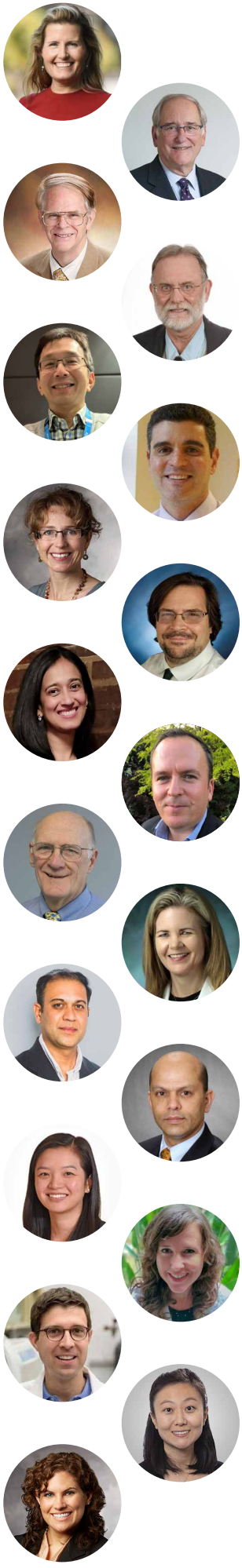

Improving Quality of Life in Patients with Autism:

Emerging Research, Evaluation, and Management of Co-Occurring Conditions

CONFERENCE
MARCH 1–2, 2024

9:00 am – 4:30 pm Central Time

A live event via webinar – hosted by Neuroimmune Institute and accredited in collaboration with The Wisconsin Medical Society

NEUROIMMUNE
INSTITUTE

Improving Quality of Life in Patients with Autism: Emerging Research, Evaluation, and Management of Co-Occurring Conditions

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Most interventions for individuals with autism are focused on improving social skills, speech, and language, addressing sensory and motor concerns, teaching self-care and daily living skills, and behavior management. Difficulty with communication, unusual presentation of symptoms, diagnostic overshadowing, and the tendency to view behaviors through the lens of "just autism" frequently lead to treatable medical comorbidities being overlooked.

The focus of this virtual conference is improving the quality of life in individuals with autism by educating physicians on medical comorbidities that are either more difficult to diagnose in autistic individuals or over-represented in individuals with autism compared to the general population as well as providing an overview of emerging research.

This conference features nationally and internationally renowned experts skilled in diagnostic and therapeutic approaches who will present a diverse range of clinical insights as well as emerging research. Presentations are carefully selected to familiarize attendees with developing research and to educate clinicians on diagnosis and treatment of co-occurring conditions in patients with autism.

Both generalists as well as specialists in pediatric and adult medicine will find the conference valuable to their practices. The intended audience is pediatricians, family physicians, gastroenterologists, psychiatrists, rheumatologists, immunologists, neurologists, and infectious disease physicians. Though the conference is designed for physicians, all are welcome to attend.

Neuroimmune Institute **neuroimmuneinstitute.org**

Friday, March 1, 2024 – Agenda

(Times all listed in central time zone) see page

Saturday, March 2 – Agenda

MARCH 1, 2024 AGENDA

(Times all listed in U.S. central time zone)

9:00 – 9:45 am CT

The Role of the Gastrointestinal Tract and the Microbiome in Individuals Who Are on the Autism Spectrum

Harland Winter, MD

Director, Center for Pediatric Inflammatory Bowel Disease, Massachusetts General Hospital for Children; Associate Professor, Harvard Medical School

Presentation Synopsis

Gastrointestinal dysfunction is common in individuals who are on the autism spectrum. Constipation, diarrhea, gastroesophageal acid reflux, bloating and intolerance to specific foods are the main causes of symptoms. However, there are no gastrointestinal disorders that are specific to autism, but associations with foods and restrictive diets are implicated as triggers for symptoms. Since some individuals who are on the autism spectrum are non-verbal and others might have altered perception of pain, interpreting behaviors becomes relevant in determining the source of potential co-morbid conditions. Behaviors such as applying pressure to the abdomen might signify constipation; chest tapping or posturing is indicative of gastroesophageal acid reflux; food refusal could be caused by esophagitis; and bloating by maldigestion secondary to lactose intolerance.

There are examples in nature of alterations in the intestinal microbiome affecting behavior. When Toxoplasma gondii infects rodents, they lose their innate fear of predators. Brucella suis is associated with mania and schizoaffective disorders, whereas rabies may cause hydrophobia. The best-known example is the association of streptococcal infections with pediatric autoimmune neuropsychiatric disorders.

The microbiome in the colon is altered in many individuals who are on the autism spectrum resulting in dysbiosis with decreased Firmicutes and Actinobacteria and increased Bacteroidetes and Protobacteria. There are also reported changes in specific bacteria in the colon—Desulfovibrio sp., Bacteroides vulgatus is increased and Prevotella, Coprococcus, Veillonellaceae, Bifidobacterium species and Akkermansia muciniphila are decreased in children with severe autism. In the duodenum, there is a relative decrease in abundance of two Bacteroides species and Escherichia coli and disaccharidase activity correlated with the abundance of Clostridium species. The metabolome, specifically glutamate, in the gastrointestinal tract of individuals on the autism spectrum, is associated with alterations in gut microbiota, specifically lower levels of Bacteroides vulgatus and higher levels of the potentially harmful bacteria Eggerthella lenta and Clostridium botulinum. In addition, epigenomic factors may play a role in modulating the intestinal microbiome and the metabolome.

Over the past 10 years the understanding of the gut-brain interaction in autism has evolved from maldigestion to dysbiosis to microbiome-epigenomic interactions. Future directions to generate new knowledge include integrating proteomic technology to identify biomarkers that could result in the discovery of novel metabolic pathways that could lead to new therapeutic targets.

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Kushak, R. I., Winter, H. S., *et al.* (2016). Analysis of duodenal microbiome in autistic individuals; association with carbohydrate digestion. *Journal of Pediatric Gastroenterology and Nutrition* 64: 110–116

Kushak R. I., Sengupta A., Winter H. S. (2022). Interactions between the intestinal microbiota and epigenome in individuals with autism spectrum disorder. *Developmental medicine and child neurology* 64(3): 296–304.

Speaker Biography

Harland Steven Winter, MD, is an associate professor of Pediatrics at Harvard Medical School and Massachusetts General Hospital for Children. His undergraduate degree in mathematics was from the University of California at Berkeley and his MD was from the University of California at Los Angeles where he did his pediatric residency. He completed a pediatric gastroenterology fellowship at Children's Hospital Boston. He joined the faculty at MGH and is the director of the inflammatory bowel disease program.

Dr. Winter was elected President of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition from 1998–2000. He organized the first World Congress of Pediatric Gastroenterology, Hepatology and Nutrition in Boston in 2000.

His scientific achievements include the discovery in 2012 of a new disorder (a mutation in the DGAT1 gene), that is found primarily in infants who have protein losing enteropathy and diarrhea in the first week of life. In addition, Dr. Winter has completed many clinical trials in IBD to determine the best treatment options for children. He is currently working on the identification of biomarkers that predict response to medications that treat Crohn's disease and ulcerative colitis, the role of the microbiome in inflammatory bowel disease and the relationship between the microbiome and behavior in individuals who are on the autism spectrum.

Dr. Winter is a consultant for Abbvie, Jannsen, Pfizer and Pediatric IBD Foundation. He also provides research support for Jannsen, Women's Wellness Foundation, Nestle, QOL, Autism Research Institute, Scipher and Abbvie. Dr. Winter receives royalties from UptoDate. All of the relevant financial relationships for this individual have been mitigated.

9:45 – 10:30 am CT

Sleep Difficulties in Autism: Investigation and Management Strategies

Ben Marlow, MBBS, MRCPCH, PGCME

Consultant Paediatrician (Neurodevelopment) ESNEFT; Clinical Director – The Synapse Centre for Neurodevelopment; Clinical Lead for Paediatrics, SNEE ICB; Visiting Senior Lecturer, Anglia Ruskin School of Medicine

Presentation Synopsis

Sleep disturbances in children on the Autism Spectrum are very common and impact the development and health of the child and whole family. Within the neurodevelopmental clinic, sleep issues stand out as being one of the most frequently raised difficulties.

This talk focusses on the different types of sleep disorders (ranging from delay in falling asleep, frequent night waking and early morning waking), disruption in sleep architecture, differences in neurotransmitter metabolism and medical comorbidities that should also be screened for (especially unmet pain needs related to GI dysfunction).

It also explores behavioral strategies and stepwise approaches to medication in the clinic and current areas of research (neuromodulation and other potential therapies) that may help within this very important area of medicine.

Speaker Biography

Dr. Ben Marlow is a Paediatric Consultant with an interest in neurodevelopment, having completed training in neurodisability at Cambridge and Luton. He is Clinical Director of The Synapse Centre for Neurodevelopment UK.

He has worked in the NHS for nearly 10 years, having completed his medical training at University College London (UCL). Prior to his role as a doctor, he completed a Masters in Biochemistry and worked for GlaxoSmithKline (GSK) and UCB Pharma in Research and Development. He also completed a research fellowship at the University of Florida. He has a keen interest in the neurobiology of neurodevelopmental disorders, especially the fields of neuroimmunology and metabolism. He is

very keen to help advocate and advance the translation of science into treatments for children with neurodisabling conditions, particularly within the field of Autism. At the beginning of 2020 he was awarded National Institute for Health Research (NIHR) local research network principal investigator support funding. Dr. Marlow is a member of the Scientific Advisory Board for Kingdom Therapeutics.

Dr. Marlow also has a keen interest in teaching and has completed a Post Graduate Certificate in Medical Education (PGCME).

Dr. Marlow has no relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

Break | 10:30 – 11:00 pm CT

11:00 am – 11:45 pm CT

A Mitochondrial Etiology of Autism and Associated Neuropsychiatric Disorders

Douglas Wallace, MD, PhD

Michael and Charles Barnett Endowed Chair in Pediatric Mitochondrial Medicine and Metabolic Disease, Director, Center for Mitochondrial and Epigenomic Medicine, The Children's Hospital of Philadelphia; Professor, Department of Pediatrics, Division of Human Genetics, Perelman School of Medicine, University of Pennsylvania

Presentation Synopsis

Metabolic studies of autism spectrum disorders (ASD) have revealed defects in mitochondrial bioenergetics (1), with a number of ASD loss-of-function loci overlapping with those associated with intellectual disabilities, epilepsy, schizophrenia, metabolic syndrome, and congenital heart disease (2), all manifestations of mitochondrial disorders (3). The mitochondrion is assembled from over a thousand nuclear DNA (nDNA) coded genes plus hundreds of copies of the mitochondrial DNA (mtDNA) which codes exclusively for mitochondrial oxidative phosphorylation (OXPHOS) genes. OXPHOS is assembled from approximately 160 nDNA proteins plus 13 mtDNA coded polypeptides, the mtDNA proteins synthesized on mitochondrial ribosomes using mtDNA tRNAs. The OXPHOS electron transport chain (ETC) encompasses complexes I, II, III, and IV which oxidizes NADH with O2 and uses the energy to generate an electrochemical gradient across the mitochondrial inner membrane. This capacitance drives the ATP synthase (complex V) to generate ATP from ADP + Pi. The ATP and ADP are exchanged across the mitochondrial inner membrane by the nDNA-coded adenine nucleotide translocators (ANTs).

ASD cases have been associated with all three classes of clinically relevant mtDNA variants. The first class is materially inherited pathogenic mutations, such as the *MT-TL1* ($tRNA^{Leu(UUA)}$) 3243A>G mutation which at 30–40% heteroplasmy can present with autism and/or diabetes in association with distinctive transcriptional and histone modification profiles (4, 5). The second class is ancient adaptive mtDNA lineages (haplogroups), and multiple European haplogroups increase ASD risk with Odds Ratios of ~2 (6). The third is *de novo* somatic mutations which are increased in the ASD siblings within families (7).

The causal role of mitochondrial defects in ASD has been proven by creation of a mouse harboring the human neurological disease mtDNA complex I gene missense mutation, $MT\text{-}ND6^{P25L}$ (8). These mice manifest all the phenotypes of ASD (9). Multiple nDNA ASD genes have also been found to cause alterations in mitochondrial bioenergetics (10).

The heterozygous chromosome 22q11.2 deletion commonly causes ASD but can also present as schizophrenia. This deletion encompasses several mitochondrial genes including a ribosomal large subunit (Mrpl40), the citrate carrier (Slc25A1), and thioredoxin reductase (Txnrd2). The deletion alters the interactions of multiple mitochondrial proteins including the heart-muscle-brain isoform of the ANTs (SLC25A4, ANT1)(11) and mice lacking Ant1 have defects in the migration of interneurons which are critical for cortical excitation-inhibition balance (12).

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Cells and neurons from 22q11.2 schizophrenia patients have defects in complex I and IV in association with reduced nDNA and mtDNA transcript levels. By contrast, 22q11.2 patients without schizophrenia have a compensatory induction of nDNA and mtDNA genes. Induction of mitochondrial biogenesis with bezafibrate and miRNA 181 antagomirs restores mitochondrial gene expression of the schizophrenic cells (13, 14), suggesting that modulation of mitochondrial function may provide a more general approach for treating ASD and other neuropsychiatric disorders.

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Speaker Biography

Douglas C. Wallace founded the field of human mitochondrial DNA (mtDNA) genetics and demonstrated that mtDNA variation has profound implications for human health and disease, the origins and ancient migrations of our ancestors, human and animal adaptation, and perhaps the origin of species. He obtained his Ph.D. in Microbiology and Human Genetics at Yale University in 1975. As part of his thesis, he demonstrated that the mtDNA codes for certain inherited traits like resistance to Chloramphenicol.

As a young faculty at Stanford University, in 1980 he showed that the human mtDNA is exclusively maternally inherited and that mtDNA variation correlates with the geographic origins of indigenous peoples. This work revealed that humans arose in Africa about 200,000 years ago, that only two mtDNAs successfully left Africa to colonize Eurasia and the Americas, and that functional mtDNA variants arose as humans moved into a new environment. From this foundation, he was the first to identify, in 1990, inherited mtDNA mutations that result in disease, initially the mtDNA missense mutation that causes Leber Hereditary Optic Neuropathy (LHON) and the protein synthesis mutation that causes Myoclonic Epilepsy and Ragged Red Fiber (MERRF) disease. Since then, he has identified multiple pathogenic mtDNA mutations causing diseases as diverse as diabetes, cardiovascular disease, and Alzheimer disease. He also demonstrated that regional mtDNAs when moved to new environments can predispose to a wide range of complex diseases.

Currently, his web-based mtDNA information service, MITOMAP, lists hundreds of clinically relevant mtDNA mutations. Wallace also showed that the accumulation of mtDNA mutations in tissues correlates with aging and age-related diseases. Wallace was the first to develop mouse models of mitochondrial disease and to invent a procedure for introducing mtDNA mutations into the mouse female germline. This revealed that single mtDNA base changes were sufficient to produce the common metabolic and degenerative disease phenotypes, providing compelling evidence that mtDNA variation is central to health and the common diseases.

Wallace was elected to membership in the US National Academy of Science in 1995, the American Academy of Arts and Sciences in 2004, the National Academy of Medicine in 2009, Accademia Nazionale delle Scienze detta dei XL (National Academy of Sciences of Italy) 2017. He was awarded the William Allan Award by the American Society of Human Genetics in 1994, the Passano Award for Mitochondrial Genetics (with G. Attardi) in 2000, the Metropolitan Life Foundation Award for Medical Research in Alzheimer 's disease in 2000, and the Pasarow Award for cardiovascular disease in 2006. In 2012, he received the Gruber Genetics Prize, as well as the American College of Physicians Award. He received Doctor Honoris Causa, Universitè Angers, France (2015), the Franklin Institute's prestigious Benjamin Franklin Medal for the Life Sciences (2017), Paul Janssen Award for Biomedical Research (2017). He accepted the Charles L. Hoppel Prize for Outstanding Contributions in Mitochondrial Research in 2019.

11:45 – 12:30 pm CT

Vasopressin: A Robust Biomarker and Promising Therapeutic for Autism

Karen Parker, PhD

Professor, Department of Psychiatry & Behavioral Sciences, Stanford University School of Medicine; Principal Investigator, Social Neurosciences Research Program, Chair, Psychiatry Major Laboratories Steering Committee, Associate Chair, Department of Psychiatry & Behavioral Sciences, Stanford University School of Medicine

Presentation Synopsis

Dr. Parker is Professor and Associate Chair of the Department of Psychiatry and Behavioral Sciences at Stanford University, where she leads the Major Laboratories Steering Committee and directs the Social Neurosciences Research Program. The principal goal of her research program is to better understand the biology of social functioning across a range of species, and to translate these fundamental insights to drive diagnostic and treatment advances for patients with social impairments. Dr. Parker's research has been supported by the NIH, Simons Foundation, and Department of Defense, published in leading scientific journals, and featured across diverse media outlets (e.g., NPR, CBS, New York Times, LA Times, Science, Scientific American). Dr. Parker received her undergraduate and graduate degrees from the University of Michigan. She completed postdoctoral training at Stanford University and joined the Stanford faculty thereafter. She is an Affiliate Scientist at the California National Primate Research Center, a fellow of the American College of Neuropsychopharmacology (ACNP), and a Kavli fellow of the U.S. National Academy of Sciences. She has attended key opinion leader meetings at the U.S. National Academies and NIH and held leadership roles on international animal research advisory committees (e.g., Society for Neuroscience's CAR, ACNP's ARC).

Speaker Biography

Autism spectrum disorder (ASD) is currently diagnosed behaviorally because its pathophysiology remains poorly understood. Consequently, there are currently no laboratory-based diagnostic tests to detect ASD and no disease-modifying medications that effectively treat its core behavioral features. The capability of rapidly detecting ASD based on neurochemical markers, however, would revolutionize ASD detection, enable more timely behavioral intervention, and provide targets for pharmacological treatment. To address these urgent unmet clinical needs, we developed a translational ASD research program, spanning studies of naturally low-social monkeys to children with ASD. Converging evidence from this body of research indicates that the neuropeptide vasopressin plays a critical and conserved role in regulating social abilities, and that brain vasopressin signaling is impaired in low-social monkeys, children with ASD, and newborn infants before the period when ASD first manifests. On the basis of this compelling evidence, we recently conducted a first-in-class double-blind, randomized, placebo-controlled pilot trial. We found that intranasal vasopressin treatment is well tolerated and significantly improves social abilities in children with ASD. These findings suggest that a neurochemical marker of impaired social

functioning may be present very early in life, before behavioral symptoms emerge, and that the vasopressin signaling pathway may hold diagnostic and therapeutic promise for ASD.

Dr. Parker receives funding from the National Institutes of Health for an investigator-initiated Vasopressin treatment trial in the form of a federal grant and study medication for the NIH trial from Endo Par free of charge. All of the relevant financial relationships for this individual have been mitigated.

Lunch break | 12:30 – 1:15 pm CT

1:15 – 2:45 pm CT

Infection and Inflammation Related Neuropsychiatric Deteriorations in Youth with Autism Spectrum Disorders: Case Presentations by the Stanford Immune Behavioral Health Team

Jennifer Frankovich, MD, MS

(presenting with Meiqian Ma, MD; Melissa Silverman, MD; and Bahare Farhadian, MSN, RN, FNP-C)

Clinical Professor, Pediatrics – Allergy, Immunology, Rheumatology; Co-Director, Stanford Children's Immune Behavioral Health Clinic; Director, Stanford Immune Behavioral Health Research Program, Stanford University School of Medicine

Presentation Synopsis

Peripheral and central brain inflammation may be playing a role in autism, with early exposures to infections/"inflammatory events" likely playing a role in priming the immune system into a more activated or pro-inflammatory state. If this is true, then one would expect that such patients are prone to further immune activation events (I.e. flares) in the settings of infection. Infections are indeed known to trigger systemic inflammation (arthritis, vasculitis, complement activation, etc) that can be recognized and treated clinically. We propose that "flares" or immune activation events that are recognized as part of a neuropsychiatric deterioration in kids with autism can be successfully treated using systematic standard clinical approaches that are used in general pediatrics, pediatric rheumatology, etc. We will present 4 cases of youth with autism who had severe neuropsychiatric deteriorations. Based on family history, clinical exam, musculoskeletal imaging, and standard clinical immune and vasculitis markers, each case had a clear clinical inflammatory picture which allowed selection of anti-inflammatory/immunomodulation that is considered standard of care for their conditions, were approved by medical insurance (but required an appeal process), and the interventions were followed by improvement in physical exam findings of inflammation, blood immune markers, and neuropsychiatric status. There are many challenges to this approach including that patients with autism in a neuropsychiatric decline are often not able to articulate the standard signs of infection and inflammation (pain, pressure, stiffness, etc) and are not always able to cooperate with the exam, thus a systematic and thorough approach to examination all tissues and markers may be necessary which is resource intense and requires a specialized multidisciplinary team (psychiatry, psychology, rheumatology, immunology, general pediatrics, imaging specialists, etc) working together to simultaneously to evaluate, treat, and monitor using a multimodal approach which employs standard of care pathways.

Speaker Biography

Dr. Jennifer Frankovich's primary research and clinical interest is in the intersection between mental health and systemic inflammation. She co-founded the Stanford PANS multidisciplinary clinic and research program. Alongside other collaborators, she is building a large biorepository of patient blood samples and clinical data to share with basic scientists around the world. She collaborates with 10 basic science labs at Stanford to characterize the immunophenotypes of active PANS compared to remission samples and age matched controls. Her ultimate goal is to understand the immunological factors contributing to mental health disturbances and to innovate effective multidisciplinary treatment regimens.

Dr. Frankovich has no relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

Meiqian Ma, MD

Clinical Assistant Professor, Pediatrics – Rheumatology, Stanford University School of Medicine

Speaker Biography

Dr. Ma is an Assistant Clinical Professor in the Department of Pediatrics, Division of Allergy, Immunology Rheumatology (AIR) at Stanford University/Lucile Packard Children's Hospital (LPCH). She completed her medical training at the Medical College of Wisconsin. She then went to Cohen Children's Medical Center/Northwell Health to complete her training in pediatrics and pediatric rheumatology. Her research in fellowship focused on the validation of the 2019 European League Against Rheumatism/American College of Rheumatology Criteria Compared to the 1997 American College of Rheumatology Criteria and the 2012 Systemic Lupus International Collaborating Clinics Criteria in Pediatric Systemic Lupus Erythematosus. She joined the Stanford PANS Program in July 2020.

Her current research involves investigating the risk of arthritis and other autoimmune conditions in patients with neuropsychiatric symptoms.

Dr. Ma has no relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

Melissa Silverman, MD

Clinical Assistant Professor, Psychiatry and Behavioral Sciences – Child and Adolescent Psychiatry and Child Development, Stanford University School of Medicine

Speaker Biography

Dr. Melissa Silverman is a Child & Adolescent Psychiatrist in Palo Alto, CA and Menlo Park, CA with 12 years of experience in the field of Psychiatry. Dr. Silverman's clinical focus is on children with Pediatric Acute onset Neuropsychiatric Syndrome (PANS) and adolescent youth with suicidal ideation. She graduated from Michigan State University College of Human Medicine and completed four years of general psychiatry training at Mayo Clinic Rochester. She completed her child and adolescent psychiatry fellowship at Stanford University School of Medicine. She is currently a Clinic Assistant Professor at Stanford School of Medicine.

Dr. Silverman has no relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

Bahare Farhadian, MSN, RN, FNP-C

Rheumatology – Family Nurse Practitioner, Stanford Medicine Children's Health

Speaker Biography

Bahare Farhadian is a Nurse Practitioner in the Immune Behavioral Health Clinic at Stanford Medicine Children's Health. She has been with this multidisciplinary team since 2014, the first of its kind at an academic institution which manages patients with pediatric acute onset neuropsychiatric syndrome and other inflammatory disorders. She has presented at regional, state, and international conferences on PANS/PANDAS and other inflammatory brain conditions.

Bahare Farhadian, FNP-C has no relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

Break | 2:45 – 3:00 pm CT

3:00 – 3:30 pm CT

Pain Panel

Harland Winter, MD; Richard Frye, MD, PhD; Jennifer Frankovich, MD; Ben Marlow, MBBS; Terry Harville, MD, PhD; Naveen Nagarajan, PhD

Synopsis

An opportunity for clinicians to ask questions related to pain in autism to our distinguished panelists.

3:30 – 3:45 pm CT

Calcium Transients in Microglia Drive ASD/OCD-Like Repetitive and Anxiety Behaviors

Naveen Nagarajan, PhD

Postdoctoral Associate, Dr. Mario Capecchi Lab, Eccles Institute of Human Genetics, University of Utah

Presentation Synopsis

The disruption of Hoxb8 in mice or genetic ablation of the Hoxb8 cell lineage, a subset of microglia, is causative for chronic anxiety and pathological over-grooming, a symptomatic phenotype found in Autistic children and patients. Further, optogenetic stimulation of Hoxb8 microglia in specific regions of the brain induces elevated anxiety, Autism specific repetitive grooming or both. Conversely, do microglia in specific regions of the brain respond to induced grooming or anxiety type of Autistic phenotype in mice? Herein, using fluorescent based calcium reporters, detected by in vivo microendoscopic imaging with single cell resolution, we show that induction of repetitive grooming or anxiety based Autistic phenotype in mice does indeed drive production of calcium transients within microglia in specific regions of the brain. In response to induced grooming, Hoxb8 microglia within the DMS and mPFC exhibit calcium transients reflective of the Autism-specific repetitive grooming pattern. On the other hand, induction of anxiety via the visual cortex results in generating calcium transients in Hoxb8 microglia residing within the vCA1 region of the hippocampus. Multiple grooming bouts induce multiple calcium transients locked to the repetitive grooming pattern. Microglial induced calcium transients within either the DMS or mPFC in response to induced grooming are not produced in Hoxb8 mutant mice! This defect appears to result from the inability of Hoxb8 mutant microglia to control their intracellular levels of free calcium concentrations. This failure may also account for Hoxb8 mutant mice exhibiting chronic anxiety and pathological Autistic-specific repetitive overgrooming. The results of induced calcium transient in normal mice, combined with the optogenetic results, provides the means for interrogating microglial/neuronal cross communication from opposite poles, from Hoxb8 microglia-optogenetic stimulation to generate autism-specific behavioral outputs and from the induced autistic behaviors in mice back to individual microglial responses with the production of calcium transients.

Speaker Biography

Dr. Naveen Nagarajan is a Postdoctoral Associate in the laboratory of Dr. Mario Capecchi at the Department of Human Genetics, University of Utah. His work is focused on investigating the microglianeuronal interaction mechanisms and the neural circuit basis of repetitive behaviors in pre-clinical mouse models using multidisciplinary neuroscience areas that include genetics, behavioral, optogenetics, miniature fluorescence endoscopy, electrophysiological, and computational approaches.

Dr. Nagarajan received his PhD in chemistry, with specialization in biophysics and neuroscience from the Department of Membrane Biophysics, Max Planck Institute for Biophysical Chemistry in Goettingen, Germany, under the able guidance of Dr. Christian Rosenmund and Dr. Erwin Neher. He completed postdoctoral fellowships in cellular neuroscience in Mark Bear's lab at the Picower Institute for Learning and Memory at MIT and systems neuroscience at the Keck Center for Integrative Neuroscience at the University of California, San Francisco with Dr. Michael Merzenich. He joined Dr. Mario Capecchi's laboratory as a Postdoctoral Fellow in 2009 to investigate the role of Hoxb8 gene function in repetitive, anxiety, and social behavioral functions.

Dr. Nagarajan has no relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

3:45 – 4:10 pm CT

Novel Autoantibody Discovery in Autism Spectrum Disorder

Melody Lun, MD, PhD

Clinical Fellow, Neonatology, Postdoctoral Fellow, Pleasure-Wilson Labs, University of California – San Francisco

Presentation Synopsis

This presentation will review the first study to comprehensively profile CSF from a large cohort of children with ASD and NDD. While this study did not identify a uniform autoantibody signature across this cohort, we report a novel autoantibody against FOXO3, a transcription factor that is a key regulator of neural stem cell maintenance and neuronal plasticity.

Speaker Biography

Dr. Melody Lun is a clinical fellow in Neonatology at UCSF and a postdoctoral fellow in Samuel Pleasure and Michael Wilson's labs. She completed her MD/PhD training at Boston University and Boston Children's Hospital, studying the regulation of signaling factors in cerebrospinal fluid during brain development. She is currently investigating the role of autoimmunity in neurodevelopmental disorders and is using phage display technology to identify autoimmune signatures in pediatric cohorts.

Dr. Lun has no relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

4:10 – 4:30 pm CT

Inflammation and The Gut-Brain Axis in Autism – Research Strides Point to Dietary Interventions

Emily Severance, PhD

Assistant Professor of Pediatrics, Johns Hopkins University School of Medicine

Presentation Synopsis

Immune dysregulation during neurodevelopment has emerged as a leading hypothetical mechanism underlying numerous brain disorders including autism spectrum disorder (ASD). In ASD and in other brain disorders suspected to have gene-by-environment etiologies, disruptions of the gut microbiome are increasingly linked to sub-clinical inflammation, and the loss of integrity of the blood-gut and blood-brain barriers. This pro-inflammatory gut-brain axis may

be triggered by infection or exposure to pathogens, commensal antigens, dietary antigens and autoantigens. These microbial triggers can activate complement systemically and, in the brain, where defects in immune surveillance interfere with such activities as synaptic pruning and neurogenesis. Healing the gut and its microbiome is achievable through many available interventions (diet, nutrition, probiotics, prebiotics, microbiota transfer), yet it is critical to recognize that the success of these interventions likely relies on a highly individualized diagnostic and treatment regime. The substantial challenges of introducing novel dietary interventions for people with ASD may be mitigated in part by keeping a food diary, identifying true food allergies or intolerances, improving digestion, and engaging nutritional and behavioral specialists to further identify and improve imbalances.

Speaker Biography

Dr. Emily G. Severance is an assistant professor of pediatrics at the Johns Hopkins University School of Medicine. She is a member of the Stanley Division of Developmental Neurovirology research team and has served with the Scott-Gentle Foundation of The Brain and Behavior Research Foundation and the Johns Hopkins Silvio O. Conte Center for Schizophrenia Research. As part of her ongoing research program, Dr. Severance focuses on the major gateway of the immune system, the gastrointestinal mucosa, where inflammation, food hypersensitivities, barrier defects and immune dysregulation can cause downstream brain dysfunction in people with psychiatric disorders. She is also involved in research studies of COVID-19 and the roles of other viral, bacterial, and fungal pathogens in mental illness. Dr. Severance earned her B.S. from the University of Maryland and her Ph.D. from the University of South Florida.

Dr. Severance has no relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

Closing | 4:30 pm CT

MARCH 2, 2024 AGENDA

(Times all listed in U.S. central time zone)

9:00 – 9:45 am CT

Atypical Presentations of AE

Ming Lim, MD, PhD

Professor of Paediatric Neurology, King's College London; HOS Children's Neuroscience, Consultant Paediatric Neurologist, Children's Neuroscience Centre, Evelina London Children's Hospital, King's Health Partners Academic Health Science Centre

Presentation Synopsis

In a child that becomes unwell and progressively and encephalopathic, an immune etiology needs to be considered as timely diagnosis and subsequently treatment can influence outcome. Seizures, movement disorders, cognitive and psychiatric symptoms are some of the symptom clusters that alerts the clinician to this diagnosis. However, in a small proportion of children are predominantly monosymptomatic at presentation occur, making recognition more difficult. In the very young child, early symptoms across a whole range of condition neurological disorders can present with communication and language skills. Ultimately the condition progresses. Aspects of early recognition, red flags and diagnostic strategies would be discussed, alongside management strategies.

Speaker Biography

Dr. Ming Lim undertook his undergraduate medical training at University Nottingham, UK. Following completing his pediatric neurology training in South London, he began his doctoral research in the Institute of Psychiatry, Psychology and Neuroscience (London) with the award of a Royal College of Pediatrics and Child Health Research Training Fellowship. He was appointed as Consultant Pediatric Neurologist at the Evelina London Children's Hospital; and is Professor of Pediatric Neurology within Faculty of Life Sciences & Medicine, King's College London.

The Children's Neuroscience Department Brain and Spine Inflammation Service at the Evelina is one of the largest in Europe with a highly successful research portfolio; leading and participating in multi-centre/multi-national investigator-led studies; contributing to industry-led studies; and collaborating in basic studies investigating the role of inflammation in neurodegeneration and immunobiology of antibody-mediated central nervous system disorders.

Dr. Ming is the clinical lead of the service and research lead for children's neurosciences and Evelina Children's Hospital and has generated a substantial grant income and published comprehensively on childhood neuroinflammation. His work has contributed to important characterization and understanding of many childhood inflammatory disorders and his team is credited in leading clinical and research programs which now seek to optimize the management of severe childhood neuroinflammatory disorders. The service infrastructure and collaborative national and international networks also provide crucial clinical and research training in pediatric neuroinflammation.

Dr. Lim has no relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

9:45 – 10:30 am CT

Neurodevelopmental Regression: Causes, Workup, and Treatment

Richard Frye, MD, PhD

President and Chief Scientific Officer, Autism Discovery and Treatment Foundation; Director of Research, Rossignol Medical Center; Sponsor and Principal Investigator, Southwest Autism Research and Resource Center

Presentation Synopsis

Sudden changes in neurodevelopment marked by loss of language, social or cognitive function and/or the development of severe repetitive, restricted and obsessive behaviors are being recognized in several neuropsychiatric disorders of childhood. In autism spectrum disorder (ASD) neurodevelopmental regression (NDR) is typically recognized to occur between 24 and 36 months, but is it being realized that similar sudden changes in symptoms occur through childhood and adolescence in individuals with ASD. The NDR changes seen in ASD parallel the course of those diagnosed with Pediatric Acute Onset Neuropsychiatric Syndrome (PANS). It is being recognized that several common underlying physiological abnormalities may drive these sudden changes in behavior in childhood, including metabolic abnormalities, such as mitochondrial dysfunction/disease, central folate abnormalities and abnormalities in transmethylation/transsulfuration, immune abnormalities such as autoimmune disorders, parainfectious processes and chronic infections, neurologic disorders such as epilepsy and neurodegenerative disorders, and rare genetic syndromes. Understanding the potential underlying etiology of NDR in childhood can pay the way for a systematic workup and treatment based on the etiological cause.

Speaker Biography

Dr. Richard Frye is a Child Neurologist with expertise in neurodevelopmental and neurometabolic disorders. He received an MD and PhD in Physiology and Biophysics from Georgetown University. He completed a residency in Pediatrics at the University of Miami, Residency in Child Neurology and Fellowship in Behavioral Neurology and Learning Disabilities at Harvard University/Children's Hospital Boston and Fellowship in Psychology at Boston University. He also received a Masters in Biomedical Science and Biostatistics from Drexel University. He holds board certifications in Pediatrics, and in Neurology with Special Competence in Child Neurology. He has authored over 300 publications and book chapters and serves on several editorial boards.

Dr. Frye is a national leader in autism spectrum disorder (ASD) research. He is President of the Autism Discovery and Treatment Foundation, Director of Research and Neurologist at the Rossignol Medical Center and Principal Investigator at the Southwest Autism Research and Resource Center (all in Phoenix AZ).

He has lead several clinical studies on children with ASD, including studies focusing on defining the clinical, behavioral, cognitive, genetic and metabolic characteristics of children with ASD and mitochondrial disease and several clinical trials demonstrating the efficacy of safe and novel treatments that target underlying physiological abnormalities in children with ASD, including open-label studies on tetrahydrobiopterin, cobalamin and leucovorin and a recent double-blind placebo controlled trial on leucovorin.

Dr. Frye has no relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

Break | 10:30 – 11:00 pm CT

11:00 – 11:45 am CT

Treatment Targeting Glutamate Dysregulation in Autism

Gagan Joshi, MD

Associate Professor of Psychiatry, Harvard University; Director, Autism Spectrum Disorder Program in Pediatric Psychopharmacology; Medical Director, The Alan & Lorraine Bressler Program for Autism Spectrum Disorder, Massachusetts General Hospital for Children

Presentation Synopsis

This presentation will provide overview of glutamate (Glu) dysregulation in autism spectrum disorder (ASD). Memantine is a glutamatergic agent that holds promise in improving social deficits in individuals with ASD. Forty-two intellectually intact youth with ASD initiated study medication and 33 completed the trial. There was a significantly higher rate of improvement in severity of autism with memantine versus placebo on the study criteria for treatment response. Treatment with memantine was well tolerated. Spectroscopic pgACC glutamate activity was significantly higher in ASD versus healthy controls. High glutamate activity was observed in 54% of ASD participants and was associated with significantly higher memantine treatment response. None of the ASD participants with normal glutamate activity responded to memantine treatment. Higher glutamate activity was associated with greater magnitude of autism response. The ROC analysis suggested pgACC glutamate activity was highly predictive of treatment response.

Speaker Biography

Dr. Gagan Joshi is the Director of the Autism Spectrum Disorder Program in Pediatric Psychopharmacology and Medical Director of the Bressler Program at Massachusetts General Hospital. He is also Associate Professor of Psychiatry at the Harvard Medical School.

Dr. Joshi trained in General Psychiatry at the Hospital of the University of Pennsylvania and subsequently completed his Fellowship training in Child and Adolescent Psychiatry at the combined program of the Massachusetts General Hospital and McLean Hospital, Harvard Medical School. He received training in cognitive-behavioral therapy at the Beck Institute for Cognitive Therapy and trained in psychodynamic psychotherapy at the Philadelphia Psychoanalytic Institute & Society.

Dr. Joshi has been the recipient of the prestigious Ethel Dupont Warren Fellowship Award through the Department of Psychiatry at Harvard Medical School, the XXVth Collegium Internationale Neuro-Psychopharmalogicum Congress Young Investigators Award, the American Academy of Child & Adolescent Psychiatry Pilot Research Award, and the Norma Fine Fellowship (2007–2011).

Dr. Joshi's clinical and research interest is in Autism Spectrum Disorder (ASD) with particular focus on the often-neglected comorbid conditions associated with these disorders. Besides coordinating Bressler clinic and providing clinical care to individuals of all ages with ASD, Dr. Joshi is facilitating translational clinical research in ASD. At the Bressler Program, in collaboration with the McLean Hospital and the Massachusetts Institute of Technology (MIT) and with research support from the National Institute of Mental Health, and the Simons Center for the Social Brain at MIT, Dr. Joshi is conducting research focused on the clinical and neural characterization and psychopharmacotheraputics of ASD and related psychopathology with a particular emphasis on designing neuro-imaging informed pharmacotherapy trials by leveraging state of the art pharmaco-imaging techniques to help identify biomarkers of disease and treatment response.

Dr. Joshi shares research updates and expertise in ASD by offering lectures and supervision to trainees in the MGH Department of Psychiatry, and by organizing educational programs for mental health providers and for families of individuals with ASD.

Dr. Joshi provides research support for Genentech and is a consultant for Eumentis Therapeutics. All of the relevant financial relationships for this individual have been mitigated.

11:45 am – 12:30 pm CT

Clinical Trials of Sulforaphane (SF) in Autism Spectrum Disorder (ASD): Efficacy and Biomarkers

Andrew Zimmerman, MD

Professor of Pediatrics and Neurology (Retired), UMass Memorial Medical Center

Presentation Synopsis

Sulforaphane (SF), an extract of broccoli and other cruciferous vegetables, is a multifunctional phytochemical that has several benefits for cellular processes relevant to ASD, including cytoprotective, antioxidant, and anti-inflammatory effects. It also supports mitochondrial and synaptic functions. In eight clinical trials published since 2014, SF has shown safety with various degrees of clinical efficacy and changes in biomarkers in children and young adults with ASD. Combined findings in the trials to be reviewed provide the basis for further studies of the mechanisms of action, as well as clarification of the patients with ASD who are most likely to respond, and the optimal preparations and dosage of SF.

Speaker Biography

Dr. Andrew Zimmerman is a retired pediatric neurologist with 38 years of experience as an autism clinician and translational researcher. Several of his and his colleagues' clinical and laboratory observations have led to immune, metabolic, and neuropathological findings in autism spectrum disorder (ASD), such as autoimmune disorders in families, maternal antibodies to the fetal brain, beta-2 adrenergic receptor overstimulation, microglial activation, and behavioral improvements with fever. Over time Dr. Zimmerman has come to appreciate that genetic and environmental factors become integrated at the cellular level, where different types of dysfunction may be manifested and underlie various phenotypes of ASD. Positive behavioral responses to fever in ASD support the hypothesis that cellular stress and heat shock responses are important components that lend themselves to treatment, such as with SF (broccoli sprout extract). With colleagues, Dr. Zimmerman has conducted two clinical trials of SF in ASD at the Lurie Center (MGH)and UMass, in collaboration with Drs. Paul Talalay, Jed Fahey and Hua Liu at Johns Hopkins. It is his view that such "off target" treatments, although they may differ from those anticipated from genetic mutations, can also lead to improved function in ASD by modulating cellular metabolism. From his experience as an autism clinician, he has a strong interest in the metabolic basis of ASD, especially as it relates to the behavioral effects of SF and several medications.

Dr. Zimmerman has no relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

Lunch break | 12:30 – 1:15 pm CT

1:15 – 2:00 pm CT

Case Presentations of the "Spectrum" of ASD

Terry Harville, MD, PhD

Professor of Pathology and Laboratory Services, and Internal Medicine; Medical Director, HLA and Histocompatibility Laboratory; Medical Director, Immunogenetics and Transplantation; Laboratory Medical Director, UAMS ABG Laboratory, The University of Arkansas for Medical Sciences

Presentation Synopsis

Dr. Terry Harville is trained in Pediatrics with subspecialty training in Allergy, Immunology, Rheumatology, and Transplantation Biology. His training included learning about streptococcal disease in the 1980s from Dr Elia Ayoub (who had trained with Dr Lewis Wannamaker). Further, Dr. Harville trained with Dr Robert Cade, who had found alpha-morphocasein and beta-morpho-gliadin (terms used in the 1980s; the literature now tends to label these as alpha-casomorphine and beta-gluteomorphin, respectively), which are partial digestion products from milk and wheat, respectively, in the dialysis fluids collected from children with autism. When injected into mice and rats, they produced autistic behaviors. In his clinical practice, patients were referred to him that were previously diagnosed with autism and needed additional evaluation and potential treatment. (Many of these were by "word-of-mouth" between families where autism was present.) Dr. Harville will present case vignettes, which illustrate and focus on the role of what he calls "post-infectious immune reactive disease" or "post-streptococcal immunoreactive disease", when streptococcal titers can be detected (this was before Dr Susan Swedo coined the term PANDAS), and the role of milk and wheat, as apparent causative processes for inducing autism spectrum disorders in children. This will be presented with an Allergist/Immunologist/Rheumatologist perspective on clinical evaluation, laboratory testing, and successful treatment modalities, for these subsets of ASD.

Speaker Biography

Dr. Harville began his post-graduate career in the field of Biochemistry and Molecular Biology, earning his doctorate from the University of Florida in 1982. He made the career decision to go into medicine, earning his medical degree in 1986 from the University of Florida. He remained at the University of Florida, specializing in Pediatrics, finishing in 1989. Dr. Harville then undertook further specialty fellowship training in a program of Pediatric Immunology, Rheumatology, and Transplantation Biology at the University of Florida through 1992. He joined the faculty at Duke University in 1992, where he specialized in dealing with patients with complex immune disorders. Many patients required bone marrow stem cell transplantation, for which he became recognized as a leader in the treatment of very rare disorders. In 1999, Dr. Harville joined the Department of Pediatrics at UAMS. He became the Chief of Pediatric Rheumatology, while still diagnosing and managing patients with complex immune disorders, allergic disorders, and asthmatic disease.

While at the University of Florida, Dr. Harville had active participation in the Clinical Immunology Laboratory and the HLA Laboratory, helping in the development, implementation, and clinical use of these specialized laboratory testing. This continued at Duke University, where he brought on board tests that had been developed while at the University of Florida. Thus, one other clinical area that he undertook as he came to ACH and UAMS was the Directorship of the Special Immunology Laboratory at ACH. In 2005, Dr. Harville joined the Department of Pathology to be the Director of the HLA, Histocompatibility, and Immunogenetics Laboratories. In 2016, he became the Laboratory Director of the ABG Laboratory at UAMS.

While at the University of Florida, Dr. Harville worked with Dr. Elia Ayoub on streptococcal disease, where in particular, he studied and dealt with post-streptococcal immuno-reactive disease, one of which was subsequently defined as PANDAS. He continued this work along with evaluation of other post-infection immune-reactive diseases at Duke University, working in the neurology clinic with Dr. Bob Delong, developing new evaluation and treatment methods for these post-infection immune-reactive disorders affecting brain function. Additionally, while at the University of Florida, Dr. Harville worked with Dr. Robert Cade, evaluating urinary products of wheat and milk digestion, alpha-gliadorphin and beta-casomorphin, respectively, which when injected into rats induced autistic behaviors.

Dr. Harville was initially Board Certified in Pediatrics in 1989, Pediatric Rheumatology in 1992, and Allergy and Immunology in 1993. In 2014, Dr Harville received further Board Certifications from the American Board of Medical Laboratory Immunology and American Board of Histocompatibility and Immunogenetics. Dr. Harville currently provides consultative services for the laboratory testing of patients and donors of organ, bone marrow, and hematopoietic cell transplantation, as well as those with complex immune and autoimmune disorders. He is also a Professor of Internal Medicine, in the Division of Hematology/Oncology.

Dr. Harville has no relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

2:00 – 2:45 pm CT

Neurobehavioural Impairments in Disorders of the Hypothalamo-Pituitary Axis

Ritika Kapoor, MBBS, PhD, FRCPCH

Consultant Paediatric Endocrinologist and Honorary Reader, King's College Hospital NHS Foundation Trust & King's College, London

Presentation Synopsis

This talk delves into the relationship between hypothalamic and pituitary hormones and their impact on behavior and cognition. Beginning with an overview of the hypothalamic-pituitary axis (HPA) and its regulatory functions, the discussion will focus on the association of rare endocrine conditions and autism. By examining phenotypes and patient presentations, attendees will gain insights into the identification and manifestations of hormone deficiencies and therapeutic targets for individuals affected by neurodevelopmental disorders/ autism.

Speaker Biography

Dr. Kapoor obtained her primary medical degree from the University of Mumbai in 1997. Following her MRCPCH in 2001, she received specialist Pediatric training at the East of England Deanery and obtained dual CCT in Pediatrics and Diabetes and Endocrinology in 2010. She trained in Pediatric Diabetes and Endocrinology at Addenbrooke's Hospital, Cambridge, and Great Ormond Street Hospital in London. She obtained a PhD from University College London on Genetics of Congenital Hyperinsulinism in 2010 and since then has been a Consultant in Pediatric Endocrinology at King's College Hospital NHS Foundation Trust. She also holds an Honorary Reader position at King's College London.

Her research interest focuses on congenital hyperinsulinism, growth hormone therapy and neuroendocrinology. She was recently awarded the MRC Clinical Academic Research Partnership (CARP) award to investigate the role of oxytocin in neurobehavioral problems in children with disorders of the hypothalamo-pituitary axis.

Dr. Kapoor has no relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

Break | 2:45 – 3:00 pm CT

3:00 – 3:20 pm CT

Modulation of the Gut Microbiome in ASD

Brittany Needham, PhD

Assistant Professor, Indiana School of Medicine

Presentation Synopsis

The central nervous system interprets external and internal cues from the surrounding environment and the body. One complex source of signals is the bacterial community in the gastrointestinal tract, which resides outside host tissue in the gut but produces signals that enter circulation and can reach the brain. This active community of microbes breaks down dietary and host components into small byproducts, or metabolites. Some gut-derived metabolites serve as messages to the brain and influence function and behavior. This has been a topic of study in the context of autism spectrum disorder (ASD). This talk will give an overview of the gut-brain axis in ASD and some specific examples. For instance, we recently showed that one bacterial signal elevated in ASD populations, 4-ethylphenyl sulfate (4EPS), can be selectively produced by engineered gut bacteria. Mice exposed to 4EPS via gut bacteria exhibited decreased maturation of myelin-producing cells, oligodendrocytes, leading to decreased insulation of neuronal axons, disorganized white matter, and elevated anxiety-like behavior in 4EPS-exposed mice. Improved understanding of the neuroactive effects of 4EPS and similar signals will advance potential therapeutics for anxiety within and beyond the context of ASD.

Speaker Biography

Brittany Needham, PhD, joined Stark Neurosciences Research Institute and the Department of Anatomy, Cell Biology and Physiology at Indiana University School of Medicine in 2022. Prior to this, she studied as a postdoctoral researcher at Caltech. She graduated from BYU with a B.S. in Molecular Biology, followed by a PhD in Molecular and Cellular Biology, with a focus on Microbiology and Biochemistry, at UT Austin.

Manipulating microbial communities and their byproducts is a rich and tractable opportunity for therapeutics. Dr. Needham first became interested in bacterial-host interactions as a graduate researcher studying the evolutionary strategies employed by bacterial pathogens to subvert mammalian immune detection. This work led her to appreciate the extreme range of potential host outcomes upon subtle structural variation of bacterial small molecules. As a postdoctoral researcher, Dr. Needham shifted her study of bacterial byproducts into commensal gut microbial molecules that influence neurodevelopment. The laboratory gained insight on the complexities of the molecular signatures that an altered gut microbiota imparts on its host. Her current work focuses on moving beyond associations of phenotypes in the gut and brain and into concrete causal effects that can be leveraged to understand host phenotypes.

Dr. Needham has no relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

3:20 – 3:45 pm CT

Role of Maternal Immune Activation and Serotonin Reuptake Inhibitors in Autism-Related Neurodevelopmental Disorders

John Lukens, PhD

Associate Professor, Department of Neuroscience, University of Virginia

Presentation Synopsis

Recent human studies suggest that autism is often associated with altered microbiota composition and gastrointestinal inflammation. This work has led to growing speculation of a potential role for the microbiome in autism spectrum disorder (ASD). However, it remains to be determined

how microbiota diversity mechanistically influences the development of autistic phenotypes. To formally investigate this, we evaluated how environmentally induced changes in gut microbiota landscape affect the incidence and severity of maternal immune activation (MIA)-induced neurodevelopmental disorders. In these studies, we discovered critical roles for prenatal microbiota composition in the development of behavioral abnormalities in an MIA mouse model of autism. Mechanistically, we showed that microflora-dependent calibration of the maternal immune response underlies the effects of the microbiome on inflammation-induced ASD-like phenotypes. Specifically, we found that neutralization of IL-17a ameliorates the ability of the microbiome to affect the development of autism-related behaviors. These results identify the immune system as a link between gut microbiota and the brain in neurodevelopmental disorders, and further suggest that targeting the microbiome and maternal immune responses during gestation may offer strategies to limit autism development in at-risk pregnancies.

Speaker Biography

Dr. John Lukens received his PhD from the University of Virginia in 2008 for his work describing roles for PD-1 and functional T cell exhaustion in persistent liver infection. For his postdoctoral training, John worked in the laboratory of Dr. Thirumala-Devi Kanneganti at St. Jude Children's Research Hospital where he identified molecular pathways involved in innate cytokine production. In Fall 2014, John returned to UVA to launch his lab in the Department of Neuroscience and the Center for Brain Immunology and Glia (BIG). His group is focused on understanding how inflammasomes and immune-based genomic sensors contribute to neurodevelopmental, psychiatric, and neurodegenerative disorders.

Dr. Lukens has no relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

3:45 – 4:30pm CT

Autism, Epilepsy, and Aggression

John Gaitanis, MD

Associate Professor of Pediatrics, Clinician Educator, Brown University School of Medicine; Director of Child Neurology, Brown Medical School; Pediatric Neurologist, Hasbro Children's Hospital

Presentation Synopsis

Autism spectrum disorder (ASD) with regression (ASD-R) involves the loss of previously attained developmental milestones, typically during the first or second year of life. As children age, it is not uncommon for them to develop comorbid conditions such as aggressive behaviors or epilepsy, which can inhibit habilitation in language and social function. Aggressive behaviors and epilepsy more commonly develop in patients with ASD-R than in those without a history of regression (ASD-NR). When considering the impact of epilepsy and aggression on quality of life, these co-morbidities effectively cause a second regression in patients who experienced an earlier regression as toddlers. Underlying etiologies for both the initial and the second regressions will be reviewed, with an emphasis on autoimmunity.

Speaker Biography

John Gaitanis, MD, is a pediatric neurologist at Hasbro Children's Hospital. Dr. Gaitanis received his medical degree from the Geisel School of Medicine at Dartmouth and The Warren Alpert Medical School at Brown University. He completed a residency in pediatrics at Strong Memorial Hospital through the University of Rochester Medical School, as well as a residency in neurology at Boston Children's Hospital through Harvard Medical School. He completed a fellowship in epilepsy and neurophysiology at Beth Israel Deaconess Medical Center through Harvard Medical School.

His clinical research focuses on finding improved biomarkers and therapeutics for epilepsy and improving EEG signal acquisition with advancements in electrode design and software processing techniques.

Dr. Gaitanis previously served as an associate professor of pediatrics at Tufts Medical School and chief of pediatric neurology at Tufts Children's Hospital. Dr. Gaitanis is now the director of child neurology at Brown Medical School.

Dr. Gaitanis is a member of several professional organizations including the Child Neurology Society, the American Academy of Neurology, and the American Epilepsy Society.

Dr. Gaitanis serves on the advisory board for Neurelis and the scientific advisory board for Kingdom Pharmaceuticals. All of the relevant financial relationships for this individual have been mitigated.

Closing | 4:30 pm CT

Hosts/Moderators

Anna Conkey

Executive Director and Founder, Neuroimmune Institute and Neuroimmune Foundation

Ms. Conkey has no relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

Juliette Madan, MD

Associate Professor, Pediatrics, Psychiatry, Epidemiology & Quantitative Biomedical Data Sciences, Department of Psychiatry, Division of Child and Adolescent Psychiatry, Dartmouth Hitchcock Medical Center, Geisel School of Medicine at Dartmouth

Dr. Madan is a physician scientist trained in pediatrics and psychiatry and is the Director of Research in the Division of Child Psychiatry at the Children's Hospital at Dartmouth. She is the Clinical Director of the Dartmouth Children's Environmental Health and Disease Prevention Research Center, and the focus of her research is on the developing microbiome in infants and children and the relationship to immune training and health outcomes that are alterable. She is a graduate of Brown University School of Medicine and trained in pediatrics followed by fellowship in neonatal-perinatal medicine at Tufts University, where she also completed a master's degree in clinical and translational research. She completed psychiatry training at Dartmouth to align her practice with her research focus on neurodevelopmental and neuroinflammatory conditions in childhood. Dr. Madan is an expert in the developing microbiome in large infant cohorts examining the relationship between exposures, the microbiome, and health outcomes (infectious disease risk, respiratory outcomes, and neurodevelopment). She is the founding co-director of the Psychiatry Immunology and Neurology Group at Dartmouth, which aims to provide clinical care and translational research initiatives in infection and inflammation mediated neuropsychiatric illnesses in children and young adults. Dr. Madan's lab is focused on the relationship between the gut microbiome and neurodevelopmental and neuropsychiatric outcomes and interventions such as nutritional, probiotic regimens and fecal transplant.

Dr. Madan has no relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

ACTIVITY DIRECTOR

Anna Conkey
Executive Director and Founder, Neuroimmune Institute and Neuroimmune Foundation

PLANNING COMMITTEE MEMBER

Amy Malik, MD

Assistant Clinical Professor, Pulmonary and Critical Care Medicine, University of Wisconsin

Dr. Malik has no relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

LEARNING AND OUTCOME OBJECTIVES

- Explain how to identify and treat causes of pain in a patient with autism.
- Describe an appropriate medical work up for a patient with autism who is exhibiting behavioral exacerbations.
- Describe clinical features of co-morbidities that are overrepresented in autism or more difficult to diagnose.
- List several medical comorbidities that can be more difficult to identify in a patient who also has autism.
- Describe symptoms that may indicate a patient with autism could be having seizures.

ACCREDITATION / CREDIT DESIGNATION STATEMENT

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of Wisconsin Medical Society and Neuroimmune Institute. The Wisconsin Medical Society is accredited by the ACCME to provide continuing medical education for physicians.

The Wisconsin Medical Society designates this live activity for a maximum of 12.0 *AMA PRA Category 1 Credit(s)™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

ACCOMMODATIONS

Neuroimmune Institute subscribes to the articles of Title III of the Americans with Disabilities Act of 1990. Should you or anyone accompanying you require special assistance, please notify us by contacting conference@neuroimmuneinstitute.org or 608-381-0367. Requests should be made as early as possible to allow time to arrange the accommodation.

CME EVALUATION AND CREDIT REQUESTS

CME evaluations must be completed no later than March 10, 2024, to receive credit. CME certificates will arrive via email. Please check your spam if you do not see your certificate.

The CME evaluation is available on our website:
www.neuroimmuneinstitute.org/autism-2024-cme-evaluation

neuroimmuneinstitute.org

The Neuroimmune Institute is a sister organization to Neuroimmune Foundation that provides high-quality continuing medical education focused on autism, immunopsychiatric, neuroimmune, and inflammatory brain conditions. Neuroimmune Institute was founded with the goal of rapidly advancing clinical medicine and research.