

# topics:

---

## **Anatol Bragin PhD**

Several million of different types of brain injury occur every year in USA. Independent of the type of the brain injury, 2% - 50% of people develop epilepsy. As yet, there is no diagnostic tool that allows identification of patients with a high risk of development of epilepsy from the entire population of people experienced a brain injury. With the NIH support, recently NeuroInDx, Inc. found that microarray analysis of peripheral blood samples allows identifying a set of genes that are expressed differently within 1st week after status epilepticus in rats that develop and do not develop recurrent spontaneous seizures. This diagnostic tool opens the way for targeting preventive treatment of epilepsy during the latent period. Discussion will focus on the potential for this tool on prevention of epilepsy and what steps should be taken for rapid implementation of this diagnostic clinical tool.

## **Richard H. Finnell PhD**

The Texas A&M Institute for Genomic Medicine (TIGM)

Animal models have played a fundamental role in the discovery and characterization of all of the currently available frontline antiepileptic drugs. Although some believe that the new paradigm to identify the next generation of AEDs will rely upon in silico or in vitro systems in order to identify compounds that act mechanistically on novel targets/pathways, animal models, specifically genetically modified mouse models, will continue to be the 'gold standard' in the drug development pipeline. Such mouse models often identify compounds with unique physiological profiles that prove to have efficacy in a range of seizure types and may also have unanticipated effectiveness in non-epilepsy diseases, such as neuropathic pain, bipolar disorder, and migraine headaches.

TIGM maintains the world's largest collection of genetically modified mouse embryonic stem cell clones (>650,000 clones in both C57BL/6N and 129 mouse strains). Collectively, the resource has over 10,000 genes inactivated, including vast numbers of ES cell clones from channel genes, and other obvious AED targets. In many instances, hundreds of different ES cell clones exist for a single gene, representing the opportunity to perform 'personalized' approaches to matching candidate drug efficacy with specific gene variants that may be identical to those in humans. This presentation will focus on how the TIGM resource might be utilized in a high-throughput screen to identify small molecules that impact on specific genetic pathways to find new candidate compounds, or be used to create knockout mice for efficacy and toxicology studies.

### **Dan Lowenstein MD**

The Epilepsy Phenome/Genome Project (EPGP) is a large-scale, international, multi-institutional, collaborative research project aimed at advancing our understanding of the genetic basis of the most common forms of idiopathic and cryptogenic epilepsies and a subset of symptomatic epilepsy; i.e. epilepsies that are probably related to genetic predispositions or developmental anomalies rather than endogenous, acquired factors such as CNS infection, head trauma or stroke. The overall strategy of EPGP is to collect detailed, high quality phenotypic information on 3,750 epilepsy patients and 1,500 parental controls, and to use state-of-the-art genomic and computational methods to identify the contribution of genetic variation to: 1) the epilepsy phenotype, 2) developmental anomalies of the brain, and 3) the varied therapeutic response of patients treated with AEDs.

EPGP is funded by a grant from the NINDS.

### **Jeffrey Noebels MD, PhD**

Sudden unexplained death in epilepsy (SUDEP) is a catastrophic complication of idiopathic seizure disorders. "Seizure-like" episodes have long been reported in patients with cardiac long QT (LQT) syndromes who may also experience syncope, but the events are typically presumed to be of cardiac origin. We report the discovery of an epileptic phenotype in mice engineered with human dominant-negative LQT1 mutations associated with the most common form of LQT syndrome and sudden death. The KCNQ1 gene encoding the cardiac KCNQ1 (KvLQT1) slow delayed rectifier potassium channel, previously unlocalized in brain, is expressed throughout cortical, hippocampal and brainstem networks where neuronal repolarization defects can produce seizures and dysregulate autonomic control of the heart. We also defined the presence for the first time in brain of its regulatory subunit, KCNE1 (MinK), another LQT gene (LQT5), demonstrating that all known cardiac LQT genes are co-expressed in brain and heart. This novel gene for epilepsy is the first to reveal the dual arrhythmogenic potential of an ion channelopathy co-expressed in heart and brain, and validates diagnostic strategies to improve risk prediction of early mortality in individuals with epilepsy.

### **Geoffrey S. Pitt MD, PhD**

SUDEP derives from unknown causes, but cardiac arrhythmias--either associated with a seizure or occurring independently in a patient with epilepsy--have been proposed as one paradigm. Mutations in ion channels underlie certain inherited forms of epilepsy and also life-threatening cardiac arrhythmias. Often times, the biophysical effect of an epilepsy-causing mutation on a neuronal ion channel

mimics the effect of a arrhythmia-causing mutation on a cardiac ion channel. Few ion channel genes are expressed both in heart and brain. A unifying mechanism in which a mutation in one ion channel gene is responsible for both epilepsy and sudden cardiac death is therefore unlikely to represent a common paradigm. In contrast, certain ion channel auxiliary subunits, which can provide profound modulation on channel function, are expressed broadly; a mutation in one of these auxiliary subunits could affect both cardiac and neuronal ion channels, thereby providing the substrate for epilepsy and sudden cardiac death. This presentation will present examples of auxiliary subunits expressed both in brain and in heart and discuss how perturbed ion channel function, as a result of a mutation in these subunits, could be a new paradigm for certain cases of SUDEP.