Blood & Marrow Stem Cell Donation: Safety, Innovation and Donor Advocacy

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Disclosure Information

Michael Linenberger, MD

I have no financial relationships to disclose

And

I WILL include discussion of investigational or off-label use of agents and procedures in my presentation.
Objectives

• Review the general methods, safety, AEs & donor experiences related to marrow harvest and peripheral blood stem cell (PBSC) mobilization and collection

• Discuss new approaches to marrow & PBSC mobilization, pre-stimulation & procurement

• Review donor eligibility and suitability

• Highlight recent issues in donor autonomy & ethical treatment
Lion King's Nala Needs Rare Bone Marrow Transplant

By SUSAN DONALDSON JAMES
July 20, 2010

- Acute myeloid leukemia (AML)
- No siblings
- Ethnic background: African-America & Hispanic
NMDP Donors & Transplants

Adult Donors: > 9 Million

NMDP Recipients: 1988 - 2010

NMDP Umbilical Cord Blood

145,000 UCB Units

Statistics: 2010

- > 40% of UCB units are from non-white donors
- > 40% of BMT pts from racially & ethnically diverse communities received UCB transplant
- **August 2010**: Shannon Tavarez receives UCB

Allo Stem Cell Sources (CIBMTR)

Pediatric (≤ 20 yrs) vs. Adult (> 20 yrs)

- Bone Marrow
- PBSC
- UCB

URD Transplants (NMDP)

<table>
<thead>
<tr>
<th>Year</th>
<th>Unrelated BM</th>
<th>Unrelated PBSC</th>
<th>Unrelated UCB</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>5500</td>
<td>5000</td>
<td>4500</td>
</tr>
<tr>
<td>2005</td>
<td>5000</td>
<td>4500</td>
<td>4000</td>
</tr>
<tr>
<td>2010</td>
<td>5500</td>
<td>5000</td>
<td>4500</td>
</tr>
</tbody>
</table>

Research Operations Department of the National Marrow Donor Program® (www.marrow.org)
SCCA/FHCRC Transplants

- **Auto – All**
- **Allo – BM**
- **Allo – PBSC**
- **Allo - UCB**

No. Transplants

Year: 2001 to 2010

Courtesy: Joe Norton, SCCA Finance
Hematopoietic Stem Cell Donors

Marrow – Late 1960’s

PBSC – Late 1980’s
UCB Licensure – October 2011

Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications

(Licensure Guidance)

~ Effective October 2011 ~

• **UCB** from licensed facility (eg. Puget Sd Bld Ctr) or under IND sponsored by – CBB, registry (NMDP), or Txpl Ctr

• **Indications:** Heme malign, AA, B-thal, congenital disease
SCCA “Standard” Donor

• Age: Neonate to > 80 yo *(NMDP: 18 – 60 yo)*
  – Donor < 14 yo: Bone marrow donation only
• Healthy *(ASA class 1 – 2; ≤ mild disease)*
• No infectious disease concerns
  – The donor is “eligible”
• No procedure-related safety concerns
  – The donor is “suitable”
• Note: A donor may be ineligible but suitable
  – Formal “justification” & documentation required
Marrow Stem Cell Harvest

Gray’s Anatomy of the Human Body (1918); Bartleby.com (2000)
Marrow Stem Cell Harvest

- Day surgery
- General / epidural / spinal anesthesia
- Posterior iliac crests; 5 – 7 mL/pull
- Ave. nucleated cell count: 22 – 32 x 10^3/μl
- Std goal: 10 – 15 ml/kg recipient weight
  2 – 4 x 10^8 nucl. cells/kg recipient weight
- Max Volume: 20 mL/kg donor weight
- Prestorage of autologous RBCs
BM Donor Acute Side Effects

Common (20 – 85% incidence)*
- Fatigue, pain (back, buttock, sitting), headache
- Nausea/vomiting, sore throat, IV pain

Less common (< 20%)*
- Fever, bleeding, syncope, chipped teeth, ↓ BP, urinary retention, post-spinal HA, infection

Autologous blood transfusion
- Historical: 70% - 90% of adults; 50% of pediatrics
- Current: Only for medical/surgical indications

* (NMDP data) Pediatr Blood Cancer 2006;46:422
3 Days post Marrow Harvest

Coronal view posterior iliac crests
3 Days post Marrow Harvest: Axial CT Posterior Iliac Crests

Avulsion Fracture Superior PIC
Retropelvic Bleed & Neuropathy

- Uncommon (0.5 – 0.7%)
- Compress sacral plexus
  - Nerve pain/weakness
- Supportive care
- Many weeks to resolve
  ± Permanent nerve damage

Bone Marrow Transplant 2000;26:705

MRI Scan: Iliopsoas hematoma

Spinal HA Post Marrow Harvest
(Inadvertent entry of the thecal sac)

- Severe post-op HA
  \(\uparrow\) sit/stand; photophobia
- Unusual Case*
  Subcut & epidural CSF
  Spino-SC fistula (arrow)
- Treatment
  Supportive care
  Analgesics
  Epidural blood patch

*Anesth Analg 2001;92:1050
BM Harvest Gr 3 - 4 AEs (NMDP)*

Serious (< 1%); Life Threatening (< 0.4%)
- Sacroiliac joint trauma; myofascial scar → pain
- Seizure, severe bleeding, neuropathy, abscess
- MI, PE, transfusion AE, arrhythmia, CVA

Risk Factors for Severe Adverse Events
- Older age (continuous variable)
- Larger harvest volume / Longer harvest time
- Regional (spinal/epidural) anesthesia
- Male donor

*Hematology Am Soc Hematol Educ Program. 2005;469
BM Harvest Gr 4 - 5 AEs (EBMT)*

Serious Adverse Events (n=12/27,770; ~ 0.043%)
- Cardiac arrest (4) [in OR or post-op]
- Severe hypertension (2)
- Stroke (1) [due to HIT Abs]
- Pulmonary edema (1)
- Bleed (1) [4 U PRBC]
- Other (3)

Fatalities (n=1; related donor)
- Massive PE/DVT day 7 post-op [ATIII deficiency]

Heme Malignancies (6 sibs; 1 URD [AML]; 1 n.r.)
- AML (2); ALL (2); NHL (3); plasmacytoma (1) [0.5-12 yr]

* Haematologica 2009;94:94
Marrow Harvest Sx’s – NMDP

Severe (grade 3) or Disabling (grade 4)
Moderate (grade 2)
Mild (grade 1)

Percentage of Donors

Back or Hip
Throat
Muscle
Headache
3 Wks post Marrow Harvest
Marrow Stem Cell
Harvest
Innovations
Automated Marrow Harvest (?)
Marrowminer™ (FDA 510(k) & CE)
"G-Primed" Marrow: Potential Benefit

Stimulated bone marrow grafts

Expansion of CD34⁺ cells, LTC-IC, and STRC

Selectively increase monocytes

Preferential increase of pDCs

Downregulation of CD28/B7 signals

Hyporesponsiveness of T cells

Lower expression of CD49d, CD54, CD62L, and CD11a on naïve T cells

Polarize T cells

G-CSF

Clin Transplant 2011;25:13
G-mobilized PBSC vs G-stimulated Marrow

- Myeloablative MRD BMT for heme malignancy
- G-CSF: 5 mcg/kg/d; days -4 → -1 (±d0 if 2nd apheresis)
  - Apheresis d -1, ±0 (≥ 2.5 x 10^6 CD34+ cells/kg)
  - BM d0 (≥ 3 x 10^8 TNC/kg; ≤ 5 mL/pull; 15-22 mL/kg)

1º Outcomes: Time to failure
  - Ext. cGVHD  - Relapse  - All-cause mortality

2º Outcomes
  - Hematologic recovery (ANC; plt; 1º graft failure)
  - Overall survival  - Quality of life parameters
PBSC Mobilization and Harvest
Allo Donor PBSC Mobilization

Cytokines (G-CSF, GM-CSF)

CD34+ blood stem cell

CXCR4

SDF-1

ICAM-1

LFA-1

Endothelial cell

Fibronectin

Marrow

Kronenwett, R et al, Stem Cells 2000; 18:320
Filgrastim (G-CSF)-Mobilized Peripheral Blood Stem Cells

FHCRC: 16 µg/kg/day
NMDP: 10 µg/kg/day

FHCRC: Start day -1 → goal
NMDP: Start day -1 (2 day) or 0 (1 day)
G-CSF vs GM-CSF Mobilized PBSC

Kinetics of CD34+ Cell Response

Fischmeister et al, Ann Hematol 1999;78:119
PBSC URD Risks & AEs: NMDP Prospective Trial (N=2408)

Filgrastim (G-CSF) - Bone Pain (95%)
Risks of G-CSF

• **Common**
  - MS pain, arthralgias
  - HA, nausea, malaise
  - Mild ↓ plts + ↑ spleen
  - ↑ LDH

• **Uncommon**
  - Fever, rash, arthritis

• **Rare**
  - ↓ ↓ plts – Thrombosis
  - Splenic bleed/rupture

Dincer et al. J Ped Hematol Oncol 2004; 26:761
Long-Term Risk of G-CSF?

- Transient tetraploidy in 0.6% myeloid precursors; no abnormalities detected in CD34+ cells\(^1\)
- Transient epigenetic changes (asynchronous allele-specific replication patterns) in PB lymphs\(^2\)
- Stable aneuploidy in PB lymphs (\(\geq 2x\) normal)\(^2\)
- No markers of DNA destabilization in PB WBC\(^3\)

\(^1\)Exp Hematol 2004;32:122 \(^2\)Bone Marrow Transplant 2003;32:31 \(^3\)Am J Hematol 2003;73:33

Haematological malignancies developing in previously healthy individuals who received haematopoietic growth factors: report from the Research on Adverse Drug Events and Reports (RADAR) project

Charles L. Bennett, \(^1,2\) Andrew M. Evens, \(^2\) et al.

British Journal of Haematology, 135, 642–650; 2006
Long-Term Risk of G-CSF?

• Allo PBSC donors f/u ≤ 6 yrs post collection
  – No ↑ incidence of AML, MDS, cytopenias
  – Occasional persistent mild lymphopenia (without infectious consequences)
  – Rare cases of persistent mild neutropenia

• URD registries: No evidence of increased incidence of heme malignancies*

• WMDA recommends Informed Consent language: Unknown long-term risk of G-CSF

*Transfusion 2008;48:2008
*Chromosomal Effect of G-CSF?*

- **G-mobilized PBSC donors (n=20) & controls (n=22)**
  - PBMNC assays: Baseline → Day 5 → 2, 6, & 12 mos
  - FISH analysis: Aneuploidy & replication timing
    - 7 chromosomes; 9 loci
- **Uncultured (CD34+) cells**: No increased aneuploidy & no asynchrony in replication kinetics
- **PHA-stimulated cells**: No aneuploidy or asynchrony
- **Conclusion**: Short-term G-CSF exposure does not induce early or late general chromosomal instability

*Hirsch et al. Blood 2011;118:2602*
PBSC Harvest by Apheresis

Anticoagulant
ACD-A (citrate) ± Heparin
PBSC URD Risks & AEs: NMDP Prospective Trial (N=2408)

Adverse Events during Apheresis

- Citrate (↓ Ca++): 51%
- Nausea: 20%
- Venous Access: 22%
- Pain, HA, ↓ BP: 1 - 6%

Frequency of all AE scores

Blood 2009;113:3604
PBSC URD Gender Risks & AEs: NMDP Prospective Trial (N=2408)

CVC Required (d5)

- Males (N = 1444)
- Females (N = 964)
- \( P < .001 \)

n = 166

n = 61

All Apheresis AEs (d5)

- Males (N = 1444)
- Females (N = 964)
- \( P < .001 \)

n = 191

n = 101

Blood 2009;113:3604
PBSC Mobilization/Harvest Sx’s-NMDP

Severe (grade 3) or Disabling (grade 4)
Moderate (grade 2)
Mild (grade 1)

Percentage of Donors

Biol Blood Marrow Transplant 2008;14 (9 Suppl):29
## PBSC URD Gr 3 - 4: NMDP (N=2408)*

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/vomiting</td>
<td>4</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1</td>
</tr>
<tr>
<td>Severe Thrombocytopenia</td>
<td>3</td>
</tr>
<tr>
<td>Citrate toxicity</td>
<td>3</td>
</tr>
<tr>
<td>Severe chest pain</td>
<td>2</td>
</tr>
<tr>
<td>Severe back pain</td>
<td>1</td>
</tr>
</tbody>
</table>

**Recently: 2 cases of intracerebral hemorrhage**

*Blood 2009;113:3604*
PBSC Donor Gr 4 - 5 AEs (EBMT)*

Serious AEs (N = 25/23,254; ~ 0.011%)

- DVT/PE (7)
- Severe Bleed (2)
- TRALI (1)
- Seizure (1)
- Other (5)

- Spleen rupture (5)
- Severe HTN (1)
- Seizure (1)
- Other (5)

Fatalities (n = 4; all related donors)

- Cardiac arrest (3)
- Subarachnoid bleed (1)

Heme Malignancies (9 sibs; 3 n.r.) [0.8 - 7 yr]

- AML (1); ALL (2); CLL (1); MPN (1)
- NHL (4); HL (1)

* Haematologica 2009;94:94
Median Age HPC Donor: EBMT (1993 – 2005; N=19,503)
NMA Transplant Donor Age: FHCRC
(1994 – 2006; N=982)

- 20-39 yo: 26%
- 40-59 yo: 60%
- > 59 yo: 14%
Older Age Affects Day 5 Pre-Apheresis Blood CD34+ Count

N = 195  (p = 0.004)
G-CSF 10 mcg/kg/day
No affect of co-morbidity

Day 5 Preapheresis PB CD34 cells/µL

<table>
<thead>
<tr>
<th>Age Decade, Years</th>
<th>% of Donors</th>
<th>Mean</th>
<th>Median</th>
<th>&lt; 20 (%)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30</td>
<td>8.7</td>
<td>109.8</td>
<td>122.5</td>
<td>0 (0)</td>
<td>23.0-247.5</td>
</tr>
<tr>
<td>30-39</td>
<td>13.8</td>
<td>111.2</td>
<td>93.5</td>
<td>1 (3.6)</td>
<td>11.0-237.6</td>
</tr>
<tr>
<td>40-49</td>
<td>22.5</td>
<td>94.6</td>
<td>84.4</td>
<td>0 (0)</td>
<td>23.4-247.5</td>
</tr>
<tr>
<td>50-59</td>
<td>45.9</td>
<td>81.4</td>
<td>68.4</td>
<td>5 (6.7)</td>
<td>5.6-421.9</td>
</tr>
<tr>
<td>≥60</td>
<td>17.4</td>
<td>65.7</td>
<td>57.8</td>
<td>2 (7.1)</td>
<td>2.0-181.9</td>
</tr>
</tbody>
</table>

Biol Blood Marrow Transplant 2009;15:1394
SCCA Retrospective Cohort Study: Donor Characteristics

**Cohort (A): 20 – 39 yo (N=146)**
- Median Age: 34 yrs
- Gender: 78 male (53%)

**Cohort (B): 40 – 59 yo (N=274)**
- Median Age: 49 yrs
- Gender: 130 male (47%)

**Cohort (C): 60 – 83 yo; (N=140)**
- Median Age: 64 yrs
- Gender: 68 male (49%)
Pre-Apheresis: CVC Requirement

CVC associated w/age (p<0.001) & gender

<table>
<thead>
<tr>
<th>Cohort</th>
<th>% Requiring CVC (F/M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A)</td>
<td>6% (9% / 4%)</td>
</tr>
<tr>
<td>(B)</td>
<td>11% (19% / 3%)</td>
</tr>
<tr>
<td>(C)</td>
<td>19% (31% / 7%)</td>
</tr>
</tbody>
</table>

JCA 2009;24:69 (abstr)
Symptoms & AEs by Cohort

Age not associated with apheresis toxicity

% of Donors with Symptom or AE

- MS pain
- Headache
- IV site pain
- Nausea
- Paresthesia

Cohort (A), (B), (C)

JCA 2009;24:69 (abstr)
CD34+ Cell Yields on Apheresis Days #1 – #3

- **Cohort (A)**: [124] [251]
- **Cohort (B)**: [134] [47] [134]
- **Cohort (C)**: [110] [5] [14] [19]

**Day #1**

- **Med #CD34+ cells/mL/kg**: [124]
- No. procedures: [251]

**Day #2**

- **Med #CD34+ cells/mL/kg**: [134]
- No. procedures: [47] [134]

**Day #3**

- **Med #CD34+ cells/mL/kg**: [110]
- No. procedures: [5] [14] [19]

JCA 2009;24:69 (abstr)
Achievement of $\geq 5 \times 10^6$ CD34+ cells/kg Recipient Weight

<table>
<thead>
<tr>
<th>Cohort</th>
<th>% Collections $\geq 5 \times 10^6$ /kg</th>
<th>1st Apheresis</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A)</td>
<td>66%</td>
<td></td>
</tr>
<tr>
<td>(B)</td>
<td>55%</td>
<td></td>
</tr>
<tr>
<td>(C)</td>
<td>28%</td>
<td></td>
</tr>
</tbody>
</table>

Median Donor Age (yrs)

# Collections to Achieve $\geq 5 \times 10^6$ CD34+/kg

JCA 2009;24:69 (abstr)
Older Age is Associated with Higher Product NK Cell Content

- No effect of CD34+ or NK cell content on engraftment/GVHD

Bone Marrow Transplant 2011;46:1296
PBSC Mobilization & Collection in Older Donors

- Medical comorbidities increase with age
- Neither age nor health risks translate into AEs
- Women & older donors require CVC more often
- **Older age →** lower pre-collection CD34+ cts, lower CD34+ cell yield/apheresis, higher NK yield
- Age correlates with $\leq 5 \times 10^6$ CD34+ cells/kg
- Age-related limitations in CD34+ cell yields can significantly affect product goals. Alternative, optimized strategies could be considered
PBSC Mobilization / Harvest Innovations
Plerixafor (AMD3100; Mozobil™)

- Reversible CXCR4 antagonist
- **FDA Label:** PBSC mobil. with G-CSF for NHL & myeloma
  - 4 days G-CSF → inject 11° pre-apheresis (on d5 after G)
- **Salvage success rate:** 60% - 80% (≥ 2.5 x 10⁶ CD34+/kg)
- **1° steady-state mobilization:** 2- to 3-x higher CD34+ yield
- **AEs:** Mild GI & inject site
Plerixafor Alone: Healthy Allo Donors

- 17/24 collected $\geq 2 \times 10^6$ CD34+ cells/kg on d1
- 20 pts txpl w/AMD PBSC: Normal engraftment; 35% gr II-IV aGVHD; 40% cGVHD (short f/u)

**Table 2. AMD3100 and G-CSF allograft content**

<table>
<thead>
<tr>
<th></th>
<th>AMD3100 (N = 24), median (range)</th>
<th>G-CSF (N = 8), median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD34, $\times 10^6$/kg</td>
<td>2.9 (1.2-6.3)</td>
<td>4.2 (2.5-18.7)</td>
</tr>
<tr>
<td>CD3, $\times 10^8$/kg</td>
<td>4.6 (1.5-7.8)</td>
<td>1.3 (1.2-6.8)</td>
</tr>
<tr>
<td>CD4, $\times 10^8$/kg</td>
<td>3.2 (1-5.7)</td>
<td>1.1 (0.7-3.2)</td>
</tr>
<tr>
<td>CD8, $\times 10^8$/kg</td>
<td>1.3 (0.4-3.4)</td>
<td>0.4 (0.3-3.4)</td>
</tr>
<tr>
<td>CD19, $\times 10^8$/kg</td>
<td>1.0 (0.2-2.4)</td>
<td>ND</td>
</tr>
<tr>
<td>CD56, $\times 10^8$/kg</td>
<td>0.3 (0.1-1.0)</td>
<td>0.2 (0.1-0.5)</td>
</tr>
</tbody>
</table>

Blood 2008;112:990
Feasibility of filgrastim (G-CSF) + plerixafor for rapid mobilization of PBSC from normal donors

1° Obj: Collect $\geq 2 \times 10^6$ CD34+ cells/kg in 1 day

2° Obj: PB & product CD34+; safety; engraft; GVHD

Day -14 -13 -12 -4 -3 -2 -1 0

Plerixafor 320 μg/kg
G-CSF 16 mcg/kg
Apheresis (20 L)
Donor Eligibility:
Safety for the recipient
# 3-Step Donor Eligibility: Potential Transmissible Infectious Agents

<table>
<thead>
<tr>
<th>(1) Questionnaire</th>
<th>(2) Screen Labs</th>
<th>(3) PE Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria; Chagas</td>
<td>Hepatitis B</td>
<td>IV Drug use</td>
</tr>
<tr>
<td>Babesiosis</td>
<td>Hepatitis C</td>
<td>Tattoo/pierce</td>
</tr>
<tr>
<td>CJD (mad cow)</td>
<td>HIV 1 &amp; 2</td>
<td>↑ Lymph nodes</td>
</tr>
<tr>
<td>Xenotransplant</td>
<td>HTLV I &amp; II</td>
<td>Oral thrush</td>
</tr>
<tr>
<td>Risk behavior for:</td>
<td>Syphilis</td>
<td>Kaposi’s</td>
</tr>
<tr>
<td>HIV</td>
<td>WNV</td>
<td>Jaundice; ↑ liver</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>Chagas</td>
<td>Sepsis/rash</td>
</tr>
<tr>
<td>STDs</td>
<td>CMV</td>
<td>Smallpox vaccine</td>
</tr>
<tr>
<td>Emerging ID risks</td>
<td></td>
<td>complications</td>
</tr>
</tbody>
</table>
Emerging ID Concerns: XMRV / MLV

- Xenotropic murine leukemia virus-related virus (gammaretrovirus)
- Previously implicated in prostate cancer
- PBMC PCR+ in 67% CFS cases & in 3.7% controls
- 2° infection in tissue culture (PBMC / plasma)
- Raised concerns for safety of blood / HPCs

Science 326, 585 (2009)

Detection of an Infectious Retrovirus, XMRV, in Blood Cells of Patients with Chronic Fatigue Syndrome

Absence of xenotropic murine leukaemia virus-related virus in UK patients with chronic fatigue syndrome

Groom et al. Retrovirology 2010, 7:10

Absence of evidence of Xenotropic Murine Leukemia Virus-related virus infection in persons with Chronic Fatigue Syndrome and healthy controls in the United States

Switzer et al. Retrovirology 2010, 7:57

Detection of MLV-related virus gene sequences in blood of patients with chronic fatigue syndrome and healthy blood donors

PNAS 2010 vol. 107 15874

Shyh-Ching Lo*1, Natalia Pripuzova*, Bingjie Li*, Anthony L. Komaroff*, Guo-Chiuan Hung*, Richard Wang* and Harvey J. Alter*1

Mouse DNA contamination in human tissue tested for XMRV

Robinson et al. Retrovirology 2010, 7:108

Disease-associated XMRV sequences are consistent with laboratory contamination

Hué et al. Retrovirology 2010, 7:111
Emerging ID Concerns: XMRV / MLV

• Disease causality not defined
• Pop. prevalence unknown
• 2º transmissibility unclear
• No FDA screening test avail.
• Donor Deferral (w/CFS): Canada, Australia & New Z.
• AABB Interorg. Task force*: Rely on current screening ("Are you feeling well today?") & passive deferral
• BPAC Rec: Active deferral (12/15/10)

*Transfusion 2011; 51:654 (March)
Failure to Confirm XMRV/MLVs in the Blood of Patients with Chronic Fatigue Syndrome: A Multi-Laboratory Study


Partial Retraction


reexamination by Silverman and Das Gupta of the samples they used shows that some of the CFS peripheral blood mononuclear cell (PBMC) DNA preparations are contaminated with XMRV plasmid DNA (2). The following
Dengue Fever / Hemorrhagic Fever

• Etiology & Epidemiology
  – *Flavivirus (DENV)*; *Aedes aegypti* mosquito
  – **Endemic**: 110 countries; 40% world pop.
  – **Sporadic**: Rio Grande, Hawaii, FL Keys
  – **CDC**: 100 x 10^6 cases/yr; ~ 500 x 10^3 HF/yr

• Signs/Symptoms
  – **Incubation period**: 5 – 8 days
  – **Triad**: Fever, HA/myalgia, rash/petechiae
  – **Bimodal**: 1st sx’s (2-4 d) → OK (1d) → rash

• Dengue Hemorrhagic Fever (DHF)
  – **Compromised**: < 10 yo; previous dengue
  – DIC; leaky capillaries/shock; MODS
  – **Mortality**: 6 – 30%

http://wwwnc.cdc.gov
Dengue Fever / Hemorrhagic Fever

• **Donor Concerns**
  - Transmission by blood & organ donation
  - **Singapore**: Up to 0.06% transfusions
  - **EU & Asia**: 28 d deferral post travel to endemic area
  - Defer until 4 wks post recovery

• **BPAC (12/15/10)**
  - 3 cases of donor-transmitted dengue (Singapore, Hong Kong, Puerto Rico)
  - Dengue area = malaria area (12 mo deferral)
  - Monitor activity & react to outbreaks; await a validated screening test
Donor Suitability:
Safety for the donor
Donor Suitability / Comorbidity

SPECIAL REPORT

Haematopoietic stem cell donor registries: World Marrow Donor Association recommendations for evaluation of donor health

N Sacchi¹, P Costea², L Hartwell³, CK Hurley⁴, C Raffoux⁵, A Rosenmayr⁶ and H Greinix⁷, on behalf of the Quality Assurance and Clinical Working Groups of the World Marrow Donor Association

- **Infect. Diseases:** Risks, exposures & screening
- **Deferrals:** Organ disorders, asthma, autoimmunity, trauma, cancer, psych diseases, coag disorders
- **Individual assessments:** Allergies, Htn, resp. illness
- **Temporary deferral:** Self-limited/resolved/controlled disorders/illnesses; vaccinations; surgeries
- **Comprehensive donor health questionnaires**
# Donor Suitability/Medical Risks

## Unrelated Donor Assessment (example)

**National Marrow Donor Program®**

**ASSESSMENT TOOL AT RECRUITMENT**

**PURPOSE:**
To provide guidance in determining medical suitability of potential donors volunteering to be listed on the Registry

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Seizures Disorders</strong></td>
<td>Evaluate underlying medical condition; accept/defer as appropriate</td>
</tr>
<tr>
<td>Assessment</td>
<td>Accept if treated and no seizures in the past 12 mos</td>
</tr>
<tr>
<td>Rationale</td>
<td>Defer if</td>
</tr>
<tr>
<td>See Notes</td>
<td>- untreated or if had a seizure in the past 12 mos</td>
</tr>
<tr>
<td></td>
<td>- uncontrolled and/or poorly controlled seizure activity</td>
</tr>
<tr>
<td></td>
<td>See also <em>Epilepsy</em></td>
</tr>
</tbody>
</table>
Psychological Impact of Donation on Donor Populations

• Equivalent pain/anxiety with BM vs PBSC
• Most RDs experience [+ ] psych outcomes
  – Donor attitude/relationship; known risks/pain
• Ambivalence predicts negative outcome
  – ↑ Education, ↓ happy, pessimistic of prognosis
• RD risks: Female, younger, not a blood donor
• URD benefit: Altruistic, intense counseling
FHCRC #2383 (M. Linenberger)
RDSafe Study (CIBMTR/NMDP)

- **Multi-center**: 40 adult, ~80 peds (3.5 yr study)
- **Enrollment in medical/toxicity study**: ~ 2300
  - All ages; F/U for 1 yr; AEs & SAEs; G-CSF; predictors
  - BM & PBSC RDs eligible, including G-stim BM
- **Enrollment in ancillary (HRQoL) study**: 400
  - Ages ≥ 5 yo; F/U for 1 yr; phone survey ($)  
  - Randomization; balanced for ages & BM ~ PBSC
- **Compare RD experiences w/contemporary URDs**
  - NMDP protocol or CIBMTR Rsrch Database Protocol
Donor Autonomy & Ethical Treatment
November 2, 2010

Shannon Tavarez Lost Leukemia Fight, Inspired 10,000 Bone Marrow Donors
Ban on bone marrow sales challenged

A lawsuit urges compensation for those who give the life-saving stem cells, hoping to broaden the pool of donors.

<table>
<thead>
<tr>
<th>% Positive Marker</th>
<th>HBsAg+</th>
<th>Anti-HBc+</th>
<th>Anti-HIV+</th>
<th>RPR+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volunteer Donors</td>
<td>0.05</td>
<td>1.23</td>
<td>0.01</td>
<td>0.07</td>
</tr>
<tr>
<td>Directed Donors</td>
<td>0.15</td>
<td>2.51</td>
<td>0.00</td>
<td>0.12</td>
</tr>
</tbody>
</table>
• Remuneration is undesirable & may be deleterious
• Raises ethical dilemmas & challenges...
• Fairness (remove autonomy; → favoritism/coercion)
• Risk of safety to patients (nondisclosure of ID risk)
• Damages the public will to act altruistically
• Compromises free exchange between registries
Donor Care & Counseling
CIBMTR Survey: 98 US Centers


Who provides donor’s care?

Donor’s provider involved in recipient care?
WMDA WHITE PAPER
Donor safety: the role of the WMDA in ensuring the safety of volunteer unrelated donors: clinical and ethical considerations
Bone Marrow Transplantation (2010) 45, 832–838

SPECIAL REPORT
Unrelated hematopoietic stem cell donors as research subjects
Bone Marrow Transplantation (2011) 46, 10–13

SPECIAL REPORT
Family donor care management: principles and recommendations
Bone Marrow Transplantation (2010) 45, 1269–1273
<table>
<thead>
<tr>
<th>Donor Evaluation &amp; Procurement</th>
<th>Processing &amp; Manufacturing</th>
<th>M.D. Personnel Training &amp; Competence</th>
</tr>
</thead>
<tbody>
<tr>
<td>FACT Standards</td>
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<td>FACT Standards</td>
</tr>
<tr>
<td>AABB Standards</td>
<td>AABB Stds</td>
<td>BMH 1/yr (3/cycle)</td>
</tr>
<tr>
<td>NMDP Standards</td>
<td>CLIA / CAP</td>
<td>PBSC 10/yr (30/cyc)</td>
</tr>
<tr>
<td>WMDA Directives</td>
<td>WMDA Directive</td>
<td>NMDP Standards</td>
</tr>
<tr>
<td>FDA (eligibility)</td>
<td>2004/23/EC &amp; 2006/17,87/EC</td>
<td>BMH 4/yr</td>
</tr>
<tr>
<td>CFR 21:1271</td>
<td></td>
<td>PBSC 3/yr</td>
</tr>
<tr>
<td>Parts A-F (part D)</td>
<td></td>
<td>FDA: Not addressed</td>
</tr>
</tbody>
</table>

- FDA: Not addressed
Summary

• Blood & marrow stem cell collection is relatively safe and generally effective
  – Related & older donor risks and limitations need to be better defined (RDSafe)

• New methods of marrow & PBSC pre-stimulation/mobilization may improve product quality and recipient outcomes

• Donor centers need to protect donor autonomy and optimize ethical treatment
"I went to the woods because I wanted to live deliberately, I wanted to live deep and suck out all the marrow in life...."

Henry David Thoreau (1817 – 1862)