Disease Modification in Epilepsy

Asla Pitkänen, MD, PhD
Epilepsy Research Laboratory
A.I.Virtanen Institute for Molecular Sciences
University of Eastern Finland (UEF),
Kuopio, Finland
E-mail: asla.pitkanen@uef.fi
1. Terminology

2. From Concepts to Study Designs to Proof-of-Principle Experiments

3. The Next Step
**Epileptogenesis**

The development and extension of tissue capable of generating spontaneous seizures, including

- Development of an epileptic condition
- Progression after the condition is established

NINDS Workshop 8/2010; Pitkänen, Epilepsia 2010:51(Suppl 3):2-17
**Disease or Syndrome Modification**

A process that alters the development or progression of a “disease”

- antiepileptogenesis
- co-morbidity modification
- reversal of pathology (related to either one)

NINDS Workshop 8/2010; Pitkänen, Epilepsia 2010:51(Suppl 3):2-17
Disease Modifying Treatment (DMT)

Definition

A treatment or intervention that affects the underlying pathophysiology of the disease and has a beneficial effect on clinical outcome (natural history)

- finite period of therapy
- prevention of signs and symptoms even after therapy withdrawal

Elements Required to Establish Disease Modification

Modified from Cummings et al. Alzheimer’s and Dementia 2009:5:406-418
Symptomatic vs. Disease-Modifying

Symptomatic treatment (AED)

Disease-modifying treatment (DMT)

Baseline

Ictogenic network

Suppressed ictogenic network

Repaired ictogenic network
Disease Modifying Treatment (DMT) in Epilepsy

Study Design - Scenario

• Disease modifying treatment (DMT) is **NOT antiepileptic**

• Administration of treatment
  • **before** epilepsy onset
    • genetic
    • acquired
  • **after** epilepsy onset
    • animals with frequent spontaneous seizures
    • patients with frequent seizures
# DMT - Outcome Measures

<table>
<thead>
<tr>
<th>Experimental Studies</th>
<th>Clinical Studies</th>
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<tbody>
<tr>
<td>Clinical Outcome</td>
<td></td>
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<tr>
<td>Prevention of epilepsy (yes/no)</td>
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<tr>
<td>Time to 1\textsuperscript{st} seizure</td>
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<tr>
<td>Seizure frequency</td>
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<tr>
<td>Progression in seizure frequency</td>
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<tr>
<td>Seizure duration</td>
<td></td>
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<tr>
<td>Behavioral severity of seizures</td>
<td></td>
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<td>Therapy resistance</td>
<td></td>
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<td>Seizure threshold (?)</td>
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## Biomarker

Biochemistry, imaging, cognitive testing, behavior, motor function
Study Design - DMT Before Epilepsy Onset
DMT Before Epilepsy Onset
Reversal of Circuitry Alterations - BDNF + FGF-2 Gene Therapy

Unilateral HC virus injection

Pilocarpine SE in rat

vEEG for 20d

Clinical outcome - Sz Frequency

Network Outcome - 28 d post-SE

- neuroprotection
- normalization of neurogenesis
- inflammation Ú
- mossy fiber sprouting Ú

Recent "12 Proof-of-Principle Success Stories"
DMT Before Epilepsy Onset

1. Atipamezole
2. Levetiracetam
3. Celecoxib
4. Rapamycin
5. α4 integrin-specific mAb
6. Erythropoietin
7. Ethosuximide
8. BDNF+FGF-2
9. Rimonabant
10. Parecoxib
11. Minozac
12. Hypothermia

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>References</th>
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<tr>
<td>Atipamezole</td>
<td>α2-adrenergic receptor SVA2</td>
<td>(Pitkänen et al., 2004)</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>COX-2 inhibition</td>
<td>(Yan et al., 2005)</td>
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<td>Celecoxib</td>
<td>mTOR inhibition</td>
<td>(Jung et al., 2006)</td>
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<tr>
<td>Rapamycin</td>
<td>Integrin alpha-4</td>
<td>(Zeng et al., 2008)</td>
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<tr>
<td>α4 integrin-specific mAb</td>
<td>Erythropoietin receptor</td>
<td>(Fabene et al., 2008)</td>
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<tr>
<td>Erythropoietin</td>
<td>T-type Ca-channels</td>
<td>(Chu et al., 2008)</td>
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<tr>
<td>Ethosuximide</td>
<td>FGF and NTRAK2</td>
<td>(Blumenfeld et al., 2008)</td>
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<tr>
<td>BDNF+FGF-2</td>
<td>CB1 receptor</td>
<td>(Paradiso et al., 2009)</td>
</tr>
<tr>
<td>Rimonabant</td>
<td>COX-2 inhibition</td>
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<tr>
<td>Parecoxib</td>
<td>Cytokine production</td>
<td>(Polascheck et al., 2010)</td>
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<td>Minozac</td>
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<td>(Chrzaszcz et al., 2010)</td>
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<td>Hypothermia</td>
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No anticonvulsant effect
Study Design - DMT After Epilepsy Onset

**Ictogenic network**

(w/AEDs)
Patients with frequent seizures (on AEDs)

DMT After Epilepsy Onset

**Humans**

- **DMT discontinued**
  - Reintroduction of DMT
    - Sz Ú only if DMT continued
  - AEDs reduced

**OUTCOME**

- **Responders**
  - Placebo
  - DMT
  - Biomarker analysis (MRI)
  - Clinical response

- **Non-responders**
  - Placebo
  - DMT

No antiepileptic effect in preclinical testing
DMT After Epilepsy Onset
Humans

Seizure frequency

100% Baseline

DMTÚ
Temporary Responders

AEDsÚ
Responders

Cure
DMT After Epilepsy Onset
Spontaneously Seizing Animals

Patients with frequent seizures (on AEDs)

DMT

Responders

Non-responders

Placebo

DMT

DMT discontinued

OUTCOME

Reintroduction of DMT

Sz Ú only if DMT continued

AEDs reduced

Sz Ú

Non-responders
DMT After Epilepsy Onset
Reversal of Circuitry Alterations - mTOR Inhibition

Everolimus

Rapamycin

No evidence in acquired models


Next Step
Understanding the Network Change and Its Molecular Basis In “Each Epilepsy Type”

... they all look the same, but...
How To Get Further?

• Identification of a realistic target population with an ictogenic network/molecular change that can be monitored

• Availability of biomarkers - monitoring of circuitry

• Duration of evolution and repair of ictogenic circuitry
  • duration of DMT treatment

• Spontaneous remission

• Elimination of the trigger maintaining circuitry reorganization

• AEDs with multiple mechanisms of action
  • disease-modification? (e.g. via epigenetic modulation)
  • how to test?
  • solution: ”multiple pills with 1 mechanism of action”
Epilepsy Research Group
A.I. Virtanen Institute, Kuopio, Finland

Postdocs
Heli Myöhänen
Jari Nissinen
Tamuna Bolkvadze
Nino Kutchiashvili

Technicians
Merja Lukkari
Jarmo Hartikainen

PhD-students
Xavier Ekolle Ndode-Ekane
Noora Huusko
Sofya Ziyatdinova
Olena Shatillo
Diana Miszczuk
Teemu Laitinen*
Antti Airaksinen*

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NMR Research Group
at A.I. Virtanen Institute
Prof. Olli Gröhn

Alzheimer Research Group
Prof. Heikki Tanila