Neural Repair and Rehabilitation

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NeuroRehabilitation Combines the Strengths of Two Important Medical Traditions

Rehabilitation Medicine
- Advanced team approach
- Sophisticated outcomes designs
- Quality of life

Neurology
- Pathophysiology
- Cell and molecular biology
- Tradition of research

NeuroRehabilitation
This concept has informed the approaches taken by both the NCMRR and the VA RR&D Service.
Scope of Rehabilitation Research

- **REPAIR**
  - Basic research to repair injured organs and tissues
  - Translational research to bring basic discoveries to clinical use

- **REPLACE**
  - Prosthetics/robotics research to replace what cannot be repaired

- **RESTORE**
  - Physiological function
  - Social integration
Significant Advances in NeuroRehabilitation Research Since NCMRR Started

- Application of Evidence-based practice to Rehabilitation
- Expanded BCI and robotic research
- Adaptation of multicenter, prospective randomized, controlled clinical trials for rehabilitation treatments (SCILT, Bruce Dobkin; EXCITE, Steve Wolf; LEAPS, Pam Duncan et al.; now many others)
- Adoption of basic science
  - Plasticity
  - Repair
- Translation of basic research on neural repair to clinical trials (Anti-Nogo; RhoA inhibitor; Autologous bone marrow progenitor cells for SCI in children, James Baumgartner; Autologous CNS stem cells for thoracic SCI, Armin Curt; many, many others in US and abroad) clinicaltrials.gov
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Brain-Computer Interfaces for Communication and Motor Control

Some of these neuroprostheses are commercial products; others are available in research settings.

1. Electrode array developed by Richard Norman, U. of Utah (a, b)
2. Implanted in R precentral gyrus (c)
3. Wired to computer, which controls cursor and other displays on monitor (BrainGate® system) (d)

Brain-Computer Interface to Operate Prosthetic Devices

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Challenges for Repairing the Injured Nervous System

• Wrong experimental paradigms of axon growth

• Scale - animal size

• Initial clinical trials employ patients least likely to respond

• Personalized medicine – Rare diseases; common disease type
Four Modes of Axon Growth

• Early Growth Cone Mediated Axon Pulling
  – Actin-Myosin molecular motor
  – Embryonic mechanism, but ? relevance to regeneration

• Axon Stretching
  – After initial target contacts made
  – In whales, can be 3 cm/day

• Collateral Sprouting

• Regeneration
Why Worry About Regeneration vs. Sprouting?

Partial SCI

- Injury
- Collateral Sprouting

Complete SCI (ASIA A)

- Injury
- No Collateral Sprouting
Does Neutralizing Nogo Enhance Axon Regeneration?

• Approaches
  – Antibodies to Nogo
  – Nogo-66 inhibitory peptide (NEP1-40)
  – Soluble piece of NgR (NgR(310)ecto-Fc)
  – Nogo knockouts
  – NgR knockouts
  – Triple knockout of Nogo, MAG and MOG

• Results
  – CST – Increase collateral sprouting but no regeneration
  – Other axon types may regenerate, but not sure

• Concerns: Antibodies to Nogo are in clinical trials (Novartis) limited to ASIA A. Will they succeed?
Similar Concerns can be Raised About Other Therapies Based on Neutralizing Growth Cone Collapse

- Rho-A Inhibitor (Cethrin)
- Chondroitinase-ABC
- Cyclic AMP
Axon Tips During the Period of Regeneration Lack Filopodia and Lamellipodia

A

Stained for F-Actin

B1

Live

B2

Stained for NF

Embryonic Chick Growth Cones in Tissue Culture

Regenerating Lamprey Spinal Cord Axons
Signaling Pathways for Regeneration

- Cyt
- Gp130 complex
- JAK-2
- Trk
- PI3K
- NT
- PIP2
- PIP3
- PTEN
- SOCS-3
- STAT-3
- mTOR
- Nogo complex
- NgR complex
- MAG
- MOG
- Nogo
- PIP3
- cAMP
- Akt
- CREB
- RhoA
- ROCK
- rPTP
- REGENERATION
Intrinsic Growth Control of Mature CNS Neurons

- Apoptosis
- Degenerating
- Myelin debris
- Glial scar

Cell Survival → Intrinsic Growth Ability → Extrinsic Environment

PTEN KO Promotes Axon Regeneration

AAV-Cre

AAV-GFP
Challenges for Repairing the Injured Nervous System

• Wrong experimental paradigms of axon growth

• Scale - animal size
  – Progressive loss of regenerative ability after axotomy.
  – Rate of regeneration is similar in all species.
  – In humans, regenerative ability from proximal lesions wanes before targets are reached.
Progressive Loss of Regenerative Ability After Axotomy

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  – When treatment for SCI involves highly invasive procedures, *e.g.*, exposing spinal cord, initial clinical trials are performed on complete spinal cord injury, since those patients have less to lose.
  – These patients have few spared axons, so collateral sprouting is less likely to be beneficial.
  – Non-invasive therapies are more likely to succeed.
Systemically Deliverable Blockers of Growth Inhibition

Shuxin Li

**TAT** = Transactivator of Transcription (GRKKRRQRRRC) to make peptide permeant
Challenges for Repairing the Injured Nervous System

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• Personalized medicine – Rare diseases; common disease type
The Challenge of Personalized Medicine: Gene Therapy

- Individually, rare diseases
- Insufficient attention by NIH
- Partnerships between patient families and qualified investigators willing to devote substantial time to preclinical and clinical research on the disease
- Institutional framework – “Center for Personalized Gene Therapy”?
LCA8: Gene- and Cell-Based Therapies

- Survival and Integration
- Differentiation
- Synapse formation
- ERG recovery

GFP (+) Retinal Progenitor Cells
P0 → P14
Conclusions

• With encouragement from the NCMRR (and VA RR&D), “rehabilitation”, and in particular neurorehabilitation, has expanded its meaning to include the application of research on neural repair and plasticity to restore function in persons with disabilities.

• Scientific fields that are contributing include:
  – Robotics
  – Evidence-based medicine
  – Functional plasticity (cognitive, sensory and motor)
  – Neural repair (axon regeneration, cell replacement, remyelination, gene therapy)

• The benefits of scientific research are both direct and indirect. Adoption of a basic science framework encourages evidence-based clinical practice, raises the impact of the field of rehabilitation medicine (e.g., NNR) and attracts the best trainees to the field.