Spinal Cord Injury Therapies

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State-of-the-Art 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)

- **Promising 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-)
  - Functional regeneration of neonatal spinal cords (Kawaguchi, 1994-)
  - Neurotrophin-secreting fibroblast transplants (Tuszynski, 1994-)
Methylprednisolone

- **NASCIS 3**
  - High dose (30 mg/kg bolus followed by 5.4 mg/kg/hr • 23h iv)
    - MP vs. Placebo: 75% vs. 59% (incomplete), 21% vs. 8% (complete)
  - More effective when started within 3 hours after injury
    - 48h MP more effective than 24h MP when started >3h after injury
  - >24h therapy may be associated with more severe pneumonia

- **Mechanisms of action**
  - Anti-inflammatory (glucocorticoid receptor mediated mechanisms)
  - Immunosuppression (suppresses cytokine & antibody production)
  - Anti-oxidant & lipid peroxidation inhibitor (high dose only)

- **Cellular effects**
  - Reduces necrosis and edema
  - Suppresses pro-inflammatory gene expression
  - Prevents apoptosis in white matter
Surgical Therapies (1995+)

- Stabilization & decompression
  - Stabilization
    - Anterior and posterior plates
    - Titanium cage & other vertebral fusion methods
  - Delayed decompression restore function (Bohlman)
  - Untethering spinal cord improves function
  - Adcon gel and other methods to prevent epidural scarring
- Urological procedures
  - Suprapubic catheterization & ileal conduits (Mitrafanoff)
  - Stents and artificial sphincters for bladder and bowel
- Syringomyelic cysts
  - Remove subdural adhesions
  - Restoring CSF flow
  - Dural grafts
- Peripheral nerve bridging
  - Implanting avulsed roots or nerves into cord for
    - Muscle reinnervation
    - Reduce neuropathic pain
    - Bladder reinnervation
  - Peripheral nerve bridging
    - Bridging spinal accessory, intercostal, and ulnar nerves to phrenic, sciatic, pudendal, and other peripheral nerves
    - End-to-side anastomoses
Drug Therapies (1995>)

- **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 of motor and sensory function on 4-AP
Rehabilitative Therapies
(1995>)

- **Bladder Function**
  - Urodynamic studies
  - Intravesicular instillation
    - Ditropan
    - Capsaicin

- **Neuropathic Pain Therapies**
  - Antidepressants
    - Amitryptiline (Elavil)
  - Anti-epileptic analgesics
    - High dose Neurontin (Gabapentin)
  - Glutamate receptor blockers
    - Ketamine
    - Dextromethorphan
  - Cannabinoids

- **Functional electrical stimulation**
  - Implanted hand muscle stimulation (Freehand)
  - FES stimulators
  - Leg/walking stimulators (Parastep)
  - FES exercise devices

- **Reversing learned non-use**
  - Forced-use training
  - Biofeedback therapy
  - Supported treadmill ambulation training
  - Robotic exercisers
Regenerative Therapies
(1995>)

- Axonal growth inhibitor blockade
  - Nogo receptor blockers (Strittmatter, 2001-)
  - Chondroitinase (Bradbury, 2002)
  - C3 rho inhibitor (McKerracher, 2001)

- Purine nucleotides
  - Inosine (Benowitz, et al. 1999)
  - AIT-082 (Neotherapeutics)
  - Adenosine (Chao, et al., 2000)

- Therapeutic vaccines
  - Spinal cord homogenate vaccine (David, et al., 1999)
  - Myelin-basic protein & copaxone (Schwartz, 2001)

- Cell Transplants
  - Activated macrophages (Schwartz, et al. 1998)
  - Olfactory ensheathing glia (Ramos-Cuetos, 2000)
  - Nasal mucosa (Lu, et al. 2002)

- Electrical stimulation
  - AC electrical currents stimulates axonal growth and orients glia (Borgens, et al. 1997)

- Growth stimulators
  - Nerve bridge & growth factor cocktail (Cheng & Olson, 1996)
  - cAMP & Rolipram (Filbin, 2001)
  - L1 (Roonprapunt, et al., 2002)
  - Combination neurotrophins NGF+BDNF+NT3 (Xu, 2001)
Remyelinative Therapies (1995+)

- Schwann cells
  - Schwann cell invasion into the injury site (Blakemore, 1990)
  - Schwann cell transplants (Vollmer, 1997)
  - Peripheral nerve transplants (Kao)

- Oligodendroglial cells
  - 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)
  - Transplanted OEG cells remyelinate axons in the spinal cord (Kocsis, et al. 1999)

- Antibody remyelination therapies
  - M1 antibody stimulates remyelination (Rodriguez, 1996-)
  - Copaxone (copolymer 2) improved recovery in rats (Schwartz, et al. 2001)
Current Clinical Trials

- Fetal spinal cord transplants to treat progressive syringomyelia
  - Gainesville Florida, Rush Presbyterian Chicago, Karolinska in Sweden, Moscow, Novosibirsk, and China
- 4-aminopyridine for chronic SCI
  - Acorda: Phase 3 trial in 82 U.S. & Canadian SCI Centers
- Activated macrophage transplants for subacute SCI
  - Proneuron: Tel Aviv, Erasmus Hospital (Brussels), Craig Hospital (Denver)
- Porcine neural stem cell transplants for chronic SCI
  - Diacrin: Albany Med. Center and Washington University in St. Louis
- Alternating current electrical stimulation for subacute SCI
  - Purdue University in Indiana
- AIT-082 (Neotrofin) therapy of subacute spinal cord injury
  - Neotherapeutics: Ranchos Los Amigos, Gaylord, Craig, Thomas Jefferson
- Olfactory ensheathing glial (OEG) transplants
  - Brisbane & Lisbon (nasal mucosa), Beijing (fetal OEG)
Olfactory ensheathing glia

- Fetal OEG cells
  - Bipolar (migrating)
  - Multipolar (directing)
  - “Fried egg” (ensheathing)

- Markers
  - Laminin
  - L1 CAM
  - Nestin
  - GFAP
  - P75 (NGF receptor)
Other Clinical Studies

- Supported treadmill ambulation training to reverse learned non-use
- Spinal cord L2 stimulation to activate locomotor generator
  - Hermann in Tucson and Dimitrijevic in Vienna
- Experimental surgical approaches
  - Omentum transplants (U.S., Cuba, China, and Italy)
  - Nerve bridging of spinal cord (University of Sao Paulo)
  - Fetal stem cell transplants (Moscow, Novosibirsk, Beijing)
  - Peripheral nerve bridging to spinal cord (Brunelli in Brescia)
  - Peripheral nerve bridging to bladder and muscle (Zhang in Shanghai)
  - Bridging spinal cord injury site with peripheral nerves & growth factor cocktail (Cheng in Taiwan)
  - Untethering, peripheral nerve transplants, omentum transplant, hyperbaric oxygen, and 4-aminopyridine (Carl Kao in Ecuador)
  - Shark embryonic transplants (Tijuana)
Upcoming Clinical Trials

- IN-1 antibody to regenerate axons in chronic SCI
  - Novartis (Schwab at University of Zurich)
- M1 antibody to remyelinate spinal cord
  - Acorda (Mayo Clinic)
- Inosine to stimulating sprouting in chronic spinal cord injury
  - BLSI (Massachusetts General Hospital)
- Olfactory ensheathing glia (OEG) transplants
  - Porcine OEG (Alexion, Yale University)
  - OEG autograft (Madrid, Miami Project)
- Schwann cell transplants
  - Schwann cell autograft for MS (Yale University) & SCI (Miami Project)
- Adult stem cell transplants
  - Autografts (adult stem cells from bone marrow, fat cells)
- Chondrotinase ABC
  - Enzyme to break down chondroitin 6-sulfate proteoglycans (Seikagaku, Japan)
Generations of SCI Therapies

First Generation Therapies

- 4-Aminopyridine (Acorda)
- Growth stimulators
  - GM1 (Fidia)
  - AIT-082 (Neotherapeutics)
  - AC electrical currents (Purdue)
- Cell transplants
  - Fetal spinal cord transplants (UFG)
  - Macrophages (Proneuron)
  - Porcine fetal stem cells (Diacrin)
  - Human fetal stem cells (Russia, China)
  - Peripheral nerve grafts (Taiwan)
  - Olfactory ensheathing glia (Beijing)
  - Nasal mucosa autografts (Lisbon, Brisbane)
  - Neurotrophin-secreting fibroblasts (UCSD)
- Locomotor training
  - Supported ambulation treadmill training (Bonn, Zurich, UCLA, etc)
  - Locomotor FES (Arizona, Vienna)

Second Generation Therapies

- Immune therapies
  - M1 antibody (Acorda)
  - Copolymer Copaxone (Teva)
- Anti-growth inhibition therapies
  - Humanized IN-1 (Novartis)
  - Rollipram (PDE-4 inhibitor)
  - C3 Rho Kinase inhibitor (BioAxone)
  - Chondroitinase ABC (Seigaku)
  - Nogo receptor blocker (Biogen)
- Growth factors
  - Neurotrophins (Regeneron)
  - Inosine (BLSI)
  - Neuregulins (CENES)
- Cell Transplants
  - Adult olfactory ensheathing glia
  - Bone marrow stem cells
  - Human neural stem cells
  - Genetically modified stem cells
  - Enteric glial stem cells
Third Generation Treatments

- Combination therapies
  - Regeneration
    - Bridging the injury site
    - Growth factors
    - Overcoming inhibition
    - Guiding axons to target
  - Remyelination
    - Stimulating remyelination
    - Remyelinating with Schwann, OEG, O2A, stem cells
  - Restoration
    - 4-aminopyridine
    - Biofeedback therapy
    - Forced use therapy
    - Activity induced plasticity

- Almost beyond imagination
  - Vaccine
    - Regenerative vaccines
    - Neuroprotective vaccines
    - Remyelinitive vaccines
  - Stem cells
    - Neuronal replacement
    - Reversing atrophy
    - Replacing motoneurons
  - Guiding axons
    - Gene therapy to express guidance molecules
    - Cell adhesion molecules direct axonal growth
    - Use of ephrins to control axonal pruning
Preparing for Recovery

- Avoid irreversible surgical procedures
  - Dorsal root rhizotomies
  - Peripheral nerve bridges
  - Tendon transfers
  - Omentum transfers
- Prevent muscle, bone, and neuronal atrophy
  - Don’t eliminate spasticity
  - Standing exercises to put stress on bones
  - Functional electrical stimulation (FES) to build muscle
  - Stem cell implants to muscle and spinal cord
- Relieve causes of continuing spinal cord damage
  - Decompression
  - Reduce syringomyelia
  - Untethering of cord
- Reverse learned non-use
  - Physical therapy
  - Activity-induced activity
    - Overground ambulation
    - Weight supported treadmill ambulation training
  - Biofeedback therapy
  - L2 locomotor generator stimulation

Prevent muscle, bone, and neuronal atrophy
Restorative Principles

- “Complete” is not complete
  - Severance or transections of the cord are very rare
  - <10% of axons can support substantial function, adding 5-10% sufficient
- Accelerating and extending recovery processes
  - Continued recovery in chronic SCI over many years
  - Spontaneous regeneration may occur in some people
- Surviving axons need to be myelinated
  - 4-aminopyridine improves conduction
  - Cell transplantation to remyelinate spinal axons
- Spinal cord capable of remarkable “plasticity”
  - Detailed specificity of reconnection is not necessary
  - Local sprouting can restore functions across the midline
- Reversing learned “non-use”
  - Even a short period of non-use can turn off circuits
  - Intensive “forced-use” exercise can restore function
Emerging Trends

- High-volume drug screening
  - Systematic drug design
  - Better tissue culture models
  - More efficient animal models

- Gene expression studies
  - Identification of endogenous repair & regenerative factors
  - Use of gene expression as an outcome measure for assess therapeutic effects

- Endogenous stem cells
  - The genes responsible for converting any cell into stem cells
  - Drugs to stimulate endogenous stem cells to proliferate and to go into reparative mode

- Immunotherapies
  - Some evidence indicates that immune cells (macrophages and lymphocytes) are reparative
  - Therapeutic vaccines to stimulate antibody production
  - Use of cytokines (i.e. IL-6) to stimulate repair and regeneration

- Molecular and Gene Therapies
  - Ex vivo gene therapies
    - Genetically modified progenitor or stem cells
    - Stem cells and lymphocytes seem to know where to go
  - In vivo gene therapy
    - Viral vectors
    - Non-viral vectors for gene delivery
Novel Remyelination Strategies

- **Cell transplantation**
  - Schwann cells
  - Oligodendroglia precursor
    - O2A cells remyelinate axons
    - Stem cells produce O2A
  - Olfactory ensheathing glia
    - Adult autograft
    - Fetal heterografts
    - Nasal mucosa
  - Stem cell transplants
    - Embryonic stem cells
    - Fetal stem cells (neural, umbilical cord blood)
    - Adult stem cells (bone marrow, neural, & skin)

- **Stimulation of remyelination**
  - M1 antibodies
    - Germ cell line IgM kappa auto-antibody that stimulate oligodendroglia to proliferate and to myelinate axons
    - IgM kappa antibodies may act as signaling molecules
    - M1 belongs in the same class of molecules as IN-1, the antibody that binds Nogo
  - Neuregulins
    - Neuregulin regulates neural precursor growth and the oligodendrocyte conversion
Progenitor Cells

Neurosphere

Nestin stain  BRDU stain
Cell Loss and Replacement

Cell Loss
- Primary Cell Loss
- Secondary Necrosis
  - Central hemorrhagic necrosis leaves rim of white matter
  - Wallerian degeneration
- Apoptosis
  - Neuronal apoptosis in gray matter at 48 hours
  - Oligodendroglial apoptosis in white matter at 2 weeks
- Cystic degeneration
  - Syringomyelia
  - Chronic myelopathy
- Muscle Atrophy

Replacing lost cells
- 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 transplants into muscle to prevent atrophy
- Stem cell therapies to reverse muscle atrophy
Each clinical trial has a limited probability of success.

To increase odds of clinical trial success, we must:
- Do systematic preclinical studies to establish and optimize therapies for clinical trials.
- Create a spinal cord injury clinical trial network.
- Randomize a larger percent of SCI patients to the best experimental therapies in comparison with best standard therapies.

The Program at Rutgers:
- Establish and disseminate well-standardized models & outcome measures.
- Sharing databases:
  - SCICure Consortium to share spinal cord injury data.
  - NGEL gene chip to share gene expression data.
- Standardized cell transplant (stem cells, precursor cells, olfactory ensheathing glia).
- Training workshops.
- Annual SCI clinical trial symposia for scientists and clinicians.