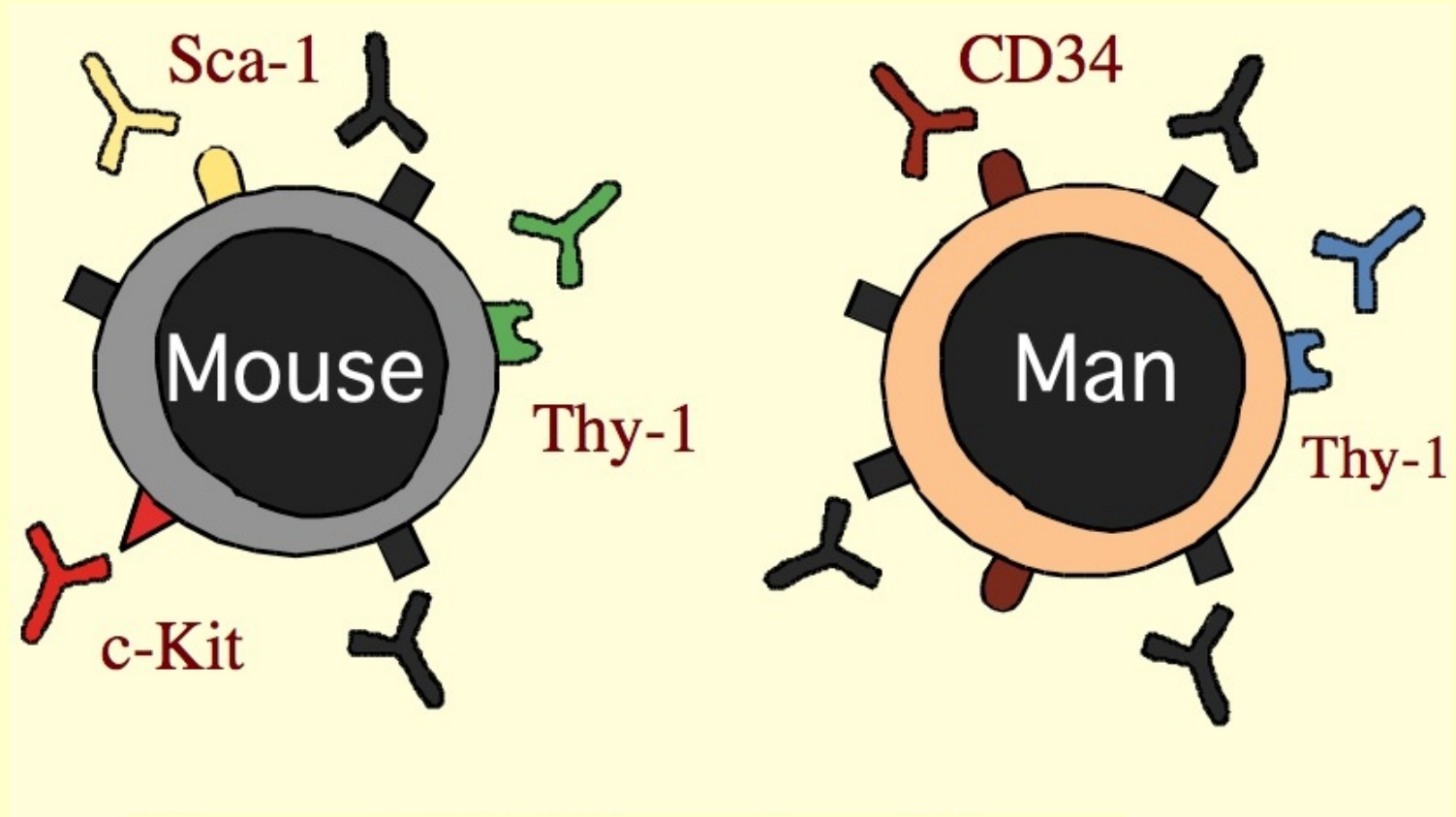


# Your Genes and Your Health

<http://bio84.stanford.edu/>

## Stem Cell Therapies

<http://bio84.stanford.edu/07%20Stem%20Cell%20Therapy.html>



Doug Brutlag, Professor Emeritus of  
Biochemistry & Medicine (by courtesy)  
Stanford University School of Medicine

# California Institute for Regenerative Medicine

<http://www.cirm.ca.gov/our-progress/stem-cells-therapies>



## CALIFORNIA'S STEM CELL AGENCY

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

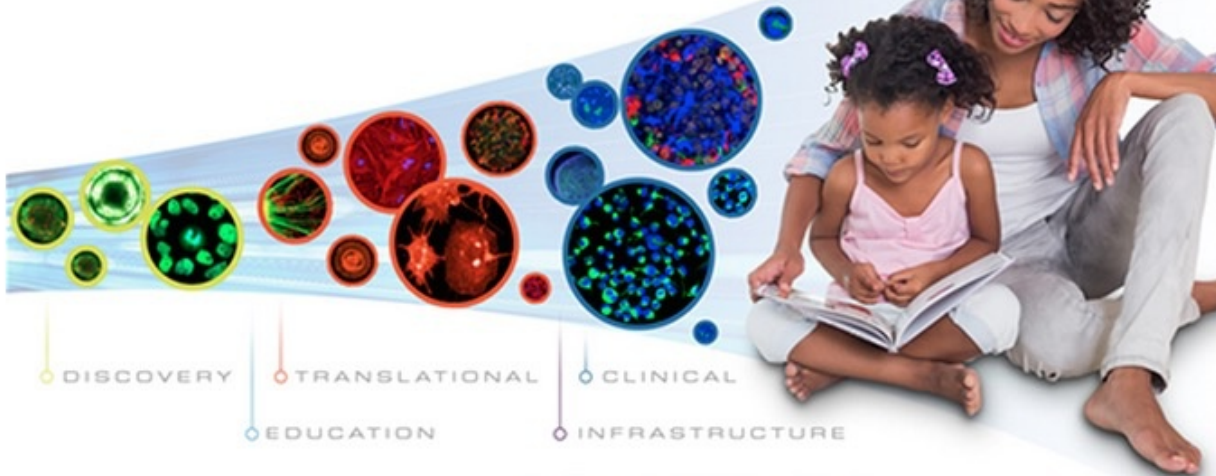
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# CIRM 2.0

CALIFORNIA'S STEM CELL AGENCY

January 21, 2015



**C. Randal Mills, Ph.D.**  
President and CEO  
California Institute for Regenerative Medicine

**CIRM 2.0 Webinar**  
Hear President and CEO C. Randal Mills discuss CIRM 2.0, a radical overhaul of the way the Agency operates.

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## Webinar Now On-Line

Turning Stem Cells Into Cures



## Turning stem cells into therapies

Stem cells have the potential to treat a wide range of diseases, including diabetes, neurodegenerative diseases, spinal cord injury, and heart disease. Learn why these cells are such a powerful tool for treating disease as well as what the current hurdles are before new therapies can become available.

- How can stem cells treat disease?
- What diseases could be treated by stem cell research?
- How can I learn more about CIRM-funded research in a particular disease?
- Are there any stem cell-based therapies currently available?
- When will therapies based on embryonic stem cells become available?
- What about the therapies that are available overseas?
- Why does it take so long to create new therapies?
  - Differentiation
  - Testing the therapy
  - Propensity for the cells to cause tumors
  - Immune rejection of the cells
  - Growing the cells in consistent conditions





## How can stem cells treat disease?

The most common way of thinking about stem cells treating disease is through a stem cell transplant. Embryonic stem cells are differentiated into the necessary cell type, then those mature cells replace tissue that is damaged by disease or injury. This type of treatment could be used to replace neurons damaged by spinal cord injury, stroke, Alzheimer's disease, Parkinson's disease, or other neurological problems. Cells grown to produce insulin could treat people with diabetes and heart muscle cells could repair damage after a heart attack. This list could conceivably include any tissue that is injured or diseased.

These are all exciting areas of research, but embryonic stem cell-based therapies go well beyond cell transplants. What researchers learn from studying how embryonic stem cells develop into heart muscle cells, for example, could provide clues about what factors may be able to directly induce the heart muscle to repair itself. The cells could be used to study disease, identify new drugs, or screen drugs for toxic side effects. Any of these would have a significant impact on human health without transplanting a single cell.

## What diseases could be treated by stem cell research?

In theory, there's no disease that is exempt from a possible treatment that comes out of stem cell research. Given that researchers may be able to study all cell types via embryonic stem cells, they have the potential to make breakthroughs in any disease.

## How can I learn more about CIRM-funded stem cell research in a particular disease?

CIRM has created disease pages for many of the major diseases being targeted by stem cell scientists. You can [find those disease pages here](#).

# FDA and Stem Cells

<http://www.fda.gov/aboutfda/transparency/basics/ucm194655.htm>



**U.S. Food and Drug Administration**  
Protecting and Promoting *Your* Health

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## FDA Warns About Stem Cell Claims

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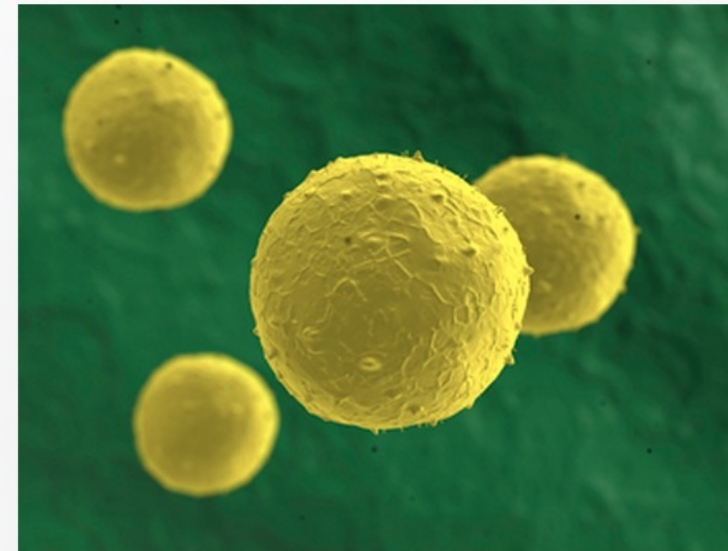
### On this page

- [Regulation of Stem Cells](#)
- [Advice for Consumers](#)
- [Thwarting a Stem Cell Scheme](#)

Stem cell therapies offer the potential to treat diseases or conditions for which few treatments exist.

Stem cells, sometimes called the body's "master cells," are the precursor cells that develop into blood, brain, bones and all of your organs. Their promise in medical treatments is that they have the potential to repair, restore, replace and regenerate cells that could then be used to treat many medical conditions and diseases.

But the Food and Drug Administration (FDA) is concerned that the hope that



Researchers hope that stem cells will one day be effective in the treatment of many medical conditions and diseases.

ISSCR



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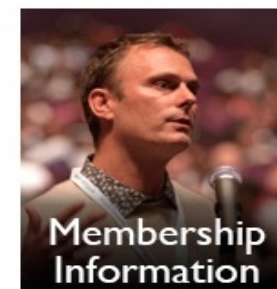
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**STOCKHOLM | SWEDEN**  
**24-27 JUNE**  
Stockholmsmässan

## For the Public



## What's New?

### The Vancouver Sun, Op Ed: Gordie Howe's Pursuit of Stem Cell Treatment Abroad is an Awakening for Continued Education and Informed Choice

05 February, 2015

An opinion piece by Drs. Judy Illes and Fabio Rossi, available here. Dr. Illes is Canada research chair in neuroethics, professor of neurology and director of the National Core for Neuroethics, Faculty of Medicine, University of British Columbia. Dr. Rossi is Canada research chair in regenerative medicine and professor of Medical Genetics Biomedical Research Centre, UBNC. Both are investigators with the Stem Cell Network.

[Read more](#)

### ISSCR 2015 Annual Meeting Abstract Submission Extended

05 February, 2015

[Read more](#)

### Member Spotlight on Beck Tsai, PhD

26 January, 2015

CIRM Postdoctoral Scholar at the City of Hope National Medical Center and podcast enthusiast Dr. Becky Tsai aims to develop tools that contribute to improving patient diagnosis and treatment. She also aids in the personal development of Southern California's youth. Find out how and why in this month's Member Spotlight.

[Read more](#)

### The International Society for Stem Cell Research Announces the 2015 Recipients of the McEwen Award for Innovation, the ISSCR-BD Biosciences Outstanding Young Investigator and the ISSCR Public Service Awards

20 January, 2015

## a closer look at **STEM CELL** treatments

[Home](#) [What to Ask](#) [Frequent Questions](#) [Other Resources](#) [From the Experts](#) [About ISSCR](#)

## *considering* **STEM CELL** *treatment?*

### Find out what's possible. Know what to ask.

We have all heard about the extraordinary promise that stem cell research holds for the treatment of human diseases. Clinics all over the world claim to offer stem cell treatments for a wide variety of conditions. But are all of these treatments likely to be safe and effective?

The ISSCR provides information to help you evaluate these claims. **Learn more about what this site can provide.** Please check back in January 2015 for new and expanded resources.

View CBS' 60 Minutes (US) 2010 segment, "**21st Century Snakeoil**"

**TOP 10** Things to Know About Stem Cell Treatments



ISSCR Patient Handbook



How Science Becomes Medicine

# FDA and Stem Cells

<http://www.fda.gov/aboutfda/transparency/basics/ucm194655.htm>



**U.S. Food and Drug Administration**  
Protecting and Promoting *Your Health*

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## About FDA

Home > About FDA > Transparency > FDA Basics

### Transparency

FDA Basics

FDA Fundamentals

Animal & Veterinary

Cosmetics

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Drugs

Food

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Radiation-Emitting Products

Tobacco Products

Vaccines, Blood, and Biologics

Ask Us: FDA Basics Webinar Series

Children

## What are stem cells? How are they regulated?

Stem cells are cells that have the ability to divide and develop into many different cell types in the body during early life and growth. Stem cells may also help repair the body by dividing to replenish cells that are damaged by disease, injury, or normal wear. When a stem cell divides, each new cell has the potential either to remain a stem cell or to become another type of cell with a more specialized function, such as a nerve cell, a skin cell, or a red blood cell.

Three types of stem cells have been identified:

1. adult stem cells
2. human embryonic stem cells
3. induced pluripotent stem cells

These three types of stem cells share properties:

- They are capable of surviving over long periods and divide to make additional stem cells.
- They are unspecialized ("blank slates" that can become specific types of cells).
- They can develop into specialized cell types (cells that do specific work in the body).

Adult stem cells can be found throughout the body. They are found as unspecialized cells among the specialized cells in tissues and organs as well as in umbilical cord blood and peripheral blood (that is, hematopoietic stem cells). An adult stem cell can either divide to make more adult stem cells, or differentiate to produce some or all of the major specialized cell types of the tissue or organ.

# Stem Cell Promise & Stem Cell Therapies

<http://www.cirm.ca.gov/our-progress/stem-cells-therapies>

---

- **Parkinson's Disease** with iPSCs (**Michael J. Fox Foundation**)
- Spinal Cord Injury with human embryonic stem cells (hESCs)
- Sickle Cell, Thalassemias, hemophilia and other blood diseases with iPSCs (**Matthew Porteus, Stanford**)
- **Bone Marrow Transplants (BMT) & hematopoietic stem cell therapy (HCT)** (**Judith Shizuru**)
  - Lymphomas and thymomas
  - Hematopoietic cells
  - Metastatic cancers of other origins
- Autoimmune Diseases with hematopoietic stem cells (HSCs)
  - Rheumatoid arthritis
  - Systemic Lupus Erythematosus
  - Type 1 diabetes mellitus
  - Multiple sclerosis
  - Pernicious anemia

# Parkinson's Treatment with Fetal Stem Cells

---

- [KQED Parkinson's Documentary](#)
- [My Father, My Brother and Me](#)

# Fetal Cell Transplants Can Cure Parkinson's



David Iverson's Frontline Film: My Father, My Brother and Me

© Doug Brutlag 2016

# Geron Stem Cell Therapy

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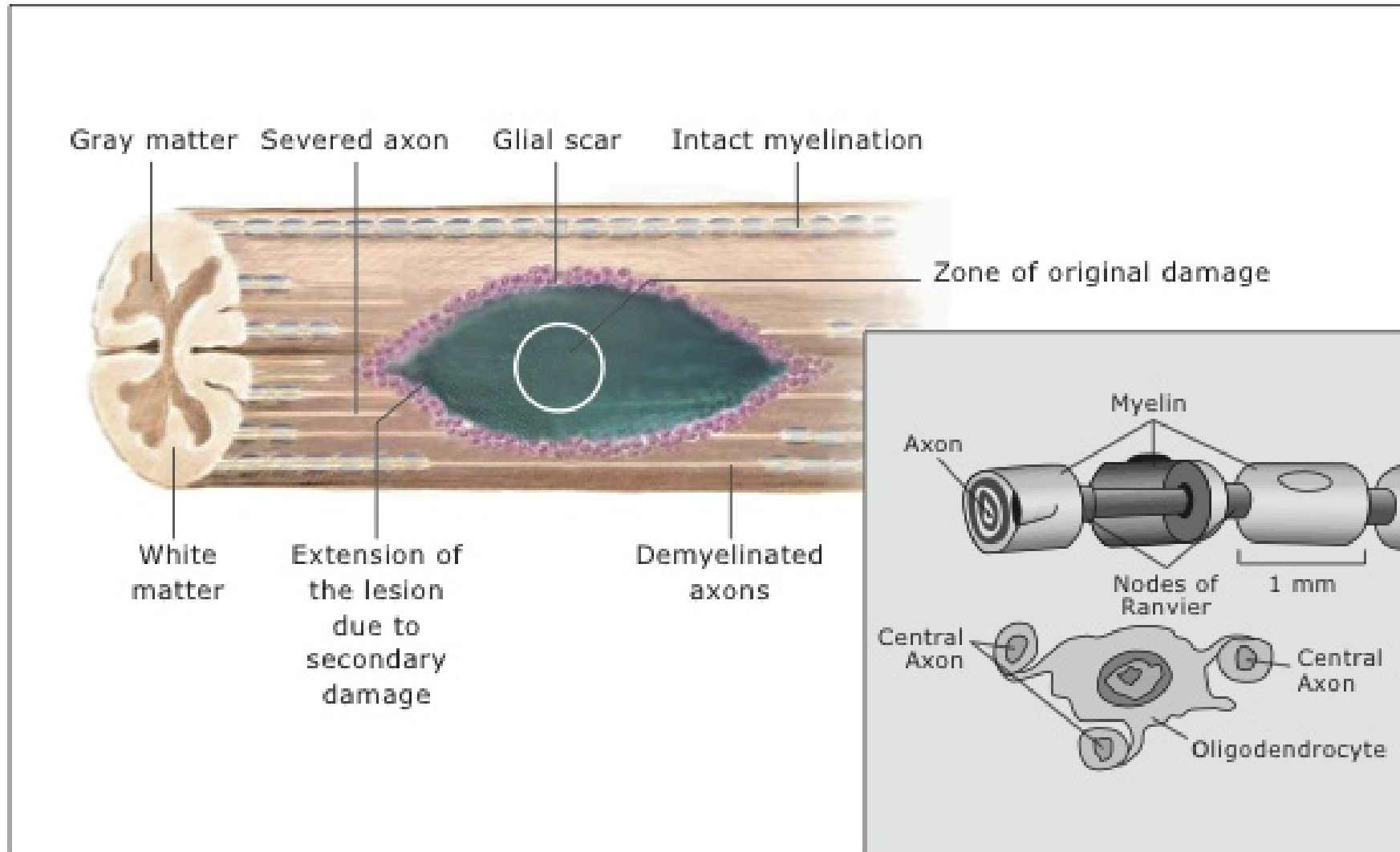
A large, stylized, 3D-rendered version of the word "geron" in a light blue color. The letter 'g' has a green circle above it, and the letters have a slight shadow effect.

**Human Embryonic Stem Cell Therapy: Pathway to the Clinic**

**Stanford University  
Stem Cell Policy Symposium:  
Understanding the Scientific and Legal Challenges Ahead**

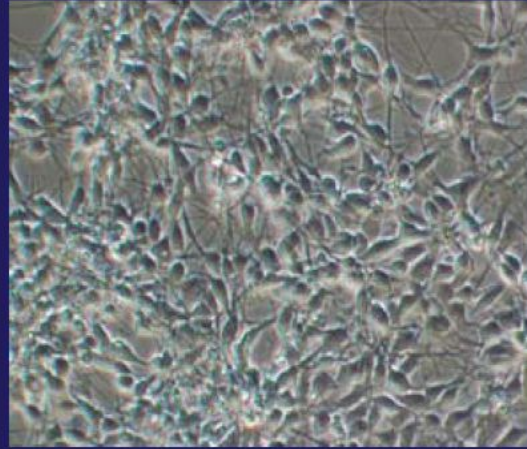
**October 2, 2009**

# Spinal Cord Injury Pathology at the Lesion



# GRNOPC1 Improves Locomotor Behavior after Spinal Cord Injury

hESC-Derived Oligodendrocyte Progenitors



Control

GRNOPC1



Journal of Neuroscience, May 11, 2005

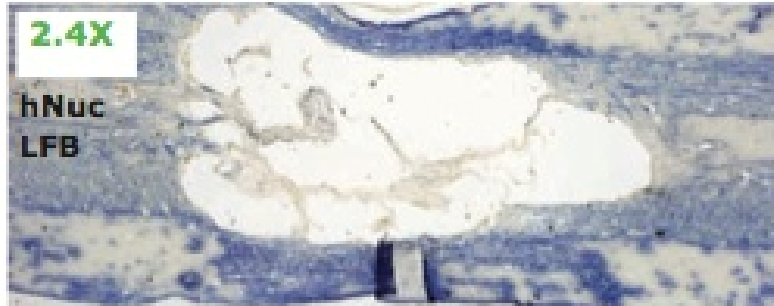
# Spinal Cord Injury

<http://www.geron.com/GRNOPC1Trial/>



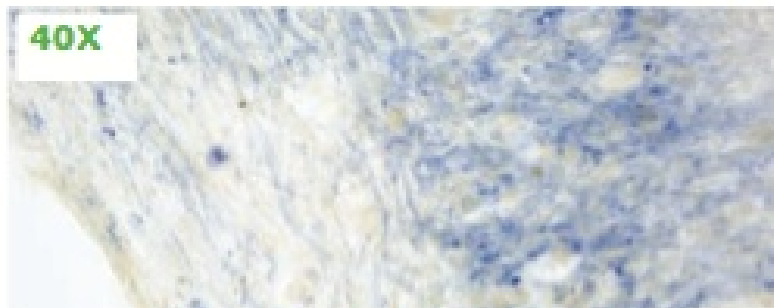
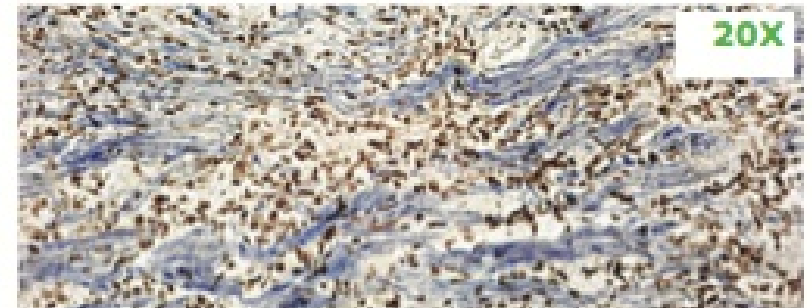
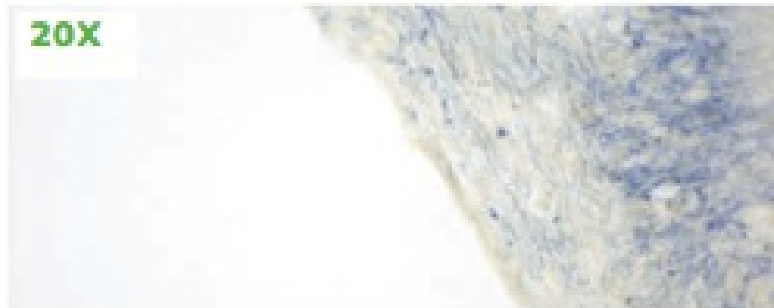
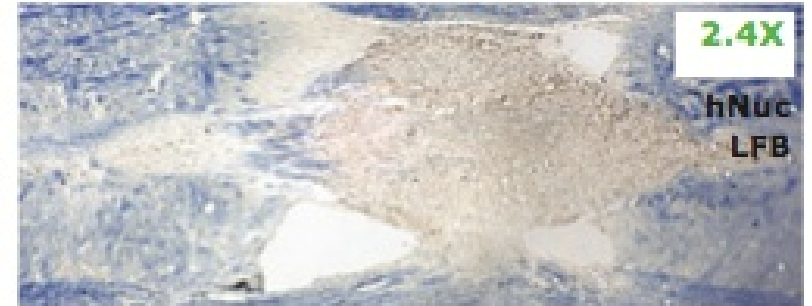
# GRNOPC1 Induces Remyelination after Spinal Cord Lesions in Rodents

**9 Months After No Treatment**

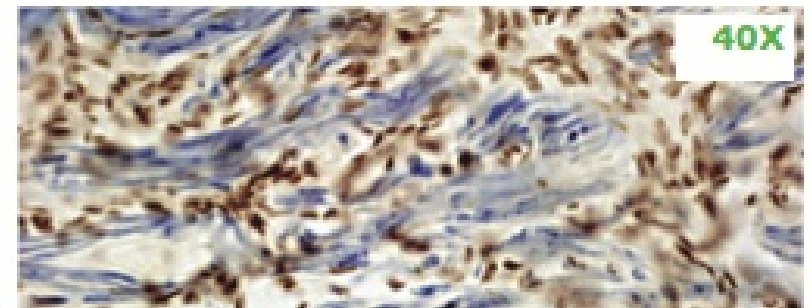


*(Damaged Zone)*

**9 Months After GRNOPC1 Treatment**

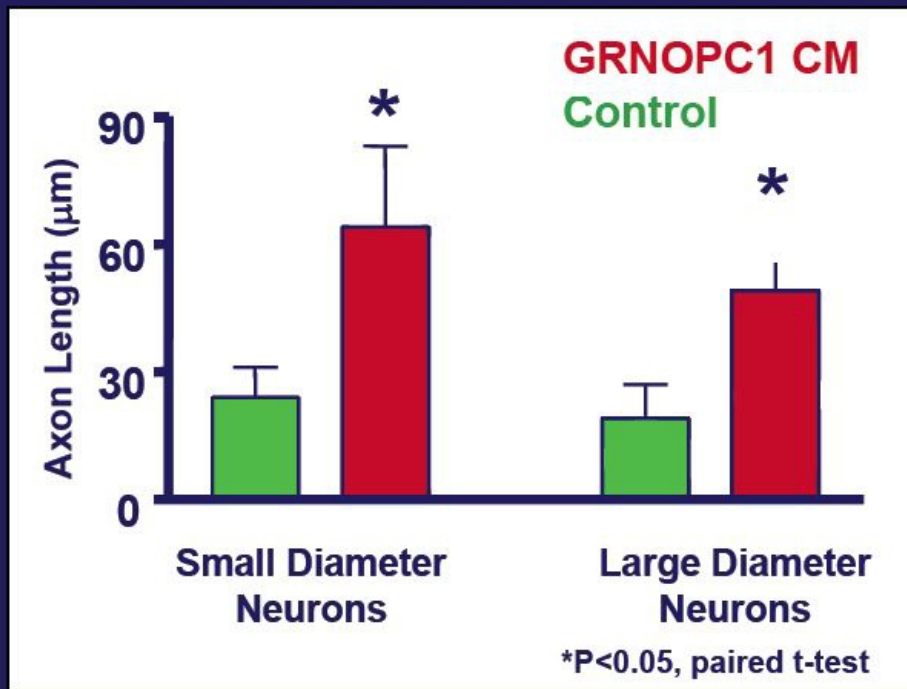


*(Loss of Neurons and Myelin)*



*(Myelinated Rat Axons)*

# GRNOPC1 Promotes Neural Outgrowth



## Concentrations of Neurotrophic Proteins in GRNOPC1 Conditioned Medium

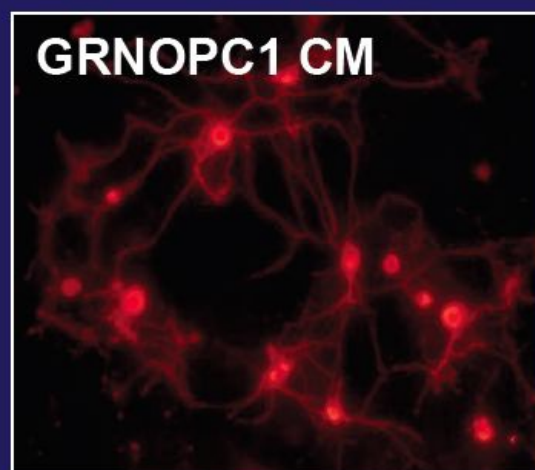
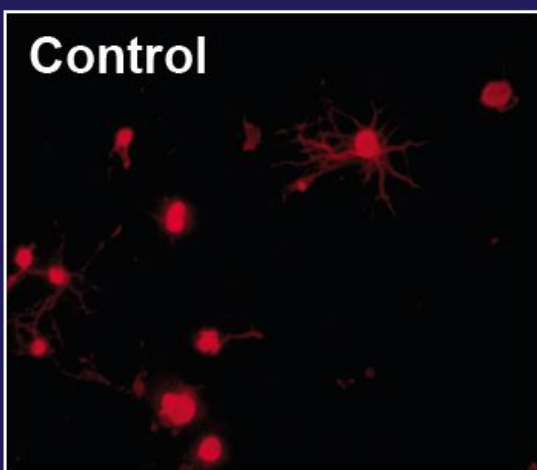
**Midkine**  $7.7 \pm 2.3$  ng/ml (n = 6)  
neurite growth-promoting factor 2

**Activin A**  $13.2 \pm 1.6$  ng/ml (n = 6)  
growth & differentiation factor in TGF family

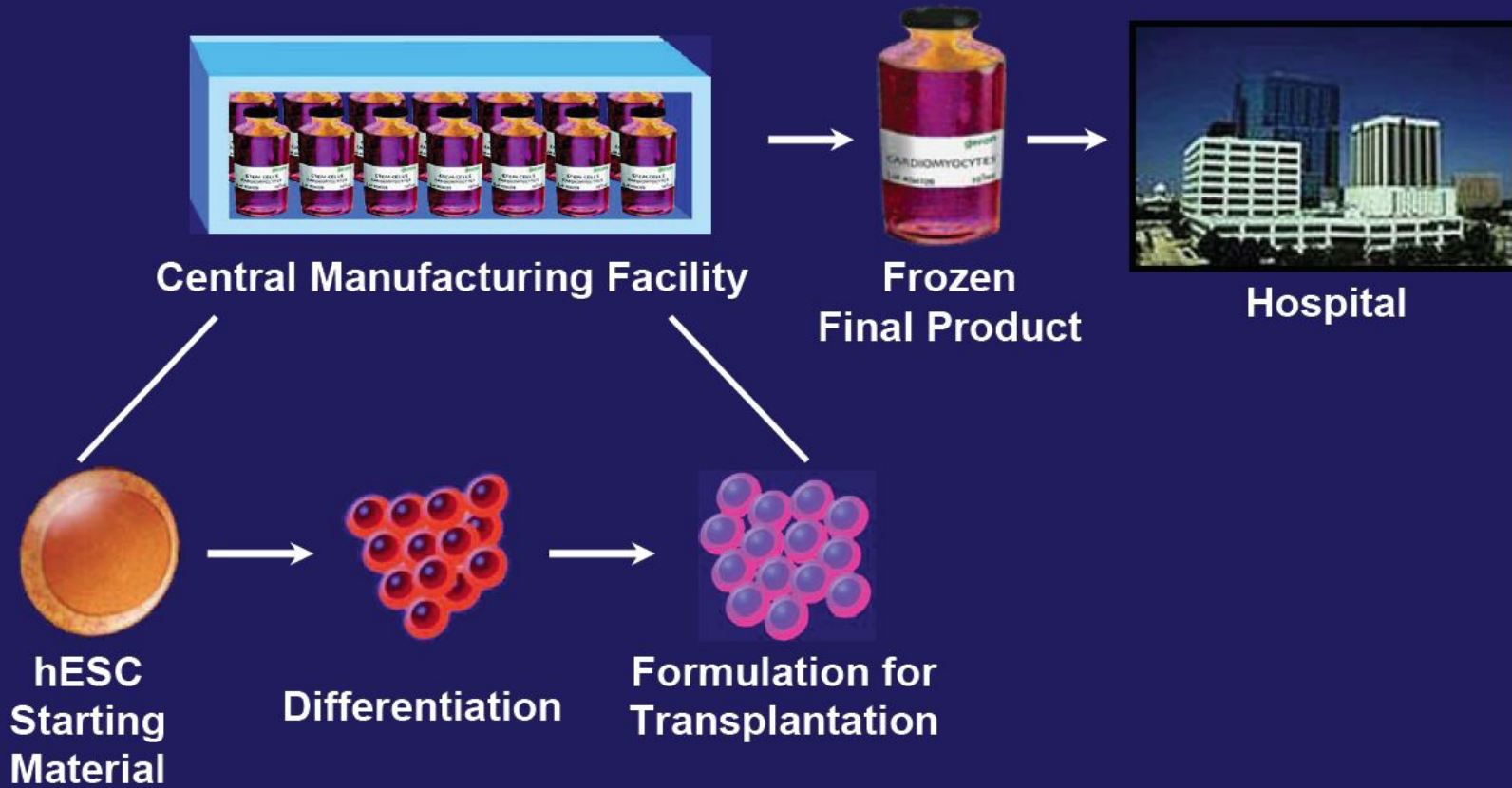
**BDNF**  $48 \pm 13$  pg/ml (n = 9)  
brain-derived neurotrophic factor

**TGF- $\beta$ 2**  $95 \pm 18$  pg/ml (n = 9)  
transforming growth factor-beta 2

**HGF**  $1.2 \pm 0.5$  ng/ml (n = 5)  
hepatocyte growth factor

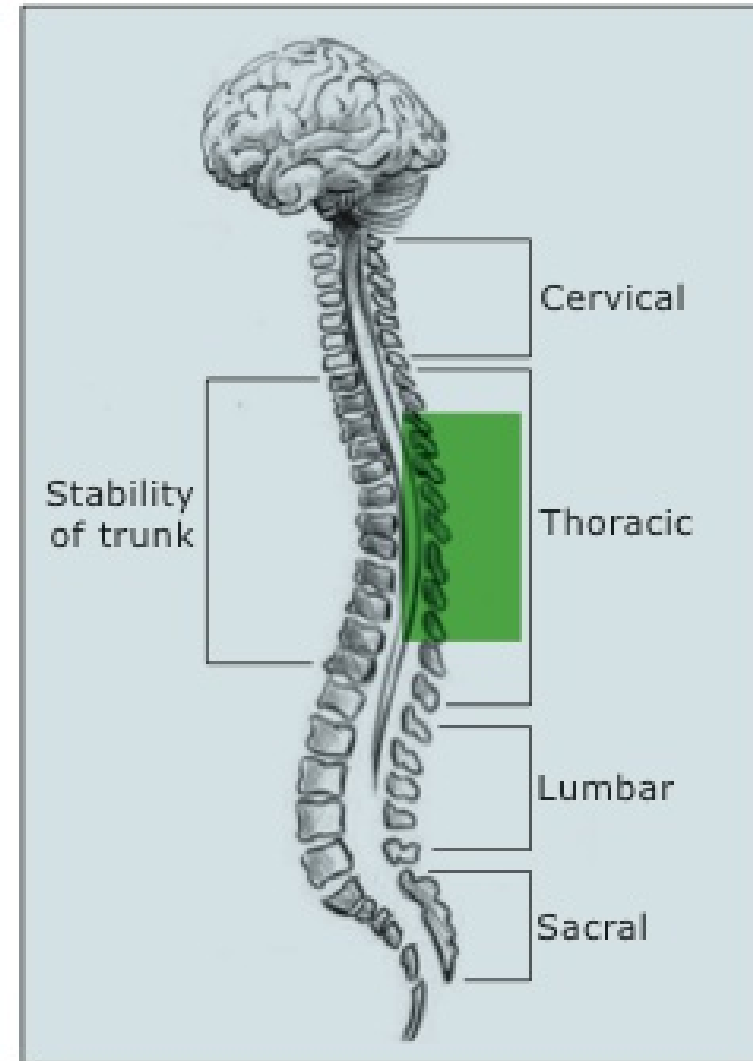


# Human Embryonic Stem Cell (hESC) Based Therapy



# GRNOP1 Phase 1 Multi-Center Spinal Cord Injury Trial

- **Open Label Trial**
- **Subacute, Functionally Complete Spinal Cord Injury with a Neurological Level of T3 to T10**
- **$2 \times 10^6$  Cells**
- **Transplant 7-14 Days Post Injury**
- **Temporary Immunosuppression with Low Dose Tacrolimus**
- **Primary Endpoint: Safety**
  - *Neurological*
  - *Overall*
- **Secondary Endpoint: Efficacy**
  - *ASIA Sensory Score*
  - *Lower Extremity Motor Score*



# Clinical Trials Database

<http://clinicaltrials.gov/>

**ClinicalTrials.gov**

A service of the U.S. National Institutes of Health

*ClinicalTrials.gov is a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world. Learn more about clinical studies and about this site, including relevant history, policies, and laws.*

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ClinicalTrials.gov currently lists **209,194 studies** with locations in all 50 States and in **192 countries**.

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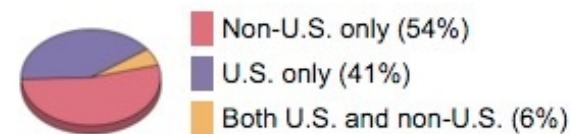
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Total N = 37,436 studies  
(Data as of February 23, 2016)

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Deborah Zarin, Director, Hum Bio Grad.

# Clinical Trials Database

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Example: "Heart attack" AND "Los Angeles"

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2	Completed	<p><b><a href="#">Haploidentical Stem Cell Transplant for Treatment Refractory Hematological Malignancies</a></b></p> <p><b>Conditions:</b> Acute Lymphoblastic Leukemia (ALL); Acute Myeloid Leukemia (AML); Secondary AML; Myelodysplastic Syndrome (MDS); Secondary MDS; Chronic Myeloid Leukemia; Juvenile Myelomonocytic Leukemia (JMML); Paroxysmal Nocturnal Hemoglobinuria (PNH); Lymphoma, Non-Hodgkin; Hodgkin Disease</p> <p><b>Interventions:</b> Procedure: Stem Cell Transplantation; Device: Miltenyi Biotec CliniMACS; Drug: Systemic chemotherapy and antibodies</p>
3	Completed	<p><b><a href="#">CARDIOSphere-Derived aAutologous Stem CElls to Reverse ventricUlar dySfunction</a></b></p> <p><b>Conditions:</b> Recent Myocardial Infarction; Ventricular Dysfunction</p> <p><b>Intervention:</b> Biological: Autologous stem cell infusion</p>
4	Recruiting	<p><b><a href="#">Reversal of Type 1 Diabetes in Children by Stem Cell Educator Therapy</a></b></p> <p><b>Condition:</b> Type 1 Diabetes</p> <p><b>Intervention:</b> Device: Stem Cell Educator</p>

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ClinicalTrials.gov

A service of the U.S. National Institutes of Health

Example: "Heart attack" AND "Los Angeles"

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2	Recruiting	<a href="#">Reversal of Type 1 Diabetes in Children by Stem Cell Educator Therapy</a> Condition: Type 1 Diabetes Intervention: Device: Stem Cell Educator
3	Recruiting	<a href="#">Allogeneic Mesenchymal Stem Cell Transplantation in Tibial Closed Diaphyseal Fractures</a> Condition: Tibial Fracture Interventions: Biological: Mesenchymal stem cell injection; Biological: Placebo
4	Recruiting	<a href="#">Stem Cell Transplantation for Stiff Person Syndrome (SPS)</a> Condition: Stiff Person Syndrome Intervention: Biological: Autologous Hematopoietic Stem Cell Transplantation

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Rank	Status	Study
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2	Recruiting	<a href="#">Neural Stem Cell Transplantation in Traumatic Spinal Cord Injury</a> Condition: Spinal Cord Injury Intervention: Biological: Autologous Stem Cell Transplantation
3	Recruiting	<a href="#">Safety and Efficacy of Autologous Mesenchymal Stem Cells in Chronic Spinal Cord Injury</a> Condition: Spinal Cord Injury Intervention: Procedure: Mesenchymal stem cell transplantation
4	Recruiting	<a href="#">Nerve Regeneration-guided Collagen Scaffold and Mesenchymal Stem Cells Transplantation in Spinal Cord Injury Patients</a> Condition: Spinal Cord Injury

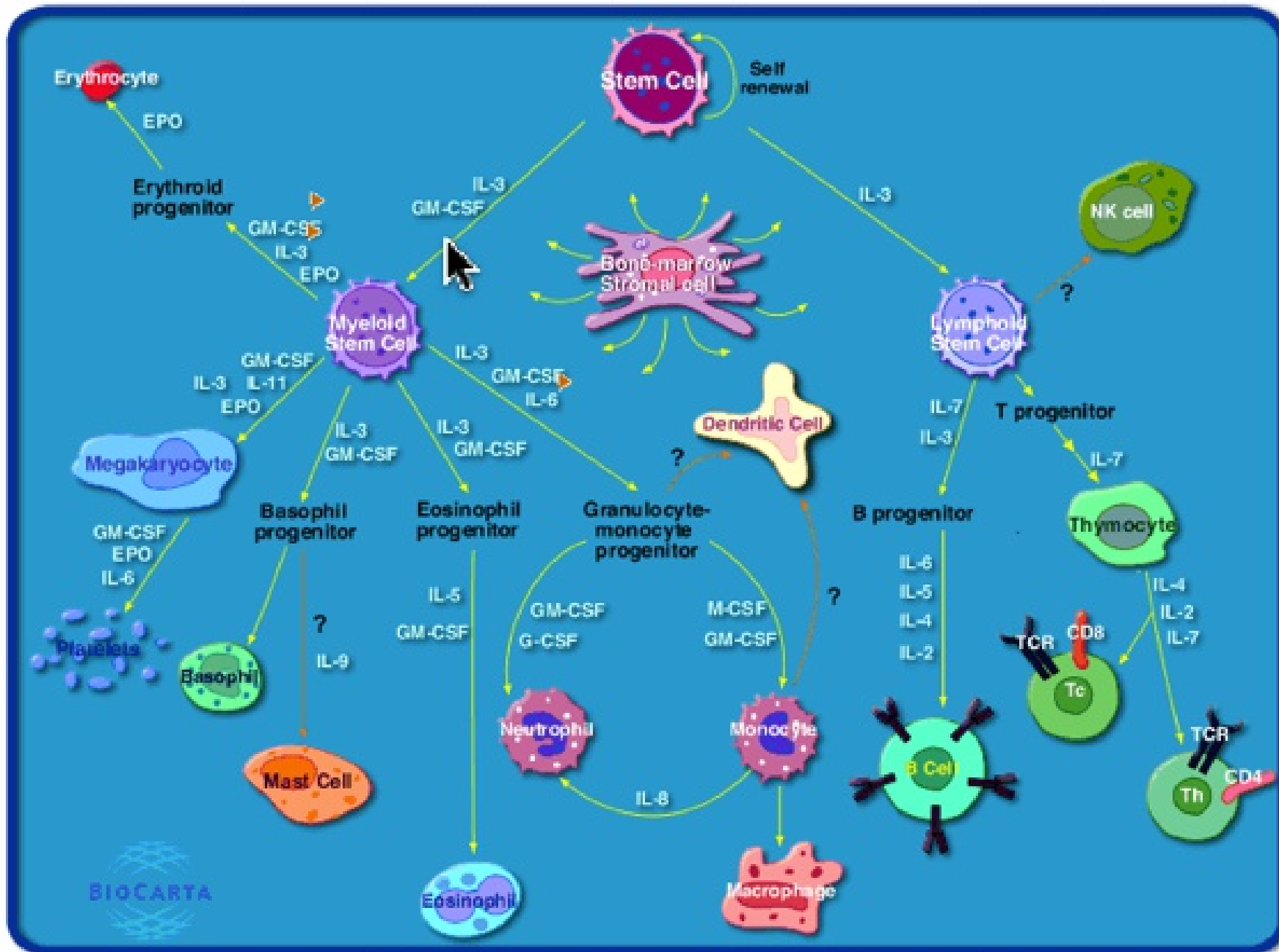
# Clinical Trials of Hematopoietic Stem Cell Transplantation

---

Judith A. Shizuru, M.D., Ph.D.  
Division of Blood and Marrow  
Transplantation  
Stanford University Medical Center

# Hematopoiesis

[http://www.biocarta.com/pathfiles/h\\_stemPathway.asp](http://www.biocarta.com/pathfiles/h_stemPathway.asp)



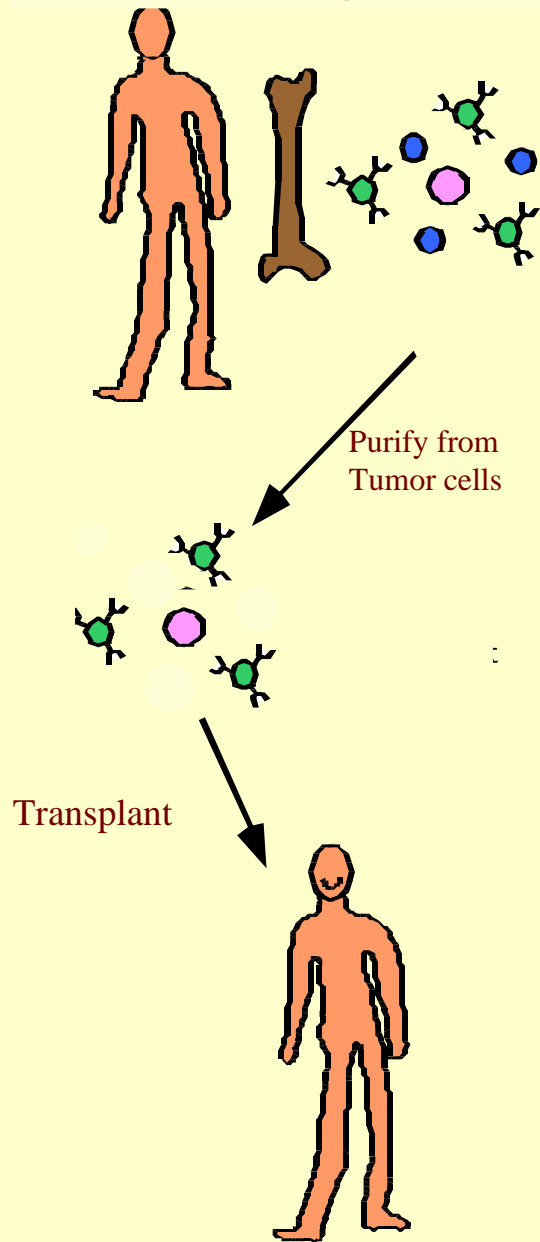
# Bone Marrow Transplants to Cure Lymphomas / Thymomas

---

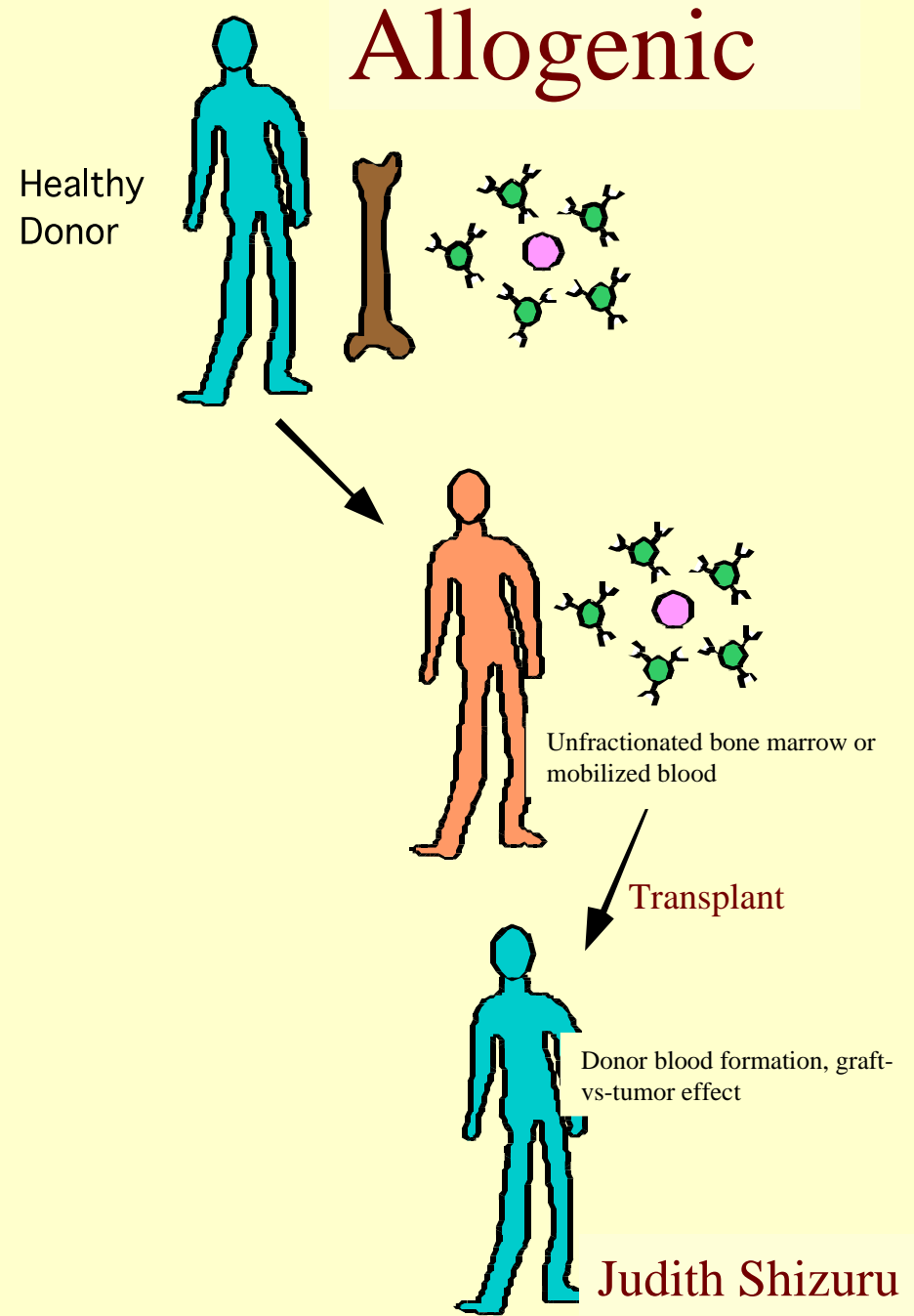
- Whole Body Irradiation to remove cancer and entire immune system
  - Also total lymphoid irradiation with antithymocyte serum
- Injection of bone marrow from a well matched donor to re-establish immune system
- Regulation of immune response to prevent graft versus host reaction.
- Autologous donation possible if one can purify and remove tumor cells, enriching for stem cells.
- Allogeneic donors have advantage of graft versus tumor reaction to kill any remaining tumor cells.
- Allogeneic donors have the disadvantage of graft versus host reaction if they are not well matched.

# Autologous vs. Allogeneic Transplants

## Autologous



## Allogeneic



# Complications of Allogeneic Transplants

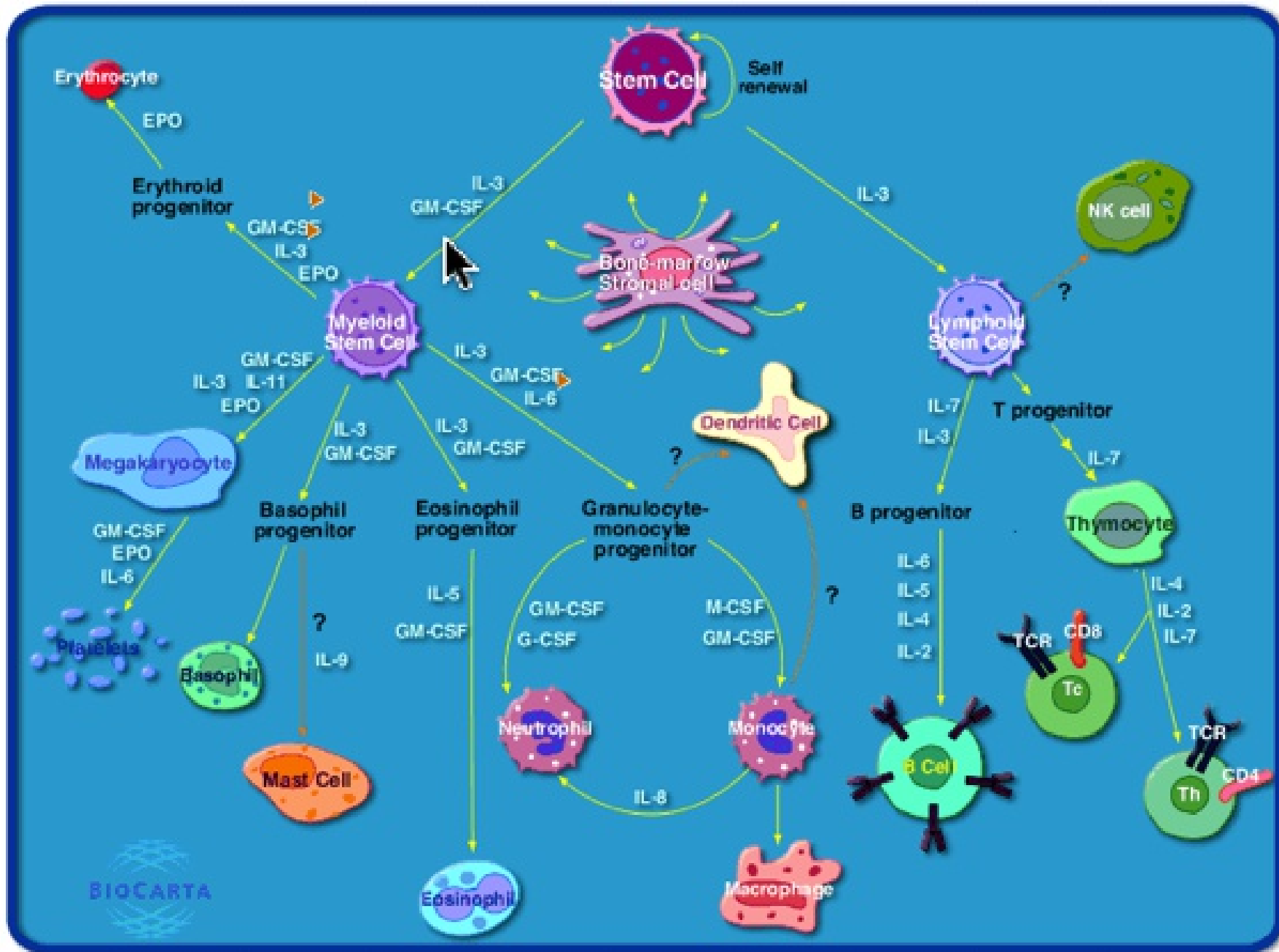
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Transplant related mortality = 10 - 15%

- Regimen related toxicity
- Infectious complications
- Engraftment failure
- Graft-versus-host disease

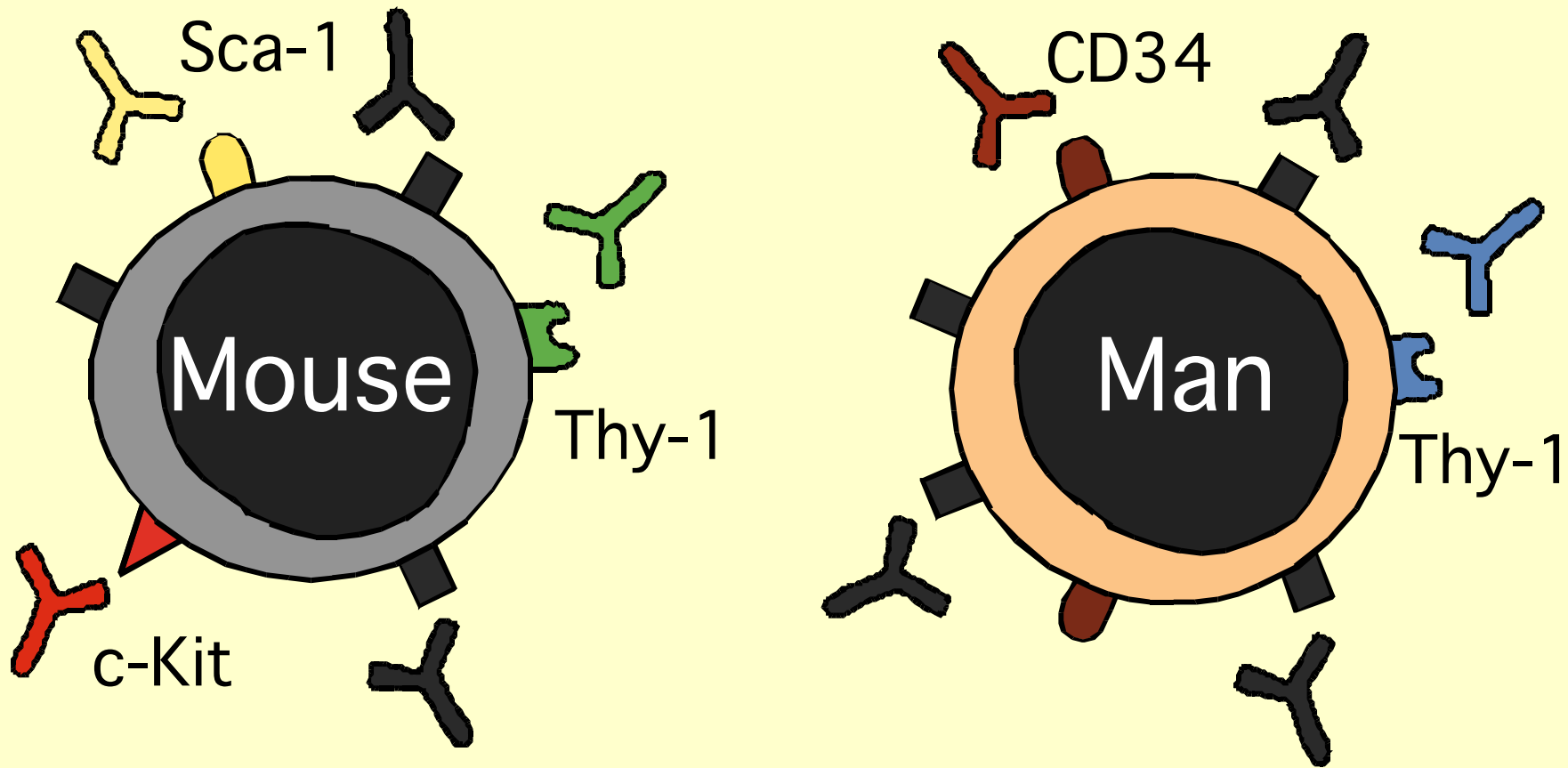
# Regulation of hematopoiesis by cytokines

[http://www.biocarta.com/pathfiles/h\\_stemPathway.asp](http://www.biocarta.com/pathfiles/h_stemPathway.asp)



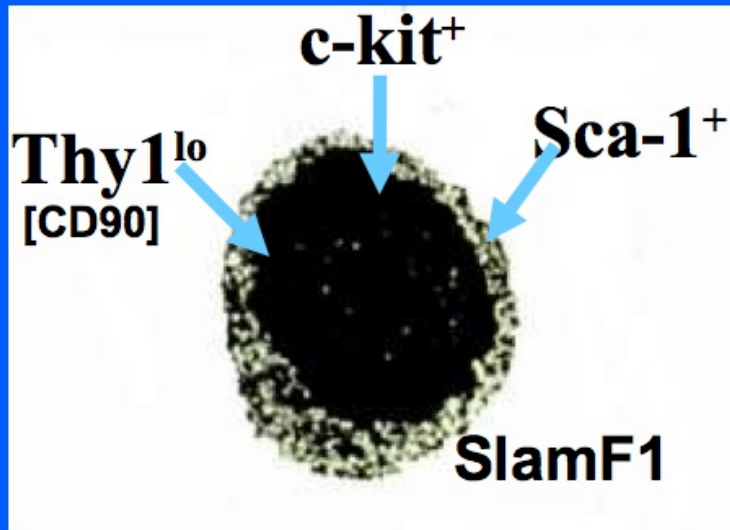
# Isolation of Hematopoietic Stem Cells

---



# Isolation of Hematopoietic Stem Cells

## MOUSE



Negative for:

B220

Mac-1

Gr-1

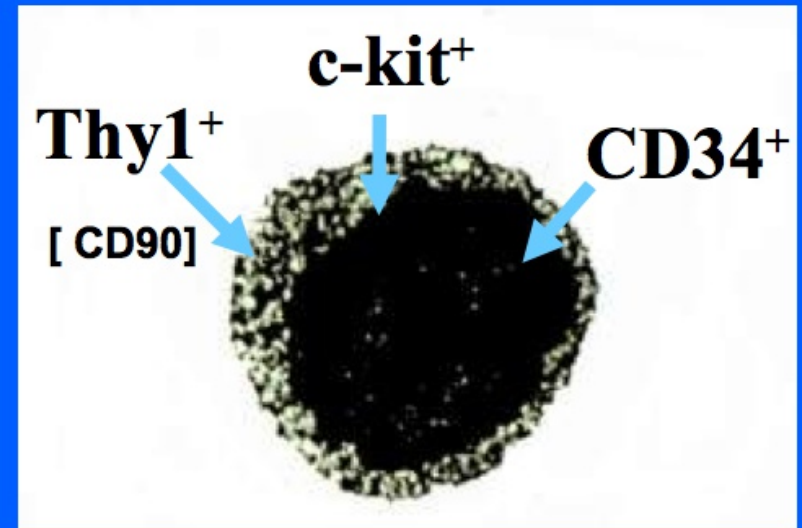
CD3, 4, 8

Ter119

Flk2

CD34

## MAN



Negative for:

CD10

CD14

CD15

CD16

CD19

CD20

CD 38

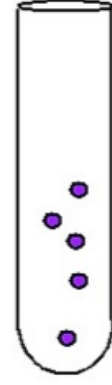
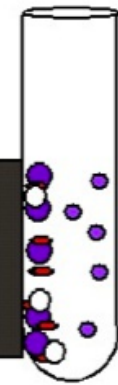
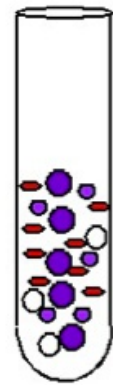
CD 3,4,8

Glycophorin A

# Isolation of Pure Hematopoietic Stem Cells



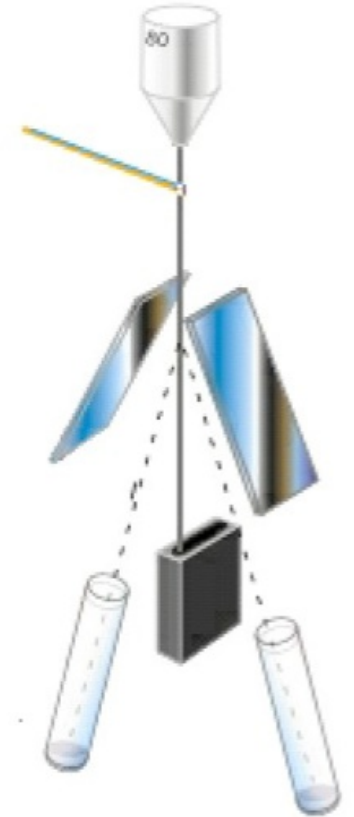
Lineage stain



magnet

HSC enriched cells

HSC stain

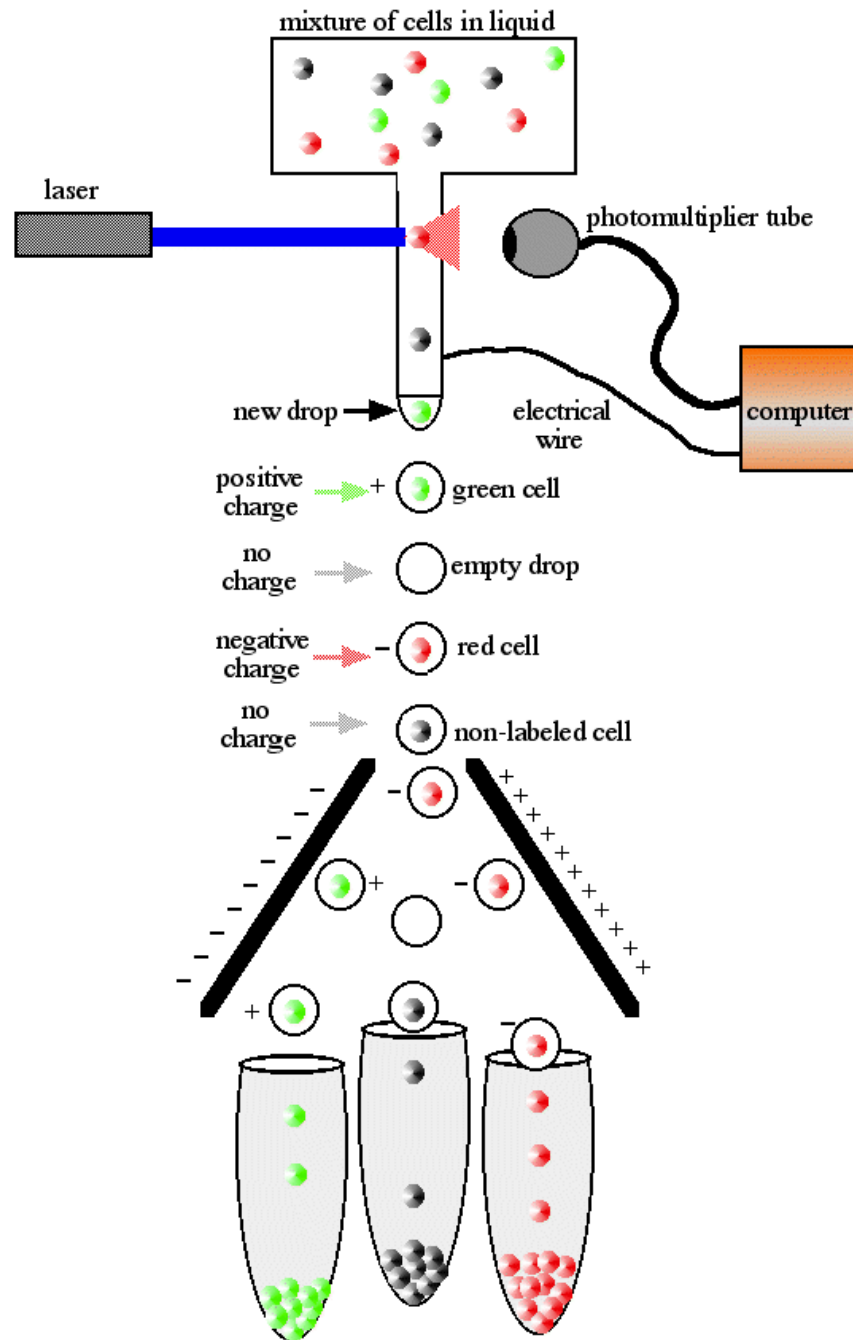


Collect bone marrow cells

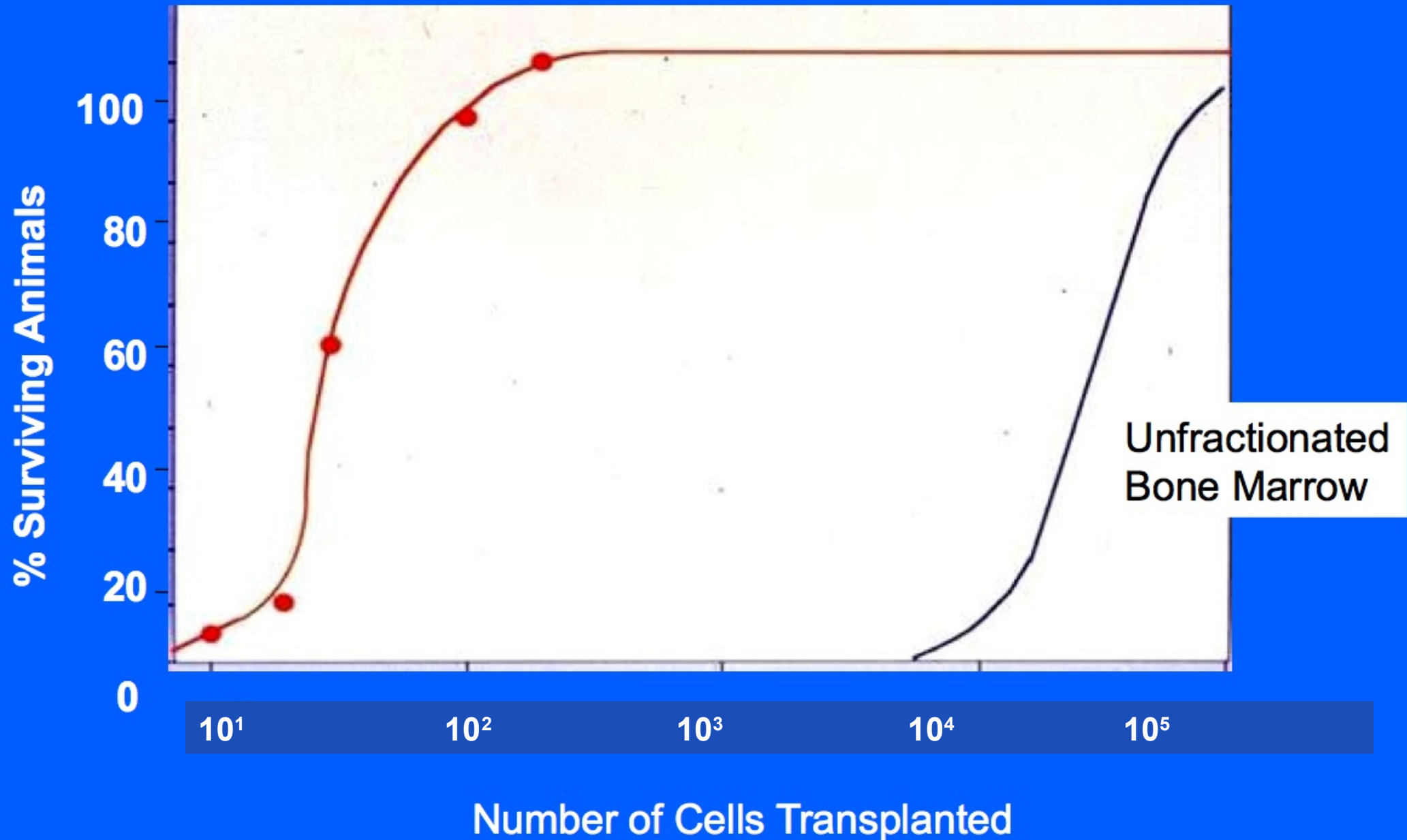
Deplete mature blood cells by labeling with magnetic antibodies

Sort stem cells

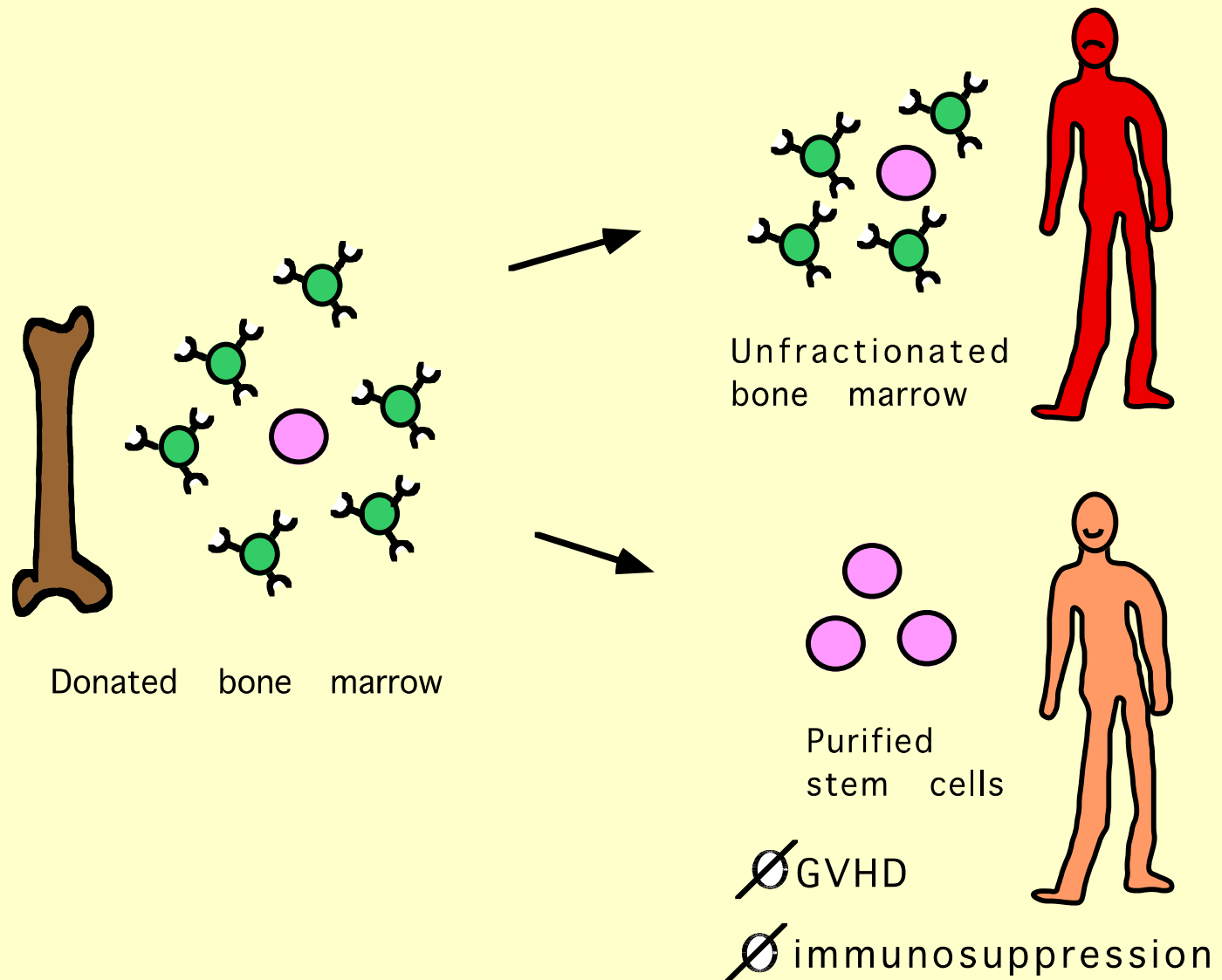
# Fluorescent Activated Cell Sorter (FACS) Herzenberg & Herzenberg



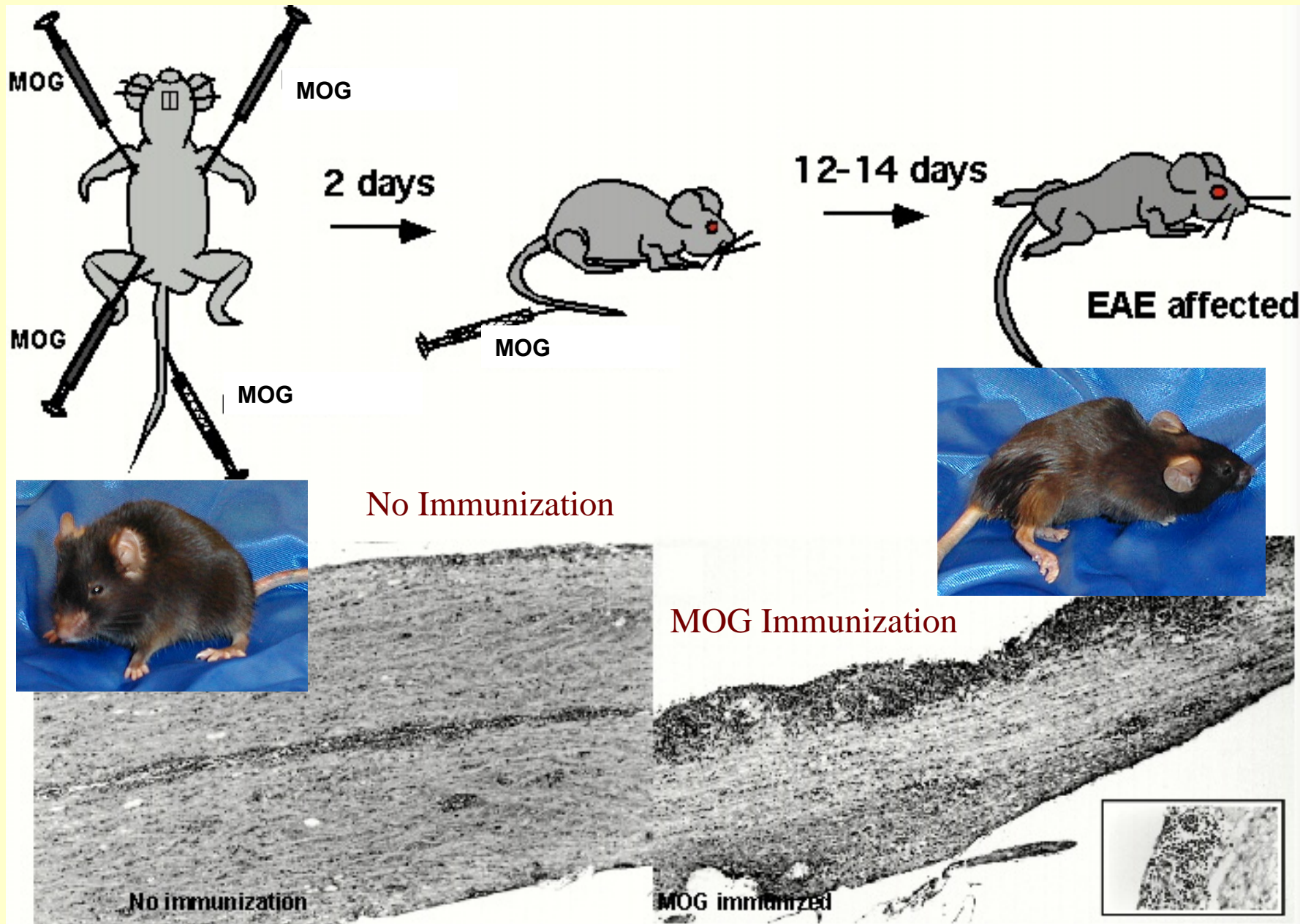
# Purified Hematopoietic Stem Cells are 2000 Times More Effective in Transplants



# Why Transplant Purified Allogeneic HSCs?



# Hematopoietic Stem Cell Therapy for Mouse Multiple Sclerosis



No Immunization

MOG Immunization

No immunization

MOG immunized

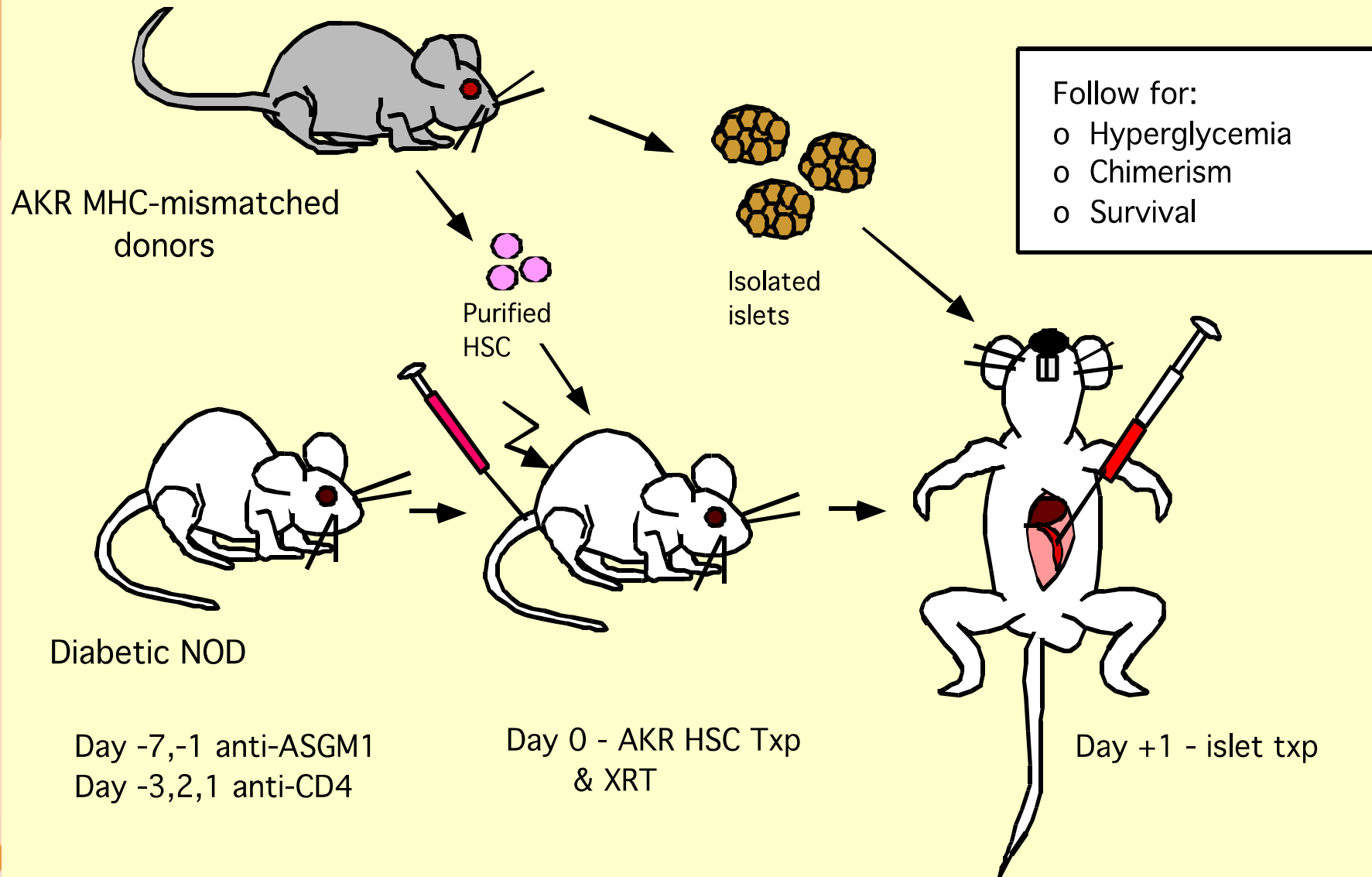


# Other Applications of Hematopoietic Stem Cell Transplantation

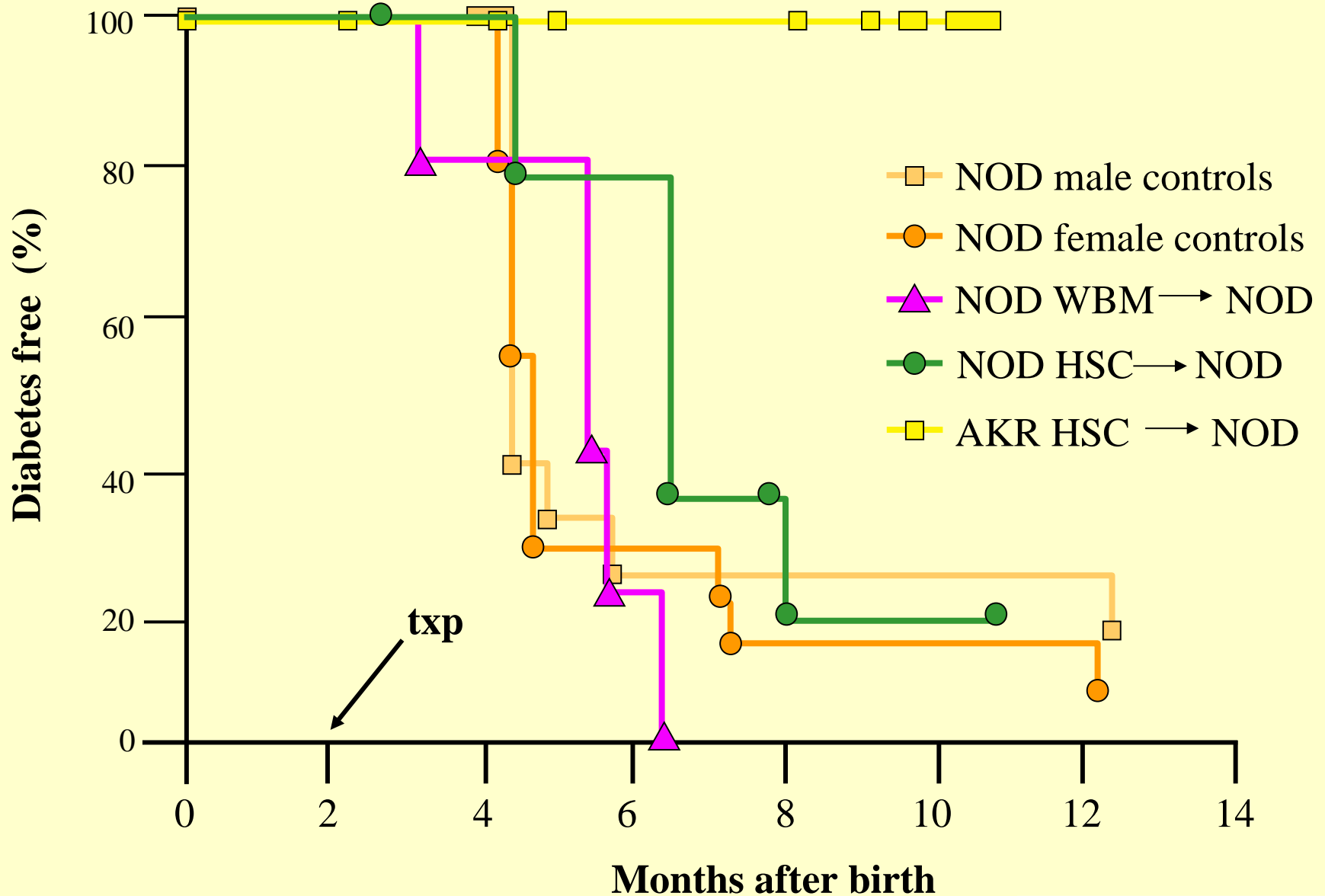
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- Treatment of autoimmune disease
  - Patients treated with bone marrow transplants are often cured of autoimmune disease
  - Bone marrow transplant donors with autoimmune disease can pass the disease on to recipients
- Organ tolerance induction
  - Mice receiving organ transplant and HSC transplant together are tolerant and no rejection occurs. No immune suppressants are needed.
- Very high dose chemotherapy
  - Breast cancer patients receive very high dose chemotherapy that kills tumor and immune system.
  - Autogenic hematopoietic stem cell transplants recover patient's immune system.

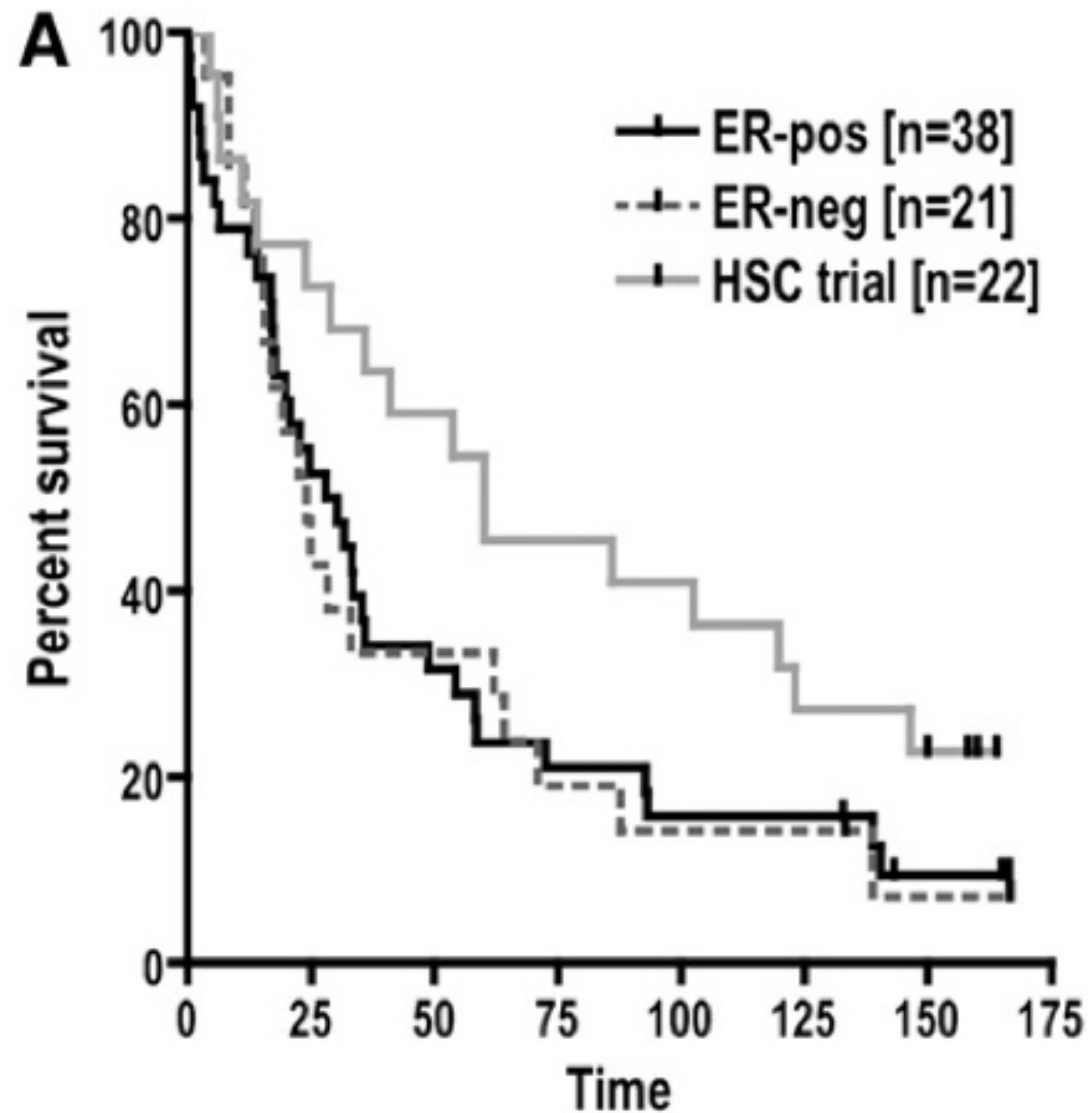
# Combined HSC & islet transplantation



# Treatment of Diabetic Mice (NOD) with Hematopoietic Stem Cell Transplants



# Hematopoietic Cell Treatment Coupled with High Dose Breast Cancer Chemotherapy



Stage Four Metastatic Breast Cancer

Müller et al. (2011) Biol. Blood Marrow Transplant