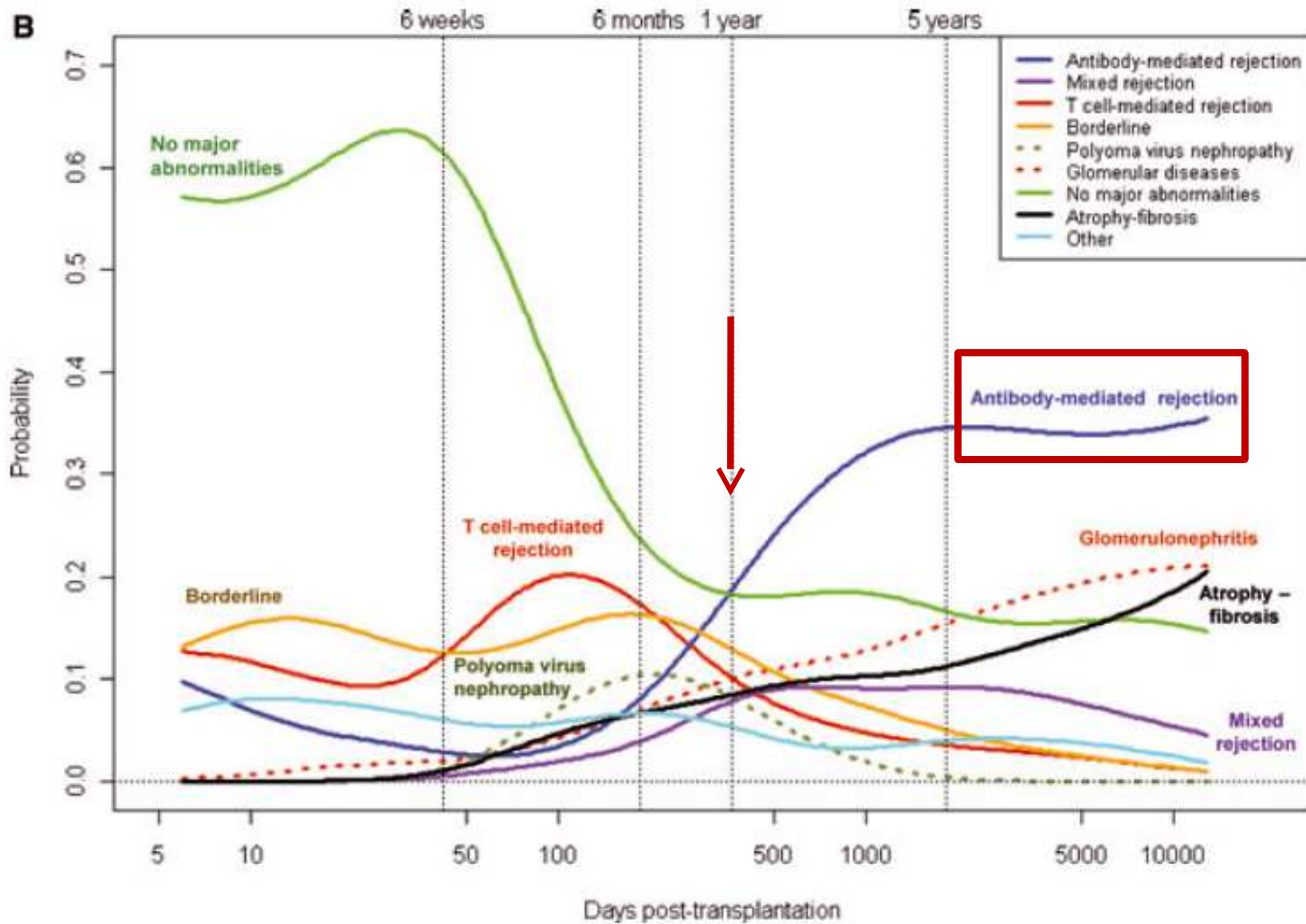
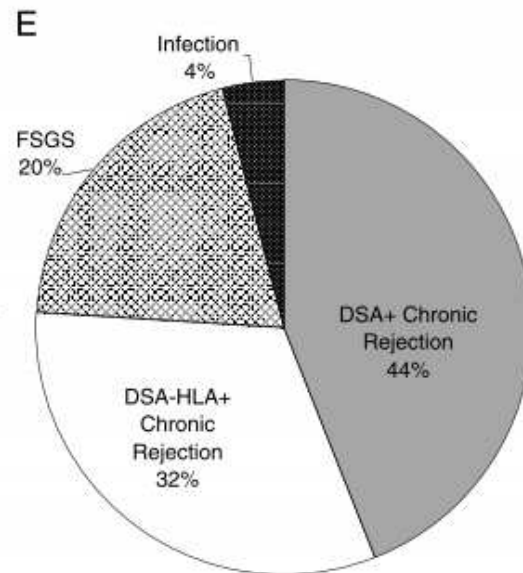
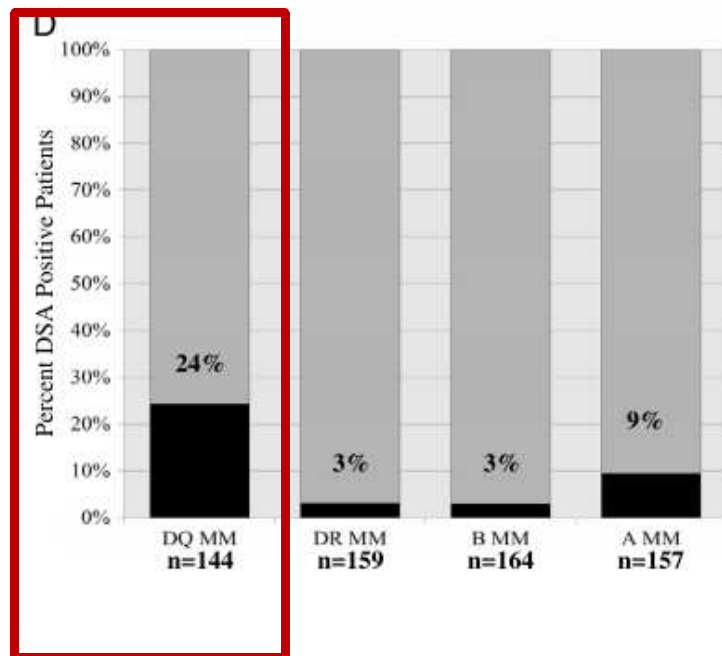
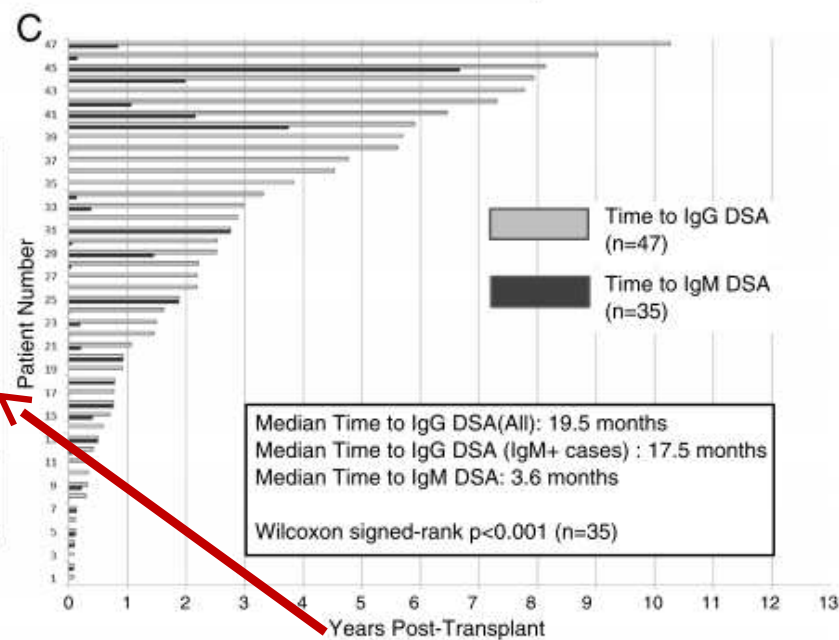
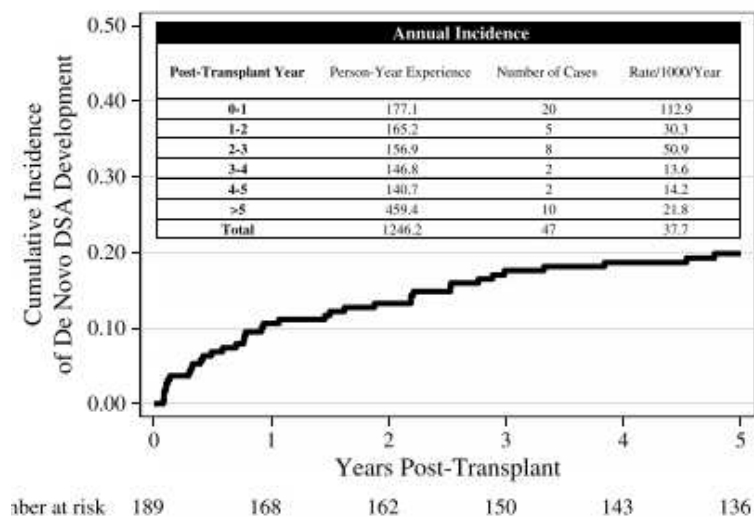


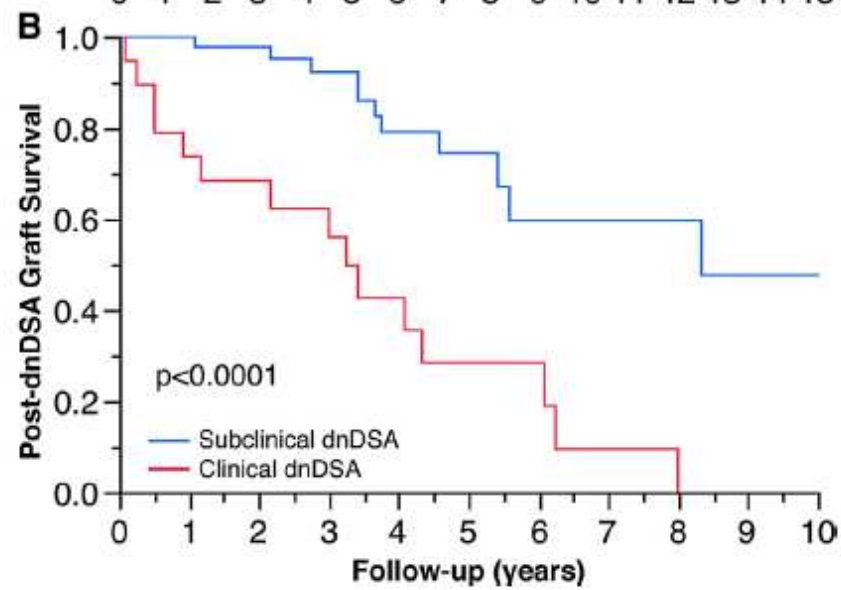
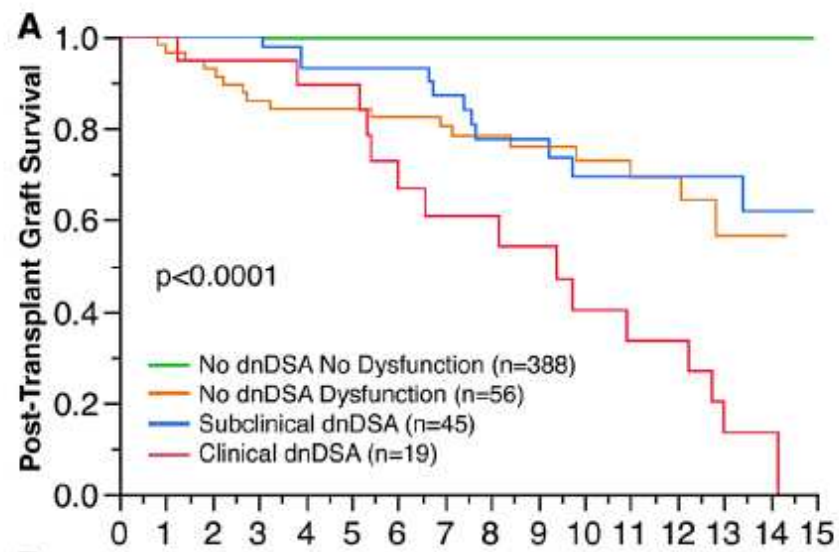
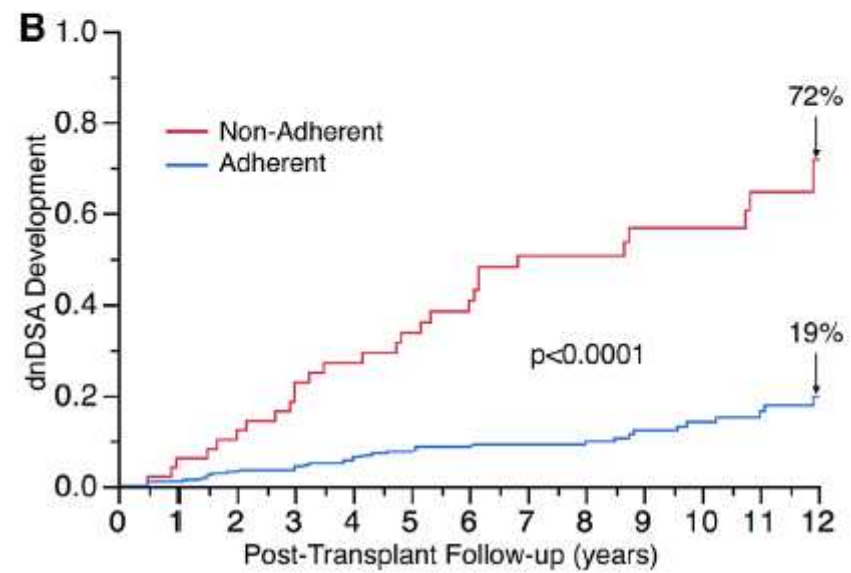
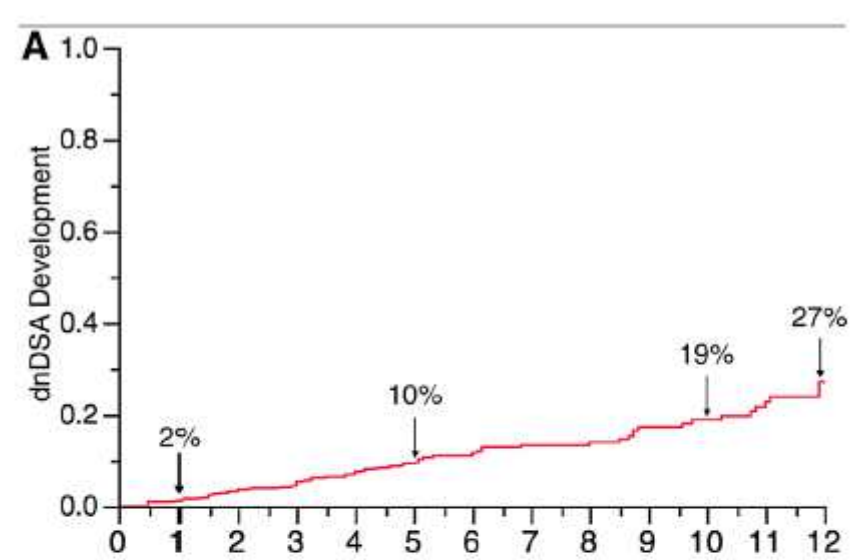
*Sellares, Am J Transpl 2012; 12: 388–399*



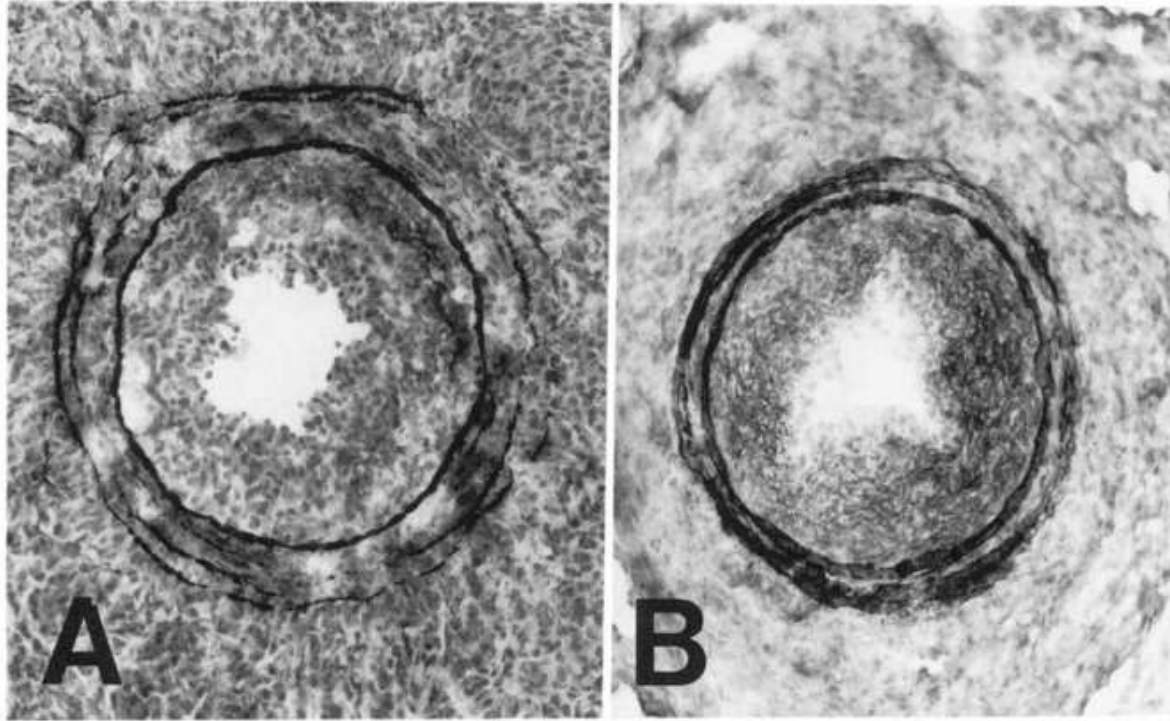
*Sellares, Am J Transpl2012; 12: 388–399*



*Everly, Transplantation 2013;95: 410-417*

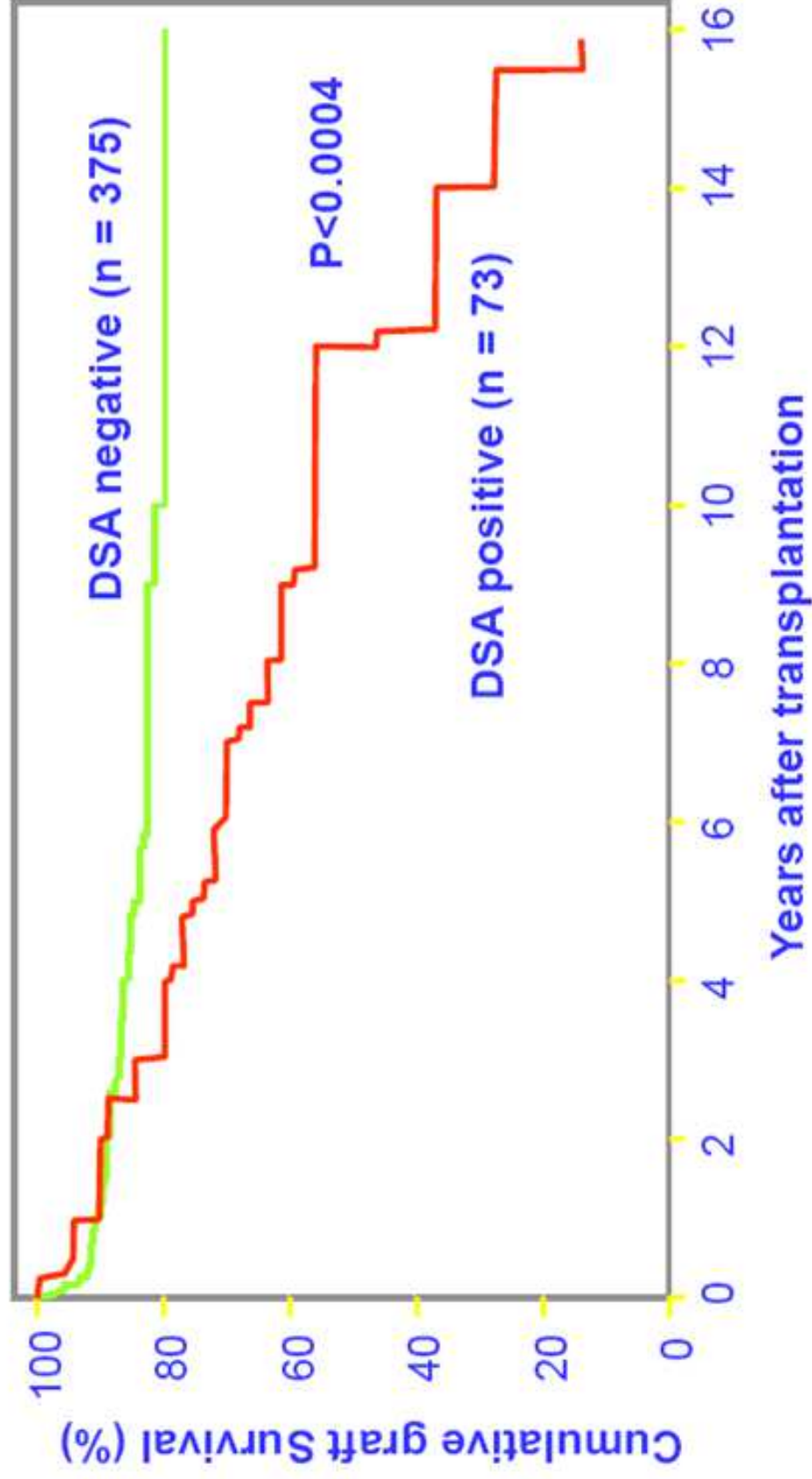


*Wiebe, Am J Transpl 2015; 15: 2921–2930*



**FIGURE 1.** Light micrographs of affected extramyocardial coronary arteries from allografts. (A) A 42 day B10.A cardiac graft in a B10.BR recipient shows marked intimal thickening, luminal stenosis, cellular infiltration, and periadventitial inflammation. (B) A 40 day B10.BR cardiac graft in a C.B-17 SCID recipient treated with passive Ab to donor Ags shows similar intimal thickening and luminal stenosis, without the periadventitial infiltrate. Elastic tissue stain,  $\times 200$ .

*Russell, Journal of Immunology, 1994, 152: 51 35.*



[Piazza et al., Clinical Transplant 2006]



Contents lists available at SciVerse ScienceDirect

## Seminars in Immunology

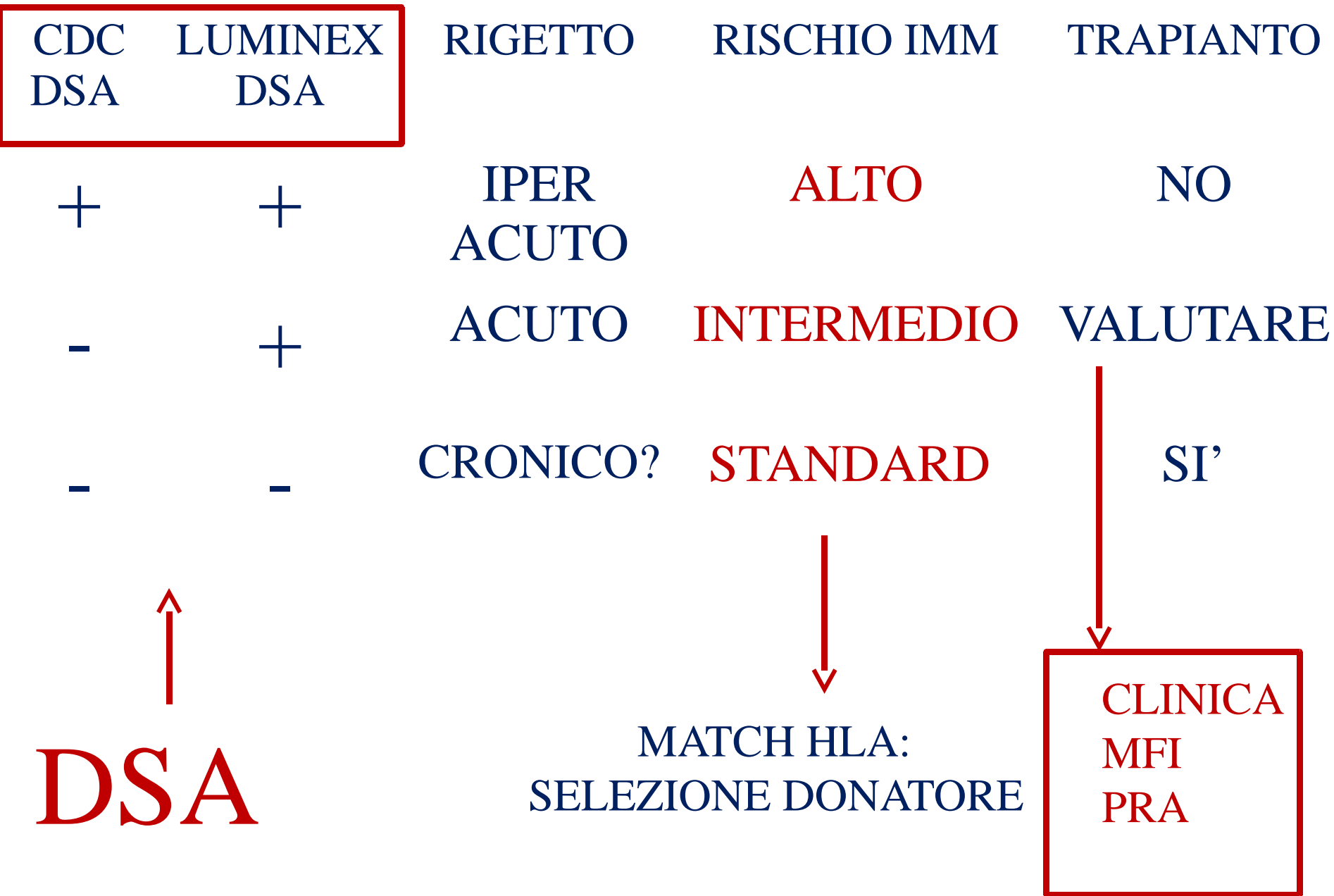
journal homepage: [www.elsevier.com/locate/ysmim](http://www.elsevier.com/locate/ysmim)

Review

### Humoral immunity and antibody-mediated rejection in solid organ transplantation

Robert A. Montgomery<sup>a</sup>, Emanuele Cozzi<sup>b</sup>, Lori J. West<sup>c</sup>, Daniel S. Warren<sup>a,\*</sup>

*Seminars in Immunology 23 (2011) 224–234*

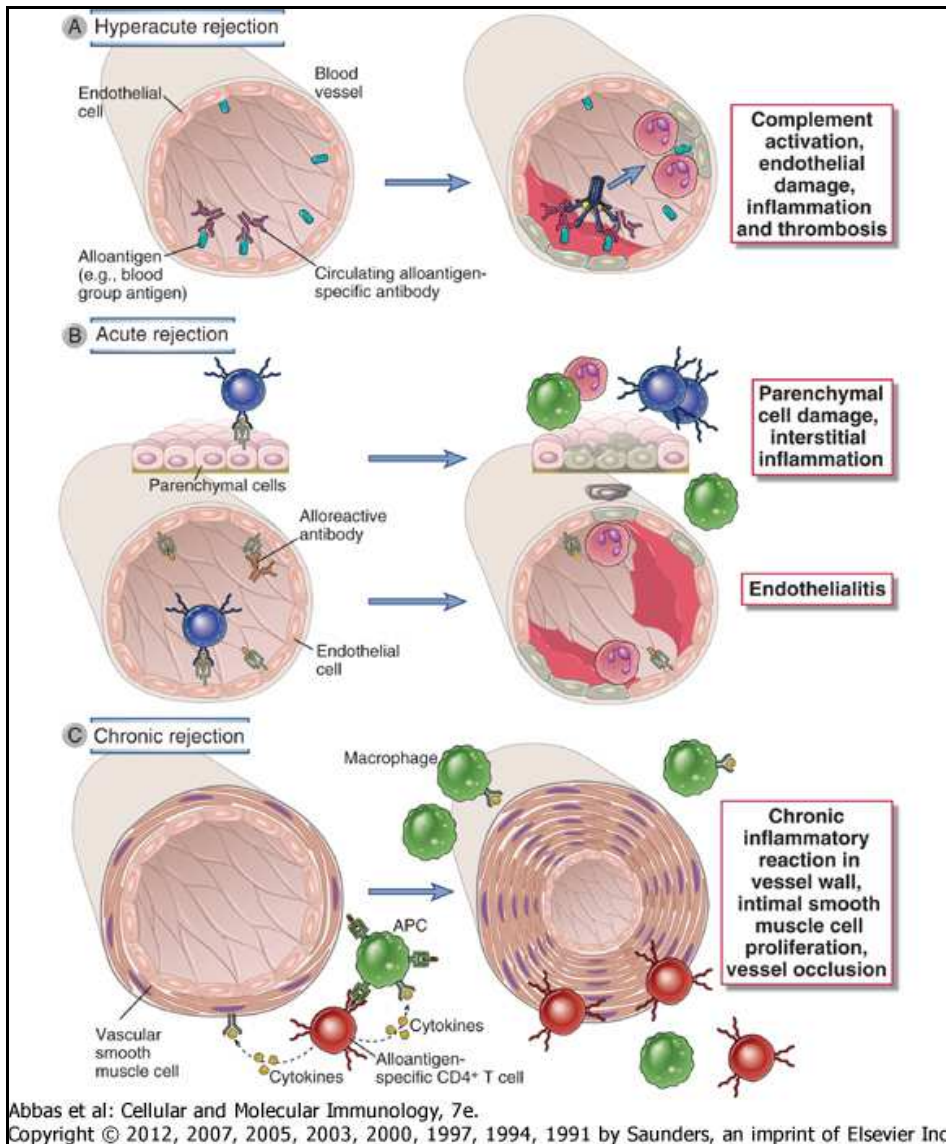


# I MECCANISMI DEL RIGETTO

IPERACUTO

ACUTO

CRONICO



# The New England Journal of Medicine

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Volume 280

APRIL 3, 1969

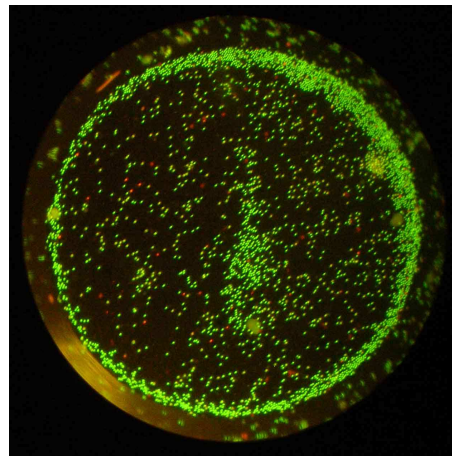
Number 14

## SIGNIFICANCE OF THE POSITIVE CROSSMATCH TEST IN KIDNEY TRANSPLANTATION\*

RAMON PATEL, M.R.C.P., AND PAUL I. TERASAKI, PH.D.

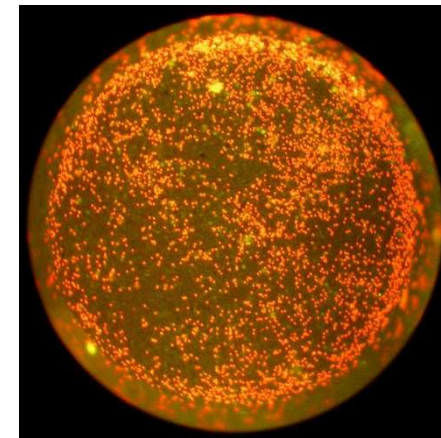
TABLE 2. *Classification of 248 Kidney Transplants Performed in 63 Recipients with and 163 without Preformed Antibodies According to the Duration of Graft Survival.*

GRAFT SURVIVAL	RECIPIENTS WITH ANTIBODIES			RECIPIENTS WITHOUT ANTIBODIES
	POSITIVE CROSSMATCH	NO CROSSMATCH	NEGATIVE CROSSMATCH	
Immediate failures	24 (80.0%)	6 (26.1%)	4 (14.8%)	4 (2.4%)
Failure within <3 mo	0	6	4	32
Failure after >3 mo	1	3	7	22
Survival for <3 mo	2	2	1	6
Survival after >3 mo	3	6	11	104
Totals	30	23	27	168



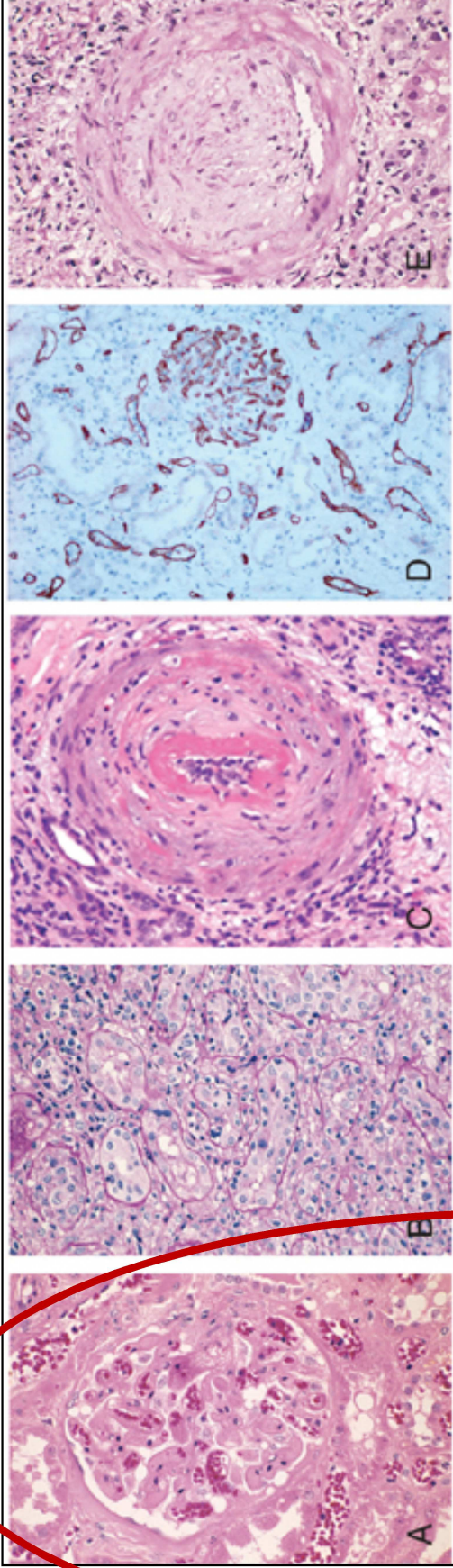
CDC XM  
NEGATIVO

TX



CDC XM  
POSITIVO

NO TX



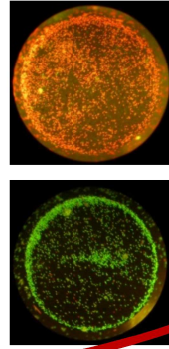
Abbas et al: Cellular and Molecular Immunology, 7e.  
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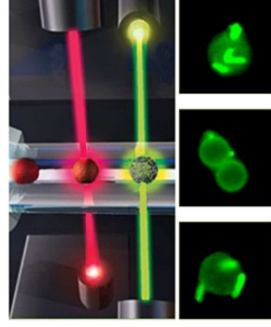
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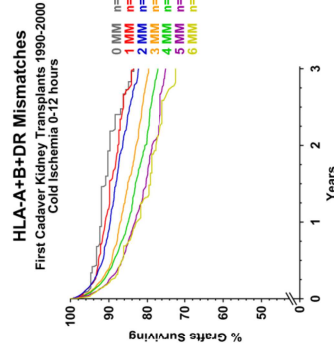
CELLULARE ANTICORPALE



CDC XM



Luminex DSA



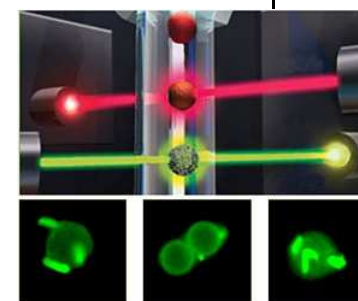
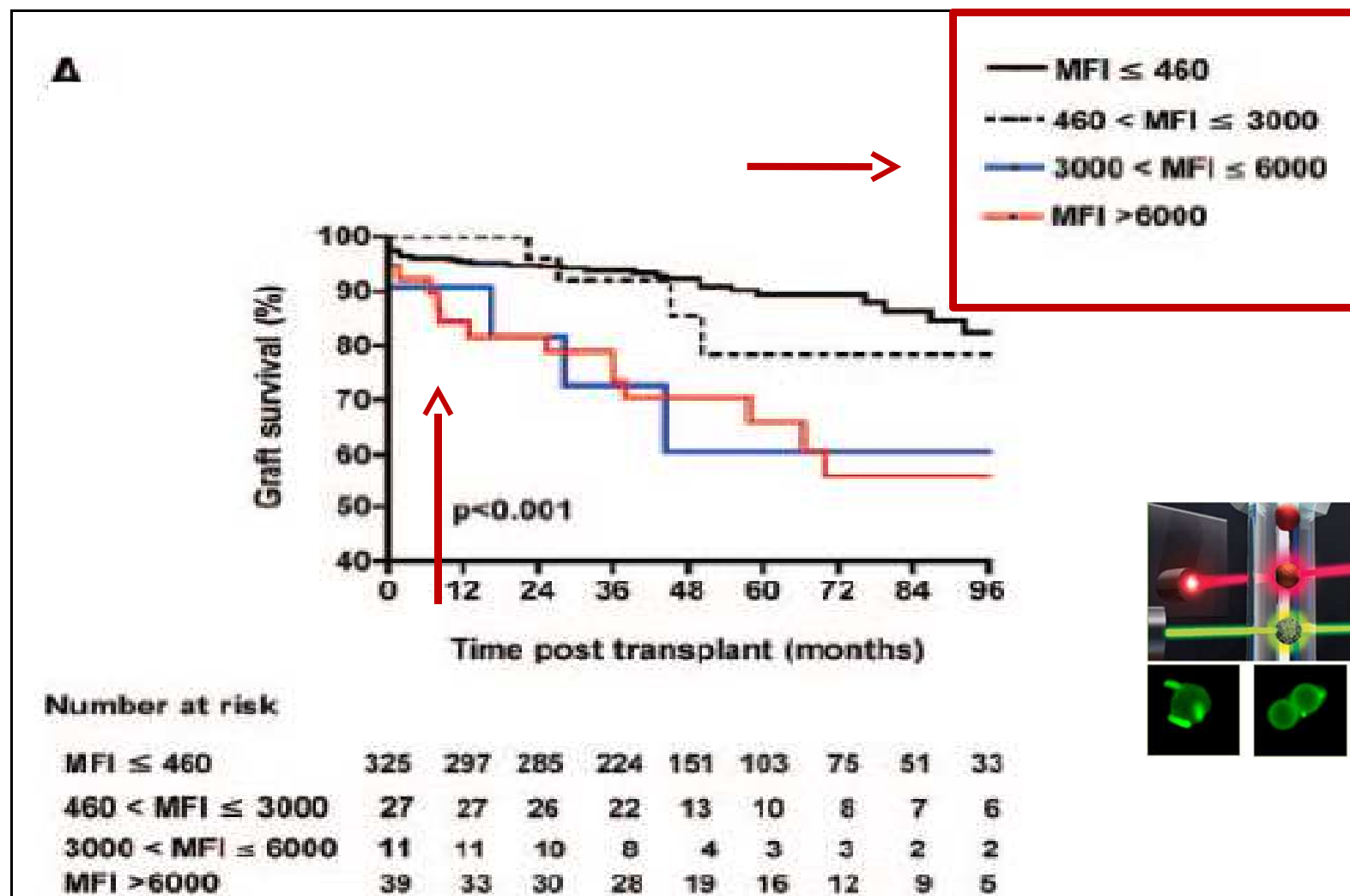
MATCH HLA

CDC DSA	LUMINEX DSA	RIGETTO	RISCHIO IMM	TRAPIANTO
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+	+	I P E R  A C U T O	A L T O	N O
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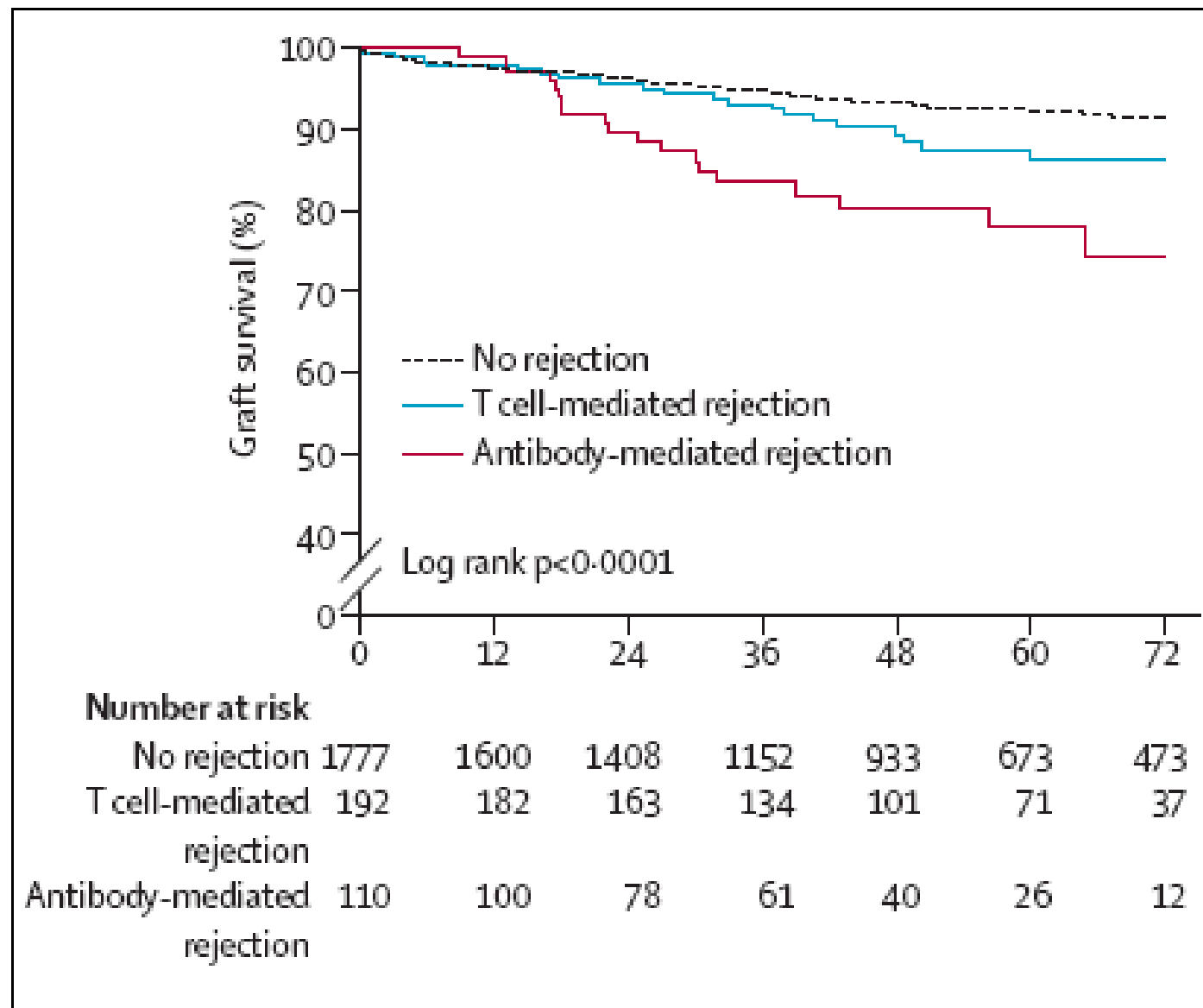
-	+	A C U T O	I N T E R M E D I O	V A L U T A R E
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-	-	C R O N I C O ?	S T A N D A R D	S I'
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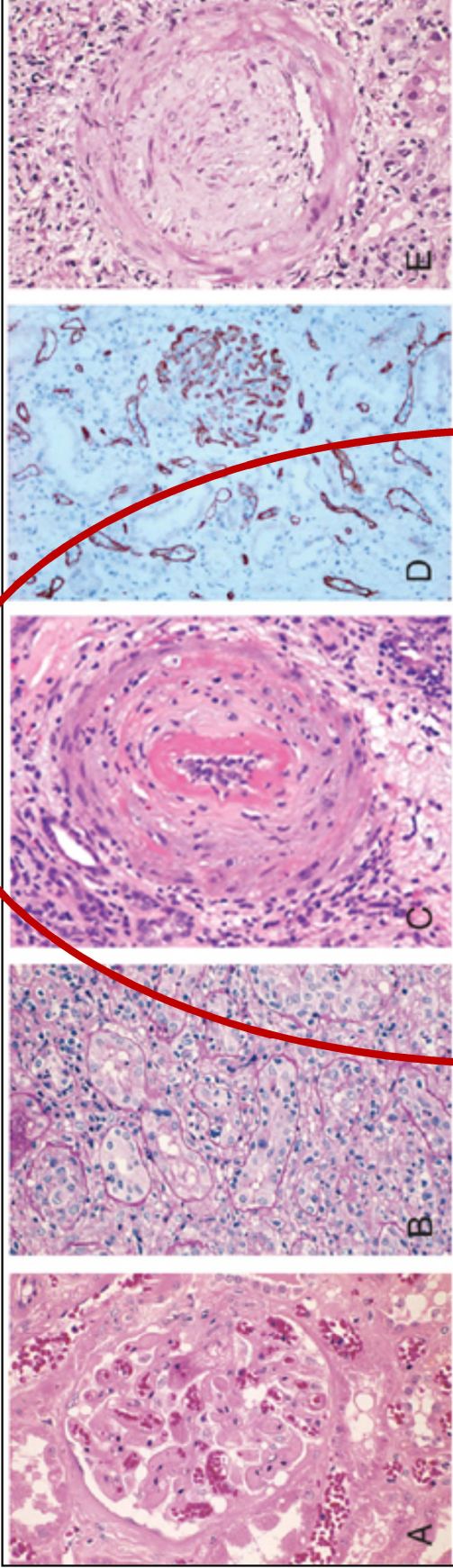


## DSA LUMINEX

*Lefaucher, J Am Soc Nephrol 21: 1398–1406, 2010*



Lefaucher, JASN 2010



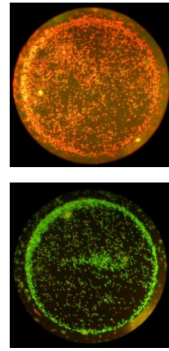
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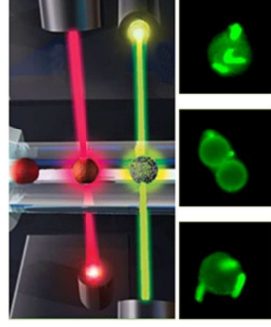
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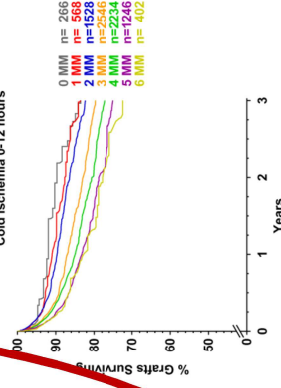
CELLULARE ANTICORPALE



CDC XM



Luminex DSA



MATCH HLA

CDC DSA      LUMINEX DSA      RIGETTO      RISCHIO IMM      TRAPIANTO

+      +      IPER ACUTO      ALTO      NO

-      +      ACUTO      INTERMEDIO      VALUTARE

-      -      CRONICO?      STANDARD      SI'

↓  
CLINICA  
MFI  
PRA

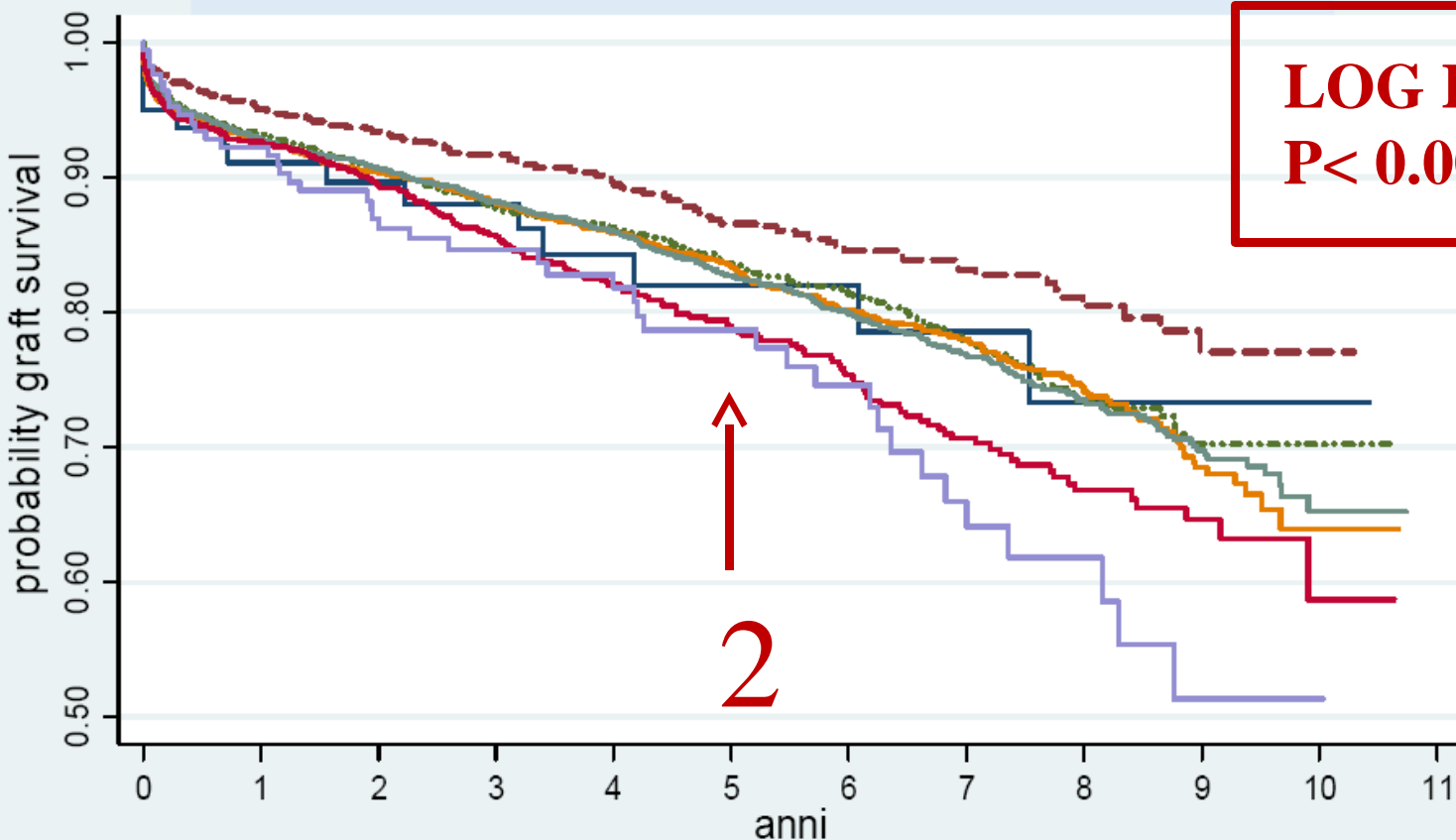
## VALUTAZIONE RISCHIO INTERMEDIO:

- URGENZA + BENEFICIO CLINICO
- PROBABILITA' DONATORE ALTERNATIVO (cPRA)
- INTERMEDIO ALTO VS. INTERMEDIO BASSO

	MFI	FCXM	C1q
ALTO	>5000	POS	POS
BASSO	<5000	NEG	NEG

## TRANSPLANT SURVIVAL – MISMATCH TOTALE

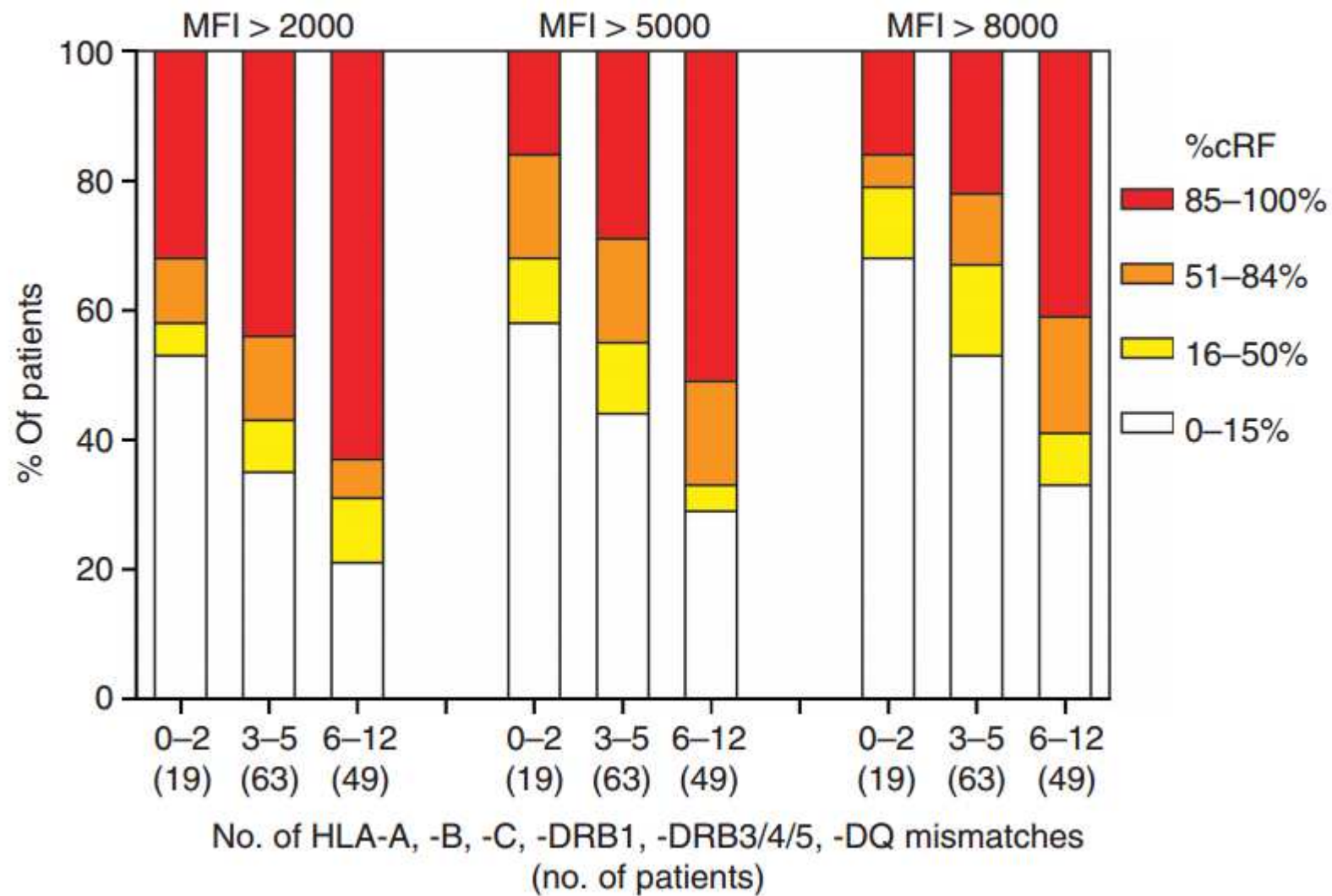
EVENTO: FALLIMENTO ORGANO O DECESSO



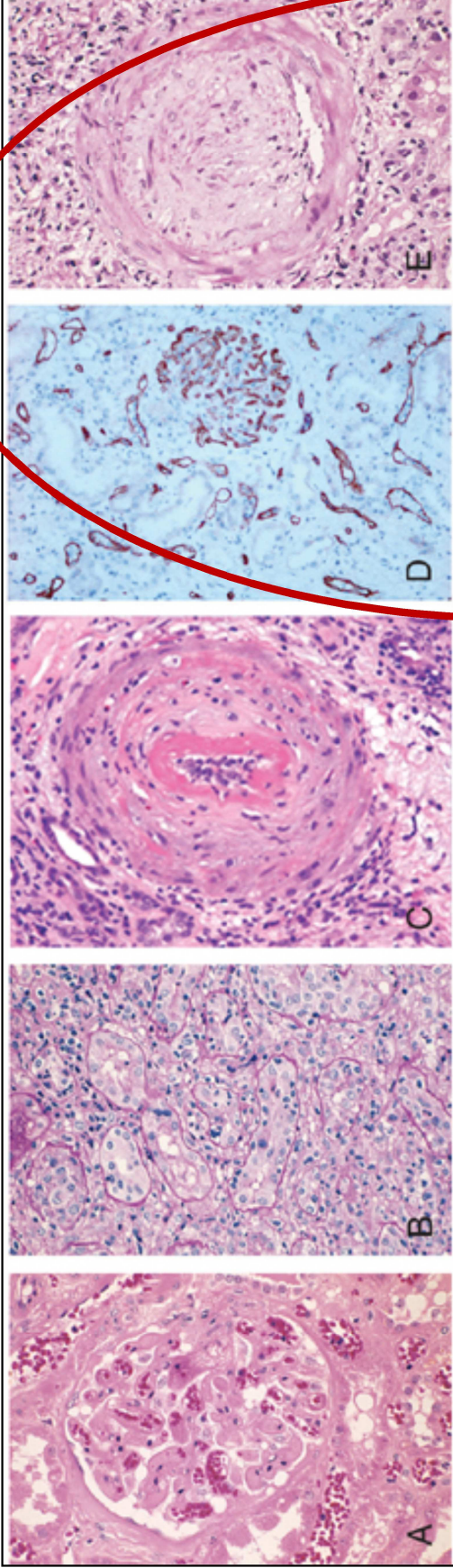
**LOG RANK TEST**  
**P < 0.0001**

↑  
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**MISMATCH HLA**



*Kosmoliaptsis, Kidney Int 2014; 86, 1039–1048*



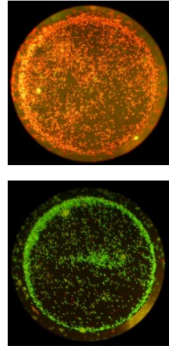
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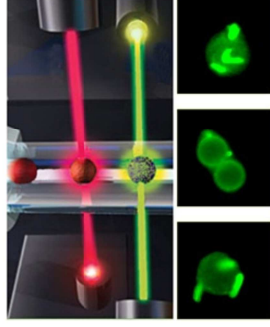
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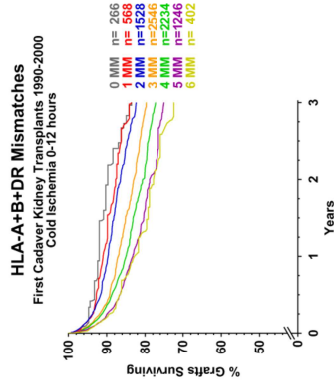
CELLULARE ANTICORPALE



CDC XM



Luminox DSA



MATCH HLA

CDC DSA	LUMINEX DSA	RIGETTO	RISCHIO IMM	TRAPIANTO
+	+	IPER ACUTO	ALTO	NO
-	+	ACUTO	INTERMEDIO	VALUTARE

-	-	CRONICO?	STANDARD	SI'
---	---	----------	----------	-----



MATCH HLA:  
SELEZIONE DONATORE

## Sensitization in Transplantation: Assessment of Risk (STAR) 2017 Working Group Meeting Report

Anat R. Tambur<sup>1,\*</sup> | Patricia Campbell<sup>2</sup> | Frans H. Claas<sup>3</sup> | Sandy Feng<sup>4</sup> |  
Howard M. Gebel<sup>5</sup> | Annette M. Jackson<sup>6</sup> | Roslyn B. Mannon<sup>7</sup> | Elaine F. Reed<sup>8</sup> |  
Kathryn Tinckam<sup>9</sup>  | Medhat Askar<sup>10</sup> | Anil Chandraker<sup>11</sup> | Patricia P. Chang<sup>12</sup> |  
Monica Colvin<sup>13</sup> | Anthony-Jake Demetris<sup>14</sup> | Joshua M. Diamond<sup>15</sup> | Anne I. Dipchand<sup>9</sup> |  
Robert L. Fairchild<sup>16</sup> | Mandy L. Ford<sup>5</sup> | John Friedewald<sup>1</sup>  | Ronald G. Gill<sup>17</sup> |  
Denis Glotz<sup>18</sup> | Hilary Goldberg<sup>11</sup> | Ramsey Hachem<sup>19</sup> | Stuart Knechtle<sup>20</sup> |  
Jon Kobashigawa<sup>21</sup> | Deborah J. Levine<sup>22</sup> | Joshua Levitsky<sup>1</sup> | Michael Mengel<sup>2</sup> |  
Edgar Milford<sup>11</sup> | Kenneth A. Newell<sup>5</sup> | Jacqueline G. O'Leary<sup>23</sup> | Scott Palmer<sup>20</sup> |  
Parmjeet Randhawa<sup>14</sup> | John Smith<sup>24</sup> | Laurie Snyder<sup>20</sup> | Randall C. Starling<sup>16</sup> |  
Stuart Sweet<sup>19</sup>  | Timucin Taner<sup>25</sup> | Craig J. Taylor<sup>26</sup> | Steve Woodle<sup>27</sup> |  
Adriana Zeevi<sup>14</sup> | Peter Nickerson<sup>28</sup>

*Tambur, Am J Transplant 2018;18:1604–1614.*

Strength of Recommendation		Patients	Clinicians	Policy
1	Recommend	Most would want	Most would do	Supports policy
2	Suggest	Majority would want but many would not	Different choices for different patients	Substantive debate to follow
3	Do not Recommend			



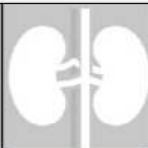
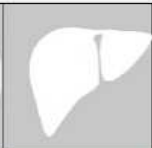
#### Quality of Evidence

A	High	RCT or Very strong evidence of association with no confounders
B	Moderate	Strong evidence of association or evidence of a dose response gradient
C	Low	Observational study
D	Very low	Other types of studies or serious limitations to study quality

EO	There is absence of evidence and/or the working group expert opinion only was used, or	
	There is no specific evidence to address recommendation, however it aligns with standard of care and would be agreed by a majority of experts that no specific evidence on the topic needs to be generated, nor would it be expected to be generated.	

**FIGURE 1** Expert assessment of strength of evidence

**TABLE 2** Organ-specific recommendations

				
<b>Peri-Transplant Evaluation (Cross-match)</b>				
A Virtual and or Prospective Crossmatch between Donor and Recipient should be performed prior to allocation ideally and at a minimum prior to transplant	1C	1C	1C	
Avoiding HLA antibody is the preferred strategy	2C	2C	2C	
<b>Post-Transplant Assessment of HLA Antibody</b>				
<b>Stable Grafts: Memory</b>				
Early in patients with active memory or at risk for latent memory	2C	2B	1A*	
Frequency depends on number and strength of pre-tx DSA	2C	2C	1A	
Not routine in liver				1D
Guided by non-liver organ in combined liver - other organ				1A
<b>Stable Grafts: Naïve</b>				
At intervals post-transplant	2C	2B	EO	EO
After modifications of immunosuppression or CNJ avoidance protocols	EO	EO	1A**	
Suspected or documented non-adherence	EO	EO	1A***	
<b>Graft Dysfunction: Memory and Naïve</b>				
As part of investigation of acute and chronic graft dysfunction	1B	1B	1B	
If there are histologic features of graft injury	1B	1B	1B	
In liver, test patients w/ steroid resistant rejection and chronic rejection or those w/ clinical or histologic features of acute or chronic AMR				EO
<b>Ancillary HLA Diagnostic Assays</b>				
Complement or Isotype assays				
May be done but the role must be determined at the center level	2C		2C	
* (34)				
** (21,35,36)				
*** (22)				

DSA, donor-specific antibody; CNJ, calcineurin inhibitor; AMR, antibody-mediated rejection.

*Tambur, Am J Transplant 2018;18:1604–1614.*

**TABLE 1** HLA diagnostic approach to assign a patient's risk for memory or naïve alloimmune response

Pretransplant donor–recipient HLA laboratory evaluation					
CDC crossmatch	Flow crossmatch	Single antigen bead	History of sensitization	HLA molecular MM	HLA identical
DSA positive	DSA positive	DSA positive			
Negative	DSA positive	DSA positive			
Negative	Negative	DSA positive			
Negative	Negative	Negative	Pregnancy or prior transplant with repeat MM		
Negative	Negative	Negative	cPRA with unknown repeat MM		
Negative	Negative	Negative			
Negative	Negative	Negative	No	High	
Negative	Negative	Negative	No	Low	
Negative	Negative	Negative	No	0	Yes
MM, Mismatch; DSA, donor-specific antibody; ABMR, antibody-mediated rejection; TCMR, T cell–mediated rejection.					

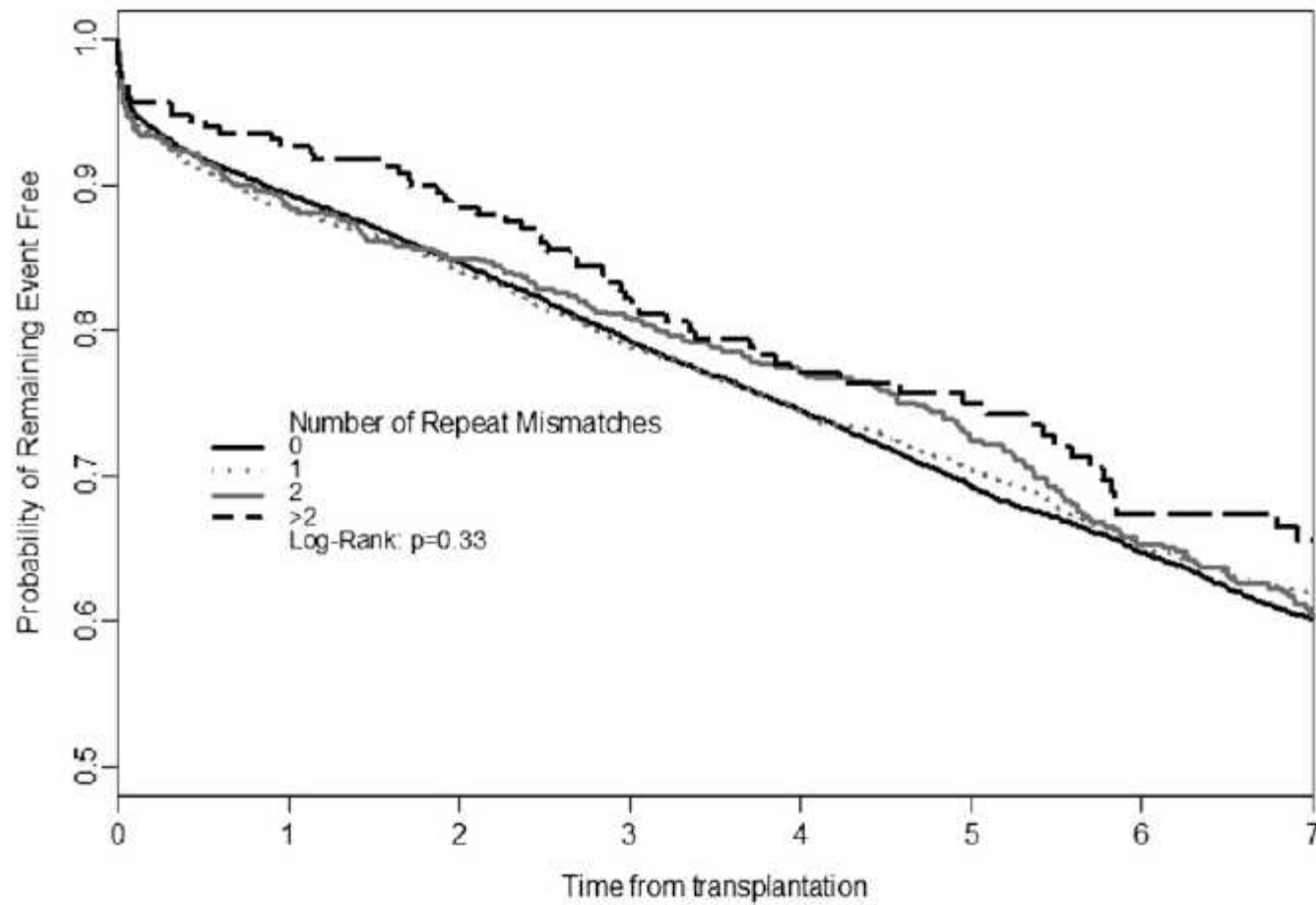
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Negative	DSA positive	DSA positive				Active memory and at risk for ABMR and TCMR
Negative	Negative	DSA positive				Active memory and at risk for ABMR and TCMR
Negative	Negative	Negative	Pregnancy or prior transplant with repeat MM			At risk for latent memory with a recall B and T cell response
Negative	Negative	Negative	cPRA with unknown repeat MM			Potential risk for latent memory with a recall B and T cell response
Negative	Negative	Negative	No	High		Increased risk for de novo alloimmune response
Negative	Negative	Negative	No	Low		Baseline risk for de novo alloimmune response
Negative	Negative	Negative	No	0	Yes	Low risk for de novo alloimmune response

MM, Mismatch; DSA, donor-specific antibody; ABMR, antibody-mediated rejection; TCMR, T cell-mediated rejection.

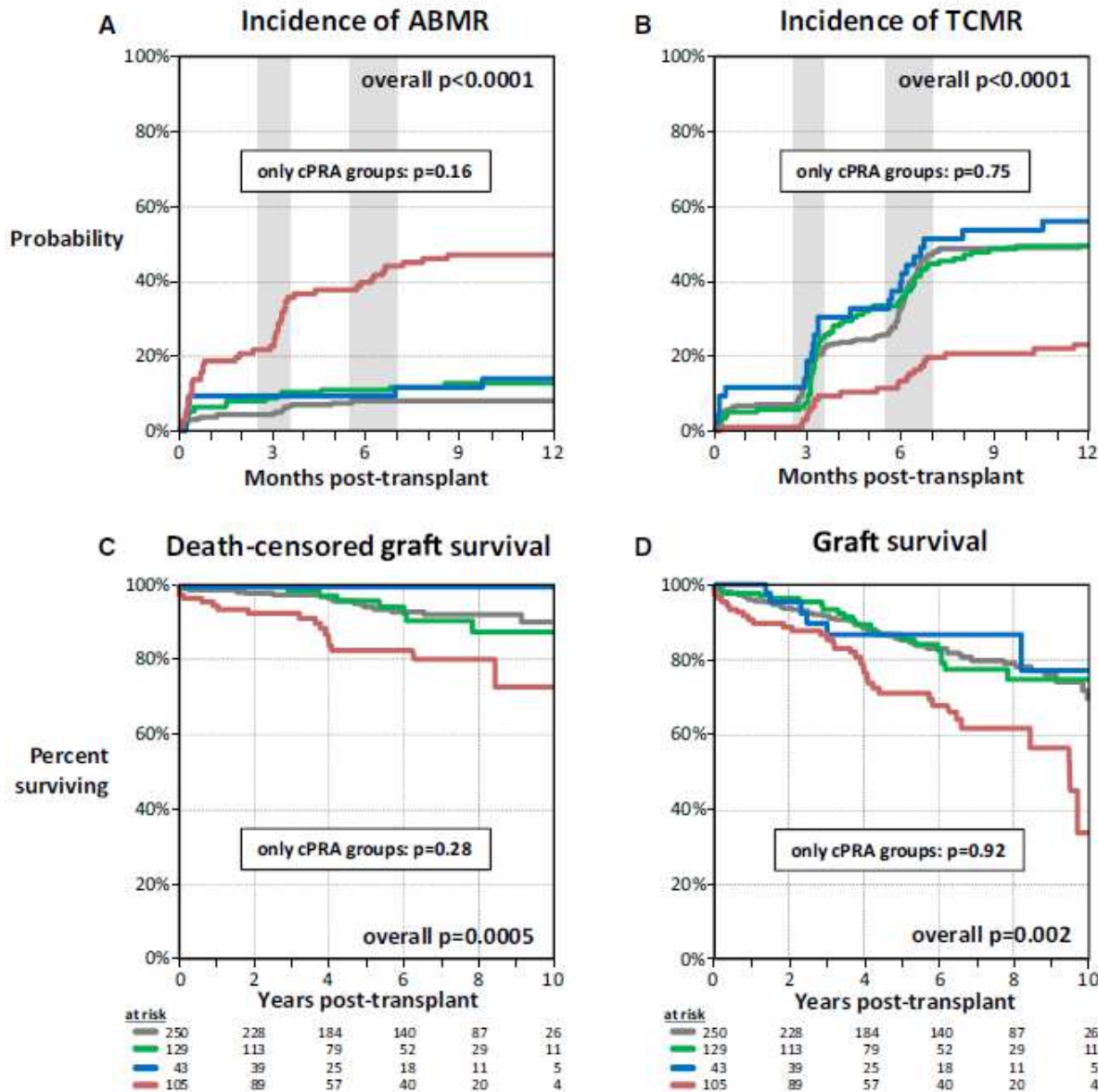
*Tambur, Am J Transplant 2018;18:1604–1614.*

# REPEATED MISMATCH



*Tinckham, J Am Soc Nephrol 27: , 2016*

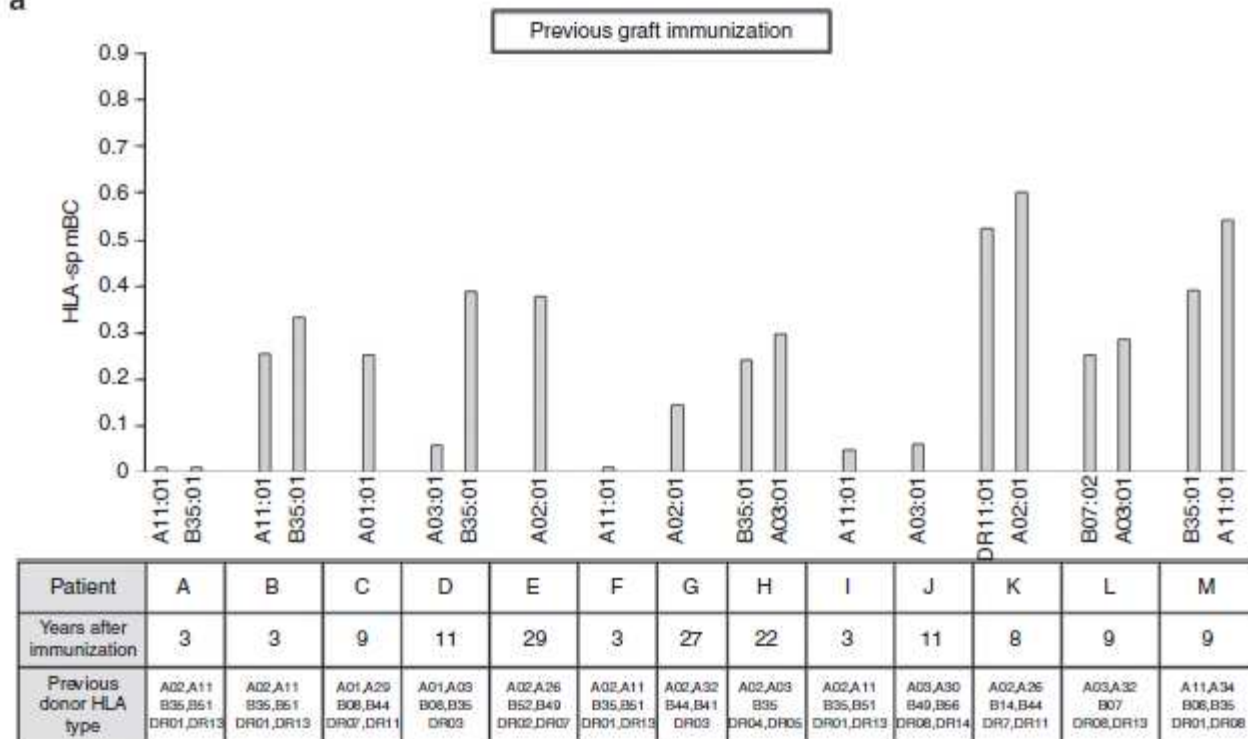
# PRA



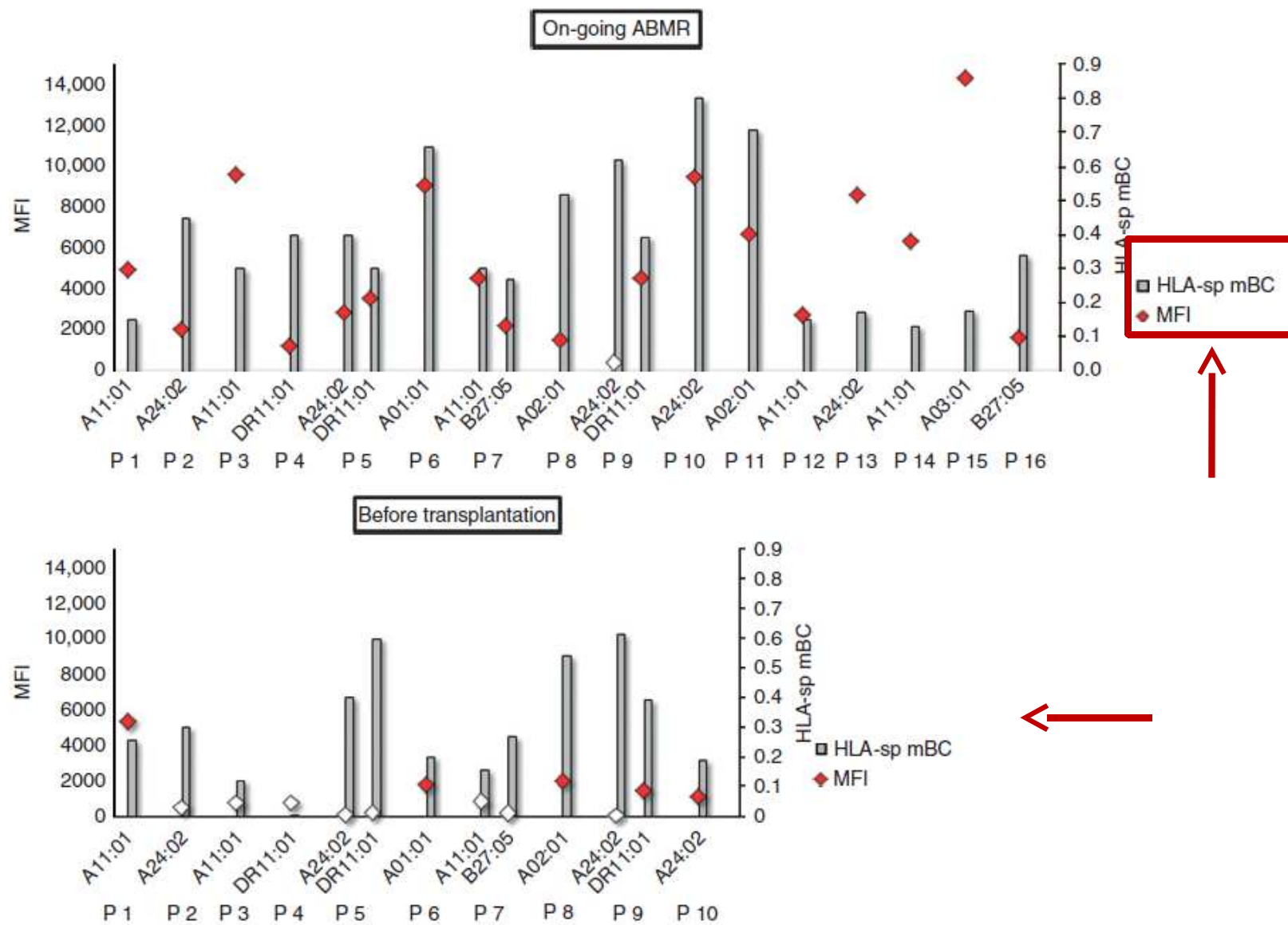
*Wehemeier, Am J Transpl 2017; 17: 2092–2102*

# HLA-specific MEMORY B CELLS

a



*Lucia, Kidney Int 2018; 88:874-887*



DONOR-SPECIFIC MEMORY B-CELL (MBC) FREQUENCIES OF KIDNEY TRANSPLANT PATIENTS  
AT THE TIME OF ANTIBODY-MEDIATED REJECTION (ABMR) AND BEFORE KIDNEY TRANSPLANTATION.

*Lucia, Kidney Int 2015; 88:874-887*

**TABLE 1** HLA diagnostic approach to assign a patient's risk for memory or naïve alloimmune response

Pretransplant donor–recipient HLA laboratory evaluation						
CDC crossmatch	Flow crossmatch	Single antigen bead	History of sensitization	HLA molecular MM	HLA identical	Immune risk assessment
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Negative	Negative	Negative	No	High		Increased risk for de novo alloimmune response
Negative	Negative	Negative	No	Low		Baseline risk for de novo alloimmune response
Negative	Negative	Negative	No	0	Yes	Low risk for de novo alloimmune response

MM, Mismatch; DSA, donor-specific antibody; ABMR, antibody-mediated rejection; TCMR, T cell–mediated rejection.



*Tambur, Am J Transplant 2018;18:1604–1614.*

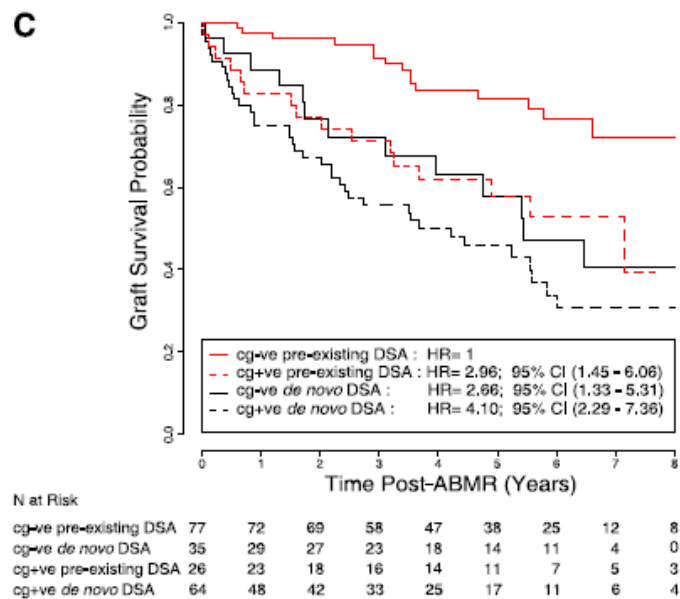
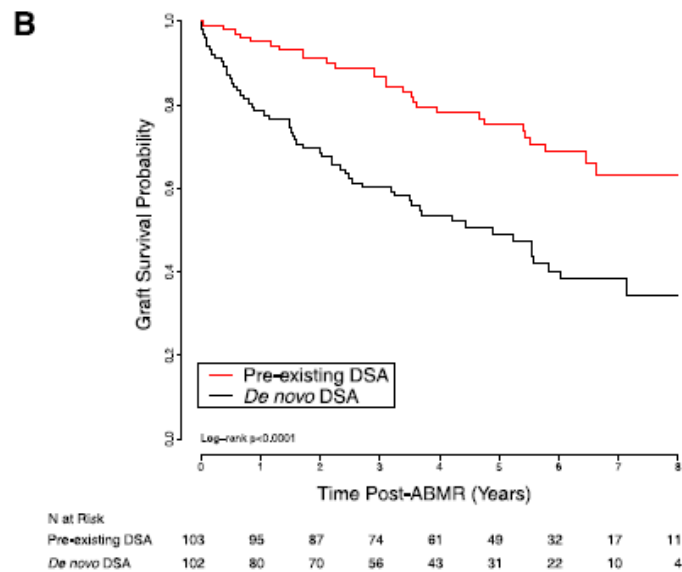
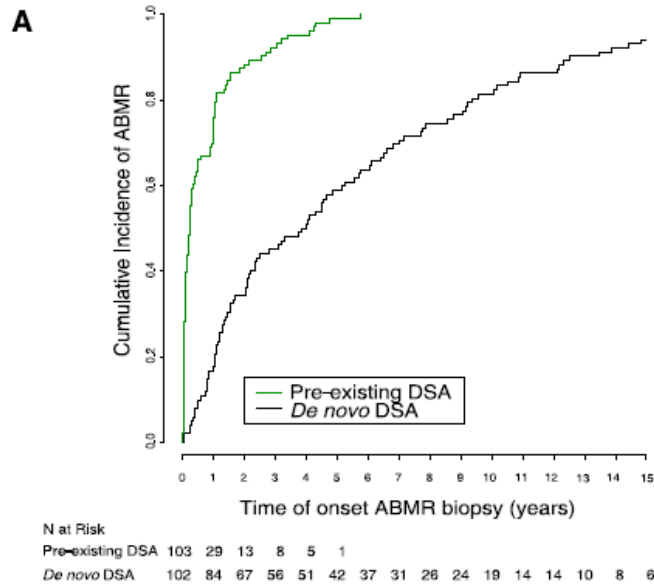
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Negative	Negative	Negative	No	0	Yes	Low risk for de novo alloimmune response

MM, Mismatch; DSA, donor-specific antibody; ABMR, antibody-mediated rejection; TCMR, T cell-mediated rejection.

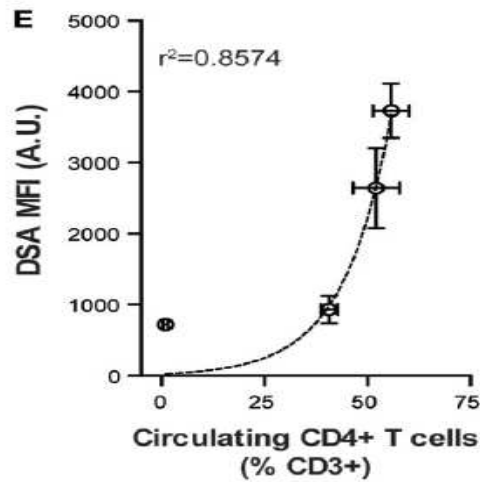
Given this complexity, the STAR Working Group concluded that in general, a **new DSA** observed in the **first 2 weeks posttransplant** likely represents a memory response. **Between 2 weeks and 3 months**, as immunosuppression is weaned and cells are repopulated from depletion therapy (when used); **then both memory and de novo alloimmunity may emerge**. **After 3 months**, the later the onset of a new DSA, the more likely that it is related to **de novo alloimmunity**.

*Tambur, Am J Transplant 2018;18:1604–1614.*

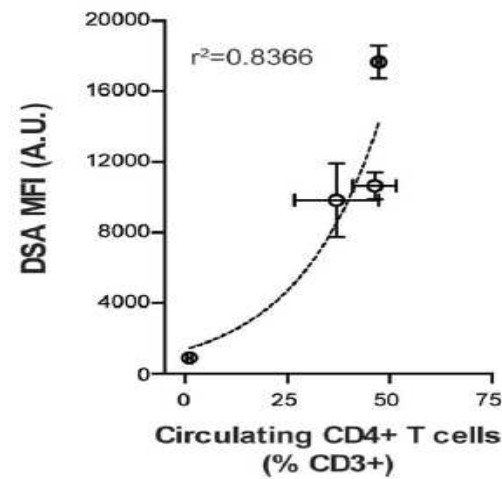


Early occurrence of preexisting anti-HLA DSA ABMR and superior graft survival compared with de novo anti-HLA DSA ABMR

*Aubert, J Am Soc Nephrol 2017; 28: 1912–1923*



NAIVE



MEMORY

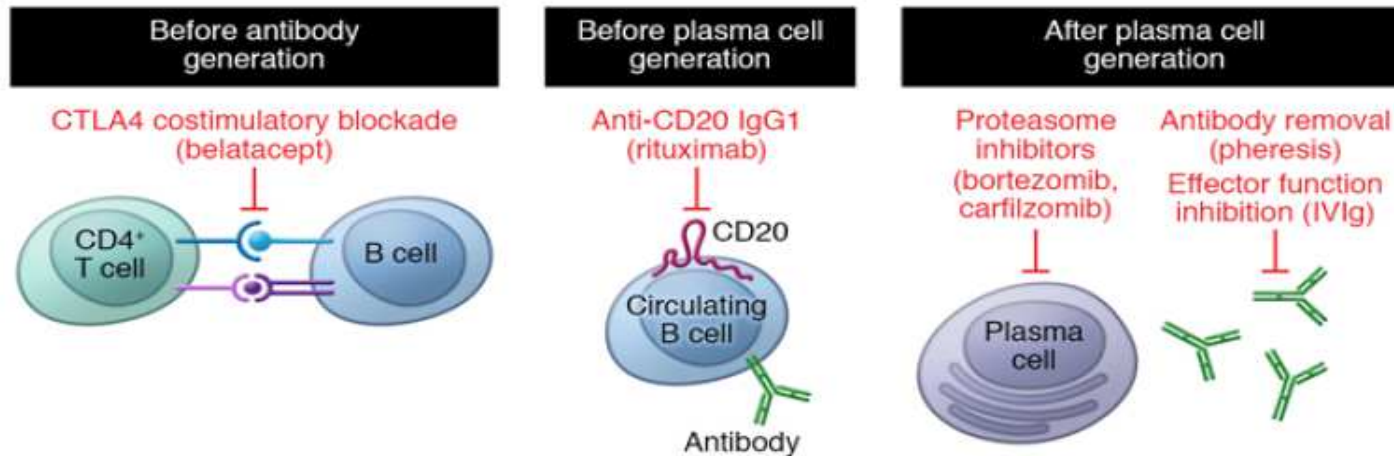
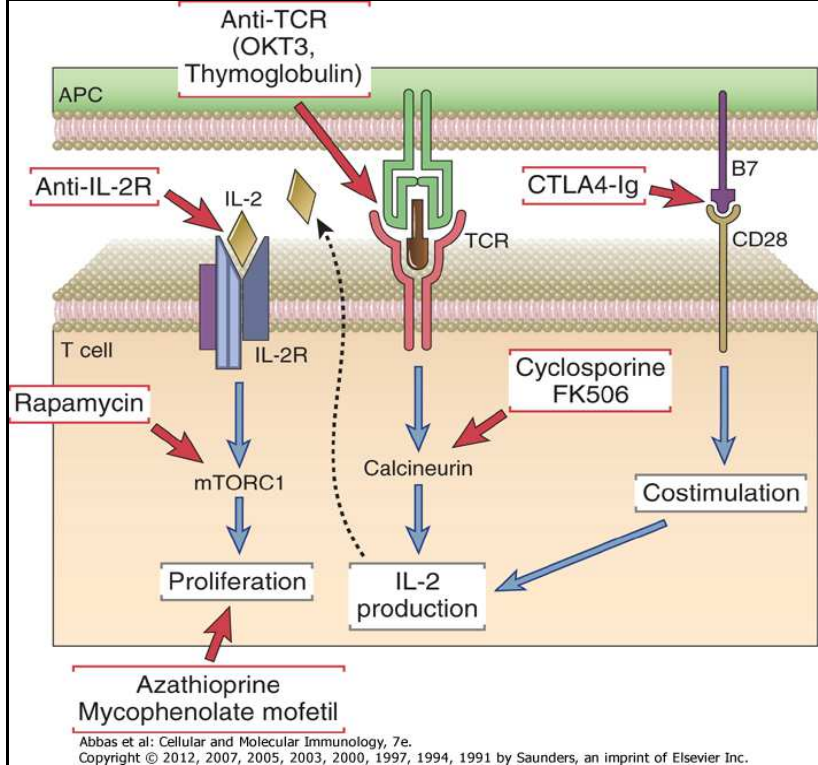
## CD4+ T Cell Help Is Mandatory for Naive and Memory Donor-Specific Antibody Responses: Impact of Therapeutic Immunosuppression



Chien-Chia Chen<sup>1,2</sup>, Alice Koenig<sup>1</sup>, Carole Saison<sup>1,3</sup>, Suzan Dahdal<sup>1,3</sup>, Guillaume Rigault<sup>1</sup>, Thomas Barba<sup>1</sup>, Morgan Taillardet<sup>1</sup>, Dimitri Chartoire<sup>1</sup>, Michel Ovize<sup>2,4</sup>, Emmanuel Morelon<sup>1,2,3,4</sup>, Thierry Defrance<sup>1</sup> and Olivier Thaunat<sup>1,2,3,4\*</sup>

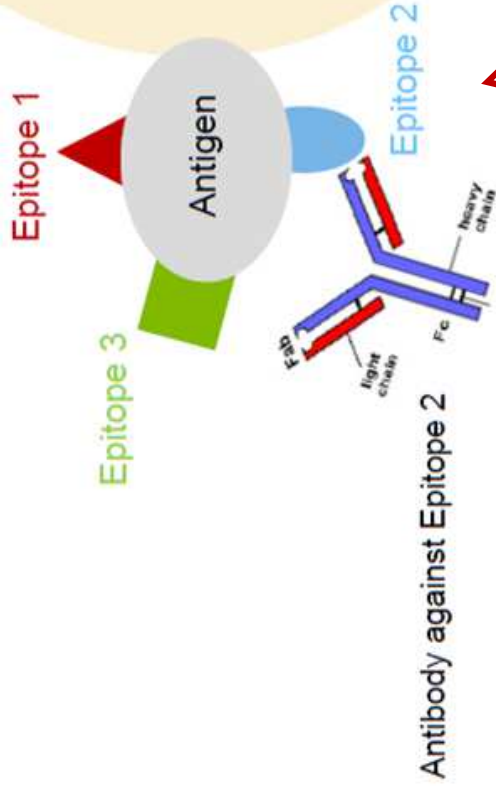
*Chen, Front. Immunol 2018; 9:275*

# TERAPIA IMMUNOSOPPRESSIVA



*Valenzuela, J Clin Invest 2017;127(7):2492–2504*

☐ Antibodies bind to Epitopes on the Antigens:

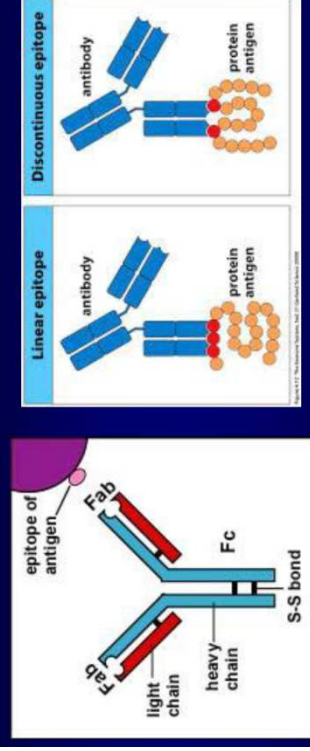


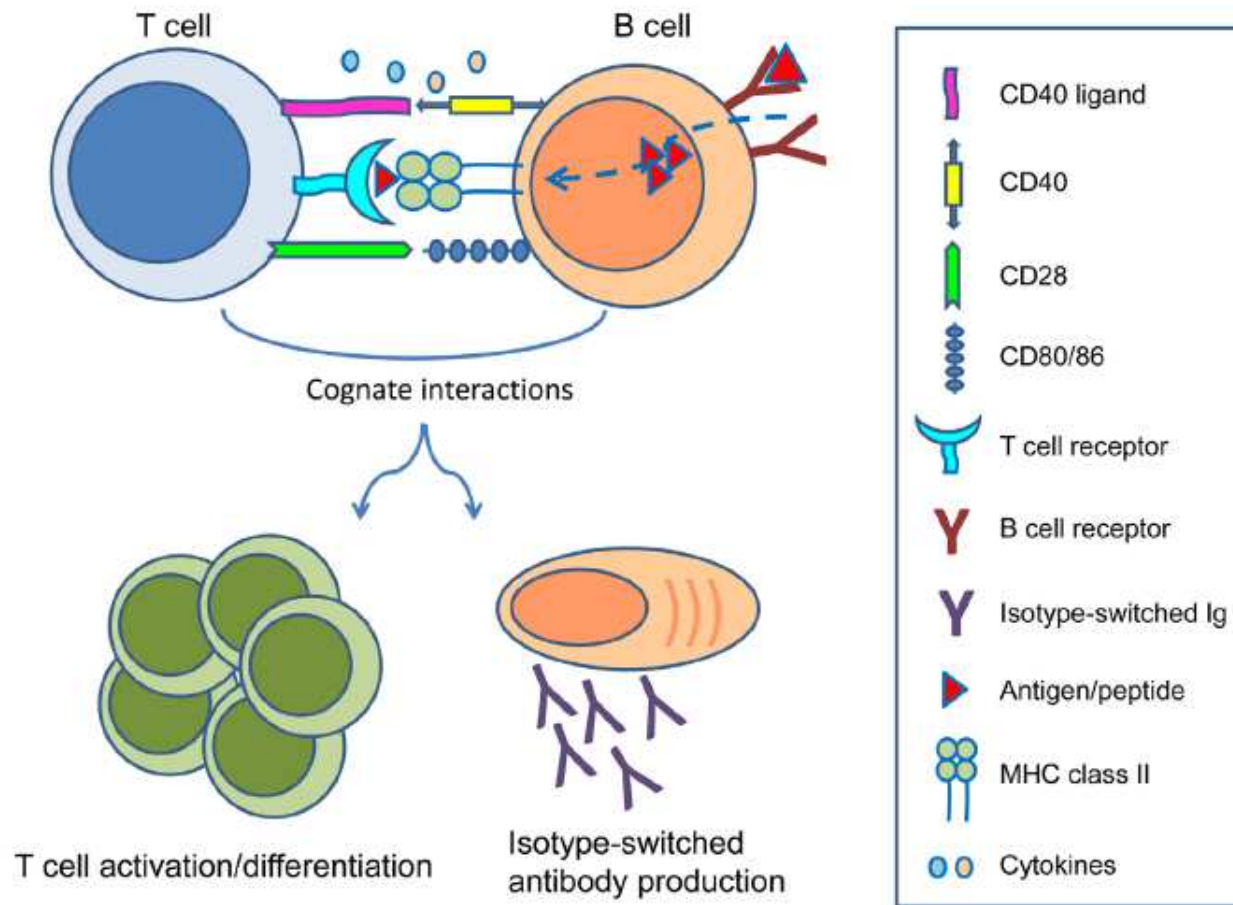
☐ Anti-HLA antibodies recognize specific epitopes on the HLA-molecule (Antigen)

These functional epitopes (“hot spots”) are represented by patches of few residues that are 3.0-3.5 Angstroms apart

Residues are in linear or discontinuous sequences

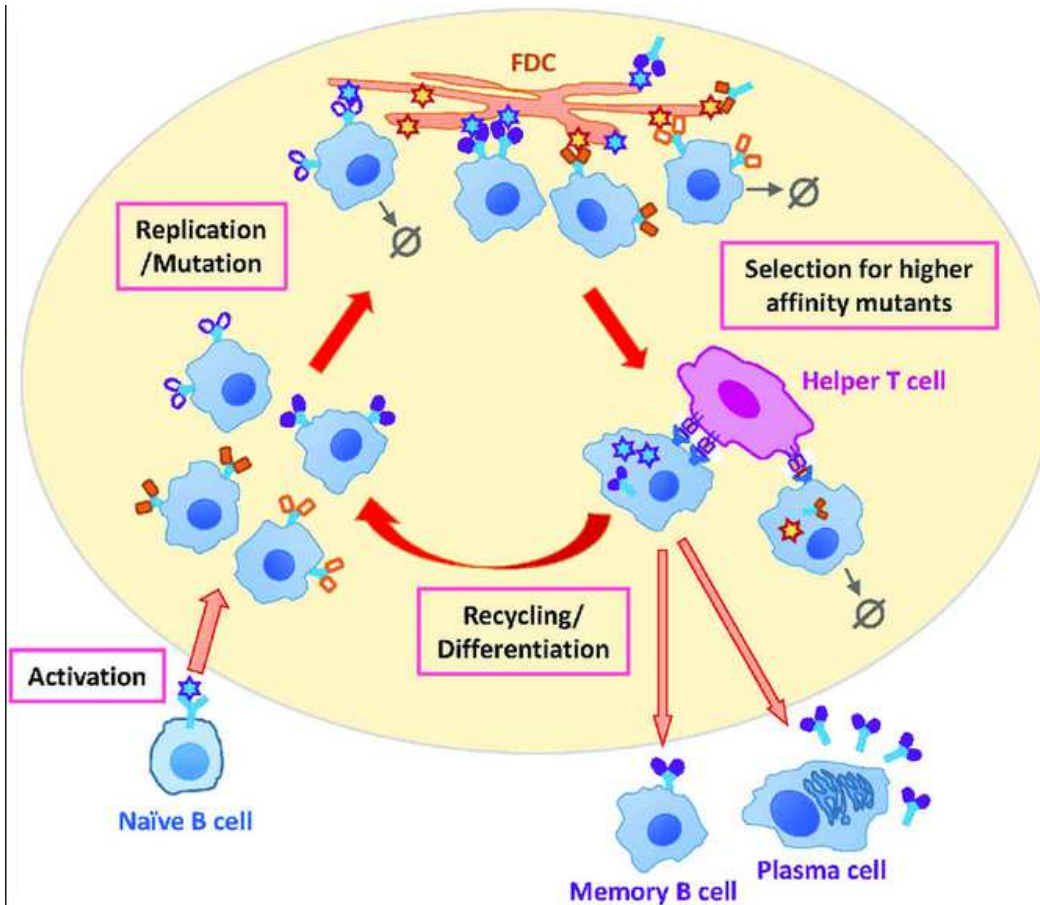
### Binding of Antibody to an Epitope



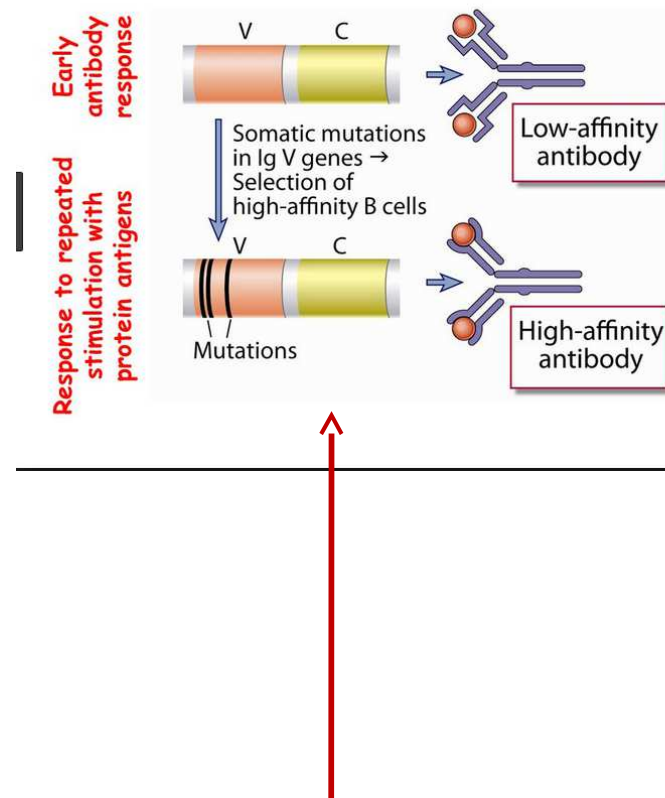


**FIGURE 1 | Reciprocal interactions between T cells and B cells.** Following B cell receptor-mediated uptake of protein antigens, activated B cells process and present antigenic peptides in the context of major histocompatibility complex (MHC) class II on their surface to cognate T cells that recognize the MHC–peptide complex through their T cell receptor. Ligation of CD40 ligand and CD28 on T cells to CD40 and CD80/86 on B cells, as well as production of several cytokines enable differentiation of both B cells and T cells into effector and memory subsets. While B cells can become isotype-switched antibody-producing plasma cells and memory B cells, T cells can become activated as effectors or differentiate into memory T cells to sustain cellular immune responses.

*Karahan, Front. Immunol. 2017; 7:686.*

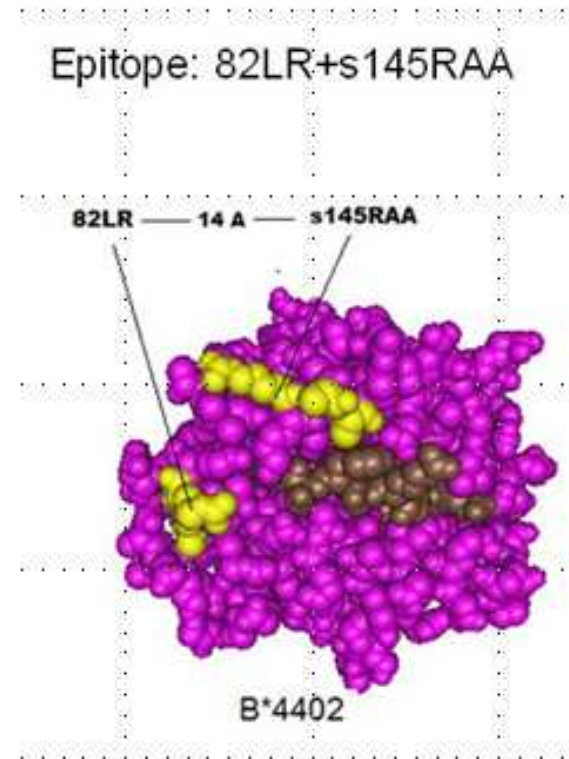
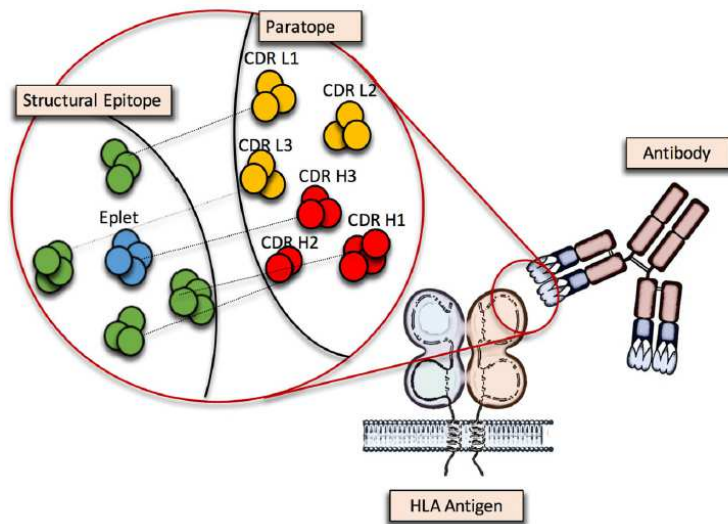


### Affinity maturation of antibodies

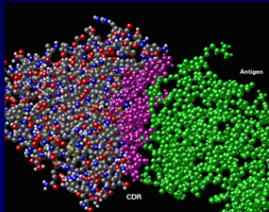


## B-CELLS DIFFERENTIATION AND AFFINITY MATURATION

# STRUCTURAL EPITOPE



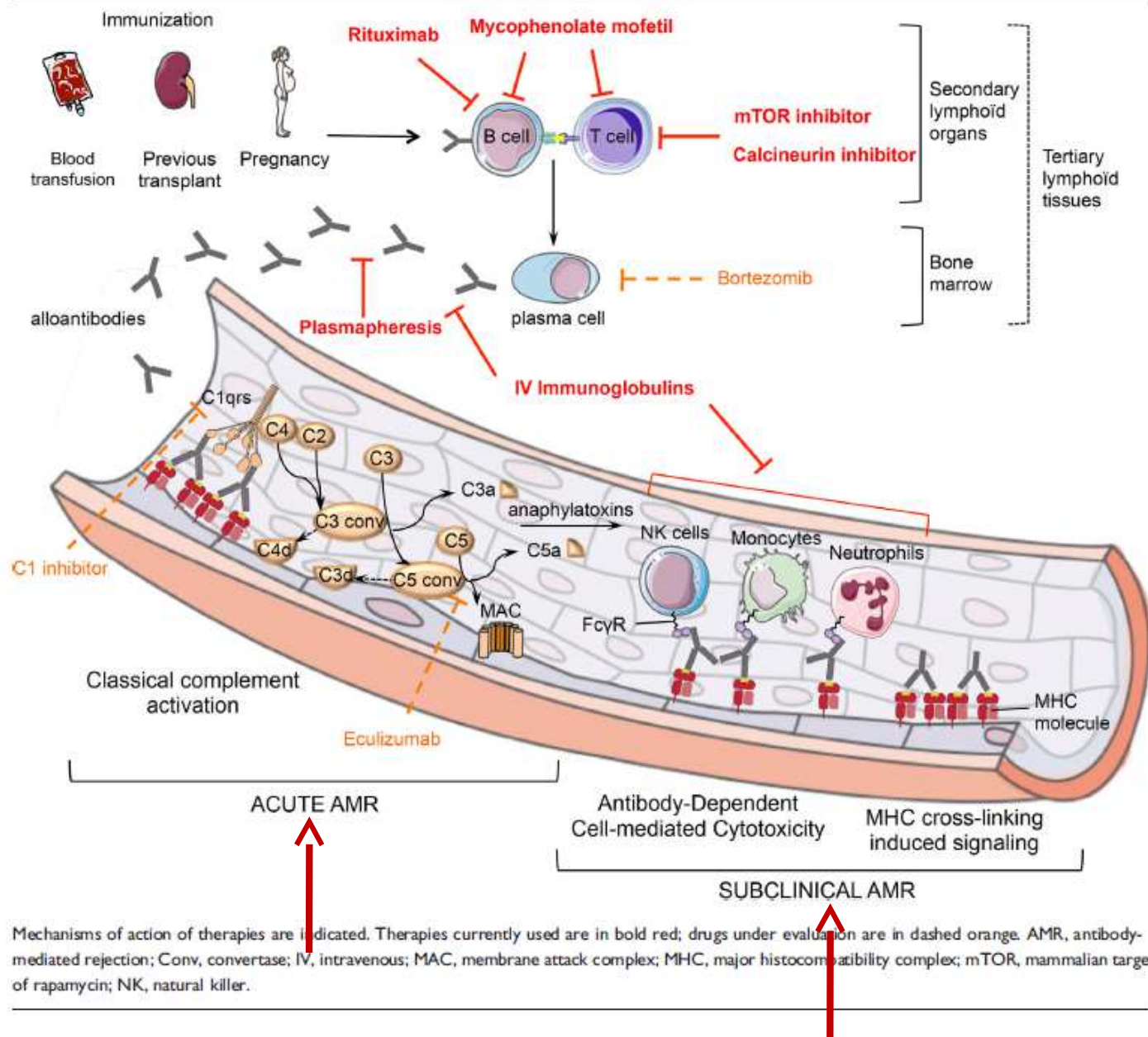
3D molecular analysis of the paratope-epitope interface



A “Structural Epitope” consists of amino acid residues that contact all six CDRs of antibody

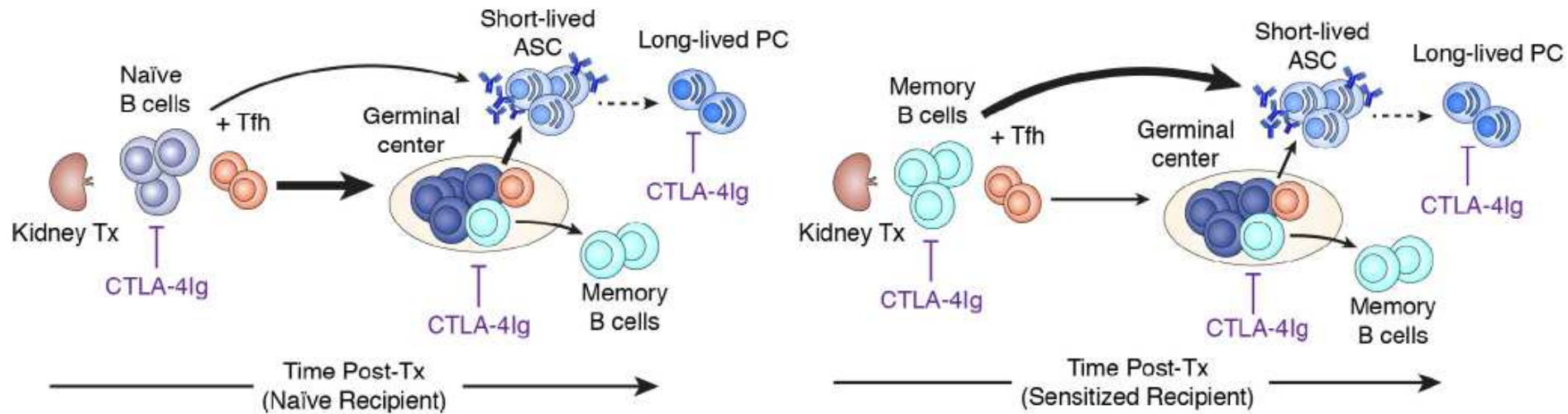
HOT-SPOT + CRITICAL CONTACT SITES (SELF OR NOT SELF) WITHIN 15 Å RADIUS

Figure 1. Schematic representation of antibody-mediated rejection pathophysiology



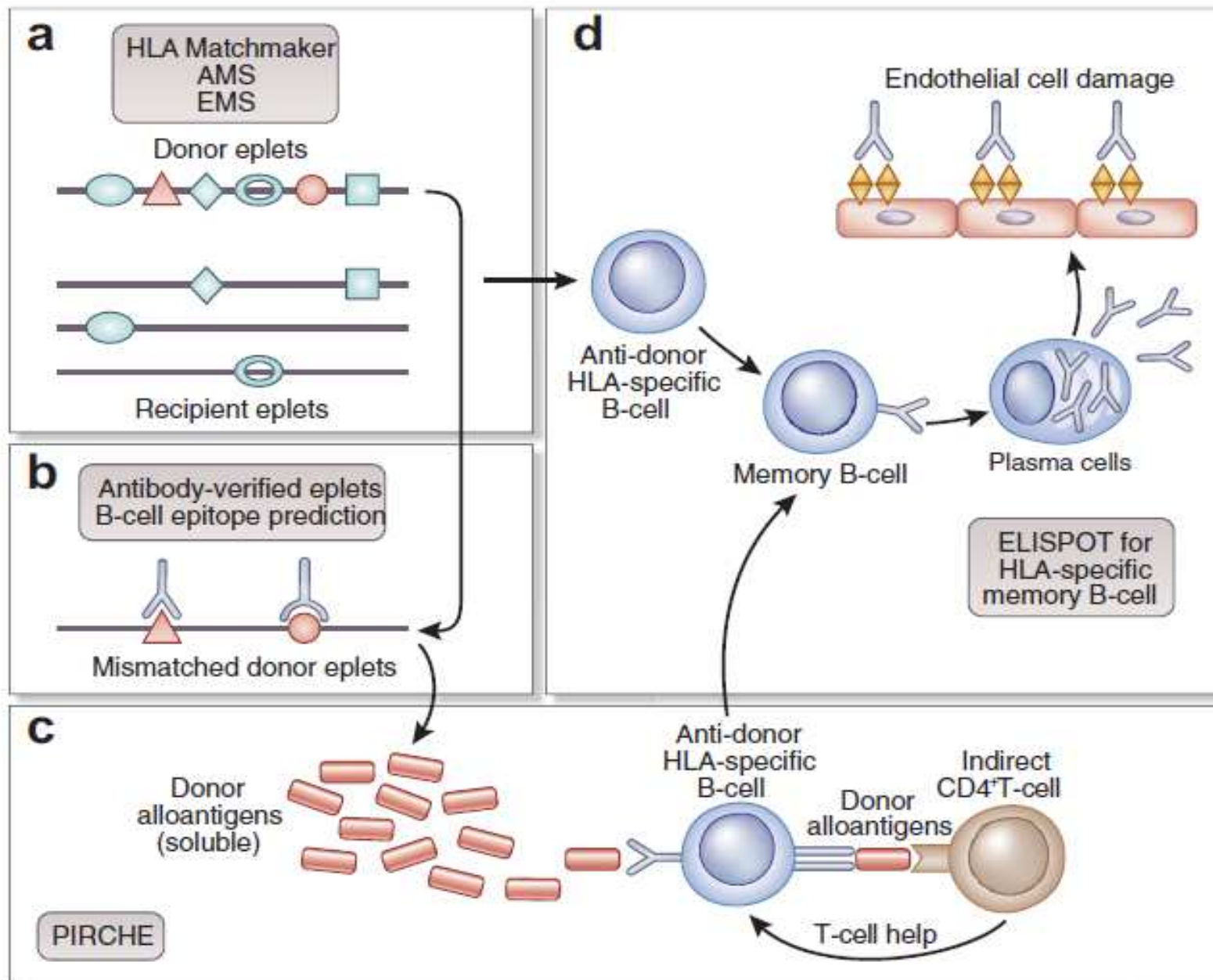
*Pouliquen, F1000Prime Reports 2015, 7:51*

ASC: Antibody secreting cell    Tfh: T follicular helper cells    → Width represents relative cell output  
 PC: Plasma cells    Tx: Transplantation    —| Inhibition by CTLA-4Ig



*Chong, Hum Imm 2019; 80 378–384*

1



› Description

› Registration

› Resources

› New Epitopes

› ABC Database

› DRB Database

› DQ Database

› DP Database

› MICA Database

## Description

This website is designed for research purposes only. The contents are not intended for making clinical c

There are five separate databases: ABC, DRB1/3/4/5, DQB + DQA, DPB + DPA and MICA.

## Their layouts display:

- 1 Epitope names
- 2 Polymorphic residue descriptions
- 3 Epitope frequencies
- 4 Antibody reactivity descriptions of "confirmed" or "provisional" antibody-verified epitopes
- 5 Information about corresponding "structural" epitopes
- 6 Epitope-carrying alleles in Luminex panels
- 7 Listings of all alleles with antibody-verified epitopes.

HLA-ABC 194 EP (56 CRYPTIC)

DRB 60 EP

DQ 15 DQB + 3 DQA EP

DP 5 EP

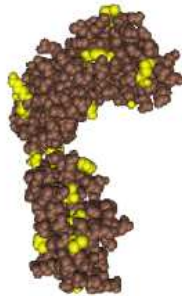
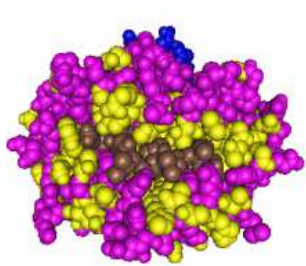
**Update of the HLA class I eplet database in the website based registry of antibody-defined HLA epitopes**

R. J. Duquesnoy

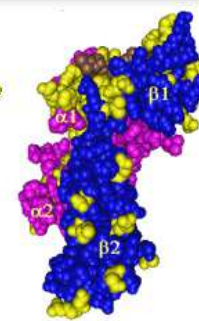
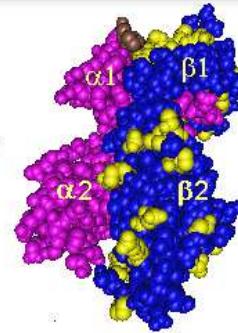
*Tissue Antigens 2014*

**H** Human MoAb    **M** Mouse MoAb

**A** Alloserum    **E** eluate-absorbed



*HLAMatchmaker*  
*An Algorithm for Epitopes*



## Welcome to the Program Download Section

To download a program, you must be signed in to google.

Downloads have been optimized for [Google Chrome](#)



HLA-ABC antibody analysis (v02) update June 2016



HLA-DRDQDP antibody analysis (v02.1) update January 2017



MICA antibody analysis (v01)



HLA-ABC matching for up to 1000 cases (v02)



HLA-DRDQDP matching for up to 1000 cases (v02.2) update 2 August 2018



Four-digit allele converter program (v01)

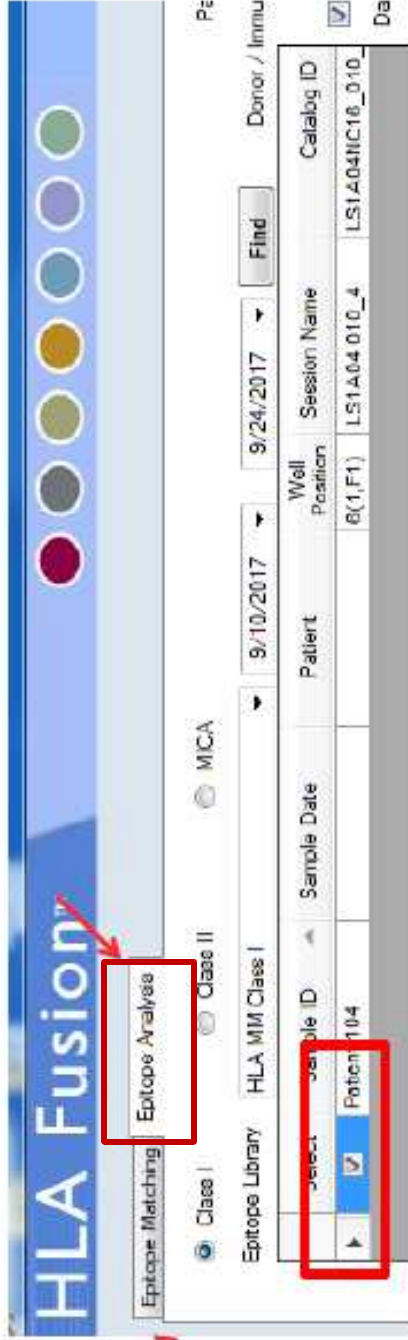
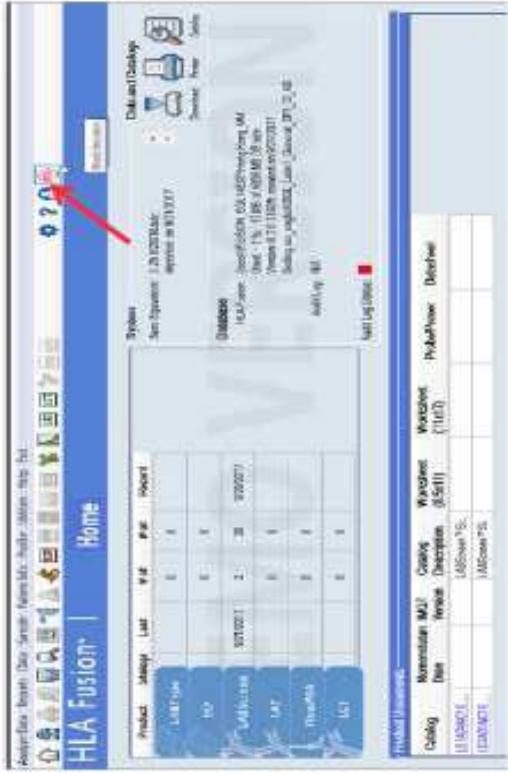
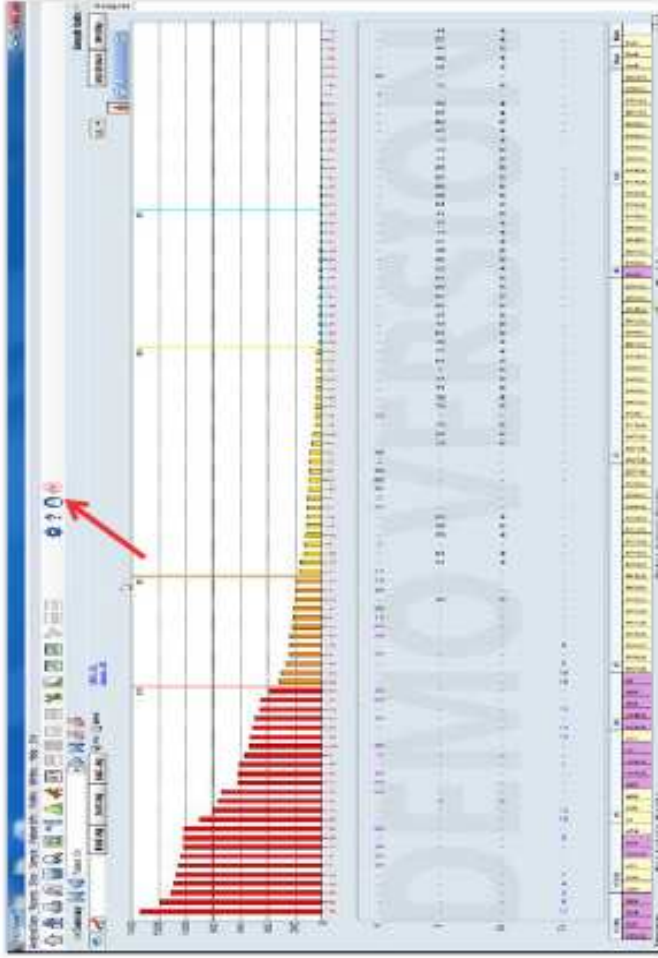


HLA Matchmaker Manual for Version 02 (May 2016)

EP-DSA

EP- MATCH

## Matchmaker - Fusion 4.2 IVD



Paul Sikorski, MS CHS (ABHI)  
One Lambda Sales Manager- US East

15 *Proprietary & Confidential*

For Research Use Only

**ThermoFisher**  
SCIENTIFIC

## Epitope Analysis

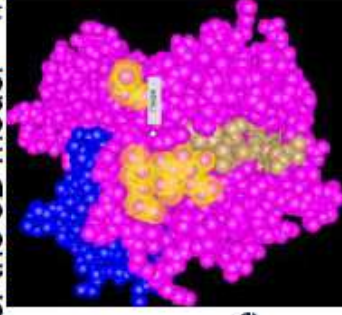
### TASK

3D model -

- Double click in any row.
- Web page will open and render the 3D model – wait for entire loading before you do anything. **WAIT!!!**

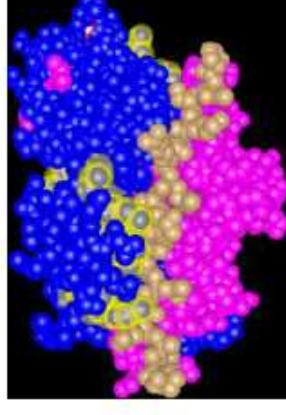
#### Class I

- Pink for Class I – alpha chain
- Blue – Beta2-microglobulin
- Brown – peptide
- Yellow – eplet site on molecule



#### Class II

- Pink for Class I – Alpha chain
- Blue – Beta Chain
- Brown – peptide
- Yellow – eplet site on molecule



- Eplets shown are those listed in the selected row.
- 3D model website can also be accessed from **Epitope Matching** (mismatches) and the **Epitope Lookup table**

To generate excel report:

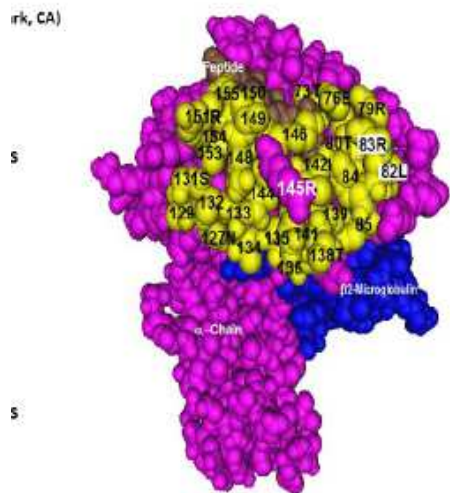
Export

- ☐ Click on “Export” > save as “matchmaker report” > “Save”.
- ☐ When export is complete, Fusion will ask if you want to open the report. Select “Yes” and review.

82LR		82L83R	<a href="#">View</a>	Yes	<a href="#">View</a>	A*23:01, A*23:02, A*24...
------	--	--------	----------------------	-----	----------------------	---------------------------

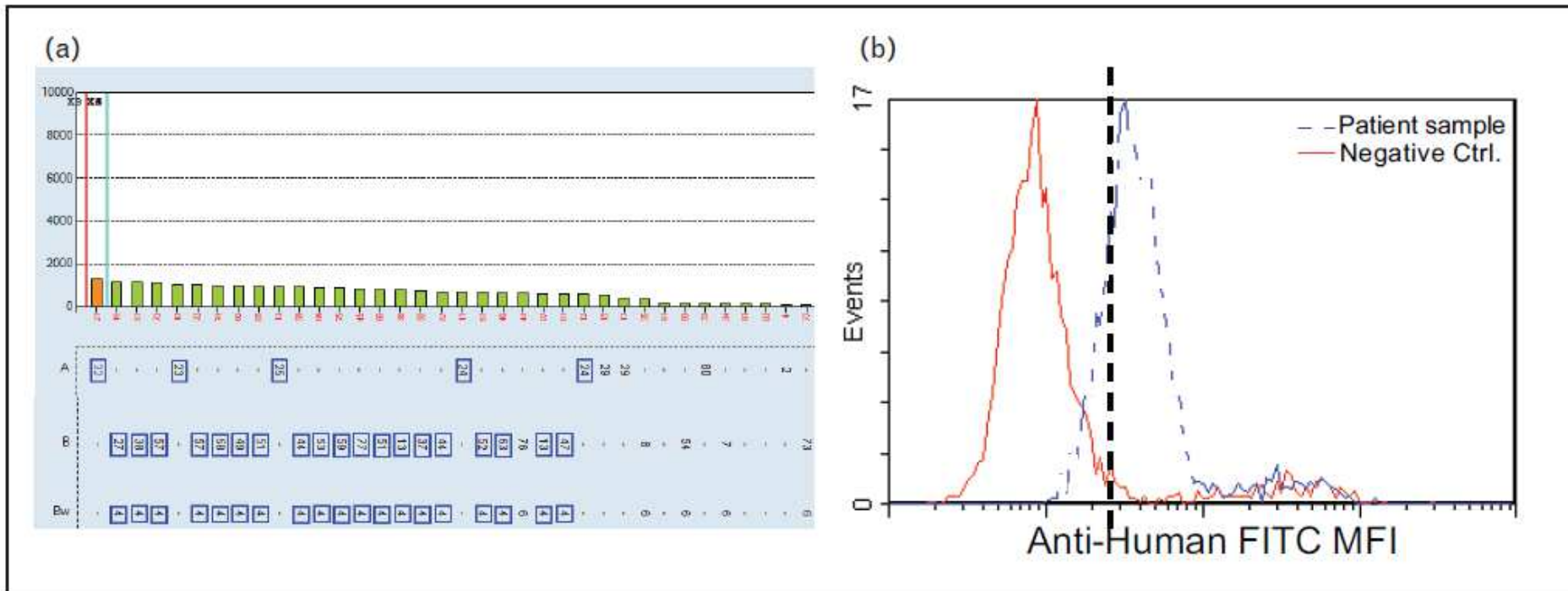
# Struct of Epitope: 82LR Yes

		Residue Differences within 15 Å									
	Eplet	12	71	77	80	81	90	138	144	145	149
A*23:01	82LR	V	S	N	I	A	A	M	Q	R	A
A*23:02	82LR	V	S	N	I	A	A	M	Q	R	A
A*24:02	82LR	V	S	N	I	A	A	M	K	R	A
A*24:03	82LR	V	S	N	I	A	A	M	K	R	A
A*25:01	82LR	V	S	S	I	A	D	M	Q	R	T
A*32:01	82LR	V	S	S	I	A	A	M	Q	R	A
B*13:01	82LR	M	T	N	T	A	A	T	Q	L	A
B*13:02	82LR	M	T	N	T	A	A	T	Q	L	A
B*15:13	82LR	M	T	N	I	A	A	T	Q	R	A
B*15:16	82LR	M	A	N	I	A	A	T	Q	R	A
B*27:03	82LR	V	A	D	T	L	A	T	Q	R	A
B*27:05	82LR	V	A	D	T	L	A	T	Q	R	A
B*37:01	82LR	V	T	D	T	L	A	T	Q	R	A
B*38:01	82LR	V	T	N	I	A	A	T	Q	R	A
B*44:02	82LR	M	T	N	T	A	A	T	Q	R	A
B*44:03	82LR	M	T	N	T	A	A	T	Q	R	A
B*47:01	82LR	M	T	D	T	L	A	T	Q	R	A
B*49:01	82LR	M	T	N	I	A	A	T	Q	R	A



Molecular model of B\*44:02 showing surface-exposed residues surrounding 145R within 15Angstroms (yellow). Single numbers refer to sequence locations of monomorphic residues and numbers with letters describe polymorphic residues shared between B\*44:02 and B\*13:02. Self residues 82L and 83R are essential components of the structural epitope.

Marrari M, Conca R, Praticò-Barbato L, Amoroso A and Duquesnoy: RJ: Brief Report: Why did two patients who type for HLA-B13 have antibodies that react with all Bw4 antigens except HLA-B13? *Transplant Immunology*, 25: 217-220, 2011



# EPITOPI CONDIVISI Bw4

*Kiernan, Curr Opin Organ Transplant 2019, 24:20–30*



(c)

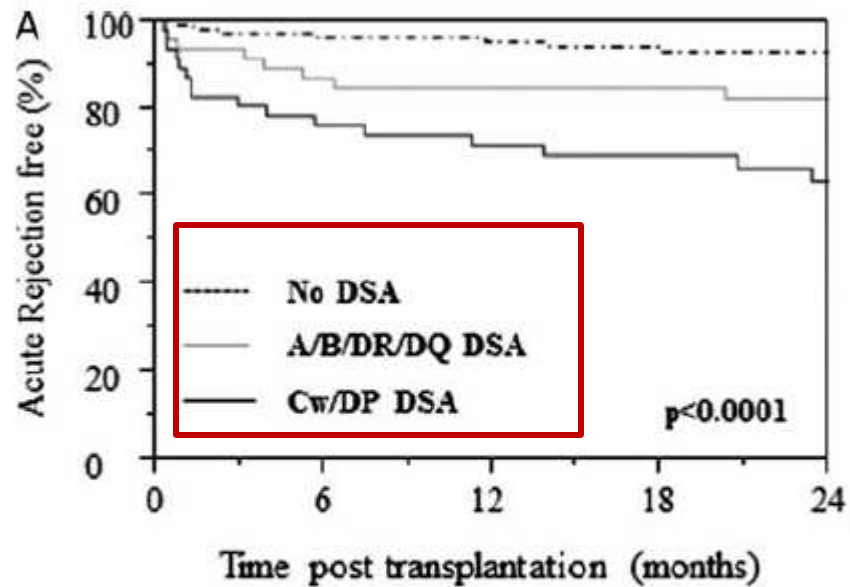
DP allele	MFI	Eplet
DPB1*04:01	352.68	SSGPM
DPB1*04:02	568.25	SSGPM
DPB1*02:01	389.18	SSGPM
DPB1*23:01	296.41	SSGPM
DPB1*18:01	251.22	SSGPM
DPB1*15:01	787.93	SSGPM
DPB1*18:01	476.63	SSGPM
DPB1*18:01	223.92	SSGPM
DPB1*28:01	341.6	SSGPM
DPB1*28:01	360.84	SSGPM
DPB1*28:01	459.96	SSGPM
NegCont	x	
PosCont	x	
DPB1*03:01	205.81	
DPB1*13:01	219.07	
DPB1*19:01	211.09	
DPB1*05:01	119.46	
DPB1*01:01	38.06	
DPB1*05:01	175.21	
DPB1*03:01	136.14	
DPB1*03:01	0	
DPB1*05:01	0	
DPB1*06:01	0	
DPB1*06:01	0	
DPB1*09:01	0	
DPB1*10:01	133.73	
DPB1*11:01	0	
DPB1*13:01	17.19	
DPB1*13:01	0	
DPB1*14:01	14.46	
DPB1*14:01	0	

← PRE-TX

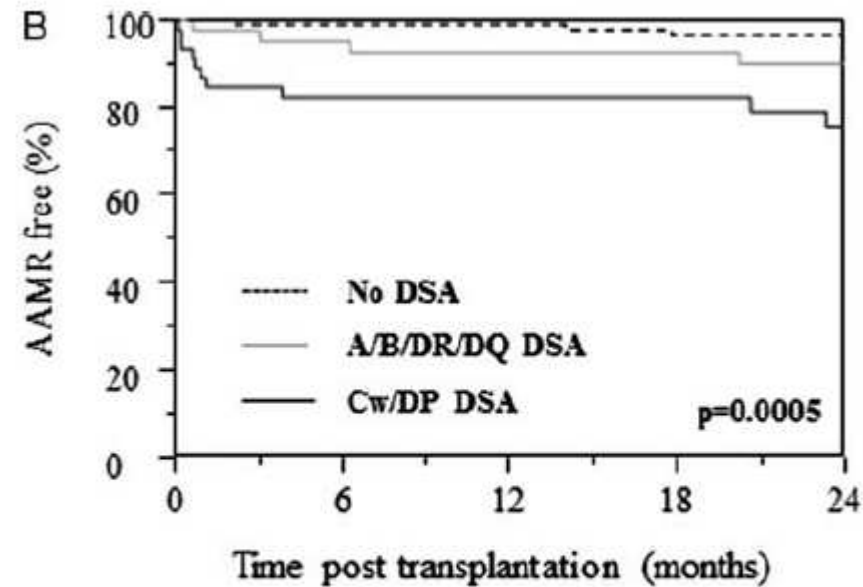
DP  
EPITOPI CONDIVISI

← POST-TX

*Kiernan, Curr Opin Organ Transplant 2019, 24:20–30*



	M0	M6	M12	M18	M24
No DSA	104	98	97	95	95
A/B/DR/DQ DSA	47	40	39	39	38
Cw/DP DSA	48	35	33	32	30



	M0	M6	M12	M18	M24
No DSA	104	100	99	98	97
A/B/DR/DQ DSA	47	44	43	43	42
Cw/DP DSA	48	38	38	38	36

DP

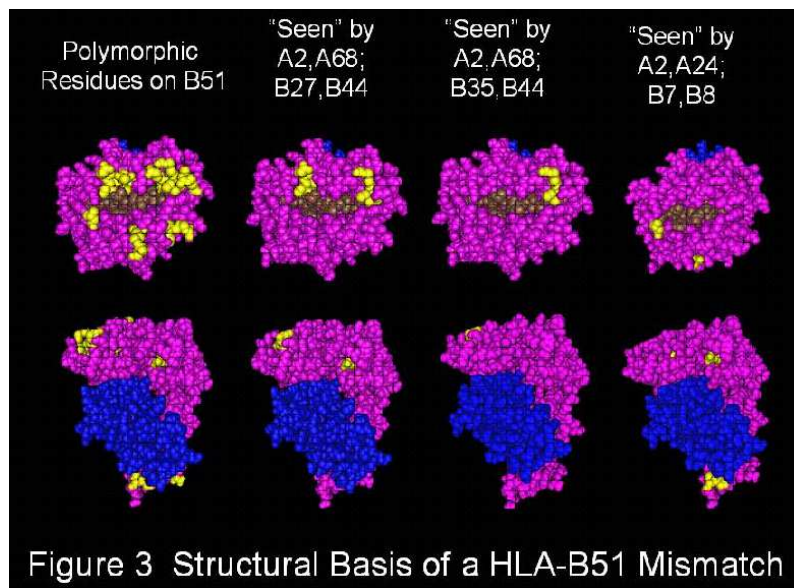
*Bachelet, Transplantation 2016; 100:159-166*

- What other alleles are associated with this epitope?
  - Enter **44KM3** into the Search Epitope box, and click the Search Epitope button
  - What does this allele list suggest if a donor was typed as A\*01:25?
  - The presence of 44KM3 could react with the donor

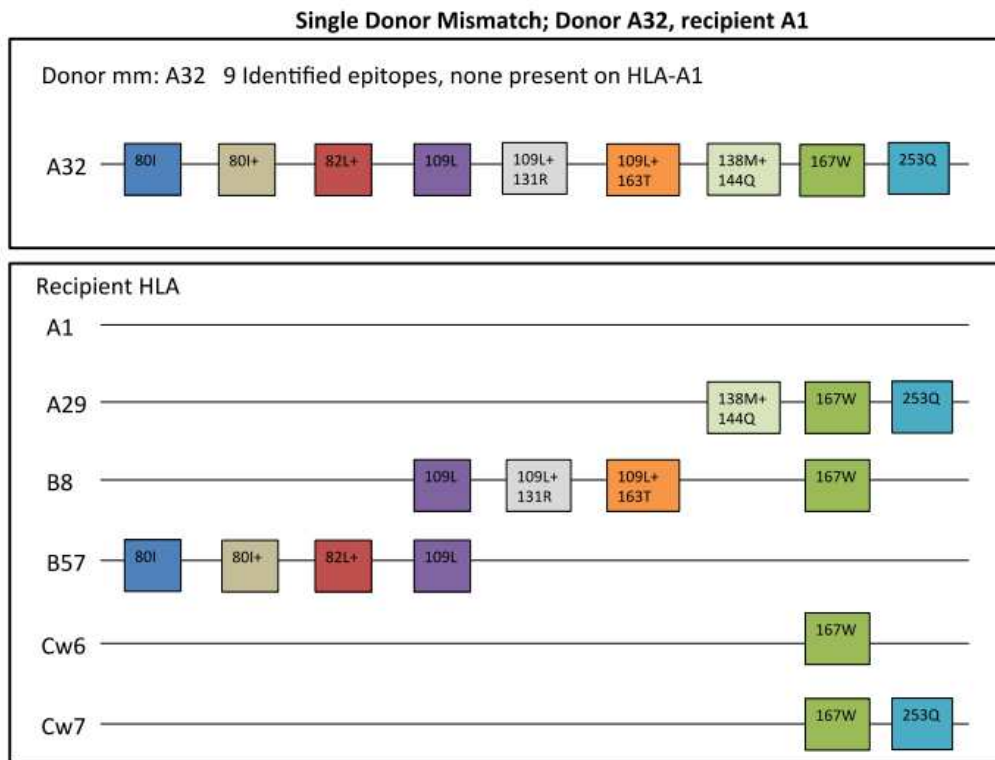
Epitope	Exposed	Antibody Reac	Antibody Verifi	Allele
44KM3	<input checked="" type="checkbox"/>	Confirmed	<input checked="" type="checkbox"/>	A*01:01
44KM3	<input checked="" type="checkbox"/>	Confirmed	<input checked="" type="checkbox"/>	A*36:01
44KM3	<input checked="" type="checkbox"/>	Confirmed	<input checked="" type="checkbox"/>	A*01:02
44KM3	<input checked="" type="checkbox"/>	Confirmed	<input checked="" type="checkbox"/>	A*01:03
44KM3	<input checked="" type="checkbox"/>	Confirmed	<input checked="" type="checkbox"/>	A*01:06
44KM3	<input checked="" type="checkbox"/>	Confirmed	<input checked="" type="checkbox"/>	A*01:07
44KM3	<input checked="" type="checkbox"/>	Confirmed	<input checked="" type="checkbox"/>	A*01:08
44KM3	<input checked="" type="checkbox"/>	Confirmed	<input checked="" type="checkbox"/>	A*01:09
44KM3	<input checked="" type="checkbox"/>	Confirmed	<input checked="" type="checkbox"/>	A*01:10
44KM3	<input checked="" type="checkbox"/>	Confirmed	<input checked="" type="checkbox"/>	A*01:12
44KM3	<input checked="" type="checkbox"/>	Confirmed	<input checked="" type="checkbox"/>	A*01:13
44KM3	<input checked="" type="checkbox"/>	Confirmed	<input checked="" type="checkbox"/>	A*01:14
44KM3	<input checked="" type="checkbox"/>	Confirmed	<input checked="" type="checkbox"/>	A*01:17
44KM3	<input checked="" type="checkbox"/>	Confirmed	<input checked="" type="checkbox"/>	A*01:19
44KM3	<input checked="" type="checkbox"/>	Confirmed	<input checked="" type="checkbox"/>	A*01:20
44KM3	<input checked="" type="checkbox"/>	Confirmed	<input checked="" type="checkbox"/>	A*01:21
44KM3	<input checked="" type="checkbox"/>	Confirmed	<input checked="" type="checkbox"/>	A*01:23
44KM3	<input checked="" type="checkbox"/>	Confirmed	<input checked="" type="checkbox"/>	A*01:24
44KM3	<input checked="" type="checkbox"/>	Confirmed	<input checked="" type="checkbox"/>	A*01:25
44KM3	<input checked="" type="checkbox"/>	Confirmed	<input checked="" type="checkbox"/>	A*01:26
44KM3	<input checked="" type="checkbox"/>	Confirmed	<input checked="" type="checkbox"/>	A*01:28
44KM3	<input checked="" type="checkbox"/>	Confirmed	<input checked="" type="checkbox"/>	A*01:29
44KM3	<input checked="" type="checkbox"/>	Confirmed	<input checked="" type="checkbox"/>	A*01:30
44KM3	<input checked="" type="checkbox"/>	Confirmed	<input checked="" type="checkbox"/>	A*01:32
44KM3	<input checked="" type="checkbox"/>	Confirmed	<input checked="" type="checkbox"/>	A*01:33
44KM3	<input checked="" type="checkbox"/>	Confirmed	<input checked="" type="checkbox"/>	A*01:35
44KM3	<input checked="" type="checkbox"/>	Confirmed	<input checked="" type="checkbox"/>	A*36:02
44KM3	<input checked="" type="checkbox"/>	Confirmed	<input checked="" type="checkbox"/>	A*36:03
44KM3	<input checked="" type="checkbox"/>	Confirmed	<input checked="" type="checkbox"/>	A*36:04

Search Allele(s)	A*24:02
Search Epitope(s)	44KM3
List All Epitopes	

ALLELI NON PRESENTI NEL PANNELLO



## B51 EPITOPES MISMATCH VS. DIFFERENT PHENOTYPES



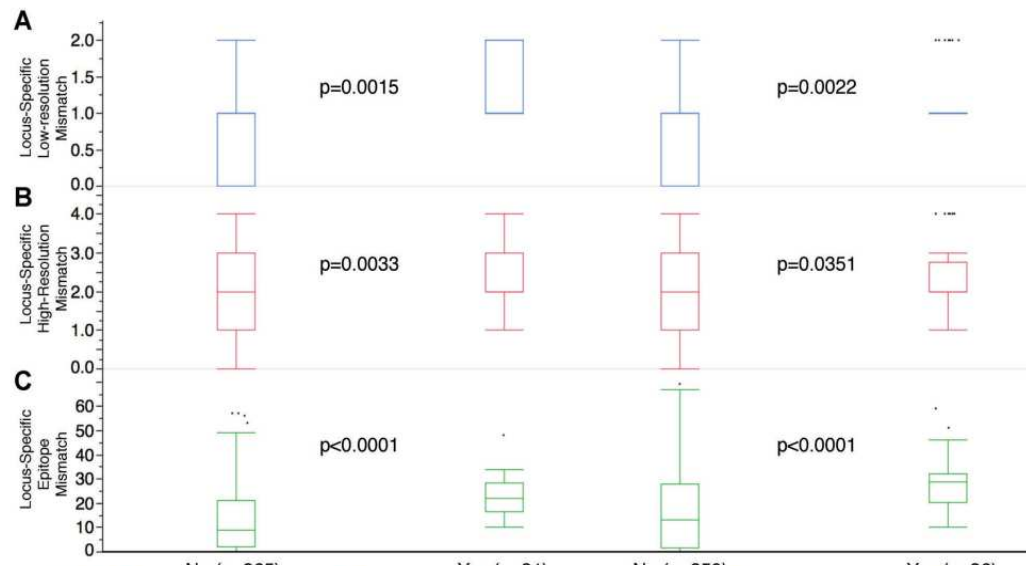
NO EPITOPES MISMATCH!

Middleton, 2014

Recipient	Donor						Antibody- Verified Eplets	Other ABC Eplets	All ABC Eplets
	1:						A*02:03,*03:01;	B*53:01,*55:01	C*04:01,*05:01
1	A*01:01	A*03:01	B*07:02	B*08:01	C*07:01	C*07:02	16	13	29
2	A*01:01	A*11:01	B*07:02	B*40:01	C*03:03	C*07:02	14	11	25
3	A*02:01	A*32:01	B*35:01	B*56:01	C*04:01	C*12:03	5	7	12
4	A*03:01	A*26:01	B*35:01	B*39:01	C*04:01	C*12:03	12	6	18
5	A*01:01	A*02:01	B*35:01	B*56:01	C*04:01	C*14:01	6	5	11
6	A*30:01	A*68:01	B*51:01	B*57:01	C*08:01	C*07:02	11	7	18
7	A*26*01	A*32:01	B*38:01	B*67:01	C*07:02	C*15:01	14	11	25
8	A*29*02	A*31:01	B*08:01	B*45:01	C*06:02	C*07:01	18	11	29
9	A*01:01	A*24:02	B*51:01	B*35:01	C*01:02	C*04:01	12	9	21
10	A*02:01	A*24:03	B*07:02	B*44:03	C*02:02	C*07:01	8	6	14

eplet loads for 10 recipients' phenotypes

Duquesnoy, Transpl 2017



HLA typing methods to predict *dn*DSA development posttransplant.

Wiebe, AJT 2013

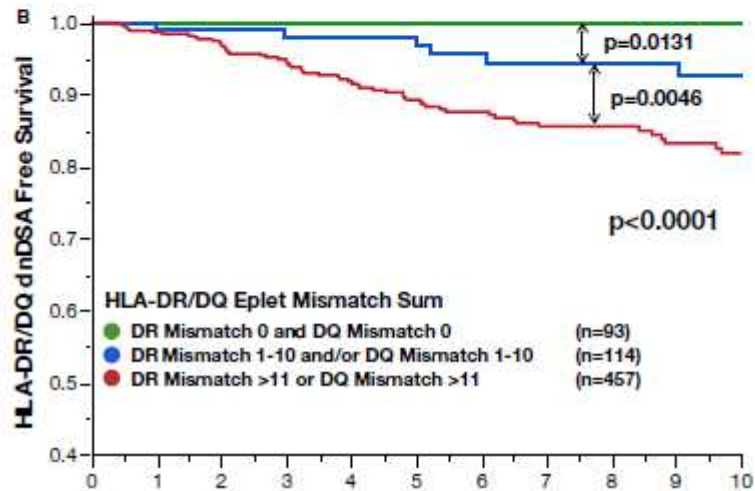
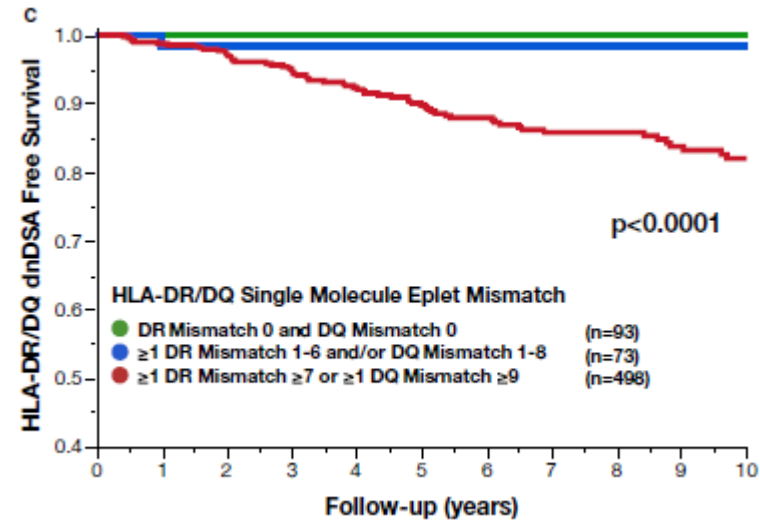
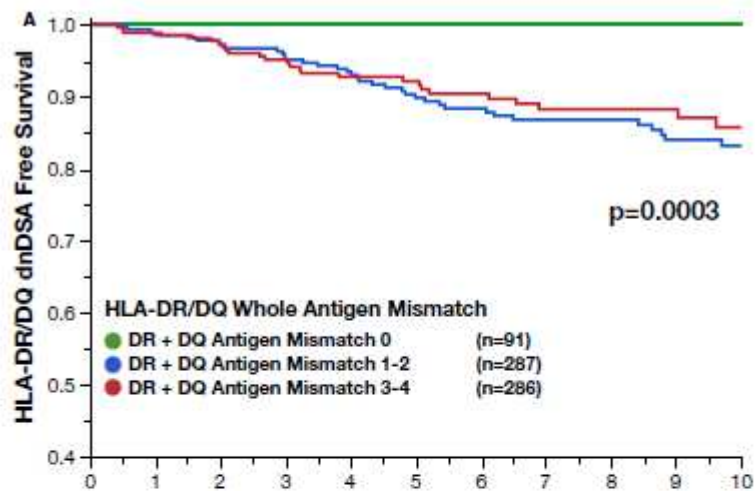
**Table 4 | Relationship between the occurrence of *de novo* DSA and antigenic, allelic, and epitopic mismatches**

No. of patients DSA + / DSA -	No. of antigenic mismatches		No. of allelic mismatches		No. of epitopic mismatches		No. of Abv epitopic mismatches	
	DSA + vs. DSA -	P	DSA + vs. DSA -	P	DSA + vs. DSA -	P	DSA + vs. DSA -	P
Class I or II DSA 29/60	6.5 ± 1.8 vs. 5.4 ± 1.8	0.015	8.2 ± 2.1 vs. 7.1 ± 2.1	0.026	44.5 ± 11.6 vs. 32.0 ± 14.2	<0.0005	21.6 ± 6.3 vs. 14.8 ± 7.0	5.7 × 10 <sup>-5</sup>
Class I DSA 5/84	4.8 ± 0.8 vs. 3.7 ± 1.4	0.07	5.0 ± 0.7 vs. 4.1 ± 1.3	0.11	23.2 ± 7.0 vs. 14.7 ± 6.1	0.014	13.2 ± 3.1 vs. 8.2 ± 3.9	0.009
Class II DSA <sup>a</sup> 28/61	2.5 ± 0.9 vs. 1.7 ± 1.2	0.003	3.8 ± 1.4 vs. 3.0 ± 1.3	0.024	27.6 ± 9.9 vs. 17.9 ± 12.4	0.0003	12.1 ± 5.4 vs. 6.8 ± 6.1	4.8 × 10 <sup>-5</sup>
DR DSA 6/83	1.2 ± 0.4 vs. 1.0 ± 0.6	0.45	1.2 ± 0.4 vs. 1.3 ± 0.6	0.41	16.8 ± 8.2 vs. 10.4 ± 7.8	0.07	7.0 ± 4.5 vs. 3.5 ± 3.5	0.04
DQ DSA <sup>a</sup> 25/64	1.3 ± 0.5 vs. 0.9 ± 0.7	0.006	1.4 ± 0.5 vs. 1.2 ± 0.6	0.18	13.5 ± 5.2 vs. 8.7 ± 8.2	0.0005	6.8 ± 3.3 vs. 3.9 ± 4.8	<0.0005

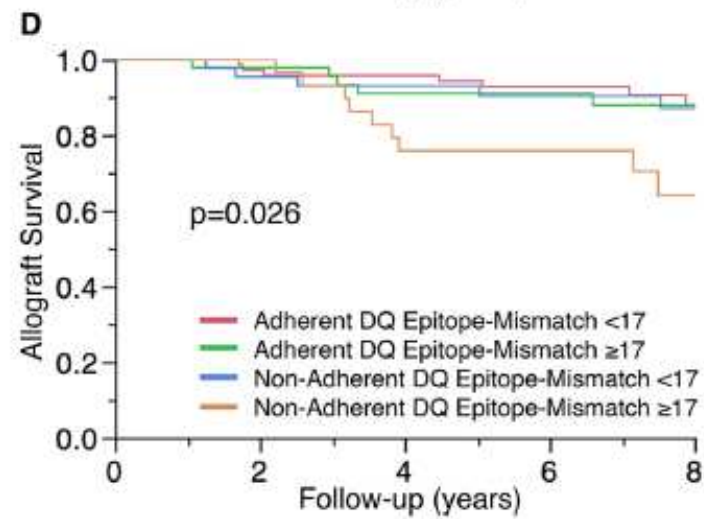
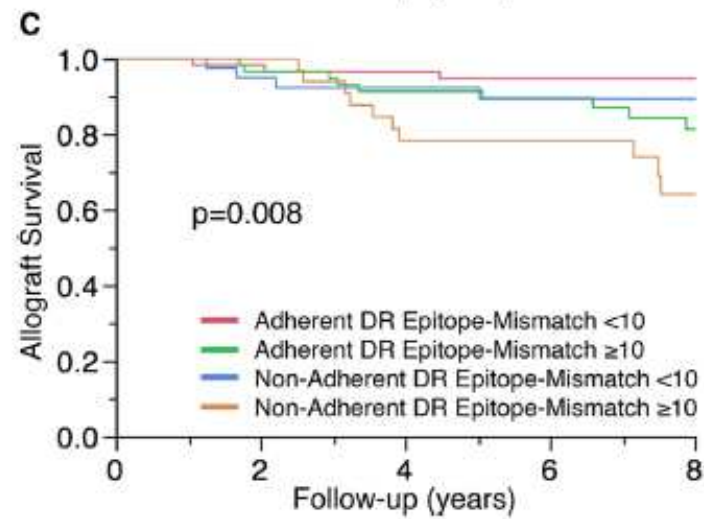
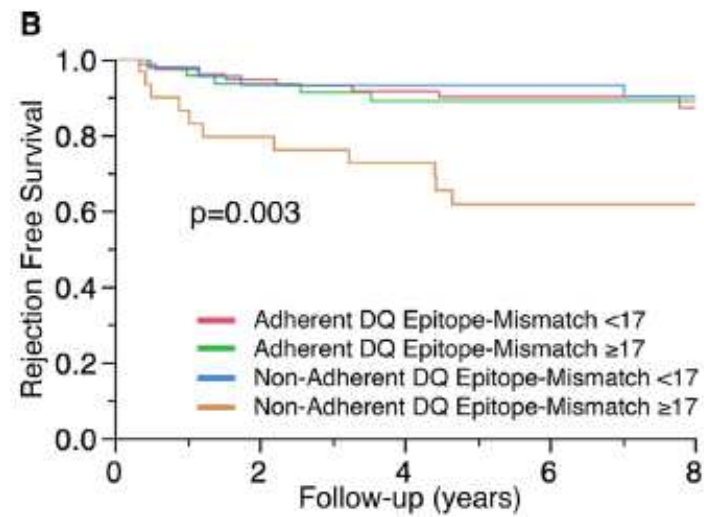
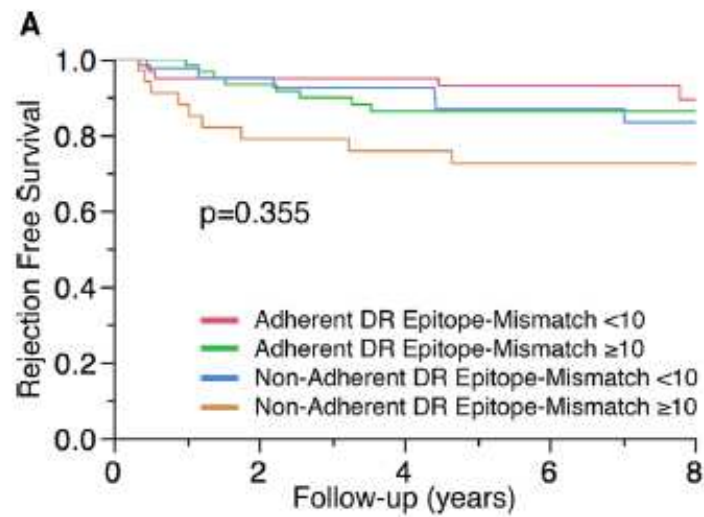
Abv, antibody-verified; DSA, donor-specific antibody.

<sup>a</sup>DQ and class II mismatches do not include DQA.

Snanoudj, Kidney Int 2019



*Wiebe, Am J Transpl 2018;1-12*



Wiebe, Am J Transpl 2015; 15: 2197–2202

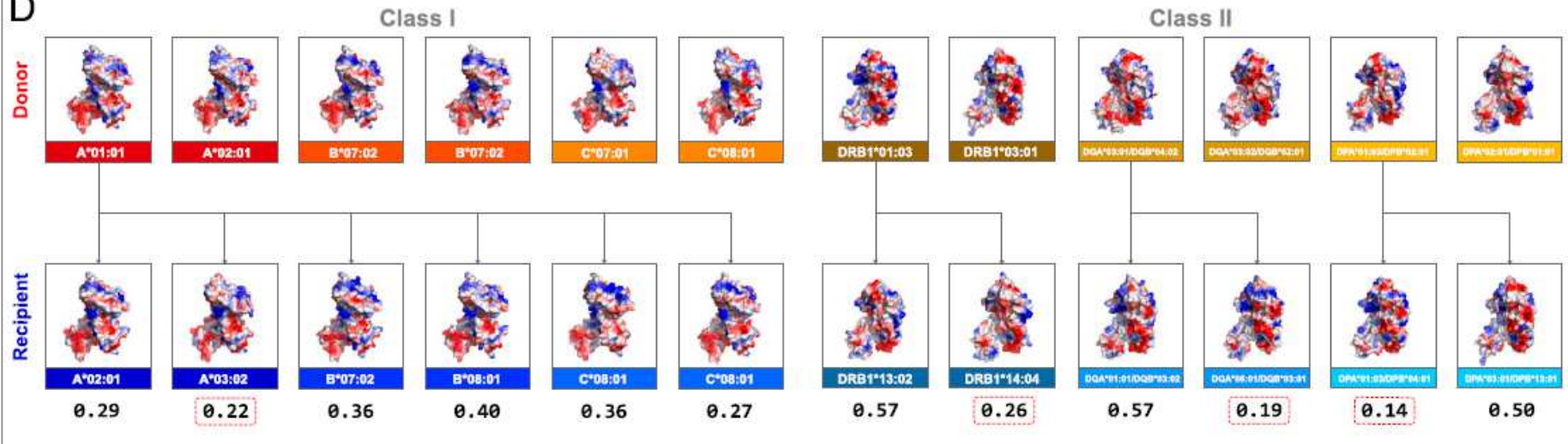
# Immunogenicity of Selected Eplet Mismatches in 62 Transplant Cases

<u>Eplet</u>	<u>Nr. Reactive (%)</u>	<u>Eplet</u>	<u>Nr. Reactive (%)</u>	<u>Eplet</u>	<u>Nr. Reactive (%)</u>
116D	0/9 (0%)	253Q	4/10 (40%)	82LR	8/11 (73%)
171H	0/9 (0%)	275EL	4/10 (40%)	180E	8/11 (73%)
113HD	1/10 (10%)	113YR	6/13 (46%)	151AHV	16/22 (73%)
116Y	1/10 (10%)	113YH	8/17 (47%)	138MT	17/22 (77%)
207S	3/15 (20%)	41T	5/10 (50%)	145KHA	17/22 (77%)
113HN	3/13 (23%)	151AHE	5/10 (50%)	167ES	7/9 (78%)
113YN	2/8 (25%)	70AQA	5/9 (56%)	177DK	8/10 (80%)
184A	5/15 (33%)	167DG	8/14 (57%)	66RKV	16/19 (84%)
193AV	5/15 (33%)	76EN	6/10 (60%)	62GE	16/18 (89%)
70AQS	3/8 (38%)	76AN	5/8 (63%)	161D	9/10 (90%)
76VD	5/13 (38%)	127K	13/20 (65%)		

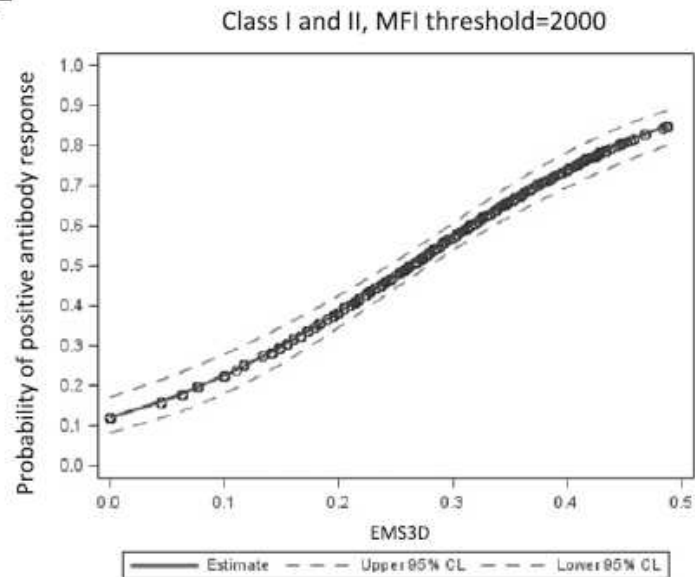
Duquesnoy, RJ and Claas FHJ: Progress Report of 14th International Histocompatibility Workshop  
Project on the Structural Basis of HLA Compatibility, *Tissue Antigens*, 69 (Suppl. 1): 1-5, 2007

# Derivation of three-dimensional electrostatic mismatch score (EMS-3D)

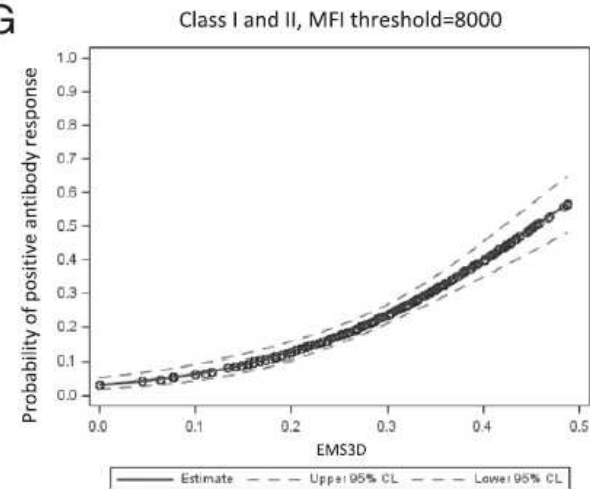
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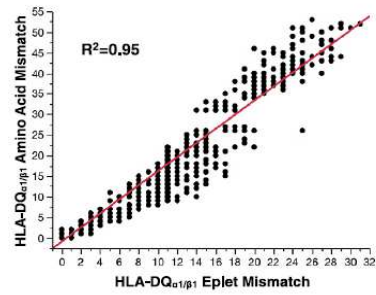
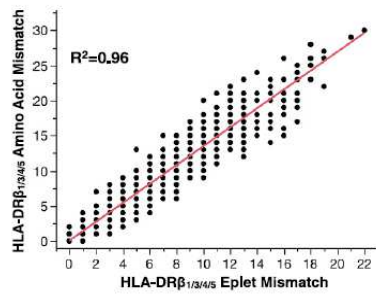
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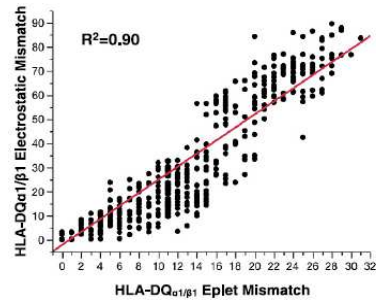
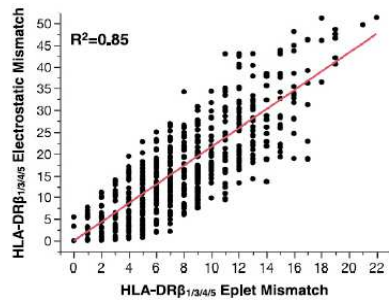
G



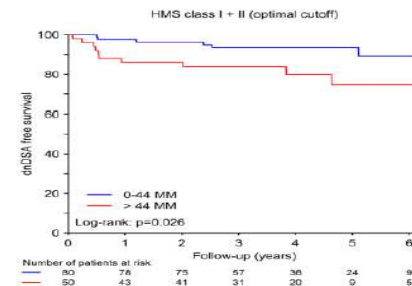
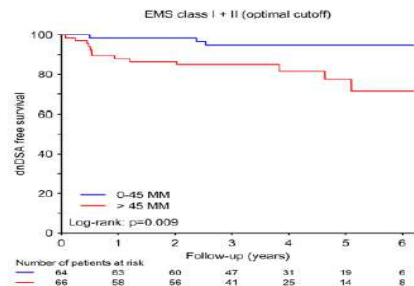
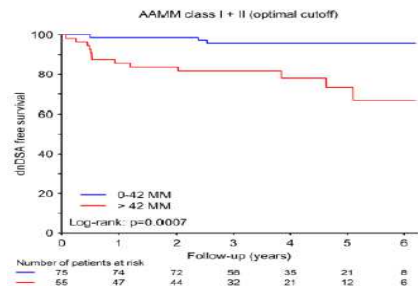
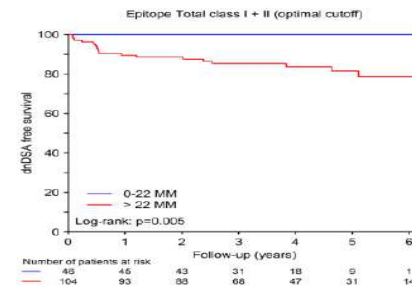
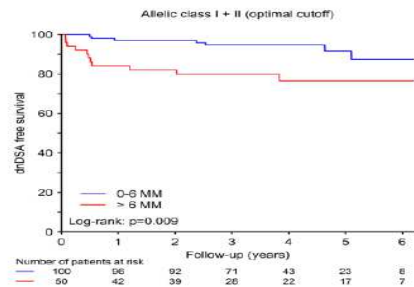
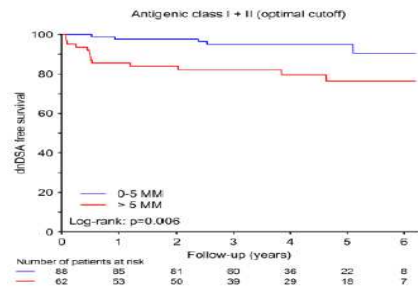
*Mallon, Journal of Immunology, 2018*



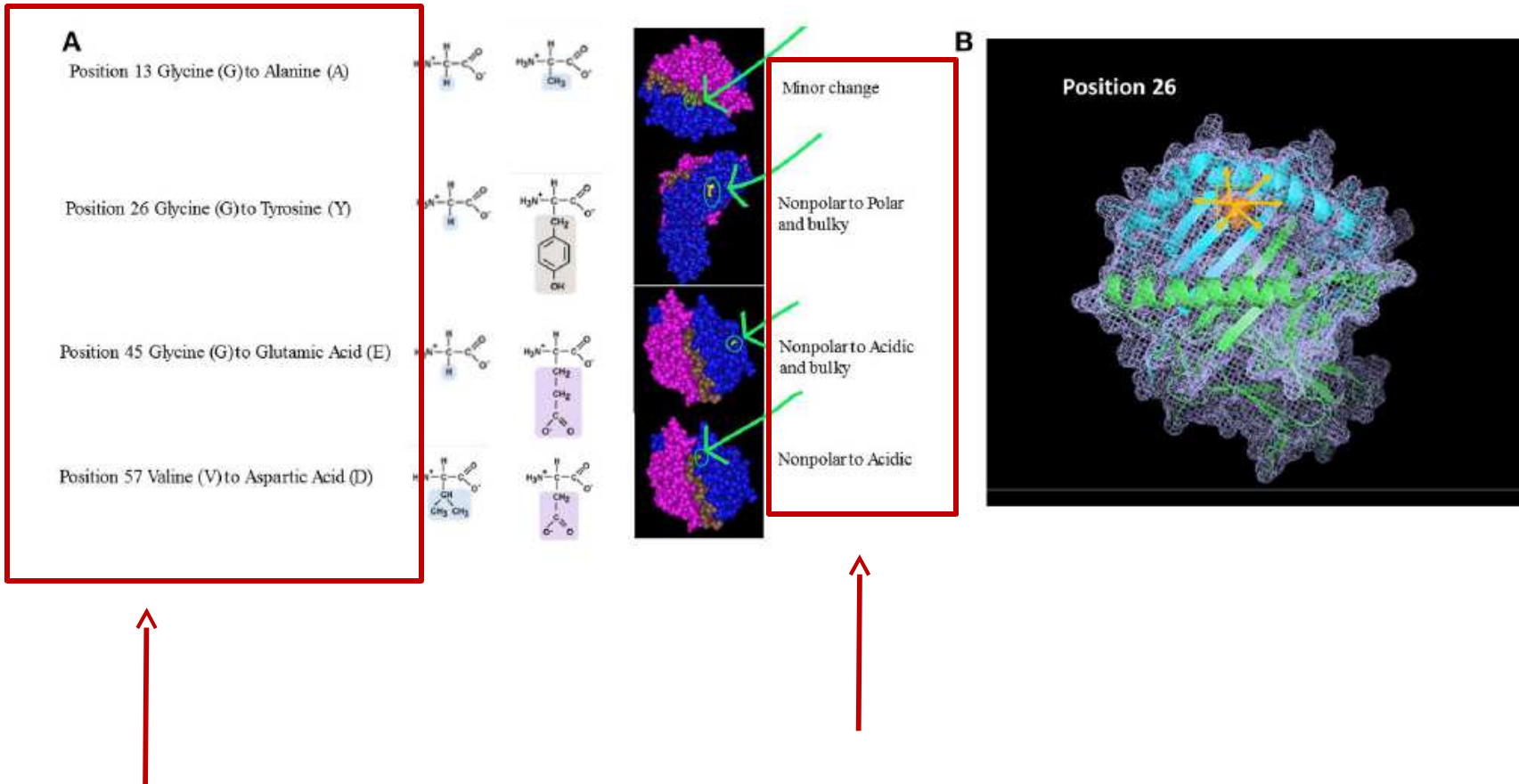
EMS vs. MM  $R^2 > 0.90$



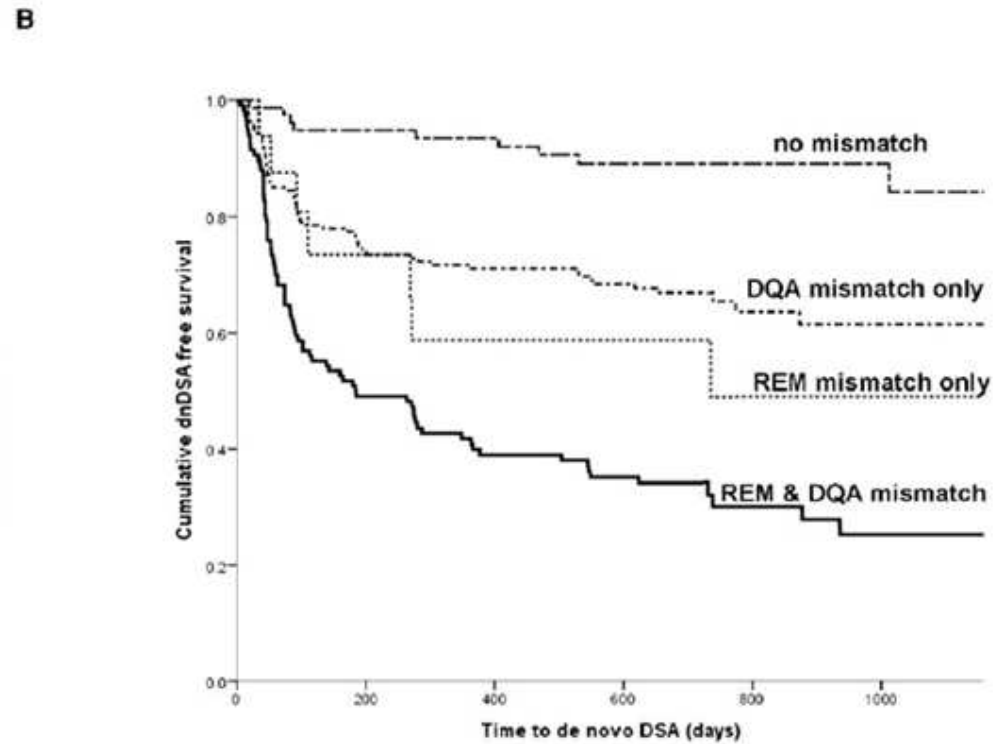
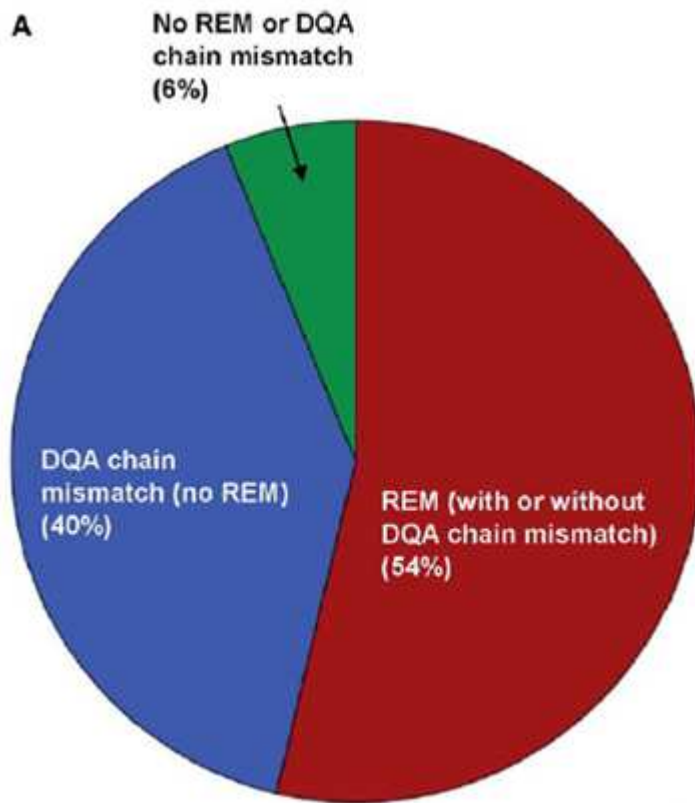
Wiebe, Transplantation 2018;102: 1338–1343



Delion, Clin Transpl 2019

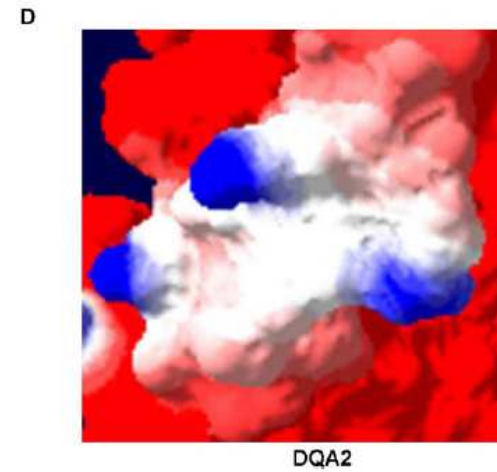
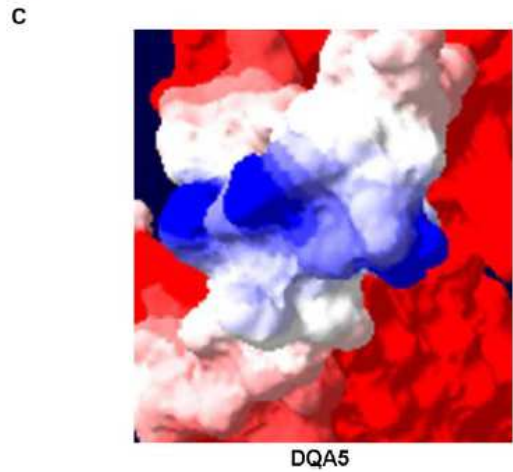
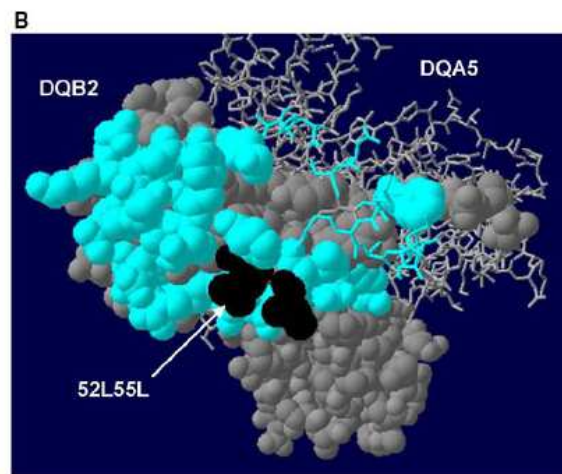
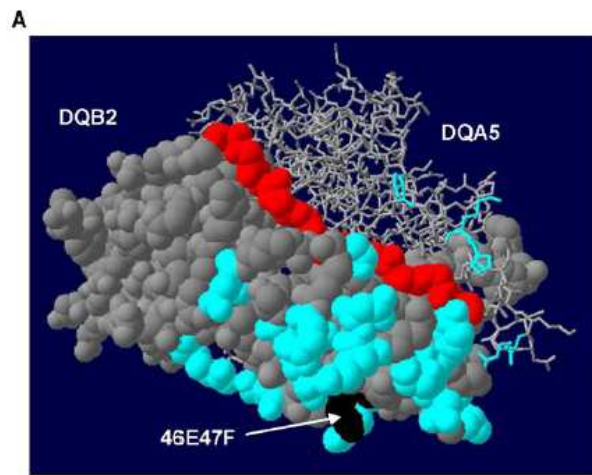


*Tambur, Front. Immunol. (2018) 9:2010.*



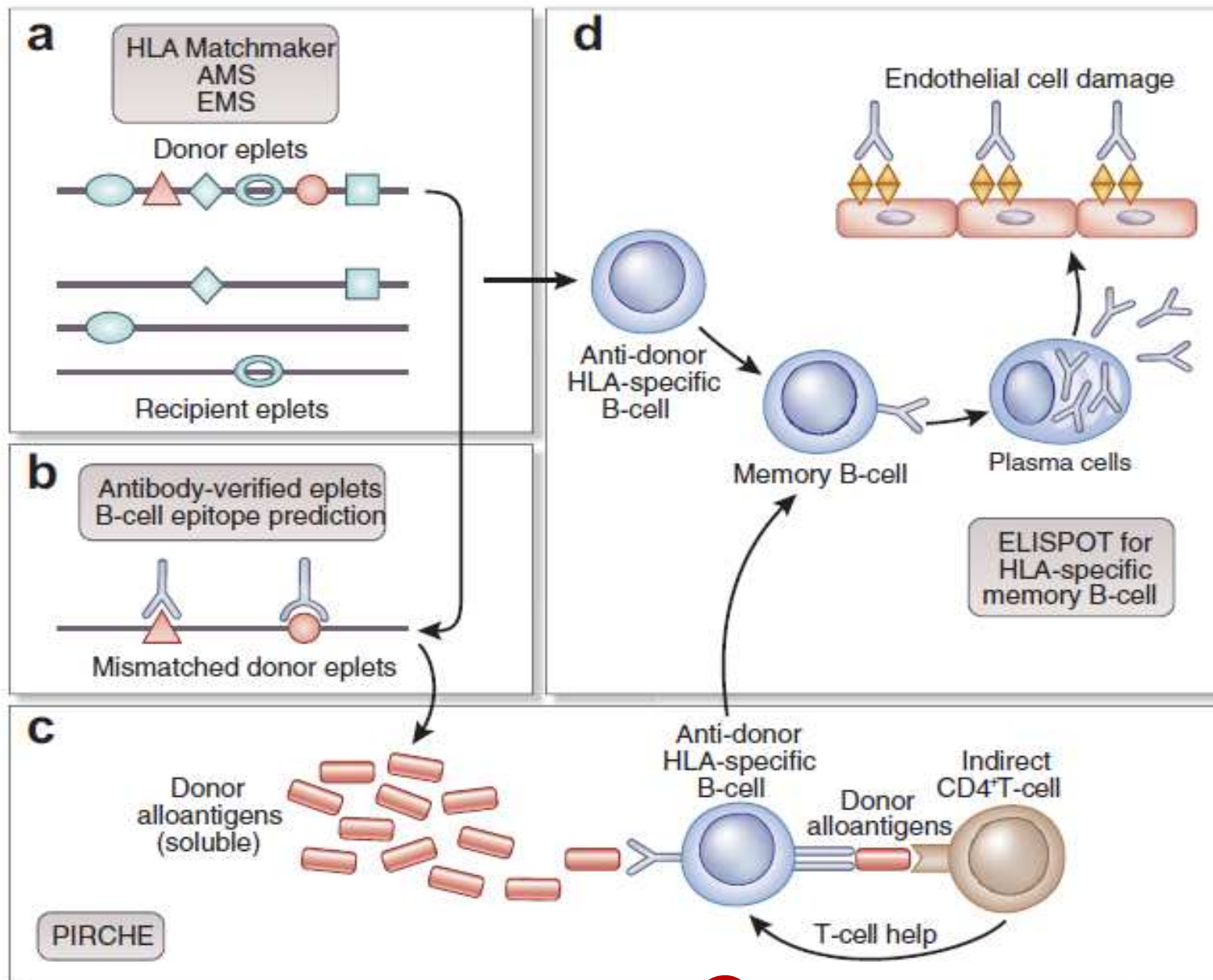
>50% DONORS “REM”  
DQA5-DQB2 o DQA5-DQB7

*McCaughan, Am J Transplant 2018;18:2924–2933.*





THE SUBSTITUTION OF SERINE FOR ISOLEUCINE AT POSITION 74 IN THE DQA5 CHAIN RESULTS IN A 4-FOLD CHANGE IN ELECTROSTATIC POTENTIAL IN THIS REGION, WHICH FORMS PART OF THE STRUCTURAL EPITOPE FOR ANTIBODIES SPECIFIC TO AN EPLET AT POSITION 45-47N DQB2.

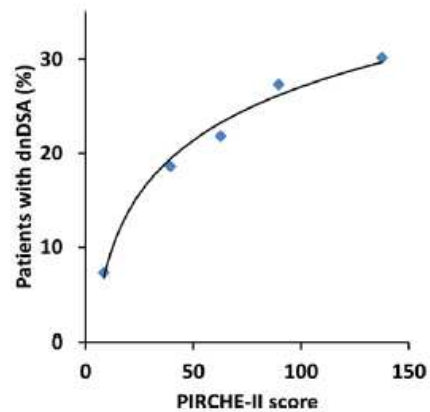
*McCaughan, Am J Transplant 2018;18:2924–2933.*



**TABLE 2** Percentage of patients, expressing different HLA-DR antigens, producing antibodies against specific HLA class I antigens

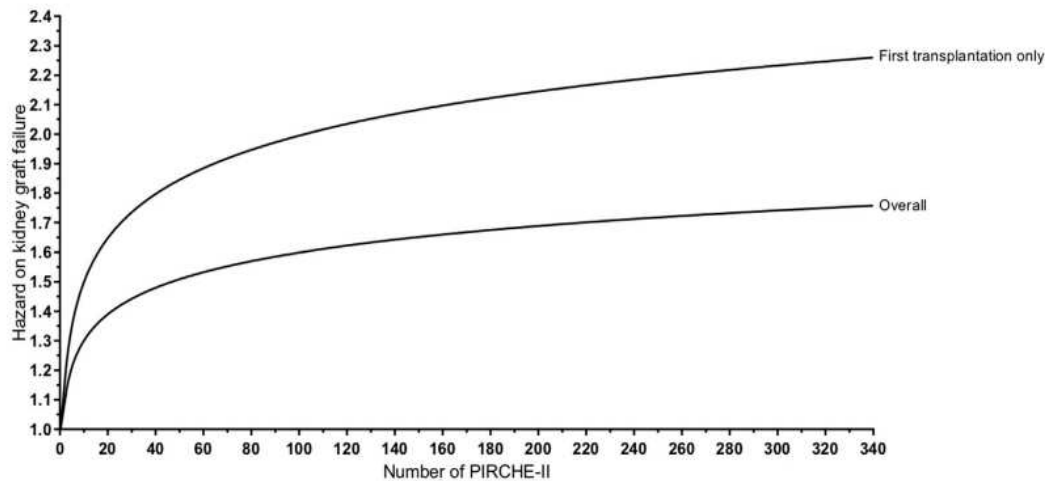
HLA class I antigen	HLA-DR antigen								
	DR1	DR2	DR3	DR4	DR5	DR6	DR7	DR52	DR53
A1	1.0 <sup>(102)</sup>	2.8 <sup>(181)</sup>	<b>0.0*</b> <sup>(61)</sup>	4.5 <sup>(223)</sup>	4.1 <sup>(122)</sup>	5.5 <sup>(200)</sup>	1.4 <sup>(74)</sup>	4.2 <sup>(383)</sup>	3.7 <sup>(297)</sup>
 A2	7.4 <sup>(68)</sup>	<b>11.0*</b> <sup>†(127)</sup>	6.2 <sup>(179)</sup>	8.4 <sup>(95)</sup>	9.5 <sup>(84)</sup>	11.9 <sup>(109)</sup>	3.9 <sup>(51)</sup>	8.6 <sup>(372)</sup>	6.9 <sup>(146)</sup>
A3	<b>0.0*</b> <sup>(65)</sup>	<b>1.6*</b> <sup>†(125)</sup>	<b>1.0*</b> <sup>(207)</sup>	<b>5.3*</b> <sup>(189)</sup>	3.3 <sup>(120)</sup>	5.0 <sup>(180)</sup>	1.2 <sup>(81)</sup>	3.0 <sup>(507)</sup>	4.1 <sup>(270)</sup>
A9	2.2 <sup>(93)</sup>	6.0 <sup>(151)</sup>	7.4 <sup>(215)</sup>	3.9 <sup>(208)</sup>	2.1 <sup>(95)</sup>	6.7 <sup>(193)</sup>	6.9 <sup>(73)</sup>	6.2 <sup>(503)</sup>	4.6 <sup>(281)</sup>
A10	3.8 <sup>(105)</sup>	3.7 <sup>(189)</sup>	4.3 <sup>(231)</sup>	4.0 <sup>(249)</sup>	5.1 <sup>(138)</sup>	<b>9.5*</b> <sup>†(221)</sup>	3.2 <sup>(93)</sup>	<b>6.4*</b> <sup>(590)</sup>	3.8 <sup>(342)</sup>
A11	<b>0.0*</b> <sup>(87)</sup>	1.6 <sup>(185)</sup>	1.3 <sup>(230)</sup>	3.1 <sup>(225)</sup>	<b>7.1*</b> <sup>(113)</sup>	<b>6.6*</b> <sup>(198)</sup>	1.1 <sup>(88)</sup>	<b>4.4*</b> <sup>(541)</sup>	2.6 <sup>(313)</sup>
A28	4.6 <sup>(109)</sup>	3.9 <sup>(205)</sup>	3.5 <sup>(232)</sup>	2.1 <sup>(238)</sup>	1.6 <sup>(126)</sup>	5.0 <sup>(201)</sup>	<b>0.0*</b> <sup>(91)</sup>	3.6 <sup>(559)</sup>	<b>1.5*</b> <sup>(329)</sup>
A19	6.0 <sup>(83)</sup>	4.3 <sup>(187)</sup>	4.9 <sup>(206)</sup>	5.5 <sup>(199)</sup>	3.8 <sup>(106)</sup>	<b>10.6*</b> <sup>†(189)</sup>	1.7 <sup>(59)</sup>	6.8 <sup>(501)</sup>	4.7 <sup>(258)</sup>
B5	3.1 <sup>(97)</sup>	2.6 <sup>(192)</sup>	<b>1.3*</b> <sup>(240)</sup>	<b>6.1*</b> <sup>(228)</sup>	3.6 <sup>(110)</sup>	4.5 <sup>(202)</sup>	2.2 <sup>(92)</sup>	2.9 <sup>(552)</sup>	5.0 <sup>(320)</sup>
 B7	3.0 <sup>(101)</sup>	5.1 <sup>(78)</sup>	5.4 <sup>(222)</sup>	<b>11.6*</b> <sup>†(218)</sup>	3.7 <sup>(134)</sup>	5.3 <sup>(208)</sup>	<b>1.1*</b> <sup>(90)</sup>	5.0 <sup>(584)</sup>	<b>8.5*</b> <sup>(306)</sup>
B8	1.8 <sup>(111)</sup>	1.5 <sup>(207)</sup>	0.0 <sup>(28)</sup>	<b>6.6*</b> <sup>(243)</sup>	<b>0.7*</b> <sup>(141)</sup>	4.9 <sup>(223)</sup>	3.2 <sup>(93)</sup>	3.1 <sup>(392)</sup>	<b>5.7*</b> <sup>(336)</sup>
B12	4.2 <sup>(95)</sup>	4.0 <sup>(199)</sup>	2.6 <sup>(232)</sup>	<b>9.8*</b> <sup>(173)</sup>	3.0 <sup>(101)</sup>	4.8 <sup>(207)</sup>	3.8 <sup>(53)</sup>	3.5 <sup>(540)</sup>	<b>8.4*</b> <sup>(226)</sup>
B15	3.9 <sup>(103)</sup>	3.7 <sup>(189)</sup>	2.1 <sup>(234)</sup>	5.3 <sup>(152)</sup>	0.9 <sup>(114)</sup>	4.1 <sup>(170)</sup>	1.1 <sup>(88)</sup>	2.5 <sup>(518)</sup>	3.8 <sup>(240)</sup>
B16	<b>0.9*</b> <sup>†(106)</sup>	<b>1.0*</b> <sup>†(198)</sup>	0.4 <sup>(237)</sup>	2.8 <sup>(250)</sup>	<b>0.0*</b> <sup>(135)</sup>	2.3 <sup>(215)</sup>	2.2 <sup>(93)</sup>	1.0 <sup>(587)</sup>	<b>2.6*</b> <sup>(343)</sup>
B17	5.3 <sup>(114)</sup>	<b>4.8*</b> <sup>†(208)</sup>	2.2 <sup>(230)</sup>	4.8 <sup>(251)</sup>	1.4 <sup>(139)</sup>	4.1 <sup>(221)</sup>	1.4 <sup>(72)</sup>	2.7 <sup>(590)</sup>	4.0 <sup>(323)</sup>
B35	5.0 <sup>(40)</sup>	<b>1.0*</b> <sup>†(194)</sup>	<b>0.4*</b> <sup>(223)</sup>	<b>2.7*</b> <sup>†(219)</sup>	<b>0.0*</b> <sup>(112)</sup>	<b>4.2*</b> <sup>(192)</sup>	2.4 <sup>(84)</sup>	1.7 <sup>(533)</sup>	2.6 <sup>(303)</sup>
B40	3.7 <sup>(108)</sup>	4.4 <sup>(180)</sup>	3.0 <sup>(232)</sup>	5.2 <sup>(213)</sup>	2.3 <sup>(130)</sup>	<b>2.5*</b> <sup>†(159)</sup>	1.2 <sup>(84)</sup>	2.7 <sup>(521)</sup>	4.0 <sup>(297)</sup>

*Dankers, Hum Imm 2004 ; 65:13–19*



**Figure 4:** Logarithmic correlation between the cumulative incidence of dnDSA and PIRCHE-II score. dnDSA, *de novo* donor-specific HLA antibodies; PIRCHE, predicted indirectly recognizable HLA epitopes. [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

# PIRCHE-II



**FIGURE 2 |** Modeling of the increased hazard on graft failure for each Predicted Indirectly Recognizable HLA Epitopes presented by recipient HLA class II (PIRCHE-II). Based on the multivariable analyses, the kidney graft failure risk is plotted as a function of the number of PIRCHE-II for both the overall cohort and for the first-transplantations only group. For example for the overall cohort, a patient with a PIRCHE-II value of 2.718 [ $\ln(2.718) = 1$ ] has a hazard of 1.13 on kidney graft failure, whereas a patient with a PIRCHE-II value of 7.388 [ $=2.718 \times 2.718$ ;  $\ln(7.388) = 2$ ] has a hazard of 1.26 (an increase of 0.13 compared with a PIRCHE-II value of 2.718) on kidney graft failure. Similar calculations were performed for other PIRCHE-II values and for the first-transplantations only group. The differences in hazard on kidney graft failure between different PIRCHE-II values decrease for higher PIRCHE-II values.

*Geneugelijk, Front. Immunol. (2018) 9:321*

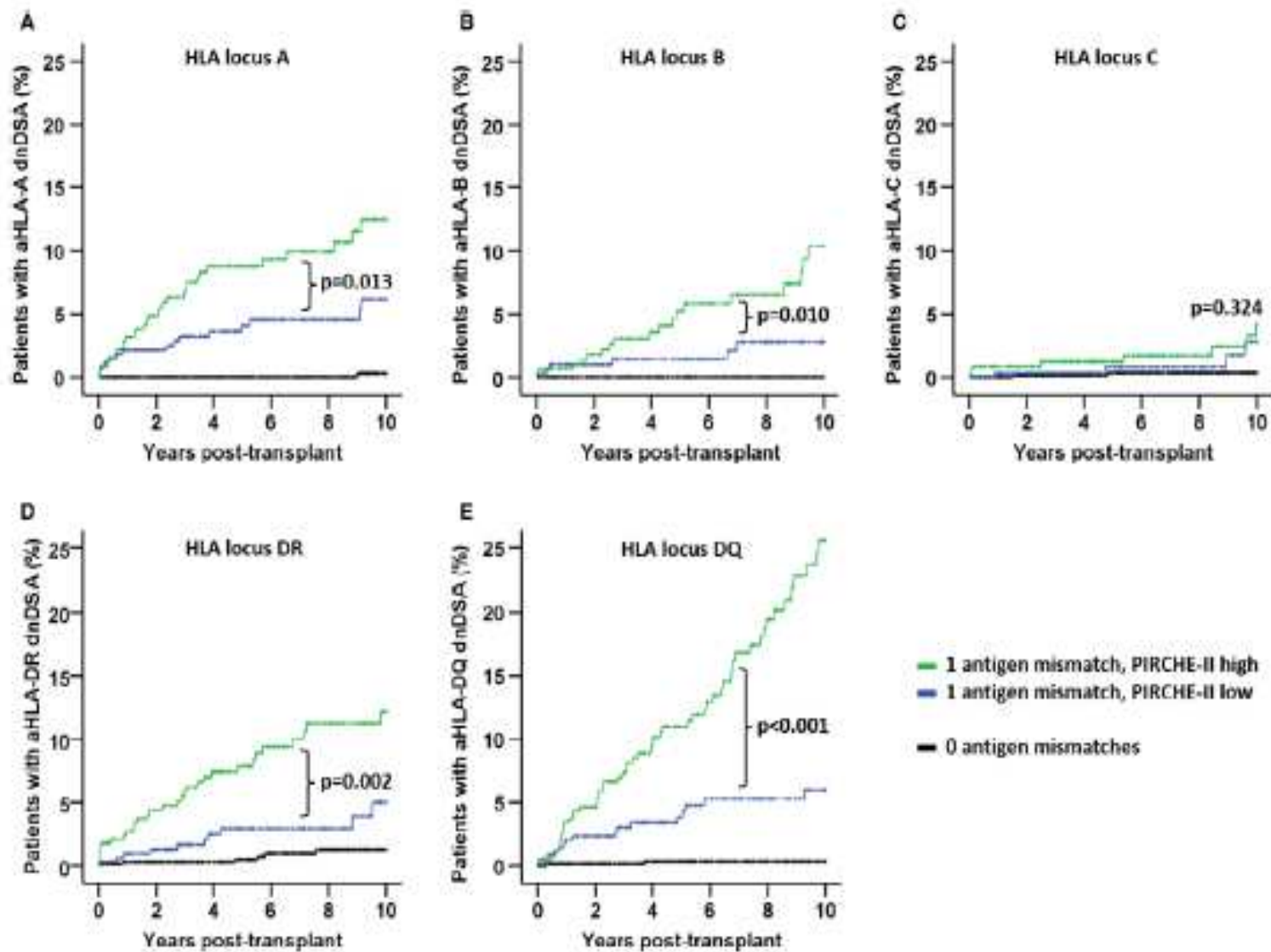
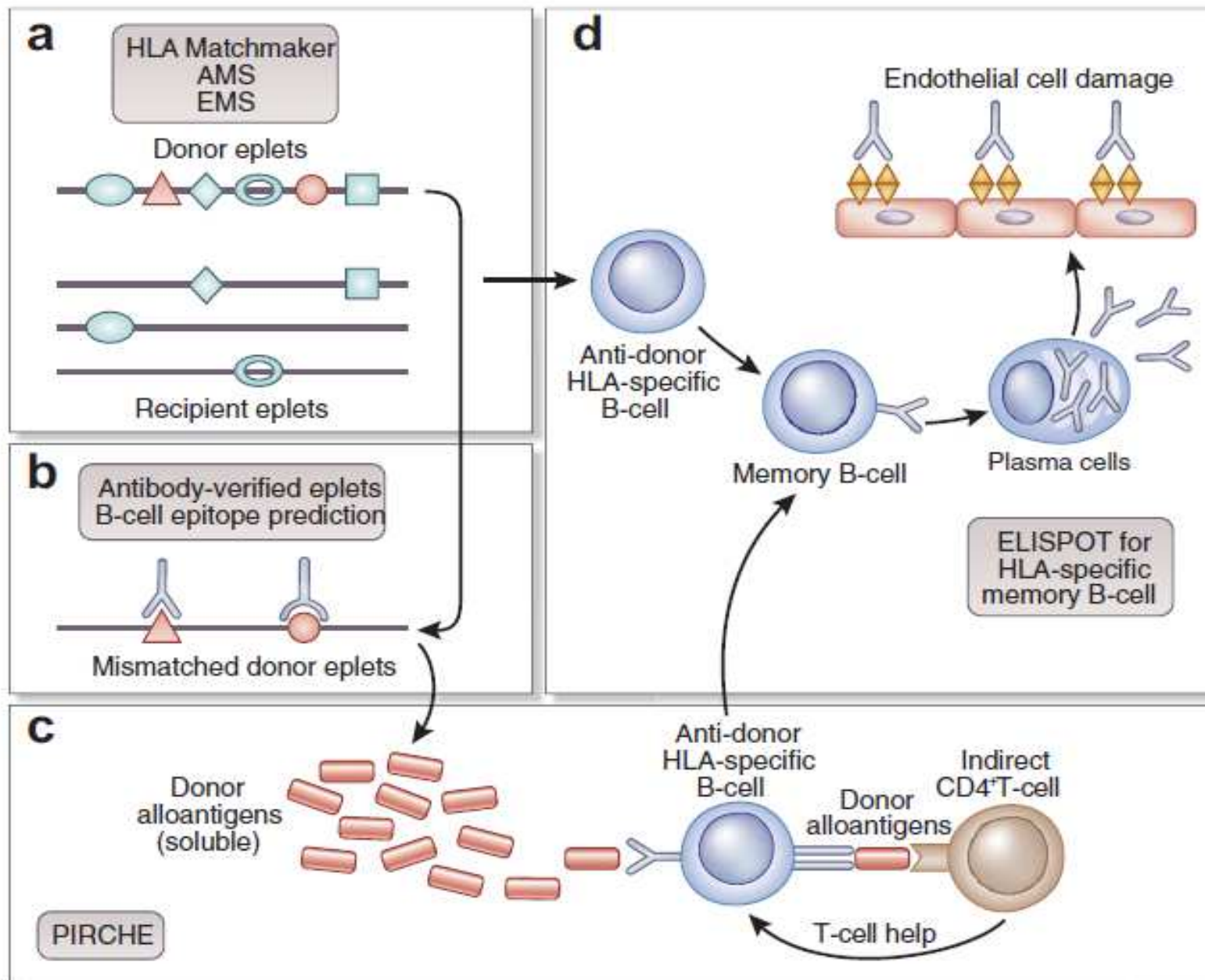


Figure 5: Cumulative incidence of dnDSA stratified according to low and high PIRCHE-II score (first vs. fourth quartile) in patients

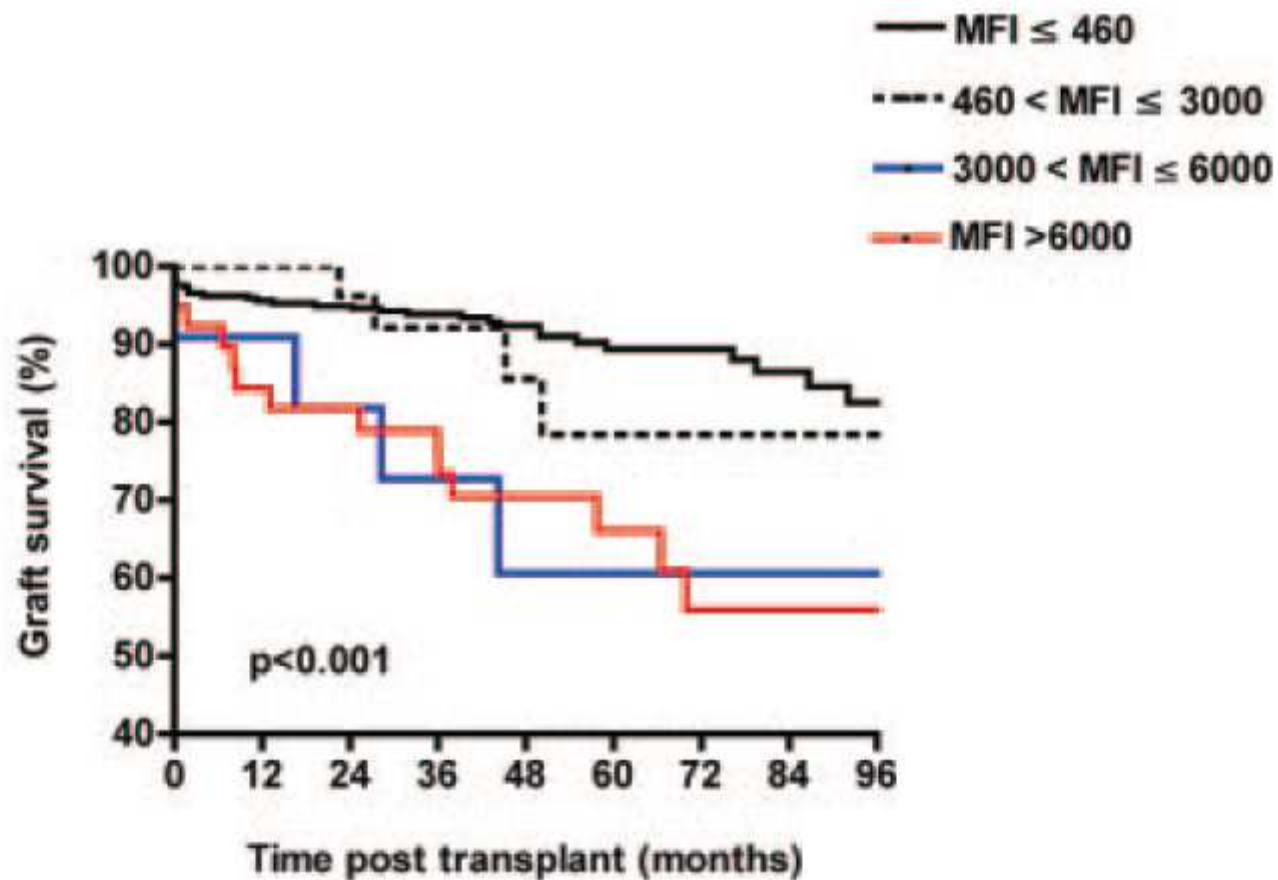
PIRCHE-II

*Lachmann Am J Transpl 2017; 17: 3076–3086*



3

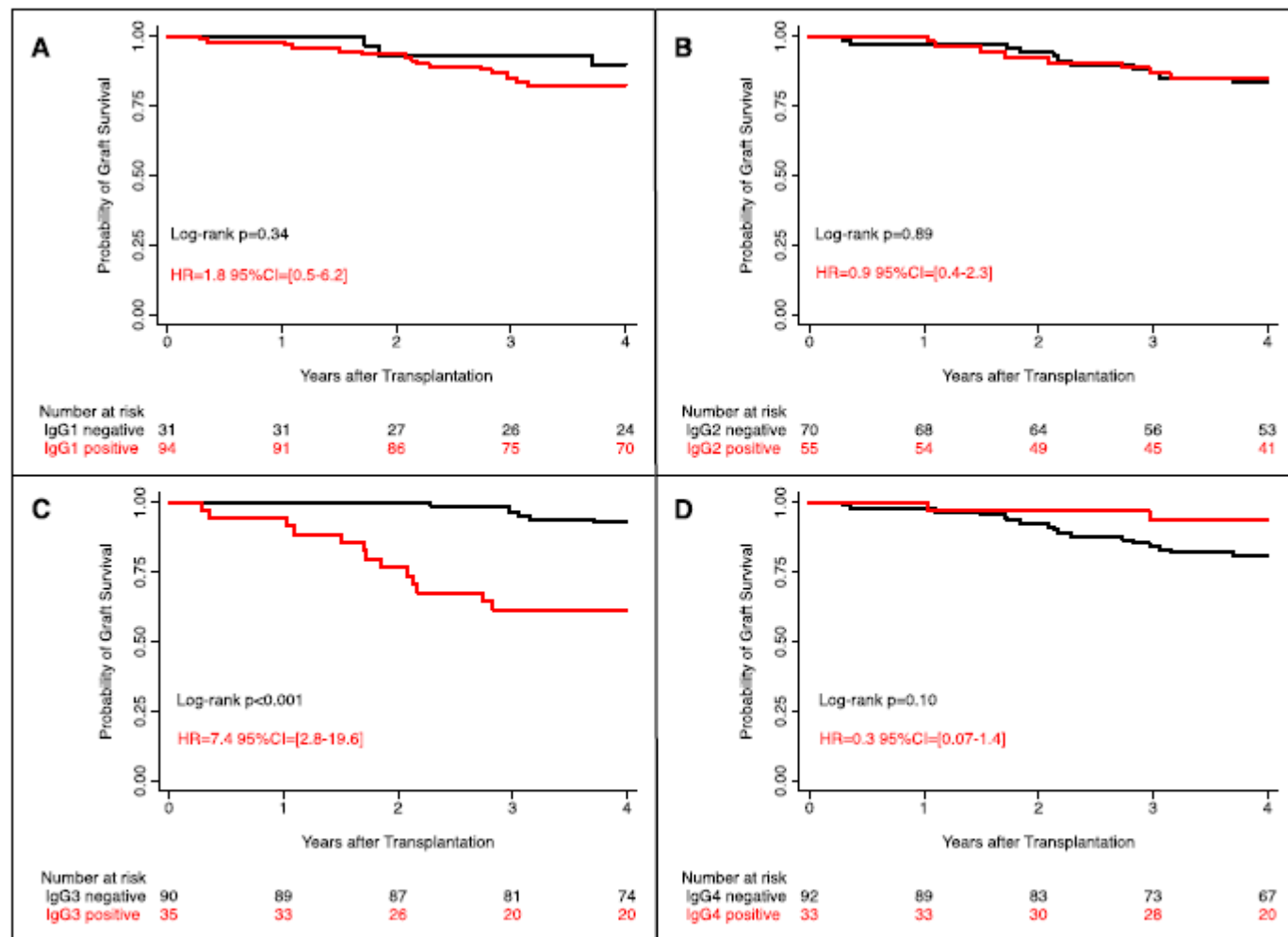
**A**



Number at risk

MFI ≤ 460	325	297	285	224	151	103	75	51	33
460 < MFI ≤ 3000	27	27	26	22	13	10	8	7	6
3000 < MFI ≤ 6000	11	11	10	8	4	3	3	2	2
MFI > 6000	39	33	30	28	19	16	12	9	5

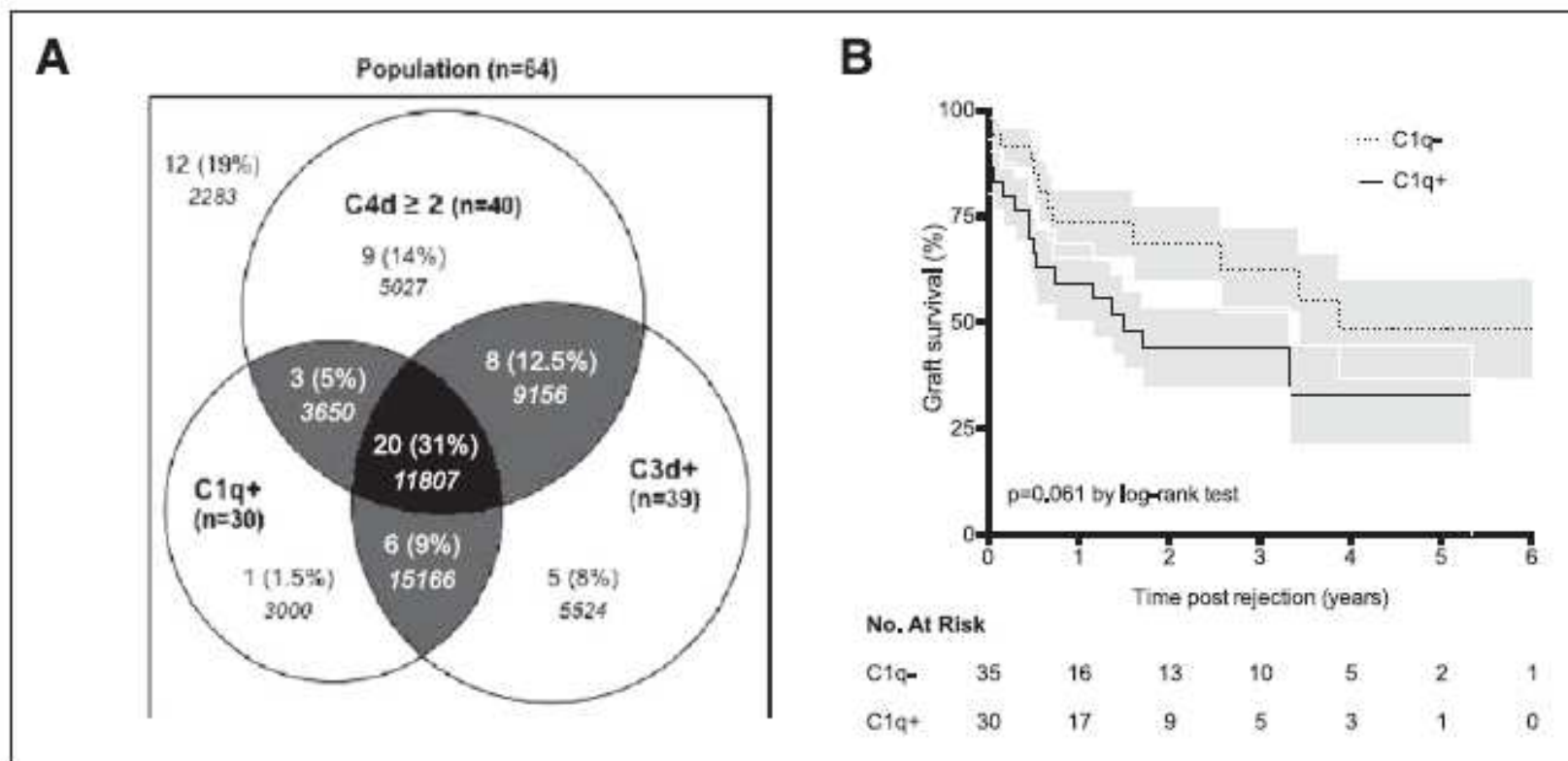
*Lefaucher, J Am Soc Nephrol 21: 1398–1406, 2010*



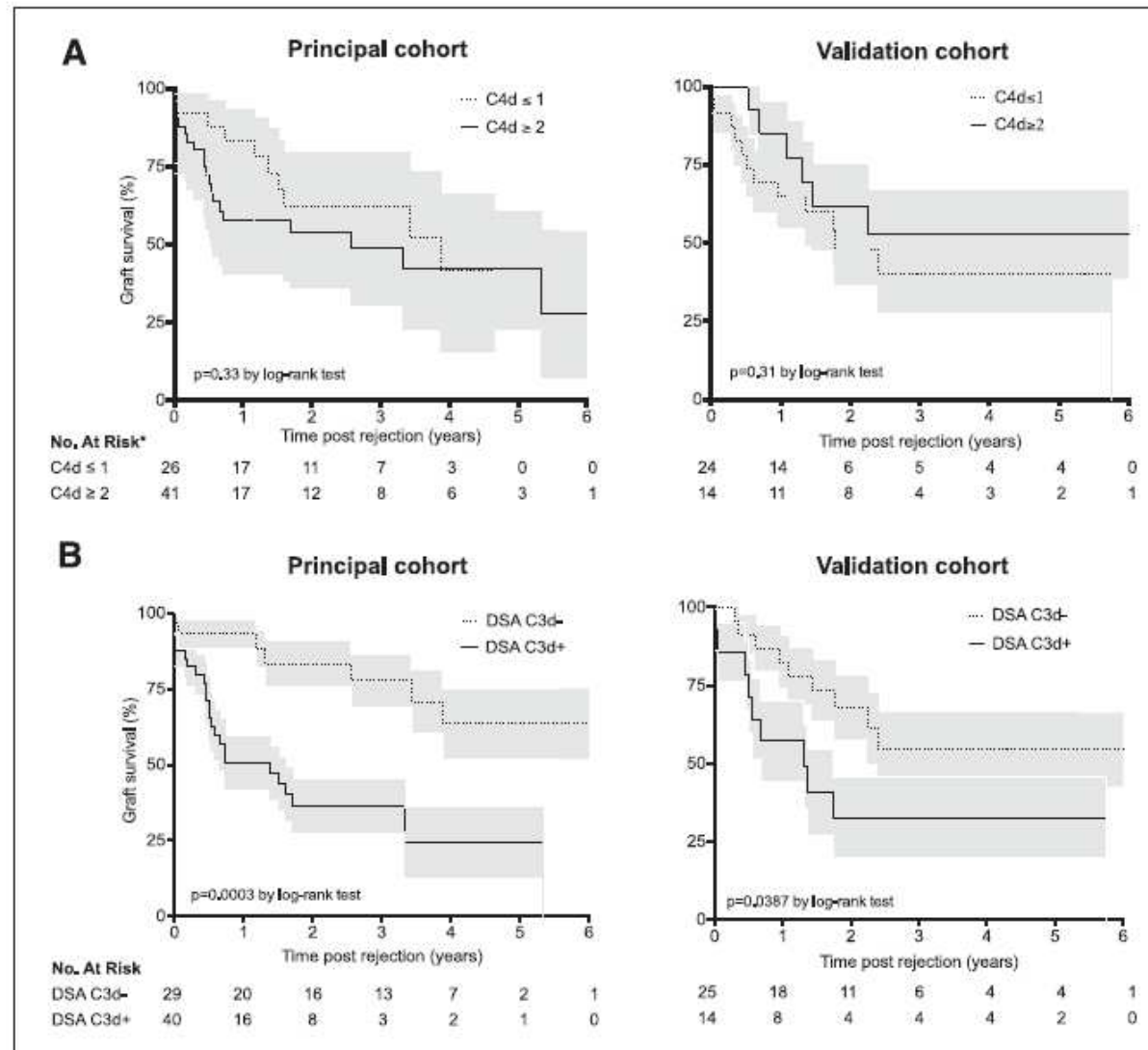
C1q  
★

**Figure 3.** Kaplan–Meier curves for death-censored kidney allograft survival according to iDSA IgG1 (A), IgG2 (B), IgG3 (C), and IgG4 (D) subclass status.

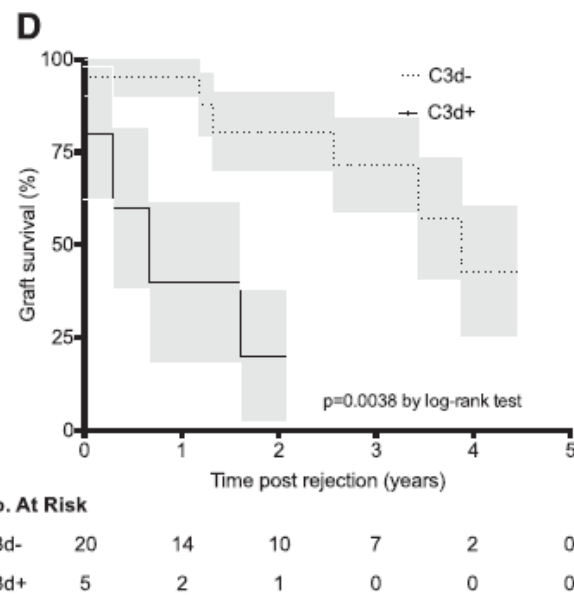
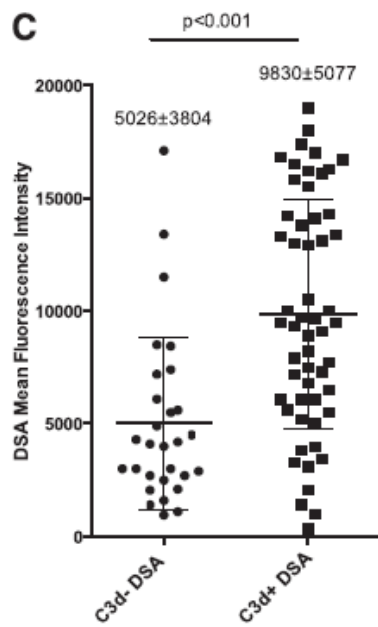
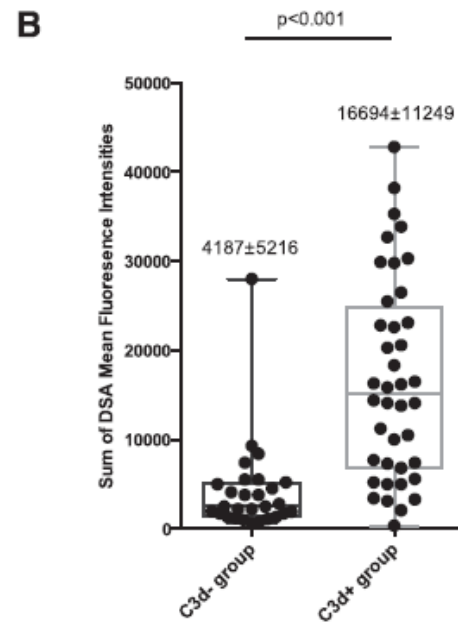
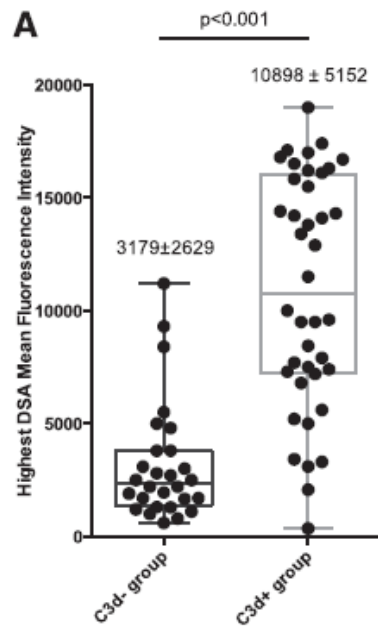
*Lefaucher, J Am Soc Nephrol 27: 293–304, 2016.*



*Sicard, J Am Soc Nephrol 26: 457–467, 2015*

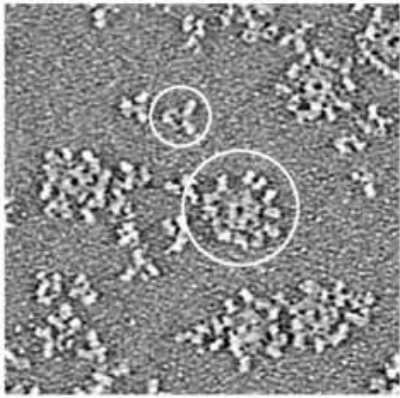
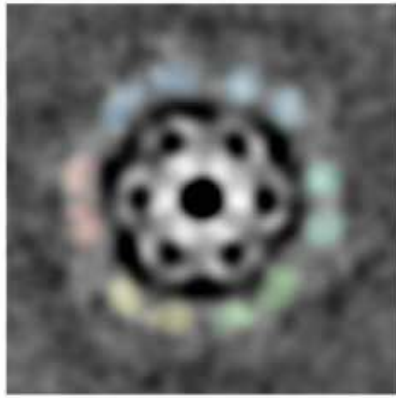
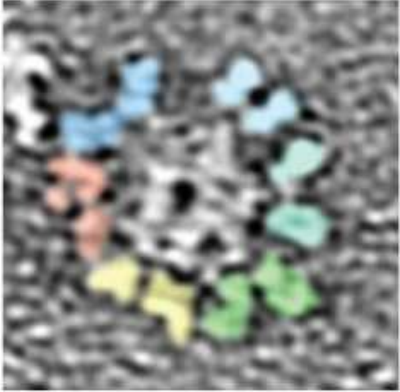
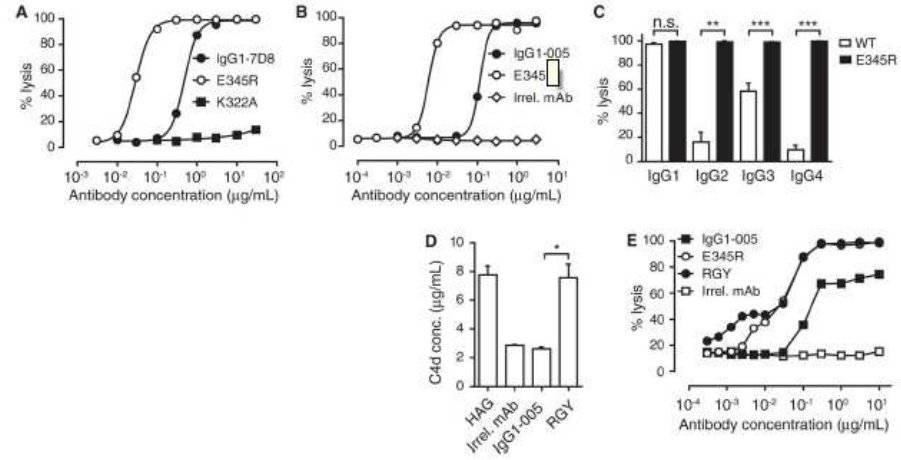


*Sicard, J Am Soc Nephrol 26: 457–467, 2015*



C3d vs. MFI

*Sicard, J Am Soc Nephrol 26: 457–467, 2015*

**C****E****D****F**

# IgG HEXAMERS BIND C1

*Dieboldier, Science 2014; 343(6176): 1260–1263.*

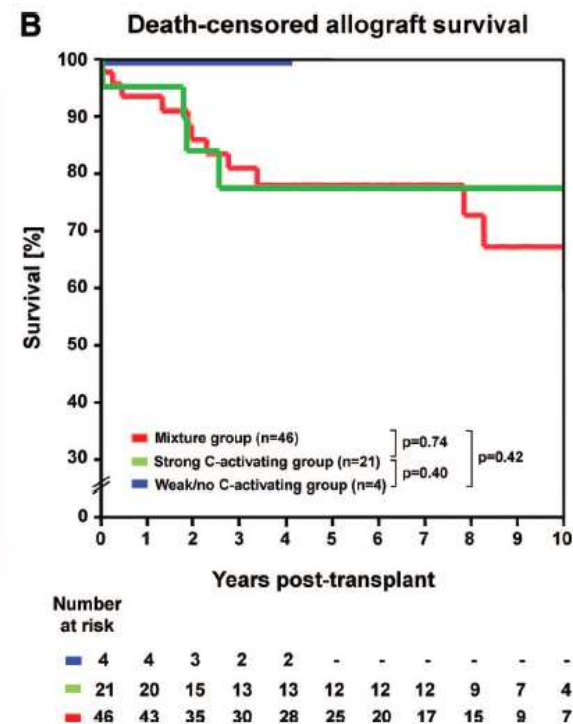
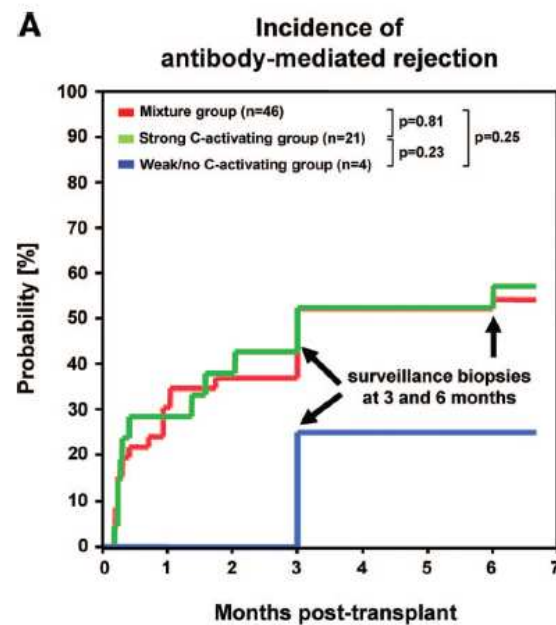
Table 1 | Properties of human IgG subclasses.

	IgG1		IgG2		IgG3		IgG4	
General								
Molecular mass (kD)	146		146		170		146	
Amino acids in hinge region	15		12		62 <sup>a</sup>		12	
Inter-heavy chain disulfide bonds	2		4 <sup>b</sup>		11 <sup>a</sup>		2	
Mean adult serum level (g/l)	6.98		3.8		0.51		0.56	
Relative abundance (%)	60		32		4		4	
Half-life (days)	21		21		7/~21 <sup>a</sup>		21	
Placental transfer	++++		++		++/++++ <sup>a</sup>		+++	
Antibody response to:								
Proteins	++		+/-		++		++ <sup>e</sup>	
Polysaccharides	+		+++		+/-		+/-	
Allergens	+		(-)		(-)		++	
Complement activation								
C1q binding	++		+		+++		-	
Fc receptors								
FcγRI	+++ <sup>c</sup>	65 <sup>d</sup>	-	-	++++	61	++	34
FcγRIIa <sub>H131</sub>	+++	5.2	++	0.45	++++	0.89	++	0.17
FcγRIIa <sub>R131</sub>	+++	3.5	+	0.10	++++	0.91	++	0.21
FcγRIIb/c	+	0.12	-	0.02	++	0.17	+	0.20
FcγRIIIa <sub>F158</sub>	++	1.2	-	0.03	++++	7.7	-	0.20
FcγRIIIa <sub>V158</sub>	+++	2.0	+	0.07	++++	9.8	++	0.25
FcγRIIIb	+++	0.2	-	-	++++	1.1	-	-
FcRn (at pH < 6.5)	+++		+++		++/++++ <sup>a</sup>		+++	



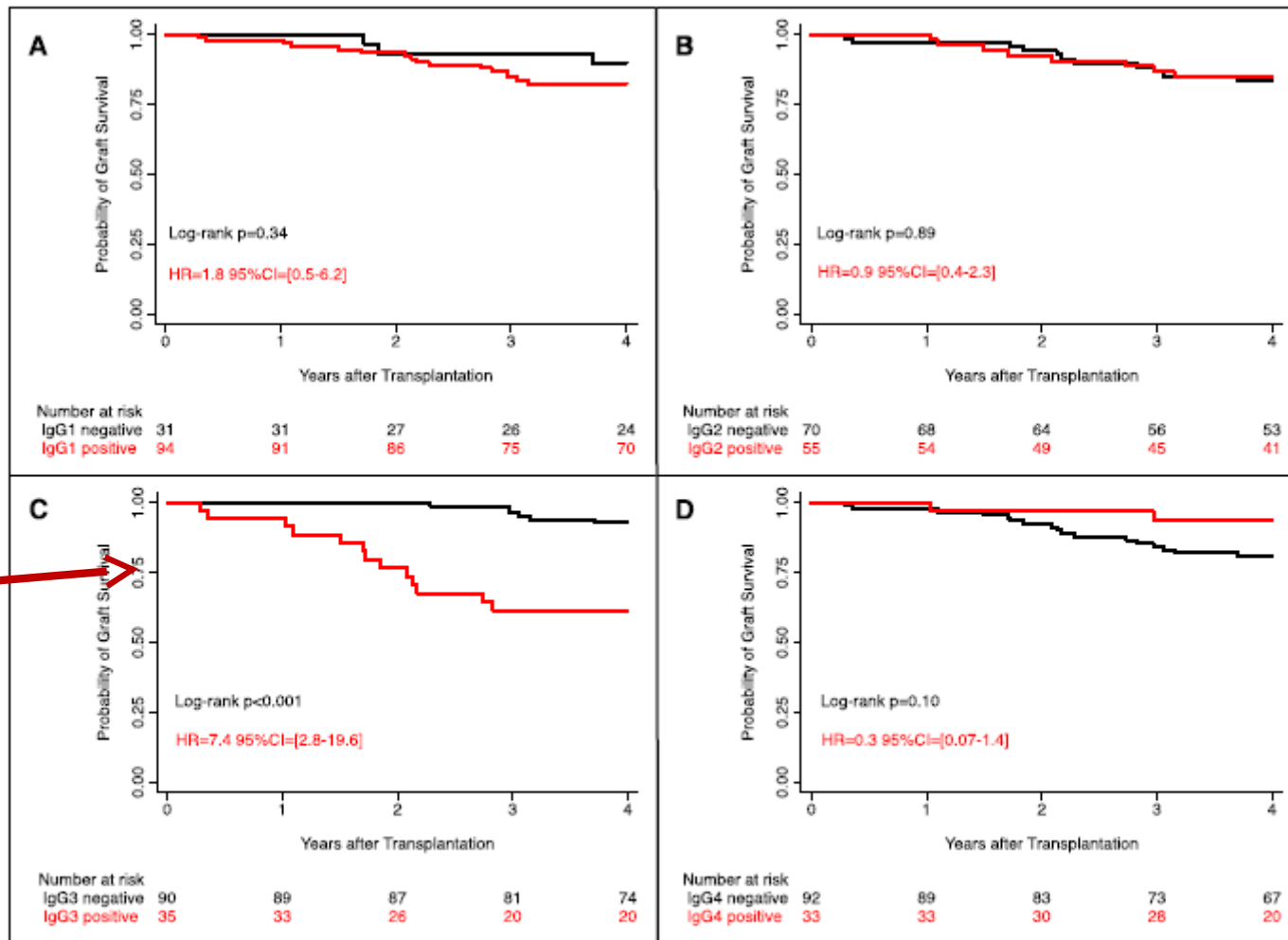
Vidarsson, Front Imm 2014

subclass pattern	biological group	N
1	strong C-activating	32
1+3	strong C-activating	14
3	strong C-activating	2
2	weak/no C-activating	6
2+4	weak/no C-activating	2
4	weak/no C-activating	1
1+2	mixture	21
1+2+3	mixture	19
1+2+3+4	mixture	14
1+4	mixture	6
1+2+4	mixture	5
2+3	mixture	2
2+3+4	mixture	-
1+3+4	mixture	-
3+4	mixture	-
no IgG1-4	all negative	17



IgG1+3 vs. IgG2+4

*Honger, Transplantation 2011;92: 41–47*



IgG3

**Figure 3.** Kaplan–Meier curves for death-censored kidney allograft survival according to iDSA IgG1 (A), IgG2 (B), IgG3 (C), and IgG4 (D) subclass status.

*Lefaucher, J Am Soc Nephrol 27: 293–304, 2016.*



# Gabry Little Hero

