2007 Epilepsy Research Benchmarks

2010 Update: Progress, Challenges, Opportunities

Anne Berg, Northwestern Children’s Memorial Hospital (co-chair, Benchmarks Area III)
Interagency Collaborative to Advance Research in Epilepsy (ICARE)
June 27, 2011
March 2000 - Curing Epilepsy: Focus on the Future
  ▪ Conference brought together scientists, care providers, and leaders of voluntary organizations
  ▪ Developed the first set of goals for the broad epilepsy research community
  ▪ Benchmarks Stewards promote and track progress

March 2007 - Curing Epilepsy: Translating Discoveries into Therapies
  ▪ Updated the original Benchmarks in light of progress made and changes in research directions
2007 Epilepsy Research Benchmarks

- Area I: Prevent epilepsy and its progression
- Area II: Develop new therapeutic strategies and optimize current approaches to cure epilepsy
- Area III: Prevent, limit, and reverse the co-morbidities associated with epilepsy and its treatment

Epilepsy Research Benchmarks: Area I

- Prevent epilepsy and its progression
  - Identify
    - unrecognized causes of epilepsy
    - underlying mechanisms of epileptogenesis.
    - biomarkers for epileptogenesis
    - approaches to prevent epilepsy or its progression
  - Develop new animal models to study epileptogenesis
  - Test the efficacy of prevention strategies
Gene discoveries and changing concepts

- Identifying mechanisms beyond ion channels.
  - \textit{TBC1D24}: gene involved in axonal guidance and development of neuronal morphology and connectivity
  - Cadherins (\textit{PCDH19}): cell adhesion

- Broadening the range of phenotypes associated with individual genes:
  - \textit{PCDH19}: gene associated with Epilepsy in Females with Mental Retardation (EFMR). Now associated with a ~phenocopy of Dravet syndrome in girls.
  - \textit{SLC2A1} (Glut1 transporter): associated with early onset absence epilepsy and multiple different epilepsies in large multiplex families, movement disorders.

- Copy number variants: previously understood as an alternative type of error in monogenic disorders (e.g. Rett disorder and \textit{MECP2} errors), now being found in “idiopathic” epilepsies:
Excitatory role of neurotransmitter GABA in early development due to balance in expression of NKCC1 (transports chloride into cell) and NKCC2 (transports out).

- Mechanism suggested bumetanide as possible therapy: blocks NKCC1 (in-going transporter). Theoretically should restore inhibitory (hyperpolarizing) effects of GABA.

- Recent studies had unexpected results
  - Tested in hippocampus and did not reduce the development of spontaneous, recurrent seizures in a rat model; phenobarbital alone did.
Area I: Non neuronal mechanisms of epileptogenesis

- **Roles for astrocytes and neuron-astrocyte interactions**
  - Glutamate transport in astrocytes
    - Astrocytic glutamate transporter expression is decreased in the **hippocampus** of patients with TLE and after traumatic brain injury
  - In a mouse model of TSC, the antibiotic ceftriaxone recovered transporter expression and reduced **seizure frequency**, **neuronal loss**, and **mortality**
Area I: Mechanisms of epileptogenesis

- **Everolimus, mTOR, inhibitor approved by FDA.**

- **mTOR signaling pathway**
  - Over-activated in Tuberous Sclerosis (TSC) and increased in other epilepsy animal models and human epilepsies
    - Rapamycin (mTOR inhibitor) has anti-epileptogenic effect in mouse models of TSC and **temporal lobe epilepsy (TLE)**
    - Preliminary data now suggest mTOR inhibitors also decrease seizure frequency in some TSC patients
    - mTOR over-activation observed in cortex in a multiple-hit model of infantile spasms
Role of Blood Brain Barrier (BBB) breakdown in epileptogenesis after hypoxic-ischemic insult.
- Allopregnanalone and progesterone reduced BBB disruption and infarct size.
- Seizures developed only in animals with infarcts.

Rapid hippocampal kindling: inflammatory challenge potentiates kindling, blocked by interleukin-1 receptor blockers.
Area I: Models of Epilepsy, Epileptogenesis and Blocking Epileptogenesis

- Parecoxib (COX-2 inhibitor) administered 18 days prior to pilocarpine-induced status epilepticus → less severe hippocampal subfield damage.

- Toll-like receptors (TLRs) and their activators (e.g. TLR4 activated by HMGB1) are released from necrotic cells. Over expression of HMGB1 → increased seizures. Antagonists of HMGB1 or TLR4 decreased seizures.

- Carisbamate suppresses spasms in multiple-hit ACTH-resistant spasms model.
Area I: Needs and Opportunities for research on epileptogenesis

- Ongoing research needs:
  - Models of non-limbic human epilepsy
  - Biomarkers for the development of epilepsy and disease progression, especially outside the hippocampus
  - Better understanding of the therapeutic window for interventions to prevent epileptogenesis for different relevant clinical scenarios.
  - Use of well-characterized genetic models to improve understanding of epileptogenesis
    - $SLC2A1$

- Opportunities
  - Studying laboratory findings with current therapeutics into human RCTs.
  - The International League Against Epilepsy (ILAE) has formed a task force for translational research focused on antiepileptogenesis
Develop new therapeutic strategies and optimize current approaches to cure epilepsy

- Identify basic mechanisms of ictogenesis (seizure generation) that will lead to the development of cures
- Develop tools that facilitate the identification and validation of a cure
- Optimize existing therapies and develop new therapies and technologies for curing epilepsy
Area II: New methods and technologies for improving use of surgery.

- High frequency oscillations as marker of epileptogenic cortex.
  - *Could be used to guide resections intra-operatively*

- 7T MRI technology: improvements in scanning times and properties reported.

- Use of co-registration techniques to localize epileptogenic zones using multi-modal information – MRI, with PET, SPECT, BOLD.
Several Phase II trials for drugs targeting a range of mechanisms from ion channels to inflammation

New clinical trial designs
- FDA accepted a new trial design developed by the epilepsy community (historical control withdrawal to monotherapy)
Area II: Challenges and Opportunities

- Despite all of the new drugs, there is little to guide their use in most patients with epilepsy.

- Barriers to assessing and improving surgical outcomes
  - Lack of standards for evaluation and assessment of outcomes.
  - Needs for high quality studies evaluating new technologies in epilepsy surgery today.
Prevent, limit, and reverse the co-morbidities associated with epilepsy and its treatment

- Identify and characterize the full range and age specificity of co-morbidities in people with epilepsy
- Identify predictors and underlying mechanisms that contribute to co-morbidities
- Determine the optimal treatments for the neuropsychiatric and cognitive co-morbidities in people with epilepsy
- Prevent or limit other adverse consequences occurring in people with epilepsy
- Develop effective methods for diagnosis, treatment and prevention of non-epileptic seizures (NES)
Area III: Identify new susceptibility factors

- Cognitive impairment
  - Neurocystercerosis (NCC), independent of seizures and their treatment, conveys a risk for some subtle cognitive impairment.
Area III: Delineate natural history

- Subtle cognitive dysfunction is seen in adults at the time of initial diagnosis before initiating treatment.

- Over time, children and adults with new-onset experience declines in memory, executive function, and psychomotor speed.
Improvements in cognitive function are seen in children after resective surgery. Substantial improvements required ~5 years to be appreciated.

Developmental scores improved in severely impaired children with Lennox-Gastaut Syndrome following surgery.
Area III: Underlying mechanisms contributing to co-morbidities

- Functional MRI studies demonstrating impaired (less efficient) language networks involving widespread brain regions in children with epilepsy.

- Imaging evidence of subtle variations in brain structure in individuals with CAE and JME.
New animal models of comorbidities associated with epilepsy

- Depression in lithium-pilocarpine model in the and WAG/Rij model of absence
- Psychosis-like symptoms in GAER
- Learning, memory and autistic like behaviors in an animal model of “symptomatic” infantile spasms.
Area III: treatment of co-morbidities in PWE

- RCT found sertraline (an SSRI) and CBT equally effective for the treatment of major depressive episodes in PWE. Sertraline did not negatively affect seizure control!

  **Important:**
  - A survey found primary care doctors did not treat depression because of fear of worsening seizures.
  - 5 center study documented the under treatment of depression and anxiety in PWE.

- Several studies of CBT and related non-pharmacologic studies as interventions in adults and adolescents with epilepsy. Phone and internet administration investigated – results all promising.
Suicidality

- Several reports and a careful review regarding risk associated with AEDs.
- Overall no compelling, consistent evidence of an increased risk of suicide associated with specific AEDs or AEDs overall.
SUDEP

Respiratory mechanisms:

- Evidence from animal models of serotonin linked to apnea and death in a genetic model of epilepsy, rescued by fluoxetine.
- PWE on SSRIs had less severe O2 desaturations during focal seizures than did PWE not taking SSRI.
Area III: SUDEP

- Prolonged-QT genes
  - Mouse models: LQT genes express dual phenotype of arrhythmias and epilepsy and sudden death.
  - Humans: presumptive epilepsy phenotype reported in patients with genotyped LQT.

- Electrocerebral shutdown hypothesis: prolonged generalized post-ictal electrographic suppression was a significant predictor of SUDEP.
  - Biomarker of SUDEP risk
Area III: Sleep

- Technological advances in portable 24-hour sleep and seizure tracking devices.
- Severity of epilepsy in children correlated to frequency and severity of sleep disorders.
- Obstructive sleep apnea more common in children with severe epilepsy (relevant to SUDEP).
Shared mechanisms:
- Familial clustering of nocturnal frontal lobe epilepsy and parasomnias (arousal disorders, nightmares)

Therapies:
- Light therapy: RCT ongoing
- Melatonin: May help regulate sleep-wake cycle for people with epilepsy
Area III: Other systemic disorders

- Osteopenia
  - Balance impaired with AEDs, particularly polytherapy and prolonged use
  - Genetic susceptibility (vit D receptor allele)

- Endocrine disturbances
  - Elevated testosterone in men recently begun on levetiracetam.

- Reproductive
  - Population-based study: 1/3 of women with epilepsy have infertility; polytherapy → increased risk
Neurodevelopmental Teratogenicity of AEDS
- VPA → substantial impact on offspring development
- Other AEDs tested (LTG, LVT) no significant impact
Area III: Non-Epileptic Seizures

- Differential diagnosis based on semiology alone is hard.
  - Only $3/48$ features helpful:
    - preserved awareness,
    - eye flutter,
    - intensification or resolution when others interact with patient)

- NES Susceptibility factors
  - Psychiatric history.
Area III: Non-Epileptic Seizures

- Treatment of NES
  - RCT of sertraline vs. placebo.
    - 45% reduction of NES in sertraline group
    - 8% increase of NES in placebo group
  - Psychodynamic interpersonal therapy: uncontrolled feasibility study:
    - 25% NES-free,
    - 40% had significant reduction in NES.
  - Venalafaxine: uncontrolled open label study: substantial improvements in NES and HAM-D scores
The Institute of Medicine has convened a panel on the public health dimensions of epilepsy. At an open workshop, March 21, 2011, Los Angeles, CA, one of the sessions addressed co-morbidities.

The 2009 Merritt Putnam symposium at the AES was devoted to a multidisciplinary presentation on co-morbidities associated with the epilepsies.
Area III: Challenges and opportunities

- Translating research into useful interventions and policies at all levels.
  - Prevention
  - Treatment
  - Accommodation
  - Education

- Several potential areas for randomized trials or other evaluations of therapies
  - SUDEP
  - Sleep
  - NES
Epilepsy Research Benchmarks: research community Stewards

Dan Lowenstein, Benchmarks Stewards Chair
Cara Allen, NINDS liaison

**Area I Benchmarks**
- Jerome Engel, Jr. (Co-chair)
- Jocelyn F. Bautista
- Solomon (Nico) Moshé
- Carl Stafstrom
- Annapurna Poduri
- Michael Wong
- Aristea S. Galanopoulou
- Richard J. Staba
- Alexander Rotenberg

**Area II Benchmarks**
- Brian Litt (chair)
- Jacqueline French
- Chad Carlson
- Greg Worrell
- William Stacey
- Kathryn Davis

**Area III Benchmarks**
- Anne Berg (Co-chair)
- Amy Brooks-Kayal (Co-chair)
- John J. Barry
- Bruce P. Hermann
- W. Curt LaFrance, Jr.
- John W. Swann
- Elson So
- Alica Goldman
- Alison Pack
- Molly Huntsman
- Madison Berl
- Timothy A. Benke
- Miya Asato
- Jack J. Lin
- Andres M. Kanner
- John T. Langfitt
- Tobias Loddenkemper
- Samden Lhatoo
- Robert C. Doss
- Tanvir Syed
- Daniel L. Drane
Q & A