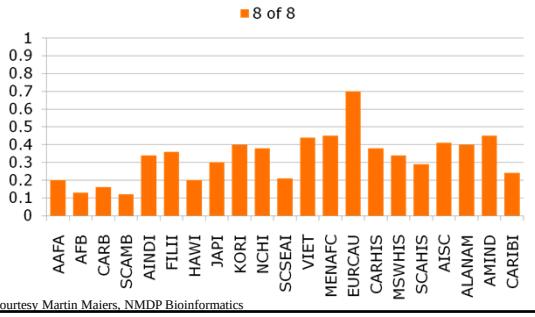
Umbilical Cord Blood and Haploidentical Stem Cells: *Transplantation for Everyone!*

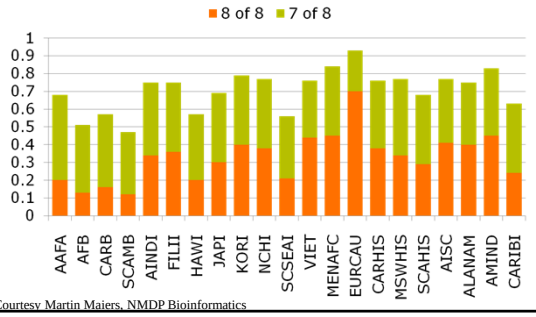
Corey Cutler, MD MPH FRCP(C)
Associate Professor of Medicine
Harvard Medical School
Dana-Farber Cancer Institute
Boston, MA

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



Courtesy Martin Maiers, NMDP Bioinformatics

7/8 and 8/8 Allele, Available-Match Rates in the Adult Donor Registry



Courtesy Martin Maiers, NMDP Bioinformatics

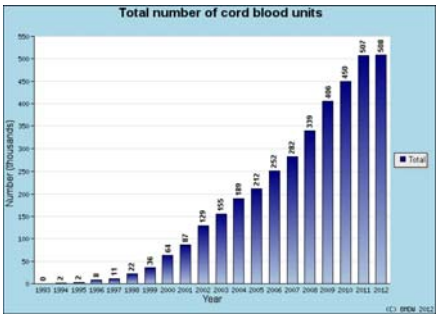
Be The Match Registry®: Adult Donor Facts and Trends

- Expanded diversity, younger donors targeted
  - 9.5+ million on Be The Match Registry
  - NMDP recruits over 400,000 donors per year; >80% <age 45
  - 41% new recruits of U.S. donors are minority
  - Over a third of the Registry is < 35 years
  - Over 50% of US donors giving confirmatory typing (CT) are < 35 years of age
- High quality HLA typing
- Comparative analysis shows that 80% of non-U.S. donors selected have potentially matched HLA types in the Be The Match Registry

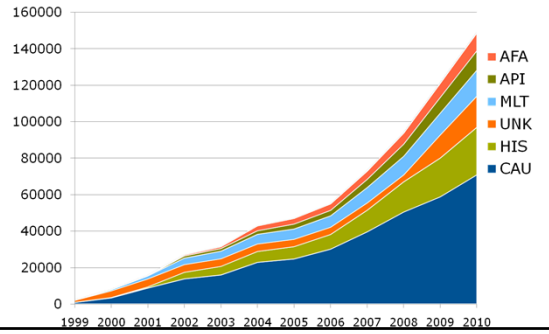
Alternatives to Closely Matched Adult Donor Stem Cells

- Umbilical Cord Blood
- Haploidentical Donor

Umbilical Cord Blood



Umbilical Cord Blood



Be The Match Registry®: Cord Blood Facts and Trends

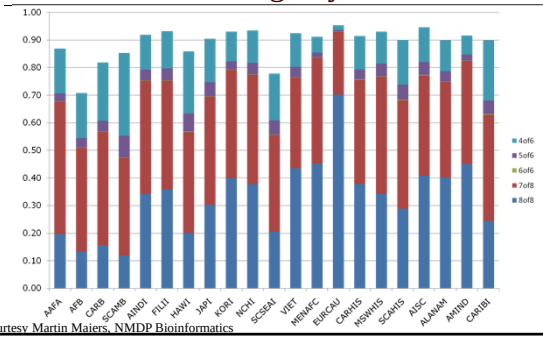
- Number of units accessible
  - Nearly 145,000 on Be The Match Registry
  - Real-time access to >185,000
  - Facilitating worldwide access to >550,000
  - More than 36,000 cord blood units added each year
- Expanded diversity and use
  - 40% minority units
  - More than 35% of NMDP-facilitated use more than one cord
  - Transplants for minority patients increased 42% 2010 vs 2008.
- Improved timing to meet Transplant Center needs
  - Domestic: 94% met 2-day request-to-ship requirement
  - International: Median 11 days request-to-CT

Umbilical Cord Blood

- ? 500 000 donors should not make a big difference in ability to find donors
  - Low Low Low T cell #s prevent GVHD

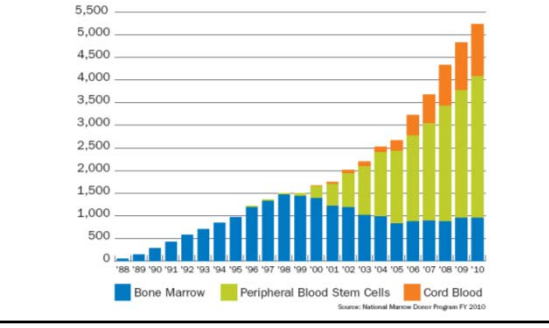
→ Very valuable resource for ethnic minorities

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

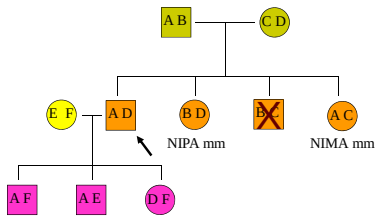


Courtesy Martin Maiers, NMDP Bioinformatics

NMDP Transplants by Cell Source



Haploidentical Transplantation



Haploidentical Transplantation

- Initially performed using extreme T depletion
- Re-introduced by Hopkins group using post-transplant Cytoxan
  - Kills rapidly dividing allo-responsive T cells
  - Stem Cells have high levels of aldehyde dehydrogenase – protects them from toxic effects of Cytoxan

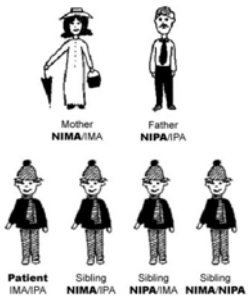
Theoretical Differences: UCB v Haplo

Search Strategy
Procurement
Engraftment
GVHD
TRM
Relapse Prevention
Cellular Therapy
Immunologic Reconstitution
Survival

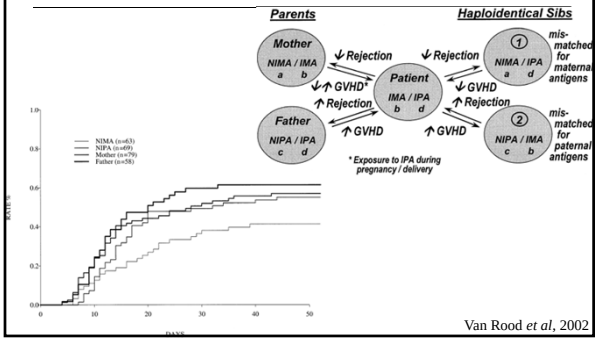
Search + Typing Strategy

- Family (sib) typing done routinely on all sibs < 60 yrs
- Haplo: *Might* require additional typing (child, parent) = $$$, time. Need to select the optimal donor if several potential identified.
- Cord: Typing complete, but selection of optimal units difficult, and difficulty is increasing

Haplo – Selection of Optimal Donor



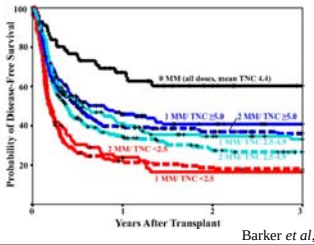
Haplo – Selection of Optimal Donor



Van Rood *et al*, 2002

Cord – Selection of Optimal Donor

- Single vs. Double
  - Probably does not matter if adequate cell dose (?)
- Size vs. HLA



(even more complex after DUCBT Avery 2011

Barker *et al*, 2010

Cord – Selection of Optimal Donor

- Other Complexities
  - NIMA/NIPA – Tricky esp. when maternal typing is not known!
  - HLA-C matters in 5/6, 6/6 but not 4/6 UCBT
  - Method of collection, red cell depletion
  - Anti-HLA antibodies
  - $CD34^+$ cell dose

Rocha et al, Eurocord
Brady et al, CIBMTR
van Rood et al, PNAS 2009
Eapen et al, *in press* 2012
Cutler et al, Blood 2011

Theoretical Differences: UCB v Haplo

Cord	Haplo
Search Strategy	
	Procurement
	Engraftment
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Procurement

Haplo

Cord

Theoretical Differences: UCB v Haplo

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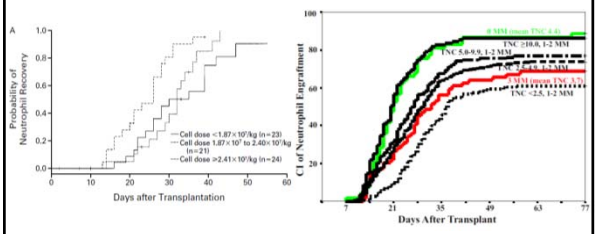
Engraftment

- What is correct comparison?
  - Single OR Double Cord?
  - Reality: > 75% of Cord Tx in adults is Double
- Engraftment FAILURE continues to pose a serious ~10% risk
- Strategies: Cord blood expansion, activation

Cord – Cell Dose Matters



Laughlin et al NEJM 2001
Barker et al, Blood 2010

Cord – Delayed Engraftment

	Days to ANC>500	Days to Plat>20K
MAC Single UCB	24 (12-68)	52 (22-275)
MAC Double UCB	23 (15-41)	53 (30-99)
RIC Single UCB	19 (13-32)	40 (25-100)
RIC Double UCB	12* (0-32)	49 (0-134)

Eapen et al
Barker et al
Uchida et al
Brunstein et al

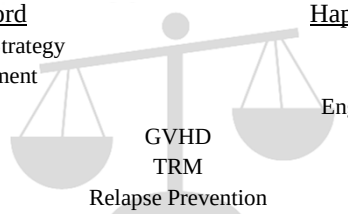
Haplo - Engraftment

- In theory, no different than URD transplantation, but…

	Related	Unrelated
ANC >500/µl	23 days	25 days
Platelets >20K	31 days	35 days
Graft failure	1/78 (2%)	3/39 (8%)

Luznik et al, Blood 2010

Theoretical Differences: UCB v Haplo



Cord
Search Strategy
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GVHD

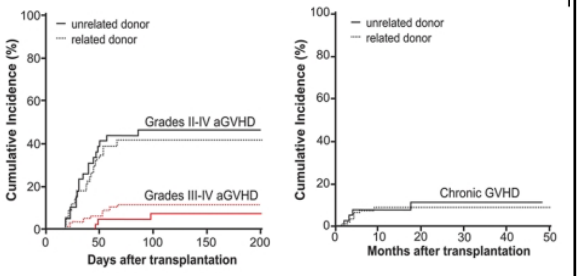
- Cord Blood: Very Low # of T cells to prevent GVHD
- Haplo: T Depletion (rare) or Post-Transplant Cy to prevent GVHD

GVHD: Cord

- As low as 10% Acute GVHD with Sirolimus containing GVHD prevention regimen
- As high as 40-60% in some Double Cord series
- In general, most is Gr II only
- Chronic GVHD very low regardless of GVHD prevention used

Cutler *et al*, 2011
Brunstein *et al*, 2010

GVHD: Haplo



Luznik *et al*, Blood 2010

Theoretical Differences: UCB v Haplo

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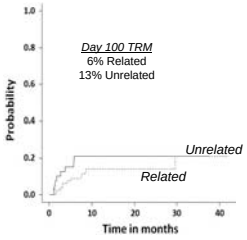
TRM

- Cord: Excessive
- ~30% 1 yr
- Infections

<u>Haplo</u>



Theoretical Differences: UCB v Haplo

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Relapse Prevention

- Very difficult to compare since treated populations are very different
- Theoretical concern over <u>increased</u> relapse with haplo due to T depletion effect
- Double cords appear to relapse <u>less</u> than single cords

Theoretical Differences: UCB v Haplo

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<u>Haplo</u>

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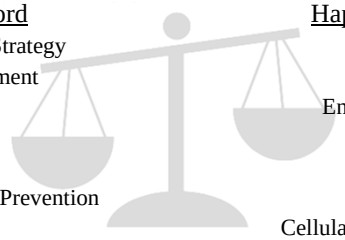
Cellular Therapy

- Cord:
  - Need to pre-emptively generate therapeutic cells: ? Treg ? Teff ?others
    - $$
  - No DLI
- Haplo: Donors generally available for post-transplant cellulur therapy / DLI

Theoretical Differences: UCB v Haplo



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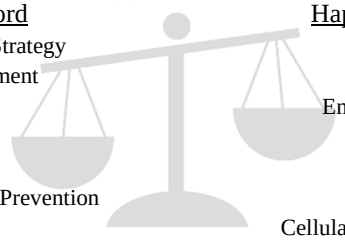
Immunologic Reconstitution

Survival

Immune Reconstitution

- No comparative data
- LOTS of late infectious complications after Cord
- EBV reactivation / lymphoproliferative disease ~ 10% incidence after cord
- No 'signals' in Haplo except T Deplete Haplo where recon is very poor

Theoretical Differences: UCB v Haplo



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Immunologic Reconstitution

Survival

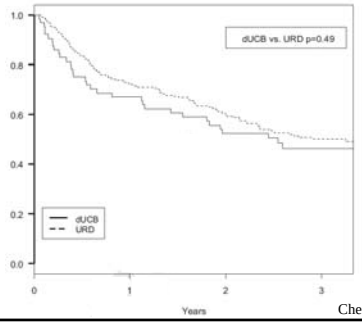
Survival

- Comparisons difficult
- Different patient populations, risks etc
- Comparing registry data vs. single center

Eurocord Single Myeloablative Transplantation

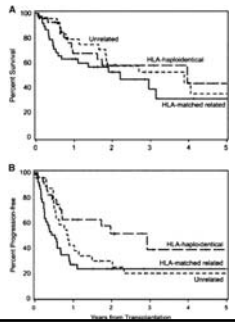
Year	N	2 Year OS
1994-1998	62	23 %
1999-2000	100	31 %
2001-2003	233	31 %
2004-2008	787	38 %

Survival – Cord with URD



Chen *et al*, 2012 in press

Survival – Haplo with URD



* Hodgkin Disease only

Burroughs *et al*, BBMT 2008

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Survival

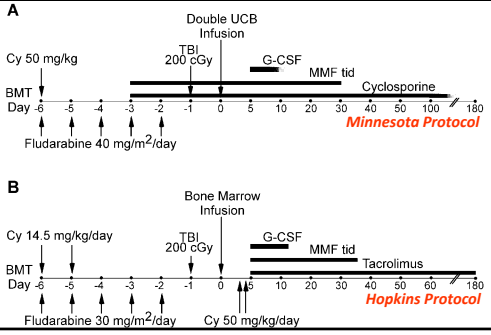
First Attempt at Comparison

- BMT CTN 0603 / 0604
- Parallel Phase II trials for high-risk hematologic malignancies (~16 participating centers)
  - Haplo-BM (0603)
  - Double UCB (0604)
- Both trials accrued 50 patients in 50% projected time
- Publication: Brunstein *et al*, Blood 2011

Patient Characteristics

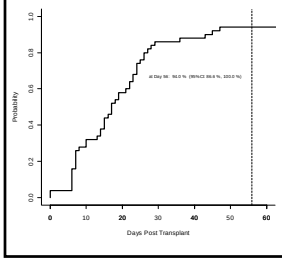
Graft Characteristics

Treatment Regimens

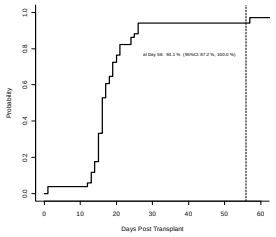


Engraftment - Neutrophils

Cord (0604)



Haplo (0603)



Engraftment - Platelets

78% (95%CI, 66-90%) at 56 days

20K

96% (95%CI, 89-100%) at 56 days

Cord (0604)

Haplo (0603)

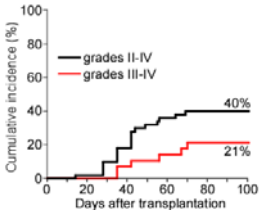
42% (95%CI, 28-56%) at 56 days

61% (95%CI, 47-75%) at 56 days

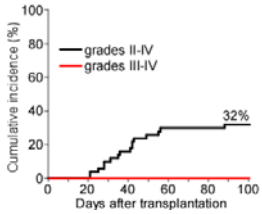
50K

Acute GVHD

Cord (0604)

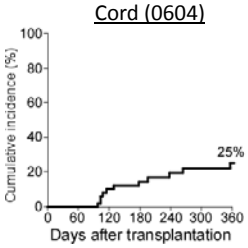


Haplo (0603)

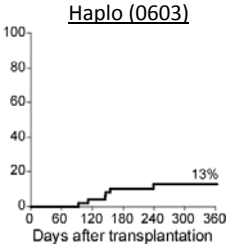


Chronic GVHD

Cord (0604)

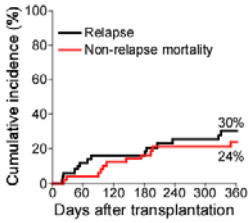


Haplo (0603)

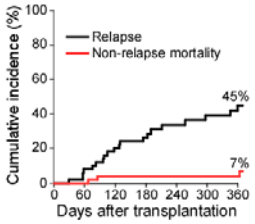


Relapse, Non-Relapse Mortality

Cord (0604)

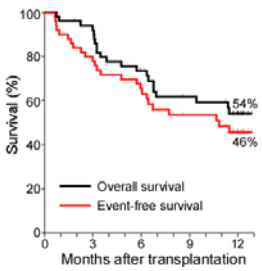


Haplo (0603)

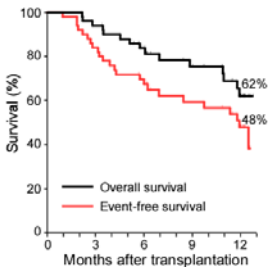


Disease-Free, Overall Survival

Cord (0604)



Haplo (0603)



BMT CTN 1101

- **Randomized Trial: 0603 vs. 0604**
- Must have both donors available for randomization
  - dUCB (0-2/6 HLA mismatches, 1.5 x 10^7 TNC/kg per unit)
  - Haplo-BM (2-4/8 HLA mismatches)
- Age ≤ 70 yr, No donor age restriction
- n = 410 over 4 years

BMT CTN 1101

- **Primary Endpoint: 2 Yr PFS**
  - **Powered to detect 15% difference**
- Secondary Endpoints
  - Hematopoietic recovery
  - GVHD
  - Infections
  - Immune reconstitution
  - Health-related Quality of Life
  - Cost effectiveness analysis
  - TRM / OS

Conclusions

- Umbilical Cord Blood and Haploidentical Transplant extend transplant alternatives to nearly ALL patients
- Theoretical advantages exist for each modality
- Randomized Trial will suggest preferable strategy
- Improvements to each strategy ongoing – not being studied in prospective trial
- Each ‘camp’ will find a way to refute trial and controversy will persist!