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Stem Cells to Clinical Trials

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Santina Muha, Moderator

Special Thanks to:

- The Central Jersey Spinal Cord Association
- Dr. Wise Young
- The W.M. Keck Center for Collaborative Neuroscience
- The Spinal Cord Injury Project
- Patricia Morton & Jim Bennet
- Santina Muha

Please Fill the Survey

- Thisabled is asking participants to assist one of our partners by filling out a survey on SCI at: http://member.assistyourteamsurveys.com/aytsreg.aspx?AID=217.
- $10.00 will go to the Central Jersey Spinal Cord Association for every survey which is completed.

The Present Situation

- We collect stem cells from blood, bone marrow, aborted fetuses, fertilized eggs, and other sources.
- Cell transplants are either autografts (from a person to self) or matched (HLA) with recipients.
- Only blood and bone marrow cells are available in sufficient diversity for matching HLA
- We don’t have reliable methods of growing large quantities of cells from blood or bone marrow.
- Stem cells are still classified by developmental stage and source, rather than what they are and do.

Current Business Models

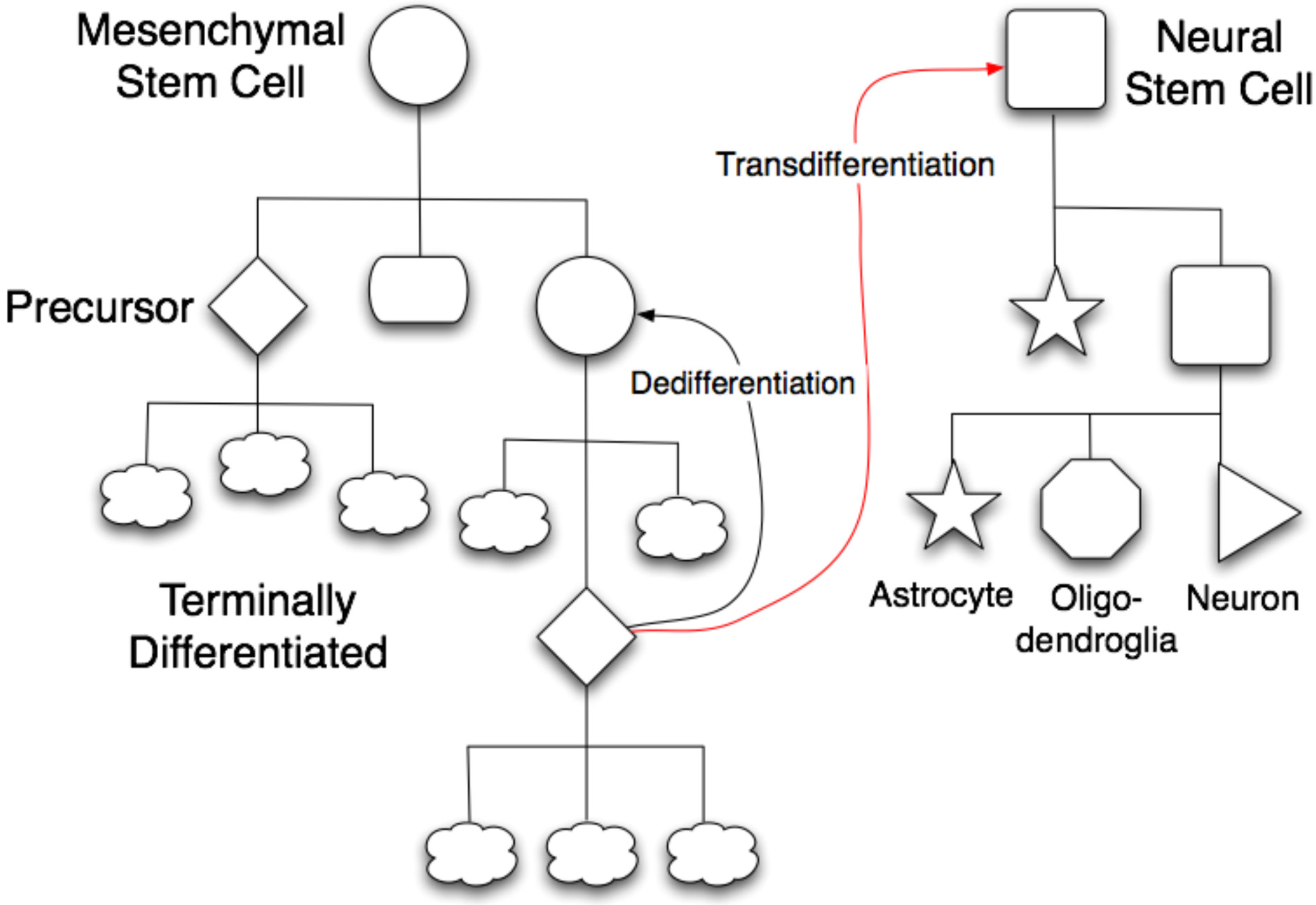
- Blood banks collect voluntarily donated blood. They test, store, match, and ship blood cells.
- In vitro fertilization clinics are repositories of fertilized eggs and blastocysts from parents.
- Private cord blood banks store umbilical cord blood cells for babies who might need them in the future.
- Public cord blood banks store umbilical cord blood to provide HLA-matched cells for patients.
- Bone marrow registries provide a database to match “walking donors” with potential recipients.

Future Business Models

- Universal stem cells. Create a population of immune-tolerized babies by *in utero* vaccination to a optimized "universal" stem cell line.
- Universal stem cell library. Develop 2000-3000 cell lines that can match HLA antigens of 90% of a given population.
- Personalized stem cell service. Provide some cell samples and come back several weeks later for a unit of your own stem cells.

Stem Cell Definition

- Old Definition: Undifferentiated pluripotent cells (able to produce many kinds of cells).
- Stem cells: Pluripotent cells that can replicate themselves.
- Progenitor cells. Multipotent cells that do not replicate themselves.
- Precursor cells. Cells that differentiate into or make a few other related cells but not themselves.
- Emerging concept that stem cells are the only cells that can replicate themselves.


Mesenchymal
Stem Cell
Precursor
Terminally
Differentiated
Dedifferentiation
Transdifferentiation
Neural
Stem Cell
Astrocyte
Oligo-
dendroglia
Neuron

Dedifferentiation

- Differentiation has long been believed to be a one-way street. The dogma is that once cells have differentiated, they cannot “dedifferentiate”.
- Scientists have long known that dediffentiation can occur. For example, Dolly the sheep was “cloned” by dedifferentiation of a breast cell nucleus.
- Dedifferentiation suggests a process by which a differentiated cell can revert to an earlier stage, all the way back to stem cells or even an egg.

Transdifferentiation

- Transdifferentiation is the process where one type of cell makes cells of another type, i.e. a bone marrow cell makes neurons.
- Many scientists consider transdifferentiation to be impossible, e.g. once a cell has differentiated into mesenchymal, it cannot make neural cells.
- Transdifferentiation would imply that a differentiated cell can produce differentiated cells of another type without first dedifferentiating to a stem cell.

Sources of Stem Cells

- Embryonic stem cells
- Fetals stem cells
  - neural stem cells
  - hematopoietic stem cells
- Neonatal stem cells
  - umbilical cord (Wharton's, lining)
  - umbilical cord blood
  - placenta
- Adult stem cells
  - hematopoieitic
    - bone marrow
    - peripheral blood
  - neural
    - hippocampus
    - subventricular
    - olfactory bulb
  - mesenchymal
  - endodermal
    - enteric glia

Embryonic Stem Cells

- Embryonic stem cells are pluripotent cells derived from the inner cell mass of blastocysts,.
- They are not “embryonic”. A blastocyst becomes an embryo after it develops a midline (primitive streak) and implants in the uterus.
- They can also be made from germ cells, by fusing with somatic cells, or by genetic induction.
- Embryonic stem cells can produce all cells of the body except for the placenta and amnion.

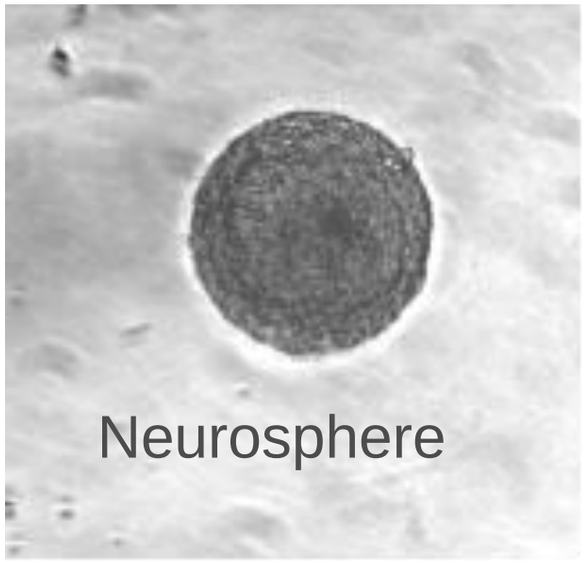
Stem Cell Mythology

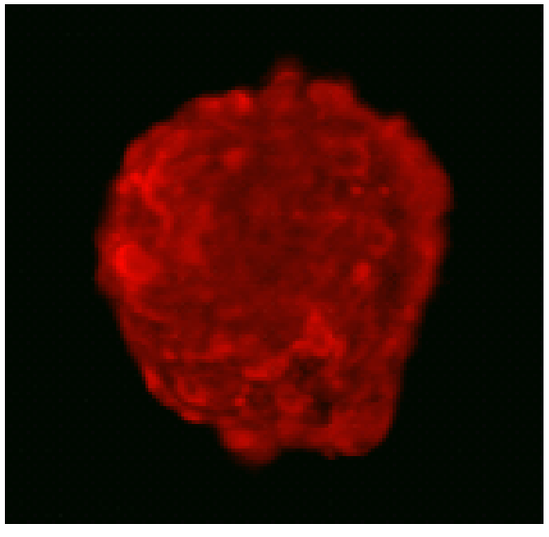
- Myth 1. Embryonic stem cells are easy to grow. They are difficult and very laborious to grow, requiring a full-time technician to maintain a line.
- Myth 2. Embryonic stem cell lines are similar. Every stem cell line turns out to be very different both in growth requirements and pluripotency.
- Myth 3. Embryonic stem cells produce all cells. They readily produce neural and mesenchymal stem cells in vitro but less readily to others.

Neural Stem Cells

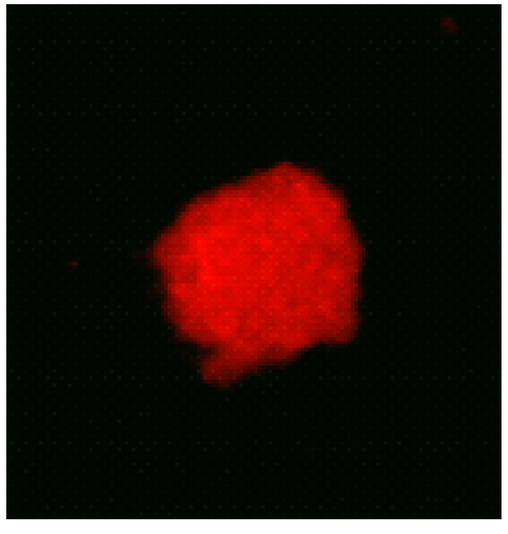
- Neural stem cells (NSC) are the first cells that embryonic stem cells produce in development. They are the “default” cell type.
- NSC make cells of the brain, including neurons, astrocytes, oligodendroglia, and microglia. They are present in brain, in the subventricular zone.
- Neural progenitors are the easiest of all stem cells to grow. They don’t need serum or feeder cells. All they need is FGF and culture medium.

Progenitor Cells

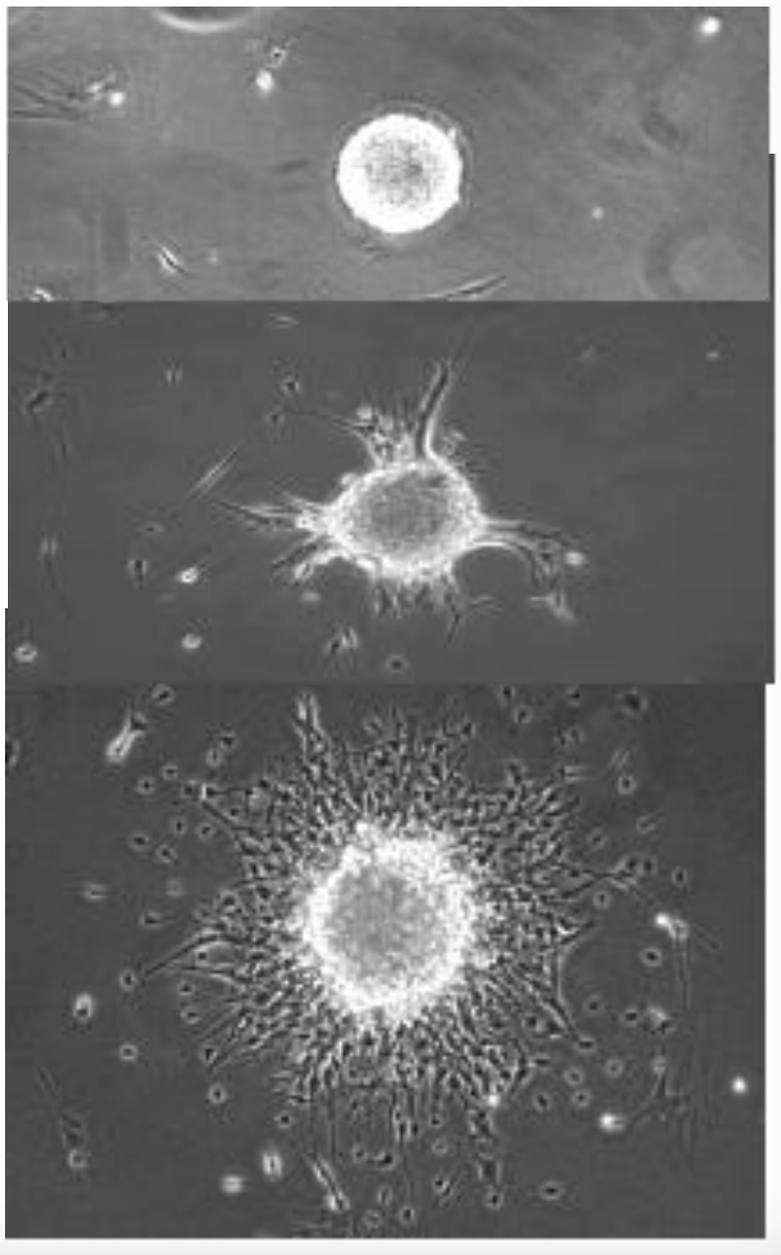




Nestin stain



BRDU stain



Mesenchymal Stem Cells

- Mesenchymal stem cells (MSC) are mesodermal in origin and form blood, bone, and muscle.
- MSC's are present in bone marrow and form all the blood cells, myoblasts, and osteoblasts.
- They can be stimulated by hormones and drugs to proliferate (GM-CSF, lithium).
- MSC's can be isolated and grown in culture from bone marrow, cord blood, and umbilical cord (Wharton's jelly).

Endodermal Stem Cells

- Endodermal cells form the yolk sac and give rise to the epithelium of the alimentary and respiratory tracts, as well as parenchyma of associated glands.
- They interact with mesodermal stem cells to form many of the internal organs (pancreas, liver, gut, gall bladder, adrenal glands, and mesenteric plexus).
- Our intestines have large numbers of stem cells. These include cells called enteric glia that make neurons and can myelinate axons.

Stem Cell Gene Therapy

- Most people think of stem cells only from the viewpoint of cell replacement therapies.
- Stem cells are well suited for gene delivery for the following reasons:
  - Transplants allow local delivery of gene products
  - The genetic manipulation can be done ex-vivo.
  - Delivery is sustained because the cells renew.
  - The cells can be programmed suicide when done.
- No gene therapy has yet been approved because viruses are not trusted as a delivery vehicle.

Stem Cell Nitches

- Stem cells are the most regulated cells of the body and for good reason. One cannot have pluripotent cells wandering our body.
- In adults, stem cells must fit into a “nitch” that tell them how much and what cells to produce. This is the only way they can make more cells.
- The cells must express appropriate antigens for immune rejection in order to prevent cancer development after transplantation.

Cancer Stem Cells

- Cancer stem cells. Only stem and cancer cells reproduce themselves, giving rise to the concept of cancer stem cells.
- Tumors have cell-nitches that tell stem cells to produce tumor cells. If so, this explains why most chemotherapies destroy stem cells.
- A therapeutic target for cancer. We can treat solid tumors by disrupting communications between tumor nitches and stem cells.

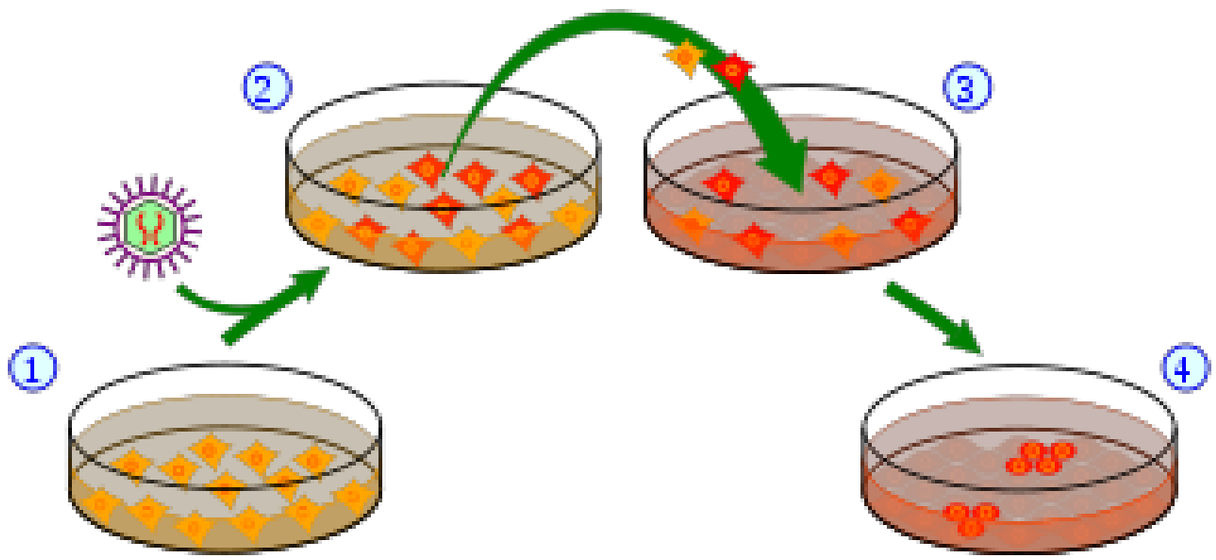
Endogenous Stem Cells

- Endogenous stem cells. There are substantial numbers of pluripotent stem cells present in adults. Why not stimulate endogenous stem cells instead of transplanting additional cells?
- Can endogenous stem cells be stimulated to proliferate and produce more stem cells? Several drugs are already known to do so:
  - GM-CSF is known to stimulate bone marrow.
  - Lithium stimulates many types of stem cells.
  - Stress and inflammatory interleukins also do so.

Immune Compatibility

- Autografts. One's own cells are obviously the most immune-compatible cells. However, autografts may not be desirable for treatment of genetic diseases.
- Popular HLA antigens. Identify cells with the most popular HLA antigens to create a library of cell lines that matches 80-90% of a population.
- Induced pluripotent stem cells. Recent studies indicate that one can make pluripotent stem cells by transfecting as few as four genes into skin cells.

Induced Pluripotent Cells



Inducting pluripotent stem cells. (1) culture differentiated somatic cells, (2) transfect with Oct3/4, Sox2, Klf4, and c-Myc, (3) grow cells on mitotically inactivated feeder cells, (4) the cells go on to make pluripotent stem cells.

A Paradigm Shift?

- Thomas Kuhn described science as periods of relative stability punctuated by revolutions that he calls “paradigm shifts”.
- We are in the midst of a biological paradigm shift that is as or more profound than transition from Newtonian physics to Einsteinein relativity.
- Stem cells have not only overturned every major assumption that we have in cell biology and some dogmas that we did not even realize were dogmas.

Dogmas Overturned

- We were born with neurons that we die with.
  - New neurons are being born throughout adult life.
- Cells do not dedifferentiate or transdifferentiate.
  - A somatic nucleus can de-differentiate to an egg.
  - Bone marrow and neural stem cells are multipotent.
- Cells are independent entities.
  - Stem cells tend to fuse with other cells.
- Cells usually replicate themselves.
  - Only stem cells routinely replicate themselves.
  - Self-replication is the exception rather than the rule.

The Future of Stem Cells

- Future stem cell therapeutics will be different from the current approach of harvesting, storing, and matching cells for transplantation.
- No stem cell source today can meet clinical demand, if any stem cell therapy is shown to be effective for any major disease or condition.
- It would be a moral catastrophe. What do we do when we discover the cure for Alzheimer's disease but do not have enough cells to cure 1% of people?

Conclusions

- The Present
  - Harvest, bank, and transplant. Limited sources of pluripotent cells. Embryonic stem cell, difficult regulatory hurdles, political interference, embryonic vs. adult stem cells, and the ethics of endless debate.
- The Future
  - Producing and cloning cells. Immune compatibility, tolerance, and privilege. Reducing tumor risk. Differentiation and progenitors. Paradigm shifts and overturned dogmas. Clinical trials.

Therapeutic Targets

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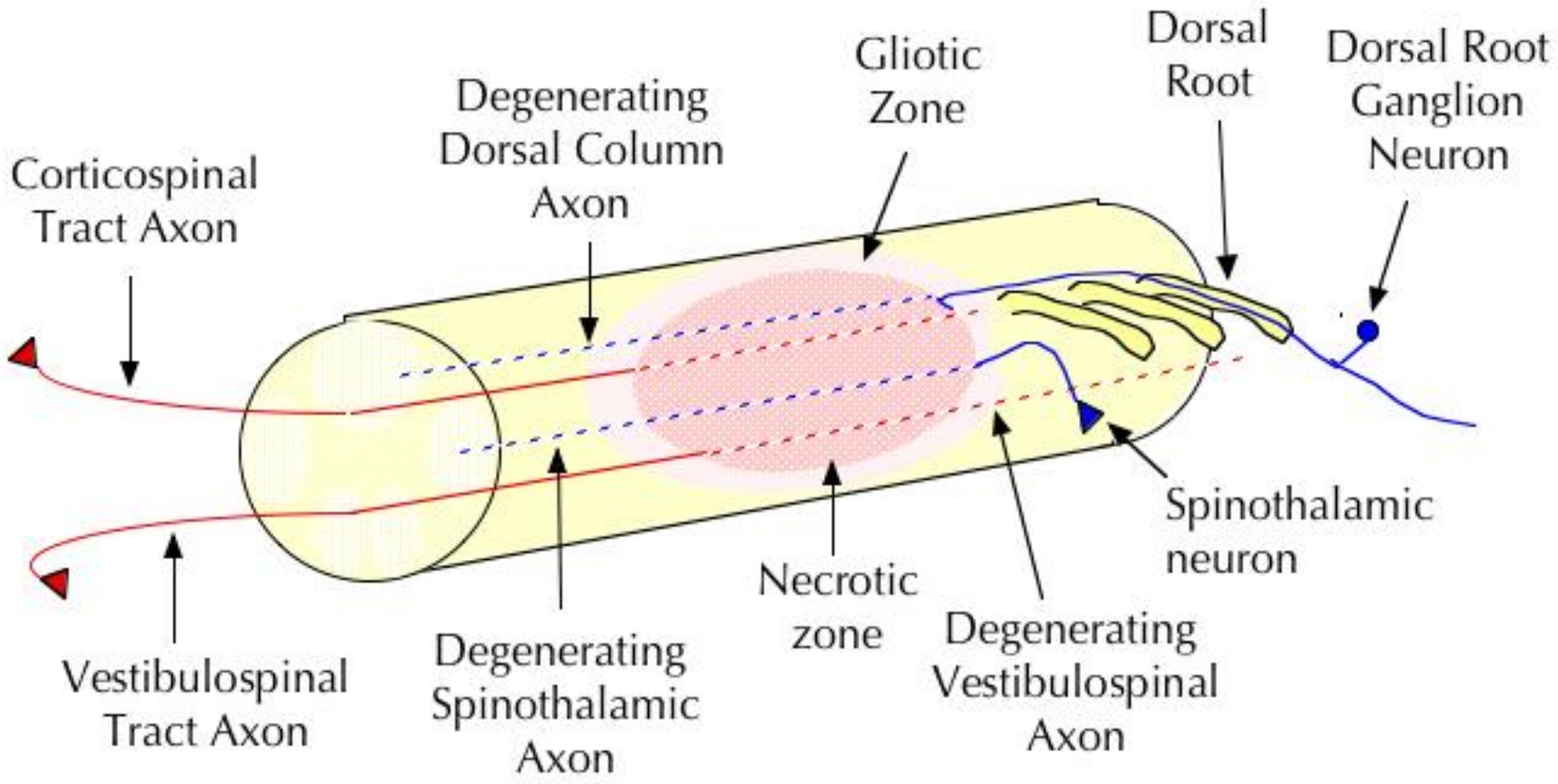
Spinal Cord Injury



Spinal Cord Injury

- Injury: contusion, compression, edema, ischemia, inflammation, calcium, free radicals.
- Repair: cytokines, stem cells, neurotrophins, gliosis, angiogenesis, blood brain barrier.
- Regeneration: regrowth, regeneration, reconnection, remyelination, restoration of function
- Recovery: reversing learned non-use, reorganization of brain and spinal cord circuitry, restoring function.

Barriers to Regeneration

- Injury site. The injury site is bereft of cell adhesion molecules and surrounded by reactive gliosis.
- Time. Axons grow no faster than hair, less than a mm per day.
- Distance. The distance of axonal growth may exceed a meter.
- Growth inhibitors. Several factors stop axon growth, i.e. Nogo, chondroitin-6-sulfate proteoglycan.

Regenerative Therapies

- Bridging the injury site. The injury site is often bereft of cell adhesion molecules and surrounded by reactive gliosis. Cells can form a bridge.
- Sustained growth support. Axonal growth takes many months and sustained growth factor support is required. Neurotrophins stimulate axon growth.
- Blocking growth inhibitors. Myelin express axonal growth inhibitor Nogo, which can be blocked by Nogo antibodies or rhok/rho blockers.

Cellular Bridges

- Cell transplants will form a living bridge across the injury site, supporting axonal growth across otherwise inhospitable terrain.
- The bridge does not have to be permanent. After the axons have grown past, the bridge can quietly disappear after several months.
- Cells injected into surrounding spinal cord will migrate into the injury site. Cells injected into the injury site form an isolated island at the injury site.

Growth Factors

- Neurotrophins stimulate axonal growth
  - nerve growth factor (NGF)
  - brain-derived neurotrophic factor (BDNF)
  - neurotrophin-3 (NT-3)
  - glia-derived neurotrophic factor (GDNF)
- The injured spinal cord produces cytokines and neurotrophins after contusion injury.
- The cytokines attract inflammatory cells and stem cells to the injury site.
- Other factors such as MIF act on CD44 to keep stem cells from migrating away.

Growth Inhibitors

- Several factors in spinal cord inhibits axon growth
  - Nogo. Located in myelin, this protein activates the nogo receptor on axons and stops growth.
  - Chondroitin-6-sulfate-proteoglycan (CSPG). This extracellular protein stops axonal growth.
  - Ephrins. These guide axon growth into dorsal or ventral cord.
- These factors explain why central nervous system does not regenerate while the peripheral nerves can. Blockade of these factors will allow regeneration.

Combination Therapy

- Bridge injury site with immune compatible cells:
  - HLA-matched cord blood mononuclear cells
  - Bone marrow mesenchymal stem cells
- Provide or stimulate growth factors
  - Lithium stimulates neurotrophin production
  - Intrathecal application of neurotrophins
- Block axon growth inhibitors (nogo, CSPG)
  - Nogo receptor protein/blocker
  - Chondroitinase

Lithium and Cord Blood Mononuclear Cell Therapy of Spinal Cord Injury

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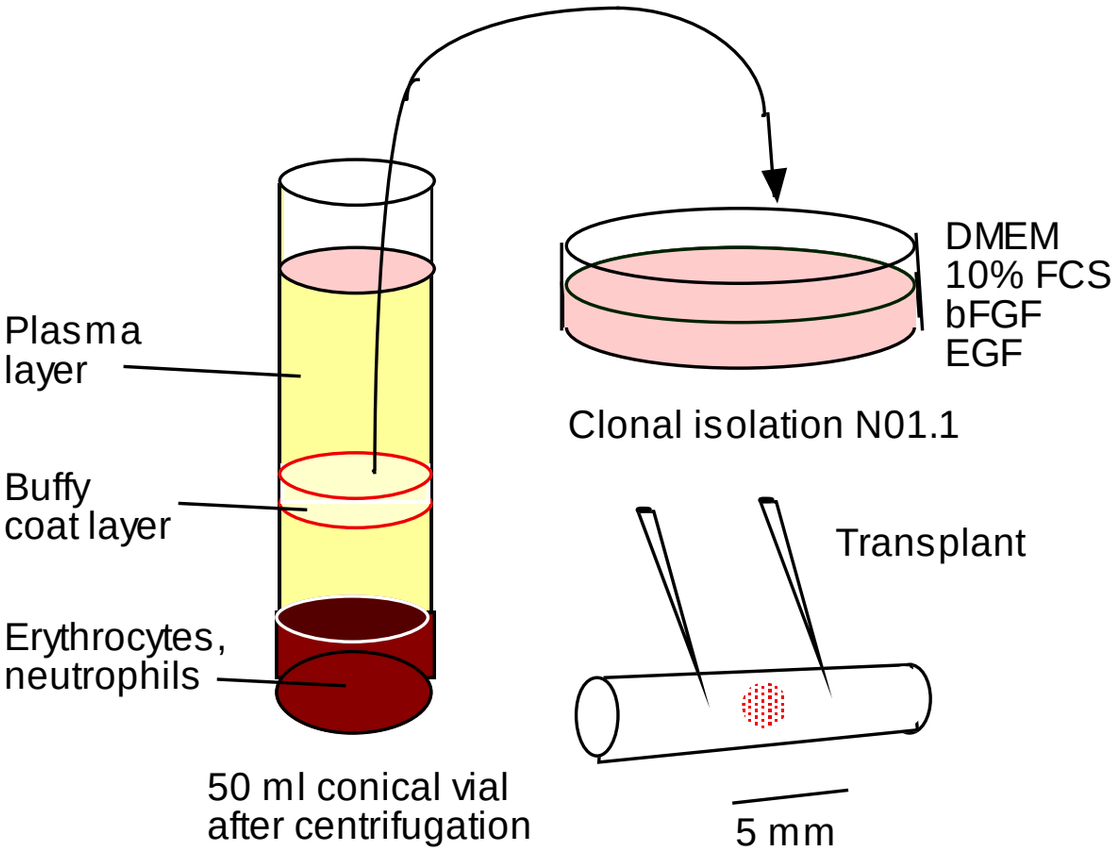
Umbilical Cord Blood (UCB)

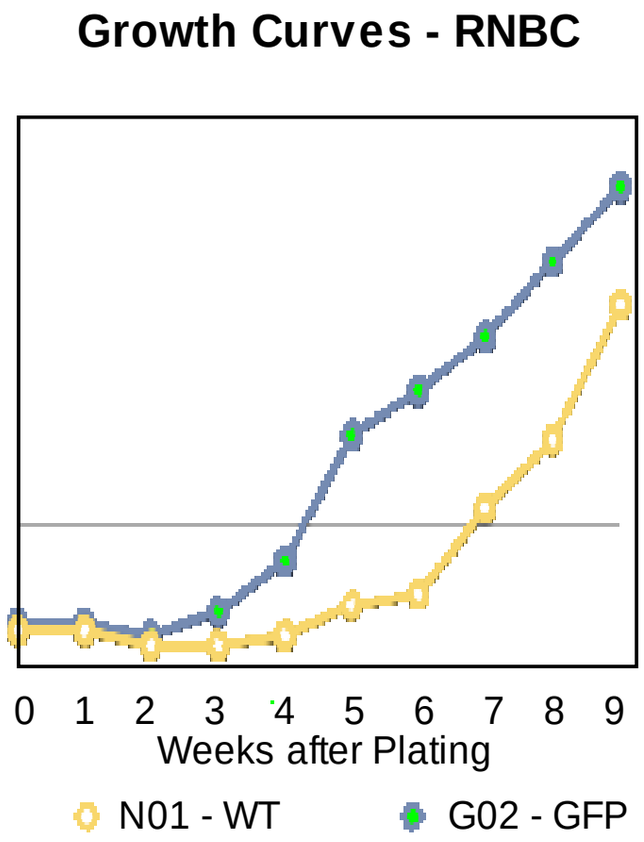
- Intravenous infusion of human UCB improves function in a rat SCI model (Saporta, et al., 2004)
- Intraspinal transplants of human CD34+ UCB cells improve recovery in hemisected rats (Li, et al., Zhao, et al, 2004)
- Intraspinal transplants of human CD34+ UCB cells plus BDNF improve recovery of spinal-injured rat (Kuh, et al. 2005)
- Human UCB CD34+ cells survive 3 weeks in contused rat spinal cords snd reduce tissue damage (Nishio, et al., 2006).
- Human UCBM mononuclear cells transplanted to contused rat spinal cords improve locomotor recovery (Dasari, et al. 2007)

UCB-treated Conditions

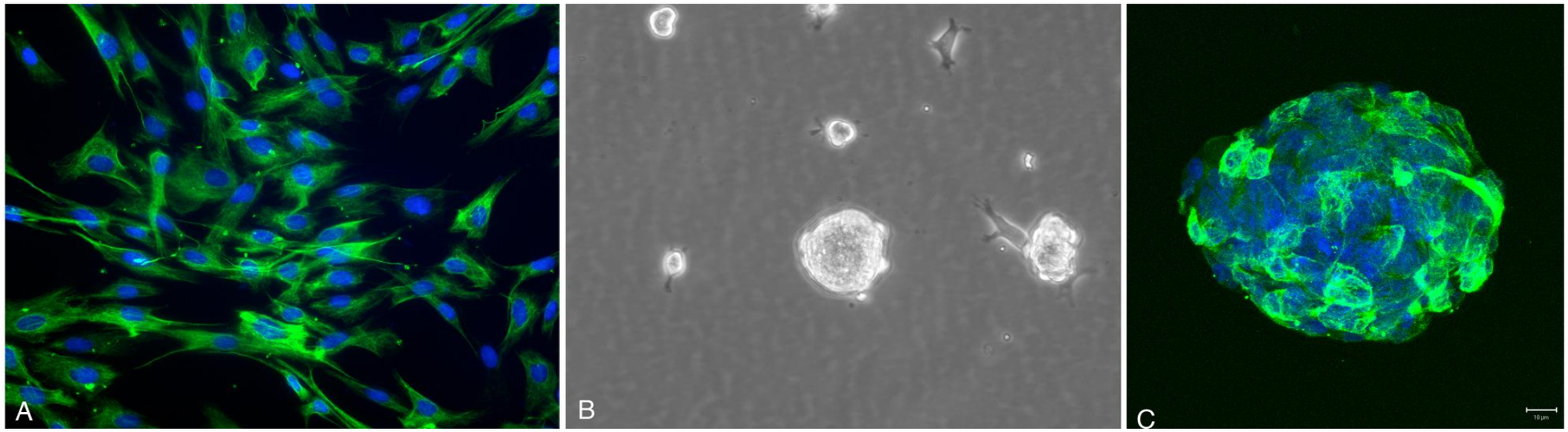
- Duchenne's muscular dystrophy (Kong, et al. 2004, Zhang, et al., 2005).
- Infantile Krabbe's disease (Escolar, et al., 2005)
- Cerebral palsy (Kurtzberg, et al., personal)
- Stroke (Lin, et al., personal).
- Autoimmune diseases.
  - Multiple sclerosis, Devic's disease
  - Systemic lupus erythematosus
  - Diabetes mellitus

Neonatal Rat Blood Culture



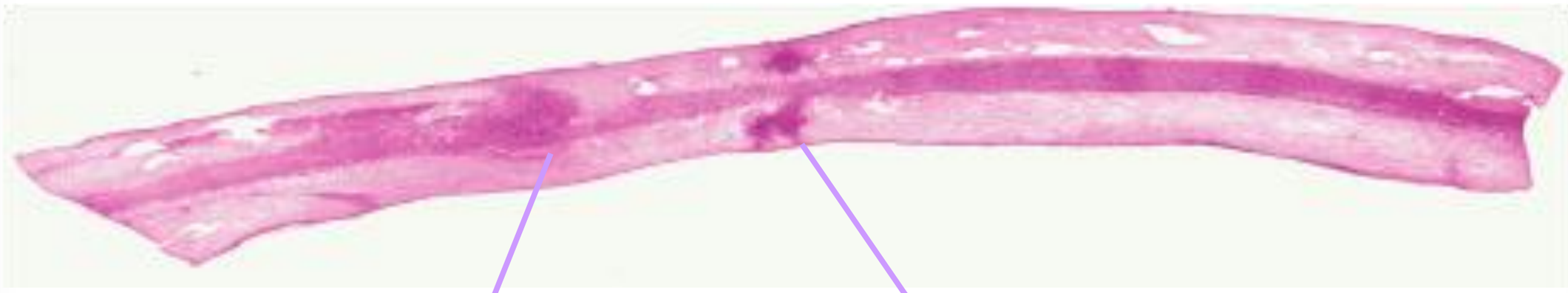


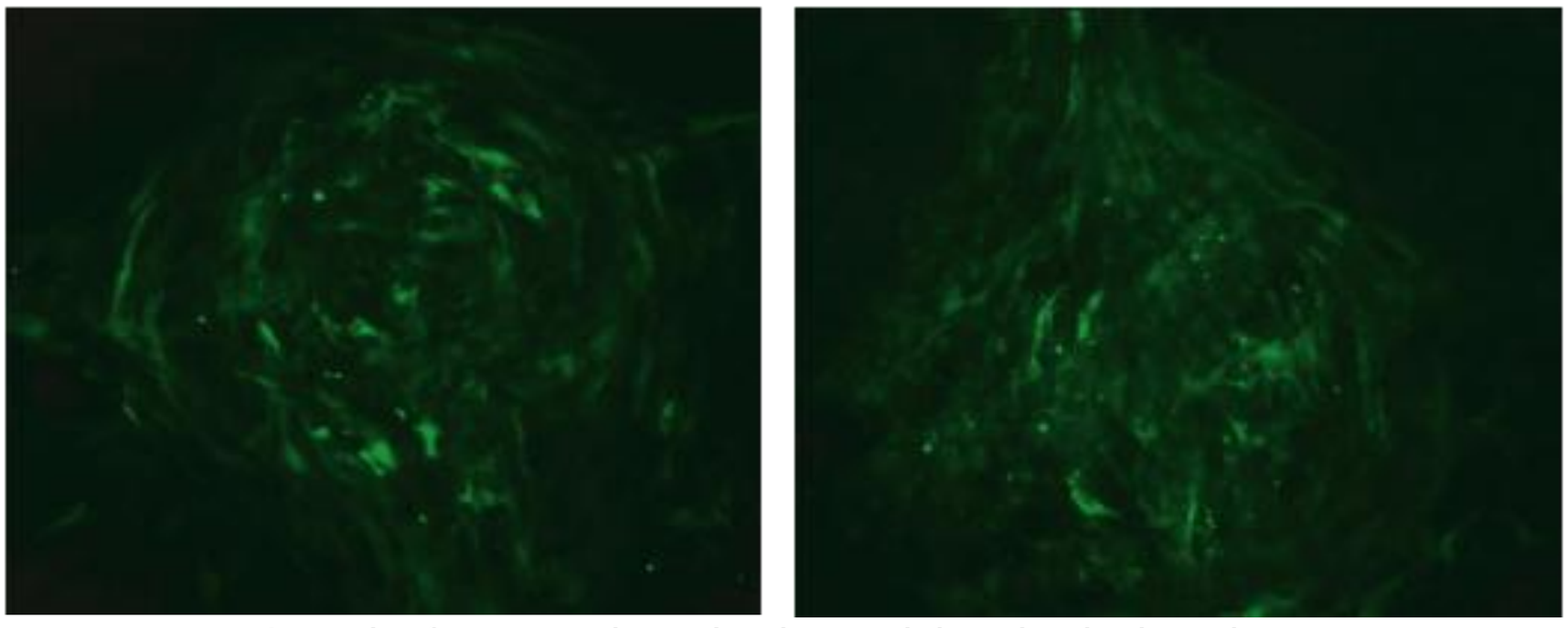
Neonatal Rat Blood N01.1 cells



N01 cells were isolated from rat neonatal blood cells of Sprague-Dawley (SD) pups and cultured in growth media with DMEM, 10%FBS, EGF and bFGF. At 6 weeks, 60% of N01 cells are nestin-positive. A clonal line was isolated and named N01.1. All cells in the clone expressed nestin (A, green). N01.1 cells can be cultured for long period of time without showing changes in morphology or nestin expression. When serum was withdrawn from the growth media, N01.1 cells formed spherical structure (B & C), similar to neurospheres formed by neural stem cells (data presented by Dongming Sun at the First Scientific Annual Meeting, Stem Cell Research in NJ)

N01.1 Transplantation





1 week after transplantation into uninjured spinal cords

Lithium (Li)

- Lithium strongly stimulates proliferation of many types of stem cells, including umbilical cord blood mononuclear (UCBM) cells.
- We recently discovered that lithium increases production and secretion of neurotrophins by UCBM cells both *in vitro* and *in vivo*.
- Lithium has long been used to treat manic depression and stimulatory effects of lithium on neural stem cells may be responsible for its effects.

Lithium and Regeneration

- Yick LW, So KF, Cheung PT, Wu WT (2004). Lithium chloride reinforces the regeneration-promoting effect of chondroitinase ABC on rubrospinal neurons after spinal cord injury. J. Neurotrauma 21: 932-43.
- Su H, Chu TH, Wu W (2007). Lithium enhances proliferation and neuronal differention of neural progenitor cells in vitro and after transplantation into the adult rat spinal cord. Exp. Neurol. 2006-307
- Dill J, Wang H, Zhou F, Li S (2008). Inactivation of glycogen synthase kinase 3 promotes axonal growth and recovery in the CNS. J. Neurosci. 28: 8914-28.

Lithium and Degeneration

- Yeh HL, Tsai SJ (2008). Lithium may be useful in the prevention of Alzheimer's disease in individuals with presenile familial Alzheimer's disease. Medical Hypotheses.
- DeSarno P, Axtell RC, Raman C, Roth KA, Alessi DR, Jope RS (2008). Lithium prevents and ameliorates experimental autoimmune encephalomyelitis. J. Immunol. 181: 338-45.
- Feng HL, Leng Y, Ma CH, Ren M, Chuang DM (2008). Combined lithium and valproate treatment delays disease onset, reduces neurological deficits and prolongs survival in an amyotrophic lateral sclerosis mouse model. Neuroscience 155: 567-72.

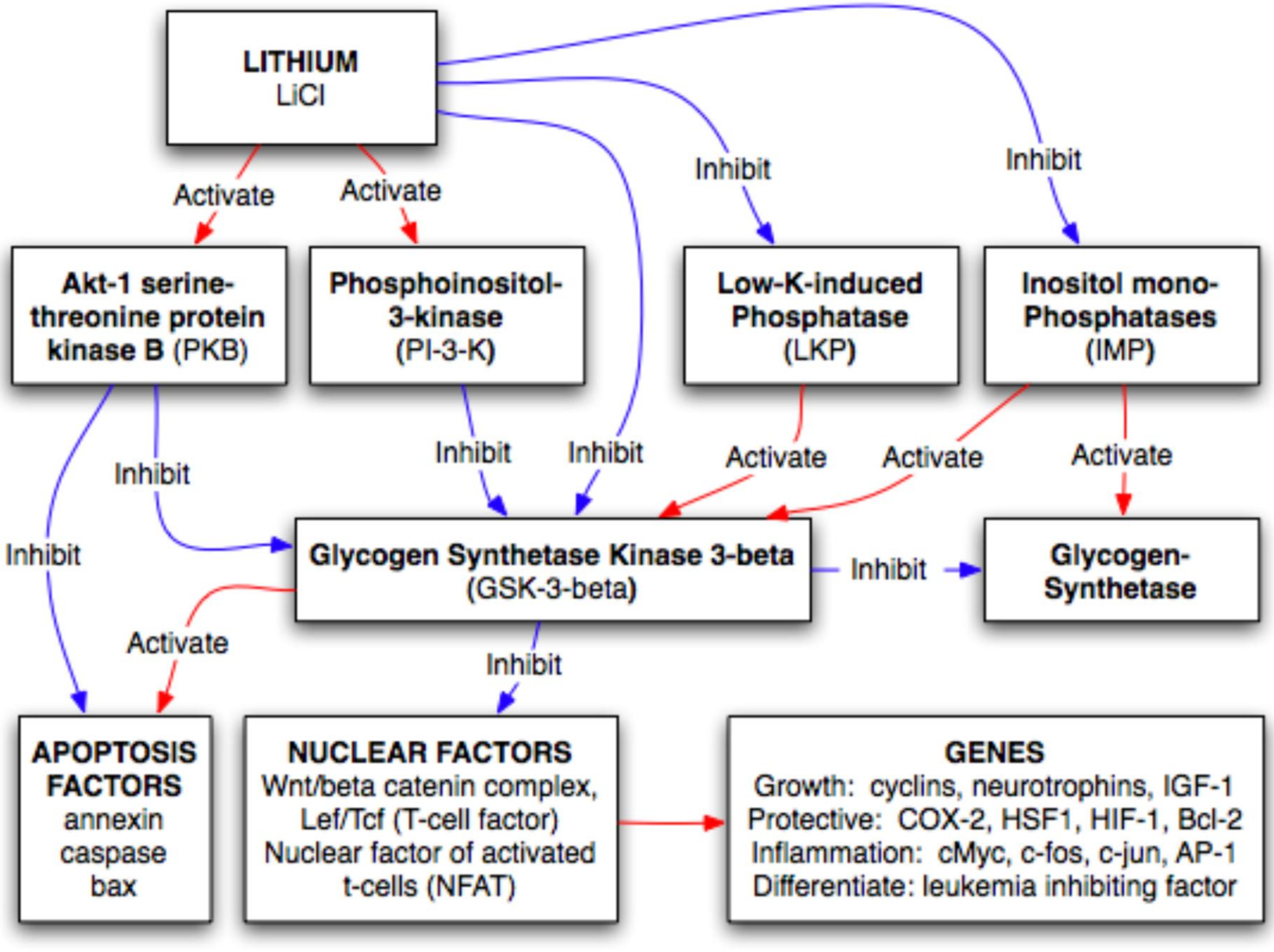
Lithium & ALS

- Fornai, et al. (2008). Lithium delays progression of amyotrophic lateral sclerosis. Proc. Nat. Acad. Sci. 105:2052-2057.
  - Daily doses of lithium (plasma level 0.4-0.8).
  - 44 patients with ALS randomized to riluzole (control) or riluzole plus lithium.
  - At the end of 15 months, 29% of control group died but none in the riluzole+lithium group.
  - Lithium group showed no significant motor deterioration whereas control group deteriorated.

Lithium and Stem Cells

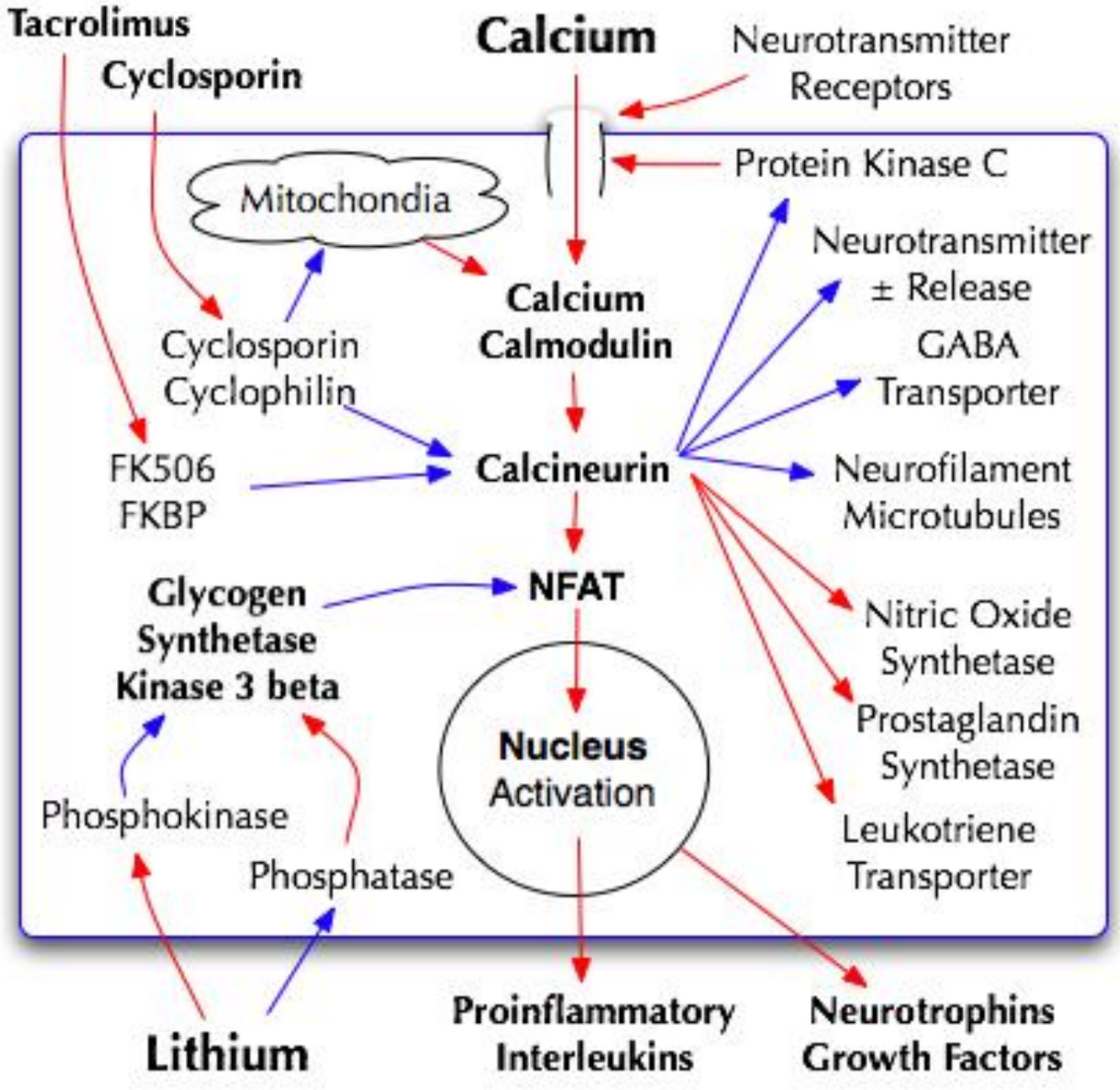
- Lithium has been used for over 100 years to treat manic depression. It was one of the first drugs to be approved by the Food and Drug Administration.
- Therapeutic serum levels of 0.6-0.8 mM stimulate proliferation of bone marrow, neural, and other stem cells *in vitro* and *in vivo*.
- Lithium-treated patients with manic depression have more gray matter and higher neuronal density in their brains.

Lithium Mechanisms

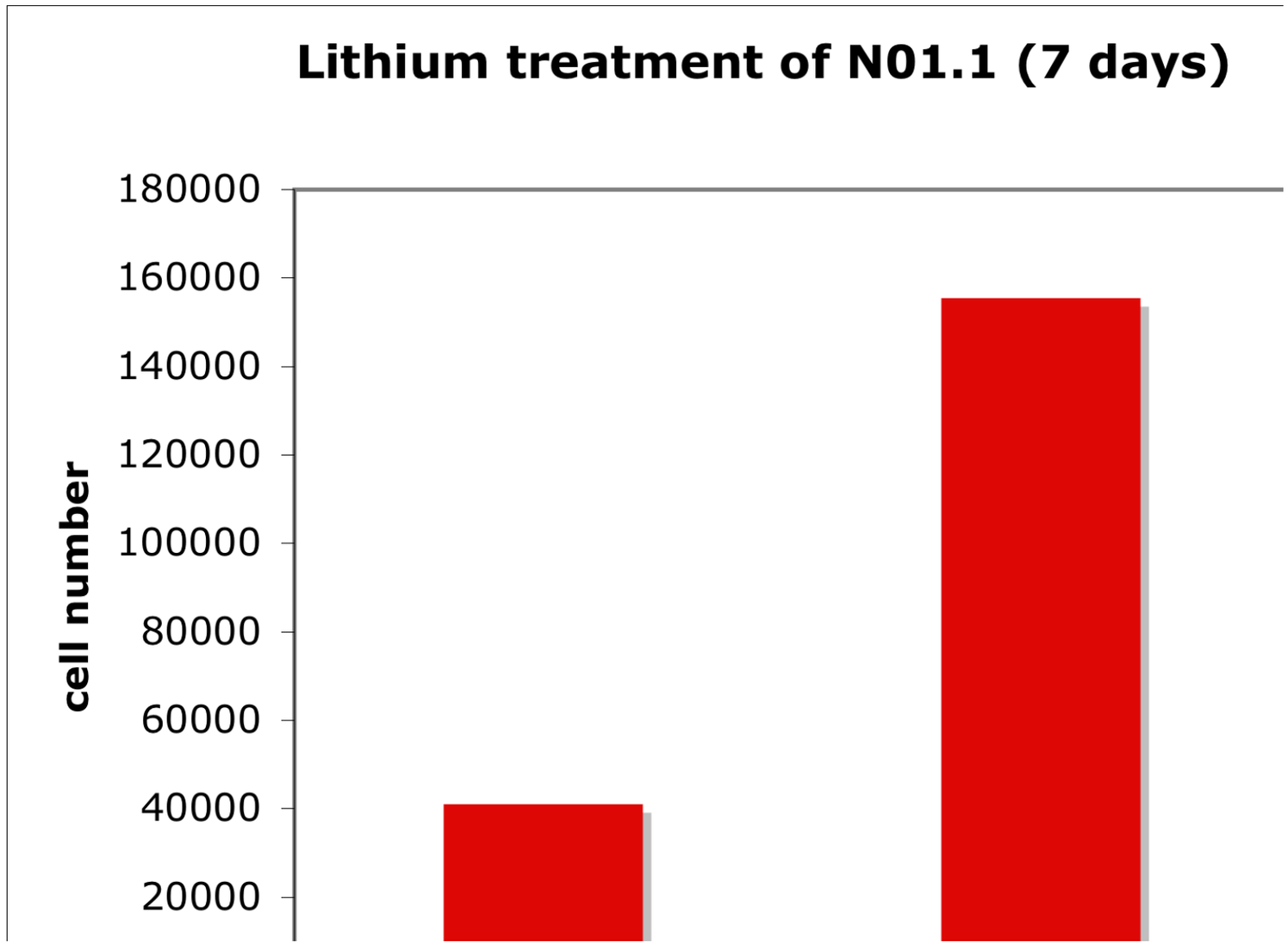


Recent Lithium Studies

- Lithium stimulates proliferation of neural and other stem cells but it stimulates neurotrophin production only in umbilical cord blood cells.
- Other glycogen synthetase kinase beta-3 (GSK-b3) inhibitors have similar effects as lithium.
- Calcineurin inhibitors (cyclosporin and FK506) block lithium, suggesting that GSK-3ß acts via NFAT (nuclear factor of activated t-cells).

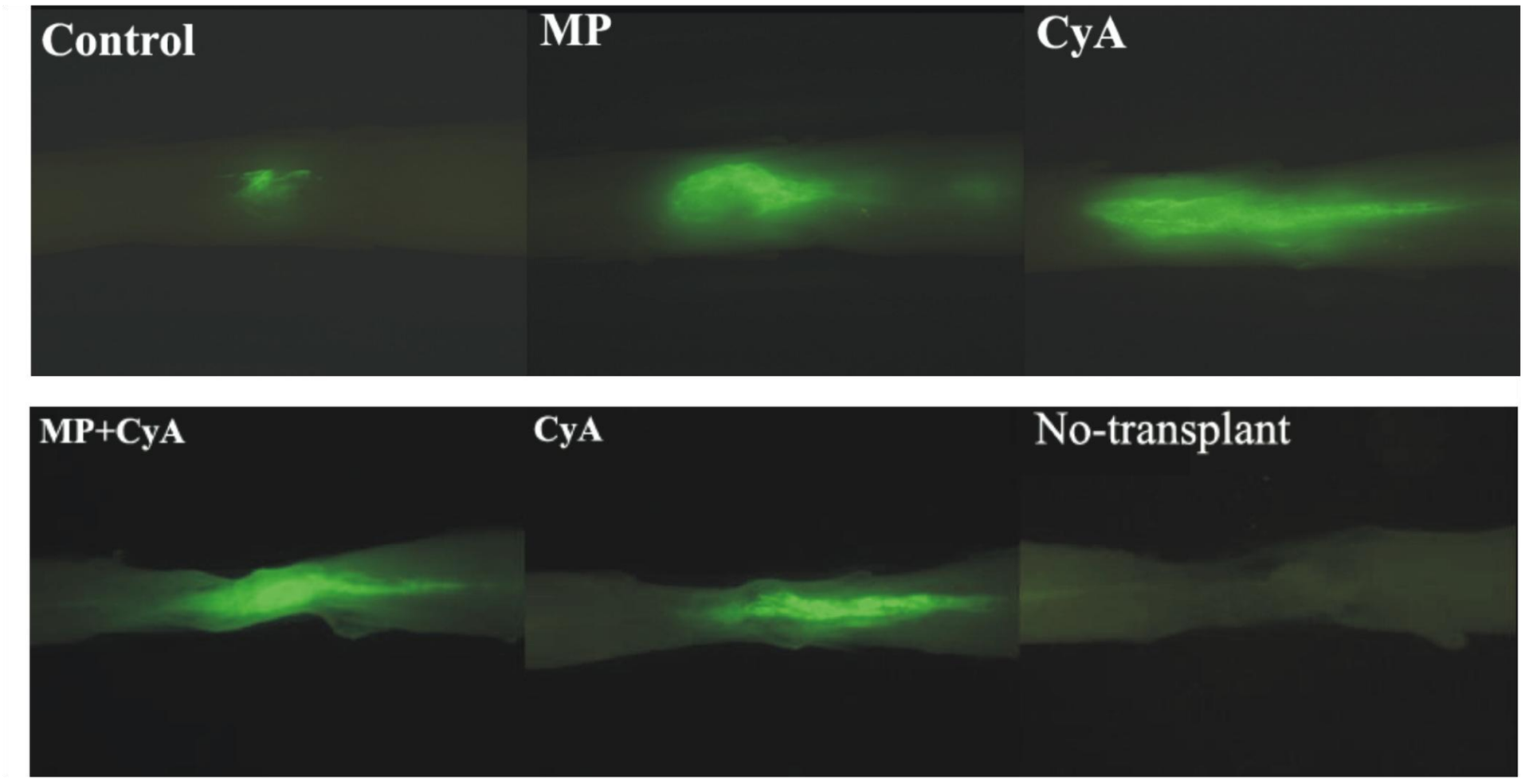

Tacrolimus
Cyclosporin
Calcium
Neurotransmitter
Receptors
Protein Kinase C
Mitochondia
Neurotransmitter
± Release
GABA
Transporter
Calcium
Calmodulin
Cyclosporin
Cyclophilin
FK506
FKBP
Calcineurin
Neurofilament
Microtubules
Glycogen
Synthetase
Kinase 3 beta
NFAT
Nitric Oxide
Synthetase
Prostaglandin
Synthetase
Nucleus
Activation
Phosphokinase
Phosphatase
Leukotriene
Transporter
Lithium
Proinflammatory
Interleukins
Neurotrophins
Growth Factors

Lithium Stimulates Proliferation



N01.1 cells were cultured in 3 mM lithium chloride for 7 days. Lithium treated cultures had 359% more cells than control cultures grown without lithium.

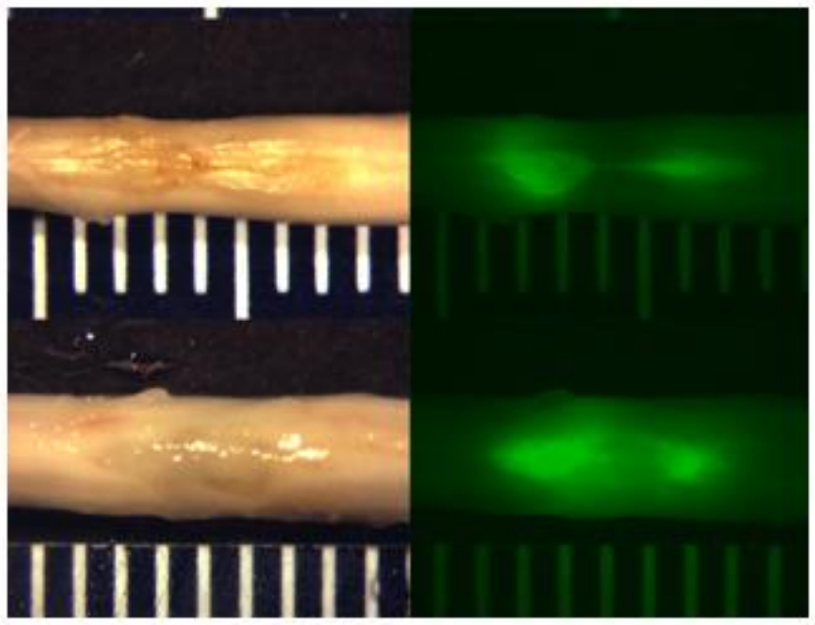
OEG Survival at 2-15 weeks



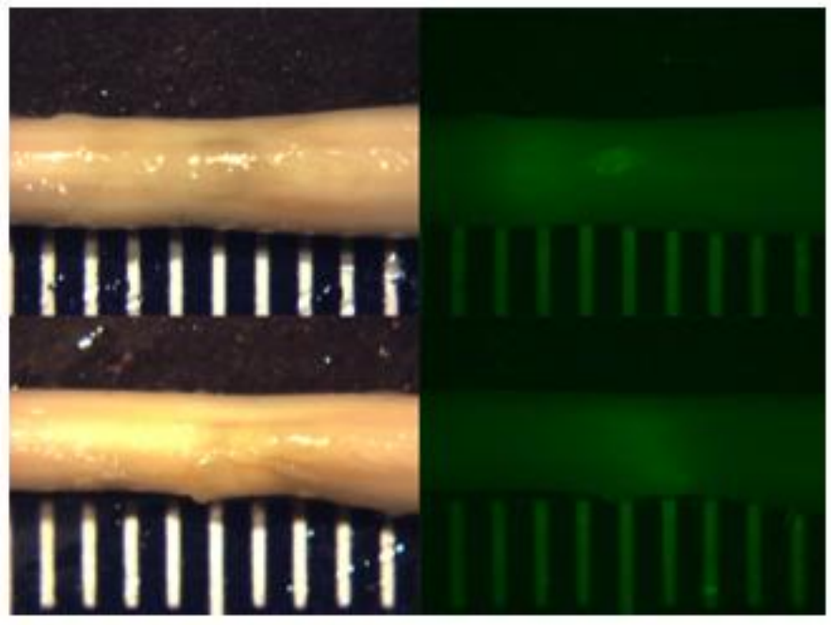
Green fluorescent protein (GFP) expressing OEG cells in whole-mounted rat spinal cord at 2 weeks (2w) or 14 weeks (14w) after a 25-mm contusion and treatment with methylprednisolone (MP) or/and cyclosporine A (CyA).

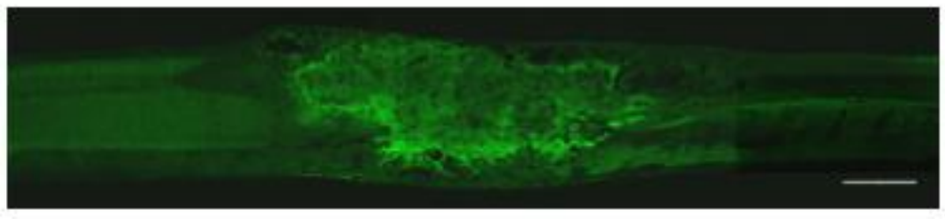
Lithium Effects on N01.1

Lithium-treated



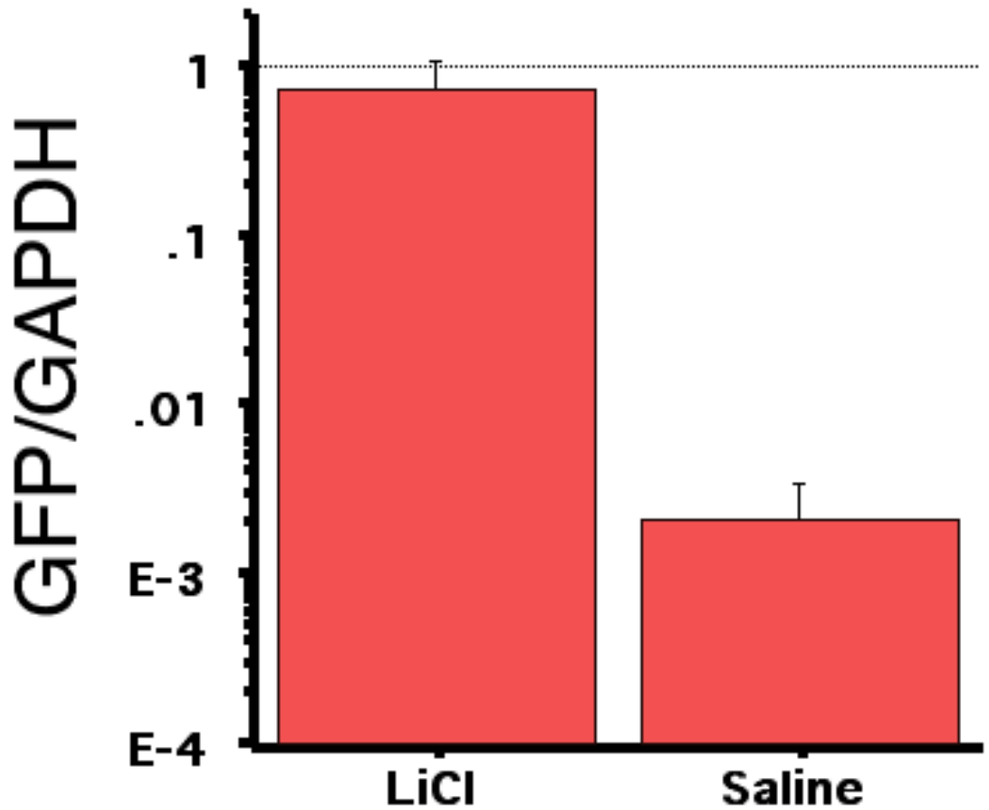
Saline-treated





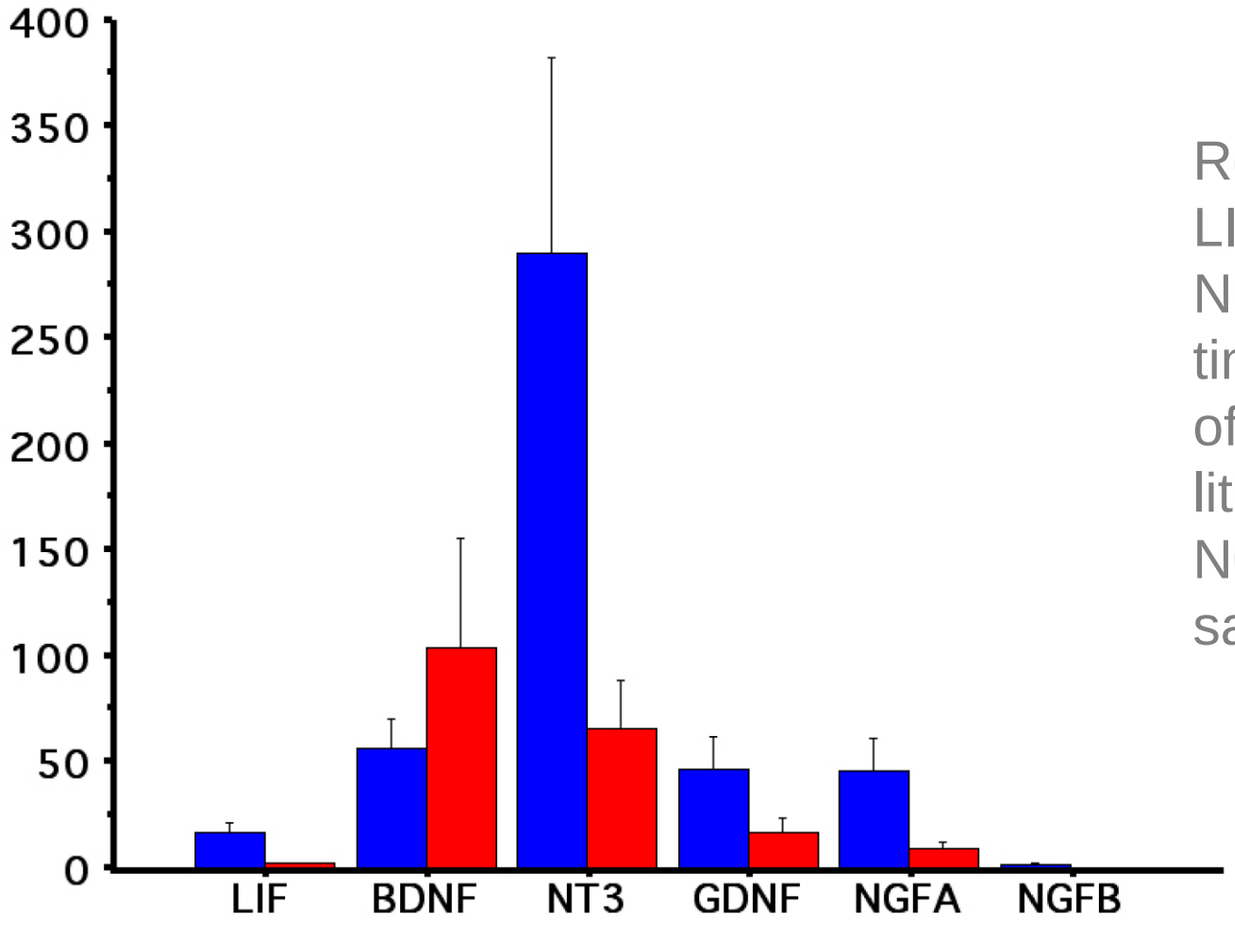
Spinal cord at 2 weeks

Lithium Effect on GFP in Vivo



GFP mRNA measured by real-time RT/PCT in un-injured rat spinal cord at 2 weeks after NO1.1 cell transplantation. GFP mRNA was detectable but very low in saline-treated rats. Lithium-treated rats had 1000x more GFP mRNA than in saline-treated rats.

Lithium & Growth Factors



Real-time PCR showed that LIF, GDNF, NT3, NGFa, and NGFb mRNA levels were 3-5 times higher in spinal cords of N01.1-transplanted and lithium-treated rats than in N01.1-transplanted (n=6) and saline-treated rat (n=6).

Rationale for Trials

- Cord blood cells have many advantages
  - Long history of cord blood safety in human use.
  - GMP source of HLA-matched cells for transplantation
  - Preclinical shows cord blood mononuclear cells are well behaved after transplantation to rat spinal cords.
- Methyprednisolone and Lithium
  - A single bolus dose of methylprednisolone (MP) markedly (4x) improves survival of transplanted cells
  - Lithium stimulates proliferation and neurotrophin production by cord blood mononuclear cells.
- Combination UCBMC, MP, and lithium.

China Spinal Cord Injury Network (ChinaSCINet)

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Genesis of ChinaSCINet

- In 1997, a 17-year old gymnast (Sang Lan) broke her neck at the Good Will Games in New York. When she was returning to China, she cried and asked how the cure for SCI would come to China.
- I told her that clinical trials in China is the only way to bring therapies to China. I promised her I would do my best to bring trials to China.
- In 2003, I met the mother of a young man with SCI (Suzanne Poon) and asked her to help raise funds for the China Spinal Cord Injury Network (ChinaSCINet).

Spinal Cord Injury in China

- Spinal cord injury (SCI) incidence in China increased tenfold (from 6.5 to 65 cases/million) from 1995 to 2005, i.e. >85,000 new cases/year.
- Prevalence of chronic SCI >800,000 in 2008 and is likely to exceed a million by 2010 in China.
- ChinaSCINet has 25 leading SCI centers in mainland China, Hong Kong, and Taiwan.
- The network can randomize 6000 subjects with acute SCI and almost unlimited numbers of chronic SCI/year

Hong Kong SCI Fund

HKU SCI Fund
Rutgers Foundation
Li Ka Shing
Foundation

China SCI Network, Inc.

Board of Directors
Kwok-Fai So and
Wise Young
Co-Chairs

Wise Young (CEO)
Wendy Chen (VP Reg. Aff)
John Chen (VP Clin Aff)

Sponsors

Stemcyte
Pfizer
Biogen
Acorda

China Spinal Cord Injury Network

Beijing: Beijing Army General Hospital, China Rehabilitation Research Centre, Peking University People's Hospital, PLA 301 Hospital, Xishan Hospital.
Chongqing: Xinquiao Hospital (Third Military Medical University)
Fujian: First Affiliated Hospital (Fujian Medical University), Fuzhou City Hospital
Guanzhou: Nanfang University Hospital, Sun Yatsen Memorial Hospital
Hong Kong: Queen Mary Hospital (Hong Kong University, Prince-of-Wales Hospital (Chinese University of Hong Kong).
Kunming: Kunming People Liberation Army General Hospital
Shanghai: Zhong Shan Hospital (Fudan University), Changhai Hospital (2nd Military Medical University), East Shanghai Medical Center (Tongji University), Ningpo #2 Hospital.
Shangtou: First Affiliated "Li Ka Shing" Hospital (Medical College of Shantou)
Taiwan: Buddhist Tzuchi General Hospitals, China Medical University Hospital, Chang Gong Memorial Hospital
Tianjin: Tienjin Medical University Hospital
Xi'an: Xi'jing Hospital (Fourth Military Medical University), Second Hospital (Jiaotong University)
Zhengzhou: Henan People's Provincial Hospital

China SCI Network

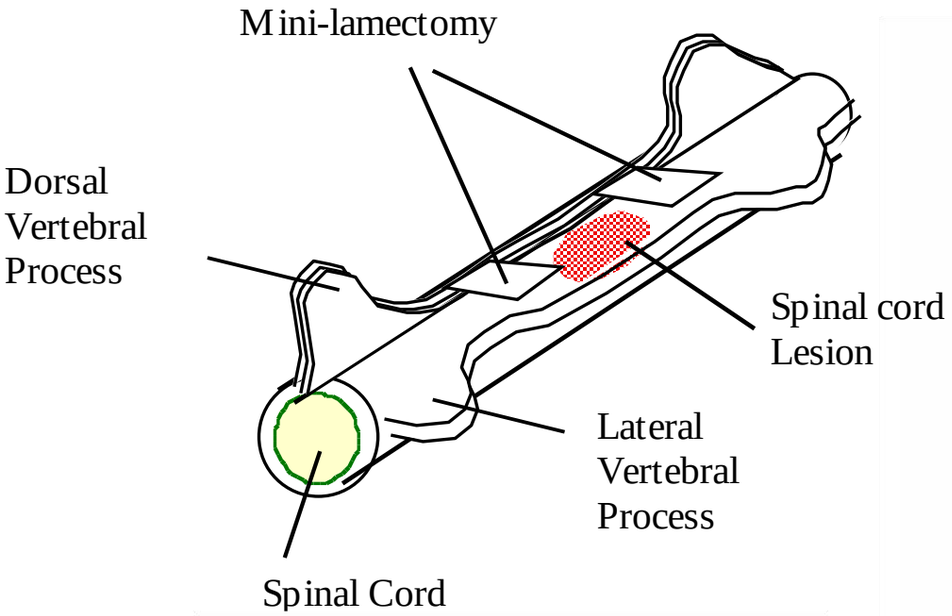
- ChinaSCINet has 25 leading spinal cord injury centers in China, Hong Kong, and Taiwan.
- Network Activities
  - 2004: recruited centers, signed trial agreements.
  - 2005: trained International SCI Classification.
  - 2006: initiated 400-patient observational trial.
  - 2007: initiated phase 1 oral lithium trial at HKU.
  - 2008: phase 2 cord blood transplant trials.
  - 2009: phase 3 cord blood + Lithium trials

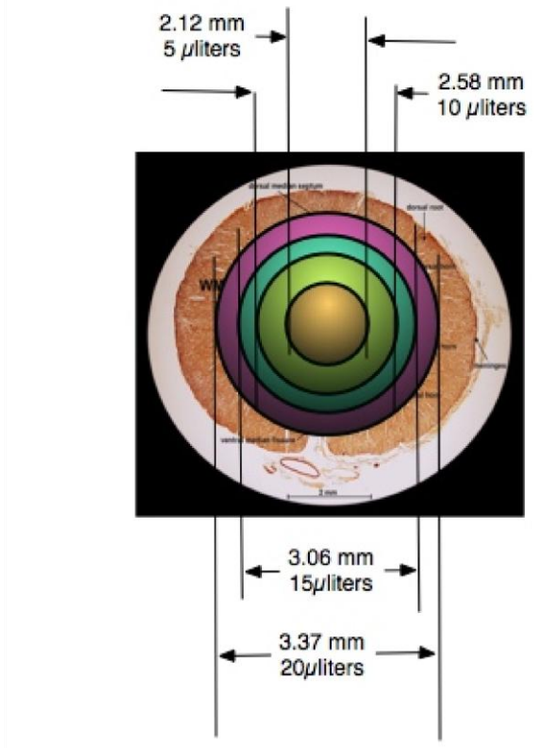
ChinaSCINet Trials

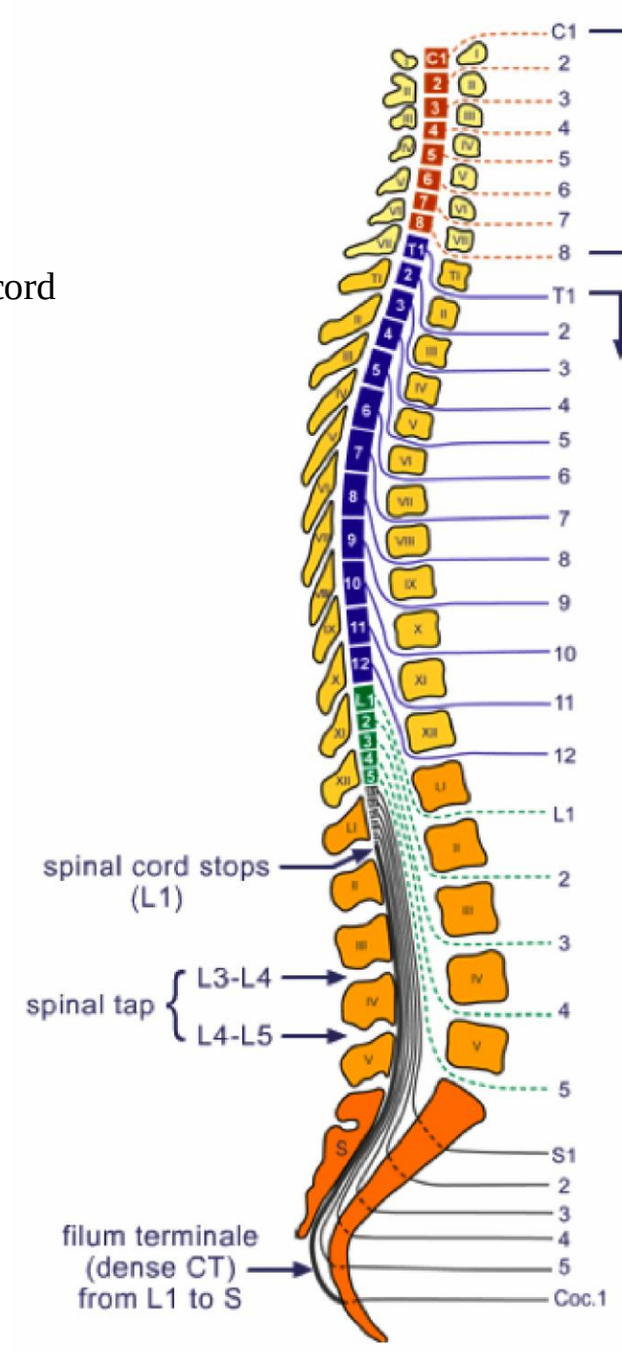
- Phase 0 Observational Study (CN100). This trial recruited 600 patients with SCI and collected data for up to a year.
- Phase 1 Open-label Lithium (CN101). This trial assessed 6-week daily oral lithium treatment of 20 subjects with chronic SCI.
- Phase 2 Lithium vs Placebo (CN102a). This double-blind trial randomizes 80 subjects with chronic SCI to lithium vs. placebo.
- Phase 2 Escalating dose cord blood mononuclear cell (CN102b). This trial evaluates safety and efficacy of 1.6, 3.2, 6.4 million HLA-matched CBMC cells transplanted to spinal cords of 40 subjects with chronic SCI, with methylprednisolone & lithium.
- Phase 3 HLA-matched UCBMC transplants ± Lithium (CN103). This trial will randomize 400 subjects that have received CBMC transplants to lithium or placebo.

Cell Transplant Experience

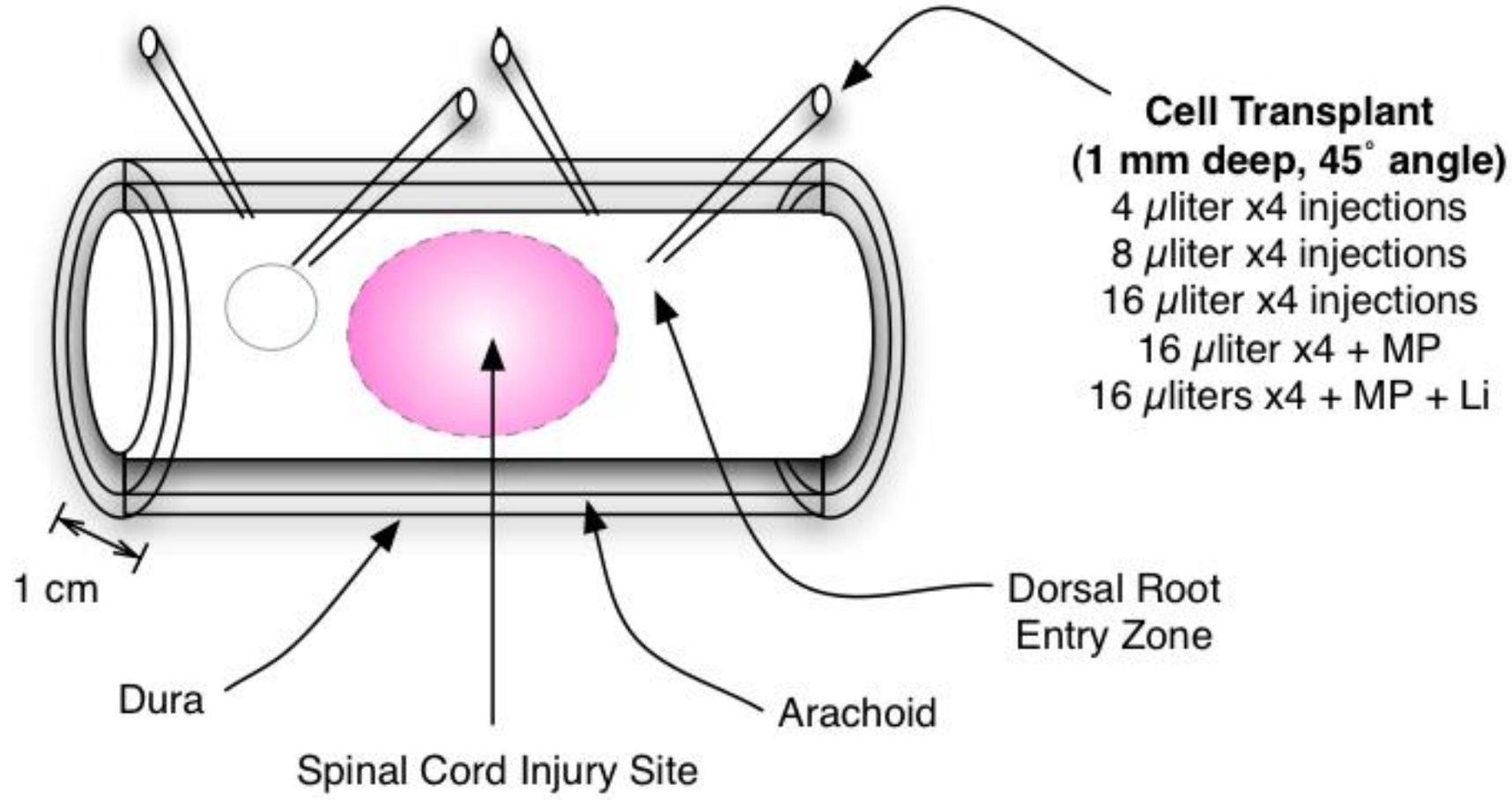
- Fetal Olfactory Ensheathing Glia
  - Hongyun Huang (Beijing Xishan) n=700.
  - Tianshen Sun (Beijing Army General) n=30.
  - Huiyong Shen (Sun Yatsen Memorial) n=57.
- Bone marrow CD34+ autografts
  - Yongfu Zhang (Zhengzhou, Henan) n=220
  - Yoon Ha (Inha Univ., Inchon) n=11.
- Schwann cell transplants
  - Hui Zhu (Chengdu Army, Kunming) n=120
  - Shiqing Feng (Tianjin Univ Hospital) n=10


Mini-lamectomy
Dorsal
Vertebral
Process
Spinal cord
Lesion
Lateral
Vertebral
Process
Spinal Cord


2.12 mm
5 µliters
2.58 mm
10 µliters
3.06 mm
15µliters
3.37 mm
20µliters


C1
on top of C1
under C7
T1
under corre
spinal cord stops
(L1)
spinal tap
L3-L4
L4-L5
filum terminale
(dense CT)
from L1 to S
S1
Coc.1

Cell Transplantation

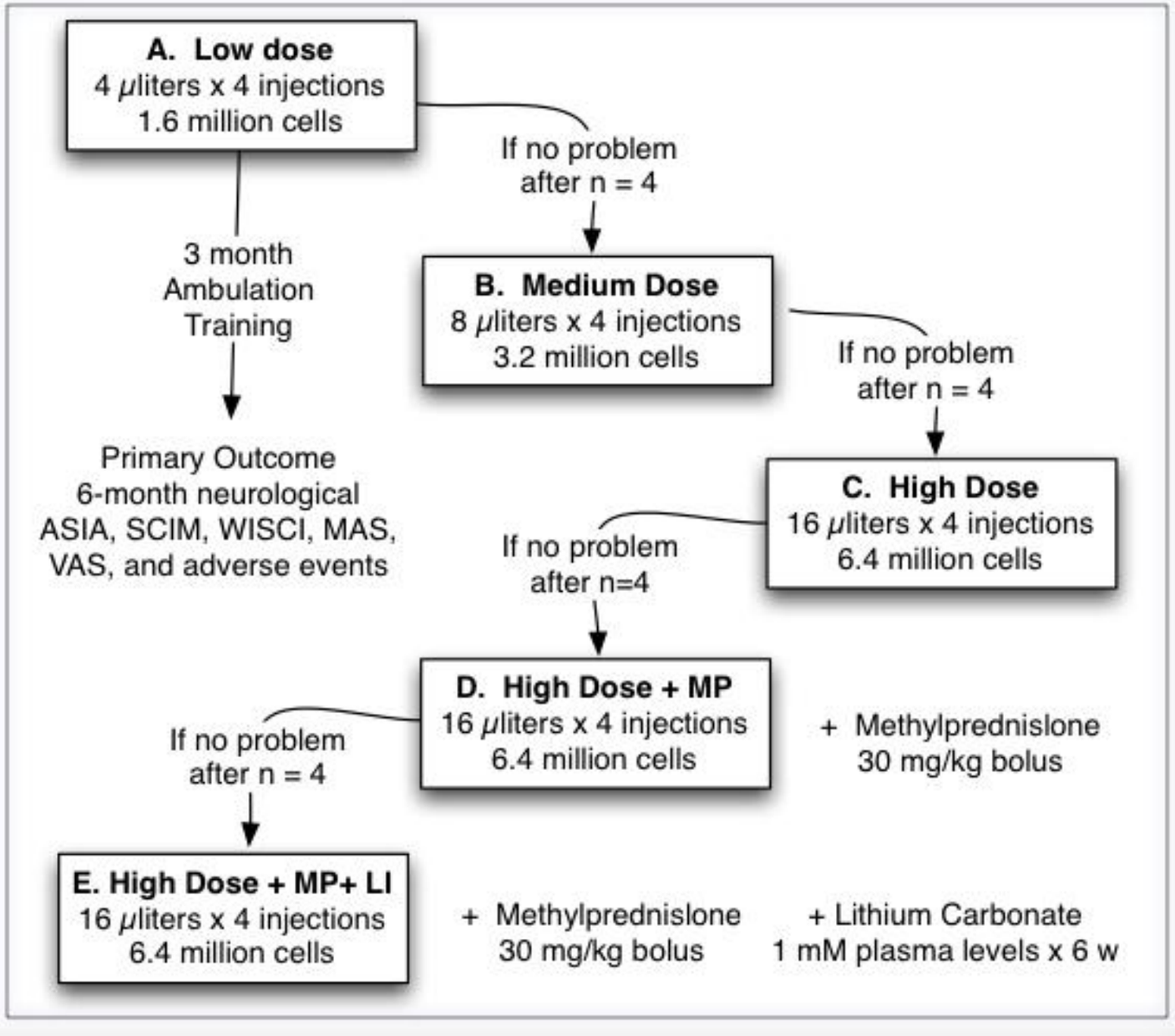


Cells will be injected into the dorsal root entry zones of the spinal cord above and below the injury site, at a 45˚ angle and 1 mm deep. The injection volume will be 4, 8, or 16 µliters of 100,000 cells/µliter.

CN102B Protocol

Cord Blood Mononuclear (CBM) Cells

HLA matched
cord blood
>4/6 match
20 subjects
chronic SCI



CN102B Goals

- Assess cord blood mononuclear (UCBM) cell dose, i.e. 4, 8, 16 µliter (100,000/µliter) into dorsal root entry zones next to injury.
- Assess whether methylprednisolone (single bolus 30 mg/kg MP) increases survival of UCBM cell transplants and improves treatment effects.
- Determine safety and efficacy of lithium after UCBM cell transplants to stimulate proliferation and neurotrophins (NGF, NT3, GDNF, LIF).

CN103 Possible Outcomes

- Neither treatment improve function. We would recommend against cord blood mononuclear cells and lithium treatment of chronic SCI.
- Both treatment improve neurological function. We will need to do a surgically controlled trial to rule out placebo and surgery-alone effect.
- Cord blood plus lithium is more effective than cord blood alone. We can strongly recommend the former combination treatment.

ChinaSCINet Summary

- ChinaSCINet is the world's largest spinal cord injury (SCI) clinical trial network. Stemcyte is the best cord blood cell transplant company.
- Lithium stimulates proliferation and neurotrophin production by umbilical cord blood mononuclear (UCBM) cells.
- ChinaSCINet will assess safety and optimal dose of HLA-matched UCBM cell transplants for SCI, combined with methylprednisolone and lithium.

SCINETUSA

- Many Americans wanted to go to China for the ChinaSCINet trials. We formed the Spinal Cord Injury Network USA (SCINETUSA).
- Several U.S. SCI centers have joined NASCINET:
  - Brackenridge Hospital (Austin)
  - UMDNJ/Kessler Institute of Rehabilitation Medicine
  - Thomas Jefferson/McGee Institute of Rehabilitaion Medicine
  - Mt Sinai Medical School (NY)
  - Long Island Jewish Hospital (NY)
  - University of Colorado at Denver
  - Shriner’s Hospital (Philadelphia).
  - Wayne State University, Rehabilitation Institute of Michigan

Proposed U.S. Trials

- NA103A. Multicenter phase 3 trial to assess safety and efficacy of umbilical cord blood mononuclear cell (UCBMC) transplants and lithium therapy of chronic SCI in adults (16-60 years old).
- NA102B. Phase 2 trial to assess feasibility, safety, and efficacy of UCBMC & lithium in older adults (age 60-80).
- NA102C. Phase 2 trial to assess feasibility, safety and efficacy of UCBMC & lithium in children (age 8-16 years) at Shriner's Hospital in Philadelphia.

Stem Cell Policy

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

U.S. Stem Cell Policy

- The Bush Administration held back federal funding of all human stem cell research, not just human embryonic stem cell research.
- The NIH spent <1% of its budget on human stem cell research from 2001 to 2007, too little considering the importance of stem cells.
- Obama passed executive order to expand federal funding of stem cell research but new draft NIH policy may restrict the research further.

Draft NIH Policy

- Limits embryonic stem cell (ESC) research to cells derived from IVF clinics only and explicitly forbids all cloned or parthenogenetically derived cells.
- Limits chimera models. New limits on ESC transplants in developing primate and in other animals that may reproduce.
- New informed consent requirements. ESC must fulfill new informed consent. Most existing ESC lines may not be eligible.

California Proposition 71

- Funding. Lawsuits have tied up Proposition 71 since 2004 but a favorable decision by the California Supreme Court in 2007 released the funds.
- The California Institute of Regenerative Medicine (CIRM) has funded “training”, “seed”, “comprehensive”, and “facilities” grants.
- The economic recession may limit funding for the coming year but CIRM recently announced a strong commitment to clinical trials.

The New Jersey Initiative

- New Jersey passed the Stem Cell Research Act in 2004, encouraging research on all stem cells, including cloned human embryonic stem cells.
- In December 2006, the legislature approved a $270 million bond to build the Christopher Reeve Stem Cell Institute in New Brunswick.
- A $500 million bond for stem cell research was defeated in 2007 and the building of the institute has been suspended.

New York State Stem Cells

- The New York State Legislature, under the leadership of now Governor David Paterson, passed a $500 million bill to fund regenerative medicine in 2008.
- The bill started funding of stem cell research in the state but it is not clear what the budget situation will be in 2009 and 2010.
- The funding of stem cell research will likely be very limited due to the severe budgetary deficits faced by the state.

Cell Therapy Industry

- A thriving cellular therapeutic industry, however, has grown up in the past 8 years in the United States with increasing investments by major companies.
- Large pharmaceutical companies are investing significantly in stem cell research, including Pfizer, Johnson & Johnson, Bristol-Myers-Squibb, Galaxo-Smith-Kline, Astra-Zeneca, and Roche.
- Many small companies are now focusing on stem cells, including devices and supply companies.

Summary

- Despite the promise of stem cell therapies, federal funding of the all stem cell research has been very limited, not only of embryonic but adult stem cells.
- States have started fund stem cell research in California, New Jersey, New York, and other states but the recent recession has cut back on funds.
- The Obama administration recently issued a draft stem cell policy that further restricts embryonic stem cells and this will hopefully change.

For Information:

SCIProject@biology.rutgers.edu

CareCure.org

To Donate:

Keck.Rutgers.edu

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Javier Robles, J.D.

President