

## OUR STORY

Citizens United for Research in Epilepsy (CURE), is the leading nongovernmental agency fully committed to funding research in epilepsy. CURE's mission is to cure epilepsy, transforming and saving millions of lives. We identify and fund cutting-edge research, challenging scientists worldwide to collaborate and innovate in pursuit of this goal.

**A BRIEF HISTORY:** The organization was founded in 1998 by Susan Axelrod and a small group of parents of children with epilepsy who were frustrated with their inability to protect their children from seizures and the side effects of medications. Unwilling to sit back, they joined forces to spearhead the search for a cure.

**OUR IMPACT:** CURE has led a dramatic shift in the epilepsy research community from simply treating seizures to enhancing understanding of underlying mechanisms and causes, so that cures and preventative strategies can be found. CURE's research program is cutting-edge, dynamic and responsive to new scientific opportunities and directions through both investigator-initiated grants and unprecedented scientific programs and initiatives.

## SIGNATURE PROGRAMS

Since its inception, CURE has been at the forefront of epilepsy research, raising over \$50 million to fund research and other programs that will lead the way to a cure for epilepsy.

### EPILEPSY GENETICS INITIATIVE (EGI)

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Many people don't know the cause of their epilepsy, but genetic research is changing that. The Epilepsy Genetics Initiative was founded to help broaden our understanding of the genetic causes of epilepsy—leading us toward personalized medicine, and bringing us one step closer to a cure.

**ABOUT THE INITIATIVE:** Made possible by a generous contribution from the John and Barbara Vogelstein Foundation, Epilepsy Genetics Initiative (EGI), a Signature Program of CURE, is advancing our understanding of the genetic causes of epilepsy. The vision is to improve the ways we prevent, diagnose, and treat this devastating disease. EGI is an initiative created to bridge the gap between people with epilepsy, clinicians, and researchers, and to advance precision medicine in epilepsy. EGI's centralized database holds the genetic (exome) data of people with epilepsy, and the data will be analyzed and reanalyzed until the cause of the patient's epilepsy is found. Findings will then be reported to the patient's treating physician and the data will be made available to advance cutting-edge research projects.

*CURE has been a leader in epilepsy genetics by:*

- Making exome data available for research.
- Identifying new genes associated with epilepsy as a result of reanalysis of exome data.

- Identifying treatments to try; treatments to avoid; and risk for SUDEP for certain genetic cases of epilepsy.
- Facilitating the collection of exome data to advance research; EGI has partnered with nearly 20 institutions, both US-based and abroad.
- Elevating awareness and funding.
- Helping doctors diagnose patients. To date 350 enrollments; with analysis already identifying a genetic diagnosis in two patients.
- Advancing precision medicine in epilepsy, exome data from EGI is currently being used to inform targeted research studies.

## POST-TRAUMATIC EPILEPSY (PTE)

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With the help of a \$10 million grant from the U.S. Department of Defense, CURE is creating a new, first-of-its-kind research program and focus on post-traumatic epilepsy (PTE) as a result of traumatic brain injury (TBI).

**ABOUT THE INITIATIVE:** This unprecedented, multi-disciplinary program will devote significant resources over five years toward research which will benefit veterans who have been affected by TBI and resulting PTE. The goal of CURE's new initiative is to establish a multi-center, multi-investigator research team that will rapidly translate patient-relevant findings at the molecular, cellular, and systems level into novel therapies to prevent the development of epilepsy from TBI. This "team science" model will establish a foundation of knowledge regarding what types of injury increase risk to development of epilepsy and how it is best studied in the laboratory.

The key aims of the program are for thought leaders in the field to address questions with a peer-reviewed approach. An External Advisory Council also provides scientific and logistical oversight over the selected investigative team. As science drives the initiative, additional funds will be awarded to further the understanding of PTE. We are committed to exploring the complex underlying mechanisms of post-traumatic epilepsy...and one day, being able to prevent it entirely.

## SUDDEN UNEXPECTED DEATH IN EPILEPSY (SUDEP)

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CURE is the leading private funder of Sudden Unexpected Death in Epilepsy (SUDEP) research, pioneering the focus on SUDEP since 2002.

**ABOUT THE INITIATIVE:** CURE launched a first-of-its-kind research program dedicated to Sudden Unexpected Death in Epilepsy (SUDEP) in 2004, funding our first grant to Carl L. Faingold, PhD. Since then, CURE has been leading efforts to create breakthroughs, and partnered with NINDS to host the first-ever scientific SUDEP meeting in 2008.

*CURE has been a leader in SUDEP by:*

- Awarding \$4.3M in SUDEP grants to date
- Collaborating with 41 SUDEP investigators
- Funding 33 total SUDEP grants/projects in 8 countries

- Revealing the link between SUDEP and genes in the brain and heart
- Funding 4 SUDEP registries
- Funding 6 animal models of SUDEP
- Elevating awareness and federal funding
- Helping established respiratory arrest as a leading cause of SUDEP
- Helping establish generalized tonic-clonic seizures as a clear risk factor
- Working with the American Academy of Neurology (AAN) and the American Epilepsy Society (AES) to create evidence-based practice guidelines for SUDEP

## INFANTILE SPASMS (IS) INITIATIVE

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The initiative's main goal is to support collaborative, milestone-driven efforts that advance the understanding of the underlying pathology of infantile spasms and lead to the development of a disease-modifying therapy or cure for infantile spasms.

**ABOUT THE INITIATIVE:** In a groundbreaking, multidisciplinary “team science” initiative, CURE awarded grants to eight teams of investigators to advance cutting-edge research to find a cure for infantile spasms, a rare childhood epilepsy syndrome. Infantile Spasms (IS) can have profoundly negative long-term developmental and cognitive consequences, and the treatments that are currently available are often ineffective and frequently associated with substantial adverse effects.

The lead investigators in CURE's IS Initiative, a scientific “dream team,” bring a wealth of expertise and perspectives that span adult and pediatric neurology, basic mechanisms of the epilepsies, animal modeling, human genetics and clinical trial design and execution.

“A big part of what we do at CURE is break down barriers—specifically barriers that have impeded progress toward a cure.” – Susan Axelrod

The projects associated with this multi-year, multimillion-dollar initiative involve investigators at multiple institutions emphasizing a novel, team approach to research. This unconventional research method encourages the investigators to function as a united team and remain focused on the common goal of identifying underlying causes and finding a cure.

“The Infantile Spasms Initiative is unique in that it involves focused multidisciplinary ‘team science’ that will be driven by the outcomes of the research in a responsive and timely manner. We are extremely excited about the potential that this focused effort has to further our understanding of the causes of infantile spasms and the translation of basic science into better treatments and eventually a cure for IS.” – Dr. H. Steve White, Senior Research Advisor, CURE

*Meet the multidisciplinary research team:*

- Chris Dulla, PhD – Tufts University
- Aristea Galanopoulou, MD, PhD – Albert Einstein College of Medicine
- Jeff Noebels, MD, PhD – Baylor College of Medicine
- John Swann, PhD – Baylor College of Medicine
- Libor Velisek, MD, PhD – New York Medical College

- Manisha Patel, PhD – University of Colorado Denver
- Doug Nordli, MD – Children’s Hospital of Los Angeles
- Elliott Sherr, MD, PhD – University of California, San Francisco

## CURE RESEARCH GRANTS

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CURE’s mission is based on the fact that research is the key to finding cures for the epilepsies. Each year, grants are funded based on promising trends in the field and the potential for breakthroughs in a specified area. These investigator-initiated grants are the cornerstone of CURE’s research portfolio.

**CURE Epilepsy Awards:** Two-year, \$250,000 awards focusing on scientific advances that have the potential to truly transform the lives of those affected by epilepsy, with prevention and disease modification as critical goals. Priority areas include: 1) Basic mechanisms of epilepsy, 2) Acquired epilepsies, 3) Pediatric epilepsies, 4) SUDEP, and 5) Treatment-resistant epilepsies.

### **2015 Challenge Awards:**

#### **LGI1 AUTOANTIBODIES AS A CAUSE AND THERAPEUTIC TARGET FOR SEIZURE CONTROL**

*David Henshall, PhD, Teresa Maloney, PhD*

*Royal College of Surgeons in Ireland/University of Oxford*

The immune system occasionally launches a strike on one of its own proteins, generating self(auto)antibodies. Autoantibodies against brain proteins have recently been discovered in patients with difficult-to-treat epilepsies of unknown cause, including some that bind a secreted protein involved in communication called LGI1. This project will test models of autoantibody transfer to determine if these LGI1 antibodies are sufficient to cause seizures and interfere with brain functions such as memory. We will also look at the molecular changes that occur after exposure to the autoantibodies to understand the mechanism by which they promote seizures.

#### **HMGB1 AS A TARGET AND A MECHANISTIC BIOMARKER OF EPILEPTOGENESIS**

*Annamaria Vezzani, PhD*

*Istituto di Ricerche Farmacologiche Mario Negri (IFRMN) - Milan, Italy*

The next generation of therapies for epilepsy needs to target the mechanisms intimately involved in making the brain susceptible to spontaneous seizures. Such drugs could be used to prevent the onset of epilepsy in susceptible individuals or favourably modify its course after the disease onset. A major area of interest in epilepsy research relates to inflammation. We have shown that one specific molecule, which is known by the acronym HMGB1, is closely involved in seizures, and its presence in epileptic brain tissue is an indicator of neuroinflammation. It is produced and released by injured brain cells and can be measured in the bloodstream. The project goals are to use experimental models to prove the HMGB1 involvement in epilepsy development and its comorbidities, the utility of blood HMGB1 for predicting disease development and the therapeutic response to treatment, and the anti-epileptogenic effects of a new combination of medically used drugs targeting HMGB1.

### **2015 CURE Award:**

#### **TARGETED DELIVERY OF CARBAMAZEPINE FOR IMPROVED ANTIEPILEPTIC DRUG THERAPY DURING PREGNANCY**

*Erik Rytting, PhD, Marxa Figueiredo, PhD*

*University of Texas, Galveston*

Because uncontrolled seizures during pregnancy can lead to serious consequences for both mother and child, pregnant women with epilepsy should continue their anti-seizure medication throughout pregnancy. However, prenatal exposure to such drugs is linked to increased risks for birth defects. The goal of this project is to develop nanoparticles that will accumulate in the brain to treat the epilepsy and thereby reduce the amount of medication crossing the placenta and affecting the baby’s development. If successful, this work will lay the foundation for preventing seizures in the mother while decreasing the risk of birth defects to the unborn child.

**2015 Pediatric Epilepsies Awards:****REGULATION OF CORTICAL INTERNEURON MIGRATION AND EPILEPSY**

*Natalia De Marco Garcia, PhD*

*Cornell University*

Many neurological illnesses including a subset of pediatric epilepsies are thought to arise during the development of the nervous system. Increasing experimental evidence points towards imbalances between the excitatory and inhibitory circuits in the brain as a prominent component in the generation of epilepsy. The goal of this proposal is to assess how environmental perturbations during a critical period of development affect inhibitory connections and lead to abnormal brain activity. We will focus our studies in a subset of inhibitory neurons since our previous work indicates that these neurons are exquisitely sensitive to environmental stress in newborns. We hope that our studies will inspire therapies to correct aberrant brain formation in epilepsy.

**A NOVEL THERAPEUTIC INTERVENTION OF DRAVET SYNDROME**

*Glenn King, PhD, Steven Petrou, PhD*

*The University of Queensland, Australia/Florey Institute of Neuroscience and Mental Health*

Dravet syndrome (DS) is a catastrophic pediatric epilepsy characterized by severe drug-resistant seizures, intellectual disability, autistic traits, movement disorders and increased risk of sudden death. Most DS cases are due to mutations in an ion channel known as Nav1.1 (gene named SCN1A) that is found in neurons responsible for calming brain activity. In DS, the aberrant function of these neurons leads to increased brain excitability and seizures. We have identified compounds that enhance Nav1.1 function in order to control seizures, and we aim to develop these molecules as therapies. This project has the potential to revolutionize the treatment of DS and related epilepsies.

**MOLECULAR GENETIC DECODING OF BRAIN SOMATIC MUTATIONS IN INTRACTABLE PEDIATRIC EPILEPSIES**

*Jeong Ho Lee, MD, PhD*

*Korea Advanced Institute of Science and Technology*

Genetic abnormalities in small areas of the brain can lead to disruption of the entire brain by interfering with normal neuronal signaling. Focal epilepsies in children are one example of this and genetic mutations arising in specific brain regions can lead to abnormally synchronized electrical discharges and seizures. In this project, we will systematically uncover mutations occurring in the brain of children with intractable epilepsies who have undergone epilepsy surgery. The identification of brain-only genetic mutations will not only reveal the cause of the epilepsy, but will also provide information on biomarkers and medically actionable targets, which are important as we seek to treat these childhood drug-resistant epilepsies.

**2015 Prevention of Acquired Epilepsies Awards:****TARGETING THE MTOR PATHWAY IN GLIOMA-ASSOCIATED EPILEPSY IN MICE AND HUMANS**

*Guy Mckhann, MD*

*Columbia University Medical Center*

Epilepsy is the most common presenting symptom of an adult glioma. A multidisciplinary team will study a mouse glioma model that closely parallels the human disease to determine when seizures arise, and we will see if we can prevent or treat seizures by blocking the mTOR pathway with an oral drug that is FDA approved for human use. We will also use EEG brain recordings before and during human surgery to determine the "seizure prone" electrically abnormal areas on the margins of tumors. Finally, we will establish a pre-clinical study in glioma patients in which we give patients an mTOR inhibitor the day prior to surgery and then study the resected tumor tissue to see whether this treatment decreases mTOR pathway activation and electrical excitability in the cells around the tumors.

**THE CONTRIBUTIONS OF CD74 TO ACQUIRED EPILEPSY**

*Karen Newell-Rogers, PhD, Lee Shapiro, PhD*

*Texas A&M University System Health Science Center*

Epilepsy occurs in 15 to 20% of traumatic brain injuries. Who acquires post-traumatic epilepsy (PTE), and why, is unknown. While injury type and severity influence who gets epilepsy, similar injuries can cause PTE in one person, but not in another. The answer to why similar injuries can have such different outcomes may lie in the differences between individuals' immune responses. TBI causes inflammation and can elicit an immune response. We have also

discovered that targeting components of the immune response can suppress inflammation after TBI. The purpose of this proposal is to determine if we can prevent PTE by selectively targeting a damaging immune response after TBI.

**MEASURING AND MODIFYING CORTICAL HYPEREXCITABILITY IN PATIENTS AT HIGH RISK FOR ACQUIRED EPILEPSY**

*Mouhsin Shafi, MD, PhD, Alvaro Pascual-Leone, PhD, Igor Korolnik, MD  
Beth Israel Deaconess Medical Center*

Epilepsy is a common complication of many acquired brain injuries such as stroke, brain infections, and traumatic brain injury. However, any one person's likelihood of acquiring epilepsy after a brain injury is usually low, and there are no tests to help identify which individuals are particularly likely to develop seizures. As a result, research to help prevent acquired epilepsy in patients has been difficult. Furthermore, there are no approved treatments that directly affect the brain processes involved in the development of epilepsy. We will utilize a noninvasive brain stimulation technique, Transcranial Magnetic Stimulation (TMS), in combination with electroencephalography (EEG) to evaluate brain excitability, and thereby the risk of developing epilepsy, in patients with an acquired brain infection called Progressive Multifocal Leukoencephalopathy (PML). We will then assess whether multiple sessions of repetitive TMS can decrease brain excitability in high-risk patients, and thus potentially prevent the development of seizures.

**2015 SUDEP Awards:****EMPLOYMENT OF IN VIVO BIOSIGNAL DYNAMICS AS BIOMARKERS OF SUDEP**

*Edward Glasscock, PhD, Leon Iasemidis, PhD  
LSU Health Sciences Center in Shreveport/Louisiana Tech University*

This research seeks to identify novel biological signal patterns that can be used as reliable markers to predict SUDEP risk. We will identify these biosignal patterns by performing innovative mathematical analyses of simultaneous recordings of brain, heart, and lung activity in a two gene model of human SUDEP (Scn2a, Kcna1 double mutant mouse). Currently, utilization of biosignal analyses for the study of SUDEP is very limited and mainly restricted to individual EEG analysis. The envisioned project has the potential to widen this field by applying bioengineering analytical principles to identify interactions and associations between biosignals that can be used to predict SUDEP risk.

**PILOT IN SILICO MORTALITY RISK ATTRIBUTION IN SUDEP AND SUDDEN DEATH IN THE YOUNG (SUDY) TO INFORM PRECISION MOLECULAR DIAGNOSTICS OF SUDDEN DEATH**

*Alica Goldman, MD, PhD, Tara Klassen, PhD, Torbjorn Tomson, MD, PhD  
Baylor College of Medicine/University of British Columbia/Karolinska Institutet*

Sudden unexpected death in the young (SUDY) is the tragic mortality affecting otherwise healthy individuals. It includes sudden death in epilepsy (SUDEP), sudden infant death (SIDS), and sudden cardiac death (SCD) syndromes and there are overlapping candidate mechanisms that seem to converge on cardiac, respiratory or autonomic (cra) pathways in all of these. We will perform whole genome sequencing on DNA samples from patients that died of SUDEP, SCD, and SIDS to understand the genomic variation in cardiac, respiratory or autonomic pathways and we will use bioinformatic analyses to understand the point of overlap in these genetic networks. The results of this work will inform models for risk prediction in SUDEP and in SUDY overall.

**PATIENT-SPECIFIC INDUCED PLURIPOTENT STEM CELL CARDIAC MYOCYTES AS PREDICTORS OF SUDEP RISK**

*Lori Isom, PhD, Jack Parent, PhD  
University of Michigan*

Mutations in ion channel genes cause Dravet Syndrome (DS) and several other forms of severe childhood epilepsy. Many of these ion channels, which are critical for electrically excitable tissues, are present in the heart in addition to the brain. We propose that heart rhythm may be altered in genetic epilepsy and that heart abnormalities may contribute to SUDEP. We were the first to demonstrate altered cardiac excitability in mouse models of DS caused by SCN1A and SCN1B mutations. Our new results suggest that DS patient-derived heart cells generated from skin cells using the induced pluripotent stem cell (iPSC) method have altered beating rates and ionic currents and may be useful in predicting SUDEP risk. We will test the hypothesis that genetic epilepsy patients who are at greater risk of SUDEP will exhibit a higher beating rate and higher levels of sodium current in their iPSC-cardiac heart cells compared to people who do not have epilepsy. If so, then our work may lead to a diagnostic test for SUDEP risk.

**Taking Flight Award:** One-year, \$100,000 awards that promote the careers of young epilepsy investigators, allowing development of a research focus independent of their mentor(s). We encourage studies that will provide new directions for epilepsy therapy, prevention, and ultimately a cure, and that will allow applicants to collect the data necessary to support a further funding by the National Institutes of Health (NIH) or other agencies.

**2015 Taking Flight Awards:**

**AUTONOMOUS SEIZURE PREVENTION USING BIOLUMINESCENCE-DRIVEN OPTOGENETICS (BLOG)**

*Omar Ahmed, PhD*

*Brown University*

Seizures arise due to over-active subtypes of brain cells. Our goal is to prevent seizures by helping individual brain cells self-regulate their own activity, without the need for invasive electrodes, monitoring devices or implanted batteries. To do so, we create a modification of optogenetics, a tool that uses light to alter the activity of specific cells. By causing brain cells to emit their own light when they get over-active, we will let them control their own activity automatically, without the need for external light sources. We call this new technique bioluminescence-driven optogenetics, or BLOG. This powerful technique holds the promise to be a novel, non-invasive way to treat many different kinds of epilepsies.

**GENETIC AND OPTOGENETIC DISSECTION OF SEIZURES IN RETT SYNDROME**

*Darren Goffin, PhD*

*The University of York, United Kingdom*

Rett syndrome (RTT) is a devastating neurological disorder that represents the second leading cause of intellectual disability in females. RTT patients suffer frequent and severe seizures that place a tremendous burden on patients and caregivers. Although models of RTT recapitulate many symptoms observed in patients, they exhibit few, if any, spontaneous seizures. Thus, the underlying cellular and circuit mechanisms leading to the manifestation of RTT-associated seizures remain unknown. We recently developed new models that exhibit robust RTT-associated behavioral and electrographic seizures. In this proposal, we will first dissect the specific cell types that mediate RTT-related seizures. Next, we will develop strategies to control seizure manifestation. These studies will provide new insights into the pathogenesis of seizures in RTT and may aid in the development of new strategies for their control.

**MODELING EPILEPTIC ENCEPHALOPATHIES IN HUMAN BRAIN ORGANOIDS**

*Gaia Novarino, PhD*

*Institute of Science and Technology, Austria*

Early infantile epileptic encephalopathies (EIEEs) are a group of devastating disorders characterized by intractable seizures, global developmental delay and intellectual disability. EIEEs are highly genetic, meaning that often a genetic mutation is the basis of the disorder, however, in most of the cases the underlying mutation is very rare. Recent data suggest that distinct EIEEs may converge along specific molecular pathways. Can we identify these points of convergence? We aim to employ human "mini brains" to compare the effect of a large number of genetic mutations and identify points of intersection between distinct forms of EIEEs. The identification of these molecules will be the basis of future studies aiming to develop novel treatments.

**EPIGENOMIC APPROACHES TO EPILEPSY**

*Gemma Carvill, PhD*

*University of Washington*

Mutations in a number of genes have been shown to cause epileptic encephalopathy, one of the most severe types of epilepsy. Many of these genes control the expression of other genes i.e. they are responsible for switching certain genes 'on' or 'off' during the development and/or functioning of the brain. Here, we will use a new genome-editing technology to introduce mutations into two of these genes and create neuronal models of epilepsy. We will then study how mutations in these genes disrupt gene expression, and which pathways are affected. Identifying these pathways is the first step in finding new targets for therapeutics and understanding how genetic mutations cause epilepsy.



**DECIPHERING THE GENE REGULATORY NETWORKS IN HUMAN INHIBITORY INTERNEURONS AND THEIR ROLE IN INFANTILE SPASMS***Ramon Birnbaum, PhD**Ben-Gurion University of the Negev, Israel*

Epilepsy is a complex and heterogeneous disease which makes it difficult to precisely diagnose and provide an effective treatment. A major cause of epilepsy could be mutations in gene regulatory elements that instruct genes when, where and at what levels to turn on or off. Disruption of these elements in human inhibitory interneurons could be a cause for infantile spasms, an early-onset epilepsy. Here, we will identify and characterize gene regulatory elements of human inhibitory interneurons that could be associated with infantile spasms. This study will pave the way for screening epilepsy patients for mutations not only in genes but also in these regulatory elements, thus improving our ability to genetically diagnose epilepsy and hence provide more effective treatments.

**Innovator Award:** One-year, \$50,000 awards that explore a highly innovative new concept or untested theory in entirely new avenues of investigation. Studies that may not be currently fundable by other agencies or other mechanisms because of their preliminary, innovative, or unconventional nature are prioritized.

**2015 Innovator Awards:****PERICYTE PDGFRB SIGNALING DURING SEIZURES: CHARACTERIZATION OF A NEW MECHANISM OF DISEASE***Nicola Marchi, PhD**CNRS Delegation Regionale Languedoc Roussillon, France*

Seizures remain difficult to control in a significant percentage of patients. Increasing evidence indicates that epilepsy can be caused by vascular disease in the brain and that abnormal neuronal activity is linked to blood vessel dysfunction in the brain. Targeting the damaged brain vasculature could represent a therapeutic approach to end seizures. We propose that a key brain vasculature receptor called PDGFRb regulates the brain's blood flow response to seizures, and we will explore whether modulation of the receptor using specific medications can stop seizures.

**EXOSOMES AS CARRIERS OF CIRCUIT ALTERATIONS IN EPILEPSY***Angelique Bordey, PhD**Yale University*

This research aims at gaining novel insights into the biological processes that lead to cognitive deficits and psychiatric problems in children with epilepsy. More specifically, this work will examine whether the transfer of small vesicles (called exosomes) between abnormal brain cells leads to changes in the surrounding brain wiring. We will focus on abnormal "epileptic" neurons, like those found in focal cortical dysplasia and tuberous sclerosis complex, and will examine whether these cells alter the structure or electrical activity of healthy, neighboring neurons through the release of exosomes. If exosomes released from "epileptic" neurons do alter the function of healthy neurons, this would open up an entirely new field of epilepsy research.

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**FRONTIERS IN RESEARCH SEMINAR SERIES**

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Epilepsy research is significantly underrepresented in University Seminar Series and Grand Rounds that take place at institutions across the country. With the support of the Nussenbaum-Vogelstein family, the goal of this program is to expose young researchers and clinicians to exciting epilepsy research, and to provide opportunities for young investigators to interact with a senior level epilepsy researcher.

**ASTROCYTE STRUCTURE AND FUNCTION: WHAT ARE THE "OTHER" CELLS OF THE BRAIN UP TO IN EXPERIMENTALLY-INDUCED EPILEPSY?***Tuesday, February 24, 2015 at University of California, Riverside***Speaker:** Karen Wilcox, PhD**Host:** Todd Fiacco, PhD and Devin Binder, MD, PhD**Talk Summary:** Temporal lobe epilepsy (TLE) is a devastating seizure disorder that is difficult to control with currently



available anti-seizure drugs. Decades of research in animal models have generated vast knowledge regarding functional changes in neurons in TLE. However very little is currently known about the role in TLE of astrocytes, the other major cell type of the brain. Furthermore, epilepsy is recognized as a 'circuit' disorder. Thus innovative ways to evaluate the contributions that both neurons and astrocytes make to aberrant excitatory circuit activity will be critical for the understanding of the emergent network activity that results in seizures. Dr. Wilcox will describe recent findings from her laboratory that have identified structural and functional changes in astrocytes soon after a TLE-inducing insult. In addition, she will present recent genetic approaches she and her collaborators have taken to image calcium signals, a marker of activity in both neurons and glial cells, both in vivo and ex vivo. It is anticipated that this work will lead to novel insights into the process of epileptogenesis at the network level and may identify disease-modifying therapeutic targets that have been missed due to a largely neurocentric view of seizure generation.

**SUDDEN UNEXPECTED DEATH IN EPILEPSY: WHAT ARE WE MISSING?**

*Thursday, April 2, 2015 at University of Toronto, Toronto Western Hospital*

**Speaker:** Orrin Devinsky, MD

**Host:** Danielle Andrade, MD, MSc

**Talk Summary:** Sudden unexpected death in epilepsy is a leading cause of mortality in people with epilepsy. The past decade has brought significant advances in our understanding of the epidemiology, risk factors, and the role of seizures in leading to the cascade of terminal physiological changes. However, we remain uncertain about the specific mechanisms that lead a rare minority of seizures to become fatal while the vast majority of similar intensity seizures are followed by full recovery. Dr Devinsky will provide a broad overview on our current knowledge of SUDEP from both clinical and research perspectives, including the role of serotonergic function and respiratory dysfunction. One focus will be areas of current thinking that may restrict our recognition of SUDEP - from limitations of definition and diagnosis that likely lead to a significant underestimate of SUDEP, the role of status as a model of SUDEP, and Sudden Unexplained Death in Childhood where the rate of febrile seizures is ten-fold higher than population controls. He will discuss the recently funded NINDS Center for SUDEP Research (CSR) and its portfolio of studies, the North American SUDEP Registry, as well as other research efforts that are ongoing. Finally, he will present current research on SUDEP prevention - from education to reduce risk factors to monitoring devices to detect seizures.

**SODIUM CHANNELS AND EPILEPSY: NEW INSIGHTS, CHALLENGES AND OPPORTUNITIES**

*Thursday, June 4, 2015 at UC Davis Medical Center (Sacramento)*

**Speaker:** Andrew Escayg, PhD

**Host:** Christoph Lossin, PhD and James Trimmer, PhD

**Talk Summary:** Voltage-gated sodium channels (VGSCs) have emerged as important epilepsy genes with mutations in the major brain isoforms, SCN1A, SCN2A, SCN3A and SCN8A, associated with a growing list of epilepsy subtypes. This presentation will focus on recent findings from the analysis of SCN1A and SCN8A mutations. The emerging data highlights the complexity of seizure generation, but importantly, also provides new opportunities for the development of improved treatments.

**SODIUM CHANNELS AND EPILEPSY: NEW INSIGHTS, CHALLENGES AND OPPORTUNITIES**

*Friday, June 5, 2015 at University of California, Davis*

**Speaker:** Andrew Escayg, PhD

**Host:** Christoph Lossin, PhD and James Trimmer, PhD

**Talk Summary:** Voltage-gated sodium channels (VGSCs) have emerged as important epilepsy genes with mutations in the major brain isoforms, SCN1A, SCN2A, SCN3A and SCN8A, associated with a growing list of epilepsy subtypes. This presentation will focus on recent findings from the analysis of SCN1A and SCN8A mutations. The emerging data highlights the complexity of seizure generation, but importantly, also provides new opportunities for the development of improved treatments.

**A DENDRITIC MECHANISM UNDERLYING EPILEPTOGENESIS IN TEMPORAL LOBE EPILEPSY: IMPLICATIONS FOR THERAPY**

*Wednesday, June 17, 2015 at Tufts University*

**Speaker:** Heinz Beck, MD, PhD

**Host:** Jamie Maguire, PhD and Chris Dulla, PhD

**Talk Summary:** The input-output relationship of neuronal networks depends both on their synaptic connectivity and on the intrinsic properties of their neuronal elements. In addition to altered synaptic properties, profound changes in

intrinsic neuronal properties are observed in many CNS disorders. We have found pronounced changes in intrinsic excitability in experimental epilepsy, consisting of a transient conversion of regular firing to burst-firing hippocampal neurons. This conversion is due to a selective functional up-regulation of T-type Cav3.2 channels in CA1 dendrites, mediated via specific Zn<sup>2+</sup>-dependent transcriptional mechanisms. Importantly, genetic deletion of Cav3.2 subunits, or transient application of the Cav3.2 blocking anticonvulsant eslicarbazepine, strongly attenuated the development of chronic epilepsy. These results suggest that Cav3.2-dependent increases in intrinsic excitability may be an important mechanism for epileptogenesis that can be influenced by a clinically employed anticonvulsant drug.

**ADULT NEUROGENESIS, MTOR SIGNALING AND THE DEVELOPMENT OF TEMPORAL LOBE EPILEPSY**

*Thursday, August 27, 2015 at Cleveland Clinic*

**Speaker:** Steve Danzer, PhD

**Host:** Hoonkyo Suh, PhD

**Talk Summary:** Aberrant integration of adult-generated dentate granule cells is implicated in the development of temporal lobe epilepsy. It has been known for decades that the hippocampal dentate gyrus rewires in animals and humans with temporal lobe epilepsy, and physiological evidence indicates that this rewiring promotes hyperexcitability. More recently, it has been established that adult-generated neurons are responsible for much of this rewiring, directly implicating these new cells in epileptogenesis. While substantial correlative evidence now exists suggesting a role for aberrantly integrated adult-generated cells in epilepsy, however, direct evidence is limited. Dr. Danzer's research program is aimed at establishing whether adult-neurogenesis plays a causative role in the development of temporal lobe epilepsy, and whether these cells can be manipulated to develop novel therapies. Dr. Danzer will show new data characterizing the origination of these cells from distinct granule cell progenitors, and will present pre-clinical data aimed at determining whether manipulating these cells can have disease-modifying effects in epilepsy. Findings focus on clonal analysis studies of granule cell progenitors, and on results demonstrating that genetically ablating adult-generated cells after an epileptogenic brain injury can mitigate epileptogenesis. Studies designed to establish the cell signaling pathways responsibility for aberrant cell integration, with particular emphasis on the mammalian target of rapamycin (mTOR) pathway, will also be discussed.

**DEVELOPMENTAL EFFECTS OF ANTIEPILEPTIC DRUGS**

*Friday, September 18, 2015 at Georgia State University*

**Speaker:** Kimford J. Meador, MD

**Host:** Mukesh Dhamala, PhD

**Talk Summary:** Antiepileptic Drugs (AEDs) have been known to be teratogens for over 50 years, but our knowledge of differential AED effects has developed predominately in the last decades. AED-induced teratogenicity includes both anatomical and behavioral effects. Typical major congenital malformations include heart defects, orofacial clefts, skeletal, urological and neural tube defects. The highest risk of malformations exists for valproate with intermediate risks for phenobarbital and topiramate. Overall, the lowest known risks of malformations are seen with carbamazepine, lamotrigine, levetiracetam, and oxcarbazepine. However, carbamazepine is associated with an increased risk of neural tube defects although less than valproate. Further, the risks of many AED monotherapies and polytherapy combinations remain unknown. Fetal AED exposure may also affect cognitive and behavioral outcomes. The highest risk exists for fetal valproate exposure, which has dose-dependent associations with reduced cognitive abilities across a range of domains. Valproate has also been linked to a risk for autism. Phenobarbital has also been associated with reduced cognitive outcomes. The lowest risks for adverse cognitive outcomes exist for carbamazepine, lamotrigine and levetiracetam. The behavioral/cognitive risks for other AEDs are unclear. The mechanisms by which AEDs affect developmental outcomes are not well defined. A prominent hypothesis for AED-induced malformations is that they are the result of free radical intermediate metabolites in the first trimester. In regards to behavioral teratogenesis, AED-induced apoptosis and impaired synaptogenesis in the 3rd trimester is a leading hypothesis. Additional research is critically needed to better understand the risks and mechanisms of AED-induced teratogenesis.

**PERINATAL HYPOXIC-ISCHEMIC ENCEPHALOPATHY: NEONATAL SEIZURES, EEG SUPPRESSION, AND EPILEPSY**

*Monday, October 5, 2015 at Barrow Neurological Institute at Phoenix Children's Hospital*

**Speaker:** Edward Dudek, PhD

**Host:** Matthew M. Troester, DO

**Talk Summary:** At the conclusion of this session, participants will be able to: Understand cellular mechanisms that are believed to contribute to acute seizures and chronic epileps, know hypothetical mechanisms underlying pediatric

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epilepsy after neonatal hypoxic-ischemic insults, and understand principles and controversies concerning the role of neonatal seizures and/or brain injury in acquired epilepsy.

**EPILEPSY THERAPIES OF THE FUTURE: THE LATEST TRANSLATIONAL RESEARCH**

*Wednesday, October 14, 2015 at Phillips University*

**Speaker:** Professor Matthew Walker, University College London

**Host:** Braxton Norwood, PhD

**Talk Summary:** Approximately 30% of people with epilepsy do not fully respond to our present drugs yet fewer than 10% of these people are suitable for curative epilepsy surgery, often because the epileptogenic zone is too widespread or overlaps with eloquent cortex. An alternative approach to resective surgery is the use of gene therapy to reduce the excitability of excitatory neurons or to increase the excitability of inhibitory neurons in the focus. There have been considerable advances in the development of viral vectors that self-inactivate and are not immunogenic, providing safe and effective methods for gene therapy. We have successfully used a lentiviral vector to overexpress an endogenous gene that encodes the potassium channel Kv1.1 and so have cured epilepsy in a model of focal neocortical epilepsy. A different approach is to express proteins that can be modulated on demand. We have used optogenetic (the expression of channels and ion pumps that are activated by coloured light) in order to increase or decrease neuronal excitability in specific neurons. Using a system in which an implanted light is activated when a seizure is detected, it is possible through optogenetics to suppress seizure activity. Rather than using light sensitive proteins, receptors have been developed that are activated by specific drugs – Designer Receptors Exclusively Activated by Designer Drugs (DREADDs). Using gene therapy to express in specific neurons a DREADD that is sensitive to an otherwise inert synthetic ligand, clozapine-N-oxide (CNO), we have been able to suppress seizure activity by the administration of CNO. Although human trials are some way off, there is a clear route to translation and it is likely that trials of gene therapy in the treatment of epilepsy will occur within the next decade.

**SPATIAL AND TEMPORAL PREDICTION OF SEIZURES IN HUMAN FOCAL EPILEPSY**

*Friday, November 6, 2015 at Dartmouth-Hitchcock Medical Center*

**Speaker:** Greg Worrell, MD, PhD

**Host:** Barbara Jobst, MD

**Talk Summary:** Advances in computation, recording technology, and devices are poised to transform how patients with drug resistant epilepsy are evaluated for epilepsy surgery and brain stimulation devices. In this talk Dr. Worrell will review recent advances, clinical applications, and future directions.

**EPILEPSY GENETICS--FROM DISCOVERY TO PRECISION MEDICINE**

*Friday, November 20, 2015 at University of Virginia*

**Speaker:** Ann Poduri, MD

**Host:** Laura Jansen, MD

**Talk Summary:** Unavailable