COUNCIL MEETING
Sharing Our Passion for Life

Cell Source Selection- the Debate Continues

Council Meeting 2016

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Disclosures

The following faculty and planning committee staff have no financial disclosures:

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The following faculty have the following financial disclosures:

Name	Institution	Disclosure
Stephanie Lee, MD, MPH	Fred Hutchinson Cancer Research Center	One time advisory boards: Kadmon, BMS, Amgen Mallinckrodt supported travel

Learning objectives

At the conclusion of this session, attendees will be able to:

- List advantages of each stem cell source for certain clinical scenarios
- State recent clinical updates related to the use of each stem cell source for transplant

Session Overview

- Case study presented for each cell source
  - Stephanie Lee, URD
  - Juliet Barker, CBU
  - Ephraim Fuchs, Haplo
- Questions, Discussion

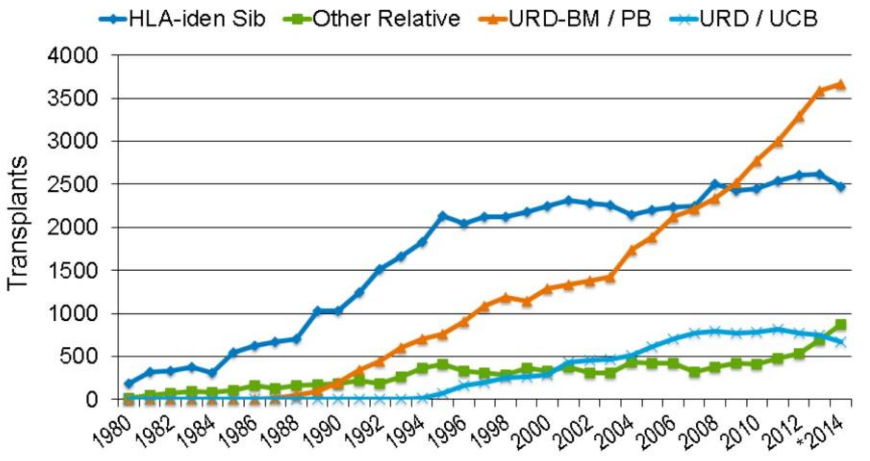
Adult Unrelated Donors

Stephanie J. Lee, MD MPH
Fred Hutchinson Cancer Research Center
November 12, 2016

Unrelated Donors

- More than 60,000 URD transplants performed since 1987
  - Longest survivor is 26 years from transplant
  - Abundant registry/international experience
- Benefits of URDs
  - Faster engraftment/lower rate of graft failure
  - Better immune reconstitution/less infection
  - (Lower risk of relapse)
  - Experienced center

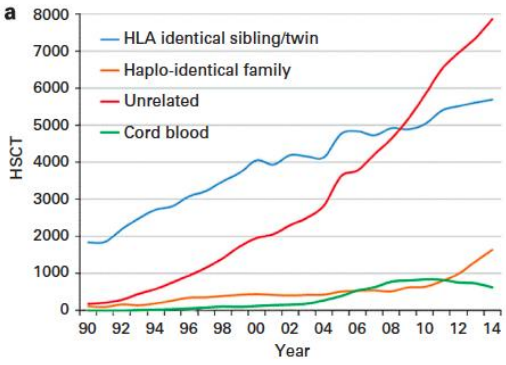
Allogeneic Transplant Recipients in the US, by Donor Type



CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

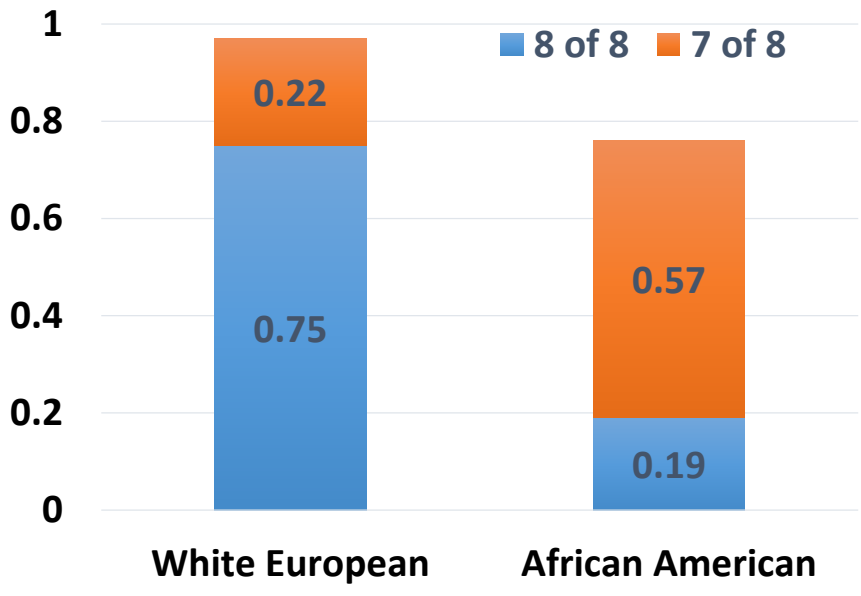
*2014 Data incomplete

4



1990-2014
EBMT Activity Survey
Europe only

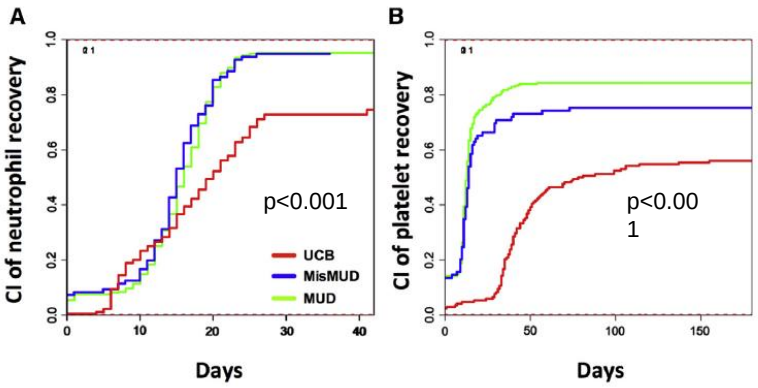
Passweg J et al, BMT 2016; 51: 786-792



GVHD, Cost

Gragert L et al, NEJM 2014; 371: 339-348

Engraftment (v. cord)



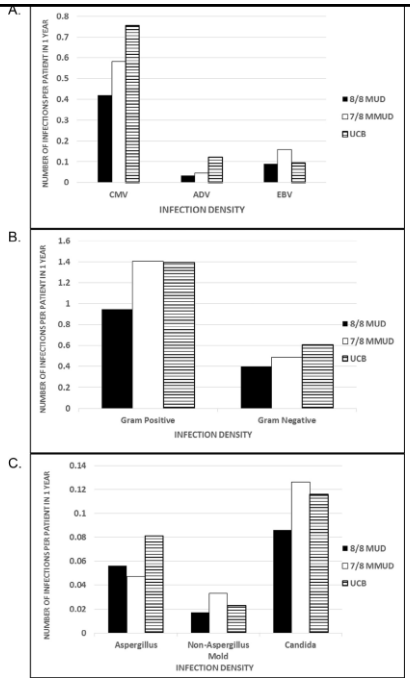
French transplant group
N=651 adult AML, NMA & RIC, 2002-2010

Malard et al 2015; 21: 1059-1067

Engraftment (v. haplo)

	AML[1] 1982 URD vs. 192 haplo MA or RIC 2009-2012	**Lymphoma[2] 491 URD vs. 185 haplo RIC or NMA 2008-2013**	**AML[3] 88 URD PB vs. 52 haplo PB (matched) 2010-2015**
Neuts	97% vs. 90% d30, p=0.02 (MA) 96% vs. 93% d30, p=0.25 (RIC)	97% vs. 94% d28, p=ns	12 vs. 16 d, p=0.002
Platelets	92% vs. 88% 6 mo, p=0.19 (MA) 93% vs. 88% 6 mo, p=0.24 (RIC)	89% vs. 63% d28, p<0.001	13 vs. 22 d , p=0.007

[1]Ciurea et al, Blood 2015; 126: 1033-1040
[2]Kanate et al, Blood 2016; 127: 938-947
[3]Rashidi et al, BBMT; 2016; 22: 1696-1701



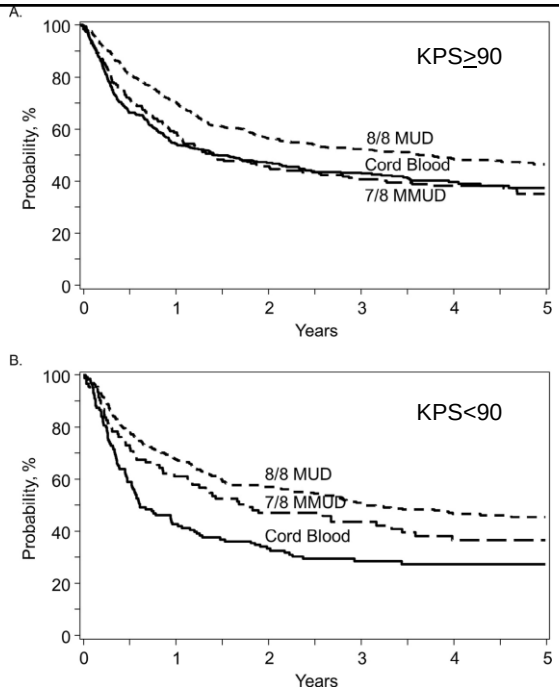
Infection (v. cord)

CIBMTR
N=1781 adults, AML/ALL in CR1/CR2, 2008-2011,

	URD	mmURD	UCB	P-value
N	930	283	568	
ATG	35%	50%	21%	<0.001
Bacterial	59%	65%	72%	<0.0001
Viral	45%	53%	68%	<0.0001
Fungal	10%	16%	18%	0.002
NRM	14%	27%	33%	<0.0001
Inf death*	31%	40%	49%	0.002

* Primary or secondary cause of death by 1 year

Ballen K et al, BBMT 2016; 22: 1636-1645

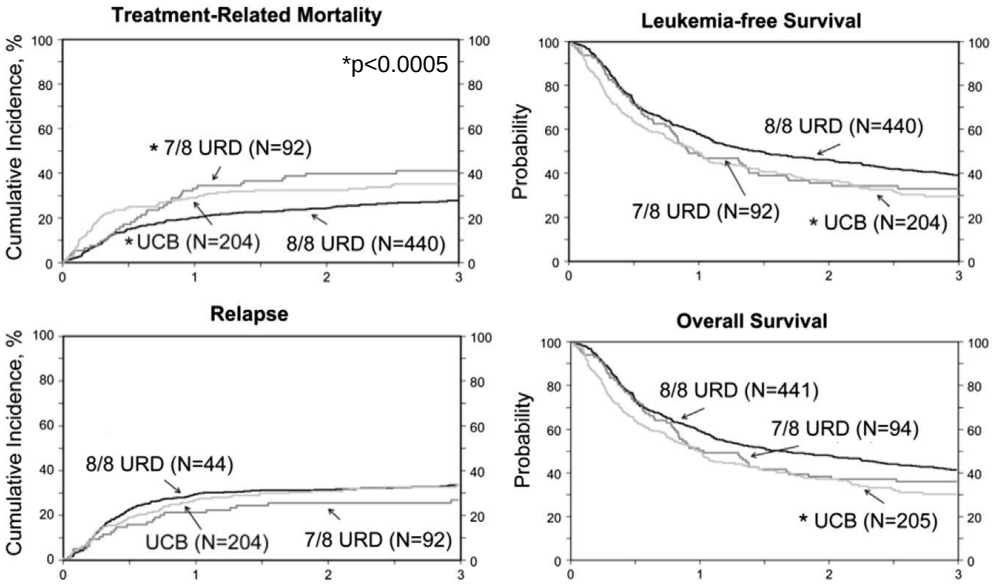


OVERALL SURVIVAL

Multivariate analysis (RR [95% CI])
MUD: 1.0
mMUD: 1.27 [1.03, 1.57], p=0.03
Cord: 1.13 [0.96, 1.34], p=0.16
Overall p=0.07

MUD: 1.0
mMUD: 1.16 [0.86, 1.57], p=0.33
Cord: 1.79 [1.39, 2.88], p<0.0001
Overall p<0.0001

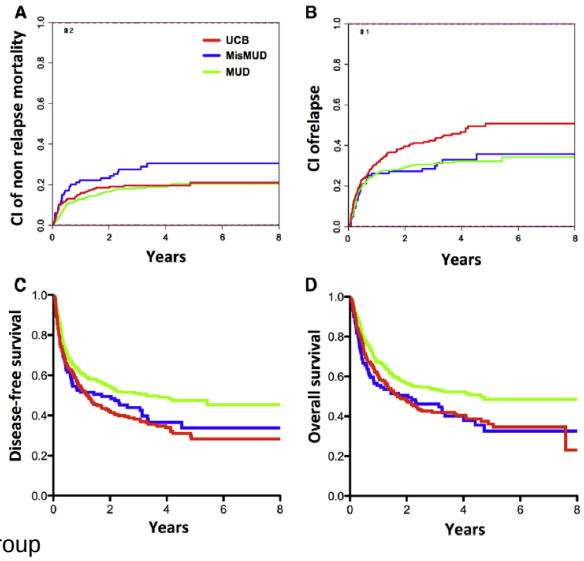
Ballen K et al, BBMT 2016; 22: 1636-1645



CIBMTR and Eurocord
N=736 adults>50, AML in CR1, 2005-2010

Weisdorf et al, BBMT 2014; 20: 816-822

Relapse (v. cord)



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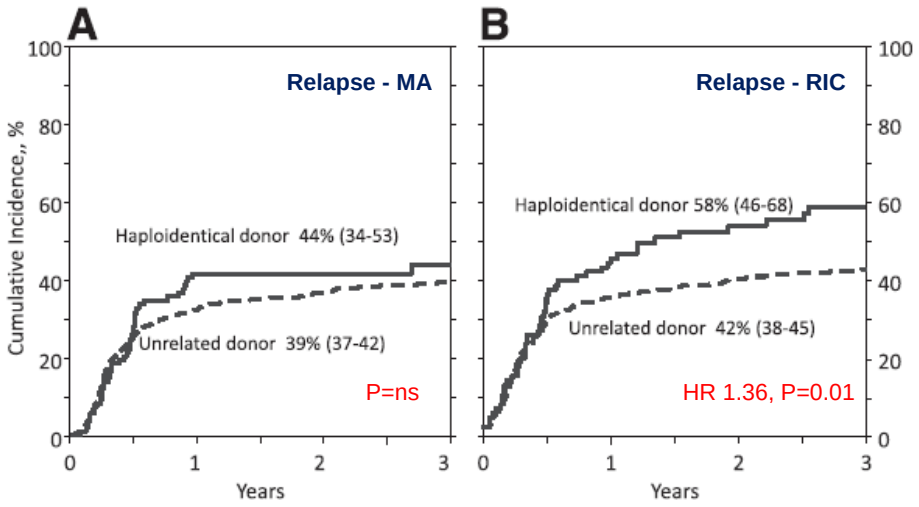
Relapse (v. haplo)



CIBMTR
N=1982 URD, 192 haplo, adult AML, 2009-2012

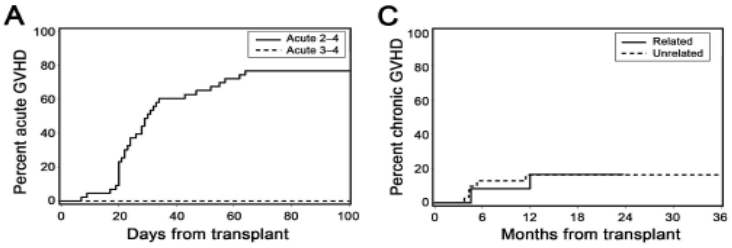
Ciurea S et al, Blood 2015; 126: 1033-1040

Unrelated Donors

- Results continue to improve:
  - Less chronic GVHD with bone marrow, post-transplant cyclophosphamide, ATG
  - Refined donor considerations
    - KIR
    - HLA-DP

URD PB + post HCT Cy

Figure 2
Mielcarek et al., BLOOD-2015-672071



N=43
MA, matched related/unrelated PBSC + PTCy
0% grade III-IV acute GVHD
16% CI chronic GVHD

Mielcarek et al, Blood 2016; 127: 1502-1508

Pretreatment with anti-thymocyte globulin versus no anti-thymocyte globulin in patients with haematological malignancies undergoing haemopoietic cell transplantation from unrelated donors: a randomised, controlled, open-label, phase 3, multicentre trial

Irwin Walker, Tony Panzarella, Stephen Couban, Felix Couture, Gerald Devins, Mohamed Elemary, Geneviève Gallagher, Holly Kerr, John Kuruvilla, Stephanie J Lee, John Moore, Thomas Nevill, Gizelle Popradi, Jean Roy, Kirk R Schultz, David Szwajcer, Cynthia Toze, Ronan Foley, on behalf of the Canadian Blood and Marrow Transplant Group

Lancet Oncol 2015
Published Online
December 23, 2015

Lancet Onc 2016; 17: 164

N=203, MA and RIC
Freedom from IST through 12 mos
37% vs. 16%, OR 4.25, p=0.0006

ASH | 58th Annual Meeting & Exposition
San Diego, CA · December 3-6, 2016

505 A Prospective Randomized Double Blind Phase 3 Clinical Trial of Anti- T Lymphocyte Globulin (ATLG) to Assess Impact on Chronic Graft-Versus-Host Disease (cGVHD) Free Survival in Patients Undergoing HLA Matched Unrelated Myeloablative Hematopoietic Cell Transplantation (HCT)

Robert J. Soiffer et al

Case 1

34 y/o man

- Ph+ ALL with CNS involvement
- recent fungal pneumonia, on anti-fungal treatment
- weight 120 kg
- eligible for a GVHD prophylaxis trial where donor = 8/8 or 7/8 unrelated donor

➢ Infection
➢ Weight
➢ Eligible for clinical trial

Case 2

64 y/o man

- myelofibrosis after a prolonged history of polycythemia vera
- splenomegaly
- no response to platelet transfusions, anti-HLA antibodies present
- anticoagulated because of a recent pulmonary embolus

➢ Engraftment concerns

Case 3

24 y/o woman

- CMML s/p induction chemotherapy
- 4% blasts in bone marrow
- CMV + with h/o reactivation and current viremia

➢ High risk of relapse

➢ High risk of CMV infection

Summary

- Unrelated donors are the most common alternative donor grafts
- More have been performed, and by more centers for longer, than other graft types
  - Registry data vs. single center data
- URD advantageous in cases of
  - Heavier recipients/higher risk of graft failure
  - Higher risk of serious infections
  - (Higher risk of relapse)
- Randomized trials are needed

Cell Source Selection- the Debate Continues
HLA-haploidentical (haplo) donors

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Outline

- Case presentation
- Just what is an HLA-haploidentical donor?
- Advantages and disadvantages of haplo donors
- Comparative outcomes of haplo stem cell transplantation

Case presentation

- 58♀ presents to emergency room with fatigue
- WBC 108K, Hb 5.9, Plts 11,000
- Diagnosis: AML with FLT3 internal tandem duplication
- Patient achieves molecular complete remission with cytarabine and daunorubicin
- Evaluation of potential family donors:
  - HLA-matched brother: 65 yo, WBC 4.6, Hb 14, Plt 160K
  - Antibody against HLA-B51 and –DR11 at +CDC XM
  - Antibody against HLA-DQ3 with MFI=1000

What is an HLA-haploidentical donor?

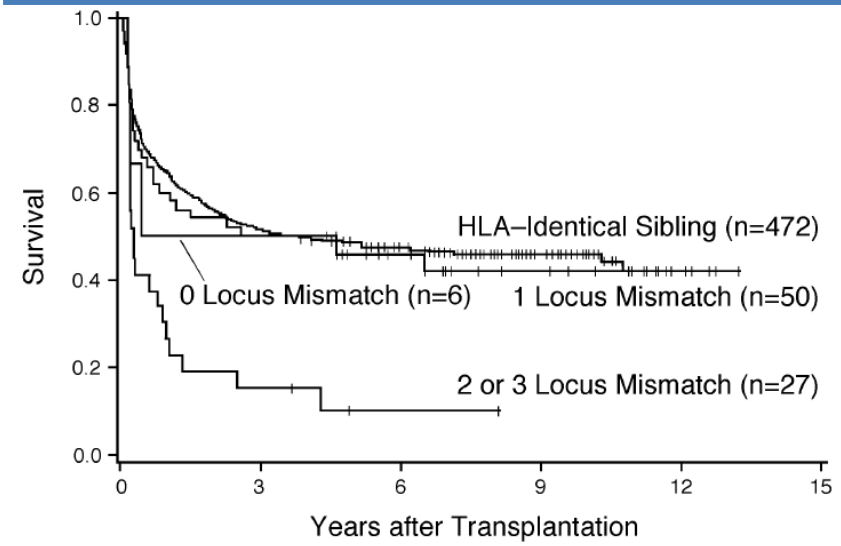
- An HLA-haploidentical (haplo) donor is a RELATIVE who shares, by common inheritance, one chromosome 6 with the patient and who is mismatched for a variable number of HLA genes (0-6) on the unshared chromosome 6
- Examples of haplo donors (likelihood of being haplo)
  - Biological parents or children (100%)
  - Sibs or half sibs, aunts or uncles, nieces or nephews, grandchildren (50%)
  - Cousins (25%)

Pros and cons of haplo donors

	10/10 MUD	Haplo	Cord
Donor availability	20-80%	90-95%	100%
Time to donation	Possibly slow	Fast	Fast
Graft failure	Lowest	Higher	Higher
GVHD	Lowest	Highest	Medium
Recurring cell source	Yes	Yes	No
Cost	High	Low	High

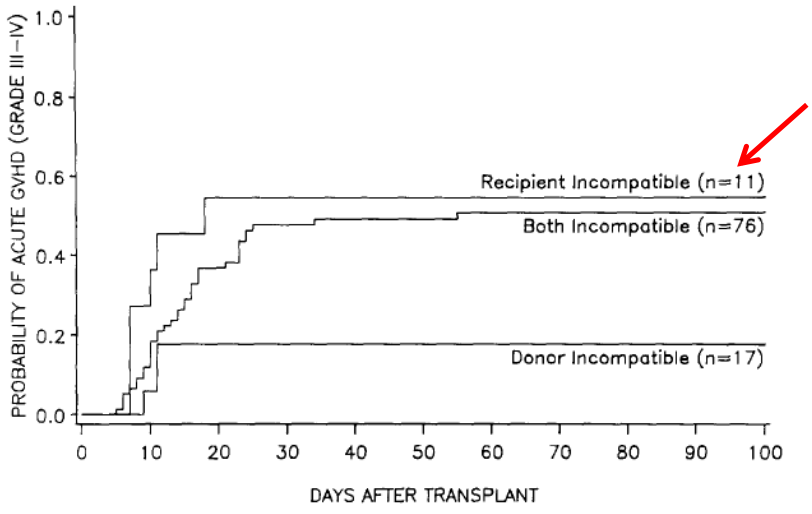
HaploBMT circa 1990

Poor outcome with heavy mismatching



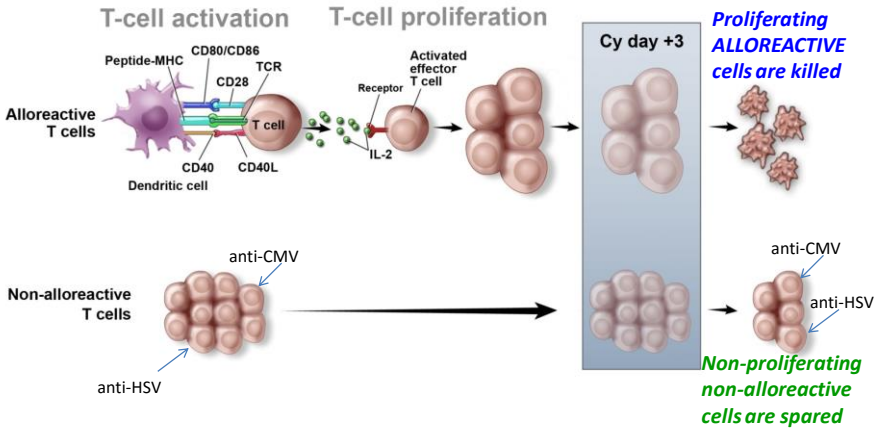
Anasetti et al., Hum Immunol 1990

Severe GVHD with single mismatch in GVH direction

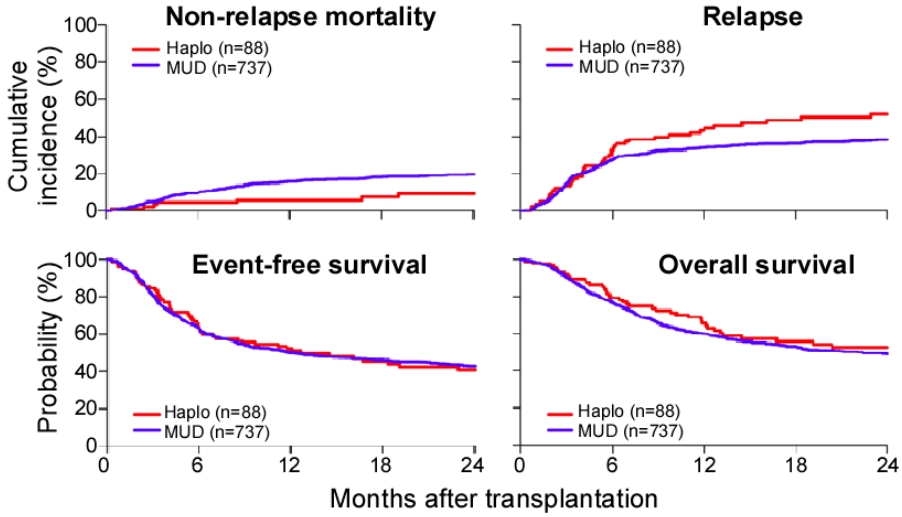


C Anasetti et al. Human Immunology, 29:79, 1990

Selective allodepletion with high dose, post-transplantation cyclophosphamide (PT/Cy)

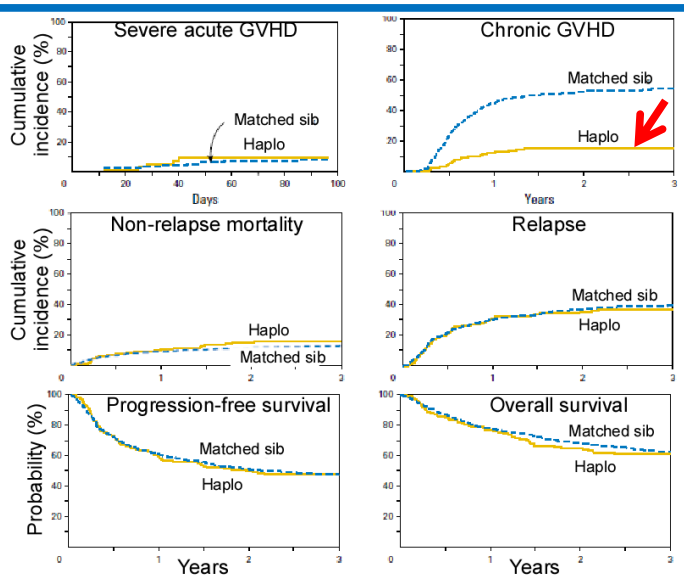


Haplo + PTCy versus MUD for AML
No difference in survival



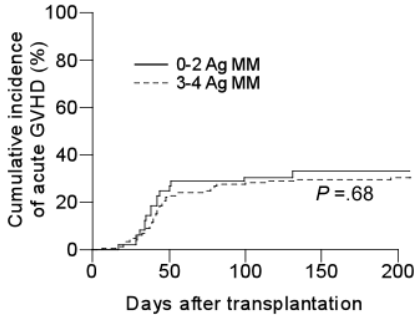
S Ciurea et al. Blood 126:1033-1040, 2015

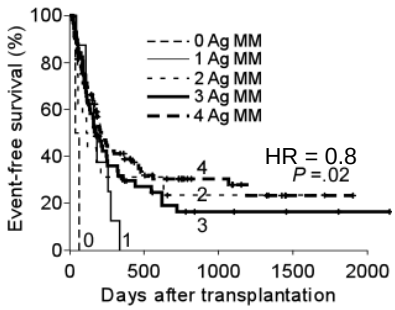
Haplo versus matched sib for lymphoma
Same outcome with less chronic GVHD



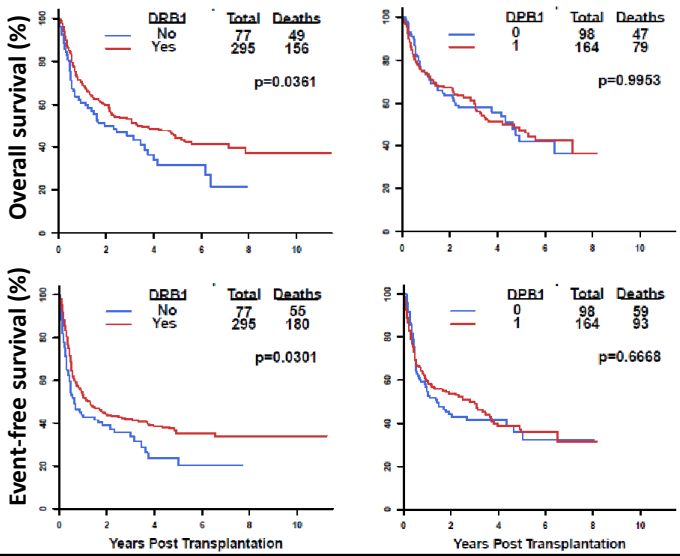
N Ghosh et al. J Clin Oncol 34:3141-3149, 2016

Increasing HLA mismatch→ *Improved EFS without ↑GVHD*





HLA-DRB1, but not –DPB1, mismatching improves survival



HaploBMT with PTCy
Conclusions

- Post-transplantation cyclophosphamide nullifies the detrimental impact of HLA mismatching on outcome of allogeneic SCT
- HLA-DRB1 mismatching in the graft-versus-host direction is associated with improved outcome of haploBMT + PTCy

Case presentation

- 58♀ presents to emergency room with fatigue
- WBC 108K, Hb 5.9, Plts 11,000
- Diagnosis: AML with FLT3 internal tandem duplication
- Patient achieves molecular complete remission with cytarabine and daunorubicin
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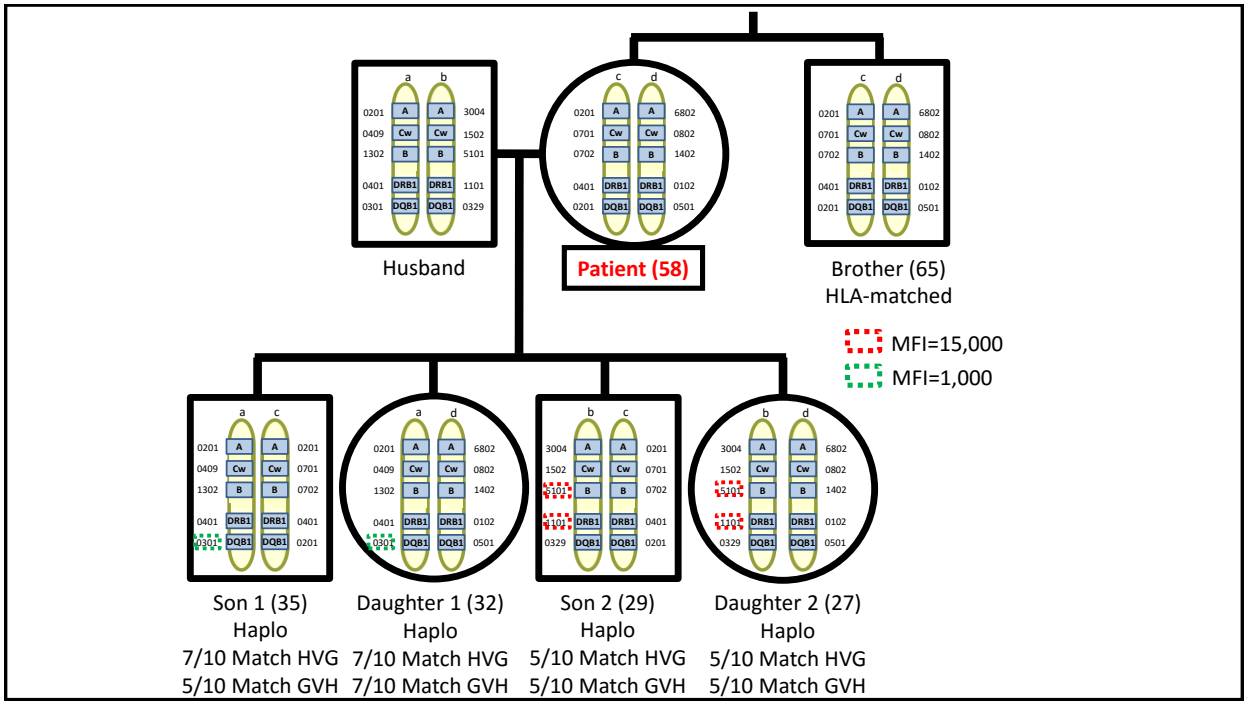

Donor selection issues in this case

- Time to donation
  - AMLs with FLT3 ITD are rapidly progressive
  - Risk of relapse while securing adult unrelated donor
- Health of potential donors
  - 6.3% cumulative incidence of donor-derived malignancy with donors>60 years old
  - AML mutation panel of sibling's blood identified clonal hematopoiesis of indeterminate prognosis (CHIP)
- Anti-donor HLA antibody
  - Two siblings ruled out due to + cytotoxic XM
  - Low level anti-DQ antibody does not preclude donation
- Benefit of HLA-DRB1 antigen mismatching
  - Patient's 35 year old son was chosen as the donor

Final comments

- Alternative graft sources have never been compared directly in a prospective, randomized trial, *therefore*
- There is no evidence that haplos are better than cords or adult unrelated donors, or vice versa, *therefore*
- **I strongly encourage transplant centers to enroll patients onto the first ever prospective, randomized trial comparing two different sources of stem cells:**

BMT CTN 1101 (cord v haplo)