brain and its correct functioning. Once validated, the models are used to test drugs for therapeutic intervention.

The genetic findings are used to group patients that share mutations in the same gene or related genes. Patients are re-contacted for a more in-depth clinical characterization that can expose shared clinical manifestations within a group. This has great repercussions on refined diagnosis, individualized patient care and therapeutics. In addition, we take what we learn from model systems to design novel treatments for the patients with similar genetic changes. We have applied this approach to children with Phelan-McDermid syndrome, including two ongoing clinical trials of novel therapeutics, and we are now extending it to patients with mutations in newly discovered genes.

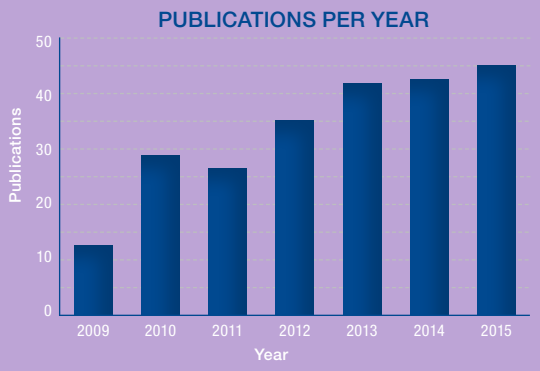
Phelan-McDermid Syndrome

Phelan-McDermid syndrome is a rare genetic disorder in which one copy of the SHANK3 gene at the end of chromosome 22 is either missing or otherwise mutated. The SHANK3 gene is key to the development of the human nervous system, and loss of SHANK3 can impair nerve cell development, function and communication.

Though symptoms can vary, Phelan-McDermid syndrome is typically characterized by low muscle tone, absent or delayed speech, intellectual disability, and minor facial or body abnormalities. Phelan-McDermid syndrome can lead to behavioral symptoms that are associated with ASD. In fact, SHANK3 deletions or mutations are estimated to occur in 1-2% of patients with ASD.

It is unknown exactly how many children are born with this condition. Current estimates indicate that more than 1,000 individuals around the world have the disorder, but studies suggest that many, many cases may go undiagnosed.

One goal of the program at the Seaver Autism Center is to investigate the role of the SHANK3 gene in autism and associated conditions and in Phelan-McDermid syndrome and to determine how best to treat these conditions. The Seaver Center, one of the leading comprehensive care centers treating ASD in the country, has recently expanded its research-based clinical program to address these types of issues.



New Grant Highlights

The Autism Sequencing Consortium: Autism gene discovery in >20,000 exomes (Supplemental Funding)

SPONSOR: NATIONAL INSTITUTE OF MENTAL HEALTH

Founded in 2010 by Joseph D. Buxbaum, PhD, Director of the Seaver Autism Center, the Autism Sequencing Consortium (ASC) is an international group of scientists who share ASD samples and genetic data. All shared data and analysis is hosted at the Icahn School of Medicine at Mount Sinai on a supercomputer designed by Mount Sinai faculty, which enables joint analysis of large-scale data from many groups. The ASC is supported by a cooperative agreement grant to four lead sites funded by the National Institute of Mental Health (NIMH), with additional support from the National Human Genome Research Institute. The ASC recently received supplemental funding from the NIMH for targeted resequencing of genes implicated in ASD.

Population-Based Autism Genetics & Environment Study (Supplemental Funding)

SPONSOR: NATIONAL INSTITUTE OF MENTAL HEALTH

Led by Dr. Buxbaum, this study is a multi-site collaboration involving researchers at the Icahn School of Medicine at Mount Sinai, the University of Pittsburgh School of Medicine, Carnegie Mellon University, the Broad Institute, and Karolinska Institutet. The study uses a population-based epidemiological sample with detailed demographic and environmental information to assess the role of inherited and *de novo* genetic variants in autism. The researchers also evaluate rare standing variation in autism, while integrating key environmental variables. This award is in addition to the original funding received to support this study, and the supplemental funding serves the purpose of increasing the sample size.

Deciphering Brain Oxytocin Circuits Controlling Social Behavior

SPONSOR: INTERNATIONAL HUMAN FRONTIER SCIENCE PROGRAM ORGANIZATION

This award is a collaboration across multiple institutions making use of a Shank3-deficient rat model developed and characterized at the Seaver Autism Center by Joseph D. Buxbaum, PhD, and Hala Harony-Nicolas, PhD. The other participating sites are the Max Planck Institute for Medical Research, the University of Haifa, the University of Heidelberg, and Paris Descartes University. This project aims to decode the oxytocin circuits in the brain that control social behavior. The study uses a comprehensive multidisciplinary approach aiming to identify, analyze, and mathematically model specific populations of nerve cells in the brain, which are differentially activated during various forms of behavior. Specifically, it will study the subpopulations of oxytocinergic cells that produce and secrete the oxytocin hormone, which has been implicated in social behavior.

Developing Scalable Measures of Behavior Change for ASD Treatments

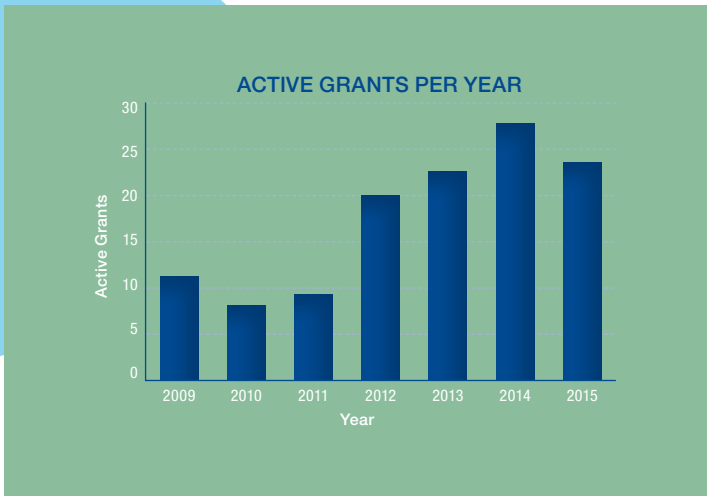
SPONSOR: SIMONS FOUNDATION AUTISM RESEARCH INITIATIVE

This study is a collaboration across four university-based centers in New York City, led by the Center for Autism and the Developing Brain (CADB) at Weill Cornell Medical College. In addition to the Seaver Autism Center at Mount Sinai, the other sites are New York University and Albert Einstein College of Medicine. Led by Dr. Kolevzon at the Mount Sinai site, the purpose of this study is to determine the sensitivity of a new instrument, the Brief Observation of Social Communication-Change (BOSCC), in measuring change in social-communication behaviors in verbally fluent children with ASD.

Integrating Large Scale Whole Exome Data with Whole Genome Data

SPONSOR: SIMONS FOUNDATION AUTISM RESEARCH INITIATIVE

This study is a collaboration between investigators at the Seaver Autism Center, the Broad Institute of MIT and Harvard, and the University of Chicago. The project aims to take advantage of the 22,000 exomes analyzed by the ASC and the ~4,000 genomes being generated by the Simons Foundation to expand the list of genes and types of genetic variation implicated in autism. At the completion of this study, there will be algorithms for identifying genetic changes at all levels in genomic data and integrating all such results into a statistical framework to reliably identify autism genes. In addition, there will be a much more detailed list of genes and genetic variation that are implicated in autism. These enhanced gene lists will allow the development of model systems and novel therapeutics.



Genetics

Within the past year, Seaver Center investigators completed four major research studies on genetic and other causes of ASD and associated syndromes, and the papers resulting from these studies represent the state-of-the-art in autism genetics for the foreseeable future.

- The first paper, titled "Insights into Autism Spectrum Disorder Genomic Architecture and Biology from 71 Risk Loci," published in *Neuron* in September 2015, is the second major genetic analysis including the Autism Sequencing Consortium (ASC), an international collaboration between over 40 research teams and co-led by Dr. Buxbaum. The ASC identified genetic mutations in over 20,000 individuals. By integrating smaller mutations with deletions and duplications, the study has identified or confirmed 65 autism risk genes and six regions in the genome that are prone to deletions and duplications in individuals with ASD.
- The second paper, titled "A spectral approach integrating functional genomic annotations for coding and noncoding variants," published in *Nature Genetics* in February 2016, stems from collaboration with Iuliana Ionita-Laza, PhD, Associate Professor at the Department of Biostatistics, Columbia University. In the study, Drs. Ionita-Laza and Buxbaum developed and validated a method to estimate the severity of human mutations. The method was successfully applied to the sequencing data from individuals diagnosed with autism, and will improve our ability to discern between genetic changes that are benign and mutations conferring risk to autism.
- The third paper, titled "Autism risk associated with parental age and with increasing difference in age between the parents," was published in *Molecular Psychiatry* in June 2015. Sven Sandin, PhD, Assistant Professor of Psychiatry, and Avi Reichenberg, PhD, Professor of Psychiatry and Preventive Medicine, led the work. The study addresses the relationship between advancing paternal and maternal ages on the risk of developing autism. By studying more than 30,000 individuals diagnosed with ASD in five countries (Denmark, Israel, Norway, Sweden and Western Australia), the study shows that increased risk for autism is associated not only with advancing paternal or maternal age alone, but also with differences in parental age.
- The fourth paper, titled "Identification of novel genetic causes of Rett syndrome-like phenotypes," came out of a collaboration between Dalila Pinto, PhD, Assistant Professor of Psychiatry and Genetics and Genomic Sciences, Mafalda Barbosa, MD, Graduate Student at Mount Sinai, and Patricia Maciel, PhD, Associate Professor at the University of Minho, Portugal. The work was published in the *Journal of Medical Genetics* in March 2016. The study investigates the genetic makeup of individuals that show clinical manifestations similar to Rett syndrome but are negative to genetic testing for this syndrome. The study has identified novel candidate genes for cases with a Rett-like phenotype.

Cell and Animal Model Systems

Rodent Models

At the Seaver Center, researchers are characterizing mouse and rat models with mutations in several ASD risk genes, including *SHANK3, FMR1, MECP2,* and *CYFIP1*. 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 IGF-1 ameliorates some synaptic plasticity and motor deficits. These findings led to ongoing clinical trials testing the effects of IGF-1 in individuals carrying mutations in *SHANK3*.

Our most recent efforts have been focused on rat models for ASD. Compared to mice, rats have specific advantages for research, such as a more complex and humanlike neural circuitry and behavioral repertoire. Use of these models will help lead to a better understanding of the deficits in brain areas relevant to ASD and the development of new therapeutic approaches. Seaver Center researchers are characterizing a rat model carrying a mutation in *SHANK3*. 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. Using this model, we discovered that treatment with the pro-social hormone, oxytocin, ameliorates the synaptic plasticity and social deficits exhibited in this model. These findings indicate that oxytocin may have therapeutic potential for multiple deficits in Phelan-McDermid syndrome and support our clinical trials with oxytocin in individuals with this 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 ASD 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 ASD medicines, as stem cells can be expanded extensively for such experiments. To date, we have collected over 300 samples from over 90 families for stem cell research.

Clinical Research

In 2015, researchers at the Seaver Autism Center recruited for six clinical trials studying five different pharmacological compounds. The trials included children, adolescents, and adults with ASD, Fragile X syndrome (FXS), and Phelan-McDermid syndrome. Researchers also developed a collaboration with Neuren Pharmaceuticals to study the effect of an IGF-1 derivative in Fragile X syndrome. In addition, we enrolled 23 participants in our largest clinical trial, the "Study of Oxytocin in Autism to improve Reciprocal Social Behaviors."

Results from a groundbreaking pilot trial of IGF-1 in children with Phelan-McDermid syndrome indicated both safety and efficacy on the primary outcome measure. Ten additional patients were enrolled in the second phase of this trial, the first ever treatment study for Phelan-McDermid syndrome. In addition, we are also studying the effects of IGF-1 in ASD more broadly.

New Collaborations

Developing Scalable Measures of Behavior Change for ASD Treatments (Simons Foundation): Developed by Catherine Lord, PhD, the goal of this study is to examine the sensitivity of a new instrument (the BOSCC) in measuring change in social-communication behaviors in verbally fluent children with ASD.

Genetics of Conotruncal Defects and Associated Neurodevelopmental Outcomes (National Heart, Lung, and Blood Institute): This study in congenital heart disease study, led by Bruce Gelb, MD, aims to discover new genes causing tetralogy of fallot and to determine whether these genes impact adverse neurodevelopmental and neuropsychological outcomes as compared to idiopathic cases.

EVALUATIONS COMPLETED BY THE ASSESSMENT PROGRAM

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 ASD, yet which 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 teeth, and one assessing exposure to persistent organic pollutants and risk for ASD. In addition, using the International Collaboration for Autism Registry Epidemiology (ICARE), we are leading projects examining the association between planned vs. emergency cesarean section and risk for ASD, and the relationship between Apgar score at birth and risk for ASD.

Assessment and Clinical Programs

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

In 2015, 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 included approximately 100 active patients in 2015, receiving comprehensive evaluations, psychotherapy, social skills group training, and/or medication management.

Sensory Assessment for Neurodevelopmental Disorders

The Sensory Assessment for Neurodevelopmental Disorders (SAND), developed by Seaver Autism Center researchers, is a novel and objective clinician-administered observation and corresponding caregiver interview that captures sensory reactivity symptoms, as per the new DSM-5 criteria for ASD (e.g., hyperreactivity, hyporeactivity, sensation seeking). The SAND is easy to administer and is appropriate across a wide range of functioning levels. The SAND represents an important new tool for both research and clinical purposes since it helps to identify subtypes of ASD, has the potential to meaningfully enhance the gold-standard assessment of ASD, and can act as a marker and measure for treatment effectiveness.

The SAND was developed over the past two years, and our initial validation studies were completed in early 2015. The results indicate that the SAND effectively differentiates between different types of sensory symptoms (hyporeactivity, hyperreactivity, sensation seeking) across three sensory domains (vision, hearing and touch) in children with ASD. Our results demonstrate feasibility of the SAND in a sample inclusive of minimally verbal children with ASD. Our current SAND studies are examining sensory reactivity in genetically defined ASD subtypes and in other neurodevelopmental disorders.

Improving Access to Care in Minority Youth with ASD using a Family Peer Advocate Model

There are significant racial and ethnic disparities in access to quality mental health care for individuals with ASD. Ethnic minorities with ASD receive diagnoses later and are significantly more likely to be misdiagnosed. There is an urgent need to design interventions that will help families in minority groups to gain access to existing services. Family Peer Advocates (FPAs) are used across healthcare to facilitate engagement in treatment. FPAs have personal experience caring for a child with special needs, and serve as role models to instill hope, encourage partnership with providers, and empower families to address their needs.

By partnering with YAI, a large community agency, we were able to work with 42 families of Hispanic or African-American descent with a child affected by ASD. These families were brought in over the course of 16 months. We found that caregiver contact with an FPA significantly reduced parental stress. As caregiver strain was associated with disruptive behaviors in the child we predict that the FPA approach will improve functional outcomes in the child.

Building on our findings, we aim to expand our project by bringing additional families in and measuring the impact of FPA contact with caregivers on functional outcomes in the child, treatment utilization and satisfaction. Our hypothesis is that focused contact with an FPA will reduce caregiver strain, improve functional outcomes in the child, and improve quality of life in affected families by increasing treatment utilization, normalizing distress, and promoting positive parent-child interactions.

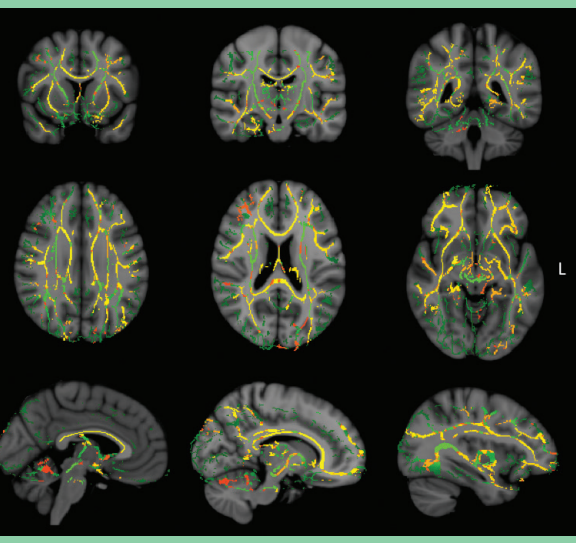
Message from the Chief Psychologist

Over the past year the Clinical and Assessment Programs at the Seaver Autism Center have remained at the forefront of the development and implementation of novel assessment tools and evidenced-based treatments. In 2015, we continued to grow our portfolio of clinical research studies with the addition of several large-scale multi-site studies and an emphasis on the inclusion of children, adolescents, adults, and family members in our research. Developing early investigators remained a priority and, with the support of the Seaver Foundation, the Seaver Clinical Fellows Program was established. Fellowships were awarded to a psychologist and a child and adolescent psychiatrist and are focused on in-depth training in neurodevelopmental disorders. Our Clinical Program continued to offer a variety of assessment and treatment services to families within the community. We apply our research findings to our clinical practices in an effort to provide all families with up-to-date assessments and empirically-grounded interventions. Our goal remains to provide all Seaver families with cutting-edge evaluations while providing unparalleled care.

Paige Siper, PhD
Chief Psychologist

Neuroimaging Program

The Neuroimaging Program uses multiple imaging techniques to better understand the neural underpinnings of ASD.



Functional magnetic resonance imaging (fMRI) is a technique used to measure brain activity. Active areas of the brain use more energy and need a greater supply of oxygen and glucose. To meet this increased demand, more blood flows to the active areas. fMRI is sensitive to changes in the oxygen content of the blood and can be used to produce activation maps showing which parts of the brain are involved in a given task.

Diffusion tensor imaging (DTI) is a method used to examine the structure and integrity of nerve fibers in the brain. DTI measures the diffusion of water molecules and takes advantage of the fact that diffusion is less restricted along nerve fiber bundles than in other directions, and therefore, can be used to detect the direction of nerve fiber tracts in the brain.

Neuroimaging in Phelan-McDermid Syndrome

Impairments in language and communication are among the most common features of both Phelan-McDermid syndrome and idiopathic autism. Using functional MRI (fMRI) in minimally verbal children with Phelan-McDermid syndrome and autism, we found that specialized brain networks for detecting communicative sounds were preserved in children with Phelan-McDermid syndrome, but not in children with idiopathic autism. In the Phelan-McDermid syndrome group, greater activity in specialized "social brain" regions was associated with better social orienting skills measured outside the scanner. These findings were published in the *Journal of Neurodevelopmental Disorders* in February 2016.

Diffusion tensor imaging (DTI) allows us to examine the white matter architecture of the brain. Using DTI, we found widespread abnormalities in white matter connectivity in children with Phelan-McDermid syndrome compared to children with idiopathic autism. This finding is striking since individuals with autism show impaired white matter structural connectivity relative to those with typical development.

Taken together, these initial studies suggest that despite shared symptoms, Phelan-McDermid syndrome and idiopathic autism may have distinct brain profiles that reflect different causes and contribute to the wide diversity observed in people with ASD.

In addition to examining structural connectivity with DTI and functional activity using task-based fMRI, we study functional connectivity using resting state fMRI. Resting fMRI examines the intrinsic functional organization of the brain and allows us to probe multiple networks without placing task demands on minimally verbal participants.

Using multiple neuroimaging techniques, we aim to comprehensively define the brain phenotype of Phelan-McDermid syndrome, which is important for developing novel treatments and identifying biomarkers for diagnosis and treatment response. Examining the common and distinct neural underpinnings of behavioral features shared between rare genetic disorders such as Phelan-McDermid syndrome and idiopathic autism has the potential to yield important insights into the diversity of ASD broadly.

Effects of Oxytocin Treatment on the Brain in ASD

A pilot study funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development takes advantage of the infrastructure provided by SOARS-B and uses fMRI to examine the impact of oxytocin treatment on "social brain" activity in children with ASD. This project uses established tasks, tapping known functional deficits to probe how oxytocin influences social behavior and whether brain activity can predict social improvement.

Training Program

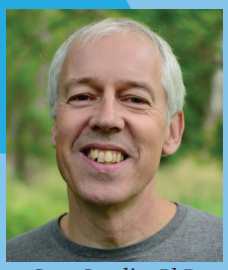
The Seaver Autism Center offers a very robust Training Program. The training opportunities available span across all programs within the Seaver Center, including genetics, model systems, and clinical research. Seaver trainees work closely with mentors, and they are encouraged to take leadership roles in projects.

Seaver Fellowship Program

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

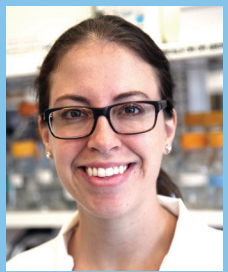
With the early career support provided by the Seaver Foundation, fellows and scholars are well-positioned to obtain further funding from foundations such as Autism Speaks, Autism Science Foundation, Phelan-McDermid Syndrome Foundation, and Simons Foundation, and federal funding from the National Institutes 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 2015, six fellows and scholars joined the Seaver Fellowship program, the most yet to join in a single year.



Sven Sandin, PhD

Reymundo Lozano, MD



Molly Heyer, PhD

Seaver Faculty Scholars

In 2015, we were joined by two new Seaver Faculty Scholars: Sven Sandin, PhD and Reymundo Lozano, MD.

Dr. Sandin, a statistician and epidemiologist, works closely with Avi Reichenberg, PhD, where he focuses on epidemiological risk for autism and other neurodevelopmental disorders, as well as clinical trials management and analysis. Dr. Sandin was a previous collaborator on two multi-site grants, and he has now joined the team.

Dr. Lozano is a pediatrician and clinical geneticist who is developing a research program focused on genetic findings in ASD while carrying out clinical genetic assessments as part of the Seaver Autism Center assessment and clinical team.

Seaver Postdoctoral Fellows

Molly Heyer, PhD, also joined the Seaver Fellowship Program in 2015. Dr. Heyer's research aims to uncover the role of miRNAs in psychiatric disorders by studying autism and schizophrenia-related behaviors in mice containing mutations of miRNAs previously associated with these disorders. She works in the laboratory of Paul Kenny, PhD, in the Department of Pharmacology and Systems Therapeutics.

Seaver Clinical Fellows

In addition to our traditional research fellowships, we also added a new category of fellowships in 2015: the Seaver Clinical Fellows. These fellowships are an opportunity for clinicians to be funded to work within the Seaver Autism Center assessment and clinical team, gain exposure to all aspects of autism diagnosis, treatment, and evaluation, and contribute to ongoing research studies.

Two fellows were selected in the inaugural year: Pilar Trelles, MD, a child psychiatrist, and Lauren Donnelly, PhD, a psychologist.

Pilar Trelles, MD

Dr. Trelles was previously a Child and Adolescent Psychiatry Fellow at Mount Sinai St. Luke's Hospital, and she served as Chief Resident from 2014-2015. Dr. Trelles is focusing on addressing the significant racial and ethnic disparities in access to quality mental health care for individuals with ASD.

Dr. Donnelly's clinical internship at the University of North Carolina School of Medicine focused on work with children and their families at the UNC TEACCH Program. She previously worked as a research coordinator and clinical extern at the Seaver Autism Center. She returned to Mount Sinai to focus on the assessment and treatment of children with ASD through group and individual treatments.

Lauren Donnelly, PhD

Seaver Graduate Fellows

The new Seaver Graduate Fellow for 2015 was Andrew Browne. Mr. Browne currently works in the laboratory of Joseph Buxbaum, PhD, on induced pluripotent stem cells, and as a fellow he will continue his work to systematically identify drugs for patients with Phelan-McDermid syndrome.

Andrew Browne

The Seaver Fellowship Program enhances all areas of research at the Seaver Autism Center, and many fellows and scholars remain at the Center after their fellowships end. We are grateful to the Seaver Foundation for this ongoing support and contribution to the research and treatment of ASD.

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. 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 from local and nationally known clinicians working in the field.

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 both through direct assessment 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 gold-standard research diagnostic instruments (e.g., ADI-R, ADOS-2); conducting baseline evaluations of cognitive, behavioral and neuropsychological functioning; assisting with social skills therapy groups; participating in weekly clinical and research meetings; and additional research activities.

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, 2015 was the fourth consecutive year that a former Clinical Research Coordinator returned to the Center for graduate training. In addition, in 2015 our didactic program grew to include trainees from other programs within our expanded hospital system.

In 2016, we are 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 people and families affected by ASD.

Danielle Halpern, PsyD
Director of Psychology Training

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 ASD.

Message from the Director of Community Outreach

This past year has been a very exciting period for the Outreach Program at the Seaver Autism Center. In 2015, we continued to focus on disseminating research and best practices to the community.

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 also hosted several distinguished lecturers from across the country on various topics related to ASD.

The Seaver Center continues to receive support from the UJA Federation of New York to help community centers develop more evidence-based social skills programming for individuals with ASD. This past year we collaborated with five different community centers on social skills programming for individuals ages 4-21. In 2015, we also 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 are collecting data on the effectiveness of the curriculum and hope to expand the program to other community centers over time. The social skills programs at each community center continue to expand, and every year we are able to serve more children and families.

Over recent years the Seaver Center has also become involved in helping cultural organizations develop programs for children and families with ASD. The Museum Tour Program, developed in collaboration with the American Museum of Natural History, continues to grow. In spring 2016, the Discovery Squad launched a third tour for children and families with ASD. 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.

2015 was a year of incredible success in terms of building and maintaining community relationships. 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.

Michelle Gorenstein-Holtzman, PsyD
Director of Community Outreach

19th Annual Advances in Autism Conference

On October 25, 2015, the Seaver Autism Center hosted the 19th Annual Advances in Autism Conference. The mixed audience of researchers, healthcare professionals, educators, and family members enjoyed the opportunity to learn about the latest findings in autism research. As in past years, the conference program included several scientific presenters, as well as multiple family members of people with autism.

This past year's conference was a rewarding experience for attendees and presenters alike. This continues to be an important event that offers a unique experience for scientists and family members to be in the same space to receive an update on current research and discuss issues in the field.

In 2016, we are celebrating the 20th Annual Advances in Autism Conference. To learn more, please visit www.seaverautismcenter.org.

19th Annual Advances in Autism Conference Speakers

Social Skills Program

In 2015, we collaborated with five different community agencies on social skills programming for children and adolescents ages 4-21.

Distinguished Lecturer Series

Helen Tager-Flusberg, PhD, Professor of Psychological & Brain Sciences at Boston University, and Professor of Anatomy & Neurobiology and Pediatrics at Boston University School of Medicine, visited the Seaver Autism Center as part of the Distinguished Lecturer Series, which features a renowned ASD researcher from an outside institution and is aimed at educating both professionals and caregivers. It is a two-day event in which the speaker gives one presentation geared towards professionals, and one geared towards parents, families, advocates, and the public.

Drs. Joseph Buxbaum, Helen Tager-Flusberg, and Alex Kolevzon

Seaver Autism Center Associates Committee "Listening Night"

Last spring the Seaver Autism Center hosted its first ever "Listening Night" for the members of the Seaver Autism Center Associates Committee. The format for the evening involved the attendees providing their perspectives as family members, caregivers, and advocates. Instead of presenting, the scientific researchers spent the evening listening. Seaver Center leadership had the important opportunity to see through the eyes of parents and other relatives of people with autism, and to gain a new perspective. Participants enjoyed and appreciated this opportunity as well.

The Associates Committee is a group of dedicated stakeholders: parents, grandparents, siblings, and others, who want to learn more and do more to support their loved ones with autism and to support the work being done at the Seaver Center. If you are interested in learning more, please contact Jessica Brownfeld (jessica.brownfeld@mssm.edu or 212-241-0349).

Autism Awareness Month

In April 2015, the Seaver Center began several new initiatives for Autism Awareness Month, including the #SeaverStories social media campaign, a Mount Sinai mural, and weekly information tables.

Members of the Seaver Autism Center team gathered to observe Autism Awareness Month.

Seaver Autism Center Team

Joseph D. Buxbaum, PhD, *Director*

Preclinical Research Team

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Principal Investigator

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Ariela Buxbaum Grice
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Elodie Drapeau, PhD
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Hala Harony-Nicolas, PhD
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Debbie Suarez

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Clinical Director

Paige M. Siper, PhD,
Chief Psychologist

Michelle Gorenstein-Holtzman, PsyD,
Director of Community Outreach

Danielle Halpern, PsyD,
Director of Psychology Training

Lauren Donnelly, PhD
Cristina Farrell, MD
Emily Fourie
Yitzchak Frank, MD
Emanuel Frowner
Shannon Gair
Julia George-Jones
Jesslyn Jamison
Reymundo Lozano, MD
Hillary Rieger
Teresa Tavassoli, PhD
Pilar Trelles, MD
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Mount Sinai

Seaver Autism Center for Research and Treatment

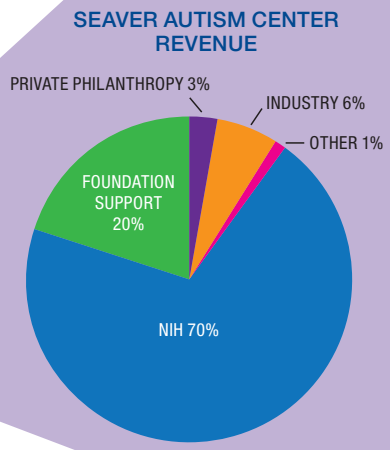
Mount Sinai

Seaver Autism Center for Research and Treatment

Committed to Research • Dedicated to Care

Our research is directed by the need to provide better care and service for families affected by ASD. Our commitment to research is driven by our compassion and dedication to patient care, as well as advancing 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 ASD.

The Seaver Autism Center is funded in large part by the Beatrice and Samuel A. Seaver Foundation and the National Institutes of Health. The Center also receives support from philanthropy, the pharmaceutical industry, and other nonprofit foundations including the Autism Science Foundation, Simons Foundation, and Autism Speaks.



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

seaver autism center for research & treatment @ mount sinai

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