seaver autism center for research & treatment @ mount sinai
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Research Update from the Seaver Autism Center

Seaver Center researchers announce exciting results from two recent studies examining genetic mechanisms in the causes of autism spectrum disorders

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▶ Treatment in a mouse model of Phelan-McDermid Syndrome restores nerve cell communication to normal levels

At the recent meeting of the International Society for Autism Research, Dr. Joseph Buxbaum presented exciting developments in potential new treatments for Phelan-McDermid Syndrome (PMS), which has behavioral characteristics that fall under the autism spectrum disorder (ASD) category. Previous research has shown that a loss or mutation in a gene called SHANK3 can cause absent or severely delayed language abilities, intellectual disability, and autism. Seaver Center researchers developed mice with a mutant SHANK3 gene and observed a lapse in communication between nerve cells in the brain, which can lead to learning problems.

The researchers then injected the mice with a derivative of a compound called insulin-like growth factor-1 (IGF1), which is FDA-approved to treat growth failure in children. After two weeks of treatment, nerve cell communication was normal and adaptation of nerve cells to stimulation, a key part of learning and memory, was restored.

"The result of IGF1 treatment of these mice is an exciting development on the road to ultimate therapies for individuals with PMS and similar autism syndromes," said Dr. Buxbaum, Director of the Seaver Autism Center. "If these data are further verified in additional preclinical studies, individuals with a SHANK3 mutation may benefit from treatments with compounds like this one."

Dr. Joseph Buxbaum examines IGF1 in the laboratory.

▶ International autism genetics consortium identifies new autism susceptibility genes

As members of the Autism Genome Project or AGP, Seaver Center investigators analyzed copy number variants (CNVs; rare submicroscopic insertions and deletions in genes) in high-density genotyping data collected from 1,000 individuals with ASD and 1,300 without ASD.

The results of the study provide further support for an emerging consensus within the scientific community that autism is caused in part by many "rare variants," or genetic changes found in one percent or less of the affected population. While each of these variants may only account for a small fraction of the cases, collectively they are starting to account for a greater percentage of individuals with autism. More importantly, they

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are also providing insights into possible common pathological mechanisms of ASD.

Additionally, the findings show that CNVs disrupting specific genes are more common in ASD than in controls. Some of the more compelling findings include CNVs in SHANK2, SYNGAP1, DLGAP2 and the X-linked DDX53–PTCHD1 locus.

The AGP explicitly tested whether genes previously implicated in intellectual disabilities but not in autism represented autism genes. The evidence was quite clear that such genes are also autism genes. The overlap between autism susceptibility genes and genes previously implicated in intellectual disabilities further supports the hypothesis that at least some genetic risk factors are shared by different psychiatric developmental disabilities.

Therapies specifically targeted to identified genetic causes ("personalized medicine") are now being tested in several neurodevelopmental syndromes associated with autism, including Fragile X syndrome, tuberous sclerosis, and Rett syndrome. The identification of additional autism genes will expand such approaches and lead to new therapies.

Commenting on the study was Bruce D. Gelb, MD, Director of the Child Health and Development Institute at Mount Sinai: "It is an exciting development to see Dr. Buxbaum and colleagues identify genes that have been linked to intellectual disabilities but not previously implicated in autism now be linked to that condition as well." Dr. Gelb, who was not affiliated with this study, said further, "This landmark study also provides a template for future research into the genetics of many other important human disorders."

The AGP consists of 120 scientists from over 50 institutions.

Highlights from the Advances in Autism Conference

The Seaver Autism Center for Research and Treatment held its annual conference, "New Insights in the Etiology, Diagnosis, Neurobiology, Genetics and Treatment of Autism," on Sunday, April 11 at the Mount Sinai School of Medicine, providing our local community with access to cutting edge biomedical research presented by internationally known investigators. The conference is the yearly highlight of the center's outreach efforts and brings together healthcare professionals, educators, service providers, and family members to address important concerns facing the field.

Pictured (L to R): Eustacia Cutler, author and advocate; Deanna Levine, Seaver Foundation Advisory Board; Sarah Spence, MD, PhD, National Institute of Mental Health; Evdokia Anagnostou, MD, University of Toronto; Bryan King, MD, University of Washington and Seattle Children's Hospital; Joseph Buxbaum, PhD, Director of the Seaver Autism Center at Mount Sinai School of Medicine; Hirschell Levine, Trustee, Seaver Foundation; Terri Rosenblum, daughter of Hirschell and Deanna Levine and long-time supporter of the Seaver Autism Center.

THIS YEAR'S conference presented research on a broad range of topics, with the pulse of the conference focused on interventions, and the challenges of addressing the needs of adults with autism spectrum disorders (ASDs). Highlights included a moving talk from Temple Grandin's mother, Eustacia Cutler, who described her tenacious path in raising an autistic child in the 1950s, and its impact on the entire family.

The day started off with a series of scientific lectures from a diverse group of renowned researchers in the field. Dr. Joseph Buxbaum, the Conference Director and the Director of the Seaver Center, gave a talk about recent findings

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Conference

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in the genetics of ASDs. Dr. Buxbaum discussed the importance of discovering genetic causes of autism and how understanding the molecular and genetic bases for ASDs could lead to the development of novel therapeutics through the use of model systems. "After a gene is identified and animal models are developed that mimic genetic abnormalities found in people with autism, we can observe how the animals function and use specific compounds in an attempt to reverse the deficits. The use of these compounds may then be explored in patients to alleviate core symptoms of autism. These sorts of approaches have led to clinical trials in Fragile X Syndrome and other neurodevelopmental disorders, including forms of autism," said Buxbaum.

DR. SARAH SPENCE, a pediatric neurologist from the Pediatrics and Developmental Neuropsychiatry Branch of the National Institute of Mental Health, spoke about research efforts to identify meaningful subtypes of ASDs. Her talk covered a broad range of issues that touch on ASDs, including genetics, epilepsy, sleep, and immunology. Dr. Spence highlighted some interesting findings from her research pointing to potential immunological factors associated with regression in children with ASD. According to Dr. Latha Soorya, Chief Psychologist of the Seaver Center, Spence's talk "was an excellent overview of progressive biomedical research in ASD today."

Dr. Bryan King of the University of Washington and Seattle Children's Hospital provided an update on pharmacological treatments in ASDs. "His fascinating studies on the placebo effect in clinical trials will no doubt lead to improved trials and eventually treatment in autism," said Buxbaum. Also during the scientific presentations, Dr. Evdokia Anagnostou, a pediatric neurologist and clinician-scientist at Bloorview Research Institute, presented recent findings in studies of ASD utilizing neuroimaging methodology, and specifically the use of magnetic resonance spectroscopy to better understand the brain circuitry underlying ASD.

Eustacia Cutler talks with a conference attendee.

THE AFTERNOON started off with a keynote address given by Eustacia Cutler, the author of *A Thorn in My Pocket: Temple Grandin's Mother Tells the Family Story.* "Eustacia provided valuable insight into how much a parent has to take on in order to fight for his or her child with autism. She took such great risks against the popular beliefs and social expectances of the day; it was truly inspiring," said a conference attendee.

The day ended with a series of workshops on various topics. Workshops were run by Seaver Center faculty as well as accomplished professionals in the field of ASDs. Dr. Alexander Kolevzon, the Clinical Director of the Seaver Center, notes that "workshops are a good opportunity to reach clinicians as well as community members and families, and provide them with resources and knowledge about best practices. Our workshop speakers are both experts in the field and also good teachers because we want to ensure that the material is accessible to everyone in the audience."

Many of the groups affiliated with the Seaver Center took part in the conference through introductory talks, workshops and exhibitor tables. Some of the groups in attendance included the Autism Science Foundation, Young Adult Institute/Premier Health Care, the Jewish Community Center of Manhattan, United Jewish Appeal-Federation, and Federation Employment and Guidance Service (F.E.G.S.)

OVERALL, THE DAY was a great success. We are extremely grateful to all the individuals and families who attend our conference and participate in our research. Our team believes the key to success lies in translating the knowledge gained from research into developing innovative treatments that meaningfully impact community care. According to Dr. Buxbaum: "Our vision is that using the latest molecular genetic, neurobiological and clinical resources, we will be able to identify genetic subtypes of ASD and develop specific therapies." For more information, please visit our website at: www.SeaverAutismCenter.org or call us at 212-241-0961.

Meet the Clinical Director

Dr. Kolevzon brings with him extensive experience working with children with autism and their families

ALEXANDER KOLEVZON, MD, Clinical Director of the Seaver Autism Center, is a child and adolescent psychiatrist and is Associate Professor of Psychiatry and Pediatrics at Mount Sinai School of Medicine. Dr. Kolevzon was appointed to the faculty at Mount Sinai in 2005, and was the Director of Clinical Services in the Division of Child and Adolescent Psychiatry before joining the Seaver Autism Center in his current role three years ago.

Dr. Kolevzon brings with him extensive experience working with children with autism and their families, both in research settings and in clinical practice. He has published numerous papers and chapters on autism and has broad clinical expertise in treating autism and related conditions with medications. As an investigator on many clinical trials, his research is focused on developing new therapies. Dr. Kolevzon collaborates closely with Dr. Joseph Buxbaum, the Director of the Seaver Autism Center, to better understand the molecular and genetic basis of autism spectrum disorders (ASDs) in order to develop novel treatment approaches.

As part of the Seaver Autism Center's initiative to advance studies in 22q13 deletion syndrome/Phelan-McDermid Syndrome (PMS), one known cause of autism, Dr. Kolevzon is actively assessing affected families in order to develop more sophisticated treatments for patients. Families coping with a 22q13/PMS diagnosis or who are looking to learn more about the condition now have several resources available to them. More broadly, in collaboration with Dr. Buxbaum's Model Systems Initiative, Dr. Kolevzon and the Seaver Center are examining the genetic causes of ASDs to prepare for clinical trials.

Another trial in progress for which Dr. Kolevzon serves as the principal investigator is evaluating the possible benefits of an investigational product called Luminenz to assess the impact on hyperactivity and other symptoms of autism in children. He is also a co-investigator with Dr. Jennifer Bartz examining the use of intranasal oxytocin to improve social cognition, both in adults and children with autism.

In addition to his clinical and research duties, Dr. Kolevzon is also extremely committed to medical student and residency training and education. He is the Associate Residency Training Director in Child and Adolescent Psychiatry and Co-Director of the Beatrix Hamburg Medical Student Training Fellowship in Child and Adolescent Psychiatry, which is sponsored by the Klingenstein Third Generation Foundation. He has written three books designed for medical student and resident education, and a fourth textbook is currently in press on ASDs.

In his role as an active teacher, mentor, and clinical supervisor, Dr. Kolevzon has received many teaching awards, as well as a grant to support innovative educational endeavors. Most recently, he received the American Academy of Child and Adolescent Psychiatry (AACAP) Outstanding Mentor Award (2009), the Excellence in Teaching Award at Mount Sinai (2007), and the Association for Academic Psychiatry (AAP) Faculty Development Award (2006).

THE SEAVER AUTISM CENTER NEWSLETTER *brings you timely updates about new developments related to research and treatment of autism spectrum disorders, as well as activities at the Seaver Autism Center. To be placed on our mailing list, please contact SeaverCenterEditor@mssm.edu or The Seaver Autism Center, Mount Sinai School of Medicine, One Gustave L. Levy Place. Box 1668, New York, NY 10029. Our phone number is 212-241-0961 and our web site is www.SeaverAutismCenter.org.*