

HLA T-cell epitopes in organ transplantation

Eric Spierings

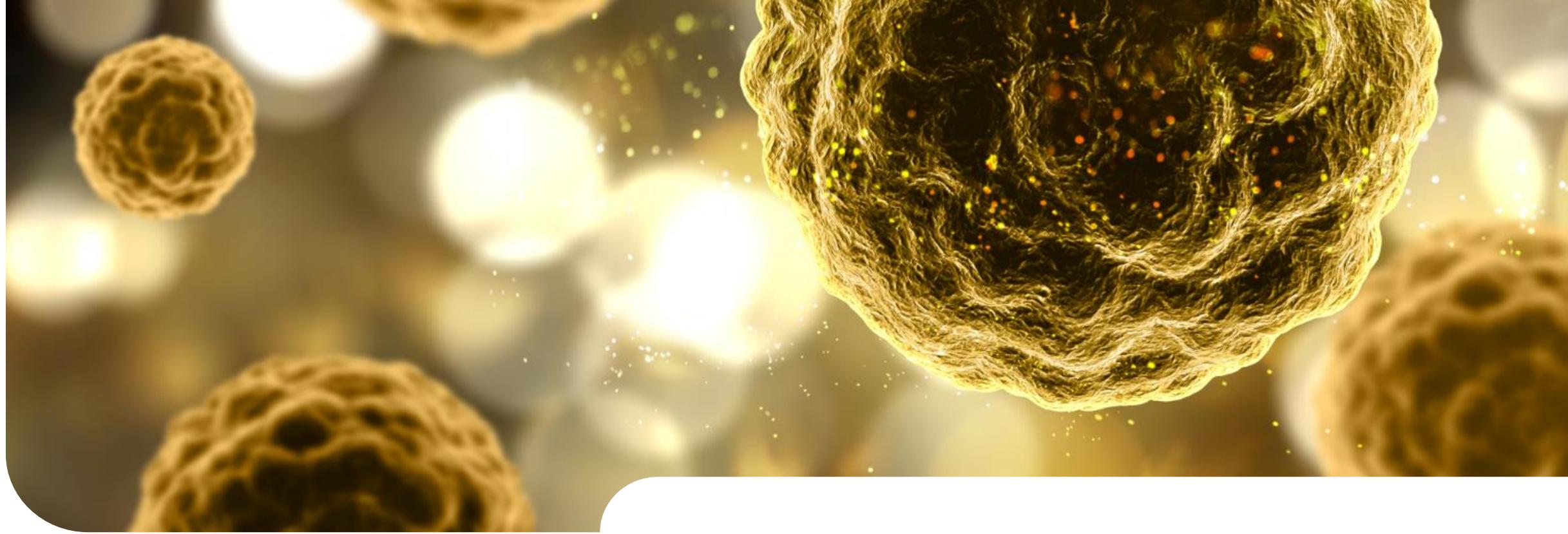
Learning objectives of these presentations

HLA antibody algorithms

- To understand the basic principles of antibody recognition
- To understand the basic concepts of HLA antibody epitope matching algorithms
- To understand the most important differences between the various HLA antibody epitope matching algorithms

HLA T-cell epitope algorithms

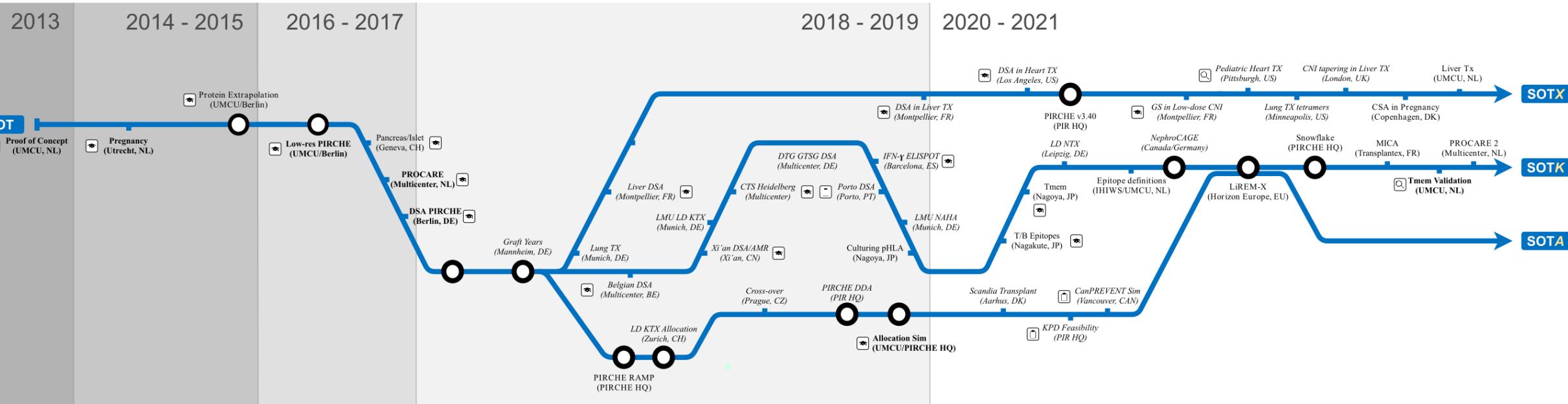
- To understand the basics of T-cell epitope recognition
- To understand the difference between PIRCHE-I and PIRCHE-II and the potential immunological consequences
- To understand how PIRCHE-II affects transplant outcome



HLA T-cell epitopes: PIRCHE: an unexpected journey

Epitope workshop ABHI
Curitiba – Friday, December 1, 2023

HLA T-cell epitopes in solid organ transplantation



PIRCHE: an unexpected journey



15th International Workshop Project on Epitope Immunogenicity

- Analyze post-allograft nephrectomy sera for antibodies against donor class I and class II epitopes
- Serum screening with single alleles (Luminex) and by CDC
- So far, 40 laboratories worldwide will contribute informative cases

Determination of Structurally Defined Immunogenic HLA Epitopes
Rene Duquesnoy, Frans Claas

Minor Histocompatibility Antigens
Els Goulmy, Eric Spierings

PIRCHE: an unexpected journey



definition of an epitope

epitope

[ēp'ī-tōp']

noun.

the **surface portion**
(τοπος) on (επι) an
antigen

B-cell epitope

[bi sĕl ēp'ī-tōp']

noun.

epitope that is capable
of eliciting a **B-cell**
immune response

T-cell epitope

[ti sĕl ēp'ī-tōp']

noun.

epitope that is capable of
eliciting a **T-cell** immune
response

definition of an epitope

epitope

[ēp'i-tōp']

noun.

the surface portion
(τοπος) on (επι) an
antigen

B-cell epitope

[bi sĕl ēp'i-tōp']

noun.

epitope that is capable
of eliciting a B-cell
immune response

T-cell epitope

[ti sĕl ēp'i-tōp']

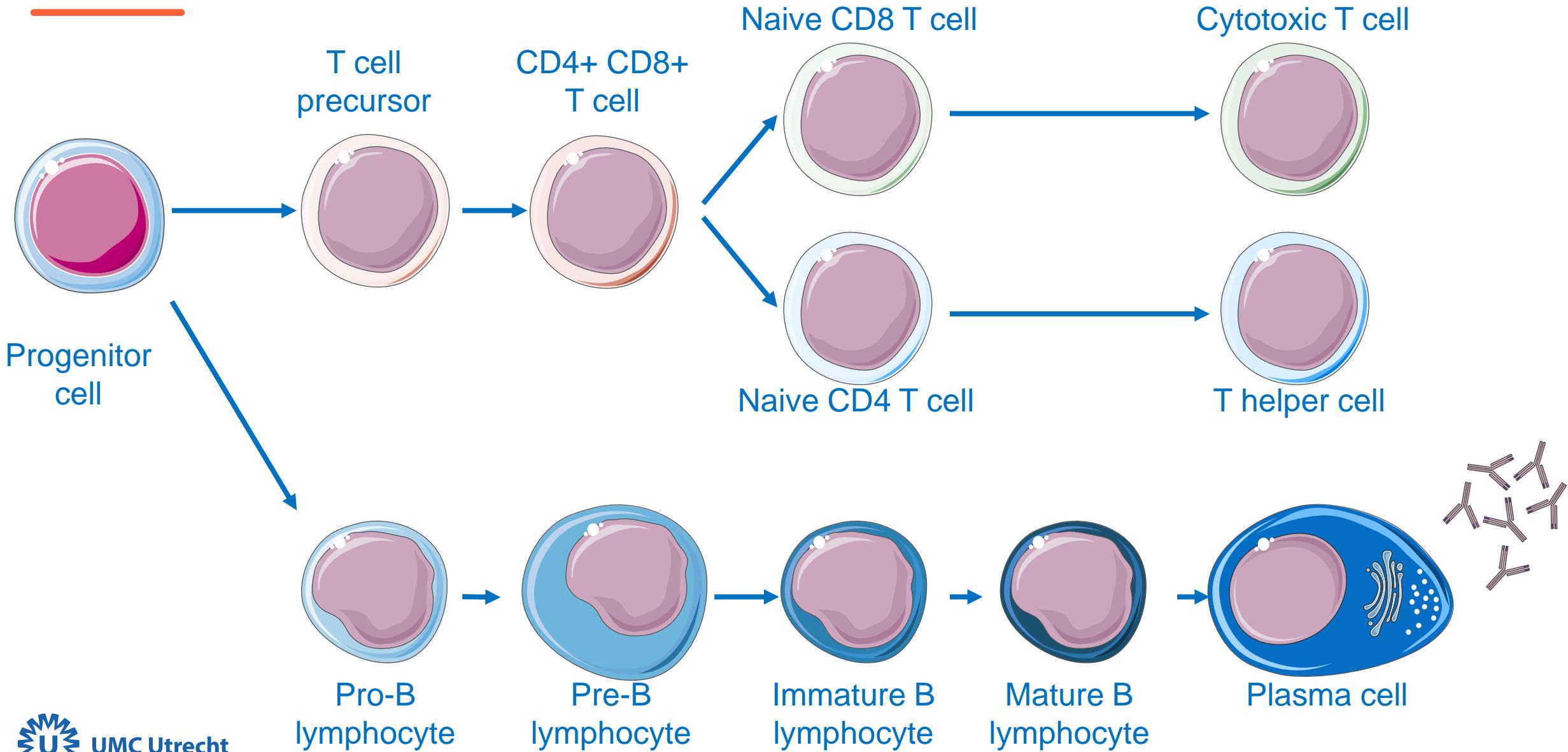
noun.

epitope that is capable of
eliciting a T-cell immune
response

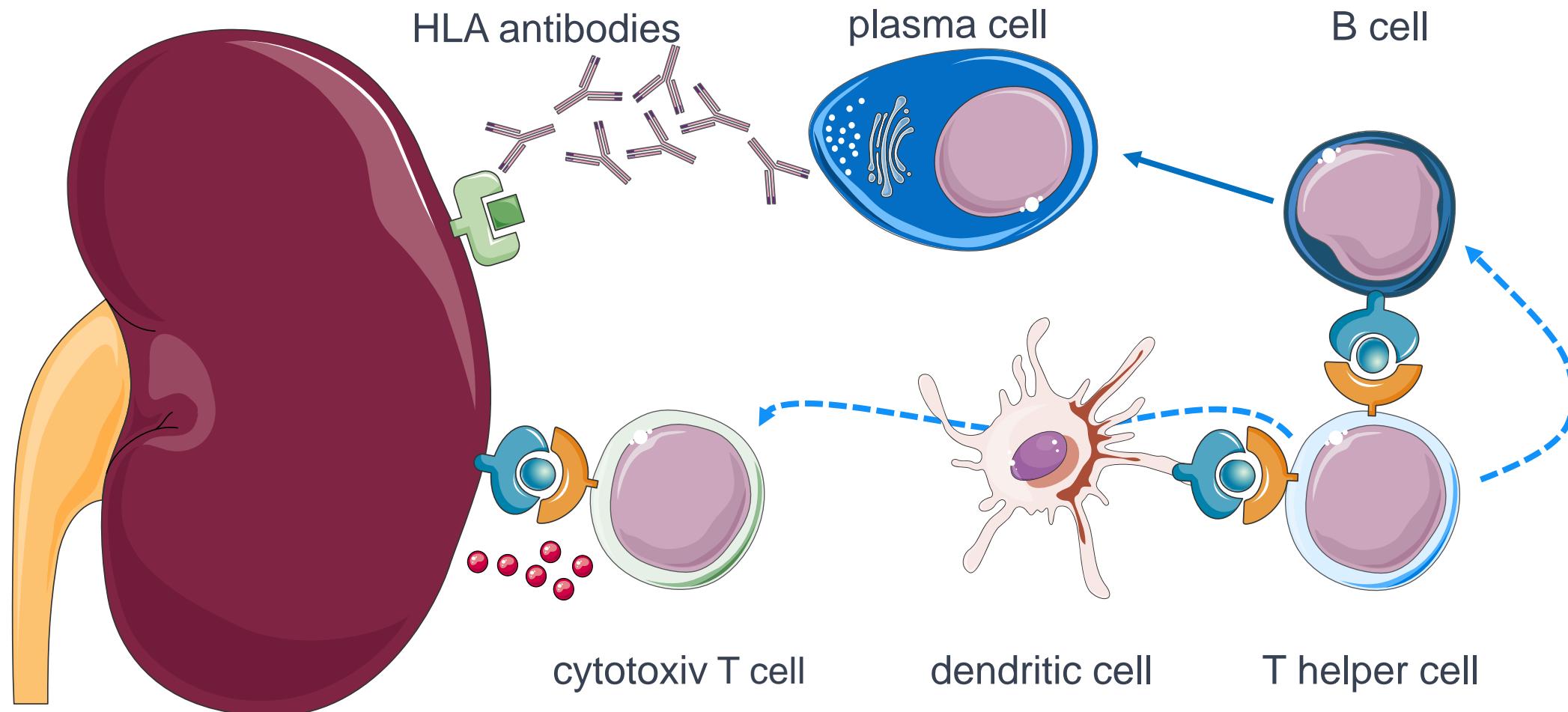


recognition by the T-cell
receptor

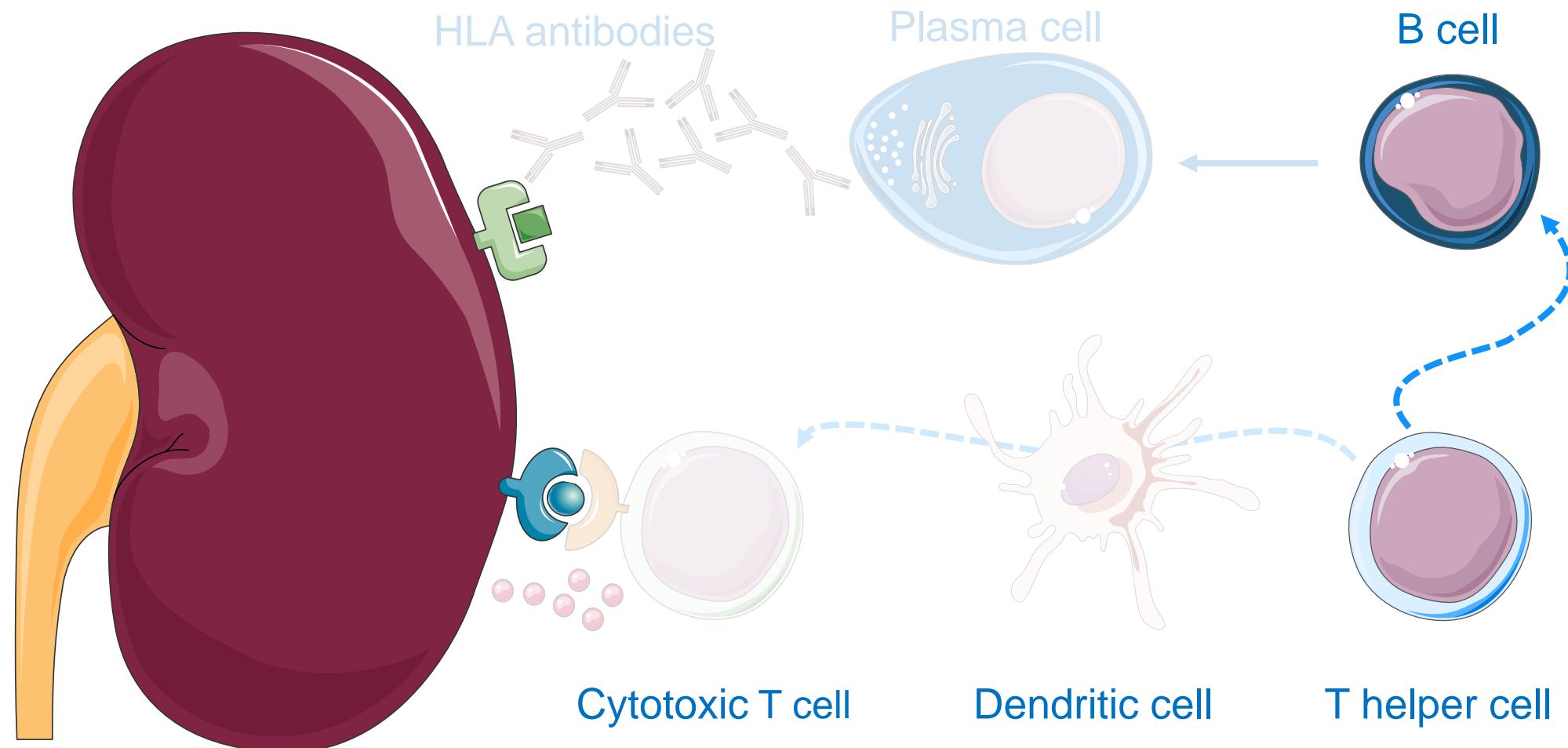
antigen-specific responses after transplantation



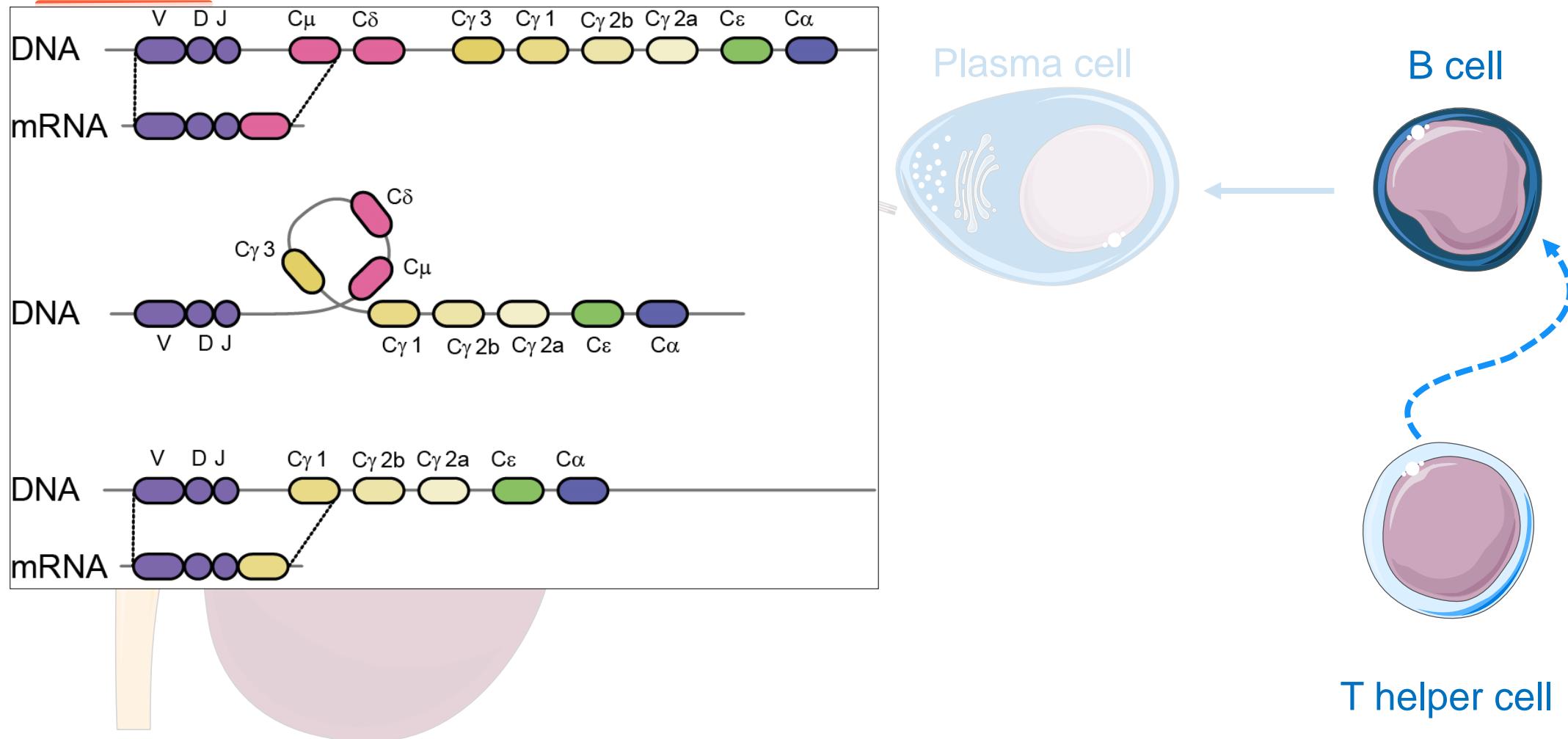
adaptive immunity in transplantation



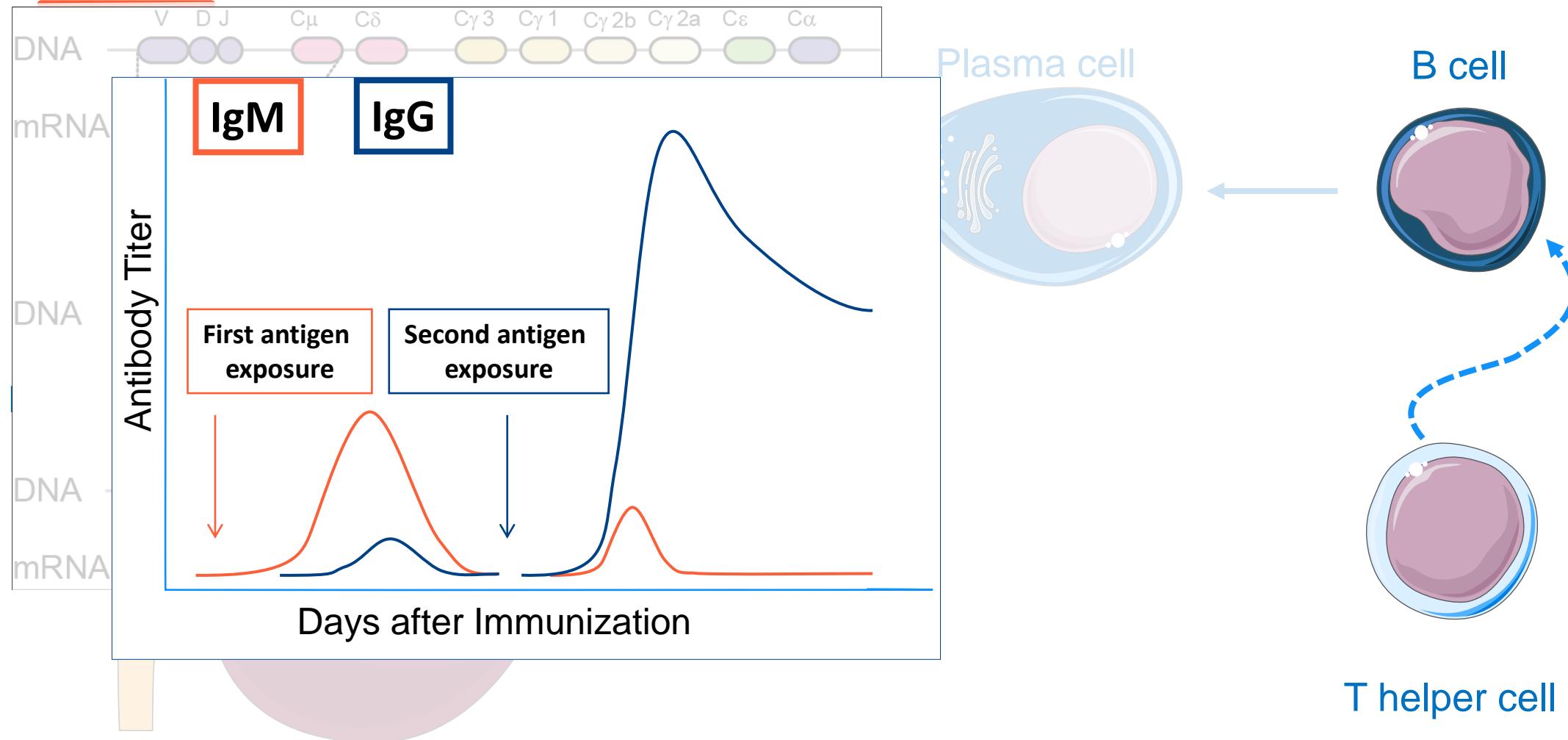
adaptive immunity in transplantation



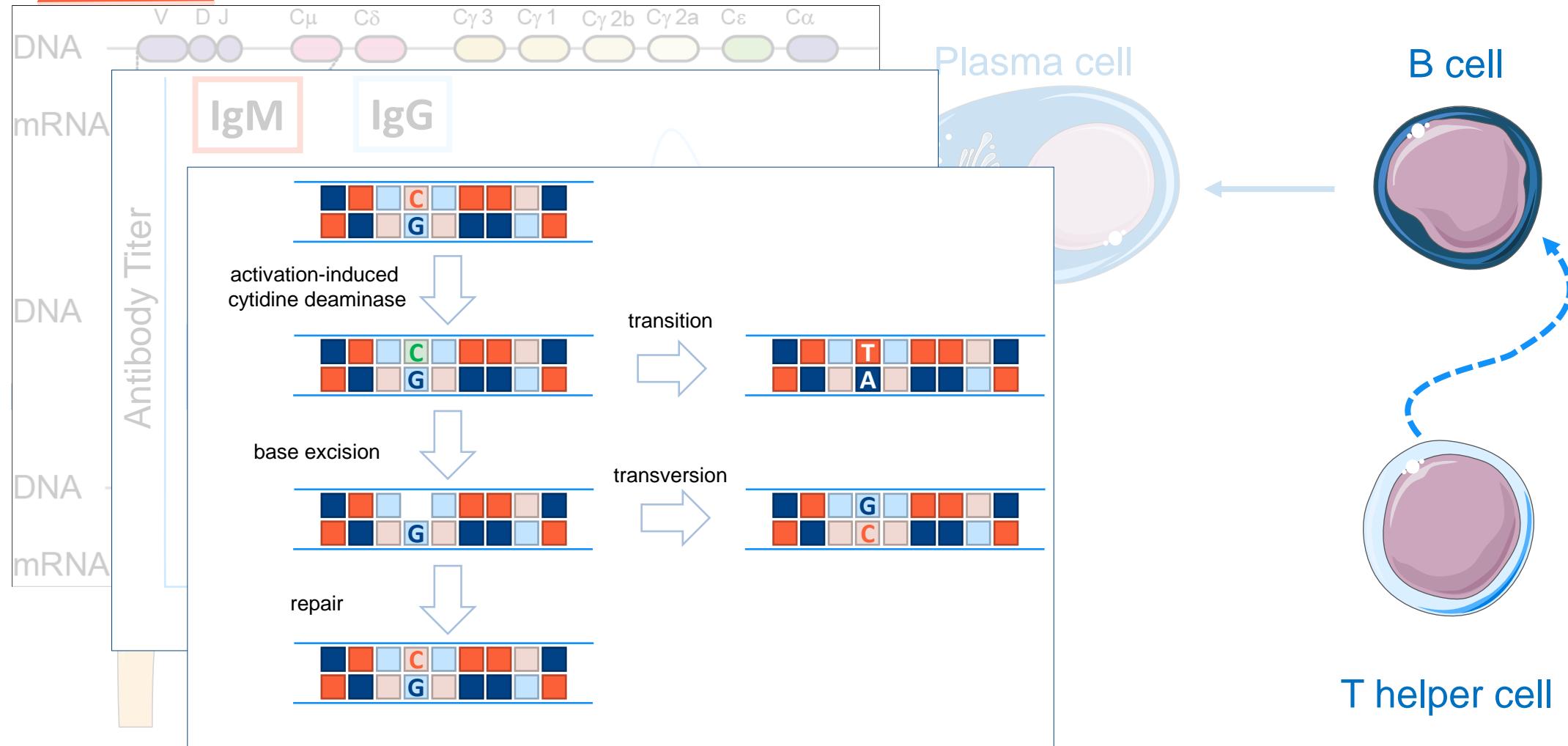
effects of T-cell help: isotype switching



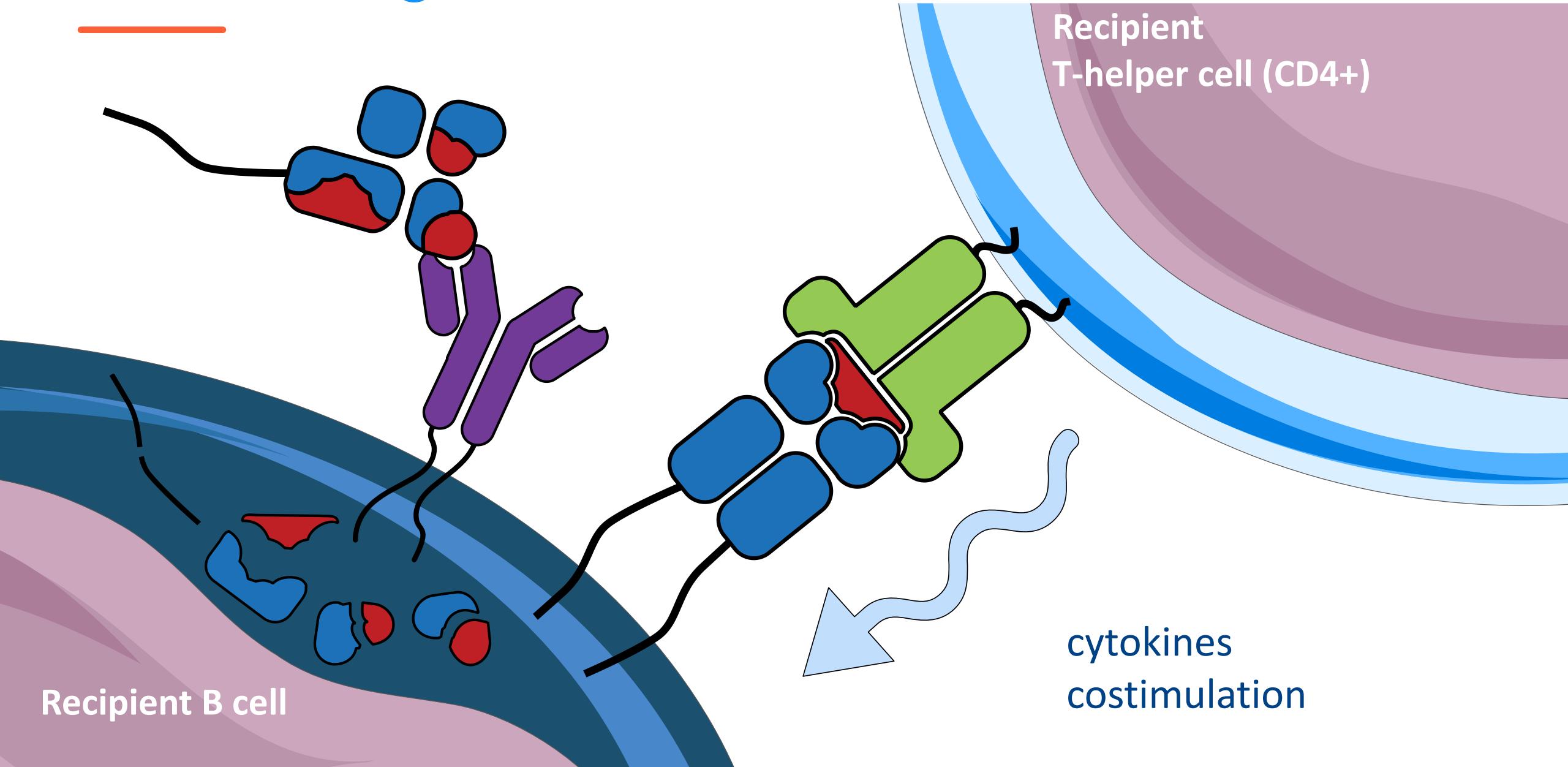
effects of T-cell help: B-cell memory



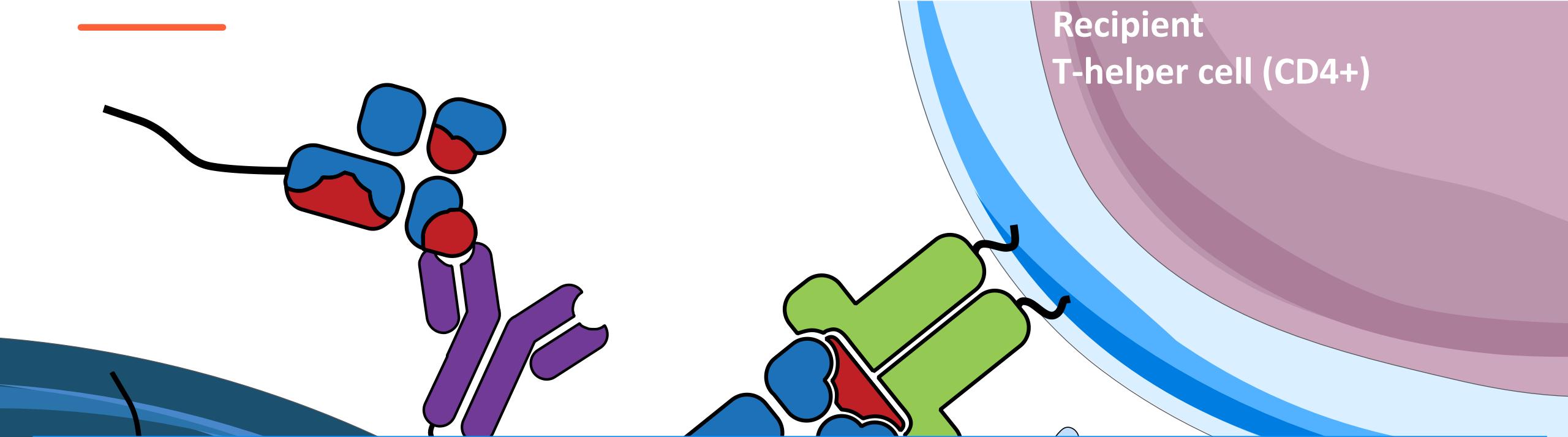
effects of T-cell help: affinity maturation



indirect recognition of HLA mismatches

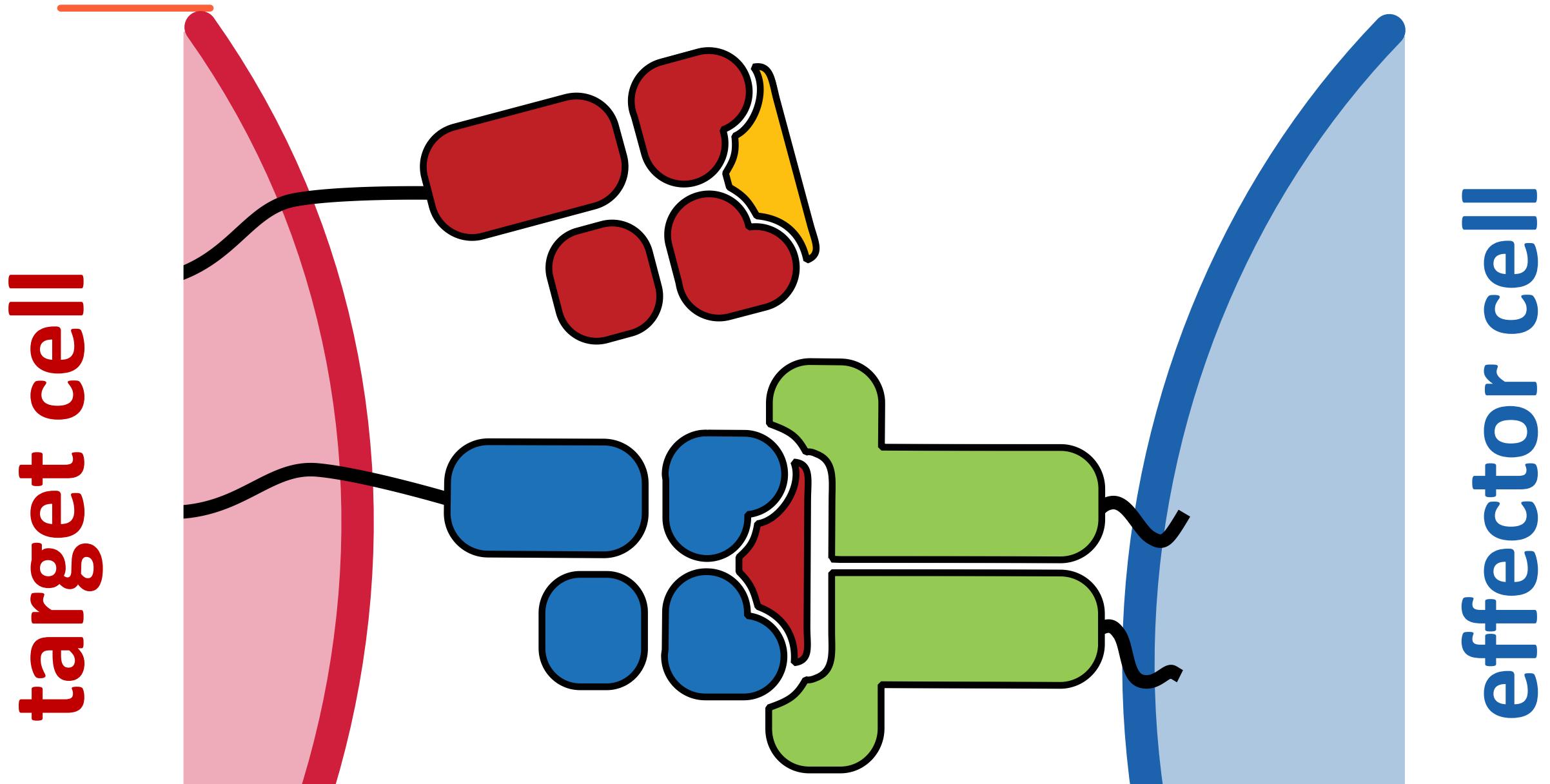


indirect recognition of HLA mismatches



Generating a mature antibody response requires the presence of both an **antibody/B-cell epitope** and an HLA class II-restricted **T-cell epitope** within the same antigen. This phenomenon is called linked recognition.

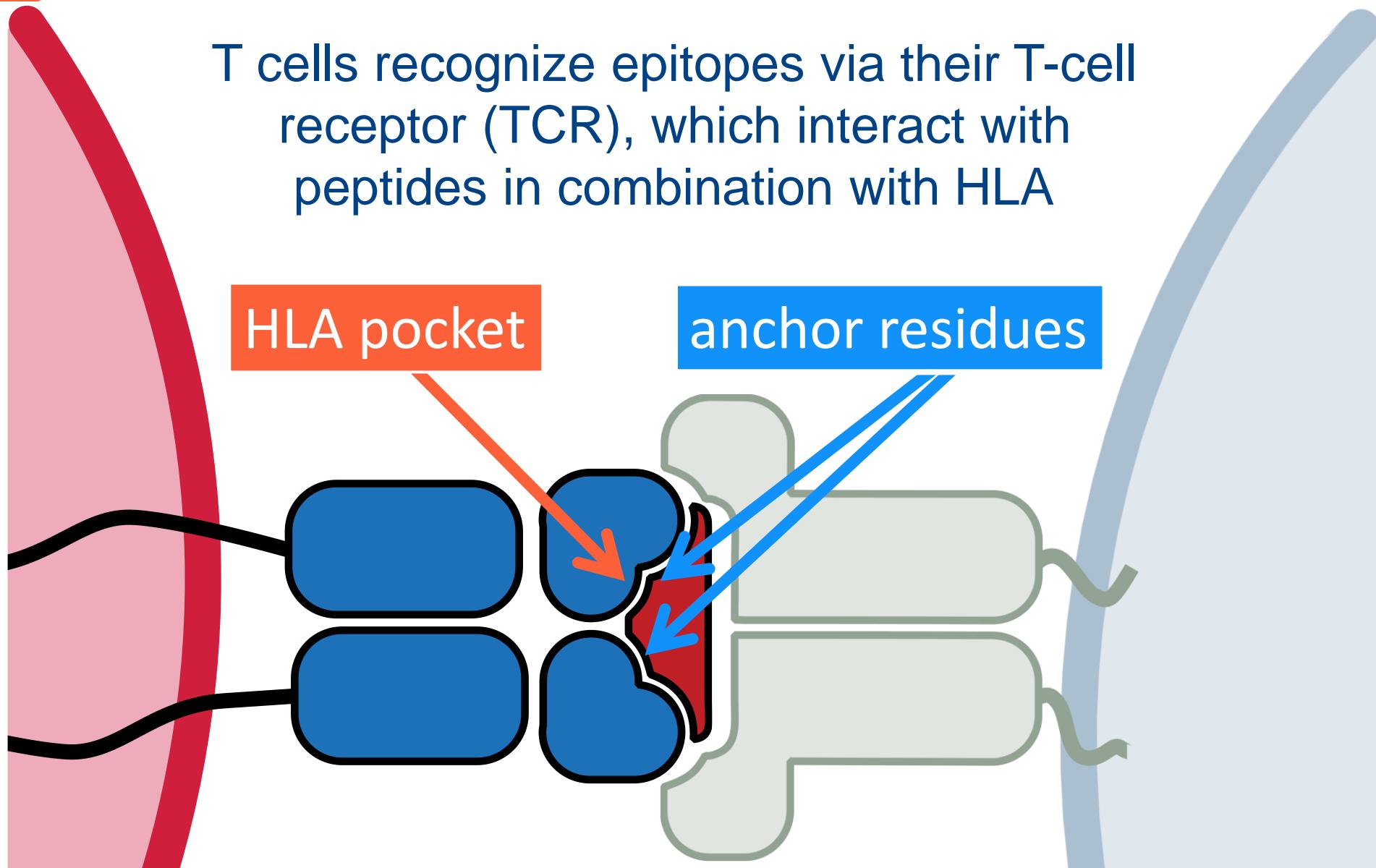
indirect recognition of mismatched HLA



anatomy of antigen presentation

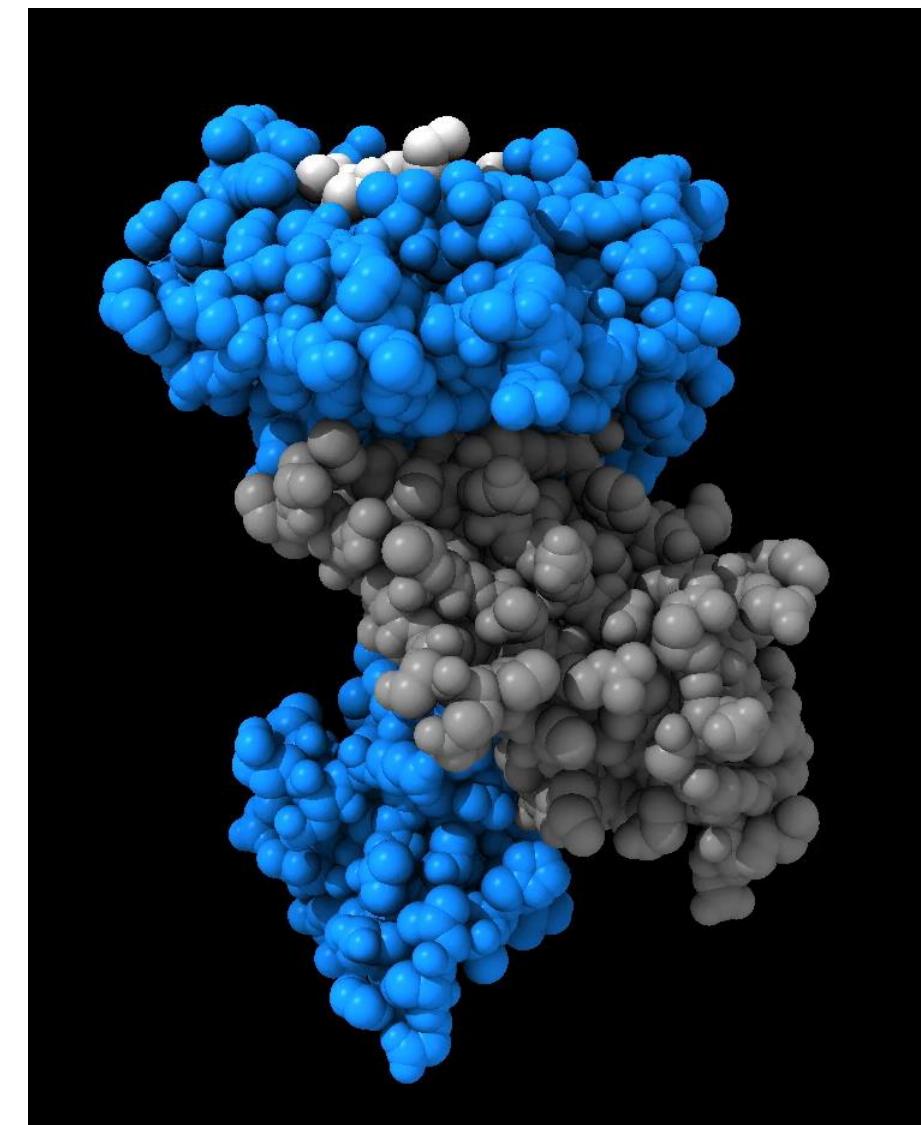
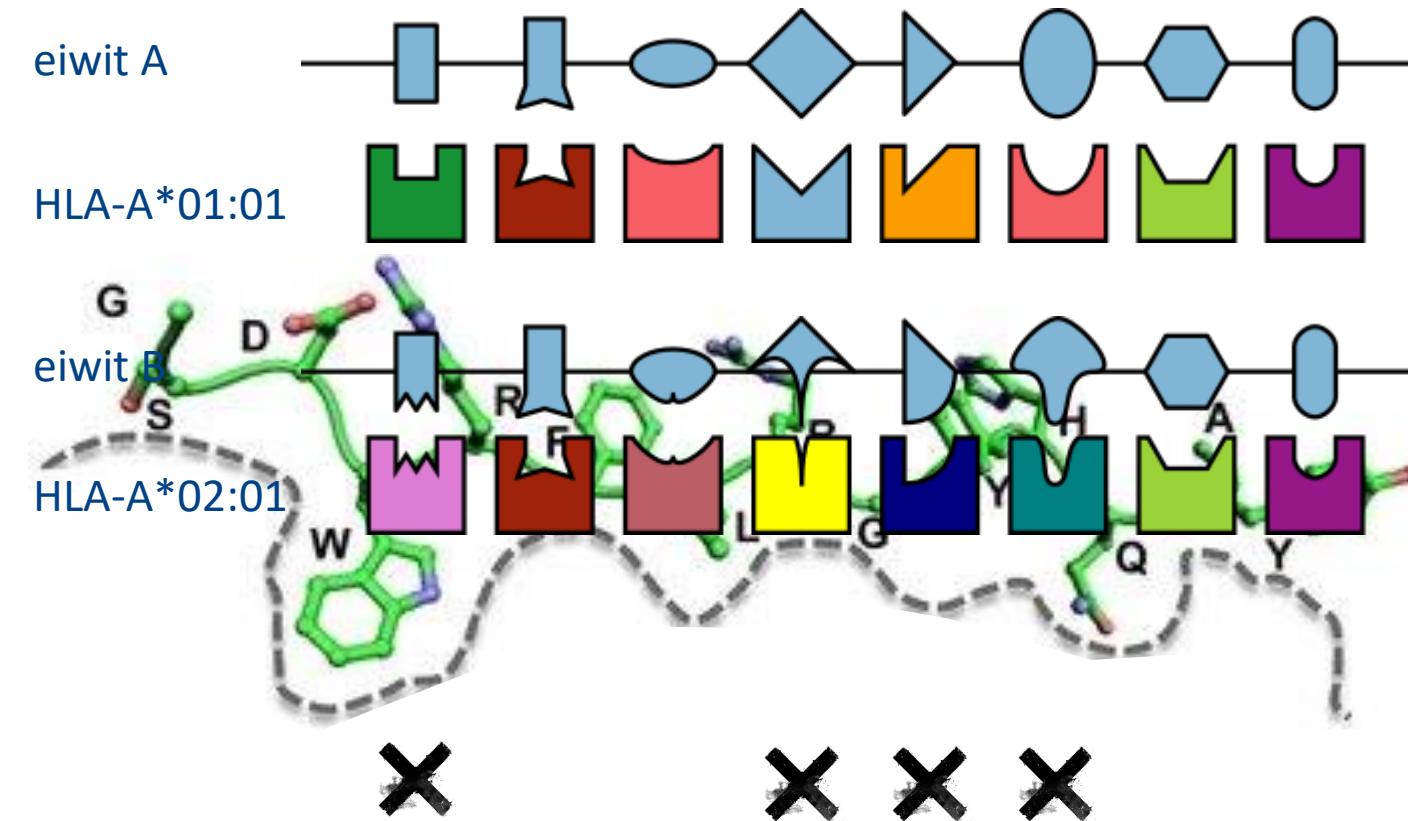
T cells recognize epitopes via their T-cell receptor (TCR), which interact with peptides in combination with HLA

target

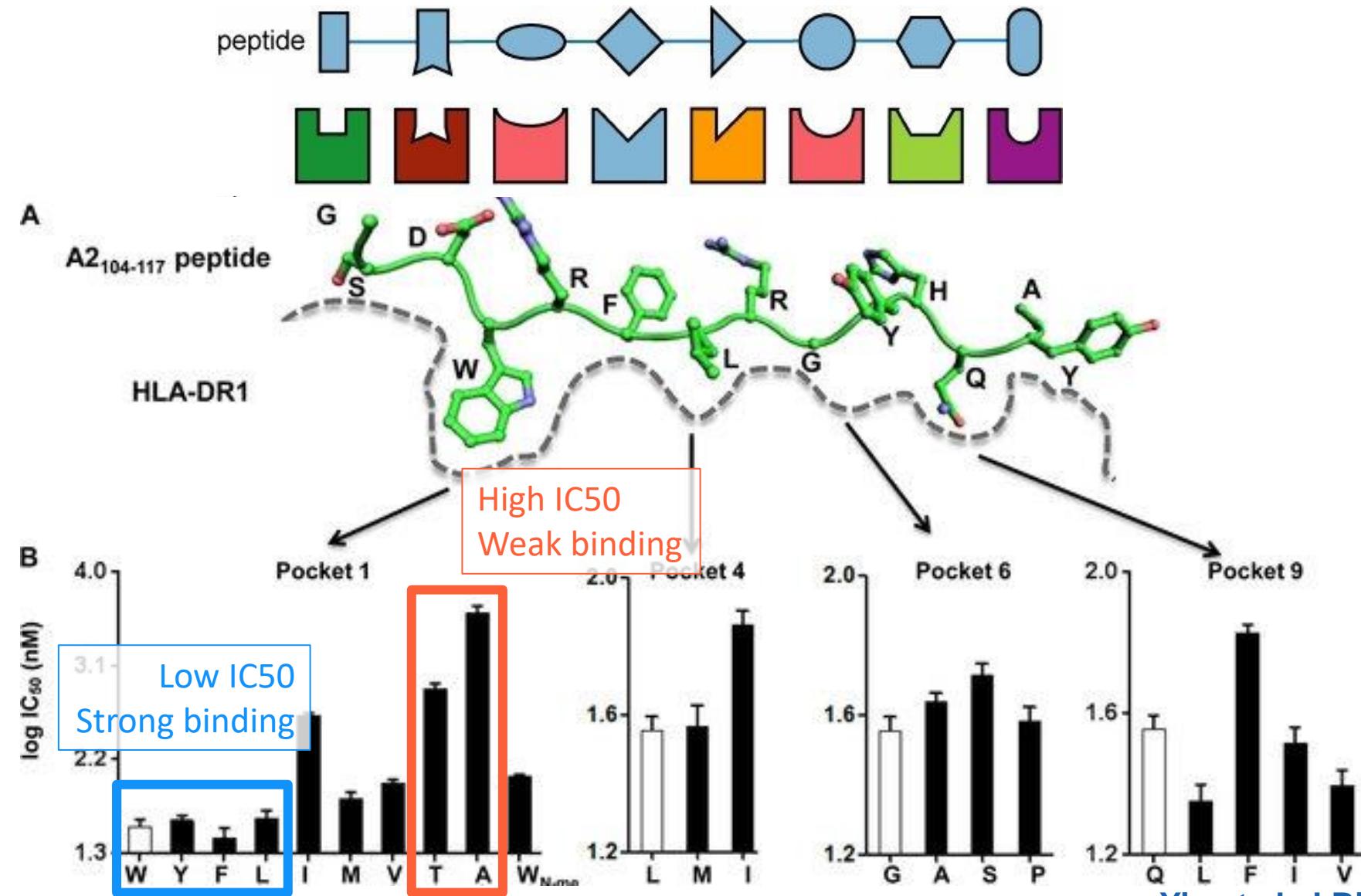


effector

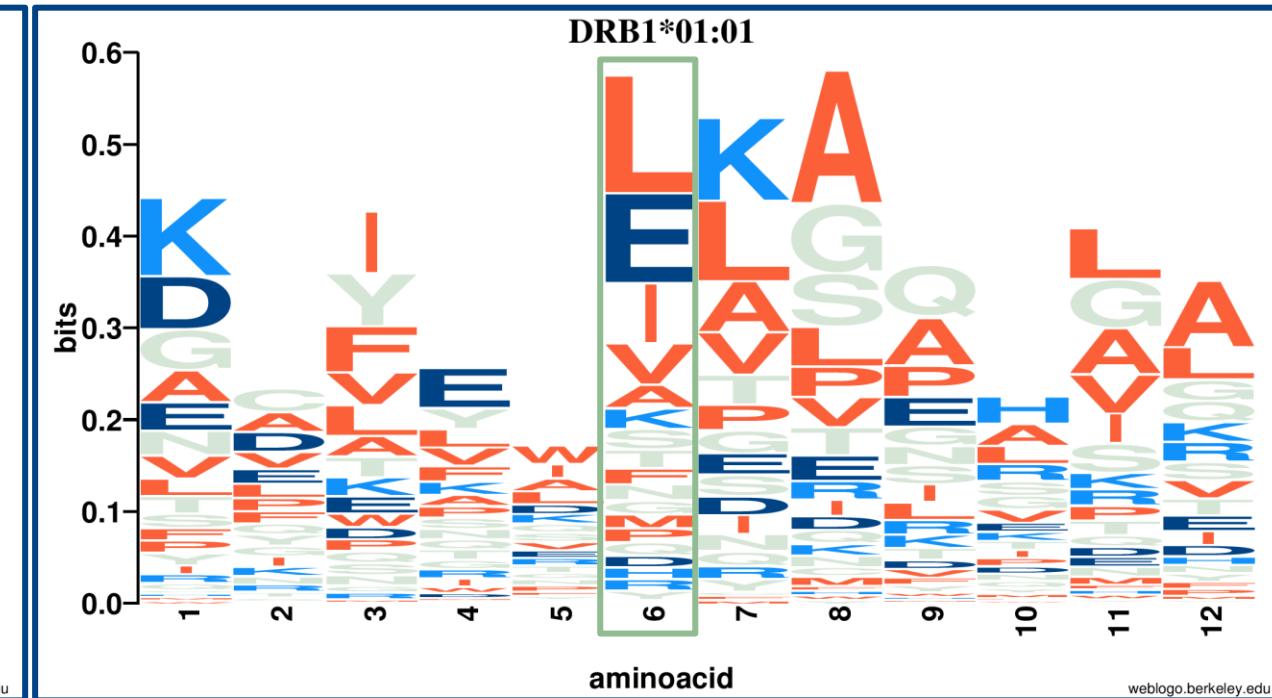
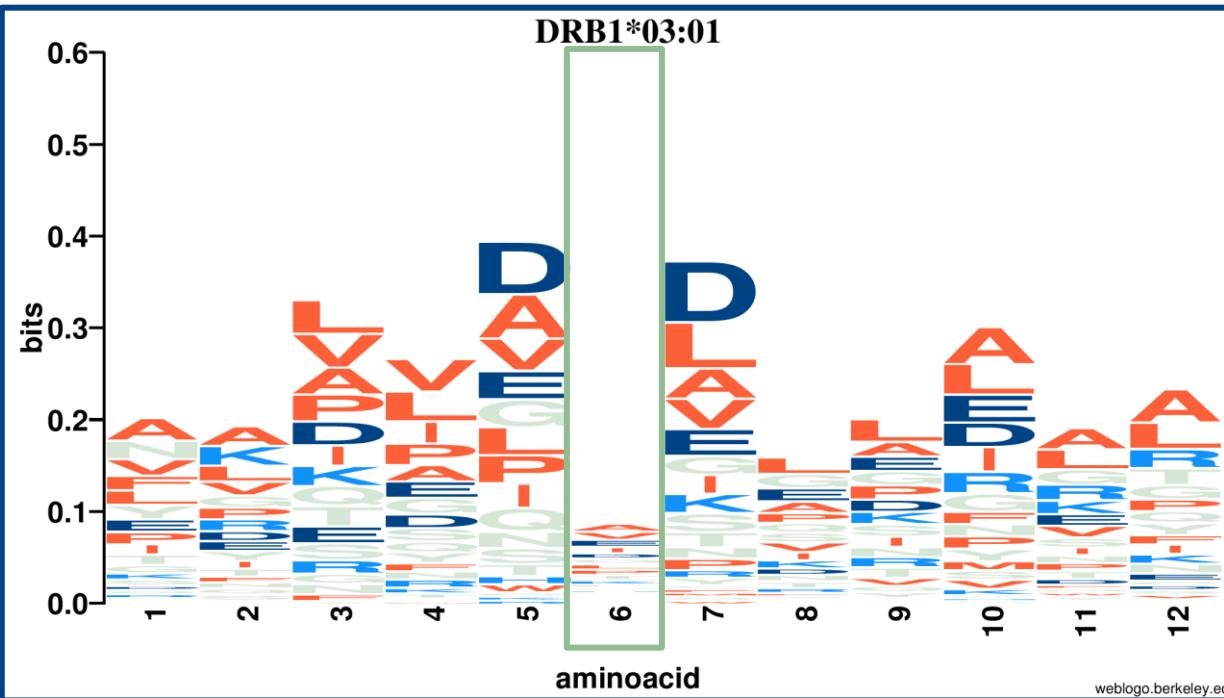
Epitope rule 3: T cells recognize small protein in HLA



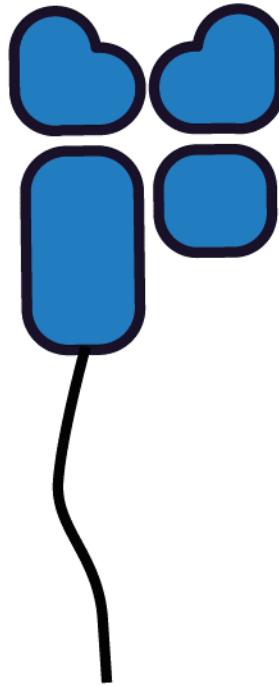
HLA pockets and anchor residues



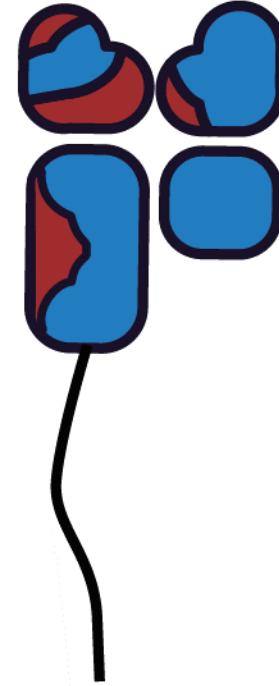
different alleles have different binding patterns



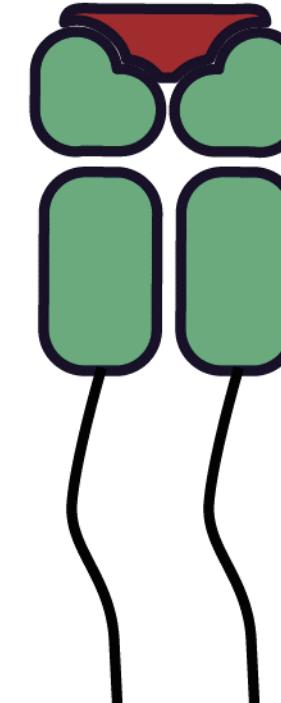
a prediction model for indirect HLA presentation



recipient
HLA class I



donor
HLA class I



recipient
HLA class II

PIRCHE ['percə]

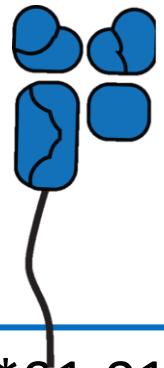
noun, acronym

Predicted Indirectly ReCognizable HLA Epitope

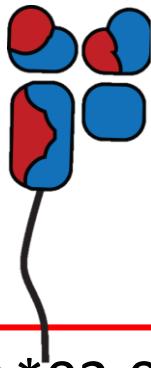
PIRCHE-I: presented by HLA class I → CD8 T cells (cytotoxic T cells)

PIRCHE-II: presented by HLA class II → CD4 T cells (helper T cells)

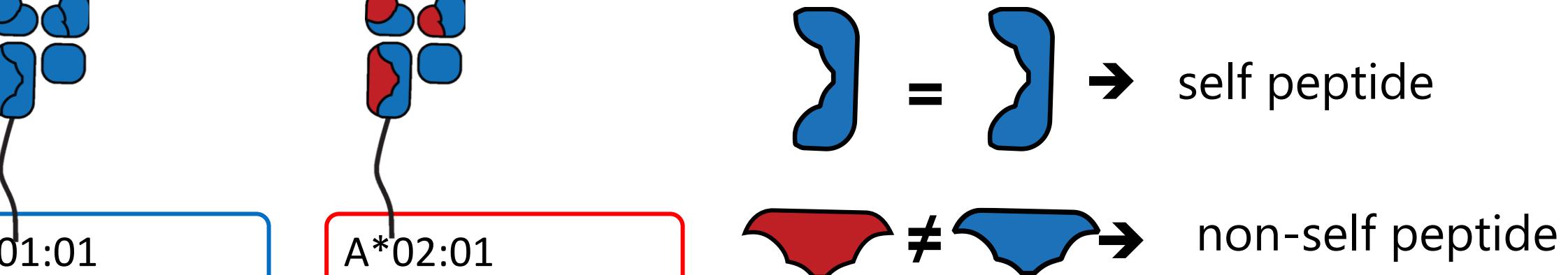
example of PIRCHE



A*01:01



A*02:01



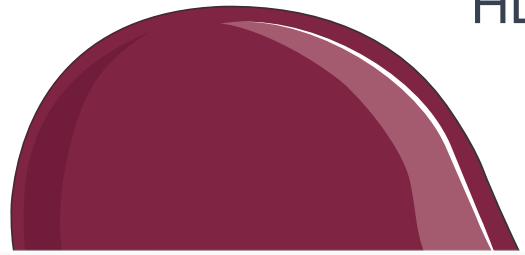
donor: A*01:01 MAVMAPRTL LLLLL GALALTQTWA

recipient: A*02:01 ----- V----- -----

A*01:01 ASQKMEPRAP WIEQEGPEYW DQE_HTRNMKA

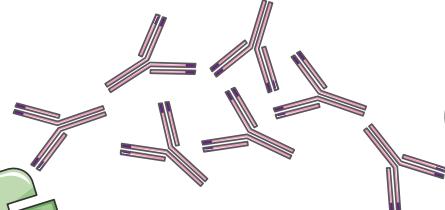
A*02:01 ---R----- ----- -G---KV--

adaptive immunity in transplantation



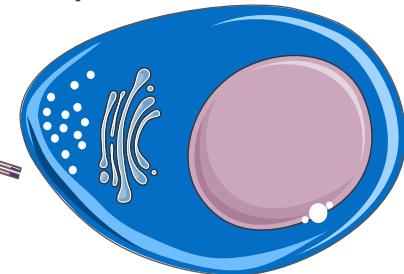
American Journal of Transplantation 2017; 17: 3076–3086
Wiley Periodicals Inc.

HLA antibodies

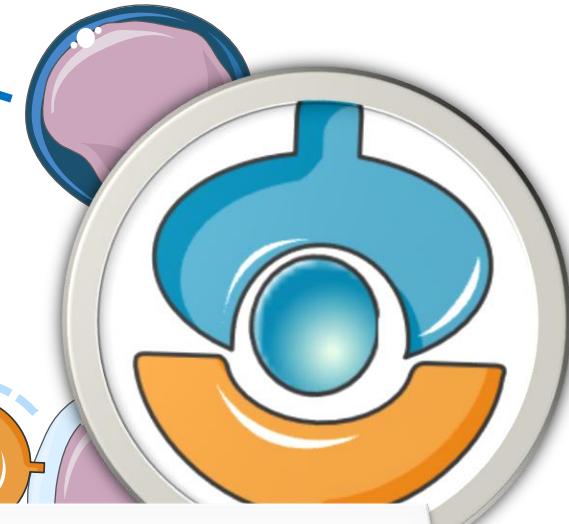


© 2017 The American Society of Transplantation
and the American Society of Transplant Surgeons
doi: 10.1111/ajt.14393

plasma cell



B cell

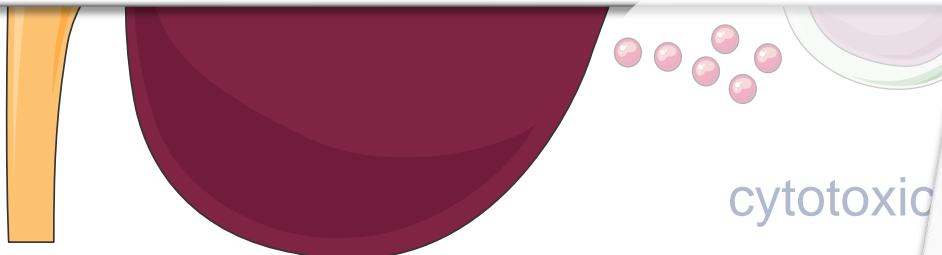


**Donor–Recipient Matching Based on Predicted
Indirectly Recognizable HLA Epitopes Independently
Predicts the Incidence of *De Novo* Donor-Specific HLA
Antibodies Following Renal Transplantation**

N. Lachmann^{1,*}, M. Niemann², P. Reinke^{3,†},
K. Budde³, D. Schmidt³, F. Halleck³, A. Prüß⁴,
C. Schönemann¹, E. Spierings⁵ and O. Staack³

¹Center for Tumor Medicine, H&L Laboratory, Charité

Abbreviations: AA, amino acid; AMR, antibody-mediated rejection; CDC, complement-dependent cytotoxicity test; CI, confidence interval; dnDSA, de novo donor-specific HLA antibodies; DSA, donor-specific HLA antibody(ies); HLAab, HLA antibody(ies);



frontiers
in Immunology

OPEN ACCESS

Edited by:
Aurore Saudeumont,
[✉ a.saudemont@chru-lille.fr](#)

**PIRCHE-II Is Related to Graft
Failure after Kidney Transplantation**

Kirsten Geneugelijk¹, Matthias Niemann², Julia Drylewicz¹, Arjan D. van Zuijen³,
Irma Joosten⁴, Wil A. Allesbes⁴, Arnold van der Meer⁴, Luuk B. Hilbrands⁵, Marije C. Baas⁵,
C. Erik Hack¹, Franka E. van Reekum³, Marianne C. Verhaar³, Elena G. Kamburova¹,
Michiel L. Bots⁶, Marc A. J. Seelen⁷, Jan Stephan Sanders⁷, Bouke G. Hepkema⁸,
Annechien J. Lambeck⁸, Laura B. Bungener⁸, Caroline Roozendaal⁸, Marcel G. J. Tilanus⁹,
Iris Vandenbroucke¹⁰, Christian E. Hoekstra⁹, Lotte Winton⁹, Elly M. van Duinenhoven¹¹

PIRCHE and the prediction of *de novo* DSA

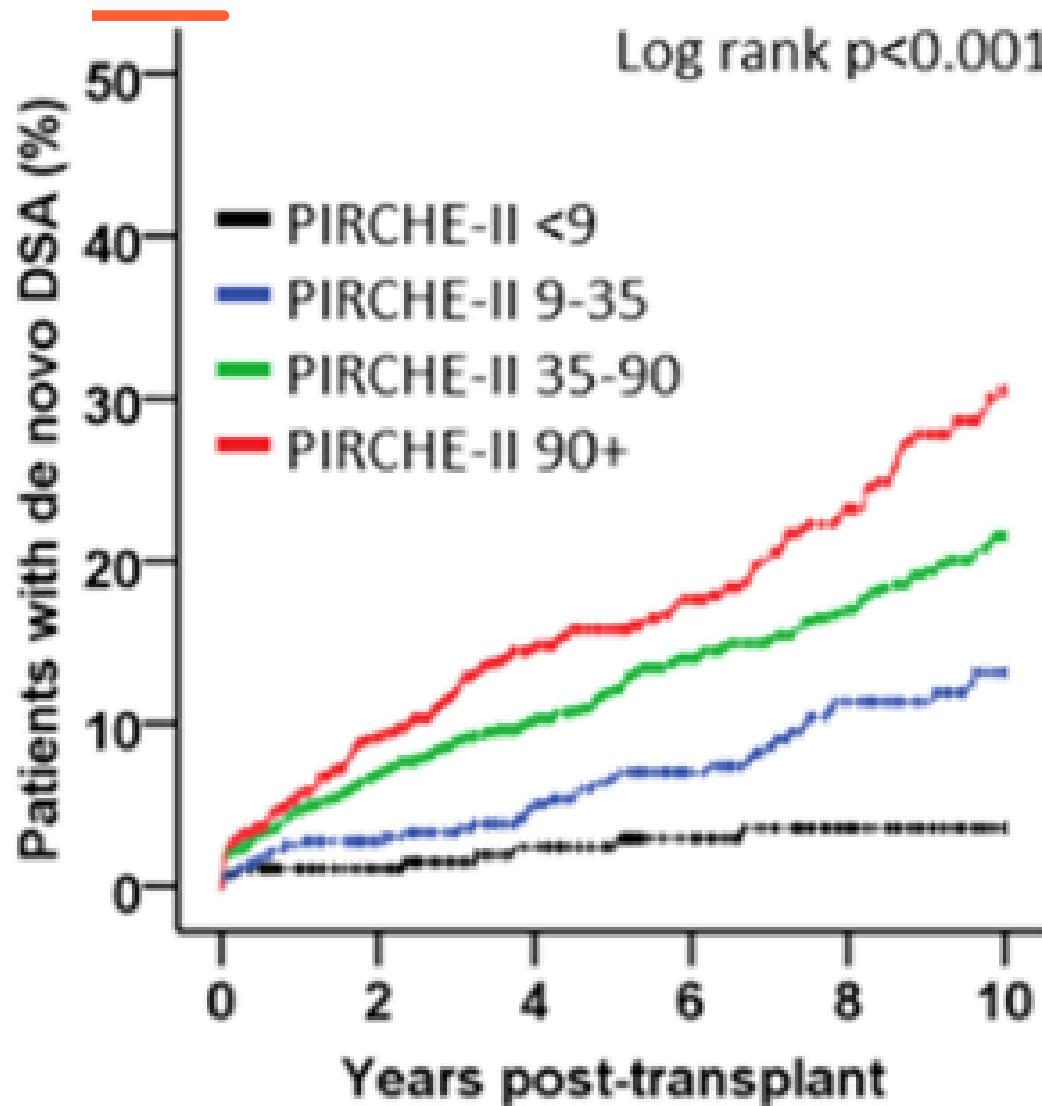
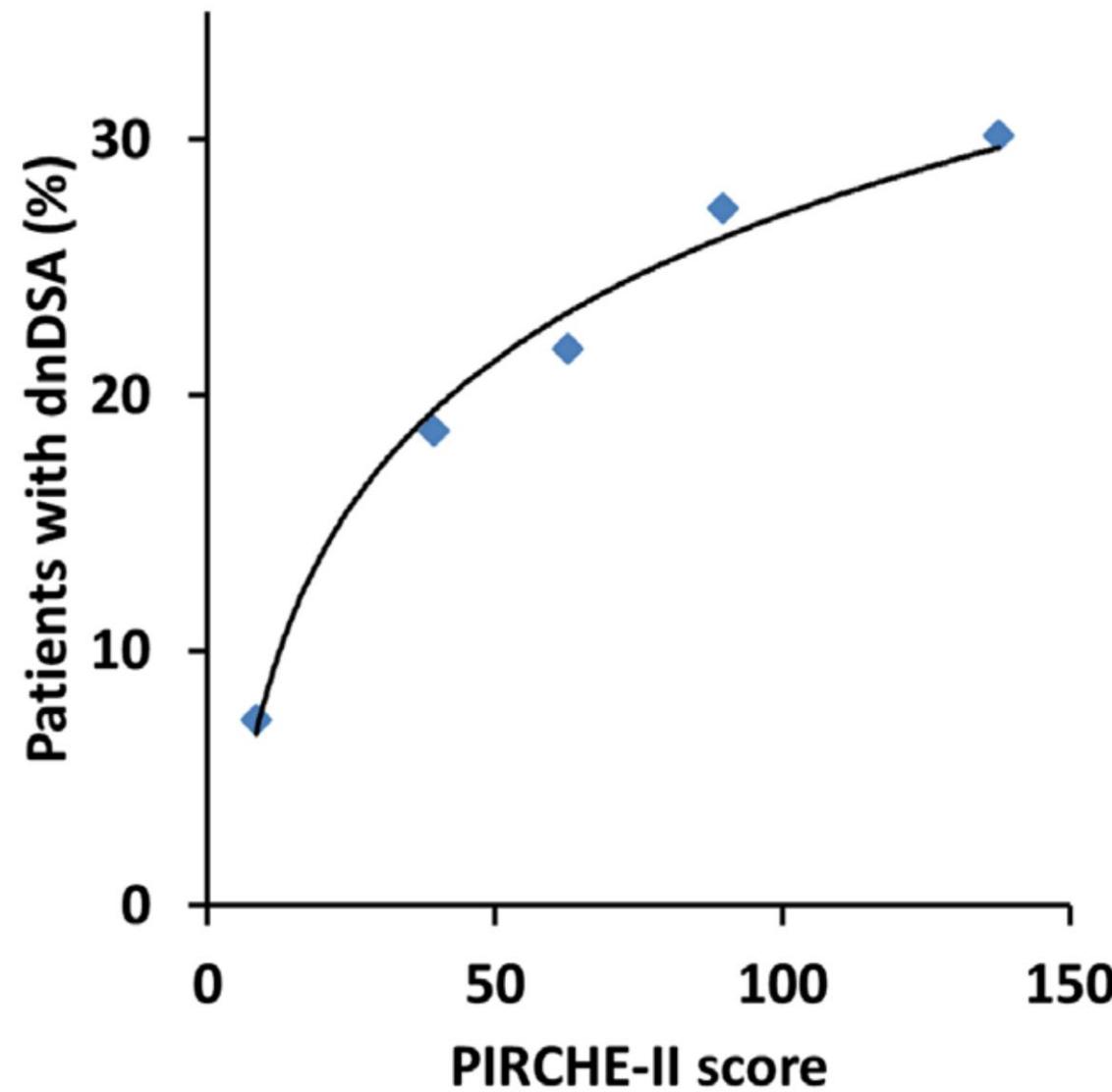


Table 1: Patient characteristics (n = 2787)

Follow-up, years (SD)	7.2 (4.8)
Recipient age, years (SD)	49.9 (13.9)
Donor age, years (SD)	50.2 (15.8)
Female gender	1095 (39%)
Time on dialysis, years (IQR)	4.8 (2.1–7.0)
Prior kidney transplantation	322 (12%)
Living donor	623 (22%)
ABO incompatible	88 (3%)
Split-HLA-mismatches (A,B,DR) (IQR)	3 (2–4)
Split HLA-mismatches (A,B,C,DR,DQ) (IQR)	5 (3–7)
Combined kidney–pancreas transplantation	159 (6%)
Cold ischemia time, hours (SD)	9.8 (5.7)
Lowest serum creatinine posttransplant, mg/dL (IQR)	1.1 (0.9–1.4)

PIRCHE-II and *de novo* DSA correlate non-linearly

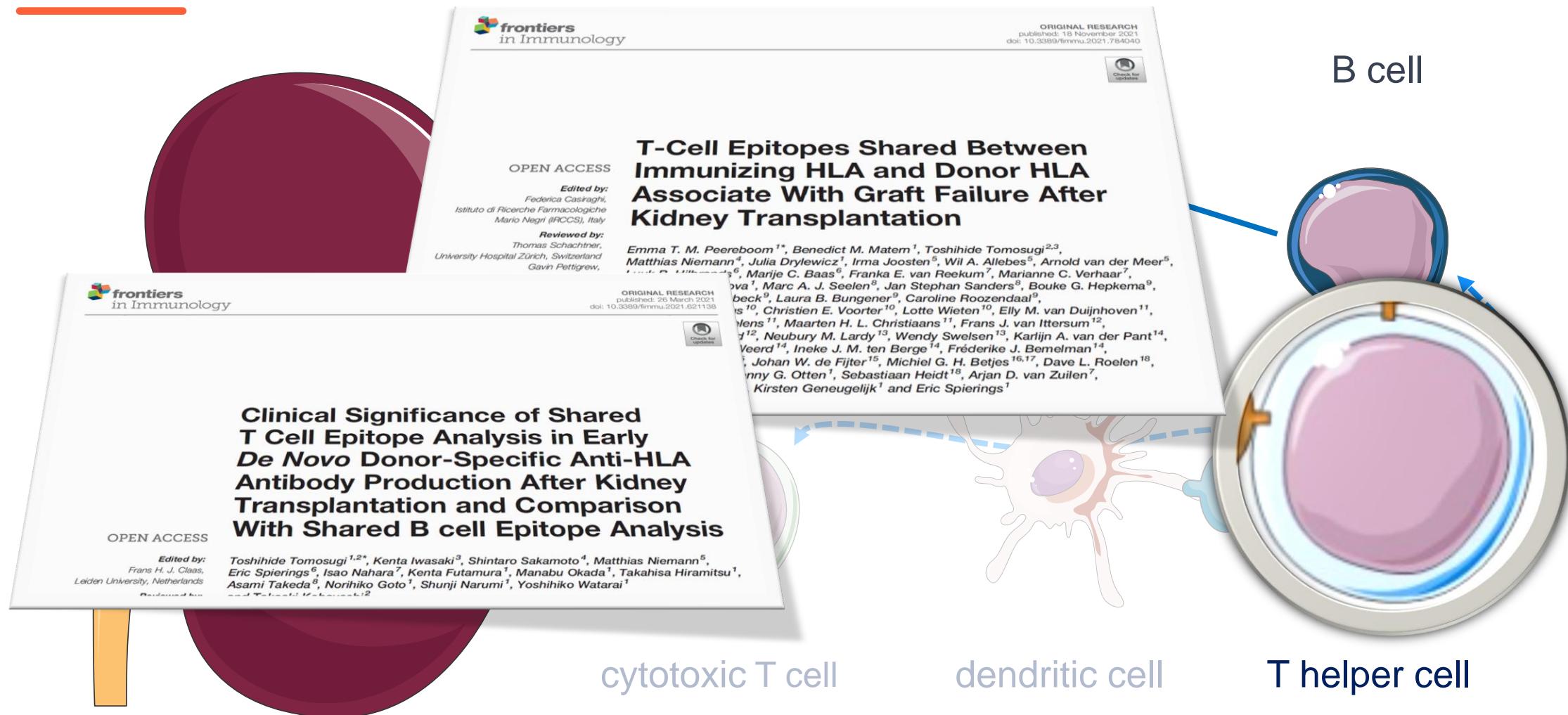


HLA factors in kidney transplant outcome

	Univariate			Multivariable model with forward stepwise selection		
	HR	95%-CI	p-value	HR	95%-CI	p-value
In(PIRCHE-II)	1.12	1.05 - 1.19	<0.001	1.11	1.04 - 1.17	0.001
Eplets	1.01	1.00 - 1.02	0.001			
Number of A/B/DR mismatches	1.12	1.05 - 1.19	<0.001			
Recipient age	0.99	0.99 - 1.00	0.002	0.99	0.99 - 1.00	<0.001
Donor age	1.02	1.02 - 1.03	<0.001	1.02	1.02 - 1.03	<0.001
Transplantation year	0.98	0.96 - 1.00	0.08	0.97	0.95 - 0.99	0.009
Recipient immunization status	1.17	1.01 - 1.36	0.04			

Cox proportional hazard analysis. All parameters as continuous variable.

Memory T cell responses in transplantation

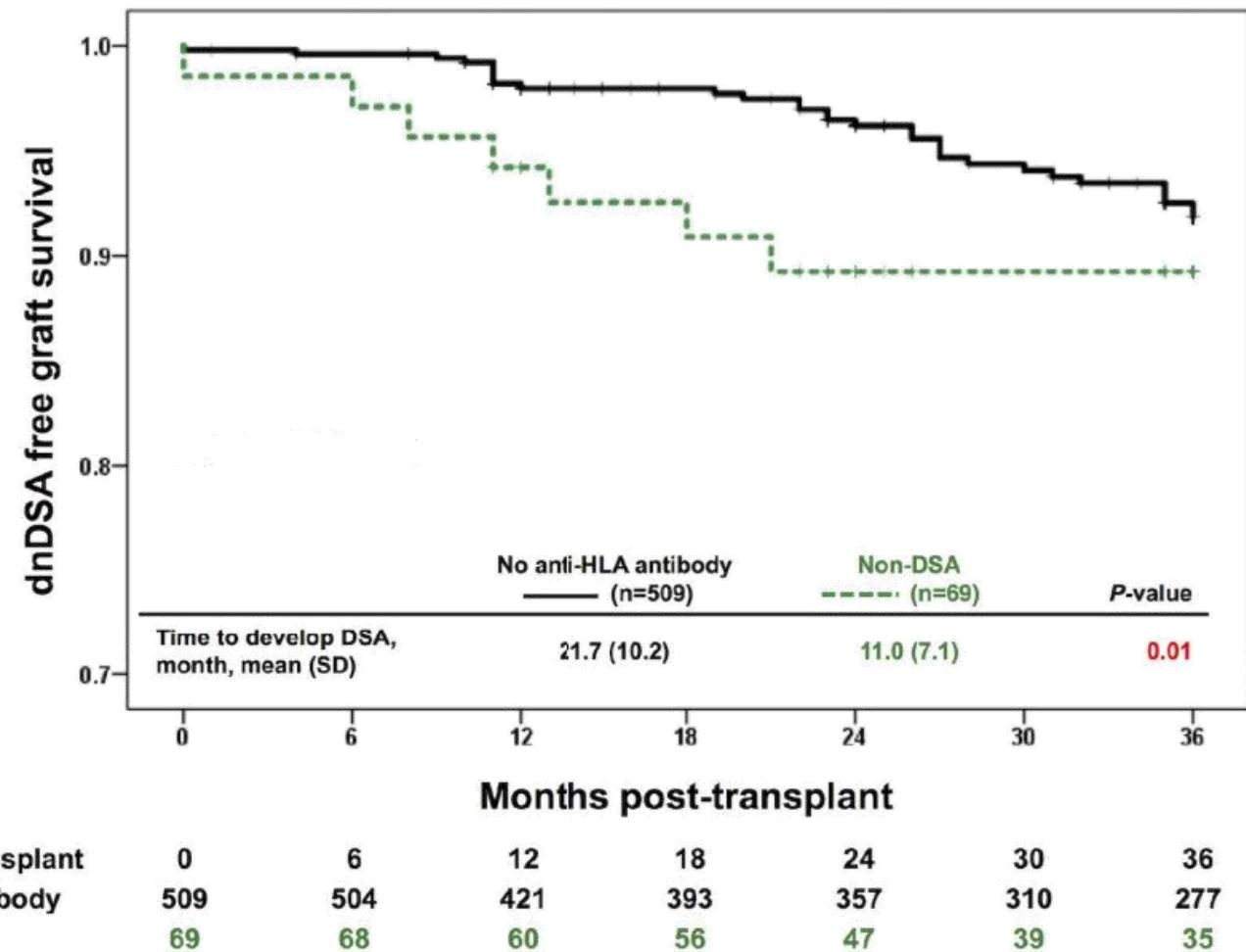


non-DSA HLA antibodies associate with decreased graft survival

Recipients with pre-transplant non-DSA HLA antibodies have a decreased graft survival¹⁻³ and diminished graft function⁴

Despite missing B-cell epitopes, there still seems to be a memory response

- Possibly a consequence of T-cell memory



¹Morath *et al.* Front Immunol. 2020

²Otten *et al.* Am J Transplant. 2012

³Tomosugi *et al.* Front. Immunol. 2021

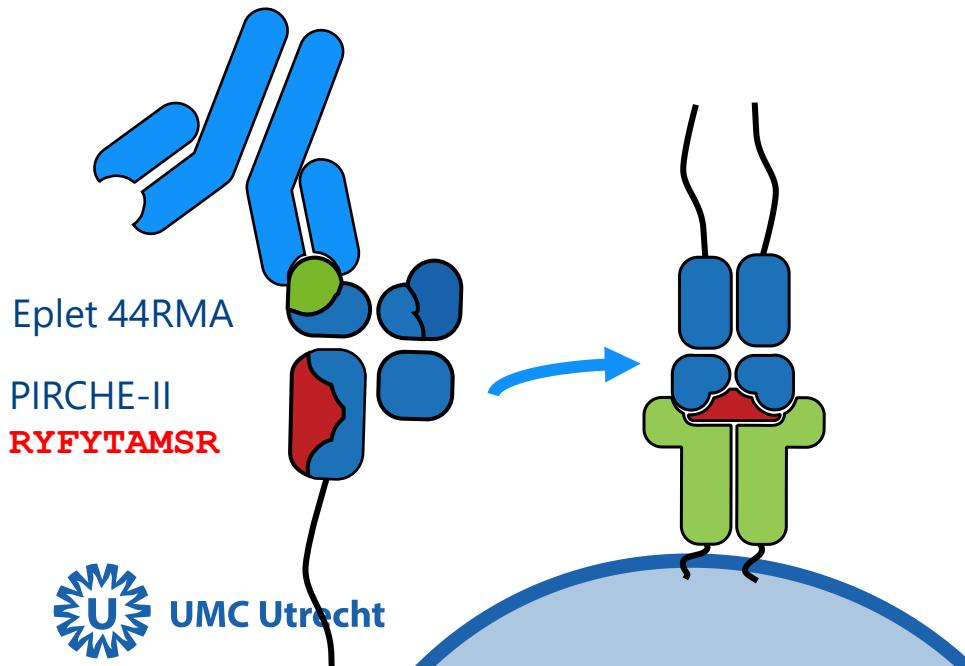
⁴von Moos *et al.* Hum Immunol. 2021

shared T-cell epitopes and allo-immune reactions post-transplantation

Pre-transplantation

Recipient with HLA-B46 antibodies
and T cells

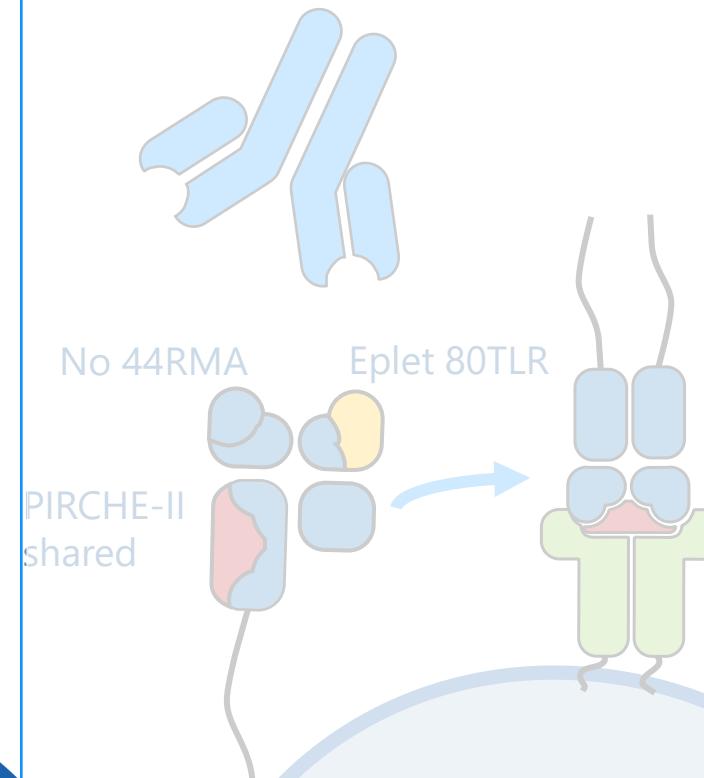
LALTETWAGS**HSMRYFYTAMSRPGRGEPRFIAV**



Transplantation

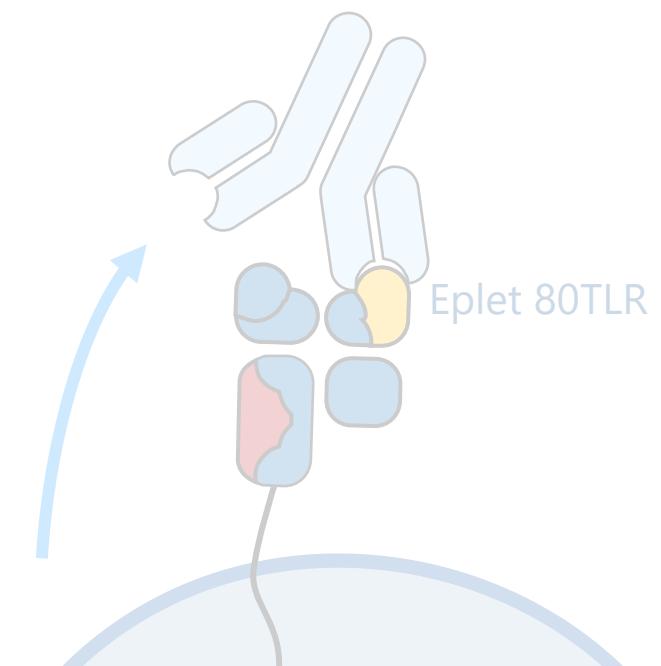
HLA-B44 donor (no DSA)

VALTETWAGS**HSMRYFYTAMSRPGRGEPRFITV**

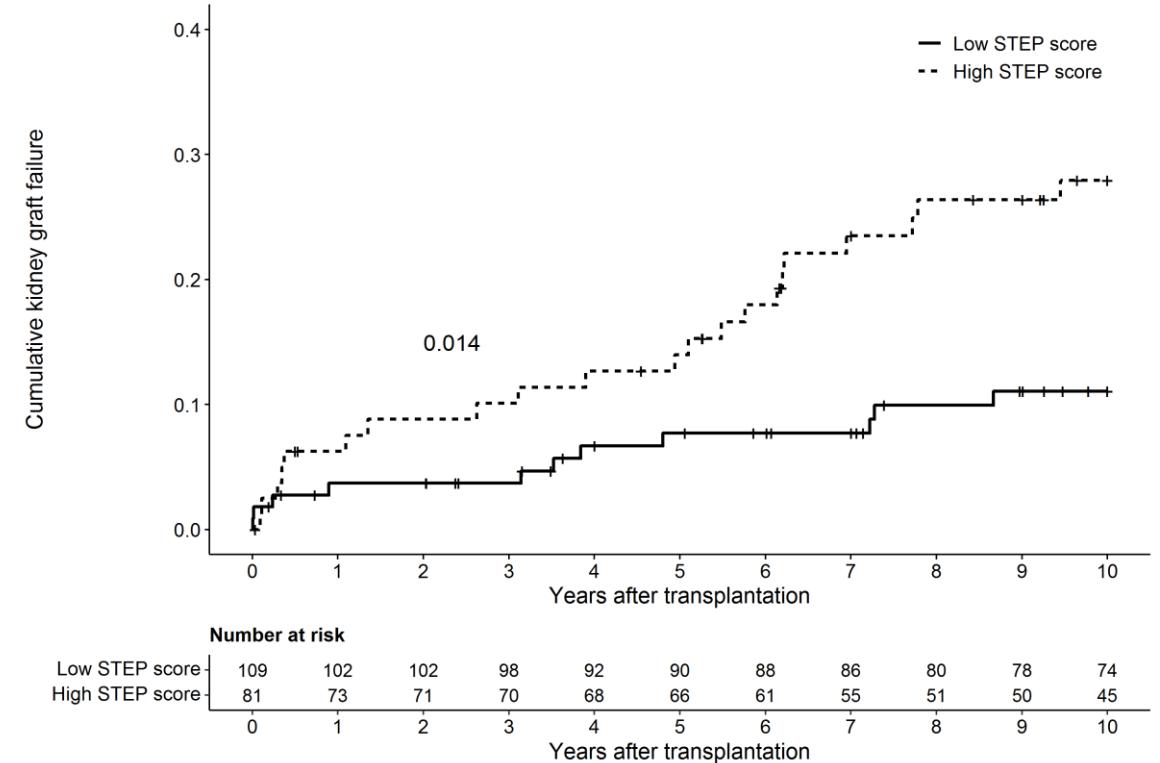
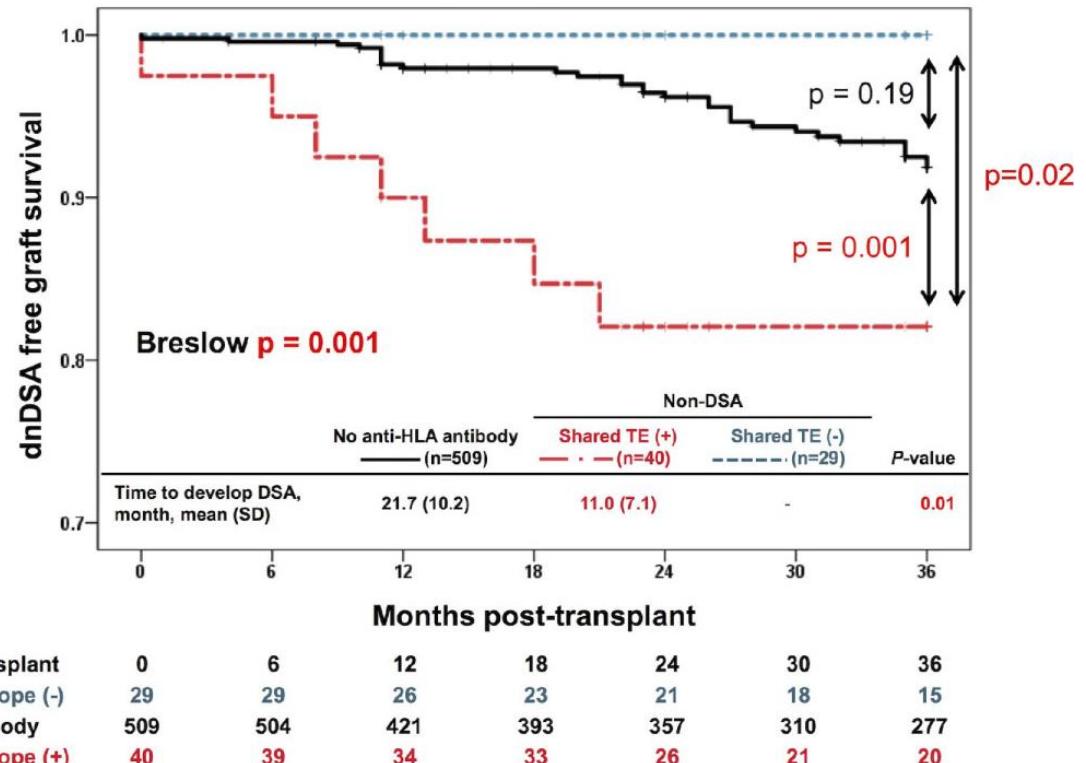


Post-transplantation

HLA-B44 antibody



shared T-cell epitopes (STEP) in DSA development and graft failure



T-cell specific responses after organ transplantation

AJKD

Original Investigation

Association of Predicted HLA T-Cell Epitope Targets and T-Cell–Mediated Rejection After Kidney Transplantation

Aleksandar Senev, Elisabet Van Loon, Evelyne Lerut, Maarten Coemans, Jasper Calleymeyn, Liesbeth Daniëls, Johan Kerkhofs, Priyanka Koshy, Dirk Kuypers, Baptiste Lamartée, Ben Sprangers, Claire Tinel, Amaryllis H. Van Craenenbroeck, Vicky Van Sandt, Marie-Paule Emonds, and Maarten Naesens

Rationale & Objective: The relationship between human leukocyte antigen (HLA) molecular mismatches and T-cell-mediated rejection (TCMR) is unknown. We investigated the associations between the different donor HLA-derived T-cell targets and the occurrence of TCMR and borderline histologic changes suggestive of TCMR after kidney transplantation.

Study Design: Retrospective cohort study.

FIMMU

Check for updates

OPEN ACCESS

EDITED BY
Mohamed Ghoneim,
Mansoura University, Egypt

REVIEWED BY
Josefina M. Alberu,
Tecnológico de Monterrey, Mexico
Kirsten Thus,
Princess Maxima Center for Pediatric Oncology, Netherlands

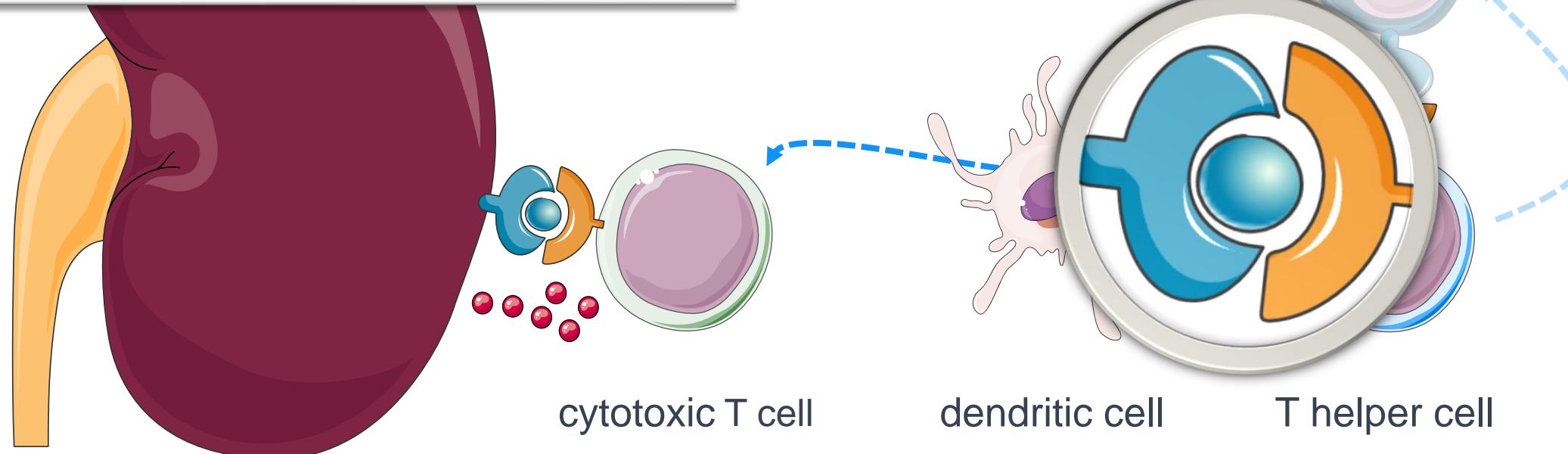
***CORRESPONDENCE**
Michiel G. H. Betjes
m.g.h.betjes@erasmusmc.nl

SPECIALTY SECTION
This article was submitted to
Alloimmunity and Transplantation,

doi: 10.3389/fimmu.2022.973968

The number of donor HLA-derived T cell epitopes available for indirect antigen presentation determines the risk for vascular rejection after kidney transplantation

Michiel G. H. Betjes^{1*}, Emma T. M. Peereboom²,
Henny G. Otten² and Eric Spierings²



T cell mediated rejection and PIRCHE – Senev 2022

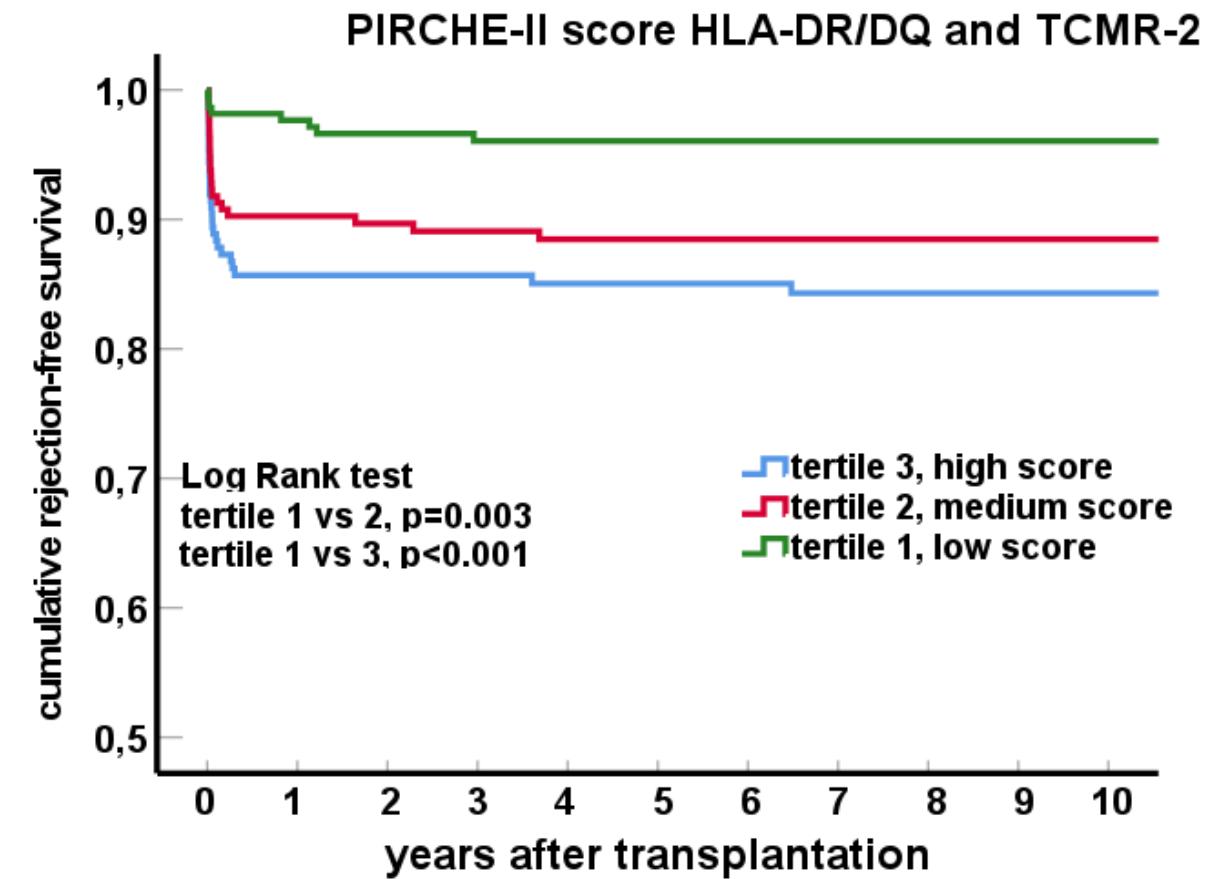
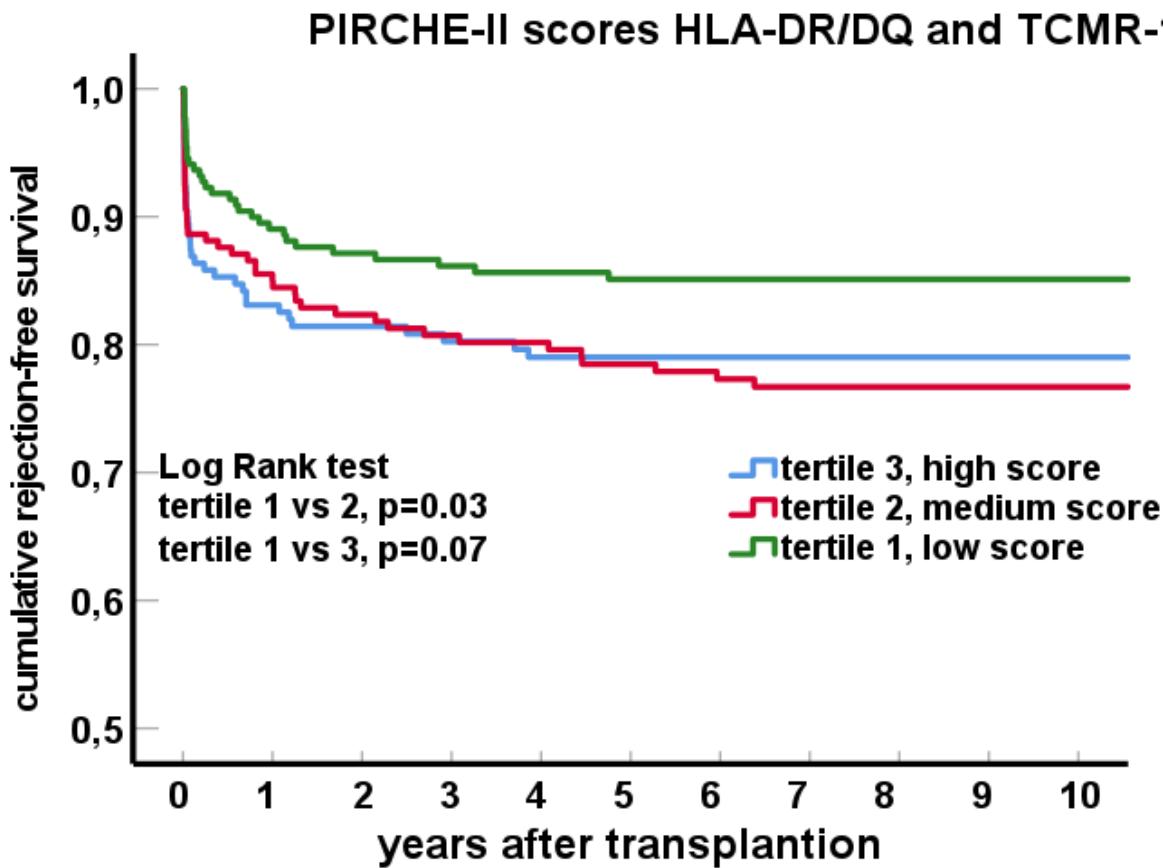
Table 1. Adjusted Hazard Ratios for Acute TCMR Only or Acute/Borderline TCMR by PIRCHE-II Score

	Acute TCMR Only (277 Events)		Acute/Borderline TCMR (411 Events)	
	AHR (95% CI)	P	AHR (95% CI)	P
Total PIRCHE-II score	1.01 (1.00-1.02)	0.009 ^a	1.01 (1.00-1.01)	0.007 ^a
PIRCHE-II score for HLA class I	1.00 (0.99-1.02)	0.7	1.00 (0.99-1.01)	0.8
PIRCHE-II score for HLA-A	1.00 (0.98-1.03)	0.8	1.01 (0.99-1.03)	0.3
PIRCHE-II score for HLA-B	1.00 (0.97-1.03)	0.9	0.99 (0.97-1.02)	0.7
PIRCHE-II score for HLA-C	1.01 (0.98-1.03)	0.5	1.00 (0.98-1.02)	0.9
PIRCHE-II score for HLA class II	1.01 (1.01-1.02)	0.002 ^a	1.01 (1.00-1.02)	0.001 ^a
PIRCHE-II score for HLA-DRB1/3/4/5	1.02 (1.00-1.04)	0.03 ^a	1.02 (1.00-1.04)	0.03 ^a
PIRCHE-II score for HLA-DRB1	1.08 (1.03-1.12)	<0.001 ^a	1.07 (1.04-1.10)	<0.001 ^a
PIRCHE-II score for HLA-DRB3/4/5	1.01 (0.98-1.04)	0.4	1.01 (0.98-1.03)	0.7
PIRCHE-II score for HLA-DQA1/B1	1.02 (1.00-1.03)	0.01 ^a	1.02 (1.01-1.03)	0.002 ^a
PIRCHE-II score for HLA-DQA1	1.02 (1.00-1.04)	0.1	1.02 (1.00-1.04)	0.01 ^a
PIRCHE-II score for HLA-DQB1	1.03 (1.01-1.06)	0.005 ^a	1.03 (1.01-1.05)	0.001 ^a
PIRCHE-II score for HLA-DPBA1/B1	1.03 (0.99-1.06)	0.1	1.02 (0.99-1.05)	0.2
PIRCHE-II score for HLA-DPA1	1.04 (0.99-1.08)	0.1	1.02 (0.98-1.06)	0.3
PIRCHE-II score for HLA-DPB1	1.05 (0.99-1.12)	0.1	1.03 (0.98-1.09)	0.2

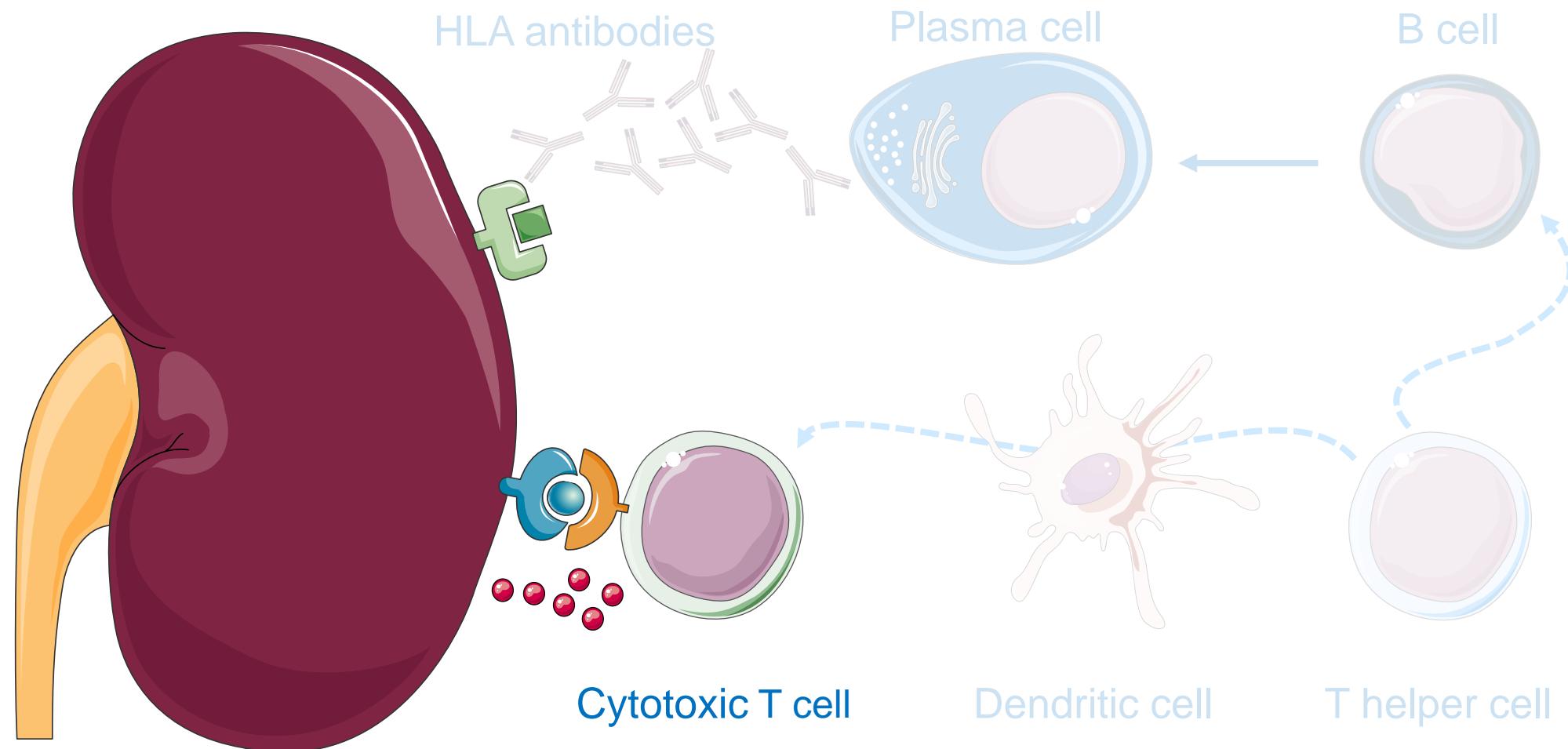
N = 893. Each row represents a separate multivariable analysis, and each hazard ratio is estimated per 10-point greater PIRCHE-II score. All multivariable models were adjusted for donor and recipient age, donor type, cold ischemia time, repeat transplantation, panel-reactive antibody (%), and induction therapy (no induction vs basiliximab vs other treatment). Abbreviations: AHR, adjusted hazard ratio; HLA, human leukocyte antigen; PIRCHE-II, Predicted Indirectly Recognizable HLA Epitopes by Recipient HLA Class II Molecules; TCMR, T-cell-mediated rejection.

^aStatistically significant value.

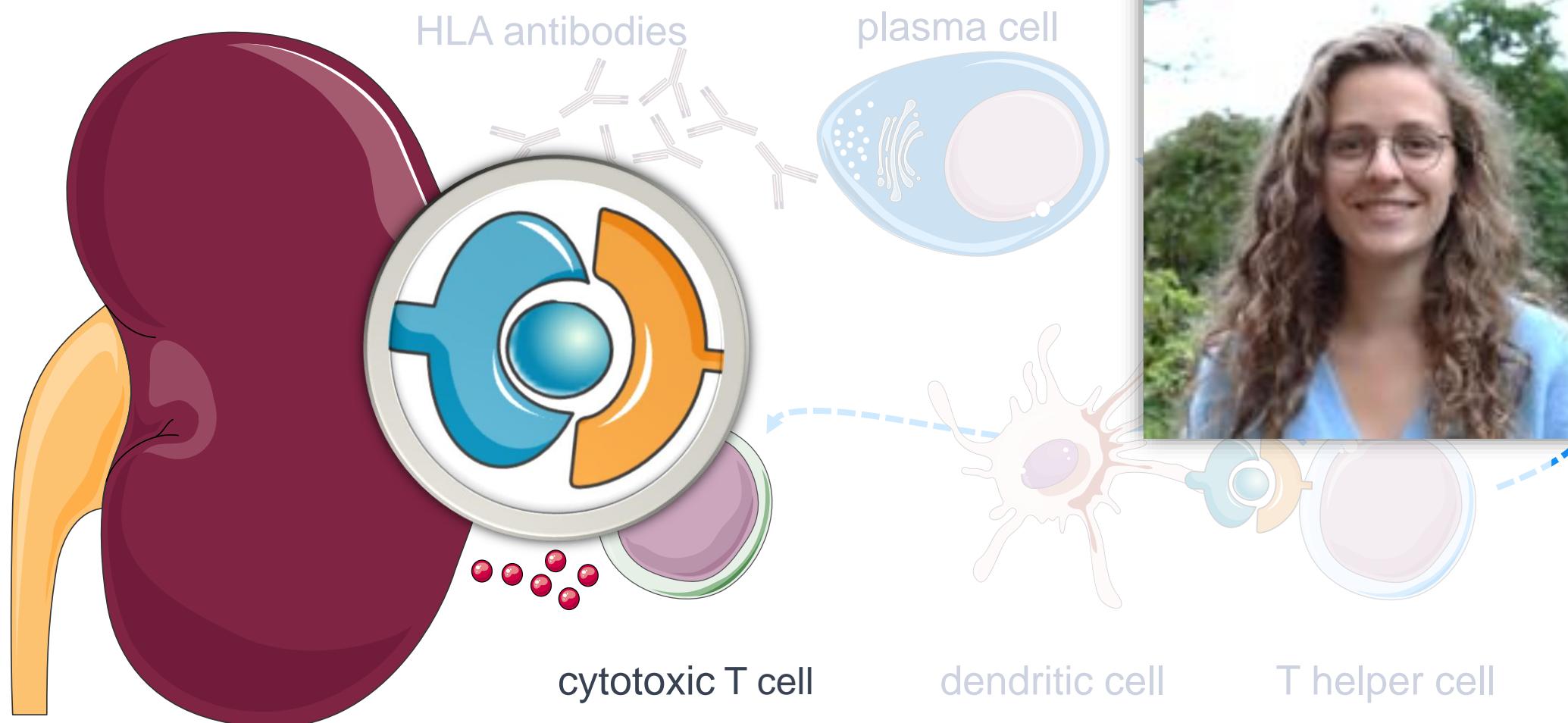
PIRCHE-II DQ/DR associate with rejection-free survival



T-cell adaptive immunity and graft rejection



Infection meets alloimmunity





Overlap between CMV and HLA mismatch affect transplantatie

Infection meets alloimmunity

Emma Peereboom

CMV and HLA can share T cell epitopes

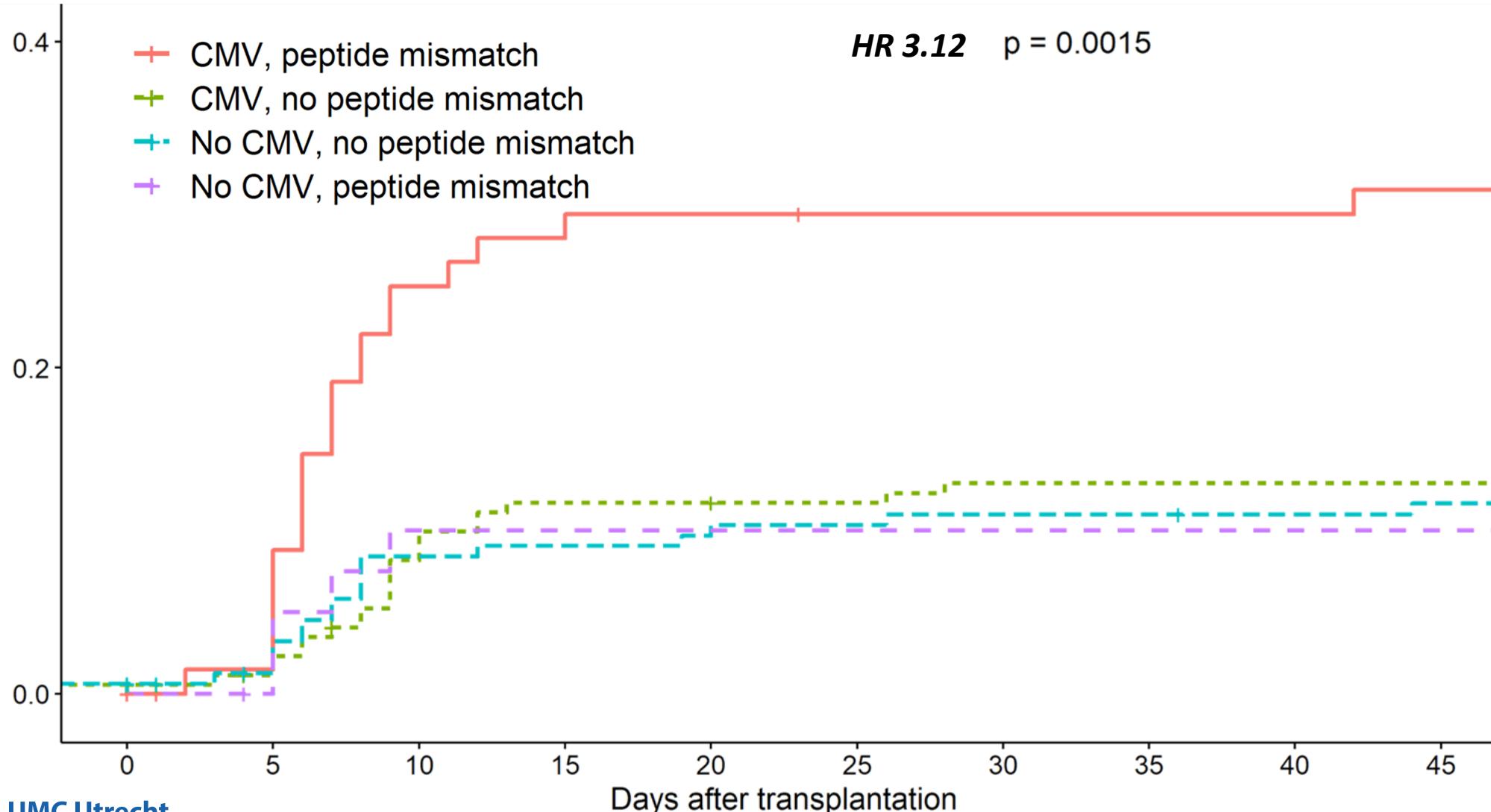
- Peptides in specific HLA class I variant are shared by the CMV protein UL40

CMV stam	Peptide	Frequentie [1]	HLA klasse I
AD169	VMAPRTLIL	~30%	HLA-C

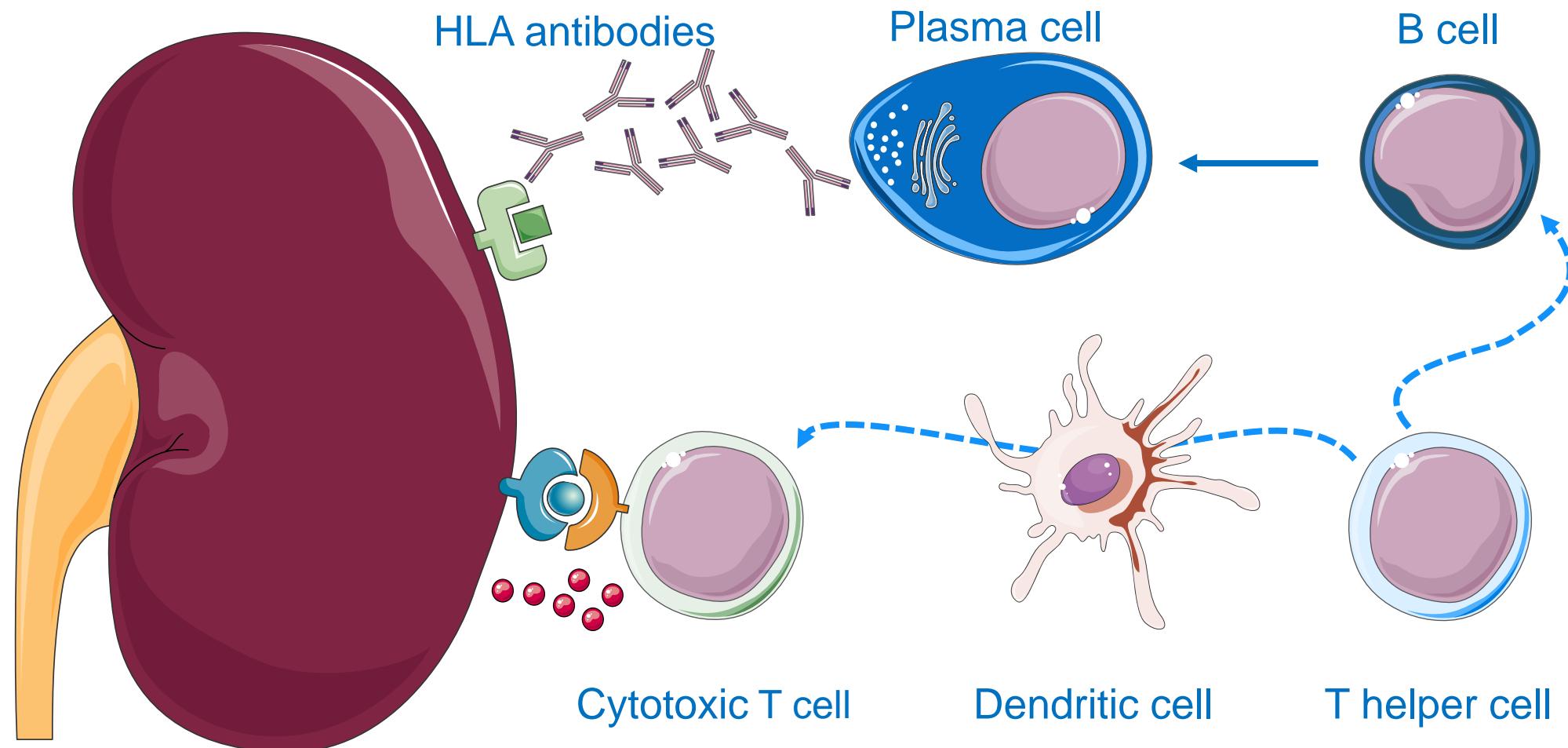
UL40--AD169	MNKFSNTRIGFTCA	VMAPRTLIL	TVGLLCMRIRSLLCSPAETTVTTAAVTSAHGPLCPLV	60
HLA-C*03:03	-----	-MRVMAPRTLIL	LLSGALALTETWAGSHSMRYFYTAVSRPGRGE-PHFI	47
HLA-C*07:01	-----	-MRVMAPRALLL	LLSGGGLALTETWACSHSMRYFDTAVSRPGRGE-PRFI	47
HLA-C*02:02	-----	-MRVMAPRTLIL	LLSGALALTETWACSHSMRYFYTAVSRPSRGE-PHFI	47

[1] Heatley *et al.* J Biol Chem. 2013, Jouand *et al.* PLoS Pathog. 2018, Vietzen *et al.* mBio. 2021.

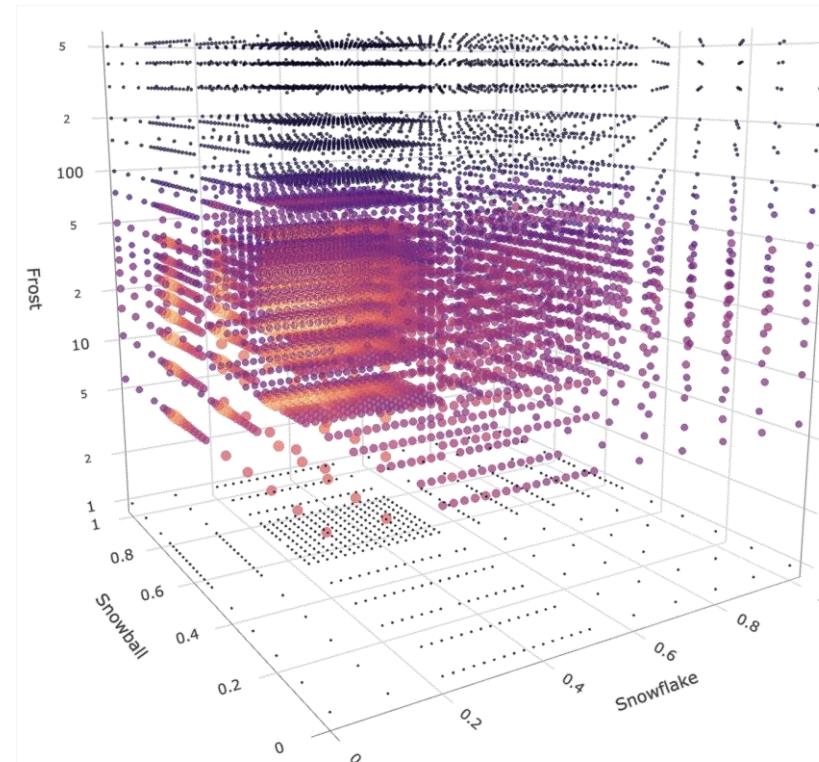
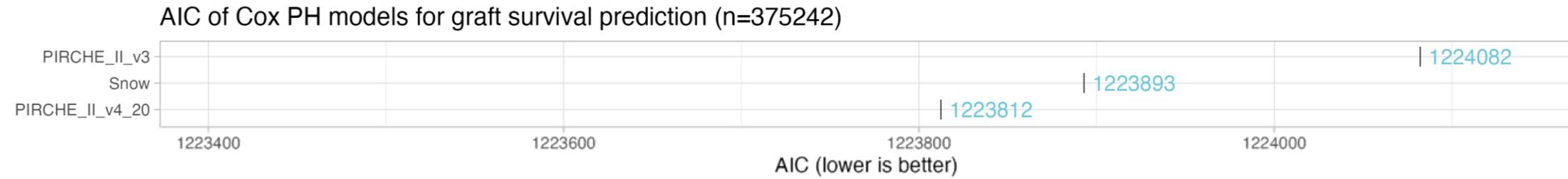
Shared epitopes increase the risk for TCMR



An integrated HLA epitope risk classification



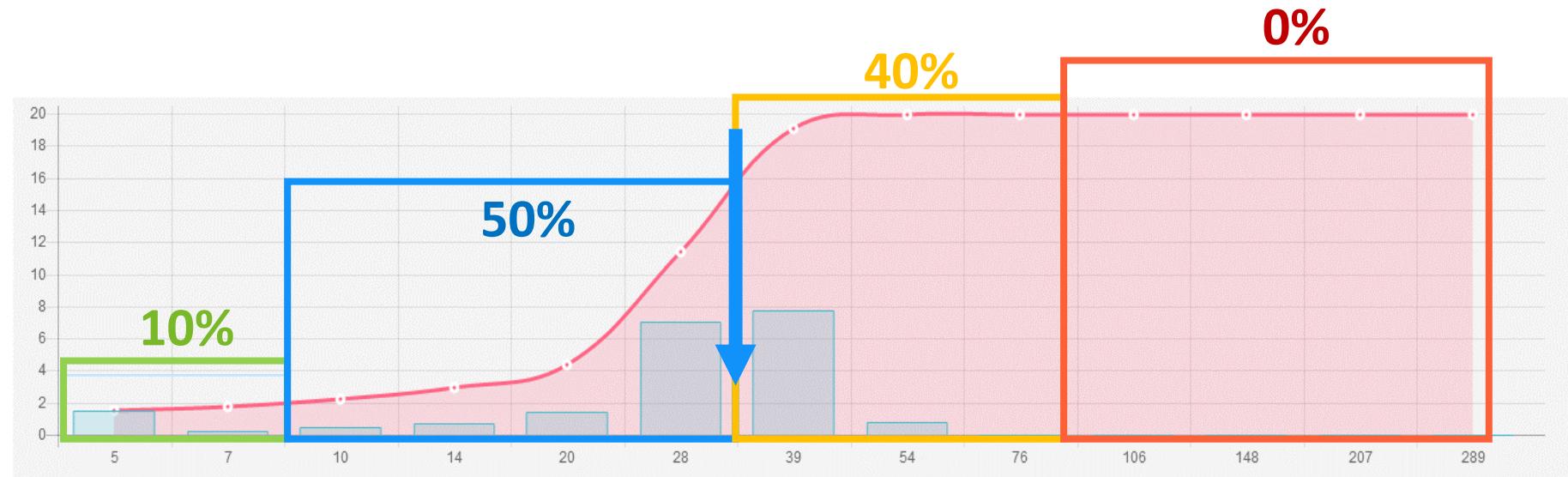
An integrated HLA epitope risk classification (SRTR)



Akaike Information Criterion (AIC) is commonly used to assess the goodness of fit and compare different Cox proportional hazards (Cox PH) models. The model with the lowest AIC value is considered the best-fitting model among the compared models.

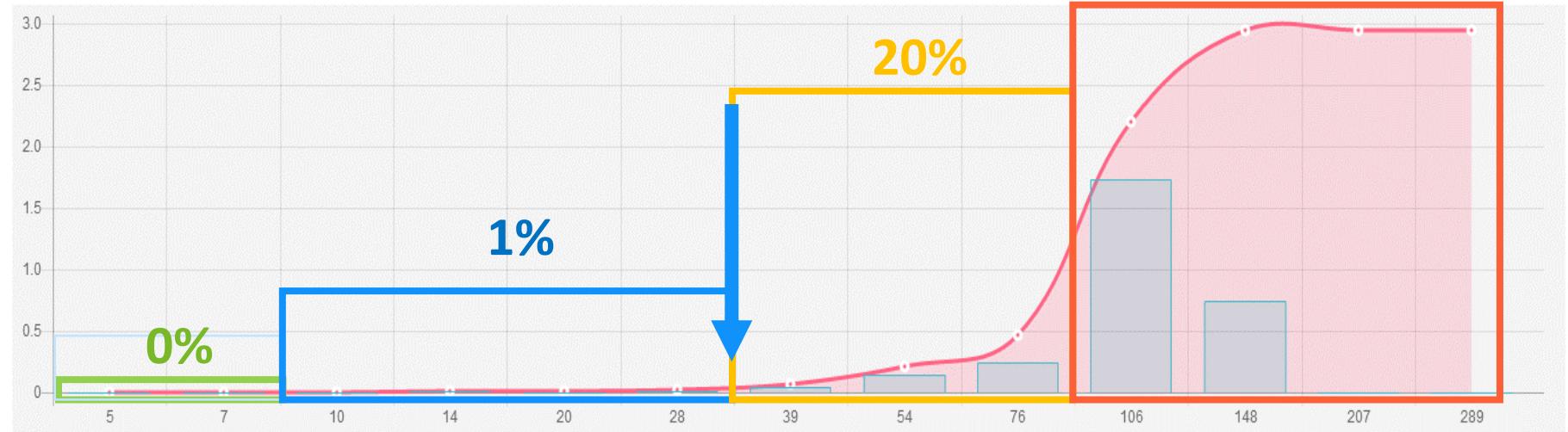
prospective PIRCHE-II mismatch probability

recipient 1



score = 33

recipient 2



Epitope scores are indicative for successfull tapering

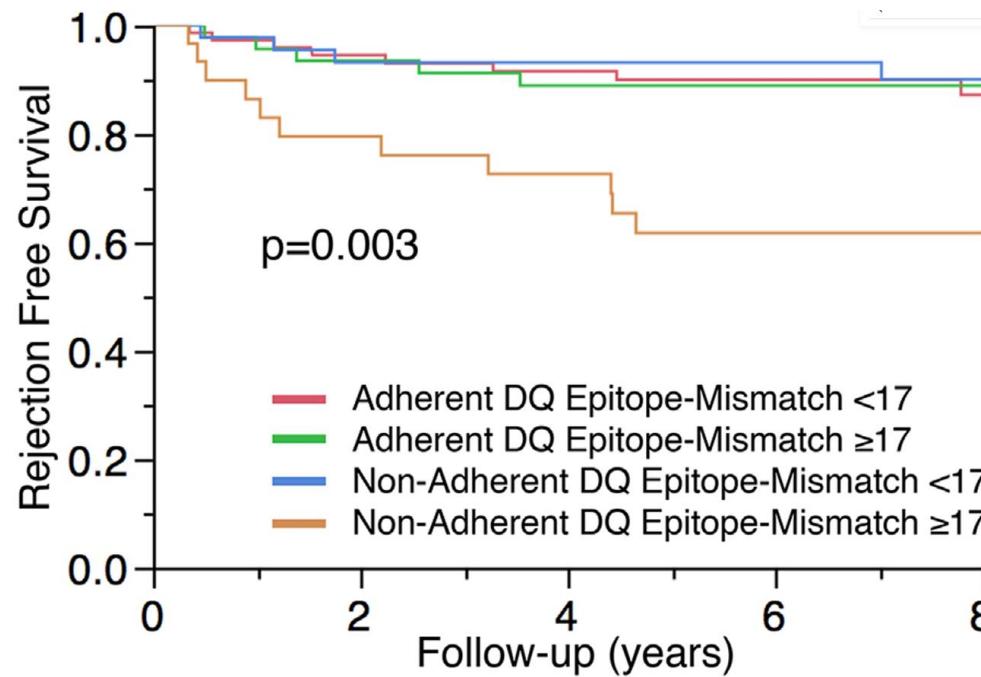
American Journal of Transplantation 2015; 15: 2197–2202
Wiley Periodicals Inc.

Brief Communication

The Synergistic Effect of Class II HLA Epitope-Mismatch and Nonadherence on Acute Rejection and Graft Survival

C. Wiebe^{1,*†}, T. E. Nevins^{2,†}, W. N. Robiner³,
W. Thomas⁴, A. J. Matas⁵ and P. W. Nickerson⁶

Received 11 August 2014, revised 13 February 2015 and accepted for publication 23 February 2015



Received: 6 December 2022 | Revised: 13 February 2023 | Accepted: 15 February 2023

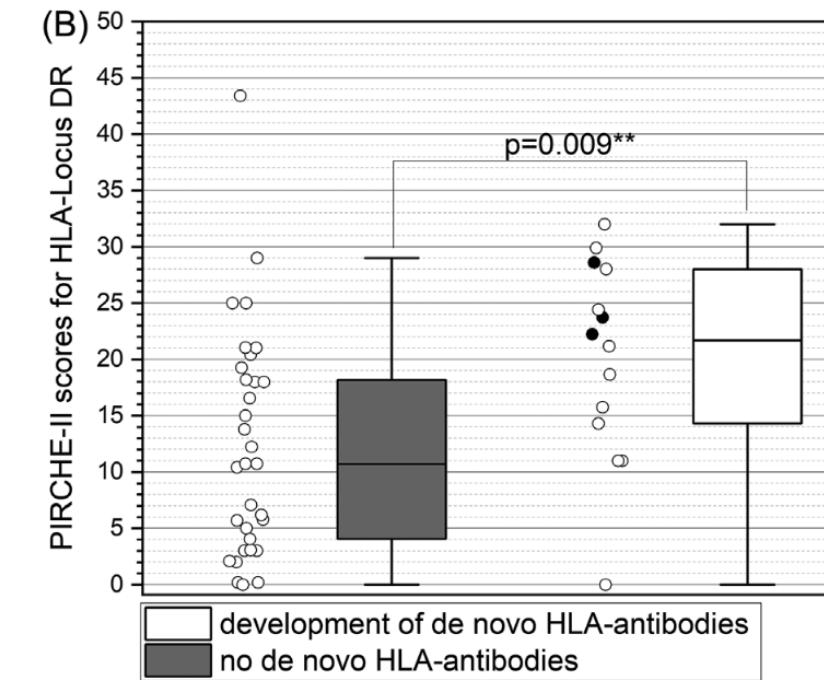
DOI: 10.1111/tid.14052

ORIGINAL ARTICLE



Association between PIRCHE-II scores and de novo allosensitization after reduction of immunosuppression during SARS-CoV-2 infection in kidney transplant recipients

Kai Castrezana-Lopez¹ | Ronja Malchow¹ | Jakob Nilsson² | Sanna M. Kokkonen¹ | Elena Rho¹ | Seraina von Moos¹ | Thomas F. Mueller¹ | Thomas Schachtner¹



Take-home messages

- **PIRCHE estimates the number of T-cell epitopes in mismatched HLA**
 - Presented by class I: PIRCHE-I
 - Presented by class II: PIRCHE-II
- **PIRCHE-II associates immunologically with CD4 T-helper responses**
 - Stimulation of antibody production
 - Stimulation of cytotoxic T cells
- **PIRCHE-II associates clinically with**
 - Increased risk for DSA development
 - Increased risk for antibody-mediated rejection
 - Increased risk for T cell-mediated rejection

Learning objectives of this presentation

HLA antibody algorithms

- To understand the basic principles of antibody recognition
- To understand the basic concepts of HLA antibody epitope matching algorithms
- To understand the most important differences between the various HLA antibody epitope matching algorithms

HLA T-cell epitope algorithms

- To understand the basics of T-cell epitope recognition
- To understand the difference between PIRCHE-I and PIRCHE-II and the potential immunological consequences
- To understand how PIRCHE-II affects transplant outcome



HLA T-cell epitopes in organ transplantation

Eric Spierings (e.spierings@umcutrecht.nl)

Epitope workshop ABHI
Sao Paulo – Wednesday, December 13, 2023