Bases for Hope for Spinal Cord Injury

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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)
Injury Site

Muscle Bridging nerve

Peripheral Nerve Bridging

Transpose, bridge and reconnect proximal root to distal nerve

Ventral roots

Bridging nerve

Injury Site

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)
Remyelinating 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)
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 patients; 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)
    - Rolipram (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
  - Regeneration
  - 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