

SCI Research and the Hope for Cure: Where are We Today?

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30 Years into the Era of Clinical Trials in SCI...

...there is still no FDA-approved treatment for improving neurological function

nor a consensus standard of care to that end

Sir Ludwig Guttmann Lecture ISCoS 2011
Washington, DC

Our Agenda...

- What happens to the spinal cord after trauma?
- Why doesn't the healing process reliably produce a recovery of function?
- What do we know about natural recovery?
- What are the opportunities for scientific intervention?
- What is the evidence basis for determining the effectiveness and safety of a new treatment?
- What is the process for regulatory approval?
- Where are we today?
- Gazing into the crystal ball...



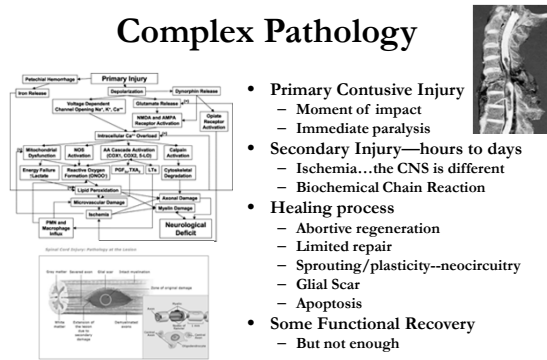
"Mr. Osborne, may I be excused? My brain is full."



The Background

Why is this research necessary?

Complex Pathology



- **Primary Contusive Injury**
 - Moment of impact
 - Immediate paralysis
- **Secondary Injury—hours to days**
 - Ischemia...the CNS is different
 - Biochemical Chain Reaction
- **Healing process**
 - Abortive regeneration
 - Limited repair
 - Sprouting/plasticity--neocircuitry
 - Glial Scar
 - Apoptosis
- **Some Functional Recovery**
 - But not enough

A “Law of Nature”?

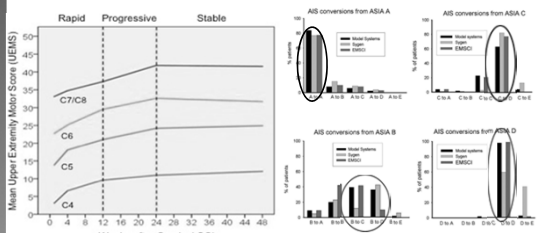
- **Fishes and some amphibians**
- **Fetal mammals**
- **Peripheral Nervous System**

Other Clues...

- **Abortive Regeneration**
- **Growth Factors**
- **Inhibitory Factors**
 - Inhibitory molecules
 - Perineural net

Natural Recovery

Most Patients Get Some (but not enough) Better



From Fawcett 2007

“Natural Recovery” in SCI

What do we need to improve upon?

- **Most SCI patients experience improvement (12-18mo)**
 - 70% of cervical patients will descend one level (Steeves 2010)
 - 30% of cervical patients will descend 2 or more levels (Steeves 2010)
 - 20-25% of initial AIS A patients will become incomplete (Fawcett 2007)
 - 8-10% of initial AIS A's patients will improve to C or D (Fawcett 2007)
- **Even “chronic” SCI can change (Kirschblum 2004)**
 - 3.5% of AIS A at one year improve to B
 - 2.1% of AIS A at one year improve to C or D
 - 20% improved motor level and NLI between 1 and 5 years

Opportunities for Intervention following SCI

- **Limit secondary damage**
 - Neuroprotection
- **Promote Regeneration**
 - Growth Factors
 - Suppress Inhibitory Factors
- **Repair Damaged Cells**
 - Remyelination
- **Replace dead cells**
 - Cell therapy implants
- **Promote Sprouting/Plasticity**
 - Enhanced cellular environment
 - Rehabilitation: Activity-dependent Therapies

Opportunities for Intervention

concepts and examples

- **Drugs/Molecules**
 - Growth factor-like
 - SUN13837 (Asubio trial)
 - Suppression of inhibition
 - Anti-Nogo antibody (ATI355 trial)
 - Ion Channel Blockade
 - Riluzole—neuroprotection
 - Fampridine-SR—improved nerve function
- **Cell based therapies**
 - Autologous Schwann Cells (University of Miami)
 - hESC-derived cells (GRNOPCI—Geron)
 - Neural Stem Cells (Stem Cells Inc and Neuralstem)
 - Bone Marrow-derived MSC (many examples)
 - Umbilical Cord Blood cells (China SCINet)

The Basis of Evidence

Building the Case for Effectiveness and Safety

Improving Neurological Function
The Variables

- **Natural recovery**—most patients improve some
- **Aspects of clinical care**
 - Acute care surgery, blood pressure control, etc.
 - Rehabilitation content/intensity/timing
- **Personal factors**—motivation/effort
- **Measurement variables**
 - Precision
 - Bias
- **Biological effect of the Experimental Treatment**

The Basis of Evidence

Building the Case for Effectiveness and Safety

- **If the patient gets better, which of the variables were responsible? Which are the “active ingredients”?**
 - Cause and Effect vs. Association
- **Narrowing the focus to the experimental Rx**
- **Elimination of bias**—everyone is hoping for improvement
 - Randomization
 - Blinding
- **The “Gold Standard”**
 - Randomized Placebo Controlled Double Blind Trial
 - Placebos and Blinding may not always be feasible
- **Clinician’s Gestalt/Patient Testimonials** *insufficient*

The Regulatory Context

What does it take to get FDA approval?

- **Preclinical (Animal Model)**
 - Proof of Concept *and* Safety
- **Human Studies**—progressive trial phases
 - Phase 1 (open label; 10-15)—feasibility, safety/tolerability
 - Phase 2 (RCT; 20-80)—How to give, what/how to measure
 - Delivery methods
 - Dose, timing,
 - Refinement of primary outcome measure
 - Phase 3 (multicenter rigorous RCT; 100’s)—pivotal trials
 - Definitive protocol
 - Two confirmatory trials required for approval
- **Five or more years, Hundreds of millions of \$**
 - The temptation to bypass this process is strong...



The Kevin Everett Story

Injury in an NFL game 9/9/2007

Has had an “excellent” recovery

Touted in the press as a “miracle”

What is the explanation?

- Natural Recovery? AIS A?
- Early decompression?
- Methylprednisolone?
- Hypothermia Treatment?



Hypothermia Rx in SCI

- **Phase I trial**—University of Miami
 - Report on 14 patients with cervical AIS A SCI (Levi, Neurosurgery 2010)
 - Appears “reasonably safe” (pulmonary, cardiac dysrhythmia AEs)
 - AIS Conversion rate 42.8% (3A→B; 2A→C; 1A→D)
- **Prospective observational trial underway**
- **Can/will a RCT be conducted?**
- **Should this therapy be a standard of care?**
- **Balancing (potential) benefits and risks**

A Cautionary Tale...

The Autologous Macrophage Trial

- Animal model studies encouraging
- Phase 1 human trial “positive”
 - AIS conversion rate 37.5% (3 of 8, A→C)
- Phase 2 multicenter RCT disappoints
 - AIS conversion rate 27% in macrophage patients
 - AIS conversion rate 59% in control patients!
- The importance of rigorous science...

Where are we today?

- **Basic Science: Explosive Knowledge Growth**
 - Fetal Cell→hESC→iPSC→iN cell
- **Translational Science: moving towards more clinical trials**
 - Expanding beyond acute to more chronic models
- **Increasing number of clinical trials underway: Drugs, Cells, Surgery, Rehabilitation**

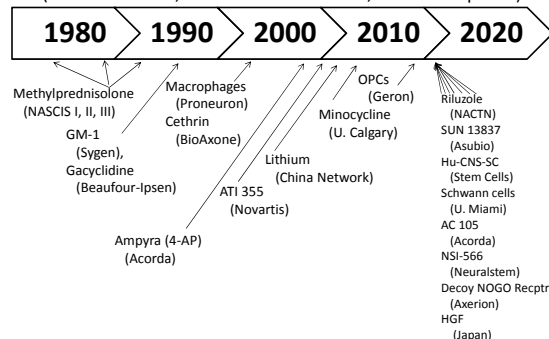
Current SCI Trials

clinicaltrials.gov lists 203 SCI trials currently open
25 Restorative Trials (www.scope-sci.org)

- | | |
|--|---|
| <p>“Restorative Trials”</p> <ul style="list-style-type: none"> • ASB113837 • AC105 (MgCl₂-PEG) • Minocycline (2) • Bone Marrow Stem Cells (5) • Human Neural Stem Cells (2) • Adipose-derived Stem Cells (2) • Umbilical Cord Blood Cells (1) • Autologous Schwann Cells (1) • Riluzole (2) • Dalfampridine • Spinalon • Human Growth Hormone (1) • Intermittent Hypoxia (3) | <p>Rehab/“Activity Based” Rx Trials</p> <ul style="list-style-type: none"> • Locomotor Therapy <ul style="list-style-type: none"> – Traditional BWSTT & Robotic • FIRTHAND system • Patterned UE FES • Complex Motion Stimulator • Somatosensory Stim/ Massed Practice Training • Others... |
|--|---|

SCI Trials – Past, Present and Projected

The neighborhood is becoming increasingly populated with treatments (small molecules, monoclonal antibodies, & cell transplants)



The Rehab Variable

- Activity-based Rehab Therapies have entered the clinical mainstream...
 - and have been accepted as an important treatment variable
- The “Black Box”: what has been proven effective?
- Preclinical studies show synergy between “biological” and “rehab” interventions
- Challenges of incorporating rehab into clinical trial protocols...how much...of what...started when...for how long? How will it be funded???

Technology

- FES
- Neuroprostheses
- Brain-Computer Interface
- Neuromodulation

What about Complimentary/Alternative Approaches?

- Acupuncture
- Chiropractic
- Vitamin therapies
- Low Power Laser

- Science is an impartial judge
- Truly effective/safe therapies will/should stand the test

The “Fringe”: Medical Tourism

Less than Quasi-science

- hESC injections (IV, IM, IT) in India
- Fetal Blue Shark Schwann Cell implantation into the spinal cord (Tijuana)
- Autologous Schwann Cell implantation into the spinal cord (Ecuador)
- Omentum Transposition to the spinal cord (Cuba, China, elsewhere)
- Autologous Bone Marrow
- Umbilical Cord Blood
- Many others...
- ***Caveat Emptor!!!***
 - *Costs, Scientific Protocol, Follow-up*

The Big Questions

- Is there any experimental therapy available that might make a difference?
- Where can we go to access experimental protocols?
- Why am I not eligible?
- How can I make sure I will be a candidate?
- Can I put my name on the list?
- Can't science be more efficient—appoint a czar?
- What do think of the work being done in Beijing? Delhi? Should I “go for it”?
- “*What have I got to loose?*”
- *When* will the cure be available?

Crystal Ball Gazing

- Combination Therapy Approaches
 - Drugs
 - Cells
 - Neuroprosthetics/technologies
 - Rehabilitation
- The initial successes will be modest
 - Subsequent advances/refinements will have impact
- The challenges of finding synergies and measuring benefit

Moving Towards Better Neurological Outcomes in Spinal Cord Injury

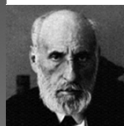
(How Can We Do Better?)

- Preclinical: More potent interventions
- Clinical: Improved conduct of clinical trials
 - More rigorous trial design
 - Improved outcome measures...and measurement
- Translational Dialogue Imperative



Final Thoughts...

The Path to Translation



“It is for the science of the future to change, if possible, this harsh decree...”

The Clinical Trial Era of SCI Research

Developing the Best of Both Worlds: The Clinical Trial Era of SCI Research

