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About Spinal Cord Injury (SCI)

Scene 1  A tetraplegic preparing for the day and concerns for the rest of the day

Scene 2  Viewing an experiment in my laboratory with comments about our results

Scene 3  Taking our experiments to the FDA for approval of a Schwann cell clinical trial
**C3-4; High Tetraplegic**

No use of arms or legs

Dependent on nurse/attendant constantly

Preparation: 3 x /week; 8:00 a.m. – noon

  Catheterized (every 5 h), start bowel emptying, stretching legs, into shower chair, shaving, dressing, into chair for the day

Concerns: sitting comfortably (special inflatable cushion), urological status (infection), lung function, sweating, temperature and blood pressure peaks, “ticking time bomb”

Exercise with FES: many benefits

Cost (insurance) $600 – 700,000 /year
C 5- Low Tetraplegic

Partial use of arms, limited or no use of hands
Dependent on attendant 2 X / day, 1h (a.m.), 2h (p.m.)
Not paid by insurance
Requires hard-to-find reliable help
Bladder catheter maintenance
Wheelchair function
Transportation availability / barriers/accessibility
Sexual relations impacted but pregnancy possible
Temperature, blood pressure and sugar, osteoporosis issues
Quality of Life Issues with SCI

- Muscle paralysis, loss of feeling
- Reduced pulmonary function
- Blood clot formation (DVTs)
- Early cardiovascular disease, stroke
- Lack of bowel and bladder control; infection, stones
- Temperature, blood pressure vary widely
- Pressure ulcers, osteoporosis
- Sexual function/fertility impaired
- Pain long – term, 80 %
- Obesity, diabetes, cognitive decline
Spinal Cord Injury

- 12,000 new cases / year in the U.S.
- Approx 1.275 million Americans with paralysis, due to SCI
- Nearly 50%, ages 16-30; 80%, males
- Higher occurrence in military
- MVAs (36.5%), falls (28.5), violence (14)
- 5.3 million in the U.S. with paralysis due to some type of CNS injury/disorder
<table>
<thead>
<tr>
<th>Severity of Injury</th>
<th>Aver Yearly Expenses (Feb 2013)</th>
<th>Est Lifetime Costs Age at Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First Year Each Subsequent Year</td>
<td>25 years old 50 years old</td>
</tr>
<tr>
<td>High Tetraplegia (C1 –C4)</td>
<td>$1,044,197 $181,328</td>
<td>$4,633,137 $2,546,294</td>
</tr>
<tr>
<td>Low Tetraplegia (C5-C8)</td>
<td>$754,524 $111,237</td>
<td>$3,385,259 $2,082,237</td>
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<tr>
<td>Paraplegia</td>
<td>$508,904 $67,415</td>
<td>$2,265,584 $1,486,835</td>
</tr>
</tbody>
</table>
Why Schwann cells?

- Promote regeneration of axons in PNS
- Produce growth factors, ECM
- Myelinate axons in CNS
- Restore axon activity
- Enter cord in large numbers/ SCI
- Are readily accessible/peripheral nerve
- Can obtain large numbers
- Can transplant person’s own cells
- Can genetically engineer
- Promising pre-clinical data in multiple species; cited for FDA approval
Transplants at 12 wk after contusion injury

Dr. Damien Pearse
Thoracic contusion model: Schwann cells

- Reduce cyst formation
- Protect spinal cord tissue from secondary damage
- Support axonal growth into SC graft
- ~5000 SC-myelinated axons in graft
- Some improvement in walking after paralysis
Combination strategies: SCs +

• Steroid (used clinically)
• Variety of growth factors
• Another cell type (olfactory ensheathing cells)
• An enzyme (to reduce scar formation)
• Elevation of a cell signaling molecule, cAMP
• Introduction of genes to improve Schwann cell efficacy

ALL THESE IMPROVED REPAIR/FUNCTION
Combination strategies: SCs +

- More myelinated axons in graft
- Increase in regenerated axons from neurons above spinal cord (Distance factor overcome)
- Exit of regenerated axons from graft into the cord
- More improvement in walking
SCs with added growth factor gene survive better and promote nerve fiber growth
Combined engineering of Schwann cell implants to secrete neurotrophin and chondroitinase promotes axonal regeneration and locomotion after SCI

H Kanno, Y Pressman, A Moody, R Berg, E Muir, J Rogers, H Ozawa, E Itoi, D Pearse, M Bunge
**Experiment**

Adult female Fischer rats (160-180g)
- Moderate contusion injury at thoracic 8 level

Schwann cell transplantation:
- 1 week after injury, 1+1 million cells

Experimental groups:
1. Vehicle (no cells) (control)
2. green/GF-SCs + red-SCs (control)
3. green/GF-SCs + red-SCs
4. green-SCs + red/ENZ-SCs
5. green/GF-SCs + red/ENZ-SCs
SC-transplanted spinal cord

Control

Combination strategy
SC myelination in implant

DMEM/F12
GFP + mCherry
GFP/D15A + mCherry
GFP + mCherry/ChABC
GFP/D15A + mCherry/ChABC

# SC myelinated axons / section

#
Combination vs single treatments

- Further increase in implant compared to GF or ENZ
- Further increase in SC myel axons compared to ENZ
- Higher number of responding neurons above cord than with GF or ENZ
- Higher number of their axons in implant and in cord beyond than with GF or ENZ
- Improved walking scores
- Lessened pain in hindpaws
Funding: MBB

- NIH Fellowship
- NIH research grant 1971-2017 (3 Javits Awards) Renewed every 5 or 7 yr
- Private Foundations
  - Donors to The Miami Project, 25 yr
  - The Buoniconti Foundation
  - The C and D Reeve Foundation, 15 yr
  - Christine E. Lynn Disting Professor, 11 yr
- State of Florida
APPROVAL FROM THE FDA FOR
OUR FIRST SC TRIAL

Phase 1 (for safety) Clinical trial: to inject person’s own Schwann cells (from peripheral nerve*) into site of SCI
SCs expanded in culture for 3-5 wk
SCs injected into lesion epicenter

*From single adult sural nerve biopsy, 100 m SCs/ 3-4 wk
Miami Project Schwann Cell Team
Milestones-1

Dec ‘07  Organized SC clinical trial team, weekly meetings

Feb-Apr ‘08  Obtained guidance from FDA consultants

Aug ’08  Held pre-pre-IND discussion with FDA

‘08- ‘09  - Developed GMP cell manufacturing procedures for human SCs
           - Obtained supporting data from chronically injured non-human primates

‘09-’10  - Tested toxicology and tumorigenicity in rats
           - SCI studies in pigs to determine safest cell injection procedure
**Milestones-2**

July ‘10  Held pre-IND discussion with FDA

‘10–’11  - More toxicology and tumorigenicity studies on rats
         - Studies in pigs to determine safest dose and volume for clinical protocol

Apr ’11  External Advisory Board meeting

July ‘11  Submitted IND application to the FDA

July ‘12  Approval!

Dec ‘12  Performed 1\textsuperscript{st} transplantation

Apr ‘13  Performed 2\textsuperscript{nd} transplantation

May’14  Performed 3\textsuperscript{rd} transplantation

Jun ’14  Permission from FDA to broaden Exclusion Criteria
IND submission
What did the FDA require?

Studies to detect: Tumors? Biodistribution? Appropriate dose (MTD)? Toxicity? Cell survival for 6 mo?

Characterization of cell product (GMP)

Every substance FDA approved

Each step in protocol recorded

Mode of SC injection
Challenges

• $$$, rats, ramping up personnel (training), paper work
• Documentation of outcome of EVERY rat, including cause of death
• SOPs for every step in every procedure
• Sectioning of entire brain and spinal cord to detect migration of transplanted SCs
• Certified Pathologist to examine sections
Thank You

The Miami Project to Cure Paralysis
“If you want to go quickly, go alone. If you want to go far, go together.” – African Proverb
The autologous hSC trial

• Open label, unblinded, non-randomized and non-placebo dose escalation study, looking at safety of transplantation of autologous hSCs with long term follow-up in subjects with subacute SCI

• Cell preparation protocols are FDA approved and cell processing is conducted in a facility with extensive experience producing clinical grade cells (GMP)

• Piece of sural nerve is harvested within 5 days post-injury

• SCs are expanded in culture for 3-5 wk

• SCs are injected into the lesion epicenter
**Inclusion Criteria**

- Traumatic thoracic SCI between levels T3-T11
- ASIA grade A, 18-50 years of age
- Consents to spinal nerve biopsy, implantation, one year follow-up and 5-year protocol

**Dose Escalation**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Target dose</th>
<th>Injections</th>
<th>Total volume</th>
<th># subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 x 10^6</td>
<td>1</td>
<td>50 µl</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>10 x 10^6</td>
<td>1</td>
<td>100 µl</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>15 x 10^6</td>
<td>1</td>
<td>150 µl</td>
<td>3</td>
</tr>
</tbody>
</table>
Exclusion criteria

- Penetrating injury
- Spinal cord transection
- Lesions involving conus
- Multi-system trauma
- Closed head injury
- Severe neuropathic pain at admission
- BMI < 35
Outcomes

• **1° outcome – assess safety**
  – Serious adverse events
  – Changes in sensory and motor scores
  – Changes in pain or spasticity
  – Electrophysiology for MEP and SSEP
  – MRI

• **2° outcome – evaluate functional scales**
  – Functional Independence Measure (FIM)
  – Spinal Cord Independence Measure (SCIM)
  – Autonomic (BP, HR, tilt table response, etc.)

• **Follow-up of above for one year**

• **Follow-up (MRI annually for 4 years after first year)**