Progress, Challenges, Opportunities

2007 Epilepsy Research Benchmarks

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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 as yet unrecognized causes of epilepsy (e.g., genetic, autoimmune and infectious)
- Identify underlying mechanisms of epileptogenesis.
- Identify biomarkers for epileptogenesis
- Identify approaches to prevent epilepsy or its progression
- Develop new animal models to study epileptogenesis
- Test the efficacy of prevention strategies
Identify as yet unrecognized causes of epilepsy

- **Gene discovery**
  - Many known genes affect ion channels or neurotransmitter signaling
  - New findings point to other processes
    - Synaptic vesicle release
    - Cadherin superfamily (development of neuronal connectivity)
    - Interneuron (inhibitory) development
  - New clues from genes linked to brain development or other disorders associated with epilepsy

- **Immune or inflammatory risk factors**
  - Acute seizures associated with H1N1 and RSV infections
  - Maternal genitourinary infections and increased seizure risk in offspring
  - Case study reporting autoantibody-mediated encephalitis
  - Interactions between genetic and environmental risk factors?
Targeting the mechanisms of epileptogenesis

- **Hypoxic-ischemic (H-I) encephalopathy**
  - Most frequent cause of neonatal seizures
  - Role for increased expression of glutamate receptor subunits
  - In rat model, drugs that block AMPA receptors reduce H-I seizures and cognitive deficits

- **mTOR signaling pathway**
  - Over-activated by mutations that cause Tuberous Sclerosis (TSC)
  - Also dysregulated 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)
New animal models of epilepsy and epileptogenesis

- **Childhood epilepsies**
  - Multiple new models developed for Infantile Spasms (IS), a devastating epileptic encephalopathy

- **Epileptogenesis in aging**
  - Increased incidence of seizures in Alzheimer’s disease
  - hAPP mouse model has non-convulsive cortical seizures

- **Acquired epilepsy**
  - Theiler’s murine encephalomyelitis virus (TMEV) as mouse model for acute symptomatic seizures and post-infection acquired epilepsy
Challenges and Opportunities

Ongoing needs
- Animal models of epilepsy development and progression for mechanistic and intervention research
- Biomarkers that predict progression in new onset epilepsy or the development of epilepsy in those at risk

Genetics
- Advancing genetic technologies present opportunities
  - Genome-wide familial and large-scale association studies
  - Application of whole genome sequencing to known loci
- Need for collaboration across studies using different patient cohorts

Acquired epilepsies
- H1N1 and RSV infections present natural experiments for studying immune-related epilepsy
- New clinical trials ongoing or beginning for post-traumatic epilepsy
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
Seizure generation, propagation and termination

- Advancing technologies for recording network activity
  - High-density intracranial EEG and microelectrode recording

- Graph theory, functional connectivity analysis of seizure activity
  - Could interventions that target ‘hub’ cells in epileptogenic tissue eliminate seizure activity without loss of network function?

- Cell signaling pathways
  - Astrocyte networks coupled through gap junctions maintain epileptiform activity
  - The acid sensing ion channel ASIC1a contributes to seizure termination
    - Opens in response to decreased pH, which occurs during seizure
    - Increases activity of inhibitory interneurons
New approaches for targeted therapies

- **Brain stimulation**
  - Some trials have shown reduced seizure frequency
  - No large scale, randomized trials yet show freedom from seizures

- **Gene therapy and other biologics**
  - Neuropeptide systems (NPY, galanin) and GABA signaling pathway are most popular target

- **Focal therapeutic delivery**
  - Adenosine
    - Suppresses seizures, but cardiovascular side effects limit clinical application
    - Adenosine-secreting matrices or cell implants
  - Other approaches under investigation include focal cooling, catheter delivery
Optimizing outcomes for surgical intervention

- *Surgical intervention remains a very good option for patients with an epileptogenic focus that can be*
  - clearly localized
  - removed without functional loss outweighing benefits of reduced seizure frequency

- *Improving the localization of epileptic foci*
  - Application of advancing imaging and recording technologies (e.g. HFOs)

- *Better understanding of functional networks involved in language and memory*
  - may improve surgical planning and ability to predict and avoid functional deficits
Challenges and Opportunities

- Despite new anticonvulsant drugs, 25-35% of people with epilepsy lack adequate seizure control

- Challenges in therapy development
  - Drugs, gene therapy, biologics, focal drug delivery
    - Need for specific targeting, long-lasting effects
  - Brain stimulation
    - Effective stimulation protocols will require better understanding of circuits involved in different epilepsies

- Challenges facing clinical trials
  - Epilepsy Study Consortium, NINDS Common Data Elements
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 and behavioral comorbidities of epilepsy

Community-based and population studies report increased:
- Depression and suicidal ideation/attempt
- Anxiety
- Cognitive deficits
- Behavioral problems
- Reported poor health, poor health-related behaviors (e.g., smoking, inactivity)

What are the relative contributions of
- Chronic seizures and their treatment?
- Overlapping biological mechanisms underlying comorbidities and the development of epilepsy?
Epilepsy Research Benchmarks: Area III

- **Risk factors for cognitive and behavioral comorbidities**
  - Young age of onset
  - Duration of epilepsy
  - Symptomatic or cryptogenic etiology
  - Presence of cognitive/behavioral deficits at onset

- **Brain imaging and neural activity correlates**
  - Many studies have shown relationships between structural and/or functional abnormalities and cognitive/behavioral deficits in epilepsy
  - Further progress anticipated from approaches that look across whole networks or apply multiple imaging/recording modalities
Animal models point to mechanisms

- In a rat model of febrile seizures, MRI abnormalities present after induced seizure predict later memory deficits
- Spatial memory deficits in a rat model of TLE
  - observed soon after induced status epilepticus and prior to the development of chronic seizures
  - associated with electrophysiological changes in the hippocampus

... and to potential treatments

- Inhibition of Interleukin-1β (IL-1β) signaling improved depressive symptoms in rat model of TLE
- In a rat model of absence epilepsy, ethosuximide prevented spike-wave discharges and improved measures of depression
Other comorbidities associated with epilepsy

- **Sudden Unexplained Death in Epilepsy (SUDEP)**
  - Increased risk of premature death with some epilepsies, especially if seizures are not well controlled
  - Advances in understanding the mechanisms of SUDEP
    - Mouse model of cardiac Long QT syndrome links one ion channel to both epilepsy and cardiac arrhythmias leading to sudden death
    - Naturally occurring SUDEP in primates (potentially new animal model)
    - Further characterization of adverse respiratory effect of seizures
  - American Epilepsy Society and Epilepsy Foundation Joint Task Force and 2008 NINDS workshop
    - Research and education/outreach needs
Reproductive outcomes in women with epilepsy

- Healthy Outcomes for Pregnancies in Epilepsy (HOPE) forum
- American Academy of Neurology (AAN) and American Epilepsy Society (AES) joint recommendations on pregnancy in women with epilepsy
- Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study interim analysis
  - children exposed to valproate had significantly lower IQ at age 3

AED use associated with effects on bone health and endocrine and reproductive function
- Contradictory results across studies point to research needs
Non-epileptic seizures

- Heterogeneous in terms of etiology and comorbidities
  - Associated with somatoform patterns, depression, anxiety, trauma/post-traumatic stress disorder, dissociation
- Recent advances in efforts to improve NES diagnosis
- No large-scale epidemiological data available regarding the types and frequency of NES in the general population or in people with epilepsy
- Cognitive behavioral therapy and psychodynamic therapy may be effective treatments
Challenges and Opportunities

- Ongoing need for research on frequency, risk factors and mechanisms of comorbidities associated with epilepsy
  - Importance of sharing data, development of shared measures
- Research on cognitive deficits has focused largely on TLE and lags behind for other epilepsies
- Opportunities in research on comorbid conditions as they appear alone, or on other disorders (Alzheimer’s disease, autism, Fragile X Syndrome) associated with epilepsy or seizures
Challenges and Opportunities (con’t)

- Continued application of brain imaging and recording technologies to research to understand comorbidities
- Ongoing need for research on risks related to AED use
  - Recent report of a genetic risk factor for potentially fatal skin reactions to carbamazepine in a subgroup of individuals of Asian ancestry
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