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DOERNBECHER CHILDREN'S Hospital
OHSU

2023 Friends of Doernbecher Grant Recipients

Andrew Arndt, M.D.
Project Title: The Effect of Music Therapy on Neonates with Neonatal Abstinence Syndrome
Award: $5,000

The primary purpose of this baseline study is to learn about the potential effects that live music therapy interventions may have on the pacification, stabilization, and development of infants diagnosed with pre-term or post term Neonatal Abstinence Syndrome (NAS) including infants with iatrogenic (hospital acquired) exposure to opioids which need to be withdrawn. Specifically, we will be examining the effects of six different modalities in music therapy, song of kin-influenced lullabies, vocal toning, contingent singing, release-holding and entrained heartbeat rhythms, and womb sounds on the symptoms of NAS that are evaluated using a standard of care scoring system. A recent study by Loewy et al. (2013) demonstrated that three music therapy interventions had an influential effect on the vital signs, feeding, and sleep of premature infants who were not diagnosed with NAS. We hope to learn if these music therapy interventions along with three other specifically designed live music interventions will help to decrease the distress symptoms associated with NAS or iatrogenic exposure to opioids that need to be withdrawn. Additionally, we hope to learn about the crying patterns (pitch range, melodic and rhythmic patterns) and potential of induced musical comfort sounds of infants diagnosed with NAS or iatrogenic exposure to opioids which need to be withdrawn. We would like to further investigate the culturally relevant influence of song of kin, developed music themes (Loewy, 2015) and the potential benefit this may have on the physiological and emotional impact of postpartum stress and its impact on caregivers and their capacity to bond in the caregiver-infant dyad (Bronkington et al., 2006).

Seshadri Balaji, Ph.D., MBBS, MRCP(UK) and James McNames, Ph.D.
Project Title: Development of a New Automated Method to Quantify Junctional Rhythm on Ambulatory Electrocardiogram
Award: $9,357.50

We aim to develop an automated method to quantify the extent of and abnormal heart rhythm called junctional rhythm (JR) on the ambulatory electrocardiogram (AECG). JR is common in certain children with heart surgery especially after the Fontan operation. The Fontan operation is done for children with a single ventricle heart. Fontan patients tend to be fragile circulation with limited ability to increase their cardiac output, so that even minor perturbations cause major deterioration. Dysfunction of the sinus node (which determines the heart rate and activation sequence) is common after the Fontan operation and results in JR (rhythm originating in the AV node, thus causing inefficiency due to loss of the contraction of the atria). We have shown that JR decreases the cardiac output and that pacing the heart's upper chamber (atrium) restores

atrial contraction, and improves the cardiac output. The long-term impact of JR on outcomes is thought to be bad but has not been studied. Automated "recognition" of JR is possible on standard ECG and AECG but quantification of JR (also known as the JR burden or %JR) on AECG is not currently possible. Manual quantification of %JR is laborious and cumbersome, involving poring through pages and pages of ECG recordings with potential inaccuracy unless done meticulously. An automated method to quantify %JR is urgently needed and would hugely impact the management of Fontan patients. We aim to develop an automated method to quantify %JR and validate it by comparing it to a meticulously performed manual quantification. The ability to quantitate %JR using an automated method will be paradigm-changing, leading to intensified follow-up using AECG in Fontan patients. Once quantified, those with a high %JR would be candidates for an atrial pacemaker which could lead to significantly improved long-term results. Also, the proposed project is needed to generate preliminary data and proof of technique for a large multi-center NIH grant application which is currently being developed. This project is a collaboration between Dr Seshadri Balaji, Pediatric Cardiologist at Doernbecher, and Dr James McNames, Professor of Computer Engineering and Signal Processing at Portland State University.

Zoe Beach, M.D./Ph.D. Candidate – Grad2
Project Title: Evaluating Efficacy of Targeted Therapies in PDGFRA Altered Pediatric Brain Tumors
Award: $22,500

Pediatric brain tumors are the most common type of pediatric solid tumor and unfortunately, are also the most common cause of cancer related death in children. Pediatric brain tumors include a broad spectrum of disease phenotypes and have 5-year survival rates ranging from 80% to almost 0%. Unfortunately, therapeutic strategies have not significantly improved and disease is often controlled through surgical resection followed by general chemotherapy and radiation. Due to the toxicity and young age at which patients receive these treatments, about two-thirds of children develop long-term health complications and are at significantly higher risk for developing a second cancer later in life. A barrier for inclusion of pediatric patients in clinical trials is often lack of robust pre-clinical data. Our goal is to provide this pre-clinical data and establish a pipeline for further data generation through creation of a brain tumor relevant mouse model to evaluate drug sensitivity. Significant progress has been made in understanding the molecular components in pediatric brain tumors and public data repositories such as Childhood Brain Tumor Network and Pediatric Bioportal, have been established making this valuable information widely accessible to researchers. Leveraging information from these datasets, we have identified alterations in the receptor tyrosine kinase, PDGFRA in 25% of all pediatric gliomas. We hypothesize that these alterations in PDGFRA represent pharmacologically actionable targets, and treatment with brain permeable PDGFRA directed inhibitors will reduce disease burden and improve survival and quality of life for these patients. The primary aims of this proposal is to 1) establish the functional significance of novel PDGFRA point mutations identified in pediatric glioma and 2) contribute preclinical data on the efficacy of targeted TKIs in the setting of RTK aberrant glial tumors, to support expansion of FDA approved usage of these inhibitors as well as support creation of new pediatric clinical trials, thus expanding potential therapeutic options for children with PDGFRA altered brain cancer.

Henry Milczuk, M.D.
Project Title: Speech, Language, and Ear Outcomes in Cleft Palate Patients
Award: $11,840

Cleft palate (with or without cleft lip) is one of the most common congenital differences in children, affecting approximately 1 in 500 births. These children and families face a number of challenges including recurrent ear disease, speech and language development, and speech understandability. For more than 20 years, clinical data for most patients who have attended the Craniofacial Disorders Clinic (CFD) at Doernbecher Children's Hospital (DCH) have been collected. Work by our team of investigators this past year, supported by a generous award from the Friends of Doernbecher, indicates that clinically important questions regarding treatment outcomes for cleft palate1, and the frequently associated problem of temporary hearing loss2, may be answered by further analysis of this large and rich data set. From our work with these data this past year we will have two presentations this Spring at two national meetings. We will report how secondary surgery for speech disorders that commonly affect cleft palate patients will only impact resonance changes in a significant way. Articulation errors and compensatory misarticulations need to be addressed with regular speech therapy1. Another presentation may affect the treatment plans used for infants who develop hearing loss before their cleft palate is repaired. The time when ear tubes are used to correct the hearing loss does not seem to affect language development2. These studies were possible from the statistical analysis funded by a Friends of Doernbecher Grant. We believe that there are other investigations which could yield further insights and improved management strategies for children born with cleft palate (with or without cleft lip). We may be able to recommend treatment strategies for school and community speech therapists, as well as the medical community that cares for children born with cleft palate, that may lead to improved outcomes and resource utilization.

Becky J. Riggs, M.D. and Erin Madriago, M.D.
Project Title: Cerebral Perfusion Mapping of Infants With Single Ventricle Congenital Heart Disease Using Contrast Enhanced Ultrasonography To Detect Cerebral Perfusion Changes Associated With Cardiac Surgery
Award: $21,332.50

Complex congenital heart disease, also known as single-ventricle physiology, occurs in infants with either a hypoplastic right or left ventricle. Advancements in single ventricle palliation surgery allow children with formerly lethal defects to survive into adulthood. The Norwood surgery, performed shortly after birth, reconstructs the aorta, creates a source of pulmonary blood flow, and removes the atrial septum. Next, the Bidirectional Glenn, which happens at 4-6 months of age, redirects blood draining from the head and arms directly to the lungs. This surgery leads to venous congestion, increased intracranial pressure, and possible changes in cerebral perfusion manifested by persistent post-surgical cerebral swelling. The final Fontan surgery, performed at 2-3 years, returns venous blood from the entire body directly to the lungs. While it is assumed that cerebral perfusion is altered by these surgeries, real-time qualitative and quantitative measures have never been reported. Approximately 80% of single ventricle survivors have significant neurodevelopmental disabilities, some of which might be triggered by alterations in cerebral perfusion caused by their life saving surgeries. Clinicians lack real-time quantifiable data about how and to what extent cerebral perfusion is altered by each of the 3 surgeries. Bedside cerebral contrast enhanced ultrasonography (CEUS) is an emerging tool with an unmatched neuroimaging capacity to non-invasively visualize cerebral perfusion and blood

flow dynamics in real-time. CEUS uses intravenous injection of ultrasound contrast agents to highlight blood vessels and tissue penetration to clearly show cerebral hypo-perfusion, hyper-perfusion, and re-perfusion injuries. Ultrasound contrast does not have any associated renal toxicity or ionizing radiation. Identification of cerebral perfusion changes associated with each single ventricle surgery could provide a therapeutic window of opportunity for interventions to correct or reverse abnormal cerebral perfusion and improve the infants' neurological outcomes. For each enrolled patient, we will perform cerebral CEUS in the operating room immediately before and after each of the three surgeries, described above, to determine precisely how cerebral blood flow is altered by each surgery. If alterations in cerebral blood flow are detected, weekly cerebral CEUS will be performed until discharge home.

Kevin Wright, Ph.D.
Project Title: Seizure Susceptibility in Mouse Models Of Dystroglycanopathy
Award: $48,039

Dystroglycanopathy is a form of congenital muscular dystrophy that is caused by defective function of the protein Dystroglycan. Dystroglycanopathy is often accompanied by a wide range of neurodevelopmental defects. Severe forms of dystroglycanopathy are characterized by widespread brain malformation, while patients with milder forms of the disease can present with cognitive defects despite having normal brain development by MRI. Patients with dystroglycanopathy also show a significantly increased incidence of seizures. Over the past several years, our lab has developed several mouse models that recapitulate the wide range of neurological defects present in dystroglycanopathy. Recently, we have identified a novel function for Dystroglycan in regulating the development and maintenance of inhibitory synapses between cells in the brain. The synaptic defects in these mouse models scale with the severity of Dystroglycan dysfunction, and results in increased seizure susceptibility. In this study, we propose to use whole-brain mapping of the neuronal activity marker c-Fos to better understand the progression of seizures in mouse models of dystroglycanopathy, and test whether synaptic defects and seizure susceptibility can be rescued by gene therapy or a novel pharmacological approach. If successful, these experiments will provide a potential therapeutic target for human patients.