



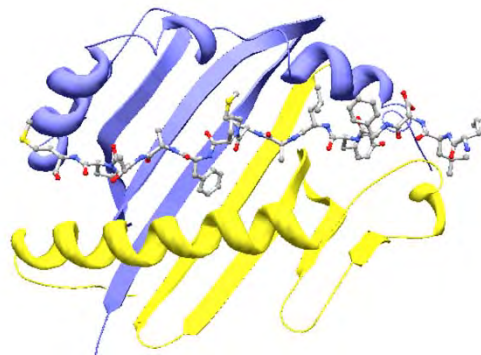
10<sup>th</sup> INTERNATIONAL SUMMER SCHOOL ON IMMUNOGENETICS  
15-18 SEPTEMBER 2013, STINTINO/SARDINIA, ITALY

SESSION 5: HLA AND TRANSPLANTATION

*Wednesday, September 18, 2013*



# Matches and Mismatches in HSCT



**Katharina Fleischhauer**

Unit of Molecular and Functional Immunogenetics

San Raffaele Scientific Institute, Milan, Italy

Institute for Experimental Cellular Therapy

University of Essen, Germany

# Historical Data

---

- 1965 HLA-identical sibling donor Bone Marrow SCT
- 1979 HLA-identical unrelated donor Bone Marrow SCT
- 1994 haploidentical family donor megadose CD34+ SCT
- 1995 HLA-identical unrelated donor PBSC SCT
- 1996 HLA-A,B,DR identical unrelated Cord Blood SCT
- 1997 Reduced Intensity Conditioning unrelated SCT
- 1995 Molecular HLA Typing Class 1+2
- 2013 Number of known HLA alleles risen to >6000

HLA Matching  
Status

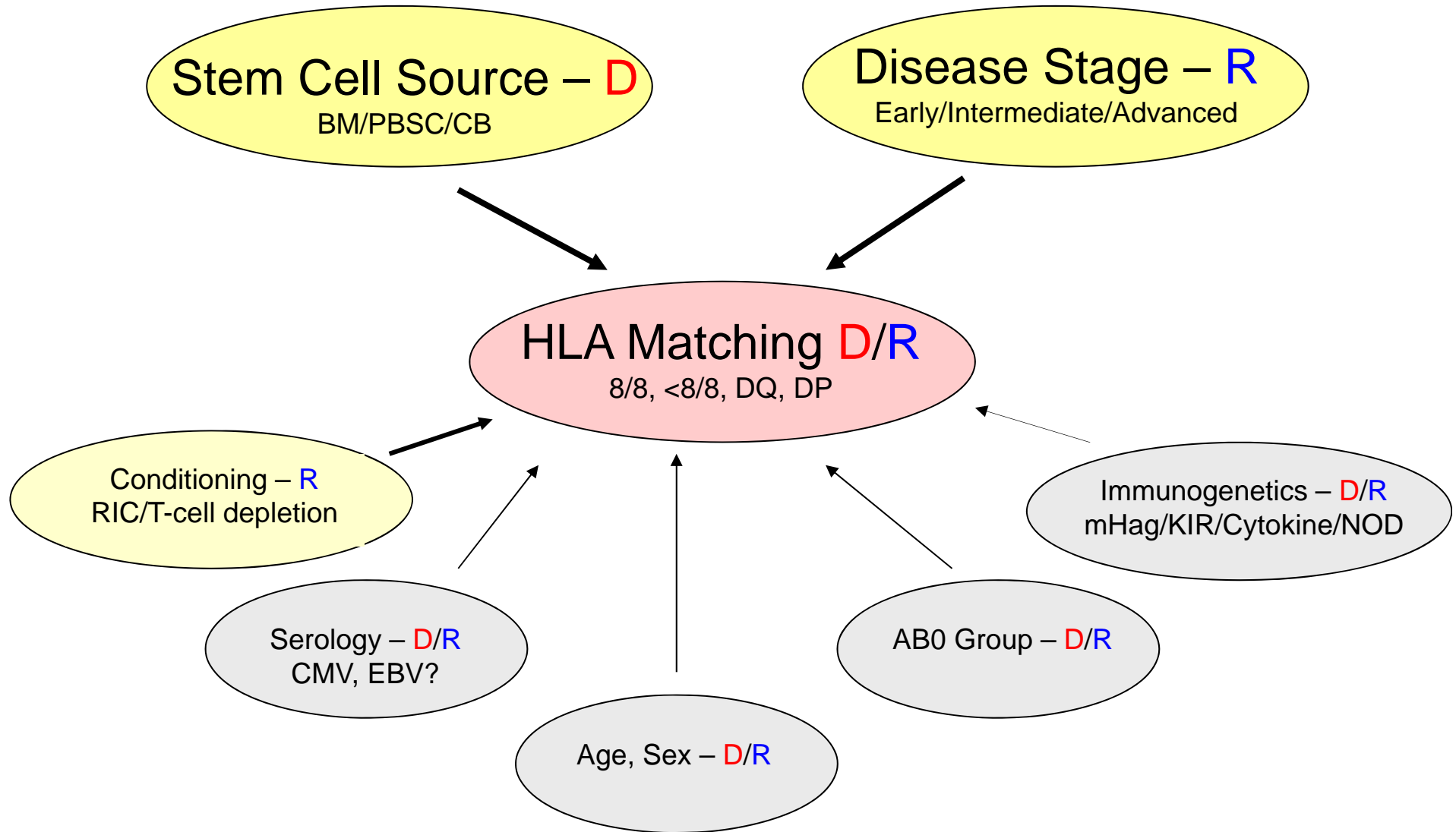
Stem Cell  
Source

Conditioning  
Regimen

HLA Typing

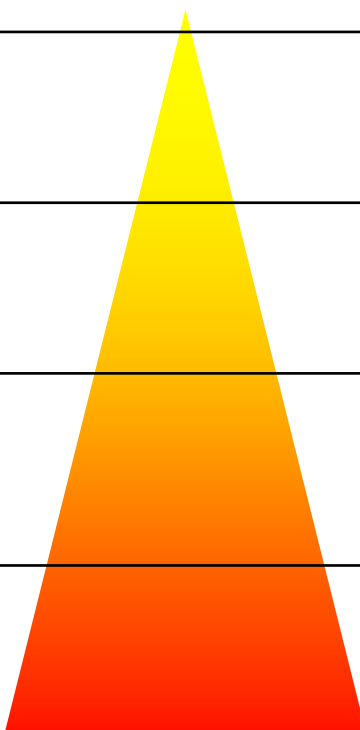
# Factors influencing outcome of HSCT

---



# Donor Matching and T cell Alloreactivity

---

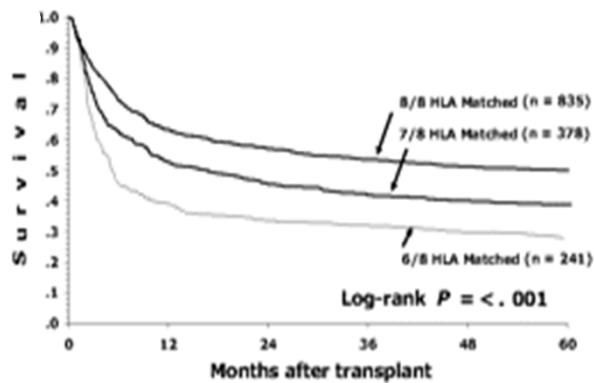
HSCT	Target Ags	GvHD/GvL
HLA-id. Sibling	Minor Ags (12/12)	
Unrelated	Minor Ags; HLA-DP (10/10)	
Cord Blood	Minor Ags; HLA-DP; HLA A,B,C,DR,DQ (>6/10)	
Haploidentical	Minor Ags; One full HLA-haplotype (>5/10)	

# Disease Stage and HLA Matching

- 3857 MUD Tx from unrelated adult volunteer donors (*Lee, Blood 2007*)

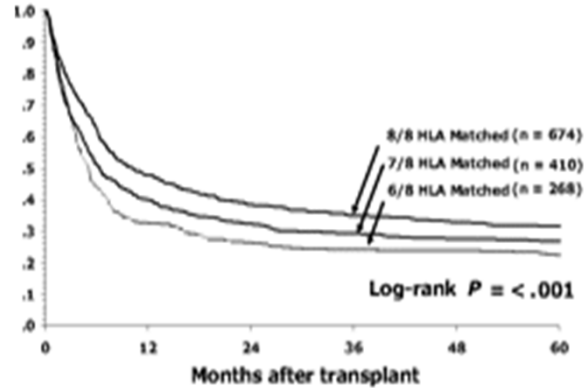
Early Stage

P<0.001



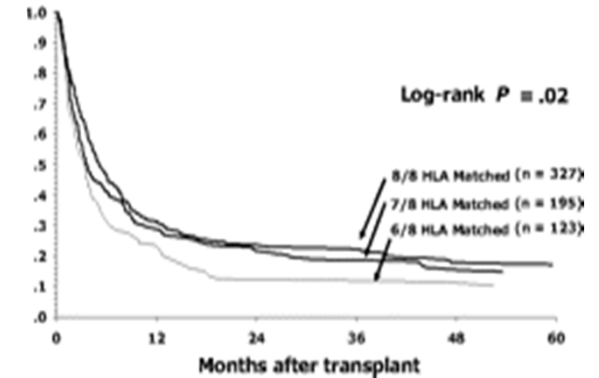
Intermediate Stage

P<0.001



Late Stage

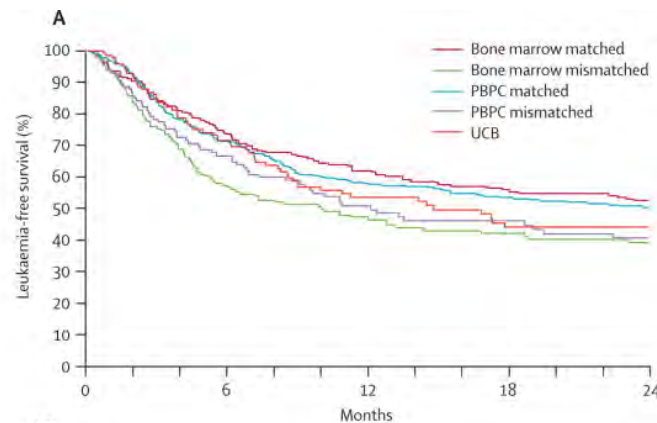
P=0.02



# HLA Matching, Stem Cell Source, Disease Stage

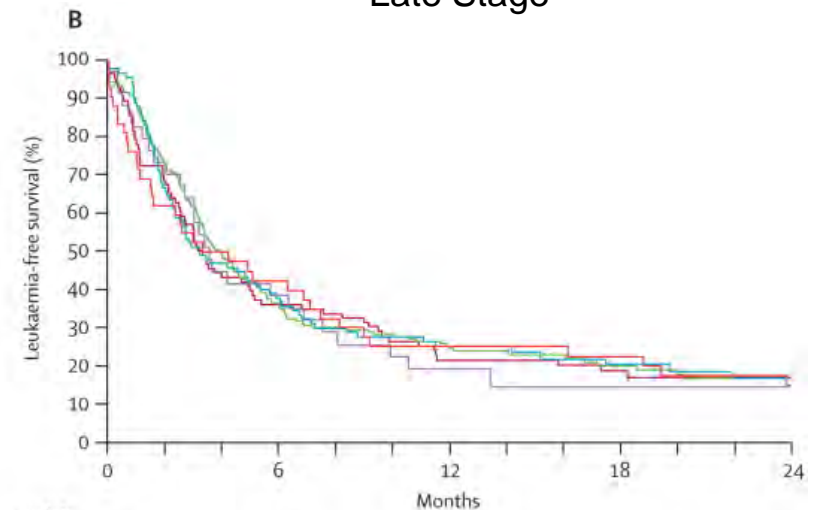
- 8/8 matched BM and PBSC have similar survival *(Eapen, Lancet Onc 2010)*
- Superior to 7/8 BM/PBSC which are similar to 4-6/6 UCB

Early Stage



Number at risk		Months				
		0	6	12	18	24
8/8 matched bone marrow	246	177	139	99	82	
7/8 matched bone marrow	106	69	46	35	31	
8/8 matched PBPC	452	316	220	143	112	
7/8 matched PBPC	166	89	66	45	36	
4/6-6/6 matched UCB	123	77	47	30	24	

Late Stage



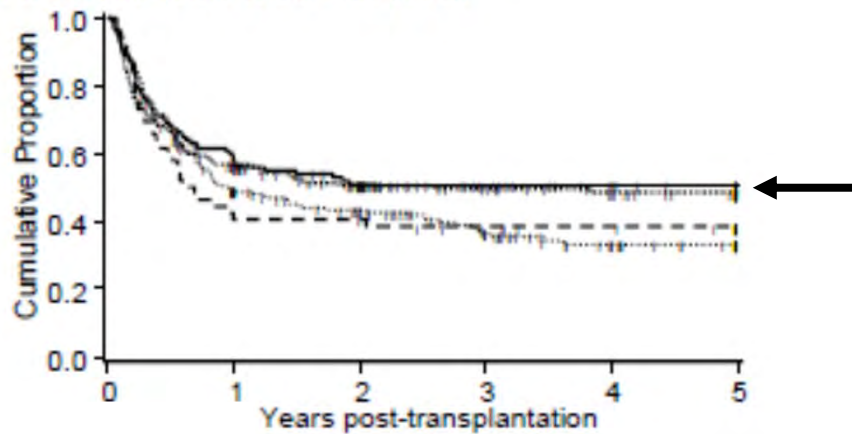
Number at risk		Months				
		0	6	12	18	24
8/8 matched bone marrow	86	31	17	13	10	
7/8 matched bone marrow	34	12	5	3	3	
8/8 matched PBPC	180	63	39	19	14	
7/8 matched PBPC	90	34	19	12	8	
4/6-6/6 matched UCB	42	17	10	9	6	

**...ONLY IN PATIENTS WITH EARLY DISEASE!**

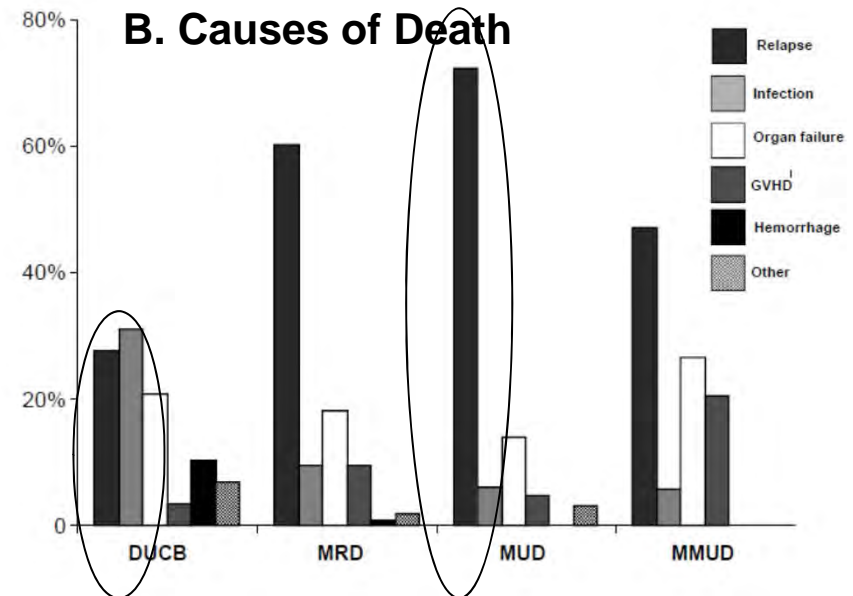
# Outcome of 4-6/6 double UCB Tx

- HLA matching is far less stringent (4/6 alleles)
- Cell dose  $>2.5 \times 10^7/\text{kg}$  TNC and  $>1.7 \times 10^5/\text{kg}$  CD34+
- Higher NRM but lower relapse than adult donors

**A. Leukemia-free survival**



**B. Causes of Death**



...mismatched HLA may be target of GvL!

(Brunstein, Blood 2010)

# Donor-specific HLA alloantibodies (DSA)

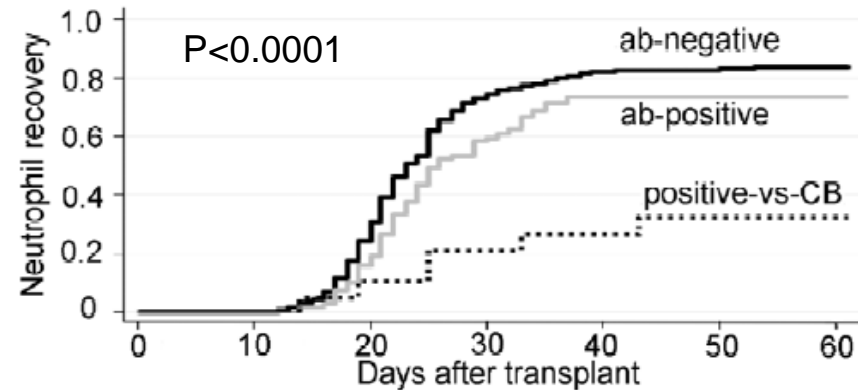
- Graft failure in HLA-mm unrelated SCT (*Spellman, Blood 2009*)
- Engraftment and survival in unrelated cord SCT (*Takanashi, Blood 2010*)

HLA-mismatched unrelated SCT

	Odds ratio	95% confidence interval	P
Class I DSA	11.34	1.49-∞	.017
Class II DSA	12.00	1.46-551.97	.014
Class I and/or II DSA	22.84	3.57-∞	<.001

>3-fold higher risk of graft failure

Unrelated Cord Blood SCT



...donor crossmatches in HLA-mismatched SCT!

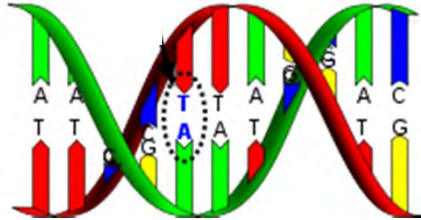


# T Cell Epitope Matching in Unrelated HSCT

## Structural versus Functional

---

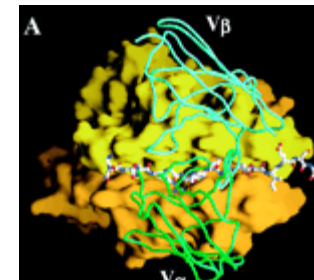
### Structural Matching



- Nucleotide Sequencing
- Allelic Matching or Disparity
- Sequence Identity for A,B,C,DRB1 (8/8)

• Classical Approach for SCT

### Functional Matching



TCR / MHC

- Shared T cell epitopes (TCE)
- TCE matching or disparity
- Functional Identity for TCE groups

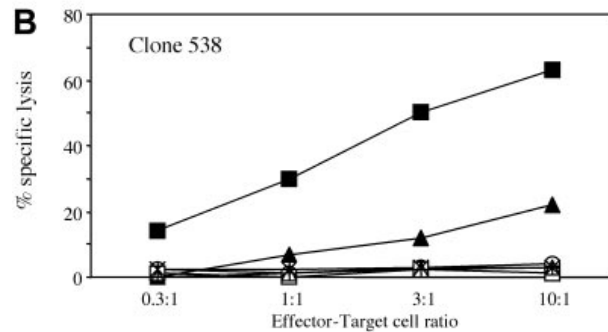
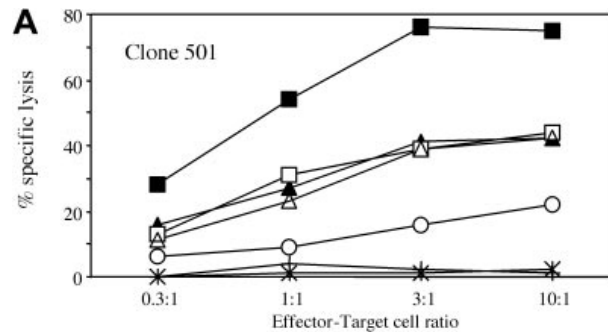
• In use for Solid Organ TX

- **Innovative for SCT**

# The three-group model TCE3

- Cross-reactivity of T cell clones from a patient with rejection
- Patient: DPB1\*0201,\*0401; Donor: DPB1\*0201,\*0901

Nominal Ag: DPB1\*0901



DPB1\*1001

DPB1\*1701

DPB1\*0301

DPB1\*1401

DPB1\*4501

Group 1: DPB1\*0901,1001,1701

Group 2: DPB1\*0301,1401,4501

Group 3: Others

DPB1\*1001

DPB1\*1701

# Functional matching by TCE3

DPB1* alleles	TCE3 group	Immunogenicity
0901 1001 1701	1	
0301 1401 4501	2	
Others	3	

TCE3 Grouping

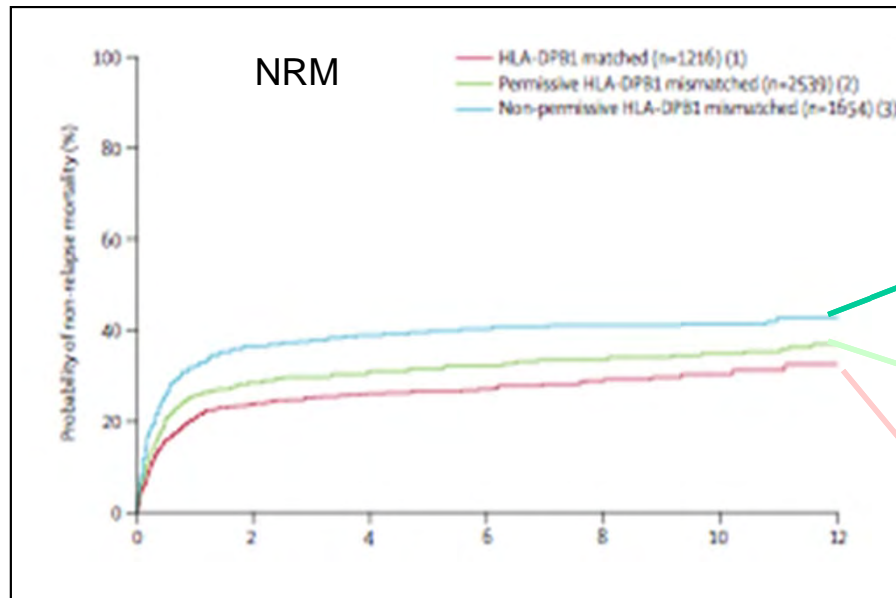
The Algorithm: 60% permissive  
40% non-perm.

		Recipient					
		1/1	1/2	1/3	2/2	2/3	3/3
D O N O R	1/1	permissive			non-permissive (HvG)		
	1/2						
	1/3						
	2/2	non-permissive (GvH)			permissive		permissive
	2/3						
	3/3						

# From Allele to T cell epitope (TCE) matching for DPB1

	HLA 10/10 match				
	Permissive HLA-DPB1 mismatch	HLA-DPB1 match		Non-permissive HLA-DPB1 mismatch	
		HR or OR	p value	HR or OR	p value
Overall mortality	1 (ref)	0.96 (0.87-1.06)	0.40	1.15 (1.05-1.25)	0.002
Non-relapse mortality	1 (ref)	0.86 (0.75-0.98)	0.03	1.28 (1.14-1.42)	<0.0001
Relapse*	1 (ref)	1.34 (1.17-1.54)	<0.0001	0.89 (0.77-1.02)	0.10
Grade 3-4 aGvHD	1 (ref)	0.84 (0.69-1.03)	0.09	1.31 (1.11-1.54)	0.001

Retrospective Analysis of 5428 UD-HSCT (10/10)



Non-permissive TCE Mismatch

Permissive TCE Match

Allelic DPB1 Match

DPB1 Allele Mismatched

# The DPB TCE Webtool

Anthony Nolan Registry

## Predicted Immunogenicity

Patient Typings: PROSPECTIVEPATIENT1

Allele	TCE Group	Predicted Immunogenicity	Comments
DPB1*04:01	3	Low	
DPB1*04:02	3	Low	

Donor Typings: PROSPECTIVEDONOR1

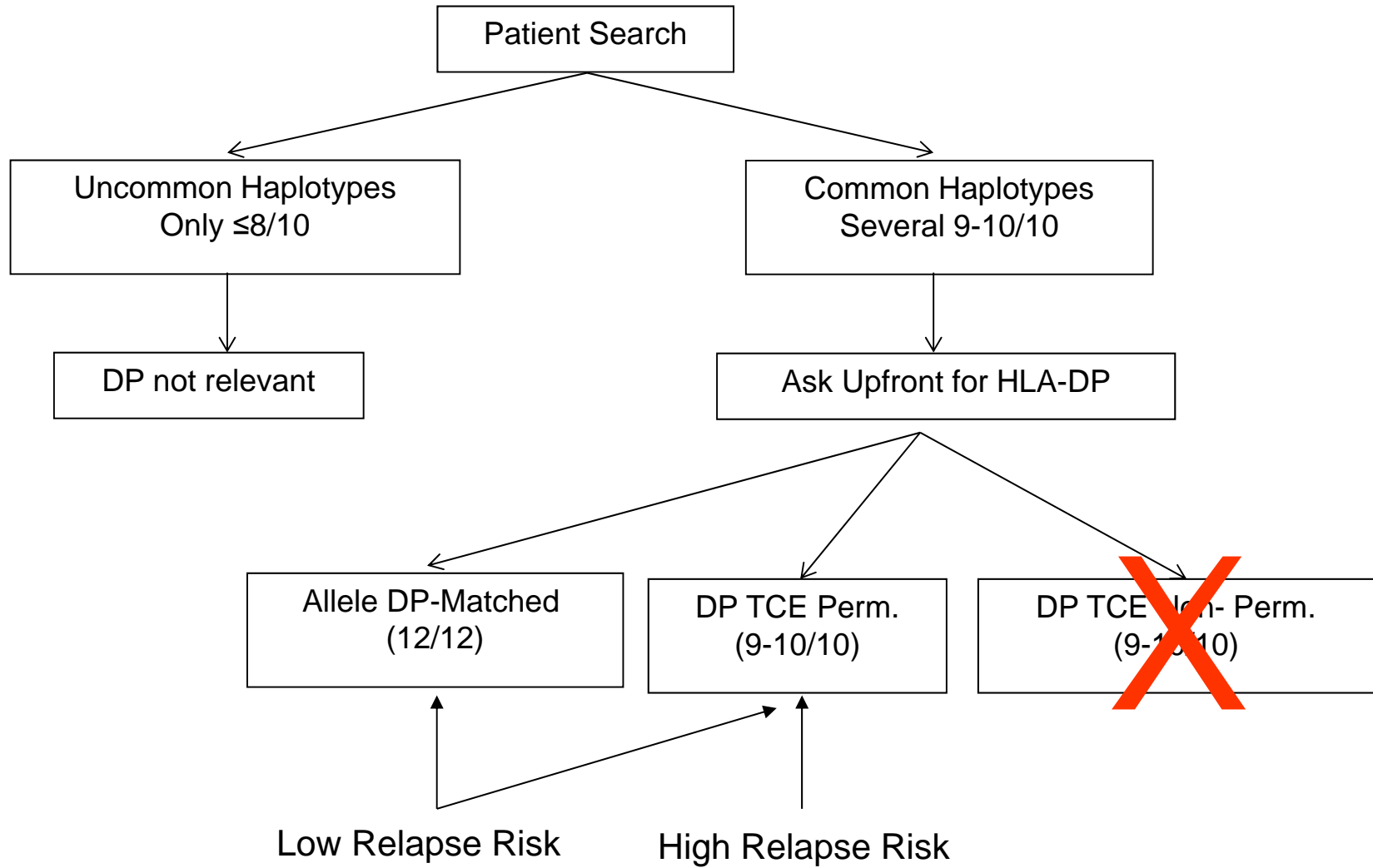
Allele	TCE Group	Predicted Immunogenicity	Comments
DPB1*04:01	3	Low	
DPB1*05:01	3	Low	
The predicted immunogenicity of the DPB1 matching for this pair is: <b>Permissive</b>			

<http://www.ebi.ac.uk/cgi-bin/ipd/imgt/hla/dpb.cgi>

Shaw et al., BMT in press

# Refined Guidelines for unrelated donor searches

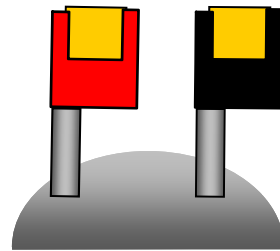
---



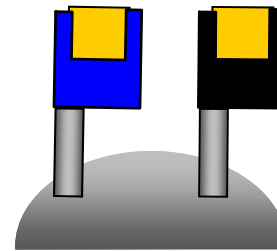
# HLA Mismatching

## Tracking Host Chimerism by HLA Typing

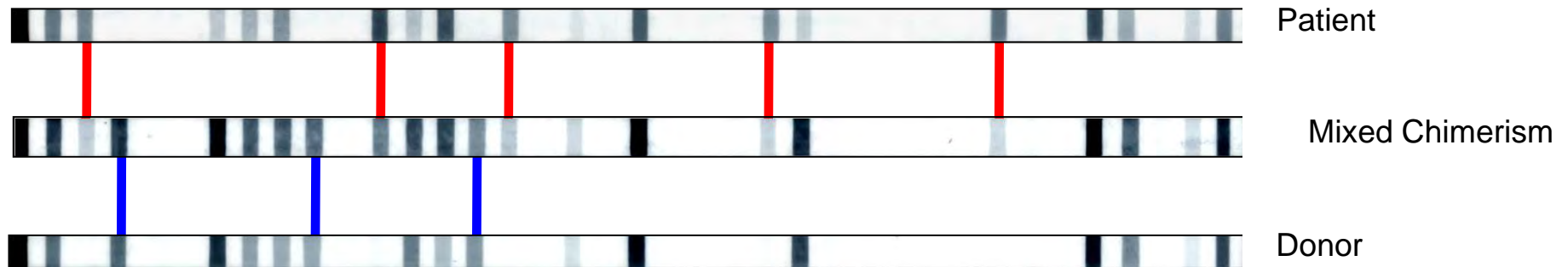
---



Patient



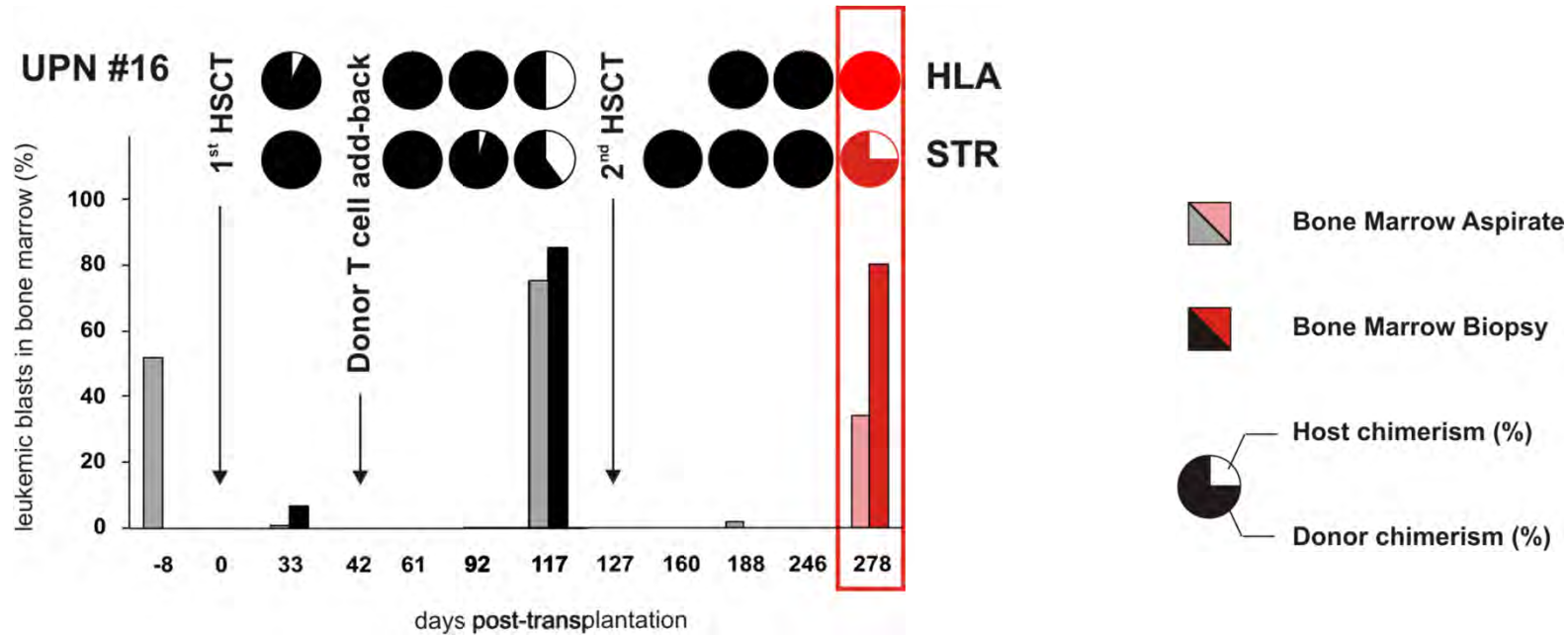
Donor



HLA typing is sensitive (1%) in detecting re-appearance of host hematopoiesis after SCT from mismatched donors

# HLA Mismatching

## HLA Loss Relapse

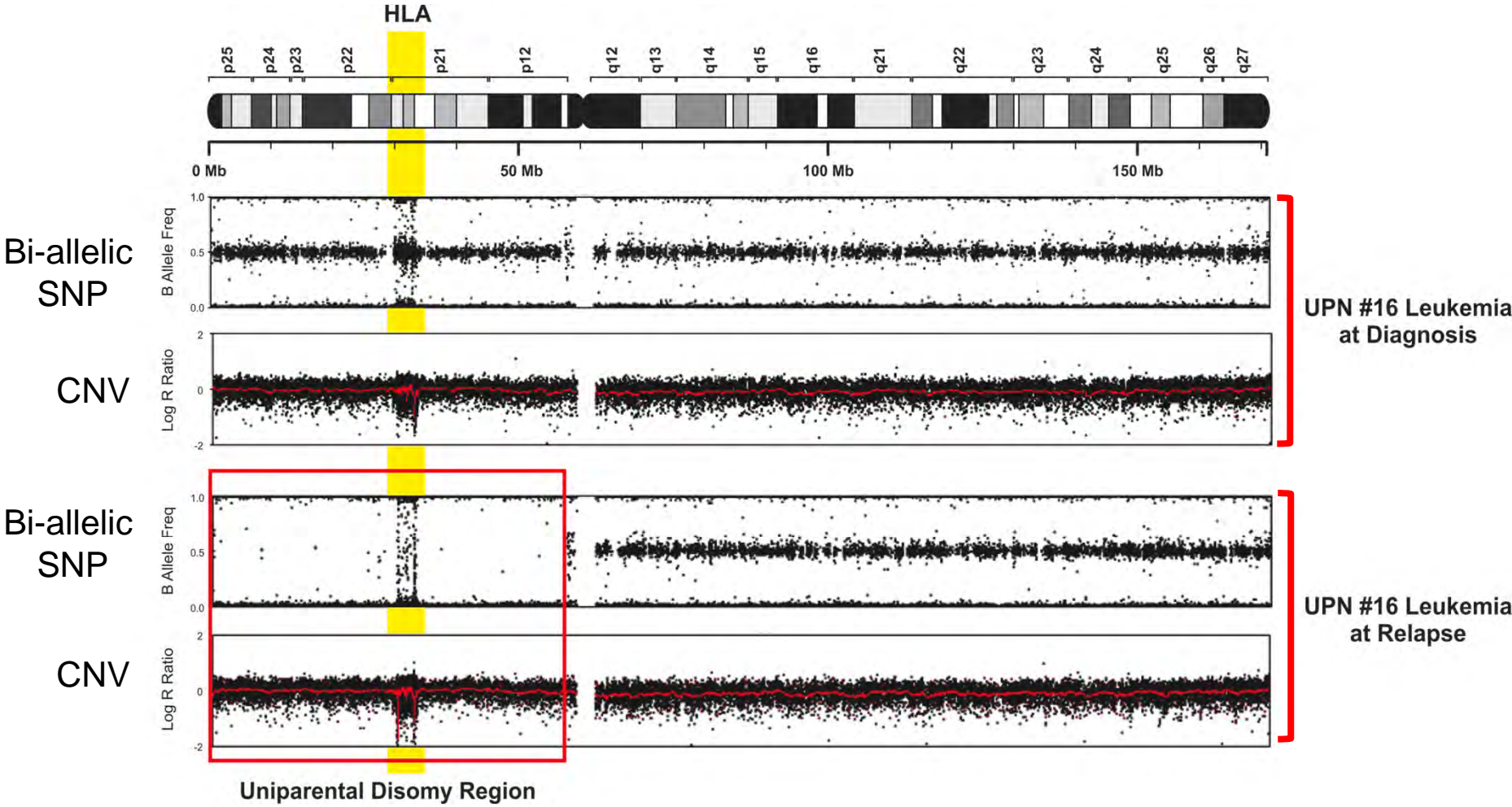


In 13/36 (36%) acute myeloid leukemia relapses after haplo-SCT, HLA typing failed to detect leukemic blasts



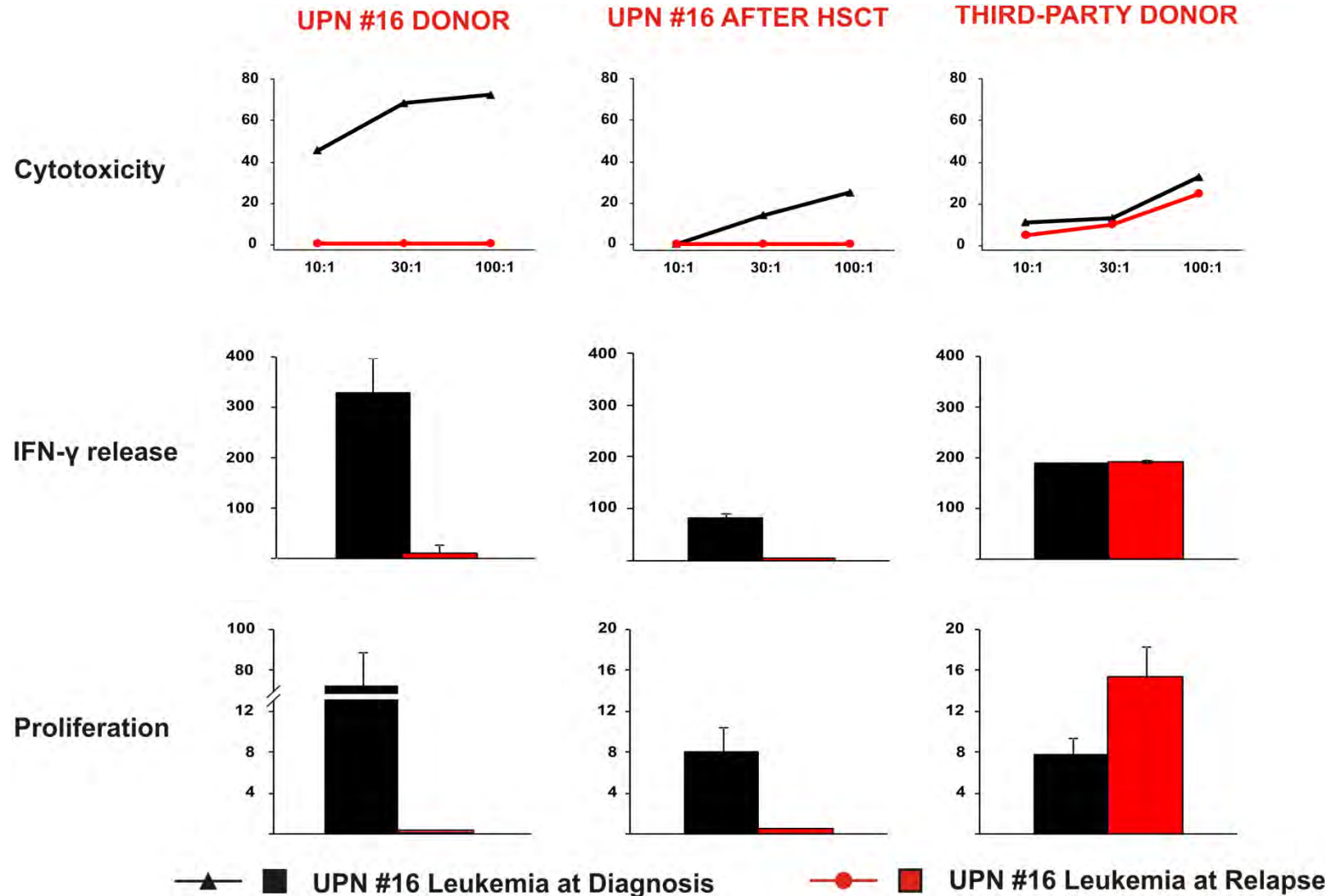
# HLA Mismatching

## UPD of chromosome 6p



# HLA Mismatching

## Specific evasion from anti-leukemia T cell response



# Take Home Messages

---

- Impact of HLA mismatches in allo-SCT is dependent on
  - Disease Stage – Transplant as early as possible!
  - Stem Cell Source (BM=PBMC 8/8; UCB 4-6/6)
- Permissible mismatches can be functionally defined
  - Concept of epitope matching
  - Added predictive value for HLA-DP in the 9-10/10 context
  - DRB? DQB1? Class 1??
- HLA loss relapses limiting factor in HLA-mismatched SCT
  - 30% of relapses after haplo-SCT; occurs also after unrelated SCT
  - Important impact on clinical treatment of relapse