

DGHO
DEUTSCHE GESELLSCHAFT FÜR
HÄMATOLOGIE UND MEDIZINISCHE ONKOLOGIE

OeGHO
Österreichische Gesellschaft für
Hämatologie & Medizinische Onkologie

SSMO
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JAHRESTAGUNG

Jahrestagung der Deutschen, Österreichischen
und Schweizerischen Gesellschaften für
Hämatologie und Medizinische Onkologie

www.haematologie-onkologie-2017.com

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STUTTGART
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Neue Konzepte im HLA Matching

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Disclosure of conflicts of interest

Other Financial Relationships

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Donor-Recipient HLA mismatches

Non-Self reactive TCR

Alloreactive T cells

HLA-A,B,C,DR,DQ,DP

GvHD and GvL

Missing-Self reactive KIR

Alloreactive NK cells

HLA-(A),B,C

GvL

Donor-Recipient HLA mismatches

Non-Self reactive TCR

Alloreactive T cells

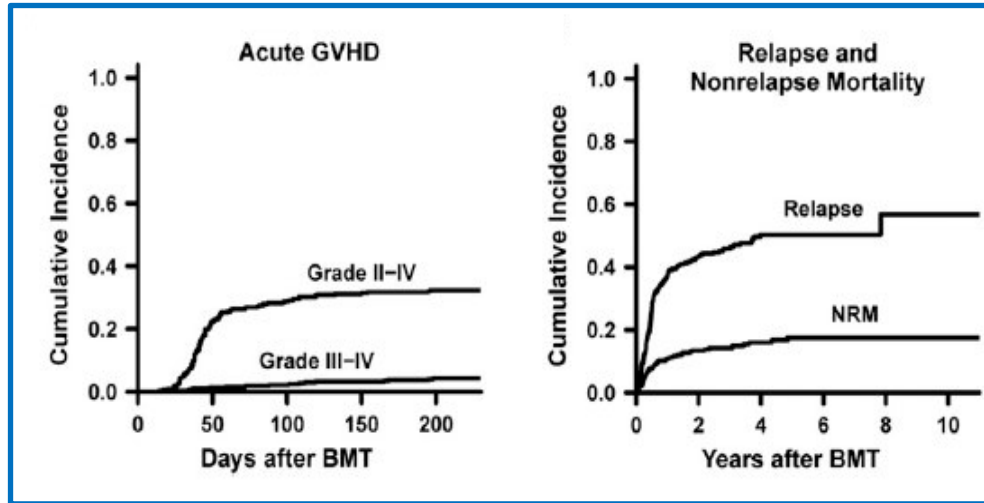
HLA-A,B,C,DR,DQ,DP

GvHD and GvL

- **Haploidentical:**
 - ✓ Full Haplotype mismatch
- **Matched Unrelated Donors (MUD):**
 - ✓ 8/8 – 7/8

Haploidentical Transplantation

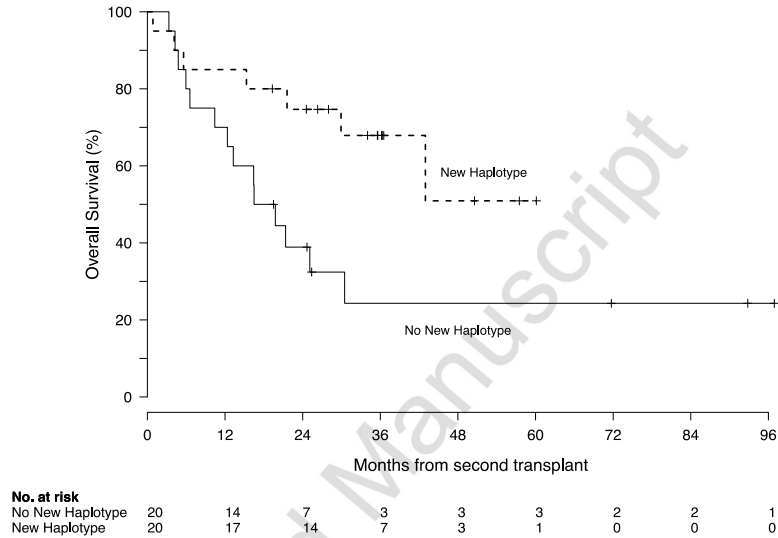
- **No definitive HLA matching concepts**
 - ✓ Number of Matches on the unshared haplotype?
 - ✓ Non-Inherited Maternal Antigens (NIMA?)



Relapse remains a problem

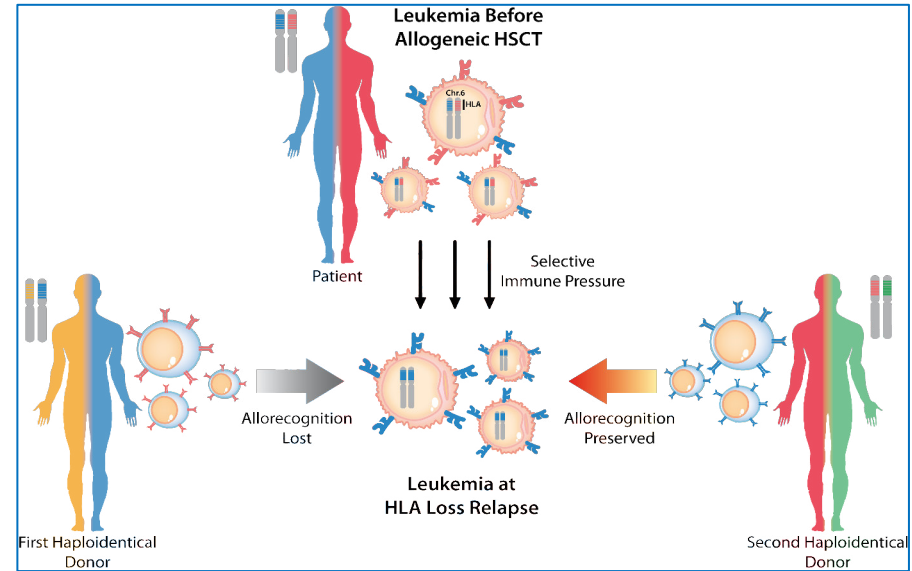
“Alternative Haplotype” for Relapse

Switch Second Donor



Imus et al., Biol Blood Marrow Transplant 2017

“HLA Loss” Immune Escape



Vago & Ciceri., Biol Blood Marrow Transplant 2017

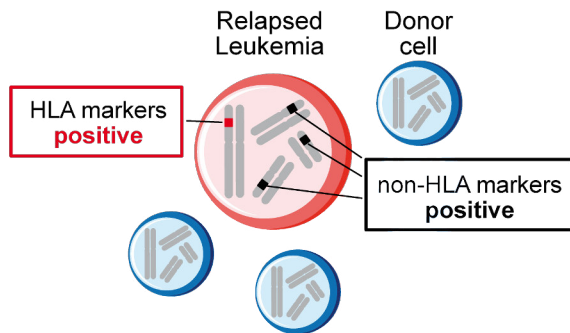
qPCR Chimerism for HLA loss relapse

"HLA" host chimerism (%)

De novo developed
HLA-A, -C, -DPB1



"Classical" relapse

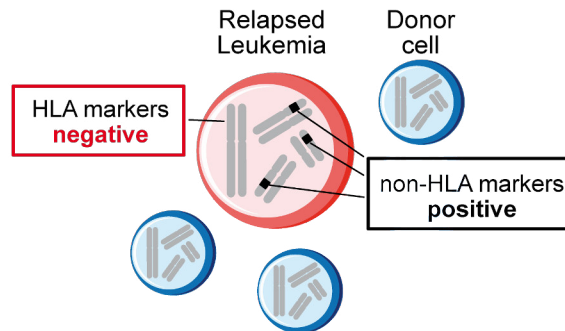


"non-HLA" host chimerism (%)

Commercially available
indels across the genome

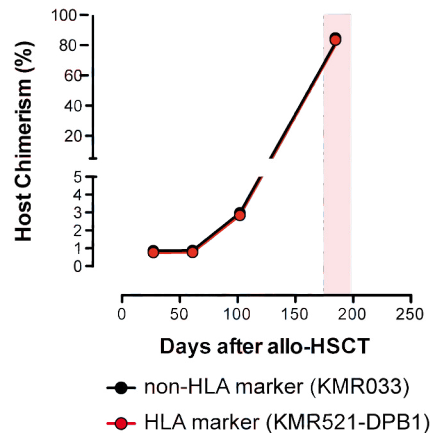


HLA loss relapse

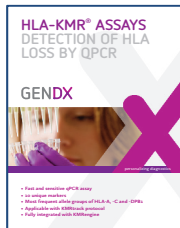
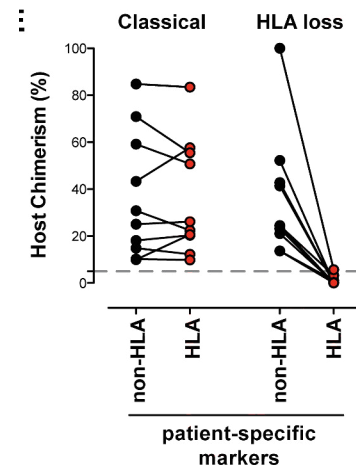
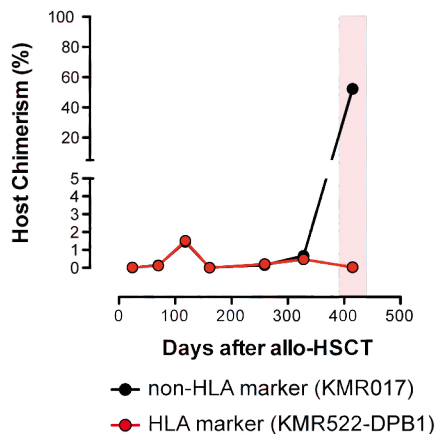


qPCR Chimerism for HLA loss relapse

Classical Relapse



HLA loss Relapse

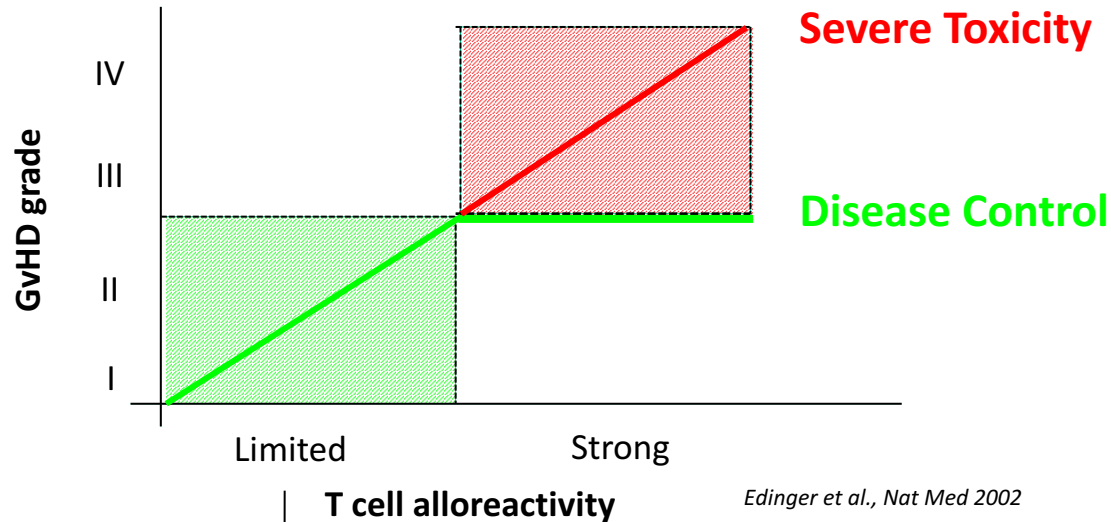


10 Reactions (HLA-A,C,DPB1)

71.6% Informativity after Haplo

Ahci & Toffalori et al., Blood 2017

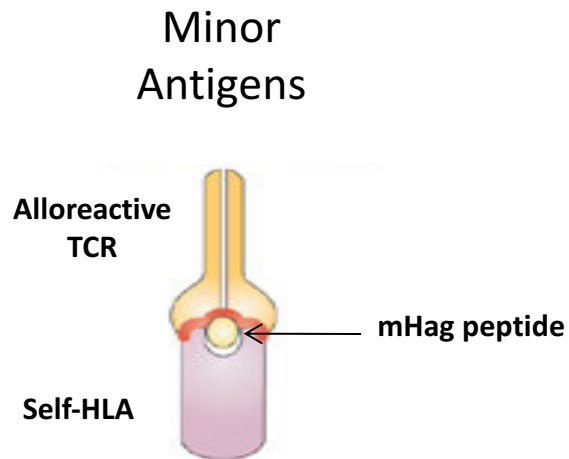
MUD: Limited T cell alloreactivity



Permissive Transplantation

- Cellular (T-depletion, Treg, ...)
- Pharmacological (CNI, PTCy, ...)
- Genetic (low T cell alloreactivity)

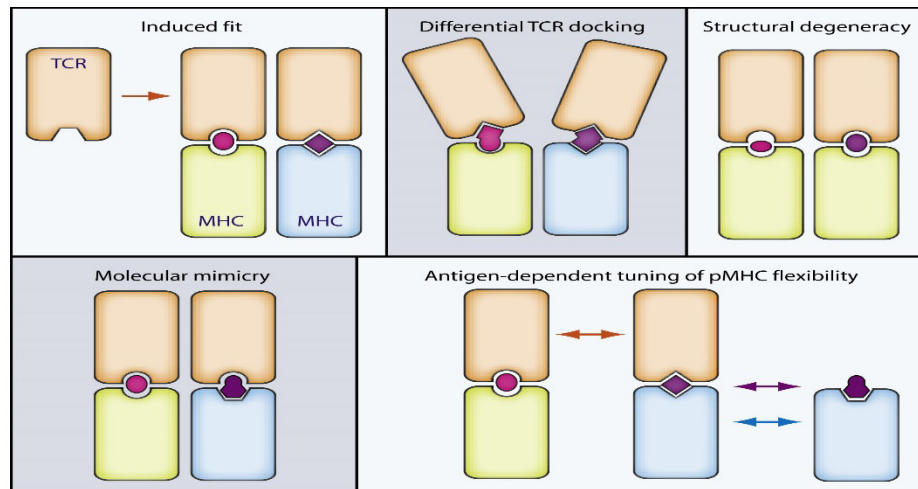
T cell alloreactivity



Conventional recognition
of polymorphic peptides

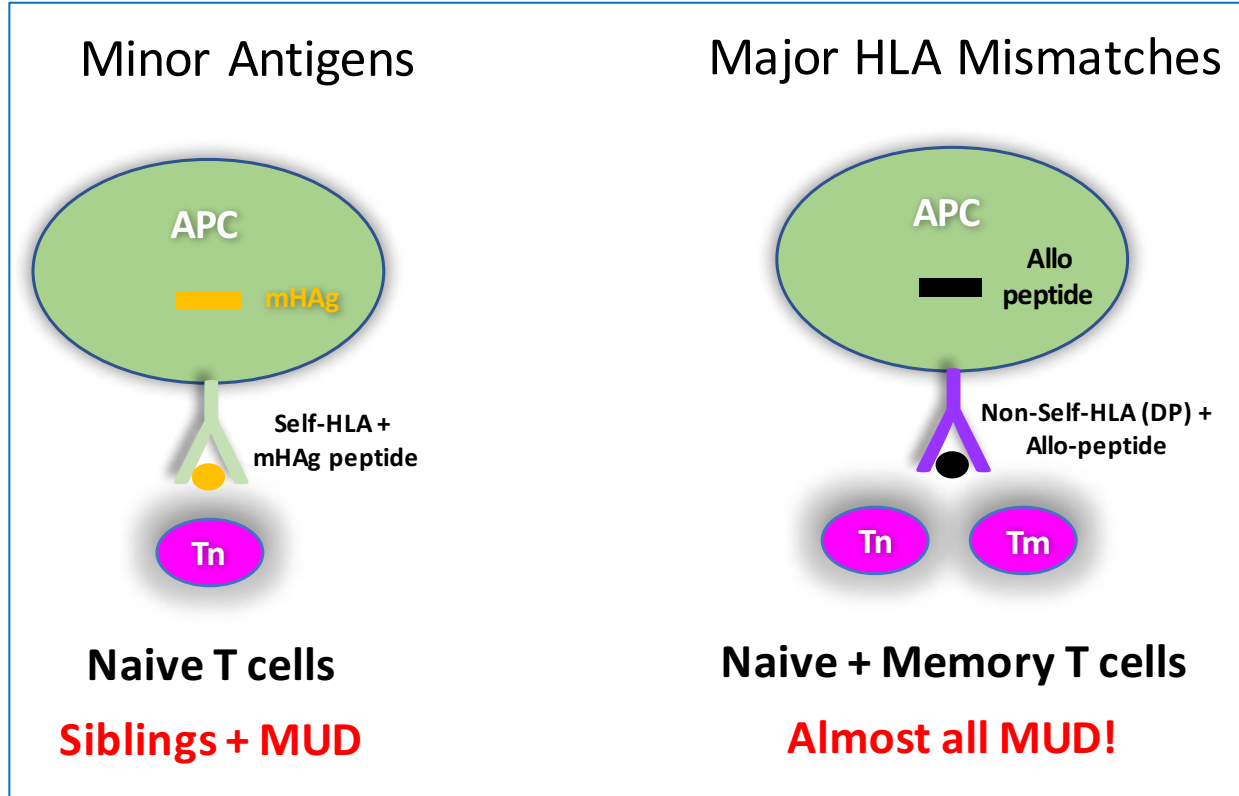
(also from mismatched HLA = PIRCHES)

Major HLA mismatches

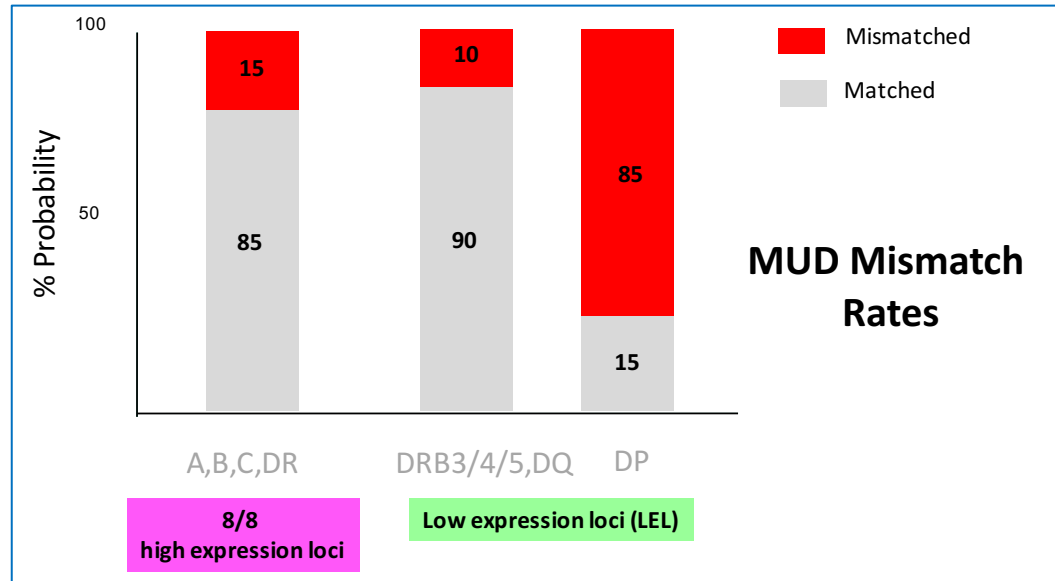
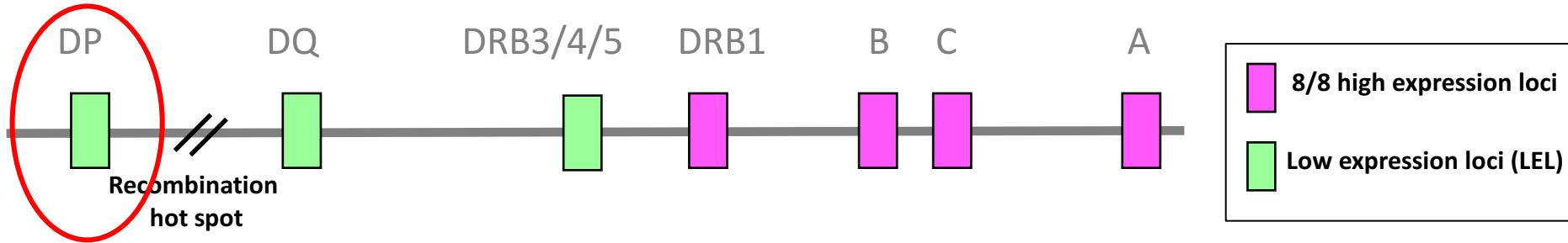


Cross-recognition of mismatched HLA

Naïve and Memory alloreactive T cells



HLA mismatches in MUD-HSCT



Permissive HLA Mismatches?

Several 9/10 MUD:

Permissive mismatch combinations (e.g. C*03:03 vs. 03:04)

Fernandez-Vina et al., Blood 2014
Kawase et al. Blood 2011

Predicted Indirectly ReCognized HLA Epitopes (PIRCHE)

Thus et al., Biol Blood Marrow Transplant 2014

Several 10/10 MUD:

HLA-DPB1 permissive T Cell Epitope (TCE) mismatches

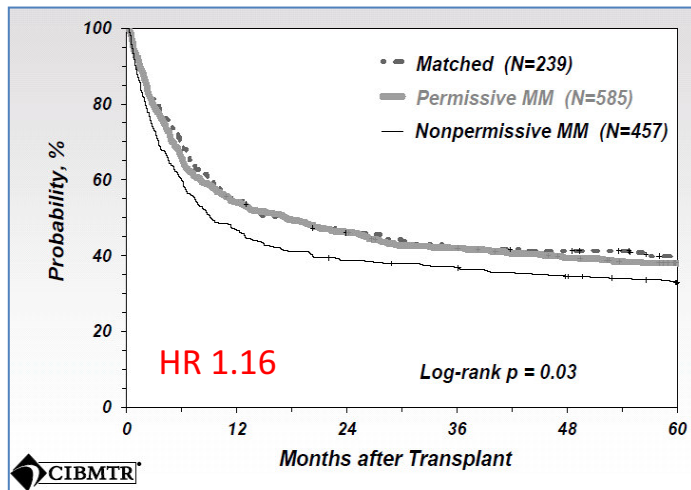
Zino et al., Blood 2004
Fleischhauer et al., Lancet Oncol 2012
Pidala et al., Blood 2014

High Expression single GvH mismatches

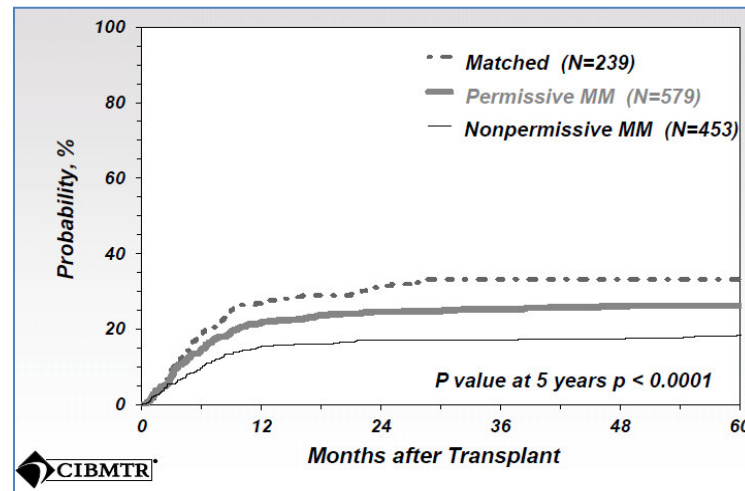
Petersdorf et al., N Engl J Med 2015

Clinical Association of TCE Mismatches

Overall Survival



Relapse



Fleischhauer et al., Bone Marrow Transplant 2014

Crocchiolo et al., Blood 2009

Fleischhauer et al., Lancet Oncol 2012

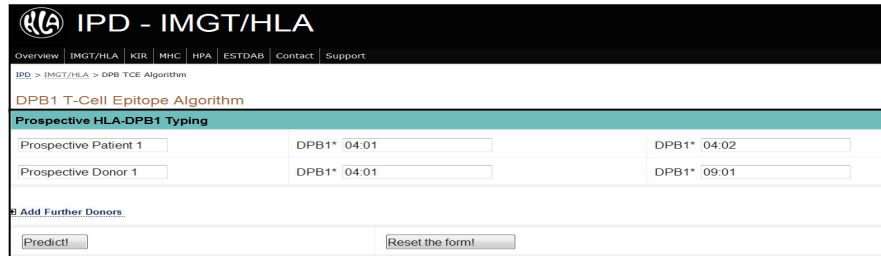
Pidala et al., Blood 2014

Fleischhauer & Shaw Blood 2017

Matched vs. Permissive	Relapse	GvHD 3-4
HR	1.31	0.96
P	0.05	0.77

Online Tools for TCE matching

DPB1 T-Cell Epitope Algorithm



IPD - IMGT/HLA

Overview | IMGT/HLA | KIR | MHC | HPA | ESTDAB | Contact | Support

IPD > IMGT/HLA > DPB TCE Algorithm

DPB1 T-Cell Epitope Algorithm

Prospective HLA-DPB1 Typing

Prospective Patient 1 DPB1* 04:01 DPB1* 04:02

Prospective Donor 1 DPB1* 04:01 DPB1* 09:01

[Add Further Donors...](#)

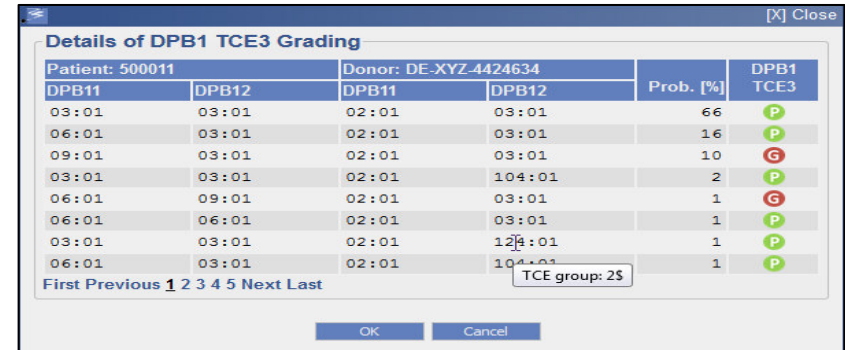
<http://www.ebi.ac.uk/ipd/imgt/hla/dpb.html>

Collaboration with SGH Marsh
(Anthony Nolan, London)



Zentrales
Knochenmarkspender-
Register Deutschland

OptiMatch®



Details of DPB1 TCE3 Grading [X] Close

Patient: 500011 Donor: DE-XYZ-4424634

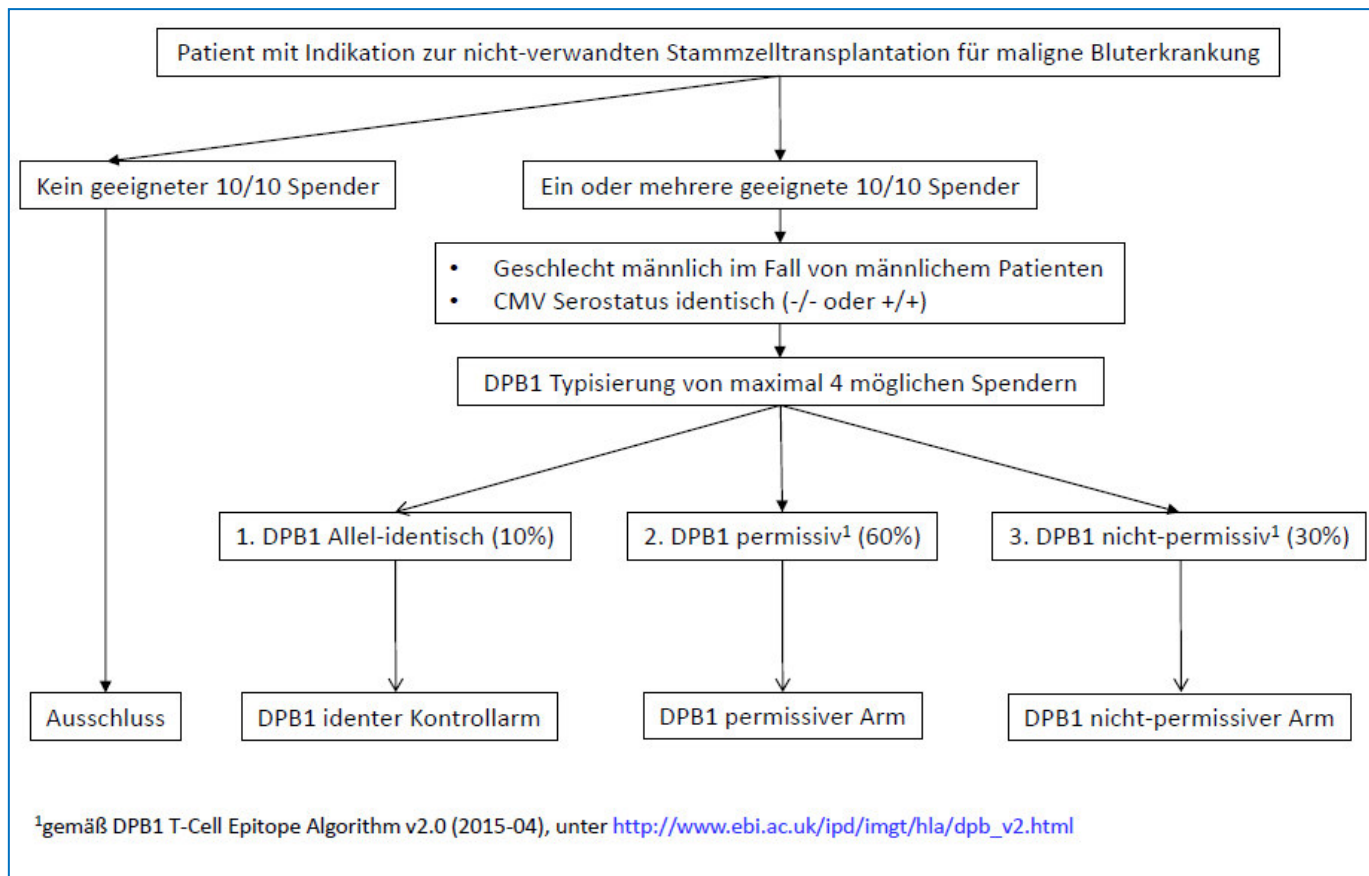
DPB11	DPB12	DPB11	DPB12	Prob. [%]	DPB1 TCE3
03:01	03:01	02:01	03:01	66	P
06:01	03:01	02:01	03:01	16	P
09:01	03:01	02:01	03:01	10	G
03:01	03:01	02:01	104:01	2	P
06:01	09:01	02:01	03:01	1	G
06:01	06:01	02:01	03:01	1	P
03:01	03:01	02:01	12:01	1	P
06:01	03:01	02:01	104:01	1	P

First Previous 1 2 3 4 5 Next Last

TCE group: 2\$

Courtesy of CH Müller
(ZKR D, Ulm)

Prospective Study HLA-DPB1 TCE Matching



Essen

Hamburg

Dresden

Heidelberg

Mainz

...

Conclusions

- Haplo-HSCT:
 - ✓ Relapse: test for HLA loss and switch to new donor at 2nd Tx
- MUD-HSCT:
 - ✓ “HLA–matched” Sibling and MUD biologically different!
 - ✓ Permissive HLA-DP TCE mismatches preserved GvL but limited GvHD
 - ✓ Prospective TCE trial open katharina.fleischhauer@uk-essen.de

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