Rosamund Stone Zander Translational Neuroscience Center Selects Four Pilot Research Grant Awardees

The Rosamund Stone Zander Translational Neuroscience Center (RSZ TNC) at Boston Children's Hospital is delighted to announce the selection of this year's RSZ TNC Pilot Research Grant awardees. The mission of the RSZ TNC is to improve the lives of children with brain disorders via timely and efficient translation of scientific research through collaboration with Boston Children's Hospital's exceptional investigators, and in partnership with the external research community. To fulfill the goal of "timely and efficient translation," this grant aims to support translational research on neurodevelopmental disorders within the domains of *Preclinical Research, Drug Discovery, Therapeutic Development, Translational Biomarkers, and Gene-based Clinical Research and Trials*.

Translational Biomarkers and Therapeutic Development for Very Young Children Diagnosed with Autism Spectrum Disorder and Co-occurring Anxiety
Susan Faja, PhD and Katherine Driscoll, PhD | Division of Developmental Medicine

This study has the broad goal of evaluating new tools that could be used to improve the clinical care of autistic preschoolers who have co-occurring anxiety diagnoses. It plans to test four measures of the physical response to stressful situations because they have been validated in older autistic and neurotypical children, are feasible for autistic preschoolers, and provide an objective way to measure elevated anxiety prior to intervention or reduced anxiety following intervention. Itwill collect these measures before intervention to examine whether baseline scores predict intervention response, one month later to ensure that they provide a reliable measure of functioning, and after a behavioral intervention to examine whether changes in scores correspond to intervention response. It will use a behavioral intervention, Being Brave, that has been successfully used to reduce anxiety with autistic preschoolers to examine the four potential measures of anxiety response and regulation.

Discovery of Exosome-Based Biomarkers of Brain Development in Preterm Infants
Christopher Elitt, MD, PhD, and Zhigang He, PhD | Department of Neurology

Premature birth is a major problem is the United States and worldwide, disproportionally impacting Black and Brown families. Infants born early are at high risk for brain injuries, particularly injuries to the cells (oligodendrocytes) that later produce the insulation (myelin) around the wires in the brain. There is increasing evidence that nutritional deficits may underlie some of these injuries. A major problem is identifying babies in the Neonatal Intensive Care Units who have abnormal brain development from insufficient nutrition or other insults. This study proposes a new approach to discover biomarkers using tiny bubbles (exosomes) that are released by all cells into the blood. The exosomes contain information from the original cell (DNA, RNA, protein) providing a window into brain development. This study has recruited nearly 50 very preterm infants with blood, urine and breast milk samples, as well as obtained a picture of their brain (MRI) when they left the hospital. It will isolate exosomes, count the number of copies of every RNA (instructions from genes to make proteins) and then determine associations of these RNAs with zinc intake, blood zinc concentrations, brain development and body growth. These experiments are likely to discover biomarkers that can be introduced rapidly into the NICU, as well as identify novel genes or pathways critical for brain development and brain injury in preterm infants.

Identifying Novel Network-based EEG Biomarkers of Drug-Resistant and Surgery-Resistant Epilepsy in Children

Eleonora Tamilia, PhD | *Department of Pediatrics*
Alexander Rotenberg, MD, PhD | *Department of Neurology*

One of the most effective treatments for children with drug resistant epilepsy (DRE) is brain surgery for the removal of the brain area(s) that cause them to have seizures. However, most children with DRE spend precious years trying ineffective drugs while continuing to experience uncontrolled seizures. It would be ideal if we could make the diagnosis of DRE as soon as a patient experience their first seizure/s: However, it is quite unknown how to recognize DRE in a child that presents seizures until the lengthy process of trying several ASMs.

Based on this premise, the first aim of this study is to test whether we can identify drug resistant epilepsy (DRE) using the scalp EEG data recorded very early in the course of the disease, by developing a new methodology that focuses on understanding the brain network. For children with DRE, a significant challenge is to understand whether they will actually benefit from brain surgery or not, since not all patients with DRE can become seizure free with brain surgery. Thus, a second aim of this is to predict whether a patient will benefit from brain surgery by analyzing scalp EEG data recorded before surgery. To this purpose, a new methodology is proposed that estimates whether the area/s of the brain that cause the seizures can be fully targeted during brain surgery (and thus stop the seizures) or not.

Developing Splice-Modulating ASO Strategies For CDKL5 Deficiency Disorder

Timothy Yu, MD, PhD | *Division of Genetics and Genomics*
Heather Olson, MD, MS | *Department of Neurology*

Antisense oligonucleotides (ASOs) are promising drugs comprised of 15-20 nucleotide snippets of chemically modified RNA molecules that can be customized to modulate specific gene-splicing patterns for treating genetic disorders. The goal of this project is to develop ASO therapeutic strategy for CDKL5 deficiency disorder (CDD), a severe developmental and epileptic encephalopathy with no established disease modifying therapies. The present authors found at least 20 patients carrying CDKL5 mutations within in-frame exons beyond the kinase domain that are skippable, and more within exons that could be skipped with a combined exon skipping strategy to maintain the reading frame. This study will develop and test ASOs to rescue CDKL5 pathogenic variants by inducing in-frame exon deletions. Successful completion of this project will provide a foundation for launching new interventional clinical trials for CDD.

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The RSZ TNC Pilot Grant awardees will begin their funded research in November 2023 and have the opportunity to apply for a second year of funding pending research progress and success. New RSZ TNC Pilot Grant awards will be offered annually.

For more information, please contact TNC@childrens.harvard.edu or visit www.RSZTNC.org.