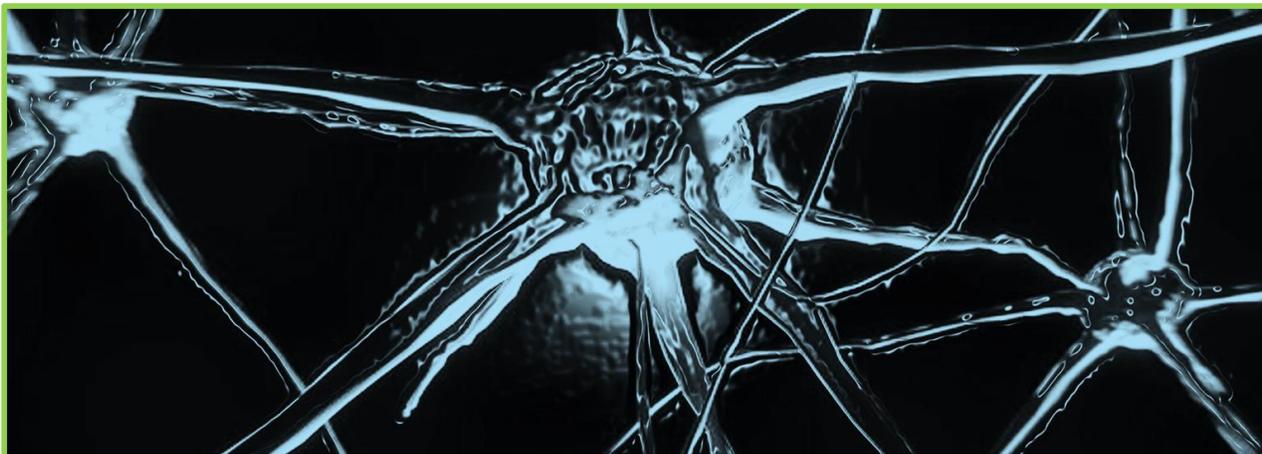


TRANSLATIONAL NEUROSCIENCE CENTER



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CLINICAL RESEARCH & REGULATORY TIPS

Inaugural Kleefstra Syndrome Family and Scientific Virtual Meeting: February 4, 2021

The Translational Neuroscience Center at Boston Children's Hospital is proud to announce a Kleefstra Syndrome Family and Scientific Virtual Meeting to be held on February 4, 2021. Please visit <https://www.idefine.org/copy-of-events> for more information. Scientific and clinical experts, including Professor Tjitske Kleefstra of Radboud University, Nijmegen, will update participants on the latest research into this rare genetic disorder. *An award from the BCH ICCTR supports this initiative.*

New England Regional Genetics Group Annual Meeting, December 3, 2020

Emerging Genomic-Based Treatments for Neurological Disorders

Part 1: Ataxia Telangiectasia

- Timothy Yu, MD, PHD
- Tori Suslovitch, MS, CGC

Part 2: Epilepsy

- Mustafa Sahin, MD, PHD
- Annapurna Poduri, MD, MPH

Registration link here:

<http://nergg.org/annual-conference/>



COVID-19 and TNC

Dr. Mustafa Sahin, director of the TNC, co-authored a Letter to the Editor titled "The Impact of COVID-19 on Individuals With Intellectual and Developmental Disabilities: Clinical and Scientific Priorities" for the American Journal of Psychiatry, which provides a critical scoping perspective from experts in the field about the impact of COVID on those with intellectual and developmental disabilities.

The Letter discusses social distancing, education, the "digital divide," and the effects of disruptions in special care and healthcare on pediatric patients, raising vital awareness, and the urgent need to develop further guidelines.

Published Online: August 28th, 2020 <https://doi.org/10.1176/appi.ajp.2020.20060780>

TNC CORE UPDATES

Human Neurobehavioral Core Service

The Human Neurobehavioral Core service (HNBCS) of the TNC, under the direction of Ellen Hanson, Ph.D., has continued to operate with Covid-19 restrictions put in place to ensure the provision of quality services has continued during the pandemic. The HNBCS aims to centralize, improve the efficiency of, and expand behavioral assessment resources at Boston Children's Hospital. The staff of the HNBCS has over 20 years of experience in research design, neurodevelopmental testing, and analysis. Consultation is provided to investigators on study conceptualization and design, grant development, IRB protocol development, appropriate instrument selection, and data analysis. The HNBCS team also assists investigators in identifying national and international programs for collaboration.

The HNBS staff have the specialized training necessary to administer over 100 phenotyping measures. Dr. Hanson is also a certified trainer for autism assessment measures (ADOS and ADI-R). The testing provided by the HNBCS involves many areas of development, including behavioral functioning and psychosocial adjustment; cognitive ability ("IQ"); neuropsychiatric (e.g., processing speed, executive functioning, attention, inhibition); adaptive functioning; motor and language development; psychiatric symptoms and diagnosis as well as diagnosis-specific measures.

The HNBCS has been able to make significant adaptations for COVID-19 restrictions. The team has modified many protocol measures to be performed via videoconference/telephone or reduced in-person contact. In addition, they have been able to add research staff to allow the expansion of hours of service to accommodate socially distanced in-person visits with ample cleaning time between visits.

Recently, Dr. Hanson has observed that some children with developmental difficulties appear to be exhibiting significant regression in a number of skills and increases in negative behaviors during the pandemic and subsequent school and therapeutic service changes, including shutdown/remote learning. These findings have been shown through clinical observation, parent reports, and preliminary review of data.

Cancellation and difficulty in accessing therapeutic services, as well as the lack of in-person interactions, are hypothesized to be the main causative factor of these issues. The TNC is currently pursuing the collection of quantitative data on returning patients to compare them to the metrics collected before the COVID pandemic. These data may provide vital information and potential guidelines for vulnerable children, including potential recommendations for increased accommodations during this time.

Additional literature recommended by TNC relevant to this issue:

Changes in access to educational and healthcare services for individuals with intellectual and developmental disabilities during COVID-19 restrictions. Jeste S, et al. J Intellect Disabil Res. 2020. PMID: 32939917



Human Neuron Core (HNC)

The HNC continues its mission to support all neurology-related screening and iPSC-based research for academic and industry investigators. While still operating at less than full capacity due to BCH Covid-19 precautions, the recent allowances to increase personnel in the laboratory propelled multiple cell-based projects towards completion. The HNC houses unique instruments representing an exceptional platform for preclinical disease modeling and drug discovery. Moreover, the HNC offers researchers the ability to become trained to use these instruments themselves in order to lower the costs for the researcher, accelerate timelines, and gain flexibility for starting new projects. Once training is complete, all instruments are available for independent use and sign-up via iLAB. Please review our new [COVID-19 standard operating procedures](#) before booking or arriving at the core.

An updated summary of the HNC equipment available for use:

Human Neuron Core Equipment
The Maestro Multielectrode Array (Axion Biosystems) is a high-throughput, electrophysiology recorder that enables analysis of neuronal activity. Ideal for large-scale cellular analysis, drug screening, and phenotyping of human neurons in multi-well plates.
The ArrayScan XTI (ThermoFisher Scientific) is an automated microscope and analysis suite detecting subsets of cells based on co-expressed markers, integrated with a live-cell imaging compound liquid handler. ArrayScan can capture real-time fluorescence changes with speeds up to 10 Hz with an enhanced CCD camera and seven-color LED light source, using 6-well to 384-well labware.
The Hamamatsu FDSS700ex is an advanced HTS-dispense and imaging system for cell-based optical detection of intracellular reactions and signal transmissions such as intracellular Ca ²⁺ flux, membrane potential, and ion channel.
The IncuCyte S3 is an industry-leading live-imaging screening incubator platform for population-based high-content analysis (HCA). It provides fully automated long-term, high-quality, live imaging of 6 labware pieces simultaneously.
The VIAFLO Liquid Handler allows for the easy exchange of liquid in 96-well or 384-well formats for changing media, adding compounds, setting up qPCR plates, making plate dilutions, plates fixing, staining, and washing.
The ImageXpress® Micro Confocal High-Content Imaging System is a state-of-the-art high content confocal imaging system with a high-resolution dual disk configuration and widefield modes. The cell incubator allows for high-content screening kinetic and time-lapse experiments, while the fluidics head performs compound addition, cell washing, facilitating assay development for High-Throughput Screens.
The Spinnaker robot arm works in conjunction with the two HCS imaging systems and the cytomat 5C hotelling incubator to provide scheduled autonomous plate imaging.
The Agilent Bravo is a versatile liquid handling platform controlled by a simple graphical user programmable interface. The 96-well microtip bravo head provides accurate liquid handling from 0.3-70µl. Our Bravo is coupled with a Benchcel plate stacker and Plateloc sealer.
The Mantis is a liquid handler with minimal priming volume for a single well-dispense of precious reagents. Fully programmable to perform NGS library prep (RNA-Seq), magnetic bead dispensing, PCR master mix, precious reagent dispensing, cell dispensing, PCR setup.
The Combi is a sterile peristaltic pump cell dispenser for 96 and 384 cell culture plates used to minimize variability. Priming volume is around 3-4ml and a 10-12 seconds dispense speed.

Biostatistical Services

Biostatistics Services are provided through the TNC by newly hired Dr. Bo Zhang, who provides study design and data analysis support for clinical and preclinical research projects. Services include developing a statistical analysis plan, sample size calculation, and grant proposal biostatistics support. Dr. Zhang is faculty in the Department of Biostatistics and the Department of Neurology and an investigator for the Institutional Centers for Clinical and Translational Research Biostatistics (ICCTR) and Research Design Center. He has supported several investigators by providing his expertise in study design and data analysis to evaluate the safety and effectiveness of clinical, biochemical, and behavioral interventions and to advance disease diagnosis and risk assessment.

Dr. Zhang is the lead biostatistician for several high-profile research programs in the Department of Neurology, including the multi-center Developmental Synaptopathies Consortium, led by Dr. Mustafa Sahin, in the Rare Disease Clinical Research Network. In a randomized, double-blind controlled trial of Everolimus in individuals with *PTEN* mutations, Dr. Zhang oversees the trial's progress along with the principal investigators and will lead the final data analysis for evaluating the safety and effectiveness. Dr. Zhang is also working with Dr. Simon Warfield on analyzing the imaging results produced by the TACERN: Tuberous Sclerosis Autism Center of Excellence Research Network consortium. These studies aim towards enhancing understanding of mechanisms underlying Autism Spectrum Disorder (ASD) and developing biomarkers thereof. All these studies draw heavily on the expertise of Dr. Zhang in the design and analysis of complex clinical trials, longitudinal data analysis, data mining, and statistical learning.

Clinical Research Highlights: Kleefstra Syndrome Clinical and Research Initiatives

A new multi-disciplinary Kleefstra Syndrome (KS) Clinic is being established at BCH through the generous support of the patient advocacy group, IDefine. Dr. Siddharth Srivastava will lead the Kleefstra Syndrome Clinic. As well as offering specialized care for individuals with this rare disorder, families will be provided the opportunity to participate in the Kleefstra Syndrome Natural History study, sponsored and led by Professor Tjitske Kleefstra of Radboud University. The Natural History study focuses on pre-adolescent and adolescent patients to better understand the regression course that has been observed in some patients. The TNC will also partner with Radboud University and Idefine to host the Inaugural Family and Scientific KS (Virtual) Meeting on February 4, 2021. This will mark the launch of the International KS Consortium for Clinical Trial Readiness, for which the TNC has been awarded a grant from the BCH ICCTR.

2020 AP-4 Research Conference Summary and Progress

Hosted by the Translational Neuroscience Center at Boston Children's Hospital, the 4th CureAP-4 Research Conference took place virtually this year, allowing participants from over ten countries to attend. Just like prior meetings, this year's conference brought together families affected by **AP-4-associated hereditary spastic paraplegia** (AP-4-HSP) and the growing community of clinicians and researchers working on a cure for this ultra-rare disease. In a series of short presentations, several research groups provided updates ranging from the cell biology of the AP-4 complex to gene therapy approaches, small molecule screens, and the first natural history study.

Alexandra Davies, Ph.D. from the Max-Planck Institute of Biochemistry in Germany, shared exciting new insights into additional cargo proteins of the AP-4 complex, including some that shed the light into the role of AP-4-mediated protein trafficking in brain development. Building on this, Darius Ebrahimi-Fakhari, MD, Ph.D., on behalf of the team at Boston Children's Hospital, reported first results from a large small-molecule screen for modulators of AP-4 function in patient-derived cells, including from a large library of novel compounds provided by Astellas Pharma Inc./Mitobridge Inc. through a joint research agreement with Boston Children's Hospital.

Next, João Cruzeiro, Ph.D., and Mimoun Azzouz, Ph.D. from the University of Sheffield and Xin Chen, MD, Ph.D. from the University of Texas Southwestern provided updates on the development of AAV9-based gene therapies for SPG47 and SPG50, including crucial proof-of-principle experiments in newly created knockout mouse models.

Finally, Darius Ebrahimi-Fakhari, MD, Ph.D., provided updates on the **International Registry and Natural History Study for AP-4-HSP**, which has now enrolled over 200 individuals from around the world. New results include a systematic quantitative analysis of brain MRI scans that identified patterns for diagnosis and disease progression and the first longitudinal clinical data from this growing cohort. The meeting was well attended by >50 researchers, clinicians, and families interested in AP-4-HSP and related disorders.

The discussion featured several topics, including strategies for developing a better understanding of the role of AP-4 in neurons, the next steps for preclinical development of gene therapy vectors, including a possible program for SPG52, and ways to promote the development of clinical and biochemical biomarkers. The next steps for obtaining approval by regulatory agencies and designing a phase 1 clinical trial for the gene therapy vectors under development were discussed.

Clinical Research & Regulatory Tips

Watch for the Tips section in future newsletters. These tips are geared towards investigators and their study teams involved in clinical research. In this edition, we address the use of remote consenting.

REMOTE CONSENT FAQs:

Due to the current COVID19 situation, many research teams may be utilizing alternative options to in-person consent/assent. There are several approved options that BCH study teams can use to obtain consent/assent remotely. A Remote Consent FAQ document was created by the Clinical Research & Regulatory Affairs Service of the TNC to provide guidance on this topic. The document is available on the [COVID-19 Research Guidance and Resources](#) website.

For any clinical research or regulatory questions, please contact one of our Co-directors of Clinical Research & Regulatory Affairs Service:

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