Merritt-Putnam Symposium:
Future Therapies: How We Will Be Treating, Preventing and Curing Epilepsy in the Year 2025

Symposium Chair:

Amy Brooks-Kayal, M.D.

Monday, December 9, 2013
Convention Center – Ballroom B, Level Three
8:45 a.m. – Noon
OVERVIEW
Multiple strategies are being forwarded for prevention and treatment of epilepsy, some of which raise the possibility of providing an eventual cure for the disorder. Signaling pathways and inflammatory processes offer promising targets for novel treatment strategies, some of which use existing medications. As stem cell research progresses, cell replacement therapy is considered a potential option to replace lost or dysfunctional neurons in the epileptic brain. Optogenetics may provide unique strategies for potential treatment of brain diseases, particularly epilepsy. Seizure detection and prediction devices suggest possible non-medication-related approaches for treatment of epilepsy. This symposium will review these topics and provide insight into emerging treatment options.

LEARNING OBJECTIVES
- Utilize novel therapies for treatment of patients with difficult to control epilepsy with resulting improved seizure control
- Assess patients for inflammatory processes which are causing uncontrolled seizures and treat with anti-inflammatory and immune therapies when appropriate.

TARGET AUDIENCE
Intermediate: Epilepsy fellows, epileptologists, epilepsy neurosurgeons, "mid-level" providers with experience in epilepsy care (e.g., advanced practice nurses, nurses, physician assistants), neuropsychologists, psychiatrists, basic and translational researchers.

Advanced: Symposium will address highly technical or complex topics (e.g., neurophysiology, advanced imaging techniques, advanced treatment modalities, including surgery).

PROGRAM
8:45 – 9:00 am  Lennox Award Presentation
9:00 – 9:15 am  Introduction
Amy Brooks-Kayal, M.D.
9:15 – 9:45 am  Cell Signaling Modulators as Novel Disease Modifying Therapies
Anne Anderson, M.D.
9:45 – 10:15 am  Anti-Inflammatory Therapy
Annamaria Vezzani, Ph.D.
10:15 – 10:45 am  Cellular Therapies
Scott C. Baraban, Ph.D.
10:45 – 11:15 am  Optogenetic Therapy
Ivan Soltesz, Ph.D.
11:15 – 11:45 am  Seizure Detection / Prediction Devices and Therapies
Gregory A. Worrell, M.D., Ph.D.
11:45 am – Noon  Conclusions
Amy Brooks-Kayal, M.D.

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The American Board of Psychiatry and Neurology has reviewed the Merritt-Putnam Symposium and has approved this program as part of a comprehensive lifelong learning program, which is mandated by the ABMS as a necessary component of maintenance of certification.

Core Competencies: Medical Knowledge and System-Based Practice

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Anne Anderson, M.D.

Dr. Anne Anderson is an Associate Professor, Departments of Pediatrics, Neurology and Neurosciences, Baylor College of Medicine and Principal Investigator in the Gordon and Mary Cain Pediatric Neurology Research Foundation Laboratories at Texas Children's Hospital as well as the Medical Director of the Epilepsy Monitoring Unit at Texas Children's Hospital. Her research focus includes understanding epileptogenesis in the immature brain and mechanisms involved in cortical dysplasia using human tissue and animal models, as well as understanding mechanisms underlying sudden unexpected death in epilepsy. As a pediatric epileptologist, Dr. Anderson is involved in the evaluation and treatment of children with epilepsy with a particular emphasis on presurgical workup of children with epilepsy.

Anne Anderson, M.D. has nothing to disclose.

Scott Baraban, Ph.D.

Scott C. Baraban is Professor of Neurological Surgery and William K. Bowes Jr. Endowed Chair in Neuroscience Research at UCSF. After graduating from Johns Hopkins University he completed a PhD at the University of Virginia and postdoctoral training at the University of Washington. His NIH-funded research focuses on translational questions and includes work on epilepsies associated with a brain malformation, zebrafish models of pediatric epilepsy, and studies to develop an interneuron-based cell therapy. He is a recipient of a Klingenstein Fellowship in Neuroscience and an NIH EUREKA award. He is a regular NIH study section member and serves on the Scientific Advisory Board of the DSF.

Scott Baraban, Ph.D. discloses receiving support as Company Ownership (incl. personally managed stocks and stock options, excluding mutual and managed funds) from Co-founder Neurona Therapeutics. No financial gain to report.

Amy Brooks-Kayal, M.D. (Chair)

Amy Brooks-Kayal, MD is Professor of Pediatrics, Neurology and Pharmaceutical Sciences and Co-Director of the Translational Epilepsy Research Program at the University of Colorado School of Medicine, and Chief and Ponzio Family Chair of Pediatric Neurology at the Children's Hospital Colorado. Her research focuses on the molecular mechanisms underlying epileptogenesis. Her clinical focus is on pediatric epilepsy. Dr. Brooks-Kayal is 2nd Vice-President of AES and has also served on the Scientific Program Committee, R&T Council, Board of Directors, Nominating Committee, Governance Committee, Awards Committee and as Chair of the Merritt-Putnam Symposium.

Amy Brooks-Kayal, M.D. discloses receiving support as Salary from Commercial Sources generating W-2 from My husband is President of a specialty chemical company, SPI pharma, that makes drug delivery systems and over the counter actives for antacids (no antiseizure drugs); as Company Ownership (incl. personally managed stocks and stock options, excluding mutual and managed funds) from We own stock in Johnson and Johnson and Myelin Pharmaceuticals; as Federal/State/Not-for Profit Funding from I have funding from NIH (R01 and mentor on K01), DOD and AES/EF (pre-doc award to my student); as Participation in Foundation or Not-for-Profit Organizations from EF, Child Neurology Foundation, CURE- I donate money and time./p>

Ivan Soltesz, Ph.D.

Ivan Soltesz Ph.D. is Chancellor's Professor and Chair of Anatomy and Neurobiology in the School of Medicine at University of California, Irvine. His research focuses on the organization and plasticity of neuronal circuits in epilepsy, employing closely integrated electrophysiological, optogenetic, morphological, imaging and large-scale computational modeling techniques. He co-founded the Gordon Research Conference on Epilepsy and served as Chair of the AES Basic Science Committee
and the CNNT NIH study section and as co-Chair of the Epilepsy Foundation Research Grants and Fellowship panel.

Ivan Soltesz, Ph.D. discloses receiving support as Federal/State/Not-for Profit Funding from NIH; as Participation in Foundation or Not-for-Profit Organizations from NIH, CURE, EF.

**Annamaria Vezzani, Ph.D.**

PhD in Neuropharmacology at the Mario Negri Institute in Milan. Post-docs at the Univ of Maryland, Univ of Stockholm and Karolinska Institute. On sabbatical in 2002 at the Albert Einstein College of Medicin, laboratory of Developmental Epilepsy. Since 1997 Head of the Laboratory of Experimental Neurology, dept of Neuroscience at the Mario Negri Institute. Past Associate Editor of Epilepsia. Former Chair of the Commission on Neurobiology, member of Commission on European Affair of ILAE. Recipient of the Research Recognition Award for translational research in 2009 by AES. Research focused on molecular mechanisms involved in the etiopathogenesis of seizures and underlying pharmacoresistance

Annamaria Vezzani, Ph.D. discloses receiving support as Research Funding from For Profit Commercial Sources/Principle Investigator from UCB pharma-unrestricted grant support for a research project.

**Gregory Worrell, M.D., Ph.D.**

Greg Worrell, MD, PhD is Chair of Clinical Neurophysiology and Professor of Neurology at Mayo Clinic. His research and clinical practice are focused on the evaluation and care of patients with drug resistant epilepsy. He is currently pursuing the integration of large-scale neurophysiology, computing, and imaging for biomarker discovery. Ongoing clinical trials are investigating brain mapping, brain stimulation, and seizure forecasting. Dr. Worrell received his Ph.D. in Physics from Case Western Reserve University, MD from University of Texas Medical Branch, and Neurology/Epilepsy training at Mayo Clinic.

Gregory Worrell, M.D., Ph.D. discloses receiving support as Consulting/Advisory Board Activity from Medtronic Inc. Neuropace Inc. NeuroVista Inc.; as Federal/State/Not-for Profit Funding from NIH; as Participation in Foundation or Not-for-Profit Organizations from Cure Epilepsy Therapy Program Epilepsy Foundation.

**Kevin Haas, M.D. (CME Reviewer)**

I am an adult neurologist and epilepsy specialist at Vanderbilt University. My basic research has focused on GABA-A receptor physiology and synaptic roles of ubiquitination, and epilepsy in Angelman syndrome. My current clinical research interests focus on epilepsy surgery, status epilepticus, treatment of neurogenetic epilepsy syndromes, and epilepsy pharmacogenomics. I am the Vanderbilt site PI for the Critical Care EEG Consortium and am actively involved in projects investigating the diagnosis and management of non-convulsive seizures and status epilepticus.

Kevin Haas, M.D., Ph.D. discloses receiving support as Participation in Foundation or Not-for-Profit Organizations from Serve on Scientific Advisory Committee for FAST.

**Paul Levisohn (Medical Content Specialist, AES)**

Dr. Levisohn is a member of the faculty of the section of Pediatric Neurology at The University of Colorado School of Medicine and Children's Hospital Colorado Neuroscience Institute, having joined the faculty over 15 years ago following a similar period of time in the private practice of pediatric neurology. His academic career has focused on clinical care for children with epilepsy with particular interest in clinical trials and on the psychosocial impact of epilepsy. Dr. Levisohn is currently a consultant on medical content for CME activities to staff of AES. He is a member of the national
Paul Levisohn, M.D. discloses receiving support as Consulting/Advisory Board Activity from CME medical content consultant to AES staff.; as Research Funding from For Profit Commercial Sources/Principle Investigator from Eisai (clinical trials); as Federal/State/Not-for Profit Funding from NIH/NINDS: Childhood Absence Epilepsy, PI. NeuroNEXT, PI.; as Participation in Foundation or Not-for-Profit Organizations from Professional Advisory Board, Epilepsy Foundation; Co-chair, Advisory Committee National Center for Project Access; Consultant to AES.

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Merritt-Putnam Symposium: Future Therapies: How We Will Be Treating, Preventing and Curing Epilepsy in the Year 2025

Cell Signaling Modulators as Novel Disease Modifying Therapies

Anne Anderson, M.D.

Slides Not Available
Learning Objectives

• To understand the role played in the pathogenesis of seizures by the inflammatory pathways activated in epilepsy
• To provide insight into emerging anti-inflammatory treatment options for drug-resistant forms of epilepsy

Chronic activation of immune system in epilepsy

Innate immune system
Microglia, astrocytes
Macrophages
Cytokines, Chemokines, PGE2, complement

Inflammation leads to brain damage/dysfunction

Adaptive immune system
Cytotoxic T cells
Auto-Abs

Inflammation in epilepsy: what is new?

Sterile inflammation
Brain: cell injury, chronic stress, seizures
Innate immune response: microglia, astrocytes

Inflammatory mediators are neuromodulators:
these "immune molecules" have CNS-specific roles independent of their role in the classical immune/inflammatory response
(Graeber et al, FEBS Letters, 2011)
Innate immunity: IL-1Receptor/Toll-like Receptor signaling

Cytokines, Chemokines, mTOR, Complement cascade
Cell adhesion Molecules
Metalloproteases
Cox-2

Post-translational modifications
Neuronal hyperexcitability
BBB/astrocyte dysfunction

EPILEPSY

Activation of HMGB1 signaling in epilepsy: TLR4 & RAGE

Temporal Lobe Epilepsy
TLR4 (neurons & astrocytes)

HMGB1 (astrocytes & microglia)

Activation of HMGB1 signaling in epilepsy: TLR4 & RAGE

Cellular localization of TLRs in RE Cerebral Cortex

HMGB1, Hsp60/70, Hyaluronan, Fibrinogen

Gram -

HMGB1/TLR4 induces MHCII
Zong et al, Ann Rheum Dis, 2013

Activation of innate immunity in human epilepsy: glia & neurons

IL-1β in mTLE

IL-1β in FCD type 2b

BBB damage Albumin+IgG

Activation of this signaling is pro-ictogenic in experimental models

Activation of innate immunity in human epilepsy: glia & neurons

Adaptive immunity in Rasmussen Encephalitis

CD8+

Bien et al, Ann Neurol, 2002; Pardo et al, Epilepsia, 2004

Innate immunity in RE

by courtesy of Jan Bauer

Link between brain inflammation and epilepsy

• Various inflammatory mediators are overexpressed in epileptogenic foci in human epilepsy with differing etiologies (e.g. RE, LE, MCD, TLE). Anti-inflammatory mechanisms are inefficient in epilepsy (Ravizza et al, Neurobiol Dis, 2006; Pernhost et al, Seizure, 2013)
• Microglia/astrocytes are common sources of inflammatory mediators in brain tissue (also neurons and endothelial cells)
• Leukocytes contribute to different extent depending on etiology of epilepsy
• BBB damage is often detected in areas of perivascular inflammation involving astrocytic endfeet

Extent of glia-derived inflammation correlates with frequency of seizures and epilepsy duration

Experimental seizures and epileptogenic brain injuries induce brain inflammation:
- Long lasting
- Precedes the development of epilepsy
- Inadequately controlled by endogenous antiinflammatory molecules

Pharmacological experiments:
- Specific anti-inflammatory treatments reduce seizures and delay their onset (see also transgenic models)
- Proinflammatory insults decrease seizure threshold


IL-1β and HMGB1 signaling is induced in glia, neurons, BBB endothelium in human and experimental epileptogenic foci

**Anticonvulsive effects**

- Neuronal nitric oxide synthase (NOS) inhibitors
- Anakinra/IL-1ra
- P2X7 antagonists (Engel et al, Faseb J, 2012)
- VX765
- ICE inhibitors

**Anticonvulsive efficacy of anti-inflammatory treatments**

- IL-1β/TLR signaling
  - Status epilepticus in rats is reduced by anakinra (De Simoni et al, 2000; Marchi et al, 2009)

- COX-2 & PGE2 promote cell loss:
  - Induction in neurons and astrocytes in mTLE (DeSimone et al, 2003)
  - Reduced hippocampal cell loss in COX-2 KO mice (Serrano et al, J Neurosci, 2011)

- EP2 antagonists are neuroprotective (Jiang et al, PNAS, 2011, 2012)
  - Parecoxib, Polascheck et al, 2010; Celocoxib, Jung et al, 2005; neuroprotective
  - SC-58236 worsens SE outcome, Holtman et al, 2010

Cytokines and acquired channelopathies

Adapted from Pitkanen & Lukasiuk, 2009

- TNF-α, IL-6, COX-2 & complement system (reviewed in Kukarni & Dhir, 2009; Vezzani et al, 2011; Aronica et al, 2012)

- Induction in neurons and astrocytes in mTLE (Desjardins et al, 2003)
- Reduced hippocampal cell loss in COX-2 KO mice (Serrano et al, J Neurosci, 2011)

- EP2 antagonists are neuroprotective (Jiang et al, PNAS, 2011, 2012)

- Parecoxib, Polascheck et al, 2010; Celocoxib, Jung et al, 2005; neuroprotective
- SC-58236 worsens SE outcome, Holtman et al, 2010
The yin and yang of the EP2 receptors in the brain

Butaprost/EP2 agonist is neuroprotective

Jiang et al., PNAS, 2011

Neuroprotection after SE: cocktail of antiinflammatory drugs

Blockade of IL-1β system in adult rats (Noe’ et al., Neurobiol Dis, 2013)

Anakinra + COX2 inhibitor in PN21 rats

Kwon et al., J Neuroinflamm., 2013

Finding master regulators

Treatments combination

Prevention & Resolution

Open questions

Activation of innate immunity and inflammation contribute to

• Seizures generation and recurrence

Anti-IL-1β drugs

Complement inhibitors

EP2 antagonists

TLR4 antagonists

Inhibitors of glia activation

Regulators of BBB integrity

Neuroinflammation & epileptogenesis

NSAID: Celecoxib, Parecoxib, Aspirin

Anti-integrins antibodies

Anti-IL-1β drugs

Complement inhibitors

TLR4 antagonists

Inhibitors of glia activation

Regulators of BBB integrity

Threshold Genetic background Inciting Event

Inciting event: Seizure or Syndrome Identification

Inflammation, ictogenesis & epileptogenesis

Adapted from: A. Pitkanen, Epilepsia, 2010

The team

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F. Noe’
Learning Objectives

• Understand current cell therapy approaches to control intractable seizures

• Discuss potential limitations in moving these approaches toward the clinic

Problem: epilepsy is a network phenomena

• Increased neuronal bursting and synchronization are a hallmark of seizures

Inhibition may be the best way to constrain an epileptic network

How do we increase inhibition?

• GABA mimetic drugs

• Modulation of postsynaptic GABA receptors

• Block GABA re-uptake

• New GABA interneurons


A strategy for cell therapy

1. Identify epileptic zone
2. Cell transplantation
3. Cell integration and seizure control

Adapted from Parent & Murphy, News & Views, Nature Neuroscience 2013

Benefits and risks of intranigral transplantation of GABA-producing cells subsequent to the establishment of kindling-induced seizures


Modulation of experimentally induced epilepsy by intracerebral grafts of fetal GABAergic neurons

Finn A, Meldrum BS. Neuropsychopharmacology 2006

A path to the clinic: preclinical studies

Obtain proof-of-principle data in an animal model of epilepsy

• Generation of inhibitory interneurons
• Functional integration following transplantation
• Disease-modifying activity (DMA) against spontaneous seizures and related co-morbidities

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Why earlier approaches did not work?

• Failure of transplanted cells to integrate
• Mixed populations of transplanted cells
• Mechanism of action??
• Not tested in appropriate animal model

How to make an interneuron for cell therapy

Source: embryonic medial ganglionic eminence (MGE)

• neuron expressing GABA
• migration in host brain
• mature firing properties
• integration in host circuitry
MGE cells migrate widely in host brain

- P2 transplant (up to 5 mm)
- P60 transplant (up to 2 mm)
- cortex, hippocampus, amygdala

MGE cells enhance inhibition in host brain

- fetal MGE progenitor cells
- iPSC onto host pyramidal
cortex and hippocampus

Optogenetic manipulation of MGE-derived interneurons following transplantation

Robert F. Hunt III

MGE cells in a genetic form of epilepsy

- Kv1.1 null mice
- P2 MGE transplant
- 96% seizure reduction

How to make a neuron: induced neural cells

- defined transcription factors direct cell fate
Features of an ideal human MGE cell line

- GABA interneuron specificity – PV, SOM, NPY
- Robust migration
- Functional integration
- Safety
- Efficacy

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Potential problems: Slow functional maturation

- NKX2.1::GFP human ES cells
- FACS sorted/neonatal cortex
- 7 months post-transplant

Potential problems: Teratocarcinoma

- undifferentiated hES cells
- hippocampus transplant
- Sox1::GFP::Ubi::RFP cells

Some currently available human stem cell lines

1. Sox3-expressing embryonic stem cells (ESC)
2. Nkx2.1-expressing embryonic stem cells (ESC)
3. induced pluripotent stem cells (iPSC) from Dravet patients


Human SC-derived interneurons in vitro

Potential problems: Slow differentiation

- NKX2.1::GFP human ES cells
- FACS sorted and transplanted into neonatal cortex
- 6 wk - 3 mo. post-transplantation: “undifferentiated appearance . . . often tipped by growth cones”
How do we address these problems?

- Learn more about the properties of fetal human MGE cells
- Improve methods or techniques for generating hMGE cells
- Develop and characterize more appropriate animal models for evaluation of human MGE cells

Properties of human MGE cells

- Subcortical origins of human and monkey neocortical interneurons. Ma et al. Nat Neuroscience 2013
- Non-epithelial stem cells and cortical interneuron production in the human ganglionic eminences. Hansen et al. Nat Neuroscience 2013

“Cerebral organoids” as MGE donors?


Human stem cell therapies that are showing some promise (but not epilepsy, yet)


A path to the epilepsy clinic

Obtain IND enabling data with a human MGE cell line

- Disease Modifying Activity (DMA) in at least one animal model of epilepsy
- Safety and “dosing” information
- Cryopreservation
- Device for delivery of human MGE cells

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(Future) Impact on Clinical Care and Practice

Tissue grafts transiently suppress evoked seizures

1987-1990
Mouse MGE cells suppress spontaneous seizures & reverse comorbidities

Tissue grafts transiently suppress evoked seizures

1987-1990 2013

Human MGE cells are safe and suppress seizures in patients

Tissue grafts transiently suppress evoked seizures

1987-1990 2013 2025
**Optogenetic Therapy**  
December 9, 2013  

Ivan Soltesz, PhD  
University of California Irvine

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**Introduction**

Epilepsies are often refractory to current anti-epileptic drugs. Therefore, a treatment option is needed that *preserves physiological neuronal function and tissue by improving selectivity* of intervention through targeting specific cell populations at specific times.

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**Learning Objectives**

- Explain how selective excitation or inhibition of brain cells can be achieved with light
- Assess the advantages and future potential of optogenetic interventions in epilepsy

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- 1979 Francis Crick’s major challenge in neuroscience: **Control one type of cell** in the brain while leaving others unaltered  
  - Electrodes and drugs are not sufficient  
  - Light?  
  **Solution:** Microorganisms produce visible *light-gated proteins that directly regulate the flow of ions across the membrane*
  
  - 1971 - Bacteriorhodopsin  
  - 1977 - Halorhodopsin  
  - 2002 - Channelrhodopsin

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2005 Following *introduction of a microbial gene alone* (without any other parts, chemicals or components) neurons became responsive to light

Boyden, E.S., Zhang, F., Bamberg, E., Nagel, G. & Deisseroth, K.  
**Optogenetics** is a control technology that allows the fast, selective excitation or inhibition of specific neurons with light by expressing light-sensitive proteins in cells.

Enables precise causal control of neuronal activity in behaving animals.

**Activation and inhibition of cells**

Examples of applications of optogenetics to study brain function and dysfunction (outside of epilepsy):

- Sleep-wake transitions (Adamantis Nature 2007)
- Gamma oscillations (Sohal Nature 2009)
- Social dysfunction (Yizhar Nature 2011)
- Fear memory (Yizhar Nature 2011)
- Anxiety (Yizhar Nature 2011)
- Depression (Covington J Neurosci 2010)

First application of optogenetics to seizures (in vitro)

Stimulation train-induced bursting (STIB) in CA3 is strongly attenuated by orange-light activation of transgene NpHR in organotypic hippocampal cultures.

Stimulation train-induced bursting (STIB) in CA3 is strongly attenuated by orange-light activation of transgene NpHR in organotypic hippocampal cultures.

2012-2013 Optogenetic seizure control in animal models of epilepsy in vivo

- Acute seizures (Sukhotinsky PLoS ONE 2013)
- Focal cortical seizures (Wykes Sci Transl Med 2012)
- Thalamocortical seizures, stroke (Paz Nature Neurosci 2013)
- Temporal lobe epilepsy (Krook-Magnuson Nature Commun 2013)
- Closed-loop control (Paz 2013; Krook-Magnuson 2013; Berenyi Science 2012; Armstrong Nature Prot 2013)
**Focal cortical seizures**

- Focal injection of tetanus toxin to induce seizures
- Lentivirus to transduce excitatory pyramidal cells in the focus
- Inhibitory opsin halorhodopsin

Conclusions:
1. Optogenetic approach can inhibit focal cortical epileptiform activity
2. Inhibition of a portion of excitatory cells at the focus is sufficient

*Wykes et al Sci Transl Med 2012*

**Temporal lobe epilepsy**

- Intrahippocampal kainate model, chronic seizures
- Transgenic mice
- On-demand, closed-loop activation of light

Conclusions:
1. Seizure control via inhibition of excitatory cells or excitation of inhibitory cells
2. Focal light delivery is effective in TLE

*Knock-Magnuson Nature Comm 2013; Armstrong Nature Prot 2013*

**Main challenges for future optogenetic therapy**

- Safe and stable opsin expression in humans
- Safe implantable device for on-line seizure detection (and prediction)
- Safe device for light delivery

**Main advantage of optogenetics: Specificity**

- Cell-type specificity
- Temporal specificity
- Spatial specificity

**Thalamocortical seizures**

- Cortical photothrombotic stroke model
- AAV with halorhodopsin; in excitatory cells
- On-demand, closed-loop activation of light

Conclusions:
1. Cortical strokes produced thalamocortical seizures
2. Optogenetics can provide insights into mechanisms of seizures

*Paz et al Nat Neurosci 2013*

**Thinking forward: Towards future human optogenetics**

- Viral vectors have been used in humans, including in the brain (Bartus Neurology 2013; Murphy Transl Res 2013)
- Gene-delivery in general is being considered for a range of neurological diseases including epilepsy (*Wykes Sci Transl Med 2012*)
- Insertional mutagenesis may be avoided using vectors that remain extrachromosomal
Optogenetics in non-human primates

Additional optogenetic applications with relevance for epilepsy

- Opsins can be light-sensitive ion channels, pumps, and G-protein coupled receptors
- Transcriptional effectors
- Opsin expression achieved through developmental origin and date of birth
  - Levels of activity at a specified time
  - Long-distance projections
- Optogenetic control through glial photostimulation
- Optogenetic manipulation of transplanted cells

Improved opsin designs for in vivo

- Red-shifted opsins: Propagation of light in tissue is proportional to its wavelength: blue is high scattering, low penetration compared to higher wavelengths such as red
- Step-function opsins (SFOs): Slow deactivation time constants, improved light sensitivity: can be used to slightly alter network contribution of different cells

Additional challenge: preserving specificity after seizures

- Important caveat for Cre-mediated selectivity: excision of DNA (e.g., removal of STOP cassette) is permanent, even if Cre-expression itself is transient
- For example, somatostatin is transiently expressed in excitatory principal cells after seizures

Optogenetic fMRI

- Monitoring brain responses to optogenetic stimulation or suppression of a given circuit (Lee Nature 2010; Desai J Neurophys 2011)

Powerful translation tool: imaging longitudinally (e.g., before and after drug administration) in conscious subjects

Conclusions

- Optogenetics is a versatile control technology to manipulate normal and abnormal neuronal activity
- Main advantage is specificity of control: time, space, cell-type
- Main challenge for future therapy: Safe opsin expression
Acknowledgements

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Seizure Detection/Prediction Devices and Therapies
December 9, 2013
Gregory Worrell MD, PhD
Mayo Clinic

Learning Objectives
• Epilepsy Devices: State of Art
• Big Data Applications
• Seizures are not Random

Devices for Epilepsy
Duty Cycle Stimulation
Responsive Stimulation
Forecasting

Responsive Neurostimulation

Challenges in Epileptology
Detection: Seizures & Quantification
• Epilepsy Diagnosis & Therapy
• Diary & EMU
Epilepsy Therapies
• Drugs, Surgery & Stimulation
Forecasting: Seizures are not Random
• Spatial Predictability
• Temporal Predictability

Disclosure
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Scientific Advisory Board
Clinical trial
Scientific Advisory Board
NIH
R01-NS063039, U01-NS073557 & U24-NS063930

Brain Stimulation and Prediction Devices not approved for Epilepsy

Responsive Neurostimulation System
NeuroPace Inc.
Seizure detection & stimulation

Responsive Neurostimulation System

Baseline Trial Phase Open Label Phase

Bilateral Independent TLE

Are Seizures Random?

- Deterministic
  - Seizures are predictable (9:45 AM May 17)
- Time Dependent Probability
  - Pre-ictal state → Seizure Forecasting possible
  - Precursory Signal
Prediction of Natural Phenomena

Complicated Problem
- Physics known
- Good “Big Data”
  - multiple scales

Good predictions
Weather Prediction - Big success

Seizure Prediction
Mormann et al. Brain 2006

"Prediction is difficult ...especially when it is about the future". Nils Bohr

Pre-ictal State ?
D. Snyder et al. JNeural Eng. 2008

Interictal Pre-ictal State Ictal State

Forecasting Seizures

Probabilistic prediction (forecasting)
- Increased risk of seizure (red-light)
- Decreased risk of seizure (blue-light)

Observation of a precursory signal
- State change: Interictal → Preictal → Ictal

Utility
- Warn patient (minutes, hours, days ?)
- Deliver pre-emptive therapy (AED, Stim....)

Machine Learning Classification
Mirowski EpilepsyRes 2009
Netoff Epilepsia 2011, Howbert PLOS-One 2013

Pre-processing
Electrophysiology Understanding
Physiology

Feature Extraction Classifier Training

Training Data Feature Selection

Classifier Optimization

Performance Measures Classify Test Set

Signal Required Pre-Processing Electrophysiology

Interictal Preictal Ictal Postictal
Forecasting Seizures

• Only 5/11 correlate

Seizure Diaries

15 People w/ Epilepsy
Responsive AED

Forecasting Canine Seizures
NIH-U01 Team: NeuroVista, UMinn, UPenn, Mayo

- Davis et al. Epilepsy Res. 2011
- Coles et al. Epilepsy Res. 2013
- Howbert et al. Plos-One 2013

Forecasting Seizures
Howbert PLOS-One 2013 & Brinkman ...2013

Human Brain Electrophysiology

Spatial Scales of Interest

Frequency Scales of interest
Electrophysiological Biomarkers
Goldensohn 1975; Schevon 2008; Stead 2010

Pathological Micro-domains ~300 μm

Clinical Impact
The Future 2025: Big Data & Machines

- Data to guide treatment
- Forecasting Risk for Epilepsy (Epileptogenesis)
  Prevention
- Spatial Forecasting (Localization)
  Surgery & Stimulation
- Temporal Forecasting
  Neurophysiologically based therapy

Path to Future: Machines & Data

- Devices, Data & Tools
  - NIH EEG Portal (ieeg.org)
  - Share Data (Reproducible Results)

- Contest (2014 AES Presidential Symposium)
  - Seizure Detection (Human iEEG recordings)
  - Seizure Forecasting (Canines & Humans)