# Permissività delle incompatibilità HLA nel trapianto di cellule staminali emopoietiche

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AIBT Summer School, Favignana, 5 Giugno 2015

# Indice

- Cenni sulla risposta alloimmune
- Perché è necessario studiare la permissività delle incompatibilità (MM) HLA ?
- Studio della permissività:
  - alloriconoscimento diretto
  - alloriconoscimento indiretto
- Considerazioni conclusive

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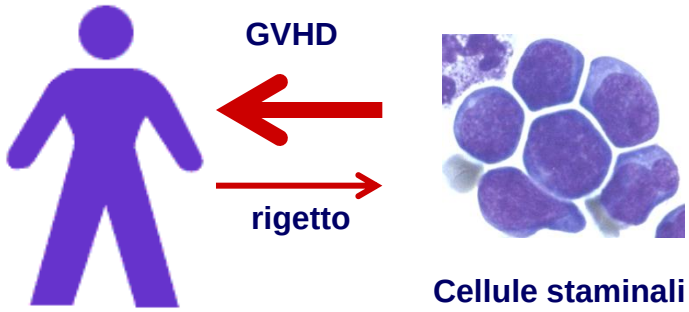
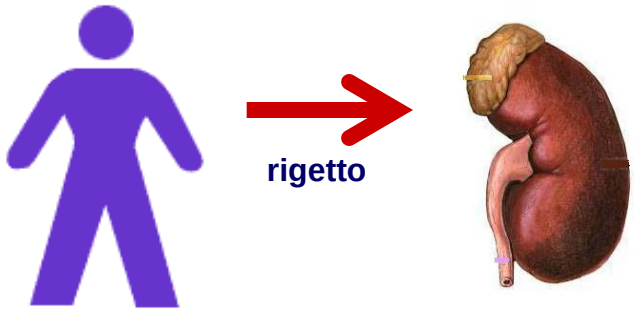
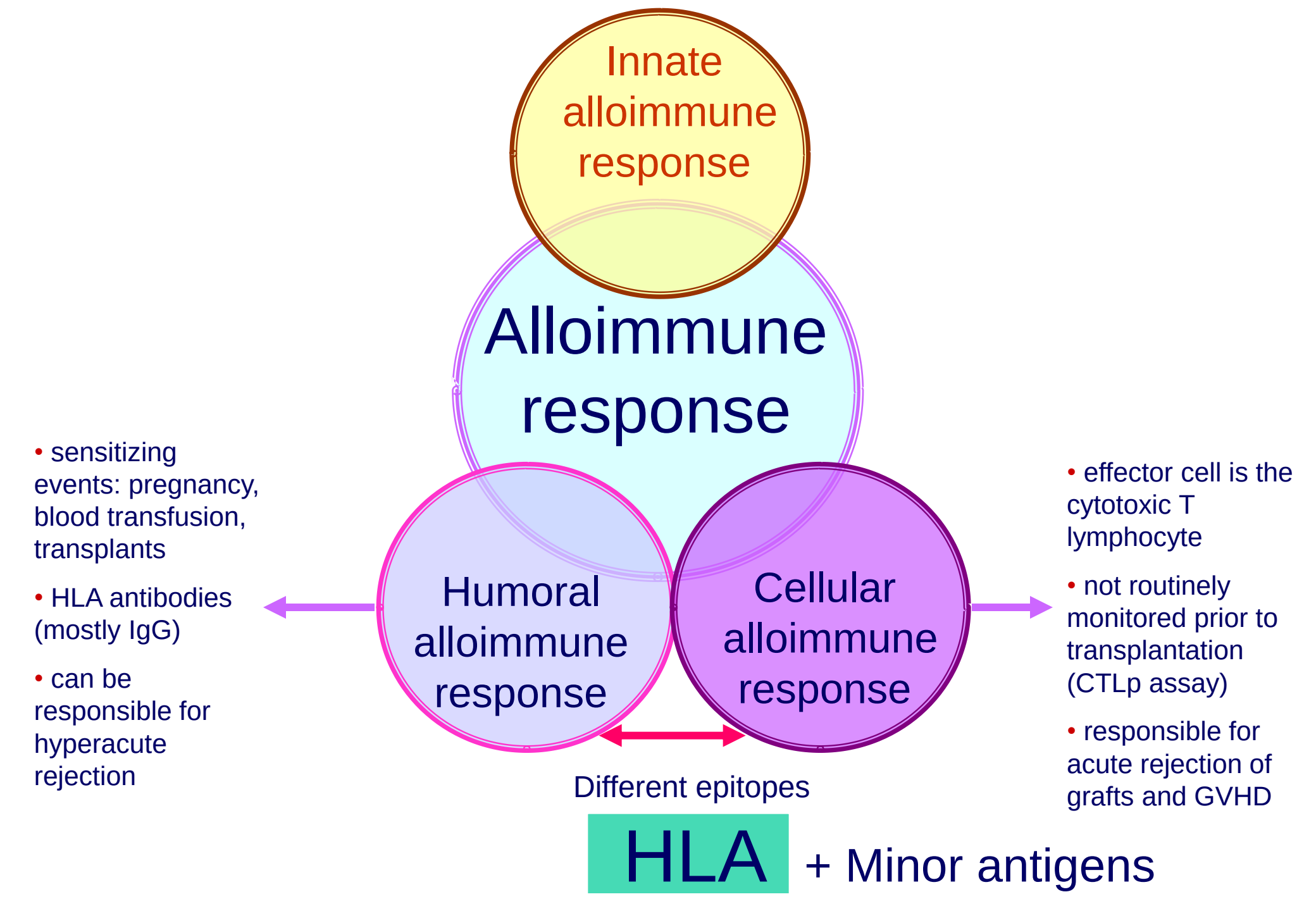
# La risposta alloimmune

- Capacità del sistema immunitario di riconoscere polimorfismi codificati geneticamente, appartenenti a cellule non-self (allogeniche)
- I principali bersagli della risposta immune ai tessuti allogenici sono le molecole **HLA**

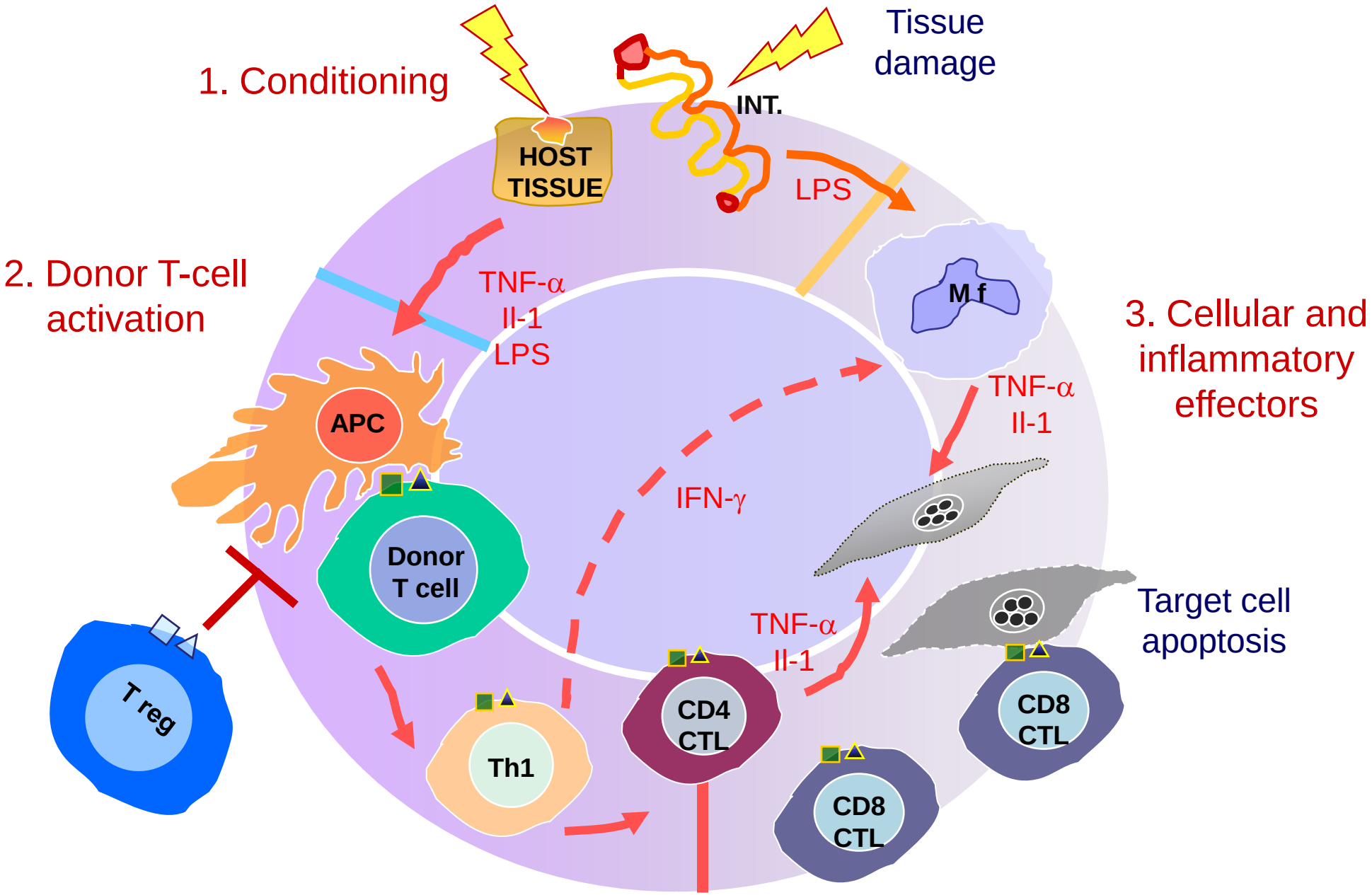


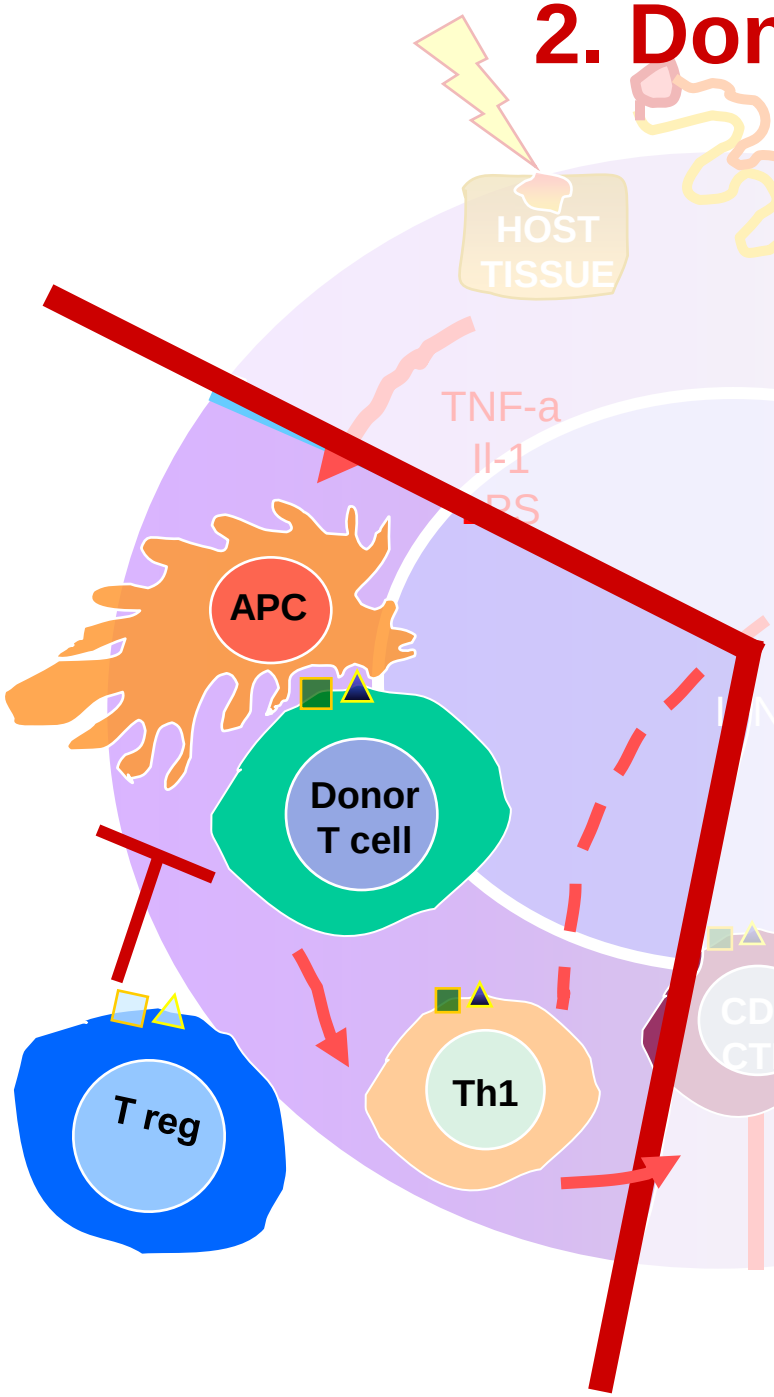

- La risposta dei linfociti T alle molecole HLA allogeniche è PARTICOLARMENTE forte, ma altre molecole polimorfiche codificate fuori dal sistema MHC (antigeni minori) possono dare origine a una risposta alloimmune


Innate alloimmune response
Alloimmune response
• sensitizing events: pregnancy, blood transfusion, transplants
• HLA antibodies (mostly IgG)
• can be responsible for hyperacute rejection
Humoral alloimmune response
Cellular alloimmune response
• effector cell is the cytotoxic T lymphocyte
• not routinely monitored prior to transplantation (CTLp assay)
• responsible for acute rejection of grafts and GVHD
Different epitopes
HLA
+ Minor antigens

# GVHD: a complicated inflammatory disease (J.L.Ferrara)



# 2. Donor T-cell activation




**Is the core of aGVHD:**

- **donor T-lymphocytes recognise mismatches in MHC molecules or minor histocompatibility antigens**
- **donor T-lymphocytes proliferate and differentiate**
- **is influenced by phase 1, which increases expression of costimulatory molecules**

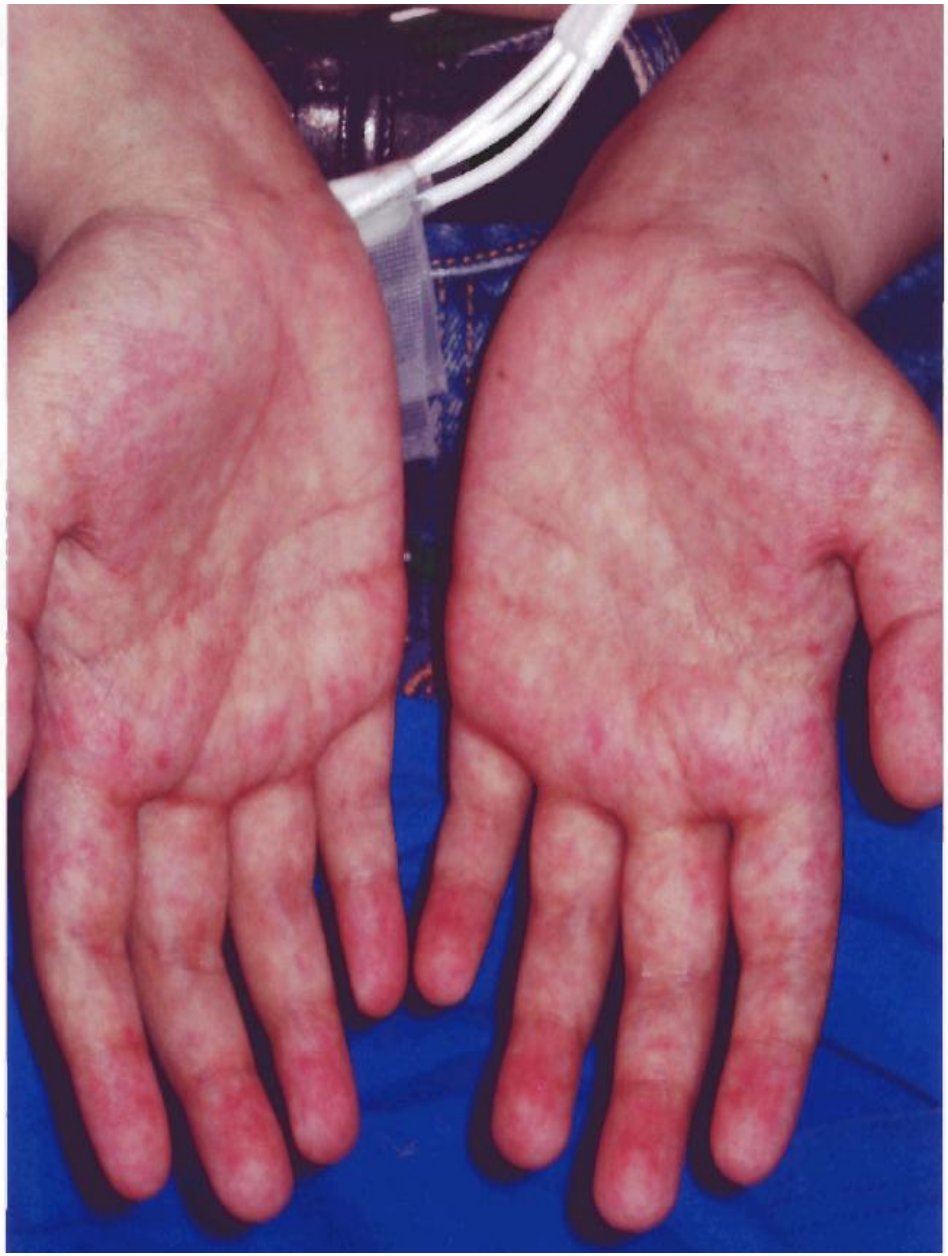
## Cytokine storm


1. Activates APCs

and enhances alloantigen presentation

2. Recruits effector cells to target organs via induction of inflammatory cytokines

3. Directly causes tissue necrosis



Acute GVHD of the skin (Grade I). Photograph courtesy of J. Levine, M.D.

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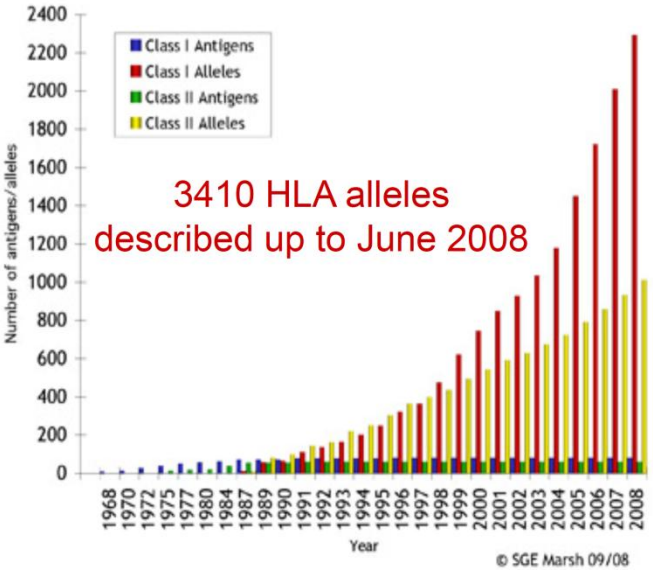
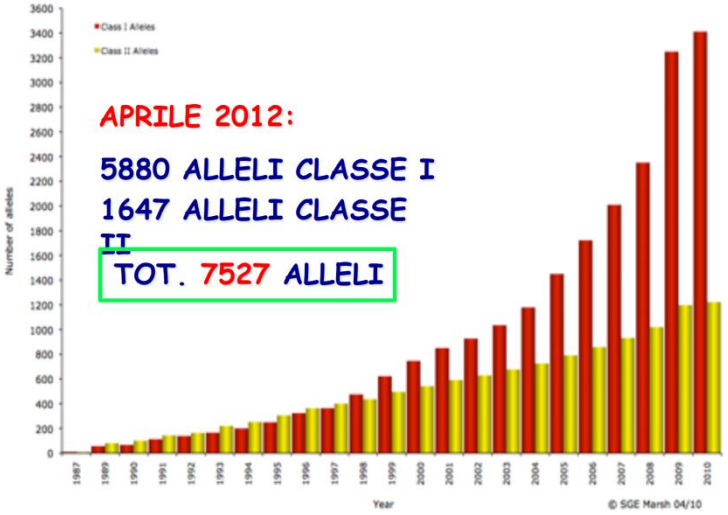



3410 HLA alleles described up to June 2008

## POLIMORFISMO DEL SISTEMA HLA

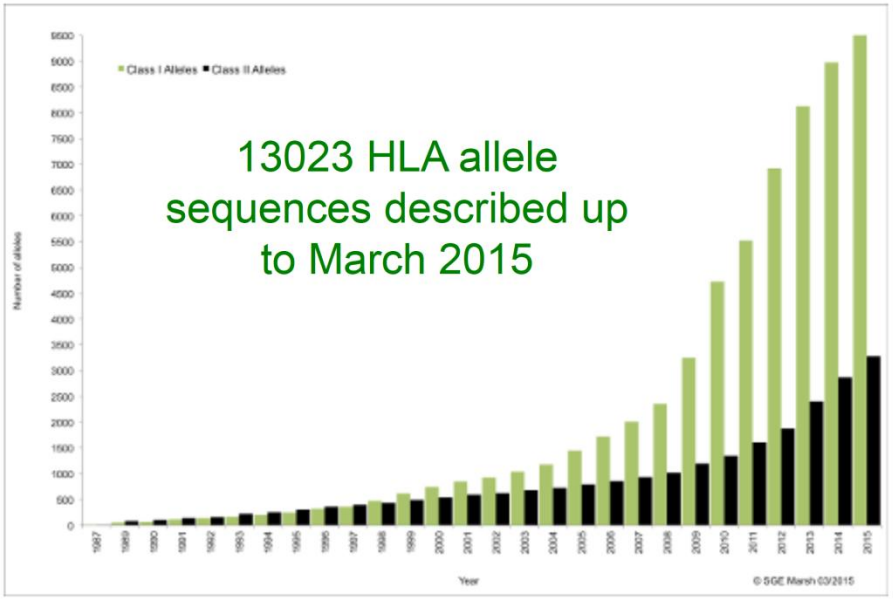



APRILE 2012:

5880 ALLELI CLASSE I

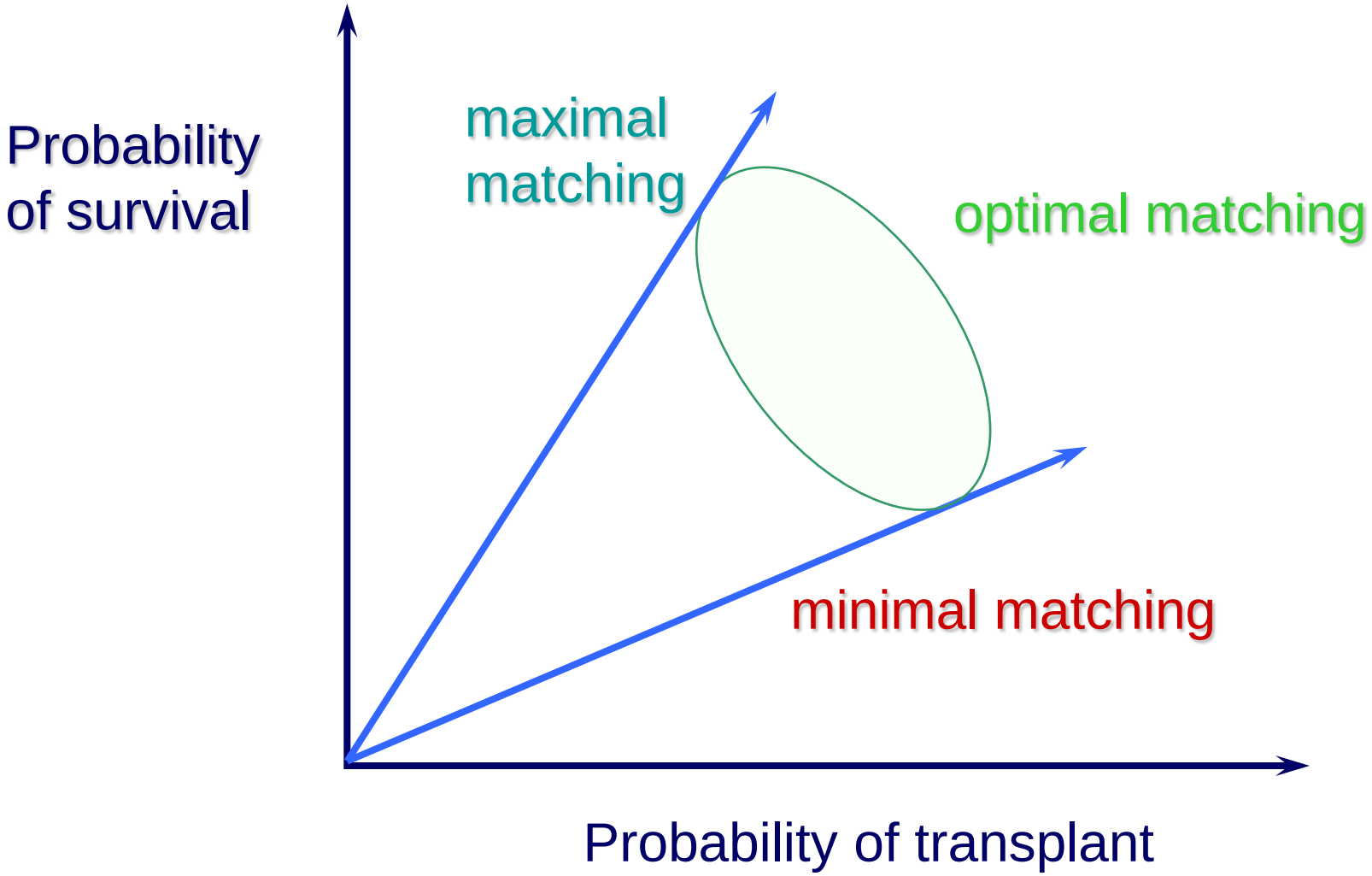
1647 ALLELI CLASSE II

TOT. 7527 ALLELI




13023 HLA allele sequences described up to March 2015

# We do not know what the optimal matching is at the moment. John Hansen, EFI 1998



# BONE MARROW–ALLOGRAFT REJECTION BY T LYMPHOCYTES RECOGNIZING A SINGLE AMINO ACID DIFFERENCE IN HLA-B44

KATHARINA FLEISCHHAUER, M.D.,
NANCY A. KERNAN, M.D.,
RICHARD J. O'REILLY, M.D.,
BO DUPONT, M.D., D.SC.,
AND SOO YOUNG YANG, PH.D.

**NEJM, 1990**

This case report demonstrates that a structural HLA Class I incompatibility limited to the substitution of a single amino acid, in the clinical setting of the transplantation of allogeneic bone marrow from an unrelated donor, depleted of T lymphocytes, can be recognized as a major histocompatibility barrier.

E’ sufficiente una differenza minima, pari a un singolo amino acido, per indurre una reazione alloimmune molto severa

MA

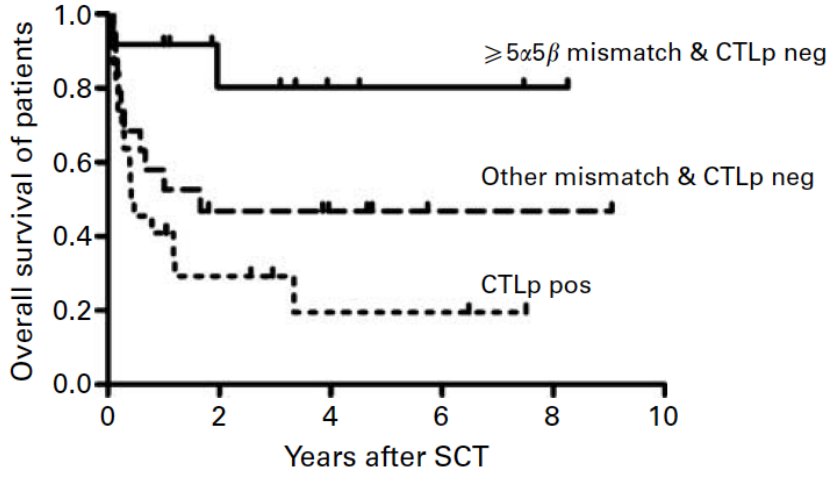
alcune incompatibilità HLA, assai diverse tra di loro, sono PERMISSIBILI

# Highly diverged MHC class I mismatches are acceptable for haematopoietic stem cell transplantation

MBA Heemskerk[1,2], JJ Cornelissen[3], DL Roelen[1], JJ van Rood[1,2], FHJ Claas[1], IIN Doxiadis[1] and M Oudshoorn[1,2]

[1]*Department of Immunohaematology and Blood Transfusion, Leiden University Medical Center, Leiden, The Netherlands;* [2]*Europdonor Foundation, Leiden, The Netherlands and* [3]*Department of Haematology, Erasmus MC/Daniel den Hoed, Rotterdam, The Netherlands*

Bone Marrow Transplantation (2007) 40, 193–200




CTLp

**Figure 2** Overall patient survival after SCT correlated with the CTLp assay outcome and $\geqslant 5\alpha 5\beta$ mismatch category. The number of pairs in each group: 12 pairs with a $\geqslant 5\alpha 5\beta$ MHC class I difference and negative CTLp assay, 19 pairs with another single MHC class difference and a negative CTLp assay and 22 pairs with a positive CTLp assay. Recipients with a negative CTLp assay outcome and a $\geqslant 5\alpha 5\beta$ MHC class I difference with the donor had a superior chance of survival compared to the other groups (hazard ratio = 0.144; 95% CI = (0.033–0.633); $P = 0.010$).

# High-risk HLA allele mismatch combinations responsible for severe acute graft-versus-host disease and implication for its molecular mechanism

Takakazu Kawase

Blood, 1 October 2007

**5210 transplants 1993-2006**

**Diseases included: ALL, ANLL, CML, MDS, hereditary disease, lymphoma, MM, AA, other**

**High-resolution HLA typing**

**HLA-A, B, C, DRB1, DQB1, DPB1**

**Table 1. Multivariable analysis of impact of mismatch pairs for sever aGVHD in HLA-A and -C**

| Mismatch combination, donor-patient | N | HR (95% CI) | *P* |
|---|---|---|---|
| **A locus match** | 4510 | 1 | NA |
| A0201-A0206 | 138 | 1.23 (0.87-1.73) | .223 |
| A0206-A0201 | 131 | 1.78 (1.32-2.41) | < .001 |
| * A0201-A0207 | 28 | 0.83 (0.34-2.03) | .699 |
| A0207-A0201 | 20 | 1.12 (0.42-3.02) | .809 |
| A0201-A0210 | 11 | 1.57 (0.58-4.23) | .367 |
| * A0206-A0207 | 27 | 3.45 (2.09-5.70) | < .001 |

**Table 2. Nonpermissive allele mismatch combinations for severe aGVHD**

| Mismatch combination, donor-patient | N | HR (95% CI) | *P* |
|---|---|---|---|
| A0206-A0201 | 131 | 1.78 (1.32-2.41) | < .001 |
| A0206-A0207 | 27 | 3.45 (2.09-5.70) | < .001 |
| A2602-A2601 | 21 | 3.35 (1.89-5.91) | < .001 |
| A2603-A2601 | 35 | 2.17 (1.29-3.64) | .003 |
| B1501-B1507 | 19 | 3.34 (1.85-5.99) | < .001 |
| C0303-C1502 | 25 | 3.22 (1.75-5.89) | < .001 |
| C0304-C0801 | 69 | 2.34 (1.55-3.52) | < .001 |
| C0401-C0303 | 42 | 2.81 (1.72-4.60) | < .001 |
| C0801-C0303 | 80 | 2.32 (1.58-3.40) | < .001 |
| C1402-C0304 | 23 | 3.66 (2.00-6.68) | < .001 |
| C1502-C0304 | 27 | 3.77 (2.20-6.47) | < .001 |
| C1502-C1402 | 50 | 4.97 (3.41-7.25) | < .001 |
| DR0405-DR0403 | 53 | 2.13 (1.28-3.53) | .003 |
| (DR1403-DQ0301)-(DR1401-DQ0502) | 19 | 2.81 (1.44-5.51) | .002 |
| DP0301-DP0501 | 49 | 2.41 (1.49-3.89) | < .001 |
| DP0501-DP0901 | 71 | 2.03 (1.30-3.16) | .002 |

T. Kawase et al. Blood 2007

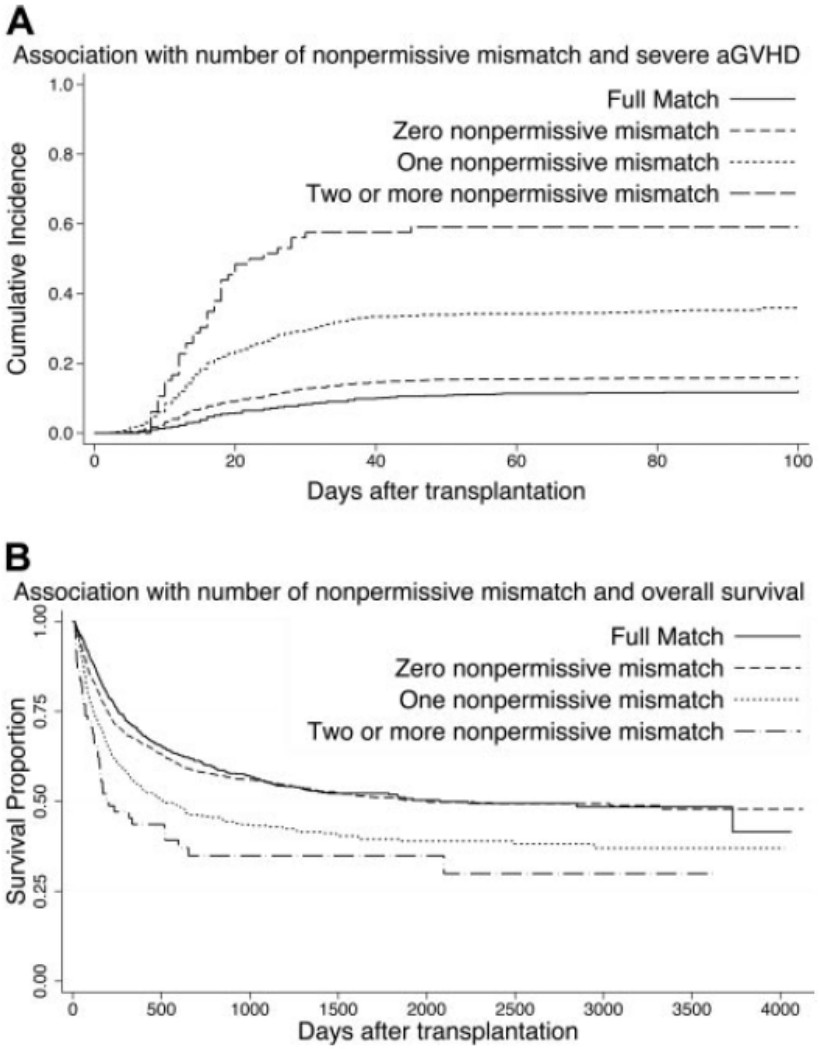



**Figure 1. Impact of number of nonpermissive mismatches on severe aGVHD and overall survival.** (A) Cumulative incidence of severe aGVHD according to number of nonpermissive mismatches. — indicates full match (in HLA-A, -B, -C, -DRB1, -DQB1, and -DPB1) group; ----, zero nonpermissive mismatch (with mismatches other than nonpermissive mismatches) group; ····, one nonpermissive mismatch (with or without mismatches other than nonpermissive mismatches) group; and – – –, 2 or more nonpermissive mismatches (with or without mismatches other than nonpermissive mismatches) group. (B) Kaplan-Meier estimates of survival according to number of nonpermissive mismatches. Each group was divided as described for panel A.

- The identification of high-risk nonpermissive mismatch, would be beneficial for the selection of a suitable donor

T. Kawase et al. Blood 2007

# Importanza di caratterizzare la permissibilità dei MM HLA

- Consentirebbe di selezionare la coppia ricevente-donatore ottimale, riducendo le complicanze post-trapianto

TUTTAVIA

- Sono necessari grandi numeri di riceventi-donatori per valutare tutte le combinazioni
- Siamo ancora ai primi passi

*Review Article*

# Unrelated Hematopoietic Stem Cell Donor Matching Probability and Search Algorithm

**J.-M. Tiercy**
**2012**

Table 1: Parameters that contribute to define a low probability estimate.

| HLA, ethnicity, nb donors | Examples and comments |
|---|---|
| ≤3 donors in BMDW | |
| Non-European ancestry | |
| Rare[(1)] allele at any locus | A*02:17, B*44:05, DRB1*11:03 |
| Rare B-C association | B*18:01-C*02:02, B*51:01-C*16:02 |
| Rare DRB1-DQB1 association | DRB1*15:01-DQB1*06:03, DRB1*0701-DQB1*03:02 |
| B*15:01, B*18:01, B*27:05, B*51:01-positive haplotypes | Higher risk of C MM |
| B*35:02/35:03/35:08-positive haplotypes | Higher risk of B*35 allele MM |

[(1)] <5% of the alleles included a given serotype.

Based on our experience of the last 10 years, still 2–5% of the patients do have a unique phenotype (not necessarily including a rare HLA variant) that is not represented in the 20 million donors-BMDW registry. A German study based on 2008-2009 searches reported a 3.3% rate [13]. The ratio is expected to be higher for patients of non-European ancestry.

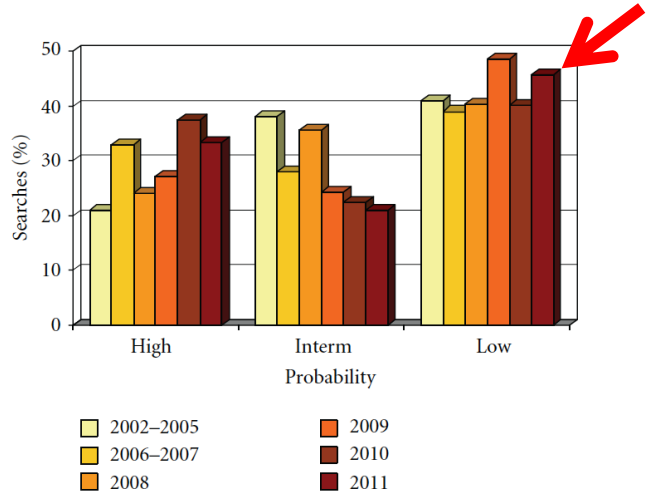



Figure 1: Relative distribution of 1244 high, intermediate, and low probability searches run from 2002 to 2011. The 2002–2005 probability estimates have been reported previously [6].

# Alloriconoscimento diretto e indiretto

•Prima di affrontare gli strumenti che abbiamo a disposizione per valutare la permissibilità dei MM HLA, è necessario ricordare che ci sono due strade (pathways) di alloriconoscimento: diretto e indiretto

# Allorecognition Pathways in Transplant Rejection and Tolerance

*Jason M. Ali, Eleanor M. Bolton, J. Andrew Bradley, and Gavin J. Pettigrew*

*Transplantation* • Volume 96, Number 8, October 27, 2013



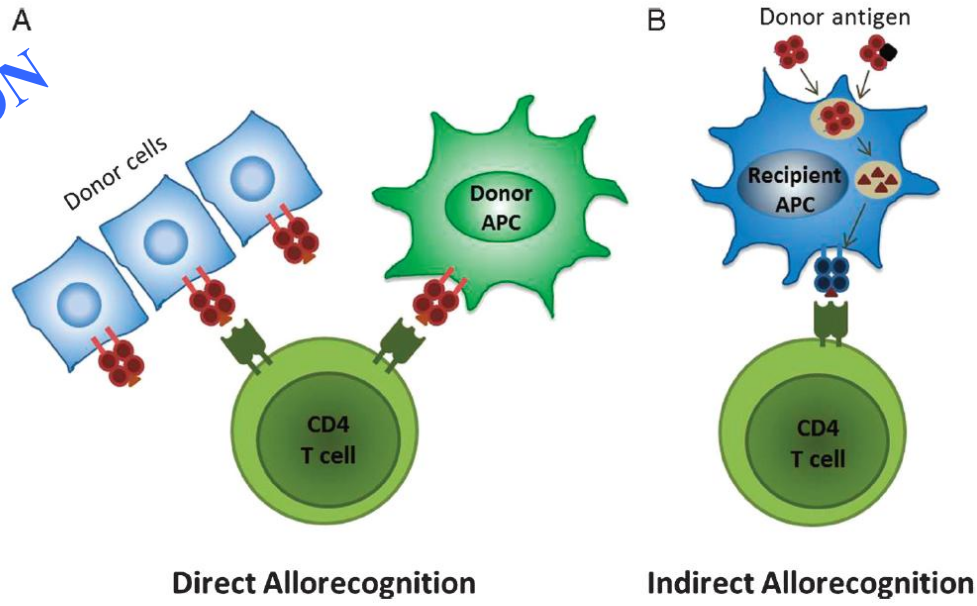
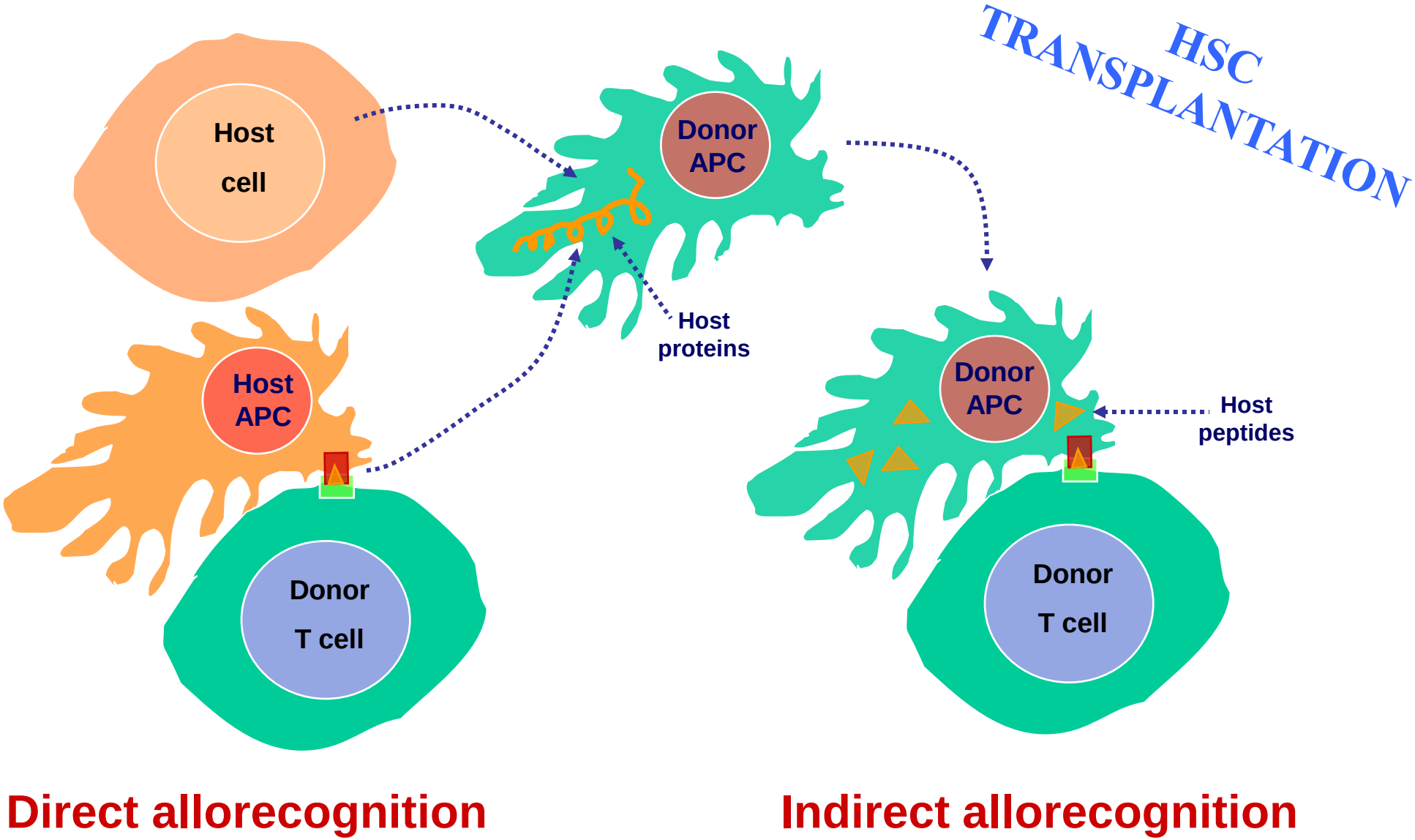



**FIGURE 1.** Direct and indirect allorecognition. A, direct allorecognition: recipient CD4 T cells recognize intact MHC class II alloantigen. This is present on donor APCs migrating from the graft and on MHC class II–expressing donor parenchymal cells. B, indirect allorecognition: donor alloantigen is internalized, processed, and presented as peptides in the context of recipient MHC class II by recipient APCs to recipient CD4 T cells.

# Presentation of alloantigen




## Direct allorecognition

## Indirect allorecognition

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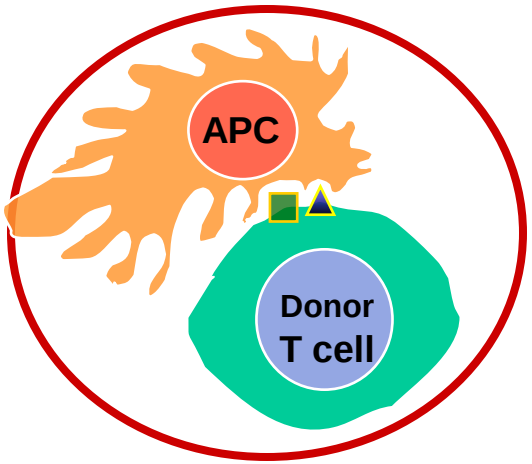



# Studio della permissività dei MM
# HLA: alloriconoscimento diretto

- Test *in vitro*

➢ Cytotoxic Lymphocyte Precursor Assay (CTLp)

- Modelli *in silico*

➢ T cell epitope

➢ Histocheck

➢ Matchmaker (per trapianto d'organi)

➢ Posizioni specifiche di amino acidi

# Cytotoxic Lymphocyte Precursor Assay (CTLp)

- Valuta l'estensione della risposta dei linfociti T alloreattivi nei confronti delle molecole HLA allogeniche
- Utile per distinguere i MM permissibili dai non permissibili
- Elevata frequenza dei CTLp correla sia con i risultati dei trapianti d'organo che degli HSCT

*Immunology*, 1968, **14**, 181.

# Quantitative Assay of the Lytic Action of Immune Lymphoid Cells on $^{51}$Cr-Labelled Allogeneic Target Cells *In vitro*; Inhibition by Isoantibody and by Drugs

K. T. Brunner, J. Mauel, J.-C. Cerottini and B. Chapuis

*Swiss Institute for Experimental Cancer Research, Lausanne, and Institute of Biochemistry, University of Lausanne, Switzerland*

(*Received* 15*th May* 1967)

# Cytotoxic Lymphocyte Precursor Assay (CTLp)

- LIMITI:
  - ➢ difficile da eseguire
  - ➢ tempi di esecuzione lunghi
  - ➢ poco standardizzabile

- Trasformazione in algoritmo in grado di predire l'alloreattività, ma non si è rivelato utile nel HSCT

# Functional versus structural matching: can CTLp test be replaced by HLA allele typing?

*M. Oudshoorn, Human Immunology 2002*

- HLA class I MM are significantly associated with CTLp frequencies (211 cases, $p<0.001$)

- Exceptions:
  - high CTLp in 14% of matched pairs
  - low CTLp in 7% of HLA-A,B MM pairs
  - successful outcome in the MM pairs with negative CTLp

- CTLp can be used as a tool to detect permissible MM when no fully matched donor is available

# A T-cell epitope encoded by a subset of HLA-DPB1 alleles determines nonpermissive mismatches for hematologic stem cell transplantation

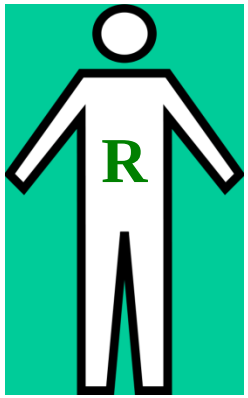
Elisabetta Zino, Guido Frumento, Sarah Marktel, Maria Pia Sormani, Francesca Ficara, Simona Di Terlizzi, Anna Maria Parodi, Ruhena Sergeant, Miryam Martinetti, Andrea Bontadini, Francesca Bonifazi, Daniela Lisini, Benedetta Mazzi, Silvano Rossini, Paolo Servida, Fabio Ciceri, Chiara Bonini, Edoardo Lanino, Giuseppe Bandini, Franco Locatelli, Jane Apperley, Andrea Bacigalupo, Giovanni Battista Ferrara, Claudio Bordignon, and Katharina Fleischhauer

**Blood. 2004;103:1417-1424**

## T cell epitope model

- Il primo modello clinicamente rilevante che stima con successo, l'effetto dell'alloriconoscimento diretto

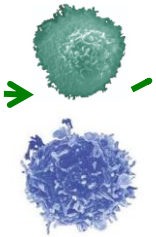
# T cell epitope
# K. Fleischhauer et al, 2004




DPB1*02:01,
04:02

Rigetto


DPB1*02:01,
09:01



2 cloni alloreattivi che riconoscono in modo DIRETTO, il MM DPB1

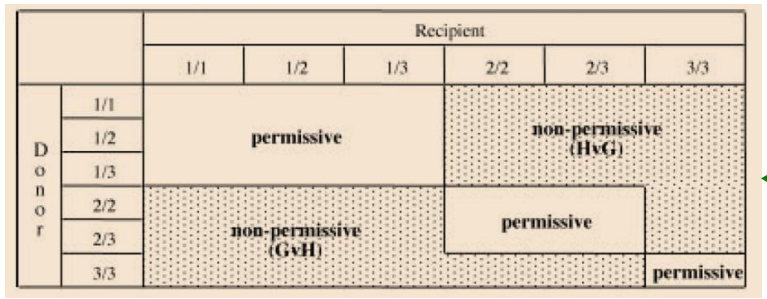
I due cloni sono stati testati con cellule con DPB1 diversi

**Table 2. Classification of HLA-DPB1 alleles according to their predicted immunogenicity**

| Groups† | HLA-DPB1* | Frequencies | | |
|---|---|---|---|---|
| | | White | Asian | African |
| 1 | 0901, 1001, 1701 | 0.018 | 0.025 | 0.325 |
| 2 | 0301, 1401, 4501 | 0.143 | 0.075 | 0.060 |
| 3 | 0101, 0201, 0202, 0401, 0402, 0501, 0601, 1101, 1301, 1501, 1601, 1901, 2001, 2301, 4601 | 0.839 | 0.850 | 0.575 |

†Based on the T-cell recognition pattern described in this study, HLA-DPB1 alleles are predicted to be immunogenic (group 1), intermediately immunogenic (group 2), or poorly immunogenic (group 3).

Classificazione degli alleli DPB1 in base all'immunogenicità




Algoritmo di permissività (immunogenicità+educazione timica)

Convalida clinica

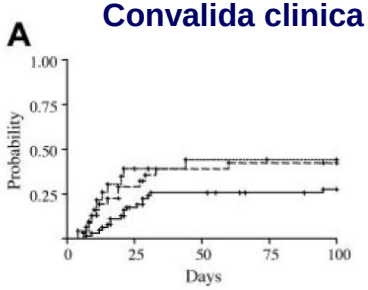
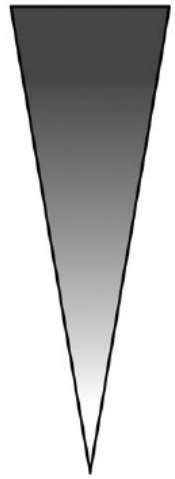
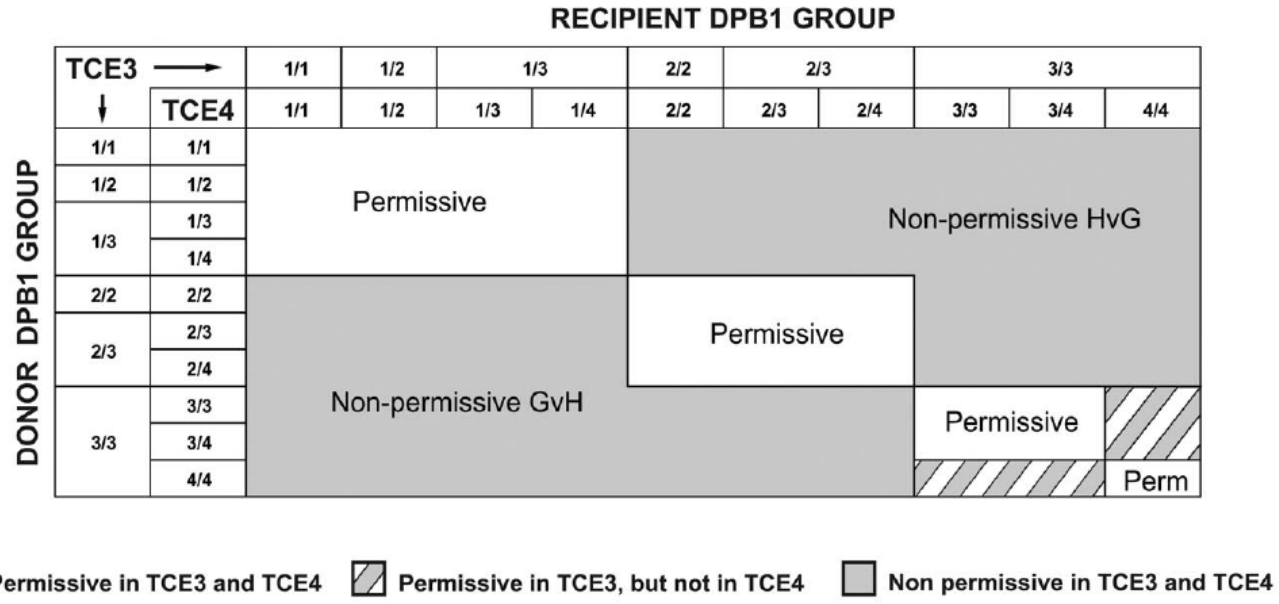


**Figure 1. An algorithm for nonpermissive HLA-DPB1 disparities according to TCE3 or TCE4.** (A) HLA-DPB1 alleles were classified into 3 groups (TCE3), or 4 groups (TCE4), on the basis of T-cell alloreactivity. TCE3 group 1 and TCE4 group 1: Alleles encoding antigens recognized by all T-cell clones studied by Zino et al.[11] TCE3 group 2 and TCE4 group 2: Alleles encoding antigens recognized by some but not all T-cell clones studied by Zino et al.[11] TCE 3 group 3: Alleles encoding antigens recognized by none of the T-cell clones studied by Zino et al.[11] "Others" refers to all alleles that can be classified according to the algorithm of Zino et al.[20] TCE4 group 3: DPB1*02, encoding antigens eliciting intermediate levels of MLR reactivity.[13,14,21] TCE4 group 4: All alleles from TCE3 group 3 except for DPB1*02. (B) The 3 or 4 groups of HLA-DPB1 alleles can be present in different combinations in diploid cells. Numbers indicate the group of the first (before the slash) and the second (after the slash) HLA-DPB1 allele of donor or recipient. Classification of HLA-DPB1 group disparities as permissive or nonpermissive in GvH or HvG direction is indicated for all possible combinations. Note that all nonpermissive TCE3 disparities are also TCE4-nonpermissive (gray boxes). In contrast, only a part of the TCE3-permissive disparities are permissive also according to TCE4 (white boxes), whereas the remaining TCE3-permissive disparities score as nonpermissive in TCE4 (striped boxes).

**A**

| DPB1* alleles | TCE3 group | TCE4 group | Immunogenicity |
|---|---|---|---|
| 0901<br>1001<br>1701 | 1 | 1 |  |
| 0301<br>1401<br>4501 | 2 | 2 | |
| 0201<br>0202<br>0203 | 3 | 3 | |
| Others | | 4 | |

**B**



# DPB1 T-Cell Epitope Algorithm

Classification of HLA-DPB1 mismatches based on T-cell-epitope groups has been shown to identify permissive mismatches and non-permissive mismatches for HLA-DPB1 after unrelated-donor haematopoietic stem cell transplantation (HSCT). Classification of HLA-DPB1 mismatches based on T-cell-epitope groups may identify mismatches that might be tolerated (permissive) and those that would increase risks (non-permissive) after transplantation. This calculator allows you to enter the HLA-DPB1 typing of a patient and donor and view the predicted T-Cell epitopes and resulting prediction of the effect of mismatching when selecting appropriate donors for HSCT recipients.

The implementation of the DPB1 T-Cell Epitope algorithm has been written in collaboration with Katharina Fleischhauer, San Raffaele Scientific Institute, Italy and Bronwen Shaw, Anthony Nolan Research Institute, UK.

Disclaimer - This tool is being offered as a tool to predict T-Cell epitope matching at DPB1 as reported in:

- Fleischhauer K, Shaw BE, Gooley T, *et al.*
  Effect of T-cell-epitope matching at HLA-DPB1 in recipients of unrelated-donor haemopoietic-cell transplantation: a retrospective study.
  Lancet Oncology (2012) **13**:366-74
- Crocchiolo R, Zino E, Vago L, *et al.*
  Nonpermissive HLA-DPB1 disparity is a significant independent risk factor for mortality after unrelated hematopoietic stem cell transplantation.
  Blood (2009) **114**:1437-44.
- Zino E, Vago L, Di Terlizzi S, *et al.*
  Frequency and targeted detection of HLA-DPB1 T cell epitope disparities relevant in unrelated hematopoietic stem cell transplantation.
  Biol Blood Marrow Transplant (2007) **13**:1031-40.
- Zino E, Frumento G, Marktel S, *et al.*
  A T-cell epitope encoded by a subset of HLA-DPB1 alleles determines nonpermissive mismatches for hematologic stem cell transplantation.
  Blood (2004) **103**:1417-24.

No information entered into this tool is collected or stored on our servers.

## IMGT/HLA

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## DPB1 T-Cell Epitope Algorithm

Classification of HLA-DPB1 mismatches based on T-Cell epitope groups has been shown to identify permissive mismatches and non-permissive mismatches for HLA-DPB1 after unrelated-donor haematopoietic stem cell transplantation (HSCT). Classification of HLA-DPB1 mismatches based on T-cell-epitope groups may identify mismatches that might be tolerated (permissive) and those that would increase risks (non-permissive) after transplantation. This calculator allows you to enter the HLA-DPB1 typing of a patient and donor and view the predicted T-Cell epitopes and resulting prediction of the effect of mismatching when selecting appropriate donors for HSCT recipients.

## Predicted Immunogenecity

### Patient Typings: PROSPECTIVEPATIENT1

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

### Donor Typings: PROSPECTIVEDONOR1

| Allele | TCE Group | Predicted Immunogenicity | Comments |
|---|---|---|---|
| DPB1*02:01 | 3 | Low | |
| DPB1*09:01 | 1 | High | |
| The predicted immunogenecity of the DPB1 matching for this pair is | | **Non-Permissive HvG** | |

Submit another job

## Disclaimer

This tool is being offered as a tool to predict T-Cell epitope matching at DPB1 as reported in:

- Fleischhauer K, Shaw BE, Gooley T, *et al.*

IMGT/HLA

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# DPB1 T-Cell Epitope Algorithm

Classification of HLA-DPB1 mismatches based on T-Cell epitope groups has been shown to identify permissive mismatches and non-permissive mismatches for HLA-DPB1 after unrelated-donor haematopoietic stem cell transplantation (HSCT). Classification of HLA-DPB1 mismatches based on T-cell-epitope groups may identify mismatches that might be tolerated (permissive) and those that would increase risks (non-permissive) after transplantation. This calculator allows you to enter the HLA-DPB1 typing of a patient and donor and view the predicted T-Cell epitopes and resulting prediction of the effect of mismatching when selecting appropriate donors for HSCT recipients.

## Predicted Immunogenecity

### Patient Typings: PROSPECTIVEPATIENT1

| Allele | TCE Group | Predicted Immunogenicity | Comments |
|---|---|---|---|
| DPB1*09:01 | 1 | High | |
| DPB1*10:01 | 1 | High | |

### Donor Typings: PROSPECTIVEDONOR1

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

The predicted immunogenecity of the DPB1 matching for this pair is: **Non-Permissive GvH**

Submit another job

## Disclaimer

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- Fleischhauer K, Shaw BE, Gooley T, *et al.*

IMGT/HLA

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# IPD - IMGT/HLA



## DPB1 T-Cell Epitope Algorithm

Classification of HLA-DPB1 mismatches based on T-Cell epitope groups has been shown to identify permissive mismatches and non-permissive mismatches for HLA-DPB1 after unrelated-donor haematopoietic stem cell transplantation (HSCT). Classification of HLA-DPB1 mismatches based on T-cell-epitope groups may identify mismatches that might be tolerated (permissive) and those that would increase risks (non-permissive) after transplantation. This calculator allows you to enter the HLA-DPB1 typing of a patient and donor and view the predicted T-Cell epitopes and resulting prediction of the effect of mismatching when selecting appropriate donors for HSCT recipients.

## Predicted Immunogenecity

### Patient Typings: PROSPECTIVEPATIENT1

| Allele | TCE Group | Predicted Immunogenicity | Comments |
|---|---|---|---|
| DPB1*03:01 | 2 | Intermediate | |
| DPB1*14:01 | 2 | Intermediate | |

### Donor Typings: PROSPECTIVEDONOR1

| Allele | TCE Group | Predicted Immunogenicity | Comments |
|---|---|---|---|
| DPB1*09:01 | 1 | High | |
| DPB1*17:01 | 1 | High | |

The predicted immunogenecity of the DPB1 matching for this pair is: **Non-Permissive HvG**

Submit another job

## Disclaimer

This tool is being offered as a tool to predict T-Cell epitope matching at DPB1 as reported in:

- Fleischhauer K, Shaw BE, Gooley T, *et al.*
  Effect of T-cell-epitope matching at HLA-DPB1 in recipients of unrelated-donor haemopoietic-cell transplantation: a retrospective study.

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# T cell epitope: convalida clinica



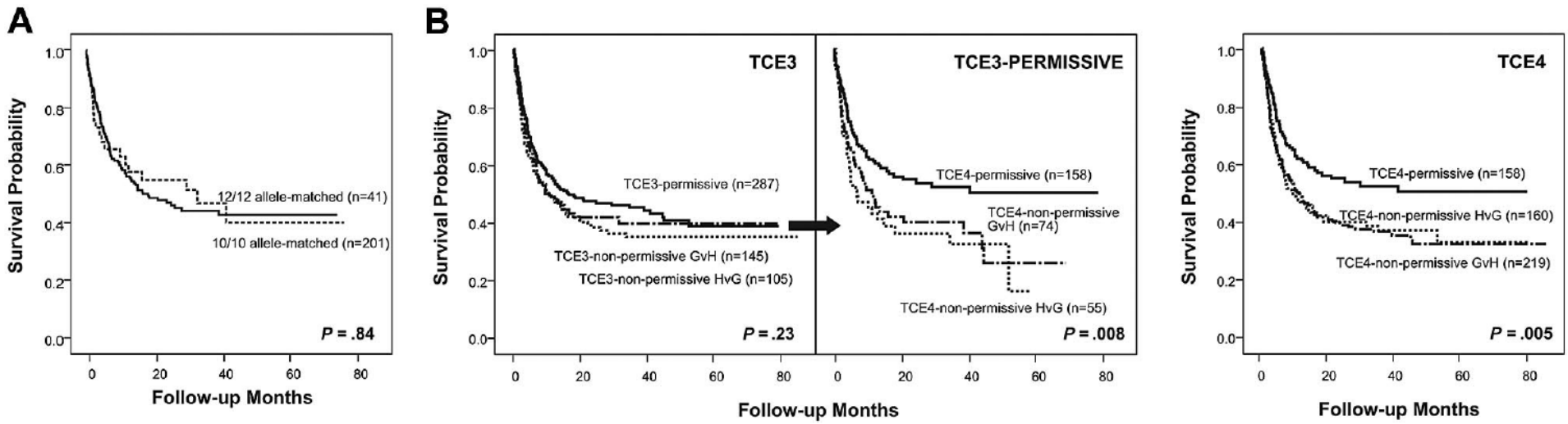



**Figure 2. Impact of allelic or allele-group HLA-DPB1 disparities on OS after unrelated HSCT.** Shown are Kaplan-Meier estimates of survival. (A) HLA-A, B, C, DRB1, and DQB1 matched transplantations (n = 242), stratified according to the presence (10 of 10; —) or absence (12 of 12; ----) of allelic DPB1 mismatches. (B) Left panel: All HLA-DPB1 mismatched transplantations (n = 537), stratified according to the presence of TCE3-permissive (—) or TCE3-nonpermissive HvG (----) or GvH (dash-dot line) mismatches. Middle panel: TCE3-permissive transplantations (n = 287), subdivided into those permissive also according to TCE4 (—), or those TCE4-nonpermissive in HvG (----) or GvH (dash-dot line). Right panel: All HLA-DPB1 mismatched transplantations (n = 537), stratified according to the presence of TCE4-permissive (—) or TCE4-nonpermissive HvG (----) or GvH (dash-dot line) mismatches.

Published in final edited form as:
*Lancet Oncol*. 2012 April ; 13(4): . doi:10.1016/S1470-2045(12)70004-9.

# Effect of T-cell-epitope matching at HLA-DPB1 in recipients of unrelated-donor haemopoietic-cell transplantation: a retrospective study

**Katharina Fleischhauer**[*], **Bronwen E Shaw**[*], **Theodore Gooley**, **Mari Malkki**, **Peter Bardy**, **Jean-Denis Bignon**, **Valérie Dubois**, **Mary M Horowitz**, **J Alejandro Madrigal**, **Yasuo Morishima**, **Machteld Oudshoorn**, **Olle Ringden**, **Stephen Spellman**, **Andrea Velardi**, **Elisabetta Zino**, and **Effie W Petersdorf** on behalf of the International Histocompatibility Working Group in Hematopoietic Cell Transplantation

**Table 2**

Multivariable regression models assessing the effect of HLA-DPB1 T-cell epitope match status on clinical outcome

| | HLA 10/10 match | | | | | HLA 9/10 match | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Permissive HLA-DPB1 mismatch | HLA-DPB1 match | | Non-permissive HLA-DPB1 mismatch | | Permissive HLA-DPB1 mismatch | HLA-DPB1 match | | Non-permissive HLA-DPB1 mismatch | |
| | | HR or OR | p value | HR or OR | p value | | 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 | 1(ref) | 0·98 (0·85–1·13) | 0·80 | 1·10 (1·00–1·22) | 0·06 |
| Non-relapse mortality | 1 (ref) | 0·86 (0·75–0·98) | 0·03 | 1·28 (1·14–1·42) | <0·0001 | 1 (ref) | 0·98 (0·82–1·17) | 0·81 | 1·19 (1·05-1·36) | 0·007 |
| Relapse [*] | 1 (ref) | 1·34 (1·17-1·54) | <0·0001 | 0·89 (0·77–1·02) | 0·10 | 1 (ref) | 1·05 (0·84–1·31) | 0·68 | 0·93 (0·78–1·11) | 0·44 |
| Grade 3-4 aGvHD | 1 (ref) | 0·84 (0·69–1·03) | 0·09 | 1·31 (1·11–1·54) | 0·001 | 1(ref) | 0·93 (0.71–1·21) | 0·58 | 1·37 (1·13–1·66) | 0·002 |

Data are HR (95% CI) for overall mortality, non-relapse mortality, and relapse, and OR (95% CI) for aGvHD. Models were done separately among HLA 10/10-matched and 9/10-matched pairs, with the permissive pairs of each group as reference. HLA=human leucocyte antigen. HR=hazard ratio. OR=odds ratio. ref=reference. aGvHD=acute graft-versus-host disease.

[*] Transplantations done for non-malignant disease were excluded from the analysis.

TRANSPLANTATION

*Blood*. 2014;124(16):2596-2606

# Nonpermissive HLA-DPB1 mismatch increases mortality after myeloablative unrelated allogeneic hematopoietic cell transplantation

Joseph Pidala,[1] Stephanie J. Lee,[2] Kwang Woo Ahn,[3] Stephen Spellman,[4] Hai-Lin Wang,[3] Mahmoud Aljurf,[5] Medhat Askar,[6] Jason Dehn,[7] Marcelo Fernandez Viña,[8] Alois Gratwohl,[9] Vikas Gupta,[10] Rabi Hanna,[6] Mary M. Horowitz,[3] Carolyn K. Hurley,[11] Yoshihiro Inamoto,[2] Adetola A. Kassim,[12] Taiga Nishihori,[1] Carlheinz Mueller,[13] Machteld Oudshoorn,[14] Effie W. Petersdorf,[2] Vinod Prasad,[15] James Robinson,[16,17] Wael Saber,[3] Kirk R. Schultz,[18] Bronwen Shaw,[16,17,19] Jan Storek,[20] William A. Wood,[21] Ann E. Woolfrey,[2] and Claudio Anasetti[1]

## Key Points

- High-resolution matching for HLA-A, -B, -C, and -DRB1 is required for optimal survival in myeloablative-unrelated donor transplantation.
- HLA-DPB1 nonpermissive mismatches should be avoided in otherwise matched transplants to minimize overall mortality.

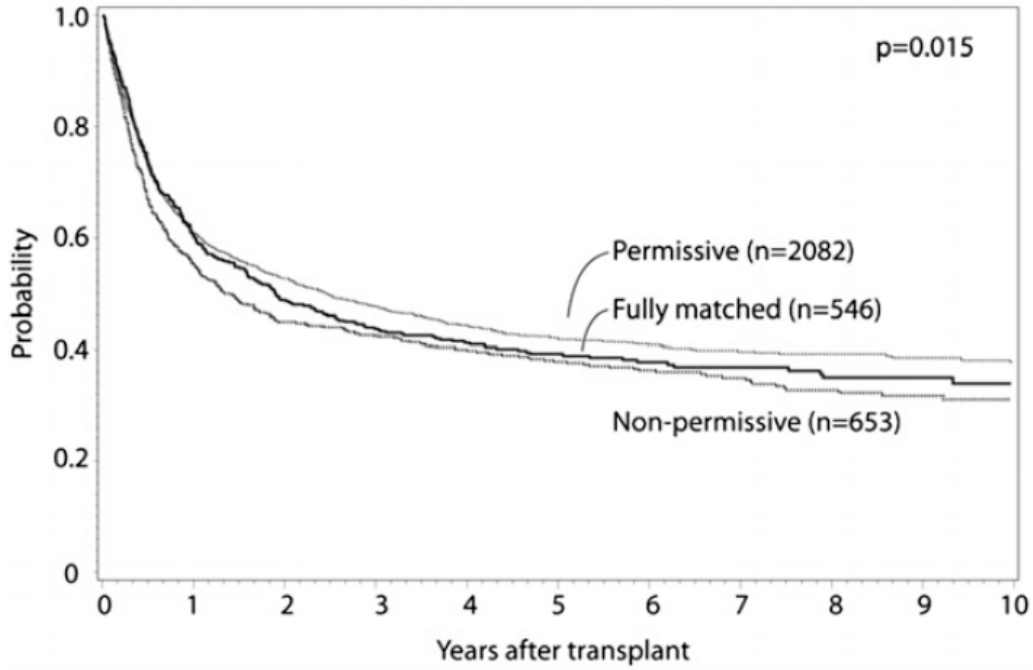



**Figure 2. Adjusted OS curves for -DPB1 matched, permissive mismatch, and nonpermissive mismatch cases.**

**HLA typing**

# *HistoCheck*: rating of HLA class I and II mismatches by an internet-based software tool

H-A Elsner, D DeLuca, J Strub and R Blasczyk

*Department of Transfusion Medicine, Hannover Medical School, Hannover, Germany*

- Un modello in silico per valutare l'alloreattività tra MM HLA di classe I e II

- Calcola uno score di compatibilità (sequence similarity matching score) in base alle differenze negli amino acidi, la loro somiglianza funzionale e la loro localizzazione nelle molecole HLA

**Table 1. Multivariable analysis of impact of mismatch pairs for sever aGVHD in HLA-A and -C**

| Mismatch combination, donor-patient | N | HR (95% CI) | *P* |
|---|---|---|---|
| A locus match | 4510 | 1 | NA |
| A0201-A0206 | 138 | 1.23 (0.87-1.73) | .223 |
| A0206-A0201 | 131 | 1.78 (1.32-2.41) | < .001 |
| A0201-A0207 | 28 | 0.83 (0.34-2.03) | .699 |
| A0207-A0201 | 20 | 1.12 (0.42-3.02) | .809 |
| A0201-A0210 | 11 | 1.57 (0.58-4.23) | .367 |
| A0206-A0207 | 27 | 3.45 (2.09-5.70) | < .001 |

## Welcome to HistoCheck - an HLA Sequence Interpreter

### Detailed Results

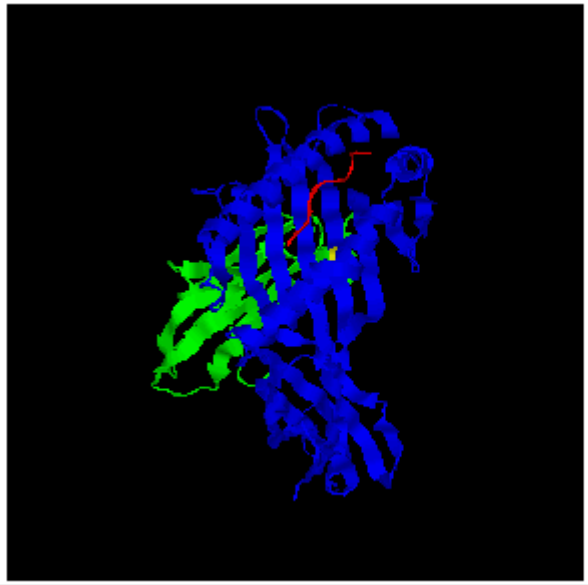
**Donor 1**

**A*02:07 -- A*02:01**

| Amino Acid Mismatch | Domains | Exon | Pockets | Position | Binding Sites | Secondary Structure | R Score |
|---|---|---|---|---|---|---|---|
| Cysteine--> Tyrosine | alpha2 | 3 | A, B, D | 99 | PEP, P1, P2, P3, P6 | beta-strand | 83 |

### Summary

| Total Differences | Affected pockets | DSS Score |
|---|---|---|
| 1 | ABD | 1.83 |



**Big GIF**
**Big Chime**
**Rasmol Script**

**http://www.mh-hannover.de/institute/transfusion/histocheck/**

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| A0206-A0207 | 27 | 3.45 (2.09-5.70) | < .001 |

## Welcome to HistoCheck - an HLA Sequence Interpreter

### Detailed Results

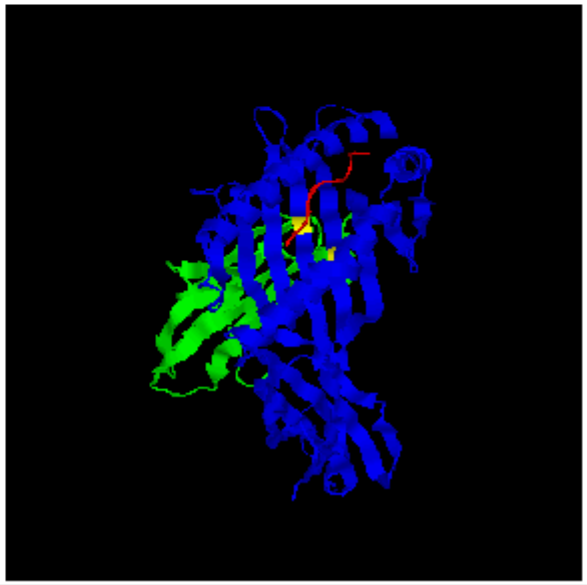
**Donor 1**

**A*02:07 -- A*02:06**

| Amino Acid Mismatch | Domains | Exon | Pockets | Position | Binding Sites | Secondary Structure | R Score |
|---|---|---|---|---|---|---|---|
| Phenylalanine--> Tyrosine | alpha1 | 2 | B, C | 9 | PEP, P2, P3, P6 | beta-strand | 4 |
| Cysteine--> Tyrosine | alpha2 | 3 | A, B, D | 99 | PEP, P1, P2, P3, P6 | beta-strand | 83 |

### Summary

| Total Differences | Affected pockets | DSS Score |
|---|---|---|
| 2 | ABCD | 2.87 |



Big GIF
Big Chime
Rasmol Script

**http://www.mh-hannover.de/institute/transfusion/histocheck/**

Welcome to **HistoCheck** - an HLA Sequence Interpreter

## Detailed Results

Donor 1

**DPB1*04:02 -- DPB1*09:01**

**R** **D**

**Il 'caso che ha dato origine al T cell epitope model**

New Query | Print

Documentation

Introduction

Algorithm

Features

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References

DISCLAIMER



### Histocheck Algorithm

| Amino Acid Mismatch | Domains | Exon | Pockets | Position | Binding Sites | Secondary Structure | R Score |
|---|---|---|---|---|---|---|---|
| Leucine--> Valine | | 2 | | 8 | | | 5 |
| Phenylalanine--> Histidine | | 2 | B, C | 9 | PEP | | 83 |
| Glycine--> Leucine | | 2 | | 11 | PEP | | 59 |
| Glutamic Acid--> Aspartic Acid | | 2 | | 57 | PEP | | 30 |
| Lysine--> Glutamic Acid | | 2 | | 69 | TCR | | 21 |
| Methionine--> Valine | | 2 | | 76 | | | 24 |
| Glycine--> Aspartic Acid | | 2 | F | 84 | | | 65 |
| Glycine--> Glutamic Acid | | 2 | | 85 | PEP | | 47 |
| Proline--> Alanine | | 2 | | 86 | PEP | | 61 |
| Methionine--> Valine | | 2 | | 87 | | | 24 |

### TCE3_EB Algorithm

| Allele | Group |
|---|---|
| DPB1*04:02 | 3 |
| DPB1*09:01 | 1 |

### TCE4_EB Algorithm

| Allele | Group |
|---|---|
| DPB1*04:02 | 4 |
| DPB1*09:01 | 1 |

### TCE4_SB Algorithm

| Allele | Group |
|---|---|
| DPB1*04:02 | 4 |
| DPB1*09:01 | 1 |

### Summary

| Algorithm | Total Differences | Affected pockets | DSS Score | Permissivenes |
|---|---|---|---|---|
| Histocheck | 10 | BCF | 11.19 | |
| TCE3_EB | | | | no |
| TCE4_EB | | | | no |
| TCE4_SB | | | | no |

Note: Additional differences found outside key domains

# Predictions in the Face of Clinical Reality: *HistoCheck* versus High-Risk HLA Allele Mismatch Combinations Responsible for Severe Acute Graft-versus-Host Disease

*Medhat Askar,[1] Ronald Sobecks,[2] Yasuo Morishima,[3] Takakazu Kawase,[3] Amy Nowacki,[4] Hideki Makishima,[5] Jaroslaw Maciejewski[5]*

*Biol Blood Marrow Transplant 17: 1409-1415 (2011)*

**Histocheck is not correlated with HSCT outcome**

# Posizioni degli aminoacidi

- Predire l'alloreattività diretta analizzando l'impatto della posizione di specifici amino acidi nelle molecole HLA
- Alcune sostituzioni di aminoacidi nella tasca di presentazione degli antigeni sono correlate ad aumento del rischio di aGVHD

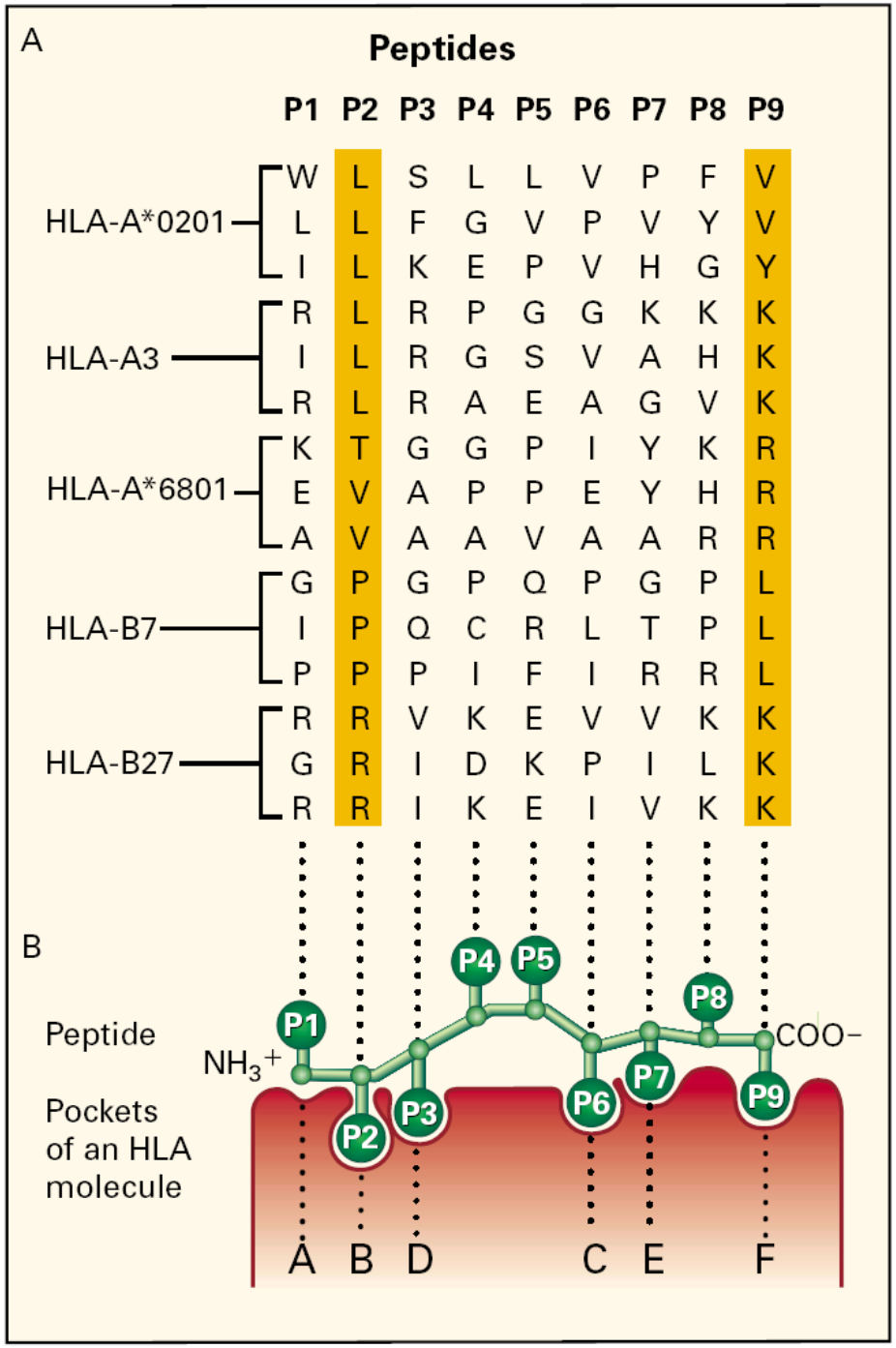
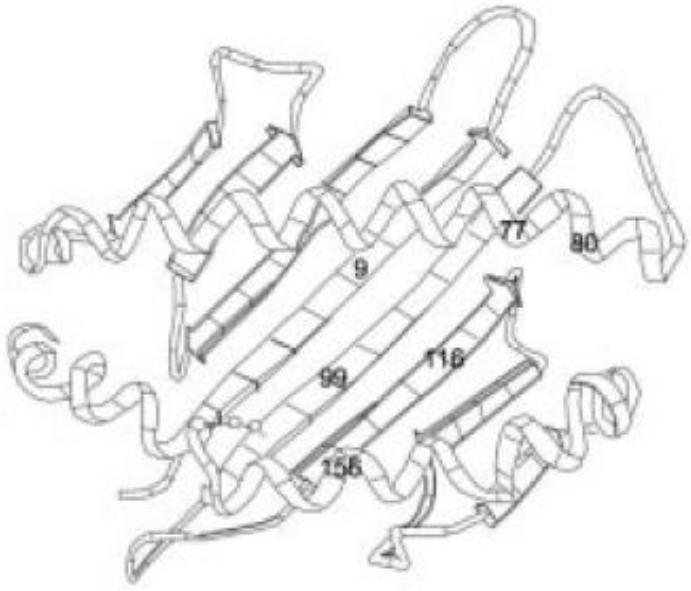



**Figure 5.** Interactions between HLA Molecules and Peptides. Panel A shows examples of peptide motifs. The listed nonamers, as well as many others,[7] have been found in complexes with the indicated HLA class I molecules. The anchor residues are highlighted in yellow. In Panel B, a longitudinal section through the peptide-binding groove of an HLA class I molecule, the side chains of amino acid residues composing the bound peptide (P1 through P9) are oriented either down into the pockets of the HLA molecule or up. The following amino acids are shown: alanine (A), cysteine (C), aspartic acid (D), glutamic acid (E), phenylalanine (F), glycine (G), histidine (H), isoleucine (I), lysine (K), leucine (L), proline (P), glutamine (Q), arginine (R), serine (S), threonine (T), valine (V), tryptophan (W), and tyrosine (Y).

Klein and Sato, NEJM 2000




| | beta-plate sheet | | | alpha helix |
|---|---|---|---|---|
| Position of HLA class I | 9 | 99 | 116 | 156 |
| Peptide-binding pocket | B C | A B D | F | D E |
| Amino acid substitution | | | | |
| HLA-A | Tyr-Phe | | Asn-Asp* | |
| HLA-C | Tyr-Ser | Tyr-Phe | Leu-Ser | Arg-Leu |

T. Kawase et al. Blood 2007

**Table 5. Multivariable analysis of impact of amino acid substitution on HLA class I molecules for severe aGVHD**

| Posisiton and kind of amino acid substitution, donor-recipient | HS | N | Event† | HR (95% CI) | *P* |
|---|---|---|---|---|---|
| **HLA-A locus** | | | | | |
| Tyr9A-Phe9A | 4.1 | 163 | 64 | 1.66 (1.19-2.32) | .003 |
| Asn116A-Asp116A | 0 | 32 | 15 | 2.25 (1.26-4.01) | .005* |
| **HLA-C locus** | | | | | |
| Tyr9C-Ser9C | 0.5 | 146 | 59 | 1.66 (1.23-2.25) | .001 |
| Asn77C-Ser77C | 2.7 | 205 | 90 | 1.87 (1.46-2.39) | < .001 |
| Lys80C-Asn80C | 0.4 | 205 | 90 | 1.87 (1.46-2.39) | < .001 |
| Tyr99C-Phe99C | 4.1 | 146 | 59 | 1.64 (1.21-2.22) | .001 |
| Leu116C-Ser116C | 4.6 | 53 | 30 | 3.40 (2.20-5.25) | < .001 |
| Arg156C-Leu156C | 8.3 | 251 | 88 | 1.48 (1.15-1.90) | .002 |

T. Kawase et al. Blood 2007

TRANSPLANTATION

*Blood*. 2013;122(22):3651-3658

# Amino acid substitution at peptide-binding pockets of HLA class I molecules increases risk of severe acute GVHD and mortality

Joseph Pidala,[1] Tao Wang,[2] Michael Haagenson,[3] Stephen R. Spellman,[3] Medhat Askar,[4] Minoo Battiwalla,[5] Lee Ann Baxter-Lowe,[6] Menachem Bitan,[7] Marcelo Fernandez-Viña,[8] Manish Gandhi,[9] Ann A. Jakubowski,[10] Martin Maiers,[11] Susana R. Marino,[12] Steven G. E. Marsh,[13] Machteld Oudshoorn,[14] Jeanne Palmer,[15] Vinod K. Prasad,[16] Vijay Reddy,[17] Olle Ringden,[18] Wael Saber,[2] Stella Santarone,[19] Kirk R. Schultz,[20] Michelle Setterholm,[11] Elizabeth Trachtenberg,[21] E. Victoria Turner,[22] Ann E. Woolfrey,[23] Stephanie J. Lee,[23] and Claudio Anasetti[1]

## Key Points

- Amino acid substitution at peptide-binding residues of the HLA class I molecule is associated with graft-versus-host disease and mortality.
- Avoidance of donor-recipient combinations that result in amino acid substitution at peptide-binding residues may improve transplant outcomes.

BLOOD, 21 NOVEMBER 2013 • VOLUME 122, NUMBER 22

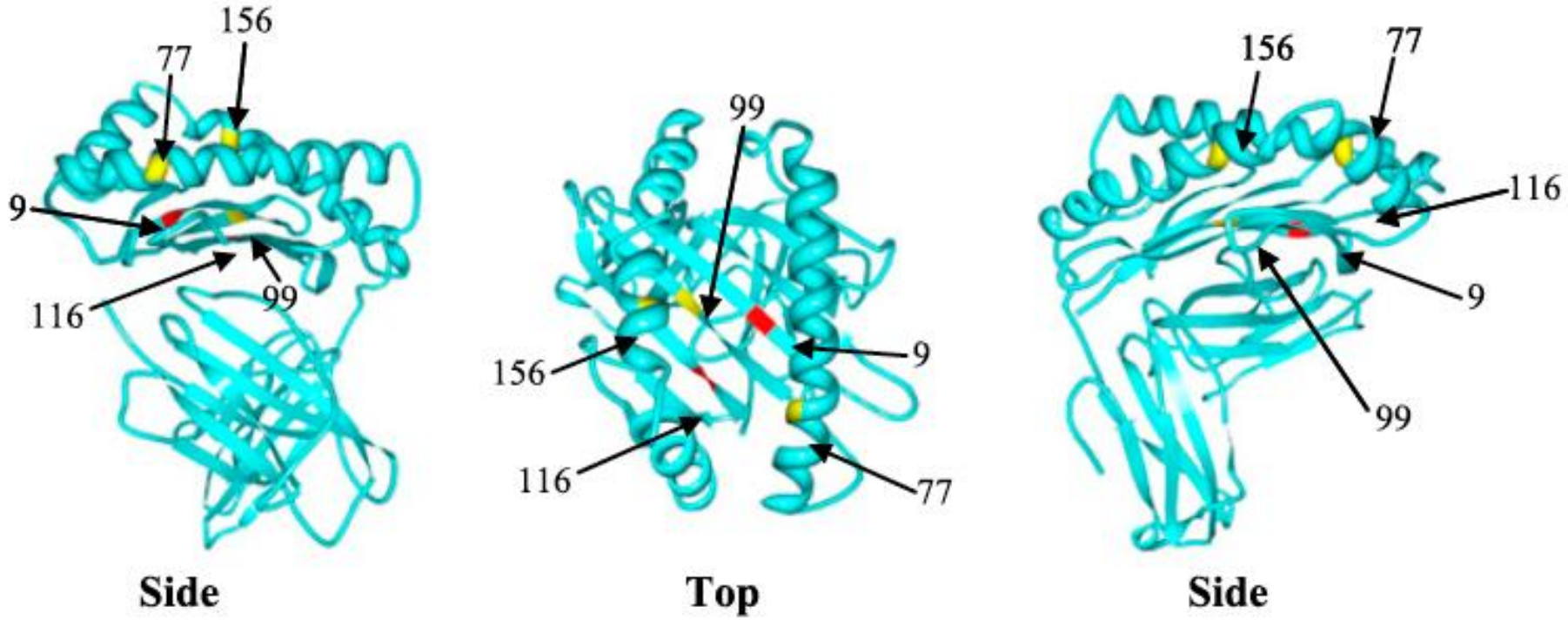



**Figure 1. Position of studied amino acid residues within the class I HLA molecule.**

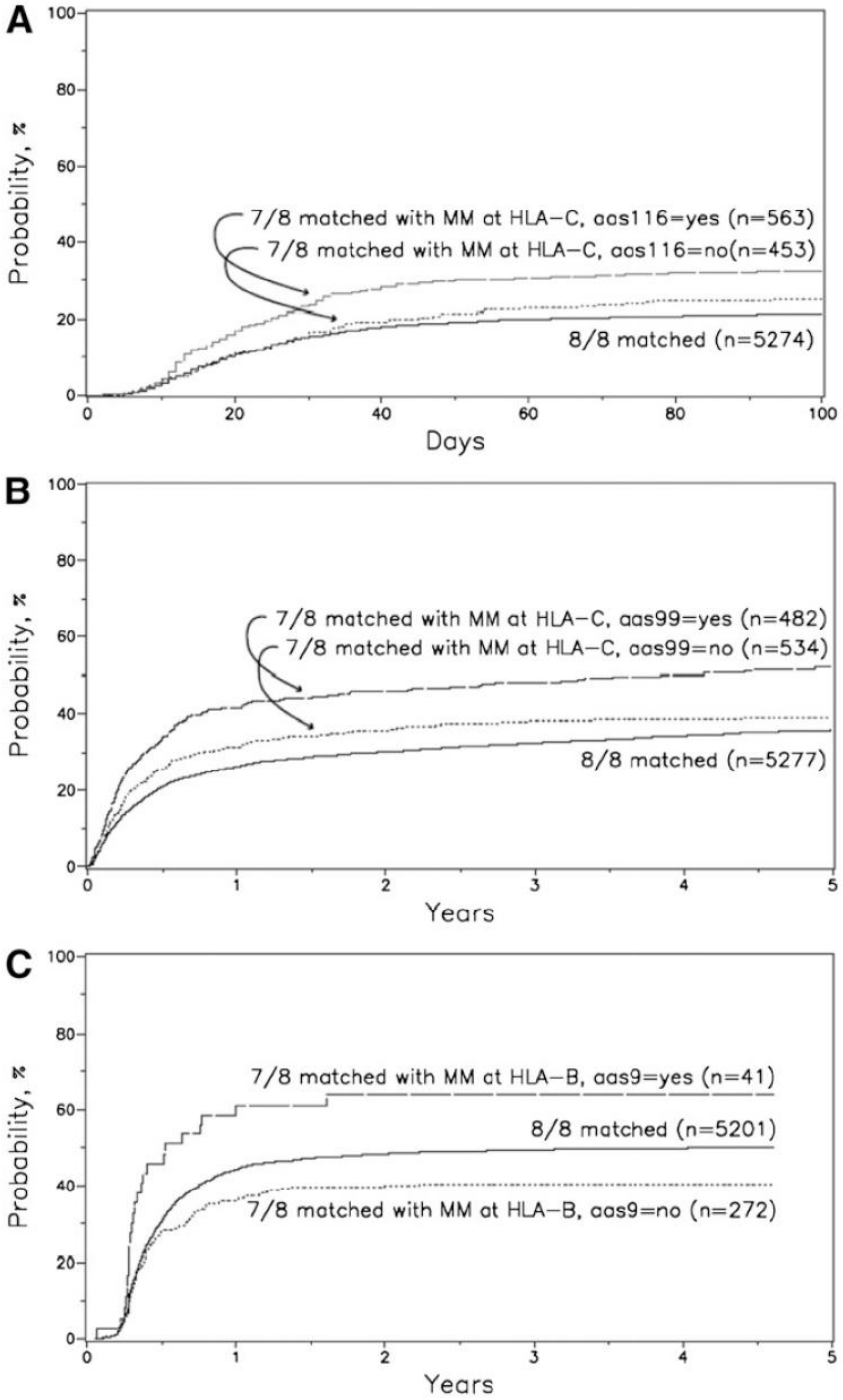



**Figure 2. Adjusted cumulative incidence of grade III-IV acute GVHD for 8/8 matched vs 7/8 HLA-C with AAS 116 vs 7/8 HLA-C without AAS 116.** (A) Adjusted cumulative incidence of grade III-IV acute GVHD at 100 days: (1) 8/8 = 21%; (2) 7/8 without HLA-C AAS 116 = 25%; and (3) 7/8 with HLA-C AAS 116 = 32%. *P* value for comparisons: (2 vs 1) $P = .071$; (3 vs 1) $P < .0001$; (3 vs 2) $P = .0088$. Adjusted variables: disease stage, graft type, Karnofsky score, patient age, sex match, disease, GVHD prophylaxis, conditioning regimen, in vivo T-cell depletion, year of transplant. (B) Adjusted cumulative incidence of TRM for 8/8 matched vs 7/8 HLA-C with AAS 99 vs 7/8 HLA-C without AAS 99. Adjusted cumulative incidence of TRM for 8/8 matched vs 7/8 HLA-C with AAS 99 vs 7/8 HLA-C without AAS 99 at 1 year: (1) 8/8 = 26%; (2) 7/8 without HLA-C AAS 99 = 31%; and (3) 7/8 with HLA-C AAS 99 = 42%. *P* value for comparisons: (2 vs 1) $P = .012$; (3 vs 1) $P < .0001$; (3 vs 2) $P = .00035$. Adjusted variables: CMV match, disease, disease stage, donor age, donor race, patient age, graft type, KPS, GVHD prophylaxis, conditioning regimen, interval from diagnosis to transplant, year of transplant. (C) Adjusted cumulative incidence of chronic GVHD for 8/8 matched vs 7/8 HLA-B with AAS 9 vs 7/8 HLA-B without AAS 9. Adjusted cumulative incidence of chronic GVHD for 8/8 matched vs 7/8 HLA-B with AAS 9 vs 7/8 HLA-B without AAS 9 at 2 years: (1) 8/8 = 48%; (2) 7/8 without HLA-B AAS 9 = 40%; and (3) 7/8 with HLA-B AAS 9 = 64%. *P* value for comparisons: (2 vs 1) $P = .0056$; (3 vs 1) $P = .023$; (3 vs 2) $P = .0012$. Adjusted variables: in vivo T-cell depletion, patient age, sex match, disease, graft type, GVHD prophylaxis, CMV match, conditioning regimen, year of transplant.

# Bone marrow transplantation from unrelated donors: the impact of mismatches with substitutions at position 116 of the human leukocyte antigen class I heavy chain

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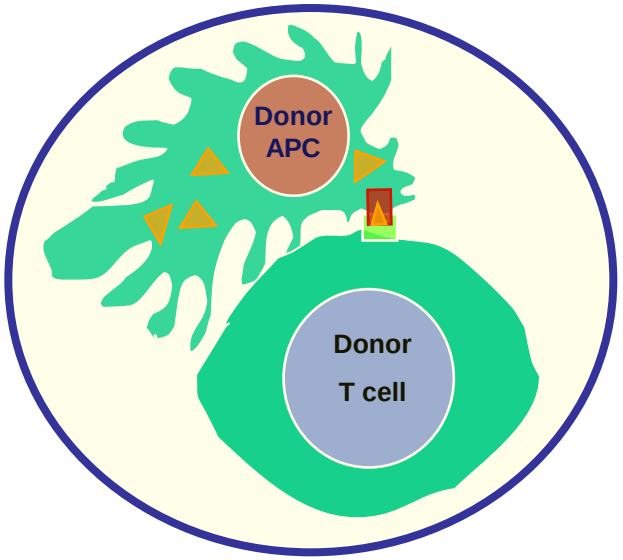
# Indice

- Cenni sulla risposta alloimmune
- Perché è necessario studiare la permissività delle incompatibilità (MM) HLA ?
- Studio della permissività:
  - alloriconoscimento diretto
  - alloriconoscimento indiretto
- Considerazioni conclusive

# Studio della permissività dei MM HLA: alloriconoscimento indiretto

- Test *in vitro*
  - Non sono disponibili
- Modelli *in silico*
  - PIRCHES



# PIRCHES – Predicted Indirectly Recognizable HLA Epitopes (Otten et al. Human Immunology 2013)

- Alloriconoscimento indiretto dipende da peptidi derivati da HLA del ricevente (nel HSCT)
- I peptidi sono presentati su HLA condiviso
- Se i peptidi sono identici tra donatore e ricevente, non c'è alloriconoscimento
- Otten et al. hanno catalogato peptidi in grado di indurre aGVHD (e rigetto nel trapianto di organi)
- Il modello utilizza strumenti informatici che 'calcolano' il processamento e la presentazione degli antigeni

# Considerazioni conclusive - 1

- I MM HLA sono in grado di provocare GVHD e rigetto del graft
- Nel HSCT, l'alloriconoscimento dei linfociti T gioca un ruolo fondamentale
- La permissibilità delle combinazioni di MM è molto variabile

# Considerazioni conclusive - 2

- Sebbene il grado di differenze nelle sequenze di amino acidi varia molto nei diversi MM, il NUMERO di differenze di a.a. non è di per sè predittivo di permissibilità
- La permissibilità dei MM è determinata da:
  - la natura del polimorfismo di a.a.
  - la posizione dell'a.a.
  - l'effetto sugli a.a. vicini

# Considerazioni conclusive - 3

- Sono state sviluppate diverse strategie per predire la permissibilità, con l'intento di migliorare le procedure di selezione dei donatori

- L'obiettivo comune di tutte le strategie, è di predire il riconoscimento delle molecole HLA allogeniche da parte dei linfociti T

# Considerazioni conclusive - 4

- L’alloreattività post trapianto difficilmente può essere attribuita a un’unica via di alloriconoscimento

- Bisogna sviluppare metodi che valutino in modo integrato i diversi pathways, poiché la via diretta e indiretta interagiscono sinergicamente

# Considerazioni conclusive - 5

• L’ulteriore miglioramento dei metodi per definire la permissibilità dei MM HLA e la loro introduzione nelle procedure di selezione del donatore, ridurranno l’alloreattività e quindi miglioreranno i risultati clinici del trapianto di cellule staminali emopoietiche.

# Grazie per l’attenzione