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 announces “Introduction to Neuroscience Drug Discovery” summer workshop series

The TNC will sponsor a summer mini-series presented as a weekly lecture on the basics of preclinical drug discovery for the neuroscience community. It is intended to give translational neuroscientists insight into the small molecule drug discovery process and an overview of the local industrial landscape in neuroscience. Lectures from local industry experts will be offered to cover different disciplines represented on small molecule drug discovery project teams. Lectures will be in CLS12 on Wednesday afternoons from 4:00-5:00 between July 14-August 12. Don’t miss this opportunity!

E-mail the TNC to register: tnc@childrens.harvard.edu

July 15, 2015 Lecture 1: An overview of small molecule drug discovery and why disorders of the nervous system are particularly challenging. Speaker: Robin Kleiman, PhD, TNC

July 22, 2015 Lecture 2: Biology; Building preclinical rationale, efficacy and biomarker packages for new molecules. Speaker: Robin Kleiman, PhD, TNC

July 29, 2015 Lecture 3: Medicinal Chemistry; Launching a Structure-Activity-Relationship (SAR) campaign to optimize drug-like properties of a brain penetrant small molecule. Speaker: D. Johnny Bennett, PhD, Merck

August 5, 2015 Lecture 4; Drug Metabolism and Pharmacokinetics (DMPK); Measuring drug levels in the body, the target organ and relating exposure to pharmacological effects Speaker: Chris Shaffer, PhD, Pfizer

August 12, 2015 Lecture 5; Preclinical Toxicology; Establishing safety of new molecules to enable launch of an Investigational New Drug (IND). Speaker: Joe Brady, PhD, Pfizer

SMA Day at Boston Children’s
Basil Darras, MD addresses the audience at the annual Boston SMA research meeting. Researchers discussed therapeutic approaches to treat Spinal Muscular Atrophy

High Content Screening platform now available to wider research community

Array scan XTI image based high content screening instrument is installed at BCH and available to researchers inside and outside BCH. New features enable live cell imaging and liquid handling to permit monitoring of responses to specific stimuli. Sign up now with iLabs!!!

Launch Meeting for Developmental Synaptopathies Consortium clinical network held

Through a grant from the NIH’s Rare Diseases Clinical Research Network (RDCRN), 10 centers throughout the country formed the Developmental Synaptopathies Consortium, directed by Mustafa Sahin, MD, PhD to study 3 rare genetic syndromes that often cause autism spectrum disorder (ASD) and intellectual disability (ID). On April 23-24th, over 50 investigators and researchers involved in the Consortium came to Boston Children's Hospital, Waltham for the 2 day launch meeting. Attendees discussed the project goals and objectives, study implementation, and recruitment plan and also met with patient advocacy group representatives providing support for the consortium.

Save the Date!! Approaches to Studying Neurodevelopmental Disorders, October 26, 2105

The TNC, in collaboration with MIT and MGH will host the inaugural Boston-wide Neurodevelopmental Disorders Symposium in the Joseph B. Martin Conference Center at Harvard Medical School. This symposium, titled “Approaches to Study Neurodevelopmental Disorders”, will focus on innovative methods to probe the brain, outcome measures and novel treatments for the brain. Open to scientists and physicians from academia, industry, foundations and government, the day long symposium will include guest speakers and poster session for graduate students and post-doctoral fellows. More information about the conference registration and how to submit a poster will appear this summer.

PRADA supports career development for Research Assistants

On June 4th, the TNC co-sponsored a seminar with the Boston Children’s Hospital Program for Research Assistant Development & Achievement (PRADA). PRADA was established in 2010 with a mission “To provide a structured, supportive learning community for research assistants to develop into tomorrow’s leaders in healthcare.” Given this core tenet and the TNC’s training initiatives, the presentation was geared towards current research assistants at BCH interested in learning about various clinical and research careers m within healthcare. The seminar consisted of 5 panelists discussing their personal experience in furthering their education through a variety of career paths. The speaker panel included a clinical trials specialist and clinical research coordinator from the TNC as well as research assistants from the BCH Kirby Neurobiology Center and Department of Neurology. A wide range of training programs were discussed including MD, PhD and MD/PhD programs as well as Masters-level training in Genetic Counseling and in Mental Health Counseling and Behavioral Medicine. Attendees were treated to an exploration of the application, interview and selection process for the different programs pursued by the panelists and participated in an informative discussion about the myriad of resources available at BCH to facilitate one’s professional development in healthcare. We were excited to have participated in this worthwhile seminar in support of the talented research staff at BCH in becoming leaders in the field.

TNC and TIDO co-host panel discussion of strategies to enhance academia-industry collaboration

On May 5th a lunchtime panel discussion was held among a full house audience to ask questions and share insight with experienced industry and academic investigators. The panelists explored a range of various industry/academic relationships including:

- The expertise gained by collaborating with industry
- Various partnership paths to different types of agreements
- Identifying strategic alignment with companies
- Identifying potential partners
- Best practices for successful relationships

The session was moderated by Robin Kleiman, PhD, Head of Preclinical Research for the Translational Neuroscience Center at Boston Children’s Hospital.

A FAQ guide for investigators considering potential collaboration opportunities with industry partners was distributed and can be found posted on the web here: http://www.childrensinnovations.org/docs/TIDO_Company_relationships_FAQ.pdf

Academia-Industry Panelists included:

John McNeish, PhD, Head of Research Regenerative Medicine DPU at GlaxoSmithKline

Bruce Zetter, PhD, Charles Nowiszewski Professor of Cancer Biology, Vascular Biology Program, BCH

Irene Abrams, Senior Director, TIDO, BCH

Thank-you to all our panelists!
On April 17, 2015 the Translational Neuroscience Center (TNC) together with the SMA Program hosted the Boston SMA Day in the Garden Conference room at Boston Children’s Hospital. The meeting was open to scientists and physicians from academia, the pharmaceutical and biotechnology industries, and foundations. The research day showcased speakers from 3 companies and 3 academic laboratories.

**SMA Day presentations included:**

- “Clinical Trials in Spinal Muscular Atrophy: An Update” Speaker: Basil Darras, MD (BCH)
- “RG7800, an oral SMN2 splicing modifier for the treatment of Spinal Muscular Atrophy” Speaker: Anne Marquet, PhD (Roche)
- “AAV Gene Therapy for SMA” Speakers: Kathy Klinger/ Alison McVie-Wylie, PhD (Genzyme)
- “Upregulation of SMN gene expression by targeting a PRC2-associated lncRNA” Speaker: Caroline Woo, PhD (Ranarx)
- “Understanding PLS3, a genetic modifier of Spinal Muscular Atrophy” Speaker: Melissa Walsh, PhD (Brown University)
- “Aberrant microRNA Expression in Spinal Muscular Atrophy Motor Neurons” Speaker: Mary Wertz, PhD (BCH)
- “Discovering Therapeutics that Improve Skeletal Muscle Regeneration” Speaker: Feodor Price, PhD (HSCI)
- “Electrophysiologic biomarkers in severe and mild SMA mouse models” Speaker: Seward Rutkove, MD (BIDMC)

**Boston SMA Day: Update on Translational Research in Spinal Muscular Atrophy**

**UPCOMING EVENTS**

- TNC monthly seminars are held at noon in CLS12 located at 3 Blackfan Circle, Boston, MA
  - Seminars and Symposia
    - 12:00-July 7, 2015: Mat Pletcher, PhD from Autism Speaks: “MSSNG – An open access database of autism family whole genome sequences”
    - August: no seminar
    - 12:00-September 17, 2015: TBA
    - 12:00-October 13, 2015: Tarik Haydar, PhD from Boston University School of Medicine
  - October 26, 2015: Neurodevelopmental Disorders Symposium at the Joseph B Martin Center, Harvard Medical School New Research Building
    - Title: “Approaches to studying Neurodevelopmental disorders”
  - 12:00-November 10, 2015: Steve Roberds, PhD from The Tuberous Sclerosis Alliance
  - 12:00-December 8, 2015: Mike Quirk, PhD from Sage Therapeutics, Inc.

**REQUEST FOR APPLICATIONS!**

The TNC currently has 2 open RFAs for principal investigators at BCH to support pilot studies in translational research. Olympia Sports is sponsoring pilot projects for Autism. The Warner Family Trust is sponsoring new research projects in arteriovenous malformations (AVM). For more information please visit our website: [http://www.childrenshospital.org/tnc](http://www.childrenshospital.org/tnc)

**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](http://www.childrenshospital.org/tnc)
TNC Pilot Project Spotlight:

Drug targets for Sturge-Weber Syndrome

The Translational Neuroscience Center supports new research into finding drug targets that will treat neurodevelopmental disorders. This month’s TNC pilot project spotlight highlights research being supported in the laboratories of Drs. Joyce Bischoff and Arin Green. Our thanks to the Credit Union’s Kids at Heart Team for providing financial support through their participation in the Boston Marathon for this important work!

Sturge-Weber syndrome (SWS) is a rare neurological disorder that is associated with capillary malformations located on one or both sides of the face, typically on the upper eyelid and forehead. Capillary malformations are also present on the surface of the brain where they are thought to contribute to the neurologic deficits in SWS. Many children have capillary malformations, often referred to as port wine stain or port wine birth mark, without SWS, but an infant’s chance of having SWS increases ~2000 fold if s/he has a capillary malformation involving the orbit, cheek, or forehead. Capillary malformations consist of excessive and abnormal capillary/venule-like vessels in which both the endothelial cells and the surrounding smooth muscle cells have a chaotic appearance (Figure 1), suggesting that one or both cell types might carry a genetic alteration.

In 2013, a somatic mutation in GNAQ (p.R183Q) was identified in both capillary malformation and SWS specimens providing a clue to what might be causing abnormal blood vessels to form and grow in both conditions. GNAQ encodes Goq, the alpha subunit of heterotrimeric G protein Goq, which links G-protein coupled receptors to phospholipase-Cβ. The discovery of the GNAQ mutation provides a foothold for mechanistic studies but it is essential to determine which cell type(s) within the capillary malformation – in the skin and leptomeninges – carries the GNAQ mutation. We set out to do this by fractionating cells from skin capillary malformation specimens into hematopoietic, endothelial, smooth muscle and stromal cells. We showed that the GNAQ mutation is enriched in the endothelial cells from capillary malformation specimens (n=6) (manuscript in press). This provides a second foothold, the cellular context, in which to study the consequences of the GNAQ mutation, and means to develop cell-based screens to identify drugs that will counter the mutation’s deleterious effects. We can also build animal models by introducing GNAQ mutant endothelial cells into skin and brain vascular beds to form capillary malformation in vivo.

Our primary goal is to find drugs that will specifically target and prevent capillary malformations in order to alleviate the tissue destruction and neurologic deficits that can last a lifetime. More broadly, our studies may uncover unique mechanisms needed for capillary blood vessel morphogenesis and homeostasis, which could apply to tissue regeneration and repair.

Enrollment for clinical trial to treat seizures associated with PCDH19 gene mutations starting in July

Annapurna Poduri, MD, MPH is leading the BCH site of a multicenter, phase 2a, open-label proof of concept study looking at the safety and efficacy of ganaxolone as an adjunctive therapy for uncontrolled seizures in females who have a mutation in the PCDH19 gene. Mutations in PCDH19 are associated with early-onset epilepsy, intellectual disability and development delay, typically restricted to females. Enrollment for this trial is projected to begin in July 2015 and include 2-3 participants. Once enrolled and baseline seizure frequency is established, participants will be treated with ganaxolone for up to 26 weeks. This trial is also taking place at the University of California, San Francisco, Miami Children’s Hospital, Nationwide Hospital, Phoenix Children’s Hospital, Riley Children’s Hospital, and Sutter Health. The study is sponsored by Marinus Pharmaceuticals.
Neurons pose a unique set of challenges to assay development. First, they are difficult to maintain in a purified culture. They typically need to be maintained in a heterogeneous mixture of cell types, which can complicate well-based assays. Second, they are electrically active and will form synapses in culture that produce spontaneous activity in neuronal networks which trigger activity dependent changes in synapse strength. The combination of these two characteristics makes neuron cultures inherently variable from preparation to preparation. Variability is the enemy of robust assay development. Thus, working with neurons requires some specialized approaches to assay development that enable reliable signal detection to support high-throughput biology and drug screening.

The Assay Development and Screening Facility (ADSF) at Boston Children's Hospital now has a live cell compatible imaging platform for developing high content screening assays. The Array Scan XTI instrument from ThermoFisher acts as an automated fluorescent microscope to automatically collect images of stained cells that use up to 5 distinctly colored labels. In addition to imaging fixed cells stained with antibodies, the platform can maintain and image live cells that are expressing fluorescent calcium sensors, such as GCaMP6, or markers of particular organelles, such as mitoDS red to detect mitochondria. The instrument is equipped with automatic image analysis software that is well suited to measuring and monitoring many endpoints unique to neurons such as the number and length of axons and dendrites, the number and density of synapses or the internalization of surface membrane receptors following activation. These responses can be monitored as an average response of all the neurons in the well, or even as a function of a particular subset of neurons within the well, allowing investigators to follow the response of a particular subtype of neuron in a heterogeneous mixture of cell types. The Bravo automated liquid handler within the core can also be programmed to carry out automated immuno-staining and washing of 96 and 384 well plates containing cells to decrease the amount of hands on labor required to prepare samples for analysis. Common assay developed in conjunction with the Array scan include:

- Receptor Activation
- GPCR internalization

All equipment within the core facility can be accessed by community researchers on an hourly basis by establishing an iLabs account for billing through the BCH core facilities web page.


Core manager Lee Barrett, PhD is available to provide training and assistance to new users:  Lee.Barrett@childrens.harvard.edu