Emerging Pharmacology of Epileptogenesis: Is Intervention Possible?

December 2, 2011

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Disclosure

Name of Commercial Interest: Lundbeck
Type of Financial Relationship: Funding for investigator initiated research project
Learning Objectives

• Understand the major elements of the translational process involved in new therapeutics for human use

• Be able to describe new areas of preclinical science addressing prevention of epileptogenesis and epilepsy progression.
Epilepsy treatment successes and shortcomings

**Epileptic patients**
0.68% 2.1 million

- **Medical control**
  63% 1.3 million

- **Refractory to meds**
  37% 800,000

  - **Unsuitable for eval**
    23% 180,000

  - **Surgical evaluation**
    45% 360,000

  - **Not referred in error**
    32% 260,000

  - **Intracranial EEG**
    50% 180,000

  - **Resection**
    50% 180,000

    - **No resection**
      24% 43,000

    - **Resection**
      76% 137,000

      - **Controlled**
        70% 126,000

      - **Refractory**
        30% 54,000

    - **Refractory to meds**
      37% 800,000

      - **Not referred in error**
        32% 260,000

      - **Intracranial EEG**
        50% 180,000

      - **Resection**
        50% 180,000

      - **Resection**
        76% 137,000

      - **No resection**
        24% 43,000

      - **Refractory**
        70% 96,000

Estimated patients controlled:
1,467,000 (70%)

Estimated refractory patients:
633,000 (30%)

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References:

Translation: what will it take to address epilepsy progression?

• Overall question is to what degree progression in refractory epilepsy shares mechanisms with de novo epileptogenesis
  – And how these relate to non-ictal symptoms of epilepsy- psychiatric/cognitive comorbidities

• Pipeline to therapy development requires work on both basic and clinical ends
  – Better preclinical models
  – Better clinical biomarkers, endophenotyping
LONG PATH TO TRANSLATION: MULTIPLE CONTRIBUTORS

Drug/Device Discovery

Target Discovery and Lead Validation

Target Selection, Assay Development & HTS / Lead Selection / Mode Definition

Lead Optimization and Testing

Lead and Mode Selection

Toxicology, Synthesis, Formulation, PK/PD modeling

Clinical Candidate Selection and Refinement

Clinical Assessment and Early CMC / Tox / PK

Safety and "Developability" Evaluation

Early Clinical Safety and Efficacy

Full Development

Clinical Proof of Concept + Proof of Developability

Academia

Industry

CROs

1 Quelle: Bain 2003
Therapy development pipeline past 25 years

SOURCE → CLINICAL TRIALS → FDA approval

26 new drugs/4+ devices
Felbamate
Gabapentin
Vigabatrin
Lamotrigine
Topiramate
Tiagabine
Oxcarbazepine
Levetiracetam
Zonisamide
Pregabalin
Rufinamide
Lacosamide
Brivaracetam
DP-VPA
Ganaxolone
Carisbamate
Seletracetam
Stiripentol
Talampanel
Valroceamide
Eslicarbazepine
Retigabine
Perampanel
Losigamone
Bumetanide

13 new drugs, 1 device
Felbamate
Gabapentin
Vigabatrin
Lamotrigine
Topiramate
Tiagabine
Oxcarbazepine
Levetiracetam
Zonisamide
Pregabalin
Rufinamide
Lacosamide
ACTH

VNS
DBS
-SANTE trial
-RNS trial
TMS

Pharma/Industry
Academia+
NIH/DOD/FDA
NGOs
Benchmarks Area I - Prevent epilepsy and its progression

- Identify underlying mechanisms of epileptogenesis.
  - Identify at least one susceptibility gene or other risk factor (e.g., viral, trauma, autoimmune) and identify how it predisposes to changes in network excitability.
  - Identify at least one epileptogenic mechanism that is reversible, or has influence at critical developmental times.
  - Identify at least one specific role for non-neural mechanisms (e.g., glia, immune cells, angiogenesis) in epileptogenesis.
  - Identify at least one neuronal mechanism in microcircuits that contributes to epileptogenesis.
New tools for mechanistic research

- Genomics
- Epigenetics
- Proteomics
- Metabolomics
- Digital EEG/extended LTM/analytical software
- Cellular imaging -
  - voltage sensitive dyes
  - Confocal microscopy
- Stem cells, iPS cells
- Optogenetics
- High throughput screening devices, cellular models of epilepsy
- Transgenic mouse models
>100 Genes Linked to Monogenic Epilepsy

Ion channels are the largest subset

**Human**
- GABRA1
- GABRB3
- GABRG2
- CHRNA4
- CHRNB2
- HTR2C
- GRIA2

**Mouse**
- DLX1
- OTX
- EMX2
- SOX1
- FCN2
- UPAR
- ARX

**Both**
- NEUROD1
- GABRB1

**Related**
- CIT
- CYSTB
- MYO5A
- TSC1, 2
- NHLRC1
- LGi1
- APP-related

[Courtesy, Jeff Noebels, MD, PhD](http://www.ncbi.nlm.nih.gov/books/NBK1318/)
Clinical technological advances and epilepsy

EMUs for animals

Post-TBI


Post-Kainate

Modeling and monitoring epilepsy

• Opportunities from LTM 24/7 monitoring units
  – Unambiguous evidence for burden of seizures
  – Video EEG essential to correlate with behavior
  – Highly labor and data intensive
• Can offer unambiguous proof of seizure control
  – EEG versus behavior
• Essential for biomarker development
  – Neurophysiologic, cellular, molecular, behavioral correlates to predict seizure susceptibility and development of epilepsy
Effects on number vs. duration of seizures

**Number of seizures**

**Seizure duration**

Blumenfeld et al, *Epilepsia*
Microcircuits can be monitored too
Case and Sotesz, Epilepsia, 2011

Morgan R J, Soltesz I PNAS 2008;105:6179-6184
Benchmarks Area I - Prevent epilepsy and its progression

• Identify as yet unrecognized mechanisms of epilepsy and its progression
  – Epigenetic modulation
  – Non-neuronal factors
    • Inflammation- astrocytes, microglia, cytokines, complement
    • Role of the BBB in pharmacoresistance
  – Metabolic causes
    • Ketogenic diet
    • Adenosine
    • 2DG
  – Post-translational protein modification
    • Neurotransmitters, transporters
The „methylation hypothesis“ of epileptogenesis

Kobow and Blümcke, Epilepsia (2011)
<table>
<thead>
<tr>
<th>DNMT inhibitor</th>
<th>Developmental stage</th>
<th>Specificity</th>
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<tbody>
<tr>
<td>Zebularine</td>
<td>Preclinical</td>
<td>DNMT</td>
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<tr>
<td>5-Azacytidin (azacytidine, Vidaza)</td>
<td>Approved 2004</td>
<td>DNMT</td>
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<tr>
<td>5-Aza-2-deoxycytidin (Dacogen, decitabine)</td>
<td>Approved 2006</td>
<td>DNMT</td>
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<tr>
<td>HDAC inhibitor</td>
<td></td>
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<tr>
<td>Valproic acid (VPA)</td>
<td>Approved 1986</td>
<td>Class I and II</td>
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<td>SAHA (Zolinza, vorinostat)</td>
<td>Approved 2006</td>
<td>Class I and II</td>
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<tr>
<td>Romidepsin (Depsitepeptid)</td>
<td>Approved 2009</td>
<td>Class I</td>
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<td>LBH589 (Panobinostat)</td>
<td>Phase II/III</td>
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<td>MS-275 (Entinostat)</td>
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<td>MGCD0103</td>
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<td>CI-994</td>
<td>Phase II</td>
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<td>PXD101 (Belinostat)</td>
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<td>Baceca</td>
<td>Phase II</td>
<td>Class I</td>
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<td>Savicol</td>
<td>Phase II</td>
<td>N.A.</td>
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<td>PCI-24781</td>
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<td>ITF2357</td>
<td>Phase I</td>
<td>N.A.</td>
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</tbody>
</table>

DNMT, DNA methyltransferase; HDAC, histone deacetylase; SAHA, suberoylanilide hydroxamic acid; N.A., information not available.
Epigenetic-based treatments attenuate epilepsy progression

Huang et al, J. Nsci 2002

McClelland et al, Ann Neurol, 2011
Neuroinflammation: a host of new targets

- Cellular
- Cytokines
- Complement cascades

Significant for new treatments as well as biomarkers

Temporal Profile of Epileptogenesis

“Time Zero”

Cascade of events?

Biomarkers?

Therapeutic targets?

EPILEPSY:
Emergence of spontaneous seizures

COGNITIVE/PSYCHOLOGICAL SYMPTOMS

Initial insult

Minutes
Days
Weeks
Worsening cognitive deficit?
<table>
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<tr>
<th>Timing</th>
<th>Target</th>
<th>Therapeutic strategy</th>
<th>Candidate agents</th>
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<tbody>
<tr>
<td>Immediate early changes</td>
<td>Post-translational</td>
<td>Kinase, phosphatase inhibitors, mTOR</td>
<td>KN-62, FK506, rapamycin</td>
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<td>phosphorylation</td>
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<td>Acetylation</td>
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<td>Valproate, SHA</td>
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<td>AMPA receptors</td>
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<td>Talampanel, topiramate, levetiracetam</td>
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<td>NMDA receptors</td>
<td>NMDAR antagonists</td>
<td>Memantine, xenon, ifenprodil, Mg^{2+}</td>
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<td>GABA receptor</td>
<td>GABAR agonists</td>
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<td>Subacute changes</td>
<td>Inflammation</td>
<td>Anti-inflammatory compounds, microglial</td>
<td>ACTH, minocycline, doxycycline,</td>
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<td>Neuronal death</td>
<td>inactivators</td>
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<td>HCN1 channels</td>
<td>i_{h}-blocker</td>
<td>ZD7288</td>
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<td>Cannabinoid receptors</td>
<td>CB1-R antagonists</td>
<td>SR14176A, SR141716</td>
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<td>Chronic changes</td>
<td>Sprouting</td>
<td>Block protein synthesis</td>
<td>Rapamycin, cyclohexamide</td>
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<tr>
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<td>Gliosis</td>
<td>Anti-inflammatory agents</td>
<td>Cox2 inhibitor, minocycline</td>
</tr>
</tbody>
</table>

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Rapamycin modifies epilepsy progression in a rodent model of MTLE

Sunnen et al, Epilepsia 2011

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• HUMAN TISSUE VALIDATION IS IMPORTANT AFTER PRECLINICAL MODELS

• NON-SURGICAL TREATMENT DEVELOPMENT IS NOT LIMITED TO PHARMACOLOGICAL AGENTS- DEVICES ARE AN INCREASING RESOURCE
Human tissue validation

- Human tissue studies
  - “Omics”
  - Electrophysiology
  - Imaging
- Target validation
- Treatment specificity

Modified from Jeffrey Loeb, MD, PhD
Device development

100 Hz Stimulation

Brain Stimulation devices
- Vagal nerve stimulation
- Deep brain stimulation
- Transcranial magnetic stimulation
- Implantable seizure detection devices


Theodore and Fisher, Lancet, 2004
Intervention

• Multiple cascades implicated in experimental models
  – Epigenetic
  – Genetic
  – Metabolomic
  – Proteomic
  – Inflammatory
• Video EEG/LTM required at present to unambiguously assess efficacy
• Biomarker development is essential for success
• Human tissue target and biomarker validation
• Endophenotyping of optimal clinical populations for early therapeutic trial
  – Mindful of the possibility that non-ictal aspects of epilepsy will play an important role in understanding mechanism, biomarker development, and treatment