AES
AMERICAN EPILEPSY SOCIETY

**Basic Science Investigators' Workshops**

| Year | Moderator(s) | Title | Description | Speakers |
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| 2021 | José Ángel Aibar, Franck Kalume | The Potential of CRISPR for Treating Epilepsies | This workshop will focus on the emerging field of gene-editing, notably CRISPR. In the past five years, nearly 20,000 papers containing the term CRISPR have been published, making it one of the mainstream topics of conversation. Advances in CRISPR genome-editing engineering technologies are sparking a new revolution in biological research, and over the next years, it will likely produce tangible and potentially wide-ranging treatments and even cures for genetic diseases, including some epileptic disorders. In this workshop, we will introduce CRISPR and discuss its applications from cell to organism in the labs and its implementations in clinics, including its challenges. | Gaia Colasante, PhD; Gabriele Lignani, PhD; Aguan Wei, PhD |
| 2021 | Sarah Muldoon, PhD; Ethan Gold | Quantitative Analysis of Epileptic Networks at Cellular Resolution | This workshop will showcase the power of computational modeling, perturbation simulations, and network science for studying large-scale epileptic networks at single-cell resolution. The speakers will discuss recent studies deploying these complex quantitative tools in a manner accessible to the broader community, with particular focus on how individual neurons and microcircuits functionally influence networks and drive pathological behavior. These presentations will emphasize diverse modeling-centric research that collectively yield novel mechanistic insights of underlying disease pathophysiology and propose clinically relevant predictions that will advance the goal of cellular scale control of epileptic circuits. | Darian Hassan Hadjiabadi, MSE; Claudia Clopath, PhD; Zhenrui Liao, BS |
| 2021 | Jaideep Kapur, MD, PhD, FAES; J | Memory Mechanisms in the Epileptic Brain | Patients with temporal lobe epilepsy experience difficulties with their memory. There has been rapid growth in our understanding of fundamental mechanisms of hippocampal memory storage and consolidation. These studies point to distinctive roles for various structures, which interact through network oscillations such as the theta rhythm, sharp wave-ripples, slow neocortical oscillations (up-down states), and sleep spindles. Furthermore, a growing number of studies demonstrate how structural and functional pathology of temporal lobe epilepsy disrupts memory formation and consolidation. The workshop will feature emerging leaders in the study of memory disruption in temporal lobe epilepsy and will stimulate research in this area. | Jaideep Kapur, MD, PhD, FAES; Tristan Shuman, PhD; Laura Ewell, PhD |
| 2021 | Vaishnav Krishnan, MD, PhD; Kir | Anatomical and Neurobehavioral Consequences of Fetal Antiseizure Medication Exposure | This investigator's workshop is designed to invite a timely and multidisciplinary dialog on the topic of anatomical/structural and neurodevelopmental consequences of fetal antiseizure medication (ASM) exposure. We will review the latest pertinent clinical data available from registry studies and critically evaluate the translational potential of preclinical models. The discussion will aim to identify transformative translational research priorities for the future, not limited to (i) developing a deeper understanding of the genetic and/or epigenetic mechanisms of ASM-induced teratogenesis, and (ii) defining avenues to design new, safe and effective ASM for use in pregnancy. | Robert Cabrera, PhD; Yi Li, MD, PhD; Vaishnav Krishnan, MD, PhD |
| 2021 | Catherine Christian-Hinman, PhD | Emerging Roles of Hypothalamus in Epilepsy and Comorbidities | This workshop will address the role of the hypothalamus in epilepsy and multiple comorbidities. The hypothalamus is the seat of multiple critical physiological functions including sleep, stress, reproduction, feeding, and temperature regulation. Growing evidence indicates changes in hypothalamic function in epilepsies characterized by seizures in extra-hypothalamic structures. The speakers will discuss recent evidence for changes in the function of multiple hypothalamic areas and circuits in diverse models of epilepsy, how these changes are related to multiple behavioral and somatic comorbidities of epilepsy, including sleep disturbances, and how altered hypothalamic function may impact the presentation of epilepsy and seizures. | Catherine Christian-Hinman, PhD; Trina Basu, PhD, Michael Wong, MD, PhD |
| 2021 | Maxime Baud, MD, PhD; Vikram | The Chronobiology of Epilepsy | Unmasking neural damage and network abnormalities allows consideration of best approaches to intervene using a range of options indicated by recently-described characteristics. | Maxime Baud, MD, PhD; Birgit Frauscher, MD, PhD; Christophe Bernard, PhD |
| 2021 | Cameron S. Metcalf, PhD; Jennifer Wong, PhD | Therapeutic Benefits of Targeting Neuropeptide | Neuropeptides have long been known to be key modulators of neurological function. Moreover, several key neuropeptides have been identified as playing an important role in epilepsy pathophysiology. Basic science and translational research in this field suggest continued potential for neuropeptides and their receptors as targets for therapy development. This Workshop will highlight recent advances in neuropeptide therapy development in general, and will focus on specific examples that demonstrate potential avenues for future and ongoing efforts. | Cameron S. Metcalf, PhD; Jennifer Wong, PhD; Esbjörn Melin, PhD |
| 2021 | Peter B. Crino, MD, PhD | Somatic Genetics of Neocortical Epilepsy: SLC35 | Patients with non-lesional neocortical epilepsy (NLNE) provide unique challenges for both medical therapy and pre-surgical evaluation and exhibit a worse post-operative seizure freedom rate. Conceptualizing how a focal area of neocortex evolves into an epileptic network in the absence of a lesion is challenging. Somatic variants in the galactose transporter SLC35A2 have been identified in resected NLNE specimens, providing a paradigm shift in understanding NLNE. We will present somatic genetic data on SLC35A2 in NLNE, review phenotypic presentations of these cases, report in vitro/in vivo studies showing how SLC35A2 variants lead to seizures, and discuss genomic strategies to investigate NLNE. | Erin Heinzen-Cox, PharmD, PhD; Melodie R. Winawer, MD, MS, Annapurna Poduri, MD, MPH, FAES; Philip Iffland, PhD |

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| **2021** | Rachel June Smith, PhD; Daniel W. Shrey, MD | Clinical Applications of Functional and Effective Connectivity in Epilepsy | This workshop will address the clinical utility of computational measures of connectivity in the epileptic brain. A diverse and expanding set of computational tools have been posited to infer functional and effective connections in the brain, and these techniques have improved diagnostic procedures, localization of the seizure onset zone, and assessment of treatment response. The speakers specialize in computational connectivity methods scalp EEG, intracranial EEG, and MEG, and will describe recent advances in their modality. Methodological challenges of computational tools to measure connectivity as well as barriers to implementation in clinical practice will be discussed. | Rachel June Smith, PhD; Beth A. Lopour, PhD; Srikantan Nagarajan, PhD |
| **2021** | Lauren Harte-Hargrove, PhD | Novel Techniques and Models to Identify Epileptogenesis in Post-traumatic Epilepsy | This workshop will address what can be learned from clinically-relevant rodent and novel porcine animal models of PTE and how new techniques and technologies can help to understand the process of epileptogenesis following TBI in the human. The latest findings from young investigators participating in the CURE Epilepsy PTE Initiative will be presented, including novel insights on promising EEG, imaging and circulating biomarkers for the prediction of PTE. | Armina Omole, MD, PhD; Federico Moro, PhD; Oleksii Shandra, MD, PhD; Kyle Lillis, PhD |
| **2020** | Jack M. Parent, MD | Using Human Brain Organoids to Study Genetic Epilepsies | This workshop will address the application of human brain organoid methods to model genetic epilepsies. The brain organoid field is advancing rapidly and offers a novel 3D culture approach to study genetic neurodevelopmental disorders and epilepsies. Advances include fusions of patterned excitatory and inhibitory organoids to model interneuron development and network integration, and the addition of non-neuronal cell types to organoids to more faithfully recapitulate human brain development. The speakers will describe using these techniques to study genetic epilepsies that include mTORopathies, Rett syndrome and ion channelopathies. Advantages and challenges of brain organoid modeling will also be discussed. | Helen Bateup, PhD; Ranmal A. Samarasinghe, MD, PhD; and Andrew M. Tidball, PhD |
| **2020** | Tristan T. Sands, MD, PhD; and Erin Heinzen, PharmD, PhD | New Vistas in the Genetic Landscape of Epilepsy: Explaining the Genetically Unexplained | This workshop will address the fact that even after exhausting the exome, the vast majority of epilepsy will remain genetically unexplained. In other words: the era of describing pathogenic variants in Mendelian epilepsy genes is coming to an end and, for most cases, we still don't have an answer to the seemingly basic question of why an individual has epilepsy. In this timely workshop, we will highlight exciting three cutting-edge avenues of investigation that are beginning to shed light genetic mechanisms underlying genetically unexplained epilepsy. | Annapurna Poduri, MD, MPH; Melanie Bahlo, BSc, PhD; and Dennis Lal, PhD |
| **2020** | Gordon F. Buchanan, MD, PhD; and Franck Kalume, PhD | Sleep and Circadian Rhythms in SUDEP: Disentangling Night Time Contributors to Seizure-Associated Death | This workshop will address sleep and circadian factors in sudden unexpected death in epilepsy (SUDEP). We will discuss the current state of knowledge regarding molecular regulation of circadian rhythms, circadian regulation of seizures, seizure threshold, and brainstem functions such as cardiovascular/ respiratory function. We will discuss how animal models will help understand these mechanisms with a focus on identifying novel ways to disentangle sleep and circadian rhythms in understanding day-night differences in seizures, epilepsy, and SUDEP. | Judy S. Liu, MD, PhD; Benton S. Purnell, BA; and Rufi Dalvi, PhD |
| **2020** | Ana Mingorance, PhD; and Gavin Rumbaugh, PhD | Beyond Seizures: Comorbidities and Genetic Rescue in Developmental and Epileptic Encephalopathies | This workshop will address the topic of comorbidities in developmental and epileptic encephalopathies and their potential treatment using genetic rescue in older animals. Presentations in this workshop will highlight the breath of epileptic and neurobehavioral alterations in translational relevant models of CDKL5 deficiency disorder, Dravet syndrome and SynGAP1 encephalopathy, and will provide preclinical evidence of the efficacy of restoration of gene expression in adult animals. Following the presentations, we will host a discussion about strategies for translating these findings into the clinic and implications for clinical trials. | Ana Ricobaraza, PhD; Zhaolan (Joe) Zhou, PhD; and Gavin Rumbaugh, PhD |
| **2020** | Esther Krook-Magnuson, PhD; and Patrick A. Forcelli, PhD | Beyond the Hippocampus: Remote Networks Important for Epilepsy Outcomes and Seizure Control | This workshop will address how regions outside the seizure focus can be effective targets for intervention, and how extra-hippocampal changes can be important for comorbidities in temporal lobe epilepsy. Specifically, we will explore 1) how cerebellar circuits can be manipulated to inhibit hippocampal seizures (including the cell-type specificity underlying successful interventions), 2) basal ganglia-brainstem networks in the control of seizures, highlighting recent findings regarding the organization of pathways in the control of absence, limbic, and generalized tonic-clonic seizures, and 3) network dysfunction in the amygdala related to comorbid anxiety in temporal lobe epilepsy. | Martha Streng, PhD; Patrick A. Forcelli, PhD; and Jamie L. Maguire, PhD |
| **2020** | Manisha N. Patel, PhD | Metabolism-Targeted Treatments for Epilepsy Revealed Through Studies of Ketogenic Diet Mechanisms | This workshop will address the emerging field of metabolism-based treatments for epilepsy- notably, with respect to mitochondrial, redox and inflammation functions. There is growing evidence that mechanisms activated by ketogenic diet treatment in various in vivo and in vitro model systems can now be exploited to develop metabolism and inflammation-targeted therapies for seizure control. While there are many distinct, parallel and intersecting mechanisms that have been invoked for ketogenic diet action, this workshop will focus on selected treatments that modulate brain metabolic function. Speakers will present recent experimental findings focused on enhancing antioxidant capacity and restoration of impaired bioenergetics. | Ashwini Sri Hari, MS; Jong M. Rho, MD; and Dominic D'Agostino, PhD |
| **2020** | Judy S. Liu, MD, PhD | How Can Study of the 'Seizure Focus' from Therapeutic Resections can Lead to Novel Insights in Epilepsy | This workshop will address the use of brain tissue from therapeutic resections in order to better understand epilepsy. Surgically resected epileptogenic human tissue samples can be used to dissect the network, cellular and molecular alterations that occur in humans normal and in epilepsy. Our workshop will address how findings from human tissue are overlapping and distinct from animal models of epilepsy with investigators using different approaches discussing different types of epilepsy, as well as the impact this has had on understanding basic sicence of human neural circuits. We will discuss how best to leverage this amazing resource. | Felix Chan, PhD; Mark Cunningham, PhD; and Costas Anastassiou, PhD |

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| **2020** | Jeffrey L. Noebels, MD, PhD | Mechanisms of Epileptogenesis in the Peritumoral Microenvironment | This workshop will address the new finding that brain tumors trigger a vicious cycle of epileptogenesis, namely, tumor-driven seizures accelerate tumor growth. Seizures occur in over 70% of brain tumors and are typically pharmacoresistant. New research establishes that malignant cells influence neurons and glia in the peritumoral microenvironment through direct synaptic and gap junction contacts, alter glutamatergic transmission, and destabilize network excitability by generating seizures and spreading depolarization, which in turn drive disease progression. Tumors are geneticallly heterogeneous, and specific gene variant profiles drive epilepsy while others do not. Biopsy-based transcriptomic approaches may soon guide individualized tumor specific epilepsy therapies. | Tara Barron, PhD; Qiqun Zeng, PhD; and Jochen F. Meyer, PhD |
| **2020** | Amy Brooks-Kayal, MD; and Scott C. Baraban, PhD | Master Regulators in Epileptogenesis: REST and all the Rest | Epigenetic regulation, and specifically Neuronal Restrictive Silencing Factor (NRSF or REST) signaling, has been implicated in neuronal reprogramming that promotes epileptogenesis. This workshop will address the contributions of REST/NRSF signaling to neuronal hyperexcitability and epilepsy and will present new and unpublished data on the contributions of REST/NRSF signaling to epileptogenesis at the cellular, network and functional levels. | Tallie Z. Baram, MD, PhD; Avtar S. Roopra, PhD; and Fabio Benfenati, MD |
| **2020** | Gary P. Brennan, PhD | Mechanisms Governing RNA Fate in Epilepsy; From Generation to Translation. | This workshop will address the increasingly complex regulatory mechanisms which govern RNA fate and how they may contribute to the development of epileptic circuits. Epilepsy-inciting events such as TBI, stroke and status epilepticus initiate global dysregulation of our transcriptome in a rapid and persistent manner at all levels of regulation including gene expression, RNA processing and translation. This IW will focus specifically on 1. epigenetic regulation of gene expression, 2. RNA modification-mediated control of RNA processing, and 3. microRNA as potent post-transcriptional regulators of RNA translation and how these canonical pathways are dysregulated in acquired temporal lobe epilepsy. | Gary P. Brennan, PhD; Farah D. Lubin, PhD; and Giordano Lippi, PhD |
| **2020** | Alfred L. George, Jr., MD; and Dianalee McKnight, PhD | VANQUISHING THE VUS: Strategies for Decrypting Variants of Unknown Significance in Genetic Epilepsies | This workshop will address multidisciplinary efforts to determine the functional and pharmacological consequences of variants associated with genetic epilepsies, and to stimulate discussion on the impact of these data on variant classification and their clinical relevance. Presentations in this workshop will also emphasize the recognition of variant-specific drug responses that have direct relevance to designing treatment strategies and may impact the design of future clinical trials for rare forms of epilepsy. | Stephen F. Traynelis, PhD; Carlos G. Vanoye, PhD; and Henrike Heyne, PhD |
| **2020** | Jenny Hsieh, PhD; and Helen Scharfman, PhD | New Therapeutic Implications for Adult Hippocampal Neurogenesis in Rodents and Humans | The workshop will address new and exciting data of adult hippocampal neurogenesis in rodent models and in human brain. Neurogenesis changes dramatically after seizures and contribute to the pathogenesis of epilepsy in rodents, but recent evidence of adult neurogenesis in humans highlight the challenges of translating this to the clinic. Animals models of Alzheimer's disease and traumatic brain injury provide a window into understanding the mechanisms regulating neural progenitor proliferation, migration, and differentiation in the adult brain. Whether these mechanisms exist in human brain remain unclear, recent work has begun to uncover the processes by which adult neurogenesis contributes to epilepsy. | Jeannie Chin, PhD; Viji Santhakumar, PhD; and Mercedes F. Paredes, MD, PhD |
| **2019** | Melissa Barker-Haliski, PhD; Angela Birnbaum, PhD; Helen Scharfman, PhD | Seizures in Seniors: How Do We Identify New and Innovative Therapies for this Growing Patient Demographic? | This workshop will address the specific therapeutic needs of the fastest growing patient demographic with epilepsy diagnosis: the elderly. Despite the greater incidence of epilepsy in the elderly, as well as the overlapping pathology and increased risk of seizures in patients with Alzheimer's disease, aged animal models are infrequently used to support antiseizure drug development1; 2. This workshop will discuss the pros and cons associated with the identification of therapeutic targets, innovation of preclinical models of aging-related seizures, and the application of comprehensive clinical pharmacology to improve therapeutic management and outcomes for aged patients with epilepsy. | Erik Roberson, PhD; Sílvia M. Illamola , PharmD, PhD; and David Alcantara-Gonzalez, PhD |
| **2019** | Melanie Boly, PhD | Neurostimulation and Neuroimaging of Subcortical Arousal Circuits in Epilepsy | This workshop will address new exciting data and techniques for imaging networks and uncovering mechanisms of therapeutic modulation by subcortical stimulation devices in epilepsy. We will provide a comprehensive update of the neuroscience of arousal and consciousness as a general field, and as applied to epileptic seizure networks, in the context of other altered states such as anesthesia, coma or sleep. Promising findings using high field opto-fMRI and multi-site stimulation in animal models allow unprecedented visualization of cortical and limbic network changes with subcortical stimulation - with ability to modulate seizure threshold or reverse seizure-induced loss of consciousness. | Melanie Boly, PhD; Jin Hyung Lee, PhD; and Hal Blumenfeld, MD, PhD |
| **2019** | Hajime Takano, PhD | Recent Advances in Microelectrode Array Technology and Its Applications | This workshop will address emerging microelectrode array (MEA) technologies and their applications. Transparent electrode arrays are of interest to many researchers who work on in vivo neuronal imaging and optogenetic stimulation. In addition, in late 2018, the novel, extremely high density silicon electrode array, "Neuropixels", became available to the general research community. Emerging innovations are not limited to the forefront of in vivo electrophysiology. Advanced materials and increased computational capability have pushed the limit of conventional MEA concepts also into in vitro assay systems. Discussion will focus on how these innovations can be implemented in the laboratory. | Flavia Vitale, PhD; Timothy Harris, PhD; and Ikuro Suzuki, PhD |

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| **2019** | Douglas Coulter, PhD | Circuit Based Therapies in Epilepsy | This workshop will address novel circuit therapies in epilepsy. Conventional systemic antiepileptic drug therapy immerses the entire brain, affecting both normal and pathogenic circuits, causing both therapeutic and negative outcomes. In addition, the neuronal circuit disruptions underlying phenotypic expression in epilepsy are mechanistically complex. Targeting individual symptoms has proven insufficiently effective in ameliorating seizures or restoring cognitive function in chronic epilepsy. Presentations in this workshop highlight that altered excitability in specific circuits is a proximate generator of both seizures and aberrant behavior in epilepsy, and that targeting these alterations in a circuit-specific manner is a viable therapeutic opportunity. | Robert F. Hunt, PhD; Julia Kahn, BS; Dimitri Kullmann, MD |
| **2019** | Jeanne T. Paz, PhD; and Daniel Lowenstein, MD | Gut Microbiome and Epilepsy: Paradigm Shifting Advances for Understanding and Treating Epilepsy | This workshop will address the timely and emerging topic of the role of the gut microbiota in epilepsy. Several publications within last year reported intriguing findings suggesting that intestinal microbiome may play a key role in epilepsy and neurodevelopmental disorders in mice. The role of the microbiome and gut-brain interactions have never been discussed at previous IW workshops. Here, we will discuss the role of the gut microbiome in the development of epilepsy and the potential implications of these discoveries for treatment. | Gloria Choi, PhD; Elain Hsiao, PhD; and Audrey Mazarati, MD |
| **2019** | Gemma Carvill, PhD; and Heather Mefford, MD, PhD | Poison Exons: From Development and Disease to Therapeutic Target | This workshop will address the role of poison exons in neuronal development, in the development of genetic epilepsies through aberrant splicing, and as potential therapeutic targets for genetic epilepsies. Poison exons, or nonsense mediated decay (NMD) exons, are small exonic regions that when spliced into an RNA transcript lead to premature truncation of a protein. Inclusion of poison exons occurs during specific times in neurodevelopment and splicing occurs in a cell-specific manner. Many of the genes implicated in epilepsy harbor these exons, including SCN1A, making them candidates for harboring disease-causing mutations, but also for targeted RNA-based therapeutics. | Gemma Carvill, PhD; Lori L. Isom, PhD; and Xiaochang Zhang, PhD |
| **2019** | Chris Dulla,PhD; and Laura Ewell, PhD | Seeing the Forest or the Trees: Does Synaptic and Cellular Heterogeneity Support Pathological Network Activity Level? | This workshop will address the topic of oligonucleotide-based therapies for the treatment of epilepsy. Oligonucleotides are artificial DNA sequences which work by binding to target RNAs (e.g. mRNA) to disrupt their function. This IW will focus on exploring this nascent field in epilepsy, which offers virtually unlimited potential to treat genetic and acquired epilepsies and is now moving to clinical trials. It will provide an over-view of the state of the art, specific use of OGNs in distinct forms of epilepsy and span the pipeline from proof-of-concept to clinical trials as well as explore risks and limitations. | Heinz Beck, MD; Xia Yang, PhD; and Krishna Jayant, PhD |
| **2019** | Vaishnav Krishnan, MD, PhD | On Melancholia in Epilepsy: Mechanistic Insights into the Comorbidity of Epilepsy with Depression and Anxiety | This workshop will address recent translationally relevant mechanistic insights into the occurrence of mood and anxiety disorders in persons with epilepsy, which contribute substantially to disability and impairments in quality of life and which remain a key NINDS/AES research benchmark. We will emphasize preclinical developments in our understanding of the shared anatomical, cellular and molecular substrates that may predispose individuals to epilepsy and comorbid mood/anxiety disorders. Following our presentations, we will host a discussion that will revolve around strategies for risk stratification and treatment. | Vaishnav Krishnan, MD, PhD; Raman Sankar, MD, PhD; and Jamie L. Maguire, PhD |
| **2019** | David C. Henshall, PhD | Oligonucleotide Therapies for Epilepsy: A New Era in Precision Medicine? | This workshop will address the topic of oligonucleotide-based therapies for the treatment of epilepsy. Oligonucleotides are artificial DNA sequences which work by binding to target RNAs (e.g. mRNA) to disrupt their function. This IW will focus on exploring this nascent field in epilepsy, which offers virtually unlimited potential to treat genetic and acquired epilepsies and is now moving to clinical trials. It will provide an over-view of the state of the art, specific use of OGNs in distinct forms of epilepsy and span the pipeline from proof-of-concept to clinical trials as well as explore risks and limitations. | Cristina Reschke, PhD; Steve Petrou, PhD; and Claes Wahlstedt, MD, PhD |
| **2019** | F. Edward Dudek, PhD; and Bruce Gluckman, PhD | Ultra-slow and DC Recordings to Study Seizures, Migraine, and Spreading Depression | This workshop will address how ultra-slow changes in membrane potential and extracellular voltage may reveal common mechanisms that link epileptic seizures with migraine. Migraine is a comorbidity of epilepsy, and spreading depression is thought to contribute to both migraine and epileptic seizures (e.g., postictal depression). During spreading depression, neurons and glia undergo prolonged depolarization. The workshop will show how DC recordings are required to measure directly the ultra-slow components of spreading depression and postictal depression, and will discuss new techniques that can be used chronically in animal models and clinically in human patients. | KC Brennan, MD; Punam Sawant, PhD; and Fatemeh Bahari, PhD candidate |
| **2018** | Jeffrey Noebels, MD, PhD | The Storm before the Quiet: Basic mechanisms of SUDEP | The Center for SUDEP Research is a multisite NINDS Center without Walls, a consortium of investigators whose major focus is to identify biomarkers and uncover basic mechanisms contributing to sudden death, the most common cause of premature mortality in patients with epilepsy. Now in its 4th year, significant progress has been made through the analysis of genes and MRI imaging of actual SUDEP cases, as well as physiological studies of preclinical animal models. This Investigators Workshop will summarize the leading hypotheses and examine the evidence supporting them. Each speaker will define the future direction of research still required to predict and intervene in order to prolong the lives of those with epilepsy. George Richerson will present human and animal evidence for forebrain pathways that depress respiratory recovery after seizures. Lori Isom will review new evidence of sodium channel-related cardiac dysfunction linked to Dravet models in mouse and rabbit. Jeff Noebels will describe the relationship between brainstem spreading depression and cardiorespiratory collapse mediated by SUDEP and migraine with aura genes. A panel discussion will explore the design of interventional strategies in patients deemed to be at risk for SUDEP. | Moderator: Jeffrey Noebels, MD, PhD; Speakers: Jeffrey Noebels, MD, PhD, George Richerson, MD, PhD, Lori Isom, PhD |

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| **2018** | John Huguenard, PhD | Do rodent models of generalized absence seizures represent human disease or simply normal rodent behavior? | The electrographic signature of generalized absence epilepsy is bilaterally symmetrical 3 Hz Spike and Wave seizures, with relatively sudden onset and offset of each seizure.  Behaviorally, these are associated with rapid and reversible mild to moderate loss of conciousness, without loss of postural tone. Rodents, felines and non-human primates have all been used to create animal models of absence epilepsy, with each showing species specific electrophysiological phenotypes, with frequencies of 3-5 Hz in cats, 2-3 Hz in papio papio, and 3-10 Hz in rodents.  SWDs are generally associated with drowsiness and/or quiet wakefulness in all cases, and produce behavioral "absences" or brief, reversible lapses in responsiveness.Recently, it has been shown that rats can be trained to control SWD through behavioral training, and it has been suggested that they are, accordingly, voluntary (PMID: 28522734).  This paper has generated some commentary in the Journal of Neuroscience and pubmed commons, and it is critical to discuss, in general, rodent models of absence epilepsy to establish whether these rodent models, which provide experimental advantages to study circuit mechanisms of seizures and antiepileptic drug actions, adequately model the human disease.Topics discussed will include comparisons between human and rat models of absence(Blumenfeld), existence of SWD in the background EEG of some rodent strains (Scharfman), voluntary modification of SWD (Barth).  Dr. Huguenard will guide discussion, which could include other investigators present at the meeting that might contribute (Dudek, Coulter, Crunelli, Leresche, Frankel, Gallegher, Noebels, O'Brien, Paz, Onat, Depaulis). | Moderator: John Hugenard, PhD; Speakers: Cian McCafferty, BSc, PhD, Helen Scharfman, PhD, Daniel Barth, PhD |
| **2018** | Mark Beenhakker, PhD | Induced Pluripotent Stem Cell Strategies to Study Neurological Disorders | In 2006 and 2007, Takahashi and Yamanaka developed induced pluripotent stem (iPS) cell  technology that quickly lead to a Nobel Prize a few years later. The recent advances in iPS cell development and differentiation technologies have provided us a unique opportunity to model neurological disorders like epilepsy in a manner that is highly complementary to animal studies, but that maintains fidelity with complex human genetic contexts. The technology has also garnered considerable attention as it has become clear that patient-specific, neurological phenotypes can be detectable when iPS cells are further differentiated into neurons. These observations have underscored the possibility that patient-specific iPS neural circuits can be interrogated for the development of patient-specific therapies. Clearly, such a possibility provides hope for devising novel therapeutic targets for patients with refractory epilepsy.In this Investigators Workshop, we review the current state of iPS cell-based technologies. We also examine how close we are to realizing the goal of iPS cell-based, personalized epilepsy treatments. The panel of experts will highlight their recent work on using iPS cell-derived neurons to better understand epilepsies associated with epileptic encephalopathies. Experts will also describe new advances in building better, more physiological neural circuits from iPS cell-derived neurons. Panel speakers include Drs. Jack Parent (University of Michigan), Zhiping Pang (Rutgers Robert Wood Johnson), and Michael McConnell (University of Virginia). | Moderator: Mark Beenhakker, PhD; Speakers: Zhiping Pang, PhD, Michael McConnell, PhD, Jack Parent, MD |
| **2018** | Tracy Dixon-Salzar, PhD and Brenda Porter, MD, PhD | Genes, models and imaging in Lennox-Gastaut Syndrome | Lennox Gastaut syndrome is a poorly understood epileptic encephalopathy.  It is defined as a constellation of multiple seizure types including tonic, atonic, atypical absence, myoclonic and localization related seizures. It develops early in life and is associated with specific EEG features including generalized and focal epileptiform features, background slowing and disorganization. Comorbidities including intellectual disabilities, behavior problems and sleep disorders are usually present. It appears to be a developmental disorder with early life brain injury and genetic causes all leading to common seizures, EEG features and comorbidities. | Moderators: Tracy Dixon-Salzar, PhD and Brenda Porter, MD, PhD; Speakers: Aaron Warren, MSc, Bpsych, Heather Mefford, MD, PhD, Jeanner Paz, PhD |
| **2018** | Kyle Lillis, PhD | Optical studies of inhibition and excitation at seizure onset in acquired and evoked epilepsy | Animal models of epilepsy have been characterized by a wide variety of changes to inhibition including loss of interneurons (de Lanerolle et al., 1989), a reorganization of inhibitory synapses (Thind et al., 2010), preictal disinhibition (Ziburkus et al., 2006), or depolarization of GABA reversal potential (Lillis et al., 2012). Together these data suggest that neurological diseases, including epilepsy, result from more sophisticated pathology than a simple imbalance in excitation and inhibition (O’Donnell et al., 2017). Recent advances in calcium imaging and cell-type specific targeting of genetically encoded calcium indicators have made it feasible to simultaneously image activity in interneurons and principals cells during seizure onset. Characterizing the nature of inhibitory and excitatory activity during seizure onset represents a key step to understanding the network interactions responsible for ictogenesis. The speakers in this workshop will present data spanning a wide range of spatial scale and resolution, each of which brings different advantages. Dr. Ethan Goldberg will present two-photon calcium imaging from awake behaving Scn1a knockout mice during hyperthermia induced seizures. Dr. Lauren Lau will describe the I/E interactions that occur during the emergence and evolution, over weeks, of seizure activity in organotypic slice cultures. Dr. Vikaas Sohal will present fiber photometry data that PV+, SOM+, and VIP+ interneurons have distinctly different activiation patterns during optogenetically-induced seizures in awake, freely moving mice. Taken together these presentations will facilitate a discussion on hypothesized I-E interactions during ictogenesis how they might be further dissected in future experiments. | Moderator: Kyle Lillis, PhD; Speakers; Ethan Goldberg, MD, PhD, Andrew Treyvelan, DPhil., MB BcH, MA, Lauren Lau, PhD |

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| **2018** | Sydney Cash, MD, PhD | Using Big Data for Basic, Translational and Clinical Research in Epilepsy | An increasing array of tools are available for collecting, managing and mining data sets which include millions upon millions of data points. This big data scientific approach has become nearly ubiquitous in our daily lives (for better or worse) but is only recently making inroads into medical science. This is true for the study of epilepsy and development of new therapies for patients with seizures.  In this investigator workshop, we will examine three case studies of using large scale data sets to understand epilepsy at basic and translational levels.  We will use these examples as springboards to discussion concerning the potential and problems of big data analysis and interpretation as well as how these approaches may change the face of basic, translational and clinical science in epilepsy. | Moderator: Sydney Cash MD, PhD; Speakers: M. Brandon Westover, MD, PhD, Gari Clifford, D.Phil, Vikram Rao, MD, PhD |
| **2018** | Phillip Iffland, PhD | GATORopathies: the Role of Amino Acid Regulatory Protein Mutations in Epilepsy and Cortical Malformations | Background: Malformations of cortical development (MCD) are common causes of  drug-resistant epilepsy and intellectual disability (Desikan and Barkovich, 2016). Many MCD have been linked to either germline or somatic mutations in genes encoding protein components of the PI3K-AKT3-mTOR pathway occurring in neuroglial progenitor cells during brain development (Iffland and Crino, 2017). Appropriate mTOR signaling provides pivotal modulation of cell proliferation, migration, axon and dendrite outgrowth, and cortical lamination during embryonic brain development and leads to the formation of the intact cerebral cortex (Switon et al., 2017). Recently, loss-of-function mutations in the amino acid regulatory arm of the mTOR pathway have been implicated in several epilepsy-associated MCD including FCD, HME, and macrocephaly.     The amino acid regulatory arm of the mTOR pathway encompasses a number of proteins and protein complexes including the GATOR1 complex (Bar-Peled et al., 2013), GATOR2 complex (Chantranupong et al., 2014), sestrins (Parmigiani et al., 2014), CASTOR1 (Saxton et al., 2016), KICSTOR (Wolfson et al., 2017), and SAMTOR (Gu, et al., 2017). Each of these components interacts directly or indirectly with GATOR1 to influence mTOR activity in response to cellular amino acid levels. When amino acid levels are low (e.g., leucine, arginine, and methionine), GATOR1 acts on Rags A/B and C/D on the lysosomal surface and accelerates the conversion of GTP to GDP. This inhibits translocation of the mTORC1 complex to the lysosomal surface and thus prevents mTOR from phospho-activating its downstream targets (e.g., phospho-S6; PS6)).     Loss-of-function mutations in DEPDC5 and NPRL3, subunits of the GATOR1 complex, have been associated with FCD and HME (Baulac et al., 2015; Poduri, 2014; D'Gama et al., 2015; Scerri et al., 2015) in which histological examination of surgically resected brain specimens revealed morphologically abnormal PS6 immunoreactive neurons (Scerri, et al., 2015; Scheffer et al., 2014; Sim et al., 2016; Ricos et al., 2015). Loss-of-function mutation in SZT2 and KPTN, both part of the KICSTOR complex (which recruits GATOR1 to the lysosome), have been associated with epileptic encephalopathy with corpus callosal abnormalities (Nakamura, et al., 2017) and macrocephaly (Baple, et al., 2014), respectively. We believe this evidence points towards mutations in this pathway as a novel subcategory of epilepsy-associated mTORopathies and have thus named them “GATORopathies.”Speaker Roles: As moderator, Dr. Crino will begin the workshop by giving a brief introduction to GATORopathies and discuss the components of the amino acid regulatory arm of the mTOR pathway and its role in epilepsy-associated MCD. Dr. Carson, a Pediatric Neurologist at the Clinic for Special Children, will discuss a novel cohort of individuals with DEPDC5 and NPRL3 mutations found in Amish/Mennonite families. He will discuss the genotypes and clinical outcomes of these patients as well as treatment strategies. Dr. Iffland, a Research Associate at the University of Maryland School of Medicine, will discuss his work in the Crino lab examining the functional consequences of DEPDC5, NPRL3 and KPTN knockdown/knockout in neural cell lines and mouse models of focal cortical dysplasia. Dr. Bordey, a Professor at Yale University School of Medicine, will discuss her work on DEPDC5 mutations in brain development and lesion formation. Dr. Crino will close the workshop with a panel discussion featuring the speakers. Speakers will answer questions prepared by Dr. Crino and also field questions from the audience. | Moderator: Peter Crino, MD, PhD; Speakers: Phillip Iffland, MD, PhD, Vincent Carson, MD, Angelique Bordey, PhD |
| **2018** | Jamie Maguire, PhD | Inhibition in the epilepsies: problematic or therapeutic? | GABAergic signaling plays a complex role in the epilepsies, with robust evidence demonstrating the ability of GABAergic inhibition to suppress seizures and other studies demonstrating a role for GABA in facilitating seizures by promoting network synchronization or directly driving epileptiform activity via excitatory actions of GABA. The objective of this Investigators Workshop will be to discuss the therapeutic potential of enhancing inhibitory synaptogenesis in treating the epilepsies. | Moderator: Scott Baraban, PhD; Speakers: Molly Huntsman, PhD, Mariana Casalia, PhD, Suzanne Paradis, PhD |

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| **2018** | Eliana Scemes, PhD | Astrocytes in Epilepsy: cause or consequence? | Much is known about neuronal contribution to epilepsy; however, despite the large body of evidence indicating that non-neuronal cells, particularly astrocytes, are key players in CNS function and dysfunction, less attention has been given to the role of astrocytes in seizure activity and epilepsy development. Thus the goal of this workshop is to provide an overview of the most current findings on the roles played by astrocytes in epilepsy with evidence indicating that these cells are potential therapeutic targets. Because astrocytes establish associations with practically all cellular types in the CNS and express a multitude of ion channels, transporters, and membrane receptors, they have the capability to sense and influence CNS function.  The release of transmitters (glutamate, ATP and D-serine) from astrocytes impact synaptic transmission such that impaired regulated secretion from astrocytes results in delayed onset and attenuation of the frequency of spontaneous recurrent seizures.   Besides this mode of neuron-glia interaction, astrocytes communicate among themselves via intercellular gap junction channels that allows direct cytoplasmic diffusion of energy metabolites (glucose, lactate) throughout the interconnected glial network; glucose trafficking from perivascular astrocytes through the coupled astrocytic network provides energy to neurons in need. Disruption of astrocyte gap junctions not only dysregulate sleep-wake cycles due to reduced transfer of energy supply from astrocytes to neurons but also promotes spontaneous recurrent seizures, particularly in response to cytokines. During epileptic seizures, a condition that leads to the consumption of excessive amounts of energy, the levels of extracellular adenosine rise to counteract, via adenosine A1 receptors, neuronal hyper-excitability; astrocytes control the adenosine tissue tone mainly via the action of adenosine kinase and nucleoside transporters that promote the flux and recycle this nucleoside into the cell energy pool.  It is expected from this workshop (1) to increase awareness of the importance of astrocytes as therapeutic targets to treat and prevent epilepsy and (2) to promote further interdisciplinary research related to neuron-glia interaction. | Moderators: Eliana Scemes, PhD, Jana Veliskova, PhD; Speakers: Jerome Clasadonte, PhD, Detlev Boison, PhD, Christian Steinhaeuser, PhD |
| **2018** | Rodney Scott, PhD | Harnessing complexity for therapeutic gain | The ultimate goal of epilepsy treatment is to maximize quality of life by minimizing the impact of seizures and associated morbidities. Therapies that both reduce seizure frequency and improve comorbidities have enormous potential for achieving this goal. Traditional approaches to identifying therapeutic targets take a reductionist approach and largely target cell signaling and membrane excitability. Embedded in this strategy is the assumption that restoring these cellular properties will have positive effects on all other epilepsy-associated abnormalities, e.g. in neural circuits, whole brain networks, etc. However, with current treatments approximately 30% of patients fail to become seizure free and very few have important improvements to comorbidities, despite introduction of several new therapies over the last 2 decades. It is becoming increasingly clear that restoring biological properties of single cells may not be sufficient for our ultimate goals, and that future treatments targeting the brain systems that maintain seizure propensity and associated morbidities in patients may be useful.  The study of these brain systems, and how they can be modulated for therapeutic gain, is best achieved within a complex systems theory framework.  This framework studies interactions between components at multiple levels including genetics, cell signaling, local neural networks and whole brain networks. A complex system is defined as any system featuring large numbers of interacting components whose aggregate activity is nonlinear and typically exhibits hierarchical self-organization under selective pressures. Thus, the brain is the ultimate complex system. The first proposed talk will describe the concepts of complex systems and how those concepts can be applied to epilepsy. The second talk will deal with the idea of networks at the level of genetics. The final talk will discuss neural dynamics and highlight the way in which dynamics can be considered system-level mechanisms of outcomes and how they can be specifically modulated for therapeutic gain.   The following talks are proposed;  An overview of complex systems theory and how it can be applied to epilepsy. Interacting Components: In the brain there are many interacting components. Genes, proteins, neurons, brain regions etc, all function within networks. Studying networks at each of these levels could provide biologically useful information, independently of findings at any other level. It is conceptually important to understand that within this complex systems framework there is no level that is biologically more relevant than any other, because in a complex system all levels interact with each other to generate emergent behaviors that can be exemplified by a specific observation, such as an EEG pattern, a metabolic process, a pathological phenotype, etc.  Hierarchy: The structure and function of a network at any given level is dependent on biological activity in networks at multiple levels; each level is required for the level above it and may feedback to the level below it. Gene expression is required for protein production which is required for cell signaling which is required for transmission across a synapse which is required for plasticity which is required for formation of microcircuits and so on up to the emergence of behavior. Feedback mechanisms allow for influences in the opposite direction as well, e.g. activity-dependent plasticity feeds back to intracellular signaling that modifies gene expression, cell morphology, and synaptic weights. This implies that intervention at any of the levels would necessarily propagate throughout the hierarchy and could alter behavior at the top of the hierarchy.  Non-linearity: Although each level is critically dependent upon the level below it, the relationships between hierarchical levels are not linear and therefore prediction of how a level will behave as a function of a lower level is inherently uncertain, even if the lower level is | Moderator: Rodney Scott, MD,PhD; Speakers: John Matthew Mahoney, PhD, Andre Fenton, PhD, Kaja Kobow, PhD |

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| 2017 | Luca Bartolini | Inflammation and epilepsy: where do we stand and where do we go from here? | This session will focus on discussing the crucial role of inflammation in epileptogenesis. This mechanism is not targeted by conventional antiepileptic drugs and may contribute to the high number of refractory epilepsy cases. We will present the results of a cross-sectional study analyzing the potential role of HHV-6 and EBV infection and the immune response in children with various forms of seizures; we will discuss evidence for inflammation in the pathophysiology of epilepsy, including immunological aspects of epileptogenesis and role of biomarkers; finally, we will exchange views on approaches to novel therapeutic trials of viral and immunomodulatory treatments aimed to decrease the disease burden. | Moderator: William H. Theodore, MD., Speakers: Luca Bartolini, MD., Annamaria Vezzani, PhD, Jacqueline A. French, MD. |
| 2017 | Michael Hildebrand | Somatic mutation: the 'hidden genetics' of brain malformations | Somatic mutation is a genetic mechanism increasingly being recognised in neurological disorders (Poduri et al. 2013). It has recently been posited that there may be a sizeable 'hidden genetics' component of epilepsy due to somatic mutation (Thomas and Berkovic 2014). This occurs post-zygotically, is largely confined to the brain and is difficult or impossible to detect in blood (Hildebrand et al 2016). At present, the route to discovery in brain is via the privileged situation of brain tissue from surgical or autopsy specimens and many somatic mutations are mosaic at very low level in brain tissue (Uchiyama et al 2016). In this workshop, we intend to push the boundaries by discussing three major challenges of this exciting field. Dr. Poduri will discuss advances in clinical evaluations including MRI that permit improved diagnostic yield even for subtle brain malformations. Dr. Hildebrand will address the need for alternative tissue sources including CSF and nasal epithelium to interrogate genetically. Dr. Matsumoto will introduce the latest molecular approaches to detect ultra-low-level somatic mosaicism. These strategies are applicable to epilepsies and other brain disorders to maximise gene discovery, clinical diagnosis and, eventually, to facilitate translation of Precision Therapies to the clinic. | Moderators: Michael Hildebrand, PhD, Heather Mefford, MD., PhD; Speakers: Annapurna Poduri, MD., Naomichi Matsumoto, MD., PhD |
| 2017 | Peyman Golshani | In-vivo imaging of network dynamics in epilepsy | New tools now enable high speed simultaneous imaging of activity in hundreds of neurons in behaving animals. We will highlight 3 speakers that show how calcium and voltage imaging of large ensembles can be used to to follow the activity patterns of large populations of precisely identified neurons in models of temporal lobe and generalized epilepsy. These approaches can be used to discover dysfunction in key cell types that may be driving initiation of seizures or network dysfunction during cognition in epilepsy. | Moderator: Peyman Golshani, MD., PhD; Speakers: Stelios Smirnakis, MD., PhD, Matthew Shrtahman, MD., PhD, Istvan Mody, PhD |
| 2017 | Christina Gross | MicroRNA-induced silencing in epilepsy-potential treatment target and biomarker | MicroRNAs control the expression of many target proteins and therefore can influence cellular function by regulating entire protein networks. In recent years, microRNA expression and function have been shown to be altered following seizures and in epilepsy. Manipulation of single microRNAs in rodent models of status epilepticus and epilepsy alters seizure susceptibility and severity, and can reduce neurodegeneration and neuroinflammation. This suggests microRNA-induced silencing as a novel therapeutic target in epilepsy that is mechanistically very different from currently available antiepileptic drugs. This workshop will discuss recent advances in understanding the mechanisms of microRNA-induced silencing in epilepsy and their implications for the development of novel therapies and biomarkers. We will cover the role of microRNAs for epileptogenesis and acquired epilepsy, as well as in genetic forms of epilepsy, and describe new technologies to quickly identify microRNAs that could be targeted to prevent hyperexcitability in the brain. Dr. David Henshall will talk about neuroprotective effects of inhibiting select microRNAs in the brain in status epilepticus and epileptogenesis. Dr. Eleonora Aronica will discuss how altered microRNA expression in Tuberous Sclerosis may influence neuroinflammation and epilepsy development. Dr. Karl Martin Klein will present recent advances in identifying genetic variation in microRNAs associated with epilepsy. The goal of this workshop is to provide insight into the current state of the field regarding the role of microRNAs in epilepsy and an assessment of what is needed to move microRNA-based therapeutics into clinical application. | Moderator: Christina Gross, PhD; Speakers: David Henshall, PhD, Eleonara Aronica, MD., PhD, Karl Martin Klein, MD., PhD |
| 2017 | Sarah Muldoon | Data-driven computational modeling of epileptic network structure | Many recent efforts in computational modeling of large-scale brain dynamics have begun to take a data-driven approach, incorporating structural and/or functional brain networks derived from patient data into the model. In this workshop, we will focus on approaches that use either structurally or functionally derived network connectivity as a base of brain network structure in virtual models of epileptic brains. This workshop will include presentations by some of the leaders in this new direction of computational research (Viktor Jirsa, Marcus Kaiser, and Ankit Khambhati), and promote discussion on how virtual experiments (lesions, resections) can guide experimental epilepsy research. | Moderator: Sarah Muldoon, PhD, Speakers: Viktor Jirsa, PhD, Marcus Kaiser, MD., PhD, Ankit Khambhati, PhD |
| 2017 | Bret Smith | Are animal models of post-traumatic epilepsy translational? | Traumatic brain injury (TBI) greatly increases the risk of medically intractable epilepsy. Several models of TBI have been developed to investigate the relationship between TBI and the development of posttraumatic epilepsy (PTE). Because the incident that precipitates development of epilepsy is known, studying mechanisms of posttraumatic epileptogenesis, identifying biomarkers to predict PTE, and developing treatments to prevent epilepsy after TBI are attainable goals. Understanding posttraumatic epileptogenesis may also inform investigations of other acquired epilepsy syndromes. Speakers will discuss the current state of animal models of PTE, the cellular similarities (and differences) between PTE and other types of acquired epilepsy, potential biomarkers specific to PTE development in the context of those associated with injury alone, and treatments that modify injury recovery and posttraumatic epileptogenesis. Understanding the processes underlying epileptogenesis after a temporally and spatially well-defined, precipitating event will provide insight into the causes of other types of acquired epilepsy. | Moderator: Bret Smith, PhD; Speakers: Bret Smith, PhD, Asla Pitkanen, MD., Robert Hunt, PhD |

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| 2017 | Joaquin Lugo | From inflammation to phagocytosis: how microglia shape vulnerable neuronal networks in epilepsy | Microglia are the brain's innate immune cells and contribute to the neuropathology and pathophysiology of epilepsy. When their microenvironment is challenged with events such as seizures microglia cells can develop an inflammatory or phagocytic response. It is widely known that microglia-mediated neuroinflammatory mechanisms play a role in neuronal hyperexcitability; however, the contribution of their phagocytic response to seizures and epilepsy is less known. Emerging evidence suggests that microglial phagocytic signaling cascades contribute to the activity-dependent modification of neuronal networks under physiological and pathological conditions. This workshop will begin by first reviewing the contributions of the microglia-mediated neuroinflammatory alterations to the hippocampal network (Sookyong Koh). The second speaker will present evidence for the role for the classical complement pathway in the regulation of the hippocampal synaptodendritic profile in experimental and human epilepsy (Amy Brewster). The third speaker will present research on the pathological role of a recently identified microglial phagocytic impairment in the hippocampus of both genetic and acquired models of epilepsy (Amanda Sierra). | Moderator: Joaquin Lugo, PhD; Speakers: Amy Brewster, PhD, Sookyong Koh, MD., PhD, Amanda Sierra, PhD |
| 2017 | Chris Dulla | NMDA receptors in epilepsy: mutations, inhibitory circuits, and personalized medicine | NMDA receptors are critical for synaptic plasticity and memory, but also contribute to multiple aspects of abnormal excitation in the epileptic brain. First, human mutations in NMDA receptors have been linked to epilepsy-aphasia syndromes, infantile spasms, and other early onset epileptic encephalopathies. Second, abnormal NMDA receptor expression and function contributes to circuit reorganization associated with epileptogenesis, the transition to the ictal state, and seizure generalization. Last, disrupted glutamate signaling acting through NMDA receptors can induce excitotoxicity, interfere with important spontaneous network activity in the developing brain, and disturb cellular and circuit maturation. Targeting NMDA receptors therapeutically, however, has been a significant challenge due to adverse side effects. Recent studies suggest, however, that pharmacological interventions in specific developmental windows, or that affect specific sub-types of NMDA receptors, may allow manipulation of NMDA receptor symptoms with reduced adverse effects. In this Investigator's Workshop, we will focus on 1) novel mutations in NMDA receptors associated with epilepsy, 2) opportunities and challenges associated with evaluating pharmacological strategies to utilize personalized medicine to treat epilepsy associated with NMDA receptor mutations, and 3) studies showing that transient disruption of specific NMDA receptor subtypes during cortical development can lead to long term circuit hyperexcitability. The session will be moderated by Dr. Heather Mefford (University of Washington), a human geneticist and epileptologist. Dr. Gemma Carvill (Northwestern University School of Medicine) will discuss "Expanding genotypes and phenoypes in the GRIN gene family". Dr. Stephen Traynelis (Emory University) will discuss "Challenges in designing strategies to exploit personalized medicine in patients with GRIN mutations". Dr. Chris Dulla (Tufts University) will discuss "Disruption of NR2C/D activity during neocortical development causes inhibitory hypofunction and network hyperexcitability". Participants in this workshop will leaving with an understanding of 1) how NMDA receptors dysfunction can contribute to epilepsy, 2) how sub-type specific disruption of NMDA receptor activity during development can lead to network hyperexcitability, and 3) the promise and difficulties in developing novel NMDA-based pharmacological tools for personalized pharmacological treatment for epilepsy. | Moderator: Heather Mefford, MD., PhD; Speakers: Chris Dulla, PhD, Steve Traynelis, PhD, Gemma Carvill, PhD |
| 2017 | Shilpa Kadam | KCC2 hypofunction in epilepsy: developing novel therapeutic strategies to modulateK+/Cl- Co-transporter 2 (KCC2) function | The KCC2 chloride co-transporter is the chief Cl- extruder in CNS neurons. KCC2 is known to co-localize with GABAA receptors but is also expressed at excitatory synapses. KCC2 plays significant roles in dendritic spine morphogenesis and glutamatergic synaptic function. KCC2 activity is both positively and negatively regulated by many pathways including phosphorylation of different sites on its protein structure. KCC2 hypofunction has now been shown to play a critical role in the emergence of seizures by multiple independent research groups. More interestingly, enhancing or preserving KCC2 function during seizures can positively impact seizure outcomes and therefore highlight the need to develop true enhancers of KCC2 as a novel therapeutic strategy. | Moderator: Stephen Moss, PhD; Speakers: Shilpa Kadam, PhD, Tarek Deeb, PhD, Anatoly Buchin, PhD |
| 2017 | Tallie Z. Baram | Divergent and overlapping mechanisms contribute to epilepsy and its comorbidities | Epilepsy is defined by spontaneous seizures. Whereas the seizures have been the central focus of epilepsy research, they are commonly accompanied by cognitive and emotional problems including memory, decision-making deficits and depression, that contribute to poor quality of life. These co-morbidities are observed in many types of epilepsy, and cognitive and emotional problems are especially prominent in temporal lobe epilepsy, involving the hippocampal-limbic circuit. Whereas the mechanisms underlying the impairments are remain unclear, recent work has begun to uncover mechanisms that uniquely contribute to cognitive/ emotional problems after a genetic or acquired 'insult'. Concurrently, recent and emerging studies are identifying common molecular, cellular and circuit processes that may promote both the epileptic seizures and the cognitive and emotional impairments. | Moderators: Julia Kahn, PhD, Christophe Bernard, PhD; Speakers: Tallie Z. Baram, PhD, Christophe Bernard, PhD, Pierre-Pascal Lenck-Santini, PhD |

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| 2016 | Long-Jun Wu | Glial mechanisms of epilepsy | Traditionally, studies on epilepsy have focused primarily on 'cell-autonomous' neuronal mechanisms in seizure activities. Recent emerging evidence indicates that glial cells including astrocytes and microglia play active roles in pathogenesis of epilepsy, but glial mechanisms of epilepsy have not been well appreciated. In this symposium, Eyo will demonstrate that microglial specific receptors P2Y12 in mediating microglia-neuron interactions during kainic acid-induced seizure using 2-photon imaging. His results reveal the molecular mechanism and functional significance of microglia-neuron interaction in epilepsy. Binder will outline changes in astrocyte water channels (aquaporins) and glutamate transporters during early epileptogenesis, which may underlie the development of hyperexcitability. Wilcox will discuss the role of cytokines, which are secreted by reactive microglia and astrocytes, in contributing to hyperexcitability of neural circuits in a novel model of infection-induced epilepsy. Studies from the three speakers will shed new light on how glial cells respond to and regulate neuronal hyperactivities after epilepsy and thus provide potential therapeutic targets at glial cells for epilepsy management. | Moderator: Long-Jun Wu, PhD<br>Speakers: Ukpong Eyo, PhD, Devin Binder, PhD, Karen Wilcox, PhD |
| 2016 | Helen Scharfman | Role of aberrant neurogenesis in epileptogenesis | Neurogenesis in the adult brain is established in all mammals including humans, where it has been suggested to changed dramatically after seizures and play a role in epilepsy. However, exactly how adult-born neurons influence seizures and epilepsy is not yet clear. This workshop will allow three individuals who have contributed to this research topic to present their views, some of which are paradoxical and therefore can stimulate discussion. In addition, the speakers will address the potential effects of adult neurogenesis on behavioral 'comorbidities' found in animal models of epilepsy. We suggest Steve Danzer, Helen Scharfman and Kyung-Ok Cho as speakers because these are central contributing investigators to the field and represent diverse backgrounds (senior, junior, male, female). Steve Danzer will discuss his laboratory's findings related to induction of epilepsy by selective deletion of the mTOR pathway modulator PTEN. Helen Scharfman will discuss the "good" and "bad" effects of adult-born neurons in animal models of temporal lobe epilepsy. Kyung-Ok Cho will discuss her work, from the laboratory of Jenny Hsieh, which shows that aberrant adult-born neurons play a role in the pilocarpine model of epilepsy. Jenny Hsieh will also be a moderator. | Moderator: Jenny Hsieh, Ph.D<br>Speakers: Helen Scharfman, PhD, Kyung-Ok Cho, MD., PhD, Steve Danzer, PhD |
| 2016 | Jenny Hsieh | Emerging strategies using stem cells to prevent epilepsy | In many genetic and acquired syndromes of epilepsy, patients are refractory to standard antiepileptic drugs for unknown reasons. Therefore, developing accurate and powerful biological models for epilepsy has been a challenge. The use of pluripotent stem cell technology has provided a new approach. This workshop will bring together two senior and one junior investigator (male and female) using stem cell technology in various settings to understand and treat epilepsy. Jack Parent will talk about the use of human induced pluripotent stem cells to model patient epilepsies. Jenny Hsieh will expand on this theme and talk about the use of 3D stem cell organoid technology to model human brain development and function. Robert Hunt will talk about cell therapy approaches to stop seizures and other comorbidities by grafting new inhibitory interneurons in animal models of epilepsy. | Moderator: Helen Scharfman, PhD<br>Speakers: Jenny Hsieh, PhD, Jack Parent, MD., Robert Hunt, PhD |
| 2016 | Peter Carlen and Marco de Curtis | Seizure termination: multiple mechanisms | This symposium will explore both the macro and micro aspects of seizure termination. On examining intracranial EEG in seizure patients, it is often remarkable how large areas of the seizing brain will suddenly and simultaneously cease seizing followed by relative cerebral silence. Although little studied, there are several biophysical and neurotransmitter mechanisms, which come into play by the end of a seizure, including presynaptic depression of glutamate release, augmentation of GABA release, increased ambient adenosine, raised intracellular calcium, and depressed metabolism. Understanding these mechanisms could lead to improved strategies for preventing and aborting seizures. | Moderators: Peter Carlen, MD., Marco de Curtis, MD.<br>Speakers: Marco de Curtis, MD., Peter Carlen, MD., Paolo Bazzigaluppi, PhD |

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| 2016 | Manisha Patel | Peripheral and imaging biomarkers in epilepsy | Currently, the epilepsy field suffers from a lack of biomarkers able to reliably stratify or diagnose patients with drug resistant or drug-responsive epilepsy. Biomarkers of early epileptogenesis are lacking. Despite severe epileptogenic brain insults, a fraction of individuals go on to develop epilepsy. Biomarkers that identify a high-risk group for development of epilepsy post-brain insult are particularly desirable. Such biomarkers could also enrich clinical trials by including only those most likely to develop epilepsy. The ideal situation would be the identification of a panel of biomarkers preferably via blood sampling or imaging that would assess the entire epileptogenic process covering the immediate post-insult epileptogenic period through ictal and interictal phases. The field of biomarker research has blossomed in recent years with the advent of brain imaging technologies, neurophysiology, genomics, proteomics, and metabolomics. Peripheral or imaging biomarkers are particularly useful in brain disorders such as epilepsy as they can are non-invasive. Inflammation, metabolic impairment and oxidative stress are important processes associated with epilepsy for which novel peripheral biomarkers have being rapidly developed. Oxidative stress and metabolic dysfunction are activated by epileptogenic injuries and can contribute to seizures and comorbidities. Plasma biomarkers of redox and metabolic perturbations based on mass spectrometry and other analytical methods have been identified in animal models of acquired epilepsy. These biomarkers can provide important information regarding the epileptogenic potential of an insult, disease progression and/or drug resistance. Brain inflammation is the key mechanism for brain repair after an insult and it has an important role in the pathophysiology of various types of epilepsy. During epileptogenesis this balance shifts towards a strong pro-inflammatory response including activation of parenchymal microglial cells, increased expression of pro-inflammatory cytokines and infiltration of peripheral immune cells due to the leakage of the blood brain barrier (BBB). A candidate imaging target of brain inflammation in epilepsy is translocator protein (TSPO), a protein localized primarily in the mitochondrial membrane. TSPO is expressed in glial cells in low amounts under healthy conditions, but as a consequence of inflammatory response microglia and astrocytes overexpress TSPO. The available Positron Emission Tomography (PET) ligands for TSPO have shown increased signal in vivo in patients in several epilepsy disorders with neuroinflammatory components. In addition, in animal model of epilepsy a substantial TSPO increase had been demonstrated during epileptogenesis and chronic epilepsy in several brain regions using post-mortem and recently, in vivo techniques. | Moderator: Manisha Patel, PhD, Stefanie Dedeurwaerdere, PhD<br>Speakers: Stefanie Dedeurwaerdere, PhD, Svenja Heischmann, PhD, William Theodore, MD. |
| 2016 | Chris Dulla | Novel intracellular signaling cascades and epilepsy: Is there untapped therapeutic potential? | In this workshop, we will investigate new and exciting cellular signaling pathways that may have important relevance to epilepsy. A great deal of recent work on cell signaling cascades, such as the mTOR pathway, have invigorated the field and provided promising new therapeutic targets. There are many signaling cascades, however, which may have particular relevance to epilepsy, but have not yet been fully explored or understood in this context. In this IW session, Dr. Michele Jacobs (Tufts University School of Medicine) will present a talk entitled “Identifying New Molecular Targets for Infantile Spasms”. She proposes a novel molecular model of infantile spasms (IS) that is centered on aberrant activation of the b-catenin pathway. b-catenin is a central molecule in an important cell signaling network, and its dysregulation in the brain leads to improper neuronal maturation and network function. Both human and mouse genetic studies provide strong support for the b-catenin malfunction model of IS. Next, Dr. Angelique Bordey (Yale University School of Medicine) will share her work on the role of the MEK-ERK pathway on neurodevelopment and neurological disease. Her talk, entitled “ERK-Filamin A dysregulation in an mTOR-associated neurological disorder” will examine how abnormalities in MEK-ERK signaling can lead to disruption of cortical development, synaptic function, and neuronal morphology. While disruptions in MEK-ERK signaling have not yet been linked to seizures, this presentation will inform epilepsy researchers how mutations in genes responsible for other neurological diseases may also play a role in the development of epilepsy. Lastly, Dr. Gaia Novarino (Institute of Science and Technology Austria) will discuss exciting new technologies that allow us to identify novel signaling pathway disruptions related to epilepsy and to screen for novel therapeutic agents. Her talk, entitled “Aligning pathway and exome analysis links amino acid homeostasis to epilepsy: strategies for the development of aetiology-based treatments” will demonstrate how cutting-edge induced pluripotent stem (IPS) cell-based approaches provide additional evidence that mutations in cell signaling pathways can have a significant impact on neurological pathophysiology. In summary, this workshop will highlight novel signaling pathways which are relevant to the development of epilepsy, but that are not widely discussed within the epilepsy community. Furthermore, we will focus on cutting-edge IPS cell-based cerebral organoids approaches to identify and understand how novel cell signaling disruptions are involved in epilepsy. | Moderator: Chris Dulla, PhD<br>Speakers: Gaia Novarino, PhD, Michele Jacob, PhD, Angelique Bordey, PhD |

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| 2016 | Dr. Jana Veliskova | Autistic traits in epilepsy models: Why, when and how? | Autism is significant comorbidity of epilepsy. Current research indicates that there are autistic traits present in mice and rats with seizures used to build epilepsy models. These traits may be different in different models as per the observations. However, a systematic approach for testing these autistic traits is necessary. Therefore, there will be three speakers most suited to draw an outline for systematic approach to testing autistic features in the animal models: Jaqueline Crawley, PhD, UC Davis spent most of her career developing and testing rodents (mostly mice) for autistic features, developing new tools and modifying available tools to standardize research in autistic features in rodents. Therefore, she can provide expert information on what should be tested and how exactly this should be done consistently. Andrey Mazarati, PhD, UCLA published several papers analyzing autistic features in rodents with epilepsy. Thus, he can provide first hand expertise in testing autistic features in rodents with recurrent seizures. Last but not least, Melissa Benson, a Junior Investigator, received her PhD at University of Brisbane working with Dr. Karin Borges on autism, neuroinflammation and epilepsy. Currently, she is working on her postdoctoral training with Dr. Jana Veliskova, at NYMC in Valhalla, NY continuing research in neuroinflammation and epilepsy in those models particularly prone to demonstrate autistic features. | Moderator: Jana Veliskova, MD., PhD<br>Speakers: Melissa Benson, PhD, Jill L. Silverman, PhD, Pierre-Pascal Lenck-Santini, PhD |
| 2016 | Devin K. Binder (co organizer: Viji Santhakumar) | Neurovascular Unit in Seizures and Epilepsy | The neurovascular unit composed of a capillary segment and associated pericytes, basement membranes, astrocytes, microglia and extracellular matrix has been found to play significant roles in shaping neuronal and network activity in the normal and epileptic brain. Brain vasculature, is central component of the neurovascular unit, can show both acute functional changes during seizures and chronic alterations in epilepsy which can regulate brain metabolism and excitability. Similarly, changes in the extracellular space in which the neurovascular unit operates profoundly influence s distinct elements of the neurovascular unit and their interaction. Thus the impact of the neurovascular unit on brain activity extends beyond the classical discussions of blood-brain-barrier permeability and changes in the immune status of the brain. The speakers in this workshop will present recent findings which highlight the diverse and novel ways in which the neurovascular element can influence seizures and epilepsy. Nicola Marchi (CNRS, France) will present new advances in the role of pericyte inflammatory modification on neurovascular coupling in epilepsy and its implications for pharmacological interventions. Todd Fiacco (University of California, Riverside) will discuss how edema, astrocytic swelling and perturbations in extracellular space impact neuronal excitability, with implications for many diseases that display edema including seizures. Cam Teskey (University of Calgary) will explore the role of postictal hemodynamic changes in functional alteration which could provide long awaited clues to the mechanisms underlying post-ictal paralysis. | Moderators: Devin Binder, PhD, Viji Santhakumar, PhD<br>Speakers: Nicola Marchi, PhD, Todd Fiacco, PhD, G. Campbell Teskey, PhD |
| 2016 | Dan Xu, PhD and Sookyong Koh, MD. PhD | Novel Immunomodulatory Therapies in Epilepsy | Despite increasing evidence of active involvement of brain inflammation and peripheral immunity in epileptogenesis and reported efficacy of steroids in treating refractory epilepsies, high dose chronic steroid therapy or other immunomodulatory drugs cannot be prescribed to otherwise responsive patients with epilepsy due to increased risks of infection, neoplasia, neuropsychiatric complications, and other severe side effects. Development of disease modifying, better-tolerated immunomodulatory therapy that specifically target brain inflammation and restrict infiltration of peripheral immune cells into the brain can thus be a highly desirable epilepsy therapy. A panel of well-established therapies that are either FDA-approved or in the late phase of clinical trials targeting unwanted or dysregulated immune responses have not been tested in epileptic disorders. A number of reasons contributed to this lack of cross-field translation, including inadequate understanding of the immune mechanisms in epileptogenesis, the scantiness of appropriate animal models for drug-testing, and a relative paucity of neuroimmunologists involved in epilepsy research. The workshop will feature a panel of immunologists as well as epileptologists. Dan Xu, PhD (Junior Investigator from Northwestern University) will start the session with a brief review of immunological contributions to chronic epilepsy and rewiring of immune circuitry in the epileptic brain. She will also discuss her recent findings on autologous regulatory T cell therapies that are being used in cancer and autoimmune diseases for the treatment of epilepsy. Braxton Norwood, PhD (Phillips Universitaet Marburg, Germany) will then discuss novel animal models, such as TLR-deficient mice that develop spontaneous seizures, to test commercially available substances for prevention of epilepsy. Annamaria Vezzani, PhD (Istituto di Ricerche Farmacologiche Mario Negri, Italy) will stimulate discussions on the use of experimental models to prove involvement of immune mediators in epileptogenesis and on novel therapies currently in clinical trials. Robert Fujinami, PhD (University of Utah) will be a backup presenter to discuss the use of a viral infection model of spontaneous seizures in the development of novel antiepileptogenic therapies. | Moderators: Dan Xu, PhD, Sooky Koh, MD., PhD<br>Speakers: Dan Xu, PhD, Eleonora Aronica, MD., PhD, Teresa Ravizza, PhD |

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| 2016 | Sam Berkovic, Melbourne (co-chair Ingo Helbig, Philadelphia) | Whole exome sequencing in the epilepsies: making sense of the sequence data. | Whole exome sequencing (WES) has become a practical and affordable clinical test for many patients with presumed genetic disorders. However, many of us in the clinical and research fields are faced with the challenge of making relevant and reliable conclusions based on the WES findings. Dr Weckhuysen will discuss how data from patients with epileptic encephalopathy can influence clinical practice, including copy number variant and whole exome sequencing findings. Over a third of epileptic encephalopathies can now be diagnosed on the basis of a genetic aberration; however, this leaves over a half of patients with a severe epileptic encephalopathy genetically undiagnosed. Drs Petrovski and Krause are analyzing large data sets of whole exome data from subjects with the more common Genetic Generalized Epilepsies. This common and highly heritable group of epilepsies has to-date largely defied attempts to identify pathogenic variants, yet there are remarkable patterns emerging from these data that suggest great promise from analyzing large data sets to provide new insights into pathogenesis and treatment. | Moderators: Sam Berkovic, MD., Ingo Helbig, MD.<br>Speakers: Sarah Weckhuysen, MD., Slave Petrovski, PhD, Roland Krause, PhD |
| 2015 | Michael Wong, Darcy Krueger | A Model Approach for Developing Antiepileptogenic Drugs: Targets, Biomarkers, and Barriers | Current medications for epilepsy suppress seizures symptomatically, but do not have antiepileptogenic or disease-modifying effects to prevent epilepsy in high-risk patients. A “holy grail” of epilepsy research is to develop an antiepileptogenic drug, but at this point there is no established, proven antiepileptogenic drug therapy in people. There are number of limitations and barriers to establishing an antiepileptogenic drug, including a paucity of proven drug targets with antiepileptogenic properties, lack of predictive biomarkers for future epilepsy to identify high-risk candidates for antiepileptogenic therapy, and practical issues in design and recruitment for a preventative trial in asymptomatic patients. Tuberous sclerosis complex (TSC) represents a model disease for developing antiepileptogenic therapies for several reasons. First of all, patients with TSC are increasingly diagnosed in infancy due to non-neurological findings, making them feasible candidates to identify prior to onset of epilepsy. Secondly, TSC patients are at very high risk for developing epilepsy, including drug-resistant epilepsy, justifying initiating prophylactic therapy in asymptomatic patients. Finally, the mTOR pathway, which is directly linked to the genetic defect of TSC, represents a rational, mechanistically-based drug target for antiepileptogenesis in TSC, and mTOR inhibitors are already clinically-available for other indications in this disease. This IW will adopt a very practical workshop approach in analyzing the critical barriers to overcome and steps to take towards developing a first antiepileptogenic drug for epilepsy, using TSC as a model disease for accomplishing this goal. In the introduction, the moderators will briefly outline the requirements and barriers to developing an antiepileptogenic therapy in general and the features that make TSC a model disorder for this purpose. Michael Wong will then review rational mechanistic targets, focusing on the mTOR pathway, in animal models with potential antiepileptogenic properties in TSC. Joyce Wu will discuss the importance of predictive biomarkers for identifying candidate patients for antiepileptogenic therapy and present data supporting use of EEG as such a biomarker in TSC. Martina Bebin will overview the practical pitfalls and barriers to designing and implementing a preventative trial in asymptomatic infants, including issues with recruitment and regulatory approval. Finally, a focused, interactive discussion period engaging the audience will further explore other practical barriers and solutions to establishing an antiepileptogenic drug and extend these principles to other types of epilepsy beyond TSC. | Martina Bebin, Michael Wong, Joyce Wu |
| 2015 | Joaquin Lugo and Amy Brewster (co-organizer) | The role of fragile x mental retardation protein in epilepsy, ion channels, and behavioral comorbidities | Loss of FMRP in FXS leads to intellectual disability, autism, neuronal hyperexcitability and epilepsy, but its role in pathological changes after epileptic seizures is not well understood. Seizures are often associated with dysregulation of dendritic ion channels (channelopathies) and cognitive deficits. In both genetic and acquired epilepsies there are reported disruptions in mRNA, protein levels, and phosphorylation of the dendritic ion channel Kv4.2. Aberrant expression of Kv4.2 is associated with neuronal hyperexcitability, spontaneous recurrent seizures, and behavioral comorbidities. Evidence suggest that cellular signaling cascades such as the PI3K/AKT/mTOR alters fragile x mental retardation protein (FMRP), which may contribute to the regulation of Kv4.2 channels in adult and developmental epilepsy. Given that activation of PI3K/AKT/mTOR and FMRP is enhanced by seizures and in some models of chronic epilepsy, it is possible that they play a role in Kv4.2 channelopathies and learning deficits. In this workshop evidence for PI3K/AKT/mTOR and FMRP-mediated dysregulation of Kv4.2, neuronal excitability and behavior will be presented and discussed. Dr. Joaquin Lugo (AES member) from Baylor University will show evidence of learning deficits, alterations in synaptic proteins, and alterations in dendritic ion channels from a PTEN KO model. Dr. Christina Gross (non member) from Cincinnati Children's Hospital Medical Center will show how elevation in the PI3K/AKT/mTOR pathway may contribute to behavioral defects and neuronal hyperexcitability in a fragile x syndrome mouse model. Dr. Tim Benke (AES member) from University of Colorado-School of Medicine will show how early-life seizures lead to long-term learning deficits and dysregulation in FMRP. | Joaquin Lugo, PhD, Christina Gross, PhD, Tim Benke, MD, PhD |

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| 2015 | Karen Wilcox & Doug Coulter | Emerging technologies for imaging the neural circuits underlying seizures | Epilepsy is a neural circuit disorder and there has been significant progress in the technologies that can be used to image these circuits in real time in rodents and other model organisms. This workshop will introduce the participants to some of these new techniques and how to practically implement them into their own research. The participants we plan on asking to speak have considerable expertise in imaging and protein development/use and will provide an engaging discussion format for the practical and financial aspects of using 2-photon in vivo microscopy and fMRI in rodent models of epilepsy. In addition, discussion will also focus on the latest developments in genetically encoded calcium and voltage indicators, which have proven to be superior to synthetic dyes and indicators for imaging in adult, rodent neural networks. We anticipate that this will be an important workshop that will contribute to the participants' understanding of the impact these new experimental techniques can have on their own work and in the field of epilepsy research. Drs. Coulter and Wilcox will serve as co-chairs and facilitate discussion between the speakers and the audience. The three talks will all be limited to 15 minutes each with a 5-minute question and answer period. The remaining time (~20 minutes) will be devoted to a panel discussion of all the speakers. | Jin Hyung-Lee, PhD , Hajime Takano, Loren Looger |
| 2015 | Chris Dulla | Energy metabolism and dynamic brain states | This workshop will examine the role that slow metabolic changes have in driving seizure activity. Our interest in this question comes from two clinical and experimental facts: 1) any brain can be made to seize if the conditions are correct, and 2) seizures are extremely idiopathic, arising when some set of undefined parameters are met. Recent modeling work has given the field new insight into how seizures begin, are sustained, and terminate. Furthermore, novel imaging, electrophysiological, and biochemical studies have identified metabolic pathways which affect excitability. In this workshop we will discuss the hypothesis that slow metabolic processes in the brain underlie the idiopathic nature of seizures. Dr. Christophe Bernard (INSERM) will present on "The role of slow molecular, including metabolic, processes in seizure genesis and propagation". Seizure genesis and propagation correspond to a change in dynamic regime, requiring a force driving neuronal networks over a threshold that separates "healthy" and "seizure" brain states. Dr. Bernard will show how metabolic processes may underlie seizure induction and propagation. Dr. Mark Beenhakker (University of Virginia, Junior Investigator) will present on "Thalamic circuit modulation by hypoglycemic conditions". Dr. Beenhakker will present data in support of a role for ATP-sensitive potassium channels in modulating neuronal activity in the thalamus during hypoglycemic conditions. Dr. Susan Masino (Trinity College) will discuss "The ketogenic diet and adenosine - linking metabolism and excitability". The ketogenic diet mimics the antiseizure effects of fasting by altering metabolism and thus neuronal excitability. In recent years Dr. Masino's group has accumulated in vitro and in vivo evidence for several mechanisms, including the neuromodulator adenosine, as key to the success of a ketogenic diet. These mechanisms form a dynamic link between metabolism and neuronal excitability, and offer predictions for multiple neurological conditions. In summary, this workshop will provide a framework by which we can understand how slow changes in metabolic processes can link to pathological brain state transitions. We will then go onto discuss example molecular sites of metabolic modulation. Lastly we consider the idea that the idiopathic nature of seizures may be due to changes at these, and other, sites of metabolic modulation. | Mark Beenhakker, Christophe Bernard, Susan Masino |
| 2015 | Viji Santhakumar and Anne Anderson | Immune and non-cannonical effects of inflammation in seizure disorders | Activation of neuroinflammatory signals is widely observed in chronic epilepsy and following epileptogenic insults such as status epilepticus. Neuroinflammation is often associated with neuroprotection and tissue repair mechanisms; however, substantial evidence suggest that pathological inflammatory signaling also may contribute to the epileptogenic process and the neuropathology of epilepsy. Studies examining the role of inflammation in epilepsy have shown that immune molecules and receptors may act through non-immune mechanisms including synaptic and neurotransmitter systems to enhance excitability and contribute to epilepsy. The complete repertoire of classical immune pathways and non-immune mechanism activated by epileptogenic insults are less clear and still an area of active investigation. Equally unknown is whether the immune and non-immune mechanisms are mechanistically separable and can be independently modified to alter disease outcome. With the increasing drive to use immunomodulators to prevent and treat epilepsies, it is timely to discuss the diversity of inflammatory signaling in epilepsy and if specific pathways can and need to be preserved while others are better suppressed to limit epileptogenesis. Amy Brewster (Junior Investigator from Purdue) will start the session off with new advances in the role for classical immune mechanisms, namely the complement cascades in experimental acquired epilepsy. Lisa Boulanger (Princeton University) will discuss the evidence for neuronal major histocompatibility complex (MHC) class I, its dynamic regulation by electrical activity in developing and adult circuits and role in synaptic plasticity and neurological diseases. AnnaMaria Vezzani will discuss therapeutic options targeting the classical and non-classical immune responses in epilepsy. Quentin J. Pittman (Calgary) and/or Nicola Marchi (Cleveland Clinic) will serve as discussants and provide a different perspective from sterile inflammation and discuss the mechanisms of systemic inflammation on brain development and seizure susceptibility. | Amy Brewster, Lisa Boulanger, Annamaria Vezzani |

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| 2015 | Omar Jamil Ahmed | Role of potassium ions and channels in shaping seizure dynamics | It has long been appreciated that increases in neuronal activity lead to increases in extracellular potassium concentration. Such increases in extracellular potassium can in turn alter the activity of neurons. In this Investigator Workshop, we will highlight recent advances in understanding the mechanistic relationship between potassium and seizures. The session will be chaired by Omar Ahmed, a young investigator who has worked extensively on inhibitory-excitatory neuronal dynamics during human seizures. The session will include presentations by Drs. Steven Schiff, Attila Gulyas and Bernardo Rudy, all renowned cellular and computational physiologists with massive amounts of experience in understanding seizure dynamics. Dr. Schiff will present a unified theory based on experimental and computational work to show how changes in potassium and oxygen concentrations can lead to transitions between normal and epileptic brain states. Dr. Gulyas's talk will examine the mechanisms of inhibitory-excitatory neuronal interactions during high potassium states in the slice. Dr. Rudy will highlight the role of specific potassium channels in epileptogenesis. The central goal of this workshop will be to highlight the importance of understanding the critical role of potassium concentrations and channels in different cell types in shaping epileptic activity. | Steven Schiff, Atilla Gulyas, Bernardo Rudy |
| 2015 | Kristina A. Simeone and Manisha Patel | Targeting mitochondrial function as an antiseizure strategy | Mitochondria actively participate in neurotransmission by providing energy (ATP), sequestering calcium and maintaining normative concentrations of reactive oxygen species (ROS) in both presynaptic and postsynaptic elements. In human and animal epilepsies, ATP-producing respiratory rates driven by mitochondrial respiratory complex (MRC) I are reduced, calcium buffering is impaired, antioxidant systems are diminished and oxidative damage is increased. This workshop will introduce the participants to some of latest studies on mitochondria and neurotransmission. The proposed speakers have considerable expertise in mitochondrial bioenergetics, oxidative species, and electrophysiology. We anticipate that this will be an important workshop that will contribute to the participants' understanding of the importance of mitochondrial health in neurotransmission. Drs. Simeone and Patel will serve as co-chairs and facilitate discussion between the speakers and the audience. The three talks will all be limited to 15 minutes each with a 5-minute question and answer period. The remaining time (~20 minutes) will be devoted to a panel discussion of all the speakers. Speakers we plan to invite are: 1. Kristina Simeone, PhD Assistant Professor (Creighton University) who has considerable expertise in mitochondrial bioenergetics in epilepsy models 2. Dr. Patrick Sullivan, PhD (Professor at University of Kentucky) with extensive experience in mitochondrial function in neurodegenerative diseases. 3. Elizabeth Jonas, MD. Associate Professor of Medicine (Yale University) with considerable experience with mitochondria and synaptic plasticity. | Kristina A. Simeone , Patrick G. Sullivan, Elizabeth Jonas |
| 2015 | Annapurna Poduri; Bill Dobyns | Genetics, Biology, and Treatment of the Early Life Epilepsies | Early life epilepsies, occurring in the first few years of life, compromise a broad spectrum of disorders that involve errors in a large number of genes involved in brain development and function. These include infantile spasms, Dravet syndrome, Lennox-Gastaut syndrome, Ohtahara syndrome, and epilepsy of infancy with migrating focal seizures. In the past several years, we have seen a growing identification of genetic causes of early life epilepsies, with significant improvement in our understanding of the underlying biology of these disorders. This has resulted in major changes to our understanding of the relationship between genotype and clinical phenotype and expanded appreciation for the integral relationship between early life epilepsy and a broad spectrum of developmental brain disorders. These discoveries change the way that we frame these disorders and will ultimately change our classification approaches for the epilepsies. Further, as the molecular biological underpinnings of early life epilepsy are increasingly understood, the implicated mechanisms and pathways provide promising targets for developing new therapies and therapeutic approaches. The speakers in this symposium will address a) the relevance of biologically-based classifications to diagnosis and treatment and the advantages the molecular-based approach promises over the clinical classifications historically used in the field; b) the emerging understanding of nuclear transcription factors and their contributions to early life epilepsies and other errors in brain development; (c ) specific molecular pathways and functions involving brain growth, channel function, and synaptic functions; and (d) treatment implications of these different mechanisms and pathways. | Alex Paciorkowski: Early life epilepsy caused by mutations in genes of the synapse, Ghayda Mirzaa: Somatic and germline mutations in growth and signaling pathways, Anne Berg: Toward a molecularly-driven classification of early life epilepsy |
| 2015 | Brian Litt, MD | Cutting Edge Technologies for Multi-Scale Recording in Epilepsy | The BRAIN initiative is pushing technology development to image and recording brain activity down to the cellular level, in the hope of finding new ways to improve health and treat disease. No field is poised to benefit more from these developments that epilepsy. In this workshop, speakers will introduce cutting edge technologies for imaging brain, relating activity in individual cells to population discharges, to signals that we interpret clinically in patient care. Speakers will bridge nano-scale events in single cells to clinical recording in patients with epilepsy. | Duygu Kuzum, PhD, UPenn (Transparent graphene electronics for simultaneous optical and electrophysiology recording in brain), Adam Cohen, PhD, Harvard (Optical electrophysiology reporting in epilepsy), Lee Bassett, PhD, UPenn (Nano-diamonds and optogenetic molecules for ion channel sensing) |

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| 2014 | Tallie Z. baram | On status epilepticus and 'epileptic neurons': energy, molecular signaling, epigenetics | A large and growing body of work on epileptogenesis has demonstrated altered expression of numerous important neuronal genes. The changes expression and hence function of these genes, in the aggregate, promotes hyperexcitability and epilepsy. These data raise two crucial questions: (a) is there a coordinate, orchestrated regulation of genes implicated in epileptogenesis (or is each one regulated independently). If orchestration exists, then who are the master regulators? and (b) who are they activated by epilepsy-promoting insults such as status epilepticus? In other words, what aspect of the insult triggers early and persistent coordinate changes in gene expression. Answers to these questions will facilitate intervention and prevention of epileptogenesis. The workshop will capitalize on recent findings demonstrating that energy imbalance triggers molecules that signal to the chromatin and influence expression of select gene clusters. Whereas such imbalances have, to date, been described in obesity and restricted diets, they are highly germane to epilepsy: SE is a state of high energy demand with limited supply, and there is evidence that similar processes take place. The workshop will engage a junior investigator and an expert from outside of the field of epilepsy to illuminate novel concepts and methodologies that will be tremendously informative to the study of epileptogenesis. | Katja Kobow, Jong Rho, R. Coppari ( McNight as backup)- expert on mechanisms by which excessive cellular energy demand activates mastter regulators of gene expression |
| 2014 | Jack M. Parent, MD | Modeling Epilepsies with Patient-Derived Induced Pluripotent Stem Cells | Kevin Ess will present his latest work using patient-derived iPSCs to model Tuberous Sclerosis Complex or Glutaric Aciduria Type 2. Jack Parent will present data on iPSC modeling of Epilepsy in Females with Mental Retardation (EFMR) due to PCDH19 mutation or Polyhydramnios, Megalencephaly Symptomatic Epilepsy (PMSE) syndrome due to Strad-A mutations. Lori Isom will describe studies of Dravet Syndrome or GEFS+ using patient-derived iPSCs. If this is picked as a translational workshop and we can have a fourth speaker, Ricardo Dolmetsch may give background on the iPSC approach and talk about his work with iPSC-derived neurons from patients with Phelan-McDermid Syndrome (autism and epilepsy) caused by Shank3 mutations. | Kevin Ess, Jack Parent, Lori Isom |
| 2014 | Sam Berkovic | Unraveling the basis of heterogeneity in genetic epilepsy | Many human epilepsies can be attributed directly to a genetic cause. Heterogeneity is a common finding among the genetic epilepsies. Specifically, clinical heterogeneity is characterized by variability in seizure phenotype, severity and penetrance. Conversely, genetic heterogeneity refers to the finding that variation in several genes can manifest in identical or similar epilepsy syndromes. Appreciating the complexity underlying such heterogeneity is central to our ability to understand epilepsy mechanisms and for ultimately utilizing data from the personal genome. In this symposium we propose to highlight recent human and animal model studies addressing this heterogeneity with the promise of helping deliver better diagnostic and therapeutic outcomes for the genetic epilepsies. | Christopher Reid, Dennis Dlugos, Peter Crino |
| 2014 | Kamil Detyniecki, MD | Cannabinoids in Epilepsy | Epilepsy is one of the most common, serious neurological disorders, affecting an estimated 50 million people worldwide. The condition is typically treated using antiepileptic drugs, of which there are 20 in widespread use. Despite this plethora of drugs about one third of epileptic patients become drug resistant. (Kwan 2000, Mohanraj 2006). There is a great need for new medications, in particular those agents that affect novel receptors. Cannabinoid compounds have been used as a natural remedy for nearly 2000 year. There has been an increased interest in the use of marijuana for medical purposes, which led to advances in medical marijuana laws. In 1974, Karler et al. found that delta-9-tetrahydrocannibinol (THC), the primary psychoactive compound in marijuana, displayed anticonvulsant properties in maximal electroshock-induced tonic-clonic convulsions. The non-psychoactive marijuana constituent cannabidiol (CBD), was also shown to be protective in this seizure model. Since this initial research, several cannabimimetic compounds have been synthesized and evaluated in vitro for their effects on neuronal hyperexcitability. The studies assessing the effects of THC, CBD, and other derivatives on seizure threshold and kindling reveal marked variability for the different derivatives in different models with anti- or proconvulsive effects. Preliminary, uncontrolled clinical studies suggest that cannabidiol may have antiepileptic effects in humans. Given the body of animal research that suggests an anticonvulsant effect of cannabinoids and the insufficient amount of clinical human data there is an important need for large, properly designed, high quality clinical trials. In this workshop we propose to: 1) Review the pharmacology and mechanism of action of cannabis and cannabinoids. (20 min. Dr. Hill). 2) Review the effects of cannabinoids in in vitro & in vivo models of epilepsy. (20 min, Dr. Whalley). 3) Explore the human evidence on the use of cannabinoids for the treatment of epilepsy with updates from recent clinical trials. (20min, Dr Devinsky) | Charlotte Hill, PhD, Benjamin J. Whalley, BPharm, PhD, Orrin Devinsky, MD |

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| 2014 | P. Elyse Schauwecker, PhD | The role of noncoding RNAs in epilepsy pathogenesis: novel therapeutic targets? | Epilepsy leads to extensive temporally orchestrated changes in mRNA expression in both rodent and human studies. Recent progress in genetics has identified a new class of noncoding RNA molecules called microRNAs, which function as post-transcriptional regulators of protein levels within cells. MicroRNAs introduce a novel concept of regulatory control over gene expression and have been implicated in the pathogenesis of a variety of neurological disorders, including more recently, epilepsy. MicroRNAs are attractive candidates as upstream regulators of epilepsy pathophysiology because miRNAs can post-transcriptionally regulate an entire set of genes. Because deregulation of the rate of transcription and/or translation of a normal gene may be phenotypically similar to the disruption of the gene itself, the exploration of these noncoding RNA molecules might provide candidate genes for common epilepsies and give additional clues about the possible role of miRNA-dependent pathways in the pathogenesis of epilepsy. This IW will provide an overview and focus on recent developments in the elucidation of miRNA involvement in the molecular pathogenesis of epilepsy. Dr. Gorter will discuss miRNA regulation of signaling pathways during epileptogenesis. Dr. Schauwecker will discuss how miRNAs can regulate a critical subset of candidate cell death responsive genes and serve as putative biomarkers of susceptibility to seizure-induced cell death. Lastly, Dr. Henshall will discuss recent animal studies showing that targeting miRNAs using locked nculeic-acid-modified oligonucleotides (“antagomirs”) can have potent effects on status epilepticus and seizure-induced cell death. The identification of miRNAs that act as regulators of gene expression and determination of their functional relevance via miRNA inhibition to post-seizure pathological events, should aid in the understanding of their dynamic interactions with downstream targets and upstream transcription factors and open new avenues for therapeutically targeting neuronal death and dysfunction following seizures. | Jan Gorter, PhD (or a Junior investigator from the lab), Elyse Schauwecker, PhD, David Henshall, PhD (or a Junior investigator from his lab) |
| 2014 | Gordon F Buchanan, MD, PhD | SUDEP mechanisms: a basic science perspective | Sudden unexpected death in epilepsy (SUDEP) is the leading cause of death in patients with epilepsy, and as such is a major public health problem. A great deal has been learned about likely mechanisms for SUDEP from witnessed SUDEP and near-SUDEP cases. However, SUDEP is difficult to study in a controlled fashion in patients, making it difficult to develop preventative strategies. Therefore we must turn to animal models where variables may be systematically manipulated and putative preventive measures identified. In this Basic Science Investigators' Workshop we will discuss the current understanding of respiratory (George Richerson, University of Iowa College of Medicine), cardiac (Jeffrey Noebels, Baylor College of Medicine) and arousal (Gordon Buchanan, Yale School of Medicine) mechanims for SUDEP rom a basic science standpoint and disucss relevant animal models related to each mechanism. | Gordon F Buchanan, MD, PhD, Jeffrey L Noebels, MD, PhD, George B Richerson, MD, PhD |

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| 2014 | Slavé Petrovski | Finding risk alleles in generalized epilepsies: Next generation sequencing and the virtues of large collaborations | Across the neurological disorders, genetic studies of the epilepsies have been considered among the most successful in yielding definitive causal genes. However, despite this success, the genetic risk factors for the common epilepsy syndromes encountered in clinical practice still remain largely unexplained. Here, we focus on the generalized epilepsies and the collective efforts from three international teams that are leveraging the most recent technological and methodological developments to better interpret the genome of patients with epilepsy. We propose to use this IW platform to share our most recent data emerging across the three international consortia, and to discuss experiences in developing new analytic methods to identify risk alleles and genes. We will particularly emphasize the increased opportunity to discover new genes owing to large, complementary collaborations. 1) Slavé Petrovski: Genetic heterogeneity in the multiplex families and pairs from Epi4K. Dr Petrovski will present an update from the Epi4K Center Without Walls "Multiplex Families and Pairs" project 2. This includes the sequencing of individuals from ~1000 Epilepsy Phenome/Genome Project (EPGP) first-degree relative pairs, and ~250 international multiplex families. He will then introduce existing analytical approaches and further methodological developments that have arisen from a need to interpret the sequence data generated as part of large sequencing efforts. In particular, Dr Petrovski will discuss how to use genic intolerance scores as an aid in interpreting association results and identifying pathogenic mutations in the epilepsies, and he will also discuss real-world challenges regarding the appropriate implementation of collapsing statistical approaches on large cohorts of individuals ascertained for common generalized epilepsies. He will then present results from the application of these methodological advances to Epi4K's recently sequenced multiplex families and first-degree relative pairs. 2) Roland Krause: Burden analyses and family studies in the EuroEPINOMICS/CoGIE project. Dr Krause will introduce the gene discovery strategies analyzing the exome sequencing of over 250 families with genetic generalized epilepsy in the EuroEPINOMICS/CoGIE project. He will compare whole genome sequencing to whole exome sequencing in selected example families. He will discuss the contextualization of the many variants found in such studies. A focus will be on analysis of pathways and networks on the heterogeneous variants found in GGE. Collaboration with European epilepsy projects focusing on other syndromes or research areas such as epigenetics will be presented. 3) Patrick Cossette: Whole genome sequencing approaches in CENet. Dr Cossette will present the advantages of using whole-genome sequencing in ~200 GGE families, notably with respects to coverage of exonic regions and detection of structural variants. He will discuss the power of studying such a large collection of French-Canadian families together with the family cohorts obtained from the Canadian Epilepsy Network (CENet) to unravel the complex genetic architecture of familial epilepsy syndromes. 4) Steven Petrou: Translational studies of risk alleles identified through sequencing patients with GGE. If selected as a Translational IW, Dr. Steven Petrou will kindly give an update on the most current opportunities to pursue functional characterization of epilepsy risk alleles identified among the human GGEs. Identified mutations can now be characterized at the individual neuron and greater network levels. The latter through the use of multielectrode array platforms to identify network-level disruptions that might be important aspects of the phenotype(s) that would otherwise be missed through traditional single neuron assessments. | Slavé Petrovski, Roland Krause, Patrick Cossette |
| 2014 | Mohamad Koubeissi, MD | Low-frequency stimulation in epilepsy | Electrical stimulation for treatment of epilepsy has been used for decades targeting various intracranial and extracranial structures. Deep brain stimulation of numerous brain structures using high frequencies has achieved limited success, and low frequency stimulation (LFS) continues to be under-investigated. In the past two years, extensive animal data have been published that illustrated the anti-epileptic action of LFS, and started to unveil its mechanism of action. In addition, some human data have found that low-frequency stimulation of a white matter tract reduced interictal epileptiform discharges and seizures in patients with intractable mesial temporal lobe epilepsy, without affecting memory. In this IW, Dr. Durand will discuss mechanisms of LFS, focusing on his recent findings of LFS-induced long lasting hyperpolarization; Dr. Teskey will summarize effects of LFS on seizures in various kinds of animal models of epilepsy, and on neuroplasticity, specifically in the motor system; and Dr. Koubeissi will go through translational implications. | Mohamad Koubeissi, MD, George Washington University, Washington DC, Dominique Durand, PhD, Case Western Reserve University, Cleveland Ohio, G. Campbell Teskey, PhD, University of Calgary, Calgary, Alberta, Canada |
| 2014 | Catherine Schevon (Columbia University) | Which parts of the brain participate in seizures, and why does it matter? | Recent results, combining animal research with human microelectrode recordings, have shown that it is helpful to consider focal cortical seizures in terms of two spatially distinct regions: a seizure core, displaying the well established, seizure-defining firing patterns (hypersynchrony and paroxysmal depolarizing shifts), and a penumbra which is being bombarded by excitation arising from the core, but where a strong inhibitory response restrains firing. These findings have been matched to clinical recordings of spontaneous seizures containing both visual-band EEG discharges and high frequency oscillations, thus putting the core and penumbra concepts into a practical context. We will discuss how this new conceptualization of cortical seizure involvement may be applied to surgical epilepsy treatment, and its implications for the mechanism of impairment of consciousness during focal seizures. We will also highlight how electrographic signals should be used for basic or translational research into areas such as understanding focal pathological mechanisms, and early detection or prediction of seizure initiation. | Andrew Trevelyan (Newcastle University, UK), Hal Blumenfeld (Yale University), Catherine Schevon (Columbia University) |

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| 2014 | Chris Dulla and Aristea Galanopoulou | Understanding Infantile Spasms: A Pathogenic Perspective | Infantile spasms (IS) constitute a catastrophic childhood epilepsy syndrome. Patients suffering from IS have unique neonatal and juvenile seizure phenotypes, neither of which are normally well clinically managed. The pathophysiologic changes that cause IS are poorly defined but their identification is critical to developing effective therapeutic interventions. In this scientific session we will highlight novel genetic and acquired models of infantile spasms and discuss their utilization in a pre-clinical framework directed at developing novel therapeutic interventions. The session will be chaired by Dr. Aristea Galanopoulou, a leader in the field of infantile spasm research. The session will include presentations by Dr. Chris Dulla (junior investigator), Dr. Galanopoulou, Dr. Jeff Noebels, and Dr. John Swann. Dr. Dulla will present a novel genetic model of IS and the role of Wnt/b-catenin signalling in developmental epilepsies. Dr. Noebels will talk about the ARX model of IS as well as highlight exciting findings demonstrating therapeutic interventions which ameliorate seizures in this model. Dr. Swann will discuss another acquired model of IS and novel extracellular signalling molecules with significant therapeutic potential. The goals of the proposed IW will be to highlight the most current developments in pre-clinical IS model development, signaling pathways which are disrupted in IS models, and potential therapeutic strategies. | Chris Dulla, Jeff Noebels, John Swann |
| 2013 | Michael Miles | Mitochondrial abnormalities in malformations of cortical development | Mitochondrial abnormalities have been reported in patients with treatment-resistant epilepsy. This workshop will explore neurological, neuropathological, and biochemical methods for evaluation of mitochondrial abnormalities in resected brain tissue. Investigation of mitochondrial abnormalities in cortical malformations may provide new therapeutic targets, biomarkers, and understanding of epileptogenesis in patients with intractable epilepsy. | Hansel Greiner, Lili Miles, Michael Miles |
| 2013 | Ed Cooper | The KCNQ2-associated epilepsy and encephalopathy spectrum : bedside to bench and back | 2013 marks the 15th anniversary of the discovery that inherited mutations in KCNQ2 and KCNQ3 underlie BFNS and that these genes encode M-channel subunits. In 2012, compelling evidence appeared that de novo missense mutations in KCNQ2 underlie severe, neonatal-onset epileptic encephalopathy (Weckhuysen et al., Saitsu et al.; both Annals Neurology). What explains the broad KCNQ2 phenotype-genotype spectrum? Why was its appreciation so delayed? Given the availability of KCNQ-selective openers including the recently approved agent, ezogabine/retigabine, could KCNQ2 encephalopathy potentially be treatable? Can new lab-based understanding of KCNQ channel regulation be leveraged to make the most of the available therapeutic tools? Millichap will provide a clinical overview of the neonatal-onset KCNQ2 (and KCNQ3) phenotypic spectrum and the associated genotypes. Shapiro will explain how KCNQ2/3 channels work, as a nexus for regulation by both voltage and intracellular signals, and how their expression and activity is acutely and dramatically altered by status epilepticus in the systemic pilocarpine and kainate models (Neuron 2012, in press). Shah will give a neuron-to-network view of KCNQ2/3 channel function, based on studies combining patch clamp recording in hippocampal slices and computational modeling. Cooper will describe studies of KCNQ2 mutant mice that model BFNS and KCNQ2 encephalopathy, studies of human KCNQ2 encephalopathy mutations aimed at understanding the phenotype spectrum, and efforts towards KCNQ2 epileptic encephalopathy treatment trials now underway by a North American clinical network. | John Millichap, Northwestern Lurie Children's Memorial (Doug Nordli Group), Mark Shapiro, UT San Antonio, Mala Shah, Univ. College London School of Pharmacy |

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| 2013 | Peter B. Crino MD., PhD | Translational Neurogenetics of Hemimegalencephaly | Hemimegalencephaly (HME) is a unique malformation of cortical development characterized by marked enlargement and severe morphological abnormalities in one cerebral hemisphere. HME is associated with infantile spasms and intractable seizures, and is viewed as a catastrophic epilepsy syndrome. HME is typically diagnosed radiographically in the neonatal period when babies exhibit severe unremitting seizures, and a growing experience suggests that HME can be readily identified on prenatal ultrasonography or fetal MRI. HME almost universally will require epilepsy surgery in an attempt to control seizures and improve neurological and neurocognitive morbidity. Epilepsy surgery can result in significant patient morbidity and is successful in less than 50% of cases. Thus, new therapies that could potentially replace invasive neurosurgery are warranted. Many cell types within the affected hemisphere exhibit mTOR activation evidenced by phosphorylation of p70S6kinase (an mTOR substrate) and its substrate, ribosomal S6 protein. A link between mTOR activation and HME has yielded new insights into the pathogenesis of this disorder. For example, HME has been reported in patients with Proteus-like syndrome who express a mutation in the phosphatase and tensin homolog on chromosome 10 (PTEN) gene, a known upstream inhibitor of AKT and mTOR. An HME phenotype has been reported in TSC (Cartright et al. 2005). We had previously proposed (see Crino, 2007; 2010) a functional link between mTOR hyperactivity and HME pathogenesis. Recently, this hypothesis was confirmed when somatic activating mutations in mTOR regulator genes such as PI3K and AKT3, as well as mTOR itself were reported in a small cohort of HME patients (Poduri et al., 2012; Lee et al., 2012). Furthermore, germline mutations in mTOR regulatory genes such as PI3K, AKT, and STRADA lead to bilateral megalencephaly (Dobyns et al., 2012; Orlova et al., 2010). Clearly, mTOR pathway mutations in HME provide a molecular basis and rationale for therapeutic development. This IW will provide a translational overview and focus on recent and exciting developments in the molecular pathogenesis of HME. Dr. Flores-Sarnat will provide an overview of known syndromic or isolated HME presentations, as well as relevant maternal-fetal issues (fetal imaging, seizures in the delivery room, typical EEG findings), and diagnostic evaluation. Dr. Poduri will discuss the recent molecular genetics of HME including mutations in Akt3 and PI3K. Dr. Crino will integrate mTOR pathway activation, neuropathological subtypes, epileptogenesis, and therapeutic development in HME. Dr. Harvey Sarnat will serve as a discussant for neuropathology, Dr. Erin Heinzen will serve as a discussant for the molecular biology, and Dr. Gregory Heuer will serve as a discussant for questions regarding surgical therapies. Because this is a workshop, Dr. Crino will pause each talk at specific times to solicit interactive information from the audience, for example, how many have cared for HME patients, what unique syndromes or presentations have caregivers seen for HME, how can fetal MRI be helpful, what EEG features have audience members seen, what genetic tests have been ordered historically to evaluate HME, how many HME patients are referred immediately for surgery, can genetic testing be used in a clinical setting. | Annapurna Poduri MD., Laura Flores-Sarnat MD., Peter B. Crino MD., PhD |
| 2013 | Chris Dulla | Astrocyte control of the extracellular environment – pathological and therapeutic implications | The contribution of astrocytes to neuronal function and brain homeostasis is a rapidly developing, exciting field of study. No longer are astrocytes thought of as passive metabolic support cells but are known to contribute to synaptogenesis, respond to injury, modulate neuronal activity, and more. In this proposed IW session we will focus specifically on one role that astrocytes play in the brain, regulation of the extracellular environment. Through numerous transporters, ion channels, and receptors, astrocytes sense and respond to the extracellular milieu. Astrocytes are tasked with maintaining extracellular glutamate and potassium levels, both critical to synaptic communication and neuronal excitability. Dys-regulation of these pathways can potentially lead to acute changes in neuronal function and long-term circuit level pathology. Furthermore, changes in the extracellular environment have been reported in human epileptic foci and may underlie seizure initiation. In this session we will bring together experts on how astrocytes maintain the extracellular environment, how that maintenance is disrupted in the epileptic brain, and how emerging therapies may target these processes for therapeutic intervention. Dr. Chris Dulla (Tufts University School of Medicine, junior investigator) will discuss how disruptions in glutamate uptake and potassium buffering by astrocytes in the developing brain can have particularly significant effects on circuit formation and function. He will also discuss novel imaging and electrophysiological techniques to assay astrocyte glutamate uptake. Dr. Daniela Kaufer (University of California, Berkeley) will discuss the relative roles that changes in potassium buffering and glutamate reuptake play in modulation of circuit function. She will also highlight recent work on how acute compromise of the blood brain barrier alters astrocyte glutamate uptake. Dr. Harald Sontheimer (University of Alabama, Birmingham) will discuss the role of system xCT dysfunction in different models of epilepsy including tumor-associated epilepsy. He will also discuss novel therapeutic interventions aimed at the system xCT pathway. Lastly, Dr. Alexander Rotenberg (Harvard University, Children's Hospital Boston) will serve as the session discussant. Dr. Rotenberg has recently completed the Epilepsy Research Benchmark section on the Glial Contribution to Epilepsy and is actively investigating the therapeutic potential of increasing astrocytic glutamate reuptake following brain injury. We believe we have assembled an excellent group of participants to present a cutting edge perspective how astrocytic control of the extracellular environment may contribute to epilepsy and may be a target for therapeutic intervention. | Chris Dulla, Daniela Kaufer, Harald Sontheimer |

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| 2013 | Manisha Patel PhD and Helen Scharfman | Engaging Basic Scientists in the Early Stages of Drug Discovery | TIW AES 2013 IW Proposal Co-Chairs/moderators: Manisha Patel (University of Colorado) and Helen Scharfman (Nathan Kline Institute and New York University Langone Medical Center) Speakers: Dr. Rajesh Ranganathan (NINDS), Dr. Ray Dingledine (Emory University), Dr. Kevin Staley (Mass. General Hospital), Dr. Annamaria Vezzani (Mario Negri Institute) and Dr. Jackie French (New York University Langone Medical Center). Title: Engaging Basic Scientists in the Early Stages of Drug Discovery Background: Drug discovery represents a pipeline that involves multiple steps from the original idea to the finished product which can take up to 15 years and cost more than $1 billion dollars. Early drug discovery is a critical step that involves target identification and target validation, both steps occurring in basic science laboratories. This initial effort is well aligned with research in most basic science laboratories and generates data to develop a hypothesis that the inhibition or activation of a protein/pathway will result in a therapeutic effect in a disease state. The outcome of this activity, i.e. target identification, is the selection of a target which may require further validation, i.e. target validation, prior to advancement in the drug discovery process. Rationale for Translational IW: As incoming chair of AES's Basic Science committee (Dr. Manisha Patel) and co-chair of AES's Translational Taskforce (Dr. Helen Scharfman), our combined goal is to (re)engage basic scientists in translational research focused on drug discovery. As stated above, the early steps in the drug discovery process i.e. target identification and target validation primarily involve basic science research. Towards this goal, this interdisciplinary Translational IW is designed to introduce the drug discovery process to AES's basic/translational scientists and specifically highlight areas where basic science can drive the drug discovery process. Dr Rajesh Ranganathan, (Director of Translational Research, NINDS) who has extensive experience in pharmaceutical industry and development of the NCATS institute will discuss the drug discovery landscape, importance of early drug discovery efforts and role of industry/government agencies. The second speaker, Dr. Ray Dingledine (Emory University) has recently identified the EP2 receptor for PGE2 as a target for neuroinflammation in epilepsy and conducted elegant high throughput studies resulting in small molecule inhibitors shown to be active in vivo and in vitro. Dr. Kevin Staley will discuss chloride transporters as targets for antiseizure drugs and the discovery/repurposing of bumetanide. Dr. Annamaria Vezzani has conducted pioneering research in identifying and validating neuroinflammation as a target in epilepsy. Dr. Jackie French has collaborated with Dr. Vezzani in the clinical development of a candidate drug that targets interleukin-1 beta as a therapy to inhibit seizures. Together, they will discuss their basic science (Vezzani) and clinical (French) efforts on targeting neuroinflammation. The moderators will organize the TIW, introduce the workshop and speakers, moderate the question/answer/discussion and provide feedback to the IW/CIW committee, Basic Science committee and the Translational Taskforce. | |
| 2013 | Audrey Yee | Cell Signaling Pathways in Epileptogenesis | --Cell Signaling pathways are emerging as essential in providing critical changes during status epilepticus (SE), and the epileptogenic period, 7-14 days after SE. --Cell signaling pathways are frequently under heavy scrutiny in other conditions, but also provide insight in brain function and development epilepsy. --Our speakers examine cell signaling pathways essential in the epileptogenic period and present exciting new data from their labs own laboratories about how augmenting or blocking these pathways may alter epileptogenesis | Marco Gonzales, Molly Huntsman, Audrey Yee |
| 2013 | Christophe Bernard | Controlling Seizures with Electrical Light Orchestra | Therapeutical research in epilepsy faces three challenges: 1) controlling seizures when epilepsy has appeared, 2) preventing the occurrence of epilepsy after an epileptogenic insult and, 3) avoiding the side effects of the therapies. The goal of this workshop is to show that it is possible to address these issues with new technological approaches that are not based on chemical compounds. In this worshop, we introduce three different techniques, which have been devised to control seizures in experimental models of epilepsy: transcranial stimulation, optogenetics and gene therapy. Transcranial stimulation consists in imposing a strong electrical field, effectively stopping seizures. The optogenetics solution consists in injecting a virus in affected regions, which will make neurons express halorhodopsin. When activated by light, halorhodopsin triggers an influx of chloride ions in the cells, decreasing their excitability. The gene therapy consists in injecting a virus, which will make cells overexpress a native potassium channel, decreasing their excitability. Closed loop systems have been designed to detect seizure onset, triggering the electrical or light stimulation, stopping seizures. Importantly, the gene therapy cured established epilepsy without deleterious side effects. It also prevented the occurrence of epilepsy following the initial insult. These different strategies raise the possibility to develop on-demand treatments only targeting epileptogenic regions. They constitute promising alternates to conventional drug treatments. | Jeanne Paz or John Huguenard, Gyuri Buzsaki, Robert C Wykes or Dimitri Kullmann |

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| 2013 | Steve White, PhD and Nicholas Poolos, MD, PhD | Antiepileptic drug and device development--what does the future hold? | "In this Translational Investigators' Workshop we will address the question of what the future of antiepileptic therapy development holds from the perspective of industry and academic leaders who are directing such efforts and are key decision-makers on the viability of new treatment approaches. We will specifically focus on efforts to treat refractory epilepsy, and ask whether there are novel approaches to be pursued to this problem. Our speakers comprise individuals at the cutting edge of antiepileptic drug and device development who can best educate the audience on the barriers to therapy development at present, and how they may be surmounted in the future. Speakers will include: 1) Henrik Klitgaard, MD, UCB Pharma, SA who will discuss new pharmaceutical approaches in the UCB pipeline; Marty Morell, MD, Stanford and NeuroPace, Inc., who will detail the promise and pitfalls of implanted devices; 3) Christopher Wright, MD, PhD, Vertex Pharmaceutical, who will discuss the potential of anti-inflammatory drug targets particularly with reference to the recent VX-765 project. | Henrik Klitgaard, PhD, UCB Pharma, SA, Marty Morell, MD, Stanford Univ., and NeuroPace, Inc., Christopher Wright, MD, PhD, Vertex Pharmaceutical |
| 2013 | Michael Wong | Dendritic injury in epilepsy: mechanisms and consequences. | A variety of structural abnormalities in dendrites have been documented in pathological brain specimens from epileptic patients and animal models of epilepsy, such as dendritic beading, loss of spines, and other morphological changes in dendrite size and shape. However, the underlying mechanisms and functional consequences of these dendritic abnormalities are poorly understood. Seizures may directly cause dendritic injury. In turn, dendritic abnormalities may contribute to progressive epileptogenesis and cognitive deficits in epilepsy patients. The objective of this IW is to explore the characteristics, mechanistic basis, and functional consequences of seizure-induced dendritic injury. First, Michael Wong will overview the range of dendritic abnormalities associated with epilepsy and demonstrate the evolving time course of dendritic injury following seizures documented by serial multiphoton imaging in vivo. Next, John Swann will describe the effects of early life seizures on hippocampal dendrite growth and associated spatial learning deficits. Anne Anderson will then discuss studies implicating the mTOR signaling pathway in dendritic pathology and associated memory dysfunction following status epilepticus. Finally, a targeted discussion period will debate the clinical implications of structural damage to dendrites in epilepsy and discuss potential therapeutic approaches to prevent dendritic injury. | Anne Anderson, John Swann, Michael Wong |
| 2013 | Aristea Galanopoulou, Karen Wilcox | Translating seizure terminology, modeling, and detection from rodents to humans is consensus possible? | There is an ongoing joint AES/ILAE effort to optimize the preclinical epilepsy research to de-risk the process of translating preclinical discoveries into clinically meaningful findings and therapies. One of the areas that plays fundamental importance in interpreting preclinical research is the definition of seizure and the translatability of seizure and epilepsy models into the human seizure types and epilepsy syndromes. Currently these definitions and the purposing of the existing animal models vary significantly among research papers. The generation of more uniform and more widely acceptable definitions for seizures and the re-evaluation of existing animal seizure models are the active tasks of a joint AES/ILAE working group. The purpose of this translational investigators' workshop would be to present the summary of the proceedings of this working group presented by preclinical investigators involved in this working group, involve as discussants clinicians with expertise in seizure classification and syndromology and human EEG interpretation, and finally solicit the feedback of the audience, before finalizing these recommendations. The first two talks will summarize the summary of the proceedings on definition and classification of seizures (Dr Galanopoulou) and models (Dr Wilcox). The third session will be organized so that spot presentations of challenging "ictal" EEGs or video-EEGs in rodents are presented for discussion. Audience response will be solicited via the audience response system (is it a seizure or not?) and a panel of clinicians (Drs Solomon Moshé, Alexis Arzimanoglou, Brian Litt) will comment on the clinical relevance of the EEG of clinical ictal patterns. The expectation is that the working group will utilize the feedback obtained from this session, to optimize their definition-classification proposals. Chairs: Aristea Galanopoulou and Karen Wilcox Topic 1: Towards a unifying definition of seizures and epilepsy syndromes in preclinical epilepsy research: Possible lecturer: Aristea Galanopoulou Topic 2: Do (and can) animal models model human seizures and epilepsies: successes, challenges, gaps. Possible lecturer: Karen Wilcox Topic 3: Case presentations or rodent EEG and video-EEG events and discussion on seizures and their models. Panel discussants: Nico Moshé, Alexis Arzimanoglou, Brian Litt. | Aristea Galanopoulou, Karen Wilcox, Discussants: Solomon Moshé, Alexis Arzimanoglou, Brian Litt |
| 2013 | Chris Dulla | Young Investigators Workshop | Featuring young investigators | |

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| 2012 | Alica Goldman | Predictive Genes, Basic Mechanisms, and Clinical Biomarkers of SUDEP | This translational workshop will explore, from the bench to the bassinet, and from the EMU bedside back to the stem cell laboratory, ways to measure genetic, cellular, and clinical parameters in epilepsy patients that may predict the risk of SUDEP. The speakers will raise questions to identify the gaps in our understanding. Where are the therapeutic opportunities to predict and prevent SUDEP? What is the evidence that it is fundamentally a deficiency of a post-ictal respiratory drive arising in the brainstem? An inherited cardiac arrhythmia? A failure of autonomic activation? An idiosyncratic antiepileptic drug withdrawal reaction? And most importantly, can a subclinical deficiency be identified in a patient before it is too late? Discussion will center on specific experimental data emerging from laboratories analyzing mouse models (EEG/EKG/vagal single axon recordings, videos of IPS caardiomyocytes from Dravet Syndrome patients) and human patients (EMU oximetry,introoperative analysis of brain serotonin levels)that display risk factors for premature death in epilepsy, and possible future clinical trials with existing medicines to prevent cardiopulmonary depression. Alica Goldman, MD, PhD (Baylor) will introduce the topic and briefly review the design of a world wide rare disease repository for DNA from SUDEP families and how it will be analyzed. Speakers: George Richerson, MD, PhD (U. Iowa) will present data on brainstem mechanisms of respiratory depression and experiments in serotonergic mouse mutants and extracellular serotonin levels in epilepsy patients. Lisa Bateman, MD (UC Davis) and Doug Nordli, MD (Northwestern) will outline the obstacles, current findings, and practical solutions to accurate measurement of peri-ictal cardiorespiratory biomarkers in the adult and pediatric EMU. Jeff Noebels, MD, PhD (Baylor) will describe human and mouse models illustrating the genes that predispose to combined seizures and cardiac arrhythmias, and highlight the challenges to evaluating cardiac arrhythmia risk in humans. Jack Parent MD,PhD (U. Michigan) will discuss the exciting use of induced pluripotent stem cells (IPS) derived from Dravet Syndrome patient fibroblasts engineered to form an actively beating syncytium of cardiomyocytes that can replicate cardiac arrhythmias, and how this model system can be used to assess the pathogenicity of individual patient variants and screen for effective therapies, ushering in an era of personalized drug selection in epilepsy. 3 Invited Discussants to be named will highlight other SUDEP hypotheses, including unexplained depression in brain activity following seizure termination, as well as controversies raised by the audience during an interactive discussion. The goal of this workshop is to stimulate interest in the development of the NINDS SUDEP Center Without Walls, and encourage prospective investigators to contribute fresh hypotheses and proposals for inclusion in the future Center research program. | Alica Goldman, MD,PhD (introducer), George Richerson, MD, PhD (speaker), LIsa Bateman (speaker) |
| 2012 | Scott Baraban & Ed Dudek | Swimming toward a new path for drug discovery in epilepsy: an open discussion of novel approaches using zebrafish, mice and induced pluripotent stem cells | The epilepsy community is currently involved in an active discussion of how best to identify new drugs for intractable forms of epilepsy. Thirty years of traditional acute seizure models in rodents have generated more than a dozen new AED's that have clearly helped a population of patients with epilepsy. Further modification and merits of this approach continue to be actively debated. However, 30-40% of patients remain pharmaco-resistant, and this has not improved. This workshop seeks to bring together groups working to refine this traditional approach, with those considering novel medium- throughput rodent strategies focused on anti-epileptogenesis and newly emerging high-throughput programs using zebrafish or human induced pluripotent stem (iPS) cell lines. Each of these approaches has its advantages and limitations and this workshop will provide a forum to discuss these important issues. Moderator: Ed Dudek (University of Utah) 1. Traditional AED drug screening in acute seizure models: H. Steve White (Utah) 2. Anti-epileptogenic strategies using organotypic slice models coupled with long-term EEG monitoring: Kevin Staley (MGH) 3. Novel high-throughput strategies using a zebrafish model of pediatric epilepsy: Scott Baraban (UCSF) 4. Patient-specific strategies using human induced pluripotent stem cells: Jack Parent (Michigan) | H. Steve White, Kevin Staley, Scott Baraban |
| 2012 | Tallie Z. Baram, MD, PhD | It takes two to tango: Dance of neuronal ion channels and their auxiliary subunits. | Changes in the abundance, subcellular localization and surface expression of ion channels contribute to altered excitability in the epileptic brain. In recent years, novel and exciting data have been emerging regarding the involvement of channel-interacting (auxiliary) proteins in these processes. The goal of this session is to discuss new developments in our understanding of the molecular complexes that control ion channel trafficking and function. The session will focus on proteins that regulate several key ion channels, and their potential relevance to epilepsy and epileptogenic process. 1. Yoav Noam will discuss novel data on the involvement of the actin-binding protein filamin A in ion channel trafficking and surface expression. 2. Lori L. Isom will discuss recent work on the involvement of sodium channels beta subunits in familial forms of epilepsy. 3. Dane M. Chetkovich will discuss the importance of the auxiliary protein TRIP8b in regulating dendritic targeting of HCN channels, and implications of these processes to the epileptic brain | Yoav Noam, PhD (Dec 2011), Lori Isom, PhD, Dane Chetkovich, MD, PhD |
| 2012 | Scott Baraban | What's Next? A Young Investigator Workshop | Each year the American Epilepsy Society and Epilepsy Foundation of America award pre-, postdoctoral and young investigator awards grants to an array of innovative, timely and cutting-edge research projects. Historically, many of these funded projects result in top-tier publications and several of these awardees have moved on to successful careers in epilepsy research. To highlight this research and provide a glimpse into what may be next, this workshop brings together four recent awardees. Scott C. Baraban (UCSF) will introduce and moderate the session. Together these talks should stimulate discussion on emerging topics and techniques in epilepsy research while providing a forum for a new generation of investigators. | |

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| 2012 | Christophe Bernard | What does it mean to be interictal spikes - do we have a predictive value? | Interictal spikes are a diagnostic hallmark of some epilepsies. Although the regions generating interictal spikes may not necessarily correspond to the epileptogenic region, they may carry untapped, clinically relevant information. This is the concept that we will develop in this translational workshop, which includes clinician-researchers and basic scientists. Massimo Avoli will present and develop the notion of green and red interictal spikes in order to provide a conceptual framework, and discuss the possibility that some spikes may prevent the occurrence of seizures, whilst others may precipitate them. But interictal spikes are not only linked to ictogenesis, they may also play a role in epileptogenesis, the process leading to epilepsy. Experimental models of temporal lobe epilepsy have shown that interictal activity precedes the occurrence of recurrent spontaneous seizures. Kevin Staley will show that interictal activity is predictive of epilepsy in several experimental models, although suppression of interictal activity did not prevent epileptogenesis in a chronic in vitro preparation. Christophe Bernard will show that the evolution of some parameters characterizing interictal spikes during epileptogenesis is predictive of the first spontaneous seizure in rodents. Finally, Elaine Wirrell will show how interictal spikes can predict the course of epilepsy and its remission in Human. This workshop is thus meant to bridge basic and clinical research, and show the potential translational value of interictal spikes. It should appeal to a wide audience. | Massimo Avoli, Kevin Staley, Christophe Bernard + 4th speaker Elaine Wirrell |
| 2012 | Sam Berkovic | Massively Parallel Sequencing in Epilepsy | Massively Parallel Sequencing (Next Generation Sequencing) is a very new technology that allows whole exomes (entire coding sequence) and whole genomes to be efficiently sequenced. In 2011, two large long-term projects in epilepsy were launched - an NIH funded Centre without Walls project called "Epi4K" aimed at sequencing 4,000 epilepsy patients in 5 years and a European project with sequencing largely at the Sanger Center called "EuroEPINOMICS". The two groups have agreed to work collaboratively. This Investigators Workshop proposal is from both groups. Lead projects from both groups involve early childhood encephalopathies and this is the proposed focus of the Workshop. The purpose is to engage the wider epilepsy community with an interest in this remarkable genetic technology and to serve as a collaborative forum between the two groups. It is expected that significant new results will be available by December 2012. It is intended to present and share data and we anticipate this will be of broad general interest. Our proposal is for the Workshop to be co-chaired by Sam Berkovic (Melbourne) and Peter De Jonghe (Antwerp) with the following 3 speakers: - David Goldstein (Duke) will present an overview of the technology, the pipeline of discovery and the impact of Massively Parallel Sequencing so far in epilepsy and in general. - Heather Mefford (Seattle, junior investigator) will present the Epi4K strategy and results to date in subjects with infantile spasms and Lennox-Gastaut syndrome. - Ingo Helbig (Kiel, junior investigator) will present the EuroEPINOMICS strategy and results on a broad range of epileptic encephalopathies. | Heather Mefford (Seattle), David Goldstein (Duke), Ingo Helbig (Kiel, Germany; also a junior investigator) |
| 2012 | Anne Anderson | Dysfunctional phosphorylation signaling in epilepsy | Title Dysfunctional phosphorylation signaling in epilepsy Abstract Post-translational modification of proteins by phosphorylation is a ubiquitous cellular signaling mechanism. There is increasing evidence that altered phosphorylation signaling occurs in epilepsy and may underlie both epileptogenesis and altered neural excitability in chronic epilepsy. In this session we will discuss how phosphorylation-dependent mechanisms underlie some forms of both genetic and acquired epilepsy, and what therapeutic possibilities exist for pharmacological targeting of phosphorylation. James Trimmer, PhD will review the regulation of ion channel properties by phosphorylation and how recent technical advances in mass spectrometry now allow large-scale measurement of ion channel phosphorylation state. Nicholas Poolos, MD, PhD will discuss how altered phosphorylation signaling in an acquired epilepsy model underlies the loss of HCN channel expression and function, a key player in epileptogenesis. Amy Brewster, PhD will describe recent research in the Pten model of cortical dysplasia, and how modulation of phosphorylation activity can alter the course of epileptogenesis. Anne Anderson, MD will serve as a discussant. | Amy Brewster, PhD, Jaimes Trimmer, PhD, Nicholas Poolos, MD, PhD |

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| 2012 | Raimondo D'Ambrosio | Neocortical Focal Seizures in Etiologically Realistic Models of Acquired Epilepsy | Several models of acquired epilepsy based on realistic etiologies have been introduced in the last decade. These include, but are not limited to, epilepsy induced by head injury, stroke, febrile status, perinatal hypoxia, encephalitis, glioma. A consistent finding in these models is that the overall pathology induced by the insult differs in many ways from that commonly induced by agents such as pilocarpine or kainate in classic status epilepticus-based models of epilepsy. Consistent with the different pathology, the ensuing epilepsy syndromes are also different, including seizures that do not originate from the hippocampus but from the neocortex. Most basic scientists are more familiar with hippocampal seizures, but the human neocortex is highly epileptogenic and neocortical seizures are often difficult to treat. The specific aims of the session are: 1) Familiarize basic scientists with the semiology of acquired human neocortical focal seizures, and clinicians with rodent neocortical seizures. 2) Present neocortical focal seizures in the rat in two different realistic models in which the neocortical origin of some of the chronic seizures has been verified. 3) Discuss similarities/differences between the realistic animal models and the human data, and between neocortical seizures and temporal lobe seizures. Potential speakers, all of whom have accepted the invitation to participate, and their proposed topics are as follows: -Ramon Diaz Arrastia, MD., PhD Professor of Neurology, Uniformed Services University of the Health Sciences, is an epileptologist with specific expertise in human posttraumatic epilepsy. He will present acquired neocortical focal seizures in humans. -Harry Sontheimer, PhD, Professor of Neurobiology, University of Alabama Birmingham, is a basic scientist with specific expertise in glial biology and electrophysiology. He will present video/ECoG data of acquired focal neocortical seizures in the rat induced by glioma. -Raimondo D'Ambrosio, PhD, Associate Professor of Neurosurgery, University of Washington, is a basic scientist with expertise in in vivo and in vitro electrophysiology and in posttraumatic epilepsy. He will present acquired neocortical focal seizures in the rat after head injury. | Raimondo D'Ambrosio, PhD, Ramon Diaz-Arrastia, MD., PhD, Harry Sontheimer, PhD |
| 2012 | Aristea Galanopoulou | Validation of epilepsy biomarkers in humans: goals, successes, challenges | The development of valid clinically relevant biomarkers for epilepsy is an essential need in the development, validation, and implementation of new therapies for epilepsy. This translational IW proposal aims to highlight examples of studies conducted in human tissue with the task of addressing feasibility, translationability from preclinical data, and also discuss the challenges (ie database issues, historical and tissue heterogeneity, age-related issues etc). The proposed talks are : 1) Laura Jansen: Developmental changes in GABAA receptor expression and function in pediatric epilepsies 2) Gilles Huberfeld: Reversal of GABAA receptor function in temporal lobe epilepsy 3) Joeff Loeb: Utilization of human tissue for biomarker validation: opportunities and challenges | Laura Jansen , Gilles Huberfeld , Joeff Loeb |
| 2012 | Brenda Porter | The extracellular matrix in epilepsy | Recent data has suggested that one of the regulators of synaptic plasticity is the extracellular matrix. It appears to stabilize neurite outgrowth and synaptic plasticity. Following head injury, stroke and status epilepticus there is a break down in the extracellular matrix due to upregulation of proteases. Recent work in transgenic animals has suggested that the destruction of the extracellular matrix contributes to epileptogenesis. | Paulette Mcrae- Will talk about the perineuronal net following status epilepticus at different ages., Chris Ikonomidou- Will talk about MMP-9 destruction of the extracellular matrix and contribution to epileptogenesis, This is the problem! Have been back and forth with several European and Japanese groups and still working on the final person. |
| 2012 | Kai Kaila | Brain pH in the generation and suppression of seizures | Changes in pH exert a strong modulatory effect on neuronal signaling under normal and pathophysiological conditions, whereby alkalosis enhances and acidosis reduces brain excitability. Convulsive seizures have long been known to produce a profound acidosis both due to reduced ventilation and build-up of lactic acid. This acidosis is not a mere bystander but contributes to the termination of seizures. Similarly, respiratory alkalosis produced by hyperventilation has been a standard way to provoke absence seizures for many decades. Identifying the pH-dependent mechanisms operating in various compartments and levels of organization does not only shed light on the process of epileptogenesis but, importantly, provides powerful insights for the development of novel anticonvulsant therapies based on manipulation of brain pH. Kai Kaila will present novel data on cellular mechanisms which point to a key role of brain pH changes in the generation of birth asphyxia seizures. The main implication for clinical work is that standard resuscitation paradigms have to be modified because they may, in fact, induce seizures caused by an abrupt fall in systemic $CO_2$ and a consequent pathophysiological "rebound" increase in brain pH. Steven Petrou will present data on the effect of $CO_2$ on thermally triggered and spontaneous SWD seizures in mouse models of human genetic epilepsy and then describe the impact on brain network stability using brain slices and field potential recordings. The overall goal of this work is to begin to unravel the potential breadth of applicability of $CO_2$ therapy and reveal mechanisms of action. Saul Mullen will present data from a clinical trial evaluating carbogen (5% $CO_2$ in 95% oxygen) as an acute anticonvulsant. Patients in an Epilepsy Monitoring Unit to investigate focal seizures receive either carbogen or oxygen in a blinded, crossover trial with the primary outcome being seizure length. This work aims to develop mild respiratory acidosis as an acute antiepileptic, avoiding the sedation and depression of respiration seen with the currently used benzodiazepines. | Saul Mullen, Steven Petrou, Kai Kaila |

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| 2011 | Michael A. Rogawski | Neurobiological Mechanisms of Comorbidities | There has been increased interest among clinical epileptologists in epilepsy comorbidities, such as migraine, cognitive impairment, depression and autism spectrum disorder. These comorbidities can dramatically impact the quality of life of people with epilepsy. Until recently, the basis for these comorbidities was obscure and the lack of scientific knowledge raised doubt as to whether the disorders are truly related to epilepsy and not chance associations. Studies in animal models have begun to provide insight into the neurobiological mechanisms underlying the neurological and psychiatric conditions that commonly occur in patients with epilepsy. For example, it is now recognized that recurrent seizures during early development are associated with significant impairment in learning and that these deficits are due to alterations in the function of hippocampal place cells. Recent studies implicate inflammatory mediators, including interleukin-1b, that are expressed with seizures in the development of a depression-like state in rats with chronic epilepsy. Epilepsy occurs in a high proportion of patients with autism. In fragile X, a genetically-defined autism syndrome, there is evidence of deficient GABAA receptor subunit expression which leads to diminished GABAergic function and epilepsy susceptibility. The importance of addressing the issue of comorbidities of epilepsy has been emphasized by the NINDS, which identified them as a high-priority area of epilepsy research in its 2007 Benchmarks. The objective of this Investigator's Workshop is to stimulate interest in further laboratory-based research on mechanisms of comorbidities of epilepsy. While the some aspects of this subject have been addressed during the Merritt-Putnam symposium in 2009, the proposed workshop will focus on neurobiological aspects of psychiatric comorbidities of epilepsy, so as to educate clinicians and researchers on the molecular and physiological basis of these conditions and to provide a rationale for the development of therapies. As moderator, Dr. Rogawski will set the stage for the three talks by briefly describing the common neurobiological bases of epilepsy and migraine, where there is substantial understanding from a genetic and cell biology perspective of the comorbidity mechanisms. Migraine therefore provides an example of how research on other comorbidities can be advanced. Dr. Rogawski's introductory remarks will be followed by these three talks: Depression Andrey M. Mazarati, MD., PhD It is estimated that on average 30% of epilepsy patients suffer from concurrent depression. This talk will focus on the recent experimental evidence that depression associated with temporal lobe epilepsy has neurobiological basis, rather then being merely a psychosocial and/or an iatrogenic phenomenon. Data will be presented that seizure-associated hippocampal inflammation may lead to depression via inducing perturbations in the hypothalamo-pituitary-adrenocortical axis, downstream plasticity of presynaptic serotonin 1A receptors, and ultimately compromising the adaptive function of ascending serotonergic pathways. Cognitive Impairment and Behavioral Disorders Gregory L. Holmes, MD. It has been well established that patients with epilepsy commonly develop cognitive and memory impairments. This presentation will discuss the role of seizure-induced impairments in the functioning of hippocampal place cells and the resulting memory deficits. Fragile X Syndrome and Autism Carl Stafstrom, MD., PhD Fragile X is a genetically-defined autism syndrome with a 30% incidence of epilepsy. Recent work indicates that reduced expression of GABA-A receptors due to the genetic defect may be the cause of the epilepsy. | Andrey M. Mazarati, MD., PhD, Gregory L. Holmes, MD., Carl Stafstrom, MD., PhD |
| 2011 | Michael Wong | Cell signaling pathways and epileptogenesis | Cell signaling pathways play essential roles in regulating and integrating a variety of physiological functions, such as cellular growth, proliferation, metabolism, and membrane excitability. Under pathological conditions, dysregulated cellular signaling may trigger multiple downstream actions that promote epileptogenesis, including inflammatory responses, synaptic reorganization, neuronal death, and abnormal expression and function of ion channels. In contrast to traditional anticonvulsant drug therapies that directly modulate neurotransmitter receptors and ion channels, these signaling mechanisms may represent novel, upstream targets for potential antiepileptogenic therapies. In this IW, the role of different cell signaling pathways in epileptogenesis in a variety of epilepsy models will be investigated. Dr. Daniela Kaufer will examine the contribution of TGF-beta pathway activation in promoting epileptogenesis in an injury-induced model of blood-brain barrier breakdown. Dr. Amy Brooks-Kayal will discuss the regulation of GABAa receptors by the JAK/STAT pathway in the pilocarpine model. Dr. Michael Wong will describe the role of the mTOR pathway in models of both genetic and acquired epilepsies. Overlap and interactions between different signaling mechanisms and the potential for antiepileptogenic therapeutic interventions targeting these signaling pathways will be discussed. | Daniela Kaufer, Amy Brooks-Kayal, Michael Wong |

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| 2011 | Russell Ferland, PhD | The importance of subcortical structures in epilepsy | Clinical studies have shown that individuals with epilepsy, overtime, often have increasing more complex seizure manifestations, with little known as to the reasons why. This can result in forms of epilepsy which are often resistant to treatment. It has been shown that the progression of epileptiform discharges into new networks in the brain (i.e., subcortical and brainstem structures) may contribute or mediate this intractability. In other words, recruitment of new brain regions into the epileptic network may result in seizures with increasing complexity and severity that are resistant to treatment. Interestingly, recent studies utilizing BOLD fMRI and SPECT imaging have revealed the importance of subcortical and brainstem structures in the expression of seizures in humans. The proposed workshop will present and discuss data relating to 1) our understanding of the role of subcortical and brainstem structures in seizure propagation (all speakers), 2) the identification of connections between the forebrain seizure circuitry (required for clonic seizure expression) and the brainstem seizure system (necessary for brainstem seizure expression), which can result in increasingly more complex seizure manifestations (Ferland), 3) the role of the brainstem in sudden unexpected death in epilepsy (SUDEP)(Faingold), and 4) discussion of the evidence for the involvement of subcortical and brainstem structures in human epilepsy (Blumenfeld and Ferland). | Russell Ferland, PhD, Hal Blumenfeld, MD, PhD, Carl Faingold, PhD |
| 2011 | Manisha Patel | Novel therapeutic target identification for epilepsies from the ketogenic diet research | Controlling seizures and epileptogenesis by modulation of metabolic pathways is an emerging topic that is now being rapidly exploited in epilepsy research. Based on the success of the ketogenic diet to control seizures associated with diverse types of epilepsies, there is great interest in the research community to explore ways to modify neuronal excitability by alteration of metabolic pathways. Importantly, research on the ketogenic diet is leading to identification of metabolic pathways that may be amenable to therapeutic intervention by pharmacological agents. This IW would highlight recent ongoing research on the ketogenic diet that identifies novel therapeutic targets for controlling seizures. Each talk will highlight a specific pathway or mechanism identified in the ketogenic diet and its therapeutic implication in epilepsy. Topics: 1) Metabolic role of hypothalamic hormones (Liu Lin Thio)or Control of seizures and epileptogenesis by the mTOR pathway (Mike Wong) 2) Control of neuronal excitability by ketone bodies (Jong Rho) 3) Manipulating cellular redox status (Manisha Patel) 4) Exploiting the Warburg Effect with 2DG and beyond (Tom Sutula or Carl Stafstrom) Alternate speaker: 5) Controlling epileptogenic tumor excitability by ketone bodies (Anne Willliamson) | Lui Lin Thio or Mike Wong, Jong Rho , Manisha Patel |
| 2011 | Ingmar Blumcke | The "methylation hypothesis": does epigenetic chromatin modification play a role in epileptogenesis ? | Many brain lesions provoke epilepsies, although onset and progression of seizures as well as response to antiepileptic drug (AED) treatment remain difficult to predict in each patient. Recent studies point to a pathogenic role of epigenetic chromatin modifications during epileptogenesis. Epigenetic mechanisms are covalent posttranslational modifications of histone proteins and DNA, which can produce lasting alterations in chromatin structure and gene expression. They are increasingly recognized as fundamental regulatory processes in central nervous system development, synaptic plasticity, and memory, and also play a role in neurological disorders, such as schizophrenia or spinal muscular atrophy. This investigator's workshop is aimed to discuss a novel methylation hypothesis, which proposes that seizures directly induce epigenetic chromatin modifications, thereby aggravating the epileptogenic condition. Unravelling epigenetic pathomechanisms will open also new strategies to identify molecular targets for pharmacological treatment in epilepsies. Dr. Kobow (Junior investigator) will summarize published evidence that seizures induce epigenetic changes in experimental TLE models. She will further present her recent data showing increased levels of DNA promoter methylation and gene silencing in human TLE specimens. Dr. Boison has discovered dysregulation of adenosine and its key metabolic enzyme adenosine kinase as key contributors to the epileptic state. The association between adenosine metabolism and the transmethylation pathways will raise fascinating new perspectives for the "methylation hypothesis". Dr. Mehler may discuss his expertise in translational studies aiming at new concepts for epigenetic medicine and drug development. If our proposal will be elected as translational workshop, we would like to invite also Dr. Eric Hahnen to review his cutting-edge experience in epigenetic drug treatment applied already in other neurological disorders, such as spinal muscular atrophy. Our speaker panel bring together an extraordinary level of experimental expertise and knowledge, which will likely attract a large AES audience and promote fruitful discussion about novel translational strategies in AED tretament. | Dr. Katja Kobow, Dr. Detlev Boison, Dr. Mark Mehler |

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| 2011 | John Jefferys | Mechanisms of high frequency activity in epileptic foci | Chronic epileptic foci produce high frequency oscillations (HFOs; >100 Hz). Activity faster than 200-300 Hz, known as fast ripples, appears specific for epileptogenic tissue and can be useful in presurgical evaluation for epilepsy surgery. More fundamentally, the mechanisms responsible for this pathological HFO may provide clues on the structural and functional changes that make the neuronal networks epileptogenic. Fast ripples are an emergent property of the activity of populations of neurons, each firing much more slowly than their collective activity. Several theories have been proposed for the mechanism of this process, including: entrainment of pyramidal cells by fast spiking inhibitory neurons, ephaptic interactions or gap junction coupling between principal cells, and out-of-phase firing of principal cells that could arise from conduction delays along local synaptic pathways. The workshop brings together key workers in the area to assess recent advances on mechanisms of pathological HFO and their implications for our understanding of the pathophysiology of the epileptic focus. PJ will introduce pathological HFO and present new work on multielectrode recordings in vivo from the tetanus toxin model of chronic temporal lobe epilepsy used to assess the spatial relationship between epileptic HFO and primary epileptogenic tissue. LMP will use multi-site and juxtacellular in vivo data to discuss the dynamical behaviour of HFOs evaluated by the event-to-event variability of their spectral properties. KS will discuss calcium imaging of the pathways of activation of the epileptic network during interictal activity. These pathways may provide a mechanism for the out-of-phase activity hypothesized to underlie HFO. Spike-to-spike variation in these pathways may explain the imperfect correlation between HFOs and other forms of interictal activity. FED will discuss the effects of anticonvulsants such as carbamazepine on seizures and HFOs. AB will round off the session by discussing the functional and clinical implications of these recent advances. | Premysl Jiruska, Liset de la Prida, Kevin Staley |
| 2011 | Ed Dudek | Neuronal death and pediatric epilepsy: Any effect of early-life seizures? A cause -or not- of later epilepsy? | A long-standing hypothesis from several studies on animal models of pediatric epilepsy is that early-life seizures generally do not lead to neuronal death, and even in cases where they do, neuronal death is not necessary for the subsequent development of acquired epilepsy. Two diametrically opposed hypotheses have been proposed, and supported by different lines of evidence: (1) Neuronal death after a brain insult early in development is not required for the subsequent development of acquired epilepsy, or (2) Neuronal death, regardless of the stage of development, is essential for acquired epilepsy. This Investigators' Workshop will essentially debate present data in search of a compromise or consensus view. Jensen and Kadam (Junior Investigator) will discuss ongoing experiments concerning animal data from hypoxia and hypoxia/ischemia models, while Staley will report on recent results from an in vitro model of epileptogenesis based on organotypic slices. In addition to the central issue, other related questions will be addressed: What is considered a seizure characteristic of acquired epilepsy in these developmental models of acquired epilepsy? Which mechanisms might be engaged by neuronal death? Which ones are likely independent of neuronal death? How compelling are the data that these mechanisms actually participate in acquired pediatric epilepsy? Is there a middle ground? | Shipa Kadam, Frances Jensen, Kevin Staley |
| 2011 | Scott C. Baraban | What's Next? A Young Investigator Workshop | Although SIGs, Poster Sessions and other special events such as the EF Fellows Reception offer young investigator's an opportunity to participate in the annual meeting, there are no real opportunities to highlight the exciting research they are working on. Each year EFA awards between more than two dozen pre- and postdoctoral fellows awards to an excellent and often cutting-edge group of research projects. This workshop will choose three of these projects for participation in a "young investigator workshop". It is proposed that the investigators/research chosen for this workshop will be selected by the current Chairs of the scientific review committee (Anderson and Soltesz) in collaboration with a moderator (Baraban). The format can be arranged around a given theme each year, or not. | TBD - recent EF postdoc awardee, TBD - recent EF postdoc awardee, TBD - recent EF predoc awardee |

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| 2011 | Paul Buckmaster | Seizure localization: A clinical challenge to basic scientists | Abstract The major goal of the proposed session is to promote interactions between basic and clinical epileptologists within the Society. The format of the proposed session is based on an approach published by Bob Fisher (2009). The session will focus on seizure localization. The specific aims of the session are the following. (1) Expose scientists to what epilepsy actually looks like in real life and what tools are used to treat it. (2) Show clinicians what techniques and models are used in research and what they could offer. (3) Present a clinical conundrum (seizure localization) to provoke discussion among clinicians and basic scientists. Speakers Bob Fisher will serve as moderator and begin by briefly presenting a case that illustrates the need for seizure localization and the difficulties encountered in the clinical setting. In this way, he will set up the challenge to investigators. Carolyn Houser will present recent anatomical approaches to identify areas of seizure onset in epileptic pilocarpine-treated mice (Peng and Houser, 2005; Houser et al., 2008; Li et al., 2010). Paul Buckmaster will present new findings on field potential and unit recording approaches to localize seizure onset regions in epileptic pilocarpine-treated rats (Bower and Buckmaster, 2008; Toyoda et al., 2010; unpublished data). If the committee would prefer to highlight up-and-coming talent, a graduate student, Izumi Toyoda, DVM, can give this presentation. Greg Worrell will show how new broad band field potential and unit data from patients with temporal lobe epilepsy is being used to localize seizure onsets (Stead et al., 2010; Warren et al., in press). Bob Fisher will briefly wrap-up by identifying remaining challenges of seizure localization that require more attention from investigators. Bob, Greg, and Carolyn have agreed to participate. If the proposal is chosen for a regular IW session instead of a Translational IW session, we welcome suggestions from the IW committee regarding which three of the four speakers to include. We submitted a proposal last year that had the same overarching goal -- to help make basic scientists aware of the needs of patients and clinicians. Feedback from the IW committee suggested last year's proposal was inadequately focused and lacked sufficient presentation of new data. Therefore, the present application focuses on a more specific, single clinical problem (seizure localization) and includes speakers who will present novel results. References Bower MR, Buckmaster PS (2008) Changes in granule cell firing rates precede locally recorded spontaneous seizures by minutes in an animal model of temporal lobe epilepsy. J Neurophysiol 99:2431-2442. Fisher R (2009) What clinicians want to know from epilepsy researchers. Epilepsia 50:364-367. Houser CR, Huang CS, Peng Z (2008) Dynamic seizure-related changes in extracellular signal-regulated kinase activation in a mouse model of temporal lobe epilepsy. Neuroscience 156:222-237. Li Y, Peng Z, Xiao B, Houser CR (2010) Activation of ERK by spontaneous seizures in neural progenitors of the dentate gyrus in a mouse model of epilepsy. Exp Neurol 224:133-145. Peng Z, Houser CR (2005) Temporal patterns of fos expression in the dentate gyrus after spontaneous seizures in a mouse model of temporal lobe epilepsy. J Neurosci 25:7210-7220. Stead M, Bower M, Brinkmann BH, Lee K, Marsh WR, Meyer FB, Litt B, Van Gompel J, Worrell GA (2010) Microseizures and the spatiotemporal scales of human partial epilepsy. Brain 133:2789-2797. Toyoda I, Bower M, Leyva F, Buckmaster PS (2010) Where do spontaneous seizures initiate in a rat model of temporal lobe epilepsy? Program No. 150.23. 2010 Neuroscience Meeting Planner. San Diego, CA: Society for Neuroscience. Online. Warren CP, Hu S, Stead M, Brinkmann BH, Bower MR, Worrell GA (in press) Synchrony in normal and focal epileptic brain: The seizure onset zone is functionally disconnected. J Neurophysiol. doi:10.1152/jn.00368.2010. | please see below, please see below, please see below |
| 2011 | Brian Litt, MD., Gregory Worrell MD, PhD | Studying High Frequency Oscillations, Microseizures and Human Microelectrode Recordings Using the International Epilepsy Electrophysiology Database (IEED) and Cloud Computing | Recent evidence suggests that high frequency oscillations, microseizures and human microelectrode recordings may be important to seizure generation and epileptogenesis. Most investigators do not have access to high bandwidth human recordings or the computational resources required to analyze them. There are many unanswered questions regarding the significance of high bandwidth EEG in epilepsy that cannot be addressed by qualitative studies of small data sets using visual analysis . The IEED is funded by the NIH and European Union to make high quality multi-scale human and animal intracranial EEG data available to the world research community. This workshop will give participants hands-on experience using cloud computing and the international database to analyze human microelectrode recordings with open source tools. The presenters and discussants will frame questions, run studies on line interactively, and analyze results with participants, projecting them on screen. Participants will also be able to log onto the database and computing platform during the session, and encouraged to bring their laptop computers to the session. At the end of this workshop participants will not only understand the current state of human microelectrode recording research, but will be able to conduct their own studies using the IEED. | S. Matt Stead MD, PhD (Mayo Clinic) , Zachary Ives, PhD, computer science/ cloud computing (UPenn), Javier Echauz PhD (JE Research) and Justin Blanco PhD (UPenn) |

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| 2011 | John J Hablitz | Molecular, Cellular and Network Aspects of HCN Channel Function in Epilepsy | Alterations in Ih and HCN expression occur in a variety of seizure models. HCN1 subunit specific knockout mice have a reduced seizure threshold whereas HCN2 knockout mice exhibit an absence epilepsy phenotype. Paradoxically, hyperexcitability has been associated with both up- and downregulation of Ih. Despite the relatively well-characterized role of Ih in cellular excitability, its contribution to network activity in epilepsy is not well understood. Maturation of rhythmic slow-wave sleep activity patterns is dependent on the density and the properties of Ih during development. Theta activity in hippocampus and sub-threshold oscillations in enthorinal cortex are disrupted by Ih blockers. The timing of interictal bursts in the neonatal rat hippocampus is positively modulated by Ih. The contribution of Ih to network hyperexcitability in epilepsy has not been established. In the proposed session, one speaker would address activity dependent regulation of HCN channel trafficking. Potential speakers would be Tallie Baram. A second speaker, Bina Santoro, who was involved in cloning the HCN1 gene, would talk on epilepsy in mice lacking HCN1. Finally, I would talk about our recent brain slice studies looking at HCN channel modulation of spatial-temporal spread of activity the freeze-lesion model of cortical dysplasia. A discussion of possible role of lamotrigine in modulating HCN effects at network level could also be a part. This session would thus consider HCN channel modulatory actions across the spectrum from molecular to intact animal. | Bina Santoro, Tallie Baram, John Hablitz |
| 2010 | Lisa R. Merlin, MD | Endogenous regulation of mGluR-mediated epileptogenesis | Group I mGluR activation has been shown to have epileptogenic potential. A variety of intracellular pathways converge and interact, having both positive and negative effects on this mGluR-induced excitation, suggesting the possibility of potential targets for antiepileptogenic therapies | Henri Tiedge - Endogenous regulation of group I mGluR signalling and epileptogenesis, Eric Klann, PhD - Signal transduction mechanisms involved in group I mGluR signalling, Randi Hagerman, MD - Clinical significance of group I mGluR mediated hyperexcitability in Fragile X |
| 2010 | Detlev Boison | Adenosine and epilepsy - promising start into a new century: the first decade | The focus of this workshop is recent translational research on adenosine, a powerful anticonvulsant neuromodulator in hippocampus and cortex. Adenosine has long offered much promise for epilepsy, and new insights into the ongoing metabolic and astrocytic regulation of adenosine, as well as advances in adenosine-releasing cells and polymers, bring significant new promise to adenosine-based therapies. Adenosine is effective in halting all types of seizures, including pharmacoresistant seizures, and is well known to promote sleep and protect neurons from injury. Thus, the implications of emerging research on adenosine, offers new hope for epilepsy and related co-morbidities. Tom Swanson will provide a general introduction into the role of adenosine within the context of epilepsy and will provide a Clinician's perspective of this timely topic. Phil Haydon will discuss the role of astrocytes in regulating adenosine levels and seizure susceptibility. Susan Masino will conclude with novel adenosine-based therapeutic approaches that include the ketogenic diet and focal adenosine augmentation approaches. | Tom Swanson, University of Montana, Phil Haydon, Tufts University, Susan Masino, Trinity College |
| 2010 | Christophe Bernard | Epigenetic mechanisms of epileptogenesis | Epileptogenesis is associated with the downregulation and upregulation of hundreds of genes. Identifying the mechanisms underlying changes in mRNA expression would provide invaluable information on epileptogenesis and the way to prevent/delay it. All speakers are focusing on the gene repressing element REST/NRSF, which has the potential to regulate the expression of over 1800 genes. They will present evidence that NRSF is critically involved in acquired channelopathy, changes in synaptic receptors and growth factors during epileptogenesis, identifying REST/NRSF as one major switch involved in the transformation of a "normal" into an "epileptic" brain. New therapeutic strategies will also be presented. If one speaker cannot make it, Doug Coulter could be a replacement speaker (all speakers have agreed to participate). | Ray Dingledine, Atvar Roopra, Tallie Z Baram |
| 2010 | Verena C Wimmer | The emerging role of the axon initial segment in epileptogenesis | Information processing in neurons relies on the integration of excitatory and inhibitory inputs to make a yes-or-no decision whether to fire an action potential (AP) or not. In most neurons, this decision is made at the axon initial segment (AIS), a specialized domain of the axon proximal to the soma where APs are initiated. Recently, the AIS has been in the spotlight of scientific interest because of its important roles in neuronal output and protein compartmentalization, and its cell-type specific properties and unique forms of plasticity have only recently been recognized. This workshop will focus on a novel perspective that suggests a critical role of the AIS in epileptogenesis. AIS function is dependent on high density clustering of a multitude of different ion channels, and an intriguing number of these channels have been associated with human epilepsy, in particular Na+-channel alpha and beta subunits, K+-channels and Ca2+-channels. This workshop will highlight recent advances in the understanding of AIS dysfunction in neuronal pathogenesis and is hoped to stimulate intense discussion as well as future research directly targeted at the impact of epilepsy mutations on the AIS. Prof Rasband will start the session with an overview of the molecular anatomy of the AIS and present his work on proteolytic mechanisms affecting the AIS in neuronal injury. Prof Cooper will present functional studies on the vital role of potassium channels in the AIS and Dr Wimmer will provide direct evidence for AIS-based pathogenic mechanisms in epilepsy. | Ed Cooper, Matthew Rasband, Verena C Wimmer |

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| 2010 | Asla Pitkanen | Peptidopathy, channelopathy or bad network - what causes epilepsy in Alzheimer's disease? | Chair: Asla Pitkanen, MD, PhD (asla.pitkanen@uku.fi) Co-Chair: Helen Scharfman, PhD (HScharfman@NKI.RFMH.ORG) For a long time, patients with Alzheimer's disease (AD) have been known to have myoclonic seizures. Recently it was shown that the risk of unprovoked partial or generalized seizures is up to 86-fold in patients with early onset of AD. Moreover, it was hypothesized that daily cognitive fluctuations in AD could relate to the occurrence of undiagnosed complex partial seizures. Many different mouse strains overexpressing APP show spontaneous seizures and have interictal epileptiform discharges. The question is: what triggers multiple seizure types or hyperexcitability in AD? Recent data suggest that processing products of amyloid precursor protein (APP) can modulate several ion channels. Further, enzymes contributing to APP processing may use Na-channel subunits as substrates, and consequenty, affect Na-channel trafficking and composition in cell membranes. In this IW we first discuss what the different mutations in mice and patients with AD pathology predict about the causes of epilepsy in AD. Then we discuss whether amyloidogenic APP processing can affect neuronal excitability via several mechanisms to the extent that leads to seizure generation. Moreover, can these data be expanded to other epileptogenic etiologies like stroke or traumatic brain injury which also show amyloidogenic APP processing in the aftermath of axonal injury? 1. Genetics of mice and humans with Alzheimer's disease and epilepsy: what does it predict about epileptogenic mechanisms? Goal: To analyze the current knowledge on the genetics of AD-epilepsy,and to discuss, whether it would indicate any specific epileptogenic mechanisms? Speaker: Jeff Noebels 2. What is the evidence that APP processing products modulate neuronal excitability? Goal: To analyze what channels or channel proteins are affected by extracellularly or intracellularly located APP degradation products. Speaker: Helen Scharfman 3. What is the evidence for Na-channelopathy in AD, and does it explain AD-epilepsy? Goal: Data is accumulating that altered trafficking of sodium channel subunits in AD could result in altered neuronal excitability. Here we ask a question: in which neurons that happens, and what are its functional consequences. Speaker: Jorge Palop(back up speaker DM Kovacs) 4. What is the evidence that neuronal network is epileptogenic in AD-epilepsy? Goal: To analyze the current data about the cellular changes taking place in AD-epilepsy brain. Should we focus on neurons like in idiopathic epilepsies, or should we investigate more the changes in neuronal networks, vasculature, or inflammatory response. Speaker: Asla Pitkanen NOTE TO THE IW COMMITTEE: We have now listed 4 speaker (15 min each plus 5 min for discussion). That is because we think that it is important to have junior people invited (Palop), individuals outside AES (Kovacs) but also "senior" people who can bring to the IW the type of "scholarly" presentation the IW needs (Pitkanen, Noebels, Scharfman). This topic needs - as an IW - the ideas of a geneticist (Noebels), network person (Pitkanen) and cellular person (Scharfman) or it will be superficial. If it is absolutely required, we could combine talks 2 and 3 (Scharman gives the talk). Other possibility is that network aspect is shortly brought up in Introduction by Pitkanen, and then talk 4 is deleted. We would greatly appreciate IW Committees opinion what to do. | Jeffrey Noebels, Helen Scharfman, Jorge Palop (back up DM Kovacs), Asla Pitkanen |
| 2010 | Elizabeth Powell | "Interneuronopathies" -Diversity in the phenotypes of genetic mutations that alter forebrain GABAergic interneuron ontogeny | Disturbances in genes that control GABAergic neuronal generation and migration share a common outcome of seizure susceptibility. However, the overall anatomical characterizations are diverse, with some mutations leading to severe malformations, whereas losses of other genes have brains that appear to be largely normal. The affected subpopulations are biochemically unique, such that in the Arx mutant, calbindin expressing cells are loss, but parvalbumin and calretinin are intact. In contrast, mutants lacking Npn2 or Met demonstrate significant loss of parvalbumin expressing populations. The reported onset and types of seizure behaviors varies with genetic manipulation and interneuron repertoire. This workshop will review the common developmental origins of the forebrain interneurons and compare anatomical and physiological outcomes with genetic disruptions. Where possible, strategies for correcting or repairing the deficits will be discussed. | Karen Muller Smith, PhD, Eric Marsh, MD, PhD, Molly Huntsman, PhD |
| 2010 | Anatol Bragin | Earlier Detection of Epileptogenesis and Search for Effective Protective Treatment in Experimental Models and in Clinic | Prevention of epileptogenesis after acute brain damaging insults like status epilepticus, or febrile seizures is a major task for prevention of epilepsy occurrence. There is a need to develop interventions that could prevent the occurrence of epilepsy in these patients. The clinical challenge for testing and applying antiepileptogenic therapy is in identifying the subset of those out of approximately 2 million experiencing an IPI who eventually became epileptic and specifically apply preventive treatment. At the present time no clinical trials have identified an intervention during the latent period that clearly prevents the occurrence of epilepsy. Recently, a new biomarkers that predict the likelihood of developing epilepsy after a status epilepticus are described. This open the way to facilitate assessment of antiepileptogenic interventions in patients. | Asla Pitkanen, Stanislav Karsten, Raman Sankar |

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| 2010 | Ruth Ottman, PhD | Neurobiological Mechanisms in Genetic Focal Epilepsies: the Case of LGI1 | Mutations in the leucine-rich, glioma-inactivated 1 gene (LGI1) have been identified in approximately half of families with autosomal dominant partial epilepsy with auditory features (ADPEAF), a genetic form of epilepsy with auditory symptoms or receptive aphasia as major ictal manifestations. These symptoms suggest localization of the epileptogenic zone to the lateral temporal lobe; hence the syndrome is also called autosomal dominant lateral temporal lobe epilepsy (ADLTE). Unlike many other genes identified in families with Mendelian forms of epilepsy, LGI1 has no homology to any ion channel. Recent studies have made progress in elucidating the mechanism by which mutations in this gene cause epilepsy. Initially, protein homology suggested that the mechanism might relate to CNS development. Later findings pointed to either a potassium channel or glutamatergic mechanism, and determined that defects in secretion of the protein product were important for pathogenesis. Most recently, studies in transgenic mice demonstrated that LGI1 mediates the postnatal development of glutamatergic circuits in the hippocampus, and mutations cause epilepsy by impairing this process. In this workshop we will discuss clinical and molecular approaches for study of the mechanisms of epileptogenesis in focal epilepsies, using research on LGI1 as a model. | Ruth Ottman, PhD, Columbia University: Clinical and Genetic Approaches, John K. Cowell, PhD, DSc, FRCPath, Medical College of Georgia: Transcriptional Profiling, Cell Culture, Proteomics, and Mouse Knockout Approaches, Matthew P. Anderson, MD, PhD, Harvard Medical School: Bacterial Artificial Chromosome Engineering and Transgenic and Neural Circuit Approaches |
| 2010 | Astrid NEHLIG, INSERM U 666, Strasbourg, France | The endocannabinoid system and temporal lobe epilepsy | For centuries cannabis has been used to treat epilepsy. Several recent studies seem to confirm the anticonvulsant role of the cannabinoid system which could allow the development of novel therapeutic agents, with one already on the market. The focus of the present workshop will be to outline the general physiological properties of the endocannabinoid system and the distribution and role of the receptors (Grant). The two other groups have worked on animal models of temporal lobe epilepsy (TLE) and in humans normal subjects and patients with TLE to study the distribution of the receptor mainly involved in central effects (CR1) (Goffin) and the time dependent changes in the distribution of CR1 that occur after status epilepticus (de Lorenzo). The two groups studied and showed the large involvement of this sytem in the regulation of seizure activity. | I Grant, UC San Diego, La Jolla, CA, USA, R. de Lorenzo, Virginia Commonwealth University, Richmond, VA, USA, K. Goffin, University of Leuven, Belgium |
| 2010 | David Prince | Control of synapse formation and epileptogenesis | Cannabis and endocannabinoid receptor play many role in vivo but may also induce addiction. The review of their properties should be of interest to the epilepsy community mainly because one of these drugs is already on the market. I chose the group from La Jolla for the general presentation since they wrote a nice and comprehensive review on this sytem. The two other groups have already performed several convincing studies on the role of this system as an endogenous modulator of the activity of neural circuits. This data is not much known to epileptologists and should be of great interest for the epilepsy community. | Ben Barres, Z.David Luo, David Prince |
| 2009 | Andre Lagrange | Epilepsy and Depression- The Two Faces of BDNF/Jak Depenent Neurogenesis | Depression is an extremely common comorbid illness in patients with epilepsy. While there are usually several presentations about epilepsy and neurogenesis, I think many of us are less familiar with the idea that neurogenesis plays a role in depression. By hosting a workshop describing the scientific endeavors of both epileptologists and psychiatrists, I thought we might help increase the dialog between our highly interdependent fields. | Linda Overstreet- Wadiche (Univ of Alabama) - Epilepsy and Neurogenesis, Shelley Russek- BDNF Dependent Changes in Neurotransmision, Francis Lee (Cornell)- Animal Models of Neurogenesis in Mood Disorders, |
| 2009 | Jack Parent and Scott Baraban | Stem Cells and Epilepsy | Neural progenitor or "stem" cells are receiving increasing attention in society and in biological research. Several areas are especially exciting and beginning to greatly impact epilepsy research. First, studies of cell transplantation as an antiepileptic therapy are gaining increasing attention. Second, investigations into how neural stem cells are disrupted in temporal lobe epilepsy are generating exciting new data. Third, the idea of using induced pluripotent stem cells to generate neurons from epilepsy patients offers an unprecedented opportunity to study mechanisms of epilepsy mutations and to develop new therapies using high throughput drug screens. Here we propose an IW focused on these three issues. Experts both in the broader community of "stem cells" along with those with long-standing interests in epilepsy research have been chosen as speakers. The talks would include: 1) Introduction to neural stem/progenitor cell biology - Hongjun Song, Johns Hopkins; 2) Cell transplantation to treat epilepsy - Scott Baraban, UCSF; 3) Influence of endogenous neural stem cells in temporal lobe epilepsy - Jack Parent, Univ. of Michigan; 4) Using induced pluripotent stem cells (IPS) to study sodium channel mutations in human epilepsy - Miriam Meisler or Lori Isom, Univ. of Michigan. | Hongjun Song, Scott Baraban, Jack Parent, Lori Isom or Miriam Meisler |
| 2009 | Theodore H. Schwartz | Optical imaging of epilepsy - hemodynamic and light scattering changes in the brain | Optical imaging of the brain has shown that focal changes in perfusion, oxygenation and light scatter accompany epileptiform events. In some circumstances these effects precede the onset of seizure activity. Whether optical imaging will be clinically useful to supplement or even replace electrical recordings is uncertain. Nevertheless, optical mapping has provided insights into neurovascular coupling mechanisms and changes in the extracellular environment associated with epilepsy. This panel will bring experts in the field together to diccuess their recent findings and examine the future of this technology. | Theodore Schwartz, Michael M. Haglund, Syd Cash, Devin Binder |
| 2009 | Kevin Staley | Imaging synchrony with activity-dependent dyes: the nuts and bolts | Our understanding of how seizures start, how they end, and how interictal and ictal activities differ could be substantially advanced by a bird's-eye view of neural networks that ideally would provide information on the activity of every neuron simultaneously. Activity-dependent dyes can provide such information from large arrays of cells, but so far there are no perfect experimental designs; each dye and imaging technique has advantages and disadvantages. The speakers will provide descriptions of their techniques, including pitfalls and potential applications, describe some interesting results, and answer questions. | Rosa Cossart - Calcium imaging of synchronous discharges in the developing brain, Douglas Coulter - Voltage and calcium activities in acute slices, Kevin Staley - Calcium and chloride activities in organotypic slices; organizing results, John White - new microscopic techniques for activity-dependent imaging |

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| 2009 | Annamaria Vezzani, PhD | The impact of neuroinflammation on neuronal excitability and excitotoxicity | Emerging evidence highlights pathophysiological interactions between inflammatory mediators and classical neurotransmission (i.e. Gaba and Glutamate) in CNS. These interactions include non-conventional mechanisms of regulation of receptor trafficking and ligand gated ion channels post-translational modifications induced by neuroinflammation that may underlie neuronal network hyperexcitability and excitotoxicity occurring in epilepsy. This IW will discuss these novel findings and their relevance for normal brain physiology and epileptogenesis as well as for developing novel therapeutic antiepileptogenic strategies. | A. Volterra-Department of Cell Biology and Morphology, University of Lausanne, Rue du Bugnon 9, 1005 Lausanne, Switzerland.Title: Neuron-astrocyte cross-talk during synaptic transmission: implications for CNS disorders characterized by neuroinflammation., E.C. Beattie -California Pacific Medical Center Research Institute, San Francisco, California 94107, USA.Title:TNFalpha-AMPA receptor interactions in CNS neurons; relevance to excitotoxicity, M. Maroso-Mario Negri Inst for Pharmacol Res,, Dept Neuroscience, Milano, Italy. Title: Toll-like receptor signaling in neuronal hyperexcitability |
| 2009 | Steven Petrou | Rodent models of febrile seizures. | Febrile seizures are a consistent feature of many familial epilepsy syndromes. Yet, despite knowledge of the underlying genetic lesion and years of basic research there are still many open questions regarding the mechanisms underlying their genesis. Recently, several studies have begun to shed light on potential mechanisms, ranging from cytokines to respiratory alkalosis. In addition there has been active debate as to relative merits of the various models for generating "febrile" seizures in rodents, from hot-pots, hair dryers to infra red light heaters. This workshop will bring together key workers in this field to discuss mechanisms of epileptogenesis in the various models and their relationship to febrile seizures in humans. | Tallie Baram, Kai Kaila, Bill Catterall, Solomon Moshe |
| 2009 | Christian Steinhaeuser | Neuron-glia signaling and epilepsy | Current anticonvulsant drugs and complementary therapies are not sufficient to control seizures in about a third of epileptic patients. Thus, there is an urgent need for treatments that prevent the development of epilepsy and control it better in patients already inflicted with the disease. A prerequisite to reach this goal is a deeper understanding of the cellular basis of hyperexcitability and synchronization in the affected tissue. Epilepsy is often accompanied by massive reactive gliosis, but the role of glial cells in seizures and epilepsy is still elusive. Several recent studies clearly indicate that glial cells take an active part in the formation, function and plasticity of synapses. Actually, the contribution of glial cells to CNS signalling can be considered one of the most exciting new fields in the neurosciences. It is the aim of the proposed symposium to present new developments and findings on the neuron-glia crosstalk in the epileptic brain. The focus will be on astroglial glutamate- and ATP-related mechanisms as well as the role of proinflammatory cytokines in seizure generation. This symposium intends to bring together established and junior scientists with various backgrounds to discuss different aspects of this new, topical field. The contribution of G. Carmignoto will demonstrate the impact of astrocytic glutamate and ATP release on excitability and blood flow control in experimental seizure models. A. Vezzani will report on the role of cytikines in the pathophysiology of epilepsy while Devin Binder will discuss the impact of dysfunctional glial water channels in epileptogenesis. Finally, C. Steinhaeuser will present findings of dysregulated astrocytic function in the context of seizure generation in human hippocampus. | Giorgio Carmignoto, Annamaria Vezzani, Christian Steinhaeuser |
| 2009 | Maria Roberta Cilio, MD, PhD | Do neonatal seizures per se cause brain damage? New insights from mutations of potassium channels | Experimental data provide strong evidence that seizures early in life produce long-lasting alterations with cognitive impairment and increased risk of developing epilepsy. However, clinical studies suggest that long-term outcome correlate best with etiology rather than with the presence of seizures or their duration. Controversies persist whether seizures per se are injurious to the immature brain. Benign Familial Neonatal Seizures (BNFS) is a genetically determined seizure disorder in which affected newborns experience partial or generalized seizures occurring many times daily. Mutations in neuron-specific KCNQ2 and KCNQ3 potassium channels have been found associated with BNFS. Through a mechanism of loss of function , these mutations induce a reduction of K+ current which leads to neuronal hyperexcitability. While newborns with BNFS may suffer from multiple episodes of seizures, this syndrome is usually not associated with any neurodevelopmental sequelae. Mouse models of human BNFS seem to parallel this benign neurocognitive outcome. The workshop is intended to discuss the dilemma with new insights from clinical and basic research on BNFS. Dr. Tim Benke will begin the session by showing the morphological and molecular changes associated with neonatal seizures. Dr. Maria Roberta Cilio will discuss the unique clinical and neurophysiological phenotype of BNFS. Dr. Maurizio Taglialatela will present his work on the cellular and developmental basis of neuronal excitability and seizure discharge in BNFS individuals, and finally Dr. Nanda Singh will expose her recent work on mouse models of human KCNQ2 and KCNQ3 mutations. The workshop will conclude with a panel discussion that will include insights from Dr. Greg Holmes into the relevance of basic research to clinical data. | Timothy Benke, MD, PhD, University of Colorado, Maria Roberta Cilio, MD, PhD, Bambino Gesu' Children's Hospital, Rome, Italy, Maurizio Taglialatela, MD, PhD, University of Naples, Italy, Nanda Singh, PhD, University of Utah |

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| 2009 | Ley Sander | Possible Mechanisms of SUDEP: towards prediction and prevention | Sudden unexpected death in epilepsy (SUDEP) is a markedly underreported catastrophe bedevilling people with epilepsy and their care-givers. The unpredictability of these events and pathophysiological hypotheses are the subject of this workshop. The proposal is to review briefly the astounding epidemiology of this condition which is unfortunately not uncommon, particularly in chronic epilepsy (JW Sander). Then a discussion of the relevance of the neurodynamics of epilepsy and how this relates to the unpredictability of seizures in general and to SUDEP in particular will be presented (S Kalitzin). The dominant hypothesis of seizure-related central apnoea and cardiac arrhythmias, and contributing clinical and possibly anatomical factors, will then be elaborated (BJ Murray). Finally, from a cellular perspective, hypotheses regarding how seizures can trigger respiratory or cardiac arrest will be discussed, with particular focus on the role of seizure-induced raised potassium initiating respiratory neuronal shutdown (PL Carlen). Vigorous and animated discussion is expected on this critical problem in epilepsy care in the hope that it will generate ideas that may eventually translate into prediction and preventative measures. | JW Sander , S Kalitzin, BJ Murrary, PL Carlen |
| 2009 | Russell Sanchez | Curing the disease by replacing the defective gene: is it so straightforward? | Gene therapy is viewed as a promising tool for the treatment of epilepsy, particularly given the increasing identification of human genetic mutations associated with the disease. An overriding notion is that having identified a gene defect that causes epilepsy, rescue of genotype by replacement of the defective gene should rescue the phenotype, and therefore, cure the disease. Optimism has been raised by studies that have successfully demonstrated inhibition of seizures after viral delivery of genes with subsequent expression of seizure-inhibiting product. However, such success has been achieved using over-expression in animal models of epilepsies that are not linked to a deficit in the gene being over-expressed, and thus, could be viewed more as a non-pharmacological approach to anticonvulsant delivery. Surprisingly, despite demonstrations of the feasibility of cell- or region-specific gene delivery, rescue of identified epilepsy gene mutations has thus far been ineffective in rescuing the disease phenotype. In this workshop, we will review progress and attempt to identify critical remaining obstacles to achieving a true cure for hereditary epilepsies by gene therapy approaches. Are these obstacles conceptual or largely technical? Do we simply need better control of targeting and expression of the gene, or do we require more thorough understanding of its dynamic regulation of function and mechanistic contribution to seizure susceptibility? Importantly, how do we determine if the brain is simply irretrievably altered by the presence of a particular genetic defect throughout embryogenesis and/or postnatal development? | Tom McCown, Beverly Davidson, Franceso Noe |
| 2009 | Aristea Galanopoulou MD PhD | Rapamycin: from tuberous sclerosis and beyond. | Tuberous sclerosis is a genetic disorder that manifests with early life epilepsy, often intractable to conventional antiepileptic therapies, tumors, and frequently cognitive impairment. The elucidation of the neurobiology of this condition have revealed a role for rapamycin, the inhibitor of mTOR pathway, as a potential therapy in this condition. An increasing number of studies have recently supported the positive therapeutic effect of rapamycin in animal models of tuberous sclerosis and extended its potential usefulness in other seizure models. This IW will aim to summarize these advances and provide a forum to discuss and better understand the broad range of involvement of the mTOR pathway and rapamycin analogs in the neurobiology of epilepsies and their treatment. Specifically, the role of mTOR pathway in the neurobiology of tuberous sclerosis will be addressed by Dr Peter Crino. Dr Michael Wong will discuss the effects of rapamycin in a mouse model of tuberous sclerosis. Dr Paul Buckmaster will present evidence that rapamycin inhibits mossy fiber sprouting in a rat model of temporal lobe epilepsy. Dr Aristea Galanopoulou will discuss the role of rapamycin in a model of symptomatic infantile spasms. | Peter Crino, MD., PhD, Michael Wong, MD., PhD, Paul Buckmaster, D.V.M., PhD, Emmanuel Raffo, MD., PhD |
| 2008 | Tallie Z Baram | Ion channel traffic jams in epilepsy | Excitability of neurons and neuronal compartments (e.g., dendrites) is governed by several ion channels, and it is likely that the ratios among different currents, rather than absolute expression levels, determine the nature of the electrical response. An eloquent example is the interaction between Ih and I-A, that sets the rate of post-inhibitory rebound. Activity dependent trafficking and of dendritic expression of I-A (Kv4.2) and Ih (HCN channels) have been described recently, and may contribute to circuit hyperexcitability. Here we aim to synthesize these recent data, provide the molecular foundation of the ion channel redistribution, and attempt to integrate their combined effect on neuronal and circuit excitability. | Dax Hoffman , Dane Chetkovich, Tallie Z Baram, Christophe Bernard |
| 2008 | Marco de Curtis | reconsidering focal ictogenesis | The identification of the mechanisms that control the initiation of a seizure is crucial to understand ictogenesis and, ultimately, to develop new strategies to cure epilepsy. Focal seizure onset correlates with the occurrence of small amplitude fast EEG activity that precedes synchronous, rhythmic discharges typically associated with epilepsy. Pre-surgical intracranial recordings in pharmacoresistant patients confirmed that fast activity is commonly recorded in diverse cortical regions at ictal onset. The main objective of the proposed Investigator's Workshop is to review the cellular and network mechanisms responsible for fast activity at seizure onset in temporal lobe. The findings will be integrated and discussed with data obtained from pre-surgical studies with intra-cerebral recording electrodes in human temporal lobe focal epilepsies. | Anatol Bragin, Miles Whittington, Richard Miles, Peter Carlen |

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| 2008 | Carl E. Stafstrom, MD, PhD | Catastrophic Childhood Epilepsies: Emerging Mechanisms from Experimental Models | The catastrophic epilepsies of childhood are among the most devastating and least understood neurologic disorders. Recently, however, several laboratories have generated animal models that may begin to allow investigations of the underlying seizure mechanisms. After a brief overview of the childhood catastrophic epilepsies by Dr. Stafstrom, Dr. Galanopoulou will discuss a model of symptomatic infantile spasms (IS) created by a combination of postnatal doxorubicin and lipopolysaccharide to produce structural damage followed by PCPA to reduce serotonin levels. Dr. Lee will then present on a new model in which spontaneous spasms and hypsarrhythmia are produced by chronic TTX infusion. Dr. Marsh will review a genetic model of symptomatic IS involving ARX gene mutations. Finally, Dr. Velisek will discuss a 2-hit model of IS-like seizures induced by prenatal betamethasone followed by postnatal NMDA. Understanding the neurobiological mechanisms of IS and related age-dependent epilepsies is prerequisite to the development of novel treatments. | Aristea Galanopoulou, Chong Lee, Eric Marsh , Libor Velisek |
| 2008 | Douglas A. Coulter | The Dentate "Gate": What is it, what regulates it, and is it compromised in epilepsy? | The dentate gyrus has been hypothesized to function as a "gate", regulating relay of pathological, synchronous afferent activity into the hippocampus proper. Despite its prevalence as a concept, there is a relative paucity of information demonstrating this putative function of the dentate in normal brain, and even less that this function is compromised in epilepsy. In this workshop, using a combination of functional imaging, patch clamp recording, gene targeting, and computational approaches, we (Coulter, Soltesz, Brenner, and Mody) will present studies demonstrating dentate gate function, describe mechanisms mediating this property, and discuss how, when, and why "gate" function is compromised during the disease process underlying epilepsy. | Douglas Coulter, Ivan Soltesz, Istvan Mody, Robert Brenner |
| 2008 | Molly Huntsman | The comorbidities of epilepsy: The unification of multiple disease states through basic mechanisms. | Epilepsy is a common comorbidity diagnosed with multiple diseases such as Fragile X, Autism and Alzheimer's. It is not known if the appearance of non-provoked seizures exacerbates the primary disease or is a protective mechanism brought about to achieve homeostasis. While different disease states manifest with distinct symptomatologies, the underlying mechanisms can be one in the same. For example, metabotropic glutamate receptor dysfunction is implicated in fragile X and also as the mechanism behind seizures induced in fragile X mice. Recently, the mechanism behind seizures in Alzheimer's patients may be related to amyloid precursor protein. Also, the common mechanism underlying seizures which appear in autism may implicate BK channels. This symposium would bring together experts both within and outside of epilepsy research in order to investigate the basic channelopathies and mechanistic dysfunction that underlie the comorbidities of epilepsy. | RKS Wong, Kevin Ess, L. Mucke, Alison Barth |
| 2008 | Alon Friedman | Interactions within the neurovascular unit and epileptogenesis | The term "neurovascular unit" refers to the composite of the endothelium, extracellular matrix, astrocytes, pericytes and neurons. Recent series of studies from several laboratories indicate that proximal trigger events in the endothelium play an important upstream role in altering the extracellular composition and causing the dysfunction of astrocytes and neurons. These studies point to disturbed "blood-brain communication" as a critical causative factor in determining astrocytic functions and ionic homeostasis, angiogenesis and inflammation -eventually affecting brain plasticity and neuronal excitability. In the proposed session presentations will focus on molecular, electrophysiological and modeling studies which present new mechanisms emerging from altered "blood-brain communication" and its role in the dynamic functions of neuronal networks during epileptogenesis. | Daniela Kaufer, Berkeley, Christian Steinhauser, Bonn, Brian MacVicar |
| 2008 | Jong M. Rho, MD | Do Anticonvulsants Injure the Immature Brain? | Since the late 1990's, investigators have reported that anticonvulsants and certain volatile anesthetics induce apoptotic cell death in immature rodent brain. Agents that block NMDA receptors, voltage-gated sodium channels, and enhance GABAergic transmission appear to induce dose-dependent programmed cell death in developing neurons over a "clinically relevant" range. In contrast, newer generation anticonvulsants appear less toxic in this regard. Finally, basic studies in rodents have suggested more advantageous combinations of anticonvulsants with respect to drug-induced cell death. While there is a growing experimental literature indicating that immature neurons "commit suicide" in response to various anticonvulsants, the clinical relevance of these findings remains uncertain. After years of such intriguing observations, it is timely to review this topic and suggest strategies to determine whether anticonvulsant-induced cell death in immature brain really occurs in humans, and whether treatment strategies should be altered to minimize iatrogenic injury. | Chrysanthy Ikonomidou, Richard H. Finnell, Kimford Meador |
| 2008 | Terence J. O'Brien, Melbourne, Australia | ABSENCE SEIZURES AND THE CORTICAL FOCUS | Abstract: The International League Against Epilepsy (ILAE) dichotomizes types of seizures into focal and generalized types on the basis of whether they are appear to start in a geographically localized region of one hemisphere or bihemispherically in a diffusely distributed manner. One of the most classical and common examples of a "generalized" seizure type is absence seizures, which are characterized by abruptly commencing bihemispheric synchronous spike and wave discharges on the EEG. However evidence is accumulating that absence seizures may actually commence in a geographically localized "focus" within the somatosensory cortex. Most of this data comes from electrophysiological studies in genetic rodent models, but there is some emerging data from electrophysiological and functional imaging studies in human with absence epilepsies. The proposed workshop will present and discuss data relating to the localization, neurophysiology and underlying pathological basis of the generator of absence seizures in the cortex of rodents, as well as debate the evidence that this may be translatable to human suffers of these absence epilepsies. | Gilles van Luijtelaar, PhD, Nijmegen, The Netherlands, Didier Pinault, PhD, Strasbourg, France, Graeme Jackson, MD. Melbourne, Australia |

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| 2008 | Martin J. Gallagher MD, PhD | Idiopathic Generalized Epilepsy Ictogenesis and Epileptogenesis: a Cross-disciplinary Discussion from Molecule to Human Brain | This session is designed to be a participatory workshop focused on addressing questions of ictogenesis and epileptogenesis in idiopathic generalized epilepsy (IGE) via a cross-disciplinary approach. Four investigators from the fields of molecular neuroscience, thalamocortical network physiology, transgenic animal physiology/behavior, and human/animal neuroimaging will serve as workshop speakers. To provide a basis for discussion, the speakers will use the first half of their presentation time to describe the relevant work from their respective laboratories. In the second half of their allotted presentation time, the speakers and workshop attendees will discuss how the results obtained in the speaker's experimental system address questions of IGE ictogenesis and epileptogenesis and complement the work done in other experimental systems. Participants will also use this time to "workshop" new experiments that could be performed within the speaker's area of scientific expertise that would answer questions deemed important to IGE investigators from all disciplines. | Robert Macdonald MD, PhD, John R. Huguenard, PhD, Steven Petrou, PhD, Hal Blumenfeld MD, PhD |
| 2008 | Karen Wilcox | New developments in neuroprotection | Although neuronal damage is associated with status epilepticus, traumatic brain injury and several epilepsy syndromes, neuroprotective strategies remain controversial. Recent evidence showing neuroprotective effects of several anticonvulsants has led to a renewed interest in neuroprotection in epilepsy. Several anticonvulsants have been shown to exert neuroprotection by mechanisms that include modulation of calcium homeostasis, histone deacetylases, mitochondrial function, antioxidant functions, iron chelation, and increased conduction through potassium channels. In addition, the development of neuroprotection assays with higher throughput may lead to a greater rate of discovery of novel neuroprotective agents. This workshop will provide an update on new developments and novel strategies for neuroprotection in epilepsy. | Karen Wilcox, Manisha Patel, D.M. Chuang, H.Steve White |
| 2008 | Ed Dudek | Surrogate markers in animal models of acquired epilepsy: The good, the bad and the ugly. | Acquired epilepsy is generally considered to be the time-dependent development of spontaneous recurrent seizures after an insult to the brain. To monitor for and confirm the presence of bona fide seizures can be technically demanding and resource-intensive, particularly when one considers the time required for the development of chronic epilepsy after a brain insult and the effort necessary to detect and validate the actual seizures, which have a range of specific electrical properties and typically last 10's of seconds to minutes. The use of alternatives to these actual seizures, or surrogate markers, for epileptogenesis has a long history, but is founded on several unproven assumptions. Examples of surrogate markers for experimental epilepsy include (1) "hyperexcitability" to extracellular stimulation, (2) increased seizure susceptibility to challenges with chemo-convulsants (e.g., kainic acid and flurothyl), and (3) brief (i.e., <15 seconds) rhythmic activity in the EEG. Although each of these changes could be interpreted as being pro-excitatory and, by extension, pro-epileptogenic, the actual basis for each of these changes and their implications for the development of epilepsy are poorly understood. This workshop will debate the pros and cons of these different surrogate markers, which are often used to validate animal models of acquired epilepsy, to test hypotheses about mechanisms of epileptogensis, and ultimately, to discover anti-epileptogenic therapies. We will present opposing positions, and invite the audience to comment on the potential utility and predictive value of each of the markers. | F. Edward Dudek, Tallie Z. Baram , Frances E. Jensen, Edward H. Bertram |
| 2007 | Carl E. Stafstrom, MD, PhD | Metabolic control of epilepsy | The ability to control seizures via modulation of metabolic pathways is a burgeoning topic that is just beginning to be exploited in epilepsy research. Following on the success of the ketogenic diet to control seizures in a substantial fraction of intractable pediatric epilepsy, researchers are now exploring ways to modify neuronal excitability by alteration of metabolic pathways. After an introduction to the topic (Stafstrom), the role of ketones and fatty acids in neuronal excitability will be discussed (Rho). The effects of mitochondrial metabolism on seizure susceptibility and excitotoxicity will be explored (Patel). Genetic control of mitochondrial biogenesis and anticonvulsant action will then be analyzed (Bough), followed by a discussion of the mechanisms by which glycolysis and its inhibitors might reduce epileptic firing (Roopra). | Jong Rho, MD, Manisha Patel, PhD, Kristopher Bough, PhD, Avtar Roopra, PhD |
| 2007 | Peter Carlen | Raised extracellular potassium: convulsant and anticonvulsant mechanisms | Raised extracellular potassium is well known to be associated with seizures both as a causal factor and as a consequence. Membrane depolarization and neuronal bursting are known to be brought on by raised potassium. Diffusion of extracellular potassium can cause spread of epileptogenic activity. There is now increasing evidence that raised potassium can also play a very significant role in seizure cessation. This can be through depolarization blockade, activation of Ih, or blockade of axonal conduction. Recent findings now warrant an in depth discussion of the role of potassium in seizure generation, spread and cessation. | Peter Carlen, Dominique Durand, Igor Timofeev, Yoel Yaari |
| 2007 | Annamaria Vezzani | The proliferating brain and its role in epileptogenesis | This workshop is meant to discuss the emerging role of proliferating cells in the brain in the process of epileptogenesis. The focus will be on neuronal and glial progenitors, astrocytes, activated microglia and proliferating endothelial cells describing their morphological and functional changes in epileptic tissue and discussing the impact of these changes on neuronal network excitability and epileptogenesis. Experimental evidence in animal models and observations in human epileptic tissue will be presented. | Jack Parent, Eleonora Aronica, Teresa Ravizza, Mireille Lerner-Natoli |

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| 2007 | Gregory Worrell, MD., PhD, and Brian Litt, MD. | Broad-Band Intracranial EEG In Patients with Epilepsy: A Window On Functional Human Networks | Recent years have seen tremendous interest in broad-band intracranial recordings in humans, driven by new therapeutic neuro-devices and brain-computer interface research. These large scale, broad-band data sets, spanning unit ensembles to large scale networks enable us to investigate hypotheses related to normal network function, such as memory, cognition, and motor control, as well as pathologic processes such as seizure generation, movement disorders and psychiatric disease. Patients implanted with intracranial electrodes during evaluation for epilepsy surgery provide unprecedented access to the brain for this research. This workshop reviews basic advances in the field of human brain electrophysiology. | Gyorgy Buzaki, MD., PhD Large-Scale Recordings of Functional Networks in Brain, Michael Kahana, PhD Mapping Memory from Human Recordings, Christoff Koch PhD Visual perception and visual Consciousness |
| 2007 | David C. Henshall | Emerging cell & molecular targets for anti-epileptogenesis | Interrupting the process of epileptogenesis offers significant therapeutic potential for treatment and prevention of epilepsy. The cell and molecular mechanisms by which epilepsy develops remain incompletely understood but are thought to involve neuronal remodelling, neurotransmitter receptor changes, neuronal death, neurogenesis and gliosis. The purpose of this Investigator's workshop will be to showcase new findings on potential targets for anti-epileptogenesis. Investigators will highlight new and evolving animal models for studying epileptogenesis. New experimental techniques and technologies will be a particular focus. This workshop will highlight mouse models with reference to new models of preconditioning, traditional knockout/transgenic mice as well as approaches such as gene trapping. Emerging genomic (e.g. DNA microarray) and proteomic findings will feature that may provide a more complete molecular map of the myriad changes during epileptogenesis. Finally, up to date findings from evaluated therapeutic strategies in animal models will be placed into context by translational research work using clinical material. | Asla Pitkanen, Yurri Bozzi, David Henshall, Detlev Boison |
| 2007 | Melanie Tallent | The Transition from Interictal to Ictal Bursting: An Update | Interictal spikes are present in patients with epilepsy. These spikes reflect cortical hyperexcitability but do not underlie the seizure itself. The relationship between interictal spikes and sustained ictal events is controversial. Further, using interictal spike characteristics to predict seizure events has proven problematic. The goal of this workshop is to explore the relationship between interictal and ictal events. We will discuss ongoing studies in human tissue and rat models of epilepsy. Topics of discussion will include: (1) How specific patterns of perforant path input can convert interictal spikes into ictal-like events in post-seizure hippocampus that has undergone mossy fiber sprouting. (2) What is the role of injury-induced alterations in the pathways of excitation through the hippocampus? We will present modeling and experimental data suggesting that if an interictal spike is initiated in precisely the wrong area of the injured hippocampus, it is possible to trigger ictogenic recurrent loops of excitation. 2) How do preictal discharges in subiculum trigger ictal events? Our data in epileptic human tissue shows that a "switch" from hyperpolarizing to depolarizing GABA responses is critical. 3) Are their critical postsynaptic mechanisms that prevent the conversion of brief interictal bursts to sustained ictal events? Our findings suggest that the K+ M-channel plays such a role, and is especially critical in immature brain. This workshop should provide new insight on the mechanisms involved in generation of ictal events, and will generate a platform for interesting discussion on this topic. | Gilles Huberfeld, Li-Rong Shao, W. B. Swiercz, Melanie Tallent |
| 2007 | Manisha Patel | Mitochondrial (dys)function and epilepsy | Mitochondria are the principal source of cellular energy and play a key role in the control of free radical production, cell death (apoptosis and necrosis), fatty acid oxidation and calcium homeostasis. These organelles are dynamically transported along lengthy neuronal processes, presumably for appropriate distribution to cellular regions of high metabolic demand and elevated intracellular calcium, such as synapses. The removal of damaged mitochondria that produce harmful reactive oxygen species and promote apoptosis is also thought to be mediated by transport of mitochondria to autophagosomes. Each of these vital mitochondrial functions is important in epileptogenesis and/or seizure-induced cell death. Mitochondrial function and dysfunction can therefore have a major impact on epilepsy. The workshop will provide insight into the role of mitochondrial function and dysfunction with implications to human and experimental epilepsy. | Mitochondrial redox changes following status epilepticus (M. Patel), Mitochondrial trafficking and morphology in healthy and injured neurons (I.J. Reynolds, Merck), Mitochondrial dysfunction in temporal lobe epilepsy (W. Kunz, Univ. Bonn), Mitochondrial dysfunction during neuronal activation in the ex vivo hippocampus (Uwe Heinemann) |
| 2007 | Amy Brooks-Kayal | Mechanisms regulating gene expression in epileptogenesis | This workshop will focus on a number of recent studies addressing the regulatory mechanisms underlying changes in gene expression seen in acquired epilepsy models. The speakers will each address different signaling pathways that have been shown to be important regulators of gene expression during epileptogenesis including neuron restrictive silencing factor and histone deacetylases (NRSF and HDAC)- Ray Dingledine; NRSF and BDNF-Avtar Roopa (Nature Neuroscience Nov 2006), early growth response factors (EGRs)- Shelley Russek (PNAS 2005, JBC 2006) and CREB family members (Amy Brooks-Kayal). Group discussion will then focus on how best to study how these signaling pathways and others may overlap and interact to coordinately regulate the multiple gene expression changes that occur during epileptogenesis. | Ray Dingledine- Emory, Avtar Roopa- University of Wisconsin, Shelley Russek- Boston University, Amy Brooks-Kayal- University of Pennsylvania/CHOP |

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| 2007 | Russell Sanchez | Varied Roles of BK-type Potassium Channels in the Regulation of Neuronal Excitability: Which are Important for Epilepsy? | Potassium channels have long been viewed as having the singular role of controlling neuronal excitability, as K+ channel inhibitors promote epileptiform activity in vitro and are pro-convulsant in vivo. BK channels are high-conductance Ca++- and voltage-dependent K+ channels that contribute to action potential repolarization and generate the fast afterhyperpolarization following an action potential. Thus, their activation intuitively also would be expected to dampen neuronal excitability. Consistent with this, enhancement of BK channel function has been shown to inhibit epileptiform activity in some experimental models. However, a human genetic mutation recently was identified to be associated with generalized epilepsy and paroxysmal dyskinesia, and this mutation paradoxically was found to cause a gain of function of a neuronal BK channel. Additionally, a directed neuronal BK channel gain-of-function mutation was found to cause limbic epilepsy in mice. Thus, the precise roles of neuronal BK channel function would appear to be varied, possibly cell-specific, and may critically depend on their interactions with other neuronal voltage- and/or Ca++-dependent channels. In this workshop, we will discuss recent evidence on the multiple roles of BK channels and attempt to reconcile human and experimental data on the relationship of BK channel regulation and epilepsy. Dr. Johan Storm will discuss the precise roles of BK channels as intrinsic regulators of neuronal excitability and discharge patterns in the brain. Dr. George Richerson will discuss functional properties of the human mutant BK channel, and how these might lead to epilepsy and paroxysmal dyskinesia. Dr. Alison Barth will present evidence of BK channel plasticity in an experimental model of epileptogenesis. The workshop will conclude with a panel discussion that will include insights from Dr. Jeff Noebels into the emerging relationship between BK channel regulation and epilepsy. | Johan Storm, George Richerson, Alison Barth |
| 2007 | David Prince | Sick axons and epileptogenesis | Although axonal sprouting and formation of new/abberant connections is a potentially important mechanism in epileptogenesis, lesion-induced intrinsic physiological abnormalities of axons themselves in epileptogenic cortex, and/or the effects of abnormal activity on axonal function, have received less attention. This is obviously an important issue, as small changes in axonal terminal function can significantly alter release of glutamate and GABA. Further, terminals possess a large number of receptors, voltage-gated channels and transporters that can be altered by genetic and acquired pathologies. This workshop will 1) focus on a few key intrinsic mechanisms for regulation of axonal terminal function; 2) provide examples of disorders in these mechanisms that either result from or give rise to epileptogenesis and 3)allow speculation regarding identification of novel presynaptic axonal targets for development of antiepileptic drugs. | David Prince, Rafael Gutierrez, David McCormick |
| 2007 | Heinz Beck | Homeostatic plasticity and epilepsy | Neurons maintain specific functional properties in the face of continued turnover and renewal of their component proteins and lipids. This stability of functional properties therefore requires a set of regulatory mechanisms that maintain both synaptic and intrinsic properties of CNS neurons, and have been collectively termed homeostatic. In the recent years, some basic mechanisms of homeostatic plasticity have been elucidated (Marder). After an introduction into basic mechanisms and features of homeostatic plasticity (Marder), this workshop will address two basic questions. Firstly, it will explore whether homeostatic mechanisms are invoked in chronic models of epilepsy or neurotrauma, and how they might contribute to long-term changes in excitability in these models (Soltesz). Secondly, it will address the importance of homeostatic plasticity in genetic epilepsies. Single gene mutations cause a large number of adaptive changes affecting many gene products. Many of these changes will correpond to homeostatic mechanisms. We will discuss the hypothesis that mutations causing epilepsy are those that cannot be homeostatically compensated. Conversely, the large number of mutations that do not cause epilepsy may be homeostatically compensated (Noebels). In summary, this workshop will introduce the concept of homeostasis, and then explore how these concepts can apply to chronic and genetic models of epilepsy. | Eve Marder, Ivan Soltesz, Jeff Noebels |
| 2006 | Jack Parent, MD. | Aberrant neurogenesis in the epileptic hippocampal formation | Aberrant neurogenesis is increasingly recognized as an important component of plasticity in the epileptic hippocampal formation. This workshop will discuss the latest findings of how neural stem cells and neurogenesis are altered in experimental temporal lobe epilepsy (TLE) and its implications for human TLE. Topics to be covered may include 1) morphological and electrophysiological features of hilar ectopic dentate granule cell neurogenesis tin the epileptic hippocampus, 2) molecular mechanisms leading to aberrant neuroblast migration in epilepsy, 3) the use of genetic or epigenetic manipulation to block abberant neurogenesis during epileptogenesis, 4) the role of aberrant neurogenesis in hippocampal learning and memory dysfunction associated with epileptogenesis, and 5) Effects of aging on seizure-induced hippocampal neurogenesis. | Jack M. Parent, MD., Sebastian Jessberger, MD., Helen Scharfman, PhD, Lee Shapiro, PhD |
| 2006 | Claude G. Wasterlain, MD. | Receptor trafficking during epileptic seizures | We have recently learned that receptor function is not just a matter of how many receptors you have, but where they are. GABA receptors can be internalized as a result of seizure activity or be unable to move to the synaptic membrane as a result of genetic mutations, resulting in decreases in the efficiency of synaptic inhibition or in a reduced response to GABAergic drugs. The speakers, who are responsible for most of the recent epilepsy-related advances in this new field, will discuss these new aspects of the regulation of synaptic excitability and their implications for clinical epilepsy and its treatment. | Claude G. Wasterlain, MD., Jaideep Kapur, MD., PhD, Robert DeLorenzo, Robert MacDonald |

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| 2006 | Robert Schwarcz, PhD | Entorhinal glial cells and TLE: an exciting connection * combine with Beck, synchronization | Both astrocytes and microglial cells are increasingly recognized as integral components of normal brain function. As sources and targets of a large number of neuroactive substances, glial cells also participate actively in neurological and psychiatric diseases. Using electrophysiological, pharmacological, neurochemical and microscopic techniques in human and rodent tissue, the proposed speakers will provide evidence that abnormal glial cells in the entorhinal cortex (EC) are major players in the pathophysiology of TLE. Separately, the EC and glial cell physiology/pathology have received sporadic attention at recent AES meetings (Investigator's Workshops included). However, the specific role of entorhinal glial cells in the development and occurrence of spontaneously recurring limbic seizures has not been highlighted so far. It seems timely to discuss the new evidence supporting the pathophysiological significance of these cells in TLE in an Investigator's Workshop. | Guy McKhann III, Uwe Heinemann, Helen Scharfman, Robert Schwarcz, PhD |
| 2006 | Frances E. Jensen, MD. | Molecular and Cellular Alterations in TSC: Functional Implications | This workshop will examine recent advances in genetic and neurobiological research examining mechanisms of epileptogenesis in Tuberous Sclerosis Complex (TSC). Dr. P. Crino will discuss the role of dysregulation of the mTOR signaling cascade as a common mechanism in malformations of cortical development including TSC. Dr. D. Kwiatkowski will present new data on a novel transgenic mouse model of TSC, and its potential use for mechanistic study of the neurologic sequelae of TSC. Dr. F. Jensen will present evidence for neurotransmitter receptor alterations in specific subtypes of dysplastic cells in both human TSC and mouse models of TSC that may contribute to epileptogenicity. Finally, Dr. Alvarez will describe cellular and molecular changes in neurons observed as a consequence of altered expression of Tsc genes. | Peter Crino, MD., PhD, David Kwiatkowski, MD., PhD, Frances Jensen, MD., Veronica A. Alvarez, PhD |
| 2006 | Damir Janigro, PhD | Unorthodox mechanisms of epileptogenesis | While most of studies on epileptogenesis still focus on neuronal changes and altered GABA-glutamate ratios, it has become increasingly clear that astrocytes may also, perhaps especially during pathological conditions, release glutamate to synchronize neurons. Gliotransmission is thus an attractive partner to the EPSP/IPSP balance failure in epileptogenesis (Haydon). In recent years, converging evidence from epidemiological, brain imaging and neuropathological studies has led to an increasing acceptance of the notion that at least a portion of adult neurological disorders is a neurodevelopmental disorder, whereby a brain abnormality is inherited or sustained prenatally or early in life but is not fully expressed until adulthood. Dr. Marchi will present data supporting the fact that interfering with vasculogenesis during brain development leads to cortical dysplasia. He compared the effects of prenatal exposure to the putative neurotoxin methylazoxymethanol acetate (MAM) and the vasculogenesis inhibitor thalidomide (Thal) in vivo and measured the levels of angiogenic factors in animals exposed to either toxin. The fact that vascular and glial factors are, in addition to neurons, involved in seizure generation implicates the development of new in vitro models to study these complex topographic interactions and to dissect out the role of individual players. Dr. De Curtis will present data obtained from a whole brain in vitro preparation where intravascular perfusion with activated blood cells revealed surprising epileptiform changes in parenchymal neuronal activity. I will describe how recent findings on patients and in animal models support the notion that blood-brain barrier failure may be involved in the interictal-to-ictal transition or as a factor in epileptogenesis. The speakers represent a mix of basic science investigators, preclinical scientists and a practicing epileptologist who has been for several years involved in basic research. | Philip G. Haydon, PhD, Marco de Curtis, MD., Nicola Marchi, PhD, Alon Friedman, MD., PhD |
| 2006 | Matthias J. Koepp, MD., PhD | The role of opioids in epilepsy | Our current understanding of anatomical, physiological and molecular aspects of the opioid synapse is that opioid peptides act as mediators of use-dependent synaptic activity and as co-transmitters to modulate the actions of the primary transmitter, glutamate. There is a large, sophisticated and at times controversial body of animal data showing endogenous opioid release may occur following induced and spontaneous seizures. There is consensus that endogenous opioids released following seizures contribute to a raised seizure threshold. This workshop should contribute to a better understanding of endogenous mechanisms of s | Frank C. Tortella, Friedrich Zimprich, Matthias J. Koepp, MD., PhD |
| 2006 | L. Matthew Frank, MD. | Gene Therapies and Epilepsy: New Therapeutic Directions" | | Pat Iverson, Steve Wilton |

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| 2006 | Edward Bertram, MD. | New Therapeutic Directions | The epilepsies are the symptoms of a variety of brain disorders that have extremely diverse underlying pathologies and physiologies. Our understanding of these disorders has been greatly facilitated by an ever expanding number of models that are associated with seizures or some other aspect of epilepsy. For some of the models the parallels to the clinical condition is more obvious than others. Although much can be learned about the neurobiology and the function of the brain through all of these models, the potential relationship and applicability of the results from the study of these models to an increased understanding of the pathophysiology of epilepsy is not always clear. In this workshop the organizers will outline the key features (as known) of three common forms of partial epilepsy (limbic/mesial temporal lobe, post-traumatic and secondary to cortical dysplasia) that have a number of animal models. Features about these conditions that are incompletely known will also be identified. Together with the workshop participants the organizers will review the features of the reported models and compare them to the human disorder that they model. Similarities and dissimilarities will be identified as will areas for which there is insufficient information at present. Discussions will then be focused on what additional information about the models may be needed or what features the ideal model should possess in order to improve our understanding of the pathophysiology of the disorder. This workshop will be an open a discussion at the junction of the clinical and the basic, not as a process of model approval but as process for evaluating the models for what they can tell us about epilepsy, and how the results from the lab could be applied to the clinic or interpreted in light of the clinic. The workshop will be structured to allow for significant participation from all present. | Edward Bertram, MD., Amy Brooks-Kayal, MD., Daniel Lowenstein, MD., Gary Mathern, MD. |
| 2006 | Matthew P. Anderson, MD., PhD | Engineering the mouse nervous system to decipher the mechanisms of human epilepsy | Brief description of topic to be discussed: With the advent of regional and temporal restricted gene manipulation techniques, the scientific community is now poised to solve the cellular and molecular basis of complex neurological diseases. Although the traditional methods of localized pharmacology and excitotoxic lesioning remain important, there are some neuroanatomic structures which cannot be studied using these methods. For example, what is the role of cortical pyramidal neurons in layer V? This question cannot be addressed by any other methods. Up until now, the key players in the production of epilepsy have been unclear. This is particularly critical when developing in vitro models of the disease for studies of pathophysiology and in drug discovery. I will present the latest methods in use to perform these gene manipulations and provide an example of how these methods can be used in investigations of epilepsy. | Matthew P. Anderson, MD., PhD, Istvan Mody, PhD, Scott C. Baraban, PhD, Robert Brenner, PhD |
| 2006 | Nicholas Poolos, MD., PhD | H-channelophathy workshop | Maybe the time is ripe for an "h-channelopathy" workshop? I think we would explore the evidence linking h-channels to epilepsy, primarily in animal models of epilepsy. As you probably know, there have been a number of exciting developments recently showing h-channel mediation (via loss of function) of generalized seizures in animal models of absence, and also emerging evidence that h-channel downregulation occurs in models of focal epilepsy as well. I would aim for a mix of speakers that would cover both basic aspects of h-channel function and derangement in animal models. Speakers that could be invited might include the following: | Tallie Baram, MD., PhD, Thomas Budde, PhD, Nicholas Poolos, MD., PhD |
| 2006 | Douglas A. Coulter, PhD | The role of the glutamine cycle in dynamic regulation of normal and pathological function of the CNS | There is a venerable literature on the role of the glutamate-glutamine cycle in recycling neurotransmitter in the central nervous system under both normal and pathological conditions. Several new players regulating the function of the glutamine cycle have only recently been cloned and characterized, so our understanding of processes regulating neurotransmitter recycling has advanced significantly in the past few years (Edwards). However, most of our understanding of the glutamate-glutamine cycle is derived from biochemical and/or molecular studies. These studies have highlighted the significance of this cycle, but the nature of these technical approaches has limited understanding of how the glutamine cycle might couple activity levels to alterations in synaptic efficacy at the millisecond timescale where synapses operate. This limitation has been overcome in recent studies which have examined the dynamic regulation of synaptic function by the glutamine cycle using patch clamp recording techniques in both normal and epileptic animals. These studies have highlighted the critical role of the glutamine cycle in maintaining synaptic neurotransmitter levels and function (Coulter and Huguenard), and have also found significant dysregulation of the glutamine cycle in the epileptic hippocampus (Coulter and Eid). Furthermore, perturbations of this cycle have been described in tissue resected from the hippocampus of patients with temporal lobe epilepsy (Eid), and experimental blockade of the glutamine cycle in animals renders them epileptic (Eid). Therefore, the glutamine cycle may play an important role in coupling inhibitory synaptic efficacy to the ongoing history of recent activation in neuronal circuits, and so may be an important, plastic regulator of circuit excitability. Furthermore, glutamine cycle alterations in the epileptic brain may be a significant contributor to alterations in excitability underlying seizure generation, and may prove to be a viable target for therapeutic intervention in control of epilepsy. This workshop symposium will highlight new advances in understanding the glutamine cycle, will describe how the glutamine cycle regulates synaptic efficacy in a dynamic fashion, and will extend this discussion into the epileptic brain, where the glutamine cycle is disrupted, describing the consequences of this pathology on synaptic and circuit function in the epileptic hippocampus. | Douglas A. Coulter, PhD, Tore Eid, MD., PhD, John Huguenard, PhD, Robert Edwards, MD. |
| 2005 | Baraban, Scott C., PhD | Fly, fish, and worm models of epilepsy | | Guy A. Caldwell, PhD, Mark Tanouye, PhD, Scott C. Baraban, PhD |
| 2005 | Ben-Ari, Yehezkel, DSc | Do seizures beget seizures? | | Yehezkel Ben-Ari, DSc, Mircea Steriade, MD, DSc, Yehezkel Ben-Ari, DSc, F. Edward Dudek, PhD |

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| 2005 | Dudek, F. Edward, PhD | Gap junctions and electrotonic coupling in hippocampus and neocortex: which connexins couple whom? | | John E. Rash, PhD, Roger D. Traub, MD, Barry W. Connors, PhD |
| 2005 | Hochman, Daryl W., PhD | Ion cotransport and epilepsy | | Dale C. Hesdorffer, PhD, Kevin J. Staley, MD, Daryl W. Hochman, PhD |
| 2005 | Koepp, Matthias, MD, PhD | Imaging excitatory neurotransmission | | Raymond J. Dingledine, PhD, Ognen A. Petroff, MD, Matthias Koepp, MD, PhD |
| 2005 | Mathern, Gary W., MD | Epileptogenesis of cortical dysplasia: Compare and contrast animal models with mechanisms gleaned from human studies | | |
| 2005 | Mikati, Mohamad, MD | Seizure-related programmed cell death | | Claude G. Wasterlain, MD, Alexei D. Kondratyev, PhD, Mohamad Mikati, MD |
| 2005 | Pitkanen, Asla, MD, PhD | In vivo imaging epileptogenesis and epilepsy: from techniques to applications | | Jeff W.M. Bulte, PhD, Olli Grohn, PhD, Tallie Z. Baram, MD, PhD |
| 2005 | Scharfman, Helen E., PhD | Animal models of catamenial epilepsy | | Helen E. Scharfman, PhD, Jessica A. Fawley (graduate student), Jaideep Kapur, MD, PhD |
| 2005 | Schiff, Steven J., MD, PhD | Interpreting multivariate EEG and fMRI signals | | Steven J. Schiff, MD, PhD, Eshel Ben-Jacob, PhD, Ivan Osorio, MD, Bjorn Schelter (graduate student) |
| 2005 | Vezzani, Annamaria, PhD | Inflammation and epilepsy | | Tallie Z. Baram, MD, PhD, Milan Fiala, MD, Annamaria Vezzani, PhD, Raymond J. Dingledine, PhD |
| 2004 | Kevin M. Kelly, MD., PhD | Models of epilepsy in aging | | Eric M. Blalock, PhD, Peter R. Patrylo, PhD, Kevin M. Kelly, MD., PhD |
| 2004 | Massimo Avoli, MD., PhD | Plasticity of chloride transport and GABA signaling | | Melanie Woodin, PhD, Richard Miles, PhD, Francisco J. Alvarez-Leefmans, MD., PhD |
| 2004 | Arnold R. Kriegstein, MD., PhD | Origin and migration of cortical neurons | | Joseph Loturco, PhD, Stewart A. Anderson, MD., Samuel J. Pleasure, MD., PhD |
| 2004 | Jong M. Rho, MD. | Ketone bodies and neuronal excitability | | W. McIntyre Burnham, PhD, Gary Yellen, PhD, Jong M. Rho, MD. |
| 2004 | Margaret P. Jacobs | Creating new animal models of the childhood epilepsies | | Solomon L. Moshe, MD., Astrid Nehlig, PhD, Philip A. Schwartzkroin, PhD, John W. Swann, PhD |
| 2004 | John J. Hablitz, PhD | The role of kainate receptors in epilepsy | | Anis Contractor, PhD, Michael A. Rogawski, MD., PhD, Yehezkel Ben-Ari, PhD |
| 2004 | Peter L. Carlen, MD. and John G.R. Jefferys, PhD | Non-synaptic seizure mechanisms | | Dominique Durand, PhD, Ante L. Padjen, MD., Renato Rozental, MD. |
| 2004 | James O. McNamara, MD. | Neurotrophins: Epileptogenesis and electroconvulsive seizures | | James O. McNamara, MD., Helen E. Scharfman, PhD, Samuel S. Newton, PhD |
| 2004 | Scott M. Thompson, PhD and Cha-Min Tang, MD., PhD | The epileptic neuron: Changes in intrinsic neuronal and dendritic excitability | | Ivan Soltesz, PhD, Heinz Beck, MD., Dan Johnston, PhD, Scott M. Thompson, PhD |
| 2004 | Miriam H. Meisler, PhD | Sodium channel mutations in familial and sporadic epilepsy | | Peter De Jonghe, MD., PhD, Mauricio Montal, PhD, Jennifer Kearney, PhD |
| 2004 | Robert K.S. Wong, PhD | Modification of intrinsic ionic channels by metabotropic receptors: A mechanism for epileptogenesis? | | Nelson Spruston, PhD, Angel Alonzo, PhD, Lisa R. Merlin, MD. |
| 2003 | Tallie Z. Baram, MD., PhD | Transcriptional channelopathies in epilepsy | | Douglas A. Coulter, PhD, Heinz Beck, MD. |
| 2003 | John Huguenard, PhD | Neuropeptides: What do they do? Why should epileptologists care? | | Charles L. Cox, PhD, Scott C. Baraban, PhD |
| 2003 | Carl E. Stafstrom, MD., PhD | Long-term seizure monitoring in experimental animal models: Video-EEG and beyond | | Edward H. Bertram, MD., F. Edward Dudek, PhD, Jeffrey L. Noebels, MD., PhD, Mark Stewart, MD., PhD |
| 2003 | Frances E. Jensen, MD. | Post-translational modifications in epileptogenesis | | Gary Westbrook, MD., Mark Bear, PhD, Anne Anderson, MD. |
| 2003 | Ivan Soltesz, PhD | Endocannabinoids in epilepsy | | Bradley E. Alger, PhD, Benjamin Cravatt, PhD, Wade Regehr, PhD |
| 2003 | Tony DeFazio, PhD and John Huguenard, PhD | T-type calcium channels in epilepsy | | Edward Perez-Reyes, PhD, Hee-Sup Shin, MD., PhD, Terrance P. Snutch, PhD |
| 2003 | Melanie Tallent, PhD | Benign familial neonatal convulsions and the K+ M-channel: Insight into how a single gene mutation causes epilepsy | | Nanda A. Singh, PhD, Edward Cooper, MD., PhD, Karen S. Wilcox, PhD |
| 2003 | George D. Richerson, MD., PhD | The role of tonic GABA inhibition and control of brain excitability | | Istvan Mody, PhD, Robert L. MacDonald, MD., PhD, Dimitri M. Kullmann, MD., PhD |
| 2002 | Andreas Hufnagel, MD. | Stem cells in epilepsy | | Ronald McKay, PhD, Jack Parent, MD., Olle Lindvall, MD., PhD |

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| 2002 | Orvar Eeg-Olofsson, MD., PhD | Pharmacogenetics of antiepileptic drugs (AEDs) | | Rene Levy, PhD, Allan Rettie, PhD, Kenneth Thummel, PhD |
| 2002 | Manisha Patel, PhD | Mitochondria and free radicals | | Victor Darley-Usmar, PhD, David G. Nicholls, FRSE |
| 2002 | John J. Hablitz, PhD | Neurotransmitter transporters and epilepsy | | Michael Robinson, PhD, Michael Quick, PhD, Anne Williamson, PhD |
| 2002 | Philip Schwartzkroin, PhD | Functional imaging in small animal models of epilepsy | | Bart P. Keogh, MD., PhD, Scott A. Small, MD., Imad M. Najm, MD., Harley I. Kornblum, MD., PhD |
| 2002 | Libor Velisek, MD., PhD | Steroid hormones and epilepsy | | Stephen G. Matthews, PhD, Serge Rivest, PhD, C. Dominique Toran-Allerand, MD., Sc.D., Jana Veliskova, MD., PhD |
| 2001 | F. Edward Dudek, PhD | Hypoxic-ischemic insults and epilepsy: Models, circuits, and receptors | | Kevin M. Kelly, MD., PhD, Russell M. Sanchez, PhD, Philip Williams, D.V.M., PhD |
| 2001 | Jaideep Kapur, MD., PhD | The latent period -- mechanisms and controversies | | Pat R. Levitt, PhD, Douglas A. Coulter, PhD, Gary W. Mathern, MD. |
| 2001 | Paul A. Rutecki, MD. | Recording from large neural networks -- what can we learn from novel techniques? | | Matthew A. Wilson, PhD, Theodore H. Schwartz, MD., Meyer B. Jackson, PhD |
| 2001 | Amy Brooks-Kayal, MD. | Gene arrays in epilepsy research | | Robert Elliott, PhD, James J. Doherty, PhD, Peter B. Crino, MD., PhD |
| 2001 | Kevin J. Staley, MD. | Inhibition: What measures are relevant to epilepsy? | | David A. Prince, MD., Christophe Bernard, PhD, Istvan Mody, PhD |
| 2001 | Gary Clark, MD. | Functional studies of human epilepsy genes | | Daniel Burgess, PhD, Andrew Escayg, PhD, Robyn Wallace, PhD |