

FALL FY08 AWARDS ROSTER
PRE-DOCTORAL RESEARCH TRAINING FELLOWSHIPS

\$20,000 awards for one year

Name: Daniel Tice Barkmeier
Institution: Wayne State University
Project: Translating human gene expression profiles of interictal spiking into a rat model
Preceptor: Jeffrey A. Loeb, M.D., Ph.D.
Lay Summary: In addition to seizures, patients with epilepsy have another type of abnormal brain activity called 'interictal spikes.' Interictal spikes occur between seizures, and are much smaller discharges than seizures which do not spread across the brain, but they occur much more frequently than seizures. Previous studies on human epileptic brain tissues have identified a set of genes that are activated in the epileptic parts of the brain when compared to non-epileptic parts of the same patient's brain. However, the amount of gene activation did not correlate with seizure activity, but did correlate with the amount of interictal spiking in that area of brain. To determine whether interictal spiking alone is sufficient to induce the gene expression changes seen in epileptic brain areas, this project will create an animal model of interictal spiking. Gene expression changes in this animal model will be examined to see if they mirror the gene expression changes previously seen in humans. The hypothesis is that interictal spiking can induce the activity-dependent gene expression changes seen in epileptic areas, which affect neuronal connectivity and synapse plasticity.

Name: Joel Philip Baumgart
Institution: University of Virginia
Project: Structural Analysis of Low Voltage-activated Calcium Channels Associated with Absence Seizures
Preceptor: Edward Perez-Reyes, Ph.D.
Lay Summary: A region of the brain known as the thalamus acts as a relay station for nearly all of the information coming to the brain. The cells of the brain in general and those of the thalamus in particular are able to communicate information in the form of electrical currents via the flow of charged molecules known as ions. These currents are carried through specialized proteins in the cell membrane known as channels that allow various ions to travel from outside to inside the cell or vice-versa. The import of calcium into the cell is critically important to the function of brain cells, especially in the timing of cell activity. The calcium channel serves as a pore in the cell membrane through which calcium flows. A number of mutations, which modify the genetic code, have been found in calcium channels genes among those suffering from childhood absence epilepsy (CAE), which affects children between ages 3 and 10. These particular seizures produce brief episodes of blank staring associated with a characteristic 'spike and wave' pattern of firing activity among brain cells.

Those afflicted with CAE tend to have very frequent seizures. Given the important role calcium channels serve in absence epilepsy, experiments are needed to develop an understanding of the portions of these channels that determine this type of cell firing. To address this, mutant channels that are missing parts of the normal channel will be created and tested for a number of properties, namely, how much current flows through the mutant channel, how long the channel remains open or closed, and how many channels reside in the surface of the cell. The properties of the mutant channels will be measured against those of the normal channel. The studies proposed here can provide a significant advance in explaining why various mutations in certain regions of calcium channels modify the electric currents in brain cells and how such changes produce seizures. A clearer sense for the structure of ion channels provides a better chance to design effective pharmacological treatments when channel activity is out of balance, as seen in numerous forms of epilepsy. The ultimate goal in understanding the structural properties of calcium channels is to improve treatments for seizures in general, and for absence epilepsy in particular.

Name: Dario J. Englot
Institution: Yale University School of Medicine
Project: Ictal neocortical slowing in a rodent model of limbic seizures
Preceptor: Hal Blumenfeld, M.D., Ph.D.
Lay Summary: Partial seizures in patients with temporal lobe epilepsy are often associated with a loss of consciousness. This project will investigate brain activity in areas important for consciousness during partial seizures in rats. Insight into the mechanisms of loss of consciousness during temporal lobe seizures may lead to better treatments to prevent this consequence of epilepsy.

Name: Marcel Paz Goldshen-Ohm
Institution: University of Wisconsin-Madison
Project: Inter-subunit communication in the GABA_A receptor
Preceptor: Mathew V. Jones
Lay Summary: The GABA_A receptor is the major inhibitory neurotransmitter receptor in the central nervous system, and plays an important role in shaping the activity of neuronal networks required for normal cognitive function. Several mutations in this receptor are associated with epilepsy in humans, one of which may disrupt communication between the receptor's constituent subunits. The overall goal of this research is to elucidate the physical mechanisms underlying inter-subunit communication and to understand how its disruption can lead to pathologies such as epilepsy.

Sponsor: Lennox Trust Fund by American Epilepsy Society

Name: Robert F. Hunt, III
Institution: University of Kentucky
Project: Posttraumatic epileptiform activity following controlled cortical impact in mice
Preceptor: Bret N. Smith, Ph.D.
Lay Summary: Every 23s, an American sustains a traumatic brain injury (TBI), and TBI is one of the most common causes for developing epilepsy. Many patients suffer from seizures and develop posttraumatic epilepsy after TBI, and head injury patients often do not respond well to anti-epileptic drug treatments. The mechanisms by which brain injury leads to the onset of epilepsy are not well understood. One reason for this is that animal models for posttraumatic epilepsy have not been well developed. The goal of this research proposal is to identify cellular and functional changes which occur in a controlled cortical impact mouse model of head injury that are also associated with changes seen in temporal lobe epilepsy. Understanding the mechanisms by which brain injury causes seizures may help to promote more effective therapeutic strategies for treating posttraumatic epilepsy.

Name: Michelle Kron
Institution: University of Michigan
Project: Role of Adult Neurogenesis in Hippocampal Remodeling and Hyperexcitability During Pilocarpine-Induced Epileptogenesis
Preceptor: Jack M. Parent, M.D.
Lay Summary: One percent of the population, more than 3 million Americans, has epilepsy. Mesial temporal lobe epilepsy, or mTLE, is the most common type of intractable epilepsy in young adults. This proposal seeks to study changes in the brain that lead to experimental mTLE, specifically those at the cellular level that may involve neural stem cells.
Sponsor: **Fred Annegers Fellow by Epilepsy Foundation**

Name: Amber L. Martell
Institution: The University of Chicago
Project: Electrical Membrane Properties and Seizure Threshold: the Effect of NMDA on Intrinsic Bursting and Network Oscillations
Preceptor: Wim van Drongelen, Ph.D.
Lay Summary: The goal of this project is to understand the NMDA receptor interaction in seizure genesis by studying how intrinsic oscillation is generated in deep pyramidal neurons and how these neurons interact in a network to drive synchronized network bursts similar to epileptic discharges.
Sponsor: **American Epilepsy Society**

Name: Julie Beth Milder
Institution: University of Colorado at Denver and Health Sciences Center
Project: Oxidative stress-mediated adaptation: a protective mechanism underlying the ketogenic diet.
Preceptor: Manisha Patel, Ph.D.

Lay Summary: Epilepsy is a common neurological disorder. Unfortunately, as many as 30% of patients do not respond to current antiepileptic medications. For this reason, the ketogenic diet was developed, and it has been successful in treating seizures in children for many years. However, how the diet works remains a mystery. This project seeks to understand some of its underlying mechanisms with the hope of developing new therapies.

Sponsor: **American Epilepsy Society**

Name: Carol L. Peebles

Institution: J. David Gladstone Institute

Project: Elucidating Arc's role in Epileptogenesis and Synaptic Plasticity

Preceptor: Steven Finkbeiner, M.D., Ph.D.

Lay Summary: Seizure activity leads to rapid changes in the cells that make up our brain. Many of these changes fuel future seizure activity by making the cells more sensitive to excitation. However, cells also counteract these changes to prevent the harmful affects of hyperexcitation. This proposal studies how Arc, a protein produced in response to seizure, affects the brain excitability.

Name: Dalin Thomas Pulsipher

Institution: Rosalind Franklin University of Medicine and Science

Project: Thalamo-Frontal Circuitry and Executive Functioning in Childhood Idiopathic Generalized Epilepsy: A Longitudinal Study

Preceptor: Michael Seidenberg

Lay Summary: This study will examine the developmental course of cognition and brain structure in children with new-onset idiopathic generalized epilepsy (IGE). IGE is a very common pediatric epilepsy syndrome which is frequently characterized by learning and social difficulties. This study combines different methods of brain measurement and assessment of problem-solving skills in the investigation of the underlying features of brain development that may be associated with these difficulties. Specifically of interest are the thalamus (the brain's "relay station") and the frontal lobes (located at the front of the brain and responsible for impulse control, judgment, and planning). The frontal lobes and thalamus have been found to play an important role in "executive function", which consists of problem solving, planning, and organizing. These abilities are crucial for successful learning and effective social interpersonal relationships. There are now several techniques based on visualization of different aspects of brain growth which are available and capable of informing us about brain development and its relationship to learning and social abilities. For example, the researchers can look at the size of a brain region as well as its connection to other critical brain areas. However, there has been no previous attempts to use these multiple brain measurement methods in children with new onset epilepsy or to examine them over time in the same children. By comparing children with IGE to a group of children without epilepsy, new information will be gathered on the changes in brain growth and behaviors which are critical for effective learning and social interpersonal relationships. This will be the first study of its kind; combining multiple methods of brain

measurement to examine targeted areas of brain development and the examination of children at the time of their epilepsy onset and then re-examination two years later. This provides the unique opportunity to examine the initial impact of seizures and their potential influence during a critical period of development.

Name: Kerry-Ann Angella Stewart
Institution: University of Utah
Project: A novel murine model of viral encephalitis-induced seizures
Preceptor: Karen S. Wilcox, Ph.D.
Lay Summary: CNS infections are associated with an increased risk for seizures and epilepsy. This proposal aims to use a novel animal model to further elucidate the mechanisms underlying infection-induced seizures. It is anticipated that these studies will prove useful in the search for therapies to prevent epilepsy following CNS infection.
Sponsor: **American Epilepsy Society**

Name: Daisuke Takeshita
Institution: University of Missouri-St. Louis
Project: Imaging and modeling the effect of inhibition in focal neocortical seizures
Preceptor: Sonya Bahar, Ph.D.
Lay Summary: Epilepsy has been considered to be a hyper-synchronous (over-synchronized) state of neural activity in the brain although some studies have suggested that this is not necessarily the case. Some neurons are excitatory, meaning that their activity promotes activity in other neurons by chemical transmission, called synaptic transmission. Other neurons are inhibitory, meaning that their activity causes suppression in other neurons through synaptic transmission. Traditionally, epileptic seizures have been considered to result from neural hyper-excitation. Therefore, it may seem reasonable to assume that the decrease in inhibitory activity is a cause for epileptic seizures. In fact, the blockage of inhibitory neurons has been shown to cause epileptic activity in animal experiments, where basic mechanisms of epileptic seizures are investigated. However, recent studies suggest that inhibitory neurons may play a role in epileptic seizures. For example, an increase of inhibitory activity has been reported in animal models of epilepsy. Another study has shown that the blockage of inhibitory activity diminishes synchronized activity in neurons. Therefore, the role of inhibition in epileptic seizure has been controversial and further investigation is necessary to understand how epileptic seizures occur and to develop better treatment. In the proposed research project, experimental and computational approaches will be combined in order to investigate the relation between inhibition and synchrony in acute neocortical seizures. Computational studies will be performed in a nonlinear computer model of coupled neocortical neurons, where various parameters such as the ratio in number of inhibitory neurons to that of excitatory neurons will be tuned in order to gain an insight on how changes in those parameters affect synchronized activity of the network of neuron models. Experimentally,

voltage-sensitive dye imaging will be performed on an animal model of acute seizures in the rat neocortex in vivo. This research will investigate the spatiotemporal pattern in neural synchronization changes during the time course of epileptic seizure event under decreases in inhibitory activity.