Epileptogenesis and Treatment

Jerome Engel, Jr., MD, PhD

Jonathan Sinay Distinguished Professor of Neurology, Neurobiology, and Psychiatry & Biobehavioral Sciences
David Geffen School of Medicine at UCLA

American Epilepsy Society | Annual Meeting
## Disclosures

<table>
<thead>
<tr>
<th>NIH NINDS grants</th>
<th>R01 NS02808</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R01 NS33310</td>
</tr>
<tr>
<td></td>
<td>P20 80181</td>
</tr>
<tr>
<td>Elsevier</td>
<td>Royalty</td>
</tr>
<tr>
<td>Wolters Kluwer</td>
<td>Royalty</td>
</tr>
<tr>
<td>Wiley-Blackwell</td>
<td>Royalty</td>
</tr>
<tr>
<td>Oxford</td>
<td>Royalty</td>
</tr>
<tr>
<td>MedNet</td>
<td>Royalty</td>
</tr>
<tr>
<td>Best Doctors</td>
<td>Royalty</td>
</tr>
<tr>
<td>ION</td>
<td>Consultant</td>
</tr>
<tr>
<td>FDA</td>
<td>Consultant</td>
</tr>
</tbody>
</table>
Learning Objectives

1. Understand possible mechanisms of post traumatic epileptogenesis
2. Understand value of biomarkers in developing antiepileptogenic treatments
Epileptogenesis after Trauma

- Cell death
- Neuronal reorganization
- Enhanced excitation
- Decreased and enhanced inhibition
- Enhanced tendency to synchronization
Epileptogenesis

- Seizure Threshold
- Seizure
- Precipitating Factor
- Epileptogenic Abnormality

A B C D

INSULT
Cure

Seizure Threshold

Seizure

Precipitating Factor

Epileptogenic Abnormality

INSULT

A B C D E

INTERVENTION
Treatment

• Discovery and validation of antiepileptogenic interventions are impeded by the prohibitive cost of screening and clinical trials
• The variable incidence of PTE after severe head trauma, and the late-onset of seizures that can occur over 10 years after injury make huge animal and patient populations necessary and require exceedingly long follow-up
Biomarkers

Dynamic changes that indicate the presence of an epileptogenic process with a sufficiently high degree of reliability to warrant intervention

• Biomarkers of epileptogenesis
• Biomarkers of epileptogenicity
Biomarkers of Epileptogenesis

• Identify the development of brain tissue capable of generating spontaneous epileptic seizures
• Identify the progression of an epileptic condition after it has developed
Biomarkers of Epilepsy Development

• Predict epilepsy in patients with risk factors
  - genetic predisposition
  - prolonged febrile seizure
  - head trauma
  - intracranial infection
  - brain lesion
• Institute antiepileptic intervention
Biomarkers of Epilepsy Development

• Create cost-effective rapid-throughput models for screening potential antiepileptogenic interventions
• Identify subjects to enrich clinical trials of potential antiepileptogenic interventions
Target Mechanisms

- Cell loss (e.g., hippocampal atrophy)
- Axonal sprouting
- Synaptic reorganization
- Altered neuronal function (e.g., gene expression profiles, protein products)
- Neurogenesis
- Altered glial function and gliosis
- Inflammatory changes
- Angiogenesis
- Altered excitability and synchrony
Potential Biomarkers

- Hippocampal changes on MRI
- Interictal spike features, including fMRI
- Pathological high-frequency oscillations (pHFOs)
- Excitability – TMS
- AMT-PET imaging
- Gene expression profiles