

## 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.

### **2016 CURE Epilepsy Awards:**

#### **THE ROLE OF NEURO-INFLAMMATION IN A RAT MODEL OF COMORBID EPILEPSY AND AUTISM**

*Daniel Barth, PhD*

*University of Colorado – Boulder*

Thirty percent of children with epilepsy also have autism and vice versa. Dr. Barth’s group has recently discovered that suspected environmental risk factors for autism, such as maternal stress and certain common prenatal drugs, only when combined, produce autism and epilepsy in offspring. These combinations also result in marked brain inflammation, a reaction of the immune system thought to contribute to both epilepsy and autism. They developed a rat model of epilepsy/autism to study the effects of combined environmental inflammatory factors, to establish human maternal guidelines and to explore anti-inflammatory strategies to prevent or reduce this severe neurological syndrome.

#### **GENETICS OF SUDDEN UNEXPECTED DEATH IN PEDIATRICS AND HIPPOCAMPAL PATHOLOGY—A NOVEL ENTITY LINKING SIDS AND SUDC TO EPILEPSY**

*Annapurna Poduri, MD, MPH*

*Children’s Hospital Boston*

Can genetics determine which children are at risk of sudden death? Sudden unexpected death in the young, which includes SIDS (Sudden Infant Death Syndrome), SUDEP (Sudden Unexpected Death in Epilepsy), and SUDC (Sudden Unexpected Death in Childhood), accounts for more deaths in the United States than all childhood cancers combined. The causes of death and how to identify those at risk remain largely unknown. Evidence suggests a biological link between SIDS, SUDEP, and SUDC. All display epilepsy-related defects in the hippocampus, a critical region of the brain involved in seizures, as well as a higher personal and familial rate of febrile seizures. The goal of this project is to find genes that underlie the hippocampal defects seen in each of these disorders, and thereby understand the biology of how SIDS, SUDEP, SUDC and febrile seizures are linked. This work may identify genetic and brain imaging biomarkers that can help determine who among children with febrile seizures, and their siblings, are at risk of death so that prevention strategies can be implemented.

#### **EPIGENETIC REGULATION OF TONIC INHIBITION IN EPILEPSY**

*Avtar Roopra, PhD*

*University of Wisconsin – Madison*

Epilepsy can be either acquired or genetic. In both cases, seizures can trigger long-term changes such as an imbalance between neuronal excitation and inhibition. Inhibition comes in two major flavors, both mediated by the neurotransmitter GABA acting through GABAA receptors: a) fast and brief synaptic transmission and b) constant activation of receptors by low ambient concentrations of GABA (i.e., “tonic inhibition”). A growing wealth of evidence shows that increases or decreases in tonic inhibition are associated with epilepsy; however, what controls the levels of genes important for tonic inhibition is unknown. All genes are controlled by transcription factors (TFs). Some TFs

control thousands of genes and are often called “Master Regulators”. Dr. Roopra’s data suggests that a Master Regulator called Polycomb (Pc) is induced in multiple epilepsy models and suppresses a GABAA receptor gene called delta that is normally required for tonic inhibition. Importantly, there are drugs already in clinical trials for other diseases that could be re-purposed to suppress Pc and restore GABA-delta expression and thus restore healthy levels of tonic inhibition.

#### **ABNORMAL VENTILATORY RESPONSE TO CO<sub>2</sub> IN EPILEPSY PATIENTS: A POTENTIAL BIOMARKER FOR SEIZURE INDUCED RESPIRATORY DEPRESSION & MODIFICATION BY SSRI**

*Rup Kamal Sainju, MD*

*University of Iowa – Iowa City*

Specific mechanisms of death in “Sudden unexpected death in epilepsy” (SUDEP) are not well understood, but seizure related breathing problems are probably important in many cases. Dr. Sainju’s team will investigate whether patients who have a depressed interictal breathing response to rising carbon dioxide levels in the blood are more likely to have seizure related breathing abnormalities. They also plan to test the effect of fluoxetine in reversing this depressed breathing response and in reducing the severity of seizure related breathing abnormalities. This study may identify a new biomarker for patients at high risk for SUDEP and a novel treatment to be tested in future studies.

#### **OREXIN TRIGGERS AUTONOMIC DESTABILIZATION IN SUDEP**

*Kristina Simeone, PhD*

*Creighton University*

Dr. Simeone’s overall goals are to determine a central trigger of SUDEP, identify novel biomarkers to better identify risk for and imminence of SUDEP, and identify a treatment to postpone and ultimately prevent SUDEP. Key events that lead to SUDEP include cardiac and respiratory failure. Failure of these two systems is attributed to a destabilization of the autonomic nervous system. They hypothesize that a neuropeptide is a central lynchpin that over a lifetime gains influence and progressively destabilizes these autonomic cardiorespiratory responses and ultimately results in SUDEP.

#### **FUNCTIONAL AND CLINICAL EVALUATION OF NMDA RECEPTOR MUTATIONS IN EPILEPTIC ENCEPHALOPATHY**

*Stephen Traynelis, PhD*

*Emory University*

Dr. Traynelis’ group will test whether FDA-approved drugs that block NMDA receptors (NMDARs) reduce the seizure burden in children with overactive NMDARs due to GRIN mutations. They will evaluate the effect of NMDAR mutations on receptor function and the sensitivity in vitro to candidate drugs (such as memantine), which will inform the use of these agents in patients. They will monitor seizure type and frequency, EEG, and developmental assessment before and after off-label treatment with FDA-approved NMDAR inhibitors. The project has the potential to impact the lives of patients whose seizures are refractory to current therapies by providing personalized, targeted therapy.

#### **GENETIC INFLUENCES ON EPILEPTOGENESIS AND BIOSUSCEPTIBILITY TO POST-TRAUMATIC EPILEPSY**

*Amy Wagner, MD*

*University of Pittsburgh*

Traumatic brain injury (TBI) is an ongoing public health challenge, and post-traumatic epilepsy (PTE) negatively impacts the recovery of individuals already coping with TBI and its comorbidities. PTE accounts for 20% of those with symptomatic seizures and 5% of those with any seizure in the general population. Despite these numbers, there are no accepted means of identifying who is at risk for developing PTE following injury. Dr. Wagner’s team plans to conduct studies that will have a transformative impact on treatment and prevention of PTE for individuals with both civilian and military TBI. They are partnering with the principal investigator of the Vietnam Veterans Head Injury Study (VHIS) to evaluate currently identified genetic variants in the form of a “gene risk score” (GRS) that will help quantify how genetics influence PTE risk. The GRS can be used to help identify who is at greatest risk for PTE and it can be used in partnership with clinical treatment studies to evaluate how personal genetics might influence treatment response and PTE prevention measures.

**NOVEL MODELS OF EPILEPTIC ENCEPHALOPATHIES***Mingshan Xue, PhD**Baylor College of Medicine*

Epileptic encephalopathies are a group of devastating pediatric neurological disorders, manifesting with aggressive seizures and significant neurological comorbidities. Despite the rapid progress in identifying the genetic causes of epileptic encephalopathies, our understanding of the underlying pathogenesis remains limited, which hinders the development of new therapeutic interventions. Dr. Xue's team aims to generate and validate novel mouse models of epileptic encephalopathies. They will utilize these models to understand how genetic deficits alter synaptic functions and cortical circuits, and to determine the reversibility of the neurological phenotypes in adulthood.

**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.

**2016 Taking Flight Awards:****MOLECULAR MECHANISMS OF EPILEPSY-CAUSING MUTATIONS IN THE IKM CHANNEL: ANTI-EPILEPTIC EFFECT OF POLYUNSATURATED FATTY ACIDS (PUFAS) VARIANTS***Rene Barro Soria, PhD**University of Miami*

Epilepsy is characterized by abnormal neuronal activity in the brain. Mutations in the potassium channel regulating the excitability of neurons, the IKM channel, have been causally linked to some epilepsies. How mutations of IKM channels (channelopathies) cause epilepsy remains unknown. At present, available anti-epileptic drugs fail to control more than 30% of patients suffering from epilepsy. Therefore, there is a need to understand the molecular basis of the disease to create strategies to develop new anti-epileptic drugs. The goals of the present research project are a) to define the molecular basis of voltage activation of IKM channels, to understand the mechanisms by which epilepsy causing mutations affect IKM channels function and b) to design new drugs for the treatment of these IKM channelopathies. In the future, tailoring antiepileptic therapies to specific mutations will greatly improve the clinical outcome of treatments for each patient.

**EXAMINING THE LINK BETWEEN SEIZURES, SPREADING DEPRESSION AND SUDEP***Stuart Cain, PhD**University of British Columbia*

Spreading depression is a phenomenon in which brain cells go completely silent, and it is thought that if this spreads into the brainstem, it can lead to death. The goals of this project are to define the specific brain regions that promote spreading depression into the brainstem and to test whether spreading depression and death can be affected by a new, experimental, seizure-suppressing drug. If successful, this work will confirm that fatality in epilepsy is caused by spread of disabled nerve cell activity to the brainstem, either as a result of or accompanied by severe seizures. It will also define a set of brain regions and underlying mechanisms that cause fatality and potentially identify a new drug for the prevention of SUDEP. Knowledge of the key brain regions that cause spread of nerve cell inactivity and the underlying control mechanisms will allow for drug discovery targeting only those brain areas affected, thereby limiting side effects.

**PEDIATRIC EPILEPSIES: MICRORNAS DETERMINE NETWORK EXCITABILITY DURING DEVELOPMENT***Laura Ewell, PhD**University of California, San Diego*

Pediatric epilepsies arise when the assembling of the brain goes wrong, the mechanisms for suppressing activity are not in place, and neurons become hyperexcitable. To cure these diseases we need to identify and better understand the master regulators that instruct brain assembly and potentially fail in epilepsies. MicroRNAs (miRs) are great candidates. They coordinate complex developmental processes and are altered in patients with epilepsy. Dr. Ewell's team is studying the role of a miR that is abundant in inhibitory interneurons. They hypothesize that it supports the development of inhibitory neurons in networks, enabling interneurons to function properly. Functional inhibition is

crucial for protecting networks against hyperexcitability, so they hope that understanding miR regulation of inhibition during development will lead to powerful drug targets to cure pediatric epilepsies.

**GENETIC PREDICTION OF DRUG RESPONSE IN CHILDHOOD ABSENCE EPILEPSY**

*Kenneth Myers, MD, PhD*

*University of Melbourne/Austin Health*

The primary goal of this work is to assess whether the genetics of individuals with a specific seizure disorder, Childhood Absence Epilepsy (CAE), can be used to predict what medication will best control their seizures. They will study genes related to communication between two parts of the brain that are known to be disrupted in CAE. The ultimate goal is to generate data that can be used to design a rapid genetic testing protocol that will help doctors choose a medication for CAE based on an individual's genetics, taking a step closer to precision medicine. If successful, this project will demonstrate that treatment of a common epilepsy syndrome can be enhanced using genetic testing. For the children with CAE, this will mean faster control of seizures and fewer side effects. This research approach can then be applied to other genetic epilepsy syndromes, and in the long term, should improve the treatment of all people with epilepsy.

**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.

**2016 Innovator Awards:****SINEUPS TECHNOLOGY: A NEW ROUTE TO TREAT HAPLOINSUFFICIENCY-INDUCED EPILEPSY**

*Marta Biagioli, PhD*

*University of Trento, Trento, Italy*

Genetic mutations account for the majority of epilepsies. Recently, a new gene, CHD2, has been highlighted as an important risk factor. All the CHD2 characterized mutations are disruptive, mostly causing reduced protein levels in the brain, and this is thought to contribute to the development of epilepsy. Dr. Biagioli's recent discovery of a way to increase the expression of target proteins laid the basis of a new technology called SINEUP. This technology holds promise for rescuing disorders associated with protein level reductions as a consequence of genetic mutations. This proposal aims to demonstrate how SINEUP can rescue the protein deficit and treat the disease. This will be the first step towards the development of a new type of therapy to potentially impact many presently incurable genetic diseases with implications beyond CHD2 and epilepsy.

**SCALABLE TRANSCRIPTIONAL-TRANSLATIONAL THERAPY OF EPILEPTOGENIC GENE HAPLOINSUFFICIENCIES**

*Antonello Mallamaci, PhD*

*Scuola Internazionale Superiore di Studi Avanzati, Trieste, Italy*

More than one hundred distinct gene losses may lead to epilepsy. As these pathologies are individually rare and the defective genes are implicated in a variety of cellular processes, the development of effective cures is hard, due to the complexity of the problem and the huge economic investments needed. We will try to fix this issue via multilevel stimulation of the spared gene copy, by three novel enabling technologies, which comply with endogenous gene regulation needed for neuronal function. If successful, this approach will be exploitable for scalable, personalized cures of epileptogenic gene loss.

**REPROGRAMMING NG2 GLIAL CELLS INTO INHIBITORY NEURONS IN AN EPILEPSY MODEL**

*Akiko Nishiyama, MD, PhD*

*University of Connecticut*

NG2 glial cells are non-neuronal cells that are widely distributed in the adult brain. Their primary role is to generate oligodendrocytes that make myelin to allow fast conduction of electrical signals, but they also communicate with neurons in the neural network. Dr. Nishiyama has found that NG2 cells can be reprogrammed to become inhibitory interneurons in culture by a transcription factor. The goal of this project is to test the potential of local NG2 glial cells as a source of functionally active interneurons in the seizure environment using a mouse model of temporal lobe epilepsy.



**EPILEPTOGENIC NEURONAL HOMEOSTASIS AFTER INJURY: FOCUS ON NEUROFILAMENTS***Kevin Staley, MD**Massachusetts General Hospital*

Chloride ions carry most of the signals that stop seizures in the brain. However, when the anticonvulsant signaling molecule GABA activates chloride signaling, the expected anticonvulsant effect does not always occur. Dr. Staley's team proposes that brain cells change their chloride content in response to a variety of conditions. They will ask if brain cells vary their local chloride content by using "salt substitutes". Salt substitutes are molecules that carry the same amount of electrical charge as chloride, but are unable to stimulate the action normally associated with chloride. The team will focus on actin, a highly charged structural molecule that likely can act as a "salt substitute". If they find that brain cells alter the effect of GABA by changing local actin, they can target this mechanism to treat epilepsy. Many of these mechanisms are already well-studied in other diseases and could be readily refocused to treat uncontrollable epilepsy.

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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.

**GENE DISCOVERY IN THE EPILEPTIC ENCEPHALOPATHIES: AN UPDATE***Monday, March 21, 2016 at Northwestern University Feinberg School of Medicine***Speaker:** Heather Mefford, MD, PhD**Host:** Alfred L. George, Jr., MD & Stephan Schuele, MD

**Talk Summary:** The introduction of next-generation sequencing technologies in the past 10 years has accelerated our understanding of the genetic architecture of the epilepsies. A significant advance has been the recognition that the epileptic encephalopathies - the most severe of the epilepsy syndromes - are often due to de novo mutations. Numerous genes have been identified in the past decade through both targeted and whole exome sequencing approaches. Dr Mefford will provide an overview of recent advances in gene discovery, with an emphasis on the encephalopathies. Proteins encoded by genes in which mutations cause epilepsy function in a wide variety of cellular processes. Understanding the genetic etiology of disease in patients may lead to more precise therapies as drugs are developed to target specific pathways and processes.

**TARGETED INTERVENTIONS IN ACQUIRED AND GENETIC EPILEPSIES***Friday, April 8, 2016 - 12:30pm to 1:30pm at University College London (UCL) School of Pharmacy***Speaker:** John Huguenard, PhD**Host:** Mala M. Shah, PhD

**Talk Summary:** Our understanding of the local and extended neural networks implicated in seizure genesis has greatly expanded in recent decades. This, coupled with advances in targeted control (opto- or chemo-genetics), is leading to rather sudden improvement of epilepsy treatment, so far at least in animals. Prof. Huguenard's presentation will describe their work in post-lesional (stroke) epilepsy models as well as genetic generalized epilepsy models (absence epilepsy), with identification and effective therapeutic targeting of key neuronal cell types.

**INDUCED PLURIPOTENT STEM CELL MODELING OF GENETIC EPILEPTIC ENCEPHALOPATHIES***Tuesday, April 26, 2016 - 4:00pm to 5:00pm at University of Connecticut Health Center (Low Learning Center)***Speaker:** Jack Parent, MD**Host:** Eric Levine, PhD

**Talk Summary:** Reprogramming somatic cells to a pluripotent state via the induced pluripotent stem cell (iPSC) method offers an unparalleled approach for neurological disease modeling using patient-derived neurons. My lab has applied the iPSC approach to model severe childhood genetic epilepsies with patient-derived cells. We initially generated patient-derived neurons to study epilepsy mechanisms in Dravet Syndrome (DS), a catastrophic childhood epilepsy caused by de novo dominant mutations in the SCN1A gene that encodes the voltage-gated sodium channel Nav1.1. The talk will describe our findings of altered sodium currents and excitability in DS patient neurons. I will also



discuss studies in which we generated DS patient-derived cardiac myocytes to explore potential mechanisms of SUDEP (Sudden Unexpected Death in Epilepsy), which occurs at increased frequency in DS. We compared findings from electrophysiological recordings of DS iPSC-derived cardiac myocytes with those of cardiac myocytes from a DS knock-in mouse model. In the last part of the seminar, I will describe recent work examining potential epilepsy mechanisms in another ion channelopathy, the severe childhood epilepsy known as SCN8A-Associated Epilepsy. Compared to control iPSC neurons, mutant SCN8A patient-derived neurons show increased persistent sodium current and hyperexcitability. Using a multi-well multielectrode array for drug screening, we are validating the model with drugs known to work or to be ineffective in patients with SCN8A-Associated Epilepsy. Taken together, our work suggests that the iPSC approach offers great promise for modeling childhood epileptic encephalopathies and should provide a useful platform to identify novel therapies.

**JAK/STAT REGULATION AFTER BRAIN INJURIES: POTENTIAL NEW TARGETS FOR DISEASE MODIFICATION FOR ACQUIRED EPILEPSY?**

*Wednesday, April 27, 2016 - 3:30pm to 4:30pm at Baylor University (Baylor Science Building, Room C105)*

**Speaker:** Amy Brooks-Kayal, MD

**Host:** Joaquin Lugo, PhD

**Talk Summary:** 1 in 26 Americans will be impacted by epilepsy at some point in their lives. Although there are many symptomatic anti-seizure medications, none of them change the course of the disease or treat the underlying causes of the epilepsy. Many types of brain injuries are known to lead to epilepsy, but there are currently no preventative therapies that reduce the rate or severity of epilepsy development in those at risk. Many types of epilepsy worsen over time, but there are no therapies that can inhibit this progression. A number of novel strategies are in preclinical development for prevention and treatment of epilepsy, some of which raise the possibility of providing disease modification, prevention or even cure for this disorder. Signaling pathways offer promising targets for novel treatment strategies, some of which use existing medications. In this seminar I will discuss alterations in JAK/STAT pathway regulation of GABA(A) receptor expression and effects of JAK/STAT inhibition on epilepsy development and behavioral outcomes after experimental brain insults including status epilepticus and traumatic brain injury, and discuss the potential of JAK/STAT inhibitors as disease modifying agents for acquired epilepsies.

**THE GENETIC BORDERLAND OF EPILEPSY: A NOVEL GENE MECHANISM LINKING EPILEPSY AND MIGRAINE**

*Wednesday, May 18, 2016 - 10:00am to 11:00am at Vollum Institute, Oregon Health and Science University (M1441, Vollum Institute seminar room)*

**Speaker:** Jeff Noebels, MD, PhD

**Host:** Gary L. Westbrook, MD, Senior Scientist and Co-Director, Vollum Institute

**Talk Summary:** Monogenic causes of epilepsy now exceed one hundred genetic loci and give rise to a diverse biological spectrum of neural network synchronization disorders in the developing brain. The aberrant circuit excitability gives rise to clinically distinctive syndromes manifested by different seizure types and comorbidities, including autism, cognitive deficits, and even premature mortality. Sudden unexplained death in epilepsy (SUDEP) is the most common cause of death in idiopathic epilepsy and second only to stroke in the number of human life years lost. Until recently the underlying mechanisms were unknown. Studies in our laboratory have definitively linked mutations in ion channel genes for human cardiac arrhythmias with epilepsy and sudden death, providing the first validated genetic biomarker for SUDEP risk in individuals with epilepsy. New research in genetically engineered mouse models of SUDEP now demonstrates that a slow depolarizing wave, similar to that underlying the aura of blindness and hemiplegia that precede some genetic forms of migraine headache, is triggered following a seizure and silences brainstem pacemaker regions in the dorsal medulla causing cardiorespiratory collapse. Genes and mechanisms for migraine with aura are now also implicated in sudden death.

**ZEBRAFISH AS A MODEL FOR EPILEPSY RESEARCH AND DRUG DISCOVERY**

*Friday, May 20, 2016 - 12:00pm to 1:00pm at University of Vermont Medical Center (Davis Auditorium)*

**Speaker:** Scott Baraban, PhD

**Host:** Gregory L. Holmes, MD & Rodney Scott, MD, PhD

**Talk Summary:** Zebrafish (*Danio rerio*) have emerged as a promising and valuable model organism. The increasing popularity of this small vertebrate is evident from the growing numbers of publications, and new discoveries associated with the use of zebrafish for studying development, brain function, human disease and drug screening. Owing to the development of novel technologies, the range of zebrafish research possibilities is constantly expanding with new imaging, electrophysiological, and gene editing tools enhancing traditional techniques. Despite the

widespread success of zebrafish in the neuroscience community, epilepsy research using this organism is more limited. To address this issue, we began to adapt zebrafish for epilepsy related studies in the mid-1990s. Similar to rodents, these early studies utilized chemoconvulsants and monitored wild-type zebrafish larvae for changes in behavior, electrical activity and early gene expression. With the rapidly expanding molecular and neuroscience tool box, we are now using zebrafish models mimicking human pediatric epilepsies with genetic causes. These genetically modified zebrafish are amenable to rapid drug screening, long-term EEG monitoring or whole-brain calcium imaging, and hold great potential to advance our understanding and treatment of epilepsy. In this lecture, I will highlight the past and present techniques which have made, and continue to make, zebrafish an attractive model organism in epilepsy research. I will also focus on *scn1* mutant zebrafish mimicking a catastrophic form of pediatric epilepsy known as Dravet syndrome, and our efforts to screen repurposed drug libraries to identify novel lead compounds for this disorder.

#### **THE ROLE OF THE DENTATE GYRUS IN TEMPORAL LOBE EPILEPSY**

*Wednesday, May 25, 2016 - 12:00pm to 1:00pm at University of Wisconsin-Madison*

**Speaker:** Paul Buckmaster, DVM, PhD

**Host:** Matt Jones, PhD

**Talk Summary:** What causes temporal lobe epilepsy? The dentate gyrus in patients with temporal lobe epilepsy displays many functional and structural abnormalities. Some possibilities include synaptic reorganization, aberrant hub cells, and dysfunction or loss of inhibitory interneurons. Which (if any) are most responsible for generating spontaneous seizures? Recent anatomical and electrophysiological results from animal models of temporal lobe epilepsy will be presented.

#### **INFLAMMATION AND MICRORNA BASED REGULATION OF INFLAMMATORY RESPONSES IN EPILEPSY-ASSOCIATED PATHOLOGIES**

*Friday, June 24, 2016 - 12:00pm to 1:00pm at Stanford University (Munzer Auditorium in the Beckman Building)*

**Speaker:** Eleanora Aronica, MD, PhD

**Host:** John Huguenard, PhD

**Talk Summary:** The role of inflammation in the pathophysiology of human epilepsy has received increasing attention in recent years. Accumulating evidence suggests that activation of both innate and adaptive immune system occurs in human epilepsy and that the inflammatory response may contribute to the generation of seizures and to seizure-related neuronal damage. Both clinical observations in drug-resistant human epilepsies and experimental findings in clinically relevant models will be discussed, highlighting specific inflammatory pathways that could represent potential targets for antiepileptic, disease-modifying therapeutic strategies. Attention has been recently focused on the role of microRNAs (miRNA) in the regulation of the innate and adaptive immune responses. Specific miRNAs play a key role in regulating inflammatory pathways involved in epilepsy and represent attractive targets for further preclinical studies in neurological disorders associated with a chronic deregulation of the inflammatory response.

#### **DIAGNOSIS OF EPILEPSY AND TREATMENT COURSE**

*Monday, July 25, 2016 at Bhutan Society of Epilepsy and Neurology, Thimphu (Bhutan)*

**Speaker:** Dr. Manjari Tripathi

**Host:** Dr. Devender Bhalla

**Talk Summary:** It is estimated that the epilepsy affects approximately 50 million people, around 40 million of them living in developing countries (World Health Organization, 2000). 80% of the burden of epilepsy is in the developing world, where in some areas 80% to 90% of people with epilepsy receive no treatment at all. This higher incidence rates in developing countries, is thought to be attributable to parasitosis particularly neurocysticercosis, HIV, trauma, perinatal morbidity, and consanguinity. The diagnosis of epilepsy is clinical but is also helped by videos made by the caregiver showing the complete seizure. Complimentary tests include EEG, CT head, MRI Brain. 70 % of persons with epilepsy respond to first line medicines used in combination. The most common medicines used are Phenytoin, carbamazepine and valproic acid. Newer drugs like levetiracetam, lamotrigine, topiramate, clobazam, lacosamide are also effective and may have a better adverse effect profile. When people with epilepsy continue to have frequent seizures despite multiple-drug therapy, epilepsy surgery may be indicated. Surgery can provide a significant improvement in the quality of life for some of the 20% to 30% of people with epilepsy who continue to have seizures while taking appropriate medication. A video EEG, MRI brain epilepsy protocol, PET, SPECT may be required before epilepsy surgery. Special diets are also an effective method specially in children. My talk will cover the diagnosis of epilepsy and management approach.

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**EPILEPSY AND ALZHEIMER'S DISEASE**

*Wednesday, September 21, 2016 at Dalhousie University*

**Speaker:** Helen Scharfman, PhD

**Host:** Bernd Pohlmann-Eden, MD, PhD

**Talk Summary:** It has been suggested that neuronal hyperexcitability contributes to Alzheimer's disease (AD), based on the observations of seizures in both clinical studies and animal data. In animals it has been shown that robust seizures exist in mice that have mutations in the genes that regulate amyloid beta and tau, the two molecules that are considered to be central to AD neuropathology. Nevertheless, the exact relationship between hyperexcitability and AD is still unclear. In this presentation we will review clinical and basic research studies to date, and then discuss recent experiments of our laboratory that focus on the earliest ages of two mouse models where amyloid beta is increased due to mutations in its precursor (amyloid precursor protein, APP) that either mimic a Swedish or London cohort with AD. We also have examined a transgenic mouse with APP overexpression without any mutation, and a mouse model of Down's syndrome, where APP is increased and AD develops in almost all individuals. Together our data suggest that one of the earliest characteristics of these mouse models and Down's syndrome are interictal spikes that can be recorded in widespread regions of the hippocampus and cortex. The spikes occur during sleep initially but then develop in other behavioral states as well. The mechanisms, use of spikes as a biomarker, and the therapeutic benefit of blocking spikes will be discussed.