Embryonic MGE Cells as a Treatment for Epilepsy
December 1, 2012

Scott C. Baraban, PhD
University of California, San Francisco
<table>
<thead>
<tr>
<th>Name of Commercial Interest</th>
<th>Type of Financial Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurona Therapeutics</td>
<td>Co-founder</td>
</tr>
</tbody>
</table>
Learning Objectives

- Recognize that an interneuron-based cell transplantation strategy could provide a novel approach for correcting network dysfunction (and co-morbidities) associated with epilepsy

- Review data concerning transplantation of interneuron progenitor cells in rodent models of epilepsy
NINDS Epilepsy Research Benchmarks

Research Objectives

Benchmarks Area I: **Prevent epilepsy and its progression**

Benchmarks Area II: **Develop new therapeutic strategies** and optimize current approaches to cure epilepsy

Benchmarks Area III: **Prevent, limit, and reverse the co-morbidities associated with epilepsy** and its treatment
Interneurons mediate inhibition in the CNS

- Primarily mediated by GABA
- Modulates cortical output
- Regulates neuronal proliferation/migration
- Dysfunction = schizophrenia, autism, bipolar disorder or epilepsy
New interneurons could provide a powerful "surround" inhibition


Where do interneurons come from?

Cortical interneurons originate in the embryonic medial ganglionic eminence (MGE)
A Strategy for Generation of New Interneurons in the Postnatal Brain
Transplanted embryonic MGE cells migrate widely in the host brain

Arturo Alvarez-Buylla & colleagues (1999-2012)
MGE-GFP cell distribution in the host brain

Joy Y. Sebe
MGE-GFP cells integrate as interneurons in the host brain.

MGE-GFP cells form synapses in the host brain
MGE-GFP cells function as inhibitory neurons in the host brain.

1. Record MGE-GFP cell

2. Examples of electrophysiological recordings.

Alvarez-Dolado et al. 2005
Baraban et al. 2009
MGE-GFP cells enhance GABA-mediated inhibition in the host brain

1

record host pyramidal cell

2

control

100 μM SNAP-5114 + 20 μM NO711

100 μM gabazine

grafted

100 μM SNAP-5114 + 20 μM NO711

100 μM gabazine

mean tonic current (pA)

control
grafted

n = 22

n = 21

Alvarez-Dolado et al. 2005
Baraban et al. 2009
Phasic inhibition does not scale with MGE-GFP cell density

NINDS Epilepsy Research Benchmarks
Part One

Benchmarks Area II: Develop new therapeutic strategies and optimize current approaches to cure epilepsy

• A.2. Define underlying mechanisms of initiation, propagation and cessation of seizures in the epileptic brain as targets for treatment
Cortical interneuron density is reduced in Dlx1 mutant mice


- Reduced interneuron density
- Reduced synaptic inhibition
- Reduced synaptic excitation
- Altered intrinsic excitability
- Abnormal EEG
Hippocampal excitability defects in Dlx1 mutant mice

Inhibition

Excitation

Intrinsic

MacKenzie A. Howard
MGE transplantation into Dlx1 mutant mice (hippocampus)
Hippocampal excitability defects in Dlx1 mutant mice rescued by P2 MGE transplant
NINDS Epilepsy Research Benchmarks
Part Two

Benchmarks Area II: Prevent epilepsy and its progression

• D.2. Identify interventions that prevent, interrupt or reverse the epileptogenic process
P2 MGE cell grafts interrupt epilepsy in Kv1.1−/− mice

Baraban et al. PNAS (2009)
Benchmarks Area II: Develop new therapeutic strategies and optimize current approaches to cure epilepsy

• C.2. Developed a new approach (e.g., GABA progenitor cells) for targeted cell therapy

Benchmarks Area III: Prevent, limit, and reverse the co-morbidities associated with epilepsy and its treatment

• B.3 Developed and implemented a cell therapy treatment for the amelioration of behavioral and cognitive co-morbidities in an animal model of epilepsy
A Strategy for Generation of New Interneurons in the Adult Brain

Status epilepticus (Pilocarpine) → P51

Video monitoring → P60

MGE transplant → P65

Behavior Physiology Anatomy → 60 DAT

MGE transplant into hippocampus

MGE transplant into amygdala

MGE transplant into CA3

MGE transplant into BLA

Robert F. Hunt
MGE progenitors migrate widely in adult epileptic hippocampus.
MGE progenitors migrate and differentiate into GABAergic interneurons in adult hippocampus.
MGE-GFP interneuron subtypes 60+ DAT in adult hippocampus
Pilocarpine model of epilepsy

- P51
- “latent” period
- P70-P80
- ~P130

Acute pilocarpine SE
1st spontaneous seizure
Spontaneous seizures, hippocampal pathology, behavioral & cognitive deficits

Pinnacle Technology

Electroencephalogram (EEG) tracings:
- Channels 1, 2, 3, 4
- 100 μV
- 200 ms
MGE rescue of epilepsy phenotype in the Pilocarpine model

Continuous 24/7 video-EEG monitoring; 7-10 days
Seizure duration > 15 sec
MGE rescue of behavioral co-morbidities in the Pilocarpine model

(a) Mean score
(b) Distance traveled (x1000 cm)
(c) Time on Rota-rod (m:ss)
(d) Time in open arm (sec)
(e) Open arm entries

(f) Time immobile (sec)

(g) Visible
(h) Hidden
(i) Probe

(j) Control S1 MGE-AMG S6 Probe

Key:
- Control
- Epilepsy
- MGE-HC
- MGE-AMG

* indicates significant difference
NINDS Epilepsy Research Benchmarks

Research Completed

Benchmarks Area I: Prevent epilepsy and its progression
- MGE progenitor cell transplantation into Kv1.1 KO or Pilocarpine mice

Benchmarks Area II: Develop new therapeutic strategies and optimize current approaches to cure epilepsy
- GABA progenitor cell transplantation to generate new and functionally integrated interneurons in the host brain

Benchmarks Area III: Prevent, limit, and reverse the comorbidities associated with epilepsy and its treatment
- MGE progenitor cell transplantation into the adult hippocampus in Pilocarpine model

American Epilepsy Society | Annual Meeting 2012