Proposal Submission Confirmation

Submission ID: (2459)

Title: Bedside to Bench and Back: Translational Medicine in Epilepsy Genetics

Type: Proposal Submission

Status: Entered

Submitted By: (Lacey Smith, lacey.smith@childrens.harvard.edu)

Finanical Interest: No

Agreed to Terms and Agreement: Yes

Signature Date: 04/22/2016

Signature: Lacey Smith

Description:

The epilepsies are among the most common neurological conditions, affecting approximately 1% of the general population and are most common in childhood, affecting approximately 70 out of 100,000 children under the age of two years. Seizures are commonly encountered in the genetics clinic, as they are a common comorbidity of many known Mendelian disorders and many epilepsy syndromes have a strong genetic component. Recent data show that de novo alterations play an important role particularly in the early-onset epileptic encephalopathies.

Treatment for the epilepsies may be directed by seizure type, and many patients try multiple medications until they find one, or a combination of several, that help control seizures. In one of out every three people with epilepsy, seizures remain uncontrolled despite multiple medications. In some patients, the identification of the underlying molecular etiology can have therapeutic implications, leading to more targeted therapies. Recent technological advances in gene sequencing have led to a rapid increase in genes leading to epilepsies, particularly severe epilepsies of childhood. However, despite the success in gene discovery, the ability to provide targeted therapies has not paralleled this influx. The field of epilepsy genetics has now shifted efforts from focusing solely on gene discovery to investigating the mechanisms of seizure susceptibility and identifying targeted therapies in the laboratory that can be translated back to the clinic. In this session, we will present a translational approach to the diagnosis, providing examples of how gene discovery in the epilepsies has led to a better understanding of the underlying mechanisms, forming a basis for precision medicine.

During this session, we will have four speakers covering topics of translational epilepsy genetics. The first speaker will provide a comprehensive clinical overview of the genetic epilepsy syndromes, including important features relevant to the pediatric genetics clinic. The second speaker will discuss current available testing options for patients with epilepsy, including next generation panel testing and whole exome sequencing, the clinical utility and diagnostic yield, and challenges in variant interpretation in the context of the epilepsies. The third speaker will discuss current translational studies and clinical trials harnessing genetic

diagnoses to forge a path for precision medicine. This talk will cover many of the ongoing clinical trials for genetic epilepsies and outline the overall framework for future drug development. The fourth speaker will discuss functional analysis of identified genetic variants and screening of potential antiepileptic medications in zebrafish models of genetic epilepsies. This talk aims to present the spectrum of screening model systems for genetic epilepsies and will demonstrate how pathogenic variants identified in patients can be used for compound screening, allowing for rapid discovery of new compounds targeted at specific genetic epilepsies.

Target Audience: Clinicians, fellows, genetic counselors, laboratory personnel

Level of Audience: Intermediate

March of Dimes Clinical Genetics Conference/Plenary Session: No

R. Rodney Howell Symposium: No

Learning Objective 1:	Identify current gaps in knowledge that make obtaining a definitive genetic diagnosis in epilepsy particularly challenging
Learning Objective 2:	Outline efforts to provide functional analysis for variants in genes associated with epilepsy as well as efforts for drug-screening in animal models
Learning Objective 3:	Describe examples of how findings have translated back to the clinic to inform patient care, and identify ways in which such efforts need to be expanded
Learning Objective 4:	Describe ongoing collaborative efforts in clinical research relevant for patients with seizure disorders

Presenters:

First Name	Last Name	Email
Ingo	Helbig	helbigi@email.chop.edu
Topic: Seizures in the genetics clinic: a comprehensive update of genetic epilepsy syndromes		
Amanda	Bergner	abergner@ambrygen.com
Topic: Genetic testing in the epilepsies: Testing options, diagnostic yield, and unique challenges in variant interpretation		
Annapurna	Poduri	annapurna.poduri@childrens.harvard.edu
Topic: Personalized medicine approaches to specific genetic epilepsies: the 2017 landscape		
Jeremy	Ullman	jeremy.ullman@childrens.harvard.edu
Topic: Drug screening in zebrafish as a model system for genetic epilepsies: the path to precision medicine		

Moderators:

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Lacey	Smith	lacey.smith@childrens.harvard.edu
Ingo	Helbig	helbigi@email.chop.edu