Adult stem cells…great potential

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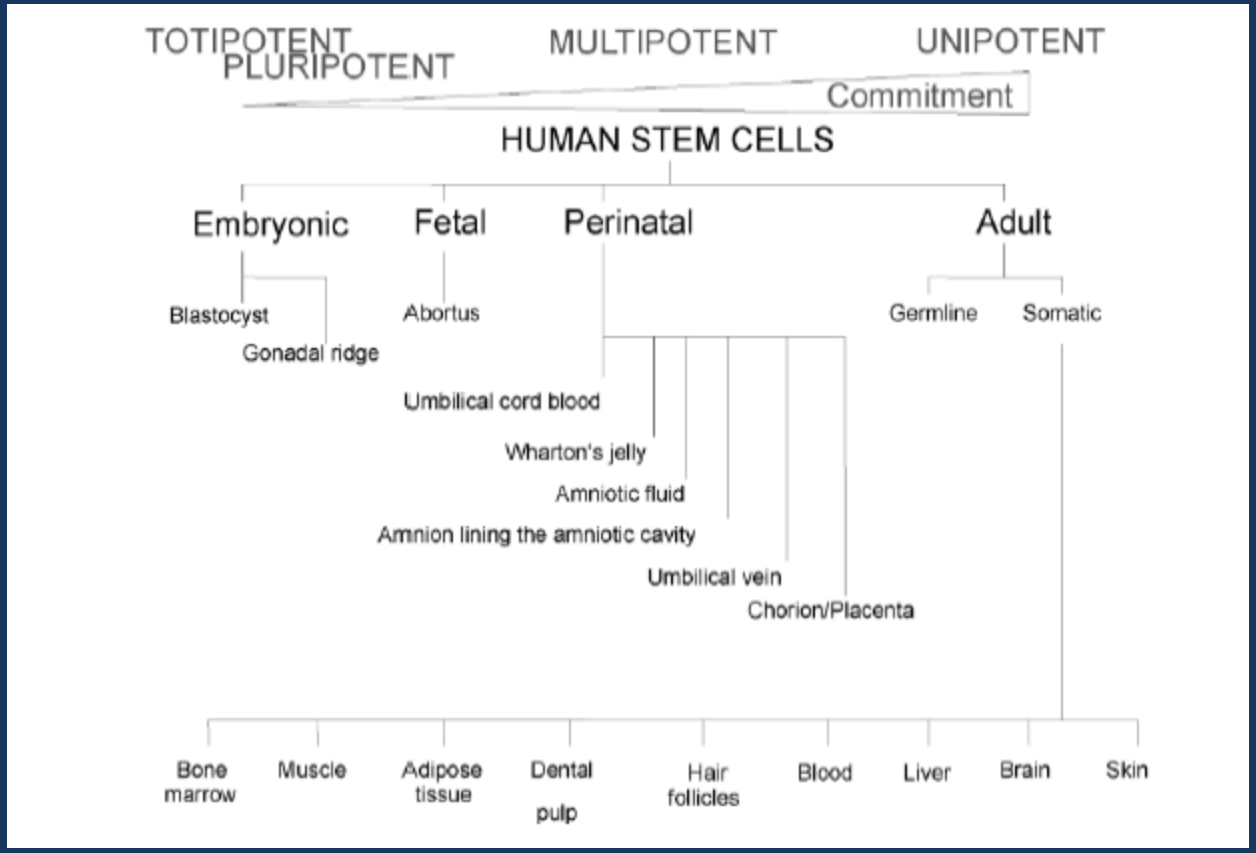
Stem cells

- Biological cells present in all multicellular organisms
- Characteristics:
  a. Divide through mitosis
  b. Differentiate into diverse specialized cell types
  c. Self-renew

Stem cell types

- Two broad types of stem cells:
    a. Embryonic stem cells
    b. Adult stem cells

Human stem cell hierarchy and classification



CELLULAR & MOLECULAR BIOLOGY LETTERS
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Umbilical cord blood stem cells

First successful umbilical cord blood (UCB) transplant (1988)

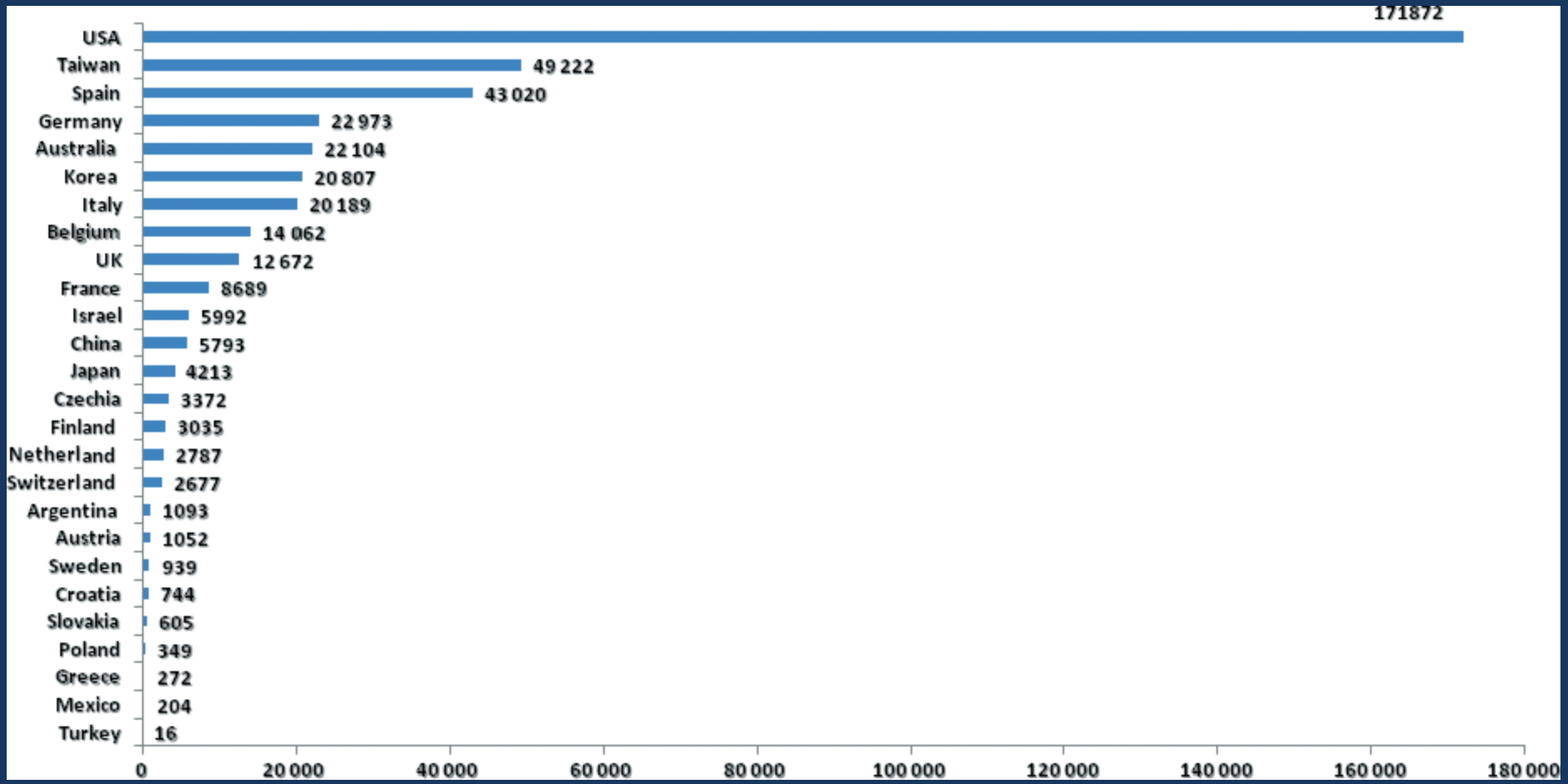
Matthew Farrow
(recipient)

Umbilical cord blood extraction

- A major collaborative effort across the Atlantic:
- A patient of Dr. Joanne Kurtzberg
- The cord blood was banked by Dr. Hal Broxmeyer
- Dr. Eliane Gluckman performed cord blood transplant in Paris

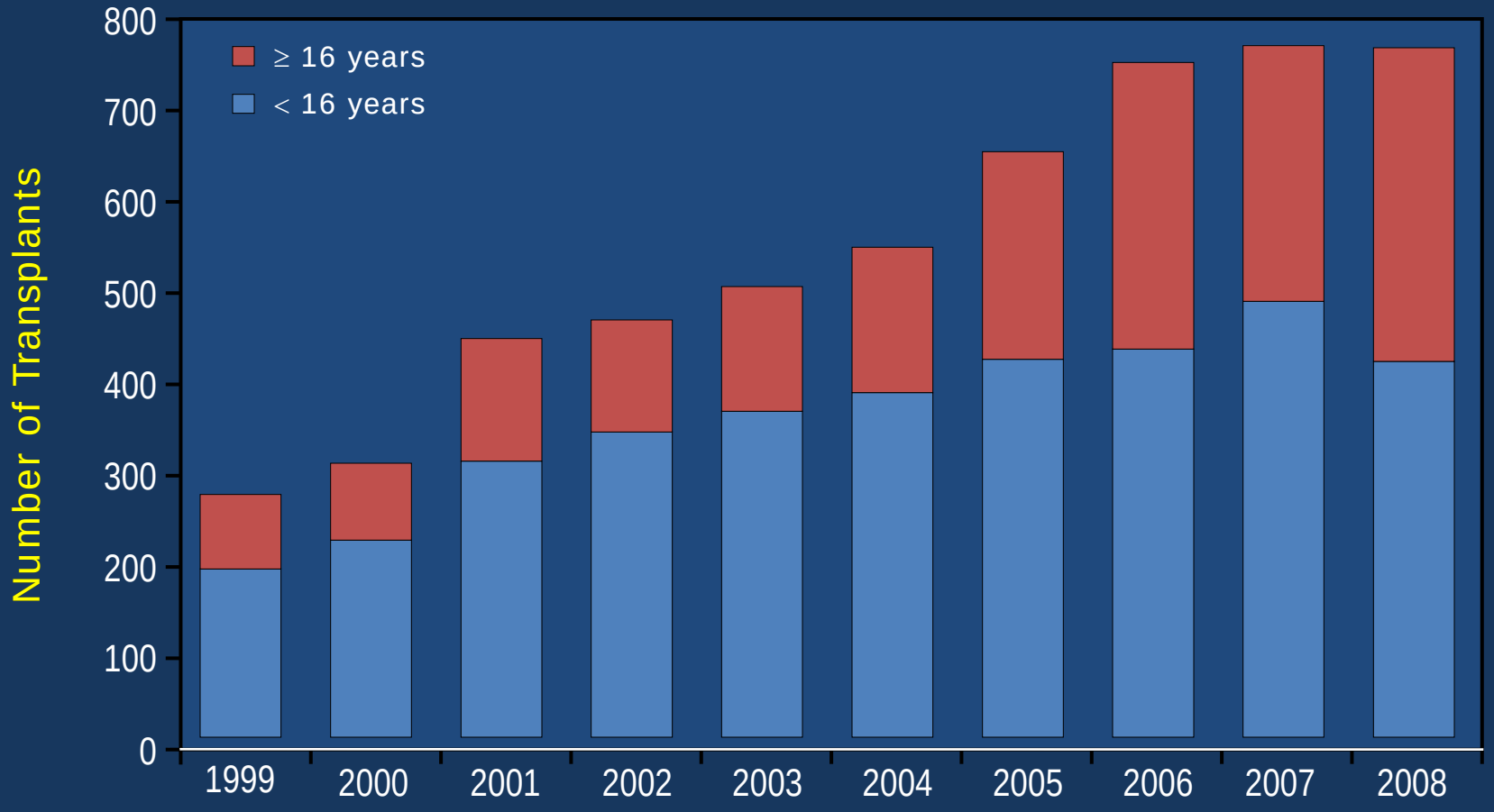
*Since the first successful UCB has been used as a graft source for over 14 000 patients with both malignant and non-malignant diseases (Broxmeyer et al, 2009).

Over 419 000 umbilical cord blood samples are stored in public registries worldwide

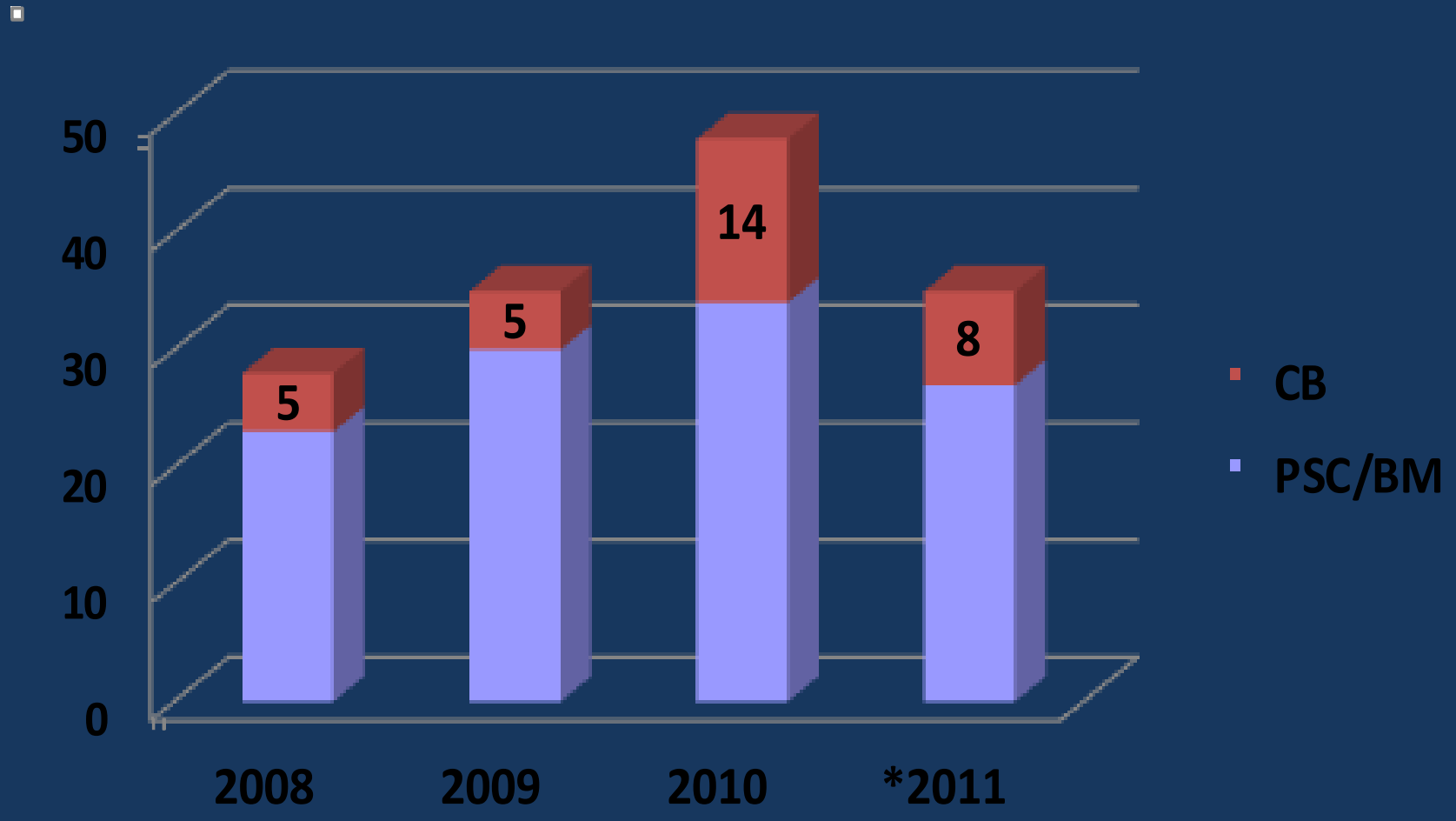


Cell Prolif., 2011, 44 (Suppl. 1), 60–69

Unrelated cord blood transplantation registered with CIBMTR 1999-2008



Matched Unrelated Donor HSCT Volume-KUMC



*2011 volume as of 9/1/11

Indications

Table 1
Numbers of hematopoietic stem cell transplants in Europe 2008 by main indication and use of related and unrelated CB products. Numbers refer to patients with first HSCT only. BM, Bone Marrow; CB, Cord Blood; PB, Peripheral Blood. Proportion: Percentage of CB as stem cell source amongst allogeneic HSCT.

Main indication	Family		Unrelated		Total	Proportion	Autologous		Total	
	BM/PBSC	CB	BM/PBSC	CB	Allo	CB Allo	BM/PBSC	CB	BM/PBSC	CB
Leukemias	3514	11	3413	456	7394	6.3	936	0	7863	467
Acute	2584	8	2262	337	5191	6.6	810	0	5656	345
Chronic	930	3	1151	119	2203	5.5	126	0	2207	122
Lymphoproliferative disorders	855	0	728	53	1636	3.2	12,908	0	14,491	53
Solid tumors	46	0	14	1	61	1.6	1400	0	1460	1
Non-malignant disorders	822	36	319	115	1292	11.7	168	0	1309	151
Bone marrow failures	380	9	176	34	599	7.2	2	0	558	43
Congenital disorders	440	26	138	80	684	15.5	7	0	585	106
Auto immune disease	2	1	5	1	9	22.2	159	0	166	2
Others	33	1	28	14	76	19.7	25	0	86	15
Total	5270	48	4502	639	10,459	6.6	15,437	0	25,209	687

A. Gratwohl, H. Baldomero / Transfusion and Apheresis Science 42 (2010) 265–275

UCB as a Graft Source for transplantation

- **Advantages:**

a. Ease of procurement

b. Absence of donor risks

c. Reduced risk of transmissible infections

d. Availability for immediate use

e. Lower incidence of graft versus host disease (GVHD)

f. Extends transplant to minority populations

- **Limitations:**

a. Delayed blood count recovery, engraftment, and higher rates of graft failure post transplant

b. Delayed immuno-reconstitution post transplant

c. Limited options to treat post transplant relapse

UCB non-hematopoietic stem cells

Table 1
CB-derived non-hematopoietic stem cells for regenerative medicine.

Field of research	Haematology	Orthopedics	Cardiology	Vascular	Neurology	Metabolic disorders	Diabetes
Pre clinical studies	MSCs to support expansion of HSC [26,27]	Differentiation into osteoblasts [30-34] and chondrocytes [35-38]	Recovery after MI in animal models [25,41-46]	Differentiation into endothelial cells [49-52]; In vivo angiogenesis [52] and blood flow restoration [53,54]	Differentiation into neural cells [56-65]; Protection in animal models of stroke [66-72], heatstroke [74], TBI [76], CP [77], PD [78,79], ALS [80,81], AD [82], SCI [83,84]		Differentiation into insulin-producing cells [92,93]; Reduced blood glucose levels and improved symptoms in T1D and T2D animal models [94-96]
Clinical case-study				Buerger's disease [55]	SCI [85]		
Phase I clinical trials	Improved engraftment [00823316]			Limb ischemia [01019681, 00951210]	Brain injury [00593242]	Krabbe's [87] and Hurler's [88] diseases	TID [97]
Phase II clinical trials	Prevention of GVHD [00504803]	Severe osteoporosis [00775931]			Chronic SCI [01046786]	Krabbe's/ Hurler's/other metabolic inherited diseases [01046786]	TID [00305344]
Phase III clinical trials		Articular cartilage defect or injury [01041001]					

Numbers in square brackets represent either reference numbers (one or two digits) or the last eight digits of the numbers of clinical trials, assigned according to the U.S. National Institute of Health registration http://www.clinicaltrials.gov/ct2/show/

Abbreviations: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; CP, cerebral palsy; GVHD, Graft versus host disease; HSC, hematopoietic stem cells; MI, myocardial infarction; MNC, mononuclear cells; PD, Parkinson's disease; SCI, spinal cord injury; TBI, traumatic brain injury; T1D, type 1 diabetes; T2D, type 2 diabetes.

H. Arien-Zakay et al. / Best Practice & Research Clinical Haematology 23 (2010) 291–303

Mesenchymal stem cells

- Multipotent stem cells that can differentiate into a variety of cells types.
- Differentiation patterns:

  a. Osteoblasts (bone cells)

  b. Chondrocytes (cartilage cells)

  c. Adipocytes (fat cells)

  d. Neuronal cells (nerve cells)

  e. Cardiomyocytes (cardiac muscle cells)

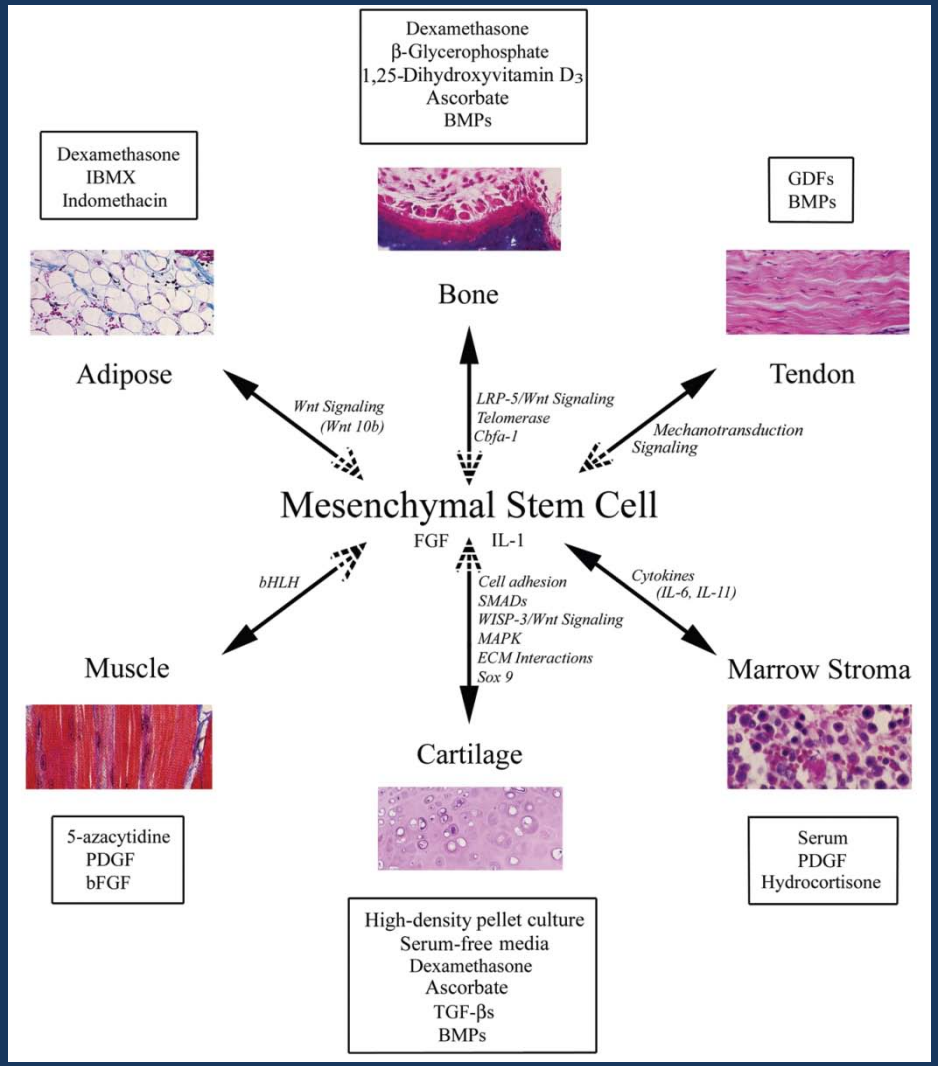

Dexamethasone
β-Glycerophosphate
1,25-Dihydroxyvitamin D3
Ascorbate
BMPs
Dexamethasone
IBMX
Indomethacin
GDFs
BMPs
Bone
Adipose
Tendon
Wnt Signaling
(Wnt 10b)
LRP-5/Wnt Signaling
Telomerase
Cbfa-1
Mechanotransduction
Signaling
Mesenchymal Stem Cell
FGF
IL-1
bHLH
Cell adhesion
SMADs
WISP-3/Wnt Signaling
MAPK
ECM Interactions
Sox 9
Cytokines
(IL-6, IL-11)
Muscle
Marrow Stroma
Cartilage
5-azacytidine
PDGF
bFGF
Serum
PDGF
Hydrocortisone
High-density pellet culture
Serum-free media
Dexamethasone
Ascorbate
TGF-βs
BMPs

Table 4. Clinical Trials of Stem Cell Therapy for Chronic Myocardial Ischemia and/or Heart Failure With ≥20 Patients.

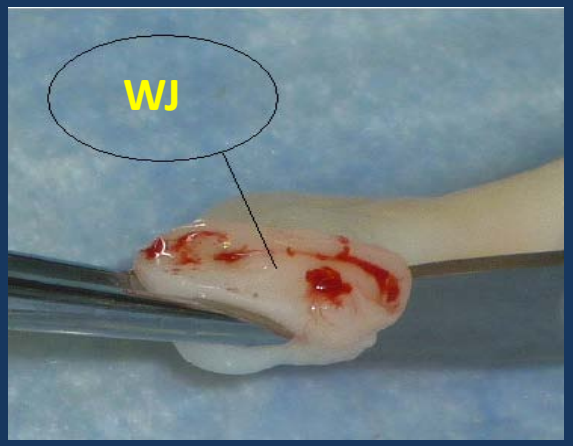
Table 4. Clinical Trials of Stem Cell Therapy for Chronic Myocardial Ischemia and/or Heart Failure With ≥20 Patients

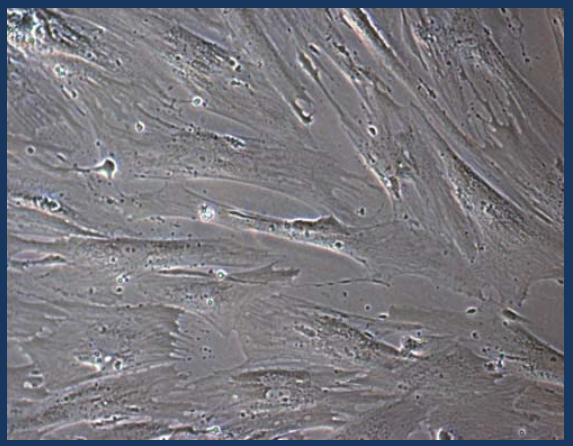
Source	Trial Type/Name of	No. Patients	Follow-up, mo	Stem Cell Route	Stem Cell Source	LVEF Outcome; Comment
Assmus et al,[87] 2007	TOPCARE-CHD	121	19	Intracoronary	Bone marrow	Improved mortality in high-order CFUs injected
Losordo et al,[97] 2007	Randomized	24	12	Intramyocardial	CD34	Not examined
Manginas et al,[96] 2007	Unblinded	24	28	Intracoronary	CD133, CD34	Improved LVEF and left ventricular volumes
Stamm et al,[99] 2007	Unblinded	40	6	Intramyocardial	CD133	Improved LVEF
Assmus et al,[86] 2006	TOPCARE-CHD Randomized	75	3	Intracoronary	Bone marrow/ CPCs	Improved with bone marrow
Beeres et al,[93] 2006	Single group	25	12	Intramyocardial	Bone marrow	Improved LVEF, CCS angina score, perfusion
Chen et al,[95] 2006	Unblinded	45	12	Intracoronary	Mesenchymal	Improved ischemia, NYHA class, and LVEF
Fuchs et al,[92] 2006	Single group	27	12	Intramyocardial	CD34	Improved CCS angina score
Gao et al,[94] 2006	Unblinded	28	3	Intracoronary	Bone marrow	Improved LVEF, improvement in CHF
Hendrikx et al,[91] 2006	Randomized	20	4	Intramyocardial	Bone marrow	NS
Mocini et al,[98] 2006	CABG + cells or CABG alone	36	12	Intramyocardial	Bone marrow	Improved LVEF and wall motion
Erbs et al,[84] 2005	Randomized	26	3	Intracoronary	CPCs	Improved
Patel et al,[90] 2005	Randomized	20	6	Intramyocardial	CD34	Improved
Strauer et al,[85] 2005	IACT[a]	36	3	Intracoronary	Bone marrow	Improved
Perin et al,[88] 2004	Sequential enrollment; treatment or control	20	12	Intramyocardial	Bone marrow	NS
Perin et al,[89] 2003	Single group	21	4	Intramyocardial	Bone marrow	Improved

Abbreviations: CABG, coronary artery bypass graft; CCS, Canadian Cardiovascular Society; CFU, colony-forming unit; CHF, congestive heart failure; CPC, circulating progenitor cell; IACT, Intracoronary Autologous Bone Marrow Cell Transplantation in Chronic Coronary Artery Disease; LVEF, left ventricular ejection fraction; NS, not significant; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; TOPCARE-CHD, Transplantation of Progenitor Cells and Recovery of Left Ventricular Function in Patients With Chronic Ischemic Heart Disease.

[a] Control group refused treatment with bone marrow-derived cells.

Burt, R. K. et al. JAMA 2008;299:925-936





Wharton's Jelly (WJ) mesenchymal stromal cells (MSCs)

A research project involving UCB and WJ MSCs at KUMC

A Wharton's Jelly Mesenchymal Stromal Cell Derived 3D Osteogenic Niche for Cord Blood Expansion

Background

- Delayed blood count recovery and graft failure-post UCB transplantation:

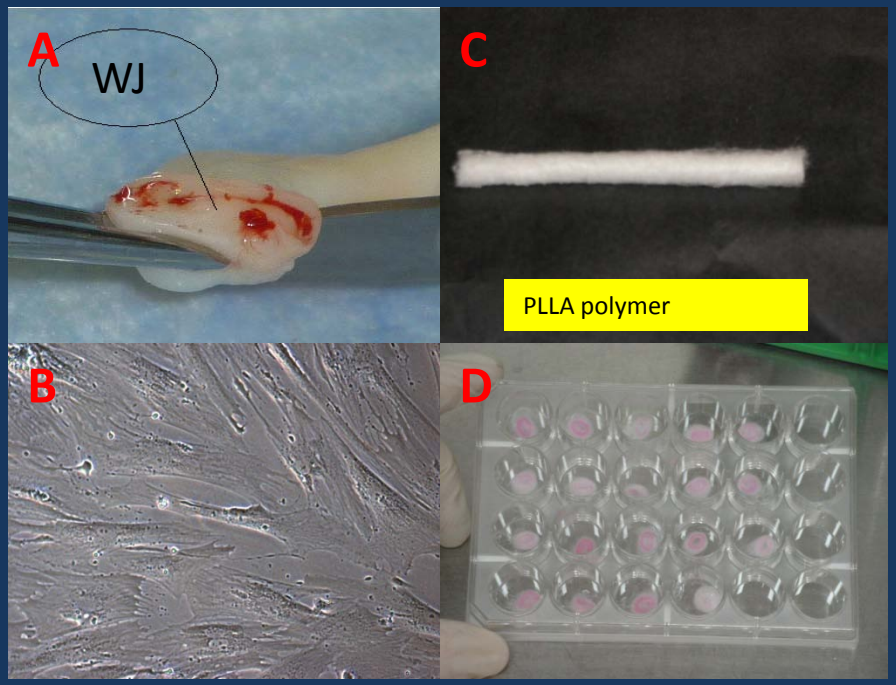
a. Limited cell dose in umbilical cord blood units

b. Defects in UCB stem cell homing to bone marrow

- ***Rationale:*** Time to engraftment is inversely related to the cell dose given during transplantation

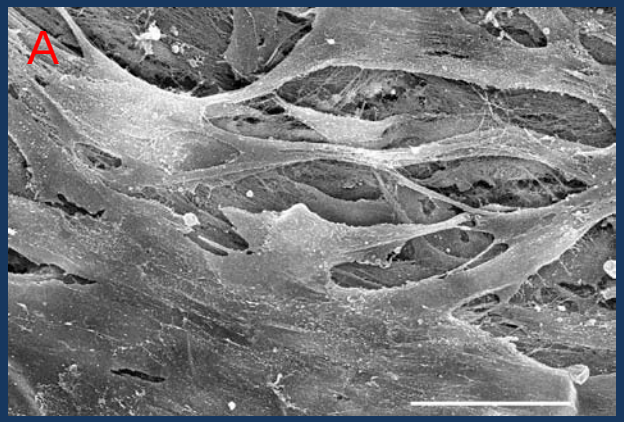
Components of the 3D model

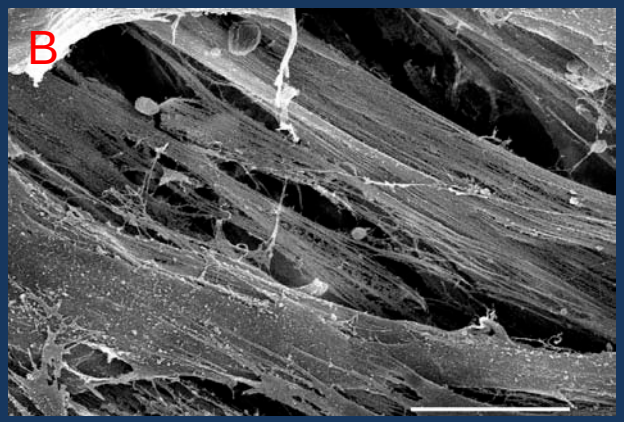
- Occupying cells: mesenchymal stromal cells isolated from umbilical cord Wharton's jelly matrix (A and B)
- Synthetic scaffolds(PLLA) to provide the 3D frame (C and D)

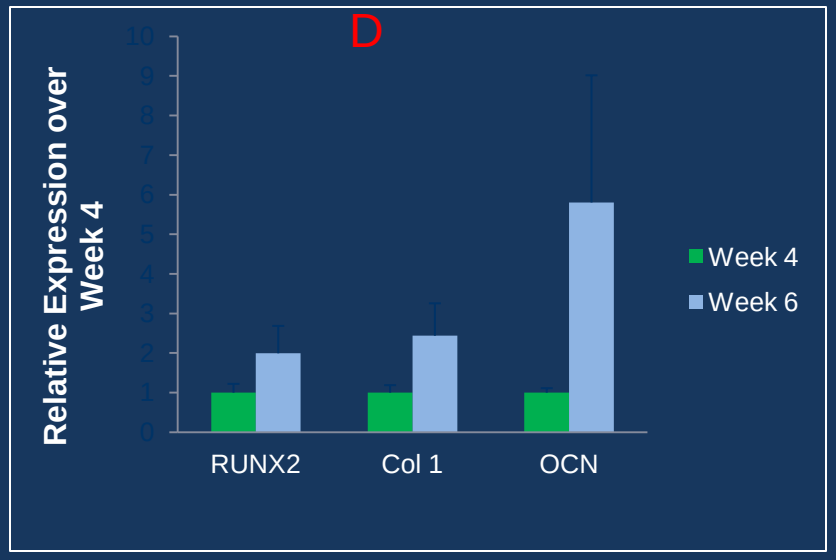


Cells positive for CD 90, CD105, CD 73 and negative for CD 34, CD 45, and isotype consistent with MSC phenotype

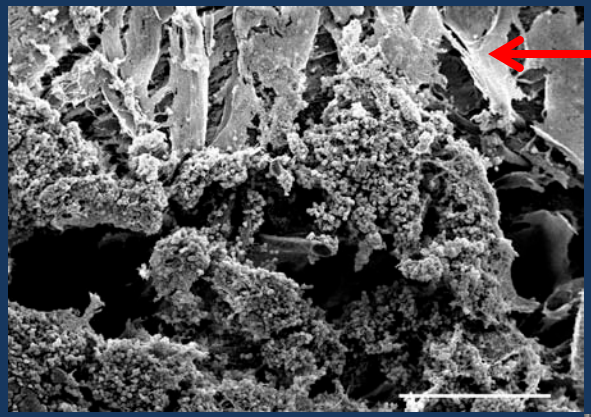
Verification of Osteogenesis (bone differentiation)







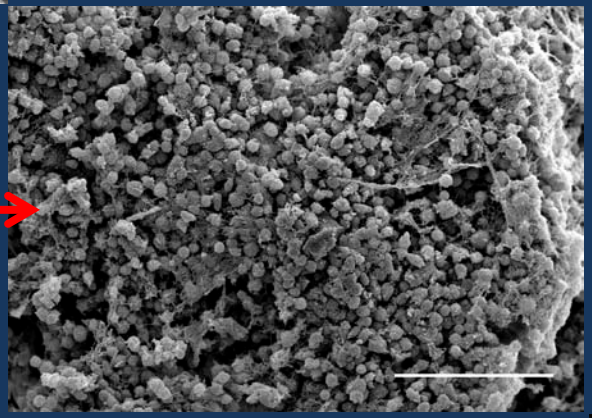
Verification of Osteogenic differentiation in 3D model. Scanning electron microscopy pictures of the scaffold after 6-weeks of osteogenic differentiation. Notice the spindle shaped cells consistent with osteogenic progenitors (A) and the collagen fibrills produced (B). Alizarin red stain of the scaffold after 6 weeks of exposure to osteogenic differentiation media (C). D: Relative expression of molecular markers of osteogenesis at 6 weeks of osteogenic differentiation (red bars) compared to 4 weeks (blue bars) . Runx2 (runt-related transcription factor 2) is an early stage differentiation marker, and OCN (osteocalcin) is a late stage differentiation marker. (Aljitawi et al 2010, unpublished)

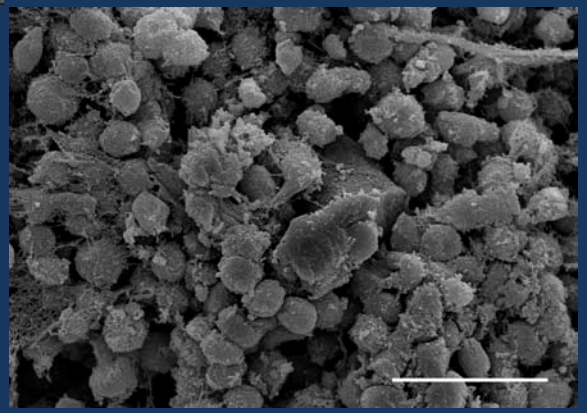


osteongenic matrix cells

UCB CD 34+ cells attach to osteongenic matrix cells

UCB CD 34+ cells





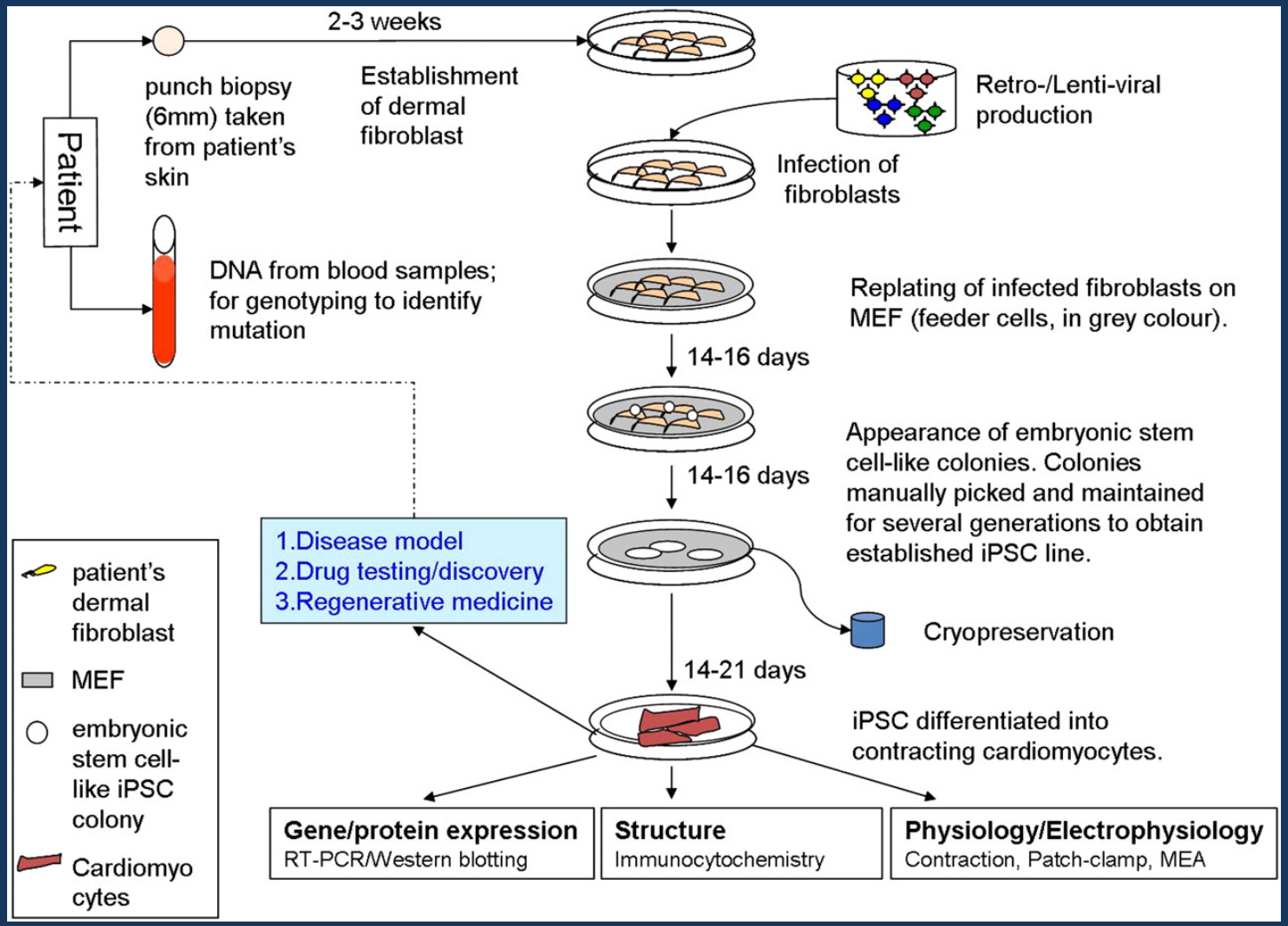
Green investment

Benefit of mankind

Regional economic opportunity

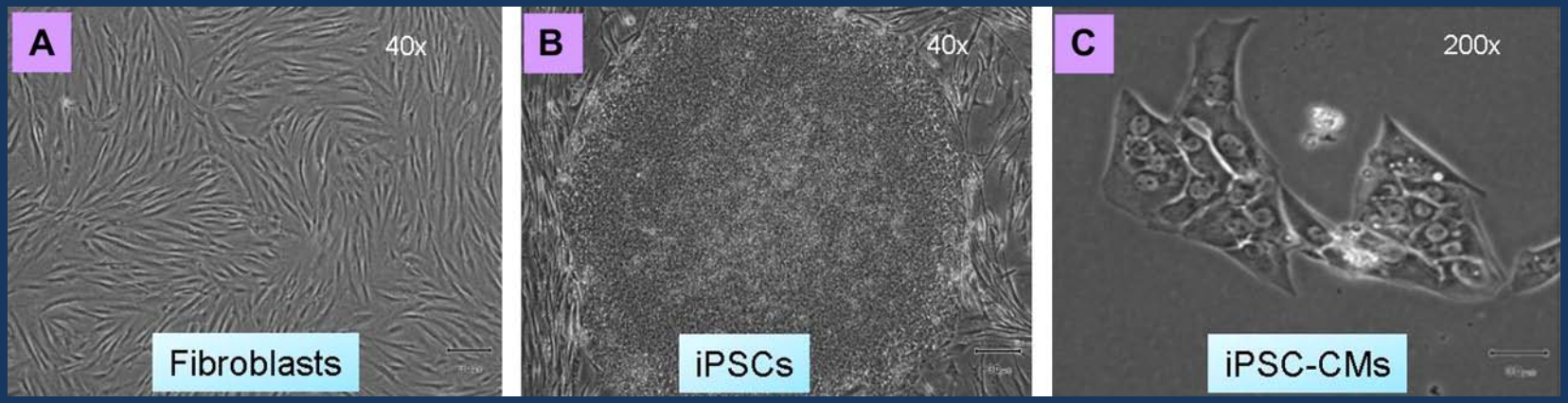
An alternative to embryonic stem cells…Induced pluripotent stem cells

Schematic diagram showing the generation of induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) from human dermal fibroblasts.



Oh Y et al. Heart doi:10.1136/heartjnl-2011-301317

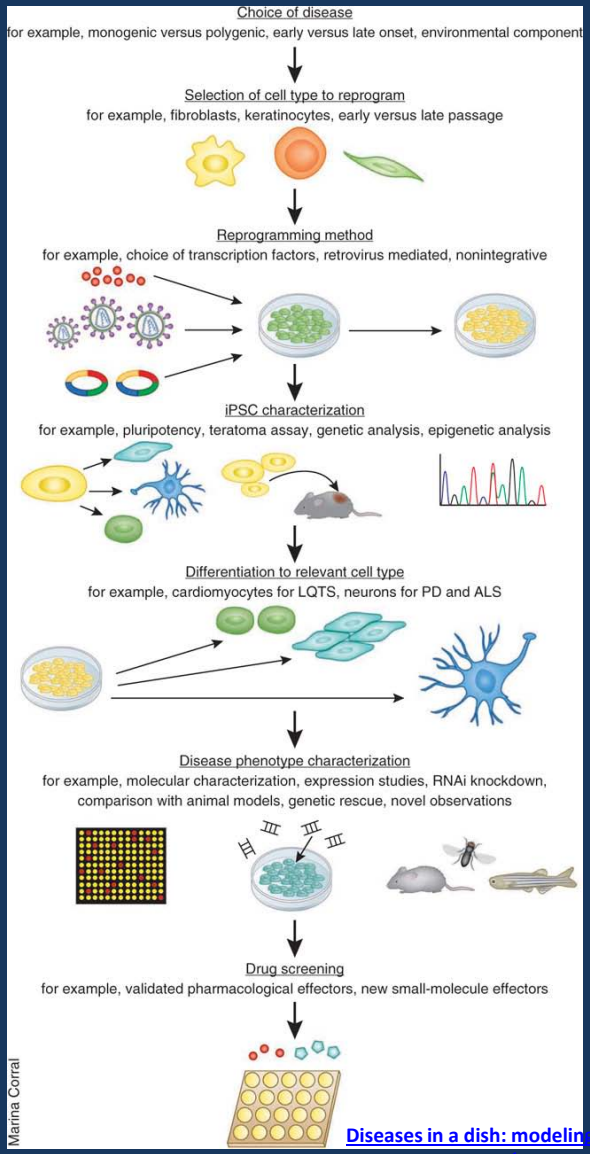
Light microscopic images of typical dermal fibroblasts, human induced pluripotent stem cells (iPSCs) and iPSC-derived cardiomyocytes (iPSC-CMs).



Oh Y et al. Heart doi:10.1136/heartjnl-2011-301317

HEART

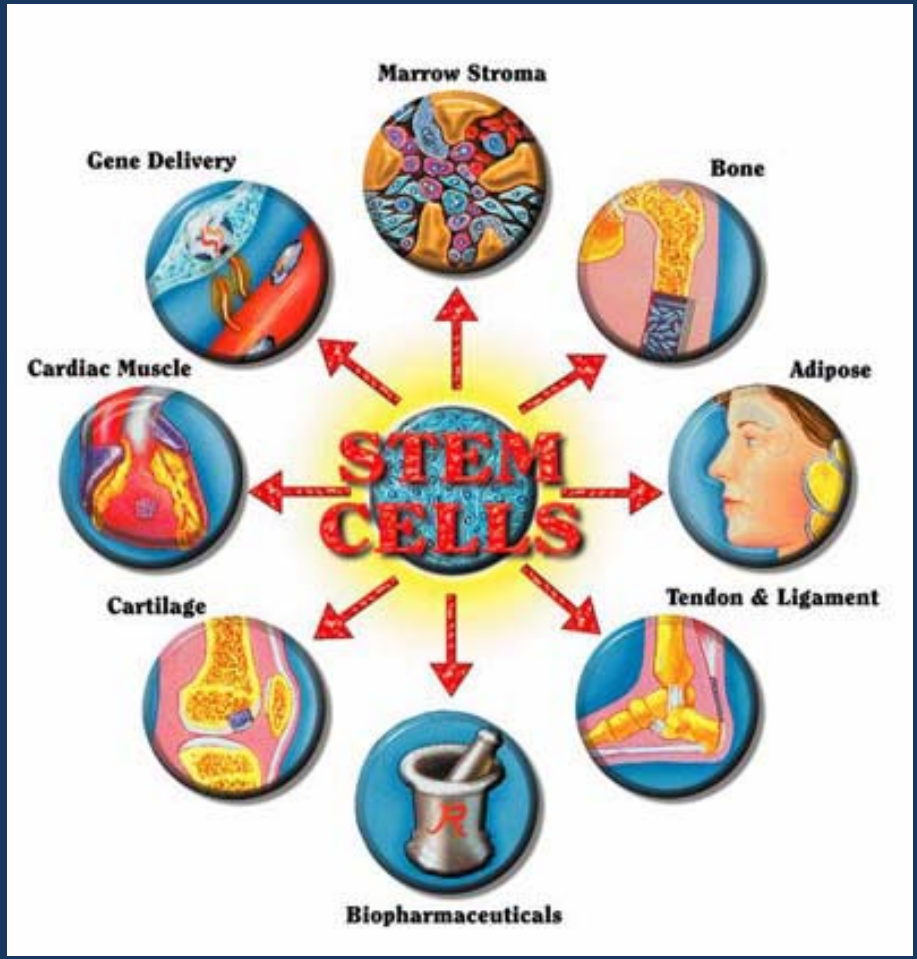
iPSCs…an opportunity to study diseases in the lab.



Diseases in a dish: modeling human genetic disorders using induced pluripotent cells. Gustavo Tiscornia[1], Erica Lorenzo Vivas[1], Juan Carlos Izpisúa Belmonte[1, 2]

Nature Medicine Pages: 1570–1576 Year published: (2011)

Potential stem cell uses



http://blog.lib.umn.edu/huber195/myblog/2011/10/neural-plasticity-stem-cells-a-solution.html

Summary

- There are multiple stem cell sources with diverse differentiation potential
- Umbilical cord blood represents a viable stem cell source for curative transplantation
- Umbilical cord blood stem cells and Wharton's Jelly mesenchymal stromal cells are being investigated for use in several regenerative medicine applications
- KU and other regional institutions have been involved in stem cell research
- Research that involves discarded perinatal tissues represents an example of green investment

Questions?