The Translational Neuroscience Center (TNC) was launched by the Boston Children’s Hospital (BCH) departments and divisions of Developmental Medicine, Genetics and Genomics, Neurology, Neurobiology, Neurosurgery and Psychiatry to accelerate efficient translation of new ideas from today’s science into effective prevention, diagnosis, treatments and cures for pediatric nervous system disorders.

TNC awards pilot funding for projects in Autism Spectrum Disorders, Arteriovenous Malformations and Sturge-Weber syndrome

The TNC awarded 3 pilot grants to BCH investigators to for projects in translational neuroscience. Award recipients included: The Olympia Sports Autism Research Fund was awarded to Louis Kunkel, PhD, for the “Generation of conditional dystrophin knockout mice”. The Credit UnionKids at Heart Research Fund was awarded to Arin Greene, MD, and Joyce Bischoff, PhD, for “Endothelial cells with somatic mutations in GNAQ as a model for discovery of new therapies for Sturge-Weber syndrome”. The Warner Family Translational Research Fund to Katie Priclola, MD, and Edward Smith, MD, for “Axonal guidance factors as novel diagnostic and therapeutic targets in cerebral arteriovenous malformations”.

Congratulations to all our award recipients!

Alcobra conducting clinical trials for Fragile X at BCH

Investigators from Boston Children’s Hospital’s Fragile X Program including Lisa Prock, MD, MPH, (Developmental Medicine) Jonathan Picker, MD, PhD (Genetics and Genomics) and Kaizad Munshi, MD (Psychiatry) are currently involved in a randomized double blind placebo controlled clinical trial of Metadoxine extended release (XR) with Alcobra Pharma targeting inattention symptoms in adolescents and adults with Fragile X Syndrome. Inattention is often a significant clinical concern in individuals with Fragile X Syndrome. Based on improved measures of cognitive performance in a mouse model of Fragile X, Metadoxine is thought to be active on GABAergic and glutamatergic neurotransmission, but not active on dopamine and norepinephrine transmission. Metadoxine is therefore hypothesized to have a different mechanism of action than currently available stimulant and non-stimulant medications used to treat patients with ADHD symptoms - and potentially may have a positive therapeutic impact with a different side effect profile than currently available medications to treat symptoms of inattention.

MLSC awards 2.26 million dollars to BCH to construct Human Neuron Core facility to make stem cell derived neurons available to broad research community

BCH will consolidate the existing TNC Human Neuron Differentiation Service and FM Kirby Neurobiology Assay Development Screening Facility into a state of the art core facility to support phenotypic screening with patient derived neurons.
Autism Spectrum Disorder Biomarker trial nears completion

Boston Children’s Hospital is the coordinating site for the Autism Consortium’s Biomarkers in Autism: Bridging Basic Research with Clinical Research project. This pilot study is aimed at:

1) Developing process experience in engaging busy clinicians in clinical translational research within a collaborative multi-site study.

2) Determining correlations between a selected set of biomarkers (including behavioral history, physical findings and biochemical measures) and clinical presentation in children with autism spectrum disorder (ASD).

The project is multidisciplinary as it includes investigators and clinicians from developmental pediatrics, neurology and psychiatry. Clinicians at 5 clinical sites within the Autism Consortium are participating in this collaborative study: Boston Children’s Hospital (PI: Carolyn Bridgeman, MD), Lurie Center at Massachusetts General Hospital (PI: Yamini Howe, MD), The Floating Hospital for Children at Tufts Medical Center (PI: Monica Utman, MD, and Karen Miller, MD), Boston Medical Center (PI: Laura Sices, MD) and the University of Massachusetts Medical Center (PI: Jean Frazier, MD). The team at Boston Children’s includes Carolyn Bridgeman, MD (PI; Developmental Medicine), Stephanie Jo Brewster, MS, (project manager; Translational Neuroscience Center), Kate Pawlowski (study coordinator; Developmental Medicine & Genetics and Genomics) and study clinicians Leonard Rappaport, MD, MS, Elizabeth Harstad, MD, MPH, Alison Schonwald, MD and Laura Weissman, MD in Developmental Medicine and Sarah Spence, MD, PhD and April Levin, MD in Neurology.

(continued on Page 4)

Phase 2 trial of Everolimus in Tuberous Sclerosis completed at BCH

Mustafa Sahin, MD, PhD, led an investigator-initiated phase 2 clinical trial looking at the effect of everolimus on neurocognition and autism in individuals with tuberous sclerosis complex. Enrollment for this trial, which was launched in 2011, closed in July 2014 and the last patient’s last visit occurred in December 2014. The trial also took place at Cincinnati Children’s Hospital Medical Center led by Darcy Krueger, MD, PhD. Study participants were randomized into a treatment with everolimus or placebo group for a 6 month period. The study was sponsored by the TS Alliance, Autism Speaks and Novartis Pharmaceuticals.

Data from the trial is set for analysis in February 2015 and results are expected to be released in the spring.

MLSC Neuroscience Consortium awards BCH investigators grants to fund translational research

The MLSC sponsored an industry consortium of Massachusetts pharmaceutical companies working to develop new therapeutics for brain disorders. The consortium includes Abbvie, Biogen Idec, EMD Serono, Janssen, Merck and Sunovion Pharmaceuticals. This precompetitive consortium has awarded 2 grants to BCH investigators to initiate projects in translational neurosciences. The award recipients included:

Thomas Schwarz, PhD, for his proposal: “High Content Screen for modulators of mitochondrial motility”.

Hanno Steen, PhD, for his proposal: “Co-regulation Proteomics to identify targets of LRRK2 in Parkinson’s”.

TNC to spearhead rare disease study network with NIH grant

Under a five year, $6 million grant, the TNC will lead 10 medical centers in studying 3 rare genetic syndromes that often cause autism spectrum disorder (ASD) and intellectual disability (ID). While both ASD and ID have a variety of known genetic causes, some of them have been shown to impair similar cellular pathways in the brain. The 3 conditions to be studied by the Consortium are tuberous sclerosis complex (caused by mutations in the TSC1 and TSC2 genes), Phelan-McDermid syndrome (caused by SHANK2 mutations) and PTEN Hamartoma Tumor Syndrome (caused by PTEN mutations). These 3 rare diseases seem to affect certain shared pathways influencing the development of brain connections, or synapses.

The study’s ultimate goal is to launch clinical trials of new treatments and develop “biomarkers” that can be used to monitor treatment effectiveness for the 3 rare syndromes and possibly for broader groups of ASD/ID patients.

Through the grant, from NIH’s Rare Disease Clinical Research Network (RDCRN), the 10 centers have formed the Developmental Synaptopathies Consortium. The RDCRN is an initiative of the Office of Rare Disease Research (ORDR) and the National Center for Advancing Translational Sciences (NCATS). The grant is funded by collaboration among NCATS, NIH, NINDS and NCHD. The leading investigators in the Developmental Synaptopathies Consortium are:

Mustafa Sahin, MD, PhD, Principal Investigator, Boston Children’s Hospital
Audrey Thurm, PhD, Principal Investigator, NIH
Darcy Krueger, MD, PhD, Principal Investigator, Cincinnati Children’s Hospital Medical Center
Charis Eng, MD, PhD, Principal Investigator, University of California at Los Angeles
Antonio Hardan, MD, Principal Investigator, Stanford University
Martina Bebin, MD, Principal Investigator, University of Alabama at Birmingham
Joyce Wu, MD, Principal Investigator, University of California at Los Angeles
Hope Northrup, MD, Principal Investigator, University of Texas Health Sciences Center at Houston

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Joyce Wu, MD, Principal Investigator, University of California at Los Angeles
Hope Northrup, MD, Principal Investigator, University of Texas Health Sciences Center at Houston
National showcase of speakers
Dr. Elizabeth Berry-Kravis from Rush University Medical Center in Chicago spoke about current clinical trials in Fragile X Syndrome.

Academia and Industry Poster Session
Over 58 posters from 10 different organizations were available for discussion during the noon lunch break.

REGISTERED SYMPOSIUM ATTENDEES
30%
30% of those registered to attend came from industry or foundations

49%
49% of those registered to attend came from academia. 21% attendees could not be categorized based on their email address.

DON'T MISS OUT ON TNC NEWS!
To be added to the TNC distribution list contact us at: TNC@childrens.harvard.edu
Visit our website: http://www.childrenshospital.org/tnc

Inaugural Translational Neuroscience Center Symposium: “Translating Neural Circuits and Pathways into Treatment”

On October 29, 2014, the Translational Neuroscience Center (TNC) at Boston Children’s Hospital hosted its inaugural symposium at the Joseph B. Martin Conference Center at Harvard Medical School. The Symposium was open to scientists and physicians from academia, the pharmaceutical and biotechnology industries, disease-based foundations, and government. The all-day symposium showcased speakers from across the country to cover 3 scientific themes:

Preserving Neuromuscular Circuits:
“Translation of Gene Therapeutics in Neuromuscular Disease”
Brian Kaspar, PhD
Research Institute at Nationwide Children’s Hospital, Columbus, OH

“New Frontiers in ALS Research”
Merit Cudkowicz, MD, MSc
Massachusetts General Hospital, Boston, MA

Translating Neurodevelopmental Circuits:
“Translation of Targeted Treatments for Fragile X Syndrome: Hurdles and Hope”
Elizabeth Berry-Kravis, MD, PhD
Rush University Medical Center, Chicago, IL

“Correcting Disorders of Critical Period Brain Development”
Takao Hensch, PhD
FM Kirby Neurobiology Center
Boston Children’s Hospital, Boston, MA

Monitoring and Regenerating Neural Circuity
“Tools for Mapping and Fixing Brain Computations”
Ed Boyden, PhD
Massachusetts Institute of Technology, Cambridge, MA

“Neural Stem Cells in Models of Spinal Cord Injury”
Mark Tuszyński, MD, PhD
University of California, San Diego, CA

We are very grateful to our sponsors who provided funding to help support the cost of this educational event. Our sponsors included: Amgen, AstraZeneca, Biogen, Lundbeck and Merck.

UPCOMING EVENTS
TNC seminars are held in CLS12 located at 3 Blackfan Circle, Boston, MA
February 17: Jose Antonio Enriquez Dominguez, PhD
Centro Nacional de Investigaciones Cardiovasculares
(1000-1200 pm)
March 10: Yongjie Yang, PhD
Tufts University
April 14: Helen Tager-Flusberg, PhD
Boston University
May 15: George Mentis, PhD
Columbia University
June 9: Gerard Berry, MD
Boston Children’s Hospital

Stay tuned for Spinal Muscular Atrophy Research Day coming in April! Contact the TNC if you want to present your research.
Biomarkers for Early Onset Psychosis

The Developmental Neuropsychiatry Clinic (DNP) at BCH provides clinical care to children and adolescents with psychosis and high risk states for psychosis. Joseph Gonzalez-Heydrich, MD directs the clinic as well as a multidisciplinary team of researchers whose overarching goal is to translate insights from the pathophysiology of psychosis into treatments. A necessary step towards this goal is the characterization of endophenotypes that can detect if a potential translational therapy is performing as predicted in reversing psychotic pathophysiology. To that end the team has been using high density electroencephalograms (EEGs) to measure resting state coherence in brain activity and evoked response potentials to repeated simple auditory stimuli, measures of early information processing, to identify abnormalities in brain plasticity and network functioning in the psychosis high risk state and early psychosis. MRI measures of cortical thickness, connectivity, and inflammation are being gathered on the same subjects characterized electrophysiologically to look for correlations between MRI and EEG based measures. Given the goal of developing translational therapies, EEG and MRI measures that can be implemented in rodent models were chosen for study. Using genetic tools, the team has identified a high rate of copy number variants in patients with very early onset psychosis and is using exome sequencing to find additional genetic deficits in these children. The team is collecting fibroblasts and blood from patients with identified genetic defects associated with psychosis for generation of inducible pluripotent stem cell (iPSC) lines. Cellular biological characterization of neurons differentiated from the iPSC lines derived from these patients will be correlated with the endophenotypes characterized through behavioral, EEG, and MRI testing in the same patients. In vitro human neuron models from these well characterized patients will become an important research tool for high throughput screening to identify new treatments reversing cell autonomous deficits detected in these models. These treatments can be further studied in rodent models and early human studies in which the EEG and MRI endophenotypes can quickly detect the presence or absence of predicted reversal of pathophysiology leading to psychosis. Treatments successful at ameliorating cell autonomous defects in neuronal cultures and at correcting network level endophenotypic disturbances in rodent and short exposure human trials can then be brought into longer efficacy trials testing their ability to ameliorate behavioral deficits and halt or reverse the progression to psychosis in patients.

This comprehensive multidisciplinary program is directed by Joseph Gonzalez-Heydrich, MD (Psychiatry) in collaboration with Eugene D’Angelo, PhD (Psychology), Frank Duffy, MD (Electrophysiology-Neurology), Catherine Brownstein, MPH, PhD (Genetics), Robin Kleiman, PhD (iPSC and rodent models), Michelle Bosquet, PhD (Infant Psychology), Simon Warfield, PhD (MRI), and Ellen Grant, MD, PhD (MRI).

Autism Spectrum Disorders Biomarker trial nears completion (cont. from Pg. 2)

The identification of clinically validated biomarkers for ASDs could create a paradigm shift in the way clinicians diagnose and treat ASDs. Correlation of biomarkers with physical and behavioral phenotypes could also help with predicting and tracking outcomes and potentially, in the future, allow for targeting specific treatments. Biomarkers under study include platelet serotonin (5-hydroxytryptamine, 5-HT) and urinary melatonin as well as dysmorphology and neurological exam findings in children aged 5-10 years of age seen during a routine clinic visit. While increased levels of platelet serotonin have been reported in ASDs and the relationship between melatonin in sleep and neurodevelopment is well known, this study will examine the pre-pubertal levels of serotonin and melatonin and how they correlate with cognition, disruptive behavior and mood symptoms. In collaboration with Hanno Steen, PhD, (Boston Children’s Hospital), urinary proteomic studies are also being conducted to identify additional biomarkers for ASD. Proteomics has resulted in the identification of biomarkers for a variety of conditions including those linked to inflammatory response and autoimmune disease which is of particular interest given the increasing evidence of a link between ASD and alterations in inflammatory and immune responses.
Boston Children’s Hospital awarded $2.26 Million Dollars as part of the 2014 Competitive Capital Program from MLSC to build a Human Neuron Core

The promise of using in vitro human neuron disease models for drug screening is starting to bear fruit across a variety of neurological disorders that are vastly underserved by available therapies due, in part, to the paucity of translatable preclinical disease models. New examples of human iPSC-derived neuron models of neurological disorders have identified disease relevant phenotypes for these disorders including Alzheimer's disease, Amyotrophic lateral sclerosis (ALS), Parkinson's disease, Rett syndrome, and several copy number variants (CNVs) associated with neuropsychiatric disorders and autism. One recent example is the breakthrough Alzheimer's disease model wherein Rudy Tanzi, PhD and colleagues from MGH working with Clifford Woolf, MB, BCH, PhD and his lab at BCH successfully recapitulated amyloid-β and tau pathology in a single 3D human neural cell culture system derived from stem cells (Choi et al., Nature 2014). Another recent publication from Dr. Woolf's lab at BCH in collaboration with Kevin Eggn, PhD, at HSCI has highlighted techniques for reprogramming human fibroblasts into human nociceptive neurons to model mechanisms inherent in inflammatory pain hypersensitivity, and chemotherapy-induced neuropathy (Wainger, Buttermore, et al., Nature Neuroscience, November, 2014). Finally, a recent study from the same group identified the FDA approved drug Retigabine as a potential therapy for ALS (Wainger et al., Cell Reports 2014). This was hypothesized on the basis of drug induced reversal of hyperexcitability exhibited by human iPSC derived spinal motor neurons in vitro and has led to the initiation of a clinical trial for this drug in ALS at Massachusetts General Hospital (MGH). This new paradigm for disease modeling combined with drug screening has the potential to reshape the future of drug discovery for select disorders where a cell autonomous phenotype can be linked to an identified genotype.

Boston Children's Hospital has been awarded a $2.26M grant from the Massachusetts Life Sciences Center to create a Human Neuron Core that will operationalize this new paradigm for disease modeling using human neurons derived from clinically and genetically characterized patients to support preclinical screening of potential drugs in a core facility that is aligned with a broad network of Harvard neuroscience, neurology and stem cell expertise. The core will house personnel and newly purchased equipment in 1,500 square feet of renovated space provided by Boston Children’s Hospital (BCH) to enable fee-for-service provision of characterized human neurons derived from patient and healthy control inducible pluripotent stem cells (iPSC) lines generated by investigators throughout the Massachusetts research community. The core will help investigators develop phenotypic assays suitable for drug screening and repurposing. The MLSC will enable the TNC's existing human neuron differentiation service to merge with the FM Kirby Neurobiology Center's existing cellular assay development and screening core into a newly renovated core facility. It will also support the purchase of new equipment to support standardized phenotypic characterization of neurons and drug screening in a facility large enough to support requests from the basic and clinical research community within and outside of Harvard Medical School (HMS). The creation of this resource at BCH will accelerate research into new treatments that will specifically benefit children with neurodevelopmental, psychiatric and neurological disorders as well as neurological and psychiatric disorders to broadly facilitate new avenues of research for clinical investigators who lack direct experience in stem cell biology.

The core will be overseen by an experienced scientific team led by Mustafa Sahin, MD, PhD, Director of the Translational Neuroscience Center at Boston Children’s Hospital, Clifford Woolf, MB, BCH, PhD, Director FM Kirby Neurobiology Center and Director of Neuroscience Program, Harvard Stem Cell Institute and Robin Kleiman, PhD, Director of Preclinical Research, Translational Neuroscience Center at Boston Children’s Hospital.