HEIDELBERG
UNIVERSITY
HOSPITAL

50 JAHRE
TRANSPLANTATIONSZENTRUM
FREIBURG

20 JAHRE
TRANSPLANTATIONS-WORK-
SHOP HINTERZARTEN

Histokompatibilität – Neue Konzepte

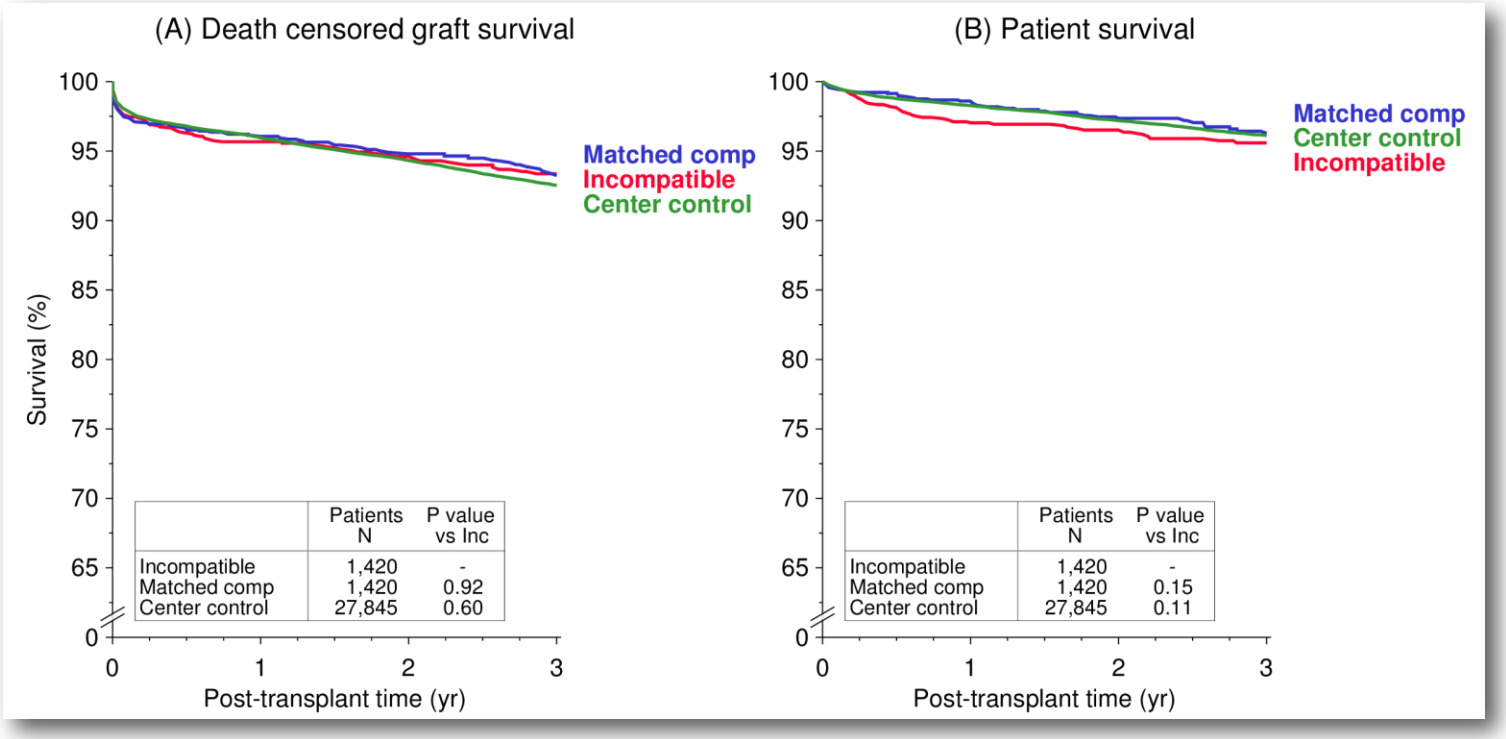
Prof. Dr. med. Caner Süsal

For Rejection Reactions Responsible Antigen Systems

ABO Blood Group Antigen System

ABO-incompatible Living Donor

Kidney Transplantations

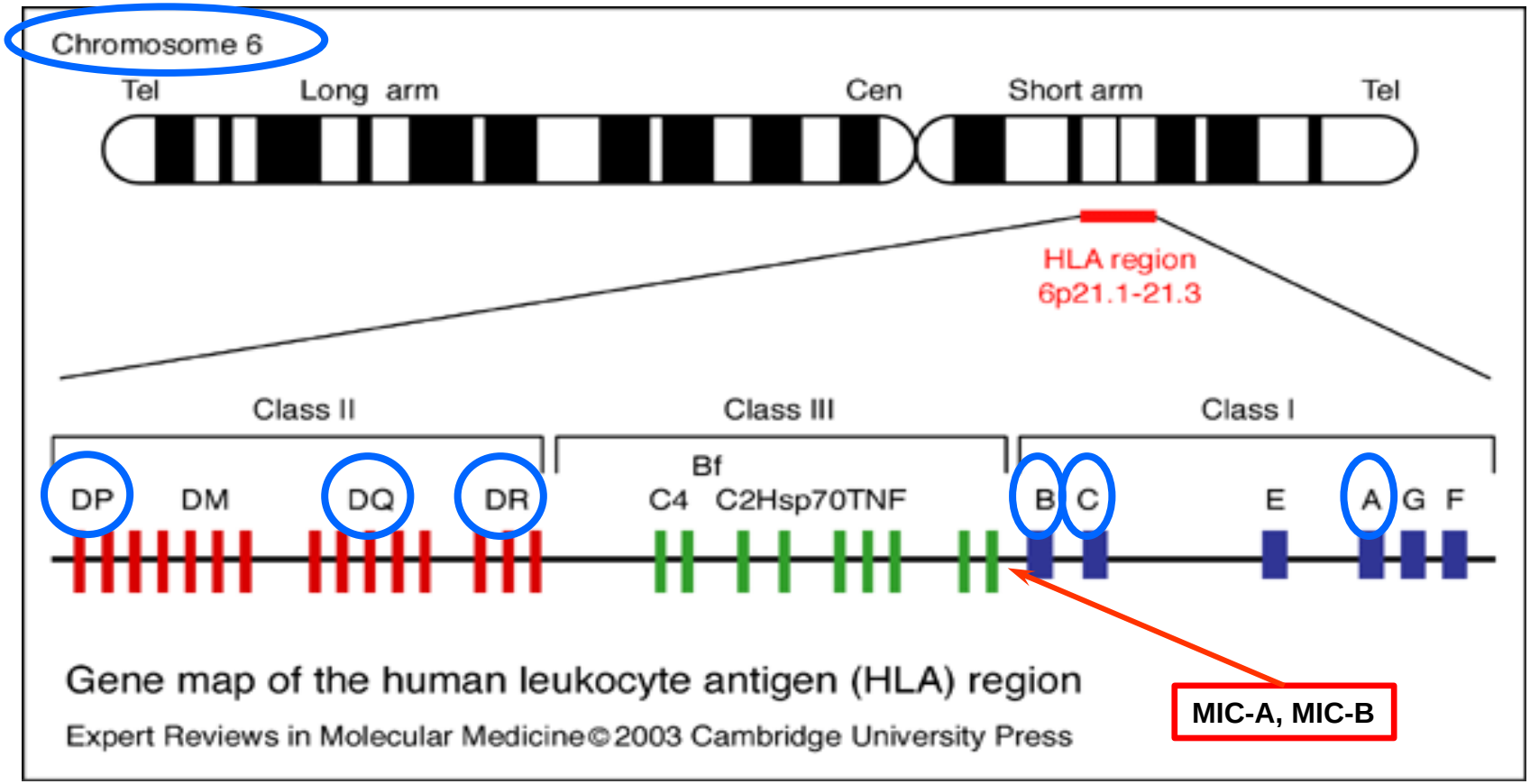


For Rejection Reactions Responsible Antigen Systems

ABO Blood Group Antigen System

HLA-Antigen System

HLA Genes


Chromosome 6
Tel
Long arm
Cen
Short arm
Tel
HLA region
6p21.1-21.3
Class II
Class III
Class I
DP
DM
DQ
DR
Bf
C4
C2Hsp70TNF
B
C
E
A
G
F
Gene map of the human leukocyte antigen (HLA) region
Expert Reviews in Molecular Medicine©2003 Cambridge University Press
MIC-A, MIC-B

Example of a Family-Typing of HLA Antigens

Müller, Hans (Father)

A	1	2
B	7	8
DR	3	4

Müller, Brigitta (Mother)

A	-	32
B	62	39
DR	1	7

	Patient		Brother 1		Sister 1		Brother 2		Sister 2	
A	1	32	2	-	1	32	1	-	24	32
B	7	39	8	62	7	39	7	62	17	39
DR	3	7	4	1	3	7	3	1	4	7

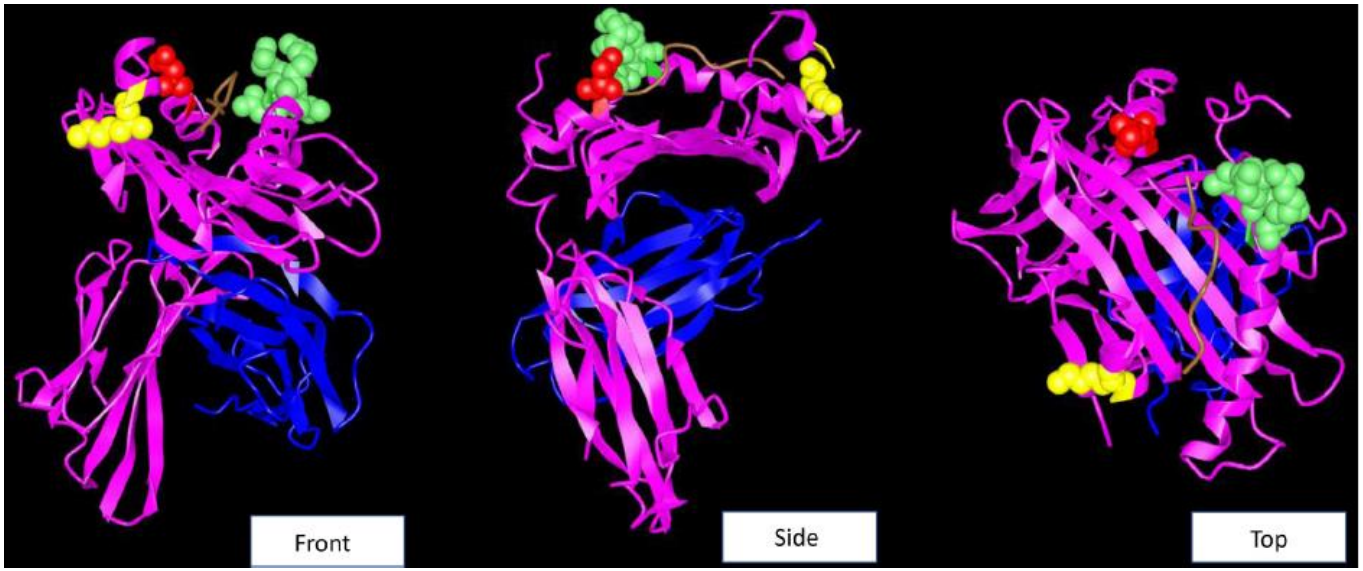
HLA-Antigen System
is the antigen system with the
highest grade of polymorphism
in the human genome!

Number of Characterized Alleles
December 2018 (hla.alleles.org)

HLA Class I	14,800
HLA Class II	5,288
MIC-A	107
MIC-B	47

Polymorphism = Great Barrier Organ- and Stem Cell Tx

3-Dimensional Crystallographic Structure of HLA-A*01:01



Allelic differences are effectively recognized by the T- and B-Ly

ET Manual 2016

4.7.2 HLA antigen frequency

HLA gen frequenties 2014 excl. HLA-A -B splits

HLA-A	2014	HLA-B	2014	HLA-DR	2014
A1	0,1534	B5	0,0738	DR1	0,1151
A2	0,3007	B7	0,1227	DR2	0,1645
A3	0,1490	B8	0,1025	DR15	0,1277
A9	0,1138	B12	0,1217	DR16	0,0368
A10	0,0642	B13	0,0322	DR3	0,1114
A11	0,0555	B14	0,0236	DR17	0,1112
A19	0,1195	B15	0,0758	DR18	0,0002
A28	0,0441	B70	0,0023	DR4	0,1328
A36	0,0001	B16	0,0454	DR5	0,1463
A43	0,0001	B17	0,0453	DR11	0,1261
A203	0,0001	B18	0,0540	DR12	0,0202
A210	0,0001	B21	0,0232	DR6	0,1639
A80	0,0001	B22	0,0252	DR13	0,1314
		B27	0,0483	DR14	0,0325
		B35	0,1027	DR7	0,1164
		B37	0,0140	DR8	0,0312
		B40	0,0684	DR9	0,0087
		B41	0,0111	DR10	0,0096
		B42	0,0004		
		B46	0,0002		
		B47	0,0034		
		B48	0,0008		
		B53	0,0027		
		B59	0,0001		
		B67	0,0002		
		B73	0,0002		
		B703	0,0001		
		B78	0,0002		
		B81	0,0001		
		B2708	0,0001		
		B82	0,0001		
		B83	0,0001		

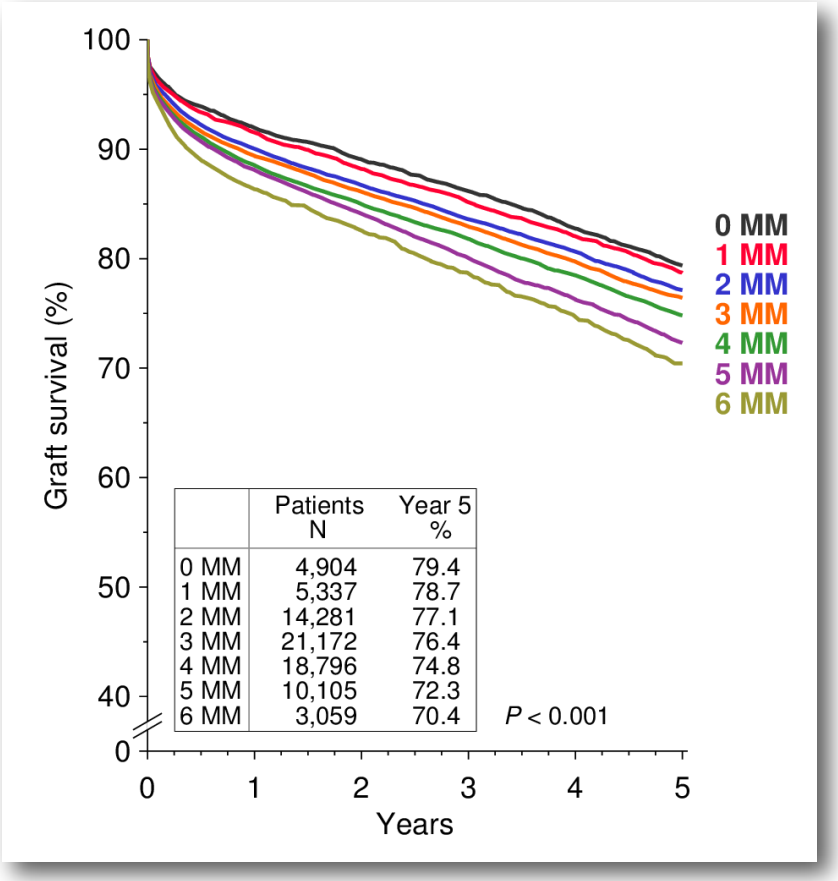
ET Kidney Allocation System

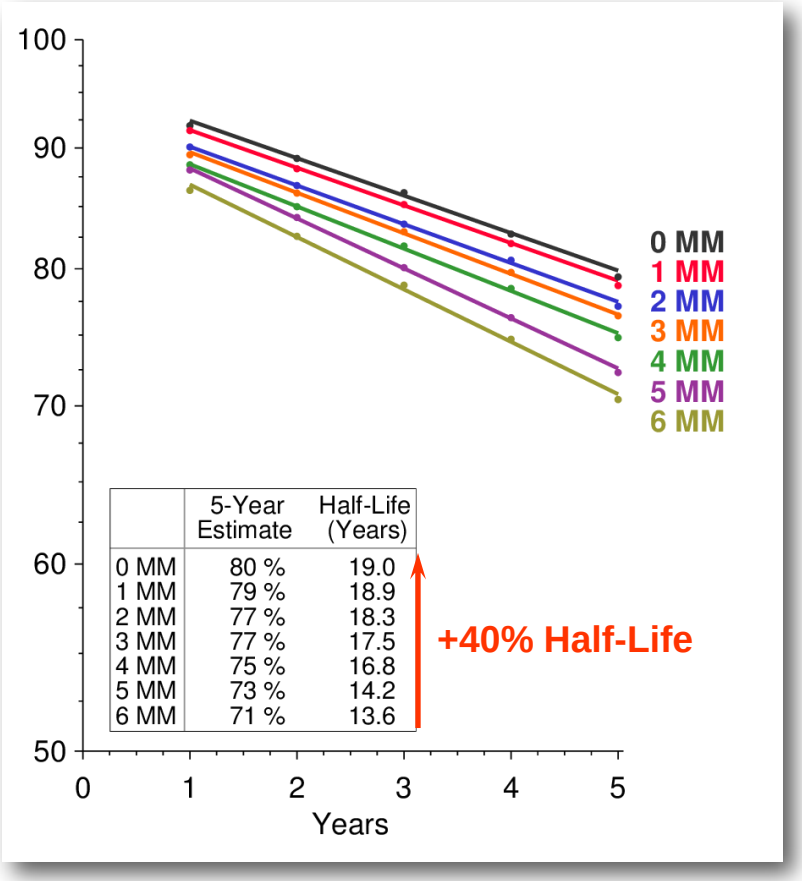
Point Score System

	Max. Points
HLA-A, -B, -DR Matching	400
Mismatch Probability	100
Waiting time (per day)	0.09
Distance Factor	300
National Balance	no max

HLA-A+B+DR Mismatches

Deceased Donor Kidney Transplants 2005–2014





Other Reasons for HLA Matching

- Less side effects
- Less sensitization

Increased Immunosuppression

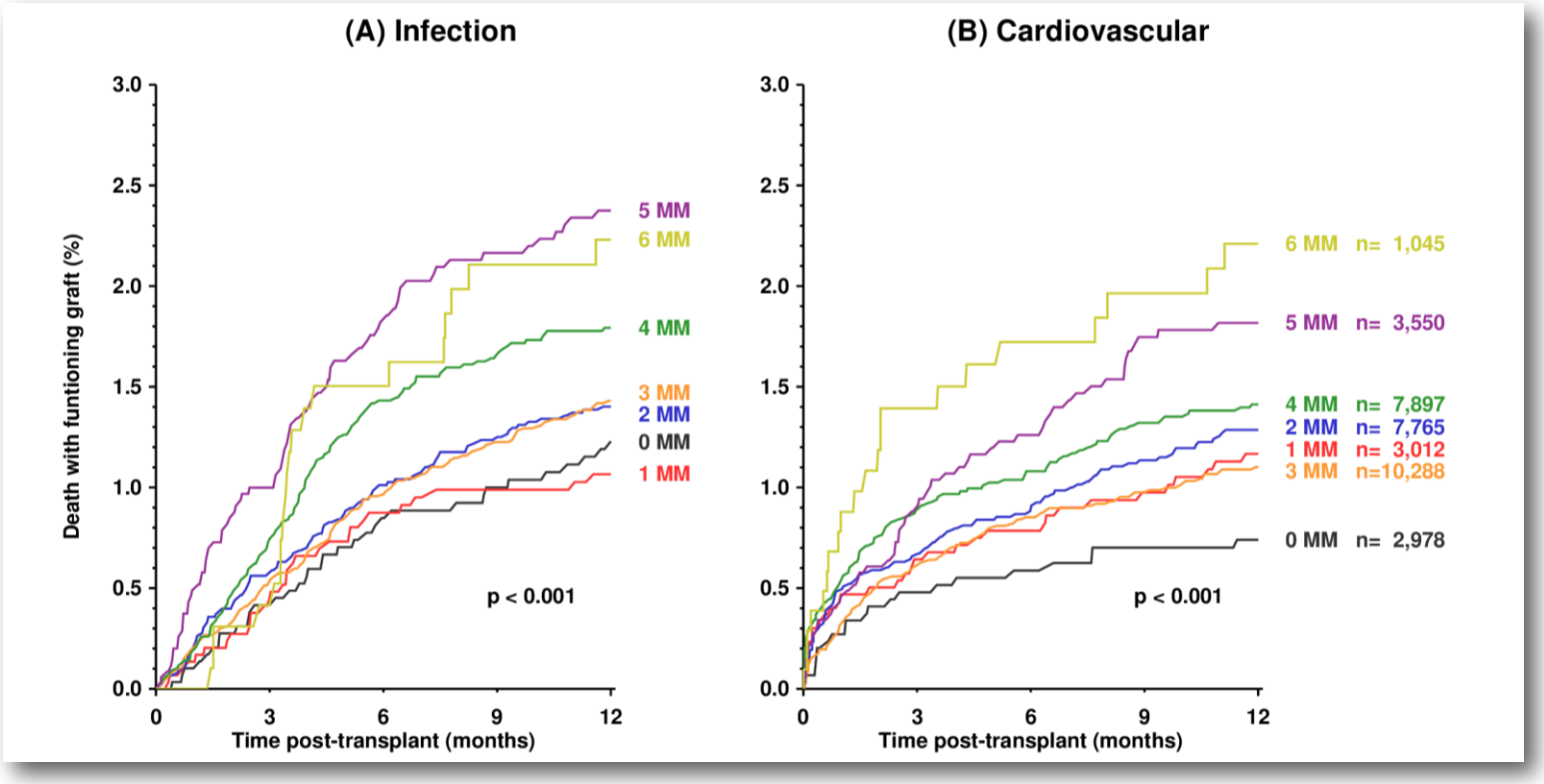
One Year Post-Transplant	HLA-DR mismatches			P
	0 MM	1 MM	2 MM	
Treated Rejection	21.4 %	26.5 %	31.7 %	<0.001
ATG or OKT3	26.3 %	27.8 %	31.3 %	<0.001

One Year Post-Transplant	HLA-DR mismatches			P
	0 MM	1 MM	2 MM	
High dosage of *				
CsA	8.9 %	10.8 %	12.3 %	<0.001
Tac	8.8 %	10.7 %	10.1 %	0.052
MMF	9.0 %	10.9 %	10.2 %	0.010
Steroids	7.5 %	9.5 %	12.5 %	<0.001
** > 90-Percentile*				

Opelz et al, Transplantation 2010

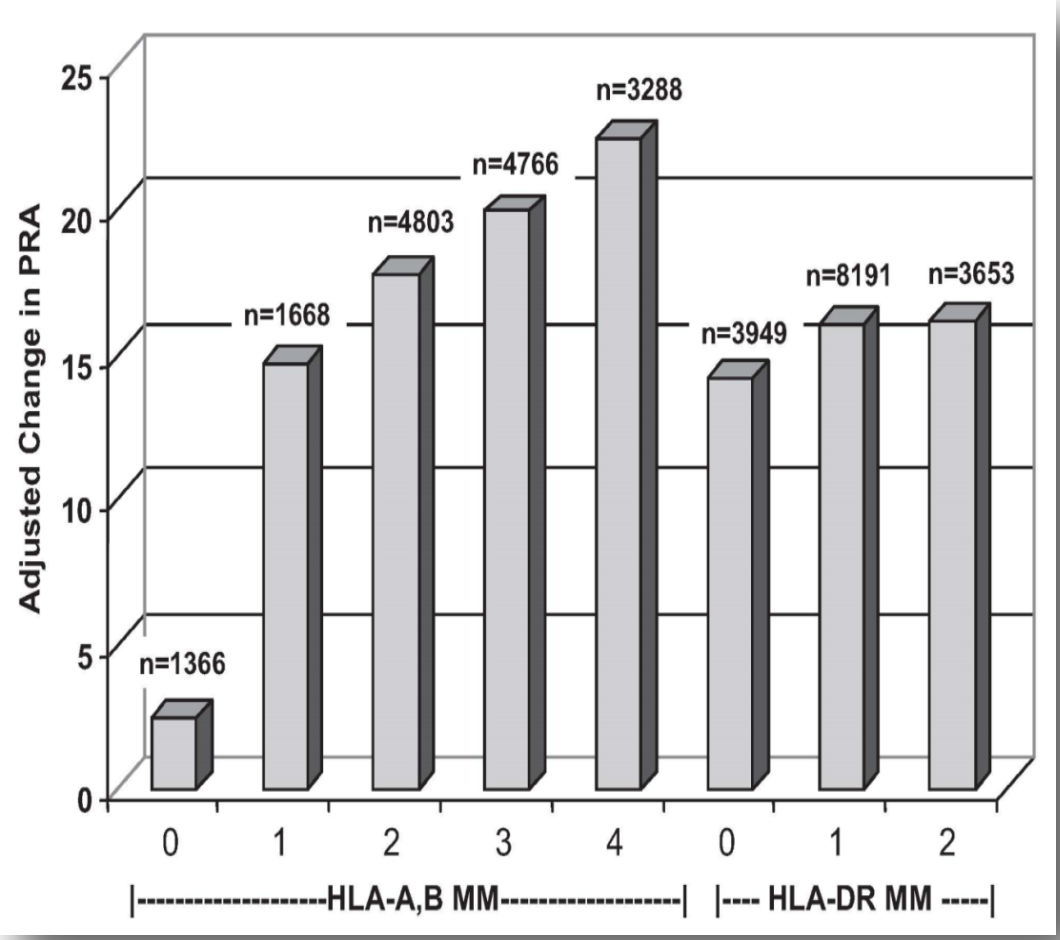
Death with Functioning Graft – A+B+DR Mismatches

Deceased Donor Kidney Transplants 2005–2009



Opelz and Döhler, Am J Transplant 2012

HLA-Mismatches – Panel Reactive Abs at Relisting



"Many patients are negatively impacted from poor HLA matching of their first kidney transplant when needing a second transplant"

Meier-Kriesche et al, Transplantation 2009

PRA and Median Waiting Time

UK 1998–2005

PRA <5%	788 days
PRA 61–84%	1,696 days
PRA ≥85%	2,232 days

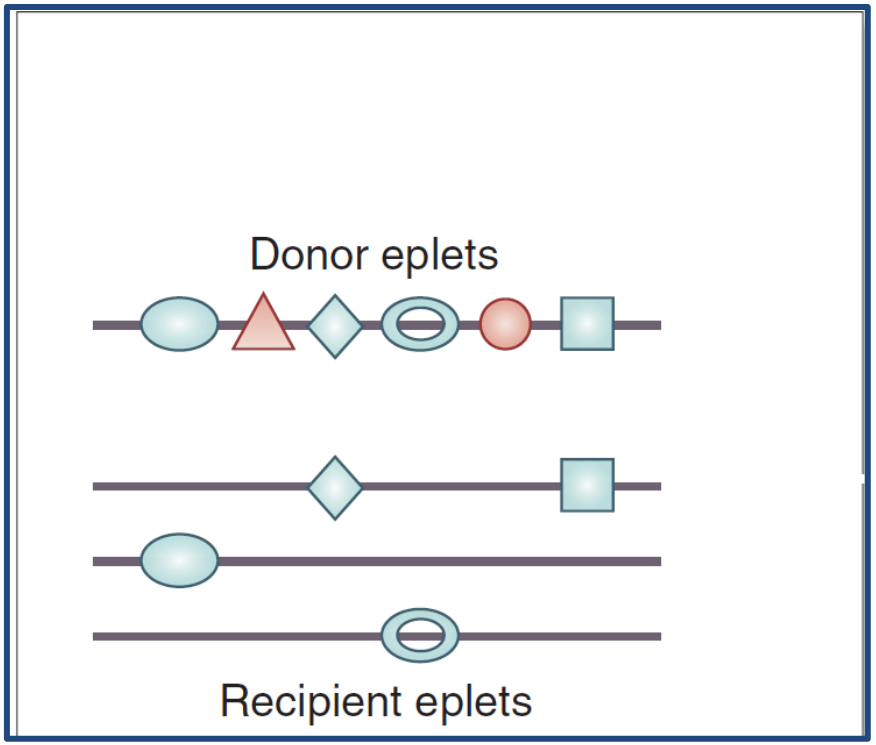
Fuggle and Martin, Transplantation 2008

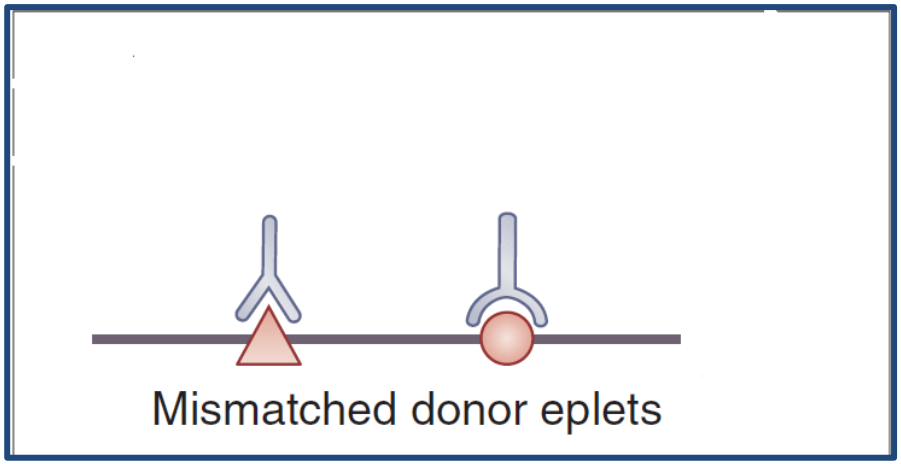
Epitope vs. HLA Matching

private and public epitopes

B-Cell/Antibody Epitopes

Direct Recognition

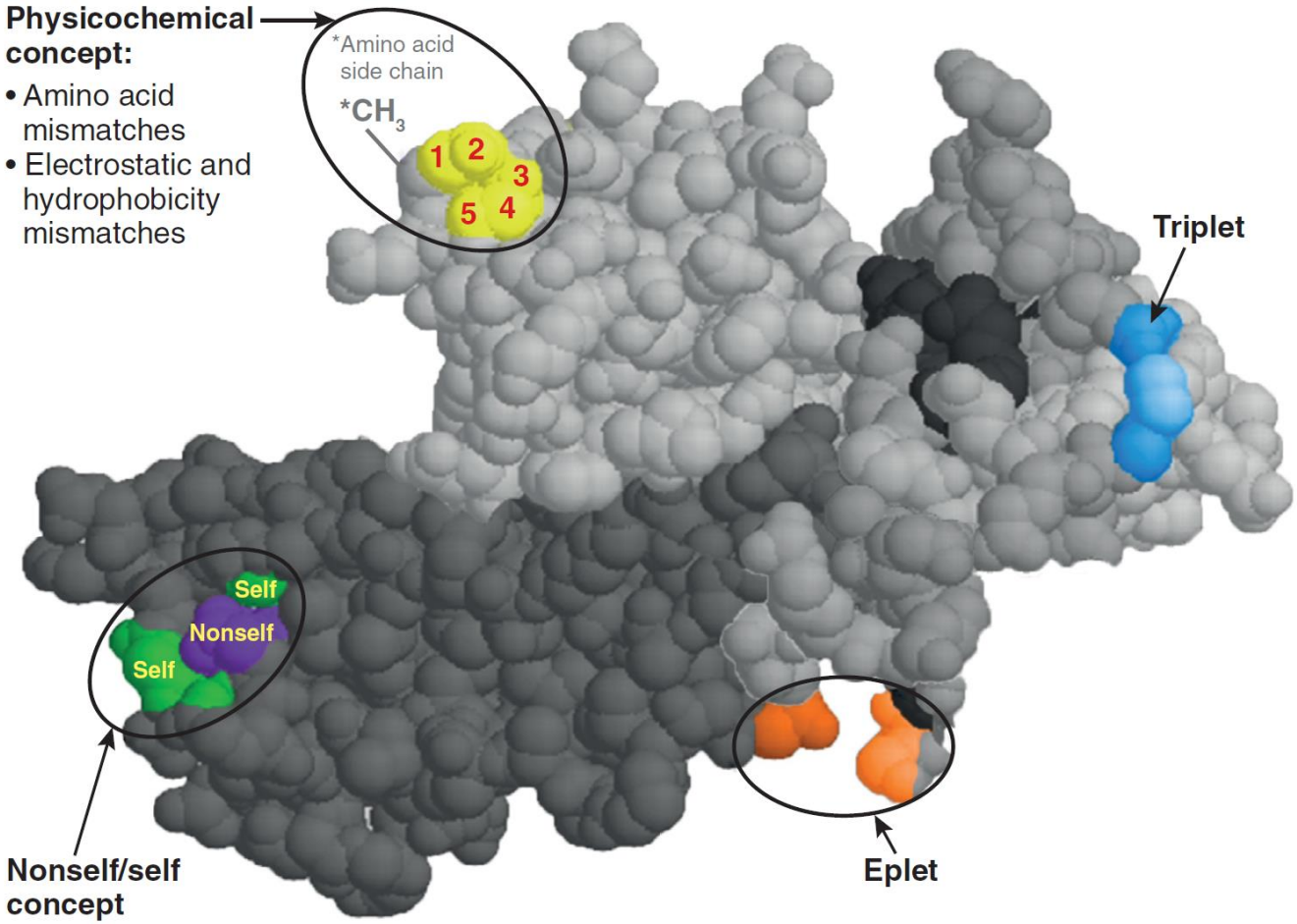




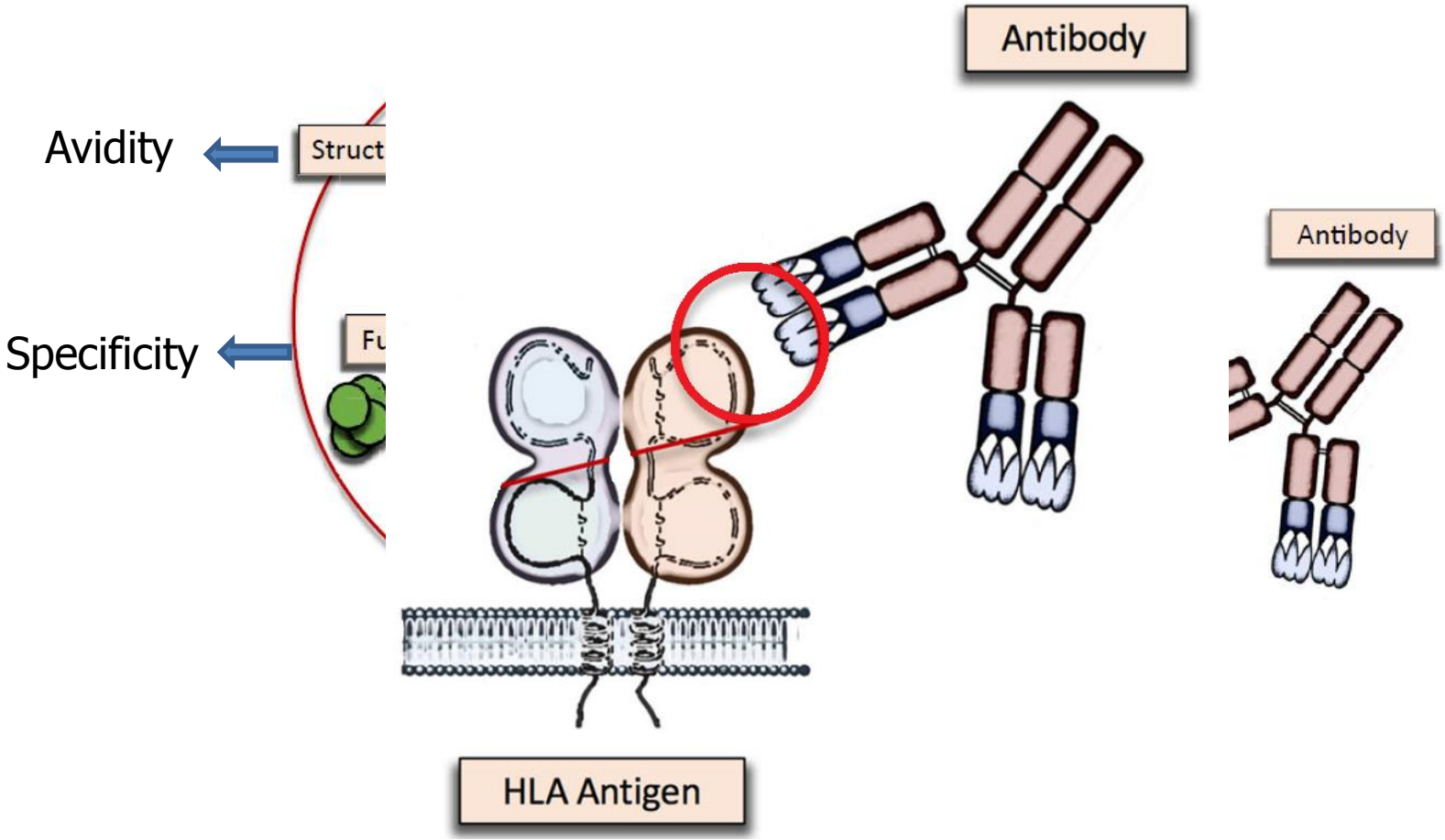
HLA-Matchmaker (Duquesnoy)
Terasaki Epitopes (El-Awar)
Physicochemical Concept (Kosmoliaptsis)

Lim et al, Kidney Int 2018

3-Dimensional Structure of a Class II HLA Molecule



Interface Between Antibody Paratope and Antigen Epitope



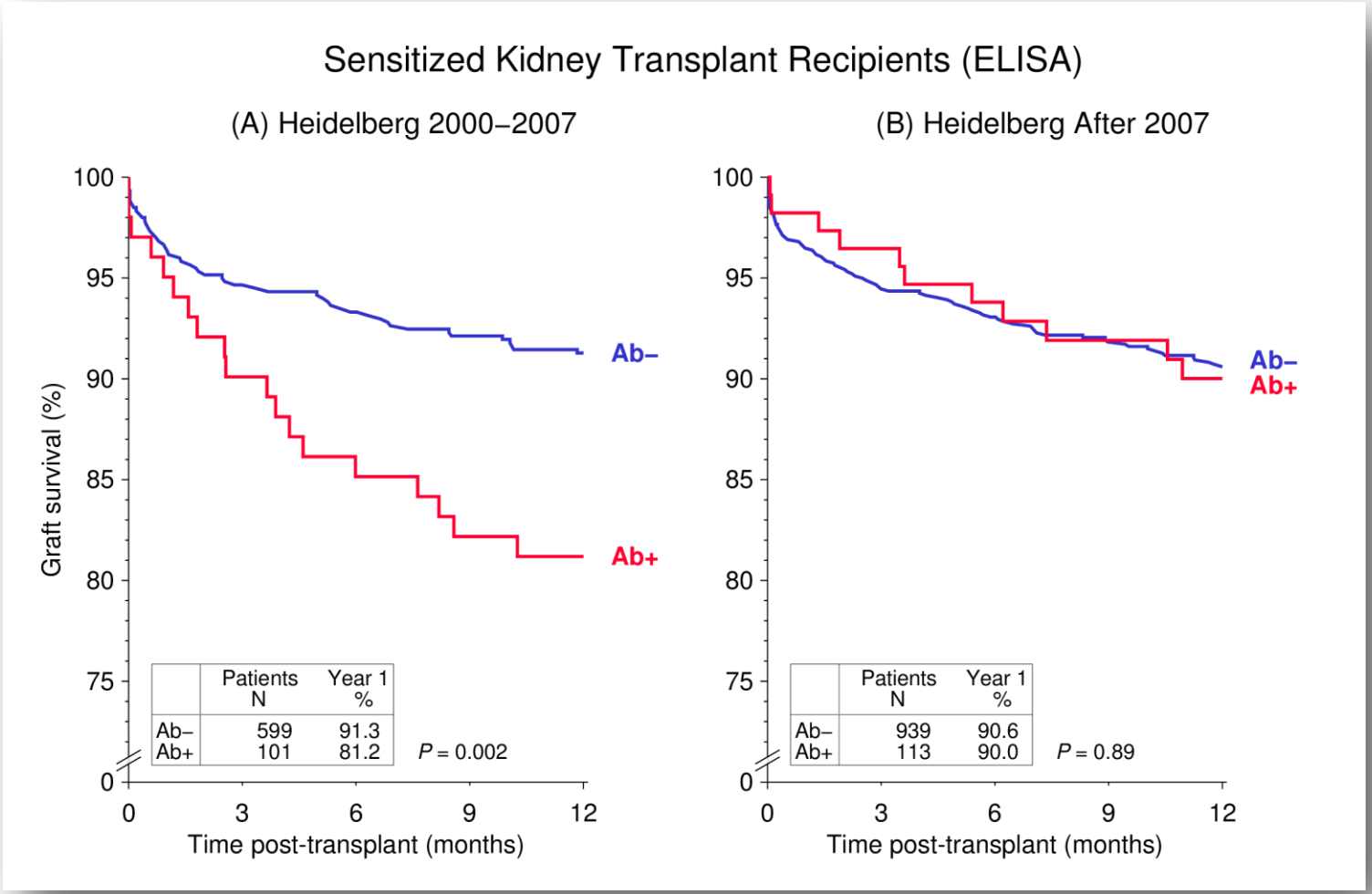
Prevention of Early Damage in Graft

Pre-Tx DSA

Pre-Tx X-Match

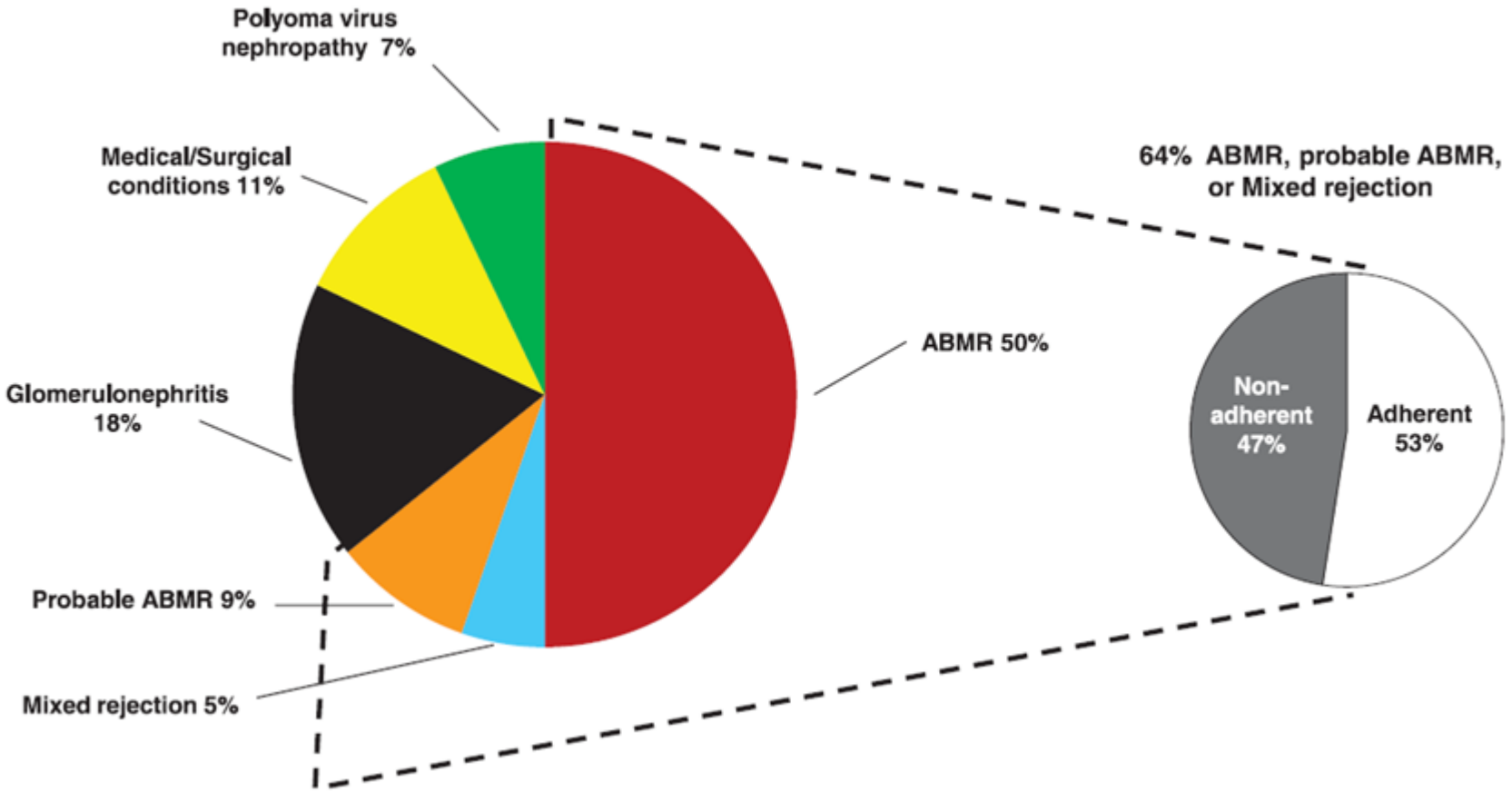
Pre-Tx Ab Screening "Unacceptables"

Impact of Pretransplant HLA Antibodies



ABMR as the Main Cause of Late Graft Loss

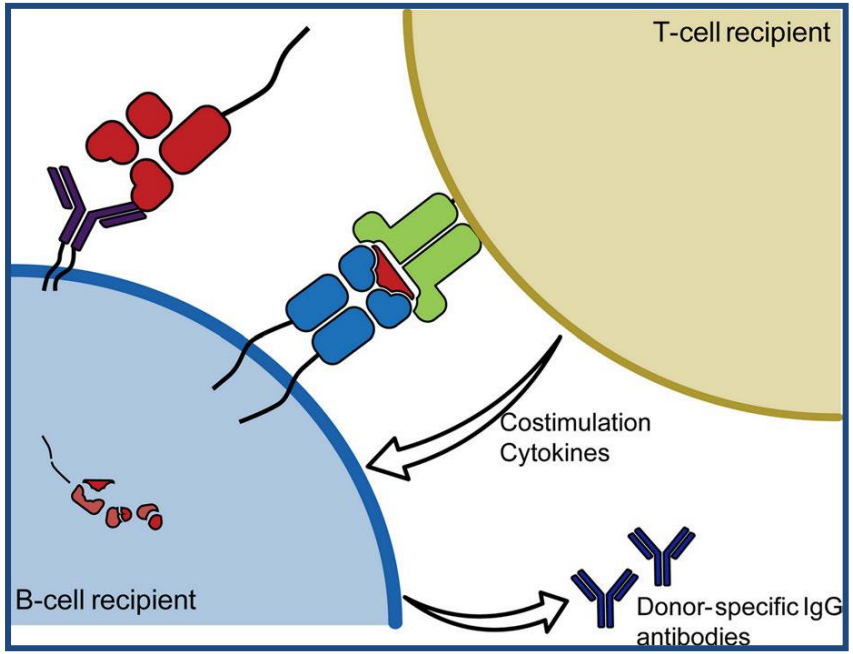
315 patients with indication biopsy

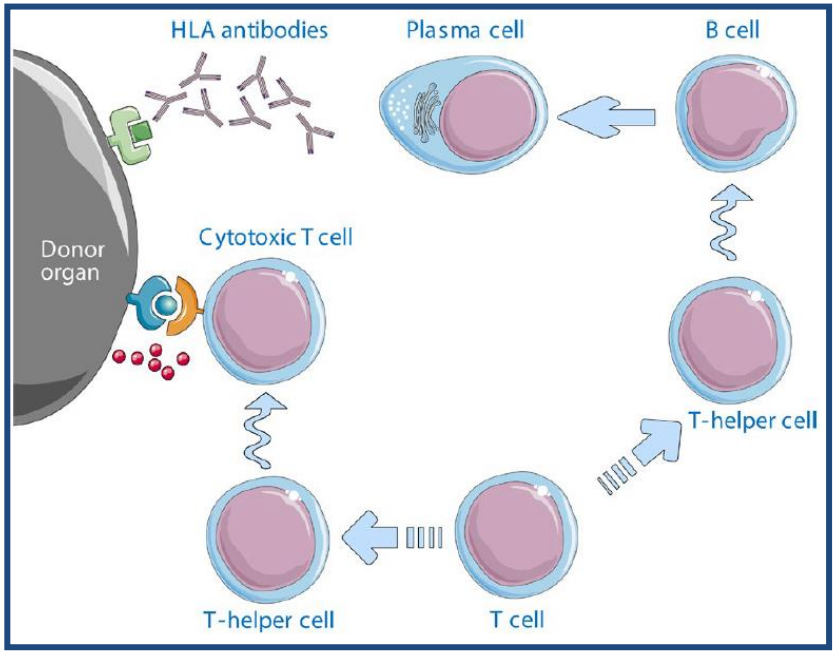


Sellarés et al, Am J Transplant 2012

T-Cell Epitopes

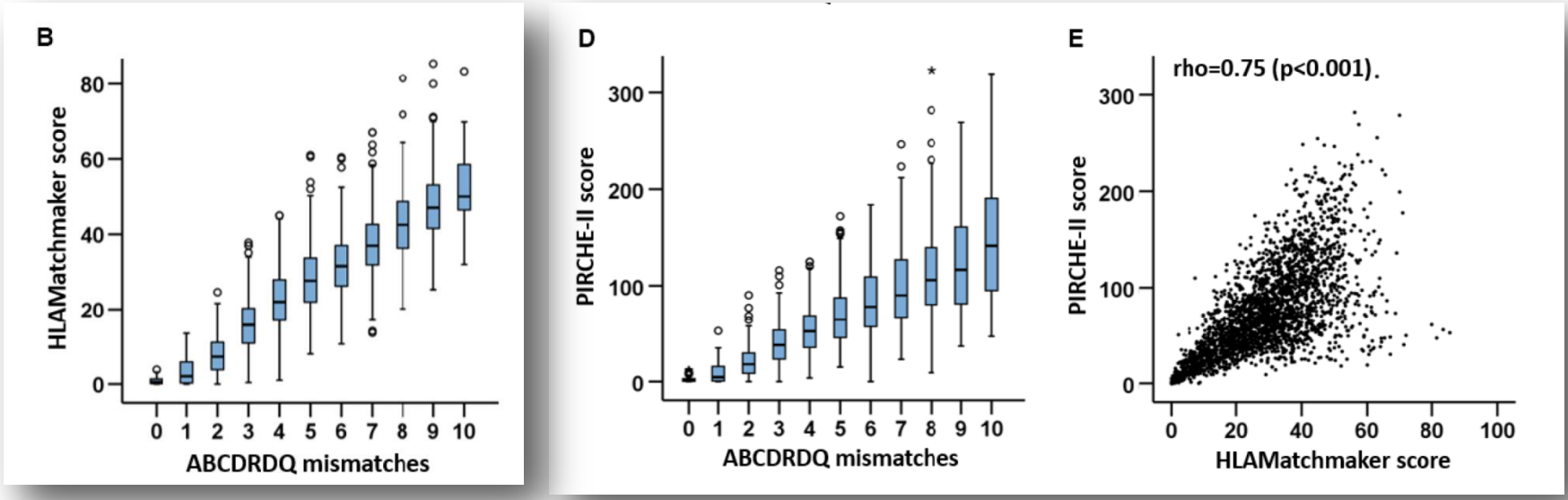
Indirect Recognition



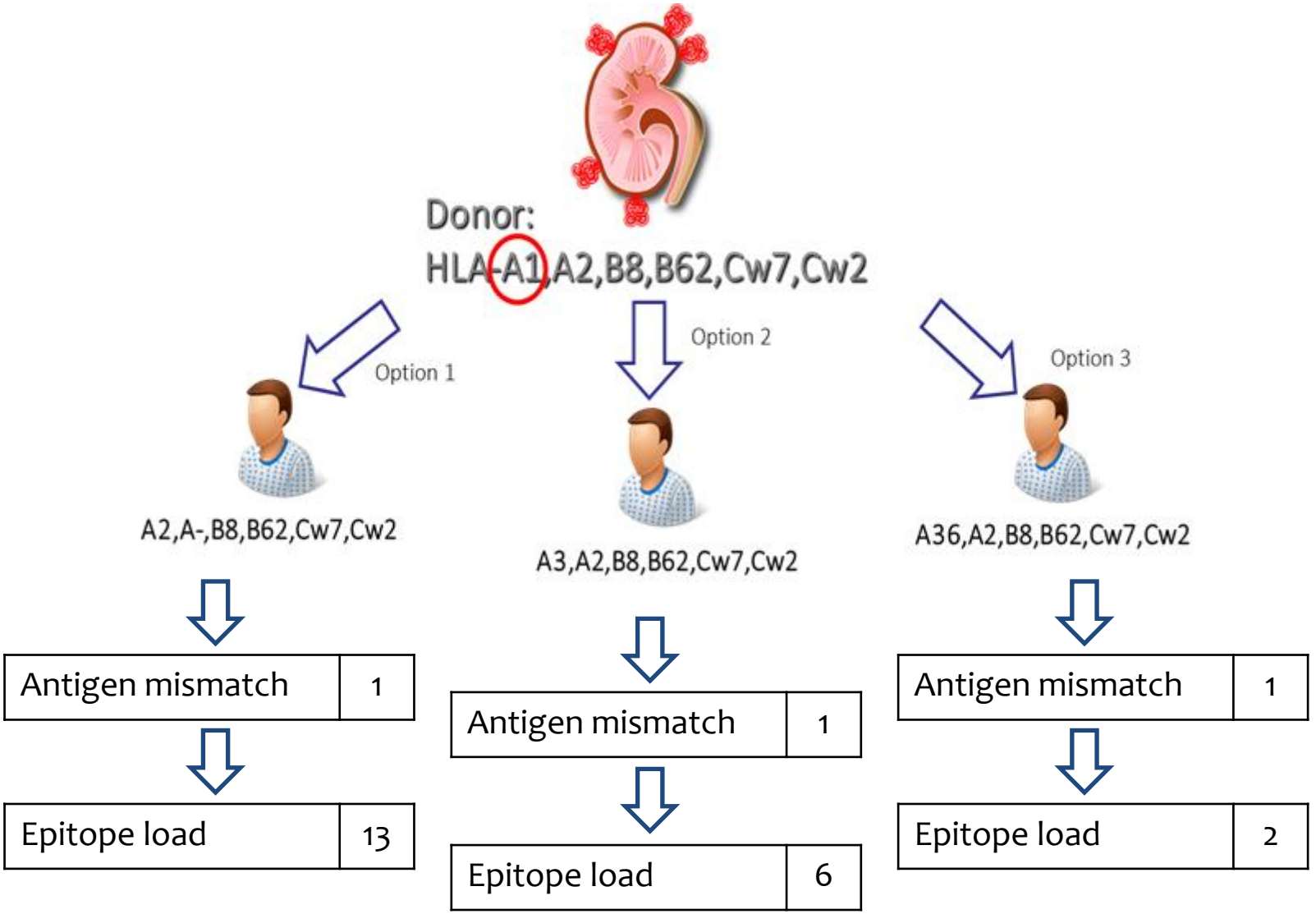


PIRCHE II: Predicted Indirectly Recognizable T-Cell HLA Epitopes

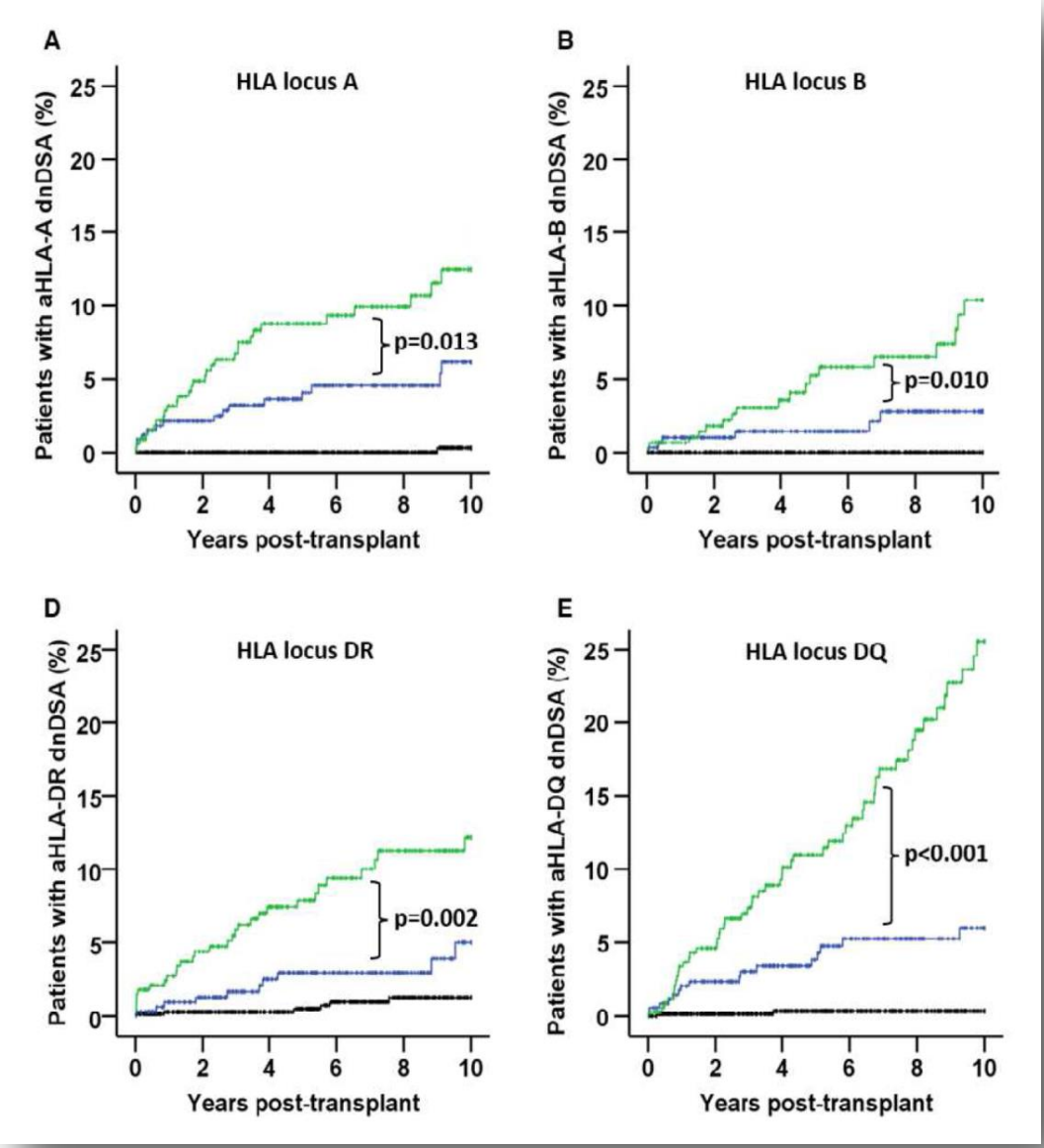
Association of ABCDRDQ Mismatches, PIRCHE II and HLA-Matchmaker Scores



HLA vs. Epitope Matching (PIRCHE II)

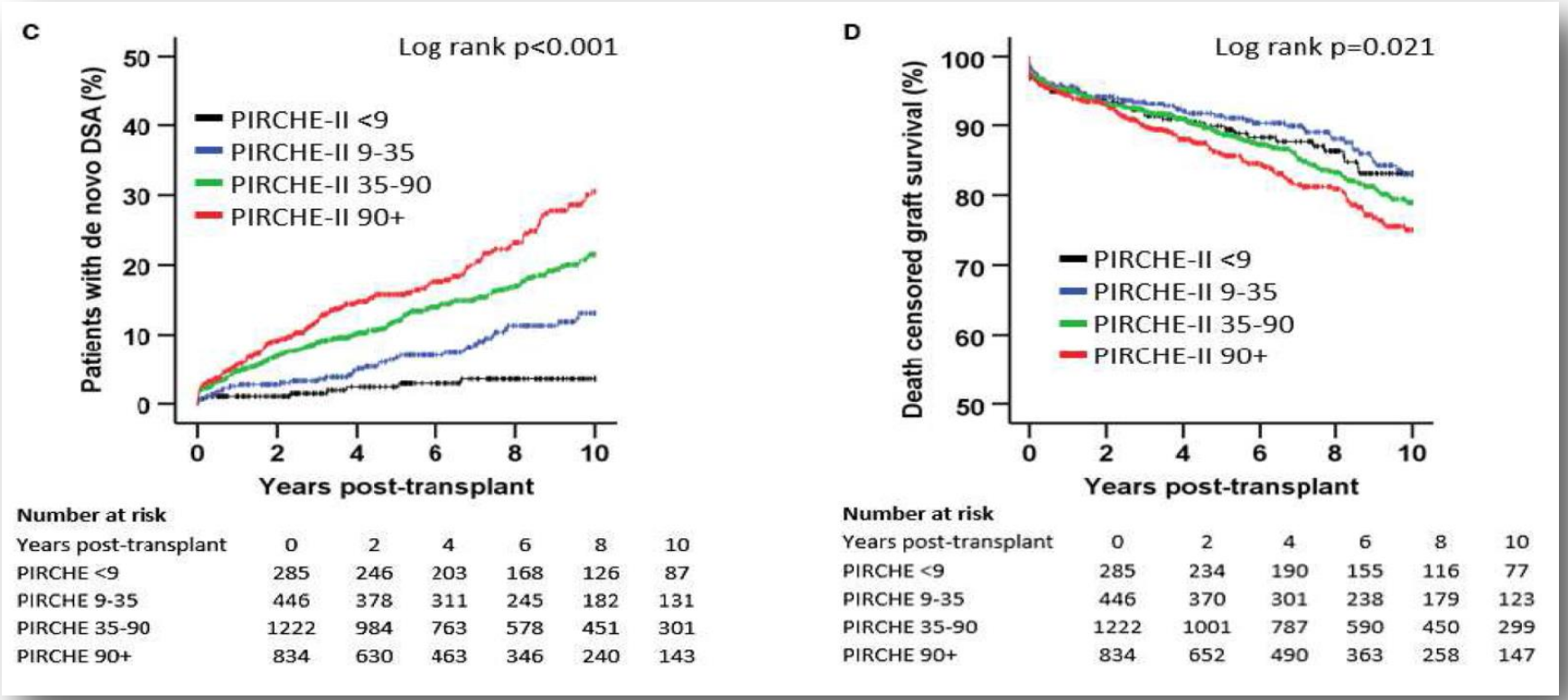


Patients with one HLA mismatch and de novo DSA



Lachmann et al, Am J Transplant 2017

Epitope Matching
de novo DSA Development and Graft Survival
(1995-2015)



Number at risk

Years post-transplant	0	2	4	6	8	10
PIRCHE <9	285	246	203	168	126	87
PIRCHE 9-35	446	378	311	245	182	131
PIRCHE 35-90	1222	984	763	578	451	301
PIRCHE 90+	834	630	463	346	240	143

Number at risk

Years post-transplant	0	2	4	6	8	10
PIRCHE <9	285	234	190	155	116	77
PIRCHE 9-35	446	370	301	238	179	123
PIRCHE 35-90	1222	1001	787	590	450	299
PIRCHE 90+	834	652	490	363	258	147

Lachmann et al, Am J Transplant 2017

Epitope Matching – Graft Survival

(1995-2005, Dutch Patients)

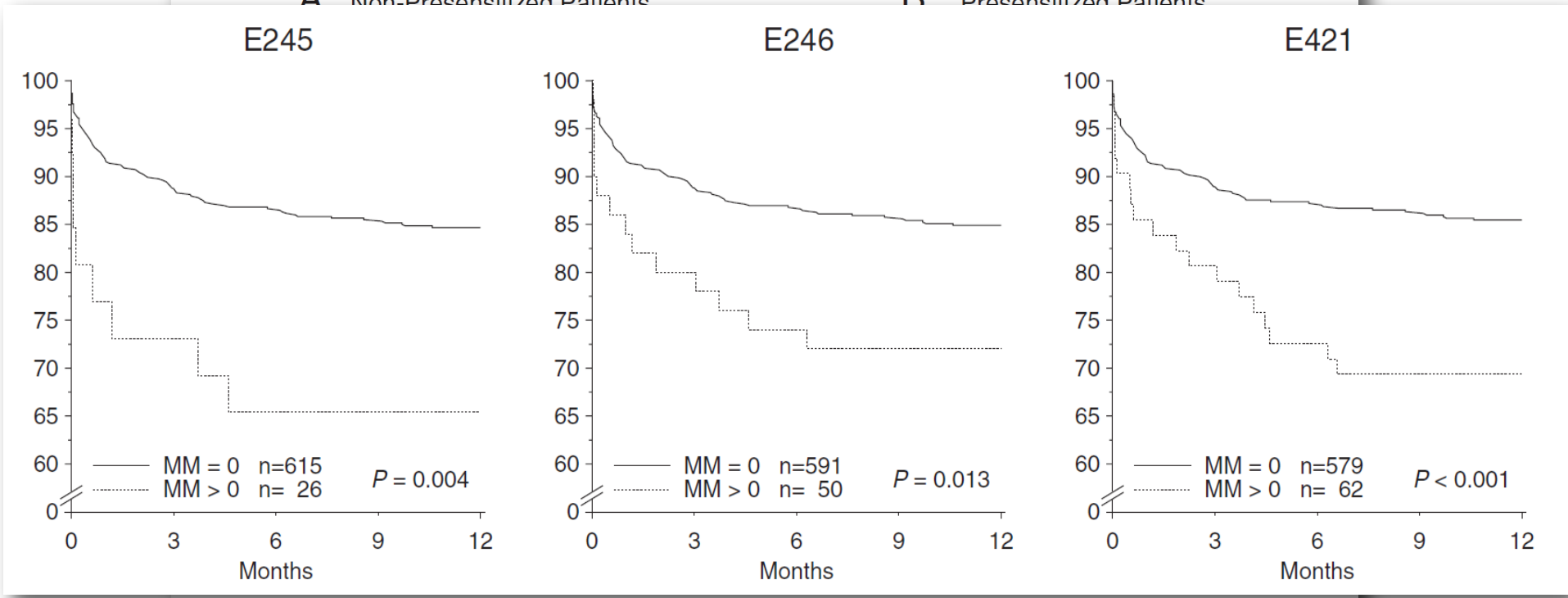
TABLE 2 | Univariate and multivariable hazard ratios (HRs) of graft failure for ln(PIRCHE-II), eplets, number of HLA-A, -B, and -DR mismatches, age, year of transplantation, retransplantation, and recipient immunization status in the overall cohort.

	Univariate			Multivariable model with forward stepwise selection		
	HR	**95% CI**	***p*-Value**	**HR**	**95% CI**	***p*-Value**
ln(PIRCHE-II)	1.15	1.06–1.25	0.001	1.13	1.04–1.23	0.003
Eplets	1.01	1.00–1.01	0.01			
Number of A/B/DR mismatches	1.11	1.04–1.18	0.002			
Recipient age	0.99	0.99–1.00	0.003	0.99	0.99–1.00	0.002
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	0.06	0.97	0.95–0.99	0.015
Previous transplantations	1.62	1.34–1.95	<0.001	1.56	1.29–1.89	<0.001
Recipient immunization status	1.16	0.99–1.35	0.06			

Immunogenicity of TerEp Epitopes

HLA-C Mismatch Effect in Presensitized Patients (CDC-PRA >10%)

1988-2008 Deceased Donor Kidney Transplants



Epitope Matching

Epitope load

Immunogenicity

HLA Epitope Registry
http://www.epregistry.com.br

Number of Described Epitopes
(December 2018)

HLA Class I	**223** (72 Ab-verified)
HLA Class II	**292** (66 Ab-verified)
MIC-A	**58** (22 Ab-verified)

Thank you very much for your attention!

Epitope-Based Kidney Allocation

Avoid allocation of organs with high epitope load

Prevent allosensitization (dnDSA)

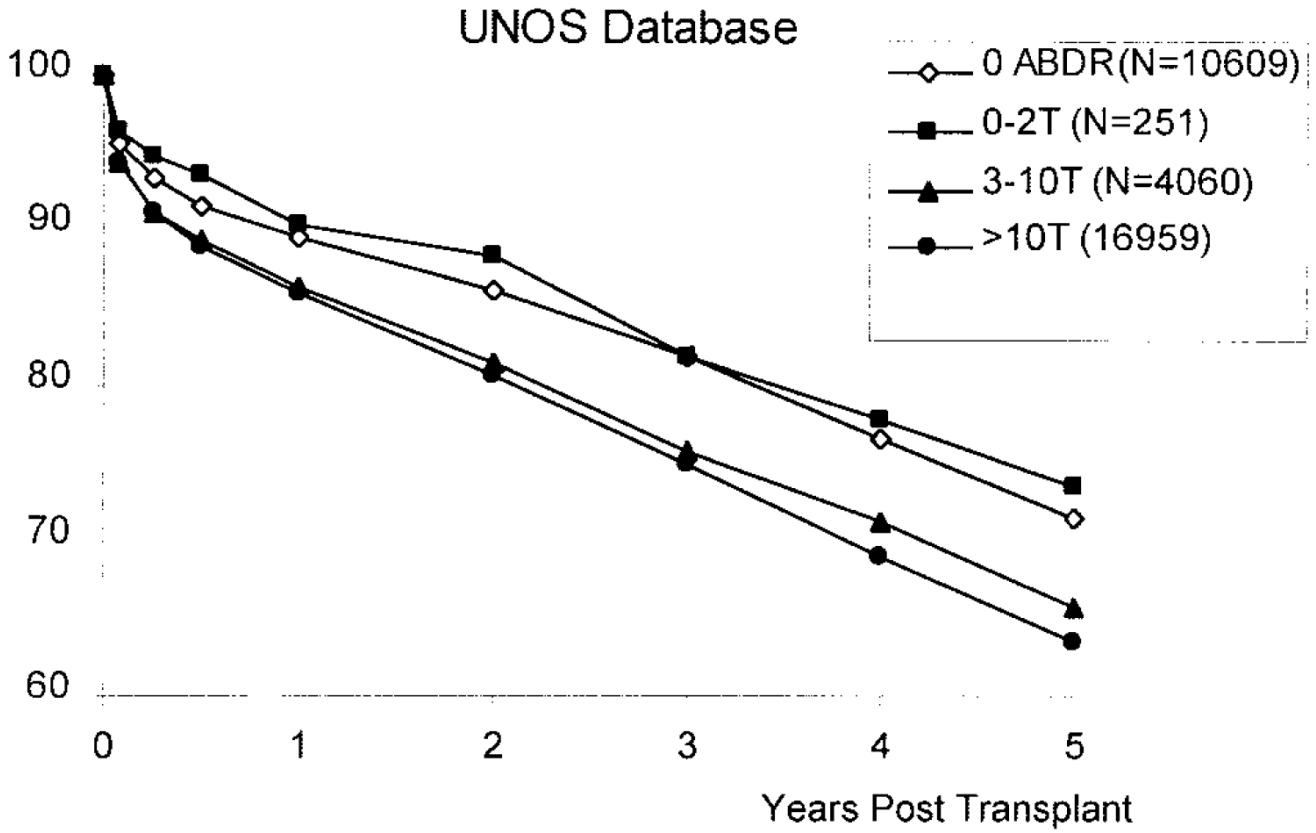
Improve long-term outcome

Expansion of donor pool in highly sensitized patients by precise identification of acceptable and unacceptable immunogenic epitopes

Fragen

- Welcher Algorithmus ist besser?
  - Matchmaker;
  - Pirche II,
  - Electrostatic (Kosmoliaptsis)
  - Ab-Verified (Brasil-Register, TerEp)
- Welche Epitope sind immunogener?

HLA-A,B triplet matching in zero-HLA-DR–mm kidney transplants (UNOS 1987-1999)



Epitope-Based Concept in the Kidney Allocation Systems

Avoidance of allocation of donor kidneys with a high load of immunogenic epitopes

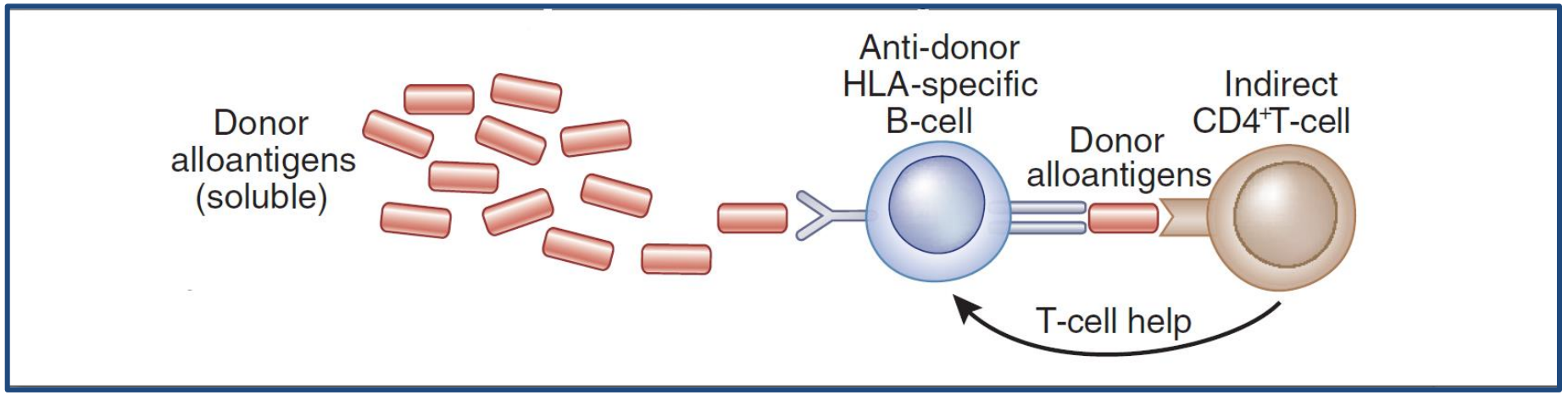
Prevention of future allosensitization (dn DSA)

Expansion of donor pool in highly sensitized patients by identification of acceptable and unacceptable immunogenic epitopes

Identification of rare HLA alleles

Elimination of false positive reactions

T-Cell Epitopes



PIRCHE II: Predicted Indirectly Recognizable T-Cell HLA Epitopes

PIRCHE score and dnDSA
(after adjustment for antigen mismatching and HLA Matchmaker epitopes)

Table 3: Uni- and multivariate Cox regression models of HLAMatchmaker score, ln(PIRCHE-II) score, and count of ABCDRDQ mismatches to predict the incidence of dnDSA (n = 2787)

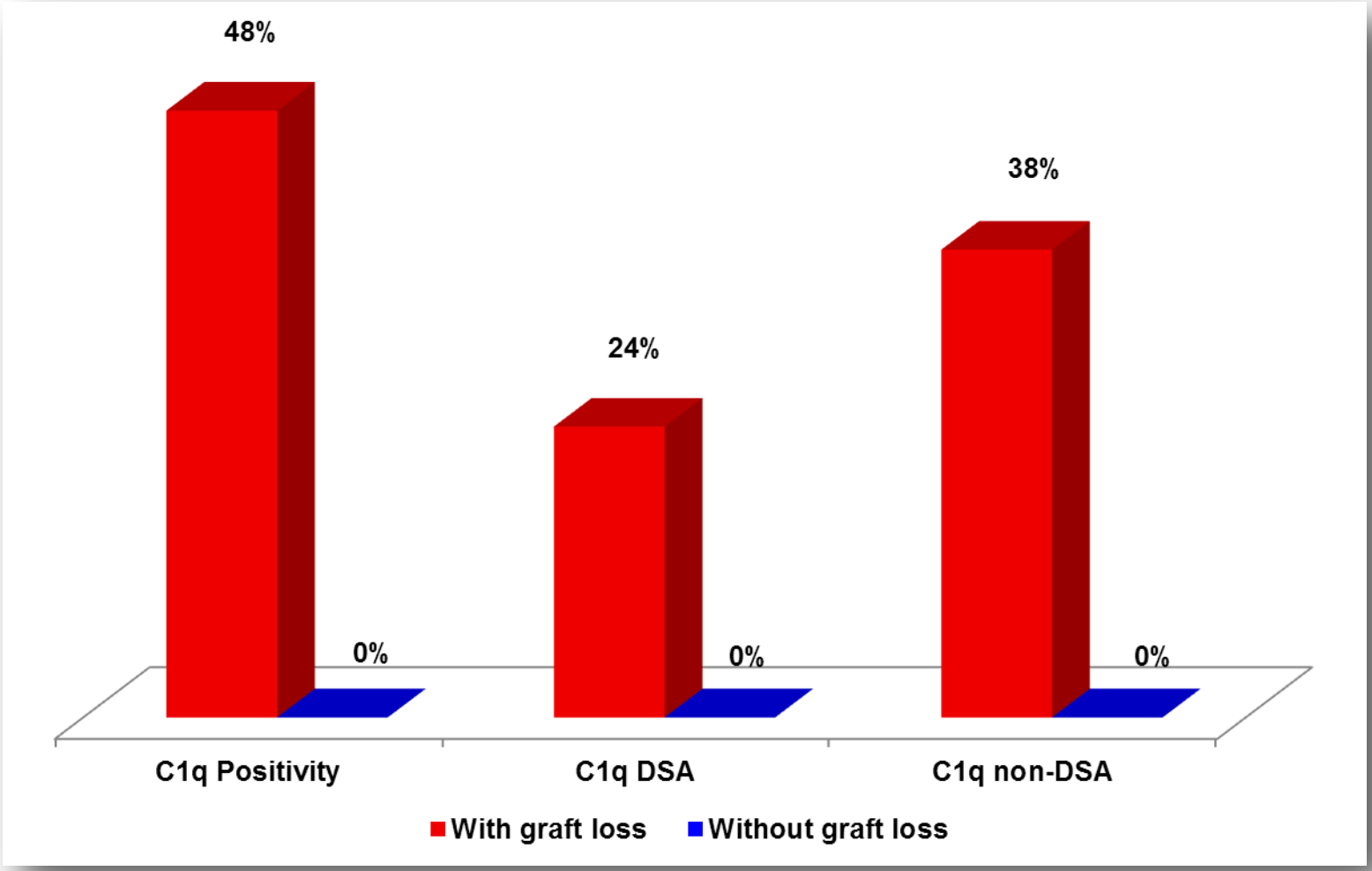
	Univariate analysis		Multivariate analysis[1]	
	HR (95% CI)	p	HR (95% CI)	p
HLAMatchmaker score per 10 increment	1.30 (1.23–1.38)	<0.001	1.23 (1.10–1.37)	<0.001
ln(PIRCHE-II) score	1.63 (1.46–1.83)	<0.001	1.44 (1.22–1.69)	<0.001
ABCDRDQ mismatches per MM	1.16 (1.12–1.21)	<0.001	0.96 (0.89–1.04)	0.299

CI, confidence interval; dnDSA, *de novo* donor-specific HLA antibodies; HR, hazard ratio; PIRCHE, predicted indirectly recognizable HLA epitopes.

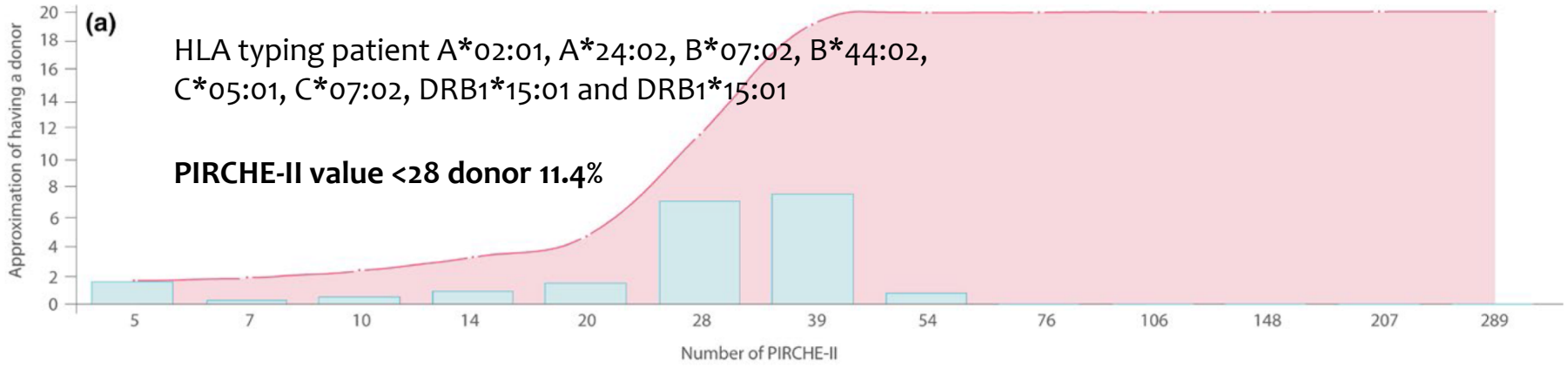
[1]Adjusting for ln(PIRCHE-II), HLAMatchmaker score, recipient age, donor age, and count of ABCDRDQ mismatches.

CTS Serum and DNA Studies

C1q-Positivity in DSA-Positive Patients (n=51, cut-off 300 MFI)

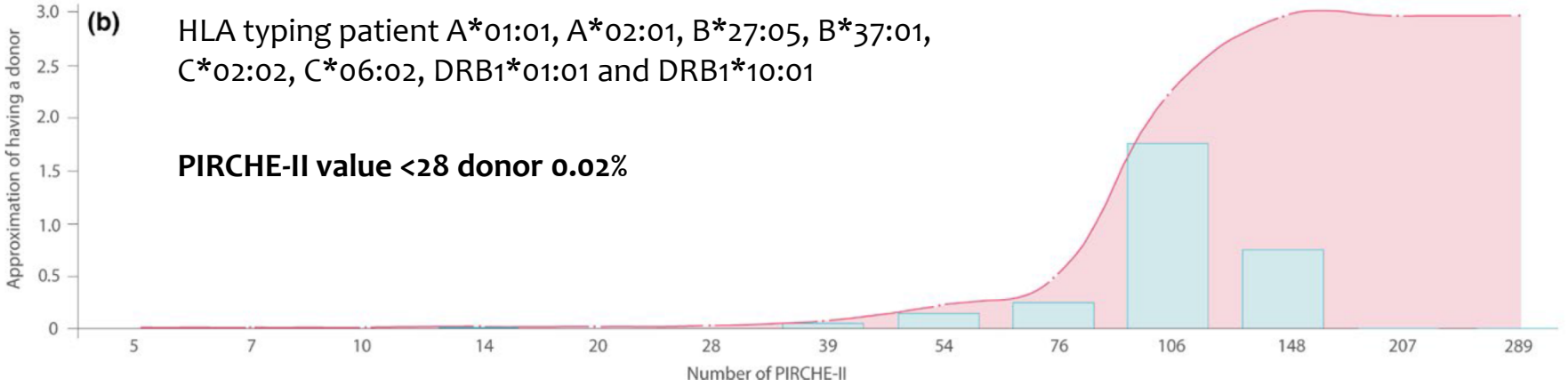


Match Probability Calculations
PIRCHE-II



HLA typing patient A*02:01, A*24:02, B*07:02, B*44:02, C*05:01, C*07:02, DRB1*15:01 and DRB1*15:01

PIRCHE-II value <28 donor 11.4%



HLA typing patient A*01:01, A*02:01, B*27:05, B*37:01, C*02:02, C*06:02, DRB1*01:01 and DRB1*10:01

PIRCHE-II value <28 donor 0.02%

Methods

HLA Typing

- **Serological (cells):**
  - CDC
- **Molecular (DNA):**
  - PCR-SSP
  - PCR-SSO
  - PCR-SBT

Cross-match

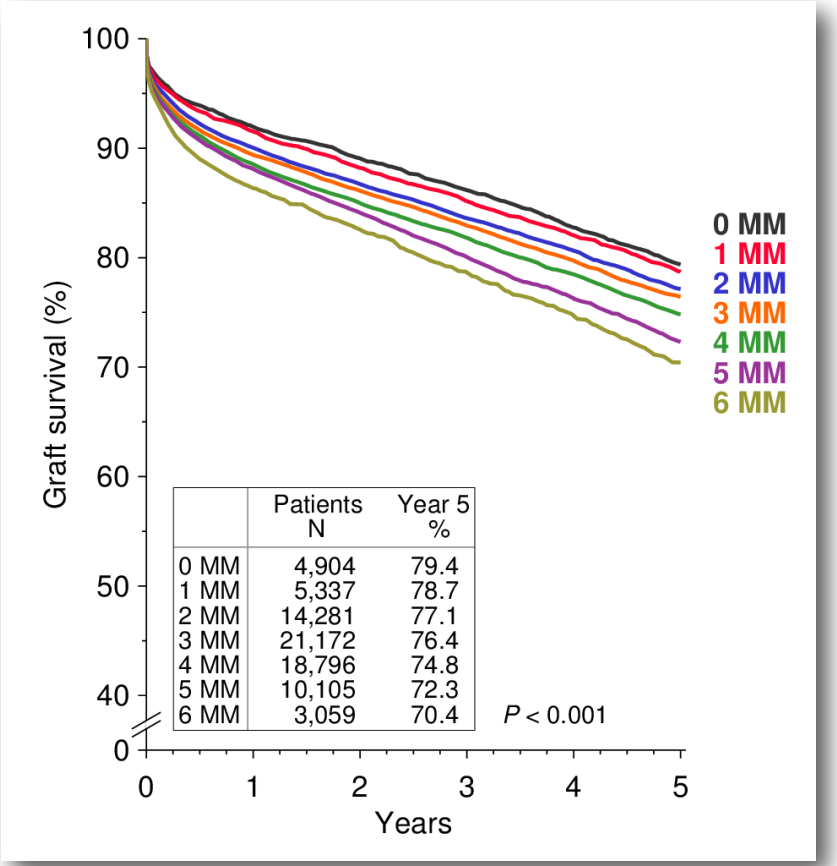
- CDC
- Flow
- ELISA
- Luminex®
- XM-One®

HLA Antibody Detection

- CDC
- ELISA
- Luminex® beads (mixed, PRA, Single Antigen → IgG, IgM, IgG1-4; C1q, C3d)

HLA-A+B+DR Mismatches

Deceased Donor Kidney Transplants 2005–2014



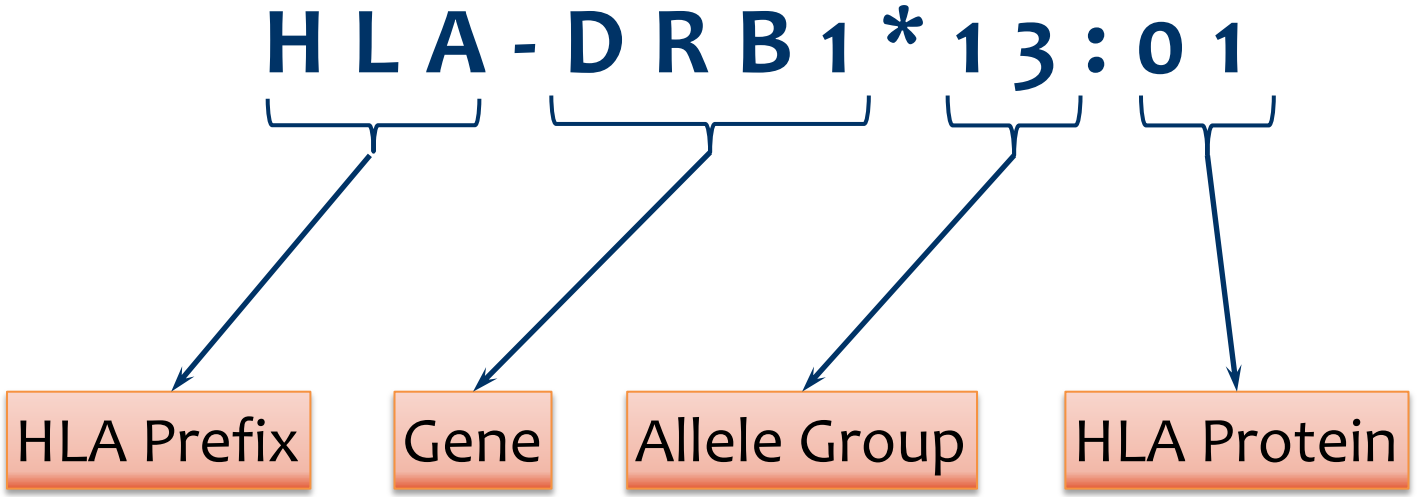
Matching

Kidney Tx: HLA-A, -B, -DRB1

Stem cell Tx: HLA-A, -B, -C, -DRB1, -DQB1

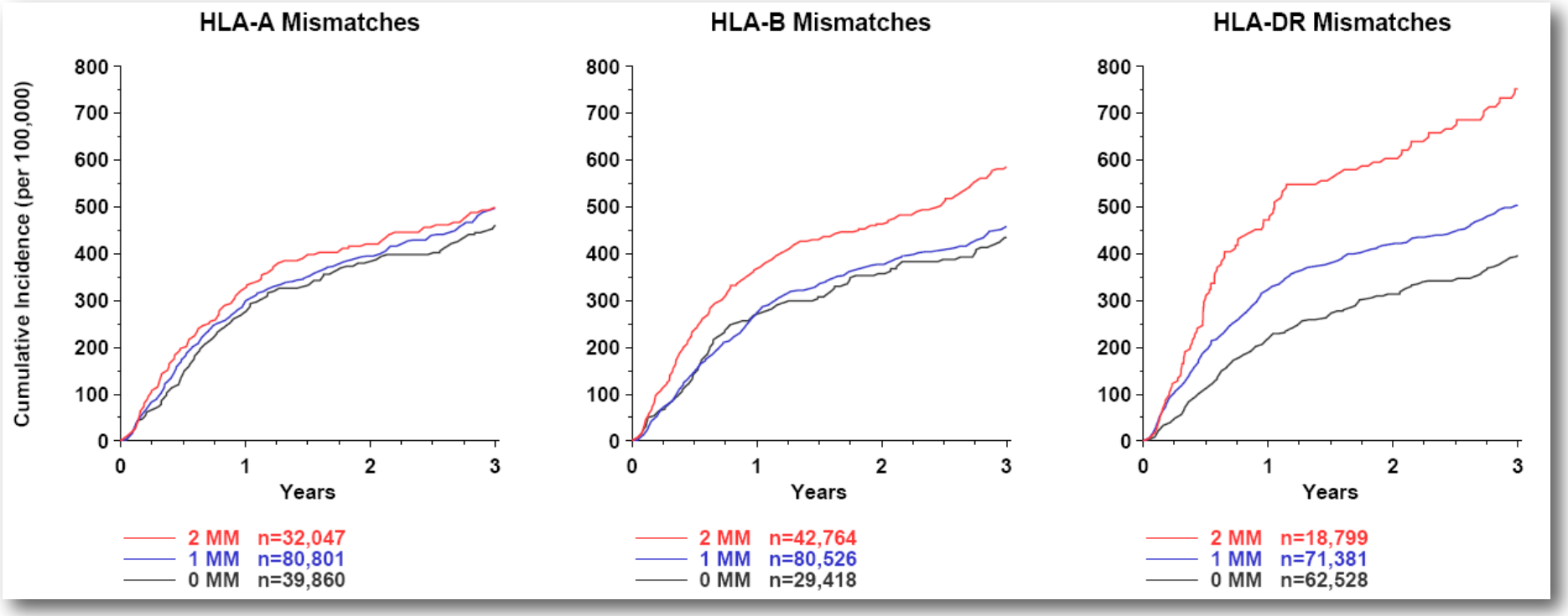
Nomenclature

Reporting of Molecular DNA Typing Results



Non-Hodgkin Lymphoma

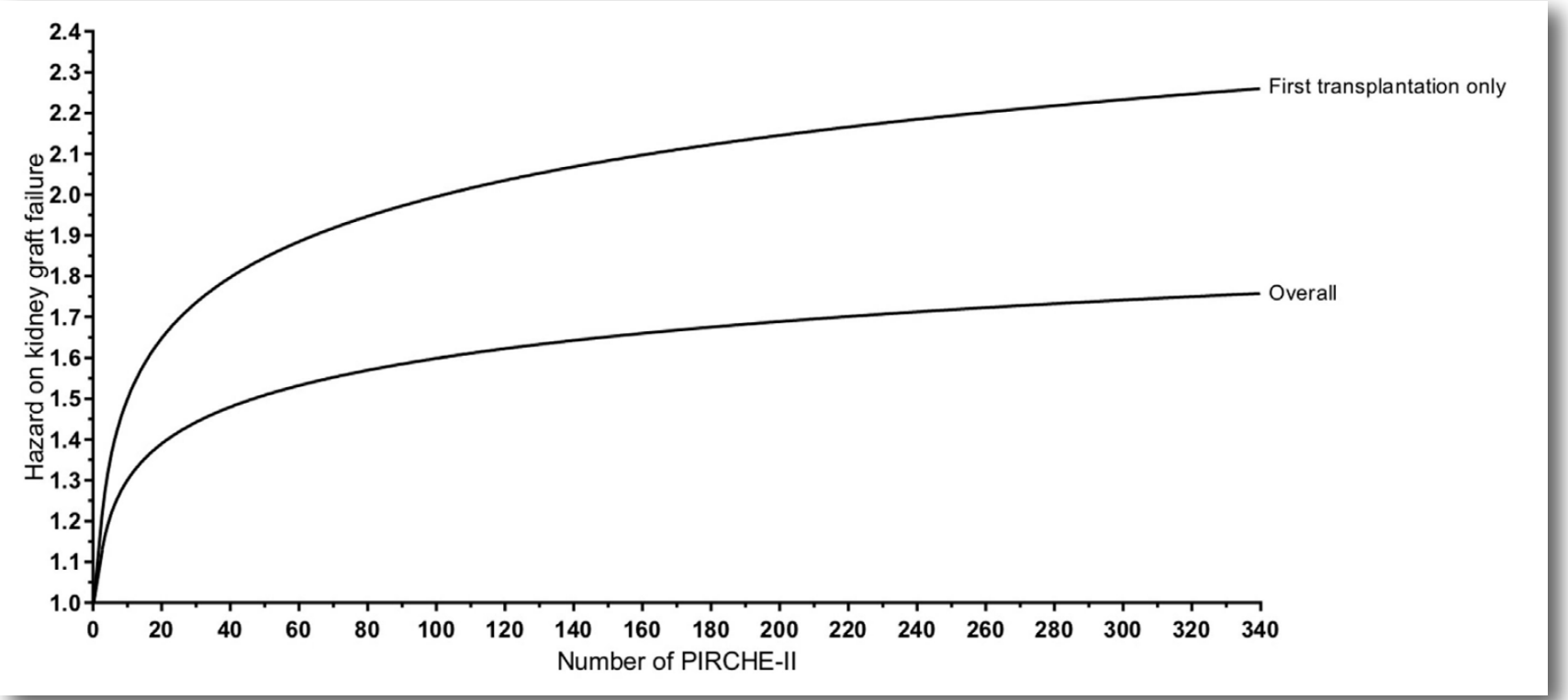
Deceased Donor Kidney Transplants



Opelz and Döhler; Transplantation 2010

Epitope Matching – Graft Survival

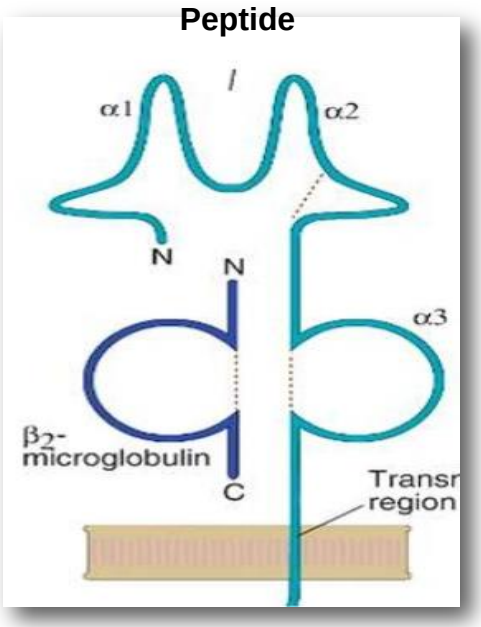
(1995-2005, Dutch Patients)



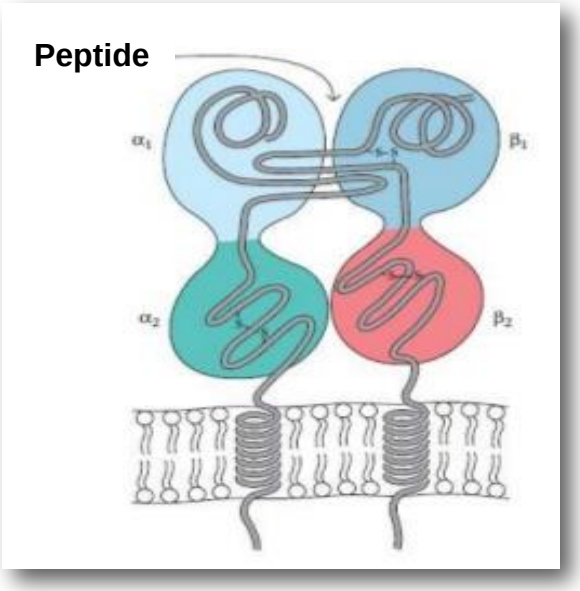
Increasing PIRCHE-II scores were a risk factor for kidney graft failure after Tx (p=0.003), especially in first transplants (p<0.001)

Geneugelijk et al, Front Immunol 2018

Schematic Structure of HLA Molecules



HLA Class I



HLA Class II