# Neural Repair and Rehabilitation

## NICHD 50th Anniversary Colloquium

December 5, 2012

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(*Center for Neural Repair and Rehabilitation*)



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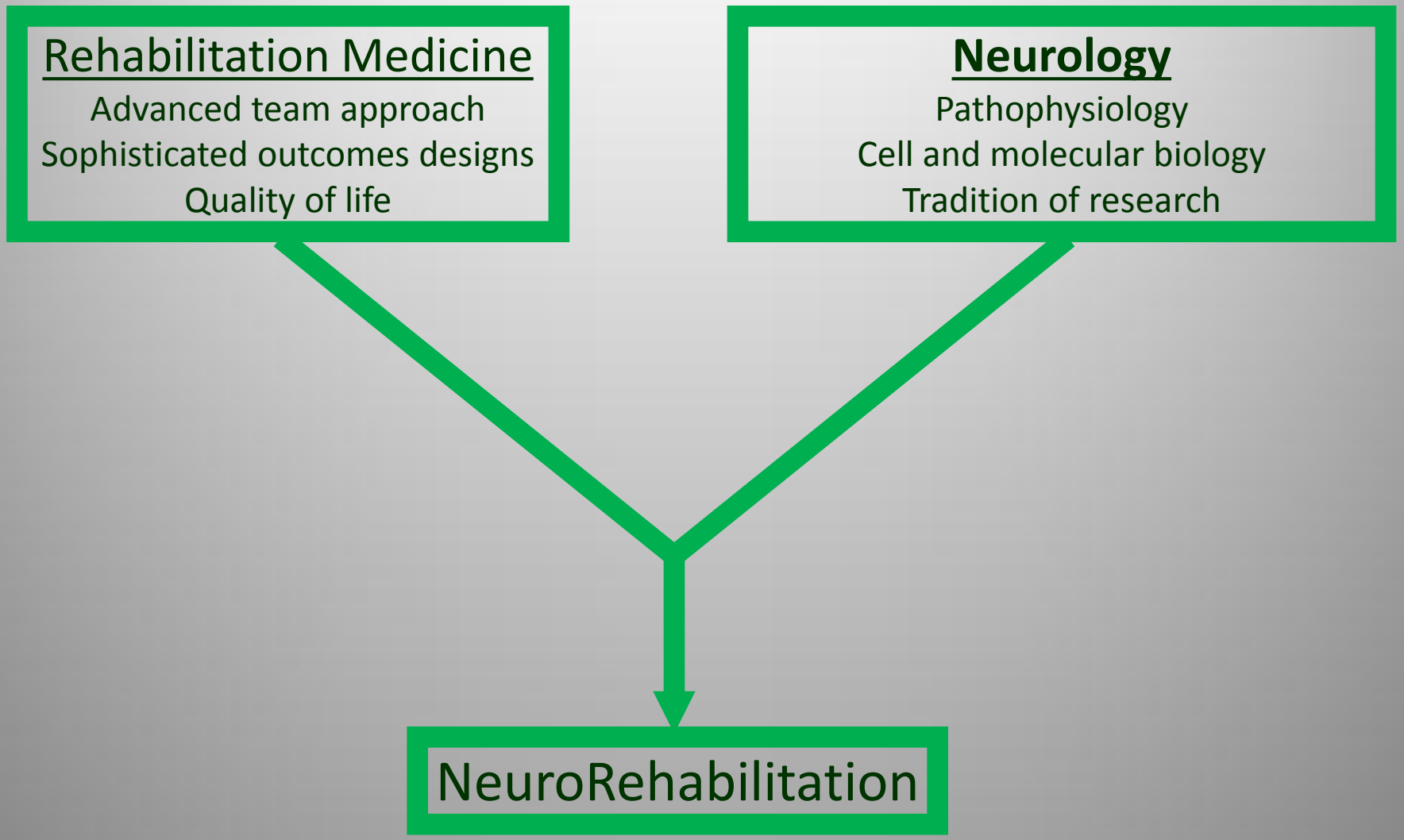
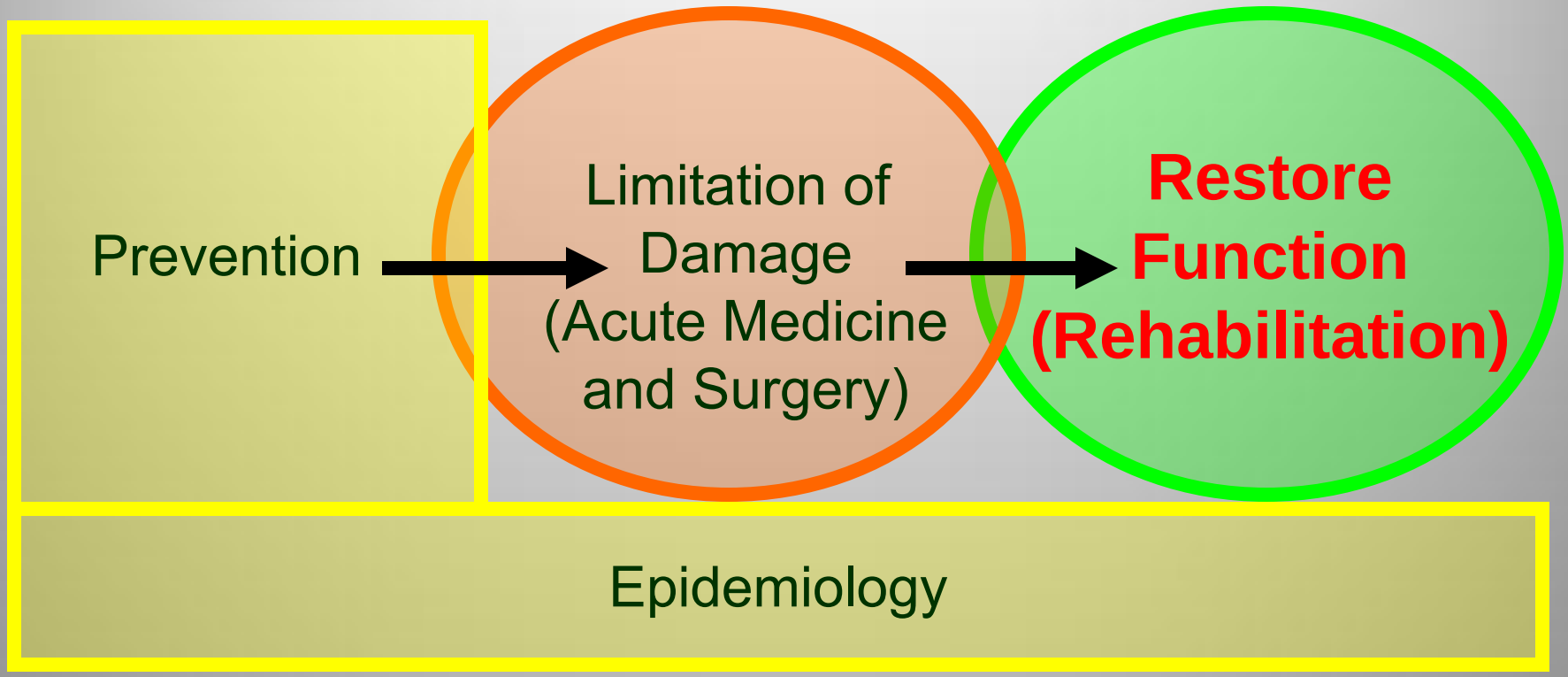
# NeuroRehabilitation Combines the Strengths of Two Important Medical Traditions



# Interdisciplinary Time Model of Medicine




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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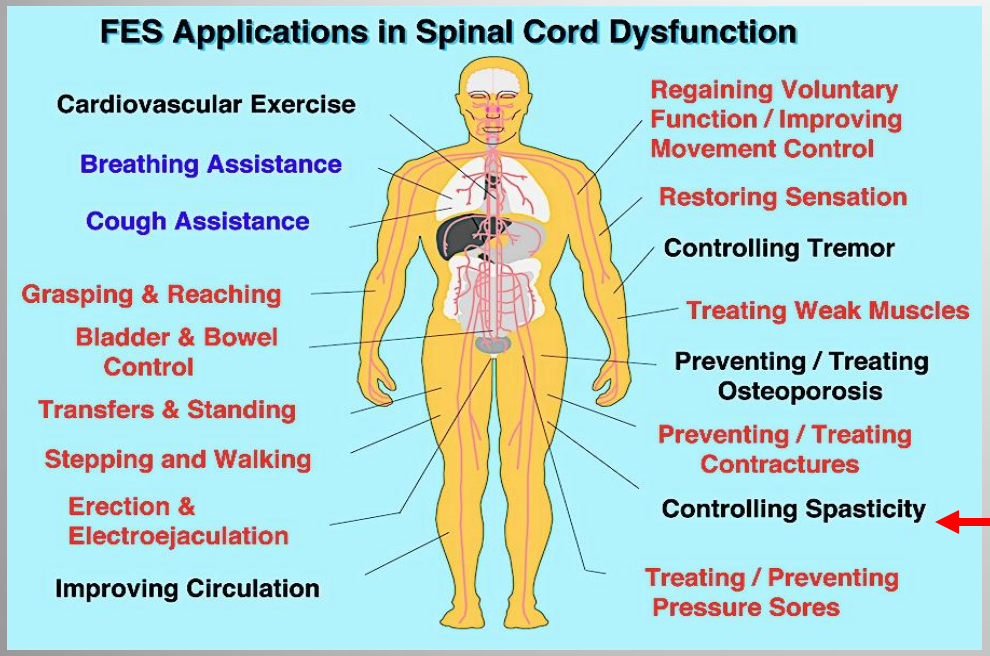
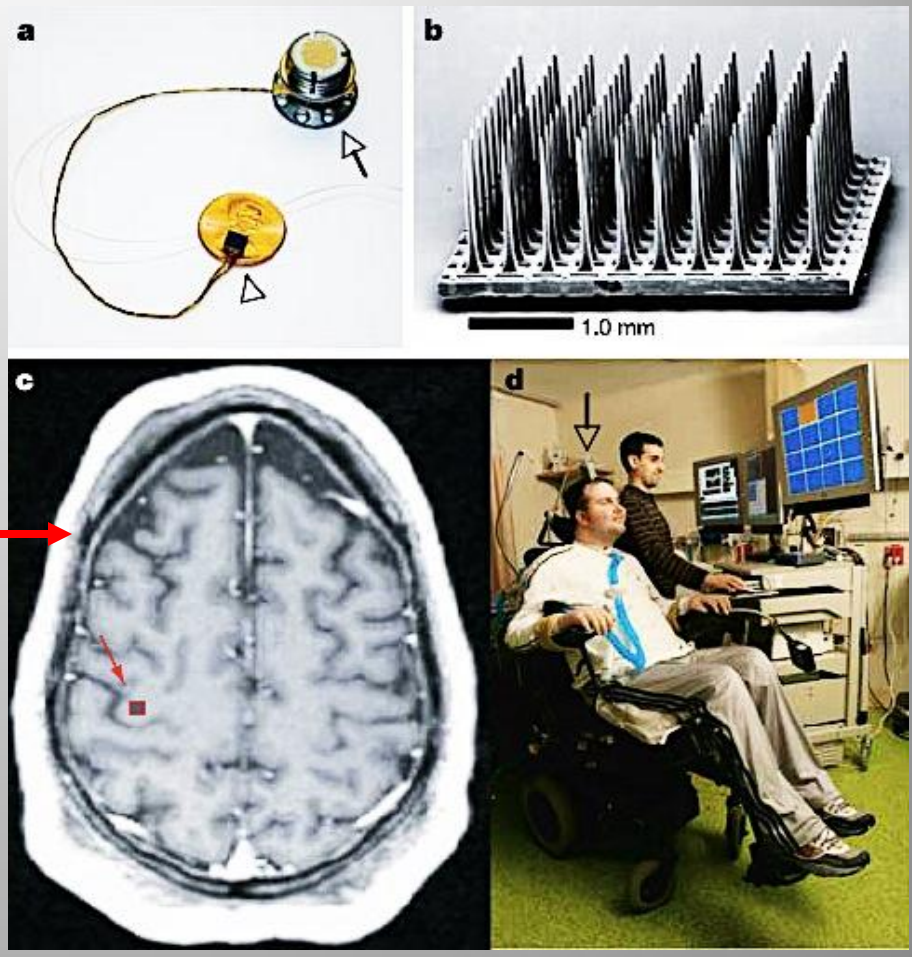
# Brain-Computer Interfaces for Communication and Motor Control



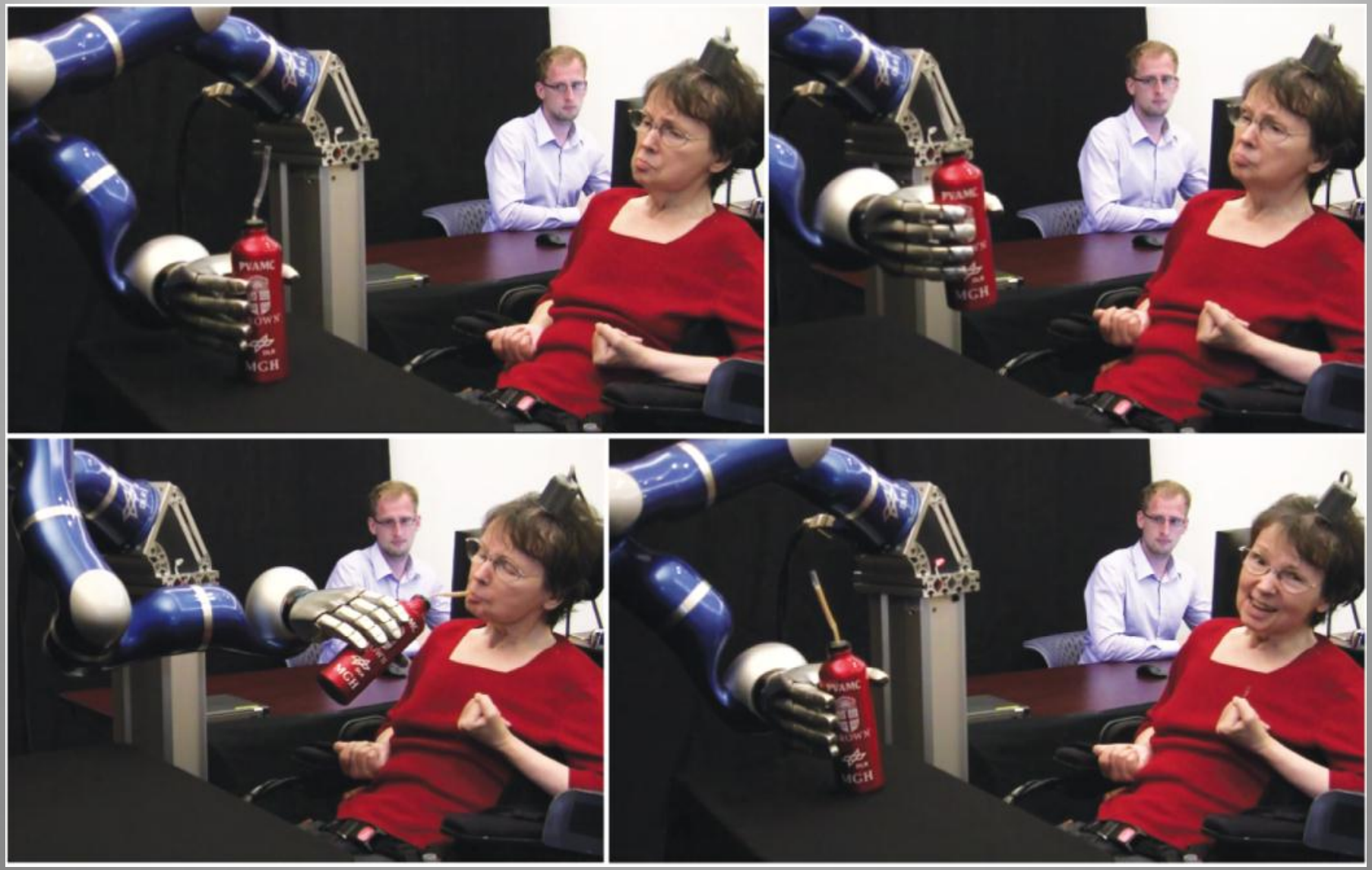




**Some of these neuroprostheses are commercial products; others are available in research settings.**

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)

Hochberg LR *et al.* Nature 442: 164-71, 2006

# Brain-Computer Interface to Operate Prosthetic Devices



Hochberg LR, Bacher D, Jarosiewicz B, Masse NY, Simeral JD, Vogel J, Haddadin S, Liu J, Cash SS, van der Smagt P, Donoghue JP. Reach and grasp by people with tetraplegia using a neurally controlled robotic arm. *Nature 485:*372-7, 2012

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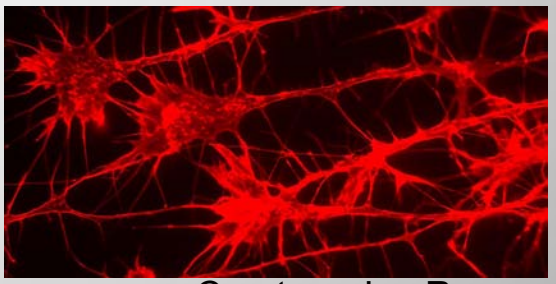
# Challenges for Repairing the Injured Nervous System

- 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

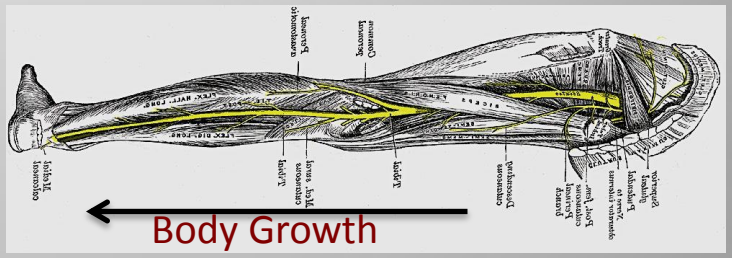
# Four Modes of Axon Growth

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

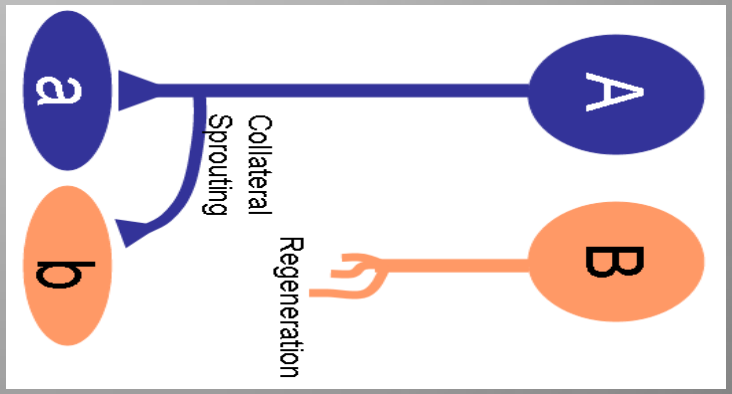


Courtesy Jon Raper

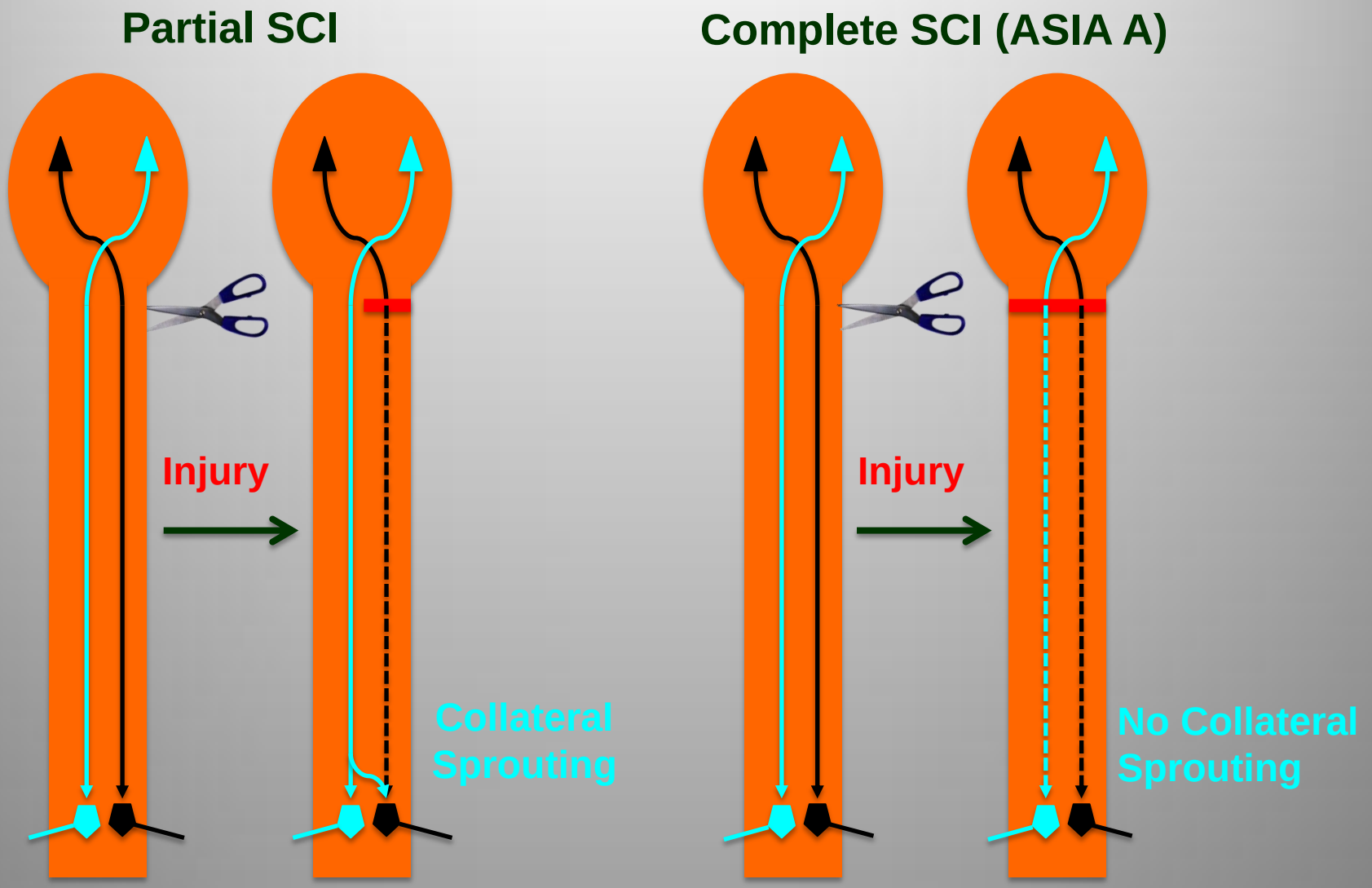
- Axon Stretching
  - After initial target contacts made
  - In whales, can be 3 cm/day




- Collateral Sprouting
- Regeneration



# Why Worry About Regeneration *vs.* Sprouting?



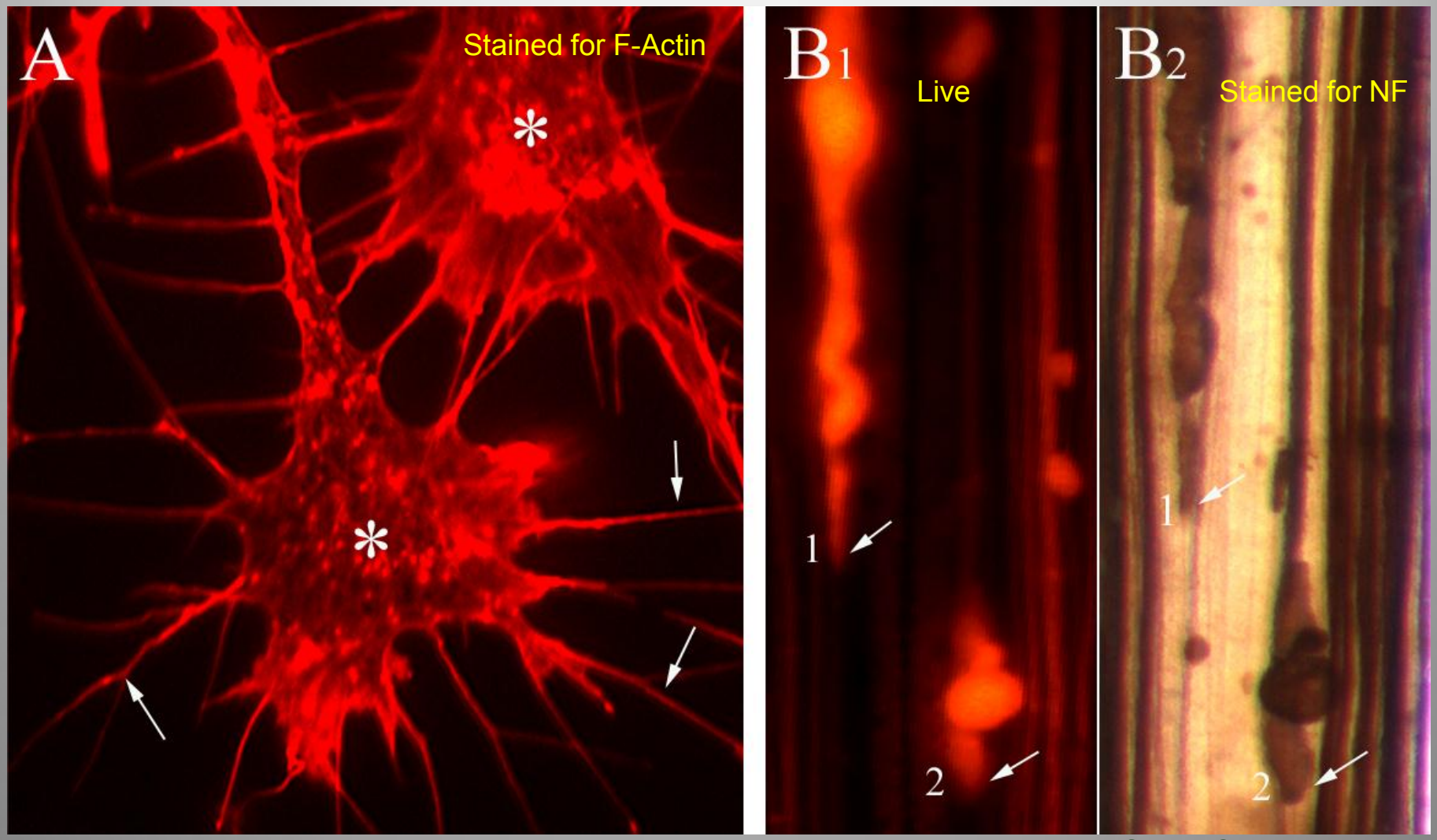
# Does Neutralizing Nogo Enhance Axon Regeneration?

- 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 Neutralizating Growth Cone Collapse

- Rho-A Inhibitor (Cethrin)
- Chondroitinase-ABC
- Cyclic AMP

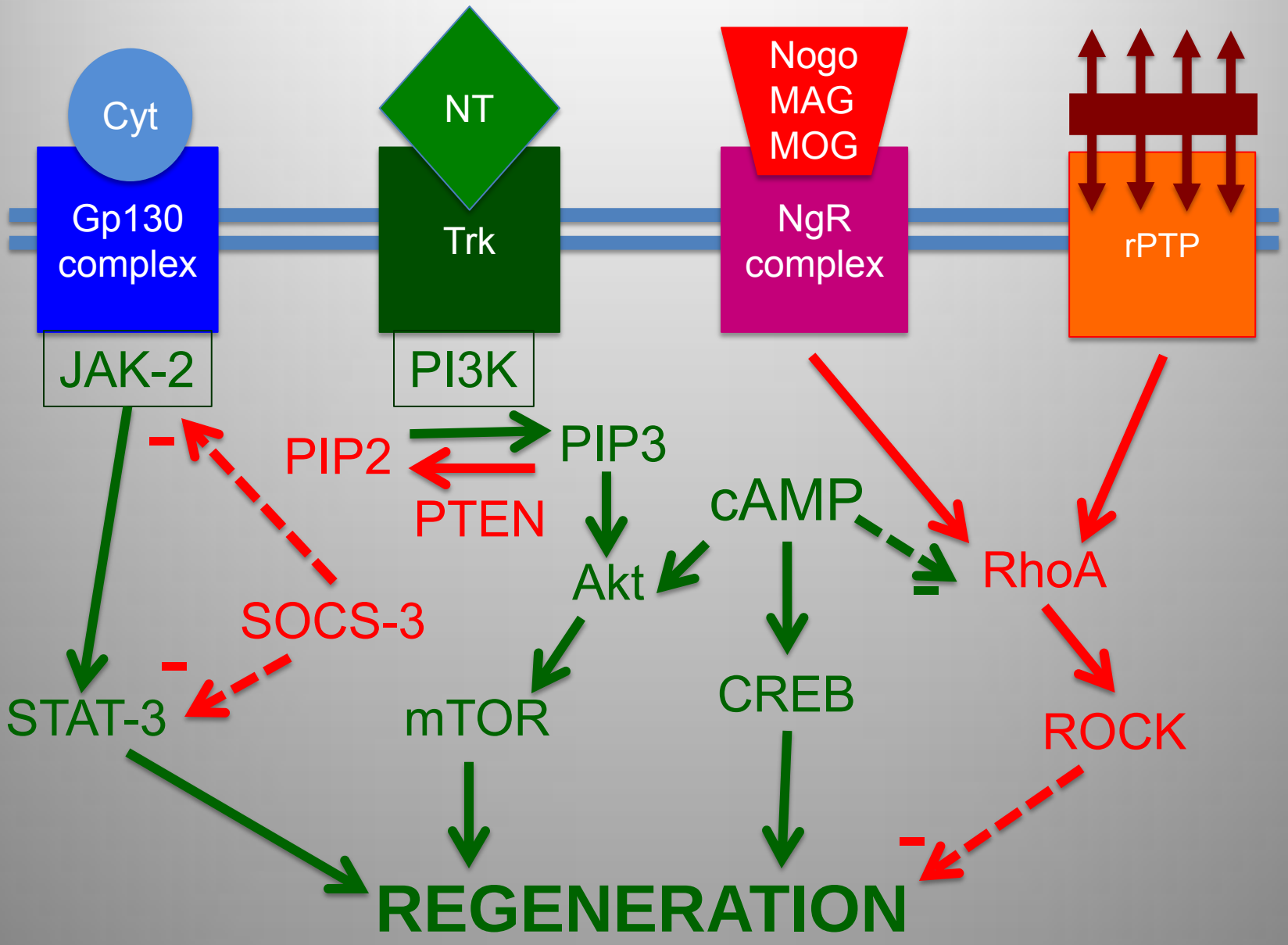
# Axon Tips During the Period of Regeneration Lack Filopodia and Lamellipodia



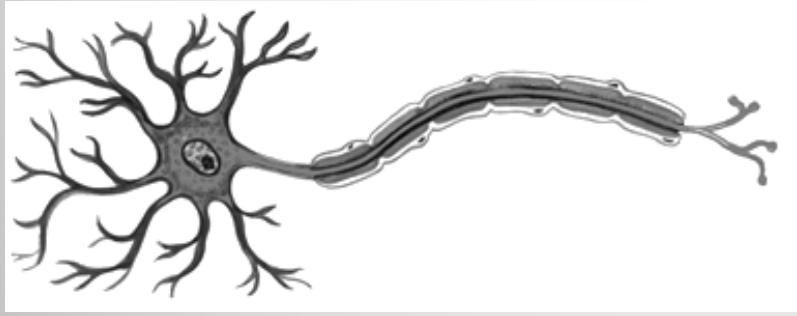

Embryonic Chick Growth Cones in Tissue Culture

Regenerating Lamprey Spinal Cord Axons

# Signaling Pathways for Regeneration



# Intrinsic Growth Control of Mature CNS Neurons



Apoptosis

Degenerating

Myelin debris

Glial scar

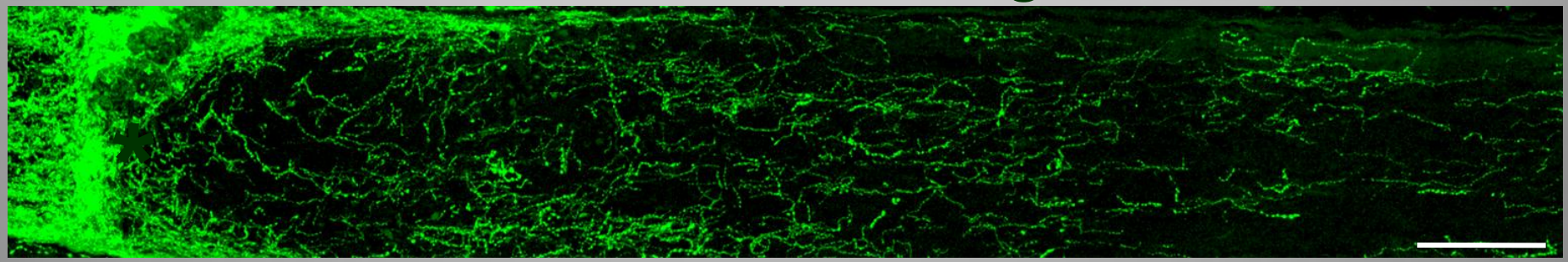
Cell Survival

Intrinsic Growth Ability

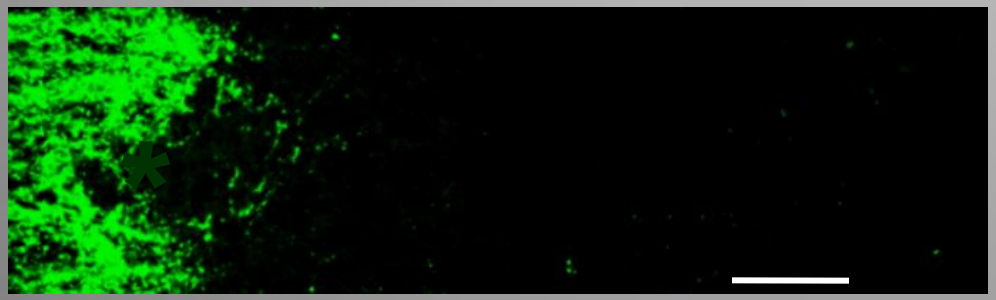
Extrinsic Environment

## PTEN KO Promotes Axon Regeneration

AAV-Cre



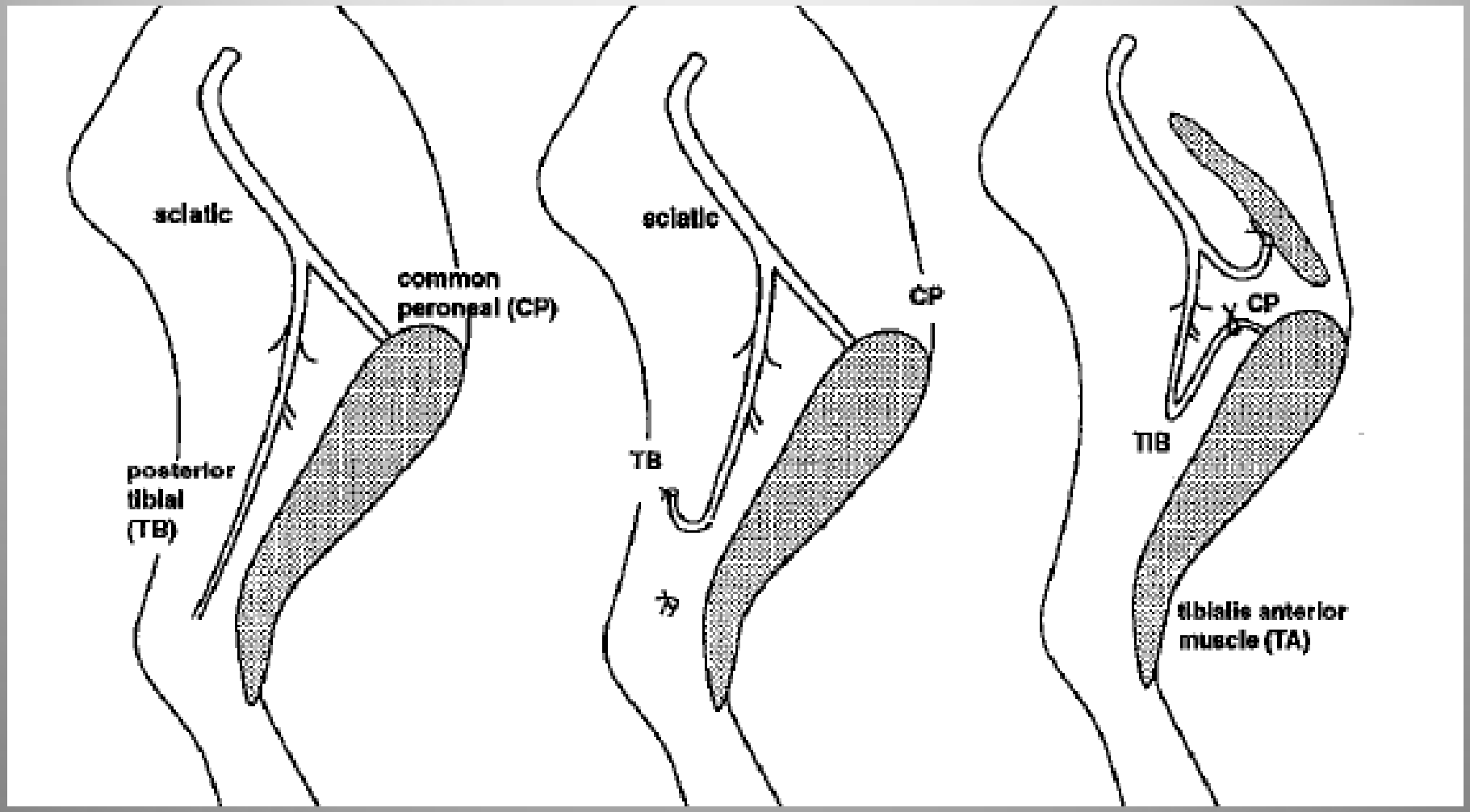
AAV-GFP



# 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



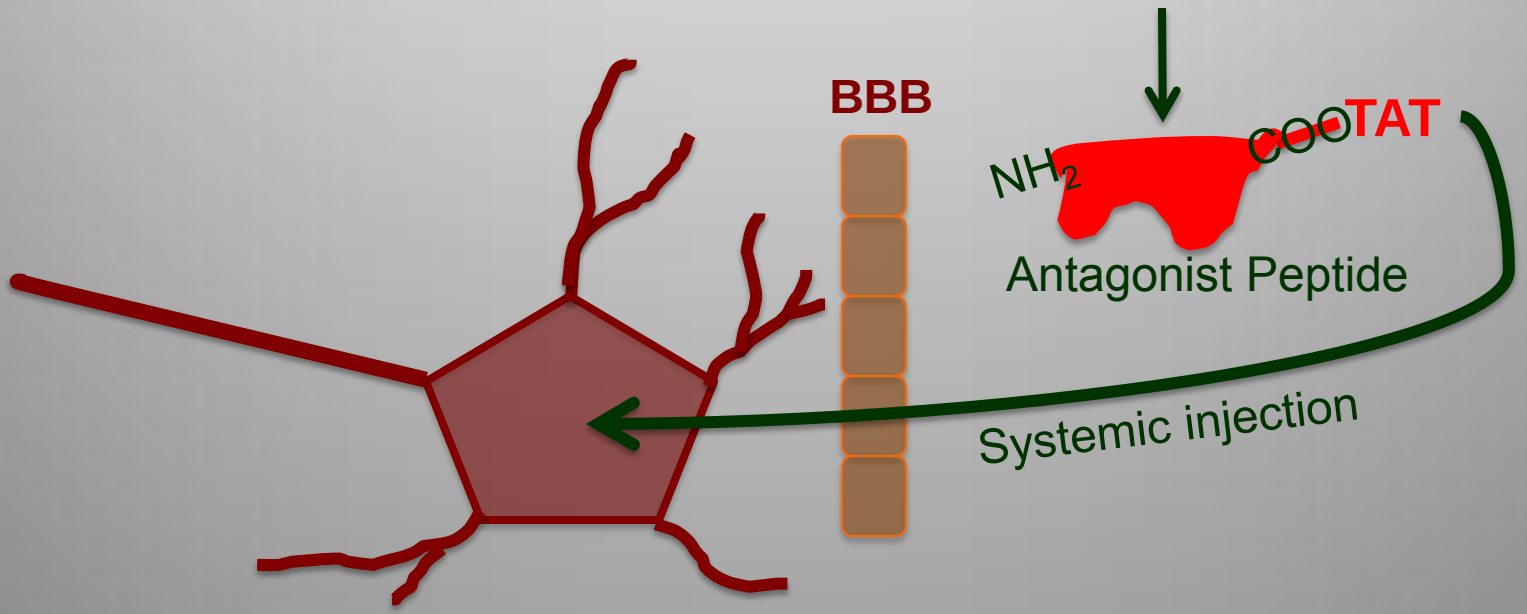

Fu SY, Gordon T (1995) Contributing factors to poor functional recovery after delayed nerve repair: prolonged axotomy. J Neurosci 15:3876-3885.

# 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
  - 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

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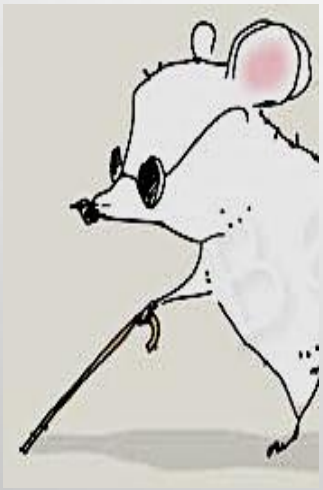
# The Challenge of Personalized Medicine: Gene Therapy

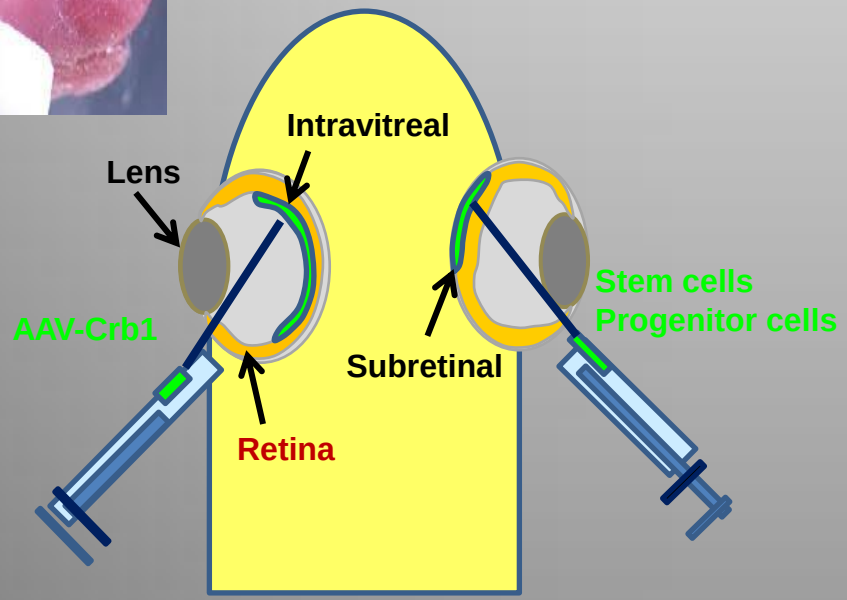
- Individually, rare diseases
- Insufficient attention by NIH
- Partnerships between patient families and qualified investigators willing to devote substantial time to preclinical and clinical research on the disease
- Institutional framework – “Center for Personalized Gene Therapy”?

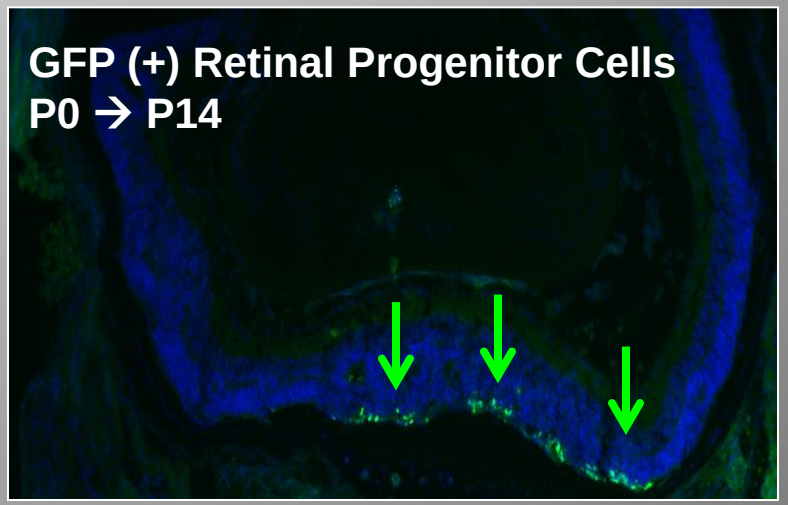
# LCA8: Gene- and Cell-Based Therapies

Seo-Hee Cho



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



# Conclusions

- With encouragement from the NCMRR (and VA RR&D) , “rehabilitation”, and in particular neurorehabhilitation, 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.