

# *Permissività immunologica nel trapianto di CSE*

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**Trapianto di CSE**

04 Ottobre 2019

# Pavia

03.10.2019



**Essen**

01.10.2019



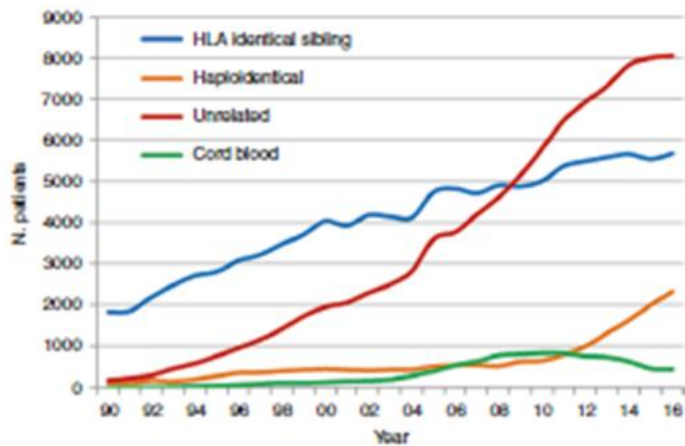
**Essen**

27.09.2019



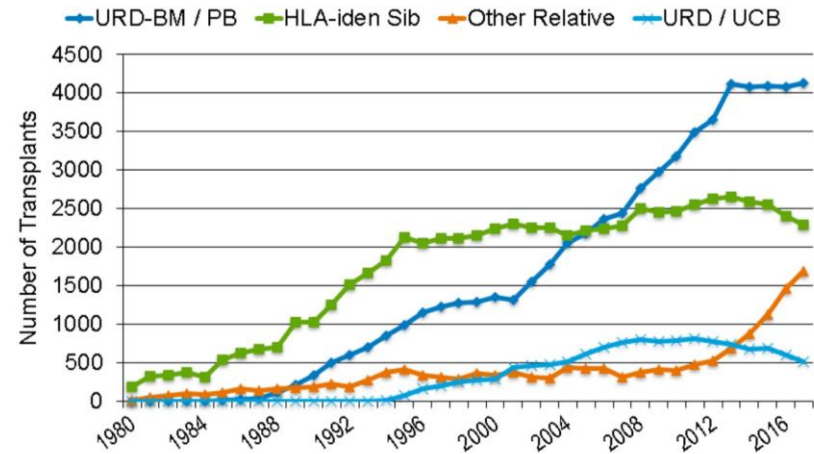
# HCT Donor Types 2016

## Europe

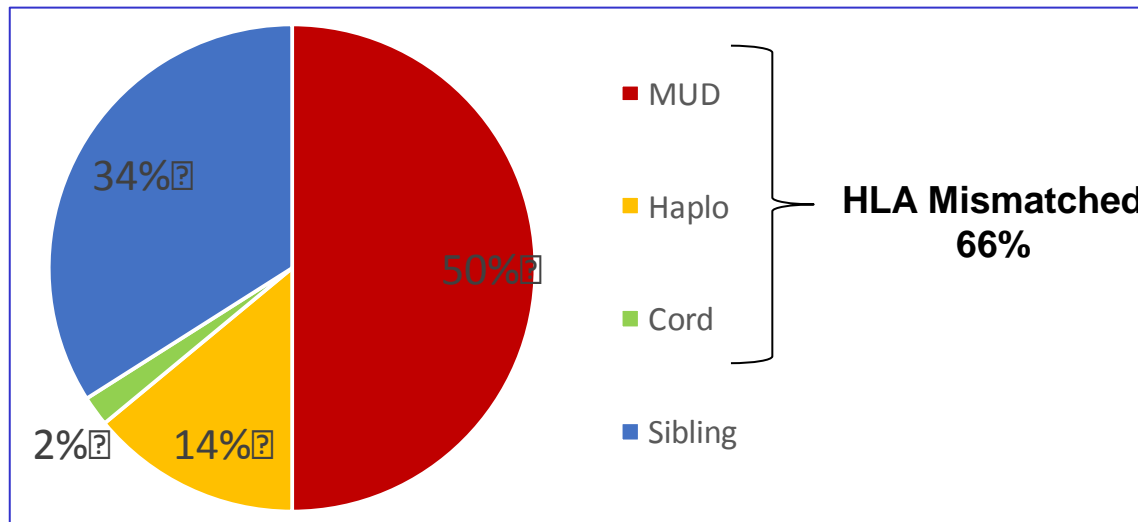


Passweg et al., BMT 2018

## United States

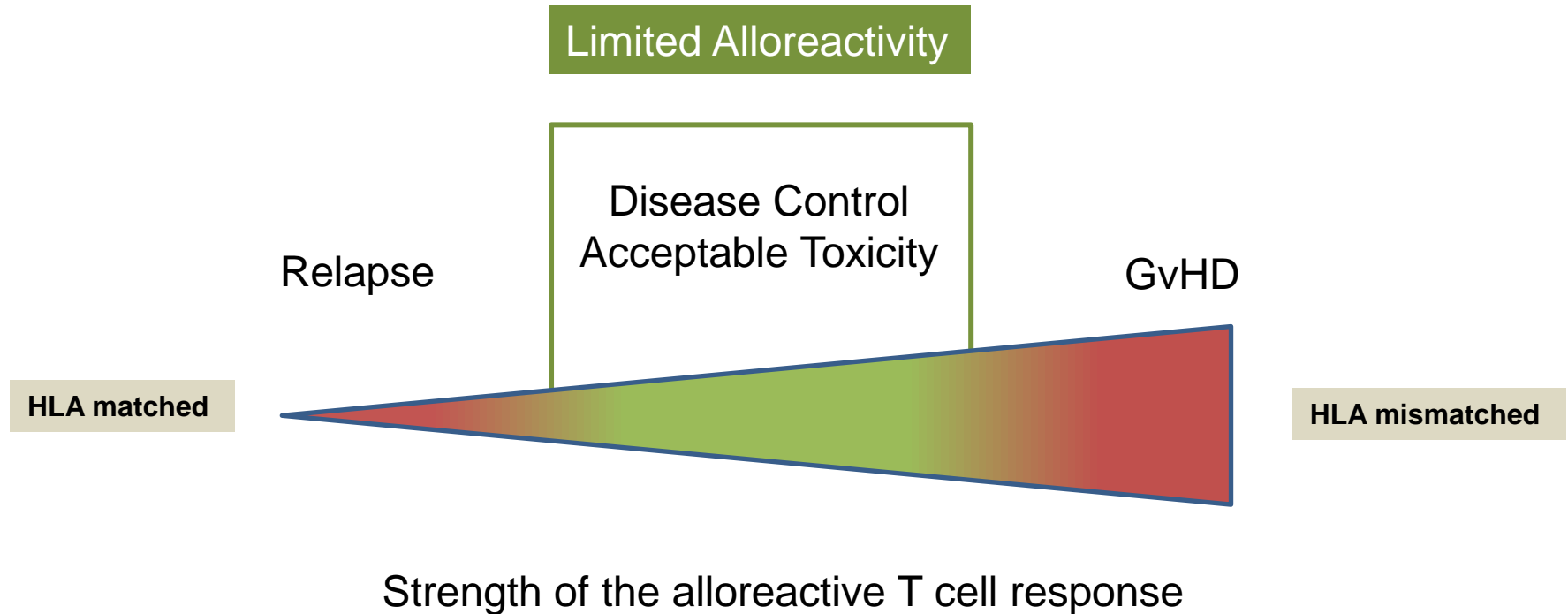


CIBMTR Summary Slides, 2018





# The Window of Opportunity



## GvHD Prophylaxis

- MUD: Methotrexate + Cyclosporine +/- ATG
- Haplo: Post-transplant Cyclophosphamide (PtCy)

# How to achieve Limited Alloreactivity?

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## T Cell Epitopes (TCE)

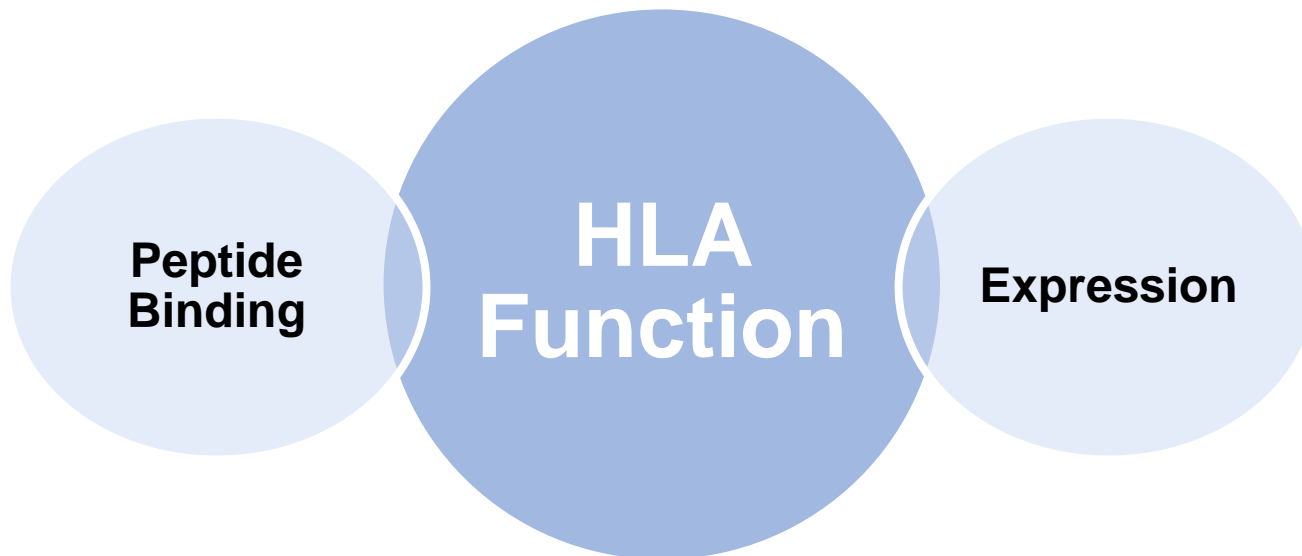
Tolerance to Self

Overall Alloresponse / TCR Diversity

## HLA Expression Levels

Genetic Regulation

Tissue / Cytokine Dependency



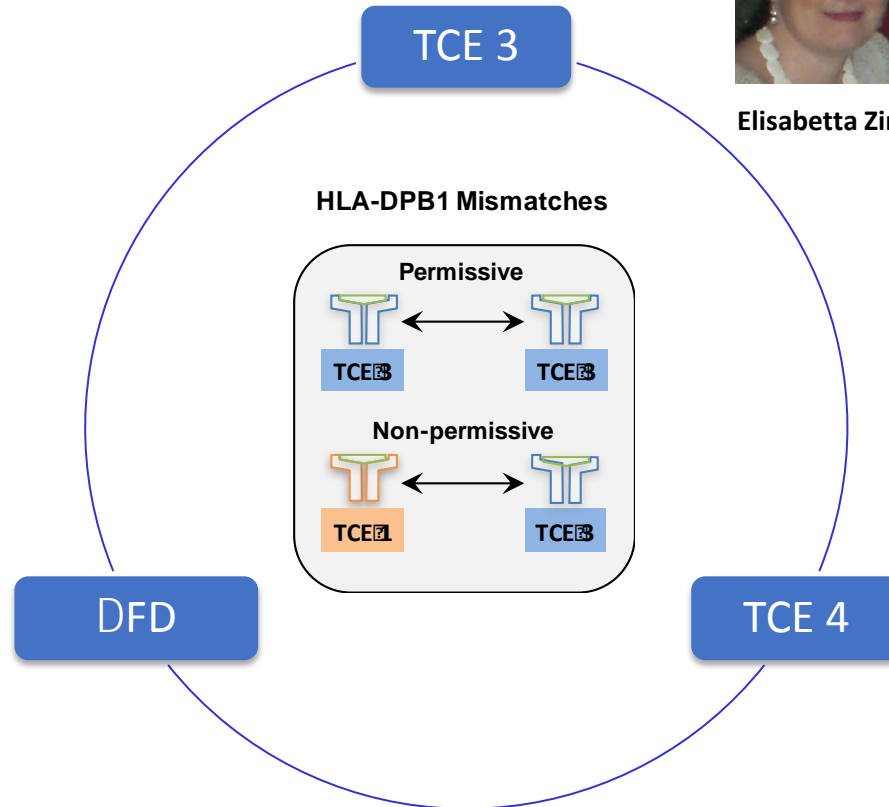
Combine Both?

# HLA-DP TCE Models



Elisabetta Zino

Zino, Blood 2004  
Fleischhauer, Lancet Oncol 2012  
Pidala, Blood 2014



Pietro Crivello

Crivello, Blood 2016  
Arrieta-Bolanos, Blood Adv 2018

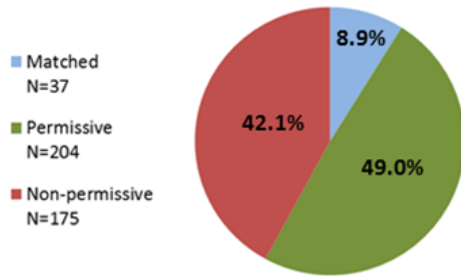


Roberto Crocchiolo

Crocchiolo, Blood 2009  
Lorentino, Haematologica 2019

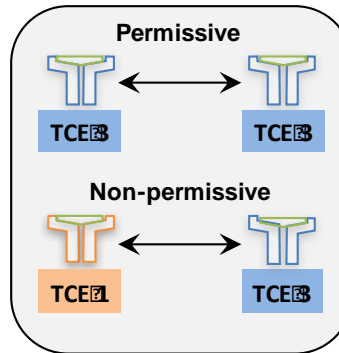
# Clinical Relevance: Survival

**TCE3**



**TCE 3**

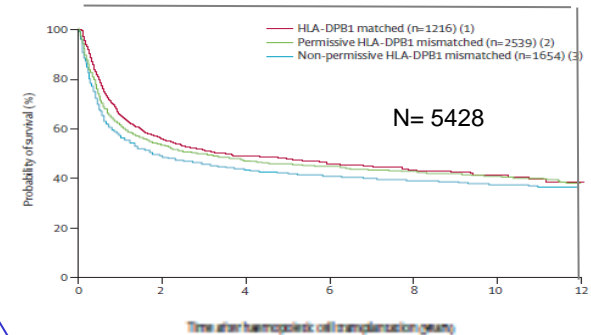
**HLA-DPB1 Mismatches**



**DFD**

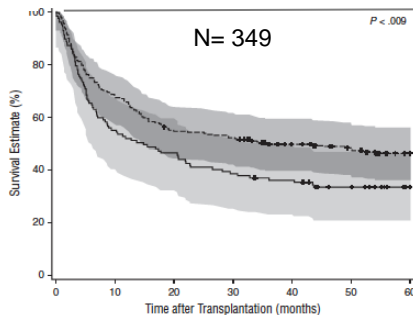
**TCE 4**

**15th IHIW**



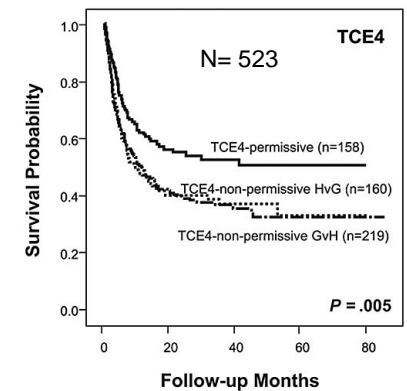
Fleischhauer, Lancet Oncol 2012

**Essen**



Crivello, Blood 2016

**IBMDR/GITMO**

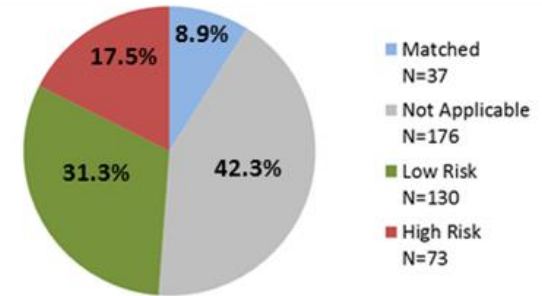


Crocchiolo, Blood 2009

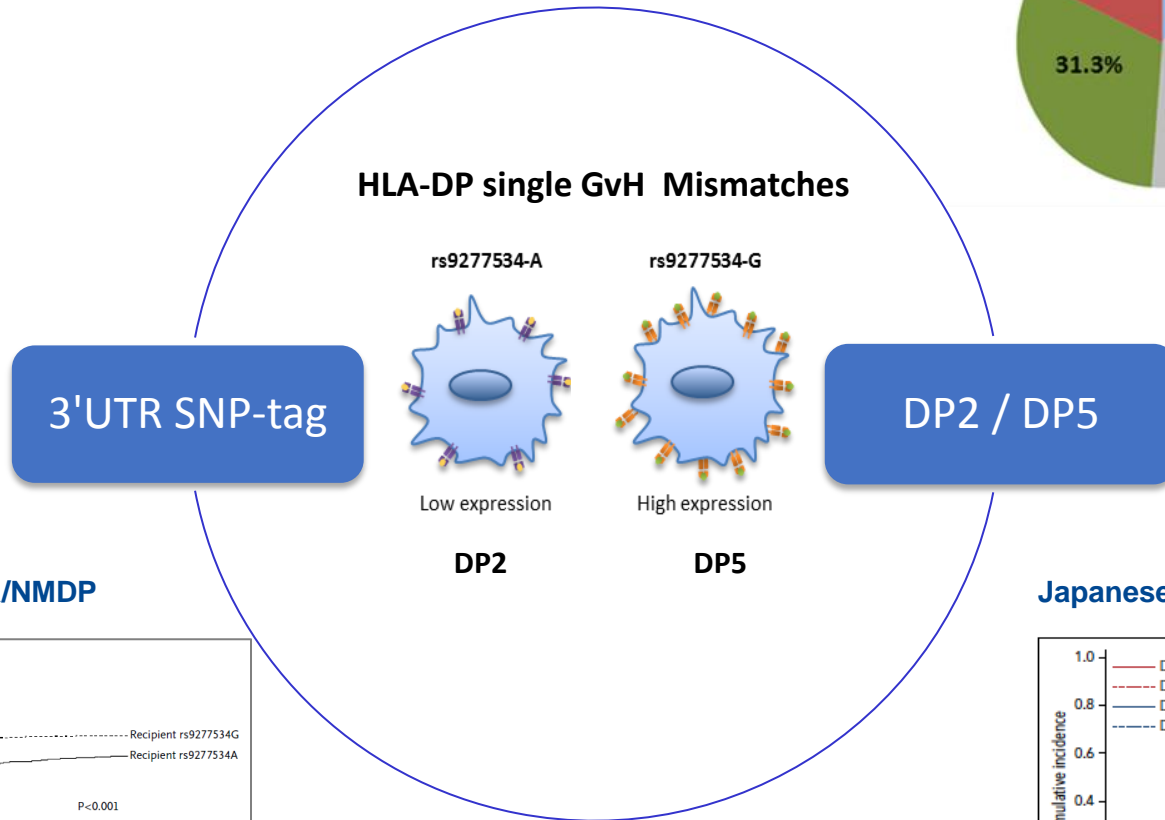


# HLA-DP Expression Models

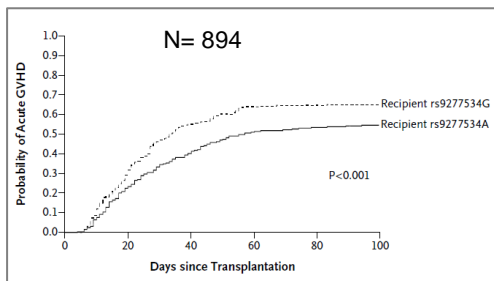
## Clinical Relevance: acute GVHD



### HLA-DP single GvH Mismatches

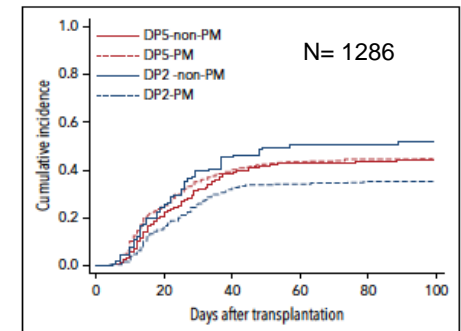


### CIBMTR/NMDP



Petersdorf, N Engl J Med 2015

### Japanese Marrow Donor Program



Morishima, Blood 2018

# Overlap TCE and Expression





## Linkage TCE – 3'UTR SNP

 TCE1  
 TCE2  
 TCE3

DPB1*-rs9277534-rs2281389 Haplotypes			
DPB1*	rs9277534	rs2281389	HLA-DP Expression Levels
02:01, 02:02, 04:01, 04:02, 17:01, 23:01, 40:01, 46:01, 55:01, 71:01, 94:01, 105:01, 128:01	A	A	 Low
01:01, 05:01, 11:01, 13:01, 15:01, 18:01, 19:01, 85:01	G	A	 High
03:01, 06:01, 09:01, 10:01, 14:01, 16:01, 20:01	G	G	 High

### TCE-Expression cross tabulation

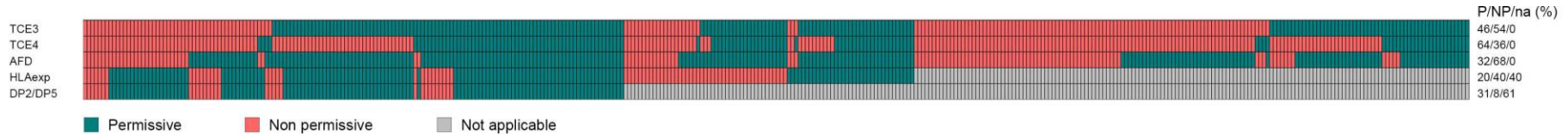
		Expression matching	
		Low Risk	High Risk
TCE group matching	Permissive	48.2%	15.8%
	Non-permissive	15.8%	20.2%

 Concordant Permissive/Low Risk  
N=98  
 Concordant Non-permissive/High Risk  
N=41  
 Discordant Permissive/High Risk  
N=32  
 Discordant Non-permissive/Low Risk  
N=32

**68.4% Concordance**

# Comparison between 5 Models

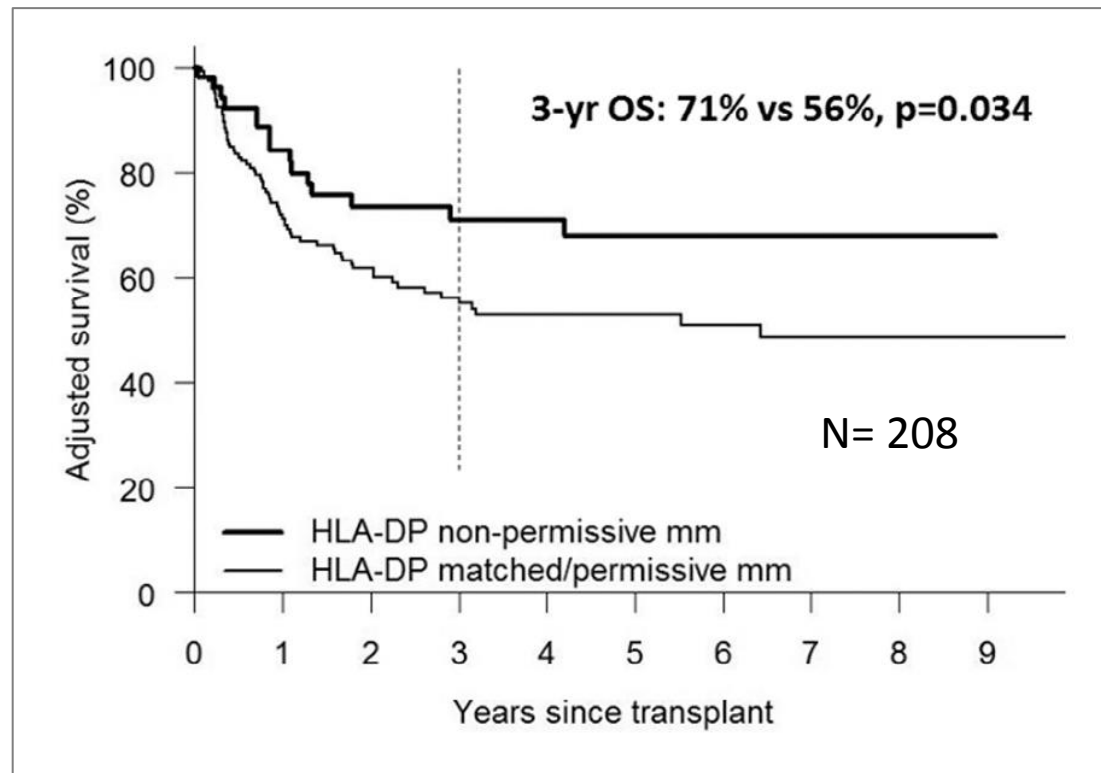
## Studio IBMDR / GITMO 2009-2016



	OS		GRFS		Relapse		NRM		aGvHD $\geq 2$		aGvHD $\geq 3$		cGvHD		Ext cGvHD	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
<b>TCE4<sup>1</sup>: NP vs P</b>	<b>1.7 (1.1-2.4) 0.008</b>		<b>1.4 (1.1-1.9) 0.01</b>		1.1 (0.7-1.7) 0.7		<b>1.9 (1.1-3.2) 0.01</b>		1.3 (0.8-2.1) 0.2		1.5 (0.7-3.2) 0.3		<b>1.7 (1.1-2.6) 0.02</b>		<b>3.6 (1.4-9.5) 0.01</b>	
<b>Matched vs P</b>	<b>2.1 (1.2-3.7) 0.01</b>		1.5 (0.9-2.4) 0.09		<b>2 (1.1-3.7) 0.03</b>		2 (0.9-4.8) 0.09		Not applicable <sup>o</sup>		Not applicable <sup>o</sup>		0.8 (0.3-2) 0.6		0.9 (0.1-7.5) 0.9	
<b>TCE3<sup>2</sup>: NP vs P</b>	1.1 (0.8-1.6) 0.5		1.1 (0.8-1.4) 0.5		1 (0.6-1.5) 0.9		1.1 (0.7-1.8) 0.6		1.2 (0.8-1.9) 0.4		1.4 (0.6-2.9) 0.4		1.2 (0.8-1.8) 0.4		1.7 (0.8-3.6) 0.1	
<b>Matched vs P</b>	1.6 (0.9-2.7) 0.09		1.2 (0.8-1.9) 0.3		<b>1.9 (1.1-3.4) 0.04</b>		1.4 (0.6-3) 0.4		Not applicable <sup>o</sup>		Not applicable <sup>o</sup>		0.6 (0.2-1.5) 0.3		0.5 (0.1-3.6) 0.5	
<b><math>\Delta</math>FD<sup>3</sup>: NP vs P</b>	1 (0.7-1.5) 0.8		1 (0.7-1.4) 0.9		1.3 (0.8-2) 0.3		0.9 (0.5-1.5) 0.7		0.9 (0.5-1.4) 0.6		0.8 (0.4-1.9) 0.6		1 (0.7-1.6) 0.9		0.9 (0.4-2.1) 0.9	
<b>Matched vs P</b>	1.5 (0.9-2.5) 0.1		1.2 (0.8-1.9) 0.4		<b>2 (1.1-3.6) 0.02</b>		1.3 (0.6-2.7) 0.5		Not applicable <sup>o</sup>		Not applicable <sup>o</sup>		0.6 (0.2-1.4) 0.2		0.3 (0.1-2.5) 0.3	
<b>Expression<sup>4</sup>: high vs low risk</b>	1 (0.6-1.6) 0.9		0.8 (0.5-1.2) 0.2		0.6 (0.3-1.1) 0.1		1.1 (0.6-2.2) 0.7		<b>2.2 (1.1-4.2) 0.02</b>		1.9 (0.6-6.2) 0.3		1.2 (0.7-2.2) 0.4		1.7 (0.6-4.5) 0.3	
<b>Matched vs low risk</b>	1.6 (0.9-2.8) 0.08		1.1 (0.7-1.7) 0.7		1.4 (0.7-2.5) 0.3		1.5 (0.7-3.4) 0.3		Not applicable <sup>o</sup>		Not applicable <sup>o</sup>		0.7 (0.3-1.7) 0.4		0.5 (0.1-3.7) 0.3	
<b>DP2/DP5<sup>5</sup>: high vs low risk</b>	1.2 (0.5-2.5) 0.7		0.8 (0.5-1.6) 0.6		0.9 (0.4-2.2) 0.8		1.3 (0.5-3.7) 0.6		<b>3.8 (1.5-9.6) 0.006</b>		<b>6.9 (1.5-31) 0.01</b>		1.1 (0.4-3.1) 0.8		4.1 (1-17) 0.05	
<b>Matched vs low risk</b>	1.8 (1-3.2) 0.05		1 (0.6-1.7) 0.9		1.6 (0.8-3.2) 0.2		1.5 (0.6-3.7) 0.3		Not applicable <sup>o</sup>		Not applicable <sup>o</sup>		0.5 (0.2-1.5) 0.2		0.6 (0.1-4.7) 0.6	

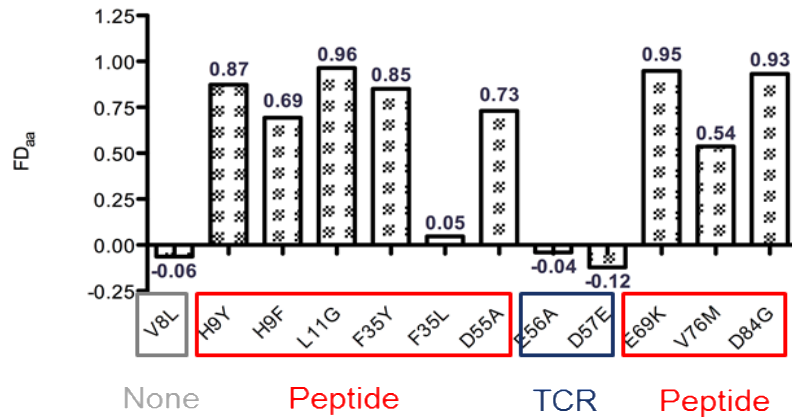
# PtCy: A Game Changer?

## Survival after haploidentical HSCT



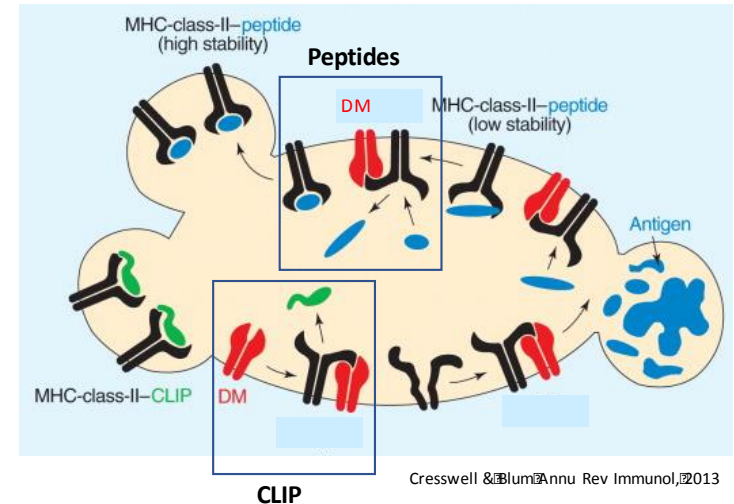
# Non-Classical HLA-DM: Role in TCE?

Peptide Contact Residues



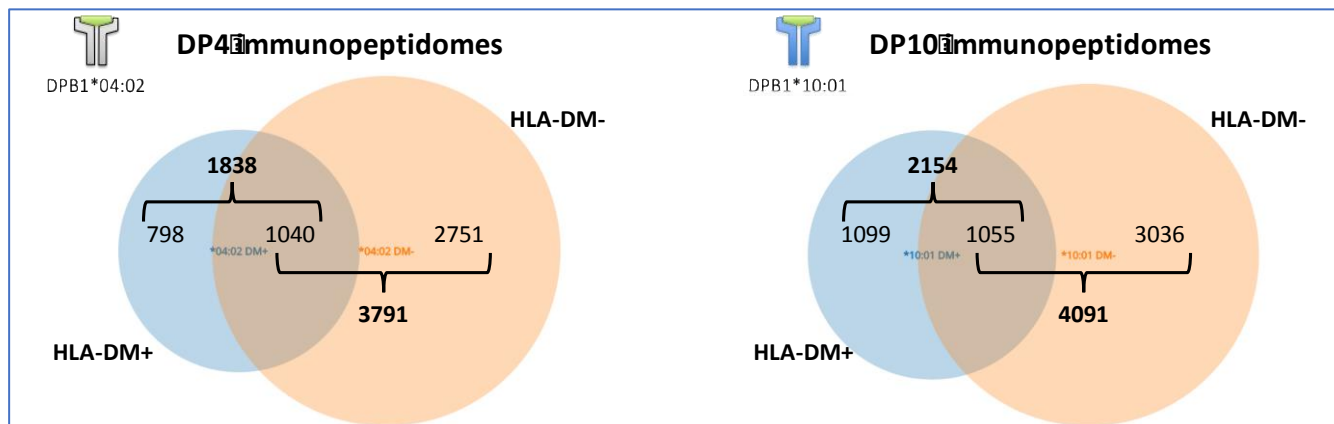
Crivello et al. Blood, 2016

HLA-DM edits Class II peptides



Cresswell & Blum Annu Rev Immunol, 2013

Peptide Mass Spectrometry of TCE3 vs TCE1

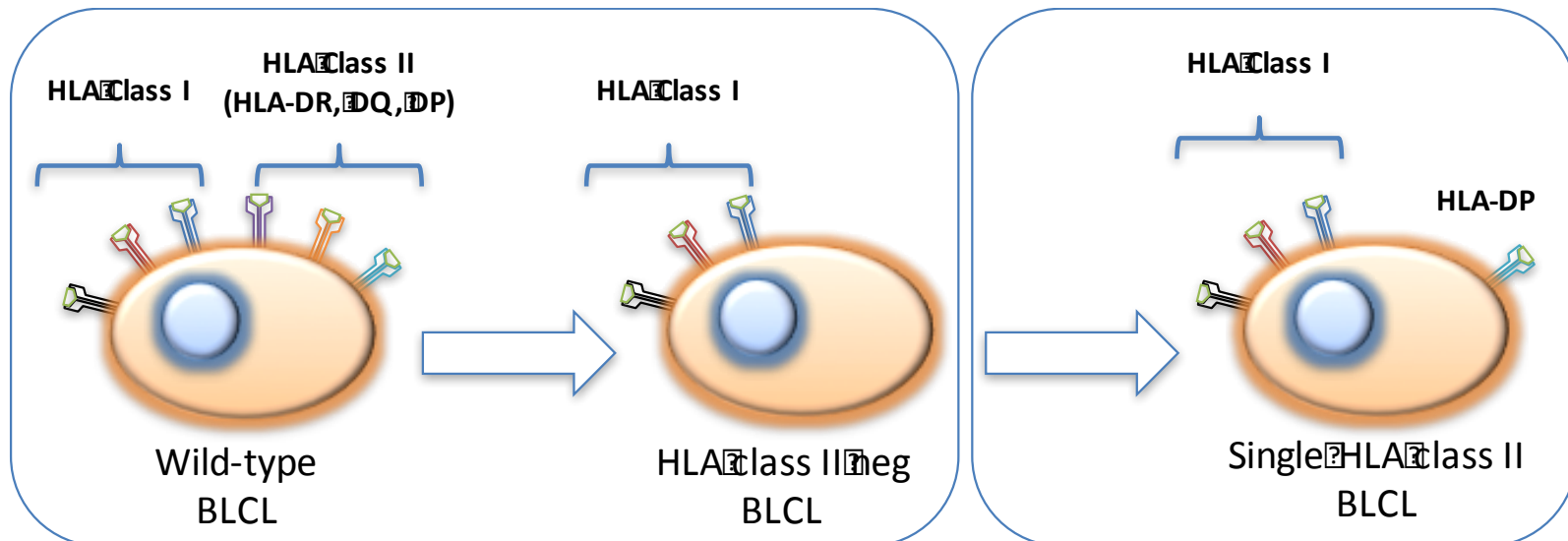


# Single HLA-DP expressing BLCL

## Multiple Knockout of Classical HLA Class II $\beta$ -Chains by CRISPR/Cas9 Genome Editing Driven by a Single Guide RNA

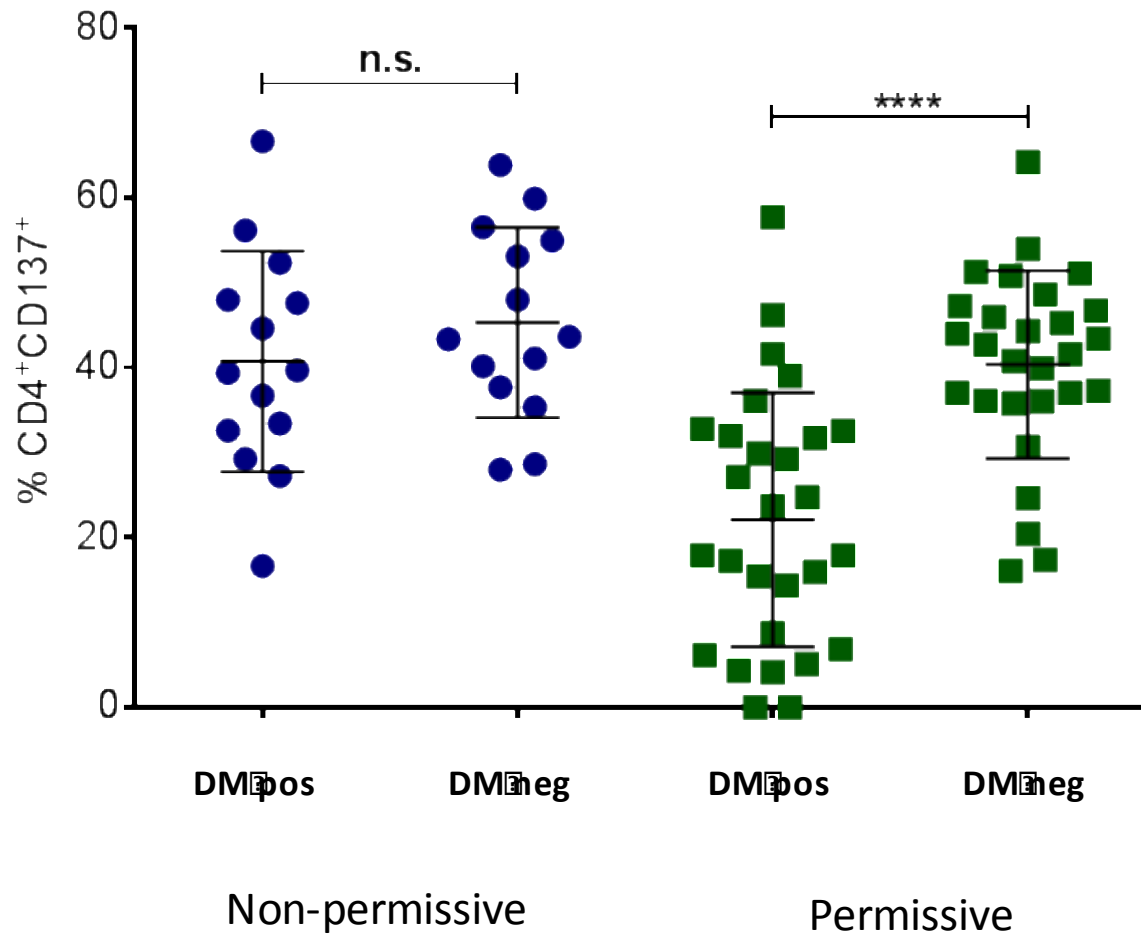
The Journal of Immunology

Pietro Crivello,\* Müberra Ahci,\* Fabienne Maaßen,\* Natalie Wossidlo,<sup>†</sup>  
Esteban Arrieta-Bolaños,\* Andreas Heinold,<sup>†</sup> Vinzenz Lange,<sup>‡</sup> J. H. Frederik Falkenburg,<sup>§</sup>  
Peter A. Horn,<sup>†</sup> Katharina Fleischhauer,\* and Stefan Heinrichs<sup>†</sup>

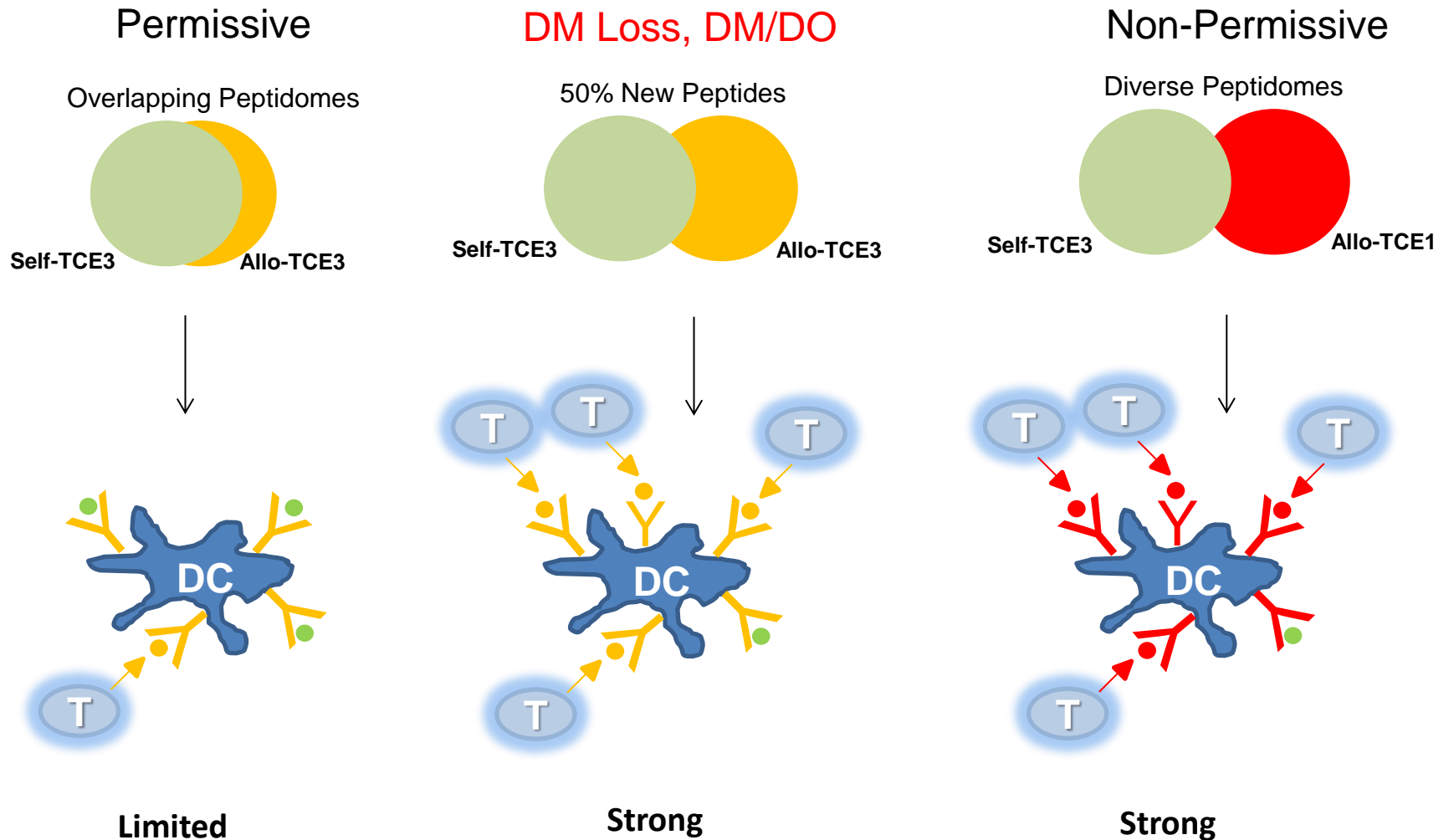




# HLA-DM mediates Permissiveness



# HLA-DM mediates Limited Alloreactivity



# Take Home Messages

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- >65% Allo-HSCT have HLA Mismatches (MUD, Haplo, Cord)
- Permissive / Low Risk by Limited T Cell Alloreactivity
- Overlap between TCE and Expression due to LD in HLA-DP
- TCE associates with Mortality, Expression with aGvHD
- PtCy is a likely Game Changer: Advantage of Non-Permissive for Relapse?
- Peptide Diversity and Editing by HLA-DM regulate T Cell Alloreactivity

# Acknowledgements



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