

## Postdoctoral Research and Training Fellowship 2009 Award Recipients

**Name:** Camin Dean  
**Institution:** University of Wisconsin-Madison (Board of Regents University of Wisconsin System)  
**Project:** Regulation of BDNF Release by Synaptotagmin IV During Seizures  
**Preceptor:** Meyer Jackson, Ph.D.  
**Lay Summary:** Brain-derived neurotrophic factor (BDNF) is a molecule that is secreted by neurons, and increases the excitability of neuronal networks. If too much BDNF is secreted, neuronal excitation in the brain could increase to a point where a seizure is induced. It was recently discovered that a molecule called synaptotagmin-IV reduces BDNF secretion. Brain slices from mice that do not have syt-IV have stronger seizures than normal mice. This project proposes to test the hypothesis that BDNF induces seizures, and that syt-IV can prevent seizures by reducing BDNF release. The researchers will test this by inducing seizures in brain slices and studying where seizure activity occurs, examine the effect of increasing or decreasing BDNF on seizures, and see if genetically-modified mice that do not have BDNF have less seizure activity. Finally, using brain slices from a mouse where neurons that have increased syt-IV protein become fluorescent, the researchers will examine if seizure responses are reduced in brain areas that have more syt-IV (and therefore less BDNF secretion). These experiments could lead to new treatments for preventing and controlling seizures by changing the levels of BDNF in the brain.

**Name:** Chris Dulla  
**Institution:** Stanford University  
**Project:** Increased Evoked Glutamate Release in a Model of Polymicrogyria  
**Preceptor:** John R. Huegenard, Ph.D.  
**Lay Summary:** Some of the most difficult forms of epilepsy to treat occur when cortical development does not occur properly. This project will study an example of cortical malformation known as polymicrogyria. In a model of this disease, it has been found that there is increased neurotransmitter release as well as altered activation of neuronal networks in the malformed cortex as compared to healthy cortex. Using simultaneous imaging and electrical recording, the researchers will attempt to discern the cellular and molecular changes which result in the generation of epileptiform brain activity in this model of polymicrogyria. The

hope is that these studies will shed new light on why cortical malformations lead to epilepsy and provide novel molecular targets for therapeutic intervention.

**Name:** Leonardo Faria  
**Institution:** Stanford University  
**Project:** Function of presynaptic inhibitory terminals in undercut rats  
**Preceptor:** David A. Prince, M.D.  
**Lay Summary:** Decreased inhibition has been associated with different types of epilepsies and can be observed in all animal models and in patients. In the “undercut” model, previous investigations suggest that inhibition is decreased after injury. The preliminary results indicate that terminals are damaged and the probability of GABA (the main inhibitory neurotransmitter in the brain) release is decreased. Transmitter release is directly dependent on calcium dynamics. Therefore, the researcher will record from connected pairs of interneuron – pyramidal cell and investigate changes in the expression of calcium channels and its effect on inhibition. In addition, this project will study the probability of GABA release on fast spiking cells. These cells are inhibitory interneurons that influence the activity of principal cells.

**Name:** James Heida  
**Institution:** The TAMUS Health Science Center Research Foundation  
**Project:** The role of cytokines in the pathophysiology of hypoxic seizures in the rat  
**Preceptor:** Russell M. Sanchez, Ph.D.  
**Lay Summary:** Seizures caused by low oxygen are a common occurrence in newborns and infants. In some cases children go on to develop epilepsy afterwards. Understanding the processes by which the brain becomes rewired to a state of epilepsy after these seizures is of great importance. In this study, the researchers aim to examine new pathways involved in this rewiring that relate to components of the immune system, which affect the brain. The goal of this project is to be able to identify targets in the brain’s immune response that can be used to improve outcome after these and other types of early life seizures.

**Name:** Xiaolong Jiang  
**Institution:** The Rector and Visitors of the University of Virginia  
**Project:** L1 Interneuron Mechanisms Promoting Bursting in L5 Pyramidal Neurons  
**Preceptor:** J. Julius Zhu, Ph.D.  
**Lay Summary:** Excitability of neurons in the brain is tightly controlled by inhibitory signals. It is generally thought that seizures occur when inhibitory signals are pathophysiologically decreased, resulting in a

vicious circle of hyperexcitability within a large group of neurons. However, evidence supporting increased inhibitory signals has also been found in several types of epilepsy, including recent evidence in autosomal dominant nocturnal frontal lobe epilepsy. This proposed work and information thus obtained may provide a feasible explanation why both the decrease and increases in inhibition could result in seizure activity.

**Name:** Anna Korzeniewska  
**Institution:** Johns Hopkins University, School of Medicine  
**Project:** Preoperative discrimination of epileptogenic vs. eloquent cortical networks  
**Preceptor:** Nathan Earl Crone, M.D.  
**Lay Summary:** Epilepsy is caused by abnormal activity that spreads through brain networks that might otherwise be used for normal brain function. These networks can be studied with a newly developed method for analyzing EEG signals that measures the interactions between different brain regions during seizures or during normal brain functioning. The proposed research will study the activity of human cortical networks under both normal (cognitive) and abnormal (seizure) brain states, and will test whether this technique can help in planning epilepsy surgery, by identifying abnormal brain networks to be surgically removed, as well as normal brain networks to be spared.

**Name:** Sang Hun Lee  
**Institution:** The Regents of the University of California (Irvine)  
**Project:** The impact of blocking CB1R during febrile seizures on GABA release  
**Preceptor:** Ivan Soltesz, Ph.D.  
**Lay Summary:** Fever-induced (febrile) seizures affect about 4 percent of infants and young children between the ages of 3 months and 5 years in the United States and worldwide. Because of the high number of children exposed to febrile seizures, it is important to know if prolonged febrile seizures early in life result in long-term changes in neuronal excitability. In the proposed research, the aim is to examine the potential roles of cannabinoid receptors (which mediate the psychoactive effects of the biologically active compound of marijuana) in the brain on epilepsy using electrophysiology, immunocytochemistry, and neuroanatomy.

**Name:** Asht M. Mishra  
**Institution:** Yale University School of Medicine  
**Project:** Neuroimaging biomarkers and prevention of spike-wave epileptogenesis  
**Preceptor:** Hal Blemenfeld, M.D., Ph.D.

**Lay Summary:** Early treatment was recently found to suppress the development of generalized epilepsy in rats. For human clinical trials, a non-invasive method is needed to track brain changes during epilepsy development, and suppression of these changes with treatment. This project will validate an MRI method for monitoring treatment in a rat model, for application in humans.

**Name:** Eduardo Pineda  
**Institution:** The Regents of the University of California, Los Angeles  
**Project:** Long-Term Effects of Seizures in the Presence of Pre-Existing Inflammation  
**Preceptor:** Raman Sankar, M.D., Ph.D.  
**Lay Summary:** The proposal examines the role of inflammation of the brain that occurs early in life, in the development of epilepsy. Using an animal model of epilepsy, the researchers will study whether inflammation that coincides with early-life seizures exacerbates the course of epilepsy at an older age, and whether the use of anti-inflammatory drugs will prevent or alleviate the development of epilepsy. This study will be useful for the development of effective treatments for chronic epilepsy.

**Name:** Karthik Rajasekaran  
**Institution:** The Rector and Visitors of the University of Virginia  
**Project:** AMPA receptor mediated neurotransmission in prolonged status epilepticus  
**Preceptor:** Jaideep Kapur, Ph.D.  
**Lay Summary:** Seizures lasting more than 30 minutes (status epilepticus) can threaten life and must be stopped. Many patients with these seizures however fail to respond to currently used drugs. It is therefore necessary to develop new drugs that can control these seizures. The proposed study will help in the development of new drugs to control the condition.

**Name:** Noah Roy  
**Institution:** New York University School of Medicine  
**Project:** Cellular and molecular mechanisms of an epileptic phenotype  
**Preceptor:** Bernardo Rudy, M.D., Ph.D.  
**Lay Summary:** Healthy brain function depends on a precise balance of excitatory and inhibitory processes. This project addresses the role of a protein known to cause epilepsy in humans when mutated in regulating the activity of inhibitory cells in the mouse brain. Mice lacking this protein have epilepsy. One goal of this project is to study the changes in inhibitory cell activity in these mice. Another is to attempt to restore normal brain function in these mice by expressing the protein in a specific population of inhibitory cells.

This project will contribute to our understanding of the cellular and molecular mechanisms of epilepsy.

**Name:** Sridhar Sunderam  
**Institution:** The Pennsylvania State University  
**Project:** State of Vigilance Tracking for Seizure Prediction in a Rodent TLE Model  
**Preceptor:** Bruce J. Gluckman, Ph.D.  
**Lay Summary:** The long term goal is to develop, for use in implantable seizure control devices, methods for real-time tracking of state of vigilance in human epilepsy patients. The availability of a behavioral measure of seizure onset probability will improve the performance of existing seizure prediction and control algorithms.

**Name:** Satoko Tokuda  
**Institution:** The Jackson Laboratory  
**Project:** Spatial and temporal role of GRIA4 in a genetic model of absence epilepsy  
**Preceptor:** Wayne N. Frankel, Ph.D.  
**Lay Summary:** Absence seizures result from abnormal activity between two brain regions, the cerebral cortex and the thalamus. A cell-surface molecule called GRIA4 carries out excitatory activity in this circuit, and mice that lack GRIA4 are known to experience absence seizures. By using genetically engineered mice in which GRIA4 can be expressed conditionally, this study aims to understand a basic mechanism of epilepsy, by focusing on regional and temporal roles of GRIA4 in the development of disease.

**Name:** Thomas Urban  
**Institution:** Duke University Medical Center  
**Project:** Genome-wide association study of drug response in epilepsy  
**Preceptor:** David Benjamin Goldstein, Ph.D.  
**Lay Summary:** Epilepsy is a debilitating disorder affecting over two million people in the U.S. alone. Although many medications exist for the treatment of epilepsy, a large fraction of patients require several trials of different medications to achieve improvement in their condition, and some may never achieve complete seizure control with medication alone. Even among patients that achieve seizure control, many also suffer side effects from the medications, some with important impacts on quality of life. Thus, current standards of treatment for epilepsy are far less than optimal. In the current proposal, we aim to discover genetic variants that predict therapeutic response to anti-epileptic drugs in a large group of chronic epilepsy patients, using a genome-wide approach to capture the effects of all common genetic variation on treatment response. The goal of the study is to find genetic predictors that

may ultimately be used as diagnostic tests to guide treatment decisions for epilepsy patients. In addition, the study will help us to understand the biological reasons for the observed variability in treatment response among patients, and may guide future development of safer and more effective anti-epileptic drugs.

**Name:** Simon Waldbaum

**Institution:** University of Colorado Denver, Anschutz Medical Campus

**Project:** The role of mitochondrial oxidative stress in network synchronization

**Preceptor:** Manisha Patel, Ph.D.

**Lay Summary:** Epilepsy is a recent addition to the diverse neurological disorders in which mitochondrial oxidative stress and dysfunction has been implicated as a contributing factor. The fact that epilepsy occurs as a consequence of many inherited mitochondrial disorders and in mice deficient in mitochondrial antioxidants suggests that excessive mitochondrial reactive oxygen species (ROS) formation and resultant dysfunction can lead to increased seizure susceptibility contributing to epileptogenesis. The proposed experiments address the mechanisms between mitochondrial oxidative stress and epilepsy by examining the effects of modulating oxidative stress levels on network synchronization in the hippocampus. This proposal utilizes a genetically modified mouse completely lacking SOD2, a critical mitochondrial antioxidant, which has spontaneous and recurrent seizures to investigate the link between mitochondrial oxidative stress and epilepsy and develop novel targets for attenuating epileptogenesis aimed at mitochondrial bioenergetics and oxidative stress.