Bases for Hope for Spinal Cord Injury

Wise Young, Ph.D., M.D.

W. M. Keck Center for Collaborative Neuroscience

Rutgers University, Piscataway, New Jersey

The Bases for Hope

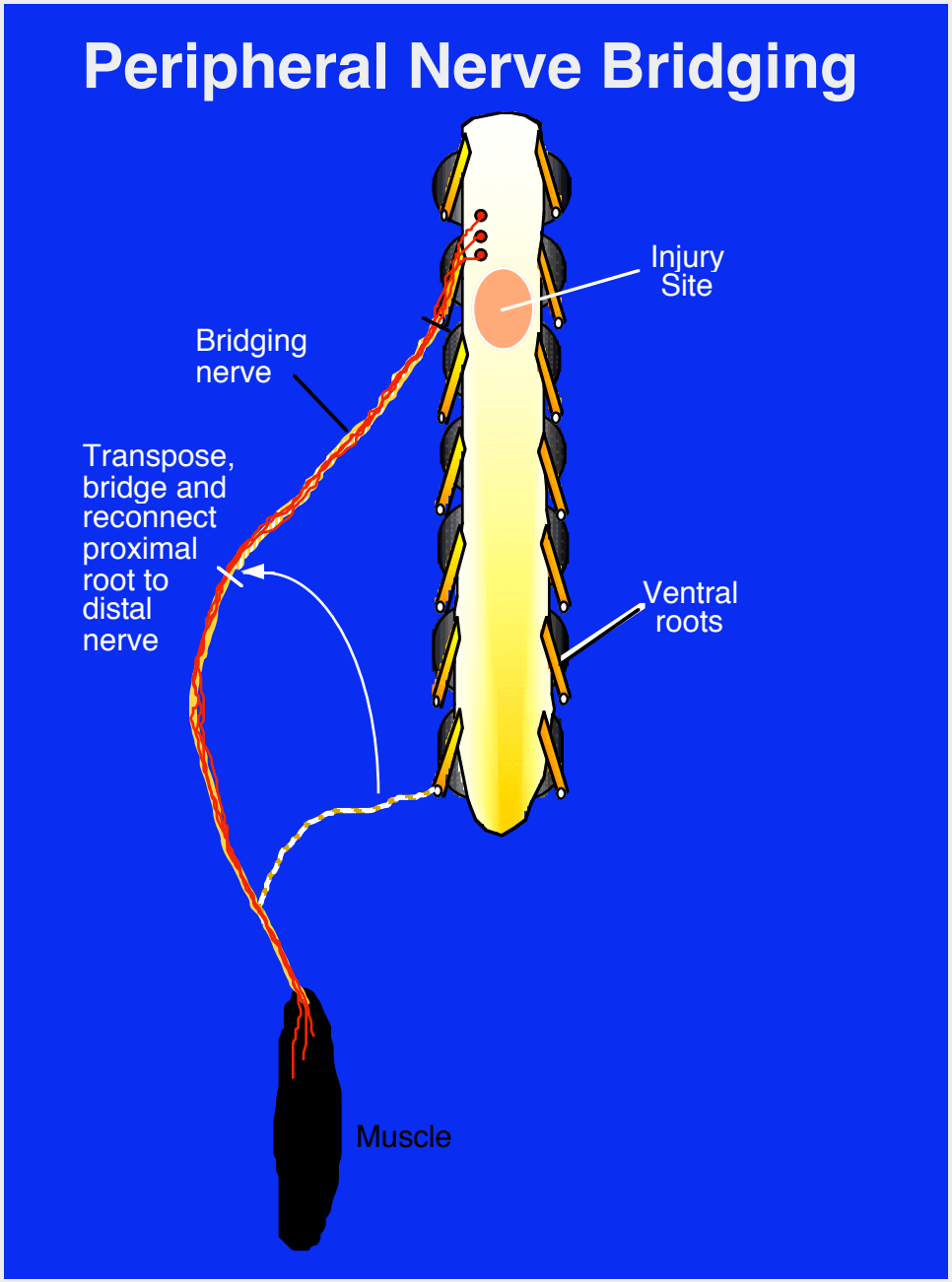
- Advances in surgical, medical, and rehabilitative care of people have significantly improved recovery from spinal cord injury.
- Researchers have discovered many therapies that are regenerating and remyelinating animal with spinal cord injury.
- Clinical trials of first generation therapies are underway. Second generation therapies will start soon. There has never been a more exciting time for spinal cord injury research.
- Hope is once more in the hearts and minds of scientists
  - The traditional dogmas that the spinal cord cannot repair or regenerate itself have been decisively overturned.
  - Most scientists believe that regenerative and remyelinative therapies are not only possible but imminent.

State-of-the-Art in 1995

- Acute and Subacute Therapies
  - Methylprednisolone is neuroprotective (NASCIS, 1990)
  - GM1 improves locomotor recovery in humans (Geisler, 1991)
- Spasticity and Pain Therapies
  - Intrathecal baclofen pump (Medtronics)
  - Tricyclic antidepressant amitriptyline (Elavil)
- Emerging Therapies
  - IN-1 antibody stimulates regeneration in rats (Schwab, 1991-)
  - Intravenous 4-aminopyridine improves function in people with chronic spinal cord injury (Hansebout, 1992-)
  - Fetal tissue transplants survive in animals (Reier, 1992-)
  - Neurotrophin-secreting fibroblast transplants (Tuszynski, 1994-)

Surgical Advances

- Decompression and stabilization of the spine
  - Anterior and posterior plates
  - Titanium cage vertebral repair
  - Delayed decompression restores function (Bohlman) even years after injury
- Urological procedures
  - Suprapubic catheterization
  - Mitrafanoff procedure
    - Use of the appendix to allow people to catheterize the bladder through the belly button
  - Vocare sacral stimulation
- Syringomyelic cysts
  - Removing adhesions and untethering of the cord will collapse syringomyelic cysts with lower rate of recurrence
  - Restoring CSF flow is key to preventing cyst development
- Peripheral nerve bridging
  - Implanting avulsed roots or nerves into the spinal cord (Carlstedt, et al. 2000)
    - Muscle reinnervation
    - Reduces neuropathic pain
  - Bridging nerves from above the injury site to organs below (Zhang, 2001; Brunelli, 2000)


Peripheral Nerve Bridging
Injury Site
Bridging nerve
Transpose, bridge and reconnect proximal root to distal nerve
Ventral roots
Muscle

Drug Therapies

- Acute & Subacute Therapies
  - NASCIS 2:
    - 24-hour methylprednisolone <8h better than placebo
  - NASCIS 3:
    - 48-hour methylprednisolone (MP) is better than a 24-hour course of MP when started >3 hours after injury (1998).
    - 48-hour course of Tirilazad mesylate after an initial bolus of MP is similar to 24-hour course of MP
  - MP+GM1
    - accelerates 6-week recovery compared to MP alone but not one year (Geisler, 1999)
- Chronic Therapies
  - Tizanidine
    - Reduces spasticity with less side-effects
  - Intrathecal baclofen
    - Effectively reduces even severe spasticity with minimal side-effects
  - Oral 4-aminopyridine
    - May reduce pain and spasticity (Hayes, et al. 1998)
    - May improve bladder, bowel, and sexual function
    - A third of patients may get improvement motor and sensory function on 4-AP

Advances in Rehabilitation

- Bladder Function
  - Urodynamic studies
  - Vesicular instillation of Capsaicin and ditropan for spasticity
- Neuropathic Pain Therapies
  - Amitriptyline (Elavil)
  - Anti-epileptic drugs
    - Carbamapezine (Tegretol)
    - High dose Neurontin (Gabapentin)
  - Glutamate receptor blockers
    - Ketamine
    - Dextromethorphan
  - Cannabinoids
- Functional electrical stimulation (FES)
  - Freehand hand stimulator
  - External hand stimulators
  - Leg/walking stimulators
  - FES exercise devices
  - Bicycling devices
- Reversing learned non-use
  - Forced-use training
  - Biofeedback therapy
  - Supported treadmill ambulation training
  - Robotic exercisers

Regenerative Therapies

- Axonal growth inhibitor blockade
  - Humanized IN-1 to block Nogo (Schwab, 2001)
  - Nogo receptor blockers (Strittmatter, 2001)
  - Chondroitinase (Fawcett, 2000)
- Axonal growth factors
  - NGF+BDNF+NT3 (Xu, 2001)
  - Inosine (Benowitz, 1999)
  - AIT-082 (Neotherapeutics)
  - Adenosine (Chao, 2000)
  - Lithium chloride (Wu, 2004)
- Therapeutic vaccines
  - Spinal cord homogenate vaccine (David, et al., 1999)
  - Myelin basic protein & copaxone (Schwartz, 2001)
- Cell Transplants
  - Activated macrophages (Schwartz, et al. 1998-2000)
  - Embryonic and fetal stem cells
  - Olfactory ensheathing glia (Ramos-Cuetos, 2000)
  - Schwann cell transplants (Xu)
- Cell adhesion molecules (L1)
- Axonal growth messengers
  - Increase cAMP (Filbin, 2002)
    - Rolipram PDE4 inhibitor
    - Dibutyryl cAMP (Bunge, 2004)
  - C3 Rho or rho kinase inhibitor (McKerracher, 2001)
- Electrical stimulation
  - Alternating electrical currents (Borgens, 1997)

Remyelinative Therapies

- Schwann cell transplants
  - Schwann cell invasion into the injury site (Blight, 1985; Blakemore, 1990)
  - Schwann cell transplants (Vollmer, 1997)
  - Peripheral nerve transplants (Kao)
- Oligodendroglial cell transplants
  - Endogenous stem cells produce oligodendroglial precursor cells (Gage, 1999)
  - O2A cells remyelinate spinal axons (Blakemore, et al. 1996-)
  - Transplanted embryonic stem cells produce oligodendroglia that remyelinate the spinal cord (McDonald, 1999).
- Stem cells
  - Mouse embryonic stem cell to rats (McDonald,et al 2000)
  - Porcine fetal stem cells (Diacrin)
  - Human fetal stem cells (Moscow & Novosibirsk)
- Olfactory ensheathing glia (OEG) transplants
  - Transplanted OEG cells remyelinate axons in the spinal cord (Kocsis, et al. 1999)
- Antibody therapies
  - M1 antibody stimulates remyelination (Rodriguez, 1996-)
  - Calpaxone (copolymer 2) improved recovery in rats (Schwartz, et al. 2001)

Clinical Trials since 1995

- Fetal cell transplants to treat progressive syringomyelia (Gainesville Florida, Rush Presbyterian Chicago, Karolinska Sweden, Moscow, Novosibirsk, China)
- 4-aminopyridine for chronic SCI (Acorda,Phase 3, Model SCI Centers)
- Activated macrophage transplants for subacute SCI (Proneuron, Israel)
- Porcine neural stem cell transplants to spinal cord injury site (Diacrin Albany Med. Center and Washington University in St. Louis)
- Alternating current electrical stimulation for subacute SCI (Purdue University in Indiana and also Dublin, Ireland)
- AIT-082 therapy of subacute spinal cord injury (Neotherapeutics trial at Ranchos Los Amigos, Gaylord, Craig,Thomas Jefferson Rehab Centers)
- Peripheral nerve bridging with neurotrophic cocktail (Cheng in Taiwan)
- Theophylline therapy to restore respiratory function in ventilator-dependent patients (Goshgarian, Wayne State University).
- Other Trials: Many clinical trials have tested various rehabilitative therapies, and treatments for spasticity and neuropathic pain.

Other Clinical Therapies

- Supported treadmill locomotor training to reverse learned non-use
  - U.S. NIH Multicenter trial (NICHD) to test treadmill ambulatory training
  - Laufband (treadmill) trials in Germany and Switzerland
- Spinal cord stimulator to activate spinal cord central pattern generator (University of Arizona, Tucson)
- Experimental surgical approaches
  - Decompression-untethering, peripheral nerve transplants, omentum grafts, hyperbaric chamber, 4-aminopyridine (Dr. C. Kao in Ecuador)
  - Fetal stem cell transplants for chronic SCI (Dr. A. S. Bruhovetsky's Moscow)
  - Fetal stem cell plus olfactory ensheathing glia (Dr. S. Rabinovich, Novosibirsk)
  - Peripheral nerve bridging of transected spinal cords
    - Barros at University of Sao Paulo bridged 6 patients
    - Cheng in Taiwan has bridged >20 patient; Beijing also has a trial
  - Ulnar to sciatic nerve bridging (Brunelli, Italy)
  - Omentum transplants (Cuba, China, and Italy)
  - Shark embryonic transplants (Tijuana, Mexico)

Treatments in trial or soon to be

- Olfactory ensheathing glia (OEG) transplants
  - Human fetal OEG (Beijing, Russia)
  - Human nasal mucosa (Lisbon)
  - Human nasal mucosa OEG autografts (Brisbane, Australia)
- IN-1 antibody to regenerate chronic SCI (Novartis, University of Zurich)
- Nogo receptor blockers (Biogen, Yale University)
- Inosine to stimulate sprouting in chronic spinal cord injury (BLSI, MGH)
- Schwann cell autografts (Yale & Miami Project)
- Stem cell transplants
  - Bone marrow stem cells (mesenchymal stromal cells)
  - Umbilical cord blood stem cell transplants
  - Genetically modified stem cell autografts (BDNF & NT-3)
- Chondroitinase (London, China)
- Rolipram & dibutyryl cAMP combined with cell transplants

Recent Therapeutic Advances

- Embryonic stem cell (ESC)
  - Transplanted ESCs will produce motoneurons in the spinal cord (Harper, et al. 2004; Wisconsin, 2005)
- Nogo receptor blockers
  - Nogo receptor protein & blockade (Strittmatter, et al., 2004)
- Chondroitinase
  - Chondroitinase stimulates spinal cord regeneration and improve functional recovery
- Eph receptors
  - EpH receptor blockade stimulates regeneration in rats
- Glial derived neurotrophic factor
  - GDNF is neuroprotective and improved functional recovery in rats
- Combination Therapies
  - Embryonic stem cell transplants combined with dibutyryl cAMP or rho kinase inhibitors produce motoneurons that send axons out the ventral roots (Harper, et al., 2004)
  - Schwann cells combined with dibutyryl cAMP and rolipram (Bunge, et al.)
  - Schwann cells combined with chondroitinase and GDNF (Xu, 2003)
  - Schwann cell transplants and combination neurotrophins, I.e. BDNF, NGF, NT-3 (Xu, 2002)
  - Chondroitinase and lithium combination better than either alone (Wu, et al, 2004).
  - Neural stem cells and L1 cell adhesion molecule (Grumet, et al., 2004)

Generations of Therapies

- **First Generation Therapies**
  - 4-Aminopyridine (Acorda)
  - Growth stimulators
    - GM1 (Fidia)
    - AIT-082 (Neotherapeutics)
    - Electrical currents (Purdue)
  - Cell transplants
    - Fetal cells (UFG)
    - Macrophages (Proneuron)
    - Porcine stem cells (Diacrin)
    - Human fetal stem cell
    - Peripheral nerve grafts
  - Locomotor training
    - Supported ambulation treadmill training (UCLA)
    - Locomotor FES (Arizona)
- **Second Generation Therapies**
  - Antibody therapies
    - Humanized IN-1 (Novartis)
    - M1 antibody (Acorda)
    - Copolymer Calpaxone (Teva)
  - Growth factors
    - Neurotrophins (Regeneron)
    - Inosine (BLSI)
    - Rollipram (PD-4 inhibitor)
  - Cell Transplants
    - Olfactory ensheathing glia
    - Bone marrow stem cells
    - Human neural stem cells
    - Human embryonic stem cells
    - Genetically modified stem cells
    - Umbilical cord blood stem cells

Third Generation Therapies

- Combination therapies
  - Regeneration
    - Bridging the gap
    - Growth factors
    - Overcoming inhibition
    - Guiding axons to target
  - Remyelination
    - Stimulating remyelination
    - Schwann, OEG, O2A, stem cell transplants
  - Restoration
    - 4-aminopyridine
    - Biofeedback therapy
    - Forced use therapy
- Not imagined in 1995
  - Regenerative and remyelinative vaccines
  - Stem cells
    - Neuronal replacement
    - Reversing atrophy
    - Replacing motoneurons
    - Intravenous administration of cells
  - Guiding axons
    - Cellular adhesion molecules (L1 and EpH)
    - Radial cells and olfactory ensheathing glial to guide growing axons

New Scientific Trends

- High-volume Screening
  - High-volume drug screening methods
  - Better tissue culture and animal models
- Gene Expression Studies
  - Surrogate measures for regeneration (RAGs)
  - Genetically modified stem cells to deliver growth factors and genes to the spinal cord
- Recombinant Molecular and Gene Therapies
  - Ex vivo and in vivo gene therapy
  - Non-viral vectors for gene delivery
- Immunotherapies
  - Activated macrophage and t-lymphocytes
  - Therapeutic vaccines to stimulate endogenous antibody production

Preparing for Recovery

- Avoid irreversible surgeries
  - Dorsal root rhizotomy
  - Ileal conduits
  - Peripheral nerve bridges
- Prevent muscle, bone, and neural atrophy
  - Don’t eliminate spasticity
  - Standing exercises to put stress on bones
  - Use neuronal circuits

- Reversing learned non-use and atrophy
  - Physical therapy
  - Fampridine
  - Standing frame
  - Vibration platform
  - Forced use training paradigms
  - Functional electrical stimulation
  - Biofeedback therapy
  - Exercise programs

Restoring Function

- "Complete" is not complete
  - Transection of the cord is a rare phenomenon
  - <10% of axons can support substantial functional recovery
  - Even "complete" injuries recover some function
- Surviving axons need to be myelinated
  - 4-aminopyridine improves conduction
  - Stem and other cells remyelinate spinal axons
- Reversing learned "non-use"
  - Even a short period of non-use can turn off circuits
  - Intensive "forced-use" exercise to restore function

Cell Loss and Replacement

- Cell Loss
  - Primary Cell Loss
  - Secondary Necrosis
    - Central hemorrhagic necrosis
    - Wallerian degeneration
  - Apoptosis
    - Neuronal apoptosis in gray matter at 48 hours
    - Oligodendroglial apoptosis at 2 weeks
  - Cystic degeneration
    - Syringomyelia
    - Chronic myelopathy
  - Muscle Atrophy
- Treating Cell Loss
  - Endogenous stem cells
    - Ependymal cells = stem cells of the spinal cord
    - Ependymal scaffolding support axonal growth
  - Cell Replacement Therapies
    - Embryonic stem cells
    - NRPs and GRPs
    - Intrathecal stem cell
    - Systemic stem cell
    - Fetal neuronal or stem cell transplants into muscle to prevent atrophy

Solutions

- More spinal cord injury research
- Systematic preclinical testing of promising therapies
- Spinal cord injury clinical trials in the United States
- Diverse and abundant source of transplantable stem cells
- Genetically modified stem cells optimized for specific conditions
- Combination therapies

- Programs at Rutgers
  - Teach laboratories to carry out spinal cord injury research
  - Provide tools for improving spinal cord injury research
  - SCICure & NGEL databases
  - Standardized cell transplant therapies
  - Annual symposia for scientists and clinicians
  - China SCI Network
  - North America SCI Network