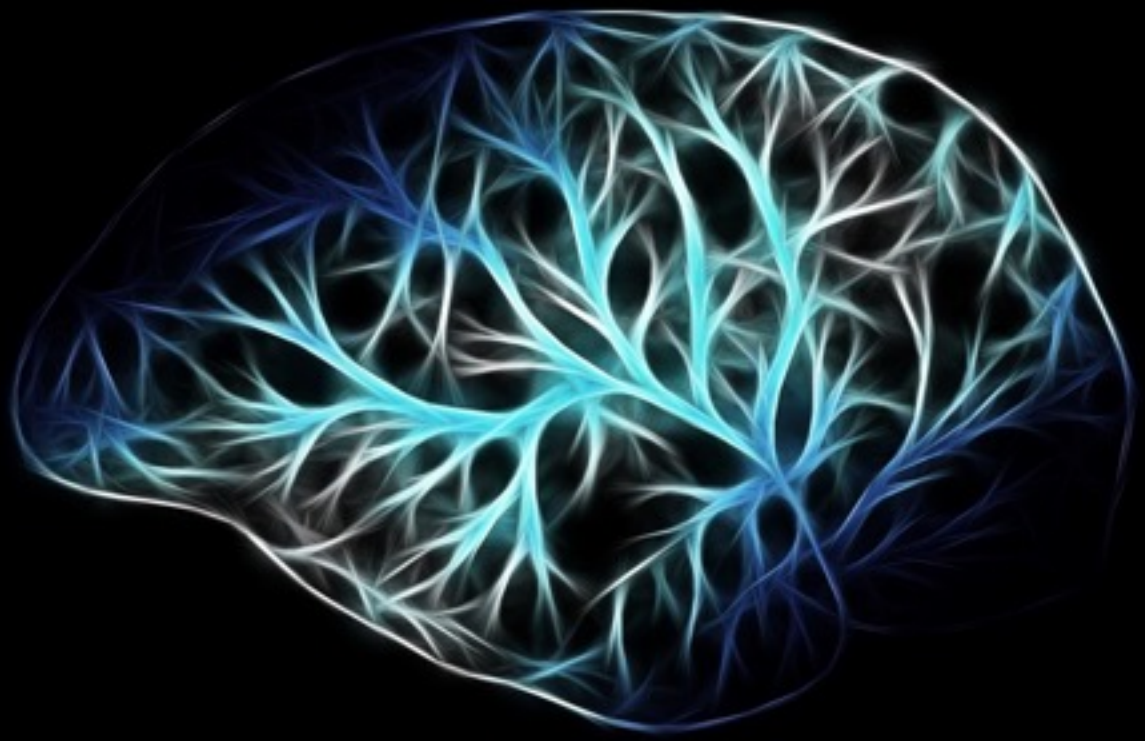
Synchrony 2021

From Bench to Biopharma



ABSTRACT BOOK

the brain foundation

December 11-12
synchronysymposium.com

About The Conference

Synchrony is the first and only international symposium on translational research in autism, that brings together academia, biotech, pharmaceutical companies, and venture partners from around the world with the mission to improve the health and quality of life of people with autism.

The abstracts below cover the latest in basic and translational research and the opportunities being pursued by biotech and pharmaceutical companies to develop FDA-approved therapeutics to benefit individuals with autism.

Several of these presentations reflect research updates from BRAIN Principal Investigators reporting results from basic science research projects or treatment studies funded by The BRAIN Foundation.

About The BRAIN Foundation

Our mission is to support translational research that will lead to the development of FDA-approved treatments and an improved standard of care for co-morbidities in individuals with autism.

Our vision is health, independence, and well-being for every person on the planet with neurological conditions, including Autism Spectrum Disorder diagnosis.

ABSTRACTS

SCIENTIFIC AND TRANSLATIONAL RESEARCH

Richard E Frye, MD, PhD
Neurologist
Phoenix Children's Hospital and University of Arizona College of Medicine, Phoenix

Update on Mitochondrial Research

The Brain Foundation has graciously funded three ongoing projects on mitochondrial function at our center.
The first project, a double-blind placebo-controlled crossover trial of a supplement to support mitochondrial function in children with autism spectrum disorder (ASD) who have mitochondrial dysfunction, is ongoing, but the results are still blinded. So far, major findings include the fact that children with ASD have a difficult time ingesting anything greater than a small quantity, making the delivery of the powder product challenges. We are working on encapsulating the product to improve delivery to many children.
The second project examines the effect of treatments on a fibroblast model of mitochondrial dysfunction in ASD. We have found unique changes in mitochondrial function in fibroblasts from children with ASD and modulatory effects of N-Acetyl-Cysteine, Rapamycin, and Metformin.
The third project examines fresh brains in children with and without ASD and/or epilepsy. Unique types of mitochondrial dysfunction are found in different types of epilepsy, and these changes in mitochondrial function correlate with gene expression data from these regions. Ongoing studies will correlate mitochondrial function with high-frequency oscillations and examine mitochondrial and gene expression differences between those with and without ASD.

Edward Quadros, PhD
Professor, Department of Cell Biology
State University of New York

Folates, Folate Receptor Autoantibodies, and the connection to Autism Spectrum Disorders

Autism is a behavioral disorder because of a disordered brain development during fetal life and early childhood. The cause remains unresolved, and consensus dictates that its multifactorial. Folate (vitamin B9) plays a pivotal role in fetal as well as neonatal brain development because of its role in cell replication, production of neurotransmitters and control of gene expression. Folate receptor autoantibodies are present in ~70% of the children with ASD and can block folate transport to the brain. These antibodies are prevalent in families with ASD children with >38% of the parents positive for the autoimmune disorder.
Leucovorin has shown great promise in the treatment of ASD with significant improvement in speech, communication, and social interaction. It holds most promise perhaps in the prevention of ASD by Identifying and treating the parents prior to conceiving. Screening for folate receptor antibodies, reducing antibody titer and providing adequate folate are critical for a positive outcome. Maternal and cord blood testing for folate receptor antibodies could provide for follow up and early intervention in the newborn to prevent development of ASD.

Harris Huberman, MD
Professor of Pediatrics, The Children's Hospital
State University of New York

Folate auto-antibody trajectories and ASD identification in early childhood

Folate receptor auto-antibodies (FRAA's) disrupt folate receptor alpha, the main route for folate transport into the central nervous system (CNS), resulting in CNS folate deficiency, and have been strongly linked to increased risk for ASD.
Treatment with leucovorin, a vitamin B9 derivative that bypasses the folate receptor and corrects CNS folate deficiency, has been shown to significantly improve core symptoms of language and social communication in children with ASD. FRAA positivity also runs in families with findings that 60-70% of parents and non-affected siblings are also FRAA+, raising the question, why does FRAA+ lead to an ASD picture in some individuals but not in others?
The answer likely lies in the timing of FRAA exposure during brain development and the interplay of metabolic, genomic and environmental factors. This presentation reviews the rationale for our current BRAIN Foundation study which will examine the trajectory of FRAA status, clinical manifestations of ASD and brain functioning correlates in infants at heightened risk for ASD based on familial ASD history, to lay the groundwork for designing both post-natal and prenatal approaches to ameliorate and/or reducing ASD incidence.

T. Atilla Ceranoglu, MD
Director, Psychiatry Service, Shriners Hospital for Children
Massachusetts Gen. Hospital, Boston, Massachusetts

Evaluation of Transcranial Photobiomodulation in Autism Spectrum Disorder: Double-Blind, Placebo-Controlled, Randomized Clinical Study of a Novel Approach

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by variable presentation of difficulties with socialization, reciprocal communication, and restrictive/repetitive behaviors. Currently, there exists no approved treatments for core features of ASD. Transcranial Photobiomodulation (tPBM) is a novel treatment approach based on application of an invisible, non-ionizing electromagnetic wave that results in metabolic modulation in tissues targeted. A recent, prospective, 8-week open-label treatment trial in adult patients with ASD revealed that tPBM was well tolerated and was effective in reducing symptom severity of ASD. In addition, tPBM treatment was associated with improvements in executive functions. Presently, an 8-week, prospective, placebo (sham) controlled, double-blind randomized clinical trial to evaluate the efficacy, safety, and tolerability of tPBM with near-infrared light in intellectually capable adults with ASD is underway. Up to 36 participants will be randomized at 1:1 ratio to receive daily tPBM or sham treatments for 8 weeks. The participants will be assessed on measures of efficacy and safety at regular scheduled visits throughout the study. A responder will be defined as those with a ≥25% reduction in Social Responsiveness Scale-2nd Edition, and a score of 2 or 1 on the Clinical Global Impression of ASD Improvement Subscale.

Karen Parker, PhD
Associate Professor and Associate Chair, Department of Psychiatry and Behavioral Sciences Stanford University

Vasopressin: A promising neurochemical marker and therapeutic for autism

Autism spectrum disorder (ASD) is currently diagnosed behaviorally because its pathophysiology remains poorly understood. Consequently, there are no laboratory-based diagnostic tests to detect ASD and no disease-modifying medications to 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.

Randy Blakely, PhD (Session Chair)
Executive Director
Stiles-Nicholson Brain Institute and Florida Atlantic University College of Medicine

Bidirectional Neuroinflammatory and Serotonin Signaling: Basic and Translational Perspectives

Sixty years ago, Schain & Freedman reported elevated serotonin (5-HT) in the blood of individuals with autism, a finding well-substantiated but still of enigmatic significance. We and others have shown using genetic and biochemical approaches that blood & CNS 5-HT levels are not directly related, raising questions as to whether changes in molecular pathways common to the regulation of brain and peripheral 5-HT synthesis, signaling and/or inactivation may link hyperserotonemia to ASD. We identified multiple, rare coding variants in the antidepressant 5-HT transporter (SERT, SLC6A4) in ASD multiplex families, each displaying hyperactivity. Expression of one of these substitutions (Gly56Ala) in transgenic mice leads to hyperserotonemia, elevated CNS 5-HT clearance, changes in pup vocalizations & adult social behavior, & repetitive behavior. These studies reinforced our efforts to understand how SERT activity is normally enhanced, leading to the discovery that SERT can be rapidly activated by the inflammatory cytokine IL-1beta (and TNFalpha), whose receptor (IL-1R1) is highly expressed by CNS 5-HT neurons. Moreover, SERT Ala56 mice display elevated expression of pro-inflammatory cytokines in the CNS and periphery, supporting a bidirectional link between the innate immune system and 5-HT signaling that may induce specific and reversible ASD traits and/or ASD comorbidities.

Aurelio Galli, PhD, DSc
Director for Gastrointestinal Biology Research
University of Alabama at Birmingham

Watch Flies Teaching Us Mechanisms of Neuropsychiatric Disorders

The human dopamine (DA) transporter (hDAT) mediates clearance of DA. Genetic variants in hDAT have been associated with DA dysfunction, a complication associated with several brain disorders including autism spectrum disorder (ASD). We investigated the structural and behavioral bases of an ASD-associated in-frame deletion in hDAT at N336 (ΔN336). We uncovered that the deletion promoted an unobserved conformation of the intracellular gate of the transporter, likely representing the rate limiting step of the transport process. It is defined by a “half-open and inward facing” state (HOIF) of the intracellular gate that is stabilized by a network of interactions conserved phylogenetically, as we demonstrated it both in hDAT by Rosetta molecular modeling and fine grained simulations as well as in its bacterial homolog leucine transporter by EPR analysis and X-ray crystallography. The stabilization of the HOIF state is associated with both DA dysfunctions demonstrated in isolated brains of Drosophila melanogaster expressing hDAT ΔN336 and with abnormal behaviors observed at high-time resolution. These flies display increased fear, impaired social interactions, and locomotion traits we associate with DA dysfunction and the HOIF state. Our results describe how a genetic variation causes DA dysfunction and abnormal behaviors by stabilizing a HOIF state of hDAT.

Harumi Jyonouchi, MD
Allergy and Immunology
Saint Peter's University Hospital

Biomarkers of Innate Immune Memory in Autism Spectrum Disorders

This is a progress report of the research project funded by the Brain Foundation.
Aim 1: Determine the state of innate immune memory (IIM) in the ASD subjects with the use of peripheral blood monocytes (PBMCs).
In initial screening of histone modification markers in purified PBMCs, we found the most significant changes in the expression of H3K27ac. Unlike animal models of IIM, H3K27ac tended to be up-regulated in ASD PBMCs at high frequency. We are in the process of conducting super-enhancer CHIP sequencing using H3K27ac as a target molecule in the 1st 12 samples that include ASD subjects with or without up-regulated H3K27ac. These results will be correlated with the functional assay results of monocytes.
Aim 2: Determine the feasibility of circulatory 7 miRNAs selected as the biomarkers of neuroinflammation. Seven circulating miRNAs selected based on our previous study were measured by qRT-PCR in 200 samples from both ASD and non-ASD subjects. In ASD subjects with sleep/seizure disorders had low circulatory levels of the miRNAs and did not reveal close associations with monocyte cytokine profiles. In contrast, ASD subjects without sleep/seizure disorders tended to have higher levels of these miRNA with negative associations with monocyte cytokine production.

Sarkis Mazmanian, PhD (Session Chair)
Luis B. and Nelly Soux Professor of Microbiology
California Institute of Technology

Gene-Microbiome Interactions in an ASD Mouse Model

Individuals with autism spectrum disorder (ASD) display deficits in social interaction and restricted behaviors, and are at least three times more likely to experience chronic gastrointestinal (GI) symptoms than the general population. Mutations in the Shank3 gene, which encodes a major scaffolding protein in the postsynaptic density of excitatory neurons, contribute to approximately 1% of ASD cases. The Shank3B-/- mouse is depleted in the major forms of SHANK3, resulting in behavioral phenotypes in mice that are similar to those observed in ASD. We show that Shank3B-/- mice display an increase in whole GI transit time (WGTT) and ex vivo colon migrating motor complexes involved in propulsive contractions, indicating altered GI motility compared to wild-type mice. Following colonization with a gut microbiome derived from wild mice, Shank3B-/- mice exhibit pronounced anxiety phenotypes. Intriguingly, depletion of SHANK3 in adult neurons using AAV-mediated delivery of Cre-recombinase in Shank3flox4-22 mice results in decreased WGTT compared to controls. Taken together, the data suggests complex gene x environment interactions impact behavior and GI comorbidities. As GI symptoms can impact quality of life, this research may lead to novel strategies to improve non-behavioral features of ASD.

Stuart Lipton, MD, PhD
Hannah and Eugene Step Chair; Professor; Co-director, Neuroscience Translational Center Department of Molecular Medicine
The Scripps Research Institute, La Jolla, CA

Potential of MEF2 Transcriptional Activator Therapy for ASD

Dr. Lipton will present new, unpublished work on the development of activators of the transcription factor MEF2C to treat Autism Spectrum Disorders (ASD)/Intellectual Disability (ID). He will present the rationale for this form of treatment, the methodology involved in screening for such drugs, and early preclinical trial results with one such drug. Dr. Lipton will also update the audience on the drug he presented last year at SYNCHRONY 2020, NitroSynapsin, with its anticipated launch into human clinical trials.

Acknowledgments
This work is supported in part by The Brain Foundation, the MEF2C Association, and the California Institute for Regenerative Medicine (CIRM).

Kazue Takahashi, PhD
Assistant Professor, Department of Radiology
Gordon Center for Medical Imaging, Harvard Medical School, Massachusetts

Mannose Binding Lectin in Health and Diseases

MBL (mannose-binding lectin) is a pattern recognition molecule and a component of innate immunity, the first line of the host defense system against pathogens, foreign bodies, altered self, and excess amounts of own molecules. MBL deficiency is common in humans, and it was initially identified as a risk factor among children with recurrent infections. We have generated mouse models of MBL deficiency in order to confirm clinical findings, in particular infectious diseases. Unexpectedly, these model studies have uncovered novel roles of MBL and evidence of its interaction with other molecules of the innate immune system. More recently, hyper-MBL levels in plasma have been identified and associated with diseases. At last, MBL is a disease modifier, and that MBL imbalance (hypo-, hyper, dysfunction) affects underlying disease conditions, including metabolic diseases.

Arthur Krigsman, MD
Pediatric Gastroenterologist
Private Practice, New York

Stephen Walker, PhD
Professor, Wake Forest Institute for Regenerative Medicine
Wake Forest School of Medicine, North Carolina

Molecular Studies to Provide Mechanistic and Diagnostic Insight in GI-Symptomatic Children With ASD

Chronic gastrointestinal (GI) issues are a common, yet understudied, occurrence in children with autism spectrum disorder (ASD) that can negatively impact all aspects of the child's life, including sleep, behavior, cognition, and the ability to receive proper nutrition. Our group has endeavored to construct an evidence-based framework from which to develop an effective standard-of-care diagnostic and treatment template for these underserved children. This lecture will present three primary goals of the molecular work that comprises this framework as follows: (1) to describe, at the molecular level, an IBD-like disorder in children with ASD, (2) to develop a sensitive and specific biomarker that can be used as a non-invasive diagnostic tool, as well as a molecular proxy for treatment efficacy, and (3) to explore the creation of relevant model systems (e.g., using patient-derived gut organoids) to examine the gut-brain-microbiome axis as tools to help us better understand the interrelationship between GI dysfunction and Neurodevelopment.

Alessio Fasano, MD
Division Chief, Pediatric Gastroenterology and Nutrition
Director, Center for Celiac Research and Treatment
Director, Mucosal Immunology and Biology Research Center
Massachusetts General Hospital for Children

Marcy Kingsbury, PhD
Assistant Professor of Pediatrics
Massachusetts General Hospital / Harvard Medical School

Using a Humanized Mouse Model And Human Intestinal Tissue to Evaluate the Zonulin Pathway For Personalized Treatment of Autism Spectrum Disorder

Autism spectrum disorder (ASD) is a heterogeneous and complex neurodevelopmental disorder that affects social communication and behavior. Many children with ASD also have gastrointestinal (GI) symptoms and dysfunction. However, whether these GI comorbidities contribute to the core behavioral hallmarks of ASD remains unknown. Pre-haptoglobin-2 protein (pre-HP2) is the archetype of the zonulin family that reversibly regulates barrier permeability by modulating intercellular tight-junctions. Clinical studies have reported increased intestinal permeability and elevated serum zonulin in ASD patients. Moreover, an imbalance in gut microbes triggers zonulin release, increasing gut permeability, antigen trafficking, and inflammation. Zonulin release can also increase blood-brain-barrier (BBB) permeability, triggering neuroinflammation. Importantly, ASD patients show changes in the diversity and composition of their gut bacteria. However, it is unknown whether their altered gut microbiota acts through the zonulin pathway to exacerbate behavioral symptoms. We are using zonulin-expressing transgenic mice (characterized by increased intestinal permeability), human gut organoids obtained from ASD children, and the zonulin antagonist AT1001, to determine whether a genetic predisposition for increased intestinal permeability (HP2-2 genotype) interacts with ASD gut microbiota to induce “leaky” gut and blood-brain barriers (BBB) and behavioral deficits. We intend to generate robust pre-clinical data leading to innovative targeted ASD treatments.

Robert K. Naviaux, MD, PhD
Professor of Genetics
Biochemical Genetics and Metabolism
Departments of Medicine, Pediatrics, and Pathology
Co-director, The Mitochondrial and Metabolic Disease Center (MMDC)
University of California, San Diego

Emerging therapeutics for ASD—shifting paradigms and improving outcomes with mitochondrial cell danger response (CDR) and healing cycle research

Broad-spectrum metabolomic and exposomic analyses were conducted in 4 independent cohorts of autism spectrum disorder (ASD). These results were compared to 12 other chronic complex disorders using machine learning techniques. Over 30 biochemical pathways were dysregulated in ASD. A core set of about 20 metabolic pathways was shared with ASD and coordinately dysregulated in every chronic complex disorder studied. These core pathways defined the cell danger response (CDR), which we found to persist abnormally and block healing in each disorder. Three programmed transformations in mitochondrial function, designated M1, M0, and M3, were required to progress from inflammation, to proliferation, and remodeling—the 3 stages of healing. Promising clinical trial results from Paxmedica using the drug suramin, and Jelikalite using transcranial optodynamic therapy (ODT) have recently been reported. In addition, a third promising approach using ATP efflux inhibition by pannexin channel blocking drugs being developed by Pannex Therapeutics may prove to be synergistic with the other approaches. Each of these three new approaches acts to restore normal mitochondrial dynamics needed for progress through the molecular stages of the healing cycle. These restore a more normal microbiome, autonomic nervous system balance, neuroendocrine signaling, improve sleep, and dozens of other neurotransmitter, chemical, and synaptic abnormalities present in ASD.

INDUSTRY PRESENTATIONS

Stewart Campbell, PhD (Session Chair)
CEO, Axial Biotherapeutics

Targeting bacterial metabolites as a strategy to manage irritability associated with autism

Research has shown that the gut flora of autistic children is different compared with non-autistic children. Axial Therapeutics and collaborators have identified certain bacteria-derived metabolites (neuroactive microbial metabolites) that are produced in the gut and have been shown in preclinical models to reach the brain resulting in altered myelination patterns and certain behavioral characteristics associated with autism. Axial is developing AB-2004, a novel gut-restricted therapeutic that removes these metabolites from the gastrointestinal (GI) tract, in an effort to help manage co-occurring conditions in those with autism.

A study of AB-2004 was conducted as an open label, single cohort, 8-week multiple dose escalation study in 12- to 17-year-olds designed to establish safety, tolerability, and adherence to the three-times-per-day dosing regimen. Thirty subjects were enrolled at three sites in Australia and New Zealand and 26 successfully completed the study. Safety was assessed by spontaneously reported adverse events as well as physical exams, blood samples, and urine samples. Exploratory endpoints included changes in key neuroactive microbial metabolites, changes in core and non-core autistic traits, and GI symptoms.

AB-2004 was found to be safe and well-tolerated with no drug-related adverse events. Significant reductions in plasma and urinary levels of several neuroactive microbial metabolites over the 8-week treatment were also observed, demonstrating target engagement of AB-2004 in the GI lumen. Additionally, irritability and anxiety assessment scores, as measured by the Aberrant Behavior Checklist-Irritability Subscale and Pediatric Anxiety Rating Scale, respectively, showed significant improvement over the 8-week treatment. Taken together, these data support that AB-2004 was safe and well-tolerated and informed the design of a currently enrolling global Phase 2 double-blind, randomized, placebo-controlled trial targeting irritability associated with autism in adolescents.

Eugenia Seingold, PhD
Chief Science Officer, JelikaLite Corp.

Transcranial Photobiomodulation (tPBM) May Reduce Symptoms of Autism in Children: a Randomized, Double-Blind, Placebo-Controlled, Randomized Study

Authors: Yuliy Fradkin, M.D., Sergey Burd, Ph.D., Luis De Taboada, Michael Hamblin, Ph.D., Margaret Naeser, Ph.D., Eugenia Steingold, Ph.D

Objective: To examine the effect of tBPM on the symptoms of Autism in 2-6 year old children.

Rationale: Multiple small pilot studies demonstrated that tPBM may be helpful in reducing symptoms of Depression (Cassano, et al 2018), TBI (Naeser et al, 2014; 2015), Dementia (Chao, 2018) and Autism (Leisman et al 2018, Ceranoglu et al, 2019). Furthermore, recent research has shown that tPBM improves brain connectivity (Dmochowski et al 2020) and alters brain oscillations (Zomorrodi et al 2019). The effect of tPBM on improving functional brain connectivity may make it an effective treatment of symptoms of Autism.

Method: We conducted a Randomized, Placebo Controlled clinical trial, with 30 participants (16 in treatment condition and 14 in sham-control condition). The participants were 2-6 year old children with a previous diagnosis of Autism. The treatment was administered twice a week, for 8 weeks. The treatment was administered through a Cognilum, a medical device, specifically designed for young children, which received Non-Significant Risk designation from the FDA. Cognilum delivered pulsed Near InfraRed Light to targeted brain areas. Childhood Autism Rating Scales was used to measure changes in participants' symptoms before and after the course treatment. Weekly interviews about children's behaviors and functioning were conducted with each parent. In addition, EEG was collected during each section.

Results: We found a significant reduction of symptoms as measured by Childhood Autism Rating Scales in treatment condition only (Mixed Design, ANOVA was used to analyze the results, $F=9.45$; $p<.05$). We also found a significant reverse correlation in the intensity of Delta brainwaves and the number of received treatment (for treatment condition only), $R2=.7845$, $p<.05$.

These results indicate that tPBM affects children's electrophysiology and may be an effective treatment of ASD. Furthermore, in the future, EEG could be used to guide the treatment and monitor a child's progress.

Neil Littman
Founder & CEO, Bioverge Inc.

Democratizing Access to Early-stage Healthcare Investments

Bioverge is an investment platform and syndicate that connects individual investors with highly curated investment opportunities at the intersection of health + tech (or TechBio). We help our members invest in the health-related causes they care about most and we help companies bridge the valley of death. At Bioverge, we believe we can all do well by doing good.

John Slattery
Co-founder, President & CEO, BioROSA

Metabolic Autism Prediction (MAP) Study: A multicenter prospective double-blind case/control study assessing metabolic prediction of ASD from a developmental pediatrics waitlist

BioROSA will give an update on their ongoing clinical trial for metabolic prediction of autism using BioROSA-developed laboratory methods.

Mark Smith, PhD
CEO, Finch Therapeutics

FIN-211, an investigational microbiome therapeutic in development for autism

Finch Therapeutics will give an update on the development of a therapeutic related to the microbiome, to benefit individuals with ASD.

Stephen O'Quinn, Pharm D
Vice President, Medical Affairs, Zynerba Pharmaceuticals

ZYN002 Cannabidiol Transdermal Gel Efficacy and Safety: Recent Clinical Research Advances in the Treatment of Autism and Fragile X Syndrome

ZYN002 is a pharmaceutically produced cannabidiol transdermal gel in development for the treatment of behavioral symptoms associated with autism spectrum disorder (ASD) and Fragile X Syndrome (FXS). FXS is the most common monogenic cause of ASD. The results of recently completed trials evaluating the safety and efficacy of ZYN002 in ASD and FXS will be discussed. The design of a new Phase 3 trial in FXS, RECONNECT, will also be reviewed. Data suggest that ZYN002 is well tolerated in children and adolescents aged 3 through 17 years. The most common treatment-related adverse event in patients receiving ZYN002 has been application site pain; occurring in less than 7% of patients and generally mild in severity. There have been no reports of significant laboratory changes, including liver function. Open-label efficacy data in ASD suggest ZYN002 may improve behavioral symptoms of ASD, including irritability, social withdrawal, and anxiety, as well as some core symptoms of ASD. Controlled clinical trials in ASD are warranted to confirm these effects. Data also demonstrate short-term and longer-term improvements in social avoidance in FXS in patients with complete or near complete methylation of the FMR1 gene. The RECONNECT trial is planned to confirm results in patients with FXS.

Erik Won
President & CMO, Wave Neuro

Biometric-Guided TMS for Kleefstra Syndrome

Kleefstra syndrome is a rare genetic condition that affects development and involves many body systems. Children with Kleefstra syndrome exhibit features of autism, developmental delay, communication difficulties, and low muscle tone (hypotonia). The condition is caused by a mutation in a gene called EHMT1 or the deletion of a specific region of chromosome 9 that includes EHMT1. Biometric-Guided TMS has shown some early promise in the treatment of Autism Spectrum Disorder (ASD), and based on the success of a Kleefstra Syndrome case there are plans to conduct a collaborative clinical trial between Wave Neuroscience, Boston Children's Hospital, Radboud University Nijmegen Medical Centre (Netherlands), and iDefine (501c3). This session will review scientific principles of the treatment approach, clinical outcomes, and the firsthand experience of a physician who is also the parent of a child with Kleefstra Syndrome.

Uli Chettipally, MD, MPH
CEO, Sirica Therapeutics

Sirica Therapeutics – Making Therapy Fun!

Autism spectrum disorder diagnoses are accelerating. Currently, behavioral therapy services are being strained. There is a growing demand that cannot be met in the future. The pandemic has shown that the traditional model of having the therapists do one on one sessions is harder due to the constraints of social distancing, vaccination requirements and wearing of masks. There is also the problem of inconsistent data, coming in slowly from these sessions to make quick, meaningful changes that will improve patient outcomes. We are building a therapeutic device by putting together a combination of technologies namely, robotics, virtual reality and machine learning that can solve some of the biggest challenges faced by this population. This device will use physical, mental and psychological tools to help create a program to calm behaviors, improve achievement and enhance neuroplasticity. Several thousand data points will be collected automatically and are stored in the cloud. Machine learning algorithms can make changes to the program very quickly. It can generate automatic progress reports. A therapist could run a few machines simultaneously while in the clinic or even remotely from a patient's home. It will be designed to be an adjunct to the one-on-one therapy.

Colleen Kraft, MD, MBA, FAAP
Senior Medical Director, Clinical Adoption, Cognoa
Professor of Pediatrics, Keck School of Medicine, University of Southern California

Streamlining the Current Autism Diagnostic Pathway

Lack of diagnostic tools for Autism Spectrum Disorder (ASD) in primary care settings and long wait lists for specialist assessment contribute to an average delay of 3 years between first parental concern and diagnosis. This prospective multi-site double-blind active comparator study compared the performance of an artificial intelligence-based device intended to aid primary care providers (PCPs) diagnose ASD, to specialist clinician diagnosis. Participants were 18-72-month-olds with developmental delay concern (425 completers). Comparison of device results to specialist diagnosis found the PPV: 80.8%, NPV: 98.3%, sensitivity: 98.4%, specificity: 78.9% for subjects with determinate device results. Device use could potentially expand timely, accurate and equitable ASD diagnosis in primary care.

James N. Woody, MD, PhD
CEO, MARAbiosystems

MaraBio, A Precision Medicine ASD Diagnostic Company

Mara Biosystems is an early-stage ASD precision medicine diagnostic and therapeutic company. The technology is based on the decade-long work of Dr. Judy Van de Water, of the UC Davis Mind Institute who discovered that the cause of a subset of autism was that 15-25% of mothers with ASD children had maternal antibodies directed against eight infant brain proteins. These maternal antibodies can cross the placental barrier at about day 100 and damage the child's brain in utero. Our test detects these antibodies in mothers. The initial use will be in families that have a child who has missed developmental milestones, has a positive M- Chat etc. even before definitive symptoms develop. The test can provide actionable information if the mother has MARA (Maternal Autism Related Autoantibodies) as the child is likely to be autistic and can enter early interventional therapy for the best outcomes. We have performed retrospective and prospective studies with over 1000 samples analyzed. Future indications include mothers with a prior ASD child, contemplating having another child, if MARA positive can provide risk. The company will not be testing pregnant women at this time but has a potential therapeutic to eliminate such antibodies that will be discussed.

Eugene Prahin
CFO, Yamo Pharmaceuticals

L1-79 for treatment of core symptoms of autism

Yamo proposes L1-79, a racemic mixture of DL-alpha Methyltyrosine e (DLAMPT) for the treatment of the core deficits in social communication and interaction in adolescents and young adults with the autism spectrum disorder (ASD). L1-79 is a tyrosine hydroxylase inhibitor known to decrease catecholamine biosynthesis by inhibiting the conversion of tyrosine to dihydroxy-phenylalanine (DOPA), the rate limiting step in catecholamine synthesis. L1-79 reduces the imbalance in the catecholaminergic system in a broad way that cannot be mimicked by selective receptor blockers (e.g. risperidone & aripiprazole) or lytic enzyme measures. Unlike dopamine receptor antagonists, whose targets are predominantly limited to more specific (and potentially less relevant) subtypes of central dopaminergic activity, L1-79's catecholamine-based mechanism of action (MOA) is the first therapy based on a rationale that allows for a more expansive theory of ASD. By taking a broader spectrum approach in modulating multiple neurotransmitter systems that play a key role in social communication, interaction as well as autonomic function, L1-79 has the potential to improve the core symptoms of autism underlying the condition.