2007 Epilepsy Research Benchmarks

2010 Update:
Progress, Challenges, Opportunities

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Epilepsy Research Benchmarks: history and development

- 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

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
Area I: Identify as yet unrecognized causes of epilepsy

- **Gene discoveries and changing concepts**
  - Identifying mechanisms beyond ion channels.
    - TBC1D24: gene involved in axonal guidance and development of neuronal morphology and connectivity
    - Cadherins (PCDH19): cell adhesion
  - Broadening the range of phenotypes associated with individual genes:
    - PCDH19: gene associated with Epilepsy in Females with Mental Retardation (EFMR). Now associated with a ~phenocopy of Dravet syndrome in girls.
    - 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 MECP2 errors), now being found in “idiopathic” epilepsies:
Area I: Targeting mechanisms of epileptogenesis

- 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.
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)
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)
Cognitive impairment

Neurocystercercosis (NCC), independent of seizures and their treatment, conveys a risk for some subtle cognitive impairment.
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 comorbidities

- 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.
Area III: Preventing consequences

- **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 arrythmias 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
Area III: Other systemic disorders

- 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.
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
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