Cord blood in hematopoietic stem cell transplantation and beyond

Marcos de Lima, MD

University Hospitals Seidman Cancer Center

NCI CCC A Comprehensive Cancer Center Designated by the National Cancer Institute

Case Western Reserve University | Case Comprehensive Cancer Center

Disclosures

Celgene and Seattle Genetics : consultant

Outline

Cord blood transplantation for hematologic malignancies : limitations and new strategies to improve engraftment

Use of cord blood cell subtypes

Family cord blood banking and potential new uses of cord blood to treat a variety of conditions

Allogeneic Stem Cell Transplantation

- Treatment of choice for selected high-risk patients with:

- Acute Leukemia (ALL, AML)
- Chronic Leukemia (CML, CLL)
- Follicular Lymphomas
- Aplastic Anemia
- Several Genetic and Immunologic Diseases

- Less than 30% of patients have a related donor

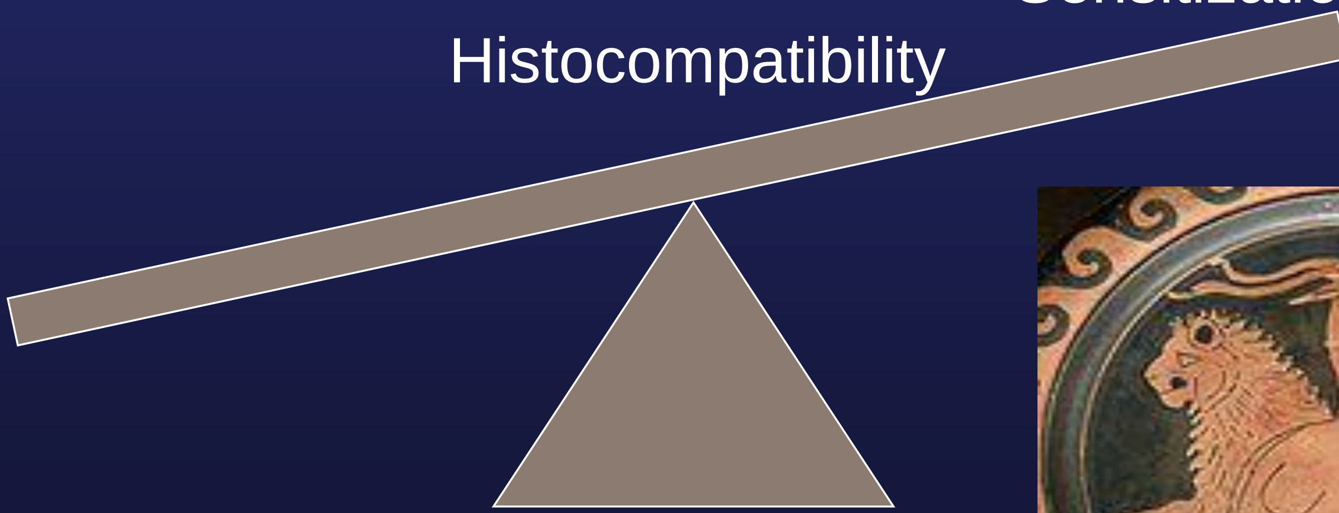
Engraftment

Graft

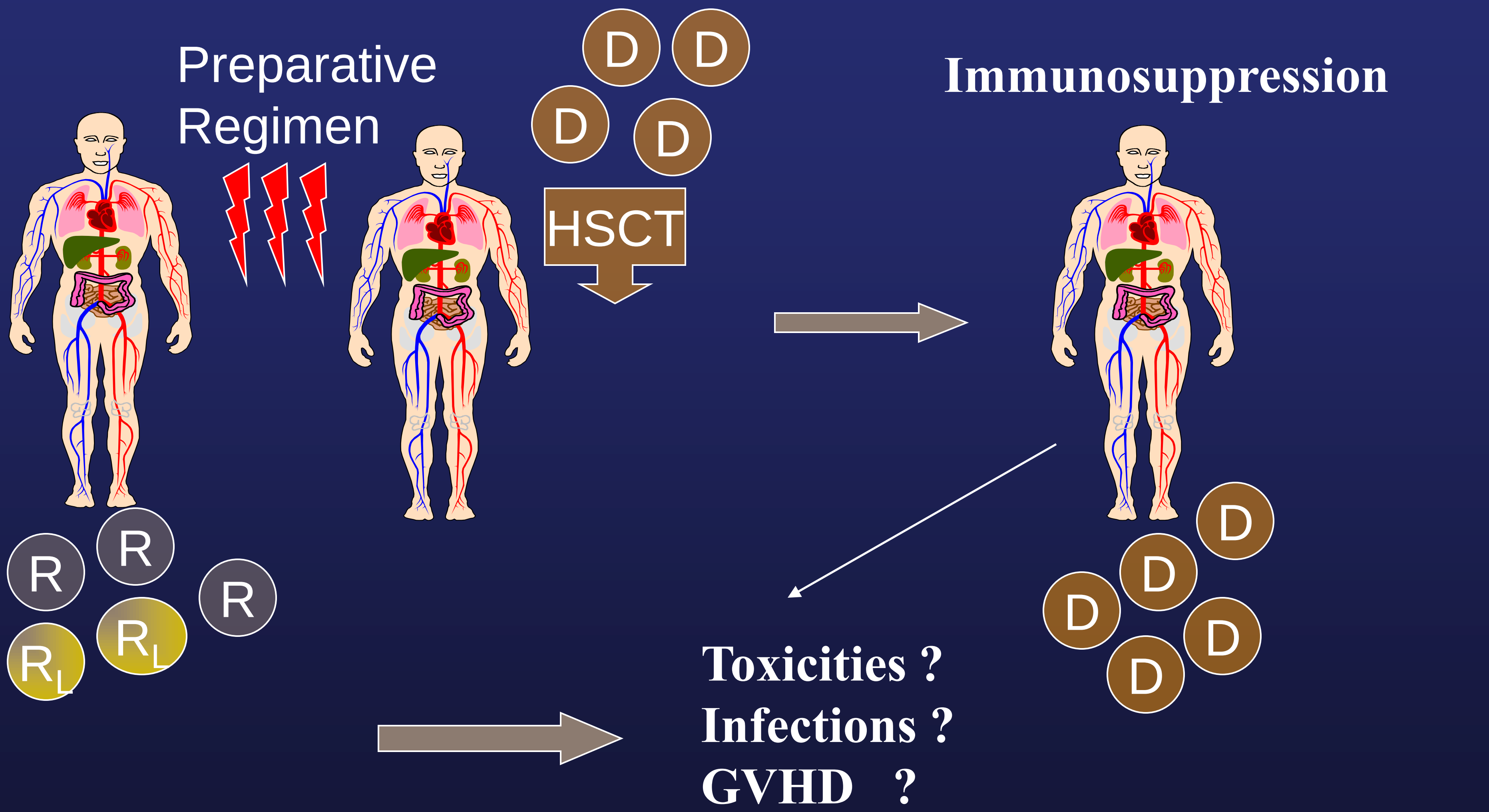
Stem cell dose
T-cell dose (CD8)
Graft-facilitating cells
Stromal stem cells?

Host

Immunosuppression
Preparative Regimen
Post transplant Rx
Disease effects
Sensitization



Hematopoietic Stem Cell Transplantation



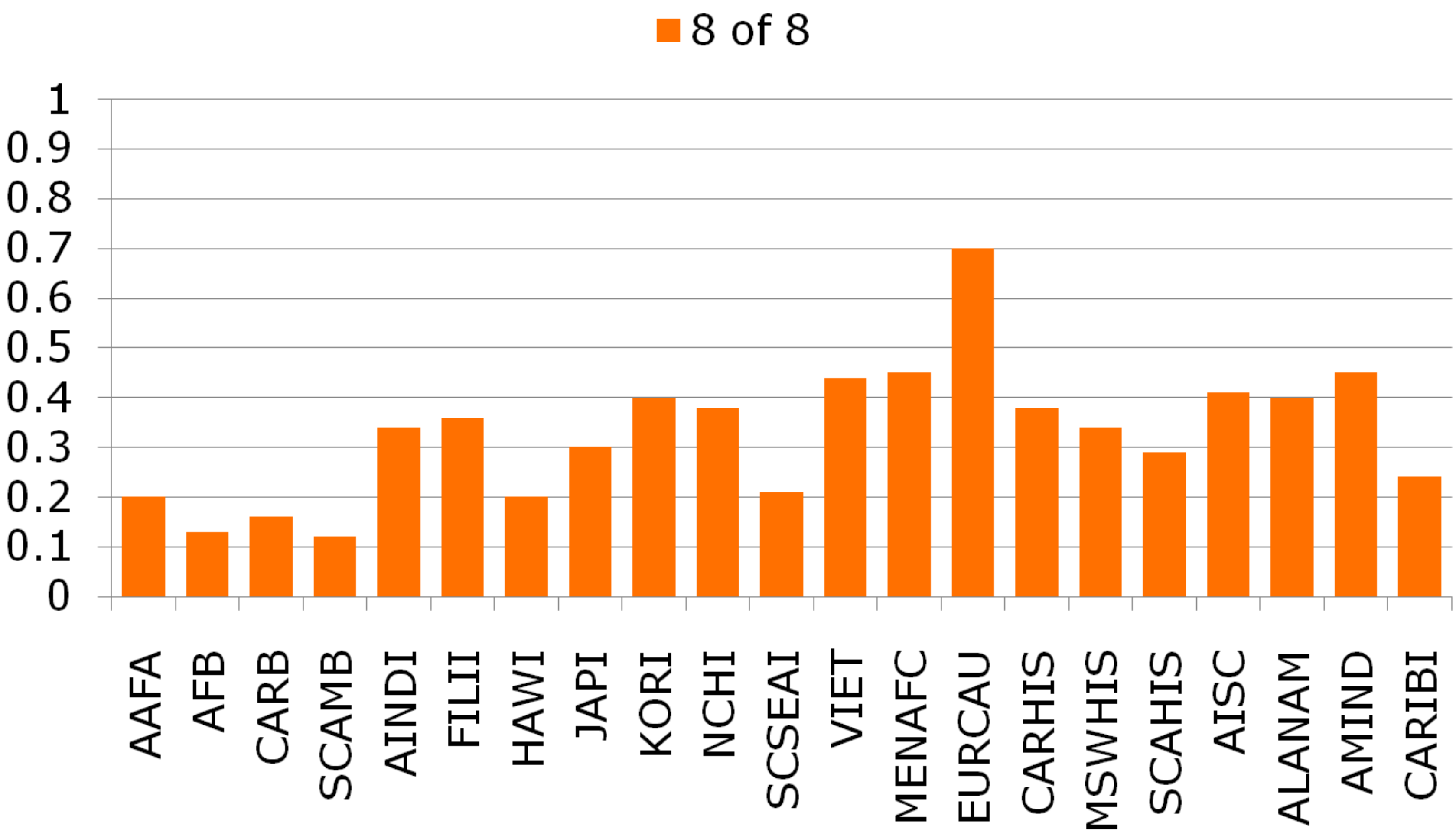
Umbilical cord blood (UCB) as a source of hematopoietic stem cells for hematopoietic reconstitution

Advantages	Disadvantages
• Rapid procurement	• Low cell dose
• Less stringent HLA matching	• Delayed engraftment
• Expanded donor pool	• Poor immune reconstitution
• Less graft-versus-host disease	• Increased graft failure rate

PBPC remains the “gold standard” against which performance of CB should be compared:

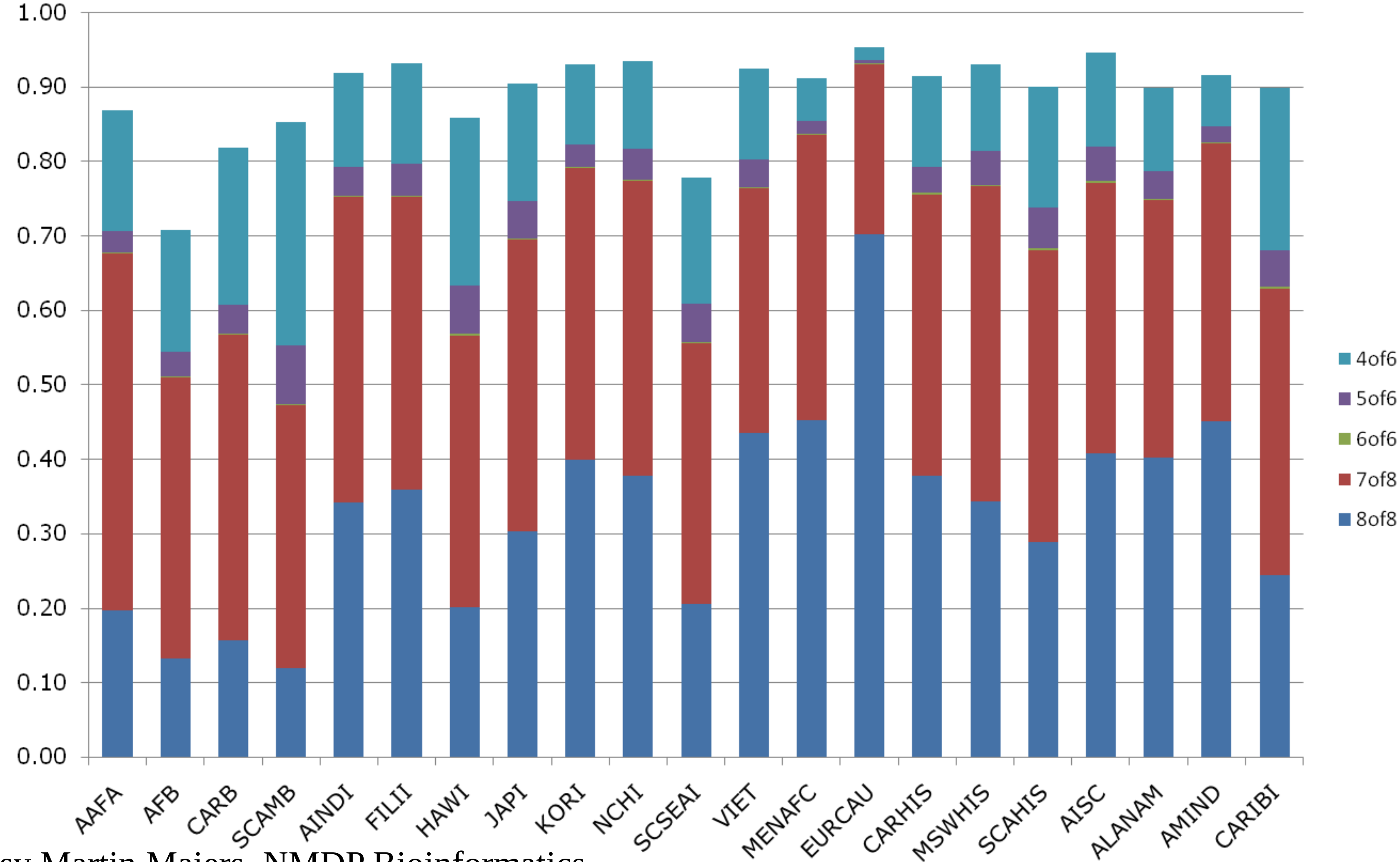
• Neutrophil engraftment (>500/µl)	11 days
• Platelets engraftment (>20,000/µl)	13 days
• Engraftment failure rate	<1%

8/8 Allele, Available-Match Rates in the Adult Donor Registry



Courtesy Martin Maiers, NMDP Bioinformatics

7/8 and 8/8 Allele Adult and Cord, in the Adult Donor Registry



Courtesy Martin Maiers, NMDP Bioinformatics

Single unit CB transplant

- Cell dose is key

  Laughlin et al. NEJM, 344:1815-1822, 2001

- HLA matching is also key, but mismatches are better tolerated than with bone marrow or peripheral blood.

- Engraftment failure rate is 5-20%.

- Time to neutrophil and platelet engraftment is delayed.

Umbilical cord blood (UCB) as a source of hematopoietic stem cells for hematopoietic reconstitution : can we improve current outcomes ?

- Improve collection procedures
- Double Cord Transplantation
- Ex Vivo Expansion
- Intra osseous transplant
- Haploidentical (CD34 selected) and CB co-transplantation
- Improve homing

Strategies to Improve the Results of Cord Blood Transplantation

Double Cord Blood Transplants

Double cord blood transplants

- one unit prevails (unable to predict which one)
- less relapses (improve survival (?))
- no graft-versus-graft effect, but more GVHD
- Single versus double: controversy is unsolved!

Barker J, Brunstein C and Wagner J.

Strategies to Improve the Results of Cord Blood Transplantation

Ex vivo expansion of cord blood progenitor cells

MDACC Expansion Trial

100% fraction

CD133+ enrichment

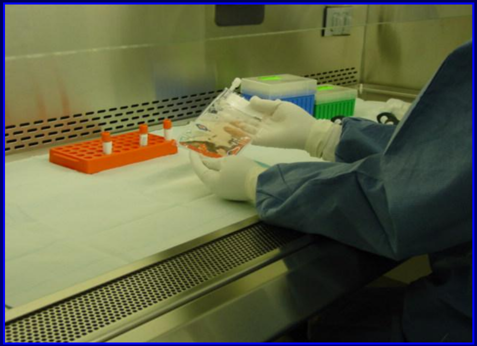
Ex-Vivo Expansion
with G-CSF, SCF, FLT3 ligand and TPO

14 days

MDACC Cord Blood Expansion Trial

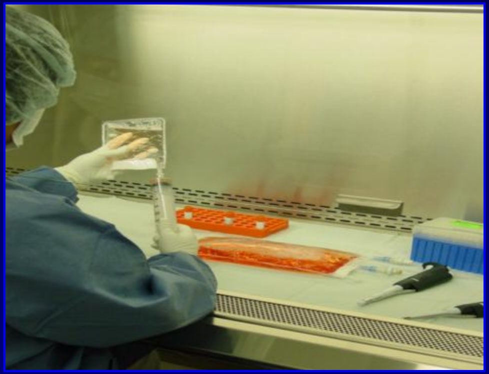
CB CD133^{+} cells cultured in SCF, Flt3L, G-CSF & TPO

Method developed by McNiece *et al*.



Day 0

50 ml



Day 7

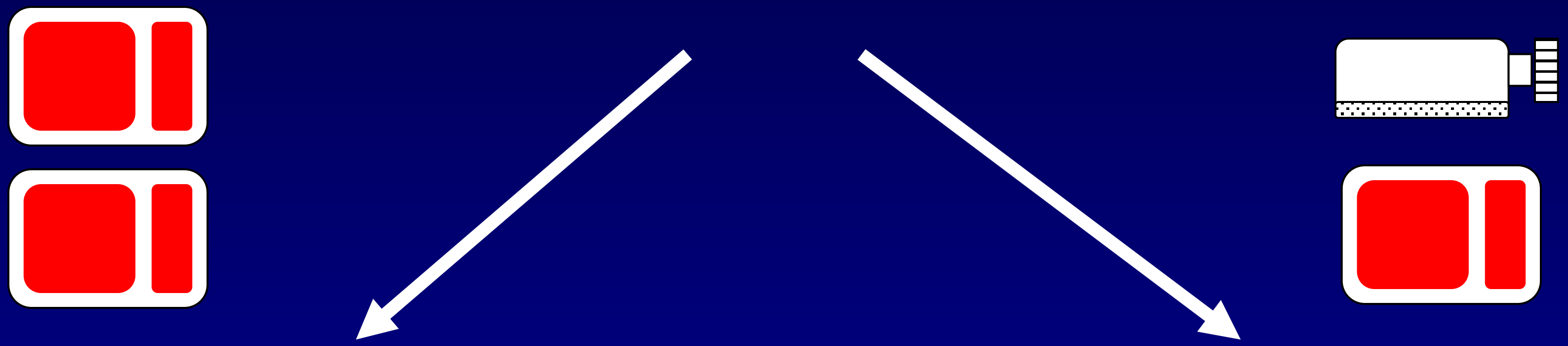
800ml

Day 14

Harvest

Patients with Hematologic Malignancies

Randomize (50 *per* arm)



Two Unmanipulated Cords

One *Ex Vivo* Expanded and One Unmanipulated Cord

MD Anderson Randomized Cord Blood Expansion Trial
P.I. Marcos de Lima - Protocol 02-407; IND 7166
Co P.I.: E. J. Shpall

Engraftment after Myeloablative Therapy

	Unmanipulated	Expanded
Days to ANC >500/µl	23 (21,NA)	**21** (19, NA)
Days to platelet >20,000/µl	50 (41, NA)	**48** (40, NA)

Selection Data

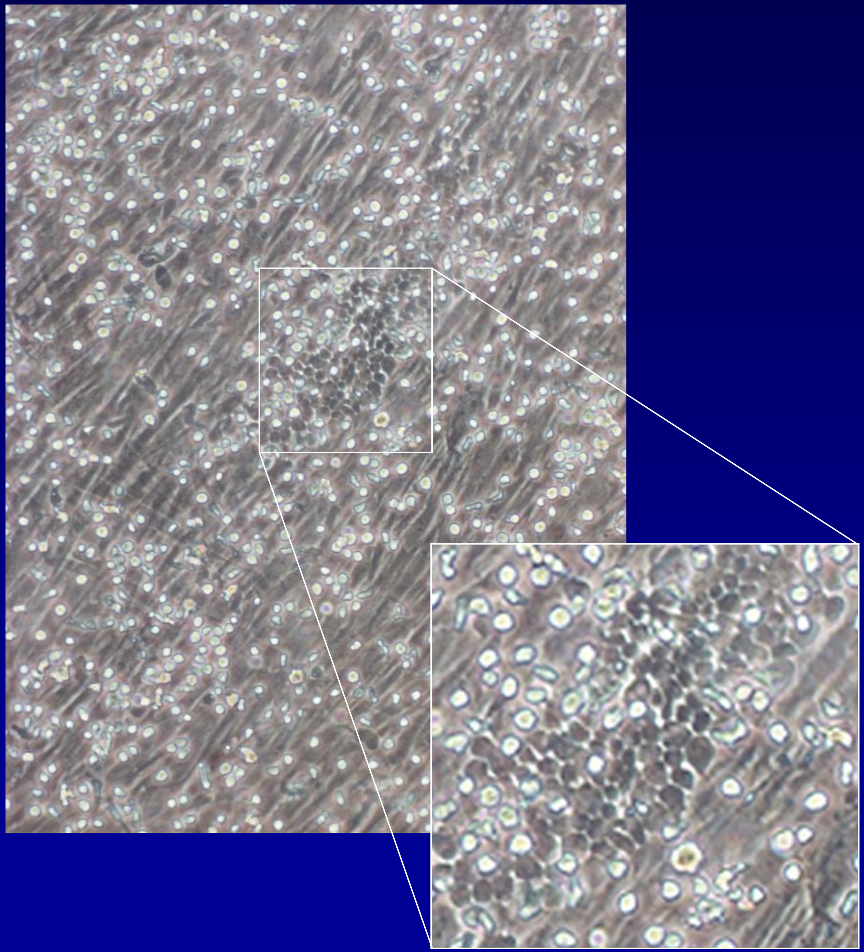
Post-selection $CD34^+$ cell recovery 46% (range 2-70%)

Expansion Data

Median TNC expansion 26-fold (range 0.4-275)
Median $CD34^+$ cell expansion 2.2 fold (range 0-18)

Positive-selection reduces $CD34^+$ cell yield

Mesenchymal Stem Cells (MSC)

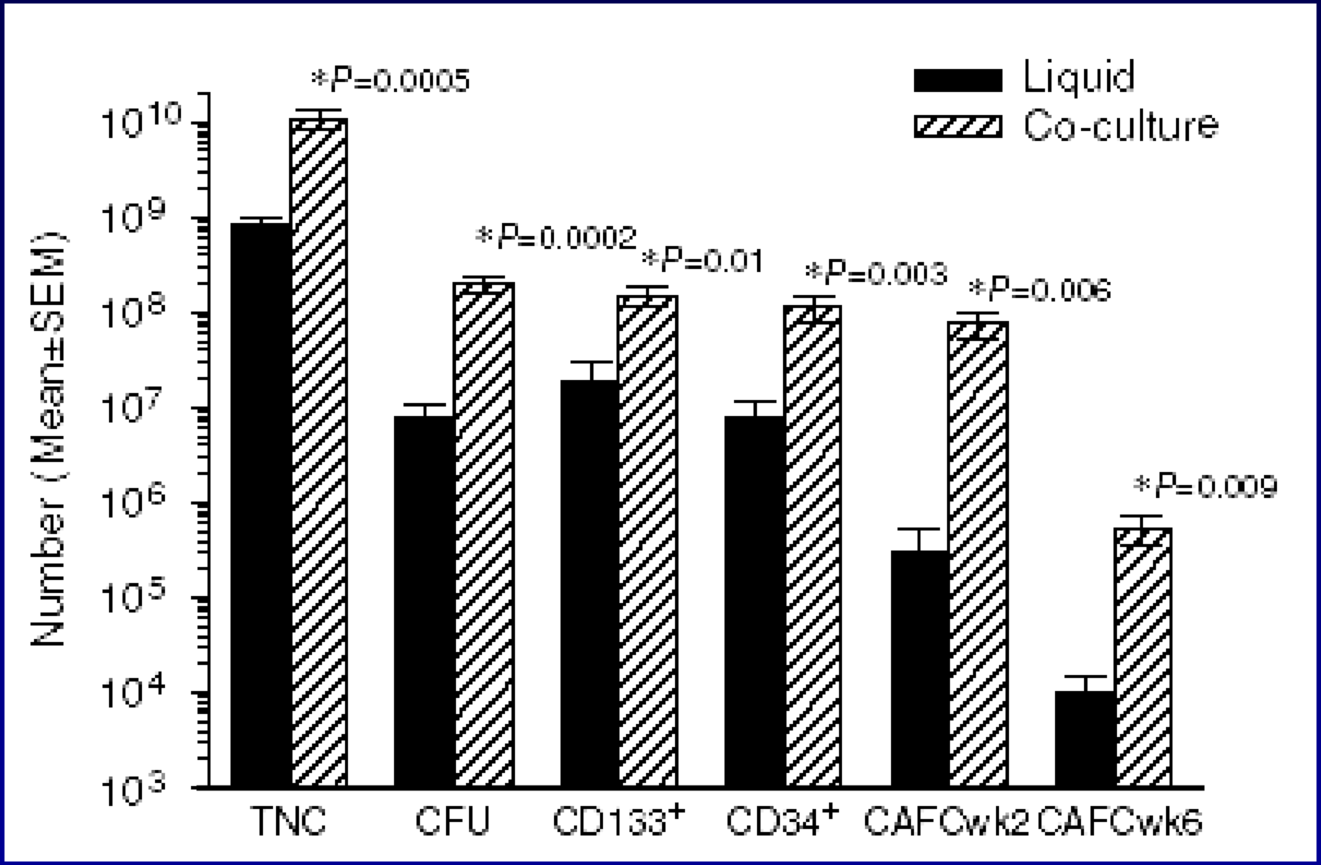


- MSC are a stromal component of the hematopoietic microenvironment.

- They provide cellular and extracellular components of the stem cell “niche”.

- When isolated and used *in vitro* in combination with cytokines, MSC markedly increase the expansion of CB hematopoietic progenitors.

Co-culture with MSC significantly enhances *ex vivo* expansion of CB cells



Fold increase x13 x25 x7 x14 x200 x44

Day 14 hematopoietic output from liquid culture of $CD133^+$ (solid bar) *vs*. co-culture of non-selected CB cells with MSC (striped bar)

Robinson *et al.* Bone Marrow Transplantation (2006) 37, 359-399

Hypothesis

Double cord blood transplant in which one unit is expanded in MSC-based co-cultures will lead to more rapid hematopoietic engraftment

Part #1: MSC Generation
(Family member, N=8)

100 mls bone marrow aspirate

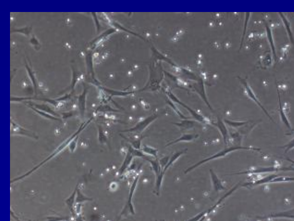
Ficoll density separation

MNC

MNC cultured 2-3 days.

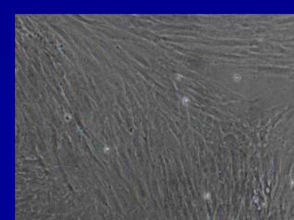
Non-adherent (hematopoietic) cells removed

Adherent cell (MSC) culture continued (7-10 days) to ~70% confluence



Medium: αMEM + 10% FBS

Passage: 6x150cm^2 flasks

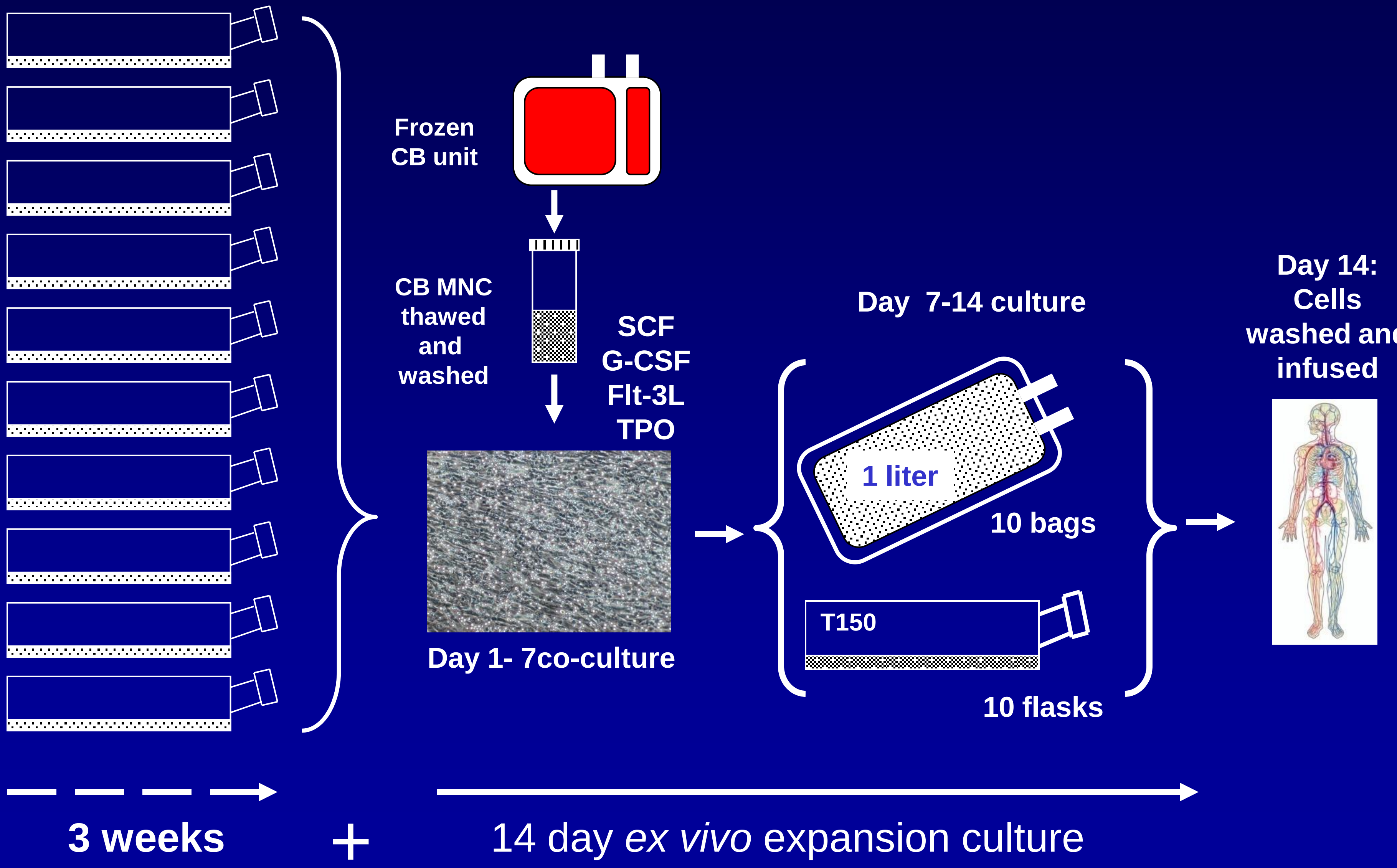


Passage: 12x150cm^2 flasks

3 weeks

Part #2: Cord blood expansion (Family member, N=8)

Two-step culture system



Limitations of the family member-derived MSC

- Family member donor not always available
- Logistics harvesting 100 ml marrow in clinic difficult
- Conscious sedation expensive
- MSC expansion procedure time consuming (approximately 3 weeks to generate sufficient cells)

Identification of Stromal Cell Precursors in Human Bone Marrow by a Novel Monoclonal Antibody, STRO-1

By Paul J. Simmons and Beverly Torok-Storb

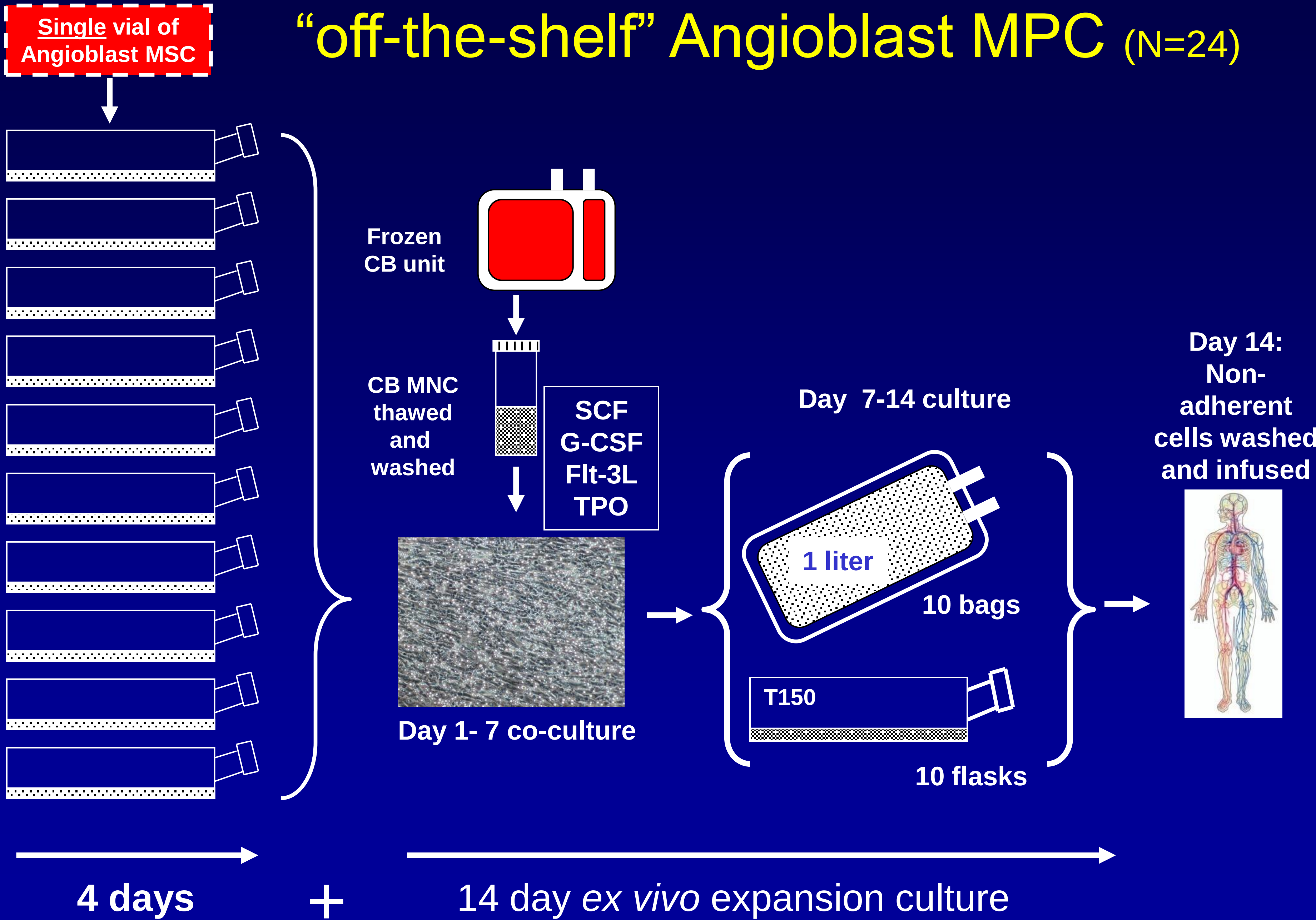
Murine IgM monoclonal antibody STRO-1 identifies a cell surface antigen expressed by stromal elements in human bone marrow (BM). STRO-1 binds to approximately 10% of BM mononuclear cells, greater than 95% of which are nucleated erythroid precursors, but does not react with committed progenitor cells (colony-forming unit granulocyte-macrophage [CFU-GM], erythroid bursts [BFU-E], and mixed colonies [CFU-Mix]). Fibroblast colony-forming cells (CFU-F) are present exclusively in the STRO-1$^+$ population. Dual-color cell sorting using STRO-1 in combination with antibody to glycophorin A yields a population approximately 100-fold enriched in CFU-F in the STRO-1$^+$/glycophorin A$^-$ population. When plated under long-term BM culture (LTBMC) conditions, STRO-1$^+$ cells generate adherent cell layers containing multiple stromal cell types, including adipocytes, smooth muscle cells, and fibroblastic elements. STRO-1$^+$ cells isolated from LTBMC at later times retain the capacity to generate adherent layers with a cellular composition identical to that of the parent cultures. The STRO-1–selected adherent layers are able to support the generation of clonogenic cells and mature hematopoietic cells from a population of CD34$^+$ cells highly enriched in so-called long-term culture-initiating cells. We conclude that antibody STRO-1 binds to BM stromal elements with the capacity to transfer the hematopoietic microenvironment in vitro.

Simmons PJ, Torok-Storb B. Blood. 1991;78:55-62

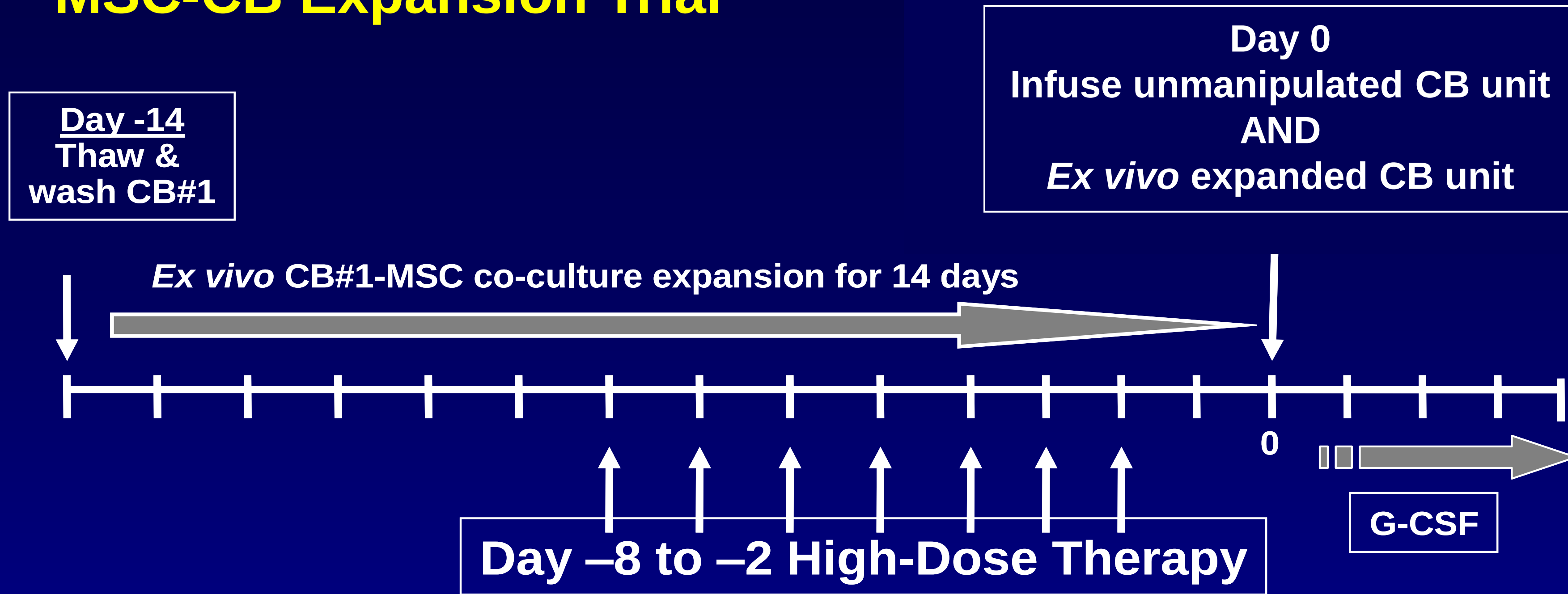
Angioblast generate GMP-grade, BM-derived, 3rd party, “off-the-shelf” MSC isolated using the STRO-1 antibody.

Frozen aliquots of STRO-1-selected MSC from Angioblast required only 3-4 days to generate sufficient MSC for co-culture and provided comparable CB expansion to family member derived MSC.

M. D. Anderson CB Expansion Trial with "off-the-shelf" Angioblast MPC (N=24)



MSC-CB Expansion Trial



Day	Preparative regimen	
-9	Hydration Therapy	
-8	Melphalan 140 mg/m^2	
-7	Thiotepa 10 mg / Kg	
-6	Fludarabine 40 mg/m^2	
-5	Fludarabine 40 mg/m^2	
-4	Fludarabine 40 mg/m^2	Rabbit-ATG
-3	Fludarabine 40 mg/m^2	Rabbit-ATG
-2	Rest	
-1	Rest	
0	CB Infusions	

G*v*HD Prophylaxis: Tacrolimus and MMF

M. D. Anderson MSC-CB Expansion Trial
Protocol 05-0781, IND 13,034

Eligibility

- Patients with a high-risk hematologic malignancy
- Two 4-6/6 HLA matched CB units with > 1×10^7 TNC/Kg each

Statistical Design

- Safety and feasibility phase I
- Primary endpoint = time to engraftment
- Stopping rule for engraftment failure or excessive G*v*HD

Demographic and Clinical Characteristics of the Patients and Controls.

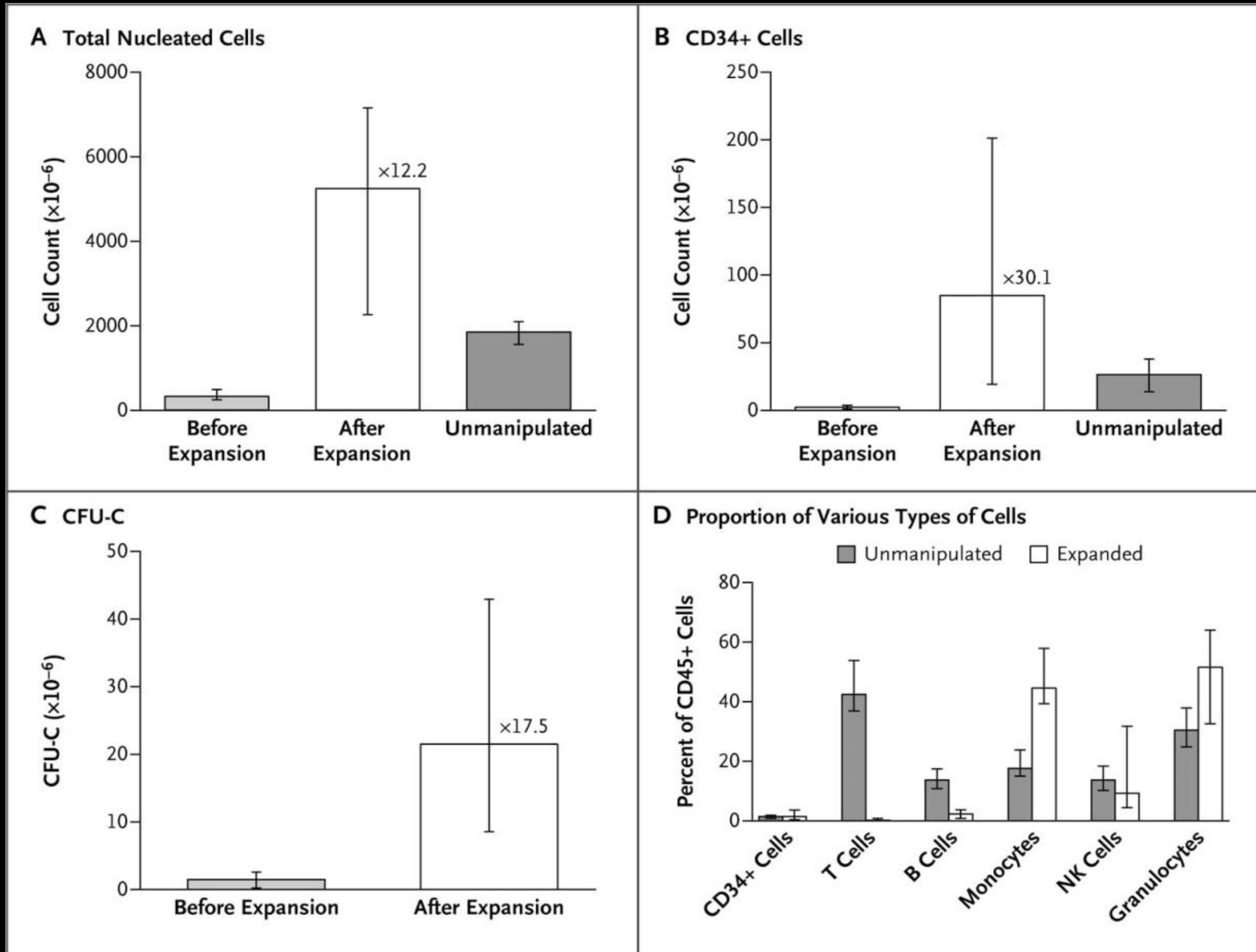
Table 1. Demographic and Clinical Characteristics of the Patients and Controls.*

Characteristic	Patients		Controls	
	Haploidentical Mesenchymal Stromal Cells (N=7)	STRO-3+ Mesenchymal Progenitor Cells (N=24)	MDACC (N=60)†	CIBMTR (N=80)
Weight — kg				
Median	79	75	75	82
Range	53–95	51–118	48–122	40–170
Age — yr				
Median	31	39	32	36
Range	26–55	18–61	18–64	18–61
Diagnosis — no. (%)				
AML or MDS	5 (71)	16 (67)	31 (52)	52 (65)
ALL	1 (14)	4 (17)	15 (25)	20 (25)
Non-Hodgkin's or Hodgkin's lymphoma	0	3 (12)	5 (8)	7 (9)
CLL	1 (14)	1 (4)	2 (3)	1 (1)
CML or other MPD	0	0	6 (10)	0
Myeloma	0	0	1 (2)	0
Disease status at time of transplantation — no. (%)				
Complete remission	1 (14)	12 (50)	26 (43)	49 (61)
First remission	1 (14)	2 (8)	8 (13)	17 (21)
Second or subsequent remission	0	10 (42)	18 (30)	32 (40)
Active disease	6 (86)	12 (50)	34 (57)	31 (39)
Donor–recipient HLA compatibility — no. (%)				
6/6	0	1 (4)	4 (7)	4 (5)
5/6	3 (43)	3 (12)	13 (22)	14 (18)
4/6	4 (57)	20 (83)	43 (72)	58 (72)
3/6	0	0	0	2 (2)
Not reported	0	0	0	2 (2)

* ALL denotes acute lymphocytic leukemia, AML acute myeloid leukemia, CIBMTR Center for International Blood and Marrow Transplant Research, CLL chronic lymphocytic leukemia, CML chronic myeloid leukemia, MDS myelodysplastic syndrome, and MPD myeloproliferative disorder.

† Two controls from the M.D. Anderson Cancer Center (MDACC) were excluded owing to lack of engraftment and chimerism documentation.

Expansion of Cord Blood with Mesenchymal Stromal Cells.



E Doses in Units of Unmanipulated Cord Blood and Mesenchymal-Cell–Expanded Cord Blood (N=31)

	Unmanipulated Cord Blood	Expanded Cord Blood	Total
		median (range)	
Total Nucleated Cells/kg$\times 10^{-7}$	2.28 (1.57–4.82)	5.84 (0.03–14.37)	8.34 (1.66–19.19)
CD34+ Cells/kg$\times 10^{-6}$	0.38 (0.07–1.74)	0.95 (1.60–9.34)	1.81 (0.09–9.88)
CFU-C/kg$\times 10^{-5}$	Not done	3.00 (0.00–13.70)	3.00 (0.00–13.70)

de Lima M et al. N Engl J Med 2012;367:2305-2315

The NEW ENGLAND JOURNAL of MEDICINE

Engraftment in Recipients of Ex Vivo Expanded Cells and MDACC and CIBMTR Controls.

Table 2. Engraftment in Recipients of Ex Vivo Expanded Cells and MDACC and CIBMTR Controls.

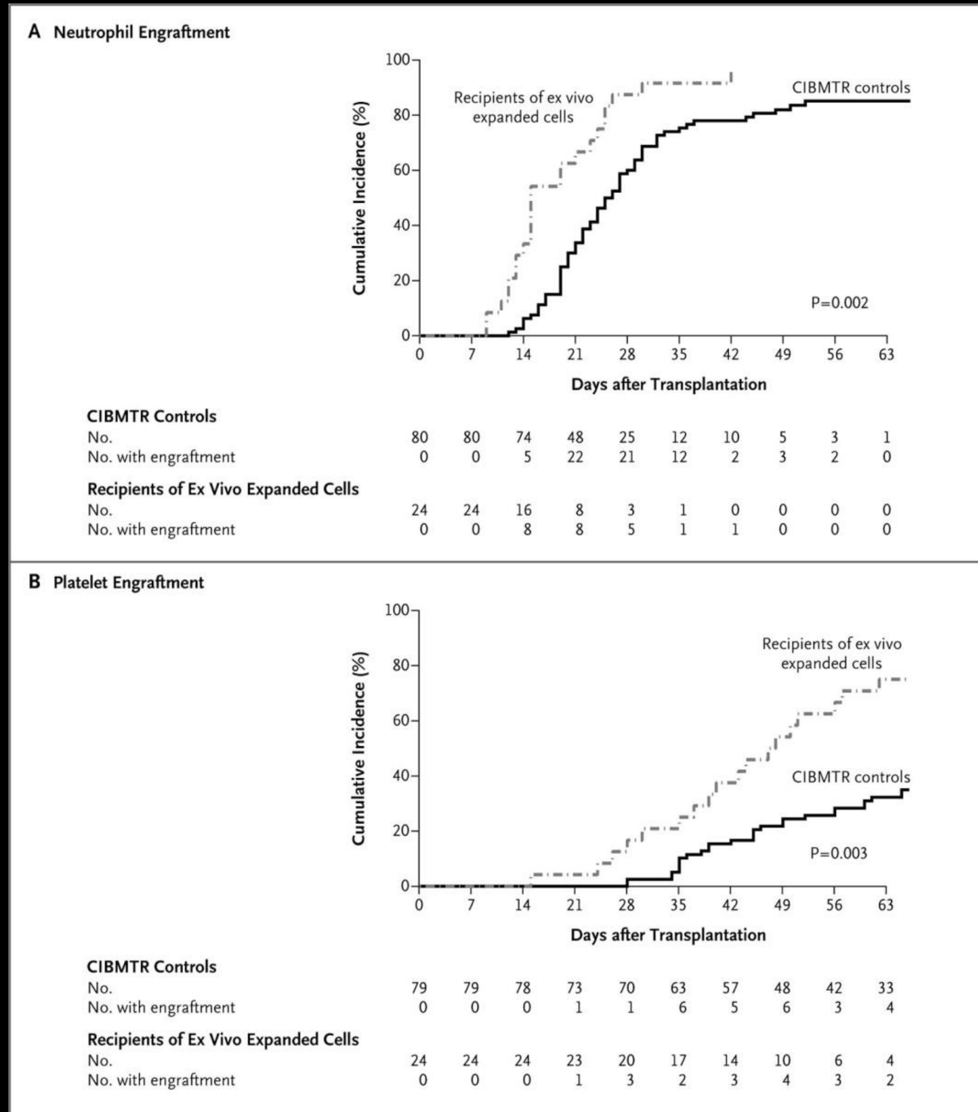
Engraftment	Recipients of Ex Vivo Expanded Cells (N=24)	MDACC Controls (N=60)	P Value*	CIBMTR Controls (N=80)	P Value†
Neutrophil engraftment					
No. of patients	23	51		67	
Time to engraftment — days					
Median	15	21	0.08	24	<0.001
Range	9–42	6–45		12–52	
Cumulative incidence — % (95% CI)					
By 26 days	88 (66–96)	62 (48–73)	0.006	53 (41–63)	<0.001
By 42 days	96 (74–99)	83 (71–91)	0.05	78 (67–86)	0.005
Platelet engraftment					
No. of patients	18	38		37	
Time to engraftment — days					
Median	42	41	0.33	49	0.03
Range	15–62	26–126		18–264	
Cumulative incidence — % (95% CI)					
By 60 days	71 (48–85)	52 (38–63)	0.10	31 (21–41)	<0.001
By 180 days	75 (53–88)	63 (50–74)	0.28	46 (35–58)	0.01

* P values are for the comparison between recipients of STRO-3+ mesenchymal precursor cells and MDACC controls.
† P values are for the comparison between recipients of STRO-3+ mesenchymal precursor cells and CIBMTR controls.

de Lima M et al. N Engl J Med 2012;367:2305-2315

The NEW ENGLAND JOURNAL of MEDICINE

Cumulative Incidences of Neutrophil Engraftment and Platelet Engraftment.



A Neutrophil Engraftment

	0	7	14	21	28	35	42	49	56	63
CIBMTR Controls										
No.	80	80	74	48	25	12	10	5	3	1
No. with engraftment	0	0	5	22	21	12	2	3	2	0
Recipients of Ex Vivo Expanded Cells										
No.	24	24	16	8	3	1	0	0	0	0
No. with engraftment	0	0	8	8	5	1	1	0	0	0

B Platelet Engraftment

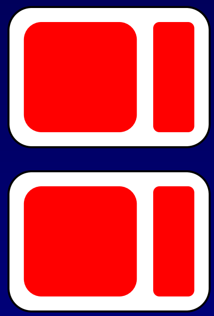
	0	7	14	21	28	35	42	49	56	63
CIBMTR Controls										
No.	79	79	78	73	70	63	57	48	42	33
No. with engraftment	0	0	0	1	1	6	5	6	3	4
Recipients of Ex Vivo Expanded Cells										
No.	24	24	24	23	20	17	14	10	6	4
No. with engraftment	0	0	0	1	3	2	3	4	3	2

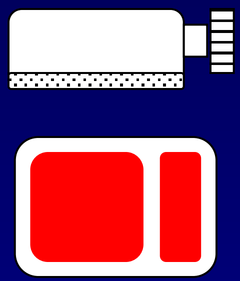
de Lima M et al. N Engl J Med 2012;367:2305-2315

The NEW ENGLAND JOURNAL of MEDICINE

What is next for MSC-based ex-vivo expansion ?

Randomize





Two Unmanipulated Cords

One *Ex Vivo* Expanded and One Unmanipulated Cord

International, multicenter study sponsored by Mesoblast

Ex-vivo expansion

- Engineered Notch Ligands

  Delaney et al, Nat Med. 2010 Feb;16(2):232-6

- StemRegenin-1 SR-1 (Novartis). Univ of Minnesota

- Gamida cell: nicotinamide-based ex vivo expansion

- TEPA (Tetraethylenepentamine) – StemEx

  de Lima et al, Bone Marrow Transplant. 2008;41:771-8

Limitations of double CB platform

Use of two units – expensive.

Possibly more GVHD.

Added costs of expansion technology to the cost of two units.

Intra-Osseous Co-Transplantation of Human Mesenchymal Stromal Cells and CD34-Selected Human Umbilical Cord Blood

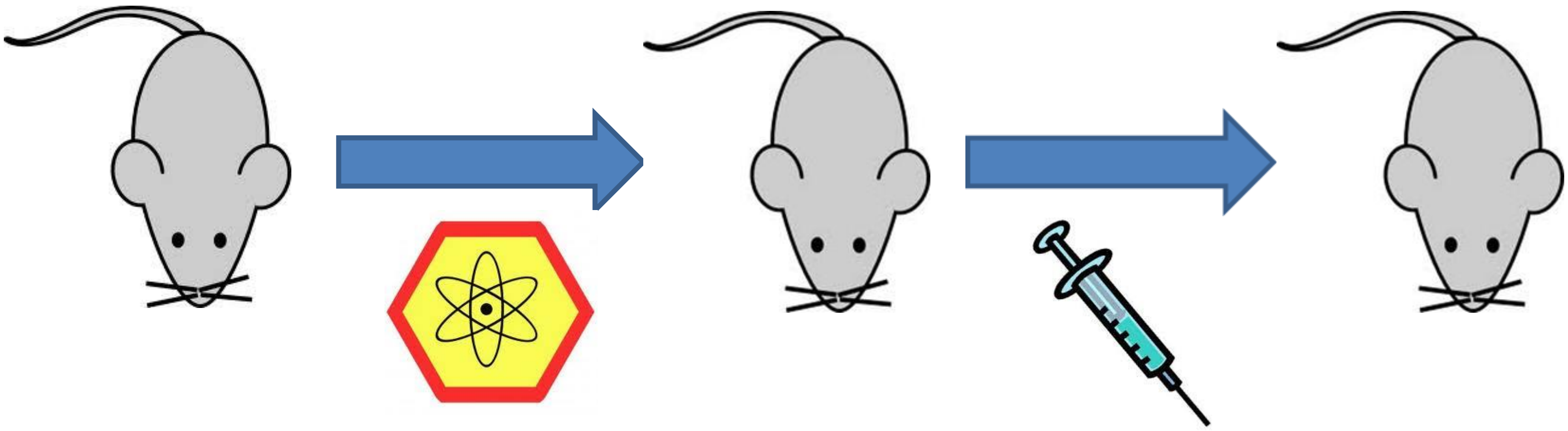
Leland Metheny M.D.
Jane Reese-Koc
Alex Huang, MD

University Hospitals Seidman Cancer Center

NCI CCC A Comprehensive Cancer Center Designated by the National Cancer Institute

Case Western Reserve University | Case Comprehensive Cancer Center

Methods



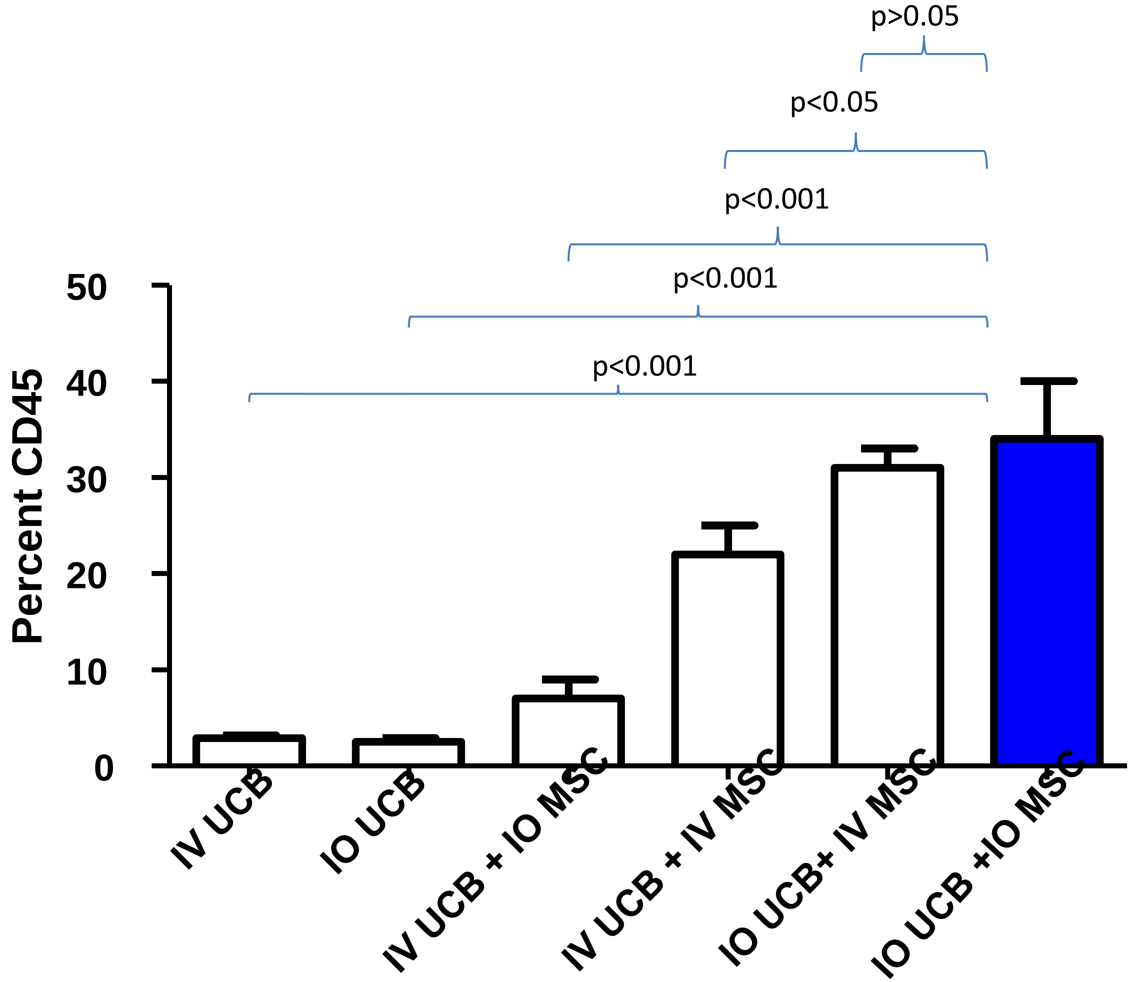
<u>Mouse:</u>
NOD/SCID-gamma

<u>Non-lethal Radiation</u>:
300 rads

<u>6 Cohorts:</u>
IV UCB
IVUCB+IV MSC
IO UCB
IO UCB+IO MSC
IO UCB+IV MSC
IVUCB+IOMSC

<u>6 Week Analysis</u>:
- Right tibia flow
- Left tibia histology

Percent CD45 in the Right Tibia Bone Marrow at 6 weeks



Cord blood as a source of cell subsets

NK cells

Regulatory T cells

Mesenchymal stromal cells

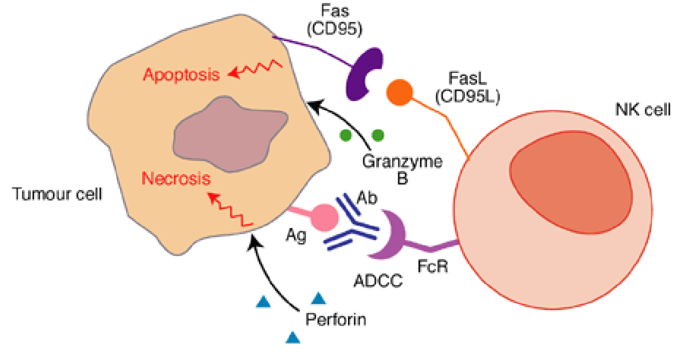
Other cell types.

Enhancing NK cell therapy through GSK3 inhibition

David Wald
Assistant Professor
CWRU/UH Hospitals
Case Medical Center

NK Cells

- Potent effectors of the innate immune response
- Make up from 1–32.6% of peripheral blood lymphocytes in normal subjects
- Large granular lymphocytes that can kill target cells
- Kill cells by cytokine/chemokine secretions (ex. IFN-γ) and/or perforin/granzyme and death receptor (ex. Fas) pathways



The natural killer (NK)-cell response to tumour cells

Expert Reviews in Molecular Medicine©2003 Cambridge University Press

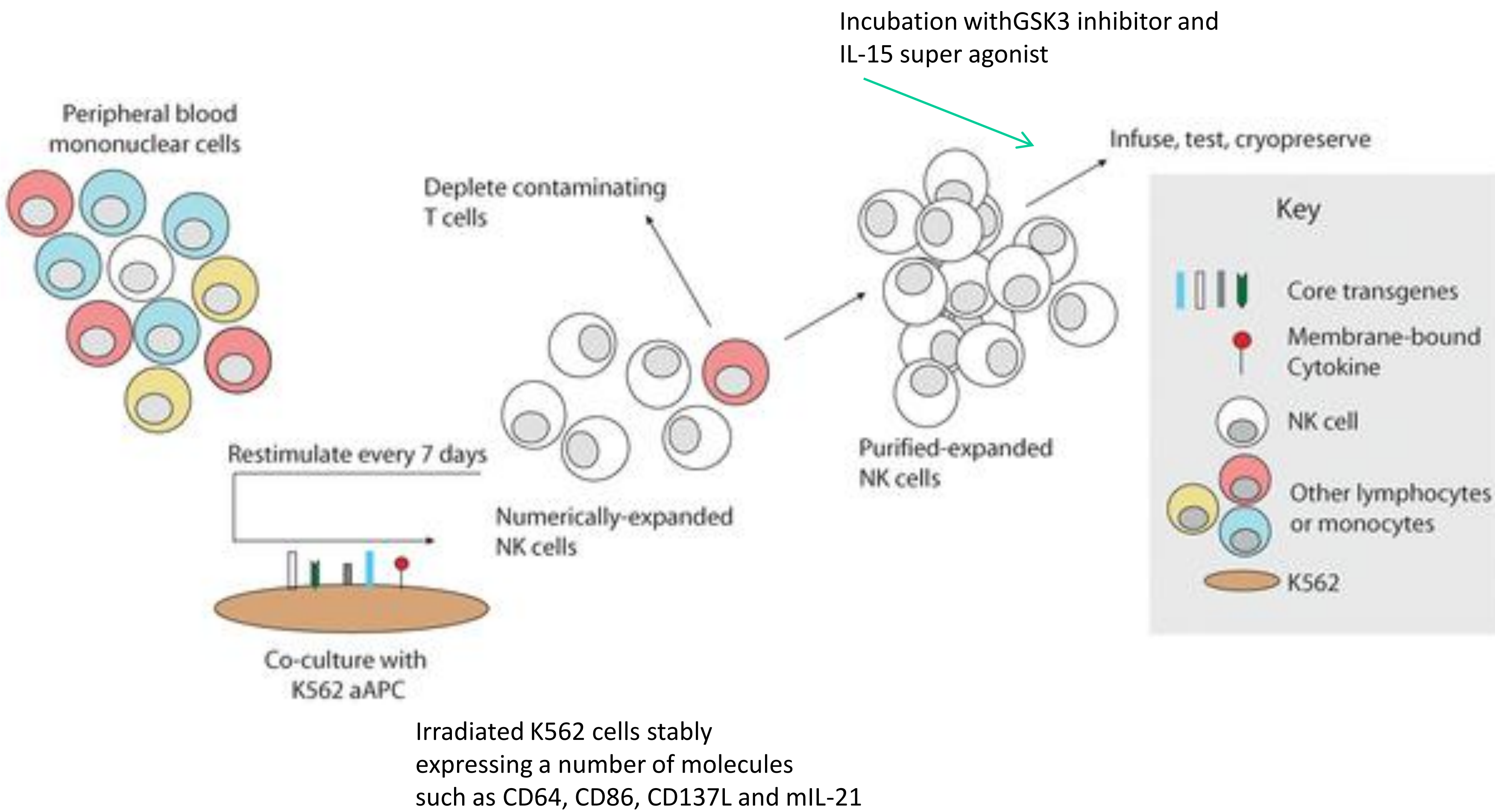
Glycogen Synthase Kinase 3

- Constitutively active serine/threonine kinase involved in a multitude of cellular processes (cell death, memory, inflammation) and signaling pathways (wnt/beta-catenin, mTor, p53, NFkB etc)

- GSK3 inhibition leads to growth inhibition, differentiation and cell death of many types of cancer cells

- Increase in NK cell-mediated AML killing in animal model and in vitro

Figure 2. Schema for NK cell manufacturing with aAPCs.



Denman CJ, Senyukov VV, Somanchi SS, Phatarpekar PV, et al. (2012) Membrane-Bound IL-21 Promotes Sustained Ex Vivo Proliferation of Human Natural Killer Cells. PLoS ONE 7(1): e30264. doi:10.1371/journal.pone.0030264
http://www.plosone.org/article/info:doi/10.1371/journal.pone.0030264

Can cord blood banks transform into induced pluripotent stem cell banks? *Cytotherapy*, 2015; 17: 756–764

HONGYAN ZHOU[1] & MAHENDRA S. RAO[1,2]

[1]*New York Stem Cell Foundation Research Institute, New York City, New York, USA, and* [2]*Q Therapeutics, Salt Lake City, Utah, USA*

Human induced pluripotent stem cells (iPSCs):

- usually derived from human somatic cell types (blood, skin)

- generated with re-programming techniques

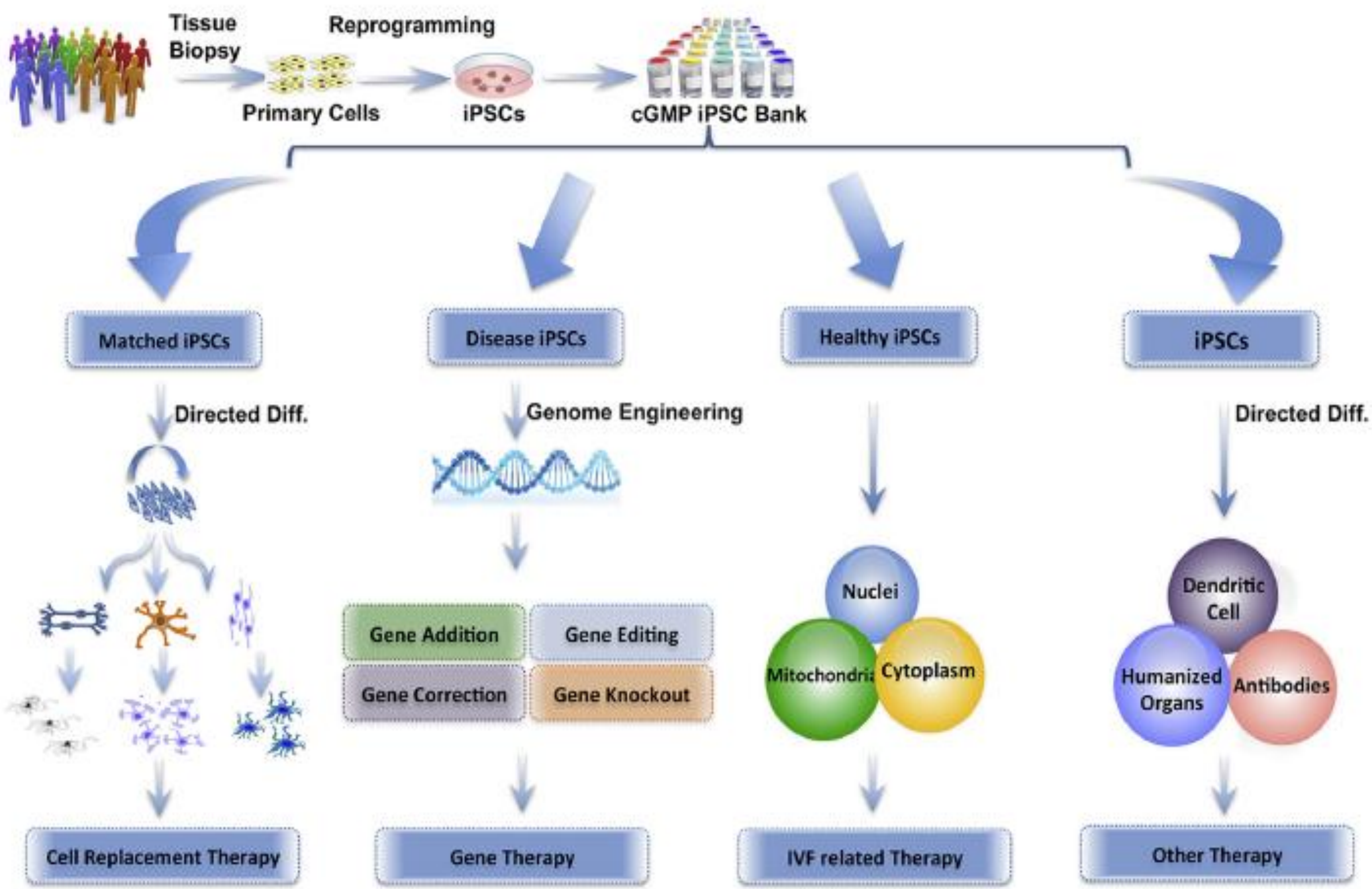
- differentiate into a variety of other cell types

Can cord blood banks transform into induced pluripotent stem cell banks?

Cytotherapy, 2015; 17: 756–764

HONGYAN ZHOU[1] & MAHENDRA S. RAO[1,2]

[1]*New York Stem Cell Foundation Research Institute, New York City, New York, USA, and* [2]*Q Therapeutics, Salt Lake City, Utah, USA*



Family Cord Blood Banking

Reasons to family bank cord blood stem cells

Autologous cord blood stem cells are an exact match

Related stem cells remain the preferred choice of transplant by many physicians,
as they cause fewer recipient problems.

- 25 percent probability of being a perfect match and a 50 percent probability of providing a suitable match for transplant use with a sibling (and possibly other family members) .

Late onset diseases : possible benefit from having cells stored.

Minority populations are under-represented in transplant registries.

Family Cord Blood Banking

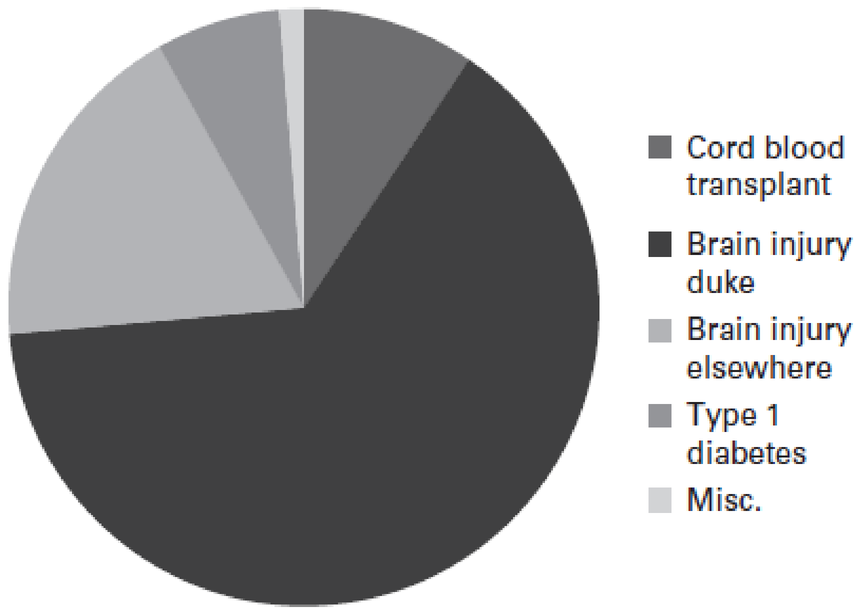


Figure 2. Autologous UCBT from family banks.

Umbilical cord blood donation
KK Ballen *et al*

Bone Marrow Transplantation (2015), 1 – 8

Family Cord Blood Banking

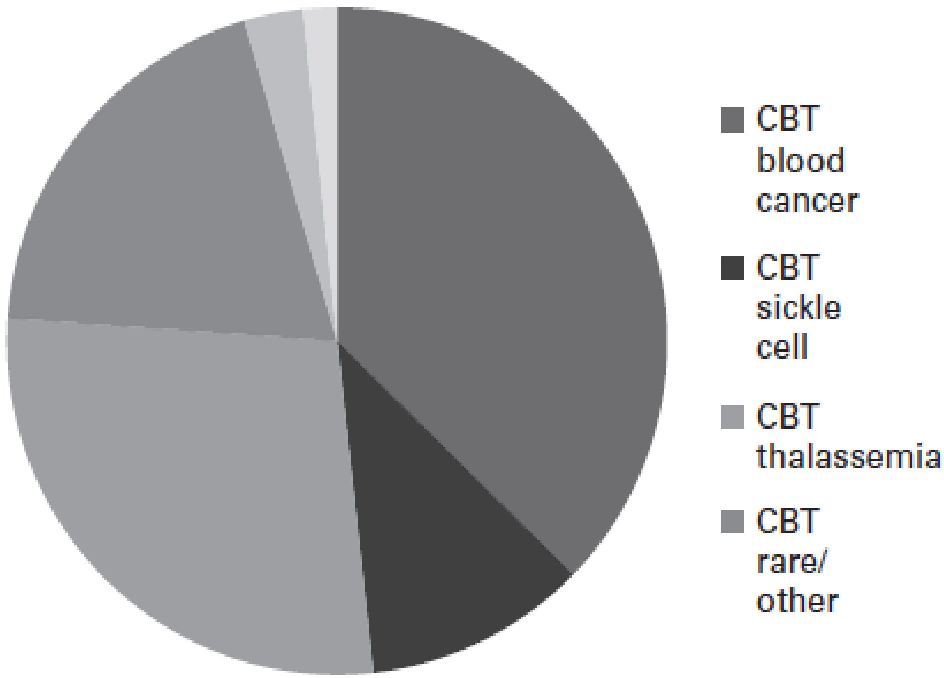


Figure 3. Allogeneic UCBT from family banks.

Current FDA-Approved Cord Blood Uses and FDA IND-Approved Cord Blood Uses

pCBB, allogenic

CD34+ Cells → Hematologic Malignancies, Anemia, SCA

Cord Blood

MNC → Critical Limb Ischemia, Spinal Cord Injury

MSC → Diabetes Mellitus, Alzheimer's, Cartilage Injury, GvHD
CD4+ CD25+ T_{reg} → Diabetes Mellitus

ALDH^{bright} → Critical Limb Ischemia, Myocardial Ischemia, Stroke

Dendritic Cells → Vaccine (Ag Viral/Fungal Infections, Anti-Tumor)

Autism, Osteopetrosis, Hypoplastic Heart, Stroke, Cerebral Palsy, Chronic Traumatic Brain Injury, Transfusion for Preterm Neonates, Neonatal Hypoxic-Ischemic Encephalopathy, Chronic Injured Spinal Cord, Acquired Hearing Loss in Children

Serum/Plasma → Eye Abrasions

fCBB, autogenic

→Treatment/Cure

→Treatment/Cure?

Current FDA BLA-Approved Cord Blood Uses and FDA IND-Approved Cord Blood Uses

pCBB, allogenic

CD34+ Cells → Hematologic Malignancies, Anemia, SCA

Cord Blood

fCBB, autogenic

→Treatment/Cure

→Treatment/Cure?

MNC → Critical Limb Ischemia, Spinal Cord Injury

MSC → Diabetes Mellitus, Alzheimer's, Cartilage Injury, GvHD
CD4+ CD25+ T_{reg} → Diabetes Mellitus

$ALDH^{bright}$ → Critical Limb Ischemia, Myocardial Ischemia, Stroke

Dendritic Cells → Vaccine (Ag Viral/Fungal Infections, Anti-Tumor)

Autism, Osteopetrosis, Hypoplastic Heart, Stroke, Cerebral Palsy, Chronic Traumatic Brain Injury, Transfusion for Preterm Neonates, Neonatal Hypoxic-Ischemic Encephalopathy, Chronic Injured Spinal Cord, Acquired Hearing Loss in Children

Serum/Plasma → Eye Abrasions

Contribution of the fCBB to Cord Blood Approvals for Alternative Uses

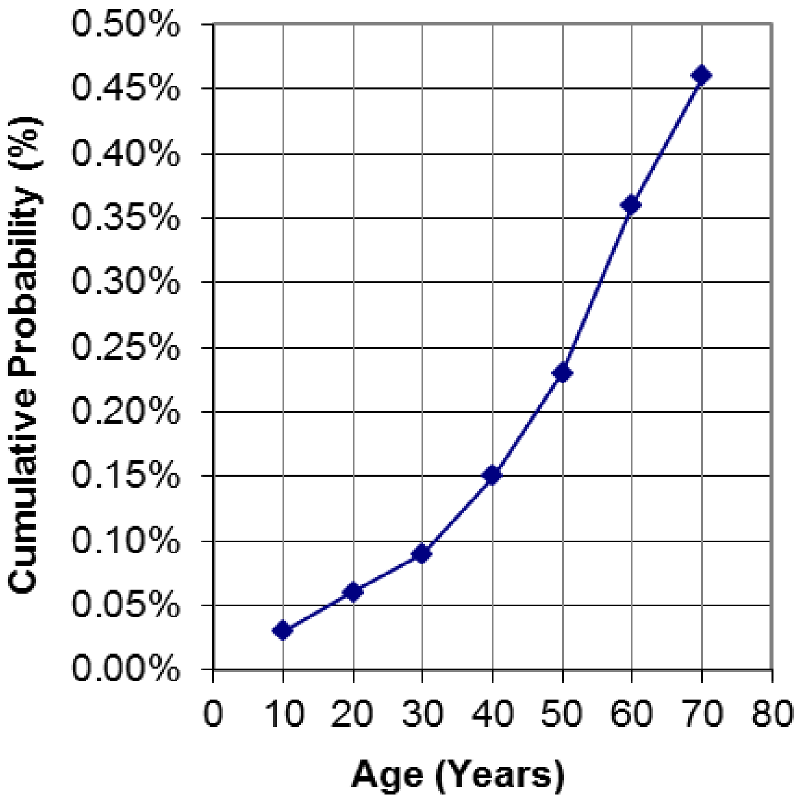
Homologous Use of Cord Blood

Homologous Use: "Use of the stem cells for the same type or purpose as the origin of that particular stem cell. A homologous use for stem cells obtained from the cord blood would be for a blood or hematological condition." (PUBLIC CBB)

Non-Homologous Use: "Use of the stem cells for any other use or purpose, e.g., using umbilical cord blood stem cells to treat a disease such as multiple sclerosis, type I diabetes or ALS."

(FAMILY CBB)

What are the Odds of Requiring a Transplant?



In the USA, 1 in 217 people have a stem cell transplant by age 70

(Nietfeld et al., 2008)

http://parentsguidecordblood.org/odds.php; Table copyright Frances Verter, PhD 2014

Summary of Clinical Trials with Cord Blood Using donor (allogeneic, + siblings) fCBB Cord Blood

Diagnosis	Occurence in USA	Trial stage	Trial registry
Cartilage Repair	10-25% adolescents have knee injuries	Approved by Korean FDA (Cartistem)	NCT01733186
Cerebral Palsy	2 per 1000 full term births	phase 2	NCT01193660 NCT01528436 NCT01639404 NCT01991145 NCT02025972
Critical Limb Ischemia	2.5 per 1000 people, over 80% of them diabetics	phase 1	NCT01019681
Premature Lungs (BPD)	25% births under 1500gm	phase 2	NCT01897987
Type 1 Diabetes	1.7 per 1000 ages birth-19	phase 2	NCT01350219 NCT01996228

http://parentsguidecordblood.org/odds.php; Table copyright Frances Verter, PhD 2014

Summary of Clinical Trials with Cord Blood Using With Autologous fCBB Cord Blood Stem Cells

Diagnosis	Occurence in USA	Trial stage	Trial registry
Acquired Hearing Loss	12.5% ages 6-19	phase 1	NCT01343394 NCT02038972
Autism	1.5% (1 in 68) children	phase 2 phase 1	NCT01638819 NCT02176317 India
Cerebral Palsy	0.2% full term births, 2.2% premature births, 1 in 300 kids ages 5-10	phase 2	NCT01147653 NCT01072370 NCT01988584 Japan
Cerebral Palsy		phase 1	Romania Slovakia Spain
Hypoplastic Left Heart Syndrome	0.2 per 1000 births	phase 1	NCT01445041 NCT01856049
Neonatal Oxygen Deprivation	0.2% full term births	phase 1	NCT00593242 NCT01506258 NCT01649648 Japan
Traumatic Brain Injury	435,000 per yr ages 0-14 #1 cause of death in kids	phase 1	NCT01251003 NCT01700166
Type 1 Diabetes	1.7 per 1000 ages birth-19	phase 1 & 2	NCT00989547 NCT00873925 CoRD

http://parentsguidecordblood.org/odds.php; Table copyright Frances Verter, PhD 2014

USA Medical Society Opinion (Family Banking)

The following medical societies have issued Opinions about cord blood banking:

ASBMT - Mar. 2008
ACOG - Feb. 2008
AMA - Nov. 2007
AAP - Jan. 2007
WMDA - Jun. 2006
RCOG - Jun. 2006
EGE - Mar. 2004

None of the medical society opinions include therapies that are in clinical trials, which are not considered standard of care.

http://parentsguidecordblood.org/odds.php; Table copyright Frances Verter, PhD 2014

Benefit of Regenerative Medicine?

- Approximately 1 in 3 Americans could benefit from regenerative medicine.

- Children whose cord blood stem cells are available for their own potential use could be among the first to benefit from new therapies as they become available.

- With autologous cells, there is no risk of the immune system rejecting the cells.

Harris DT, et al., (2007). "*The potential of cord blood stem cells for use in regenerative medicine.*" *Expert Opin. Biol. Ther.* **7** (9): 1311–1322.

Safety of Autologous Human Umbilical Cord Blood Treatment for Perinatal Arterial Ischemic Stroke (ClinicalTrials.gov Identifier: NCT02460484).

- **Principal Investigator:** James Baumgartner, MD**.**
- **Purpose:** to determine if hUCB infusion is safe, if late functional outcome is improved, if hUCB treatment improves physiologic response in the child's SSEP & EEG, and the effect of hUCB infusion in altering anatomic findings on MRI.
- **Primary Outcome Measures**: Hemodynamic Safety, Pulmonary Safety, Renal Safety, Neurological Safety
- **Secondary Endpoints**: EEG, Fine and Gross Motor

CB Infusion to Treat Type 1 Diabetes (NCT00305344)

- **Principal Investigator: M. Haller, MD, University of Florida, Gainesville.**
- **Purpose:** To transfuse autologous UCB in attempt to re-establish immune tolerance and regenerate pancreatic islet insulin-producing beta cells.
- **Design:** Open label, historic control, single group assignment efficacy study to determine if UCB can potentially be part of early treatment regimens for type 1 diabetes.

Safety of Autologous Human Umbilical Cord Blood Mononuclear Fraction to Treat Acquired Hearing Loss in Children (NCT01343394)

Cord Blood Registry
Speech Therapists for Children
The University of Texas Health Science Center, Houston
M.D. Anderson Cancer Center
Baylor College of Medicine
The Methodist Hospital System Research Institute – Houston.

Acquired hearing loss characterized by a loss of functioning hair cells in the Organ of Corti. Patients are 6 weeks to 18 months.

Cord Blood for Neonatal hypoxic-Ischemic Encephalopathy
(ClinicalTrials.govIdentifier:
NCT00593242)

- **Principal Investigator: J. Kurtzberg, MD.**
- **Purpose:** Phase I open label, historic control, single group assignment safety study to test feasibility of collection, preparation and infusion of autologous UCB if the infant is born with signs of brain injury
- **Primary Outcome Measures**: AE rates in the pilot study population will be compared between UCB recipients and historic controls from the Network Hypothermia study
- **Secondary Endpoints**: preliminary efficacy as measured by neurodevelopmental function at 4-6 mo and 9-12 mo of age

Autologous Umbilical Cord Blood Infusion for Children With Autism Spectrum Disorder (ASD) (ClinicalTrials.gov Identifier: NCT02176317)

- **Principal Investigator: J. Kurtzberg, MD.**
- **Purpose:** Prospective phase 1 single-center trial designed to determine the safety of a single intravenous infusion of autologous umbilical cord blood in children with Autism Spectrum Disorder (ASD)
- **Primary Outcome Measures: Evaluate the** number of participants with non-serious and serious adverse events.
- **Secondary Endpoints**: primary efficacy measure will be change in the Vineland Adaptive Behavior Scale

Hypothesis: umbilical cord blood cells (UCB) can offer neural protection/repair in the brain and reduction of inflammation associated with this disorder

A Randomized Study of Autologous Umbilical Cord Blood Reinfusion in Children With Cerebral Palsy (ClinicalTrials.gov Identifier: NCT01147653)

- **Principal Investigator: J. Kurtzberg, MD.**
- **Purpose:** Is Autologous Umbilical Cord Blood Reinfusion Beneficial in Children With Cerebral Palsy: A Randomized, Blinded, Placebo-Controlled, Crossover Study
- **Primary Outcome Measures**: The primary measure of efficacy will be improvement of standardized measures of neurodevelopmental function.
- **Secondary Endpoints**: to determine effects on quality of life in these children and a secondary objective is to describe functional and morphologic changes on brain MRI in these children..

CB Infusion to Treat Type 1 Diabetes (NCT00305344)

- **Primary Outcome Measures**: peak C-peptide following mixed meal tolerance test.
- **Secondary outcomes:** insulin dose, autoantibody levels, T cell functional response assays, cytokine levels, to study potential changes in metabolism/immune function leading to islet regeneration.

Reference: Haller MJ, Viener HL, Wasserfall C, Brusko T, Atkinson MA, Schatz DA. Experimental Hematology 2008 June 36, pgs 710-5.

NCT00518934: Safety and Efficacy of Therapeutic Angiogenesis for Limb Ischemia by Transplantation of Human UCB MNC

- **Principal Investigator: D. Kim, MD, Samsung Med Center, Seoul, Korea.**
- **Purpose:** to analyze the safety and efficiency of therapeutic angiogenesis for patients with limb ischemia by transplantation of UCB MNC.
- **Design:** Open label, historic control, single group assignment. Inclusion: patients with ischemic symptoms severe claudication, rest pain, or non-healing ischemic wound.

Conclusions

Umbilical Cord Blood offer the possibility of allogeneic transplantation to most patients in need.

Haploidentical donors and cord blood complement each other towards a new reality of donors for everybody.

Cord blood use is likely to rapidly diversify in the upcoming years.

Stem Cell Transplantation Program
University Hospitals Case Western Reserve University

Stanton Gerson
Hillard Lazarus
Brenda Cooper
Jane Little
Paolo Caimi
Erica Campagnaro
Basem William
Richard Creger
Bernadette McQuigg
Jane Reese-Koc
Jake Jacobberger
David Wald
Reshmi Parameswaran
Rose Beck

University Hospitals Seidman Cancer Center

NCI CCC A Comprehensive Cancer Center Designated by the National Cancer Institute

Case Western Reserve University | Case Comprehensive Cancer Center

Acknowledgements

Dana Farber Corey Cutler

THE UNIVERSITY OF TEXAS
MD Anderson ~~Cancer~~ Center
Making Cancer History®

Elizabeth Shpall
Richard Champlin
Simon Robinson
Ian McNiece

Borje Andersson
Gabriela Rondon

angioblast systems

Paul Simmons
Silviu Itescu
Michael Schuster
John McMannis

UNIVERSITY OF MIAMI

Krishna Komanduri

CIBMTR®
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Mary Horowitz
Mary Eapen

MSKCC **Sergio Giralt**

Cleveland Clinic

Yogen Sauntharajah

Marcos.delima@uhhospitals.org