Cellular Therapies
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Disclosure

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Learning Objectives

• Understand current cell therapy approaches to control intractable seizures

• Discuss potential limitations in moving these approaches toward the clinic
Problem: epilepsy is a network phenomena

- increased neuronal bursting and synchronization are a hallmark of seizures

Worrell G A et al. Brain 2004

Morgan RJ, Soltesz I. Proc Natl Acad Sci 2008
Inhibition may be the best way to constrain an epileptic network

How do we increase inhibition?

• GABA mimetic drugs

• Modulation of postsynaptic GABA receptors

• Block GABA re-uptake

• New GABA interneurons?
A strategy for cell therapy

1. Identify epileptic zone

2. Cell transplantation

3. Cell integration and seizure control

Adapted from Parent & Murphy
News & Views; Nature Neuroscience 2013
Modulation of experimentally induced epilepsy by intracerebral grafts of fetal GABAergic neurons

Fine A, Meldrum BS. Neuropsychologia 1990
Benefits and risks of intranigral transplantation of GABA-producing cells subsequent to the establishment of kindling-induced seizures

Why earlier approaches did not work?

- Failure of transplanted cells to integrate
- Mixed populations of transplanted cells
- Mechanism of action??
- Not tested in appropriate animal model
A path to the clinic: preclinical studies

Obtain proof-of-principle data in an animal model of epilepsy

• Generation of inhibitory interneurons

• Functional integration following transplantation

• Disease-modifying activity (DMA) against spontaneous seizures and related co-morbidities
How to make an interneuron for cell therapy

Source: embryonic medial ganglionic eminence (MGE)

- neuron expressing GABA
- migration in host brain
- mature firing properties
- integration in host circuitry
MGE cells migrate widely in host brain

- P2 transplant (up to 5 mm)
- P60 transplant (up to 2 mm)
- cortex, hippocampus, amygdala
MGE cells enhance inhibition in host brain

- fetal MGE progenitor cells
- IPSC onto host pyramidal
- cortex and hippocampus
Optogenetic manipulation of MGE-derived interneurons following transplantation

Robert F. Hunt III
MGE cells in a genetic form of epilepsy

- Kv1.1 null mice
- P2 MGE transplant
- 96% seizure reduction

MGE cells in an acquired form of epilepsy

- pilocarpine model of TLE
- adult MGE transplant
- 92% seizure reduction

How to make a neuron: induced neural cells

- defined transcription factors direct cell fate

Yang N, Ng YH, Pang ZP, Sudhof TC, Wernig M. Cell Stem Cell 2011
Features of an ideal human MGE cell line

- GABA interneuron specificity – PV, SOM, NPY
- Robust migration
- Functional integration
- Safety
- Efficacy
Some currently available human stem cell lines

1. Sox1-expressing embryonic stem cells (ESC)

2. Nkx2.1-expressing embryonic stem cells (ESC)

3. induced pluripotent stem cells (iPSC) from Dravet patients

Human SC-derived interneurons *in vitro*

Kevin Ess

Arturo Alvarez-Buylla, John Rubenstein
Arnold Kriegstein

Stewart Anderson
Lorenz Studer

Lori Isom
Jack Parent

Su-Chun Zhang
Potential problems: Slow differentiation

- NKX2.1::GFP human ES cells
- FACS sorted and transplanted into neonatal cortex
- 6 wk - 3 mo. post-transplantation: “undifferentiated appearance . . . often tipped by growth cones”

Potential problems: Slow functional maturation

- NKX2.1::GFP human ES cells
- FACS sorted/neonatal cortex
- 7 months post-transplant

Potential problems: Teratocarcinoma

- undifferentiated hES cells
- hippocampus transplant
- Sox1:GFP::Ubi:RFP cells

How do we address these problems?

• Learn more about the properties of fetal human MGE cells

• Improve methods or techniques for generating hMGE cells

• Develop and characterize more appropriate animal models for evaluation of human MGE cells
Properties of human MGE cells

- Subcortical origins of human and monkey neocortical interneurons. Ma et al. Nat Neuroscience 2013
- Non-epithelial stem cells and cortical interneuron production in the human ganglionic eminences. Hansen et al. Nat Neuroscience 2013
“Cerebral organoids” as MGE donors?

Human stem cell therapies that are showing some promise (but not epilepsy, yet)


HuCNS-SC oligodendrocytes, neurons and astrocytes
A path to the epilepsy clinic

Obtain IND enabling data with a human MGE cell line

• Disease Modifying Activity (DMA) in at least one animal model of epilepsy
• Safety and “dosing” information
• Cryopreservation
• Device for delivery of human MGE cells
(Future) Impact on Clinical Care and Practice

Tissue grafts transiently suppress evoked seizures

1987-1990
(Future) Impact on Clinical Care and Practice

- Tissue grafts transiently suppress evoked seizures
- Mouse MGE cells suppress spontaneous seizures & reverse comorbidities
Tissue grafts transiently suppress evoked seizures

Mouse MGE cells suppress spontaneous seizures & reverse comorbidities

Human MGE cells are safe and suppress seizures in patients

1987-1990

2013

2025