Welcome Message from Dr. Story C. Landis

Welcome to the “Curing the Epilepsies 2013: Pathways Forward” conference. This is the third conference in the “Curing the Epilepsies” series, and it follows on two very successful prior conferences: the White House–initiated “Curing Epilepsy: Focus on the Future” held in March 2000 and “Curing Epilepsy: Translating Discoveries into Therapies” held in March 2007. The 2000 conference is widely noted as a turning point for the epilepsy research community, when the goal of research shifted from merely controlling seizures to preventing and curing epilepsy. The conference also resulted in the first set of Epilepsy Research Benchmarks, a series of milestone goals that challenged the field and directed its research efforts toward clinically meaningful advances. At the 2007 conference, participants evaluated progress made in the original Benchmarks areas and recommended updates to reflect new opportunities.

Likewise, a goal of the 2013 conference is to assess the Benchmarks established in 2007 and help set the research agenda for future years. In changing the name of the conference from "Curing Epilepsy" to “Curing the Epilepsies,” we have recognized the diversity of syndromes and diseases associated with spontaneous recurrent seizures and their comorbidities. Elucidating the mechanisms responsible for the epilepsies, and developing interventions to alter or prevent them, is likely to require an equally diverse set of approaches and perspectives.

On behalf of the National Institute of Neurological Disorders and Stroke (NINDS), I’d like to thank the many people who helped to make the conference possible, including Co-Chairs Anne Berg, Sam Berkovic, and Kevin Staley; Benchmarks Stewards Chair Dan Lowenstein; each of the session chairs and speakers; all of the Benchmarks Stewards; our Federal partners; the American Epilepsy Society; and the patient voluntary organizations represented in Vision 2020.

Finally, thank you for your active participation in the conference and in updating the Epilepsy Research Benchmarks. The Benchmarks reflect the remarkable spirit of collaboration throughout the epilepsy community.
Welcome Message from Conference Co-Chairs

Since the 2007 Curing Epilepsy meeting, advances in technology and new discoveries are changing the way we study the epilepsies and our understanding of the mechanisms and pathways involved. For example, recent studies of the genetic underpinnings of epilepsy have revealed unexpected causal heterogeneity. Next generation sequencing, advances in understanding the role of the immune system in neurological conditions, innovations in engineering that provide new ways to image the structure and function of the brain and to study neuronal activity, and a growing understanding of the role of metabolic signaling in gene expression and post-translational changes are revolutionizing our concepts of what a seizure is and what the epilepsies are. In light of these discoveries, translational neuroscientists are faced with the new challenge of developing therapies for not one but many distinct pathophysologies that are manifest as epilepsies.

To meet this new challenge we have at our disposal an unprecedented armamentarium of transgenic, computational, and neuroimaging technologies. How our field embraces these technologies, builds on and adds to them and, with them, defines the best paths toward to the prevention, treatment and cure of the epilepsies is the focus of this year’s conference, “Curing the Epilepsies 2013: Pathways Forward.”

We will begin by examining the newest developments in our understanding of the causes of clinical epilepsy syndromes in the session entitled: “Progress and Future Directions in Understanding the Causes of Epilepsy.” This will be followed by a session summarizing our progress in basic scientific understanding of the pathogenesis of genetic and acquired epilepsies in the session “What Do We Know About the Paths to Epilepsy?” Real cures for the epilepsies must address the entire disorder, which often extends beyond a seizure predisposition to include a wide range of cognitive and emotional disabilities. These will be defined in the session “What Do We Know About the Paths to Comorbidities and SUDEP?” Cures for this complex, pathophysiologically heterogeneous set of disorders will require careful patient selection and analysis of risks and benefits of potentially curative therapies. Many of these issues are being addressed in currently available approaches such as epilepsy surgery, and will be discussed in the session entitled “What Do We Mean by Cures?” The session “What Do New Paths to Cures Look Like?” will examine recent, exciting developments in experimental therapies for the epilepsies. The meeting will close with a consideration by attendees of the translation of these paths forward into new research benchmarks in the session “Benchmarks for Research on the Epilepsies”.

We invite you to contribute your thoughts during the discussion of priorities for epilepsy research. From this, the next set of research benchmarks for the community will be developed.

This year’s conference has brought together an exciting group of session chairs and speakers, all stellar investigators in their own rights and also all forward thinking individuals who will provide us with an understanding of the recent advances and inspire us with the possibilities they offer. We are delighted that they have accepted this task.

We sincerely hope that you enjoy the conference, and that you take from it valuable lessons and pursue the opportunities that await our field.

Anne T. Berg, Ph.D.  Samuel F. Berkovic, M.D., F.R.S.  Kevin J. Staley, M.D.
Partners Working Group

A special thank you to the members of the Partners Working Group who assisted with development of the agenda, suggestions for speakers, and conference organization.

Sue Berry and Margaret Jacobs—American Epilepsy Society
Julie Milder—Citizens United for Research in Epilepsy
Tracy Casteuble and Roger Porter—Epilepsy Foundation
Orrin Devinsky—Finding a Cure for Epilepsy and Seizures
Gary Mathern, Nico Moshe, Emilio Perruca, and Sam Wiebe—International League Against Epilepsy
David Labiner—National Association of Epilepsy Centers
Jo Anne Nakagawa—Tuberous Sclerosis Alliance
Ilene Miller—Vision 2020 and Hope for Hypothalamic Hamartomas

Sponsors

Thank you to the sponsors of Curing the Epilepsies 2013: Pathways Forward for your support of travel awards (ILAE) and social events.

American Clinical Neurophysiology Society
American Epilepsy Society
Citizens United for Research in Epilepsy
Epilepsy Foundation
ICE Epilepsy Alliance
International League Against Epilepsy
National Association of Epilepsy Centers
Tuberous Sclerosis Alliance

Poster Selection Committee

Thank you to the members of the Poster Selection Committee for reviewing the submitted abstracts and selecting the presenters and recipients of the Travel Awards from NINDS and ILAE.

Chris Dulla, Chair
Howard Goodkin
Farah Lubin
2007–2013 Epilepsy Research Benchmarks Stewards

NINDS would like to thank the many epilepsy researchers who have volunteered to serve as Epilepsy Research Benchmarks Stewards since the first Curing Epilepsy conference in 2000. We are grateful for the Stewards’ efforts to track research advances and to build awareness of the Benchmarks among their peers and junior colleagues and in the epilepsy research community as a whole. The list below acknowledges current Stewards, including several from the original group formed in 2000 as well as Stewards who have joined more recently. For more information about the Benchmarks and to view past Stewards’ reports, please see: [http://www.ninds.nih.gov/research/epilepsyweb/2007_benchmarks.htm](http://www.ninds.nih.gov/research/epilepsyweb/2007_benchmarks.htm).

**Benchmarks Stewards Chair:** Daniel H. Lowenstein, M.D.
*University of California, San Francisco*

**Area I: Prevent epilepsy and its progression**

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<thead>
<tr>
<th>Name</th>
<th>Institution</th>
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<tr>
<td>Raymond Dingledine, Ph.D., Area I Co-Chair</td>
<td>Emory University</td>
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<tr>
<td>Jerome Engel, Jr., M.D., Ph.D., Area I Co-Chair</td>
<td>University of California, Los Angeles</td>
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<tr>
<td>Matthew Anderson, M.D., Ph.D.</td>
<td>Beth Israel Deaconess Medical Center</td>
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<td>Jocelyn Bautista, M.D.</td>
<td>Cleveland Clinic</td>
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<td>Marc Dichter, M.D., Ph.D.</td>
<td>University of Pennsylvania</td>
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<td>Aristea Galanopoulou, M.D., Ph.D.</td>
<td>Albert Einstein College of Medicine</td>
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<td>Ruben I. Kuzniecky, M.D.</td>
<td>New York University</td>
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<td>Solomon L. Moshé, M.D.</td>
<td>Albert Einstein College of Medicine</td>
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<td>Annapurna Poduri, M.D., M.P.H.</td>
<td>Boston Children’s Hospital</td>
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<td>Avtar Roopra, Ph.D.</td>
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<td>Alexander Rotenberg, M.D., Ph.D.</td>
<td>Boston Children’s Hospital</td>
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<td>Richard Staba, Ph.D.</td>
<td>University of California, Los Angeles</td>
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<td>Carl E. Stafstrom, M.D.</td>
<td>University of Wisconsin</td>
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<tr>
<td>Michael Wong, M.D., Ph.D.</td>
<td>Washington University</td>
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Area II: Develop new therapeutic strategies and optimize current approaches to cure epilepsy

Brian Litt, M.D., Area II Chair
*University of Pennsylvania*

Edward H. Bertram, M.D.
*University of Virginia*

Chad Carlson, M.D.
*Froedtert and Medical College of Wisconsin*

Kathryn Davis, M.D.
*University of Pennsylvania*

Jacqueline A. French, M.D.
*New York University School of Medicine*

Tracy Glauser, M.D.
*Cincinnati Children’s Hospital*

William Stacey, M.D., Ph.D.
*University of Michigan*

H. Steve White, Ph.D.
*University of Utah*

Karen S. Wilcox, Ph.D.
*University of Utah*

Gregory A. Worrell, M.D., Ph.D.
*Mayo Clinic*

Area III: Prevent, limit, and reverse the comorbidities associated with epilepsy and its treatment

Anne T. Berg, Ph.D., Area III Co-Chair
*Lurie Children’s Hospital*

Amy Brooks-Kayal, M.D., Area III Co-Chair
*Children’s Hospital Colorado*

Miya Asato, M.D.
*Children’s Hospital of Pittsburgh*

Timothy Benke, M.D., Ph.D.
*University of Colorado, Denver*

Robert C. Doss, Psy.D.
*Minnesota Epilepsy Group*

Daniel Drane, Ph.D.
*Emory University School of Medicine*

Alica M. Goldman, M.D., Ph.D.
*Baylor College of Medicine*

Bruce Hermann, Ph.D.
*University of Wisconsin*

Molly M. Huntsman, Ph.D.
*University of Colorado, Denver*

Andres M. Kanner, M.D.
*University of Miami*

Curt LaFrance, M.D.
*Brown University*

John Langfitt, Ph.D.
*University of Rochester Medical Center*

Samden Lhatoo, M.D.
*Case Western Reserve University*

Jack Lin, M.D.
*University of California, Irvine*

Tobias Loddenkemper, M.D.
*Boston Children’s Hospital*

Alison Pack, M.D.
*Columbia University*

Patricia Osborne Shafer, R.N., M.N.
*Beth Israel Deaconess Medical Center*

Elson Lee So, M.D.
*Mayo Clinic*

John Swann, Ph.D.
*Baylor College of Medicine*

Tanvir Syed, M.D., M.P.H.
*Case Western Reserve University*
Curing the Epilepsies 2013: Pathways Forward

April 17–19, 2013

Natcher Conference Center
Auditorium, Lower Level
National Institutes of Health
Bethesda, Maryland

Agenda

Wednesday, April 17, 2013

7:00 a.m. Registration, Poster Setup, and Sponsored Continental Breakfast

8:00 a.m. Welcome
Francis S. Collins, M.D., Ph.D., Director, National Institutes of Health (NIH)

8:10 a.m. Introduction
Story C. Landis, Ph.D., Director, National Institute of Neurological Disorders and Stroke (NINDS), NIH

8:20 a.m. Overview of the Epilepsy Benchmarks
Daniel H. Lowenstein, M.D., University of California, San Francisco

SESSION 1: Progress and Future Directions in Understanding Causes of the Epilepsies
Chair: Jeffrey L. Noebels, M.D., Ph.D., Baylor College of Medicine

8:30 a.m. Introduction
Jeffrey L. Noebels, M.D., Ph.D.

8:40 a.m. Finding the Cause: A Sibling’s Perspective
Christina Saninocencio, M.S., Lennox-Gastaut Syndrome Foundation

8:45 a.m. Gene Discoveries in the Epilepsies
David Goldstein, Ph.D., Duke University

9:10 a.m. Autoimmunity in the Epilepsies
Josep Dalmau, M.D., Ph.D., University of Pennsylvania

9:35 a.m. Viral Causes of the Epilepsies
Peter Crino, M.D., Ph.D., Temple University
**Wednesday, April 17, 2013 (continued)**

10:00 a.m. **How Neuroimaging Helps To Identify and Understand the Epilepsies**  
A. James Barkovich, M.D., University of California, San Francisco

10:25 a.m. **Summary and Discussion**  
Jeffrey L. Noebels, M.D., Ph.D.

10:45 a.m. **BREAK**

10:45 a.m. **SESSION 2: What Do We Know About the Paths to Epilepsy?**  
Chair: John Huguenard, Ph.D., Stanford University

11:05 a.m. **Introduction**  
John Huguenard, Ph.D.

11:15 a.m. **A Mother’s Journey**  
Barbara L. Kroner, Ph.D., M.P.H.

11:20 a.m. **Inherited Epilepsies: Genetic Architecture and Pathways**  
Samuel F. Berkovic, M.D., University of Melbourne

11:45 a.m. **Epileptogenesis in Genetic Syndromes: Dravet Syndrome**  
Jack Parent, M.D., University of Michigan

12:10–1:15 p.m. **SPONSORED LUNCH**

1:15 p.m. **Natural History of Structural Epileptogenesis**  
Paul Buckmaster, D.V.M., Ph.D., Stanford University

1:40 p.m. **Epileptogenesis in Acquired Insults**  
Douglas Coulter, Ph.D., Children’s Hospital of Philadelphia

2:05 p.m. **Cell-Type Specific Control of Neuronal Circuits in Epilepsy**  
Ivan Soltesz, Ph.D., University of California, Irvine

2:30 p.m. **What Can We Learn From the Macroscopic Connectome in Epilepsy?**  
Matthew Walker, M.D., Ph.D., University College London

2:55 p.m. **Summary and Discussion**  
John Huguenard, Ph.D.

3:15 p.m. **BREAK**
Wednesday, April 17, 2013 (continued)

SESSION 3: What Do We Know About the Paths to Comorbidities and SUDEP?
Co-Chairs: Bruce Hermann, Ph.D., University of Wisconsin, and Frances Jensen, M.D., University of Pennsylvania

3:35 p.m.  Introduction
           Bruce Hermann, Ph.D.

3:45 p.m.  Remembering Todd
           Wendy Mathis Parker, M.F.A., Epilepsy Foundation Central Virginia Chapter

3:50 p.m.  Cognitive Comorbidities in the Epilepsies: Lessons From the Laboratory
           Pierre-Pascal Lenck-Santini, Ph.D., Dartmouth College

4:15 p.m.  Neurodevelopmental Comorbidities in the Epilepsies
           Sarah Spence, M.D., Ph.D., Boston Children’s Hospital

4:40 p.m.  Chronobiology in Epilepsy: Treating Epileptic Seizures by the Clock
           Tobias Loddenkemper, M.D., Boston Children’s Hospital

5:05 p.m.  Psychiatric Comorbidities of Epilepsy
           Andrey M. Mazarati, M.D., Ph.D., University of California, Los Angeles

5:30 p.m.  SUDEP: Human Data and Animal Models
           George Richerson, M.D., Ph.D., University of Iowa

5:55 p.m.  Summary and Discussion
           Frances Jensen, M.D.

6:15 p.m.  Adjourn and Dinner on Your Own
Thursday, April 18, 2013

7:00 a.m.  
Registration and Sponsored Continental Breakfast

SESSION 4: What Do We Mean by Cures?  
Co-Chairs: Robert S. Fisher, M.D., Ph.D., Stanford University, and Elaine C. Wirrell, M.D., FRCPC, Mayo Clinic

8:00 a.m.  
Introduction  
Elaine C. Wirrell, M.D., FRCPC

8:10 a.m.  
Epilepsy Surgery: A Chance for a “Cure” but at What Expense?  
Craig Miller, M.D., Hope for Hypothalamic Hamartomas

8:15 a.m.  
Special Considerations for Epilepsy Therapy Early in Life: Impact on Brain Development and Long-Term Outcomes  
Karen N. Gale, Ph.D., Georgetown University

8:40 a.m.  
Improvements in the Localization of the Epileptogenic Focus  
Ruben I. Kuzniecky, M.D., New York University Comprehensive Epilepsy Center

9:05 a.m.  
Surgical Evaluation and Resection: Advances, New Frontiers, and Questions to be Answered  
Edward Chang, M.D., University of California, San Francisco

9:30 a.m.  
Epilepsy Device and Engineering Advances: Near-Term Applications  
Brian Litt, M.D., University of Pennsylvania

9:55 a.m.  
Dietary Therapies: Optimizing Efficacy and Extending Clinical Applicability  
Jong Min Rho, M.D., University of Calgary

10:20 a.m.  
Summary and Discussion  
Robert S. Fisher, M.D., Ph.D.

10:40 a.m.–12:00 p.m.  
POSTER SESSION

12:00–1:15 p.m.  
SPONSORED LUNCH

SESSION 5: What Do New Paths to Cures Look Like?  
Chair: James O. McNamara, M.D., Duke University

1:15 p.m.  
Introduction  
James O. McNamara, M.D.
Thursday, April 18, 2013 (continued)

1:25 p.m. Finding a New Path: From Heartbreak to Hope
Geraldine Bliss, M.S., Phelan-McDermid Syndrome Foundation

1:30 p.m. Exploiting Knowledge of the Molecular Pathology of Sodium Channel–Based Epilepsies for Therapy
Steven Petrou, Ph.D., University of Melbourne

1:55 p.m. Mechanism-Based Therapies in Tuberous Sclerosis Complex
Mustafa Sahin, M.D., Ph.D., Boston Children’s Hospital

2:20 p.m. Translation in Fragile X Syndrome
Mark Bear, Ph.D., Massachusetts Institute of Technology

2:45 p.m. Clinical Trials of Therapies for Specific Syndromes and Antiepileptogenesis
Jacqueline A. French, M.D., New York University School of Medicine

3:10 p.m. BREAK

3:30 p.m. Prevention Strategies for Acquired Epilepsies
Raymond Dingledine, Ph.D., Emory University School of Medicine

3:55 p.m. Novel Opportunities for Disease Modification
Annamaria Vezzani, Ph.D., Mario Negri Institute for Pharmacological Research

4:20 p.m. Summary and Discussion
James O. McNamara, M.D.

4:40–5:45 p.m. Pathways Forward Roundtable
Moderator: Greg Lewis, M.B.A., McKinsey and Company
Panelists: Katie Hood, M.B.A., Former CEO, Michael J. Fox Foundation
Joel D. Howell, M.D., Ph.D., University of Michigan
Henrik Klitgaard, Ph.D., UCB Pharma
Harald W. Sontheimer, Ph.D., University of Alabama, Birmingham

5:45 p.m. Adjourn and Dinner on Your Own
Friday, April 19, 2013

7:00 a.m.  Registration and Sponsored Continental Breakfast

SESSION 6: Benchmarks for Research on the Epilepsies
  Co-Chairs: Cara Long, Ph.D., NINDS, and Daniel H. Lowenstein, M.D.

8:00 a.m.  Benchmarks Progress: Perspectives From the Chairs of the Benchmarks Stewards
  Daniel H. Lowenstein, M.D., with Jerome Engel, Jr., M.D., Ph.D., UCLA; Raymond Dingledine, Ph.D.; Brian Litt, M.D.; Anne T. Berg, Ph.D., Lurie Children’s Hospital; and Amy Brooks-Kayal, M.D., Children’s Hospital Colorado

8:30 a.m.  Introduction to Breakout Sessions

8:35–10:15 a.m.  Benchmarks Breakout Sessions

Session 1: Benchmarks Area I—Prevent Epilepsy and Its Progression (Balcony B, Upper Level)
  Chair: Jerome Engel, Jr., M.D., Ph.D.
  Moderator: Annapurna Poduri, M.D., M.P.H., Boston Children’s Hospital
  Virtual Moderator: Aristeia Galanopoulou, M.D., Ph.D., Albert Einstein College of Medicine

Session 2: Benchmarks Area II—Develop New Therapeutic Strategies and Optimize Current Approaches to Cure Epilepsy (Room E1/E2, Lower Level)
  Chair: Brian Litt, M.D.
  Moderator: Karen S. Wilcox, Ph.D., University of Utah
  Virtual Moderator: Gregory A. Worrell, M.D., Ph.D., Mayo Clinic

Session 3: Benchmarks Area III—Prevent, Limit, and Reverse the Comorbidities Associated with Epilepsy and Its Treatment (Auditorium, Lower Level)
  Chair: Amy Brooks-Kayal, M.D.
  Moderator: Elson Lee So, M.D., Mayo Clinic
  Virtual Moderators: Daniel Drane, Ph.D., Emory University School of Medicine, and Alica M. Goldman, M.D., Ph.D., Baylor College of Medicine

10:15 a.m.  BREAK

10:35–11:50 a.m.  Breakout Session Summaries and Discussion

10:35 a.m.  Session 1
  Annapurna Poduri, M.D., M.P.H.

10:50 a.m.  Session 2
  Karen S. Wilcox, Ph.D.
Friday, April 19, 2013 (continued)

11:05 a.m.  Session 3  
            Elson Lee So, M.D.

11:20 a.m.  Full Group Discussion: New Opportunities Beyond the Current Benchmarks

11:50 a.m.  Summary and Next Steps  
            Daniel H. Lowenstein, M.D.

12:00 p.m.  Closing Remarks  
            Walter J. Koroshetz, M.D., Deputy Director, NINDS, NIH

12:15 p.m.  Conference Adjourns

12:45–3:00 p.m.  Working Meeting of Benchmarks Stewards
SESSION 1: Progress and Future Directions in Understanding Causes of the Epilepsies
Gene Discovery in the Epilepsies

David B. Goldstein, Duke University.

The Epi4K consortium was established to bring next-generation sequencing approaches to some of the most valuable cohorts of epilepsy patients currently available. Here, I describe the first Epi4K studies focused on epileptic encephalopathies (EEs) collected through the Epilepsy Phenome/Genome Project. EEs are a devastating group of childhood disorders for which the cause is often unknown. Epi4K investigators have completed a screen for de novo mutations in patients with two classical EEs: infantile spasms (IS) and Lennox-Gastaut syndrome (LGS). We exome sequenced 222 probands (117 IS and 105 LGS) and their parents and identified 247 de novo mutations. A likelihood-based analysis showed a significant excess of de novo mutations among these patients in the approximately 4,000 genes that are the most intolerant to functional genetic variation in the human population ($p = 2.36 \times 10^{-5}$). Among intolerant genes carrying de novo mutations, $GABRB3$ has de novo mutations in four patients with EE, and $ALG13$ has a de novo mutation in two different probands at the same position. Given the relevant site-specific mutation rates, the probabilities of these outcomes occurring by chance are $p = 2.9 \times 10^{-10}$ and $p = 5.5 \times 10^{-12}$, respectively. Other intolerant genes with de novo mutations that are of interest based on their roles in other neurodevelopmental diseases include $NEDD4L$, $CACNA1A$, $HNRNPU$, $MTOR$, $FLNA$, $GRIN1$, $IQSEC2$, $CHD2$, and $GRIN2B$. Overall, we show that the de novo mutations observed are enriched in specific gene sets, including genes regulated by the fragile X protein ($p < 10^{-6}$), as was reported for autism spectrum disorders (ASD). These analyses identify new genes and pathways conferring risk of EE, confirm a strong role for de novo mutations in EE, and highlight the need for genome-wide diagnostic screening of patients with complex neuropsychiatric disease. Future Epi4K plans include evaluating rare inherited variants in large case control comparisons and in multiplex families, along with sequencing genes of interest in additional cases and controls. Furthermore, to understand the highly variable outcomes for different patients, we also will study prospective cohorts to carefully correlate genetic variation to seizure control.
Autoimmunity in the Epilepsies

Josep Dalmau, University of Pennsylvania.

The recent discovery of a category of autoimmune encephalitis associated with antibodies against neuronal cell-surface and synaptic proteins has changed paradigms in the diagnosis of several novel and treatable forms of epileptic disorders previously attributed to viral or idiopathic etiologies. In some patients, the presence of an underlying tumor that expresses synaptic proteins, or a previous viral infection, appears to be involved in triggering the immune response, but in many instances no trigger is identified. The spectrum of symptoms, frequency of associated tumors, mechanisms of disease, treatment, and outcome vary according to the target antigen. The best studied of these disorders is anti-NMDA receptor encephalitis, which results in a characteristic syndrome in which 70% of patients develop seizures and/or status epilepticus. About 40% of patients are younger than 18 years; their clinical picture does not differ significantly from that of adults, but about 30% of children and teenagers present initially with seizures or status epilepticus. Other synaptic and cell surface antigens of autoimmune encephalitis include AMPA receptor, GABA(B) receptor, mGluR5, DPPX (an auxiliary subunit of the Shal Kv4.2 potassium channels), and LGI1 and Caspr2 (two proteins related to shaker potassium channels). Using in vitro or in vivo models, the antibodies of all the disorders studied to date (NMDAR, AMPAR, mGluR5, LGI1) have direct structural or functional effects on the target antigen. LGI1 is the second most common autoantigen after NMDAR. Interestingly, LGI1 is a secreted protein that forms a trans-synaptic complex that interacts with the presynaptic VGKC through ADAM23. LGI1 null mice die within the first 2 weeks of life due to tonic seizures. Mutations of LGI1 result in autosomal dominant temporal lobe epilepsy, a benign condition in humans. The encephalitis associated with antibodies against LGI1 usually affects older individuals, causing memory deficits and several types of seizures, including tonic seizures. Recognition of these seizures (also named faciobrachial dystonic seizures) as an autoimmune disorder leads to prompt immunotherapy and may prevent symptom progression to severe limbic encephalitis. The encephalitis associated with GABA(B) receptor antibodies occurs less frequently, but these patients always develop early and prominent seizures. Physicians should be aware of these disorders because some (e.g., NMDAR, LGI1 encephalitis) are relatively frequent, can affect children and adults, and are potentially lethal but respond to immunotherapy. Because the target epitopes are conformational, the antibodies are only identified with techniques that preserve this conformation, such as cell-based assays or brain tissue immunohistochemistry. Patients of any age who develop acute or rapidly progressing symptoms (presenting or accompanied by seizures or status epilepticus), usually associated with behavioral change and memory deficits, with CSF lymphocytic pleocytosis and/or oligoclonal bands of unclear etiology, or with EEG findings of encephalopathy and/or epileptic activity, should have serum and CSF studied for antibodies. About 30% of patients with anti-NMDAR encephalitis develop a characteristic EEG pattern named “extreme delta brush.” In some forms of encephalitis [LGI1, AMPAR, GABA(B) receptor], the MRI often shows increased T2-FLAIR signal in medial temporal lobes, but in other disorders, the MRI often shows normal or mild transient cortical-subcortical changes. The diagnosis is established by demonstrating antibodies in serum and CSF, keeping in mind that sometimes antibodies are detectable only in CSF. Detection of antibodies should prompt treatment with immunotherapy, such as steroids, IVlg, or plasma exchange. If these fail, the use of
second-line therapies, such as rituximab and cyclophosphamide, is often effective. The process of recovery can be very slow (e.g., anti-NMDAR encephalitis), resulting in admission to hospitals and rehabilitation centers for many months. The reasons for this remain unclear, but the effects of antibodies on neuronal circuitry are likely prominent, and evidence suggests that for some of these disorders the antibodies are produced in the CNS by inflammatory infiltrates containing plasma cells that are long-lived and difficult to eliminate.
Viral Causes of the Epilepsies

Peter Crino, Temple University.

Results from our lab and others have defined links between the mTOR pathway and cerebral cortical malformations associated with severe epilepsy, including tubers in tuberous sclerosis complex (TSC), focal cortical dysplasia type IIB (FCDIIB), ganglioglioma, hemimegalencephaly (HME), and Pretzel syndrome. Recently, somatic activating mutations in AKT3 and PI3K, leading to mTOR activation, have been reported in a subset of HME patients. Taken together, these observations provide strong evidence that altered mTOR signaling is a critical pathogenic event associated with altered cortical architecture and epilepsy, with significant public health impact. We coined the term “mTORopathies” to reflect a continuum of neurological disorders characterized by altered cortical architecture, abnormal neuronal morphology, and intractable seizures related to abnormal mTOR signaling.

FCDIIB is a sporadic developmental malformation of the cerebral cortex highly associated with epilepsy. Balloon cells (BCs) in FCDIIB exhibit constitutive activation of the mTORC1 signaling pathway. Recently, the high-risk human papillomavirus type 16 oncoprotein E6 was identified as a potent activator of mTOR signaling. HPV16 is the most common cause of cervical dysplasia and cancer and has been linked to a growing number of cases of oropharyngeal cancer. The prevalence of HPV infection has been estimated at 26% in women aged 14–59 years in the United States. Interestingly, E6 binds to TSC2, a critical negative regulator of the mTORC1 cascade and the causative gene for TSC, and targets it for ubiquitin-mediated degradation. In addition, E6 activates Akt, leading to TSC2 inhibition and subsequent mTORC1 activation. A related HPV16 oncoprotein, E7, acts synergistically with E6 to activate mTOR via Akt. In both mechanisms, mTORC1 activation is evidenced by enhanced phosphorylation of the downstream mTORC1 substrate, ribosomal S6 protein (phospho-S6), in cervical tissue in vitro and in vivo. We found the effects of HPV16 E6 on mTORC1 signaling strikingly similar to previous reports demonstrating reduced levels of TSC2, enhanced phospho-PDK1 and phospho-Akt levels, and enhanced mTORC1 signaling in FCDIIB. Interestingly, the cytopathic effect of E6 in the cervix is the appearance of koilocytes, enlarged cells also known as BCs and morphologically similar to BCs observed in FCDIIB. Thus, HPV16 E6 protein expression was assayed by immunohistochemistry in FCDIIB specimens (n = 50) and control brain specimens (n = 37). E6 DNA was assayed by PCR and in situ hybridization, and mRNA was assayed by RT-PCR. HPV16 E6 was transfected into fetal mouse brains by in utero electroporation to test the effects of E6 on cortical development.

HPV16 E6 protein was robustly expressed in all 50 FCDIIB specimens in BCs, but not in regions without BCs, or in control tissue specimens, including normal brain, control lymphoblasts and fibroblasts, and U87 glioma cells. E6 was not detected in temporal lobe epilepsy specimens or hemimegalencephaly. E6 expression in FCDIIB co-localized with phosphorylated S6 protein. HPV16 E6 and E7 DNA and mRNA were detected in representative specimens of FCDIIB, but not control cortex, and were confirmed by sequencing. Transfection of E6 into fetal mouse brains caused a focal cortical malformation in association with enhanced mTORC1 signaling.

Our results indicate a strong association between HPV16 E6 and FCDIIB. We propose a novel etiology for FCDIIB based on HPV16 infection during fetal brain development. Ours is the first description of HPV in
the human brain and the first link between HPV and a cortical malformation. Because the signaling abnormalities induced by E6 in epithelial cells exactly mirror those of mTORopathies, we hypothesized that fetal brain infection with HPV16 could be a novel pathogenic agent for FCDIIB. Because it is believed that FCDIIB forms during embryonic brain development, one possible mechanism is transplacental HPV16 infection of progenitor cells in the developing brain. The transplacental HPV infection rate among women with either genital warts or low-grade or high-grade cervical intraepithelial lesions has been reported as 12.2%. In many women, HPV16 infection is asymptomatic, and transplacental spread of HPV16 could provide a plausible and logical mechanism for infection during periods of early cortical development leading to structural changes resulting from persistent E6/E7 expression in neurons or astrocytes even in the absence of overt clinical infection. Alternatively, the possibility that FCDIIB arises as a postnatal event must be considered. HPV infection is currently an epidemic that has clear public health relevance and that has prompted a definitive preventative response by large-scale vaccination. If HPV infection is etiologically related to epilepsy and cortical malformations, then clear world health relevance will dictate surveillance both in developed and third-world countries.
How Neuroimaging Helps To Identify and Understand The Epilepsies

A. James Barkovich, University of California, San Francisco

Imaging has become a critical tool in understanding and treating epilepsy. When used properly, imaging can identify masses, hemorrhage, injury, and dysgenesis of the brain that are the sources of abnormal electrical activity resulting in epilepsy. To maximize the effectiveness of imaging, it must be tailored to each specific patient on the basis of the patient’s age, type of seizure, and localization of the epileptogenic focus according to electrophysiologic studies. This effort requires close communication among the members of the clinical epileptology team and the imaging physicians. It also requires that the imaging physician be well read and experienced in the imaging of patients with epilepsy.

The initial imaging study in nearly all epilepsy patients is magnetic resonance imaging (MRI). MRI must be optimized not only for the expected location of the epileptogenic focus but also for the age of the patient. At different ages and depending on the maturity of the brain, the appearance of the epileptogenic focus may change. In addition, the ability to detect the epileptogenic focus depends on optimizing the contrast between the epileptogenic focus and the surrounding brain, which can be difficult during times of active myelination (between ages 7 months and 24 months). Other imaging sequences with heavier T1 or T2 weighting may be useful in these settings. In addition, other imaging tools, such as positron emission tomography (PET) and magnetic source imaging (MSI), may be useful in these situations. New ligands being developed for PET may be relatively specific for certain types of malformations and tumors.

In some institutions, blood oxygen level–dependent (BOLD) MRI, MSI, or diffusion weighted imaging are used to identify eloquent areas of cerebral cortex to avoid damage to such areas during epilepsy surgery. BOLD MRI (sometimes called functional MRI or fMRI) is used in conjunction with MR–compatible EEG leads to identify the location of increasing blood volume at the time of the seizure, presumably representing the epileptogenic focus. This ability to directly identify the epileptogenic focus may be of use in future treatments.
SESSION 2: What Do We Know About the Paths to Epilepsy?
Inherited Epilepsies: Genetic Architecture and Pathways

Samuel F. Berkovic, University of Melbourne.

Genetic factors play a role in essentially every patient with epilepsy, although these roles vary from crucial to clinically trivial. For the clinician, assessment of the genetic component in an individual case should be part of a routine epilepsy consultation that is essential for answering common questions regarding the clinical genetics including etiology of epilepsy and risk to other family members. For the neuroscientist, the unraveling of the molecular genetics of epilepsy will add greatly to solving central neurobiological questions.

This presentation will give an overview of the clinical genetics of epilepsy. First, the evidence for genetic components will be briefly discussed, including data from population studies, twin analyses, and multiplex family studies. Progress in identifying genes in epilepsies with simple and complex inheritance will be reviewed. The importance of de novo mutations will be discussed; these mutations show that genetic determinants are even more important than deduced from classical clinical genetic data.

The progress of gene discovery reveals complexities in understanding genotype-phenotype correlations. Explanations for these complexities are beginning to be provided by exploring the physiology of mutations in vitro and in experimental animals. Examples will be discussed that signal a clear way forward in understanding the pathways to epilepsy from the genetic mutation to phenotype; such knowledge is key to developing cures.
Epileptogenesis in Genetic Syndromes: Dravet Syndrome

Jack M. Parent, University of Michigan.

Dravet syndrome (DS) is a severe childhood epilepsy typically caused by de novo dominant mutations in the SCN1A gene encoding the voltage-gated sodium channel Na,1.1. This catastrophic childhood epilepsy usually begins in the first year of life and manifests with intractable generalized and focal seizures, cognitive dysfunction, and other associated symptoms. Despite the development of mouse models, pathophysiological mechanisms underlying DS and related genetic ion channel epilepsies remain uncertain. Heterologous expression of mutant channels suggests loss of function in DS caused by heterozygous SCN1A mutations, raising the quandary of how loss of sodium channels underlying action potentials produces hyperexcitability. Mouse model studies suggest that decreased Na,1.1 function in interneurons causes disinhibition. Another approach to studying this disorder is to determine how mutant SCN1A affects human neurons using the induced pluripotent stem cell (iPSC) method to generate patient-specific neurons. This talk will describe studies of DS patient-derived neurons to examine epilepsy mechanisms and will discuss some newer animal models of DS using zebrafish and drosophila.

To study DS patient-specific neurons, forebrain-like neural progenitor cells were derived from two DS subjects and three human controls by iPSC reprogramming of fibroblasts. Neural progenitors were differentiated into pyramidal- and bipolar-shaped neurons and compared using whole-cell patch clamp recordings. Sodium current density and intrinsic neuronal excitability were examined. DS patient-derived neurons showed increased sodium currents in both bipolar- and pyramidal-shaped neurons. Consistent with increased sodium currents, both types of patient-derived neurons displayed spontaneous bursting and other evidence of hyperexcitability. Sodium channel transcripts were not elevated, consistent with a post-translational mechanism, and the finding of elevated Na,1.6 expression in patient neurons suggested that the increased sodium currents arose from overcompensation with a different Na, subunit. To study potential sudden unexplained death in epilepsy mechanisms, DS patient iPSCs were also differentiated into cardiac myocytes (CMs). Similar to iPSC neurons, DS patient CMs showed increased sodium current density compared with control, a finding that was also seen in a DS mouse model. These results suggest that maladaptive compensatory increases in sodium current density in DS patient neurons and CMs may lead to seizures and arrhythmias, respectively.

Recently, Na,1.1 mutant fish and fly models have been developed to study epilepsy mechanisms and identify novel therapies. Both models show seizures or seizure-like activity. The combination of drosophila, zebrafish, mouse, and iPSC models of DS offers a novel opportunity to examine shared disease mechanisms and test new therapies using a variety of assays across multiple species.
Natural History of Structural Epileptogenesis

Paul Buckmaster, Stanford University.

Structural changes in the hippocampus of patients with epilepsy were first described more than 100 years ago. Within the hippocampus, the dentate gyrus displays some of the most consistent and dramatic neuropathologic abnormalities in patients with temporal lobe epilepsy. Those changes include hilar neuron loss, GABAergic interneuron loss, GABAergic axon sprouting, mossy fiber sprouting, granule cell dispersion, and hilar basal dendrites. Additional structural changes have been described in the dentate gyrus, in other parts of the hippocampal formation, and in other brain regions. Despite extensive characterization of structural abnormalities in patients, it remains unclear which, if any, cause seizures. Much progress has been made generating similar epilepsy-related structural changes in laboratory animal models. The following animal model–based approaches are emerging opportunities for making more progress towards cures for temporal lobe epilepsy:

(1) Prioritize structural changes for in-depth testing. The list of abnormalities that might contribute to epileptogenesis is long. Testing requires time and resources. Therefore, it is necessary to prioritize. The epilepsy research field now has rigorous methods to quantify structural changes (including stereology), improved methods for measuring frequency of spontaneous seizures (including 24/7 video-EEG recording), and animal models that display spontaneous seizures at reasonable frequencies for making statistical comparisons between groups. Although improvements in all these areas would be helpful and welcome, current methods are sufficient to test for correlations with seizure frequency and identify those structural changes that are most likely to be epileptogenic.

(2) Experimentally manipulate structural changes and test the effect on epileptogenesis. Ideally, one would like to specifically block an epilepsy-related structural change to test whether seizure frequency is reduced. Existing drugs and other treatments (including genetic manipulations) that have already been employed in other research fields might be useful. An example is rapamycin, which blocks mossy fiber sprouting. This powerful experimental approach requires creative application of known reagents and development of new ones.

(3) Improve animal models. Commonly used status epilepticus–based rodent models of temporal lobe epilepsy offer many advantages. Recently, spontaneous seizures were found to originate in the temporal hippocampal formation of pilocarpine-treated rats, similar to patients. However, some structural changes do not match those in patients. For example, hippocampal damage frequently is unilateral in patients, whereas it is bilateral in chemoconvulsant rodent models. In contrast, California sea lions, which develop temporal lobe epilepsy after they are naturally exposed to the toxin domoic acid, display unilateral hippocampal damage. Animal models are useful for testing mechanisms of epileptogenesis to the extent that they replicate the mechanisms that cause seizures in patients. More work is needed to further validate existing animal models and develop new, humane models that more closely replicate structural changes found in patients.

Now is an exciting time for research on structural epileptogenesis. The field has progressed from describing epilepsy-related neuropathologic abnormalities to more rigorously testing their role in the generation of spontaneous seizures. Animal model–based approaches, including those described above, are a promising pathway forward toward curing temporal lobe epilepsy.
Epileptogenesis in Acquired Insults

Douglas A. Coulter, Children’s Hospital of Philadelphia/University of Pennsylvania School of Medicine.

Acquired seizure disorders are among the most prevalent and least therapeutically responsive epilepsy variants. These forms of epilepsy are typically associated with a predisposing event in the patient’s history, such as head trauma, CNS infection, complex febrile seizures, stroke, or an episode of status epilepticus. These injurious initiators damage the brain and can trigger the later emergence of spontaneous seizures (epilepsy). The process linking brain injury with the subsequent development of epilepsy has been termed epileptogenesis. Understanding mechanisms underlying epileptogenesis and development of therapeutic strategies to block these processes are a critical priority in epilepsy research. Effective therapeutic targeting of epileptogenesis could block the later emergence of epilepsy in at-risk patients, curing the disease before its emergence.

Significant progress has been made recently in identifying contributory factors underlying epileptogenesis, predominantly derived from studies utilizing rodent models and involving epilepsy development subsequent to an episode of status epilepticus. Diverse mechanisms on multiple scales and in multiple brain compartments have been implicated, including altered neuronal gene transcription, aberrant induction of post-translational processes in neurons and astrocytes, activation of inflammatory responses in neurons and glia, and changes in expression and function of cytokines and trophic factors. All of these diverse mechanisms have been targeted and found to blunt or block the delayed emergence of seizures in animal models of acquired epilepsy.

As an example of a triggering mechanism in acquired epilepsies, one well-characterized transcriptional regulator implicated in epileptogenesis is response element-1 (RE-1) silencing transcription factor (REST, also termed neuron-restrictive silencer factor [NRSF]). This regulator is a primary mediator of cell fate decisions during differentiation, where it is expressed in cells that are destined for a non-neuronal function. REST/NRSF expression results in REST binding to RE-1 elements expressed in promoter elements and/or introns of neuronal genes, such as ion channels, receptors, and transporters, and represses expression of these neuronal proteins through epigenetic silencing, enforcing a non-neuronal fate. However, in addition to its primary role as a master regulator during development, REST has significant roles in the adult brain. REST expression is activity dependent, and it exhibits significant upregulation in selected regions of brain time-locked to epileptogenic predisposing injuries such as episodes of status epilepticus or ischemia. Once REST is expressed after injury, it represses expression of numerous neuronal genes in a cell- and region-specific manner. Within the hippocampus, these targets include important proteins in excitability, such as AMPA receptors (areas CA1 and CA3), HCN channels (area CA1), GABA<sub>A</sub> receptors, and chloride transporters (dentate granule neurons). Repression in these critical excitability regulators then contributes to epileptogenesis through linkage of injurious stimuli to alterations in hippocampal excitability. Targeting REST upregulation after injury blocks repression in these important genes and also blunts the severity of epilepsy, which emerges subsequent to the epileptogenic injury.

Targeting these diverse mechanisms underlying epileptogenesis, including REST, may have significant translational relevance. Transcriptional, post-translational, inflammatory, and cytokine mechanisms all
are significant contributors to epilepsy initiation. Whether these diverse mechanisms require individual therapeutic interventions or might be components of one or more linked processes will determine whether mono- or polypharmacy might be obligate for controlling epileptogenesis.
Distinct interneuronal subtypes have evolved in cortical circuits to deliver GABA to specific spatial domains of principal cells at particular times during behaviorally relevant network oscillations. The precise spatiotemporal control of populations of principal cells by the GABAergic system underlies the fundamental unity of neuronal space and time, reflected in the new term “chronocircuitry.” Epilepsy, similar to several other major neurological and psychiatric disorders, is fundamentally a chronocircuit brain disorder, manifested as pathological oscillopathies at various frequencies generated by pathologically reorganized networks. Although a major challenge in understanding and treating epilepsy stems from the fact that numerous molecular, cellular, synaptic, and network properties undergo simultaneous alterations in the epileptic brain, the close integration of new experimental paradigms, such as in vivo recordings from identified cells in awake animals and imaging techniques, together with data-driven simulations performed on supercomputers, offers powerful tools towards the identification of key circuit elements that may be particularly effective in controlling epileptic chronocircuit behaviors. It has recently become possible to modulate specific subsets of excitatory and inhibitory neurons utilizing optogenetics, allowing for unprecedented specific and immediate control of cell populations of interest in the behaving animal. Optogenetic technologies have been particularly challenging to apply to epilepsy because of the unpredictable nature of the seizures. Recently, new closed-loop systems have been developed specifically for detecting and optogenetically controlling spontaneous chronic electrographic and behavioral seizures in rodents. These results demonstrate that on-demand optogenetic strategies can be extraordinarily effective at controlling epileptic chronocircuits in a spatial, temporal, and cell-type specific manner.
What Can We Learn From the Macroscopic Connectome in Epilepsy?

Matthew C. Walker, Institute of Neurology, University College London.

Brain function depends on the interconnections between different brain areas. On the macroscopic scale, connectivity can be viewed from three related but distinct perspectives: (1) structural (anatomical) connectivity, which maps the anatomical connections between brain areas; (2) functional connectivity, which maps the activity relationships between areas; and (3) effective connectivity, which maps how activity in one specific area influences another. In recent years, considerable development has occurred in methods to measure each of these, led by advances in EEG, MRI, and fMRI analysis. Such methods have been applied to the investigation of seizures and epilepsy.

Because by definition seizures require a behavioral or subjective output, and clinical seizures progress through a series of stereotypical stages, the manifestation of seizures requires the recruitment of large-scale (macroscopic) brain networks. Moreover, a number of observations indicate that epilepsy is not secondary to just an abnormally discharging focal area of cortex but arises from a complex network. Detailed assessment of grey matter often demonstrates abnormalities in brain volume beyond the apparent lesion (e.g., atrophy of striatum, neocortex, and thalamus in patients with hippocampal sclerosis). Aura symptoms can often be elicited by stimulating more than one area (often noncontiguous). Removal of the “seizure-onset zone” frequently does not cure the epilepsy, and often the patient will have unchanged auras. Analysis of functional networks using fMRI indicates that interictal and ictal activity is associated with activation/inactivation of quite disparate brain areas. If we accept that epilepsy is an abnormality of a distributed network, then understanding abnormalities in macroscopic connectivity is likely to be paramount in understanding mechanisms underlying seizure generation and propagation.

Diffusion tensor imaging has increasingly been used to map structural connectivity, and in both focal and generalized epilepsies, abnormal structural connectivity has been found. In many cases, it is unclear whether this relates to the pathology, the comorbidities (such as memory problems in people with temporal lobe epilepsy), or the pathogenesis and propagation of seizures.

Functional connectivity has perhaps been more helpful. Functional and effective connectivity are informed by the structural connectome (i.e., if there is no anatomical connection between two areas, then any functional connection must be through shared inputs rather than a connection). In the resting state in normal brain, important functional networks such as the default network exist. These resting-state networks are often abnormal in the “epileptic brain.” Moreover, functional networks change during a seizure, which is not surprising because in normal brain even microstimulations can change corticocortical signaling through recruitment of inhibitory mechanisms. Indeed, effective connectivity may be influenced by brain state and other factors. The observed changes in the functional network during seizure activity entail at first a decrease in synchronization around the seizure onset zone (seizures represent nonphysiologic, “independent” activity). Then the functional network becomes grossly altered with patterns of connectivity that are not observed in the interictal period, suggesting that seizure generation and propagation depend on aberrant network connectivity. However, a criticism of functional connectivity that has yet to be adequately addressed in epilepsy is that the “function”
measured is usually related to the input to an area (e.g., field potentials) rather than the area’s output (i.e., neuronal firing).

Overall, growing evidence exists that the substrate for the production of seizures is a widespread neuronal network (matrix) linked through connections that become altered perhaps through repeated use and/or structural pathology. Elucidating the connectome enables the development of dynamic computational models. These models have important implications for surgical treatment and for the use of other treatment modalities such as brain stimulation.
SESSION 3: What Do We Know About the Paths to Comorbidities and SUDEP?
Cognitive Comorbidities in the Epilepsies: Lessons From The Laboratory

Pierre-Pascal Lenck-Santini, Dartmouth College.

In some epileptic syndromes, cognitive impairment and behavioral disturbances can have devastating consequences on the quality of life of the patient and caregivers. In some patients, these comorbidities are of greater consequence than the seizures themselves, and the cognitive state of children with severe cases of epilepsy is often the primary concern of parents. To identify potential targets for treatment of these comorbidities, understanding the mechanisms at the origin of cognitive impairment is therefore critical. Data from animal models of epilepsy suggest that these mechanisms can be regrouped in three main origins: the seizures themselves, interictal abnormalities, and the underlying etiology.

A large set of evidence shows that seizures can have both transient and long-lasting consequences on cognitive function, particularly in newborn animals. Paralleling the clinical situation, cognitive impairment has been demonstrated in models of prolonged status epilepticus and repeated neonatal seizures. The consequences of such seizures on the morphologic and physiologic properties of brain networks are starting to unravel, and biomarkers predicting cognitive outcome after seizures are being identified.

Apart from seizures, the EEG of patients with epilepsy is also characterized by interictal spikes, epileptiform discharges that occur between seizures. Interictal spikes have been proposed to affect sensory, motor, visuospatial, and verbal processing. Recent findings in both animal models and patients with temporal lobe epilepsy show that hippocampal interictal spikes also disrupt ongoing memory processes. Therefore, interictal spikes cause transient disruption of the functions that take place in the brain region in which they occur. According to the brain region involved, their frequency, the time at which they occur, and the age of the patient, interictal spikes could therefore have important consequences for cognition.

Even when the etiology of seizures is not clearly identified, epilepsy has to be originating from abnormal network properties. It is thus logical to consider that such abnormalities also translate in functional deficits. For instance, several epilepsy syndromes are characterized by dysfunctions of GABAergic networks. These syndromes are generally associated with cognitive impairments, and the frequency and severity of seizures are not directly correlated to the extent of the cognitive deficits. However, interneurons are known to orchestrate brain oscillations, which play a critical role in information processing. Data will be presented that suggest that interneuron abnormalities, in addition to causing seizures, can have an independent consequence on cognitive function by altering oscillations.

As illustrated above, cognitive dysfunction can result from multiple origins, and it is likely that in the same patient, several causes of impairments are identified. Distinguishing between the relative effect of etiology, epileptiform abnormalities, and seizures is an important challenge and should be considered on a syndrome-to-syndrome basis.
Neurodevelopmental Comorbidities in the Epilepsies

Sarah Spence, Boston Children’s Hospital.

The prevalence of various comorbid neurodevelopmental disabilities, including intellectual disability, autism spectrum disorders, attention deficit disorder, and learning disabilities, is known to be increased in patients with epilepsy. For patients and families, these comorbidities are often as important as the seizures themselves. Unfortunately, the exact nature of the association remains unclear.

This presentation will focus on autism spectrum disorder (ASD) as a model for understanding this important association. Prevalence studies show that epilepsy is relatively common in ASD and ASD is overly represented in patients with epilepsy. In individuals with ASD, the risk factors for developing epilepsy include the presence of intellectual disability, syndromic autism, and possibly female gender. Epilepsy onset appears to occur in a bimodal distribution, with seizures starting in very young children (sometimes even predating the ASD diagnosis) or later in adolescence. How epilepsy affects the behavioral phenotype of autism is less well known.

The complexities of this relationship and how they impede research also will be addressed. A major challenge to a better understanding of this important association is the heterogeneity of both epilepsy and neurodevelopmental disorders with regard to both etiology and phenomenology. Researchers now refer to the “autisms” the way they refer to the “epilepsies,” with both being conceptualized as spectrum disorders. In addition, research is hindered by differing diagnostic classifications and measurement tools in the fields of epilepsy and neurodevelopmental disorders. Classifications not only change over time (such as new versions of the diagnostic criteria in the Diagnostic and Statistical Manual) but also between investigators, making it particularly difficult to draw conclusions across existing studies.

Collaboration between investigators from both the epilepsy and the neurodevelopmental disabilities fields will be crucial to move the field forward. Examples could include: (1) more detailed study of various single gene disorders that predispose to both epilepsy and neurodevelopmental disorders, which could identify particular overlapping molecular mechanisms that may be relevant in other patients; (2) longitudinal studies of early-onset epilepsies that focus on developmental outcomes, which could identify specific risk factors and lead to prevention; and (3) studies of genetic and mechanistic overlap between epilepsy and neurodevelopmental disorders, which could lead to novel treatment targets.
Chronobiology in Epilepsy: Treating Epileptic Seizures by the Clock
Tobias Loddenkemper, Boston Children’s Hospital.

The combination of chronobiology and epilepsy offers novel diagnostic and therapeutic management options. Knowledge of the interactions between circadian periodicity, entrainment, sleep patterns, and epilepsy may provide additional diagnostic options beyond sleep deprivation and extended-release medication formulations. It may also provide novel insights into the physiological, biochemical, and genetic regulation processes of epilepsy and the circadian clock, rendering new treatment options. Temporal fluctuations of seizure susceptibility based on sleep homeostasis and circadian phase in selected epilepsies may provide predictability based on mathematical models. Chronoepileptology offers opportunities for novel epilepsy outcome assessment tools, individualized patient-oriented treatment paradigms based on chronopharmacology, differential medication dosing, chronodrug delivery systems, and utilization of “zeitgebers” such as chronobiotics and desynchronization strategies.
Psychiatric Comorbidities of Epilepsy

Andrey M. Mazarati, David Geffen School of Medicine at UCLA.

Patients with epilepsy (PWE) frequently suffer from various concurrent psychiatric disorders. Prevalence of psychiatric disorders such as depression, anxiety, schizophrenia, attention deficit and hyperactivity disorder (ADHD), and autism spectrum disorder (ASD) is significantly higher among PWE than in the general population and in patients with other medical conditions. Psychiatric comorbidities further worsen quality of life of PWE and in addition reportedly compromise the effectiveness of anticonvulsant therapies. Understanding neurobiological mechanisms of psychiatric comorbidities of epilepsy is instrumental for the development of mechanism-driven treatment of these conditions as well as for the effective management of seizures.

Among various psychiatric comorbidities of epilepsy, depression is one of the most common: between 30% and 50% of PWE exhibit symptoms of depression. Furthermore, one of three PWE cite mood impairments and stress (both being symptoms of depression) as their top concerns, which is comparable with concerns about dependence on medications and higher than concerns regarding cognitive and memory deficits.

Depression is a multisymptomatic and multifactorial disease. Diversity of symptoms and underlying causes represent significant challenges for studying mechanisms of both major depressive disorder (MDD) and epilepsy-associated depression (EAD). Deficit of central serotonergic transmission has been widely accepted as a mechanism of hopelessness/despair (a leading symptom of both MDD and EAD) and includes reduced levels of and blunted endocrine response to serotonin (5-HT) as well as the diminished serotonergic tone in ascending raphe nuclei pathways. Clinical and experimental data suggest that, in a subpopulation of patients with EAD, central 5-HT deficiency stems from the upregulation of raphe 5-HT1A autoreceptors, which inhibit 5-HT release on a negative feedback basis.

In the absence of central serotonergic dysfunction, hopelessness and despair may develop because of perturbations in central noradrenergic transmission, particularly due to the diminished output of norepinephrine in ascending locus coeruleus projections. Underlying causes include suppressed tyrosine hydroxylase activity and upregulation of alpha2A adrenergic autoreceptors. Thus, in different patients with EAD, similar symptoms may have different underlying mechanisms.

Another key symptom of depression, anhedonia, has complex and diverse pathophysiology. At the same time, emerging evidence implicates chronic brain inflammation (the latter has been compellingly established as a hallmark of chronic epilepsy), and particularly the upregulation of the cytokine interleukin-1 beta in the hippocampus, in anhedonia associated with EAD.

Specific perturbations in sleep architecture have been well characterized in MDD patients. However, apparent differences exist in the quality of sleep impairments between MDD and EAD patients, particularly pertaining to changes in rapid eye movement sleep. Such differences suggest that EAD, while sharing some symptomatology and mechanisms with MDD, has its distinct features, and therefore EAD cannot be regarded as a mere variant of MDD.

In conclusion, mechanistic studies, diagnosis, and mechanism-based treatment of EAD should be taken into account with the multiplicity of its symptoms and underlying mechanisms. On a broader scale, effective management of psychiatric comorbidities of epilepsy is critical for the improvement of quality of life of PWE.
SUDEP: Human Data and Animal Models

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Sudden unexpected death in epilepsy (SUDEP) is “sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrowning death in a patient with epilepsy, with or without evidence of a seizure and excluding documented status epilepticus.” There is much we do not know about SUDEP. Most cases occur unwitnessed and with often limited information relating to the surrounding circumstances. No specific identifying test exists for SUDEP, and medical examiners show considerable variability in recognizing it, so determining the incidence with certainty has not been possible. What is clear is that those patients with more difficult-to-control seizures have a higher incidence; therefore, SUDEP is the most common cause of death in chronic refractory epilepsy patients, accounting for 10% to 50% of premature deaths. Although SUDEP is a huge problem, it has largely been unrecognized by the medical community.

Our understanding of the pathophysiology of true SUDEP cases comes from the relatively small percentage of cases with eyewitnesses (usually untrained) and the handful (< 10) reported cases of individuals who died in an epilepsy monitoring unit (EMU). From these cases, we know that SUDEP is a peri-ictal event, and dysfunction of respiratory control is the primary cause of death in the majority of EMU cases. It is well known that seizures alter breathing and cardiac activity. From numerous studies on cardiorespiratory function in patients monitored in EMUs, the effects on breathing are now known to be more severe and more common than most epileptologists previously thought and, surprisingly, are as common with generalized tonic-clonic seizures as with complex partial seizures. These data are not from SUDEP patients since they did not die, but it is assumed that the post-ictal mechanisms are shared. These findings indicate that respiratory monitoring should be considered for all EMU patients for safety reasons. Respiratory monitoring also would provide the opportunity to learn more about how seizures affect breathing. The field must move past the question of whether death is cardiac or respiratory—it is probably both. We now must define the specific pathophysiologic mechanisms involved, in the CNS or heart, that lead from a seizure to SUDEP.

Animal models have been instrumental in defining the mechanisms of seizure-induced death and identifying the involvement of serotonin (5-HT). It is assumed that the mechanisms of some of these models are shared with human SUDEP. 5-HT$_{2A}$ receptor knockout mice, DBA/1 mice, and DBA/2 mice all have audiogenic seizures that lead to respiratory arrest. Serotonin reuptake inhibitors (SSRIs) prevent death in DBA/1 and DBA/2 mice. This observation led to a human trial that showed SSRIs prevent postictal hypoventilation in EMU patients. Experiments are now needed to measure postictal 5-HT levels in humans and mice and to correlate this data with respiratory depression and EEG flattening. Mice also are being used to study neural pathways from the temporal lobe to the medulla that would explain postictal respiratory depression. Further experiments are needed to better define the role of 5-HT in postictal CNS depression and to discover how serotonergic agents can prevent death. It will also be important to examine interactions between cardiac and CNS mechanisms, particularly the role of long QT mutations in brainstem cardiorespiratory control.
Serotonin (5-HT) is a key regulator of breathing and wakefulness. We have used a mouse model in which nearly all CNS 5-HT neurons have been genetically deleted during embryogenesis. Seizures induced by maximal electroshock in these mice are more severe than in WT mice and mortality is greater. After those seizures that resulted in death, there was immediate flattening of EEG activity, lack of recovery of spontaneous breathing, and persistence of cardiac activity for up to 6 minutes after the last breath. These mice also had a phenotype suggestive of sudden infant death syndrome (SIDS) in which they had a high neonatal mortality. This discovery led to assessment of a possible link between SUDEP and SIDS. Many similarities were found, including a defect in 5-HT function. Our hypothesis for SUDEP is that seizures activate a descending pathway that inhibits 5-HT and possibly other monoamine neurons that are part of the ascending arousal system. The result is depression of wakefulness and respiratory dysfunction, both of which recover over the next minutes to hours. In SIDS, 5-HT neuron dysfunction is due to brainstem immaturity made worse by sleep. Alternatively, some cases of SIDS may be due to seizures in infants manifest only as apnea. Future work will need to better define the pathology of SUDEP brainstems, including the neurochemical anatomy of the medullary respiratory network, and should further examine the possibility that SIDS and SUDEP are two manifestations of a similar pathology of monoamine neurons.

Finally, a mechanistic relationship might exist with two other comorbidities discussed in this session: sleep and depression. Both are associated with 5-HT, suggesting that one underlying brainstem 5-HT defect could lead to epilepsy, depression and sleep disorders, and a predisposition to SUDEP.
SESSION 4: What Do We Mean by Cures?
Special Considerations for Epilepsy Therapy Early in Life: Impact on Brain Development and Long-Term Outcomes

Karen Gale, Georgetown University.

Seizures and epilepsy occur at an especially high rate in infancy, so effective and safe treatments for the developing brain are urgently needed. Because the developing brain is highly vulnerable to molecular and physiologic alterations, even transient interventions during sensitive developmental periods can have long-lasting functional consequences. The goal of therapy during pregnancy or early life should be to prevent seizures and their short- and long-term adverse consequences without disrupting the normal maturation of the fetal or infant brain. Thus, we need information about side effects of early-life therapy that may not appear until later in life, long after the treatment has been discontinued—long-lasting effects triggered by changing the developmental process. Because the effects of treatments, seizure history, and underlying neurologic conditions are difficult to disentangle in the clinical context, research in animal models provides essential insights. During the period of the "brain growth spurt," many antiepileptic drugs, anesthetics, alcohol, and sedatives cause a striking increase in neuronal apoptosis and lead to long-term behavioral abnormalities, but these abnormalities also can occur after exposure to doses that do not induce apoptosis. A single acute exposure to lamotrigine, phenobarbital, or phenytoin can alter the normal pattern of synaptic maturation of GABAergic and glutamatergic neurons, revealing a functional neurotoxicity that is detected in surviving neurons. However, the fact that this effect can be prevented by pretreatment with the neuroprotective agent melatonin and the fact that exposure to levetiracetam does not cause this toxicity offers the prospect that careful treatment choice or adjunct neuroprotective therapies may minimize developmental neurotoxicity, thereby allowing a broader choice of intervention for treating seizures in pregnancy and infancy. These findings underscore the need to identify and develop novel therapeutic strategies that prevent seizures without impeding synaptic maturation in the developing brain.
Improvements in the Localization of the Epileptogenic Focus

Ruben Kuzniecky, New York University Comprehensive Epilepsy Center, NYU School of Medicine.

The advent of modern neuroimaging and electrophysiologic techniques has had a major impact on epilepsy, in particular on the management of intractable epilepsy.

Current imaging techniques can detect focal structural lesions with sensitivities from 60% to 95% for patients with mesial temporal lobe sclerosis, malformations of cortical development, trauma, tumors, and other lesions. Magnetic resonance techniques such as MR spectroscopy, functional MRI, and MR connectivity (MRC) are additional tools used for localization. Through the addition of imaging and electrophysiologic techniques to the armamentarium, predictive algorithms and treatment strategies that go beyond the simple diagnosis and detection of epileptogenic lesions have been developed.

The combination of different imaging and electrophysiologic modalities has increased the sensitivity of localizing techniques in epilepsy. The co-registration of functional images such as PET, fMRI, ictal SPECT, fMRI/EEG, and MEG is now possible and allows mapping of the epileptogenic zone and network in great detail. MicroEEG studies with more than 200 channels and high sampling rates are allowing high-resolution mapping of epileptogenic areas.

Further improvements in hardware and software will enhance the likelihood of cellular and molecular imaging in the very near future and improve the detection of the epileptogenic focus while increasing our understanding of epilepsy as a focal and network disorder.
Resective epilepsy surgery is currently the only effective cure available for medically refractory epilepsy. In well-selected patients, long-term total seizure control can be achieved in up to 40% to 80% of patients. Despite randomized trials and medical guidelines, epilepsy surgery has continued to be significantly underutilized as a treatment option over the past two decades in the United States.

An important reason is patient and provider perceptions regarding the risks related to surgery. A major advance in the past decade has been the development of “minimally invasive” surgical approaches. For mesial temporal sclerosis, new selective surgical treatment options are being developed, including subtemporal selective amygdalohippocampectomy and MRI-guided thermoablation. Stereotactic radiosurgery and transcranial-focused ultrasound are also promising directions for nearly noninvasive treatment. These new directions have the promise of fewer adverse effects compared with the already low risks associated with standard temporal lobectomy and are currently being validated.

Successful outcomes in epilepsy surgery rely on (1) the localization of the epileptogenic zone and (2) the identification of at-risk eloquent brain regions. Significant progress has been made with regard to both of these goals, and we will review important advances for interrogating functional brain regions using new indices of cortical function of cognition such as high-frequency spectral mapping.

Finally, more research is needed to understand why epilepsy surgery remains underutilized and out of reach for many patients, especially compared with other treatment options with equal or poorer effectiveness. We must address awareness and education among patients and providers, pharmaceutical and device industry influence, and socioeconomic barriers to care.
Epilepsy Device and Engineering Advances: Near-Term Applications

Brian Litt, University of Pennsylvania.

One of the most successful areas of clinical translation in epilepsy research is in antiseizure devices and the engineering behind them. Two automated implantable devices, the “open loop” anterior thalamic nucleus stimulator and the “closed loop” cortical/hippocampal responsive neurostimulation device, have completed pivotal human trials and FDA panel review and are nearing approval or have been approved in Europe or the United States. Other devices for cranial nerve stimulation continue to evolve in human therapy. Rapid engineering advances to define epileptic networks using high-resolution, high-bandwidth electrophysiology, new hardware, classification/control algorithms, and mining “big” neural data are rapidly advancing the capability and hopefully the efficacy of these devices. New fields, such as optogenetics, bioelectronics and nanotechnology, ensure a rich pipeline of technologies for nearer term translation. Epilepsy will provide a preferred platform for testing these technologies in brain-network disorders.
Dietary Therapies: Optimizing Efficacy and Extending Clinical Applicability

Jong Min Rho, University of Calgary.

The most recognized and validated metabolism-based treatment for medically refractory epilepsy is the ketogenic diet (KD)—a formulation originally designed to mirror the biochemical changes associated with fasting. Despite growing international use of KD and its variants (i.e., medium chain triglyceride diet, modified Atkins diet, low-glycemic index therapy) and a greater clinical appreciation of both their indications and drawbacks, much remains unknown about their underlying mechanisms. Hence, although both clinicians and scientists have sought to improve the efficacy and tolerability of KD, substantially improved formulations (and certainly the lofty goal of creating a “KD in a pill”) have not yet been forthcoming. Efforts to optimize the clinical effectiveness of the diet rests on two principal strategies: (1) prospective controlled clinical studies designed to reveal optimum dietary constituents and formulations (e.g., types of fats, the ratio of fat to carbohydrate plus protein, protocols for administration)—an approach fraught with the limitations of serendipitous screening despite a well-framed rationale, and (2) an elucidation of key molecular and cellular mechanisms (which would be predicted to lead to novel therapeutic interventions, either dietary or otherwise, but are constrained by the usual bench-to-bedside resource needs and timelines). Studies to date suggest that the clinical effects of different dietary treatments for epilepsy are somewhat comparable, and basic science investigations have taught us that multiple parallel (and possibly synergistic) mechanisms might contribute to seizure control. Given this scenario, how could one significantly improve dietary and/or metabolism-based treatments for patients with epilepsy in an expeditious manner? Interestingly, despite clinical evidence suggesting that ketone bodies (KBs; beta-hydroxybutyrate, acetoacetate, and acetone) measured in blood and urine do not correlate well with seizure control, emerging laboratory data are demonstrating a potentially key antiseizure role for KBs. Notably, KBs have recently been implicated in the activation of ATP-sensitive potassium channels, blockade of vesicular glutamate release, and inhibition of histone deacetylases—all of which could render antiseizure, neuroprotective, and homeostatic effects on neuronal function. Furthermore, our laboratory showed earlier that KBs raise the threshold for mitochondrial permeability transition (mPT) pore activation, and in unpublished experiments, we have found that seizure control can be afforded by pharmacologic inhibition of mPT in a developmental animal model of epilepsy and that the antiseizure effects of KD can be reversed by concomitant drug-induced activation of this mitochondrial target. What is perhaps most intriguing about recent mechanistic studies of KD is the evidence for its broad neuroprotective properties and, in turn, emerging clinical and experimental data supporting its use in multiple neurological disorders, such as Alzheimer’s disease, Parkinson’s disease, brain cancer, neurotrauma, multiple sclerosis, and pain. The enormous spectrum of pathophysiologic mechanisms proposed for the aforementioned diseases would suggest a degree of complexity that cannot be affected universally by any single dietary treatment. However, because bioenergetic dysfunction has been observed for all such conditions, dietary therapies may affect the ultimate outcome of these diverse disorders, and a final common neurometabolic pathway influenced by a variety of dietary interventions might indeed exist. Much remains to be learned about epilepsy—in terms of both seizure genesis and epileptogenesis—from the study of other neurological disorders. I In turn, metabolism-based treatments such as KD may afford a degree of
disease modification in a multiplicity of neurological conditions. Ironically, accelerated progress in identifying novel therapeutic approaches toward epilepsy—aimed at providing pathways to cures—might come from the lessons provided by a nonpharmacologic treatment that is nearly 100 years old.
SESSION 5: What Do New Paths to Cures Look Like?
Exploiting Knowledge of the Molecular Pathology of Sodium Channel–Based Epilepsies for Therapy

Steven Petrou, University of Melbourne.

Epileptic encephalopathies, including Dravet syndrome, are severe treatment-resistant epilepsies with developmental regression. We examined a mouse model based on a human β1 sodium channel subunit mutation. Homozygous mutant mice shared phenotypic features and pharmacosensitivity with Dravet syndrome. Patch-clamp analysis showed that mutant subicular and L2/3 pyramidal neurons had increased action potential firing rates, presumably as a consequence of their increased input resistance. In contrast, CA1 pyramidal neurons from homozygous mutants had a distinct phenotype, with a reduction in AP firing rate and amplitude at higher stimulating currents indicating that the mutation has region-specific effects. Importantly, no changes in the firing properties of GABAergic neurons from mutant mice were observed, in contrast with Scn1a-based models of Dravet syndrome. Morphological analysis of subicular pyramidal neurons revealed reduced dendritic arborisation. The antiepileptic drug retigabine, a K+ channel opener that reduces input resistance, dampened action potential firing and, moreover, protected mutant mice from thermal seizures. These results suggest a novel mechanism of disease genesis in genetic epilepsy and demonstrate effectiveness of a disease mechanism-based therapy.
Mechanism-Based Therapies in Tuberous Sclerosis Complex

Mustafa Sahin, Boston Children's Hospital.

Tuberous sclerosis complex (TSC) is an autosomal dominant disease that affects about 1 in 6,000 people and represents one of the most common genetic causes of epilepsy. TSC is caused by mutation of one of two genes, TSC1 and TSC2, and is characterized by formation of benign tumors or hamartomas in multiple organs, such as the brain, skin, eyes, kidneys, and heart. Although many organs can be affected, neurological manifestations of TSC are usually associated with the highest morbidity. Individuals with TSC can present with epilepsy, intellectual disability, and autism spectrum disorders. Epilepsy is particularly common, affecting about 80% of individuals with TSC. In addition, it is usually severe and refractory to pharmacologic treatments.

A groundbreaking discovery in the pathophysiology of TSC was the direct regulation of the mammalian target of rapamycin (mTOR) pathway by the TSC genes. Proteins encoded by the TSC1 and TSC2 genes form a heterodimer that inhibits the mTOR pathway. The TSC-mTOR pathway controls cellular growth and differentiation in response to extracellular growth factor stimulation, nutrient availability, and intracellular energy status by regulating protein synthesis. Interestingly, in neurons, the TSC-mTOR pathway also is linked to specification of neuronal polarity, axonal guidance, dendritic complexity, and myelination. Hyperactivation of the mTOR pathway is hypothesized to be responsible for many, if not all, of the clinical and pathophysiologic features of TSC, including tumor growth and epilepsy. The identification of the mTOR pathway in the pathophysiology of TSC has had direct therapeutic implications, as mTOR inhibitors in the same class as rapamycin are now available to be tested as potential rational therapies for TSC. In fact, an mTOR inhibitor, everolimus, has recently been shown to decrease subependymal giant cell astrocytoma (SEGA) and renal angiomyolipoma growth in TSC patients, leading to FDA approval for these indications.

Overall, TSC may represent a model disease for investigating and developing antiepileptogenic therapies for several reasons. First, TSC patients are at extremely high risk for developing epilepsy (about 80%), including infantile spasms (about 35%), which is a particularly devastating type of childhood epilepsy with a poor prognosis. Thus, initiating a therapy with potential side effects in a presymptomatic stage can likely be justified in TSC patients. Second and very important, many patients can be diagnosed with TSC before birth or at the time of birth because of the presence of cardiac rhabdomyomas. It is therefore feasible to identify these patients and initiate a potential antiepileptogenic treatment at an early stage of epileptogenesis. Third, the identification of the mTOR pathway in the pathophysiology of TSC suggests that mTOR inhibitors could have antiepileptogenic properties in TSC. In fact, several preclinical studies using various mouse models of TSC strongly support the efficacy of mTOR inhibitors in preventing or stopping TSC-related seizures. Therefore, a rational, mechanism-based treatment potentially already exists and can be readily tested in TSC patients. Furthermore, progress made in antiepileptogenesis in TSC also may have broader applications to other epilepsy syndromes, such as post-traumatic epilepsy, because the mTOR pathway has been hypothesized to be involved in epileptogenesis in other types of epilepsy as well.
Translation in Fragile X Syndrome

Mark Bear, Massachusetts Institute of Technology.

Transcriptional silencing of the FMR1 gene is responsible for fragile X (FX), the most common inherited cause of intellectual disability and autism. Two key discoveries led to the current understanding of FX pathophysiology and the prospects for novel disease-modifying treatments. First, it was shown that the protein product of FMR1, FMRP, is an mRNA binding protein that functions to repress translation. Second, it was shown that a functional consequence of protein synthesis stimulated by activation of metabotropic glutamate receptor 5 (mGluR5) is long-term synaptic depression (LTD) and that LTD is exaggerated in the mouse model of FX, the Fmr1 knock-out (KO). Together, these findings suggested that exaggerated protein synthesis downstream of mGluR5 may be pathogenic and contribute to the symptoms of FX. This “mGluR theory” of fragile X has now been tested in animal models of FX (fly, fish, and mouse), and to date more than 40 distinct mutant phenotypes, including seizures, have been ameliorated or corrected by inhibition of mGluR5 signaling. These findings suggest that exaggerated consequences of mGluR5 activation provide a thread that connects widely varied symptoms of the disease and, furthermore, that an evolutionarily conserved relationship exists between FMRP and mGluR5. Human clinical trials with inhibitors of glutamate signaling and mGluR5 are underway, and preliminary results are encouraging. We stand at the threshold of fulfilling the promise of molecular medicine in fragile X. Because FX is a cause of autism, the question naturally arises as to whether FX and autism of other etiologies share a common pathophysiology, in which case they might respond to similar treatments.
Clinical Trials of Therapies for Specific Syndromes and Antiepileptogenesis

Jacqueline A. French, New York University School of Medicine.

It is hoped that over the next several decades a number of promising candidates will be put forward for both antiseizure treatment and potential disease-modifying and antiepileptogenic therapy. However, for these therapies to be successfully translated to the clinic, they will have to proceed through the "gauntlet" of phase I, II, and III clinical trials acceptable to the U.S. Food and Drug Administration for registration. It will be important to create phase II trial designs that have high sensitivity and specificity for good candidates. (In other words, they will rapidly identify the most promising candidates while not inappropriately rejecting potentially useful drugs.) This will be easier for antiseizure drugs than for antiepileptogenic or disease-modifying therapies, for which phase II trial designs are lacking. Unfortunately, even good drug candidates that performed well recently in phase II trials failed to separate from placebo during larger phase III trials. This was likely due to an increase in patient heterogeneity.1 Continued attention to this issue will be needed, and hopefully mechanisms will be put in place that will reduce the chances of trial failure.

Clinical trials to prove antiepileptogenic/disease-modifying activity of a drug remain particularly difficult. Issues to be considered in design of such trials include (1) Pre-clinical model: How closely related is the model to the patient population? Is the degree of injury similar to humans? When are you intervening? Is it consistent with possible timing of intervention in humans? (2) Clinical population: How many patients are available? Of those, what percentage will develop epilepsy? Where are the patients? Could they be identified in time to administer an intervention? When do you intervene? For how long? (3) Proposed intervention: Is it a novel therapy or an established agent? Is there known (or unknown) risk? Will physicians be willing to administer in a population who may or may not develop epilepsy?

In summary, it is important to consider future trial designs even during the preclinical phases of development of an antiseizure, antiepileptogenic, or disease-modifying drug.
Prevention Strategies for Acquired Epilepsies

Raymond Dingle, Emory University School of Medicine.

It has not been for lack of trying that effective epilepsy prevention therapies have so far been elusive. Several lessons can be gleaned by the nearly 50 antiepileptogenesis clinical trials that have failed to show efficacy. First, we need novel molecular targets that go beyond ion channels. The gradual process of lowering the seizure threshold to the point at which spontaneous seizures appear (i.e., epileptogenesis) is likely to involve quite different molecular mechanisms from those responsible for the end-state hyperexcitable condition (i.e., epilepsy). Second, the typically long lead time between an initiating brain insult and the development of epilepsy will, for economic reasons, probably force the development of surrogate biomarkers for an epilepsy prevention clinical trial. Biomarker selection and validation is itself a considerable undertaking. Third, more attention should be paid to aligning animal models with the clinical question. Retrospective epidemiologic studies indicating that prolonged status epilepticus (SE) increases risk for epilepsy, together with the common experimental observation that a variety of animal models of SE result in epilepsy, suggest that therapies effective in animal models of SE should be predictive for the human condition. Two strategies have emerged for animal model studies: (1) seek convergence of mechanism among diverse animal models to avoid the need to match model to human and (2) select or develop a model that aligns best with the specific clinical phenotype for which a trial is being designed. Considerable heterogeneity exists among animal models of SE and human SE; the question concerns which animal model features are most relevant to human SE.

Retrospective studies of refractory temporal lobe epilepsy in adults revealed strong association with febrile status epilepticus (FSE) in childhood. The FEBSTAT (Consequences of Prolonged Febrile Seizures) study is prospectively addressing the relationships among EEG and MRI biomarkers and clinical follow-up (cognition, epilepsy) in a cohort of 199 children who have experienced FSE. FEBSTAT is now in its 10th year and could provide a foundation on which to design a clinical trial for acquired epilepsy. A major consideration in design of a clinical prevention trial is the challenge of identifying the child most likely to develop epilepsy. The MRI findings are particularly intriguing for biomarker identification because early hippocampal T2 abnormalities (24 to 96 hours after FSE) were followed by evidence of hippocampal CA1 damage in a subset of children. Memory testing of these children is underway and should allow determination of whether MRI abnormalities portend cognitive deficits in children with FSE. The occurrence of epilepsy itself in this cohort will be followed over time. A recent independent study linked long-term memory deficits in children to the degree of hippocampal volume reduction after FSE, further supporting an imaging biomarker for early signs of hippocampal damage that might predispose to development of epilepsy. The frequent observation of hippocampal sclerosis in mesial temporal lobe epilepsy also supports the logic of using a T2 signal abnormality as a biomarker of epilepsy. Additional biomarkers that would be worth examining after FSE are the occurrence of abnormal EEG signals and levels of inflammatory cytokines in CSF or plasma. Brain inflammation is prominent in both man and rodent after most acquired epilepsies, and some inflammatory mediators (e.g., IL-1β) are known to enhance neuronal excitability and epileptogenesis in rodent models.

The study of animal models of FSE in rat pups and SE in adults is pointing to a variety of novel molecular targets that should be evaluated carefully for potential clinical therapy development. These targets
include TrkB; selected inflammatory mediators, including the prostanoid receptor EP2, caspase-1, and Toll-like receptor 4; the apoptosis-promoting BAD protein; effector enzymes of the transcriptional repressor REST (e.g., histone deacetylase 1 and 2, the G9a histone methyltransferase, and LSD1 demethylase); and mTOR.
Novel Opportunities for Disease Modification

Annamaria Vezzani, Mario Negri Institute for Pharmacological Research.

The search for antiepileptogenic treatments in experimental models of genetic or symptomatic forms of epilepsy has revealed that some of the attempted interventions, although not preventing the development of epilepsy, have indeed caused disease-modifying effects. This definition applies to therapeutic strategies that ameliorate the pathologic outcomes resulting from epileptogenesis, such as neuronal cell loss, severity of spontaneous seizures, and comorbidities. Disease-modifying treatments have been so far identified when given to animals early after injury, thus before the development of spontaneous seizures. The novel concept that epileptogenesis extends far beyond the onset of the first spontaneous seizures potentially extends the therapeutic window of intervention with disease-modifying treatments. Experimental models have given insights into the progressive phase of epilepsy after the onset of seizures as assessed, for example, by monitoring the frequency of seizures in epileptic animals over time or by MRI imaging of progressive anatomical brain modifications, some of which are also reflected in the clinical setting.

The molecular mechanisms underlying disease progression are still elusive, although for some of them a contributing role is highly suspected. Notable examples are the progressive compromission of blood-brain barrier function associated with angiogenesis and serum albumin extravasation in brain. In this context, VEGFR2 and TGF-betaR1/2 have been proposed as promising targets for resolution of the pathologic events. Intervention on mTOR pathway activation after seizure onset has been shown in some experimental and clinical settings to resolve neuropathologic features although reversibly. Gene therapy applied in already epileptic rats to augment the endogenous NPY levels provided evidence of arrest of disease progression. Evidence that epileptic phenotype of loss-of-function mutations might be attenuated by interactions with associated proteins and drugs opens up new perspectives for therapeutic “rescue strategies” also in genetic forms of epilepsy. Intervention with specific anti-inflammatory treatments also might be envisaged as a way to increase seizure threshold during the course of the disease by reversing, for example, salient pathologic features of hyperexcitability such as acquired channelopathies. Indepth characterization of disease progression in animal models of epilepsy and better understanding of the underlying molecular mechanisms are key priorities in experimental research for highlighting targets for therapeutic intervention that favorably modify the disease after epilepsy diagnosis.
A. James Barkovich, M.D.
University of California, San Francisco

A. James Barkovich, M.D., received his education at the University of California, Davis; the University of California, Berkeley; and George Washington University. He trained in radiology and neuroradiology before beginning his academic career at the University of California, San Francisco in 1986. He has been professor of radiology, neurology, pediatrics, and neurosurgery since 1994. During his training, Dr. Barkovich developed a lifelong interest in mechanisms of brain development and the way in which perturbations of those mechanisms alter normal development. This interest led to studies in developmental (genetic and disruptive) disorders of brain development, including malformations and injuries incurred during various stages of development. In particular, it is clear that different mechanisms and different genetic mutations can result in similar brain phenotypes (as assessed by MRI techniques) in the child. To organize these many different malformations and their causes, a classification of malformations of cortical development (MCD) was developed and has been updated many times. Epilepsy is common in people with MCD, and study of the causes of these malformations and their effects on cell structure and function in the central nervous system is important in the understanding of epilepsy. Currently, Dr. Barkovich is focusing on the effects on metabolic and molecular pathways of both genetic and acquired factors involved in developmental abnormalities, with the goal of understanding the optimal points of intervention, while at the same time improving tools (in particular imaging) to assess the effects of these interventions.
Mark Bear, Ph.D.
Massachusetts Institute of Technology

Mark Bear, Ph.D., is an investigator at the Howard Hughes Medical Institute and Picower Professor of Neuroscience in the Picower Institute for Learning and Memory, Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology. Dr. Bear served as director of the Picower Institute from 2007 to 2009. Before moving to MIT in 2003, Dr. Bear was on the faculty of Brown University School of Medicine for 17 years. After receiving his B.S. degree from Duke University, he earned his Ph.D. in neurobiology at Brown. He took postdoctoral training from Wolf Singer at the Max Planck Institute for Brain Research in Frankfurt, Germany, and from Leon Cooper at Brown. Dr. Bear’s laboratory has substantially advanced knowledge of the way in which the cerebral cortex is modified by experience. He made fundamental discoveries on bidirectional synaptic plasticity, metaplasticity, the molecular basis of amblyopia (a cause of visual disability in children), and the pathophysiology of fragile X syndrome (the most common inherited cause of intellectual disability and autism). Dr. Bear has been at the forefront of the efforts to translate knowledge of autism pathophysiology into new treatments.
Anne T. Berg, Ph.D.
Lurie Children’s Hospital

Anne T. Berg, Ph.D., oversees the daily workings of the study in conjunction with the project director and coordinates what has become a multi-institutional and international collaboration of investigators. She is actively involved in analyses and writing of papers as well as collaborating with, supervising, or in other ways participating in efforts by collaborators to do the same. Dr. Berg is an epidemiologist who specializes in the study of epilepsy and in particular on applying relevant clinical concepts to epidemiology studied in the general population. She is the original and continuing principal investigator of the Connecticut Study of Epilepsy (first funded in 1993) and one of the founding investigators of the Multicenter Study of Epilepsy Surgery. Her work has spanned several areas within epilepsy, including a detailed evaluation of seizure outcomes in epilepsy that has helped lead to a consensus definition of pharmacoresistant epilepsy; the cognitive, behavioral, and psychiatric comorbidities and increased risk of mortality associated with epilepsy; the natural history of hippocampal sclerosis and other hippocampal abnormalities, imaging markers, and correlates of "image-negative" epilepsy; and the use of clinically important electroclinical diagnoses in population-based studies. The last area has become a major focus of Dr. Berg’s international activities in classification of epilepsy and seizures. Some of the resulting concepts and published recommendations are being incorporated into the NINDS CDE vocabulary as well as the new ICD-11 codes for epilepsy.
Samuel F. Berkovic, A.M., M.D., F.A.A., FRACP, FRS
University of Melbourne

Samuel F. Berkovic, A.M., M.D., F.A.A., FRACP, FRS, is Laureate Professor in the Department of Medicine, University of Melbourne, and director of the Epilepsy Research Centre at Austin Health. He is a clinical neurologist and clinical researcher with a special interest in establishing close research links with basic scientists. His group, together with molecular genetic collaborators in Adelaide and Germany, discovered the first gene for epilepsy in 1995 and subsequently was involved in the discovery of many of the known epilepsy genes. This work has changed the conceptualization of the causes of epilepsy and is having a major impact on epilepsy research and on strategies for diagnosis and development of new treatments. Dr. Berkovic is currently a principal investigator of Epi4K, the NINDS Epilepsy Center Without Walls. He also has active research interests in surgical evaluation and outcomes, new onset seizures, treatment of epilepsy, and imaging in epilepsy. In Australia, he heads a large program grant integrating genetic, imaging, and physiological studies in epilepsy. Dr. Berkovic was elected a Fellow of the Royal Society in 2007.
Geraldine Bliss, M.S.
Phelan-McDermid Syndrome Foundation

Geraldine Bliss, M.S., chairs the research support committee of the Phelan-McDermid Syndrome Foundation. She lives in Houston with her husband and two sons. Her 14-year-old son has a partial deletion of the SHANK3 gene, autism, and refractory epilepsy. His severe struggles with seizures compelled Ms. Bliss to become highly involved as a patient advocate. She has a B.S. in economics from Trinity University and an M.S. in health and human performance (human factors) from the University of Houston.
Amy Brooks-Kayal, M.D.
Children’s Hospital Colorado

Amy Brooks-Kayal, M.D., is professor of pediatrics, neurology, and pharmaceutical sciences and chief and Ponzio Family Chair of Pediatric Neurology at the University of Colorado School of Medicine and Children's Hospital Colorado. Dr. Brooks-Kayal trained at Johns Hopkins University, the University of Pennsylvania, and Children's Hospital of Philadelphia. She joined the University of Colorado in 2008 after 13 years on the faculty at the University of Pennsylvania and Children’s Hospital of Philadelphia. Her area of clinical focus is pediatric epilepsy. Her research focuses on the effects of seizure activity on neurotransmitter systems, with particular emphasis on understanding the regulation of GABAA receptor expression in development and epileptogenesis, a topic on which she has published extensively.

Dr. Brooks-Kayal has been an active member of the Child Neurology Society for more than 15 years and has served on a number of committees and task forces, including the awards committee and the Phillip R. Dodge Young Investigator Award and Child Neurology Foundation Award Review Committees.

Dr. Brooks-Kayal is the second vice-president and chairs the Merritt-Putnam Symposium and COI Committees of the American Epilepsy Society. She is a member of the Executive Council of the American Neurological Association and the Professors of Child Neurology and is a former member of the Society of Neuroscience Program Committee. She acted as a session chair and organizer for the NIH Curing Epilepsy II conference and is currently co-chair and steward for the NINDS Epilepsy Research Benchmark III.

Dr. Brooks-Kayal has served on a number of other national scientific committees, including membership on NIH study sections, the Epilepsy Foundation Research Committee and Scientific Advisory Boards for Citizens United for Research in Epilepsy (CURE), and the National EpiFellows Foundation. She is the past associate editor for pediatric and developmental epilepsy for the journal Epilepsia and provides reviews for several other medical and scientific journals.
Paul Buckmaster, D.V.M., Ph.D.
Stanford University

Paul Buckmaster, D.V.M., Ph.D., is a professor of comparative medicine at Stanford University. He obtained a doctorate in veterinary medicine at the University of California Davis and a Ph.D. in physiology and biophysics at the University of Washington. Dr. Buckmaster’s research focuses on mechanisms of temporal lobe epilepsy. His laboratory uses electrophysiological and anatomical techniques.
Edward Chang, M.D.
University of California, San Francisco

Edward Chang, M.D., is associate professor of neurological surgery and chief of epilepsy surgery at the University of California, San Francisco. He specializes in neurophysiologic brain mapping methods, including awake speech and motor mapping, to safely perform neurosurgical procedures in eloquent areas of the brain. Dr. Chang directs a clinical research program that focuses on outcomes, decision-making, and safety improvement of cutting-edge treatments for epilepsy. His basic research laboratory is dedicated to discovering the basic cortical mechanisms of speech processing and transforming those insights to innovative new brain mapping algorithms. Dr. Chang is the recipient of the NIH Director’s New Innovator Award, Klingenstein Fellowship, and Young Investigator Award from the American Epilepsy Society.
Francis S. Collins, M.D., Ph.D.
National Institutes of Health

Francis S. Collins, M.D., Ph.D., is the director of the National Institutes of Health (NIH). In that role, he oversees the work of the largest supporter of biomedical research in the world, spanning the spectrum from basic to clinical research. Dr. Collins is a physician-geneticist noted for his landmark discoveries of disease genes and his leadership of the international Human Genome Project, which culminated in April 2003 with the completion of a finished sequence of the human DNA instruction book. He served as director of the National Human Genome Research Institute at NIH from 1993 to 2008. Before coming to NIH, Dr. Collins was a Howard Hughes Medical Institute investigator at the University of Michigan. He is an elected member of the Institute of Medicine and the National Academy of Sciences, was awarded the Presidential Medal of Freedom in November 2007, and received the National Medal of Science in 2009.
Douglas Coulter, Ph.D.
Children’s Hospital of Philadelphia

Douglas Coulter, Ph.D., received his Ph.D. from the Boston University Marine Program at the Marine Biological Laboratories in Woods Hole, MA. He began his career-long interest in studying the mechanisms of epilepsy during postdoctoral training in the laboratory of Dr. David Prince at Stanford University Medical Center. Dr. Coulter has maintained this research focus on epilepsy over the past 20+ years in his own laboratory, first at the Virginia Commonwealth University Medical College of Virginia and subsequently at the Children’s Hospital of Philadelphia/University of Pennsylvania School of Medicine, where he has been for the past 14 years.
Peter Crino, M.D., Ph.D.
Temple University

Peter Crino, M.D., Ph.D. received his Ph.D. degree in behavioral neuroscience from Boston University and his M.D. degree from Yale. Following a neurology residency at the University of Pennsylvania, he was a Howard Hughes postdoctoral fellow in the Department of Pharmacology. He completed a clinical epilepsy fellowship at the University of Pennsylvania and joined the neurology faculty in 1997, where he was associate professor in neurology until 2012 and served as the director of the Epilepsy Center from 2006 to 2012. Dr. Crino is currently head of the Brain Injury and Plasticity Group at the Shriners Hospitals Pediatric Research Center and professor and vice chair for research in the Department of Neurology at Temple University School of Medicine.
Josep Dalmau, M.D., Ph.D.
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Josep Dalmau received his M.D. and Ph.D. from the Autonoma University of Barcelona, where he completed a residency in neurology. He trained in neuro-oncology at Memorial Sloan-Kettering Cancer Center in New York and afterward was appointed to the faculty. Dr. Dalmau is currently adjunct professor of neurology at the University of Pennsylvania and research professor at the Catalan Institution for Research and Advanced Studies in IDIBAPS, University of Barcelona. His research is funded by NIH and the Spanish Health Institute. He also has been funded by the Charles A. Dana Foundation, the McKnight Foundation, the American Cancer Society, and the Marató TV3. Dr. Dalmau’s work has revealed a new category of disorders mediated by antibodies to neuronal cell surface and synaptic proteins, for which he has received multiple awards, including among others the distinguished George W. Jacoby Award of the American Neurological Association.
Raymond Dingledine, Ph.D.
Emory University School of Medicine

Raymond Dingledine, Ph.D., serves as chair of pharmacology and executive associate dean for research in the School of Medicine at Emory University. Dr. Dingledine received his Ph.D. in pharmacology under Avram Goldstein at Stanford in 1975. He received postdoctoral training from Leslie Iversen and John Kelly at Cambridge, UK (1975–1977), then Per Andersen at Oslo (1977–1978). Dr. Dingledine joined the Department of Pharmacology at the University of North Carolina at Chapel Hill in 1978 and rose to professor. During this time, he spent a sabbatical year in Steve Heinemann’s lab at the Salk Institute in 1990–1991. He moved to Emory University in 1992 as chair of pharmacology. Dr. Dingledine’s research focuses on the pharmacology of glutamate receptors and on the causes of epilepsy. His work as a whole integrates information from a variety of experimental strategies to contribute to a better understanding of the neurobiology of epilepsy. His work has broad implications for other brain disorders including stroke and schizophrenia. Dr. Dingledine was editor of Molecular Pharmacology; under his editorship, the journal had the highest citation index worldwide of primary pharmacology journals. His career was profiled in Nature Medicine in 2002 (vol. 8, p. 772). He received a Javitts Award from NINDS and the Basic Epilepsy Research Award from the American Epilepsy Society. In 2010, Dr. Dingledine was elected to the Institute of Medicine of the National Academies of Science.
Daniel Drane, Ph.D.
Emory University School of Medicine

Daniel Drane, Ph.D., is board certified in clinical neuropsychology through the American Board of Professional Psychology and currently serves as an assistant professor of neurology and pediatrics at Emory University School of Medicine. Dr. Drane maintains an affiliate associate professor position at the University of Washington School of Medicine in Seattle, where he served as the director of the Epilepsy Neuropsychology Program from 2001 to 2007. Dr. Drane received his doctorate degree in clinical psychology from Fuller Graduate School of Psychology, completed a residency in neuropsychology at the University of Alabama at Birmingham, and held a 2-year fellowship at the Medical College of Georgia. He is a fellow in the National Academy of Neuropsychology and Division 40 (Neuropsychology) of the American Psychological Association. Dr. Drane has authored a number of articles related to predicting and improving epilepsy surgery outcome, with a particular emphasis on studying the neural substrates of object naming, object recognition, and semantic memory. His work combines the use of cognitive assessment and neuroimaging procedures (e.g., diffusion tractography, quantitative MRI [volumetric] analysis, and functional imaging) to understand the interplay of neural networks underlying these functions and to use this knowledge to guide surgical intervention. Dr. Drane currently has a K02 award from NINDS and previously completed a K23 award granted by the same institution.
Jerome Engel, Jr., M.D., Ph.D.
David Geffen School of Medicine, UCLA

Jerome Engel, Jr., M.D., Ph.D., is director of the Seizure Disorder Center and Jonathan Sinay Distinguished Professor of Neurology, Neurobiology, and Psychiatry and Biobehavioral Sciences at UCLA. He is past president of the American Clinical Neurophysiology Society, American Epilepsy Society, and International League Against Epilepsy (ILAE) and is past co-chair of the Global Campaign Against Epilepsy. His bibliography lists more than 1,000 publications and 30 books, including Epilepsy: A Comprehensive Textbook (2008), The Treatment of Epilepsy (2009), and Seizures and Epilepsy (2013). He is principal investigator on two research grants from NINDS and has received numerous awards and honors, including a Fulbright scholarship, a Guggenheim fellowship, a Javits award, and the ILAE Lifetime Achievement Award.
Robert S. Fisher, M.D., Ph.D.
Stanford University

Robert S. Fisher, M.D., Ph.D., is Maslah Saul Professor of Neurology and director of the Stanford Epilepsy Center. He has won research awards from the Klingenstein Foundation, the Epilepsy Foundation of America, and NIH. Dr. Fisher has published more than 160 peer-reviewed articles and 5 books, and his peers named him to be listed from 1996 to 2012 in *Best Doctors in America*. He received the Ambassador Award from the International League Against Epilepsy (ILAE), the 2005 American Epilepsy Society (AES) Service Award, and the 2006 Annual Clinical Research Award. Dr. Fisher is past president of AES, has served on the board of ILAE, and has served as editor-in-chief of *Epilepsia*. He is immediate past editor-in-chief of the Web site http://www.epilepsy.com. Dr. Fisher’s research covers new devices and drugs to treat epilepsy.
Jacqueline A. French, M.D.
New York University School of Medicine

Jacqueline A. French, M.D., is a professor in the Department of Neurology at the New York University Comprehensive Epilepsy Center and director of the Clinical Trials Consortium, an academic group that has performed a number of early-phase clinical trials in epilepsy. Dr. French trained in neurology at Mount Sinai Hospital in New York and did her fellowship training in EEG and epilepsy at Mount Sinai hospital and Yale University. She is the current president of the American Epilepsy Society and has focused her research efforts on development of new therapeutics for epilepsy and new methodologies for clinical trials. Dr. French has been active in creating guidelines for the American Academy of Neurology (AAN) and the International League Against Epilepsy (ILAE). She chaired an AAN/American Epilepsy Society (AES) committee that produced two widely quoted guidelines on the use of new antiepileptic drugs. The 2005 recipient of the AES Service Award, Dr. French has served on the board of AES and is the past secretary of the American Society of Experimental Neurotherapeutics. In addition, she is the head of the Scientific Advisory Board of the Epilepsy Therapy Project and has served as chair of the ILAE North American Regional Commission and Commission on Therapeutic Strategies. Dr. French has authored more than 150 articles and chapters, is the editor of 3 books, and lectures internationally on clinical trials and the use of antiepileptic drugs.
Aristea Galanopoulou, M.D., Ph.D.
Albert Einstein College of Medicine

Aristea Galanopoulou, M.D., Ph.D., received her medical degree from the Medical School of the National and Kapodistrian University (Athens, Greece), her doctoral degree from McGill University (Montreal, Canada), and has completed an adult neurology residency and clinical neurophysiology fellowship at the Albert Einstein College of Medicine (Bronx NY, USA). Dr. Galanopoulou is currently an associate professor of neurology and neuroscience, co-director of the Laboratory of Developmental Epilepsy, and research director of the Rett Center at the Albert Einstein College of Medicine. Her research focus is the development and utilization of animal models to investigate the pathogenesis of and develop new treatments for early-life epileptic encephalopathies and their comorbidities. In addition, she is investigating the role of GABA_A receptor signaling in the pathogenesis of neonatal status epilepticus and in Rett syndrome. Dr Galanopoulou is a member of committees of the American Epilepsy Society (AES) and the International League Against Epilepsy (ILAE) that aim to improve basic science research and education and preclinical epilepsy therapy discovery. In addition, she co-chairs the Antiepileptic Therapy Symposium Committee of the American Epilepsy Society (AES). Dr Galanopoulou was a co-organizer of the Joint AES/ILAE Translational Workshop to optimize epilepsy therapy discovery (London, 2012). She is a member of the editorial board of, Neurobiology of Disease, Epilepsy Research, and Epilepsy Currents (contributing editor), the professional advisory boards of the Lennox-Gastaut Syndrome Foundation and ESSNY, and the scientific advisory board of the International Rett Syndrome Research Foundation.
Karen N. Gale, Ph.D.
Georgetown University

Karen N. Gale, Ph.D., is professor of pharmacology at Georgetown University, where she has been on the faculty for more than 30 years. As an internationally recognized leader in epilepsy research, Dr. Gale has been continuously funded by NIH for more than 35 years and has authored more than 165 papers on neuroanatomical and molecular substrates of epilepsy and other neurological disorders. Her preclinical studies with vigabatrin were instrumental in the early development of the drug as a treatment for epilepsy, and her lab was the first to identify the substantia nigra and superior colliculus as sites of GABA receptor–mediated seizure control and to define the area tempestas in the piriform cortex of rodents and primates as a site of seizure initiation. In recognition of these achievements, Dr. Gale received the Epilepsy Research Award of the International League Against Epilepsy in 1995. Her recent research on physiological and behavioral outcomes after neonatal exposure to antiepileptic drugs in animal models revealed adverse neurodevelopmental actions of specific medications. As founding director of the Interdisciplinary Program in Neuroscience, Dr. Gale is director of a multi-institute NIH training grant for interdisciplinary predoctoral training in neuroscience. An award-winning mentor, she has trained 14 predoctoral students and 25 postdoctoral trainees and facilitated the career development of numerous faculty.
Alica M. Goldman, M.D., Ph.D.
Baylor College of Medicine

Alica M. Goldman, M.D., Ph.D., is a neurologist with an active clinical practice specializing in the management of patients with epilepsy at the Comprehensive Epilepsy Program at Baylor College of Medicine. She has long-standing NINDS-funded research in sudden unexpected death in epilepsy (SUDEP), which was initiated through funding from the American Epilepsy Society/Epilepsy Foundation and continued and fully developed through the K08 Clinical Scientist Training Award. During her research, Dr. Goldman discovered the first candidate SUDEP gene, KvLQT1, under the mentorship of Dr. Jeffrey L. Noebels. Dr. Goldman is a NINDS-funded independent principal investigator and director of the Translational Epilepsy Neurogenetics Laboratory at Baylor. The molecular/genetic risk factors of SUDEP are the principal focus of her human translational research. In this regard, she has established the STOP SUDEP Program, which comprises a human tissue repository, a registry, and molecular research of SUDEP and involves national and international collaborative efforts in human SUDEP research.
David Goldstein, Ph.D.
Duke University

David Goldstein, Ph.D., is currently the director of the Center for Human Genome Variation (CHGV), the Richard and Pat Johnson Distinguished University Professor, and professor of molecular genetics and microbiology and professor of biology at Duke University. He was previously professor of genetics at University College London and moved to Duke University in 2005. Dr. Goldstein has authored more than 200 scholarly publications in the areas of population and medical genetics. Dr. Goldstein received the Royal Society/Wolfson research merit awards in the UK for work in human population genetics in 2001, the Triangle Business Journal Health Care Heroes Award and Innovator/Researcher Award in 2008, and the University of North Carolina Clinical Services Award in 2012. He currently serves on the NINDS Advisory Council and is current chair of the next Gordon Conference in Human Genetics & Genomics (2013). Dr. Goldstein currently runs a human genetics research center at CHGV, which, in the past several years, has emerged as a leading human genetics research center with a number of seminal discoveries. In particular, CHGV discovered the gene responsible for alternating hemiplegia of childhood, discovered the role of IL28B in treatment response to hepatitis C infection, and was one of the first to demonstrate the potential of next-generation sequencing to diagnose rare genetic conditions including neurological conditions. Dr. Goldstein is also a principal investigator of Epi4K, the NINDS Epilepsy Center Without Walls, and directs the genome sequencing and bioinformatic core of Epi4K. Epi4K is currently the largest epilepsy genetics project in the world and is in the process of generating whole exome and whole genome sequence data on a minimum of 4,000 patients with epilepsy.
Bruce Hermann, Ph.D., University of Wisconsin

Bruce Hermann, Ph.D., is professor and director of the Matthews Neuropsychology Laboratory in the Department of Neurology at the University of Wisconsin School of Medicine and Public Health in Madison, WI. His clinical and research interests have included the cognitive and behavioral effects of the epilepsies in children and adults as well as the neurobehavioral outcomes of epilepsy surgery. Dr. Hermann has served on the board of directors of the American Epilepsy Society and the Epilepsy Foundation (EF) and has chaired the EF Professional Advisory Board. He currently serves on the editorial board of Epilepsy & Behavior and is an associate editor of Epilepsia.
Katie Hood, M.B.A.

Michael J. Fox Foundation for Parkinson’s Research

Katie Hood, M.B.A., is currently a senior fellow and visiting lecturer with the Hart Leadership Program at Duke University’s Sanford School of Public Policy as well as an independent consultant working with philanthropists and nonprofits on projects designed to strengthen their businesses and position themselves to achieve outcomes from their work. She is the former chief executive officer of the Michael J. Fox Foundation (MJFF) for Parkinson’s Research, the largest funder of Parkinson’s research worldwide and one of the most innovative and results-oriented disease-focused foundations driving progress toward cures in the world. During her time as CEO (2007–2011), the Foundation more than doubled its fundraising and grant-making. Ms. Hood joined MJFF in September 2002; before serving as CEO, she served as deputy CEO and vice president of research programs. She is a member of several advisory boards and committees, including the One Love Foundation’s National Advisory Council, Duke University’s New York Women’s Forum Executive Committee, and the Fund Board of Jansen Hospice and Palliative Care. She is also a member of the MJFF’s Founder’s Council and has served as a member of the NINDS Advisory Council at NIH and as a board member of the Parkinson’s Action Network. Before her work at MJFF, Ms. Hood worked at both Goldman, Sachs & Co. and Bain & Company. She graduated from Duke University and Harvard Business School.
Joel D. Howell, M.D., Ph.D.
University of Michigan

Joel D. Howell, M.D., Ph.D., is the Victor Vaughan Professor of the History of Medicine at the University of Michigan, where he is also a professor in the Departments of Internal Medicine (Medical School), History (College of Literature, Science, and the Arts), and Health Services Management and Policy (School of Public Health). He received his MD and completed his residency in internal medicine at the University of Chicago and received a Ph.D. in the history and sociology of science from the University of Pennsylvania, where he was a Robert Wood Johnson Clinical Scholar. From 1993 to 2007, Dr. Howell directed the Robert Wood Johnson Clinical Scholars Program at the University of Michigan. He primarily studies the history of medical technology, examining how social and contextual factors have shaped its diffusion and clinical application. His research attempts to understand why American medicine has become so obsessed with science and technology, including a focus on health policy and an analysis of factors that have both contributed to and slowed the diffusion of medical technology. Dr. Howell is writing on the history of human experimentation and on ideas about heart attacks, and his publications have appeared widely in the medical and historical literature. His research has been supported both by Federal grants and by foundations. He received a Robert Wood Johnson Foundation Investigator Award in health policy research and a Burroughs Welcome Foundation Award in the history of medicine. As director of the Medical Arts Program at the University of Michigan, he is studying the effects of the arts on clinical practice with a grant from the Doris Duke Charitable Foundation. In April 2013, he will receive the Nicholas E. Davies Memorial Scholar Award for scholarly activities in the humanities and history of medicine from the American College of Physicians. In addition to his medical publications, Dr. Howell is the author of “Washtenaw County Bike Rides” (University of Michigan Press). He is a practicing internist and attending physician in both the outpatient and inpatient settings and regularly teaches in the Medical School, School of Public Health, College of Literature, Science, and the Arts, and Law School.
John Huguenard, Ph.D.
Stanford University

John Huguenard, Ph.D., is director of the Stanford Epilepsy Research Program and Stanford Epilepsy Postdoctoral Training Program. His research, which is funded by NINDS, focuses on mechanisms of primary generalized epileptic seizures, particularly those of the absence variety, and the underlying large-scale brain network—the thalamocortical system—in mice and rats. In addition, Dr. Hugunard studies the mechanisms through which antiseizure medications exert their actions. His research group uses electrophysiologic, optogenetic, computational, and neuroanatomical methods to determine the components within the epileptic network that are most susceptible to failure and the way in which this failure can lead to seizure initiation and/or generalization. Improved understanding of these points of failure is leading to novel approaches for treatment of epilepsy.
Frances Jensen, M.D.
University of Pennsylvania

Frances Jensen, M.D., has recently been appointed as chair of neurology at the Perelman School of Medicine, University of Pennsylvania. She was formerly professor of neurology at Harvard Medical School, director of translational neuroscience and epilepsy research at Boston Children’s Hospital, and senior neurologist at Boston Children’s Hospital and the Brigham and Women’s Hospital. Dr. Jensen is a graduate of Cornell Medical College and did her neurology residency training at the Harvard Longwood Neurology Residency Program. Her research focuses on mechanisms of epilepsy and stroke, with specific emphasis on injury in the developing brain as well as age-specific therapies for clinical trials development. She received a 2007 Director’s Pioneer Award from NIH to explore the interaction between epileptogenesis and cognitive dysfunction. Dr. Jensen also is the recipient of the 2008 American Epilepsy Society Basic Science Research Award. She was president of the American Epilepsy Society in 2012 and serves on a number of other leadership boards, including the Council for the Society for Neuroscience, the nominating committee at the American Neurological Association, and the council at the National Institute of Child Health and Human Development. In addition, she serves on the scientific advisory panel of a number of charitable foundations for medical research. Dr. Jensen has authored more than 100 manuscripts on subjects related to her research, has been continuously funded by NIH since 1987, and has trained numerous clinical and basic research fellows who now hold independent faculty positions nationally and internationally. Dr. Jensen also is the sponsor of an FDA-approved IND for an ongoing multicenter clinical trial of a novel therapy for neonatal seizures, generated from basic research in her laboratory. She is also an advocate for awareness of adolescent brain development, its unique strengths and vulnerabilities, and their impact on medical, social, and educational issues unique to teenagers and young adults.
Henrik Klitgaard, Ph.D.
UCB Pharma

Henrik Klitgaard, Ph.D., is vice-president and fellow in the neurosciences therapeutic area at Union Chimique Belge (UCB) in Braine-l’Alleud, Belgium. Following a Ph.D. in biology and postdoctoral work in academia, Dr. Klitgaard joined the pharmaceutical industry nearly 25 years ago. He has worked at Ferrosan, Novo Nordisk, and is currently an employee at UCB. During his career in the pharmaceutical industry, Dr. Klitgaard has focused his efforts on antiepileptic drug discovery and development. He has contributed numerous publications on basic and applied aspects of epilepsy research and antiepileptic drug discovery and lectures at epilepsy meetings. Dr. Klitgaard has been involved in the discovery and development of two new antiepileptic drugs (Tiagabine/Gabitril, Novo Nordisk A/S; Levetiracetam/Keppra, UCB Pharma) and several preclinical and clinical antiepileptic drug candidates.
Walter J. Koroshetz, M.D.
National Institutes of Health

Walter J. Koroshetz, M.D., was named deputy director of the National Institute of Neurological Disorders and Stroke (NINDS) in January 2007. He works with the NINDS director in program planning and budgeting and oversees the scientific and administrative functions of the Institute. Before joining NINDS, Dr. Koroshetz served as vice chair of the neurology service and director of stroke and neurointensive care services at Massachusetts General Hospital (MGH). He was also a professor of neurology at Harvard Medical School and has led neurology resident training at MGH since 1990. A native of Brooklyn, Dr. Koroshetz graduated from Georgetown University and received his medical degree from the University of Chicago, where he trained in internal medicine. Dr. Koroshetz trained in neurology at MGH, after which he did postdoctoral studies in cellular neurophysiology at MGH and the Harvard neurobiology department. He joined the neurology staff, first in the Huntington’s disease unit and then in the stroke and neurointensive care service. As a member of the NINDS intramural review and oversight committees, Dr. Koroshetz has been involved in various NINDS symposia and clinical trials and served as the Institute’s representative to the American Neurological Association’s Career Development Symposium. He was a member of the NINDS-chaired Brain Attack Coalition, a group of professional, voluntary, and governmental entities dedicated to reducing the occurrence, disabilities, and death associated with stroke.
Barbara L. Kroner, Ph.D., M.P.H.
RTI International

Barbara L. Kroner, Ph.D., M.P.H., is an epidemiologist at Research Triangle Institute and has 30 years of experience conducting clinical studies of chronic diseases, including epilepsy. She is currently working with the Children’s National Medical Center in Washington, DC, on a cohort study of children with epilepsy to examine seizure-related outcomes and the impact of epilepsy on the family. Dr. Kroner is also working with Children’s National and a team of bioengineers to develop a seizure alert device based on autonomic signals. She is a member of the American Epilepsy Society Vision 20/20 group and Partners Against Mortality in Epilepsy. Dr. Kroner has a 14-year-old child with Aicardi syndrome and treatment-resistant seizures. In today’s presentation, she will talk about the impact her daughter’s epilepsy has had on her and on their family.
Ruben I. Kuzniecky, M.D., is professor of neurology at the New York University (NYU) School of Medicine, co-director of the NYU Comprehensive Epilepsy Center, and director of epilepsy research. He trained in neurology, epilepsy, and EEG at the Montreal Neurologic Institute, McGill University, Canada, between 1983 and 1988. He began his academic career as assistant professor of neurology at the University of Alabama at Birmingham (UAB) and rose to professor and director of the UAB Epilepsy Center between 1992 and 2003 when he joined NYU. Dr. Kuzniecky’s clinical and research interests are centered on the development of imaging techniques, in particular magnetic resonance imaging (MRI), to study epilepsy. His research also includes areas relevant to malformations of cortical development and epilepsy and the development of new therapies and technologies. Dr. Kuzniecky has authored 3 books, 37 chapters, and more than 260 journal articles on a number of topics related to epilepsy and has received epilepsy research grants from NIH and numerous foundations since 1990. He is co-principal investigator of the Epilepsy Phenome Genome Project, one of the largest epilepsy genetic studies of its type funded by NINDS. Most recently Dr. Kuzniecky, in conjunction with Drs. J. French and D. Lowenstein, has launched a new research initiative, the Human Epilepsy Project, to investigate biomarkers of epilepsy progression. This project will enroll 600 patients with new-onset focal seizures and follow them up for 5 years with MRIs, EEG, DNA, RNA, and serum and urine measurements.
Story C. Landis, Ph.D.
National Institutes of Health

Story C. Landis, Ph.D., has been director of the National Institute of Neurological Disorders and Stroke (NINDS) since 2003. A native of New England, Dr. Landis received her undergraduate degree from Wellesley College in 1967 and her Ph.D. from Harvard University in 1973. After postdoctoral work at Harvard, she served on the faculty of the Department of Neurobiology there. In 1985, she joined the faculty of Case Western Reserve University School of Medicine, where she created the Department of Neurosciences, which achieved an international reputation for excellence. Throughout her research career, Dr. Landis has made fundamental contributions to the understanding of nervous system development. She has garnered many honors; is an elected fellow of the Academy of Arts and Sciences, American Association for the Advancement of Science, Institute of Medicine, and American Neurological Association; and in 2002 was elected president of the Society for Neuroscience. Dr. Landis joined NINDS in 1995 as scientific director and worked to reengineer the Institute's intramural research programs. Between 1999 and 2000, she led the movement, together with the scientific director of the National Institute on Mental Health (NIMH), to bring a sense of unity and common purpose to 200 neuroscience laboratories from 11 different NIH Institutes. As NINDS director, Dr. Landis oversees an annual budget of $1.6 billion that supports research by investigators in public and private institutions across the country, as well as by scientists working in NINDS intramural program. With NIMH Director Dr. Tom Insel, she chairs the NIH Neuroscience Blueprint, a roadmap-like effort to support trans-NIH activities in the brain sciences. In 2007, Dr. Landis was named chair of the NIH Stem Cell Task Force.
Pierre-Pascal Lenck-Santini, Ph.D.
Dartmouth College

Pierre-Pascal Lenck-Santini, Ph.D., did his thesis under the supervision of Bruno Poucet in Marseilles, France. His project focused on the functional relationships between the activity of hippocampal neurons called “place cells” and spatial behavior in rats. As a postdoctoral fellow, he joined the laboratories of Bob Muller and André Fenton in Brooklyn, NY, where he investigated the nonspatial properties of place cells and the influence of brain oscillations on their firing. Realizing that freely moving electrophysiology provides access to the internal computations of the nervous system, Dr. Lenck-Santini decided to use it as a tool to investigate the physiologic mechanisms at the origin of cognitive disorders in epilepsy. He joined the Neurology Department at Dartmouth Medical School in 2005 as a research assistant professor. With Professor Gregory Holmes, he studied the role of abnormal neuronal oscillations in cognitive impairments associated with epilepsy. Since 2011, Dr. Lenck-Santini has been assistant professor of neurology at the Geisel School of Medicine at Dartmouth. His laboratory studies the development of hippocampal function and the way in which it is affected by neurological disorders.
Greg Lewis, M.B.A.
 McKinsey and Company

Greg Lewis, M.B.A., is a Principal in the Detroit office of McKinsey and Company. Since joining the firm in 2001, he has primarily served clients in health care and employee benefits. His work often focuses on strategic planning, growth, and new business building. Mr. Lewis also has been a leader in McKinsey’s recent knowledge investments in supplemental health products and services as well as Government programs (Medicare and Medicaid). Before joining McKinsey, Mr. Lewis worked in international business development at a division of Tyson Foods, where he specialized in seafood opportunities, primarily in Russia and the former Soviet Union. He earned his M.B.A. with high distinction from the University of Michigan Ross School of Business and graduated magna cum laude from Harvard University with a B.A. in history and science. He lives in Ann Arbor, MI (go Blue!) with his wife, Toby, and two sons, Casey and Ian.
Brian Litt, M.D.
University of Pennsylvania

Brian Litt, M.D., was born in Baltimore, MD, and obtained a degree in engineering and applied sciences from Harvard University in 1982. He received his M.D. from Johns Hopkins University School of Medicine in 1986. He is currently professor of neurology and bioengineering, interim director of the Penn Epilepsy Center at the Hospital of the University of Pennsylvania, and director of the Translational Neuroengineering Laboratory in Bioengineering. Dr. Litt’s laboratory focuses on translating neuroengineering research directly into patient care through collaboration between the clinical neurosciences (neurology, neurosurgery, psychiatry), neuroscience, and engineering. Although epilepsy is the focus of his research, his multidisciplinary translational work spans other “brain network disorders” and brain-computer interfaces. His laboratory invents new device technologies and algorithms to run them and manages a large NIH-funded cloud computing facility dedicated to crowd-sourced collaboration and sharing “big data” in neuroengineering. Dr. Litt’s laboratory is a collaborative hub that houses a diverse group of medical, engineering, and other faculty from Penn’s campus and beyond. Dr. Litt is active as a clinician, teacher, and entrepreneur. He has participated in founding three companies and licensed technology through Penn for three implantable brain devices in or entering clinical trials.
Tobias Loddenkemper, M.D.  
Boston Children’s Hospital

Tobias Loddenkemper, M.D., is a pediatric neurologist and epileptologist at the Epilepsy Center at Boston Children’s Hospital and serves as an associate professor at Harvard Medical School. He trained in adult neurology, pediatric neurology, and clinical neurophysiology at Westfälische Wilhelms-Universität Münster and at Cleveland Clinic. Dr. Loddenkemper received several awards, including the Early Career Physician Scientist Award of the American Epilepsy Society and the Dreifuss-Penry Epilepsy Award of the American Academy of Neurology. His work intends to provide novel chronoepileptological approaches to rational treatment for patients with difficult-to-treat seizures and status epilepticus in an attempt to uncover relationships between biomarkers, seizure periodicity, and novel processes that set the stage for epilepsy in the developing brain.
Daniel H. Lowenstein, M.D.
University of California, San Francisco

Daniel H. Lowenstein, M.D., is the Robert B. and Ellinor Aird Professor and vice-chair of neurology, director of the Epilepsy Center, and director of physician-scientist education and training at the University of California San Francisco (UCSF). He received his B.A. in mathematics from the University of Colorado and M.D. from Harvard Medical School and completed neurology residency training at UCSF. Dr. Lowenstein is a clinician-scientist who has studied both basic science and clinical aspects of epilepsy. In recent years, he has been an organizer of large-scale, international efforts to study the complex genetics of epilepsy through the Epilepsy Phenome/Genome Project and the Epi4K Center Without Walls. Dr Lowenstein has been actively involved in advancing the cause of epilepsy at the national and international level. He served as president of the American Epilepsy Society in 2003–2004, was a member of the NINDS Advisory Council from 2000 to 2004, and has overseen the development of the NINDS Epilepsy Research Benchmarks since their inception in 2000.
Andrey M. Mazarati, M.D., Ph.D.
University of California, Los Angeles

Andrey M. Mazarati, M.D., Ph.D., graduated summa cum laude from the Odessa Medical University in Ukraine in 1986 and received his Ph.D. at the National Academy of Medical Sciences in Moscow in 1989. He completed his postdoctoral training at the UCLA School of Medicine in 1996 and presently is an adjunct professor in the Department of Pediatrics, David Geffen School of Medicine at UCLA. His contribution to epilepsy research includes studying the role of bioactive peptides in mechanisms of epilepsy and, in particular, the discovery of antiepileptic properties and underlying mechanisms of action of a neuropeptide galanin. For the past 7 years, Dr. Mazarati has been studying mechanisms of depression as a comorbidity of epilepsy. He has co-authored 70 peer-reviewed manuscripts, numerous critical reviews, and book chapters. Dr. Mazarati has been a recipient of four NIH-funded research projects, including an ongoing R01 grant from NINDS examining mechanisms of epilepsy-associated depression.
James O. McNamara, M.D.
Duke University School of Medicine

James O. McNamara, M.D., is the Duke School of Medicine Professor of Neurosciences in the Department of Neurobiology, founder of the Duke Center for the Advanced Study of Epilepsy, and former director of the Durham Veterans Affairs Medical Center Epilepsy Center. His research focuses on the mechanisms of epileptogenesis, the process by which a normal brain becomes epileptic. A member of the Institute of Medicine of the National Academies of Science, Dr. McNamara has received two NIH Jacob Javits Neuroscience Investigator Awards, an American Epilepsy Society Research Recognition Award, and a Freedom to Discover Award from Bristol-Myers Squibb. Dr. McNamara received his A.B. from Marquette University and his M.D. from the University of Michigan. He served as chief resident in neurology and completed his postdoctoral work in neuroscience at Duke. He completed a sabbatical year in the molecular neurobiology laboratory of Stephen Heinemann, Ph.D., at the Salk Institute in California and served as chair of the Department of Neurobiology at Duke from 2002 through 2011.
Craig Miller, M.D.
Hope for Hypothalamic Hamartomas

Craig Miller, M.D., is an orthopaedic surgeon specializing in sports medicine at Shady Grove Orthopaedic Associates. His son Mark was diagnosed with a hypothalamic hamartoma (HH) at age 5 after several years of incorrect diagnoses. He underwent gamma knife surgery at the University of Pittsburgh in August 2007 and is scheduled for stereotactic laser ablation in June of this year at Texas Children's Hospital in Houston. HH causes intractable epilepsy, often characterized by gelastic (laughing) seizures that are refractory to medical management and can lead to progressive cognitive decline. His family's experience with the trials and tribulations associated with finding the correct diagnosis for Mark led to the founding of Hope for Hypothalamic Hamartomas, a 501(c)3 organization dedicated to creating a single, credible source for information about the diagnosis, treatment, and support of individuals with HH. Dr. Miller completed a fellowship in sports medicine at the Kerlan-Jobe Orthopaedic Clinic in Los Angeles, a world leader in the diagnosis and treatment of orthopaedic and sports medicine injuries and illnesses. Dr. Miller is an assistant team physician for the Washington Nationals.
Jeffrey L. Noebels, M.D., Ph.D.
Baylor College of Medicine

Jeffrey L. Noebels, M.D., Ph.D., holds the Cullen Trust Endowed Chair in Neurogenetics and is professor of neurology, neuroscience, and molecular and human genetics at Baylor College of Medicine in Houston. He is vice chair of research in neurology and director of the Developmental Neurogenetics Laboratory and the Epilepsy Research Center at Baylor. Dr. Noebels received his Ph.D. in neuroscience from Stanford University and his M.D. from Yale Medical School. He completed postdoctoral training in developmental neurogenetics in the Harvard Department of Neuropathology as a William G. Lennox Fellow, neurology residency training at Massachusetts General Hospital, and was a Klingenstein Fellow at Children’s Hospital in Boston. Dr. Noebels’ major research focus has been to identify genes that cause epilepsy and trace their cellular expression in the developing nervous system. He has spoken and written widely in this area and serves on the scientific organizing committees and study sections of academic, NIH, and international organizations directed at epilepsy research. He is past president of the American Epilepsy Society (AES) and current chair of the Neurobiology Commission of the International League Against Epilepsy and SFN Neurobiology of Disease Workshop. Dr. Noebels has received numerous awards for his research on genes and basic mechanisms of epilepsy, including an NIH Javits Award, PEW Scholar Award, AES Research Award, and Michael Prize and Novartis Awards.
Jack Parent, M.D.
University of Michigan

Jack Parent, M.D., is a professor of neurology at the University of Michigan. He directs the Neurodevelopment and Regeneration Laboratory and co-directs the University of Michigan Epilepsy Program. He serves as an associate editor at Epilepsy Currents and Experimental Neurology, is a former chair of the Epilepsy Foundation (EF) Research Council Fellowships Committee, serves on the EF professional advisory board, chairs the scientific advisory board of the Dravet Syndrome Foundation, and is on the advisory boards of the PCDH19 Alliance and Global Ischemia Foundation. Dr. Parent’s research focuses on stem cell biology, disease modeling with induced pluripotent stem cells, and the role of adult neurogenesis in epileptogenesis and brain repair. He has received several research awards, including the American Academy of Neurology Dreifuss-Penry Epilepsy Award and the American Neurological Association Grass Foundation Award in Neuroscience.
Wendy Mathis Parker, M.F.A.
Epilepsy Foundation Central Virginia Chapter

Wendy Mathis Parker, M.F.A., is a journalist, playwright and children’s author. She is managing editor of a community newspaper in Midlothian, VA. Her work has appeared in a variety of publications, including Woman’s Day, Historic Preservation, and Scarab, a publication of Virginia Commonwealth University Medical College of Virginia (VCU/MCV). Ms. Parker is a volunteer for the Epilepsy Foundation of Virginia and the Central Virginia Chapter. She writes articles to raise awareness about epilepsy and is dedicated to raising funds for research to find a cure for epilepsy and SUDEP. For the past 4 years, she has served as a community advocate for research for VCU/MCV. She recently produced “reSearchlight,” a newsletter on seizure-related topics for the VCU Center for Clinical and Translational Research. Ms. Parker earned a bachelor’s degree in art from Ohio University and a master’s degree in English from VCU. She is the mother of two children and grandmother of three.
Steven Petrou, Ph.D.
University of Melbourne

Steven Petrou, Ph.D., is deputy director and head of the Division of Epilepsy, Florey Institute of Neuroscience and Mental Health, and deputy director of the Centre for Neural Engineering at the University of Melbourne in Victoria, Australia. His Laboratory of Ion Channels and Human Disease comprises 20 researchers with 11 postdoctoral fellows, 7 Ph.D. students, undergraduate students, and research associates. The research focus is in the understanding the CNS pathology of ion channel disorders, with a specialized interest in genetic epilepsy. Dr. Petrou’s work has been continuously funded by the National Health and Medical Research Council (NHMRC) for the past 10 years. He was invited to join the NIH Center Without Walls Epi4K as a principal investigator leading the functional genomic studies in epilepsy. Dr. Petrou currently collaborates with Drs. David Goldstein at the Center for Human Genome Variation at Duke University Medical Center, Darryl De Vivo at Columbia University Medical Center’s Department of Neurology, and Stephen G. Waxman at Yale University School of Medicine. Dr. Petrou also has served as a consultant in the local and international biopharmaceutical industry. His current service includes membership on the Basic Research Committee for the International League Against Epilepsy, the Scientific Advisory Board German Network of Neurological and Ophthalmological Ion Channel Disorders, the Australian Brain Bank Network Committee, and the NHMRC Assigners Academy. He has served on the editorial boards of Neurobiology of Disease and Epilepsia and has 95 publications and 4 patents.
Annapurna Poduri, M.D., M.P.H.
Boston Children’s Hospital

Annapurna Poduri, M.D., M.P.H., is board certified in neurology with special qualification in child neurology and subspecialty certification in clinical neurophysiology. She is an assistant professor of neurology at Harvard Medical School and Boston Children’s Hospital. Dr. Poduri attended the University of Pennsylvania School of Medicine, completed her pediatric residency at Boston Children’s Hospital and neurology training at Children’s Hospital of Philadelphia, and was awarded an epilepsy fellowship at Boston Children’s Hospital. She then completed a postdoctoral fellowship in neurogenetics in the laboratory of Christopher A. Walsh, where she studied the genetics of familial epilepsies (supported by a K23 from NINDS) and somatic mutations as a cause of focal developmental brain lesions. She now leads the Epilepsy Genetics Program at Boston Children’s Hospital, providing clinical consultation and running an independent research program to investigate the causes of severe early-onset epilepsy and somatic genetic causes of epilepsy. Dr. Poduri has been a site principal investigator of the NINDS-supported Epilepsy Phenome/Genome Project and co-investigator of the NINDS-supported Epi4K project.
Jong Min Rho, M.D.
University of Calgary

Jong Min Rho, M.D., is a professor of pediatrics and clinical neurosciences at the University of Calgary, division head of pediatric neurology at the Alberta Children’s Hospital, and the inaugural holder of the Dr. Robert Haslam Chair in Child Neurology. After obtaining an undergraduate degree in molecular biophysics and biochemistry from Yale University, Dr. Rho received his medical degree from the University of Cincinnati. Following a pediatric residency at the University of Southern California Children’s Hospital of Los Angeles and a neurology residency at the University of California Los Angeles (UCLA) School of Medicine, he completed fellowships in pediatric neurology at the UCLA School of Medicine and in neuropharmacology at NIH. Before his current position, he held faculty appointments at the University of Washington and the Children’s Hospital & Regional Medical Center in Seattle, the University of California at Irvine, and the Barrow Neurological Institute at the St. Joseph’s Hospital and Medical Center in Phoenix. Dr. Rho’s main research interests are the mechanisms underlying the anticonvulsant and neuroprotective effects of the ketogenic diet, the neuropharmacology of anticonvulsant compounds, and the study of surgically resected human epileptic tissue. His research activities have been sponsored by several NIH research grants as well as a variety of intramural and extramural public and private sector sources. Dr. Rho has served on the editorial boards of Epilepsia and Epilepsy Currents and has been a regular reviewer for research grants submitted to NIH. More recently, he has been an ad hoc reviewer for the Canadian Institutes for Health Research. In addition to an extensive list of publications in basic science and pediatric neurology peer-reviewed journals, Dr. Rho has written numerous book chapters, edited several books, and is a popular national and international guest lecturer.
George Richerson, M.D., Ph.D.
University of Iowa

George Richerson, M.D., Ph.D., received a B.S. in aerospace engineering from Iowa State University in 1980 and an M.D. and Ph.D. in physiology and biophysics from the University of Iowa in 1987. He did his neurology residency at Yale University, where he remained on the faculty from 1991 until 2010. While at Yale, Dr. Richerson rose to the rank of professor and was program director of the neurology residency for 14 years. He returned to Iowa City in 2010 to chair the Neurology Department. He has been principal investigator on numerous NIH grants focused on two major areas. The first is the role of GABA transporters in regulation of tonic inhibition and the way in which this role contributes to epilepsy and the mechanism of action of anticonvulsants. The second is the role of serotonin neurons as sensors of arterial PCO2 that cause arousal from sleep and increased ventilation in response to hypercapnia. His research has helped to understand the pathophysiology of sudden infant death syndrome and sudden unexpected death in epilepsy and the way in which the two may be related. Dr. Richerson was elected to the American Neurological Association in 2003 and has been on the editorial boards of the *Journal of Neurophysiology* and *Respiratory Physiology & Neurobiology*.
Mustafa Sahin, M.D., Ph.D.
Boston Children’s Hospital

Mustafa Sahin, M.D., Ph.D., is associate professor of neurology at Harvard Medical School. After receiving his B.S. degree from Brown University, he earned an M.D. and a Ph.D. from Yale University School of Medicine. After completing a pediatrics residency at Children’s Hospital of Philadelphia and a child neurology residency at Boston Children’s Hospital, Dr. Sahin did his postdoctoral research training in developmental neurobiology at Boston Children’s Hospital. He established and now directs the Multidisciplinary Tuberous Sclerosis Program at Boston Children’s Hospital where his laboratory is working to understand the cellular mechanisms of axon guidance and its relationship to neurologic dysfunction. Dr. Sahin’s research centers on tuberous sclerosis complex (TSC) and spinal muscular atrophy (SMA)—two neurological disorders whose genetic basis is elucidated but whose cell biology is incompletely understood. The laboratory has developed evidence that the TSC/mTOR pathway plays crucial roles in axon specification, guidance, myelination, and regeneration. These experiments support the notion that neurologic defects in Tsc-deficient mice can be blocked by postnatal mTORC1 inhibition. This work underpins the design of a clinical trial directed by Dr. Sahin investigating the effect of an mTORC1 inhibitor on neurocognition in individuals with TSC.
Christina Saninocencio, M.S.
Lennox-Gastaut Syndrome Foundation

Christina Saninocencio, M.S., is the founder and president of the Lennox-Gastaut Syndrome (LGS) Foundation, the only nonprofit organization in the world dedicated exclusively to Lennox-Gastaut syndrome. For more than 20 years, she has been a secondary caregiver and advocate to a person with LGS, her younger brother Michael. In addition to directing the LGS Foundation and helping with Michael’s care, Ms. Saninocencio is a freelance television producer and media professional. She holds a master of science degree in media studies. Her research interests include public health perception in television and film, health communications, and epilepsy messages within the media.
Elson Lee So, M.D.
Mayo Clinic

Elson Lee So, M.D., serves on the editorial boards of *Epilepsia*, *Epilepsy Research*, and the *Journal of Clinical Neurophysiology*. He is the incoming president of the American Epilepsy Society (AES) and has also served on the Professional Advisory Board of the Epilepsy Foundation (EF) and the Council of the American Clinical Neurophysiology Society. Dr. So is the past chair of the Section of Clinical Neurophysiology of the American Academy of Neurology. He has directed educational courses, symposiums, and plenary sessions at the American Academy of Neurology, AES, the American Clinical Neurophysiology Society, and the Organization for Human Brain Mapping. He chaired the Joint AES-EF SUDEP Task Force and the NINDS workshop on sudden unexpected death in epilepsy (SUDEP). His research interests are in advanced single-photon emission computed tomography (SPECT) imaging, SUDEP, and the natural history, treatment outcomes, and electroclinical aspects of intractable epilepsy. Dr. So is a named inventor of the Office of Intellectual Property of the Mayo Clinic.
Ivan Soltesz, Ph.D.
University of California, Irvine

Ivan Soltesz, Ph.D., is Chancellor’s Professor and chair of anatomy and neurobiology in the School of Medicine at the University of California Irvine. His research employs closely integrated experimental and computational modeling techniques to understand and control epileptic circuits and identify new possibilities for treatment. Dr. Soltesz is current chair of the Clinical Neuroplasticity and Neurotransmitters Study Section, co-founder of the Gordon Conference on Epilepsy, and recipient of the NINDS Javits Neuroscience Investigator Award, the American Epilepsy Society Research Recognition Award, and the Michael Prize.
Harald W. Sontheimer, Ph.D.
University of Alabama, Birmingham

Harald W. Sontheimer, Ph.D., received his Ph.D. in cell biology and biophysics from the University of Heidelberg in 1989. Following his postdoctoral training at Yale University School of Medicine, he was appointed assistant professor of neurology and neurobiology from 1991 to 1994. He is currently professor of neurobiology at the University of Alabama at Birmingham, with secondary appointments in cell biology, physiology, and neurology. In 2005, he was appointed director of the Civitan International Research Center, and in 2006 he became director of the Center for Glial Biology in Medicine, the first research entity exclusively dedicated to the study of glial cells and their role in health and disease. Dr. Sontheimer directs an active research laboratory with 12 graduate assistants and postdoctoral fellows studying the role of glial cells in various diseases of the nervous system. His current work focuses on mechanisms underlying brain tumor–associated epilepsy.
Sarah Spence, M.D., Ph.D.
Boston Children’s Hospital

Sarah Spence, M.D., Ph.D., is a child neurologist with a Ph.D. in neuropsychology and training in behavioral neurogenetics. She is currently the director of the Autism Program in the Neurology Department at Boston Children’s Hospital, and she is an assistant professor at Harvard Medical School. She maintains an active clinical practice specializing in comprehensive medical evaluation and treatment of children with autism spectrum disorder (ASD) and is involved in several clinical research projects. Previously, she was at the intramural research program at the National Institute of Mental Health in Bethesda, MD, where she was involved in several active protocols, including the intensive investigation of the subtypes of autism and a number of novel treatment trials. She has been involved in many initiatives focusing on the clinical care and research of individuals with ASD and related developmental disabilities, working with the Cure Autism Now Foundation, Autism Speaks, the Simons Foundation, NIH, the Dup15q Alliance, and the Tuberous Sclerosis Alliance. Dr. Spence is also a member of the Neurodevelopmental Disabilities Workgroup for the DSM 5. Her research interests include exploration of the medical aspects of autism, including the role of epilepsy and EEG abnormalities, sleep disorders, metabolic dysfunction, and genetics. She began her autism work as medical director of the Autism Genetic Resource Exchange, a unique shared resource designed to speed the pace of autism genetic research begun by the Cure Autism Now Foundation. She has always credited her autism training to the amazing families who graciously allowed her to come into their homes and learn from them.
Annamaria Vezzani, Ph.D.
Mario Negri Institute for Pharmacological Research

Annamaria Vezzani, Ph.D., obtained her Ph.D. degree in neuropharmacology in Milan at the Mario Negri Institute for Pharmacological Research. She spent her postdoctoral period in Baltimore at the University of Maryland working on the mechanisms of epileptogenesis in experimental models of epilepsy. Additional postdoctoral work was done at the University of Stockholm and at the Karolinska Institute. Dr. Vezzani was on sabbatical at the Albert Einstein College of Medicine in 2002 in the Laboratory of Developmental Epilepsy. She studies the biochemical and molecular mechanisms involved in the etiopathogenesis of seizures and of pharmacoresistance using experimental models of epilepsy with a special focus on inflammatory mediators. Since 1997, Dr. Vezzani has been head of the Laboratory of Experimental Neurology in the Department of Neuroscience at the Mario Negri Institute for Pharmacological Research, Milan. She is a member of the editorial boards of Epilepsy Currents, Epilepsy Research and Treatment, and the Journal of Neuroscience and associate editor of basic science for Epilepsia. She has been appointed chair of the Commission on Neurobiology of the International League Against Epilepsy. Dr. Vezzani received the Research Recognition Award for translational research in 2009 from the American Epilepsy Society.
Matthew Walker, M.D., Ph.D.
University College London

Matthew Walker, M.D., Ph.D., is professor of neurology at the University College London Institute of Neurology and the National Hospital for Neurology and Neurosurgery, London, where he is head of the Department of Clinical and Experimental Epilepsy. Dr. Walker studied medicine at Cambridge and London (St. Thomas' Medical School) and trained in neurology at St Thomas', Guy's, and the National Hospital for Neurology and Neurosurgery, Queen Square. He was awarded a Ph.D. in 1998 for his thesis on the treatment of status epilepticus. Professor Walker is very active in basic research, and his main interests lie in the mechanisms regulating cortical excitability and the treatment and consequences of prolonged seizures. His clinical research interests include the surgical treatment of epilepsy and EEG-fMRI. He has published more than 200 scientific articles, chapters, and books and is an associate editor of *Epilepsia* and *Therapeutic Advances in Neurological Disorders*. Dr. Walker is a member of the International League Against Epilepsy (ILAE) Commission on the Neurobiology of Epilepsy and a member of the Task Force on Translational Research of ILAE and of the Working Group on Recommendations for Preclinical Epilepsy Drug Discovery. He is chair of the executive committee of the Joint Epilepsy Council of UK and Ireland.
Karen S. Wilcox, Ph.D.
University of Utah

Karen S. Wilcox, Ph.D., is professor of pharmacology and toxicology and co-investigator of the Anticonvulsant Drug Development (ADD) Program at the University of Utah. Dr. Wilcox received her Ph.D. in physiology at the University of Pennsylvania in 1993 and remained there as a research associate until 1998, when she moved to the ADD program. Her areas of research interest include basic mechanisms of pharmacoresistant epilepsy, the role of inflammation in seizure generation and epileptogenesis, and the mechanism of action of antiseizure drugs. She was the 2012 chair of the Scientific Program Committee for the American Epilepsy Society (AES) annual meeting, has served on the Scientific Advisory Board for Citizen's United for Research in Epilepsy, is a member of the AES board of directors, and is the director of graduate studies in the Department of Pharmacology and Toxicology at the University of Utah. Dr. Wilcox is a member of several editorial review boards and has served as an ad hoc reviewer for journals in a number of areas, including pharmacology, neuroscience, and epilepsy. She was a regular member of the Acute Neural Injury and Epilepsy study section at NIH, continues to serve in an ad hoc capacity as a reviewer for NINDS, and reviews grants for a number of foundations. Dr. Wilcox also has trained a number of graduate students and postdoctoral fellows, many of whom have continued to study the basic mechanisms of epilepsy.
Elaine C. Wirrell, M.D., FRCPC
Mayo Clinic

Elaine C. Wirrell, M.D., FRCPC, is a professor of child and adolescent neurology and chief of pediatric epilepsy at the Mayo Clinic in Rochester, MN. She received her medical degree from the University of British Columbia, and she is board certified in pediatrics and neurology. Dr. Wirrell’s research interests include the epidemiology and treatment of pediatric epilepsy and its comorbidities. She has written more than 100 peer-reviewed articles, 13 book chapters, and numerous review articles. Her current administrative duties include serving as vice chair of the Neurology Examination Committee of the Royal College of Physicians and Surgeons of Canada, member of the International League Against Epilepsy Classification Committee, and co-chair of the pediatric Epilepsy Research Consortium. Dr. Wirrell is a fellow of the Royal College of Physicians and Surgeons of Canada and a member of the Minnesota Board of Medical Practice and the American Epilepsy Society.
Gregory A. Worrell, M.D., Ph.D.  
Mayo Clinic

Gregory A. Worrell, M.D., Ph.D., is chair of the Division of Clinical Neurophysiology in the Department of Neurology at Mayo Clinic. Dr. Worrell’s research is focused by an active clinical practice directed at the care of patients with medically intractable epilepsy. He is particularly interested in the evaluation of patients’ medically resistant epilepsy and the use of epilepsy surgery and direct brain stimulation for treatment. Dr. Worrell is currently investigating electrophysiological signatures of epileptogenic brain and the transition from normal brain activity to seizures.
Updating the Epilepsy Research Benchmarks

On the final day of the conference, participants will consider research opportunities to include in the Epilepsy Research Benchmarks for the next 5 to 10 years.

The current Benchmarks are organized around three main goals:

- **Benchmarks Area I—Prevent epilepsy and its progression.**
- **Benchmarks Area II—Develop new therapeutic strategies and optimize current approaches to cure epilepsy.**
- **Benchmarks Area III—Prevent, limit, and reverse the comorbidities associated with epilepsy and its treatment.**

Breakout groups (one for each area listed above) will discuss potential updates to the content and organization of these goals. Discussions should be informed by the conference’s scientific sessions and by the following background materials related to the 2007 Benchmarks and other input into research opportunities and challenges. These background materials are available on the conference website. Further guidance will be provided during the breakout sessions.

- **Integrated summary of input on research opportunities** provided by the Stewards and received in response to a NINDS RFI.

Breakout moderators will present summaries of discussions in their groups.

*The Benchmarks are not intended to be recommendations to NINDS. Rather, they should reflect the sense of the broad epilepsy research community in terms of opportunities for advancing research over the next 5 to 10 years, given the current state of the field. These goals and corresponding opportunities could be used by any individual or organization within the community to inform their plans and to facilitate communication and collaboration.*
Epilepsy is a complex and heterogeneous disease, making it difficult to precisely diagnose and provide effective treatments. A major and underexplored cause of complex disorders such as epilepsy could be mutations in gene regulatory elements such as enhancers. To test this hypothesis, we decided to focus on infantile spasms (IS), a subtype of epilepsy that begins in infancy and is associated with ventral forebrain development and forebrain synapse function. Using chromatin immunoprecipitation followed by deep sequencing (ChIP-seq) with enhancer marks (H3K27ac, RNAPoll2), we identified active enhancer candidates in mouse embryonic day 16.5 forebrain. In addition, using chromatin interaction analysis followed by paired-end tag sequencing (ChIA-PET) on the same tissue, we determined the enhancer candidates that regulate IS-associated genes. Using zebrafish transgenic assays, we showed that several of these candidates have enhancer activity in the developing forebrain. These enhancers are currently being screened for mutations in IS patients. Our results provide a novel dataset of neuronal enhancers involved in the spatiotemporal regulation of IS-associated genes. In addition, this work will shed light on neuronal gene regulation in general and identify novel genomic regions that could be involved in epilepsy pathogenesis and brain development.
Cognitive impairment is a devastating comorbidity of epilepsy. However, the mechanisms by which recurrent seizures induce cognitive impairments that persist even in seizure-free periods are not well understood. This gap in knowledge hampers the development of therapeutic interventions to reduce cognitive deficits associated with epilepsy. We found that seizure-induced increases in the transcription factor \( \Delta FosB \) trigger a chain of events leading to epigenetic suppression of immediate-early genes necessary for synaptic plasticity in the hippocampus, with consequences for cognitive function. Nuclear \( \Delta FosB \) expression was dramatically increased in dentate granule cells in both pharmacologic (kainate, KA) and genetic (Alzheimer’s disease transgenic, AD) mouse models with chronic seizures and cognitive deficits. Two key features of \( \Delta FosB \) make it stand out:

(1) \( \Delta FosB \) has an unusually long half-life, on the order of weeks, and (2) \( \Delta FosB \) epigenetically regulates gene expression in other brain regions after chronic stimulation such as occurs with brain injury or exposure to drugs of abuse. Thus, sustained increases of \( \Delta FosB \) in the hippocampus after recurrent seizures could play important roles in dysregulating gene expression necessary for synaptic plasticity and cognitive function. Indeed, in the hippocampus of both KA and AD mice, we found increased binding of \( \Delta FosB \) to the promoter of the \( c-fos \) gene, an activity-dependent immediate-early gene that is often used as a marker of neuronal activity. However, \( c-fos \)-mediated gene expression is also critical for synaptic plasticity and hippocampal function. Increased binding of \( \Delta FosB \) to the \( c-fos \) promoter led to recruitment of histone deacetylase, deacetylation of the \( c-fos \) promoter, and suppression of \( c-fos \) expression, even in the presence of ongoing seizure activity. Notably, treatment of chronically epileptic mice with an HDAC inhibitor restored induction of dentate \( c-fos \) expression upon exploration of a novel environment, indicating that removing epigenetic suppression of \( c-fos \) expression improves information processing. These results indicate that \( \Delta FosB \) plays a critical role in regulating hippocampal gene expression and information processing in mice with chronic seizures, suggesting that blocking its actions may improve cognitive function in epilepsy and AD.
More than 800 mutations have been identified in the voltage-gated sodium channel genes SCN1A and SCN2A in human epilepsies, including genetic epilepsy with febrile seizures plus (GEFS+), Dravet syndrome, and benign familial neonatal-infantile seizures. Family members with the same mutation frequently display variation in the clinical severity of the disease, suggesting that other factors modify the primary mutation. Several mouse models have been generated to study the genetic basis of epilepsy. A common feature of these epilepsy models is that genetic strain background alters the disease phenotype, suggesting that genetic modifiers contribute to epilepsy. The Scn2aQ54 transgenic mouse model has an epilepsy phenotype that varies depending on the genetic strain background. Scn2aQ54 mice congenic on the C57Bl/6J (B6) strain exhibit delayed seizure onset and improved survival compared with (B6xSJL/J)F1.Q54 mice. Two dominant modifier loci influencing the Scn2aQ54 epilepsy phenotype were mapped and designated Moe1 and Moe2. We fine-mapped the Moe1 locus using interval-specific congenic mouse strains and identified candidate modifier genes by RNA-Seq analysis. Consideration of gene function and RNA-Seq expression data identified Hlf as a strong candidate modifier gene. Hlf, hepatic leukemia factor, is a member of the proline and acidic amino acid–rich basic leucine zipper (PAR bZIP) transcription factor family and has previously been linked to epilepsy in PAR bZIP (Dbp, Tef, Hlf) knockout mice. Hlf knockouts were generated and crossed to Scn2aQ54 mice to assess the effect on Scn2aQ54 phenotype severity and seizure frequency. Alteration of the Scn2aQ54 phenotype by Hlf in double mutant mice will support its contribution as an epilepsy modifier gene. Identification of epilepsy modifier genes may suggest new targets for improved treatment of epilepsy and advance molecular diagnostic capabilities by identifying those patients who are most at risk for developing severe epilepsy.
#4 – Epigenetic Regulation of the SCN1A Gene for the Treatment of Dravet Syndrome

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Dravet syndrome is a severe myoclonic epilepsy, with age of onset in the first years of life. About 70% to 80% of Dravet cases are associated with heterozygous loss-of-function mutations in the SCN1A gene, which codes for the pore-forming subunit of a voltage-gated sodium channel (NaV1.1). The existing treatments for Dravet are ineffective and may cause detrimental cognitive and mood-altering side effects. In most known cases, Dravet mutations do not produce detectable amounts of mutant mRNA or protein, and the main characteristics of the Nav1.1-mediated sodium current are not significantly altered, although its amplitude is diminished. We found that increased expression of the remaining normal copy of the SCN1A gene can be achieved through changing its epigenetic regulation status by interfering with the activity of naturally occurring regulatory RNAs (NATs). Normally, NATs slow down the transcription of their specific target genes. Here, we show that oligonucleotide-mediated interference with the SCN1A NAT function leads to a 10-fold to 50-fold upregulation of SCN1A mRNA in vitro in human cell lines, including Dravet fibroblasts from patients with 5 different mutations. SCN1A mRNA was also upregulated by up to 30% in the brain of African green monkeys and in transgenic mouse models of Dravet with E1099X and E1130X mutations, after intrathecal injection of anti-SCN1A NAT oligonucleotides compared with vehicle control. In a mouse Dravet model, seizure frequency was reduced by 70% after a month-long treatment with an anti-SCN1A NAT oligonucleotide. These findings may lead to the development of a novel disease-modifying treatment for Dravet syndrome. Establishing the efficacy and safety of disease-modifying compounds that target naturally occurring regulatory RNAs in a cell- and gene-specific manner has important implications for a wide variety of human genetic disorders.
Epilepsy is a neurological disorder that can develop following brain injuries such as status epilepticus (SE). SE triggers molecular changes such as gene transcription that contribute to the development of epilepsy. Using the kainic acid (KA) model of epilepsy, we determined the contribution of chromatin remodeling to gene transcription changes in the hippocampus of animals with KA-induced epilepsy. We found that KA-induced SE triggered acute and persistent changes in two states of DNA methylation, 5-methylcytosine and 5-hydroxymethylcytosine, in the hippocampus. We also found significant changes in the gene expression DNA methylating enzymes in the hippocampus following KA-induced SE. Interestingly, DNA methylating enzymes are known to be active during memory consolidation in a seizure-free brain. In addition, induction of SE resulted in DNA methylation changes at the brain-derived neurotrophic factor (BDNF) genes. BDNF DNA methylation is altered during memory consolidation, and inhibition of DNA methylation disrupts memory formation. Memory deficits are a common comorbidity of human epilepsy and KA-induced epilepsy. We have hypothesized that disrupted DNA methylation may contribute to memory deficits associated with epilepsy. We found that by altering DNA methylation, we can rescue memory deficits in KA-induced epilepsy. These results suggest that chromatin structure modifications in the form of DNA methylation may serve as a candidate mechanism for gene transcription in the hippocampus after SE during memory consolidation. These studies constitute an initial step towards elucidating the role of DNA methylation in aberrant memory formation in the seizure-damaged hippocampus. Further work will determine the way in which BDNF is regulated during memory consolidation in the KA model, which will continue to clarify the role of BDNF transcription in the epileptic brain and during memory formation. In addition, we will continue to determine the role that DNA methylation plays in epilepsy and the way in which altered DNA methylation may affect memory in the seizure-susceptible brain.
Astrocytes modulate neuronal activity, synaptic transmission, and mammalian behavior by releasing neuroactive substances. Whether astrocytes play a role in epilepsy in vivo is unknown. Using a combination of astrocyte-specific molecular genetics, with the in vivo pilocarpine model of epilepsy and long-term continuous video-electroencephalogram recordings as well as an in situ model of epilepsy, we provide the first demonstration that astrocytes modulate the progressive development of epilepsy in vivo, including seizure occurrence, brain damage, and behavioral deficits. Inhibition of neuroactive substance release by the expression of a dominant negative SNARE domain in astrocytes increased the latency to onset of epileptiform activity in situ and reduced the frequency of epileptiform events. Similarly, in vivo data showed that astrocytic dnSNARE expression delayed seizure onset after pilocarpine-induced status epilepticus and attenuated the progressive increase in seizure frequency over 5 months. The reduced seizure frequency was accompanied by an attenuation of hippocampal sclerosis, including neuronal death and reactive astrocytosis, and by an attenuation of behavioral abnormalities detected in the open field. Because the delay in seizure onset and the reduced seizure frequency were mimicked by the intracerebroventricular delivery of the N-methyl-D-aspartate receptor (NMDAR) antagonist D-AP5 in wildtype littermates, and because the anticonvulsant effect of D-AP5 was prevented following astrocytic dnSNARE expression, we conclude that astrocytes modulate epileptogenesis and subsequent progressive development of seizures through a pathway involving NMDAR. Thus, these studies identify the astrocyte as a new cellular target for the development of therapeutic strategies for the treatment of epilepsy.
#7 – Probing Seizure Initiation With Light: Spatiotemporal Influence of Optogenetic Stimulation of the Cortical Focus in Rats With Absence Epilepsy

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The way primary generalized seizures are triggered and affect the whole brain remains poorly understood. Here, we investigate the initiation and propagation of absence seizures using an integrated device for combined optogenetics and multielectrode array (MEA) recordings in freely moving WAG/Rij rats, a genetic model of absence epilepsy.

We first characterized spontaneous seizures in 10 animals implanted with a 32- or 96-element MEA in the somatosensory cortex, the presumed cortical focus. We hypothesized that previously reported delays between distinct cortical sites would reflect propagating waves of epileptic activity. We consistently observed waves during the ictal period and sometimes more complex patterns on the larger arrays. It was sometimes possible to observe preictal and interictal activity restricted to a subset of electrodes, delineating the presumed focus.

We then hypothesized that seizure transitions could be triggered by random fluctuations or external inputs. We injected two animals with either channelrhodopsin2 (VSV.G-hSyn-ChR2-EYFP) or its variant C1V1 (AAV5-CaMKII-C1V1(T/T)-EYFP) and implanted them with our integrated opto-MEA. We found that optical stimulation at 10 Hz could evoke oscillations similar to spike-wave discharges (SWD), which sometimes became self-sustained after the stimulation period. Using a random stimulation protocol across several hours every day, this latter effect was found statistically significant and specific to frequencies around 10 Hz, although with a low probability of induction (around 10%).

Finally, we examined the way optically induced SWDs propagate across the cortex and compared it with spontaneous seizures. The directions of propagation are different, suggesting that the optical perturbation travels to the epileptogenic focus until the latter becomes able to sustain seizures by itself.

In sum, these results inform the way seizures are initiated and propagate in the cortex. The long-term goal is to identify factors leading to a seizure and find neuromodulation protocols able to mitigate them.


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#8 – On-Demand Optogenetic Control of Spontaneous Seizures in a Mouse Model of Temporal Lobe Epilepsy

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Temporal lobe epilepsy (TLE) is not only the most common type of epilepsy in adults but is also often medically refractory. Moreover, current systemic treatments have major negative side effects. However, because temporal lobe seizures tend to arise from discrete brain regions before overt clinical behavior, it is theoretically possible to design a temporal and target-selective intervention. To achieve temporal specificity, we developed a closed-loop response system to detect seizures online using the intrahippocampal kainate mouse model of TLE. To achieve target-specific intervention, we employed optogenetic techniques. Seizures were detected in real time, triggering light delivery to the hippocampus and activation of light-sensitive opsins, which provided immediate, temporary control of specific cell populations. Two approaches were taken. First, we selectively expressed the inhibitory opsin halorhodopsin in excitatory principal cells. Seizures were stopped rapidly with light application (57% ± 12% of seizures stopped within 1 second of light delivery; seizure duration after detection was reduced by 70% ± 8%; 6 animals, p < 0.01 for each animal). Next, the excitatory opsin channelrhodopsin was selectively expressed in parvalbumin positive interneurons, a subpopulation of inhibitory cells that make up less than 5% of neurons in the hippocampus. Even with this highly restricted opsin expression, light significantly reduced seizures (59% ± 11% stopping within 5 seconds of light delivery; 43% ± 11% post-detection duration reduction, n = 8 animals, p < 0.05; at the individual animal level, 5 of 8 animals showed a significant p < 0.05 effect). Our findings demonstrate that a temporal and target-specific intervention is possible; spontaneous temporal lobe seizures can be detected and stopped while directly affecting only specific cell populations in a spatially restricted manner. Clinical approaches built on these principles (affecting a minimum number of cells and only at the time of a seizure) may overcome many of the side effects of currently available treatment options.

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Prolonged status epilepticus (SE) in humans causes substantial mortality and morbidity accompanied by severe brain inflammation and injury. Currently, the only effective treatment is to stop the seizures quickly enough to prevent brain damage, whereas the delayed treatment that can be given several hours after SE onset is highly desired. Prostaglandin E2 (PGE2) is emerging as an important mediator of neuronal injury during brain inflammation, in large degree via its EP2 receptor subtype. Recent advances in chemical biology provide pharmacologic tools to be used for a better understanding of this key prostaglandin receptor regarding its physiologic and pathologic functions. We investigated the therapeutic effects of a novel brain-permeant EP2 receptor antagonist, TG6-10-1, in the mouse pilocarpine model of SE. A 1-hour episode of pilocarpine-induced SE in mice is sufficient to induce powerful neuroinflammation characterized by rapid and long-lasting induction of a significant number of pro-inflammatory enzymes and cytokines in hippocampus. Systemic administration of TG6-10-1 (5 mg/kg, i.p., 3 doses) in mice beginning 4 hours after SE onset reduced delayed mortality, accelerated weight regain and functional recovery, reduced the formation of inflammatory cytokines and gliosis in hippocampus, maintained the integrity of blood-brain barrier, and reduced delayed neurodegeneration in hippocampus. Intriguingly, behavioral seizure scoring and electroencephalographic recording demonstrated that the EP2 antagonist is not an acute anticonvulsant in the pilocarpine SE model. In summary, pharmacologic blockade of EP2 receptor following SE yields a broad range of beneficial effects, suggesting that EP2 receptor is a major mediator of seizure-induced neuroinflammation and neurodegeneration; thus, EP2 receptor antagonism might represent an adjunctive therapeutic strategy to treat SE along with antiepileptic medications.

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Brain-derived neurotrophic factor (BDNF) has attracted attention for its potential role in the etiology and treatment of temporal lobe epilepsy (TLE). BDNF is upregulated during seizures and is thought to contribute to hyperexcitation and development of epilepsy. Conversely, reports have demonstrated that chronic infusion of BDNF attenuates epilepsy development. These contrasting effects have prevented a full understanding of BDNF’s role in TLE. Our initial studies identified two related phenomena. First, mice in which activity-dependent BDNF expression is attenuated (BDNFK-IV) had lower seizure thresholds following kainate administration. BDNFK-IV animals showed decreased latency to seizure, increased seizure intensity, and higher mortality. Second, expression of GABAergic markers localized to dendrite-targeting interneurons (cortistatin, somatostatin, neuropeptide-Y, and tachykinin 1) was impaired. We labeled cortistatin-positive interneurons by crossing a mouse driving cre-recombinase from the cortistatin promoter (Corttm1(cre)Zjh/J) to a tdTomato reporter (B6.Cg‐Gt(Rosa)26Sortm14(CAG‐tdTomato)Hze/J). In hippocampus, 88% of cortistatin interneurons co-label with somatostatin, 5% with parvalbumin, and 2% have a perineuronal net. We crossed Corttm1(cre)Zjh/J mice with animals carrying a floxed attenuated diphtheria toxin cassette (B6;129- Gt(Rosa)26Sortm1(DTA)Mrc/J). In these mice, cre-recombinase expression in cortistatin-positive cells leads to their ablation. Seizure activity occurred in mutants between postnatal day P14 and P16 and death by P23. We asked whether BDNF signaling through its receptor TrkB contributed to hyperexcitability in these cell by crossing mice with a floxed TrkB allele (TrkBflox/flox) with Corttm1(cre)Zjh/J mice to generate animals in which TrkB was deleted in cortistatin-positive interneurons. Mutants showed hyperactivity and repetitive jumping at 5 to 6 weeks. These jumping bouts worsened, eventually leading to seizures, with a majority of animals dying by 8 to 10 weeks. To determine specificity, we crossed TrkBflox/flox animals with mice expressing cre-recombinase from the parvalbumin promoter (B6;129P2‐Pvalbtm1(cre)Abr/J). Mutants showed no hyperactivity, jumping, or seizures. Hence, BDNF/TrkB signaling in dendrite-targeting interneurons may be particularly important for preventing hyperexcitability and seizure development.
Epileptic seizures are thought to be the result of an imbalance between excitatory and inhibitory neuronal activity. One set of theories, based on slice and animal experiments, posits that a decrease in inhibition is a necessary prerequisite of epileptic activity. However, competing theories suggest that increased inhibition is necessary to synchronize the firing of excitatory cells, transforming normal activity into epileptic discharges. However, very little is known about the activity of inhibitory interneurons during seizures in humans. Here, using large-scale recordings of neocortical single units in epileptic patients, we show that fast-spiking interneuron activity initially parallels that of excitatory cells as seizures first spread through the neocortex, a finding consistent with what is known about feedforward drive of both inhibition and excitation. Unexpectedly, however, we find that inhibitory neurons cease firing well before the end of the seizures. We present evidence based on a novel set of analyses that suggests that these inhibitory interneurons stop firing because they enter depolarization block, where most sodium channels are inactivated and incapable of sustaining another action potential. It is striking that this absence of inhibitory activity is accompanied by dramatic increases in the amplitude of local seizure waves and occurs at a time when seizure symptoms are often at their worst. This pattern of human interneuron activity is seen during all spike-and-wave seizures, independent of etiology (cortical dysplasia vs. mesial temporal sclerosis) or seizure focus (hippocampus vs. neocortex). Thus, a remarkably consistent pattern of inhibitory neuronal activity appears to exist during human focal seizures with secondary generalization. These findings suggest that it may be possible to alter or prevent the spread of seizures by using pharmacologic manipulations that prevent inhibitory interneurons from entering depolarization block. This possibility represents a potentially novel and powerful therapeutic avenue in the treatment of human epilepsy.
In the postnatal developing brain, the rapid formation of excitatory synapses, especially the recurrent connections in the neocortex, could lead to runaway excitation on principal cells and instability of the cortical circuits. Many mechanisms are implemented to stabilize network activity, of which GABAergic inhibitory neurons play an essential role. The activity of individual cortical neurons critically depends on the relationship between the levels of synaptic excitation and inhibition that they receive. Disruption of the proper excitation and inhibition ratio often leads to neurologic disorders including epilepsy. We found that individual layer 2/3 pyramidal neurons in the developing mouse visual cortex exhibited highly heterogeneous spiking activity in vivo. Slice experiments showed that the more active neurons receive more excitation than the less active ones and, concurrently, the more active neurons also receive more inhibition than the less active ones. Therefore, the excitation and inhibition ratio is maintained across neurons despite their different spiking activity. We hypothesize that the spiking activity of pyramidal neurons positively regulates their synaptic inhibition to maintain the excitation and inhibition ratio. To test this hypothesis, we genetically suppressed the spiking activity of a small random subset of layer 2/3 pyramidal neurons in vivo by expressing inward rectifying potassium channel Kir2.1. Furthermore, expression of the light-activated cation channel Channelrhodopsin-2 in two molecularly distinct GABAergic neurons, the parvalbumin (PV)- and somatostatin (SOM)-expressing cells, allowed us to selectively activate these two cell types. We found that in slices Kir2.1-expressing pyramidal neurons received significantly less inhibition from PV cells compared with their neighboring control neurons, whereas the inhibition from SOM cells was similar. This result indicates that individual layer 2/3 pyramidal neurons autonomously adjust their levels of inhibition in an activity-dependent manner by selectively modulating the PV cell inputs.
Suppression of Adult Neurogenesis Enhances Response to the Convulsant Kainic Acid in Mice

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Postnatal neurogenesis (PN) in the dentate gyrus (DG) is necessary for physiological functions of the hippocampus. Seizures can increase the rate of PN, and adult-born neurons can influence DG excitability in animal models of epilepsy, although the models are complex. Because DG can be involved in seizure generation, we wanted to investigate how adult-born granule cells (GCs) affect seizures. Adult-born GCs may preferentially activate inhibitory interneurons, leading us to hypothesize that suppression of PN would increase response to a convulsant.

Two models of suppression of PN were used: in one, 6-week-old mice were subject to focal, low-dose irradiation over the hippocampus; these mice were compared with sham-treated mice. In the other method, 6-week-old transgenic mice expressing herpes simplex virus thymidine kinase (hSV-TK) in cells expressing glial-fibrillary acidic protein (GFAP) were fed valganciclovir. This medication activates TK and kills dividing neural progenitors (GFAP-expressing cells; GFAP-TK+ mice). GFAP-TK- mice were used as controls. Seven weeks after starting irradiation or valganciclovir, mice were implanted with depth EEG electrodes in each hippocampus and subdural electrodes over the frontal and occipital areas. Approximately 1 week after implantation, mice were administered kainic acid (KA) and recorded by video-EEG.

In response to 6 to 12 mg/kg KA, mice with suppressed adult neurogenesis exhibited a shorter latency to the first convulsive seizure (F (1, 28)6.345; p = 0.017) and a greater number of convulsive seizures (F (1, 28)7.644; p = 0.011). The first seizure was more likely to be convulsive in these mice (F (1, 28)9.014; p = 0.034). With a higher dose (16 mg/kg KA), we detected different effects: irradiated and GFAP-TK+ mice had shorter interseizure intervals (F (1, 33)12.987; p = 0.001). Some parameters were seen only in the GFAP-TK model: the duration of convulsive seizures was higher in GFAP-TK+ mice (F (1, 24) 5.968; p = 0.022). Four to 12 hours after KA injection, there was a higher interictal spike (IIS) frequency in GFAP-TK+ mice (p = 0.004); and 3 days later, GFAP-TK+ mice exhibited pyknosis in area CA3 of the hippocampus whereas controls did not. Both IIS frequency and neurotoxicity correlated with the number of convulsive seizures in GFAP-TK+ mice but not in GFAP-TK-mice.

These results are the first to suggest that removal of newborn cells leads to an exacerbated response to a convulsant.
#14 – A “Cryptic Injury” Animal Model of Acquired Temporal Lobe Epilepsy With Classic Hippocampal Sclerosis

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There are no substances that can prevent acquired epilepsy, and roughly 40% of adult patients with new-onset epilepsy suffer from intractable seizures. To discover more effective antiepileptic drugs, as well as the first antiepileptogenic therapies, new animal models are needed that resemble the human condition as accurately as possible. The most popular animal models of acquired epilepsy employ a precipitating insult that involves prolonged, severe behavioral seizures, that is, convulsive status epilepticus (CSE). Studies on the mechanisms of epileptogenesis and its prevention have so far been conducted primarily in CSE-based animal models, although CSE is rarely a cause of epilepsy in humans. Antiepileptogenesis experiments using animal models of traumatic brain injury (TBI) (e.g., lateral fluid percussion) are impractical because only a fraction of these animals develop epilepsy. Here, we present an animal model of acquired temporal lobe epilepsy (TLE) based on stimulation of the perforant pathway in freely moving rats that (1) does not involve CSE, (2) exhibits spontaneous temporal-onset seizures after a prolonged “silent period,” and (3) replicates a neuropathology typical of drug-refractory TLE—classic hippocampal sclerosis. The primary value of this animal model lies in its similarity to the human condition—that is, human-pattern neuropathology is produced in rats in vivo with negligible variability and no lethality, and every animal develops epilepsy after approximately 3 weeks. These qualities make this a reliable, relevant animal model in which to assay substances for antiepileptic and/or antiepileptogenic effects.
Insulin-like growth factor-1 (IGF-1) is present in the cerebrospinal fluid of healthy individuals. IGF-1 levels are elevated in brain tissues following head injury, with significant elevation in IGF-1 receptor (IGF-1R) phosphorylation after traumatic brain injury (TBI). IGF-1 is neuroprotective in animal models of hypoxic-ischemic and traumatic brain injury, exposure to toxins, and neurodegenerative disorders. However, effects of IGF-1 on epileptogenesis following brain injury have not been investigated. We used rapid-throughput screening technology in an organotypic hippocampal culture model of post-traumatic epilepsy to investigate the effects of IGF-1 and its downstream signaling on the development of epilepsy.

Organotypic cultures of rat hippocampus were maintained for up to 4 weeks in vitro. IGF-1, inhibitors, or vehicle were added directly to the culture medium starting from either 0 or 3 days in vitro (DIV). The development of epilepsy and level of cell death were rapidly assessed with lactate and LDH assays. The results were verified with electrical recordings of field potentials and counts of Nissl-stained neurons. Protein phosphorylation levels were analyzed by western blotting.

We found that addition of IGF-1 to the culture medium was neuroprotective immediately following injury (DIV 0–3) but caused increased spontaneous electrographic seizures and cell death between DIV 7 and DIV 28. We also found that inhibition of IGF-1R, PI3K, Akt, and mTOR between DIV 7 and DIV 28 decreased epileptic activity and cell death. Removal of IGF-1 significantly decreased phosphorylation of Akt and S6, a marker of mTOR pathway activation.

We concluded that IGF-1 is neuroprotective immediately following injury but promotes epileptogenesis in the long term via activation of Akt-mTOR signaling. Therapy design for head trauma patients should take differential action of this hormone into account—early treatment may need to focus on neuroprotection, whereas later treatment can emphasize inhibition of epileptogenesis.
#16 – Traumatic Brain Injury Alters Cortical Glutamate Network Function by Compromising GABAergic Control

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Traumatic brain injury (TBI) is a major risk factor for developing pharmacoresistant epilepsy. Although disruptions in cortical and hippocampal circuitry are associated with TBI, the precise mechanisms by which brain injury leads to epileptic network activity is unknown. In this study, we investigated how controlled cortical impact (CCI), a model of TBI, affects the spatial and temporal parameters of cortical glutamate network activity. Using FRET-based glutamate biosensors, we optically mapped cortical glutamate signaling in real time while simultaneously recording cortical field potentials. Ten-week-old male C57BL/6 mice underwent sham or CCI injury, and acute cortical brain slices were obtained 2 to 4 weeks postinjury, a time after injury but before the onset of spontaneous seizures. Slices from CCI-injured cortex were loaded with glutamate biosensor immediately before imaging and recording. Results were compared with slices from sham-injured mice. Electrical stimulation evoked polyphasic, epileptiform field potentials and disrupted input-output relationships in CCI-injured cortex. High-speed glutamate biosensor imaging showed that glutamate signaling evoked by electrical stimulation was significantly increased in the injured cortex. Elevated glutamate responses were consistent with epileptiform activity, were highest in the area directly adjacent to the injury, and spread via deep cortical layers. Cortical glutamate release from CCI-injured cortex was sequentially activated with the same temporal parameters as disinhibited control slices. Areas of cortical glutamate signaling were consistent with loss of GABAergic interneurons as measured by parvalbumin immunohistochemistry. Our results suggest that specific cortical subnetworks may facilitate the spread of epileptiform activity due to loss of GABAergic control following TBI. Overall, our studies suggest that cortical reorganization resulting from TBI leads to increased network excitability by altering GABAergic function.
**#17 – Erythropoietin Attenuates Loss of KCC2 and IPSCs in a Clinically Relevant Model of Preterm Brain Injury: Insights Into Epileptogenesis**

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**Introduction:** Children born preterm are prone to epilepsy. During development, the potassium chloride co-transporter KCC2 is upregulated and directs the formation of inhibitory circuits. KCC2 expression initiates effective inhibition by regulating chloride homeostasis and driving GABA receptor activation to hyperpolarization. KCC2 monomers form oligomers with maturation, and phosphorylation of KCC2Ser940 increases functional membrane expression.

**Objective:** Preterm infants with brain injury have significant KCC2 loss. Understanding how brain injury late in gestation affects circuit development will provide insights into epileptogenesis and reveal new therapeutic targets. We propose that late gestation hypoxiaischemia alters KCC2 upregulation, impairing the formation of essential inhibitory circuits.

**Methods:** Prenatal transient systemic hypoxiaischemia (TSHI) was performed on embryonic day 18 (E18) rats to mimic brain injury from placental insufficiency in infants born extremely preterm. Following TSHI, erythropoietin (EPO) or vehicle was administered from postnatal day P1 to P5 (2000 IU/kg/dose/ip). Whole-cell voltage clamp of CA3 pyramidal neurons was used to assess inhibitory postsynaptic currents (IPSCs). KCC2 mRNA and protein were assessed in microdissected CA3 from P2 through P15 using qPCR, western blot, and immunohistochemistry.

**Results:** A 28% reduction in the ratio of monomeric pSer940 KCC2 to KCC2 in the CA3 of TSHI pups was present at P7 compared with sham. After TSHI, loss of functional KCC2 was sustained, and at P11 oligomeric KCC2 was significantly reduced compared with sham (1.084 ± 0.054 vs. 0.089 ± 0.053, p = 0.009, n = 12). IPSC frequency was also markedly reduced following TSHI at P10–11 (n = 12 cells/7 rats). Significantly, EPO treatment attenuated loss of KCC2 oligomers and reversed pathological alterations in IPSC frequency.

**Conclusions:** Following prenatal TSHI, developmental KCC2 upregulation is significantly impaired and functional, membrane-bound KCC2 is decreased. Postnatal EPO normalized TSHI-induced reductions in KCC2 protein expression and IPSC frequency, suggesting it is possible to reverse abnormalities in inhibitory cortical development. KCC2 loss may be an essential component of the molecular pathophysiology of late-gestation brain insults and an important contributor to the development of epilepsy in children born very preterm.
#18 – Prophylactic Effect of In Vivo Optogenetic Stimulation on Post-Traumatic Epileptogenesis in Mice

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Traumatic brain injury initially causes a loss of neuronal activity and brain function due to tissue damage, deafferentation, and neuronal death. This loss of neuronal activity has been hypothesized to activate homeostatic regulation mechanism and contribute to post-traumatic epileptogenesis. Based on this hypothesis, we examined whether post-traumatic epileptogenesis may be prevented by stimulating cortical activity at the early stage following traumatic brain injury. In adult transgenic mice expressing Thy1-channelrhodopsin2-YFP (ChR2-YFP) in cortical layer V pyramidal neurons, we generated the undercut model of post-traumatic epileptogenesis. The mice were divided into an undercut group and an optogenetic stimulation group. In vivo chronic optogenetic stimulation was applied on the second day of injury by mounting a miniature blue LED (485 nm) on a cranial window to deliver light pulses 8 hours daily for 7 days. Two weeks after the injury, field potential recordings were made from cortical slices prepared from both groups. Epileptiform activities could be induced in 43.8% of the undercut mice. In the optogenetic stimulation group, the percentage of mice in which epileptiform activity could be evoked in slices decreased to 12.5%. Patch clamp recording from cortical layer V pyramidal neurons indicated that the frequencies of both excitatory and inhibitory spontaneous postsynaptic currents were significantly lower in the optogenetic group than the undercut group, but their amplitudes did not change. The results suggested that homeostatic mechanism of activity regulation may play a role in post-traumatic epileptogenesis and that enhancing neuronal activity at the early stage after traumatic brain injury has a prophylactic effect on post-traumatic epileptogenesis.

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The increased risk for later development of Alzheimer’s disease (AD) among epilepsy patients suggests the importance of studies that investigate epilepsy-related neuropathologic changes, especially as they may relate to specific ApoE genotypes. Hyperexcitation induces expression of β-amyloid precursor protein (βAPP), sAPPα release, and interleukin-1 (IL-1) overexpression, leading to increased expression of the precursors of the two hallmarks of AD—Aβ plaques and neurofibrillary tangles. Tissue levels and cellular expression of βAPP, ApoE, and IL-1, and numbers of Aβ plaques, were analyzed in frozen and/or paraffin-embedded tissues from temporal lobes resected from 91 patients (3 months to 71 years) with medication-resistant temporal lobe epilepsy. Glial activation with IL-1 overexpression was prominent in the first decade, as was neuronal distress evinced by elevated tissue and neuronal expression of βAPP and ApoE. Importantly, these changes varied with ApoE genotype. Patients with APOE ε3,3 genotype had larger neurons with less DNA fragmentation than other genotypes and greater numbers of activated IL-1-immunoreactive glia per neuron, suggesting neuronal resilience against stress. However, this resilience may foster plaque burden—25% of those with APOE ε3,3 genotype had plaques whereas no patient with even one APOE ε2 allele had Aβ plaques. Our findings show that the strength of the neuronal stress response elicited by epilepsy is related to patient APOE genotype without regard to patient age, perhaps explaining why Aβ plaque deposition is an early and common event in epilepsy that is abated by possession of an APOE ε2 allele. Our findings also are consistent with the idea that hyperexcitation elicits compensatory responses aimed at neuron repair and survival, but when chronic, these events give rise to the precocious appearance of neuropathologic changes. Moreover, they suggest that ApoE genotyping may be a tool in treatment decision-making.

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Progressive neurodegeneration often occurs because of prolonged and/or repetitive seizure activity. Ictal neurodegeneration has traditionally been viewed as a consequence of glutamate-induced excitotoxicity, resulting from calcium overload that activates pro-apoptotic molecular cascades. Ischemia, however, activates the same pro-apoptotic pathways as excitotoxicity. Abnormal capillary vasospasms during ictal periods, therefore, could contribute to apoptotic ictal neurodegeneration. Ischemia and local pockets of hypoxia have been observed macroscopically in regions that subsequently become epileptic foci, though the underlying vascular mechanisms are unknown. Determining the relative contribution of excitotoxicity versus ischemia is further complicated by the fact that the consequences of excitotoxicity can be tested in vitro, whereas the impact of abnormal ictal hippocampal capillary vasodynamics can be determined only in vivo. Here, we test the role of ictal pericytic-capillary vasospasms—sudden vascular constrictions that reduce blood flow—as a contributor to hippocampal neurodegeneration. We use a novel imaging technique to visualize spontaneous cerebral capillary vasospasms in vivo. In fact, the contribution of capillary vasospasm–driven hypoxia versus excitotoxicity has never before been assessed in any neurodegenerative disease model. Fiber-coupled confocal microscopy allows for direct microscopic blood flow imaging in the hippocampus of kainate model mice as well Kv1.1 knockouts, a genetic model of human episodic ataxia type 1 epilepsy, making these studies directly relevant to human temporal lobe epilepsy. We show, for the first time, normal and abnormal ictal hippocampal vasoconstrictions in vivo, in awake animals, driven by pericytes. We found that apoptotic neurons in epileptic animals are tightly coupled spatially to the hippocampal microvasculature compared with nonapoptotic cells. This indicates that abnormal capillary vasospasms contribute to ictal neurodegeneration because excitotoxicity has no known spatial association to the vasculature. These effects reveal that 54% of neurodegeneration in epilepsy is driven by abnormal blood flow and that most ictal neurodegeneration is reversible through oral administration of blood flow–regulating drugs.
#21 – Time to Pediatric Epilepsy Surgery Is Related to Disease Severity and Diagnostic and Sociodemographic Factors

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Objective: To identify clinical, diagnostic, and sociodemographic factors associated with time from epilepsy onset to surgical evaluation and treatment in a large cohort of children having epilepsy surgery.

Methods: Data were abstracted from records of 430 children (< 18 years) who had epilepsy neurosurgery at the University of California, Los Angeles (UCLA), from 1986 to 2010.

Multivariable Cox proportional hazards models were used to analyze unique associations of clinical severity, pre-referral brain magnetic resonance imaging (MRI), and sociodemographic characteristics with “time to surgery” (age of onset to surgery; median 3.25 years, IQR 1.33, 6.66), controlling for year of surgery.

Results: Shorter time to surgery was associated with active (HR 5.67, 95% CI 3.74–8.70) and successfully treated infantile spasms (HR 2.20, 95% CI 1.63–2.96; ref: no history infantile spasm); ≥ daily seizures (HR 2.09, 95% CI 1.58–2.76; ref: < daily seizures); MRI before referral regardless of imaging findings (HR 1.95, 95% CI 1.47–2.58; ref: no MRI); private insurance (HR 1.54, 95% CI 1.14–2.09; ref: Medicaid); and Hispanic ethnicity (HR 1.38, 95% CI 1.01–1.87; ref: non-Hispanic white). There were race/ethnicity by insurance interactions with shortest time to surgery for Hispanic children with private insurance (Log-rank p = 0.049).

Conclusions: Shorter intervals to surgical treatment were associated with greater epilepsy severity and insurance type, consistent with existing literature. Associations of shorter times to treatment with having a brain MRI before referral and Hispanic ethnicity were unexpected and warrant further investigation. More knowledgeable referring providers and parents with greater help-seeking capability may explain obtaining an MRI before referral. Shorter intervals to surgery among Hispanic children may relate to the same factors yielding an increased volume of Hispanic children receiving surgery at UCLA since 2000. Identifying the clinical and nonclinical impediments to timely surgery is important for developing interventions designed to improve access and outcomes.

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Both Hebbian and homeostatic synaptic plasticity are most robust during the neonatal period, in which the incidence of seizures is one of the highest across the lifespan. Neonatal seizures are often refractory to conventional antiepileptic drugs and can result in later life epilepsy, cognitive deficits, and autism. We have previously shown that early-life seizures (HS) result in acute and long-term enhancement of AMPAR function and impairment in LTP. In addition to Hebbian synaptic plasticity, homeostatic synaptic scaling calibrates neuronal excitability by adjusting synaptic strengths during prolonged changes in synaptic activity. Our recent study has shown that HS itself can evoke PLK2-mediated homeostatic modulation of seizure-induced enhancement of AMPAR function. Here, we hypothesize that neonatal seizures may alter homeostatic synaptic scaling in epileptic neurons in response to further chronic activity changes. Neonatal hypoxic seizures were induced by graded global hypoxia at postnatal day 10. We first established a new acute culture procedure that allows us to keep the brain slices in modified ACSF in vitro up to 48 to 72 hours. Whole-cell patch clamp recordings of AMPAR mEPSCs were made in cortical neurons of acutely cultured slices removed 24 to 48 hours after HS. We found that chronic activity blockade for 24 to 48 hours by 1µM TTX induced significant increases in amplitude and frequency of AMPAR mEPSCs in neurons from HS rats. However, the decrease in synaptic strength in response to elevated synaptic activity by application of 100 µM Picrotoxin at 24 to 48 hours is occluded in neurons from HS rats. Overall, our data reveal an impaired homeostatic synaptic scaling down in neurons following early-life seizures, which may, at least in part, contribute to neonatal seizure-induced long-term neuronal hyperexcitability and epileptogenesis.
Activity-dependent mechanisms play a critical role in the formation and refinement of neural circuits during brain development. When neural activity is blocked in the rat neocortex by local infusion of the sodium channel antagonist TTX, a severe seizure disorder develops. The seizures themselves and their electrographic (EEG) correlate are essentially identical to those seen in children with infantile spasms, one of the catastrophic epilepsies of childhood (Epilepsia. 2008 Feb; 49(2):298–307). The fundamental question arising from this observation is as follows: How does blockade of neuronal activity in early life produce such a severe hyperexcitable state? One possibility is that when the developing brain experiences regional hypoactivity, it compensates via homeostatic mechanisms to increase the excitability of nearby neurons or neurons at distant sites in the cortex. To determine whether remodeling of recurrent excitatory and/or inhibitory connectivity contributes to a state of compensatory hyperexcitability, a group of TTX-infused rats that exhibited frequent spasms and a group of saline-infused control animals were examined. Immunohistochemistry for GABAergic and glutamatergic markers was used to probe alterations in neuron number, axon arborization, and synapse density. Saline-infused animals revealed a wide distribution of parvalbumin (PV) and GAD65/67 positive cell bodies and processes across all the cortical layers. In contrast, in animals with spasms, the number and staining intensity of PV and GAD65/67 positive interneurons were noticeably decreased in the opposite hemisphere, immediately contralateral to the TTX infusion site. Glutamatergic nerve terminals, which were identified via VGLUT1 staining, were found to be abundant in both groups. These findings suggest that the loss of activity from callosal fibers projecting from one hemisphere of the neocortex may affect the formation and/or maintenance of cortical interneurons in the contralateral side and produce a shift in the excitatory/inhibitory balance, which likely contributes to neocortical hyperexcitability in this animal model of infantile spasms.
Infantile spasms (IS) are a class of syndromes that can result in developmental delays and full epilepsy. Few good therapeutic options exist. Elucidating the underlying pathophysiologic mechanisms is essential for developing effective interventions. Here, we present data suggesting that a mouse model with conditional knockout of the adenomatous polyposis coli (APC) gene in excitatory neurons (APC cKO) shows characteristics associated with IS. Early neonatal APC cKO mice display spasms (increased high amplitude spontaneous movements) compared with control littermates. Both spontaneous and evoked excitatory electrical activity is increased in the APC cKO cortex. Synaptic spines show increased density (number of spines per unit length) on the apical dendrite of layer 5 pyramidal neurons. In addition, adult APC cKO mice display learning and memory deficits in cognitive behavioral assays. These data suggest that the APC cKO mouse may recapitulate the developmental spectrum associated with IS.

The APC cKO mouse brain has increased levels of β-catenin and Wnt signaling, consistent with the role of APC as a negative regulator in the canonical Wnt pathway. β-catenin is known to have dual functions in the N-cadherin synaptic adhesion complex and the Wnt signaling pathway. Deregulation of both networks in the developing brain leads to altered axon guidance cues, excessive branching, and aberrant density and plasticity of excitatory synapses, all consistent with enhanced seizure susceptibility. Intriguingly, numerous genes associated with human IS (e.g. FoxG1, ARX, TSC1/2, and Magi-2/S-SCAM) also regulate Wnt/β-catenin signaling and/or synaptogenesis. Defining a common molecular framework across multiple mouse models of IS would provide essential insights for discovering novel therapeutic strategies for effective intervention in IS.
#25 – Aberrant Neurogenesis in Infantile Spasms and Ohtahara Syndrome: Implications for Cognitive Development

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Rationale: Infantile spasm (IS) and Ohtahara syndrome (OS) are early-onset epileptic encephalopathies that may be of structural, metabolic, genetic, or unknown cause. Even when spasms are controlled, developmental outcome is often poor and the incidence of autism is high. Because these syndromes have their onset during a critical period of brain development, we hypothesized that hippocampal and cortical neurogenesis may be affected in children with IS and OS.

Methods: Fluorescence immunohistochemistry studies were performed on formalin-fixed, paraffin-embedded brain sections from six infants with IS/OS (2 weeks–2 years old) and five age-matched controls.

Results: In preterm and term control infants, high densities of doublecortin (DCX)-immunofluorescent immature neurons were identified in the subgranular zone (SGZ) of the hippocampus, the subventricular zone (SVZ) of the lateral ventricles, and the cerebral cortex. This identification was associated with the presence of GFAP-labeled radial glia. DCX labeling dropped off dramatically by 3 months of age in nonepileptic specimens. In contrast, in specimens from children with IS/OS, high densities of DCX-positive neurons were present in the SGZ, SVZ, and cortex through late infancy. These neurons were frequently abnormally distributed and were often found in clusters. Phospho-AKT neuronal labeling also was identified. Excessive hippocampal neurogenesis was seen both in the absence and presence of morphologic hippocampal abnormalities.

Conclusions: Infantile epileptic encephalopathies are associated with excessive and aberrant hippocampal and cortical neurogenesis. In animal models of epilepsy, these newborn neurons are often abnormally integrated into neuronal circuits and are associated with later cognitive impairments. These findings suggest a potential mechanism for poor developmental outcomes in children with IS despite successful control of their spasms.
Rationale: Ischemia in the immature brain is an important cause of refractory seizures. The exact timing of neonatal stroke onset is usually unclear, and the diagnosis is delayed until presentation with seizures a few to several hours later. Developmental profiles of chloride co-transporter expression and function in immature brains have been proposed to underlie the efficacy of GABA-agonists to act as hyperpolarizing agents. To investigate the antiseizure efficacy of the first-line anticonvulsant and GABA\textsubscript{A}-agonist phenobarbital (PB) and NKCC1 antagonist bumetanide (BTN) as adjunct treatment on neonatal ischemic-seizures, we utilized unilateral carotid-ligation to produce ischemia and acute ischemic seizures in postnatal day 7, 10, and 12 CD1 mice.

Methods: Unilateral ischemia was induced by right carotid permanent ligation. Acute ischemic post-stroke seizures were recorded using video-EEG in P7, 10, and 12 pups with subdermal scalp electrodes. After recording baseline post-ligation video EEGs for 1 hour, we gave each pup IP injections of 25 mg/kg loading doses of sodium PB followed by BTN (0.1 mg/kg) 1 hour later. Quantitative video EEG analysis was done for the same duration of pre- and post-treatment EEGs using Pinnacle (Pinnacle Technology Inc., KS) seizure scoring and Insight software (Persyst Development Corp., AZ). Post-ligation brains were examined for stroke injury and western blot analyses to evaluate expression profiles of the adult-form electroneutral chloride co-transporter KCC2.

Results: Severity of acute ischemic seizures was highest at P7. PB was an efficacious antiseizure agent in P10- and P12-seizing pups. At P12, PB stopped both the occurrence of behavioral seizures as well as the associated electrographic seizures that were quantified as time spent seizing (n = 14) on EEG. In contrast, BTN treatment 1 hour following PB failed to act as an efficacious adjunct therapy and aggravated the ischemic seizures at P7 and P10 in females. At P7, both PB and add-on BTN treatment failed to stop both electrographic and behavioral ischemic seizures (n = 15). Post-ischemic downregulation of KCC2 expression was detected at all ages tested compared to age-matched naïve (control) brains. Similar downregulation was not detected for NKCC1 expression. At P7, a gender-specific susceptibility to severe ischemic seizures was detected in males that correlated with a lag in KCC2 expression levels in naïve males compared with females and was not detected at older ages.

Conclusion: Age-dependent susceptibility to ischemic seizure severity was detected. Anticonvulsant efficacy of PB for treating acute ischemic seizures was detected at P10 and P12 but not at P7, which is supported by published studies indicating a chloride co-transport–dependent developmental reversal of depolarizing to hyperpolarizing action of GABA by the age of P8–9 in rodents. However, as previously predicted, BTN as a follow-on adjunct treatment failed to improve efficacy of PB antiseizure activity at P7 and P10 with sex-specific aggravation in females. The age-dependent increase in the hyperpolarizing effects of the GABA\textsubscript{A} agonists has been shown to depend on the increasing KCC2 expression profile detected in the maturing CD1 mouse brains. However, this study showed that the downregulation of KCC2 under ischemic conditions may further decrease the efficacy of drug actions that depend on a hyperpolarizing chloride gradient for their anticonvulsant action. This lack of efficacy to treat post-ischemic seizures could not be rescued by blocking NKCC1 in vivo.
Sudden unexpected death in epilepsy (SUDEP) is the leading cause of death in patients with epilepsy. Cardiac and respiratory etiologies have been implicated to underlie SUDEP. Serotonin (5-HT) is a key regulator of breathing. 5-HT dysfunction has been implicated in the pathophysiology of SUDEP. With the aid of a mouse model in which nearly all 5-HT neurons were genetically deleted (Lmx1bf/f/p), we previously showed that 5-HT neuron absence contributes to seizure severity and seizure-related death. Here, we investigated whether pharmacologic manipulation of the 5-HT system could affect respiratory arrest and death. Seizures were induced via maximal electroshock in adult male wildtype (WT; 50 mA, 0.2 s, 60 Hz) and Lmx1bf/f/p (30 mA, 0.2 sec, 60 Hz) mice following pretreatment (i.p.) with vehicle, the SSRI fluoxetine, or the 5-HT2A/2C agonist DOI (n = 7 for each genotype/condition). A subset of vehicle-treated animals was mechanically ventilated during the seizure. Seizure susceptibility, severity (extension-flexion ratio) and mortality, and presence and duration of respiratory arrest were assessed. Seizures induced by electroshock following vehicle pretreatment were similar in intensity between genotypes and similar to those previously observed in our lab and resulted in the same survival rate (28.6% for both genotypes). All WT and most (6/7) Lmx1bf/f/p mice that were mechanically ventilated during the seizure survived (p < 0.05). Similarly, fluoxetine (20 mg/kg) or DOI (0.3 mg/kg) pretreatment prevented respiratory arrest and death in all WT mice (p < 0.05). The SSRI was not given to Lmx1bf/f/p mice because they lack 5-HT neurons and thus cannot reuptake 5-HT. DOI (1 mg/kg, but not 0.3 mg/kg) prevented death in most (6/7) Lmx1bf/f/p mice (p < 0.05). These results indicate that respiratory arrest contributes significantly to seizure-related death in this model and that augmenting 5-HT activity with an SSRI in WT or activating downstream 5-HT2 receptors can prevent seizure-associated death.
#28 – Sudden Unexpected Death in a Mouse Model of Dravet Syndrome

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Sudden unexpected death in epilepsy (SUDEP) is the most common cause of death in intractable epilepsies, but the physiologic mechanisms that lead to SUDEP are unknown. Dravet syndrome (DS) is an infantile-onset intractable epilepsy caused by heterozygous loss-of-function mutations in \textit{SCN1A}, which encodes brain sodium channel Na\textsubscript{V} 1.1. We studied the mechanism of premature death in \textit{SCN1A} heterozygous knockout mice and conditional brain- and cardiac-specific knockouts. Video monitoring demonstrated that SUDEP occurred immediately following generalized tonic-clonic seizures. A history of multiple seizures was a strong risk factor for SUDEP. Combined video-electroencephalography-electrocardiography revealed suppressed interictal resting heart-rate variability and episodes of ictal bradycardia associated with the tonic phases of generalized tonic-clonic seizures. Prolonged atropine-sensitive ictal bradycardia preceded SUDEP. Similar studies in conditional knockout mice demonstrated that brain, but not cardiac, knockout of \textit{SCN1A} produced similar cardiac and SUDEP phenotypes as in DS mice. Atropine or N-methyl scopolamine treatment reduced the incidence of ictal bradycardia and SUDEP in DS mice. These findings suggest that SUDEP is caused by apparent parasympathetic hyperactivity immediately following tonic-clonic seizures in DS mice, which leads to lethal bradycardia and ventricular dysfunction. These results have implications for treatment of SUDEP in DS patients.
Depression is the most prevalent comorbid condition associated with epilepsy. Approximately one-third of patients with epilepsy also suffer from depression, and patients with epilepsy are five times more likely to attempt suicide. It is becoming increasingly clear that depression and epilepsy share common pathological underpinnings. Stress is a trigger for both epilepsy and depression, and significant accumulating evidence, from both human and animal studies, suggests that the hypothalamic-pituitary-adrenal (HPA) axis may play a role in the comorbidity of these two disorders. A hallmark characteristic of major depression is hyperexcitability of the HPA axis, and epilepsy is associated with activation of the HPA axis, leading us to hypothesize that dysregulation of the HPA axis may play a role in the comorbidity of epilepsy and depression. The HPA axis is governed by corticotropin-releasing hormone (CRH) neurons in the paraventricular nucleus (PVN) of the hypothalamus, the activity of which is tightly controlled by GABAergic inhibition. Here, we demonstrate alterations in GABAA receptor (GABAAR) subunit expression in the PVN and altered GABAergic control of CRH neurons in the pilocarpine model of epilepsy. This altered GABAergic control of CRH neurons is associated with increased levels of corticosterone and increased depression-like behavior. Our data suggest that seizures activate the HPA axis utilizing mechanisms similar to stress, including a downregulation of the K+/Cl- co-transporter KCC2 and excitatory actions of GABA on CRH neurons. Dampened excitatory effects of GABA on CRH neurons in mice with deficits in the GABAAR δ subunit, specifically in CRH neurons (Gabrd/CRH mice), blunt the seizure-induced activation of the HPA axis, resulting in decreased levels of corticosterone and decreased depression-like behavior. These data suggest that seizures activate the HPA axis via altered GABAergic control of CRH neurons, which may play a role in the comorbidity of depression and epilepsy.
Epileptogenesis reorganizes cortical and hippocampal circuits, but the effects of these changes on the emergent network properties of precisely identified interneurons and pyramidal neurons are not understood. This level of understanding is essential for determining which circuit components are critical for seizure initiation and which components contribute to the cognitive deficits in epilepsy. To address these questions, our laboratory has developed techniques for performing stable whole-cell or juxtacellular electrophysiologic recordings and two-photon calcium imaging from cortical and hippocampal neurons in head-fixed mice free to run or rest on a spherical treadmill. Our recordings are exceptionally stable, allowing high-quality recordings from identified neurons for up to 90 minutes in running mice. Juxtacellular recordings are stable through tonic-clonic seizures. We combine these techniques with a virtual reality environment spanning 270 degrees of mouse vision in which movements of the mice on the treadmill result in movement of a virtual T-maze. We are training epileptic (pilocarpine) and control animals to perform a delayed working memory task in which a transient visual cue held in memory for several seconds allows mice to turn right or left on the T-maze for water reward. We will record delay-related activity (a correlate of working memory) in parietal cortical neurons and place cell-related activity in CA1 hippocampal neurons. By holding cells at the reversal potential for excitatory and inhibitory conductances, we will dissect how the underlying excitatory and inhibitory synaptic currents mediating these critical receptive field properties are altered in excitatory and inhibitory neurons in epileptic animals. Finally, using optogenetic modulation of specific neuromodulatory inputs (noradrenergic or cholinergic), we will determine whether augmentation of noradrenergic or cholinergic tone can rescue these functional deficits.
Increasing evidence points to a strong comorbidity between autism and epilepsy. Recent studies have shown that genetic deletion of genes that modulate the mTOR signaling pathway results in an autistic phenotype and plays a critical role in cortical dysplasia and tuberous sclerosis complex. Here, we evaluated the behavioral consequences of mTOR hyperactivation by using neuron subset–specific (NS-Pten) conditional knockout mice.

We examined several aspects of behavior in the NS-Pten knockouts (KO), heterozygous (HT), and wildtype (WT) mice: isolation-induced ultrasonic vocalizations, locomotion and anxiety, social behavior, repetitive behavior, and learning and memory through fear conditioning.

The KO mice displayed hyperactivity in the open field test compared with WT mice, \( p < 0.001 \). They exhibited less anxiety in the elevated-plus maze test compared with WT and HT, \( p < 0.05 \). They showed deficits in social chamber and social partition test, both at \( p < 0.05 \). The KO pups did not show a change in the number or duration of isolation-induced ultrasonic vocalizations. KO mice demonstrated alterations in repetitive behavior, as measured in the marble-burying test and hole-board test, both at \( p < 0.01 \). In addition to deficits in the behavioral features that describe autism, they have learning and memory deficits in contextual learning in the conditioned fear test \( (p < 0.01) \) compared with WT mice.

These findings demonstrate that hyperactivation due to genetic deletion of Pten results in long-term alterations in social behavior, anxiety, repetitive behavior, and learning and memory. Our data demonstrate that NS-Pten KO mice are a valuable tool to examine behavioral consequences due to mTOR hyperactivation. Future studies could examine which behavioral deficits are reversed with mTOR inhibitors.
Scalp electroencephalography (EEG) has been established as a major component of the presurgical evaluation for epilepsy surgery. However, its ability to localize seizure onset zones (SOZ) has been significantly restricted by its low spatial resolution and indirect correlation with underlying brain activities. Here, we report a novel noninvasive dynamic seizure imaging (DSI) approach based on high-density EEG recordings. This novel approach was designed to image the dynamic changes of ictal rhythmic discharges that evolve through time, space, and frequency.

This approach is achieved by measuring the electrical signals within the brain and performing “imaging” of seizure-generating areas using innovative engineering techniques. This method was evaluated in a group of eight adult epilepsy patients and nine pediatric patients. The results were evaluated using intracranial EEG (iEEG) and surgical outcome. In the seven pediatric patients with intracranial monitoring, the estimated seizure onset sources were concordant with the seizure onset zones of iEEG. Among all the analyzed patients, the DSI method achieved co-localization to surgical resection in 13 of the 17 patients, and the results of the remaining patients were in close vicinity to the resection boundary. The area-under-curve (AUC) measure was used as an overlapping index to evaluate the localization accuracy, which suggested that the DSI reconstructed the source distribution at seizure onset with great precision. The present promising results indicate the ability of DSI to precisely and accurately image dynamic seizure activity from noninvasive measurements. These results from a noninvasive seizure imaging modality for surgical evaluation show promise for the management of medically intractable epilepsy. Our promising results demonstrate that this technology warrants further development. A prospective clinical trial is required to definitively demonstrate the impact of this technique.

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#33 – Hemodynamic Low-Frequency Oscillations May Locate Epileptic Brain Lesions

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For the majority of pediatric patients with refractory epilepsy, the ideal treatment option is complete surgical removal of their epileptic lesions, when applicable. Diagnostic imaging technologies, such as MRI, often fail to reliably distinguish the lesions from normal brain tissue because of their limited sensitivity, and their availability in the operating room is scarce because of their prohibitive costs.

A hybrid optical imaging/spectroscopy system was developed to intraoperatively detect intrinsic interictal pathophysiologic characteristics, including the hemodynamic and structural characteristics of the pediatric epileptic cortex. The system was tested in a pilot study of eight patients during epilepsy surgery. The imaging function of the hybrid system was used to capture the spatial and temporal variations in the hemodynamics of the exposed cortex at 5 Hz for approximately 5 minutes. The analysis of the image sequences showed the presence of strong focal hemodynamic low-frequency oscillations (LFOs) in six of the eight patients. In four of these six patients, the areas in which the LFOs were observed coincided with the epileptic cortex defined by ECoG and fMRI. The remaining two patients had the LFOs in the functional cortical area. The two patients without strong LFOs had epileptic foci deep below the exposed cortical surface.

It was hypothesized that the origin of the LFOs was associated with malfunctions of the astrocytes regulating neurovascular coupling. To test this hypothesis, a multimodal optical spectroscopy system was developed to monitor hemodynamics, metabolism, Ca²⁺ waves in the astrocytes, and intracellular glutamate levels in the in vivo cortex. This system will be used in conjunction with an animal EEG system to study the cerebral cortex of epileptic rats to gain additional insight into the correlation between LFOs and epileptic cortex.


#34 – Modeling Electrocortical Source Dynamics of Intracranial EEG Data in Epilepsy

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Surgically removing the seizure-producing epileptogenic zone (EZ) provides the best chance of successfully stopping seizure activity for medically intractable but surgically treatable epilepsy. The current clinical gold standard for identifying cortical areas to resect relies on qualitative expert visual inspection of intracranial EEG (iEEG) data. Unfortunately, surgery for epilepsy is successful in stopping seizures in only 33% to 80% of cases. Here, we report a method for analyzing and visualizing electrocortical source dynamics in epilepsy patients undergoing invasive iEEG examination by identifying specific cortical source areas of seizure activity and modeling dynamic relationships between them. The main steps of our approach are as follows:

1. Apply adaptive mixture independent component analysis (AMICA) to iEEG data to separate and identify seizure sources.

2. Estimate the anatomical region of each iEEG seizure component by patch-basis inverse modeling using sparse Bayesian learning (SBL) applied to a realistic electrical forward head model of the patient including any craniotomies and electrode holders using the NFT toolbox (http://sccn.ucsd.edu/nft).

3. Identify and map source component clusters exhibiting high interdependencies by pairwise mutual information (PMI) across components followed by block diagonalization.

4. Analyze the dynamics of dependent ICA source clusters using a time-varying vector autoregressive model (VAR) using SIFT (http://www.sccn.ucsd.edu/wiki/SIFT); then use graph theoretic metrics to summarize and visualize the complex network dynamics of the observed ictal (or interictal) data.

These methods have been tested on data sets collected from three patients at the Mayo Clinic (Rochester, MN) and at the Hofstra North Shore Long Island Jewish Hospital (NY). Initial results suggest that spatiotemporal network dynamics of interictal data, modeled in the absence of seizure, may provide a novel source of predictive information regarding the location and likelihood of ictal dynamics. For two data sets, our localizations of the EZ were confirmed by the subsequent surgeon-selected resection zones and by the (mainly) positive surgical outcomes.

Our work to date suggests that this method (a) may improve the spatial resolution of iEEG data (in particular providing, from flat iEEG strip and grid arrays, detailed information about sulcal as well as gyral sources of ictal activity) that may assist epilepsy experts in making more accurate and objective clinical assessments and surgical plans and (b) may provide new insights into seizure genesis and propagation by revealing seizure network interactions too complex to be readily identified by visual inspection.
Currently, clinical electrode arrays with a sparse spatial density (1 cm) are used to map the seizure onset zone (SOZ) and epileptic network in patients before epilepsy surgery. However, recent research demonstrates that submillimeter cortical column-scale domains have a role in seizure generation that may be clinically significant. We use high-resolution, active, flexible surface electrode arrays in vivo to explore epileptiform spike patterns in two dimensions and the behavior of these domains leading up to seizures. Using novel high-density, 1 cm² active electrode arrays with 500 µm x 500 µm electrode spacing, we recorded subdural microelectrocorticographic (uECoG) signals in vivo from three cats. We topically administered a GABA antagonist, picrotoxin, to induce acute neocortical epileptiform activity leading up to discrete seizures. We analyzed 9 hours of data yielding 26,331 local field potential (LFP) spikes. We extracted features characteristic of spatiotemporal (ST) patterns from these events and employed k-mediods clustering to separate the data into 10 distinct classes of ST patterns. We tested the hypothesis that two dimension spike patterns during seizures were different from interictal spikes. A permutation test (with 1 million permutations) indicated that 2-D patterns can be used to distinguish spikes in the seizure state from those in the nonseizure state. Initial temporal analysis suggests that seizures in this model are not initiated by a single 2-D pathway but rather by a number of different ST-initiating events. We conclude that submillimeter-scale ST cortical arrays reveal network dynamics that may elucidate mechanisms underlying local circuit activity generating and terminating seizures. They provide a novel opportunity for therapeutic intervention at the microscale to treat epilepsy.
Current implantable brain devices for clinical and research applications require that each electrode be individually wired to a separate electronic system. Establishing a high-resolution interface over broad regions of the brain is not feasible under this constraint because an electrode array with thousands of passive contacts would require thousands of wires to be individually connected. To overcome this limitation, we have developed new implantable electrode array technology that incorporates active, flexible electronics. This technology has enabled extremely flexible arrays of 1,024 electrodes and, soon, thousands of multiplexed and amplified sensors spaced as closely as 250 μm apart, which are connected using just a few wires. These devices yield an unprecedented level of spatial and temporal microelectrocytographic (μECoG) resolution for recording and stimulating distributed neural networks. μECoG is one of the many possible applications of this technology, which also include cardiac, peripheral nerve, and retinal prosthetic devices. I will present the development of this technology and examples of retinotopic and tonotopic maps produced from in vivo recordings. I also will present examples of finely detailed spatial and temporal patterns from feline neocortex that give rise to seizures and suggest new stimulation paradigms to treat epilepsy.

Our lab has focused on developing this technology in two key areas: (1) creating and testing new electrode designs and supporting hardware to enable chronic implantation of active, multiplexed arrays and (2) developing new electrode designs that incorporate multiplexed recording and stimulation to enable a bi-directional interface with the brain. In my poster, I will present our latest progress towards these two goals, which includes long-term soak testing of devices, bench testing, and preliminary acute animal experiments.
About 30% of epilepsy patients are refractory to drug therapy but may be candidates for surgical intervention. However, not all surgeries are successful in curing epileptic seizures. Therefore, it is critical to predict the surgical outcome of individual patients to help with patient selection for surgery and maximize the chance of postsurgical seizure freedom. Therefore, comprehensive presurgical evaluation is necessary and includes using multiple modalities to characterize seizure type, frequency, site of onset, psychosocial function, and degree of debility. To this end, positron emission tomography (PET) using 2-[18F] fluoro-2-deoxy-D-glucose (FDG) may be utilized to depict interictal glucose metabolism that may relate to seizure foci. Previous PET and single photon emission computed tomography (SPECT) studies have measured and compared hypometabolism and blood flow of left and right hemispheres to localize seizure foci in temporal lobe epilepsy (TLE). Our group has recently shown that localized analysis of uptake in the hippocampi by ictal and interictal SPECT is superior to hemispheric analysis in increasing confidence in lateralization and selection of patients for surgical intervention. Ictal SPECT studies may not be feasible for all patients, but they may get interictal FDG-PET scans. This study has quantitatively analyzed the interictal FDG-PET and magnetic resonance imaging (MRI) data of 11 TLE patients. Hippocampi were segmented on T1-weighted MRI and overlaid on the PET and FLAIR MRI after coregistration. Volumes of hippocampi and their FLAIR intensities were estimated from MRI along with their hypometabolism (HM) and standard uptake value (SUV) from PET. Experimental results show that HM and SUV measures increase confidence in lateralization of TLE patients and their selection for surgical intervention. Moreover, a moderate correlation ($r = 0.64$, $p < 0.02$) exists between quantitative analysis of PET and MRI. In conclusion, localized quantitative analysis of PET may increase confidence in localizing seizure foci and consequently improve surgical outcome.
In Vivo Imaging of Epilepsy Using Hyperpolarized NMR: Translation From Animals to Man

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**Background:** Using a unique combination of invasive and noninvasive complimentary systems, we have reliably imaged epilepsies in vivo in rodent and human brain. Results reflect therapeutic interventions of ketogenic diet, membrane transport inhibitors, and GABAergic drugs.

**Experimental Design and Research Strategy:** High resolution NMR, small-animal proton MRI, 13C, 15N, and 19Si hyperpolarization equipment (DNP and parahydrogen), rodent EEG, brain dialysis, and stable isotope infusion research focused on an animal model of temporal lobe epilepsy and human epilepsy.

**Novel Findings:** Integration of brain dialysis, HPLC with high resolution NMR, provides direct quantification of the low concentrations of glutamate, GABA, and glutamine at which these neurotransmitters usually operate. In vivo metabolite enrichment of the “third space” by two stable isotopes (13C and 15N) allows tracking of the cell of origin by 13C–15N NMR co-resonances (1). In the kainate model of temporal lobe epilepsy (TLE), we established in vivo flux rates for the GABA-glutamine-glutamate cycle. The newest finding—that inhibiting glutamine uptake into neurons reduces seizure rate by 20% to 50% (2,3)—offers novel therapeutic opportunities. In human subjects treated by ketogenic diet, accumulation of intracerebral acetone points to an unexplored therapeutic option in childhood epilepsies (4).

**The Future:** Combining hyperpolarization of water, 13C, 15N, and 29Si provides metabolic flux rates in reduced time periods of 1 to 3 minutes (5). This time resolution reflects the electrophysiologic timeframe of seizures and translation to studies in clinical epilepsy.

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Identification of Eloquent Cortical Areas Using Resting State fMRI: A Validation With In Vivo Direct Cortical Electrical Stimulation in Humans

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When evaluating a patient for epilepsy surgery, it is critical to identify the "eloquent cortex" necessary for core cognitive functions such as language and motor control that must be preserved. The clinical gold standard for identifying functional areas is direct cortical electrical stimulation (DCES). DCES is effective, but it is an invasive, time-consuming procedure that increases patient risk and cannot always be fully completed due to epileptogenic DCES effects or the inability of patients to cooperate. An alternative method for defining eloquent cortex is resting-state fMRI (rsfMRI). It is well established that functionally related brain areas have similar patterns of rsfMRI, which allows them to be segregated from one another and identified via tools like independent component analysis (ICA) and cluster analysis. However, it is not clear whether rsfMRI can resolve eloquent cortex with sufficient precision to make it clinically useful. Previous work (Kokkonen et al., 2009; Zhang et al., 2009) has shown that hand sensorimotor regions identified by rsfMRI are similar to those defined by a finger-tapping fMRI paradigm, but it is not clear how well these results correspond with DCES. Here, we evaluate the ability of rsfMRI to define hand sensorimotor, tongue sensorimotor, and expressive language areas as defined by DCES in patients undergoing evaluation for surgical treatment of epilepsy. We use three methods of rsfMRI analysis to identify these areas: (1) ICA, (2) k-means cluster analysis, and (3) logistic regression. In addition, we compare the accuracy of these rsfMRI results with more conventional task-based fMRI paradigms used to define hand sensorimotor and expressive language areas. We find that ICA and cluster analysis of rsfMRI data are as accurate as task-based fMRI for identifying eloquent areas. Moreover, logistic regression of rsfMRI data was more successful than task-based fMRI and the two other rsfMRI analysis methods.
#40 – Improved Outcomes With Earlier Surgery for Intractable Frontal Lobe Epilepsy

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Objective: To explore the prognostic implications of epilepsy duration and age at surgery on seizure outcomes after frontal lobe epilepsy (FLE) surgery.

Methods: We reviewed 158 patients who underwent FLE surgery from 1995 to 2010 in our center. The primary outcome was seizure freedom at last follow-up (Engel Class IA). Analyses employed Cox proportional and multiphase hazard modeling.

Results: The mean age at surgery was 20.4 years, and mean epilepsy duration was 12.0 years. About half (52%) were children (age < 18 years). The estimated chance of seizure freedom was 66% (95% CI = 62–68) at one postoperative year, 52% (95% CI = 48–56) at 2 years, and 44% (95% CI = 39–49) at 5 years and beyond. In addition, 75% of recurrences occurred within 6 postoperative months. Both younger age at surgery (< 18 years) and shorter epilepsy duration (< 5 years) correlated with better seizure outcomes on univariate analysis, but only epilepsy duration remained statistically significant after multivariate modeling. Independent poor prognostic indicators included left-sided resections and acute postoperative seizures (APOS) [whole model LogRank test p-value < 0.0001]. APOS were particularly predictive of “early” epilepsy recurrence, starting within 6 postoperative months (adjusted risk ratio (RR) = 4.42; p-value < 0.0001), whereas long epilepsy duration correlated with later recurrences (RR = 6.25; p-value < 0.0001). Worse outcomes were seen with longer epilepsy duration for duration cutoffs of 2, 5, and 10 years in both adults and children, although statistical significance was achieved only in children (66% seizure free at 5 postoperative years if operated on within 5 years of epilepsy onset versus 31% if later; p = 0.01). Favorable outcomes with shorter epilepsy duration were independent of disease etiology, MRI findings, and extent of resection.

Interpretation: Early resection may improve seizure outcomes of FLE surgery, particularly in children. The preferential roles of APOS and epilepsy duration in “early” versus “late” seizure recurrence support distinct mechanisms for these two phases of surgical failures.
#41 – Blood-Brain Barrier Function in Epilepsy: New Targets for Therapy?

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The blood-brain barrier is altered in patients with epilepsy. Alterations include changes in expression of efflux and influx transporters, metabolizing enzymes, and development of barrier leakage. In this regard, it has been shown that seizures decrease expression levels of antiepileptic drug (AED) influx transporters while increasing expression of AED efflux transporters and AED metabolizing enzymes. These changes are thought to reduce AED brain uptake and thus contribute to AED resistance. In addition, development of blood-brain barrier leakage is, in part, a consequence of seizures and a trigger of seizures. Thus, blood-brain barrier dysfunction may contribute to both seizure genesis and AED resistance. However, the detailed mechanism(s) responsible for these pathologies is/are currently unknown, and lack of this knowledge prevents the discovery of new targets for innovative therapies. We have addressed this clinical challenge and identified the LOX/COX pathway to be critical for seizure-induced barrier dysfunction. Our data indicate that glutamate released during seizures activates LOX/COX, thereby changing expression of influx and efflux transporters and metabolizing enzymes and causing barrier leakage.

In experiments using rats, COX-2 knockout mice, and an epilepsy rat model, we found that glutamate signaling through the COX arm (Glu NMDAR cPLA2 COX 2 PGs) decreased expression of AED influx transporters and increased expression of AED efflux transporters and metabolizing enzymes. We also found that glutamate activation of the LOX arm (Glu NMDAR cPLA2 5-LOX LTs) elevated leukotriene levels and capillary permeability, which contributed to barrier leakage. Importantly, blocking the LOX/COX pathway in chronic epileptic rats abolished the glutamate-induced changes in transporter and enzyme expression levels and prevented barrier leakage.

Together, our data suggest new therapeutic targets that will potentially allow the design of a novel therapy with a twofold benefit: (1) reduced AED resistance and (2) reduced seizure genesis for improved epilepsy treatment and better seizure control in patients.
It is unclear how diseases that impair brain metabolism and cause seizures (notably, glucose transporter type I deficiency; G1D) disrupt excitability. Reduced metabolism is also characteristic of seizure foci in many epilepsies. Our goal is to understand metabolism-excitability relationships in patients and disease models for therapeutic development. Multielectrode-array recordings from mouse brain slices and simultaneous human fMRI-EEG reveal that G1D is associated with thalamocortical hypersynchronization, probably accounting for the anticonvulsant-refractory (but glucose-dependent) spike-wave epilepsy typical of G1D. This is associated with brain acetyl-coenzyme A depletion in the context of preserved tricarboxylic acid (TCA) cycle and lipid metabolism, as determined by assay of pyruvate dehydrogenase activity, $^{13}$C-NMR, and mass-spectroscopic analysis of glutamate, glutamine, GABA, and TCA intermediates. This translates into synaptic dysfunction, with moderately diminished cortical excitatory and greatly reduced inhibitory spontaneous and evoked currents under patch-clamp, together with thalamic burst firing. Therapies for G1D are modest: even-carbon ketones, generated from common dietary fat or a ketogenic diet, ameliorate seizures but are not anaplerotic. In fact, the two key metabolic roles of glucose are (1) energy production by oxidation of acetyl-coenzyme A and (2) anaplerosis, by providing pyruvate for carboxylation. Ketogenic diets address only the first metabolic role of glucose. In contrast, mouse brain NMR and mass spectrometry indicate that odd-carbon triheptanoin is anaplerotic, thus fulfilling both roles. G1D patients receiving triheptanoin experience increased oxygen cerebral metabolic rate (CMRO$_2$) by MRI, decreased seizures by EEG, and improved neuropsychological performance, suggesting that triheptanoin is effective in cerebral hypometabolic states associated with epilepsy.

#43 – A Novel Mitochondria-Targeted Antiseizure Treatment

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**Rationale:** Mitochondria regulate synaptic neurotransmission by (1) producing about 97% of the brain’s adenosine triphosphate (ATP; of which 41% is used for synaptic transmission); (2) sequestering synaptic calcium $[\text{Ca}^{2+}]_\text{m}$ to buffer a rise in cytoplasmic $[\text{Ca}^{2+}]_\text{i}$, thus directly influencing presynaptic release probabilities and postsynaptic responses; and (3) producing reactive oxygen species (ROS), which impair synaptic plasticity and synchronize mitochondria networks associated with increased action potential firing. We and others have reported that mitochondrial dysfunction is associated with epilepsy. Kv1.1 knockout (KO) mice model several idiopathic epilepsy syndromes. We found that ATP-producing rates, calcium buffering, and functional uncoupling are reduced and ROS levels are elevated in KO brain mitochondria. Here, we determined whether rescuing mitochondria with a targeted treatment (ascorbic acid tocopherol and pyruvate; AATP) has significant antiseizure effects against acute kainate seizures and/or during the epileptogenic period in KO mice.

**Results:** All mice treated with AATP 30 minutes before kainate-induced status epilepticus were protected from severe KA-induced stage 4 and 5 seizures. (Seizure burden index [SBI] was reduced by 57%.) More than two-thirds of KO mice treated with AATP for 5 days had more than 50% seizure reduction. (SBI was reduced by 62%.) Mitochondria isolated from AATP-treated KO mice were indistinguishable from WT. Specifically, ATP-producing respiration, maximal respiratory rates, and functional uncoupling were enhanced, and ROS levels were diminished.

**Interpretation:** These data suggest that AATP is a novel, efficacious antiseizure treatment. In addition, the data suggest that mitochondria and its restoration of bioenergetic homeostasis in the brain represent a novel antiseizure target.
Drug resistance acts as a critical impediment to successful treatment and a major obstacle in the development of new CNS therapies. Metabolic enzymes and transporter proteins at the blood-brain barrier (BBB) potentially contribute to the bioavailability of drugs to epileptic brain. Studies were designed to investigate the function and localization of cytochrome P450 and UDP glucuronosyl transferase (UGTs) enzymes at epileptic BBB.

Surgical brain specimens and blood samples (ex vivo) were obtained from drug-resistant epileptic subjects receiving a known antiepileptic drug before temporal lobectomies. An in vitro BBB model facilitated the establishment of primary cell culture derived from the same patient. Enzyme levels (CYP3A4 and UGT1A4) in patient brain or primary culture of human-derived endothelial cells and astrocytes were investigated by immunostaining and western blotting. High-performance liquid chromatography (HPLC) analysis was used to quantify carbamazepine and lamotrigine metabolism pattern in epileptic BBB. In addition, enzyme expression and cell survival were correlated.

CYP3A4 and UGT1A4 were expressed by BBB “epileptic” endothelial cells and neurons. Neurons staining positive for CYP3A4 and UGT1A4 enzymes were those lacking nuclear condensation of DNA. Epileptic endothelial cells expressed increased CYP3A4 and UGT1A4 levels (p < 0.05 vs. nonepileptic BBB cells). Expression levels were matched by increased antiepileptic drug (AED) metabolism compared with control brain endothelial cells. Brain endothelial drug metabolism resulted in the formation of known and previously unknown AED metabolites.

Taken together, the results support the hypothesis of local drug metabolism at the epileptic BBB. Metabolizing enzymes expressed in the brain are not only associated with drug metabolism but may also represent a cytoprotective mechanism by promoting neuronal survival.
**#45 – Effectiveness of Phenytoin-Caffeine Combination in General Seizures**

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**Background:** In the Indonesian community, coffee has been used as an antiseizure drug for centuries and has been prescribed in combination with phenobarbital for years to alleviate drowsiness. As an anticonvulsant, caffeine has the molecular action of blocking the A2, A3 receptor.

**Purpose:** To investigate the effectiveness of phenytoin-caffeine combination in general seizure.

**Methods:** Two different studies have been assigned. A pre-post study compared serum level and pharmacologic effects before and after the addition of caffeine to phenytoin in healthy subjects. A randomized, single-blind, active-controlled study compared the efficacy and tolerability of phenytoin-caffeine combination with phenytoin in general seizure. Study subjects were divided into two groups. Group I received phenytoin 5mg/kg, and Group II received phenytoin 5 mg/kg plus caffeine 2.5 mg/kg. Subjects were followed up 6 months after therapy. The primary outcomes measured were seizure frequency, seizure reduction > 50%, 6-month remission, plasma phenytoin concentration, and adverse drug reaction.

**Results:** 1. A total of 22 healthy subjects were enrolled. Caffeine added to phenytoin resulted in no significant pharmacokinetic interaction (F: 0.907, P: 0.347, CI 95%). The pharmacokinetic profile of phenytoin in phenytoin-caffeine was as follows: (Clav) 0.2571 ml min⁻¹; volume of distribution (Vd) 0.644 L kg⁻¹; elimination half-life (t ½) 34.8 hours; Ke 0.018 L hr⁻¹.

   The pharmacologic effects attributable to phenytoin were not augmented by the addition of caffeine (t = 1; P = 0.374, CI = 95%).

2. A total of 50 patients were enrolled; 2 were deemed ineligible, and the overall efficacy cohort comprised 48 patients. Six months after starting therapy, there were significant reductions in seizure frequency in Group II (90.6%) compared with Group I (70.8%) (Z = -1.93, P = 0.05, CI 95%); Group II demonstrated 92% terminal remission, which was significantly different (X = 51.95, P = 0.00, CI 95%) from Group I (78.6%); 82% (Group I) and 96% (Group II) achieved ≥ 50% seizure reduction (χ = 52.4, P = 0.00, CI 95%). Phenytoin and caffeine demonstrated a safety profile similar to that of phenytoin.

**Conclusion:** Caffeine increased phenytoin effectiveness in general seizure.
Many brain insults, including traumatic brain injury, stroke, and status epilepticus (SE), cause the later development of epilepsy. However, there are currently no treatments that reduce epileptogenesis following brain injuries. Recent data show that inhibiting the JAK-STAT pathway with the compound WP1066 at the time of brain insult attenuates the severity of the ensuing epilepsy. Specifically, rats given WP1066 at the time of pilocarpine-induced SE show a significant reduction in the frequency of spontaneous seizures compared with vehicle-injected animals up to 4 weeks following SE. Unfavorable pharmacokinetic (PK) properties of WP1066, however, limit its potential for preclinical development. WP1066 is rapidly cleared from blood and brain and only transiently reduces activation of the JAK-STAT pathway. We have started structure-activity relationship studies on newly synthesized compounds aimed at increasing the efficacy of JAK-STAT inhibition in brain following peripheral administration. One leading synthesized compound shows increased stability, improved blood-brain barrier penetration, and greater inhibition of pSTAT3 in both cultured hippocampal neurons and in brain following pilocarpine-induced SE in vivo. In our preliminary studies, this novel compound caused about a 200-fold increase in plasma and cortex concentrations compared with WP1066 1 hour after SE. In addition, western blot analysis on rat hippocampi 1 hour after SE showed about a 45% reduction in pSTAT3 levels in rats injected with the new compound. These findings suggest that novel JAK/STAT inhibitors may have promise as disease-modifying agents with the potential to reduce the development and/or severity of epilepsy following brain insults.
A large unmet need exists for new therapeutics to treat medically refractory epilepsy in children. Cannabidiol (CBD) is a nonpsychoactive compound found in the cannabis plant, which has been reported to have antiseizure properties.

We surveyed a group of parents of medically refractory epileptic children who were receiving artisanal preparations of CBD. Using RedCAP, we designed a questionnaire to assay parents’ reports of the effect of CBD on their children’s seizure burden and quality of life.

Eighteen parents responded to the survey. Twelve children had been diagnosed with Dravet syndrome, three with Doose syndrome, one with Lennox-Gastaut syndrome, one with polymicrogyria, and one had idiopathic epilepsy. All of the children had been living with uncontrolled seizures for at least 3 years. The children had tried an average of 12 drugs in their lifetime. Fifteen of the 18 parents surveyed (83%) reported a reduction in their child’s seizure frequency. Reported seizure frequency reduction ranged from 25% to 60% (in 4 children) to greater than 80% (in 11 children). In addition to better seizure control, 10 of the 15 parents (75%) reported weaning their children from other antiseizure drugs (ASDs). Overall quality of life improved—78% of parents reported better sleep and 73% reported better mood and improved alertness in their children. Common negative side effects reported on other ASDs were notably absent on CBD, including rash, vomiting, nausea, confusion, insomnia, anxiety, irritability, dizziness, and aggressive behavior. The doses of administered CBD ranged from less than 1 mg/kg/day to 9 mg/kg/day. CBD appears to be an effective ASD in a very difficult-to-control pediatric population of epilepsy. Importantly, it is reported to be extremely well tolerated. This survey provides support for a placebo-controlled double-blind clinical trial to investigate the efficacy of CBD in this challenging pediatric population.
#48 – A Novel Oligonucleotide That Directs Alternative Splicing of the AMPA Receptor GluA1 Subunit to Reduce Seizures and Postseizure Hyperexcitability

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Dysregulation of alternative splicing is widely reported in neurological disorders, including epilepsy, and likely contributes to disease etiology. AMPA receptor GluA subunit genes are expressed as two splice variants, “flip” and “flop.” GluA1-flip subunits confer higher gain channel properties compared with GluA1-flop. GluA1-flip levels increase after seizures, which would increase neuronal network hyperexcitability and augment seizures. Therefore, reducing GluA1-flip should have potent antiseizure and antiepileptic actions. Splice modulating oligonucleotides (SMOs) target splice regulatory sites of pre-mRNA to direct alternative splicing. We developed a highly potent and target-selective SMO (LSP-GR1) that redirects splicing of GluA1 pre-mRNA to reduce flip isoform expression. Intracerebroventricular (ICV) delivery of LSP-GR1 in neonatal mice results in long-term (> 60 days) dose-dependent downregulation of GluA1-flip measured by real-time PCR. Whole-cell patch clamp recordings in LSP-GR1-treated P10 hippocampal slices showed that GluA1-flip reduction yields a 40% decrease in AMPA receptor–mediated excitatory postsynaptic currents (aEPSCs) generated at Schaeffer collateral/CA1 synapses. Decreasing GluA1-flip with LSP-GR1 also provided strong protection against kainate-induced seizures in neonatal mice, with significant effects on latency and threshold and a 76% increase in kainate dose required to induce status epilepticus. Furthermore, seizure-induced upregulation of aEPSC amplitude, which contributes to epileptogenesis, was prevented by an ICV injection of LSP-GR1 2 hours after a P10 seizure. Importantly, CA1 long-term potentiation and depression, both GluA1-dependent cellular models of hippocampal-dependent learning, were unaffected by decreasing the GluA1-flip levels. Likewise, GR1 dosing at P10 produced no cognitive deficits at P30, assessed using novel object recognition/displacement tests and the GluA1-dependent Y-maze task.

Thus, LSP-GR1 is a highly potent, specific, and long-lasting modulator of GluA1 alternative splicing, which provides robust neonatal antiseizure activity without overtly affecting synaptic plasticity or cognition. Our results show that modulation of AMPA channel alternative splicing is a novel therapeutic strategy for the prevention of seizures and epilepsy.
Development of T-Type Calcium Channel Ligands for Epilepsy

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Previous studies showed that the T-type Ca²⁺ channel, Cav3.2, plays a role in epileptogenesis. In Cav3.2 channel KO mice, the neuropathologic development of chronic epilepsy, such as subfield-specific neuronal loss in the hippocampus and mossy fiber sprouting, was absent after an insult to the brain. Recent reports have shown that T-type calcium channel blockers attenuate thalamic burst firing and suppress absence seizures on administration to the Genetic Absence Epilepsy Rats from Strasbourg (GAERS) model. T-type calcium channel blockers potently suppressed absence seizures via a unique mechanism distinct from current drugs for absence seizures. Interestingly, several endocannabinoids can directly block Cav3.2 with potencies in the high nanomolar range and can trigger analgesia. Notably, these peripheral effects were abolished in a Cav3.2 channel KO mouse, showing their therapeutic potential to modulate Cav3.2 activity in vivo. In 2007, epilepsy researchers and the patient community established that developing new therapeutic strategies to cure epilepsy was a priority to guide future research directions, as stated in the Epilepsy Research Benchmarks. We therefore sought to develop a novel series of selective high-affinity T-type specific Ca²⁺ channel antagonists based on endogenous cannabinoid ligands. We screened this novel series of compounds for T-type channel-blocking activity and then tested their analgesic effects in an in vivo model of pain. Our most active compound is currently screened in vivo by the Anticonvulsant Screening Program (NIH/NINDS/OTR) for its anticonvulsive properties. Altogether, our experiments identify a novel chemotype of T-type channel ligands based on endocannabinoids but devoid of cannabinoid activity with potent in vivo properties. This novel pharmacophore also may serve as a starting point for the development of new, more potent, and more specific Cav3.2 antagonists. We will report details of the synthesis, in vitro characterization, and in vivo anticonvulsive properties of these novel compounds.
#50 – Intra-Amygdalar Transplantation of Epileptic Patient-Derived Stem Cells, Displaying a microRNA Profile of Reduced mir-34b/c and Increased mir-592, Attenuates Hippocampal Cell Loss in Epileptic Rats: microRNA Profiling as a Biomarker and Stem Cell Screening Tool for Transplantation Therapy in Epilepsy

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Epilepsy afflicts more than three million Americans, with mesial temporal lobe epilepsy (TLE) being the most common. Temporal lobectomy is the current treatment of choice, with about 85% of patients enjoying a marked improvement. However, only 25% of these patients become seizure free, requiring the need for novel interventions. This study reports the utility of microRNA profiling as a biomarker and therapy development for epilepsy. Under USF IRB approval, we harvested tissues from multiple brain regions from consenting TLE patients undergoing hippocampal resection. Assays of microRNAs revealed that miR-34b and miR-34c were significantly upregulated in the hippocampus and amygdala compared with the neocortex, with miR-34b/c expression highest in the amygdala. In contrast, levels of miR-592 were significantly downregulated in the hippocampus and amygdala compared with the neocortex. RT-qPCR data support the microRNA data; notably, levels of miR-34b/c were significantly upregulated whereas levels of miR-592 were downregulated in the hippocampus and amygdala compared with the neocortex. Immunocytochemical assays provided insights into the functional role of these miRs, demonstrating decreased cell proliferation and differentiation in the hippocampus and amygdala compared with the neocortex of TLE patients. Next, stem cell grafts derived from the neocortex (i.e., reduced miR-34b/c but elevated miR-592 expression) not only survived in the amygdala and migrated to the lesioned hippocampus but, more importantly, reduced the kainic acid–induced hippocampal cell loss in epileptic adult rats. Parallel in vitro studies revealed that the administration of the supernatant from cultured human epileptic neocortical stem cells significantly reduced the kainic acid–induced cell death in primary human hippocampal cells compared with control treatments, suggesting that the rescue of the epileptic hippocampus by the transplanted stem cells likely involves a trophic factor mechanism. These results support the use of microRNA profiling as a biomarker and a screening tool for stem cell–based therapies in epilepsy.
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