

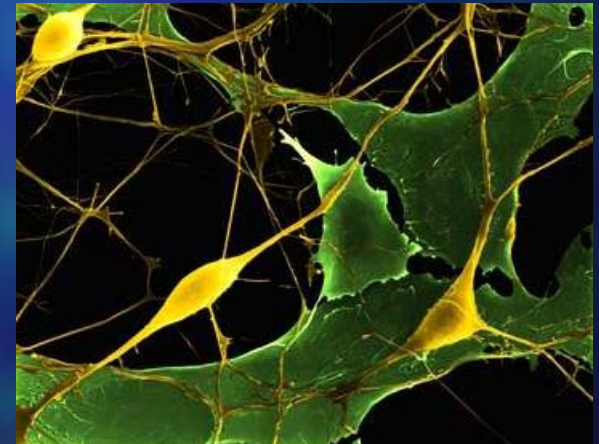
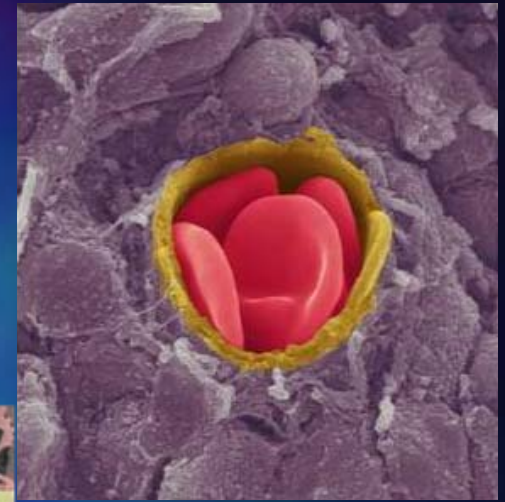
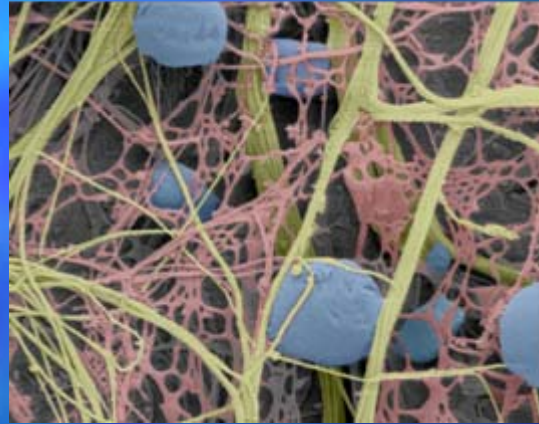
# Stem cells and cellular therapies: from research to clinic



Janis Ancans, PhD  
Faculty of Biology  
University of Latvia

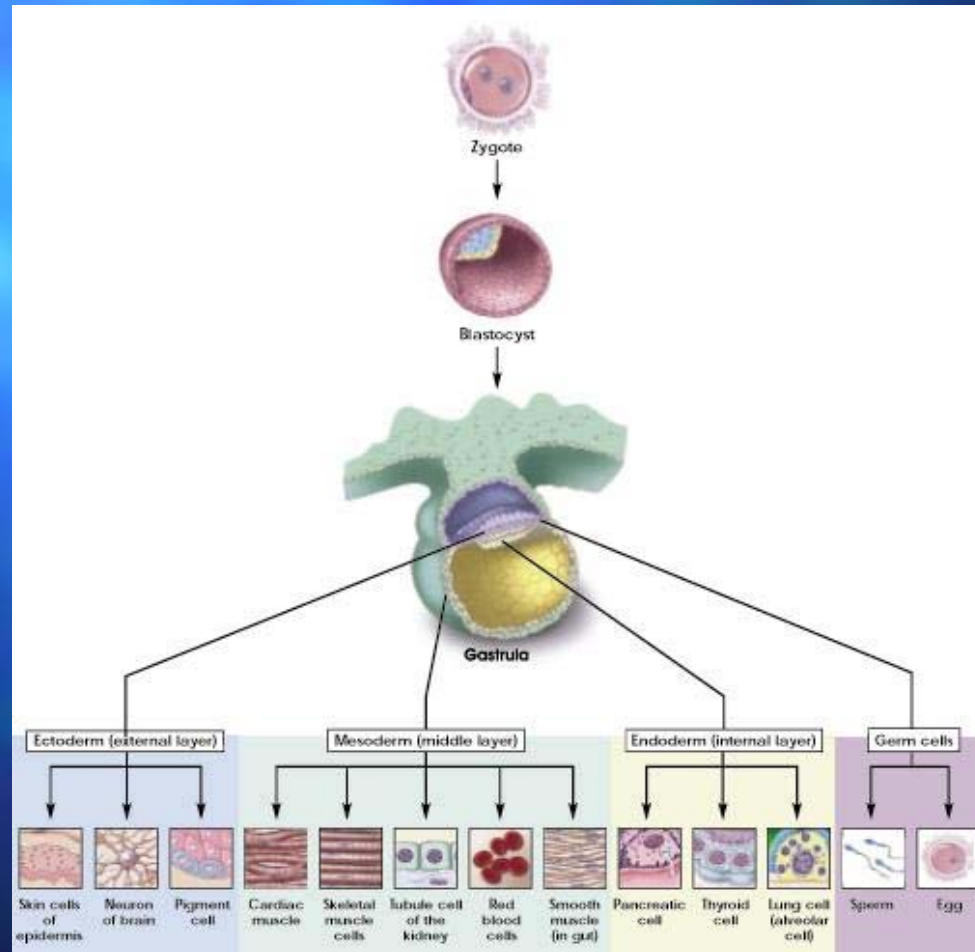


# Our cells





# Human body originates from one "stem cell"

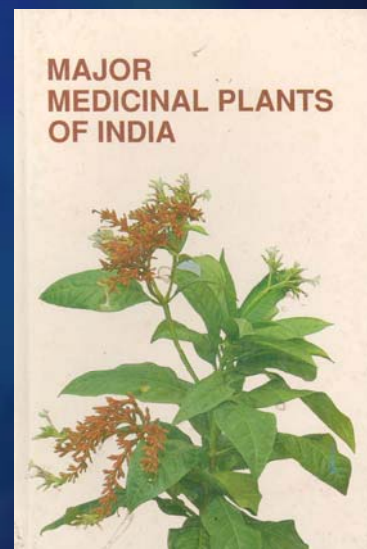
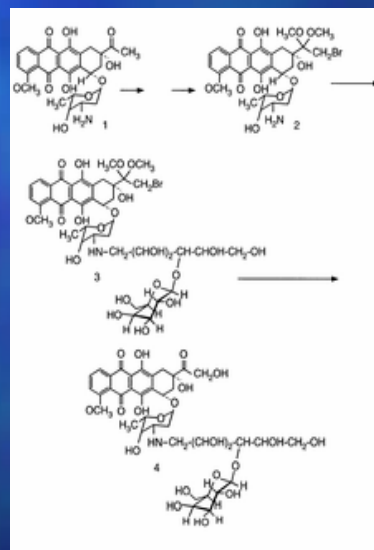




# Conventional drugs

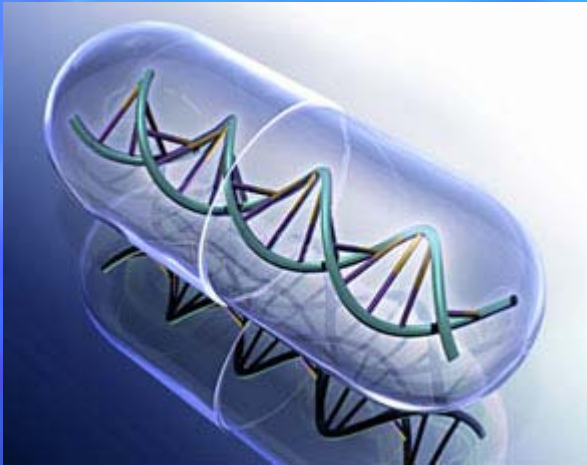


Long history of application  
Can have profound effects  
*Regeneration of cells/ tissues...?*

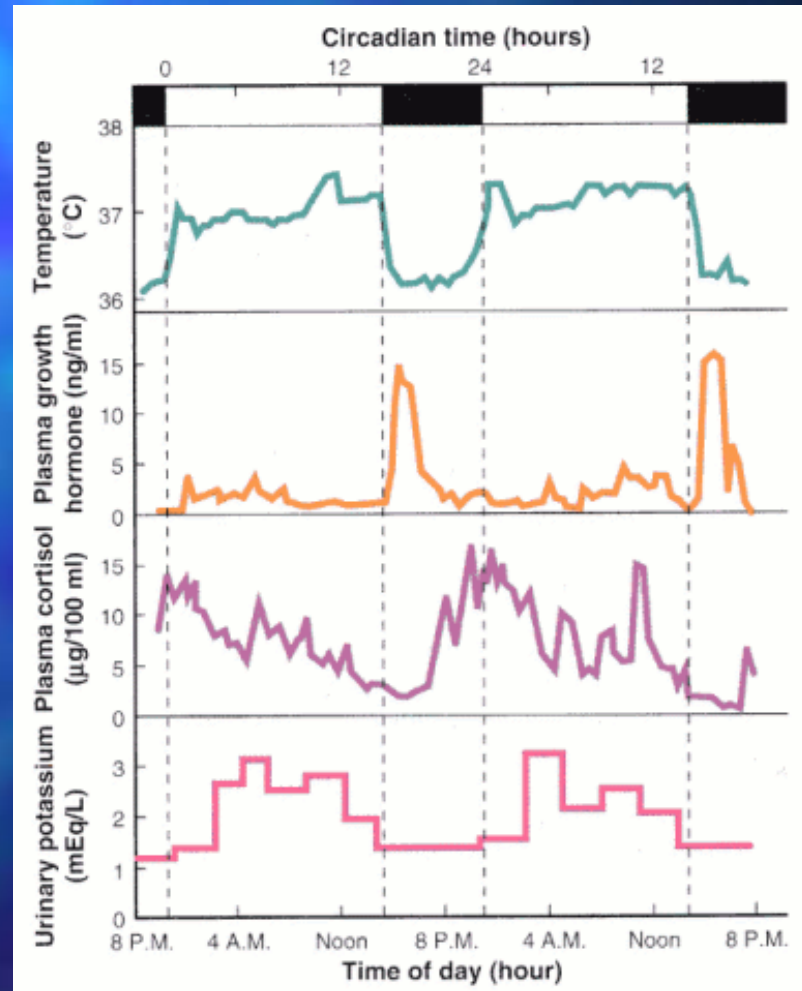




# Biologics: mimic some of cell/ tissue functions



Insulin (1923; 1982)  
Growth Hormone  
mAbs (anti TNF-alpha etc.)





# Transfusion/transplantation (cell therapy)



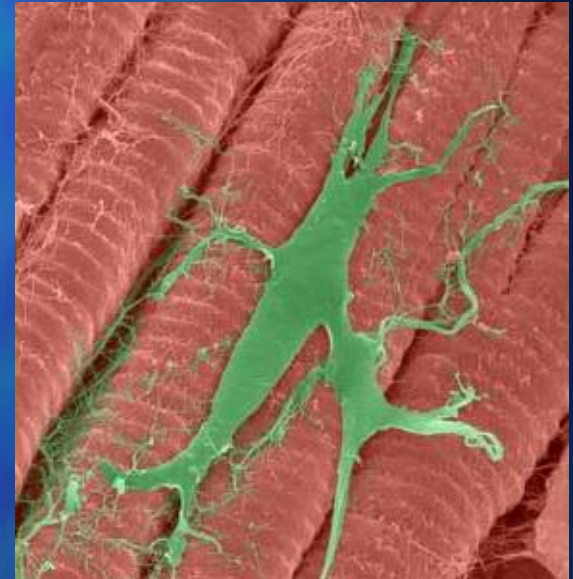
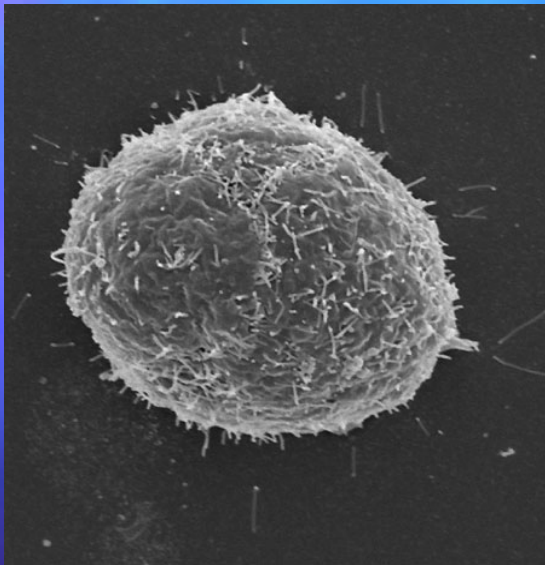
Blood transfusion (*Pope Innocent VIII* , 1492; Harvey 17th cent.; 1818 Dr. James Blundell )

Organ transplantations

Pancreatic islet transplantation



# Stem cell therapy



Bone marrow transplantation (1959; 1968- Minneapolis)

Hematopoietic stem cell transplantation (HSCT)

Cord blood stem cell transplantation (1989)

Stem cells - CD34+ , MSC, neuronal



# Stem cell therapy

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- Too much hype, incorrect perception
- New & very experimental field of therapy
- Clinical application are limited
- Currently no alternatives for regeneration of cell/ tissues functions
- Long term solution for health problems



## Products

	Indications	Preclinical	Phase I	Phase II	Phase III	Post-marketing Studies
<b><i>Osteocel</i></b> <sup>®</sup>	Focal Bone Repair					
<b><i>Prochymal</i></b> <sup>™</sup>	Steroid Refractory GvHD	FDA FAST TRACK				
<b><i>Prochymal</i></b> <sup>™</sup>	Crohn's Disease	FDA FAST TRACK				
<b><i>Prochymal</i></b> <sup>™</sup>	Acute GvHD					
<b><i>Chondrogen</i></b> <sup>™</sup>	Meniscal Repair					
<b><i>Provacel</i></b> <sup>™</sup>	Acute MI					
<b><i>Prochymal</i></b> <sup>™</sup>	Lung Disease					
<b><i>Prochymal</i></b> <sup>™</sup>	Arthritis					
<b><i>Osteocel-XC</i></b> <sup>™</sup>	Focal Bone Repair					



May 8 2008

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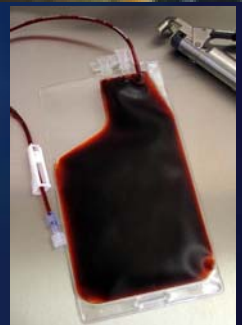
# Osiris Receives Approval for Use of Prochymal™ Under FDA Expanded Access Treatment Program

Decision makes investigational stem cell  
treatment available to critically ill children



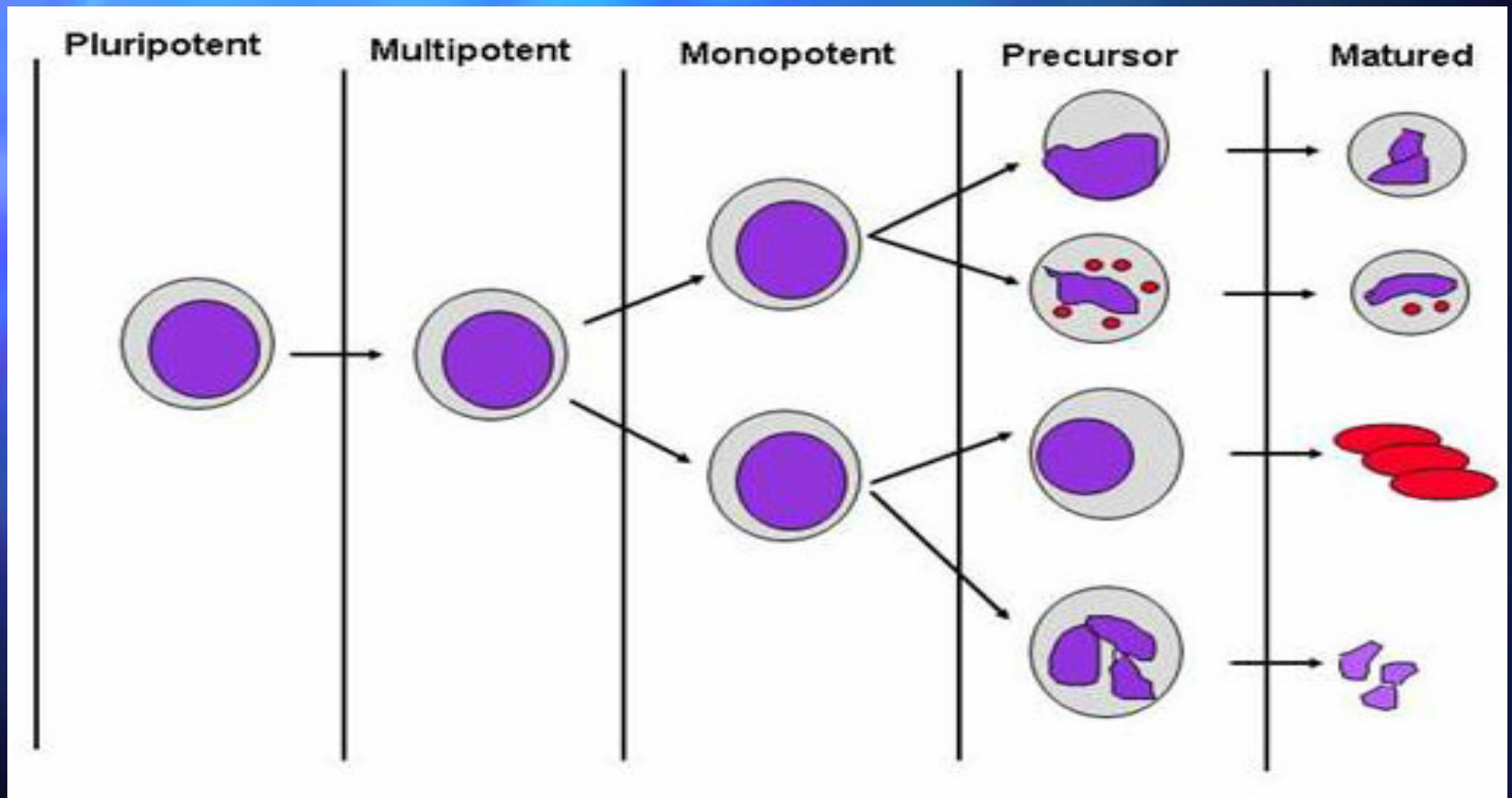
# Classification of stem cells

- hESC lines (human embryonic stem cell lines)
- Fetal tissues/ cell lines
- Cord blood (CB)
- Adult/ somatic SC (autologous, allogenic)



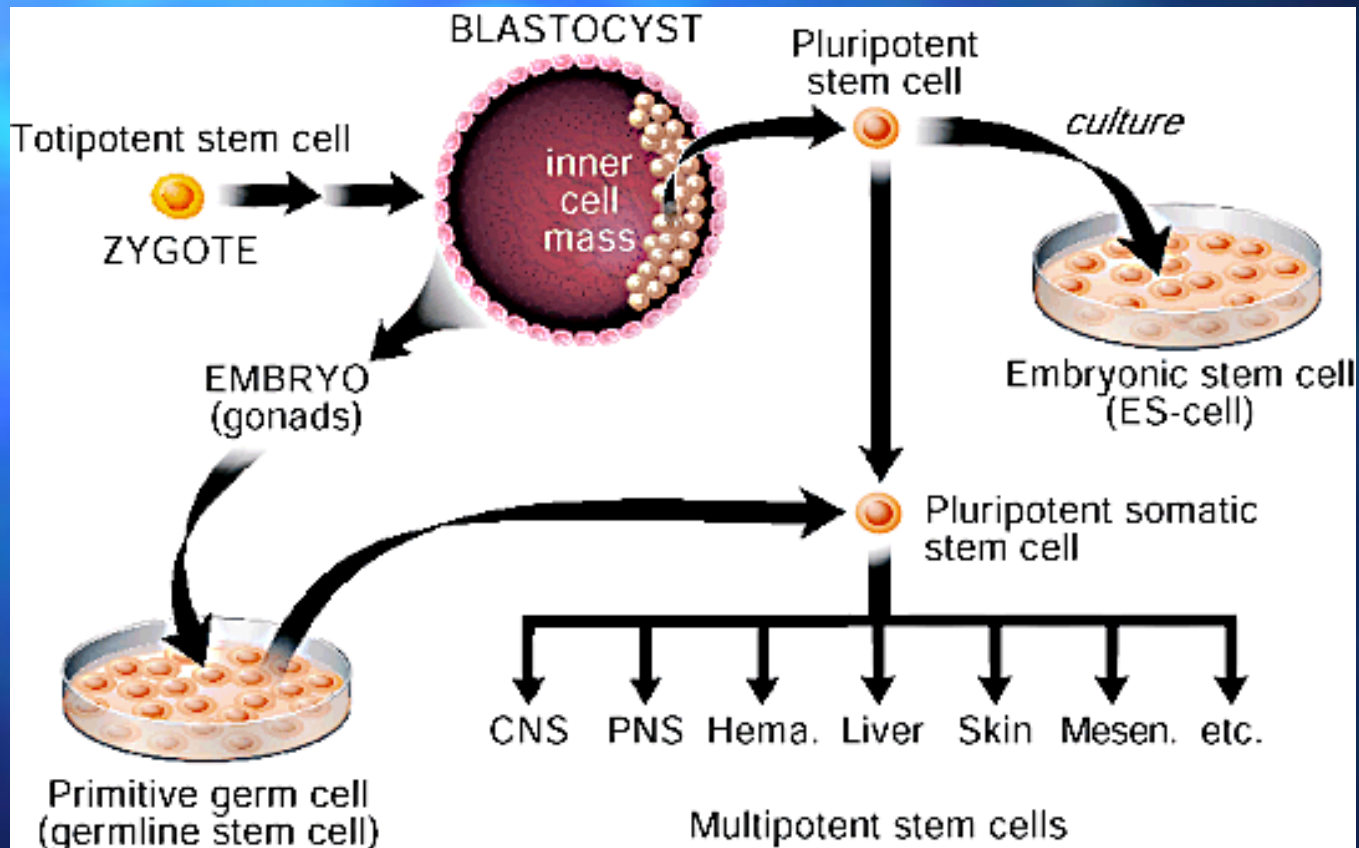


# Concept of stem cell “potency”



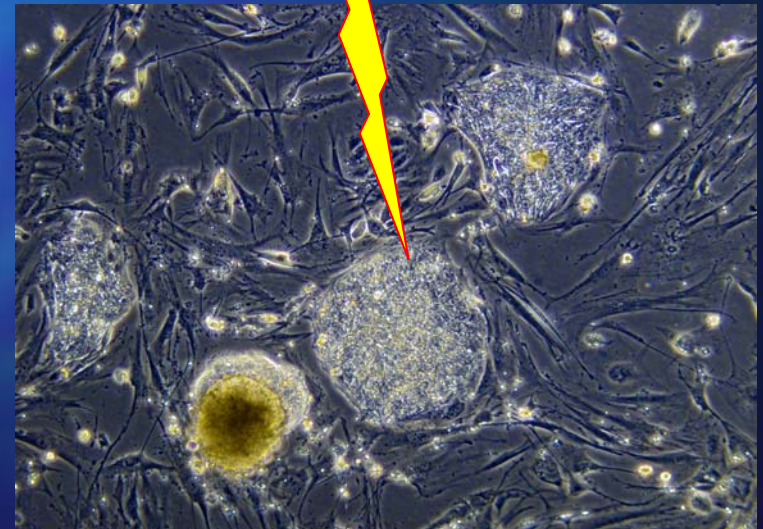
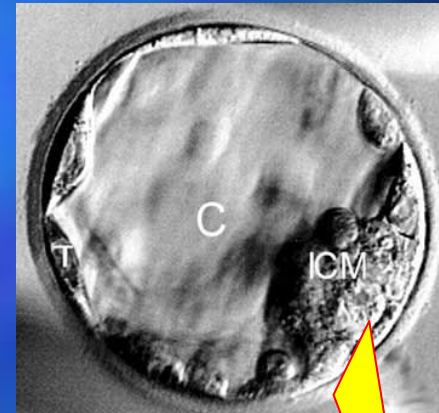
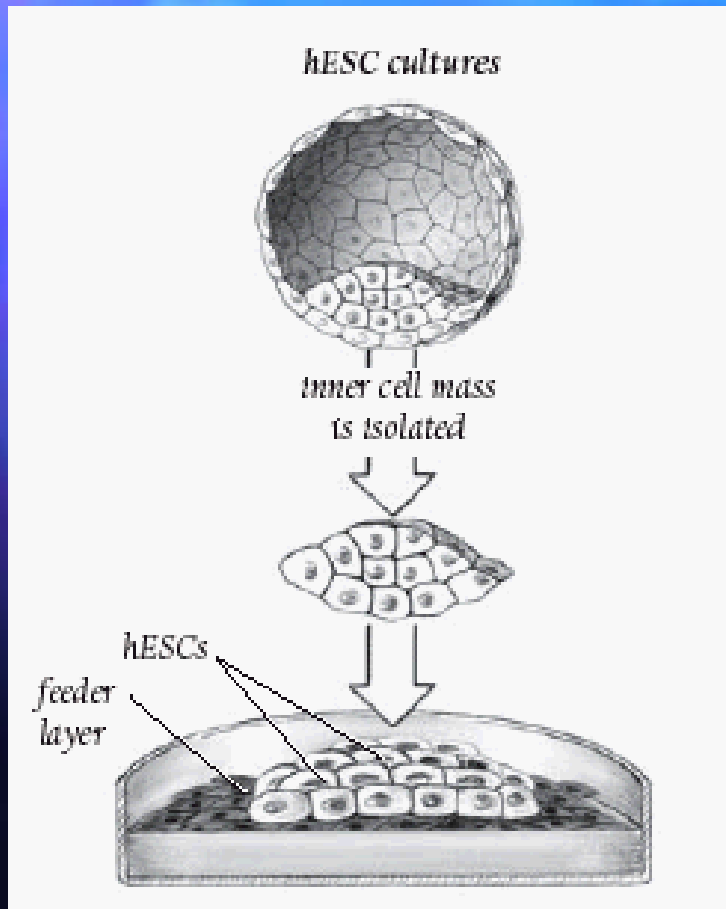


# hESC (human embryonic stem cells)



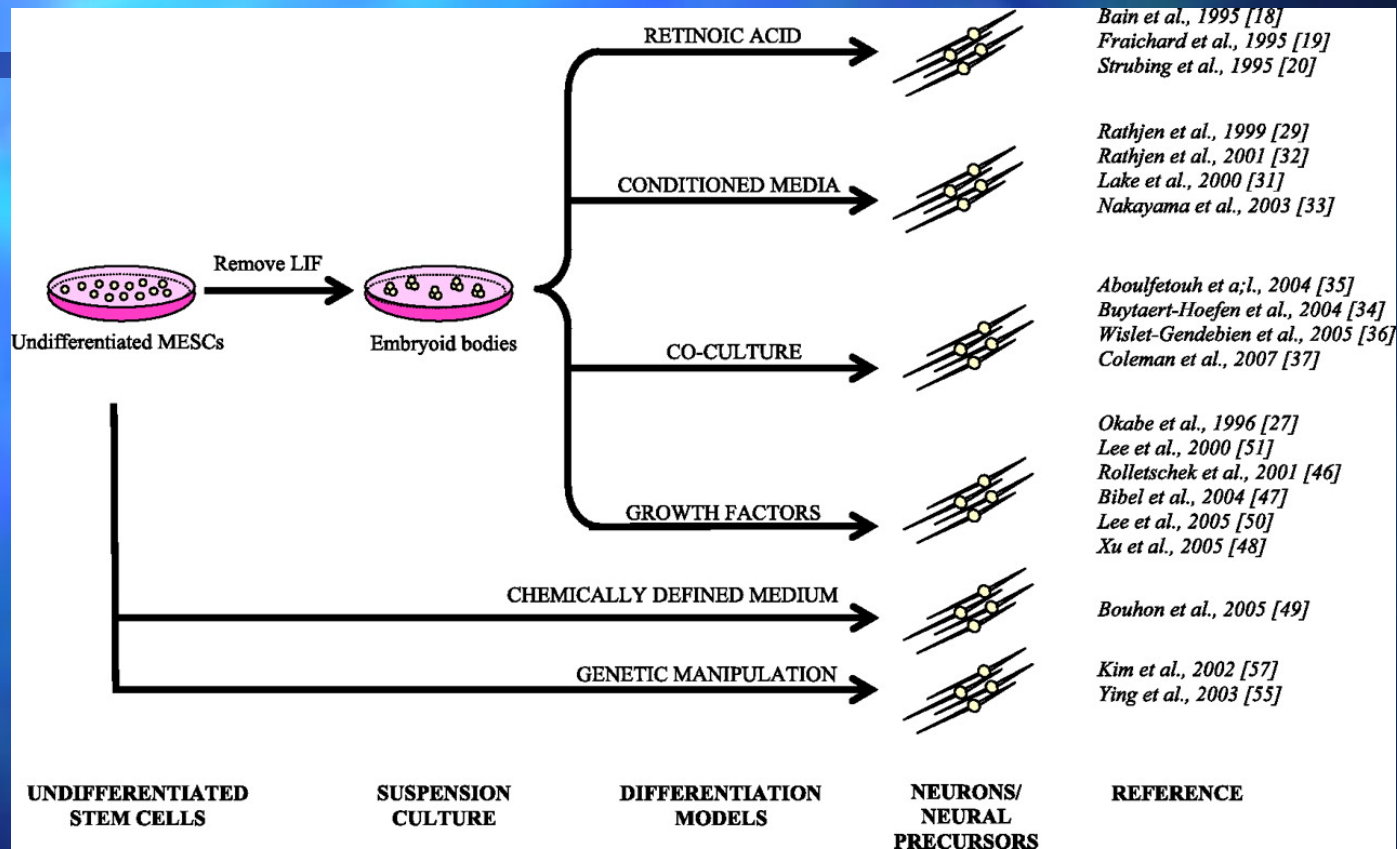


# hESC





# Pluripotency



Coleman, B. et al. Stem Cells 2007;25:2685-2694



# Elixirs of eternal youth...



Undefined biological preparation with no evidence of therapeutic effect. Possible side effects, e.g. infections



And available via internet, at  
room temperature



## Detailed Product Description

### *Laennec Fresh Cell Therapy*

*Stem cells are responsible for growth during childhood and for the repair and regeneration of human tissue throughout our lives...*

Placebo effect could be proportional to the price



# Stem cells – public perception, religion, ethics, politics





A medium shot of President George W. Bush speaking. He is wearing a dark suit, white shirt, and a blue patterned tie. He is positioned in front of a large window that looks out onto a desert landscape with mountains and sparse vegetation. To the left of the frame, a portion of the American flag is visible. In the bottom right corner, there is a small inset image showing a person at a desk.

LIVE

**Federal Funding of  
Stem Cell Research**

**C-SPAN**





## California Stem Cell Initiative

3.000.000.000 \$  
+ 3.000.000.000 \$





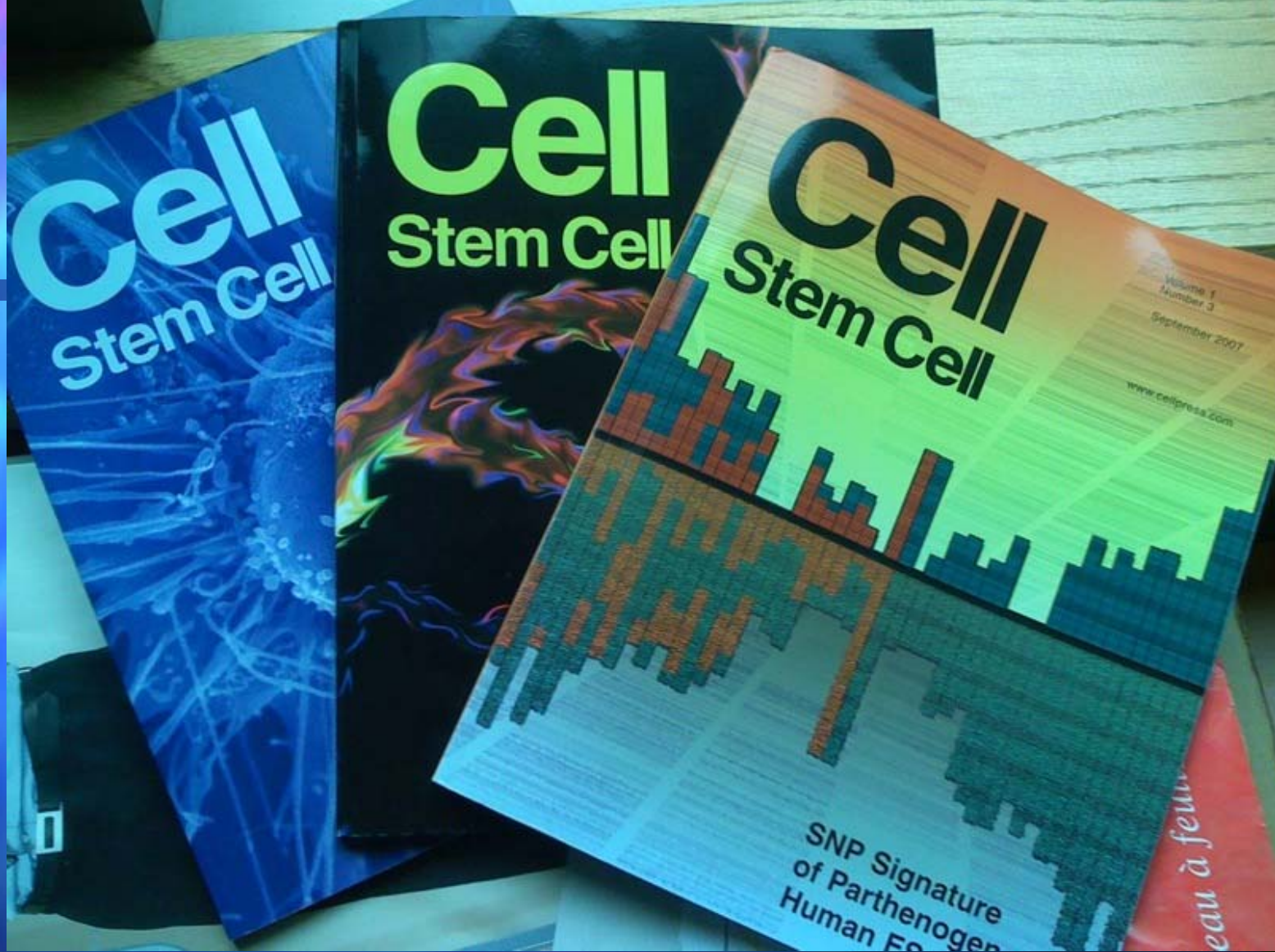
# Germany's Top Evangelical Church Leader Backs Continuing Embryonic Stem Cell Research

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BERLIN, January 3, 2008 (LifeSiteNews.com) - The Council President of the Evangelical Church in Germany (EKD), Dr. Wolfgang Huber, has declared his support for postponing the cut-off date for embryonic stem cell research (ESCR) for the sake of high-level research purposes.

According to the newspaper Frankfurter Rundschau, Dr. Huber said over the weekend that if the currently available stem cell lines were insufficient, **the deadline could be postponed for high-level research.** The Bundestag, the German national parliament, is expected to make a decision on cutting off ESCR before Easter.







# Stem cell therapy - “intelligent therapy”

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For instance, Mesenchymal stem cells (MSCs) produce different effects that depend on the medical condition (environment in the body?)



# Cells for therapy

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Accessibility of cells

- Source

*In vitro* manipulations

- Minimal
- Purification/ sorting
- Extensive (expansion etc)



# Cell therapy

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- Establish safety
- Delivery method
- “Therapeutic window”
- Evaluation of therapeutic potential  
( selection of criteria)



3 questions

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What?

When?

How?



# Potential applications (1)

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- 1) Spinal cord damage; diabetes; cardiovascular; etc.
- 2) Neurodegenerative diseases; detachment of eye retina
- 3) Restoration of hematopoiesis (CB >7000 by 2008); ischemia



# Potential applications (2)

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- 4) Regeneration of bone/ cartilage/ muscle tissue; reconstructive applications; autoimmune diseases; cardiovascular; ischemias



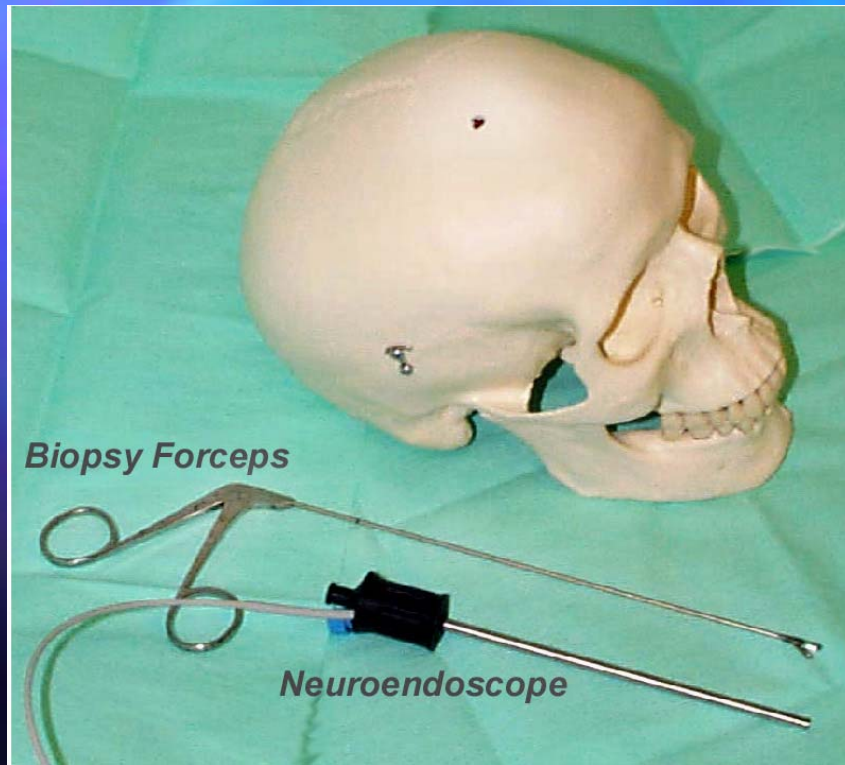
# Adult (somatic) Stem Cells

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- Human body contains multipotent cells (*somatic stem and progenitor cells*) – the cellular basis for organ homeostasis and regeneration process
- No bioethical problems; no transplant rejection (in case of autologous)

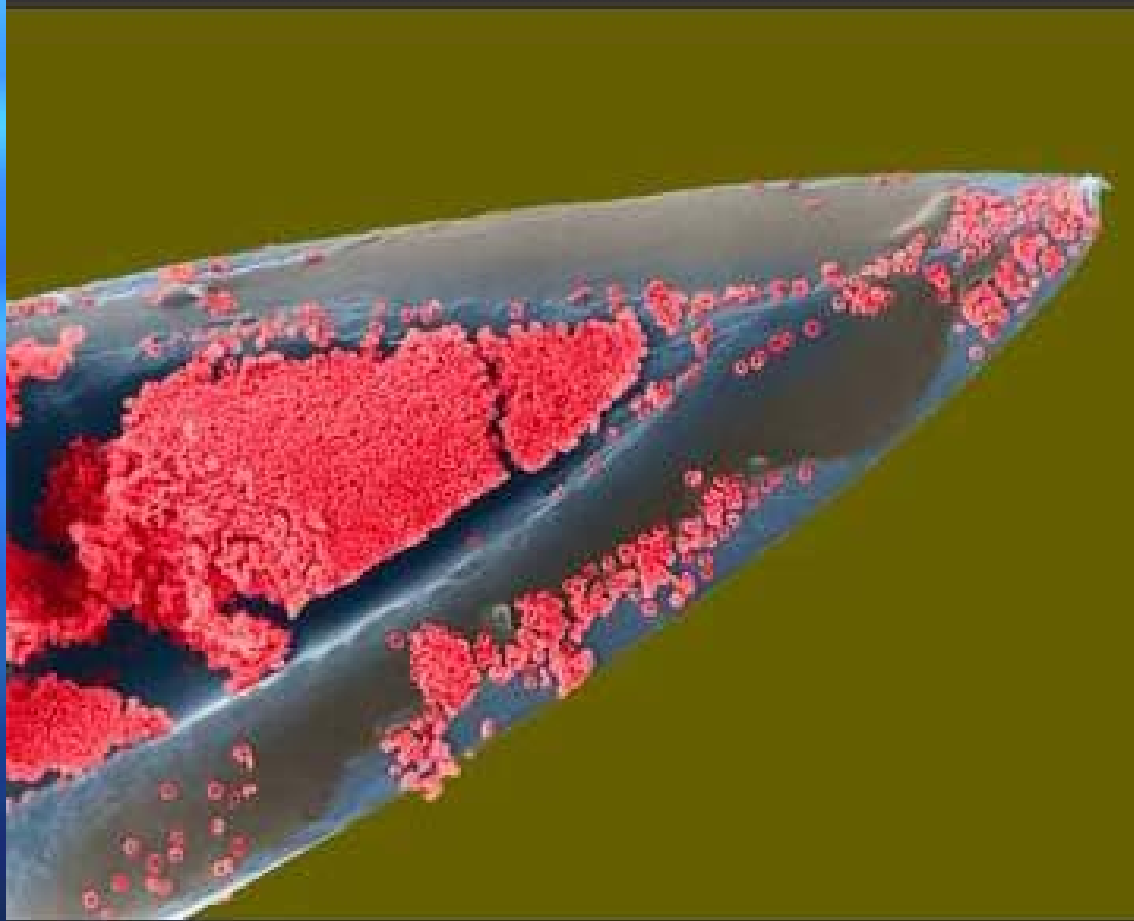


# Stem cells in every organ



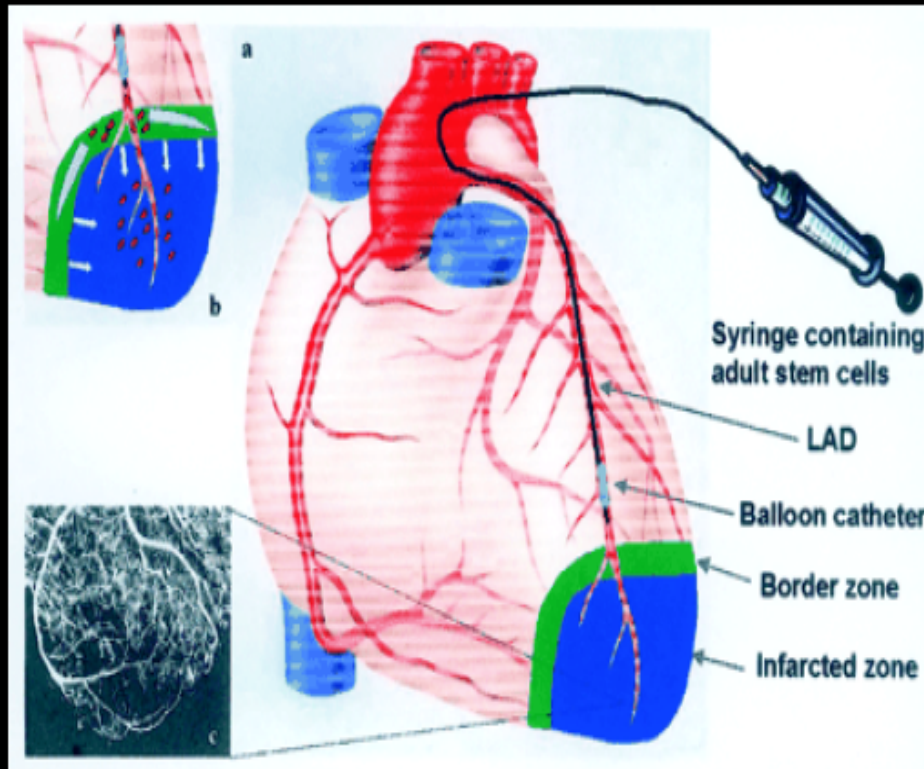


# Therapeutic applications





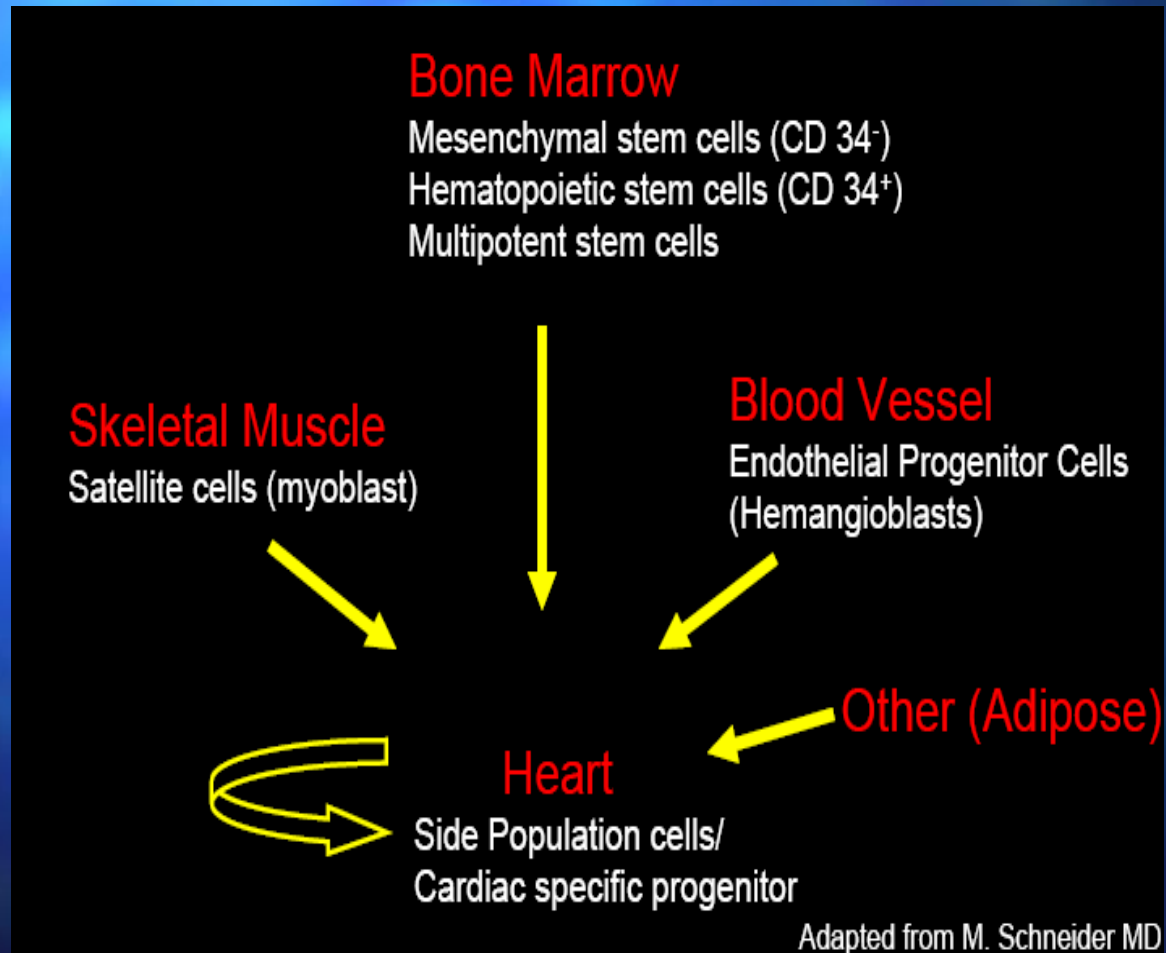
# Example: cardiovascular



Strauer BE et al Circulation 2002;106: 1913-1918

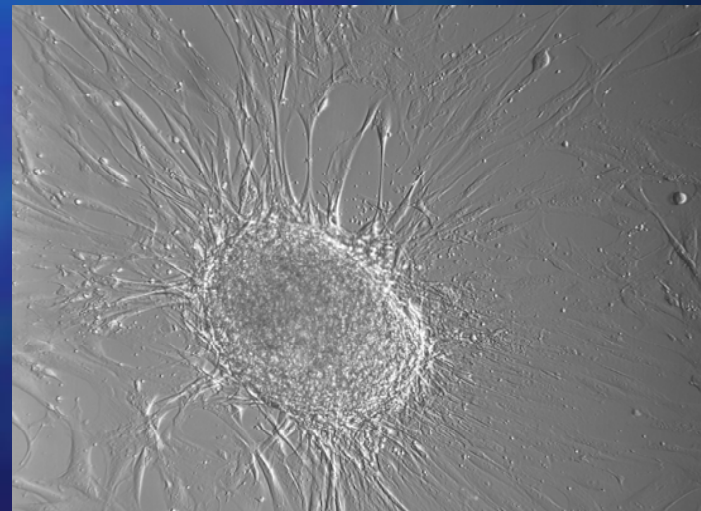
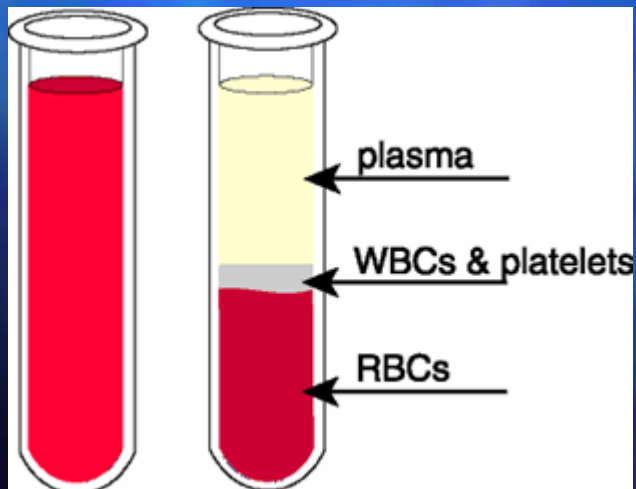
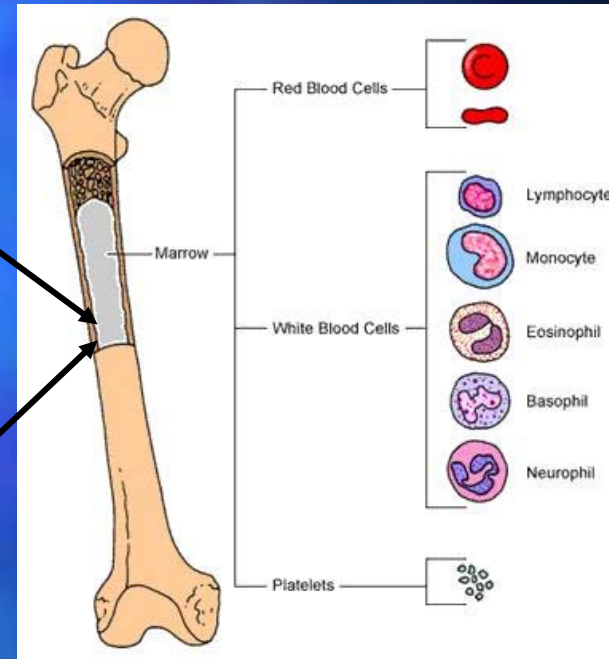
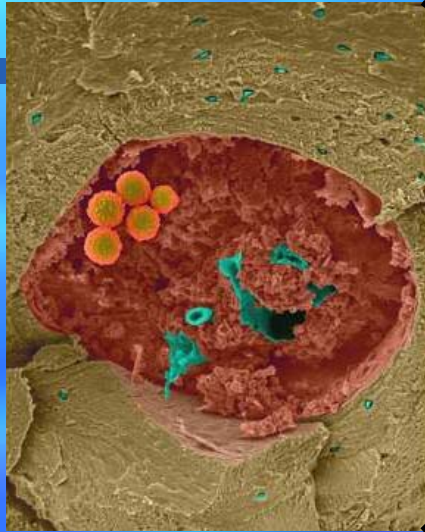


# Example: cardiovascular



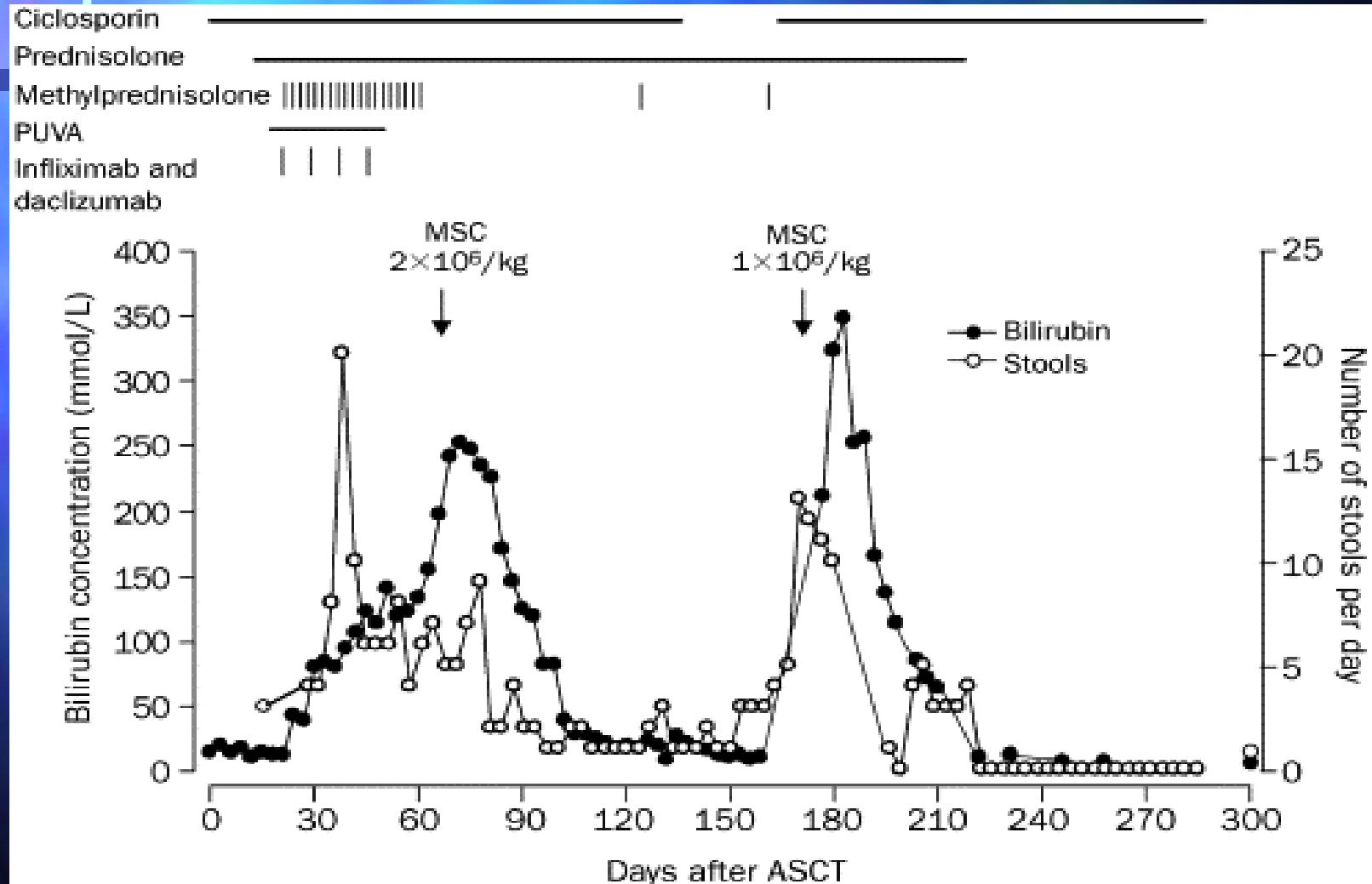


# (Bone marrow) MSCs





# Example: Immunomodulatory properties of MSCs



MSCs reduce graft-vs-host disease (*Le Blanc, Lancet 2004;363:1439-1441*)



# Example: In utero treatment (IUT) of genetic diseases

Medscape®

www.medscape.com

## Donor Cells

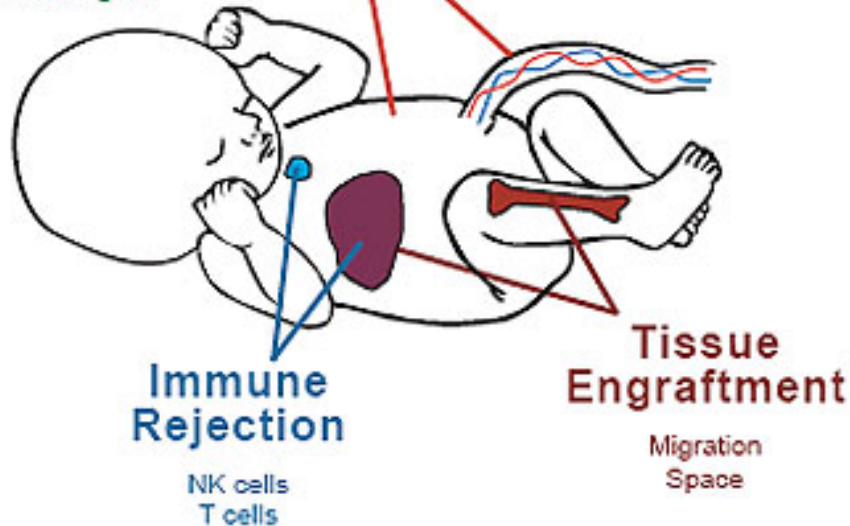
Allogeneic Fetal  
Umbilical Cord Blood  
Haplogeneic Adult  
Xenogeneic  
Modified Autologous

## Route

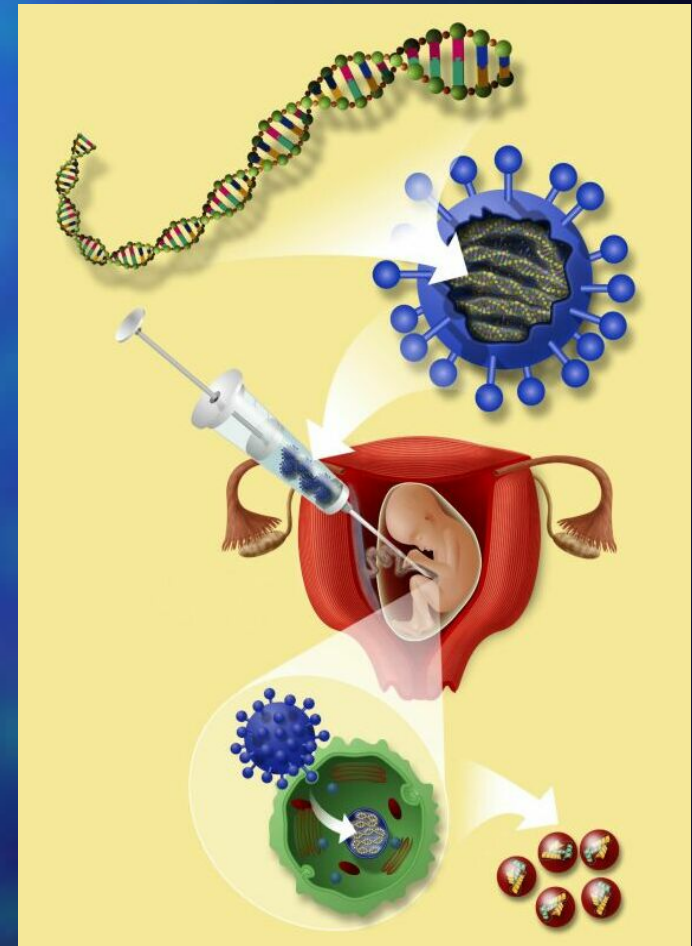
Peritoneum  
Vascular

## Administration

Single  
Multiple  
Fetal & Postnatal



Source: Cancer Control © 2004 H. Lee Moffitt Cancer Center and Research Institute, Inc.





# Example: In utero treatment (IUT) of genetic diseases

Medscape®

www.medscape.com

Indication	No. of Cases	Outcome and Comments	References
<b>Immunodeficiencies:</b>			
Bare lymphocyte syndrome	1	Alive and well with reconstitution of T cells after fetal liver and thymus transplant.	38, 86
Severe combined immunodeficiencies	9	8 cases with lymphoid engraftment and 1 case electively terminated without engraftment.	49, 50, 87-93
Chediak-Higashi syndrome	1	Born with no engraftment.	93
Omenn syndrome	1	T-cell engraftment.	92
Chronic granulomatous disease	3	2 cases born with no engraftment and 1 procedure-related death.	33, 86, 102
<b>Erythroid Disorders:</b>			
$\alpha$ -Thalassemia	2	No chimerism in 1 case and microchimerism with donor-specific tolerance noted in 1 case.	51, 96
$\beta$ -Thalassemia	12	No alleviation of disease in surviving births. Evidence of chimerism ( $\leq 4\%$ ) in 3 recipients.	86, 93-101
Sickle cell anemia	3	No engraftment.	99, 101
Rh isoimmunization	3	Donor-specific T-cell tolerance observed in 1 recipient.	103-105
<b>Storage Diseases:</b>			
Globoid cell leukodystrophy	3	No engraftment in 2 cases. Hyperengraftment and fetal death in 1 case.	106, 107
Hurler's syndrome	1	No engraftment.	108
Niemann-Pick disease (type A)	1	Patient alive and well, no engraftment data reported.	86
Metachromatic leukodystrophy	2	No chimerism.	94

\* Information on unpublished cases obtained from published reviews.<sup>104, 164</sup>



# Cell therapy center

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(from Dr. David McKenna)



# Molecular and Cellular Therapeutics (MCT), University of Minnesota

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- Built in 1992 and renovated in 1998
- Facility meets current Good Manufacturing Practices (cGMP) and current Good Tissue Practices (cGTP) standards
- Effective collaboration with University of Minnesota Stem Cell Institute, Diabetes Institute for Immunology and Transplantation, Cancer Center, and Medical Center



# Molecular and Cellular Therapeutics (MCT), University of Minnesota

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- Cell Therapy Laboratory
- Pancreatic Islet Cell Laboratory
- Cancer Center Laboratory
- Production Assistance for Cellular Therapies



# (1) Cell Therapy Laboratory

- Provides hematopoietic stem cells (HSCs) and non-hematopoietic cell types derived from a variety of sources (tissues) for somatic cell therapies;
- The laboratory processes over 700 autologous, allogeneic-related and allogeneic-unrelated peripheral blood, umbilical cord blood (UCB), bone marrow, and tissue products annually



## (2) Cell Therapy Laboratory

- HSCs from bone marrow, peripheral blood, umbilical cord blood (UCB);
- *Cardiac Therapy (BM MNCs, +/-stopflow etc., selected cells CD34+, CD133+; MSCs)*
- *Mesenchymal Stem Cells (Improvement of HCS engraftment; GVHD therapy)*
- Cord blood HSC expansion
- Skeletal Myoblasts (*stress urinary incontinence*)
- T-reg cells (T cell response inhibition, currently-PB and UCB derived; to support BM engraftment & GVHD therapy)



# (1) Pancreatic Islet Cell Laboratory

- Supports cutting-edge research in clinical islet transplantation
- Current team processes over 45 human (and 60 porcine) pancreata annually
- Above and beyond the routine islet isolation process, this team performs a host of Quality Control and Quality Assessment evaluations of the isolated islets



## (2) Pancreatic Islet Cell Laboratory

### Current clinical Trials

- ⑩ "hOKT3y1 (Ala-Ala), Sirolimus and Low Dose Tacrolimus Therapy in Type 1 Diabetic Islet Allograft Recipients"
- ⑩ "Evaluation of the Tolerogenic Efficacy of hOKT3y1 (Ala-Ala) and Sirolimus Immunotherapy in Type 1 Diabetic Islet Allograft Recipients"
- ⑩ "Anti-thymocyte Globulin, Cyclosporine, and RAD in Islet Transplantation"



# (1) Cancer Center Laboratory

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- Development of novel therapies across a wide range of application leading to clinical production
- Autologous tumor digestion and cell production and expansion
- Tumor vaccine production



## (2) Cancer Center Laboratory

- NK cell therapy (Haplo- identical; + CD34 enriched HSC graft; also *UCB derived NKs*)
- Autologous tumor cell vaccines (melanoma and renal cell carcinoma)
- Allogenic tumor cell vaccines underway (breast cancer and melanoma)



# Production Assistance for Cellular Therapies (PACT group)

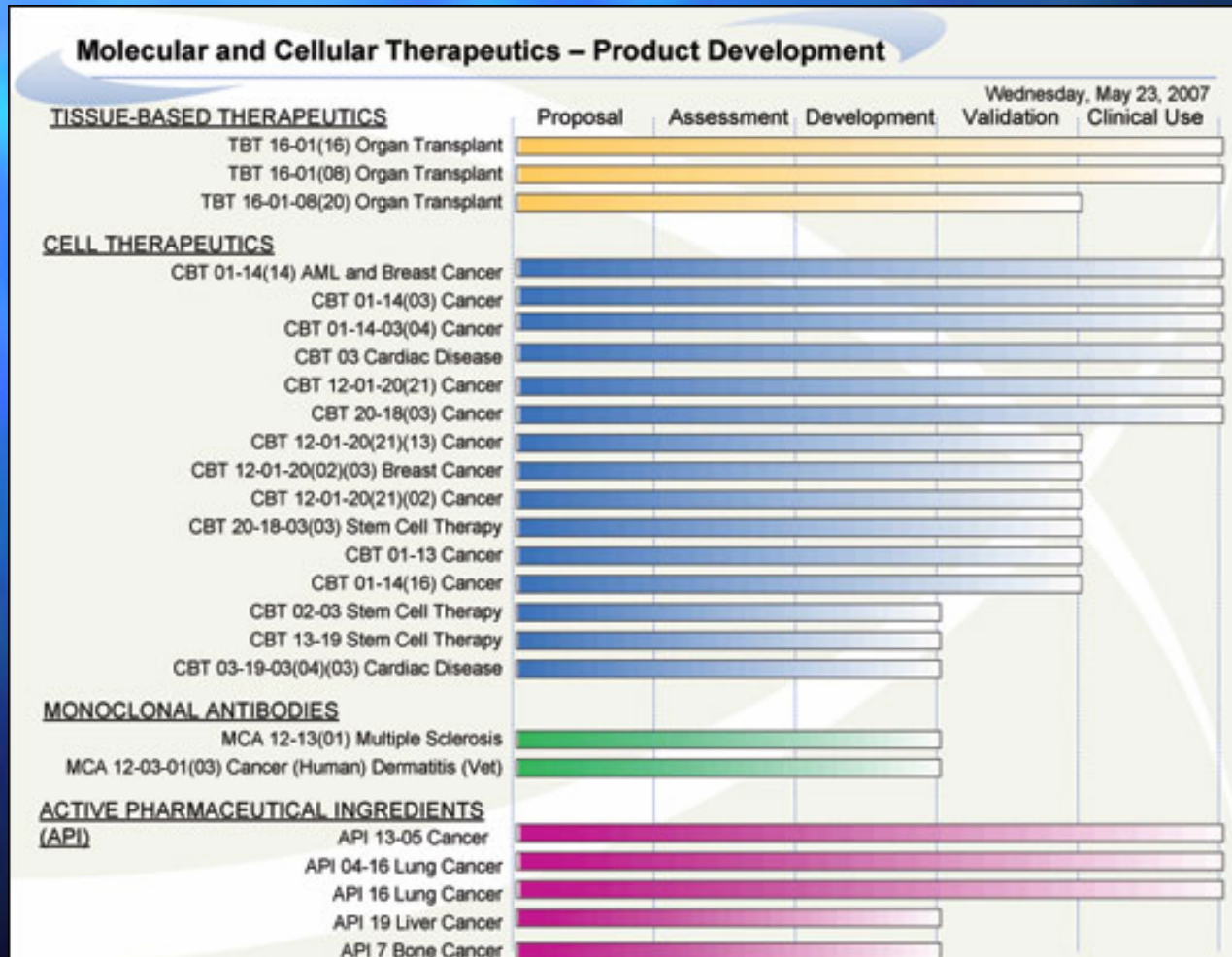
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Three facilities and an administrative center to produce novel cellular therapy products for investigators from academia and industry within the United States needing manufacturing support

E.g. "BioE" develop UCB derived MSCs cell product



# Production Assistance for Cellular Therapies (PACT group)





E.T.C. <http://www.ahc.umn.edu/mct/about/home.html>

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- Process validation: from design to implementation
- Cryopreservation program development and qualification
- Development of Shipping Validation protocols and reports to support the need to transport products worldwide



# Molecular and Cellular Therapeutics (MCT), University of Minnesota

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- Total 3.700 m<sup>2</sup>, out of which 1.020 m<sup>2</sup> are dedicated Controlled Environment Areas and areas for the development and production of advanced cell-, tissue-, and gene-based therapies
- Up to 70 (?) specialist can be involved in MTC activities



# Cell therapy in Latvia

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- Cell Therapy Laboratory, P. Stradins University Clinical Hospital, is under construction and will be operational in 2008
- Stem cell technology project for medical application initiated at University of Latvia in 2006



# Cell Therapy Laboratory, P. Stradins University Clinical Hospital, Riga, Latvia



- Total 280 m<sup>2</sup>, out of which 90 m<sup>2</sup> are dedicated cGMP area for the development and production of cell and tissue therapies (2008)
- Planned therapies- cardiac; pancreatic islets (Edmonton protocol); MSCs
- Technology implementation has already started



“Development of isolation and expansion methods for autologous stem cells with the potential for medical applications”





# Aims:

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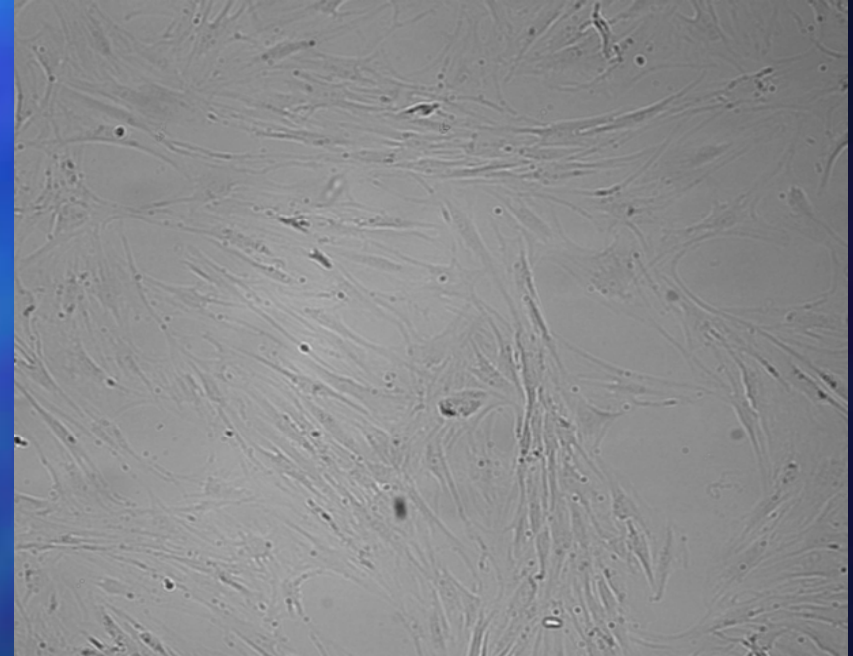
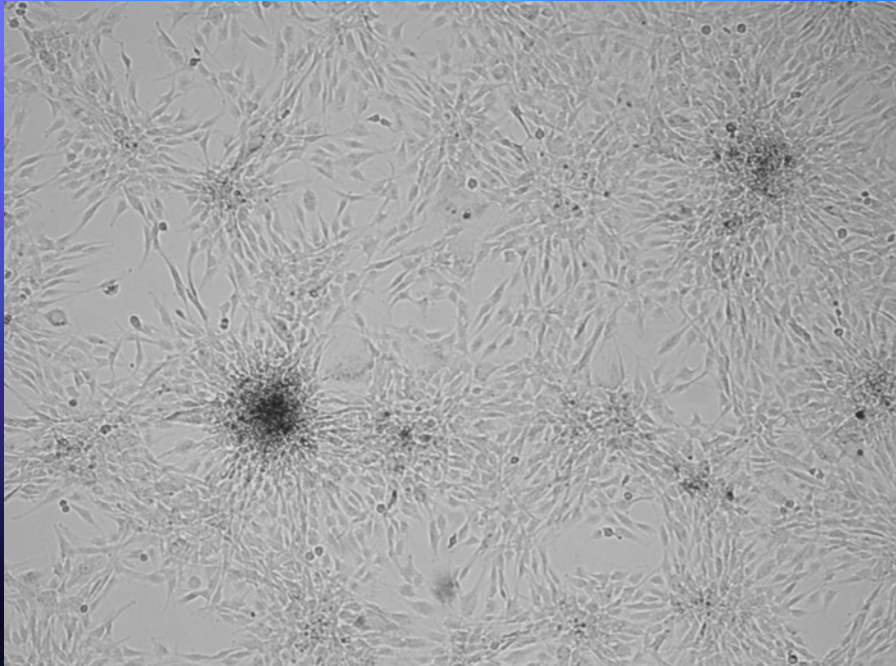
- Establish optimal MSC culture conditions
- Develop robust cell quality control
- Transfer technology to GMP production







# *In vitro* cultivation/ expansion



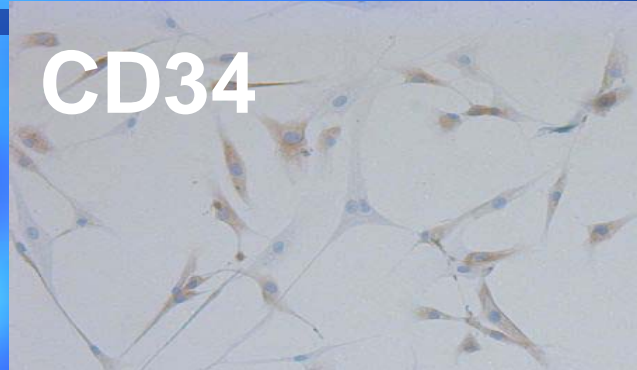


# Marker characterisation and differentiation tests

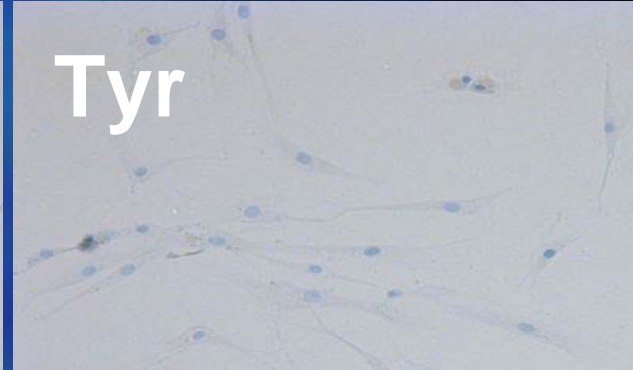
**Nestin**



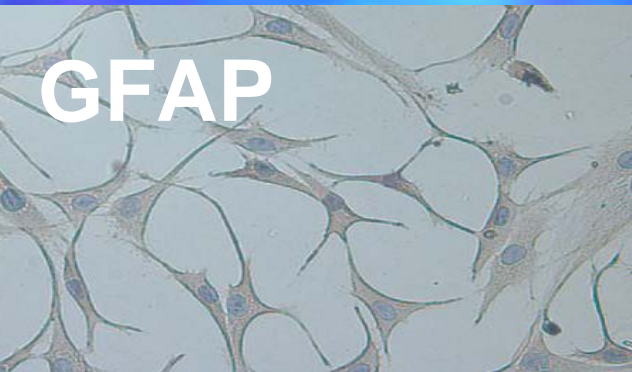
**CD34**



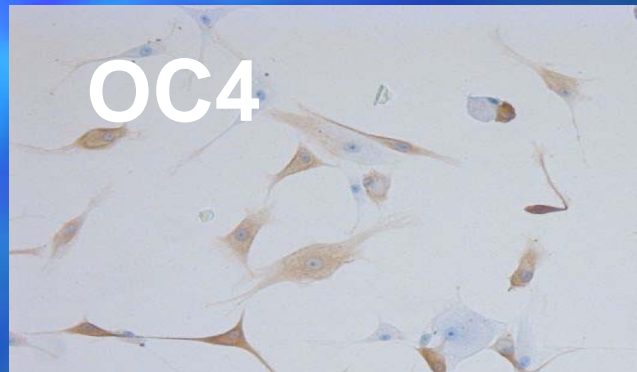
**Tyr**



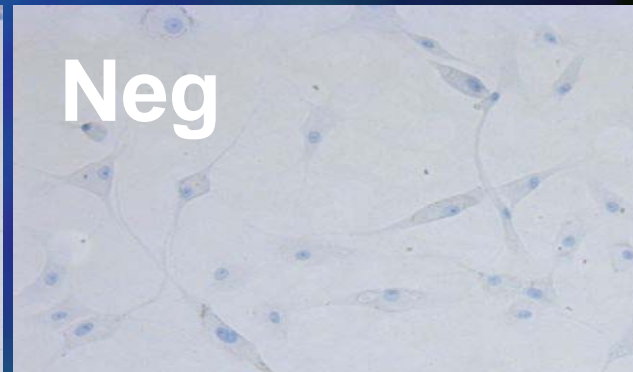
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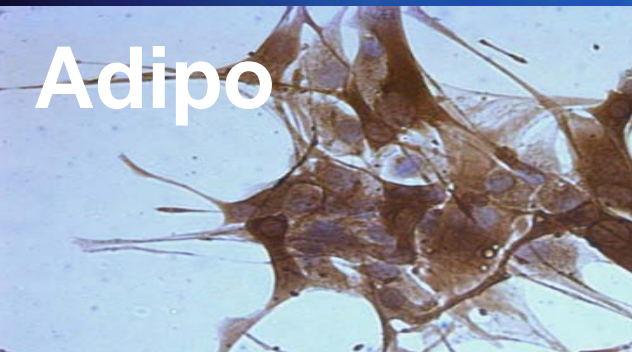
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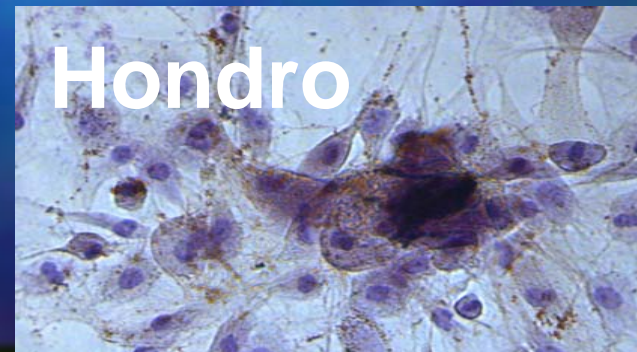
**Neg**



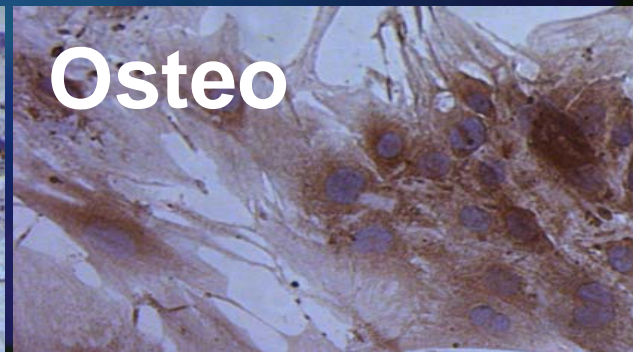
**Adipo**



**Hondro**

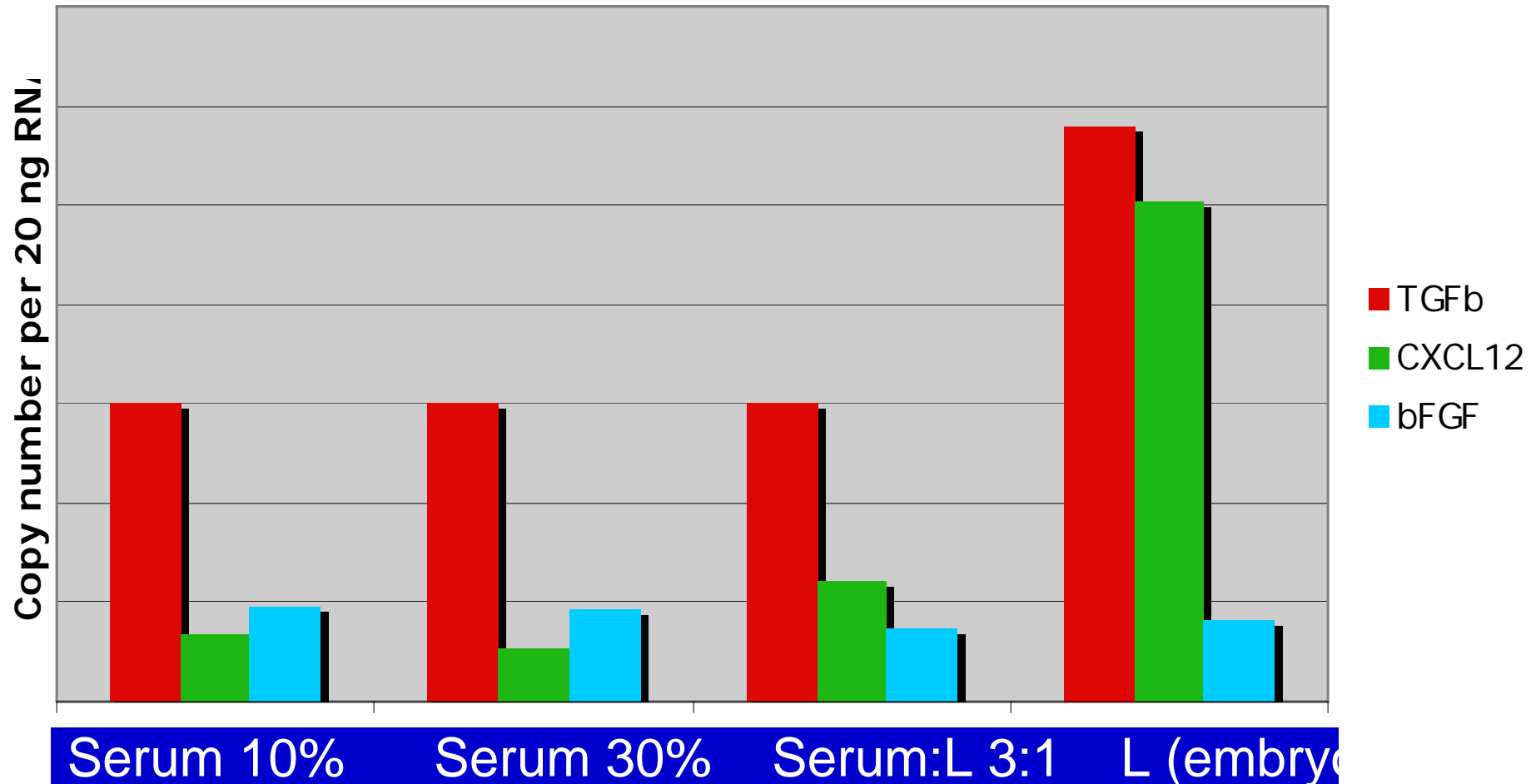


**Osteo**



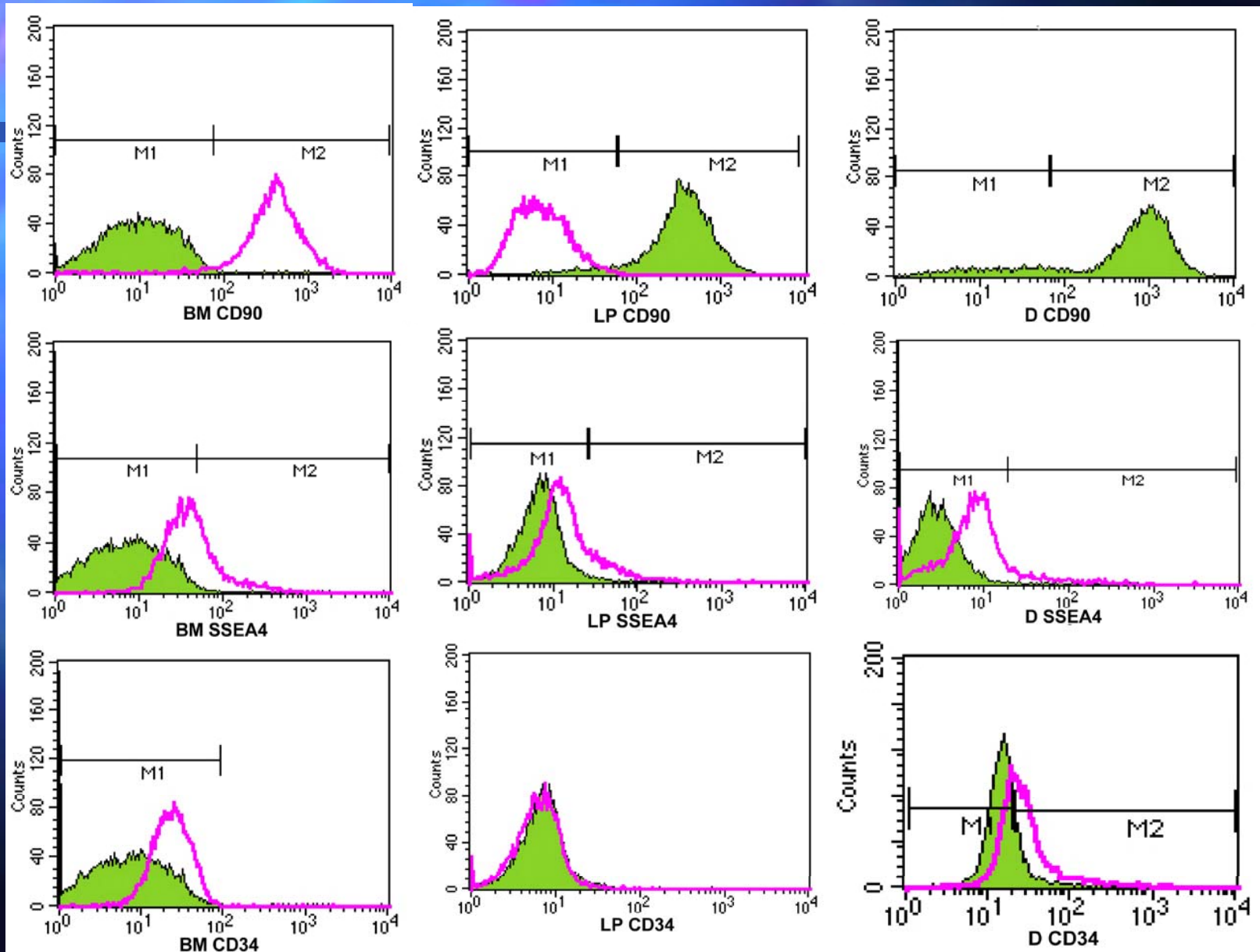


# PCR & Real time



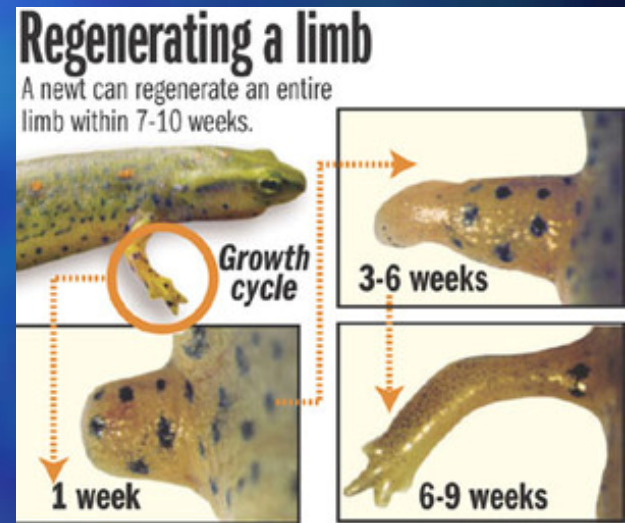


# FACS





# Exciting but philosophical questions





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**Thank you!**