New Approaches to Repair of Spinal Cord Injury

Where Discovery Begins
WHY IS THE SPINAL CORD SO VULNERABLE?

Peripheral Nerve

- Schwann Cell
- Myelin
- Collagen

DRG Neuron

Spinal Cord

- Oligodendrocyte
- Myelin
- Axon
WHY IS THE SPINAL CORD SO VULNERABLE?
WHAT HAPPENS IN A SPINAL CORD INJURY

Peripheral Nervous System

Axon or nerve fiber

Disconnection

Nerve cell

Central Nervous System

Hand

Brain

Sensation

Awareness
WHAT HAPPENS IN A SPINAL CORD INJURY

Brain

Nerve cell

Axon or nerve fiber

Degeneration

Direct injury and Secondary tissue damage

Hand

Awareness
WHAT ARE THE BARRIERS TO REGENERATION

This will occur successfully in the PNS.

Axon or nerve fiber

Hand

Nerve cell

Regrow

Brain

Reconnect
WHAT ARE THE BARRIERS TO REGENERATION

Axon or nerve fiber

Nerve cell

Scar tissue

Inhibitors

Hand

Brain

Lack of support

Lack of Growth factors

Lack of
Growth factors
Strategies for treatment

- Prevent spinal cord injuries
- Stabilize the spinal cord (surgery)
- Prevent further acute damage
- Promote healing and regeneration
  - Clear cell debris
  - Prevent inhibitors from working
  - Promote growth (cells/pharmaceuticals)
- Pain management, physical therapy and rehabilitation
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Information sources

- http://www.mcpf.org/
- http://clinicaltrials.gov/
- clinical_trials_public_guide.pdf
Cell strategies

- Immune cells (clear debris)
- Schwann cells
- Olfactory ensheathing glia
- Adult stem cells (mesenchymal stem cells)
- Embryonic stem cells
Ongoing or recent trials

**Procord/Proneuron**

- Patient-derived activated macrophages
- Initial studies in Israel
- Phase II trial in US 2005 - 2008
- 50 patients enrolled
- Suspended for “financial reasons”
Miami Project to Cure Paralysis

- Schwann cells
- Myelin-forming cells from peripheral nerves
- Patient derived
- “pre-IND”
**Olfactory Ensheathing Glia**

- Cells from patients olfactory (smell-detecting) system
- Support cell that may promote nerve growth
- Uncontrolled reports from Portugal, China, Australia
- Phase I safety trial proposed in England
Geron

- Oligodendrocyte progenitor cells (human embryonic)
- Safety study (phase I)
- Repair lost myelin
- Complete
- <14 days after injury
- Seven US centers
Mesenchymal (adult) Stem Cells (MSC’s)

- Phase I safety studies (various levels of rigor)
- China, Korea, Czech Republic, Russia, Brazil
- Cells derived from bone marrow, adipose tissue, peripheral blood
- (Umbilical cord cells)
- Work at Mayo Clinic related to ALS (Lou Gehrig’s Disease)
Ongoing or recent trials

Other Therapies

Systemic hypothermia

- Miami project single center trial (uncontrolled)
- Multicenter trial being planned

Rolipram (increases cAMP) in phase II trials

Rho inhibitors (Cethrin) planned phase II <72h after injury

Nogo antibody trials (ongoing) in Europe
1. What are the properties of the peripheral nervous system that permit regeneration?

2. Make the spinal cord more like the peripheral nerve using tissue engineering tools
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PCLF IN SCIATIC NERVE
STUDYING DIFFERENT CELL TYPES IN SPINAL CORD INJURY

PLACE CELLS INTO SCAFFOLD

Fast Blue

TRACER INJECTION
HOW ARE WE DOING?

• Normal Rat Spinal Cord ~330,000 MF/cord (at the T/L level)

• Total nerve fibers ~3,000,000/cord

• 7 channels (800/channel) ~5,600/scaffold

• 50% traverse from end to end ~2,800

• 10% travel 0.5 mm distally ~560

• 2% travel 1.0 mm distally ~1-200

• Need about 10% of normal ~300,000 nerves
New approach - adult stem cells as “delivery vehicles”
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NT3-expressing MSC’s for ascending proprioceptive pathways
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- NT3-expressing MSC’s for ascending proprioceptive pathways
- NGF-expressing MSC’s for ascending nociceptive pathways
New approach - adult stem cells as “delivery vehicles”

NT3-expressing MSC’s for ascending proprioceptive pathways

NGF-expressing MSC’s for ascending nociceptive pathways

BDNF-expressing MSC’s for descending motors pathways
How can you tell the difference

Some simple “rules of thumb”

- If it is offered in a reputable institution in North America or Europe as part of a clinical trial it is probably safe
- If you have to pay for the treatment it is probably unproven and unreliable
- If you have to go to a third country (e.g. Mexico) it is probably a fraud
A Cell Center in Europe

- ALS
- Alzheimer
- Cardiovascular diseases
- Cerebral palsy
- Diabetes
- Erectile dysfunction
- Failed Back Surgery Syndrome
- Macular degeneration
- Multiple sclerosis
- Osteoarthritis
- Parkinson
- Spinal cord injuries
- Stroke
Acknowledgements

Funding
NIH
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Neilsen Foundation
MCPF
Mayo
WHEN WILL THIS BE COMING TO PATIENTS

**Polymer scaffolds**

- Simple single channel ‘sleeves’ already in clinical use for repair of peripheral nerves in U.S. and Europe (e.g. Neurolac PCL Polyganics, Groningen; NeuraGen Collagen Integra, New Jersey)
- Plans to initiate trials of complex, biodegradable, ‘smart’ scaffolds in peripheral nerve in ~2 years (U.S.)

**Adult Stem Cells**

- Bone marrow stem cell transplants in cancer patients in routine clinical use now
- Adult MSC trial to repair damaged heart muscle planned to begin in ~ 2 years (Ireland)
- OEG/brachial plexus trial to begin this year in U.K.
Spinal Cord Injury  (a best guess)

- Proof of concept and biocompatibility studies in peripheral nerve are ongoing

- Injections of stem cells (adult autologous) and matrix-bound, recombinant growth factors 2 - 4 years
  - proof of safety
  - acute “neuroprotective”

- Injections of genetically modified stem cells ~5 years
  - proof of safety
  - Neurotrophic effects

- Reconstructive approaches with embryonic or adult stem cells in organized matrices ~ 7-10 years
• **Acknowledgements**
  • Many Colleagues at NUIG and Mayo
  • Funding from National Institutes of Health, the Wilson, Mayo, Neilsen and Morton Foundations
  • Funding from Science Foundation Ireland for the ETS Walton Fellowship
Leave you with Dr. Peter Dockery who believes that no problems are insurmountable.
• What are stem cells?
• Future success depends on multi-disciplinary collaboration.
• The central nervous system has the capacity to regenerate.
• Restoration of function depends on bridging or by-passing tissue damage
Stem Cells

- Embryonic Stem Cells
- Neural Stem Cells
- Neural Progenitor Cells
- Adult-derived Stem cells
  - Tissue derived
  - Mesenchymal
WHAT HAPPENS IN A SPINAL CORD INJURY?

- Oligodendrocyte
- Astrocyte Barrier
- Damaged Oligodendrocyte
- White Blood Cell
- Demyelinated Axons

THE END RESULT
WHAT HAPPENS IN A SPINAL CORD INJURY?

Four Major consequences
All are separate therapeutic Targets
WHAT HAPPENS IN A SPINAL CORD INJURY?

Four Major consequences

All are separate therapeutic Targets

1. Acute traumatic damage (immediate)

   Prevention - seat belts
   - sports safety
   - ban guns (U.S.)

   Rapid spine stabilisation
   - at the accident site
   - surgical fixation
WHAT HAPPENS IN A SPINAL CORD INJURY?

**Four Major consequences**

All are separate therapeutic Targets

1. **Acute traumatic damage** (immediate)
2. **Secondary haemorrhagic, inflammatory, oxidative stress** (1 - 96 hours)

**Focus of ongoing trials**
- Steroids(??)
- Anti-apoptotic agents (e.g. minocycline)
- Oxidative stress inhibitors
WHAT HAPPENS IN A SPINAL CORD INJURY?

Four Major consequences

All are separate therapeutic Targets

1. Acute traumatic damage (immediate)
2. Secondary haemorrhagic, inflammatory, oxidative stress (1-96 hours)
3. Disruption of axonal connections (0-96 hours)
4. Atrophy/dwindling of disconnected muscles, neurons, supporting cells.

Major focus of our research
Strategies to Restore Function
Strategies to Restore Function

Injury
Strategies to Restore Function

Injury

By-pass

Electronic-robotic

Injury
Strategies to Restore Function

Injury

By-pass

Electronic-robotic

Bridge