Cell Transplantation Approaches to Repair and Protect the Injured CNS

Jeffery D. Kocsis, Ph.D.
Department of Neurology and Neuroscience Research Center
VAMC
The presenter (Jeffery Kocsis) of this session has nothing to disclose.

This continuing education activity is managed and accredited by Professional Education Services Group in cooperation with the Paralyzed Veterans of America. Neither PESG nor PVA nor any accrediting organization supports or endorses any product or service mentioned in this activity.

PESG Staff and the Program Planning Committee have no financial interest to disclose.

Commercial Support was not received for this activity.
Cellular Transplantation as a Tool for Spinal Cord Repair

Repair Objectives:

• Remyelination

• Axon Regeneration/Sprouting

• Neuroprotection

• Neovascularization/microvessel repair
ENDOGENOUS REMYELINATION IS DELAYED IN THE NHP AS COMPARED TO THE RAT
Ethidium Bromide
Cell Injection
X-Irradiation
+ 3 Days
+ 3 Days
1mm

NG2 CONT

NG2 X-RT
Myelin-forming Cells Transplanted into the Demyelinated Spinal Cord leads to Extensive Remyelination

Sasaki et al., J. Neurosci 2004
Human Schwann cell transplants into spinal cord

Nav1.6

Malformed fetuses of cynomolgus monkeys exposed to thalidomide on days 26–28 of gestation.

(A) The fetus of maternal monkey given thalidomide at 15 mg/kg-d exhibiting brachydactyly in the paw, micromelia in the hindlimb, hyperflexion, ectrodactyly and brachydactyly in the foot and curled tail. (B) The fetus of maternal monkey given thalidomide at 20 mg/kg-d exhibiting amelia in the fore- and hindlimb and bent tail. Emma et al. Reproductive Toxicology; 2010 b
OECs from Transgenic Pigs Expressing human 1,2-\textit{fucosyltransferase} gene Remyelinate Demyelinated NHP Spinal Cord Axons

Radtke et al
FASEB (2004)
hESC-Derived Cellular Therapies

- Derived by Dr. James Thomson at University of Wisconsin in 1998
  From excess IVF blastocyst in accordance with ethical guidelines
  - Informed consent
  - Anonymous donors

- Immortal: Repeated derivations not required

- Pluripotent: Able to form all somatic cell types

- Suitable for clinical use:
  NIH and MRC approved
  Fully qualified for human use
GRNOPC1

- Cryopreserved Allogeneic Cell Population
- Differentiated from Human Embryonic Stem Cells
- Characterized Composition of Oligodendrocyte Progenitor Cells

Stages of GRNOPC1 differentiation

In vitro differentiation

GRNOPC1

Nestin

Progenitor population

Gal C O4

GRNOPC1

Stages of GRNOPC1 differentiation

In vitro differentiation
Demyelinated NHP spinal cord axons without cell transplantation (3 months post-lesion induction)
Human ES-derived GRNOPC1 Remyelinate the NHP Spinal cord
Vehicle injection site

GRNOPC1 injection site
Cellular Transplantation as a Tool for Spinal Cord Repair

Repair Objectives:

- Remyelination
- Axon Regeneration/Sprouting
- Neuroprotection
- Neovascularization/microvessel repair
OECs transplanted into transected spinal cord

Sasaki et al. 2006, J. Neurosci
A

Rostral

R13

14 mm

Caudal

Stim

R2

R1

3 mm

2 mm

Transection site

Transplant sites

B

Transection alone

R1

2 mm

R2

3 mm

0.5 mV

1 msec

C

Transection with OEC transplant

R1

2 mm

R2

3 mm

R3

4 mm

R4

5 mm

0.2 mV

1 msec

L4

L5

Transplant sites

Stim

Transection site
Pre-Surgery
3 Weeks Post-Surgery
3 Months Post-Surgery
Cellular Transplantation as a Tool for Spinal Cord Repair

Repair Objectives:

• Remyelination

• Axon Regeneration/Sprouting

• Neuroprotection

• Neovascularization/microvessel repair
PKH26-labeled hMSCs and BDNF-hMSCs \textit{in vitro}

Intravenous Infusion of MSCs Reduce SCI Lesion Volume

Osaka et al., 2010 BR
The Neurovascular Unit

(Endothelial cell. Pericyte, Astrocyte)
The Blood Spinal Cord Barrier Opens After SCI and Remains Open for Months

A

1 mo post-SCI

B

3 mo post-SCI
Occlusion of the MCA (M1) in the NHP as a Model for Stroke

Sasaki et al. PloS 2011
ahMSC Therapy for Stroke Patients

Honmou et al., BRAIN 2011 and Trends in Molecular Medicine, 2012
Open-field locomotor scores: MSC and DMEM (sham control)
Tracking the distribution of mesenchymal stem cells (MSCs) intravenously injected into rats

0h  6h  24h
Ex vivo imaging revealed that MSCs injected intravenously first accumulated in the lung, liver, and the spleen.
Multifunctional anti-inflammatory protein TNF-α stimulated gene/protein 6 (TSG-6)

Prockop and Oh, 2012
POSSIBLE MECHANISMS FOR FUNCTIONAL IMPROVEMENT IN SCI FOLLOWING CELL TRANSPLANTATION

- Directed axonal regeneration
- Axonal sprouting and synaptic plasticity (polysynaptic?)
- Remyelination of regenerated and spared axons
- Neuroprotection
  - Local (trophic factor release from implanted cells)
  - Remote (trophic factor release from remote sites e.g., lung)
- Angiogenesis (Neovascularization)
- Blood brain (SC) barrier stabilization
Yale University and VA (Neurology and Neurobiology)

Masanori Sasaki, MD, PhD
Karen Lankford, PhD
Christine Radtke MD, PhD (University of Hannover)
Edgardo Arroyo, Ph.D.
Kewei Yu, MD, PhD
Hajime Tokuno, MD
Eleni Makakis, PhD
Robert Brown, MD
Takashi Mutsushita, MD

Sapporo Medical University Collaboration
Osamu Honmou, MD, PhD and colleagues