
بسم الله الرحمن الرحيم

Virtual Crossmatch in Kidney Transplantation

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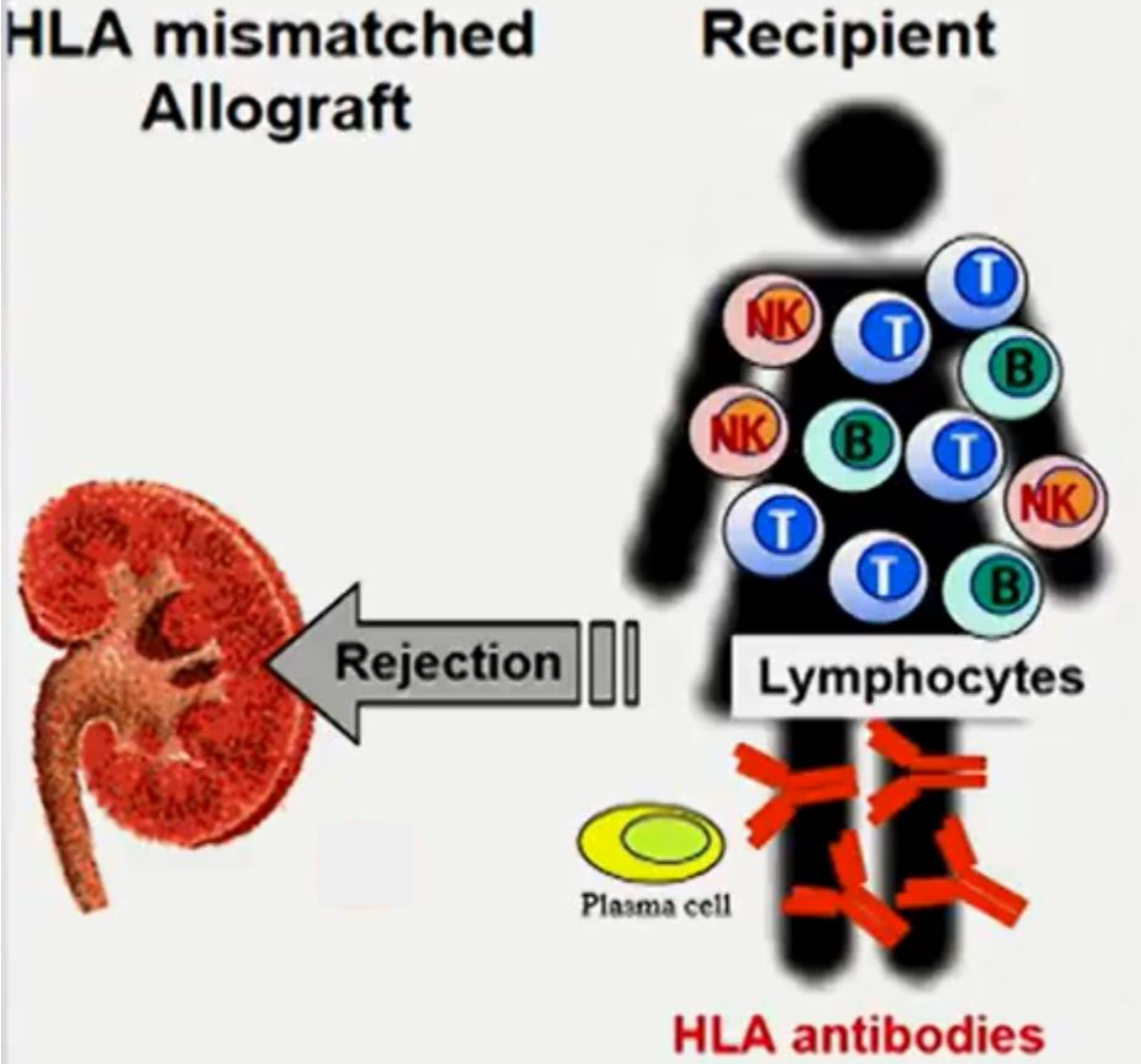
Baqiyatallah University of Medical Sciences

July 2018

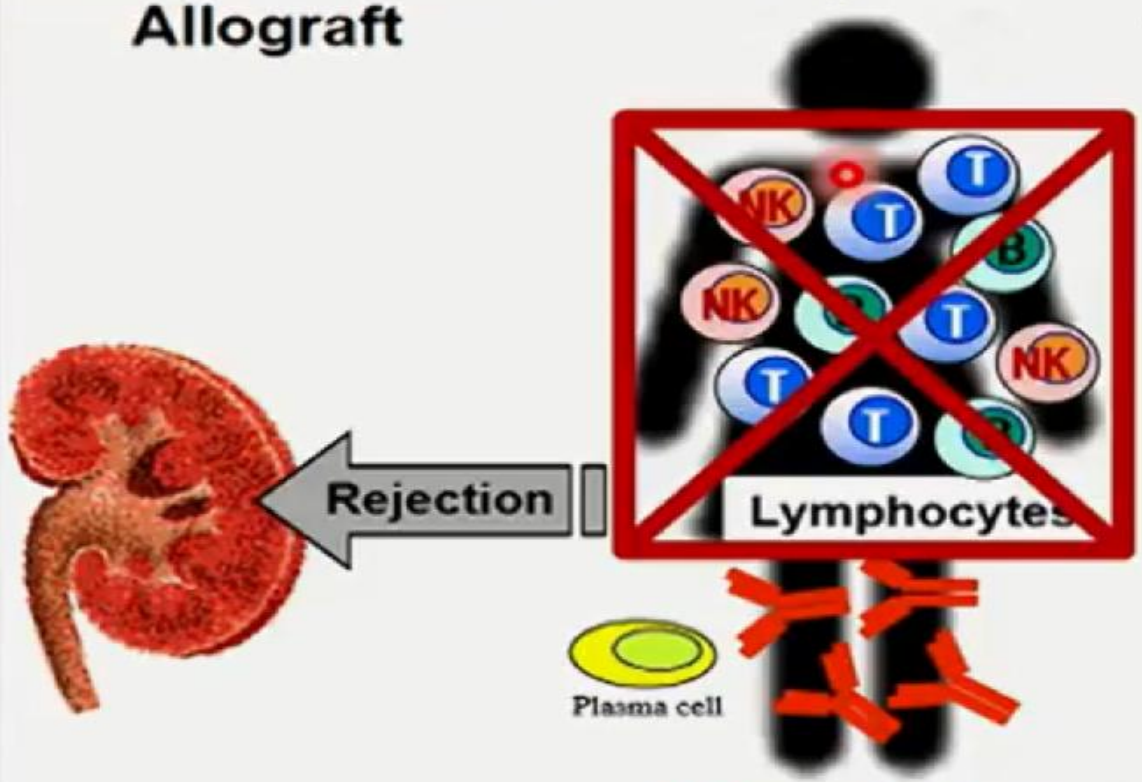
HLA is the Challenging Barrier to Transplantation



HLA is the Challenging Barrier to Transplantation

HLA mismatched Allograft

Recipient



Induction Therapy

Lymphocytes Depletion

- Anti-Thymoglobulin → T & NK cells
- Anti-CD3 → T cells
- Anti-CD25 → Activated T cells
- Anti-CD52 → mature lymphocytes
- Anti-CD20 → B cells

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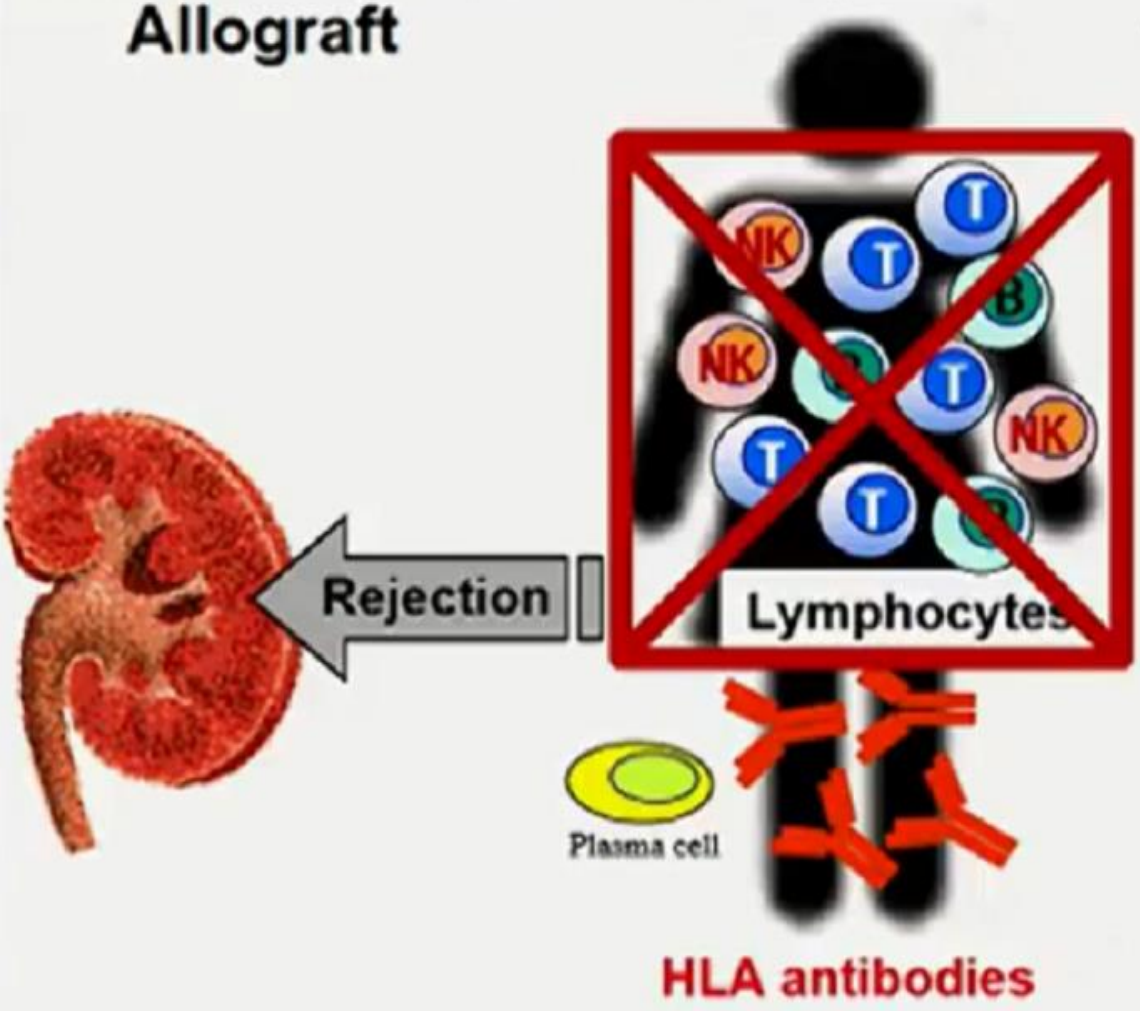

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Maintenance Therapy

Immunosuppression

- Cyclosporine
- MMF
- Steroids

HLA is the Challenging Barrier to Transplantation

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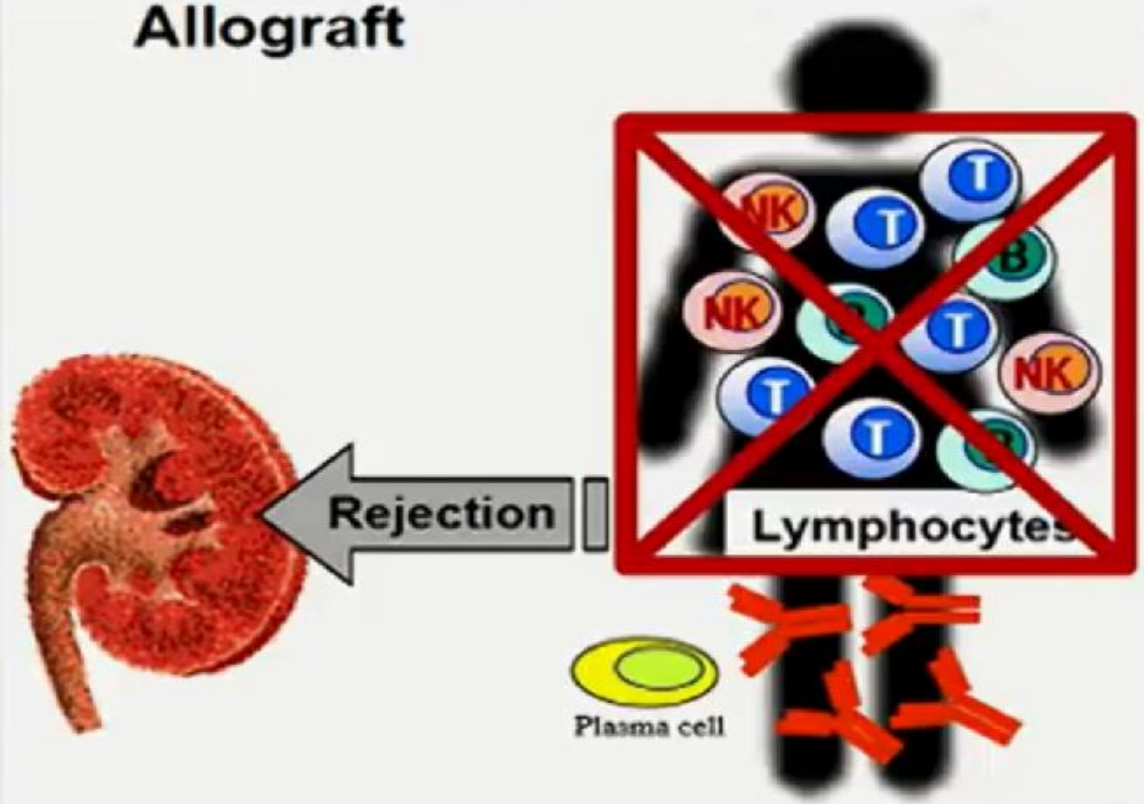

HLA antibodies

- Transplantation
- Pregnancy
- Transfusion

Induction Therapy

Lymphocytes Depletion

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Maintenance Therapy

Immunosuppression

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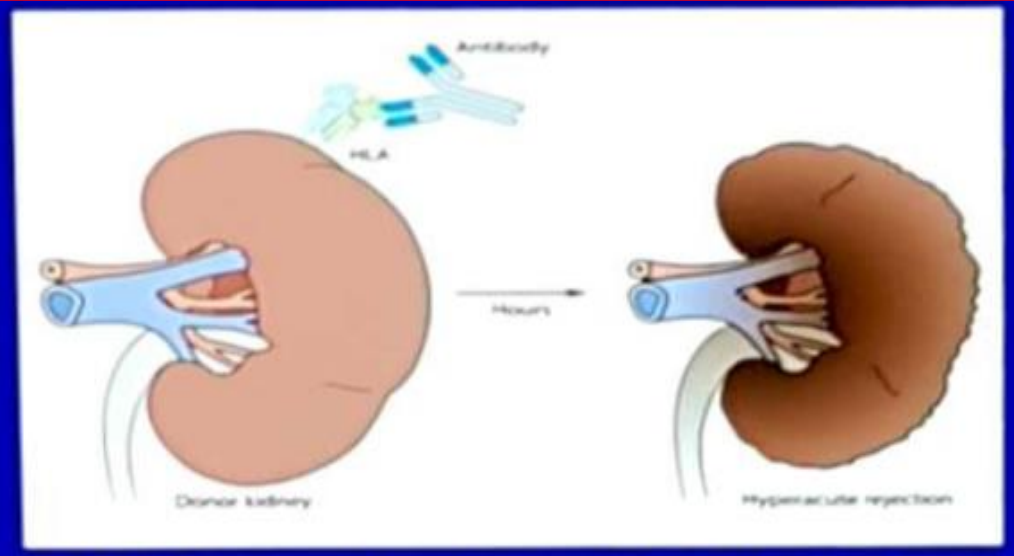
Preformed donor specific HLA antibodies lead to hyperacute rejection


The New England
Journal of Medicine



Patel & Terasaki (1969): 24/30 patients with donor specific antibodies experienced hyperacute rejection.

The introduction of a serological crossmatch and exclusion of donors toward which the patient has preformed antibodies, will prevent hyperacute rejection.

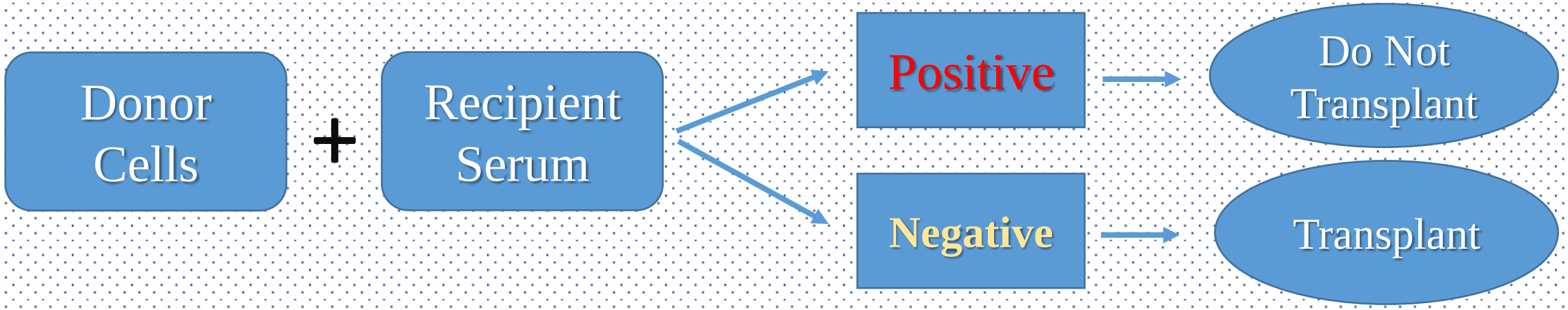
Consequences of Pre-formed Donor-Specific HLA Antibody

- Hyperacute rejection
- Delayed graft function
- Accelerated acute rejection
- Chronic rejection
- Prolonged waiting times
- No transplantation

Original PARADIGM

The pre-transplant crossmatch is the most important test performed by the HLA laboratory!

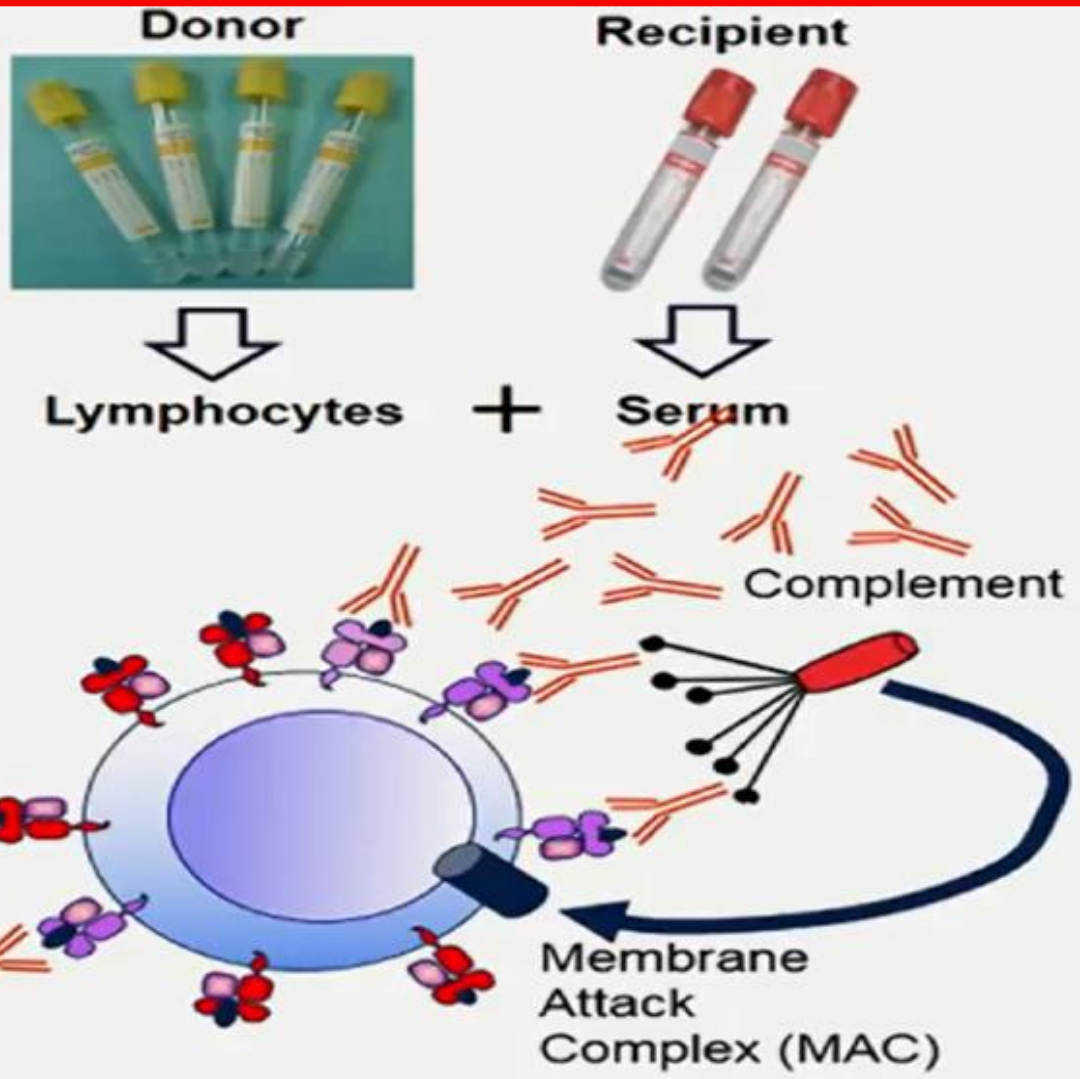
Crossmatch


Donor Cells
+
Recipient Serum
Positive
Negative
Do Not Transplant
Transplant

Crossmatch (xM)

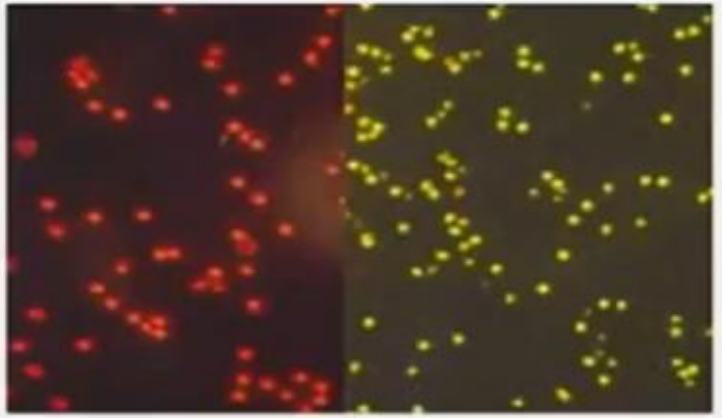
Methods	Goal
T cell xM	Class I DSA
B cell xM	Class II DSA
CDC xM	Cytotoxic Antibodies
AHG xM	Sensitive CDC xM
DTT xM	Depletes IgM
Flow xM	Sensitive xM
Pronase xM	Removes Fc/background
Endothelial cell xM	Non-HLA Antibodies
Auto xM	Auto-Antibodies
Virtual xM	Most sensitive xM

Complement Dependent Cytotoxicity (CDC) Crossmatch



Paul Terasaki

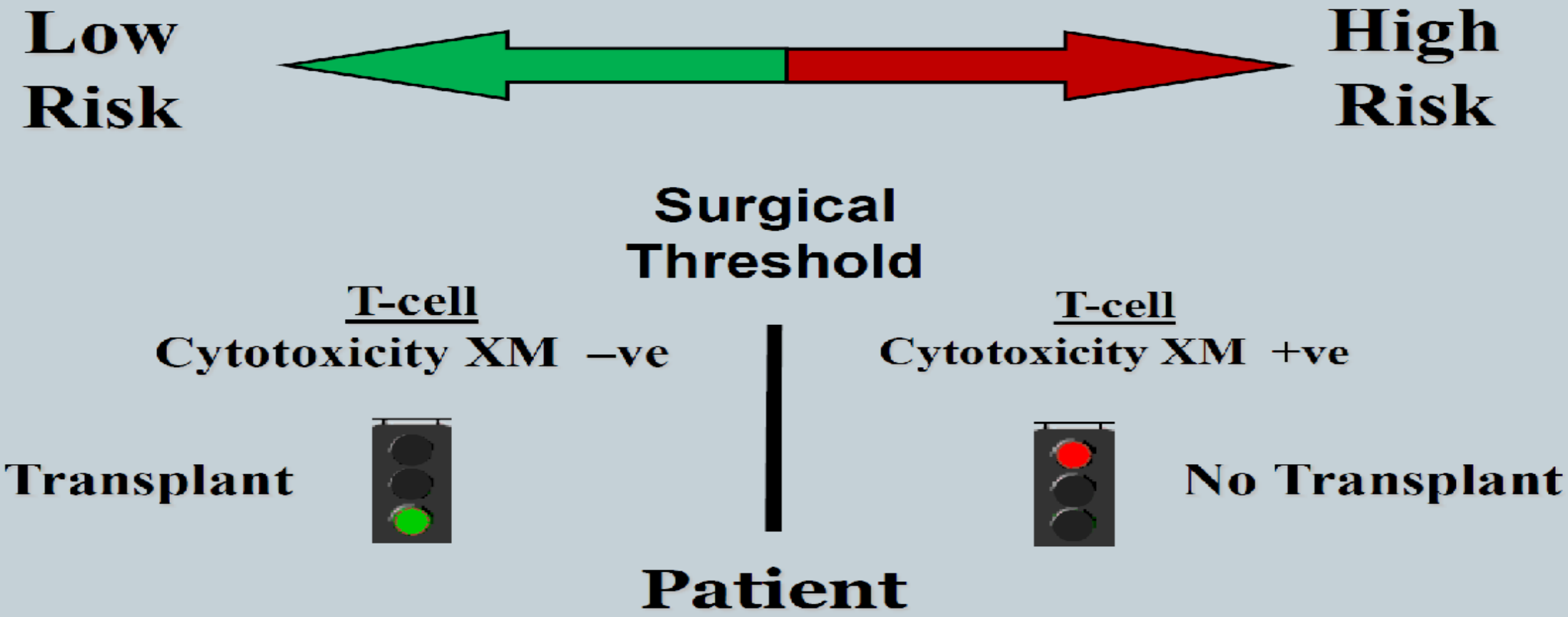
Fluorescein Diacetate +
Ethidium Bromide



Dead cells ⇩ **Positive**

Live cells ⇩ **Negative**

Clinical Paradigm (1970s-80s)



The New England
Journal of Medicine

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.

Abstract Crossmatch tests of the prospective kidney-transplant donor's lymphocytes with the serum of the prospective recipient in 225 transplants showed that eight of 195 with negative crossmatch failed to function immediately, in contrast to and patients receiving secondary transplants. The effect was not a nonspecific one, for more immediate failures occurred among transplants from unrelated than among those from related donors. The corresponding frequency of positive crossmatch

CDC xM (n=225)	Hyperacute or Accelerated Rejection	Functional Graft
Positive (n=30)	24	6
Negative (n=195)	8	187

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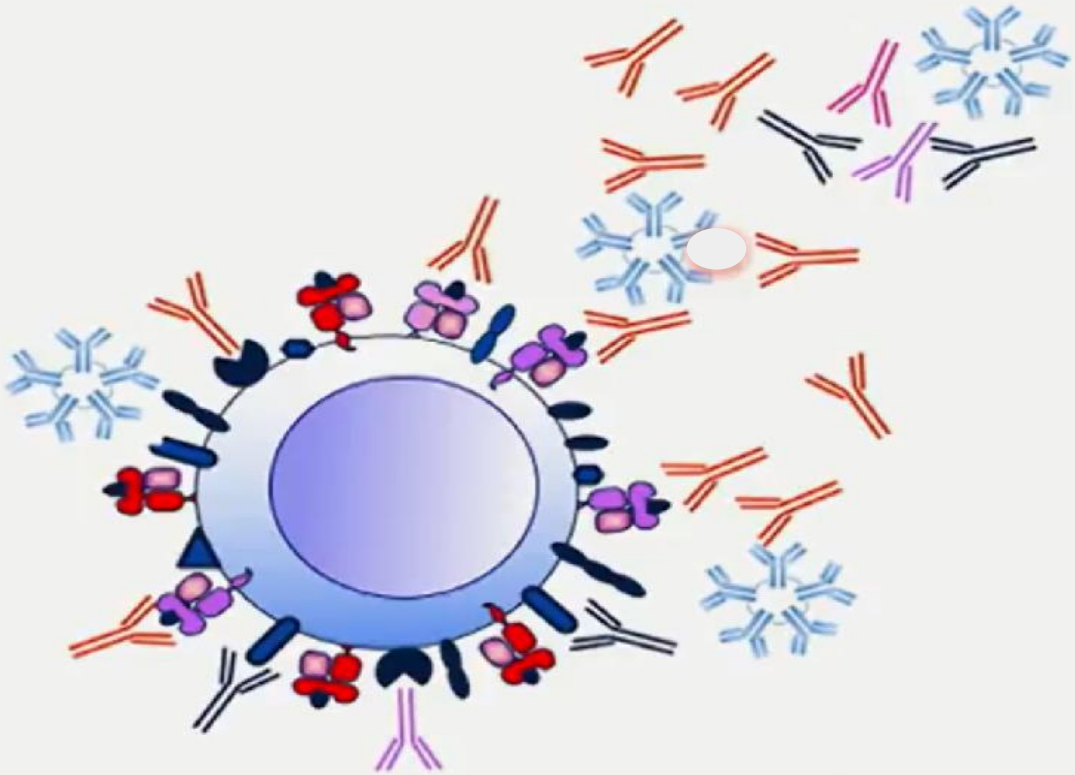
CDC xM (n=225)	Hyperacute or Accelerated Rejection	Functional Graft
Positive (n=30)	24	6 Specificity Problem
Negative (n=195)	8 Sensitivity Problem	187

Assay Improvements

Modified CDC Crossmatch



- HLA
- Non-HLA target

- HLA Antibodies
- Non-HLA Antibodies
- IgM Antibodies

to Enhance Specificity

- Deplete IgM by DTT

to Enhance Sensitivity

- Add AHG
- Extended incubation

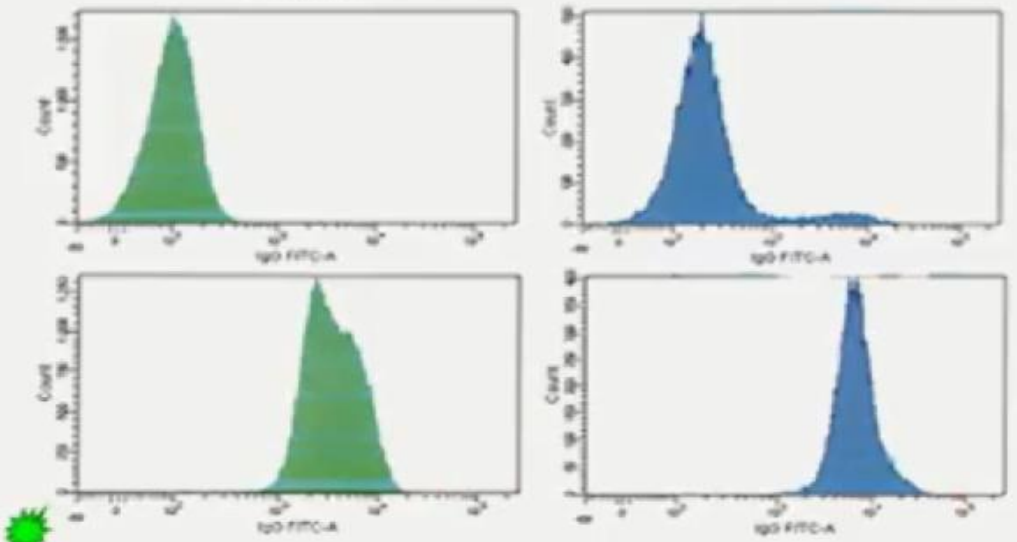
Flow Cytometry Crossmatch

Donor

Recipient

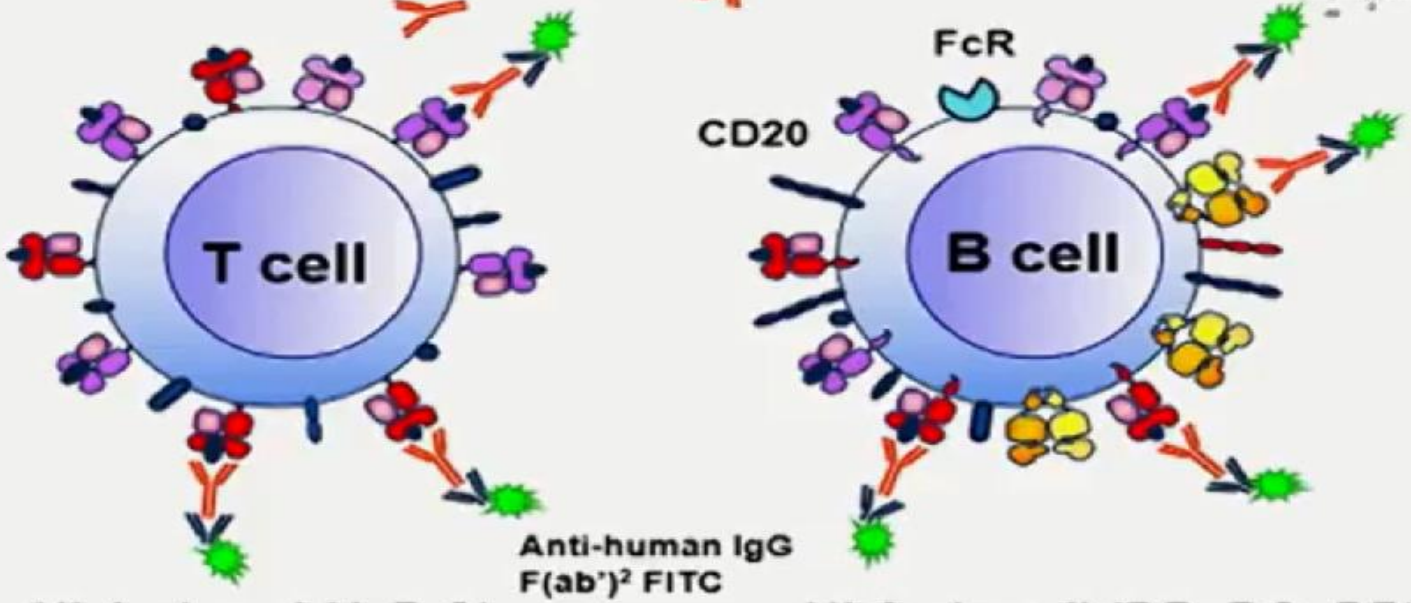
Lymphocytes + Serum

HLA antibodies



T cell MCS ≥ 50
B cell MCS ≥ 120

Measure FITC intensity
by flow cytometry



HLA class I (A,B,C)

HLA class II (DR, DQ, DP)

Flow Cytometry Crossmatch

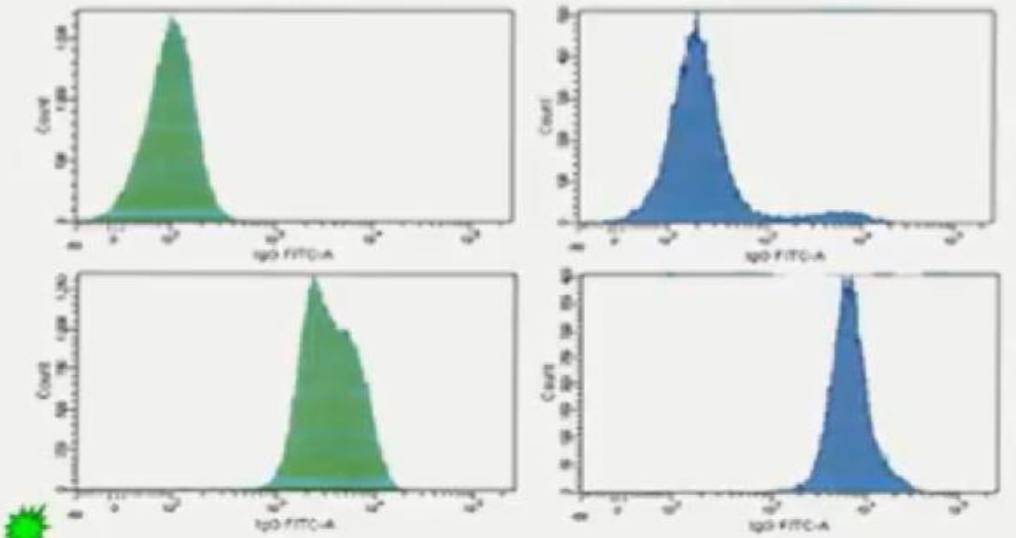
Donor

Recipient

Lymphocytes + Serum

Rituximab

HLA antibodies



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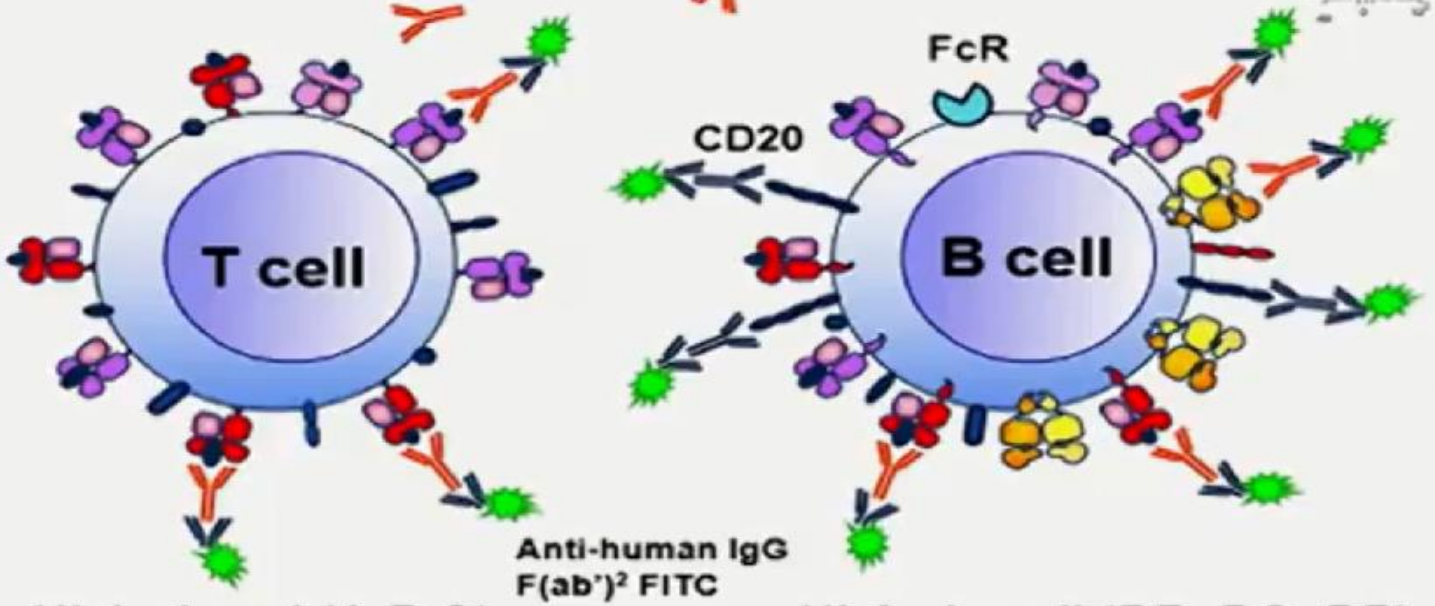


HLA class I (A,B,C)

HLA class II (DR, DQ, DP)

Flow Cytometry Crossmatch

Lymphocytes + Serum

Rituximab

HLA antibodies

Pronase

FcR

CD20

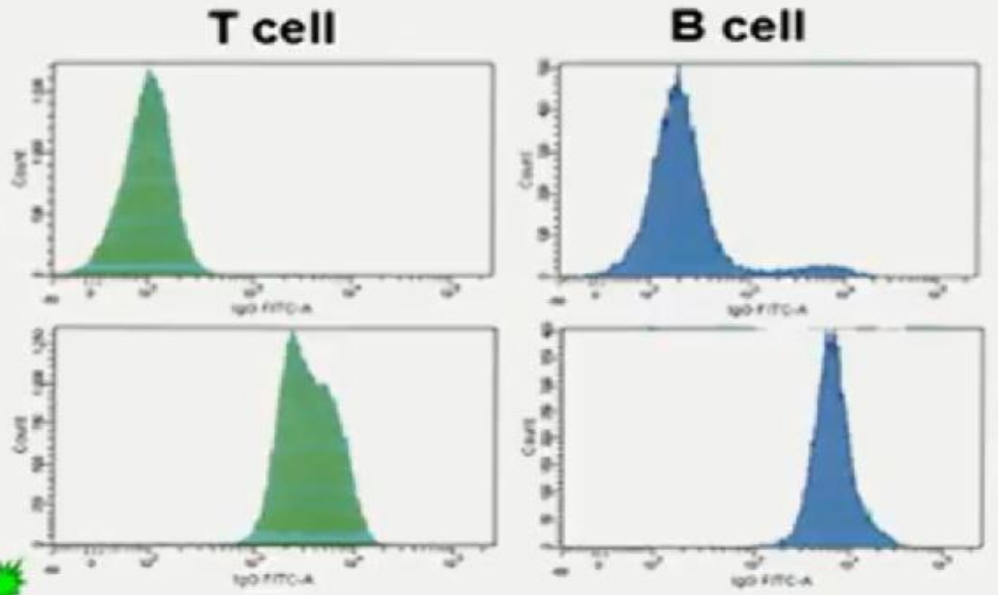
T cell

B cell

Anti-human IgG
F(ab')^2 FITC

HLA class I (A,B,C)

HLA class II (DR, DQ, DP)



T cell MCS ≥ 50
B cell MCS ≥ 120

Measure FITC intensity
by flow cytometry

Flow Crossmatch - problems

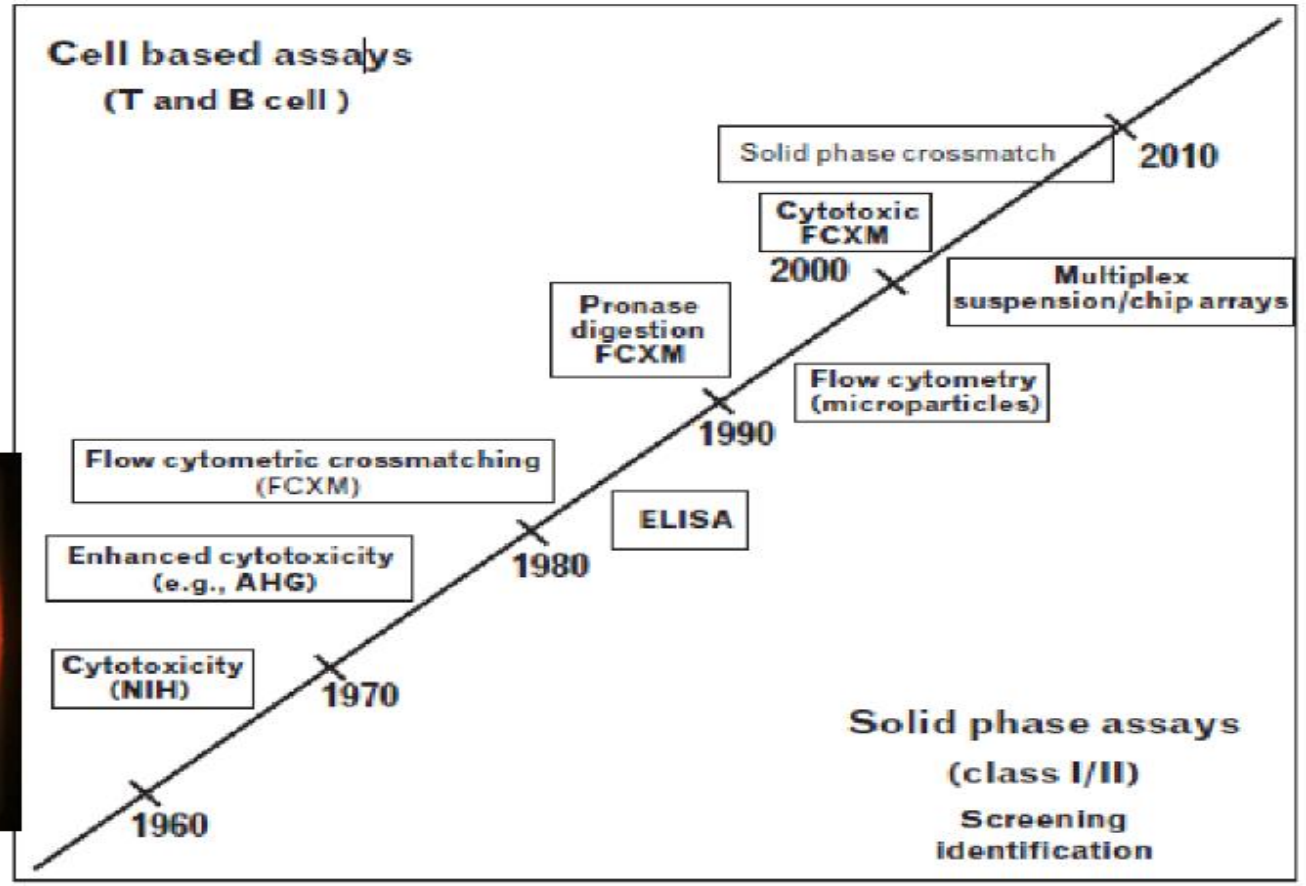
- ~8% of flow crossmatches are false positive – unneccessary exclusion
- ~7% of flow crossmatches are false negative – risk to patient

The evolution and clinical impact of Human Leukocyte Antigen technology

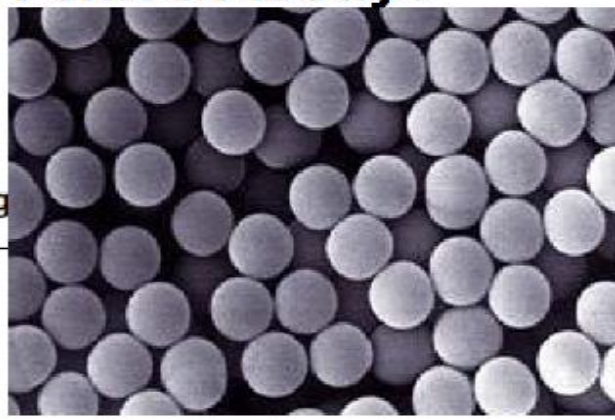
Howard M. Gebel and Robert A. Bray

Current Opinion in Nephrology and Hypertension 2010, 19:598–602

Figure 1 Evolution of human leukocyte antigen antibody testing

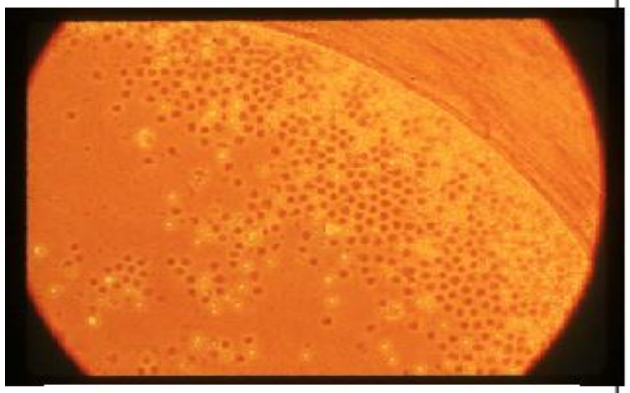


Solid Phase Assays



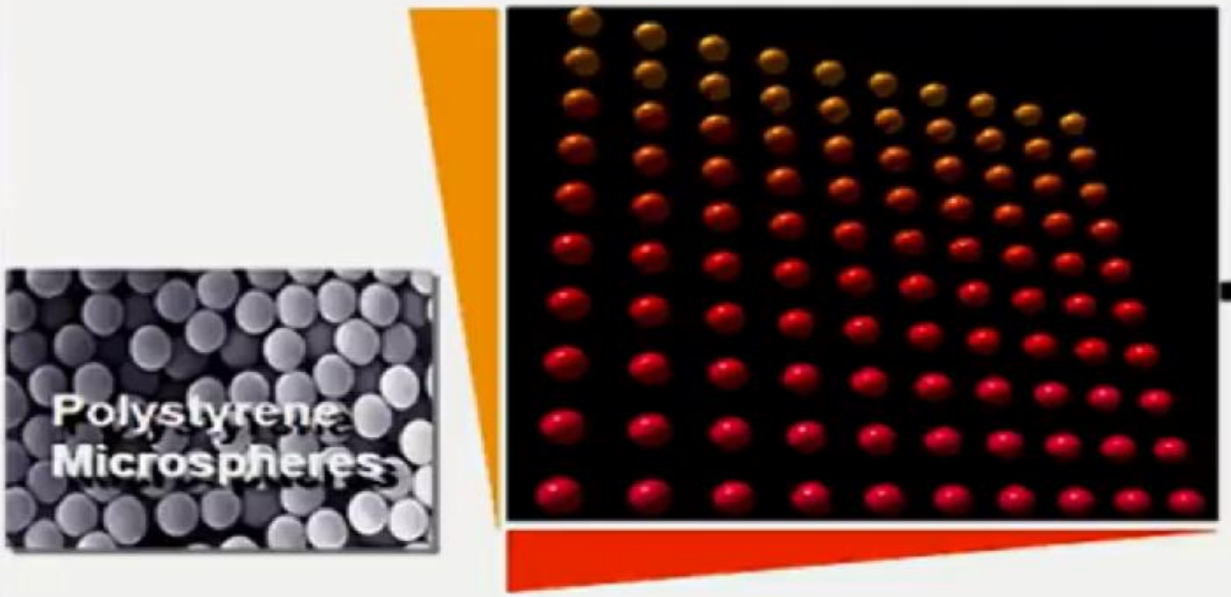
- Most sensitive
- Purified antigens
- Class I and Class II
- Molecular HLA typing

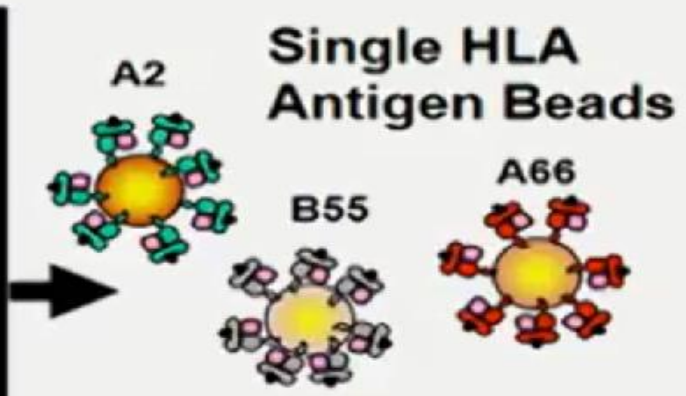
- Less sensitive
- Living cells
- T-cell (class I)
- High frequency of + B-cell XMs **NOT** due to HLA Abs

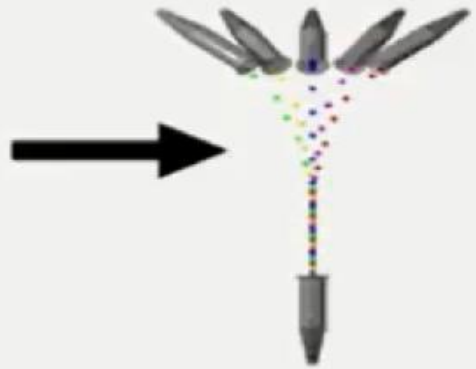


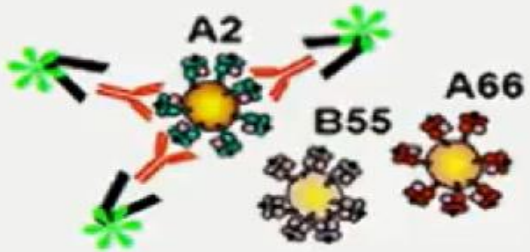
Cytotoxicity XM

Single Antigen Bead-based HLA Antibody Testing: Luminex Technology

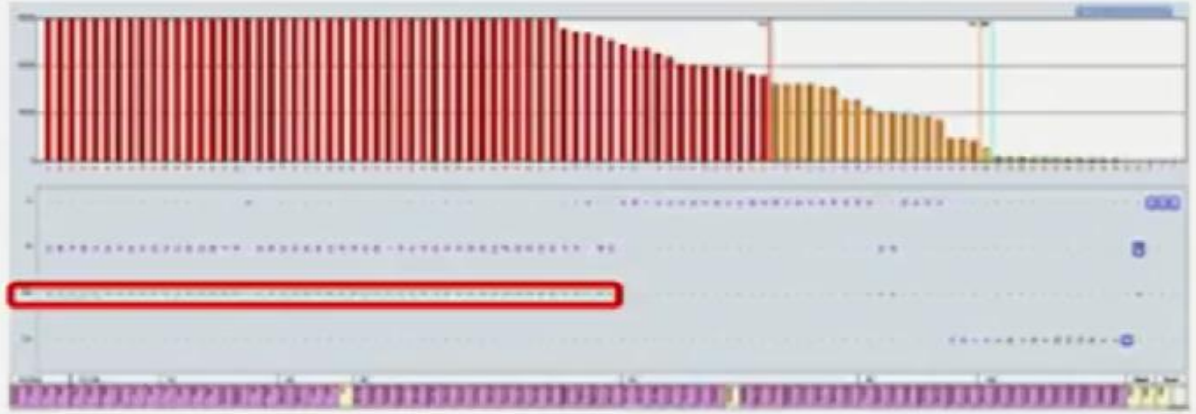








Detection & Interpretation



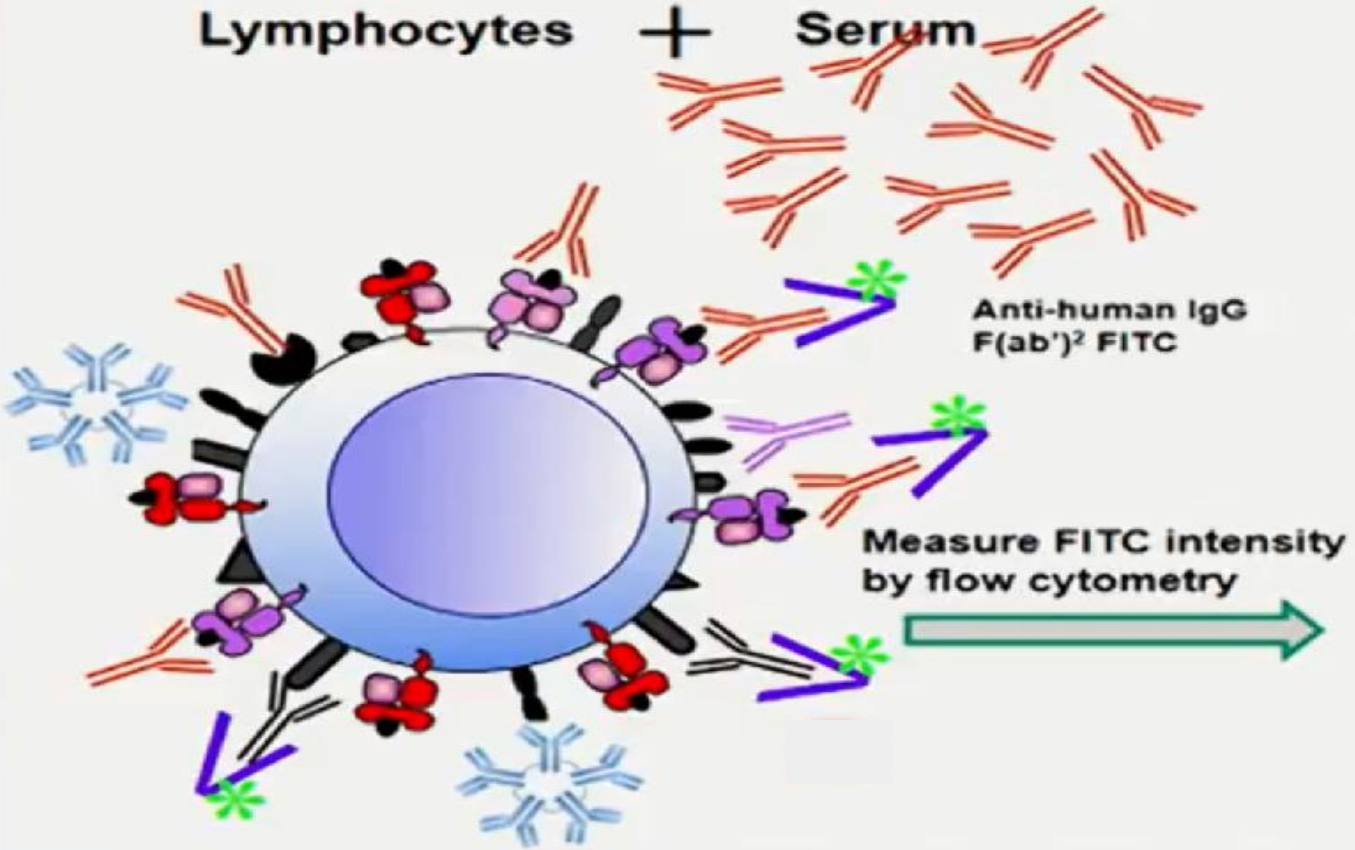
Virtual ~~Flow Cytometry~~ Crossmatch

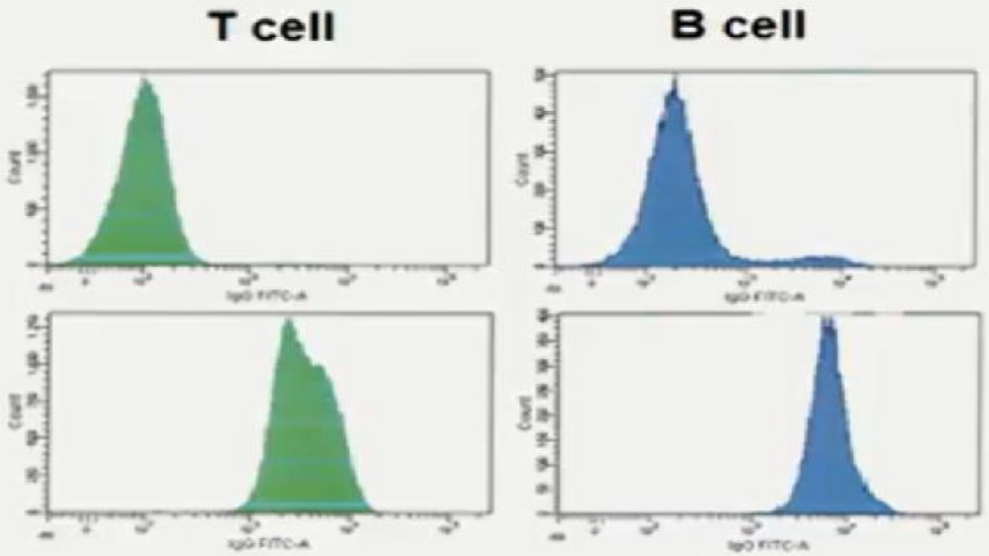
Donor

Recipient

- Median Chanel Shift (MCS) – a quantitative readout (Ag+Ab)
- Detects only IgG antibodies
- Non-specific reactivity can be reduced by Pronase digestion

Lymphocytes + Serum





T cell MCS ≥ 50
B cell MCS ≥ 120

Virtual ~~Flow Cytometry~~ Crossmatch

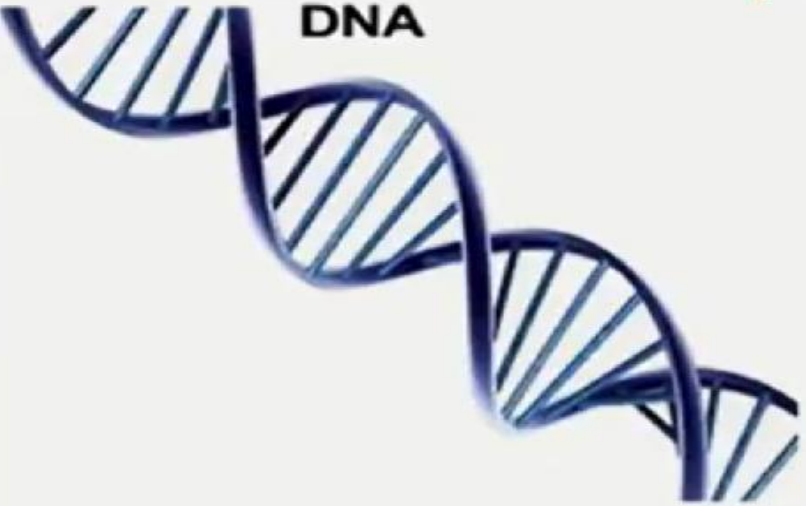
Donor

Buccal swab

Recipient

Serum

DNA

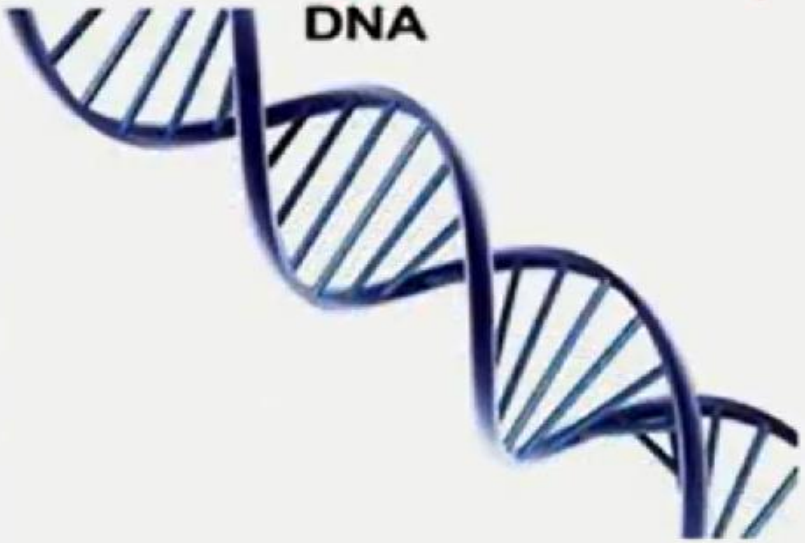


Virtual Crossmatch - Essentials

Donor

Buccal swab

DNA



Recipient

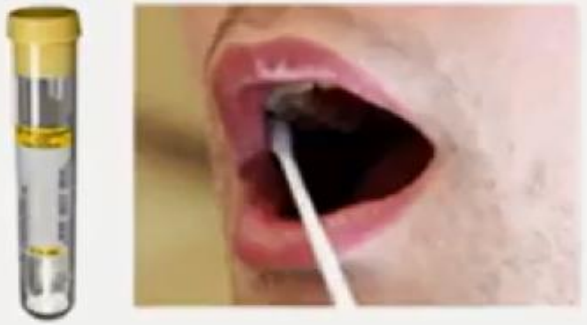
Serum

HLA Antibody Testing

HLA Typing

Virtual Crossmatch - Essentials

Donor



Buccal swab

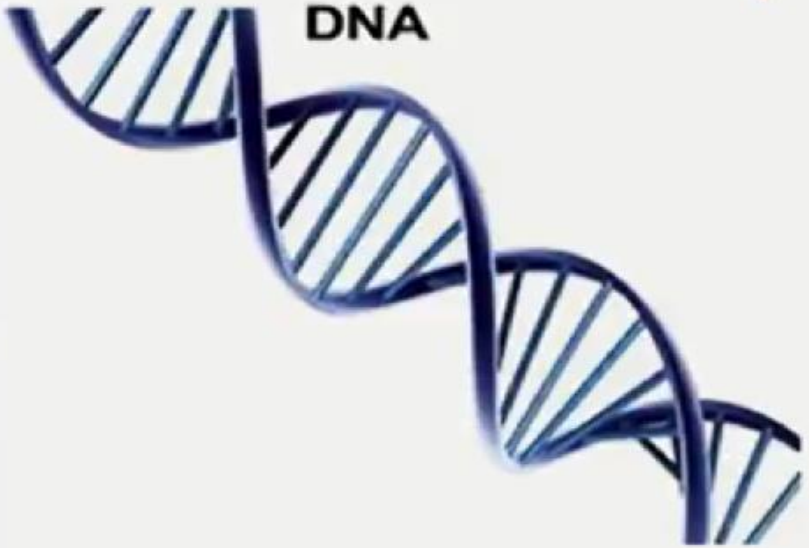
Recipient

Serum

HLA Antibody Testing

Anti HLA-A2 antibodies

DNA



HLA Typing

A2, A24, B7, B18, DR1, DR4

Virtual Crossmatch - Essentials

Donor

Buccal swab

Recipient

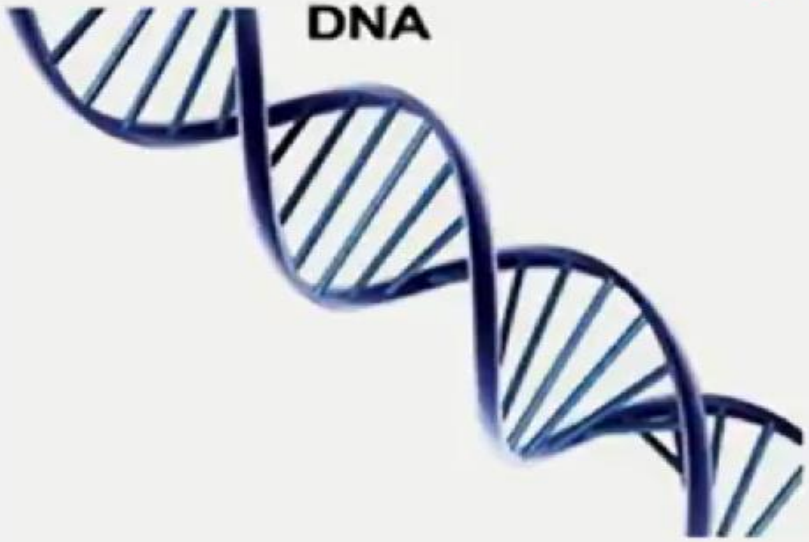
Serum

HLA Antibody Testing

Anti HLA-A2 antibodies

Virtual Crossmatch Positive

DNA



HLA Typing

A2, A24, B7, B18, DR1, DR4

Virtual Crossmatch Definition

A virtual crossmatch is an assessment of immunologic compatibility based on the recipient's alloantibody profile compared to the donor's histocompatibility antigens.

How it Works

Virtual Crossmatch = Acceptable Mismatch

Patient:

A1, A30; B7, B8 ; DR11, 15; DQ6, 7

Antibodies - DR7, DR9, DR53, DQ2

Potential Donor: complete mismatch

A25, A33; B42, B18; DR8, DR16; DQ4, DQ5

Acceptable Mismatches (AMm)

UNOS Policies

Panel Reactive Antibody (PRA)

A2 specificity:

10/30 cells positive = 33% PRA

VS

Calculated PRA (cPRA)

A2 specificity = 48% of donor pool

A2 and DR4 ?

- Assessment of HLA alloantibody via reactions with a panel of cells.
- Predominantly Class I

- Assessment of HLA alloantibody via detailed specificity determinations.
- cPRA is a calculated value based on the assigned antigens and their frequency within the donor population.

Unacceptable HLA Antigens & Virtual Crossmatch

Candidate:

anti-A2 [redacted]

Potential Donors, >12,000

A		B		DR		DQ	
1	68	8	13	4	15	2	5
2	24	7	18	1	10	5	5
2	29	13	51	8	14	4	8
23	26	49	62	1	17	2	5
2	68	39	71	15	16	5	6
1	36	7	44	9	17	4	9
69	74	55	60	4	7	7	8
3	24	18	39	1	4	4	4
11	33	51	64	15	18	5	7
24	43	27	45	4	8	4	8
2	25	39	65	9	17	4	9
2	23	44	45	13	18	7	8
1	2	8	62	4	17	4	7
2	34	57	61	11	14	2	4
66	68	27	39	4	15	8	5
3	29	35	44	1	11	7	6

Unacceptable HLA Antigens & Virtual Crossmatch

Candidate:

anti-A2 48% cPRA

Potential Donors, >12,000

A		B		DR		DQ	
1	68	8	13	4	15	2	5
2	24	7	18	1	10	5	5
2	29	13	51	8	14	4	8
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1	36	7	44	9	17	4	9
69	74	55	60	4	7	7	8
3	24	18	39	1	4	4	4
11	33	51	64	15	18	5	7
24	43	27	45	4	8	4	8
2	25	39	65	9	17	4	9
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66	68	27	39	4	15	8	5
3	29	35	44	1	11	7	6

Unacceptable HLA Antigens & Virtual Crossmatch

Candidate:

anti-A2 48% cPRA

+ anti-DR4 61% cPRA

Potential Donors, >12,000

A		B		DR		DQ	
1	68	8	13	4	15	2	5
2	24	7	18	1	10	5	5
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66	68	27	39	4	15	8	5
3	29	35	44	1	11	7	6

Unacceptable HLA Antigens & Virtual Crossmatch

Candidate:

anti-A2 48% cPRA

+ anti-DR4 61% cPRA

+ anti-DQ5 76 % cPRA

Potential Donors, >12,000

A		B		DR		DQ	
1	68	8	13	4	15	2	5
2	24	7	18	1	10	5	5
2	29	13	51	8	14	4	8
23	26	49	62	1	17	2	5
2	68	39	71	15	16	5	6
1	36	7	44	9	17	4	9
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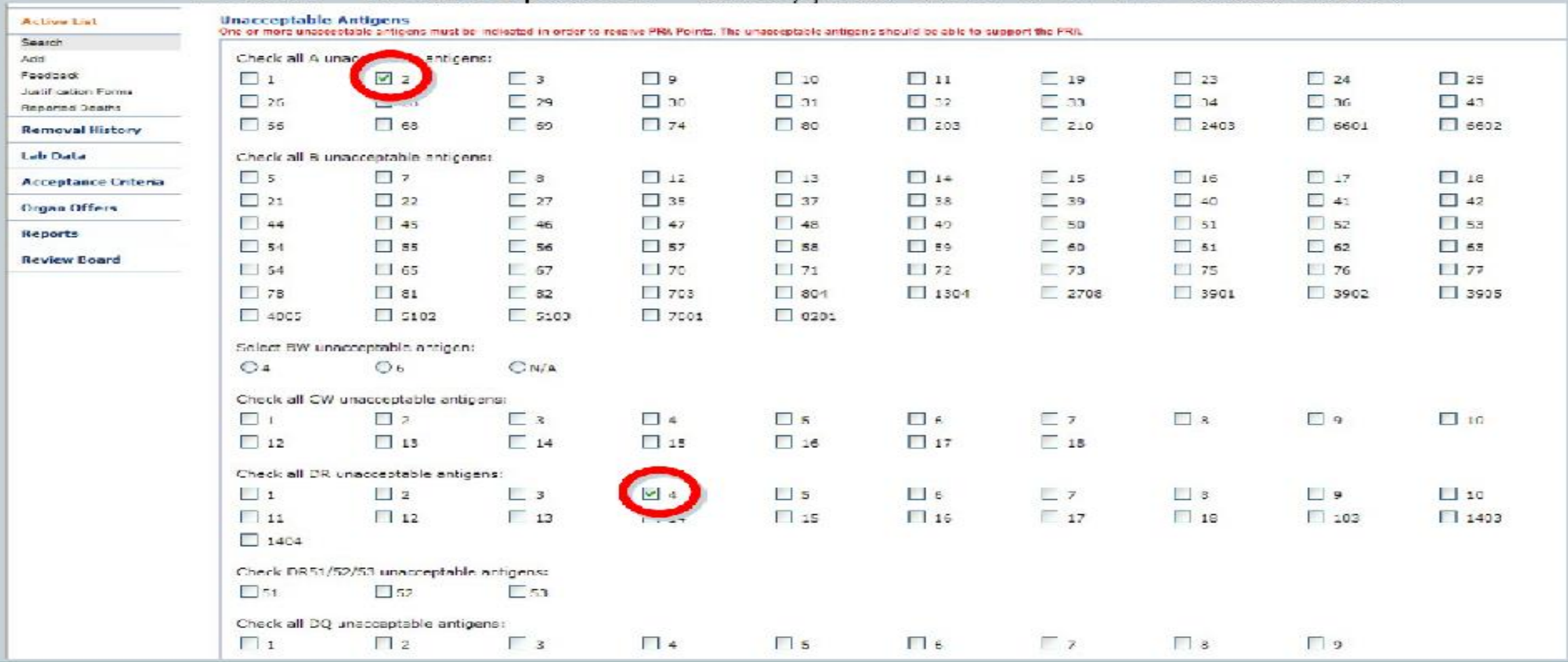
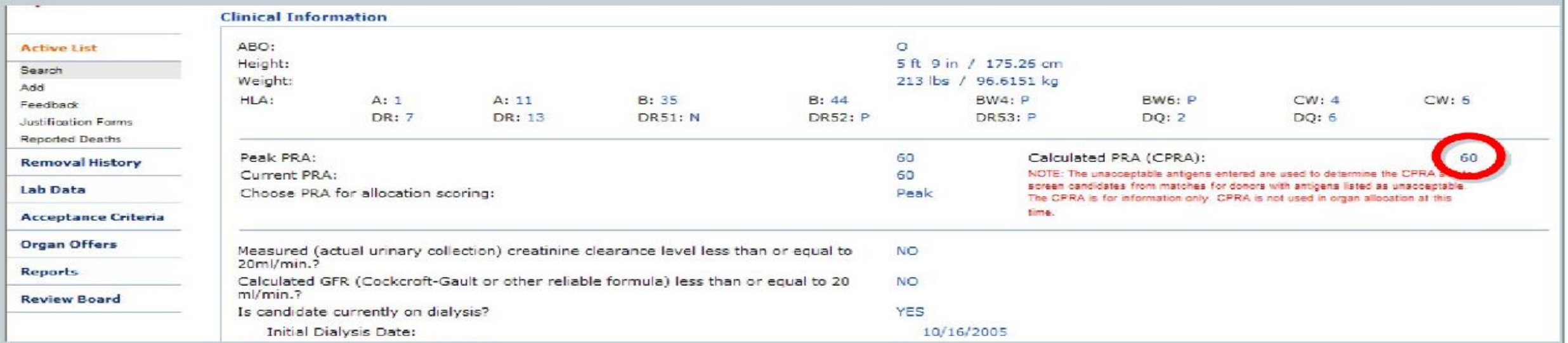
2	34	57	61	11	14	2	4
66	68	27	39	4	15	8	5
3	29	35	44	1	11	7	6

UNET – Calculated PRA

Enter "unacceptable" antigens into UNOS database.



cPRA



Clinical Information

Active List
Search
Add
Feedback
Justification Forms
Reported Deaths
Removal History
Lab Data
Acceptance Criteria
Organ Offers
Reports
Review Board

ABO:				O				
Height:				5 ft 9 in / 175.25 cm				
Weight:				213 lbs / 96.6151 kg				
HLA:	A: 1	A: 11	B: 35	B: 44	BW4: P	BW6: P	CW: 4	CW: 6
	DR: 7	DR: 13	DR51: N	DR52: P	DR53: P	DQ: 2	DQ: 6	

Peak PRA:	60	Calculated PRA (CPRA):	60
Current PRA:	60	NOTE: The unacceptable antigens entered are used to determine the CPRA s... screen candidates from matches for donors with antigens listed as unacceptable. The CPRA is for information only. CPRA is not used in organ allocation at this time.	
Choose PRA for allocation scoring:	Peak		

Measured (actual urinary collection) creatinine clearance level less than or equal to 20ml/min.?	NO
Calculated GFR (Cockcroft-Gault or other reliable formula) less than or equal to 20 ml/min.?	NO
Is candidate currently on dialysis?	YES
Initial Dialysis Date:	10/16/2005

This patient would be expected to have a positive crossmatch with **60%** of the UNOS deceased donors.

Donors with "unacceptable antigens" are <u>excluded</u> from kidney match runs.

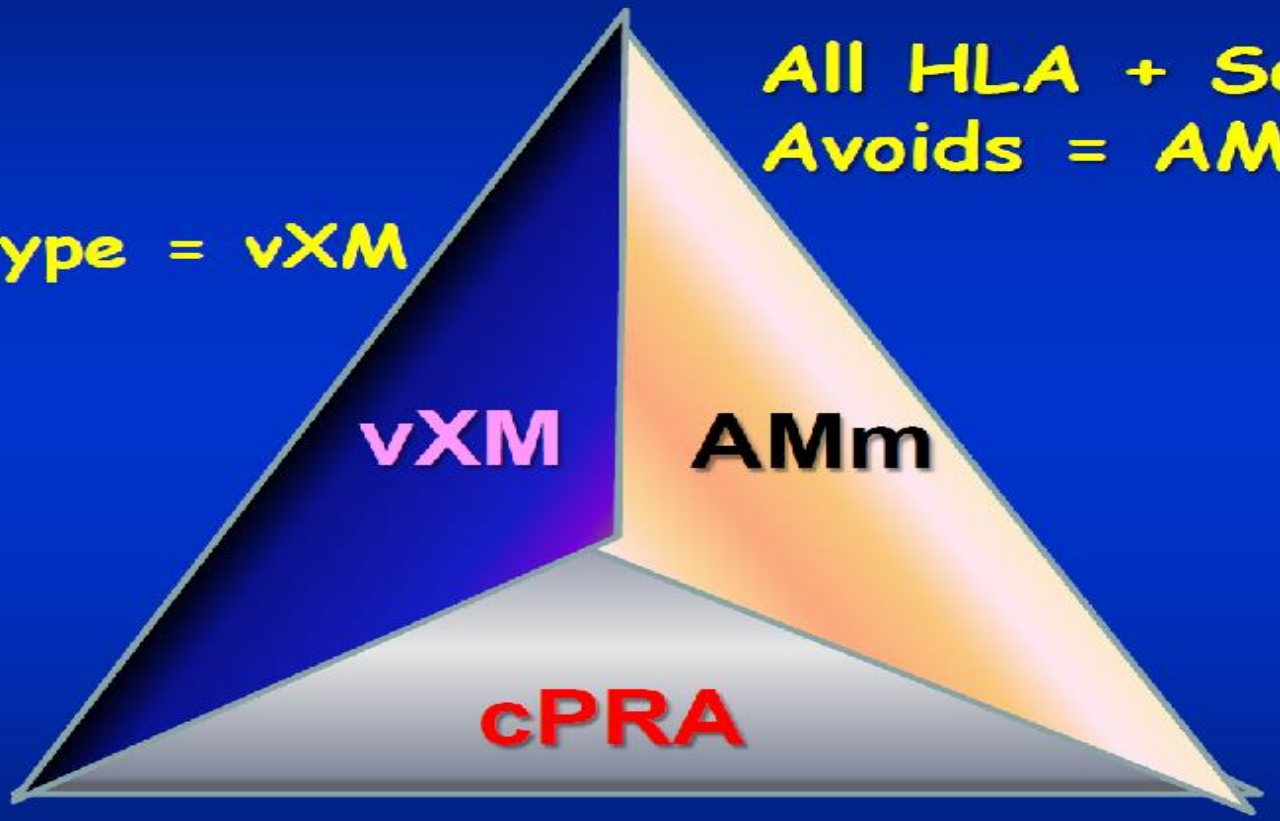
Relationship between vXM, cPRA and AMm

cPRA

$\int$ Donor phenotype = vXM

AMm

All HLA + Self HLA Ags – Avoids = AMms



Avoid Ags = cPRA

Crossmatch Methods

Crossmatch method	Sensitivity	Specificity	Cost (US $)	Turnaround time
CDC	Low	Low	600	3.5 hours
Flow	Intermediate	Intermediate	600	5 hours
Pronase	>Intermediate	>intermediate	600	6.5 hours
Virtual	100%	100%	0	10 min

Virtual Crossmatch - Advantages

- Eliminates the physical crossmatch
  - Saves 4-6 hours – cut downs cold ischemic time
  - No samples required
  - Reduces laboratory & OPO workload
  - Reduces laboratory, OPO, and Tx program cost
- Adds precision to actual crossmatch
  - CDC/flow XM prediction
  - DSA identification
- Improves allocation efficiency
- Increased rate of transplantation for sensitized patients

What are the potential benefits of virtual crossmatches for patients?

- Less time needed for evaluation of compatibility; results in more efficient use of the system
- **Reduced cold ischemia time**
- Facilitates matching over larger geographic area, renal paired donations, and the transplantation of more highly sensitized pts
- **Can result in improved access for sensitized patients**
- **Increased sensitivity and specificity of testing can lead to a better matched donor/recipient**

What are the potential benefits of virtual crossmatches for patients? -cont'd

- More specific than serologic crossmatch
- Less likely to deny access for a false positive physical crossmatch
- Reduced cost
- Does not preclude the performance of a physical XM; however, this may be completed concurrent with or after transplantation
- **Aids in risk assessment for patient desensitization needs**

Potential Benefits-cont'd

Laboratories?

- Increased efficiency, which allows for more focus on patients with problems and results in cost savings
- **Decreased on-call time expenditure by testing personnel**
- Allows for better coordination and communication with transplant programs
- Improved quality management with better patient and transplant program satisfaction

Potential Benefits-cont'd

Transplant programs?

- **Reduced ischemia time**
- Improved access to transplantation for immunologically and geographically disadvantaged candidates, which results in improved transplant physician and patient satisfaction
- Fewer unexpectedly positive physical crossmatches leads to more efficient use of transplant personnel
- Improved risk assessment for rejection
- **Allows for optimized immunosuppression and desensitization protocols**
- Flexibility in managing transplant related logistics (i.e. OR schedules)
- Cost savings

Potential Disadvantages of Virtual Crossmatches

What are the potential disadvantages of virtual crossmatches to:

patients?

- Based on the program's criteria for crossmatches, there is potential to deny use of a donor organ that could be successfully transplanted
- Requires patient to receive and understand more complicated information
- Negative crossmatch (physical or virtual) does not guarantee compatibility

laboratories?

- Potentially more difficult for staff to maintain competency in performing physical crossmatches when they are done less frequently
- Increased unreimbursed interpretation time
- Requires more coordination with transplant program

transplant programs?

- Program staff have to learn a new interpretive vocabulary
- Additional time and work to ensure that patients understand their risk and get all the information on time

others?

- No reimbursement for time/effort of professional rendering a virtual crossmatch

Most 100% CPRA candidates are sensitized to large number of HLA antigens

100% CPRA

Candidate#1:

DR :4 7 8 11 12 13 14 15 16 17 18 103
DRw:51 52
DQ :6 7 8 9

100% CPRA

Candidate#2:

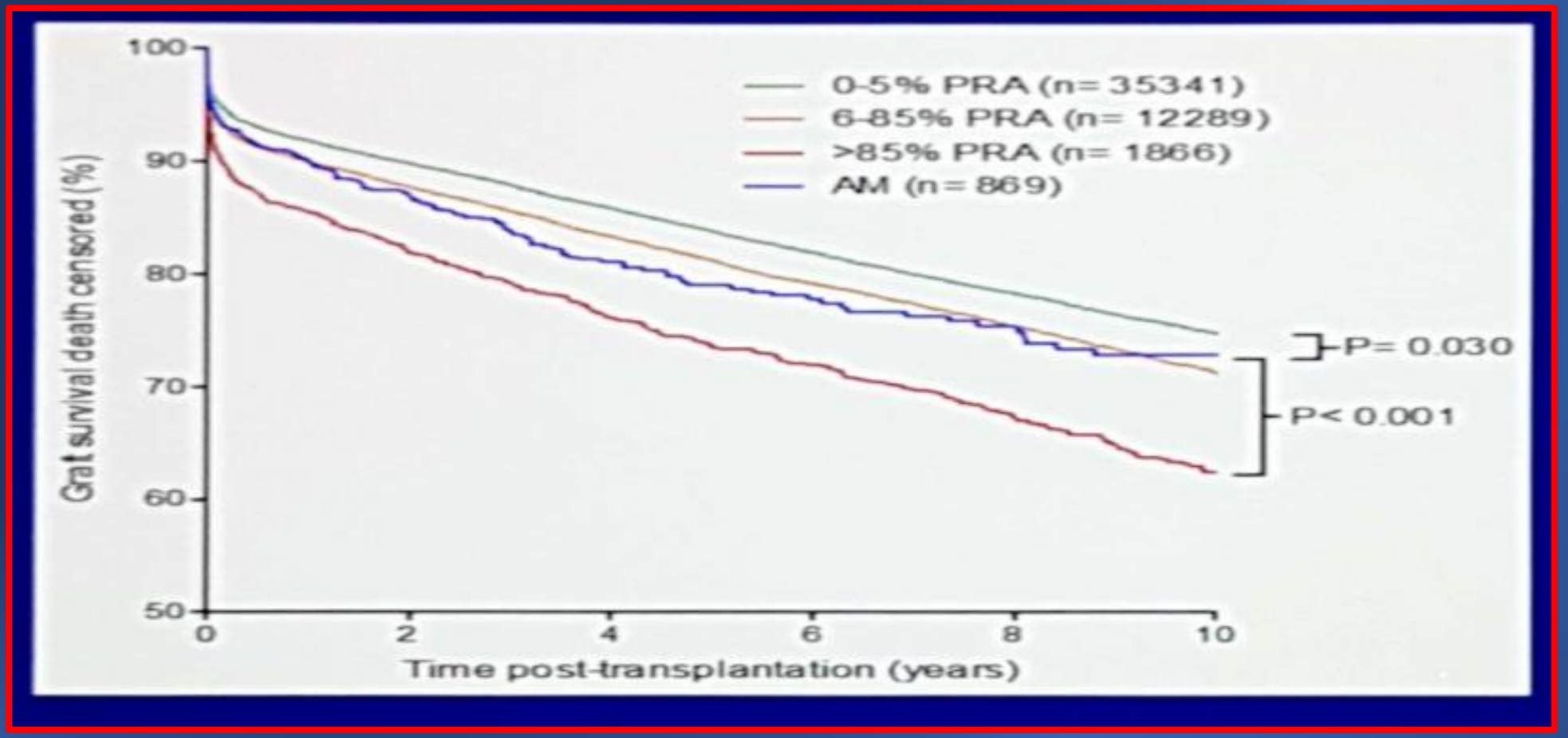
A :1 2 11 24 25 26 29 30 31 32 33 34 36 43 66 68 69 74
B :13 18 27 37 38 39 41 42 44 45 46 47 49 51 52 53 54 55 56 57 58 59 61 62 63 64 65 67 7 71 72 73 75 76 77 78 8 81 82
Cw :1 2 5 7 8 9 10 12 14 15 16 18
DR :1 4 7 8 9 10 11 12 13 15 16 103 14:02
DR :51 53
DQ :4 6 7 8 9
DQA:02 03
DP :2 3 6 9 10 14 17 18 20 28 04:02

Options for highly sensitized patients

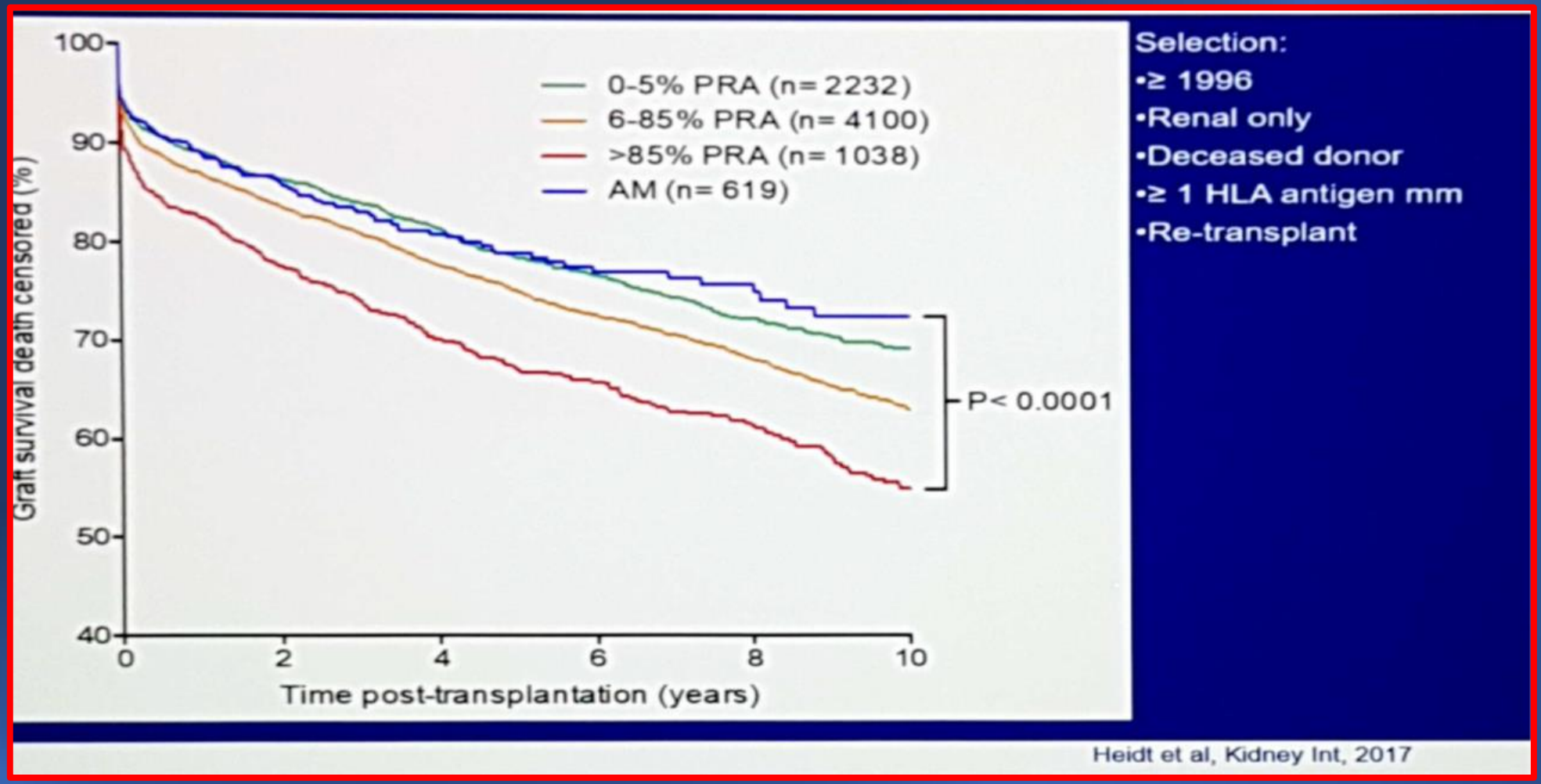
- Transplantation with an HLA identical or compatible donor.
- Do not accept that the patient is sensitized to the donor and try to remove the antibodies (desensitization).
- Accept that the patient is sensitized and try to facilitate allocation of crossmatch negative donor kidneys i.e. paired kidney transplantation.

Inclusion in the AM program increases the chance to receive a transplant

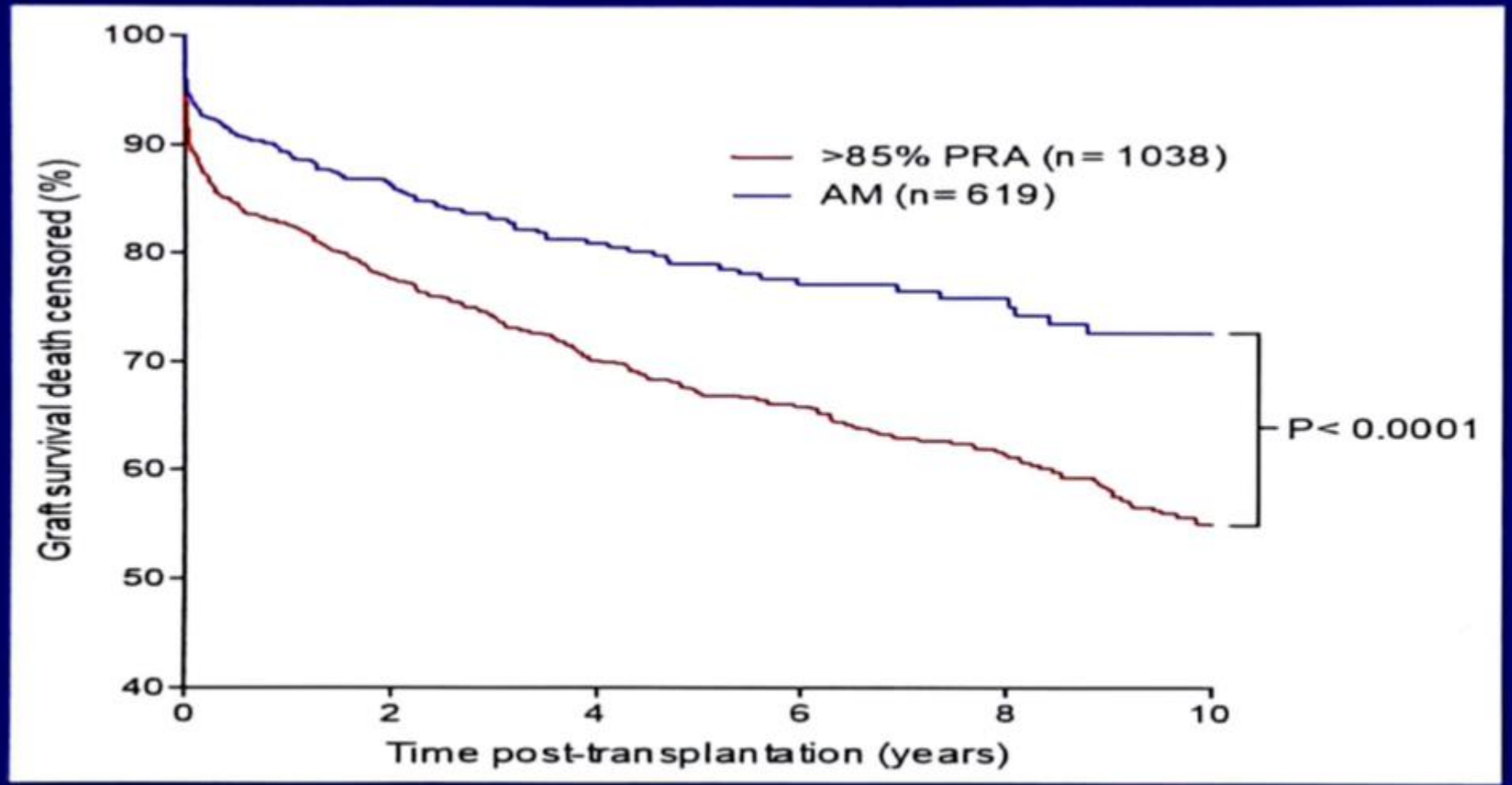
Graft survival compared to patients transplanted via standard ET-KAS



Graft survival in re-transplant recipients



Positive identification of acceptable mismatches leads to a better graft survival than avoidance of unacceptable mismatches



Selection:
- ≥ 1996
- Renal only
- Deceased donor
- ≥ 1 HLA antigen mm
- Re-transplant

Heidt et al. Kidney Int. 2017

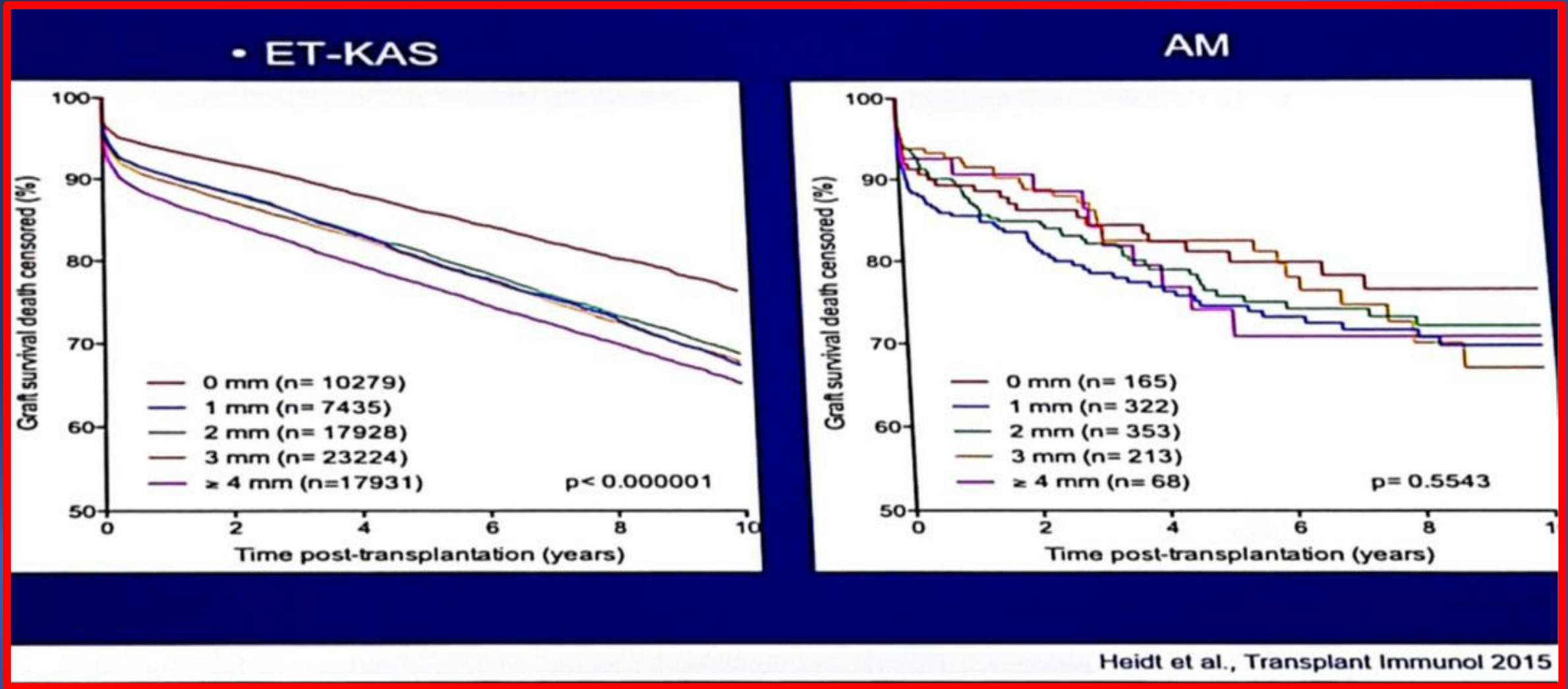
Highly sensitized patients within ET benefit from transplantation via AM program

Multivariate analysis (Cox regression)

			95% C.I.		
		HR	Lower	Upper	P-Value
A-B-DR mm	1,2,3 (ref) 4,5,6	1.32	1.047	1.671	0.019
Tx Period	1996-2005 (ref) 2006-2015	0.64	0.522	0.790	<0.001
Donor sex	Female (ref) Male	0.82	0.682	0.987	0.036
Recipient age	≤ 50 (ref) > 50	0.79	0.640	0.971	0.025
Donor age	≤ 50 (ref) > 50	1.73	1.438	2.090	<0.001
Tx via AM	No (ref) Yes	0.72	0.576	0.903	0.004

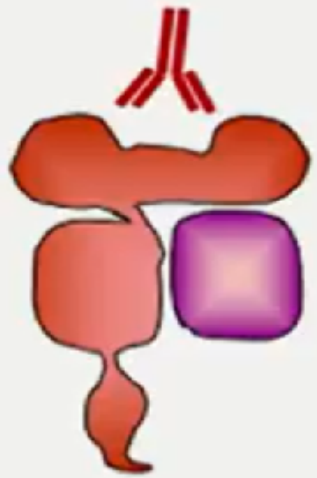
Heidt et al. Kidney Int. 2017

In contrast to ET-KAS allocation, no HLA match effect in acceptable mismatch (AM) transplant



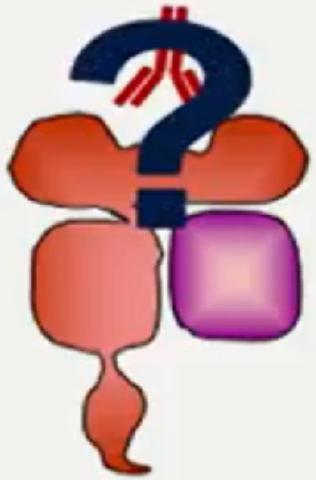
Heidt et al., Transplant Immunol 2015

Antibody Basics: Epitopes (antibody binding motif)



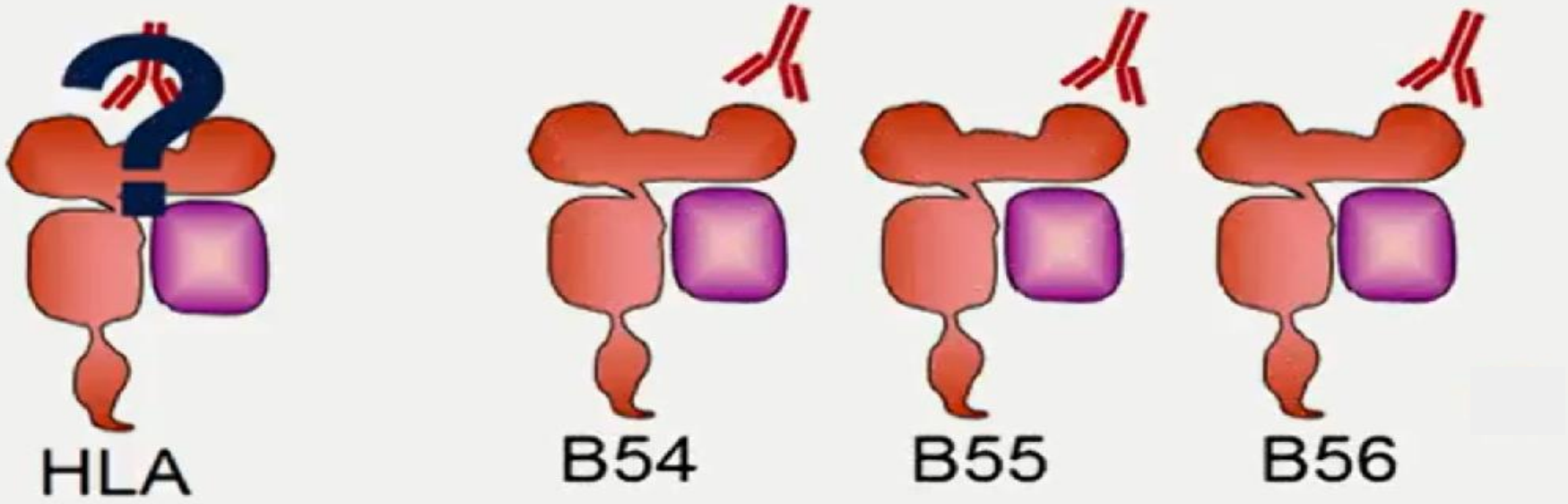
HLA

Antibody Basics: Epitopes (antibody binding motif)

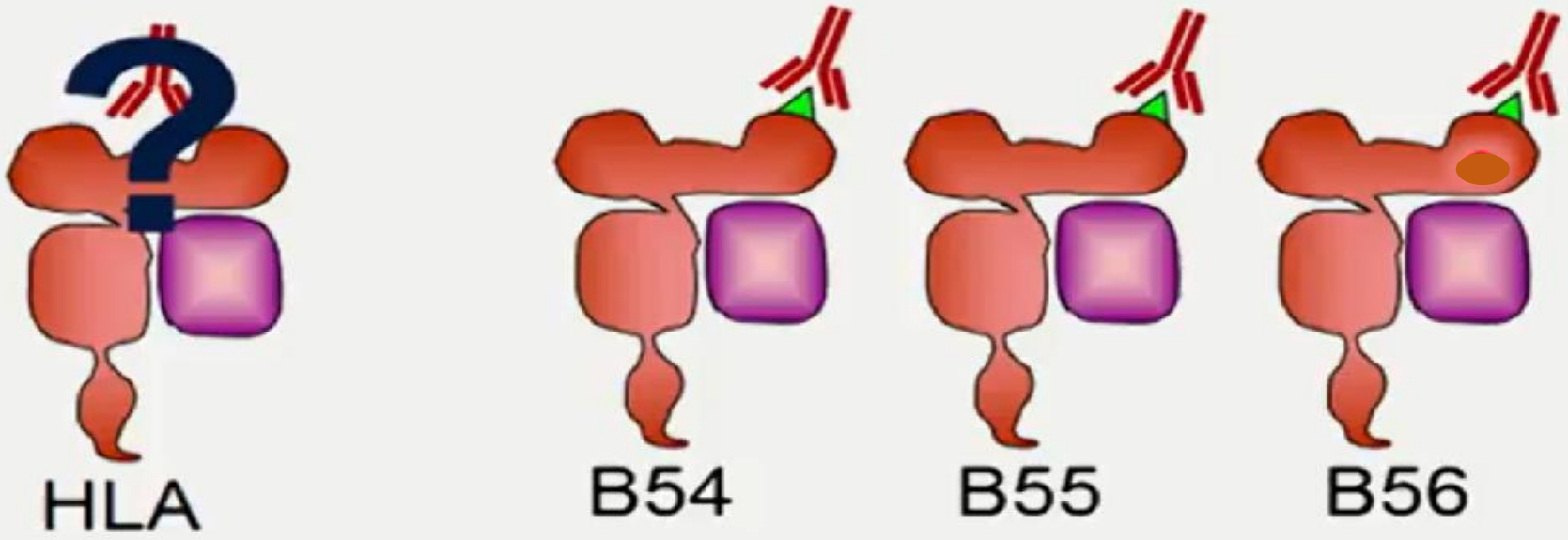


HLA

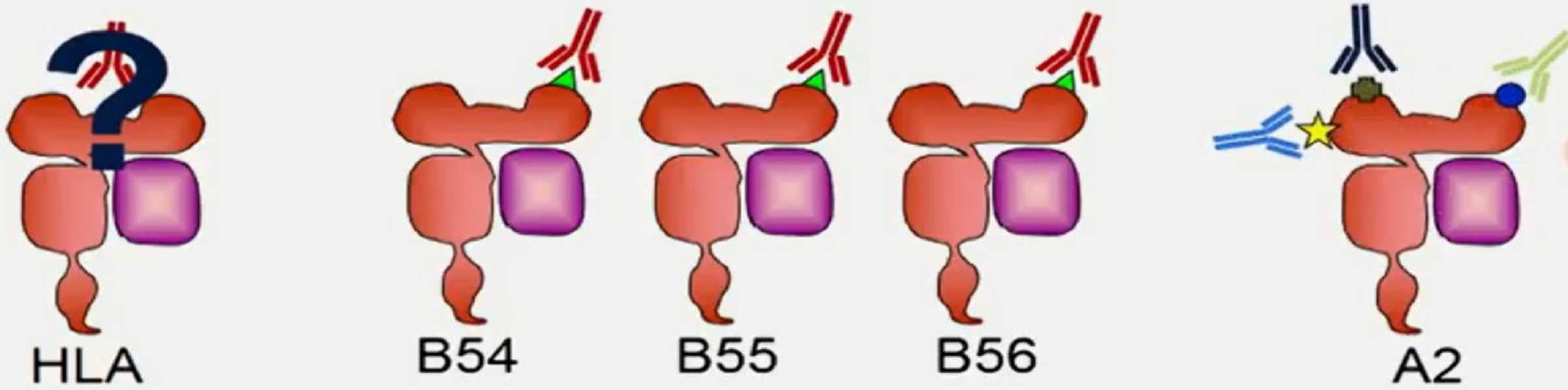
Antibody Basics: Epitopes (antibody binding motif)



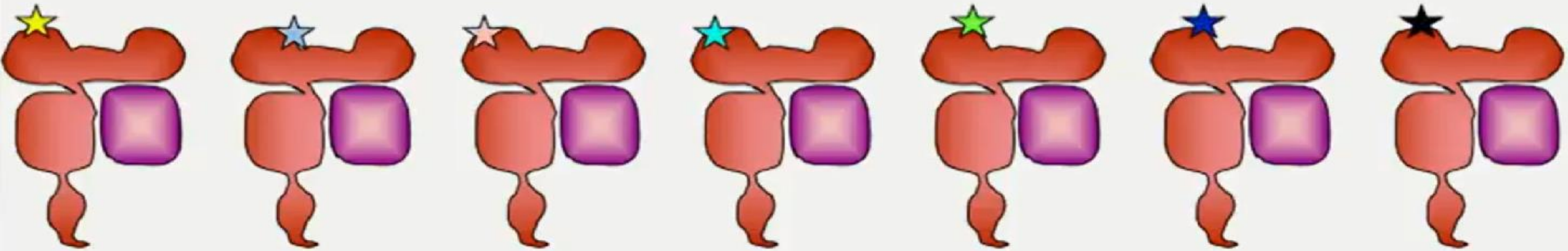
One antibody can bind to multiple HLA molecules



One HLA has multiple antibody targets



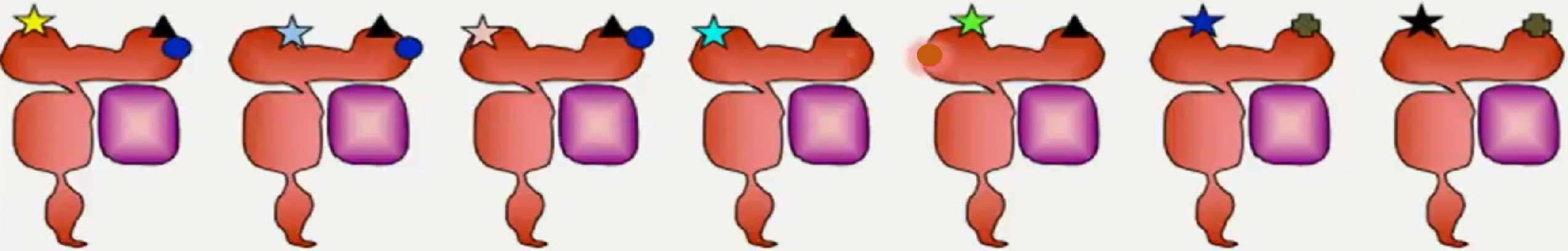
Public and Private Epitopes (antigenic determinants)



A2 A68 A69 B57 B58 A1 A36

Private Epitopes

Public and Private Epitopes (antigenic determinants)

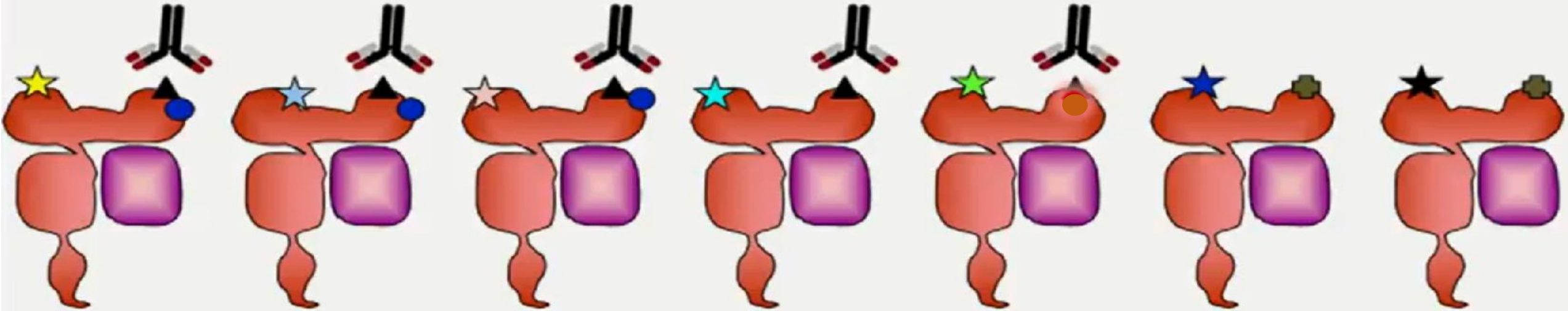


A2 A68 A69 B57 B58 A1 A36

Public Epitopes

Private Epitopes

Public and Private Epitopes (antigenic determinants)



A2 A68 A69 B57 B58 A1 A36

Public Epitopes

Private Epitopes

Cross-REactive Groups (CREG)

CREG	HLA Specificities	CPRA
A1	A1,A3,A11,A23,A24,A29,A30,A31,A36,A80	78%
A2	A2,A23,A24,A68,A69,B57,B58	75%
A10	A11,A25,A26,A32,A33,A34,A43,A66,A68, A69, A74	40%
Bw4	A23,A24,A25,A32,B13,B27,B37,B44,B47,B38,B49,B51,B52,B53,B57,B58,B59,B63,B77	74%
B5	B18,B35,B46,B49,B50,B51,B52,B53,B57, B58, B62,B63,B71,B72,B73,B75,B76,B77,B78	63%
Bw6	B7,B8,B18,B27:08, B35, B39,B40,B4005, B41,B42,B45,B48,B50,B54, B55,B56,B60,B61,B62,B64,B65,B67,B70,B71,B72, B75,B76,B78,B81,B82	85%
B7	B7,B8,B13,B27,B41,B42,B47,B48,B54,B55,B56,B59,B60,B61,B67,B81,B82	59%
B8	B8,B18,B38,B39,B59,B64,B65,B67	36%
B12	B13,B37,B41,B44,B45,B47,B49,B50,B60,B61	48%
C1	Cw1,Cw7,Cw8,Cw9,Cw10,Cw12,Cw14,Cw16,B46,B73	77%
C2	Cw2,Cw4,Cw5,Cw6,Cw15,Cw17,Cw18	66%
DR1	DR1,DR10,DR103	21%
DR51	DR51,DR15,DR16	29%
DR52	DR52,DR11,DR12,DR13,DR14,DR17,DR18	62%
DR53	DR53,DR4,DR7,DR9	50%
DQ1	DQ5,DQ6	64%
DQ2	DQ2	37%
DQ3	DQ7,DQ8,DQ9	56%
DQ4	DQ4	10%
DP1c*	DP2,DP3,DP4,DP6,DP9,DP10,DP11,DP14,DP17,DP18.DP20,DP28	----
DP2c*	DP1,DP5,DP13,DP15,DP19,DP23	----

*DP-specific antibodies that are shown to occur frequently together in UCSF waitlist population

Women alloimmunized by Bw6 motif can make antibodies to 2/3 of HLA-B types

Spouse HLA

A2-B61(Bw6)-DR4
A2-B39(Bw6)-DR4

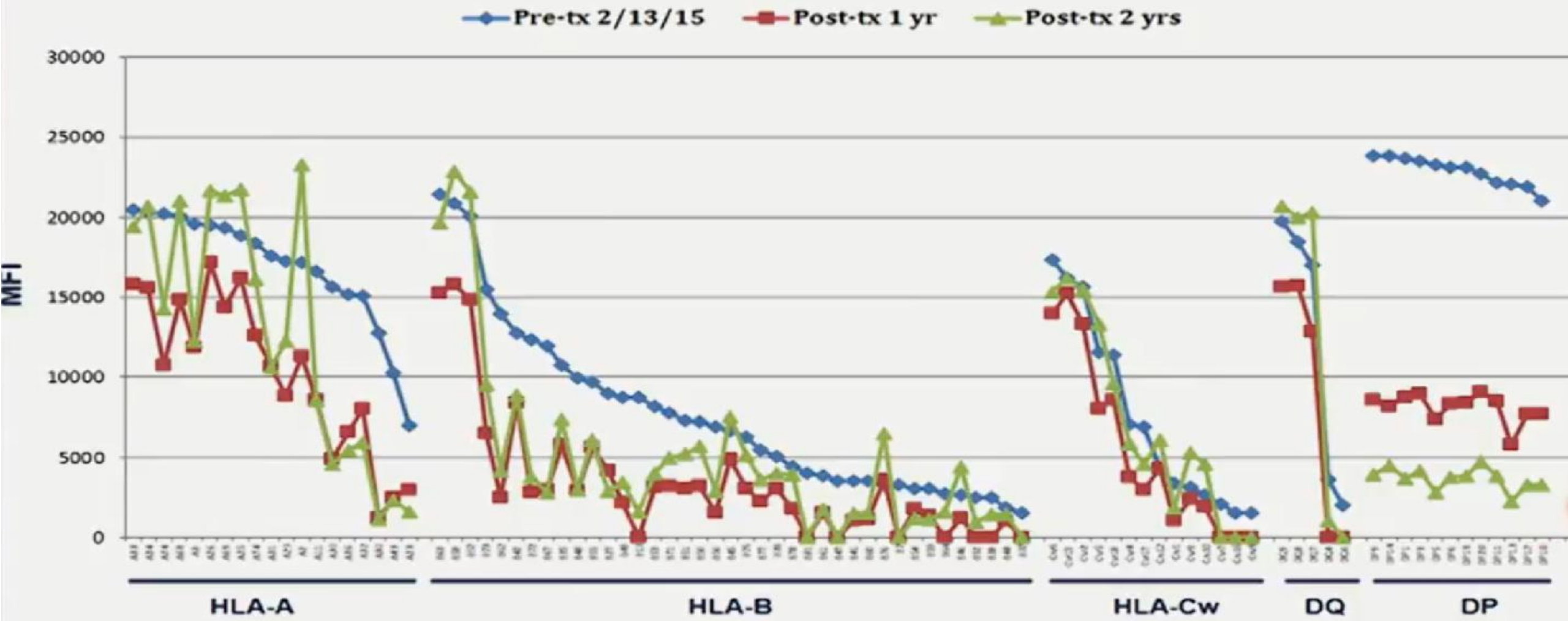
Self HLA

A2-B44(Bw4)-DR4
A2-B52(Bw4)-DR4

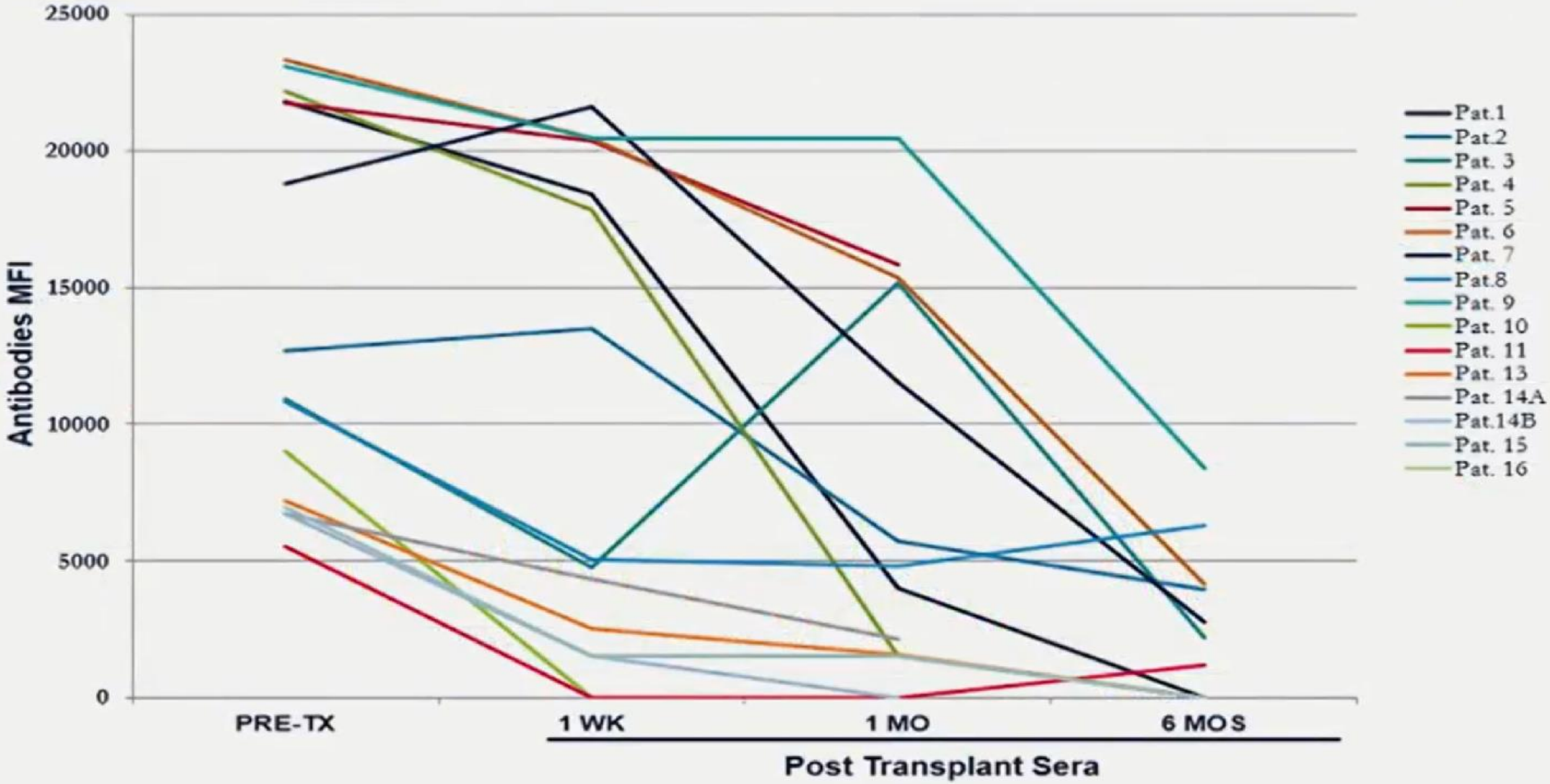
B7, B8, B14, B18, B22,
B35, B39, B40, B4005,
B41, B42, B45, B46, B48,
B50, B54, B55, B56, B60,
B61, B62, B64, B65, B67,
B70, B71, B72, B73, B75,
B76, B78, B81, B82

CPRA=85%

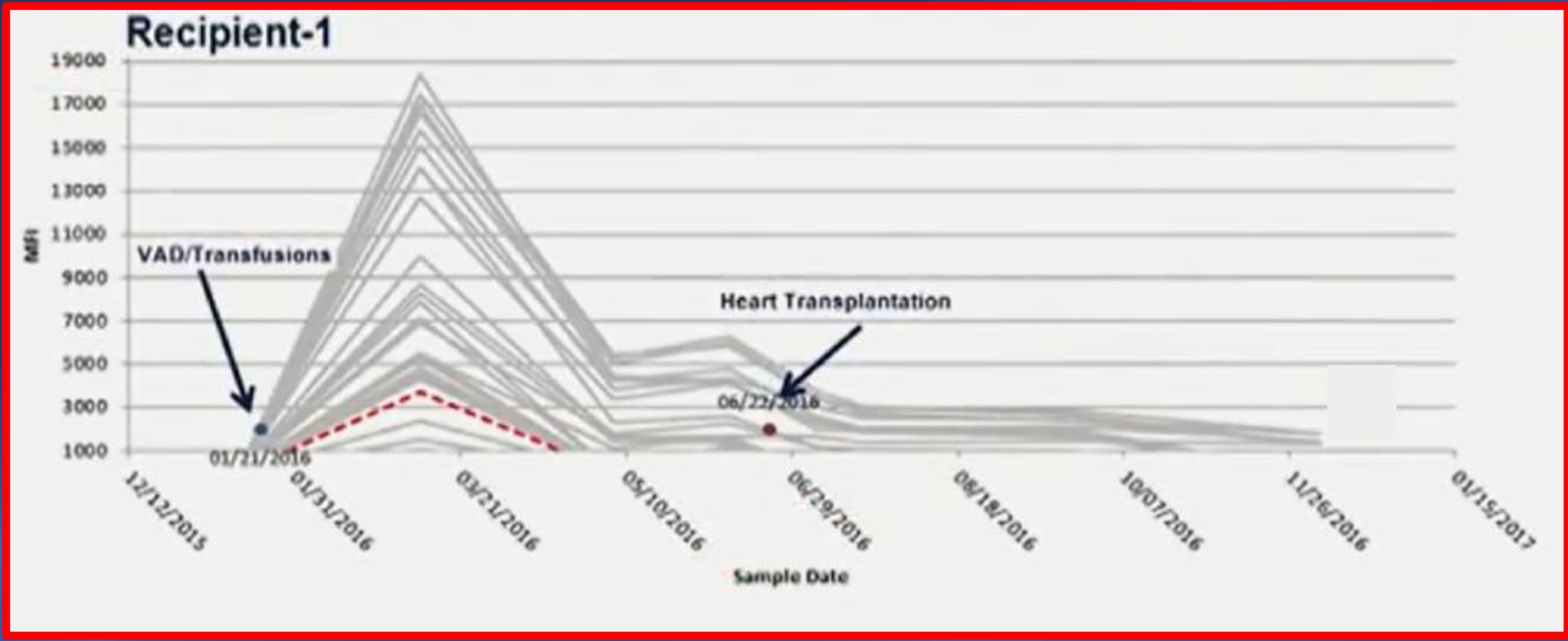
IVIG suppress HLA-DP antibodies more efficiently than the other HLA antibodies



IVIG suppress HLA-DP DSAs more efficiently in kidney transplant recipients



Transfusion-induced HLA antibodies are not stable, and do not rebound following heart transplantation



HLA Antibodies - Consideration

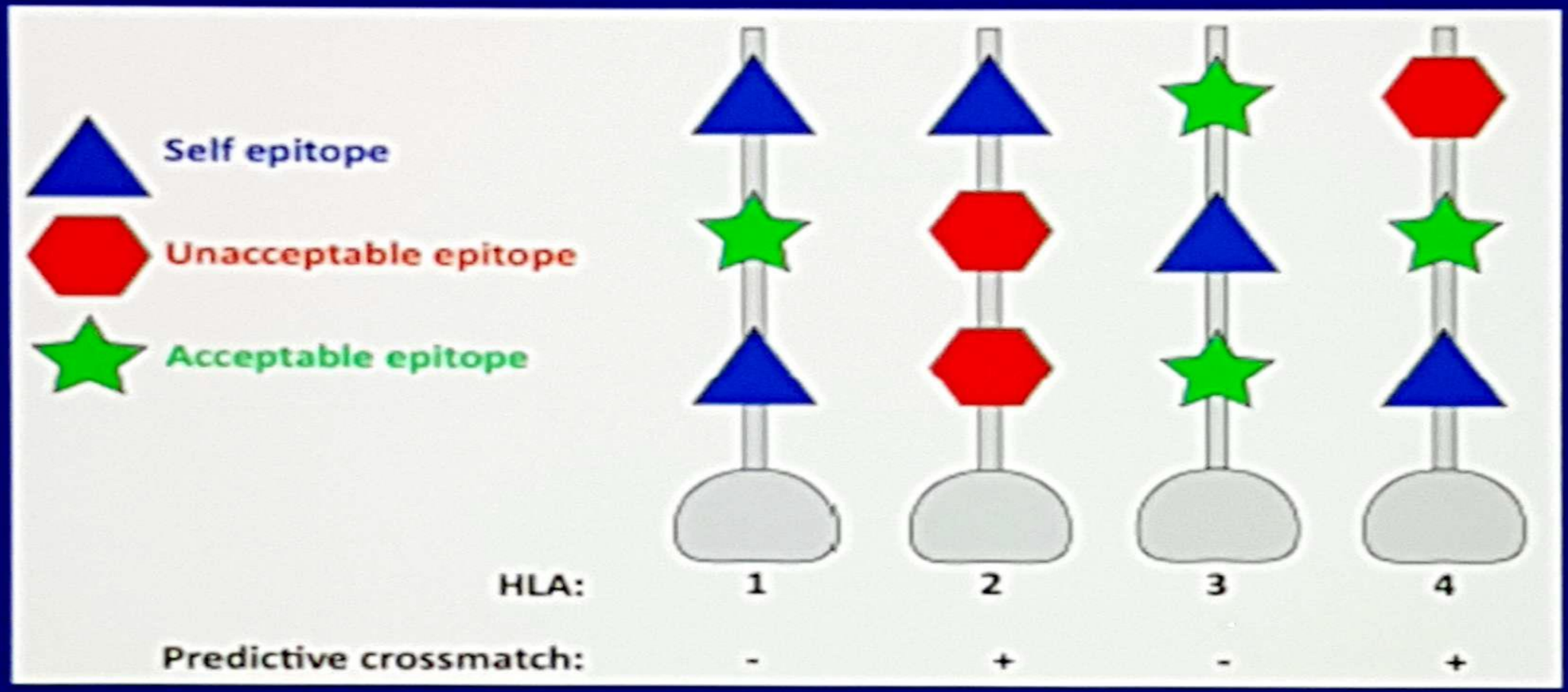
- Pts make antibodies due to prior transplant, pregnancies and transfusions
- HLA antibodies are generally reactive to multiple antigens (CREG)
- Candidates with multiple CREG Abs are hard to find a compatible donor
- HLA-DQ, DR53C, A2C antibodies are more frequent and strong, and thus most immunogenic – hard to remove; should be considered for matching
- HLA-C and DP Abs with MFI<5000 do not cause positive crossmatch
- DP antibodies are less pathogenic and amenable by IVIg
- Transfusion-induced HLA antibodies are transient, and do not rebound following transplantation

Can we do a virtual crossmatch

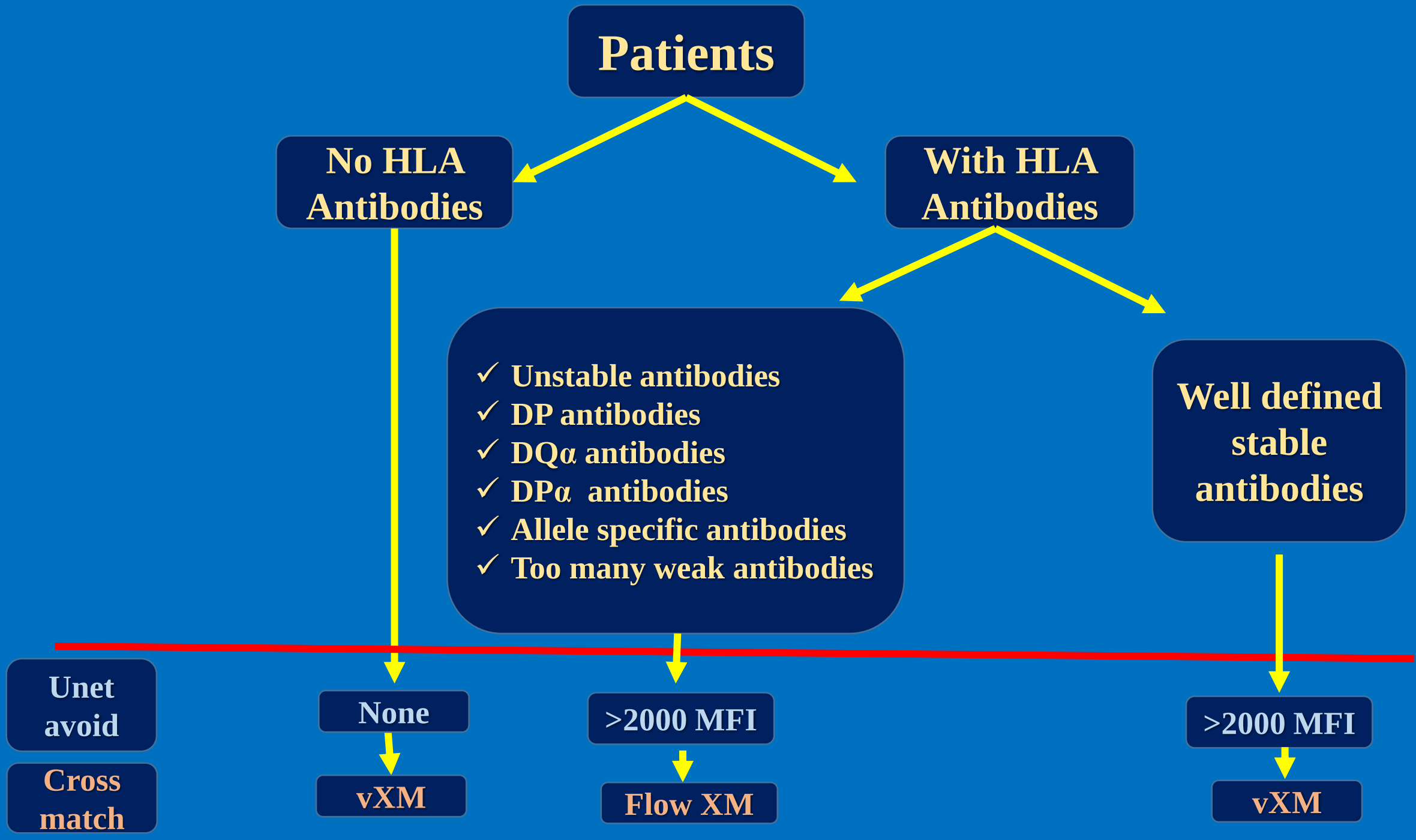
We are doing it now
(But not well…)


Thank you
all for
your
attention

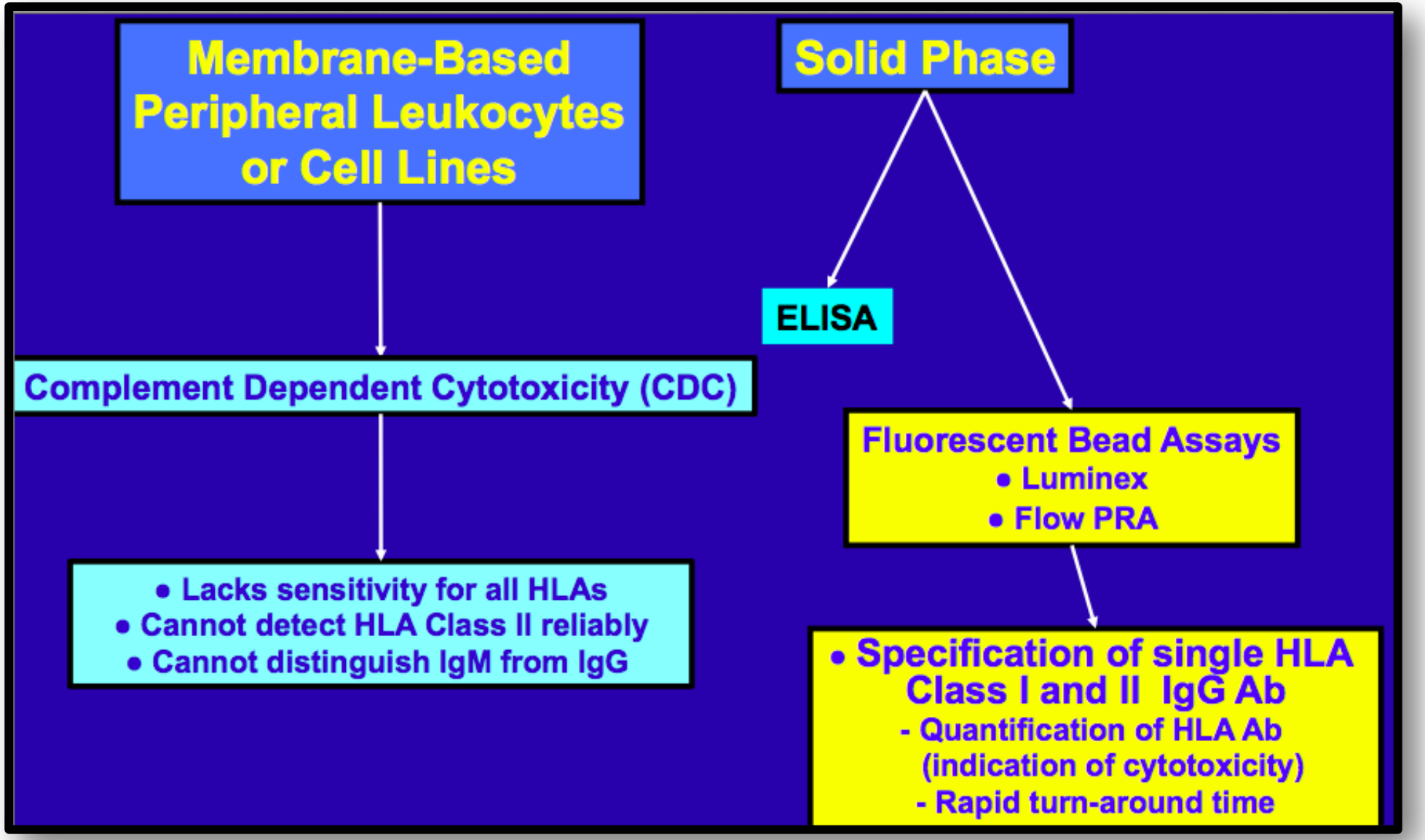
Identification of acceptable epitopes might enable prediction of additional acceptable mismatches.



Kramer et al. 2017


Patients
No HLA Antibodies
With HLA Antibodies
✓ Unstable antibodies
✓ DP antibodies
✓ DQα antibodies
✓ DPα antibodies
✓ Allele specific antibodies
✓ Too many weak antibodies
Well defined stable antibodies
Unet avoid
Cross match
None
vXM
>2000 MFI
Flow XM
>2000 MFI
vXM

Antibody Detection Methods



METHODS FOR HLA ANTIBODY EVALUATION

Antigen Non-Specific

Cytotoxicity
- Standard or NIH
- Modifications
  - Washes
  - Extended Incubation
  - Antiglobulin

Flow Cytometry (cells)
- T cell / B cell
- Pronase

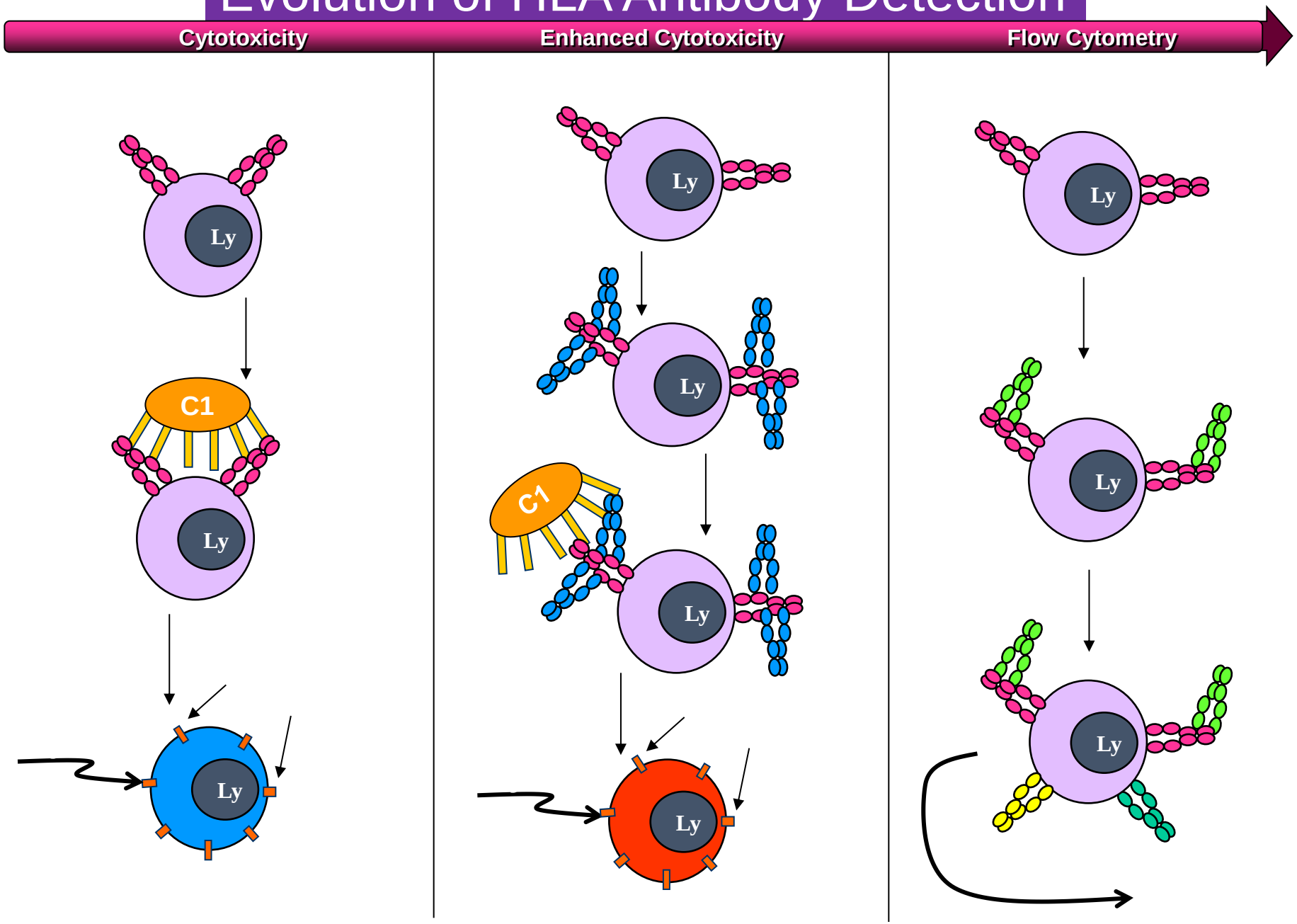
Antigen Specific

ELISA
- Yes / No
- PRA % (I & II)
- Specificity (I & II)

Flow Cytometry (beads)
- PRA % (I and II)
- Specificity (I & II)

Multiplex
- Suspension Arrays
  - Luminex

Evolution of HLA Antibody Detection



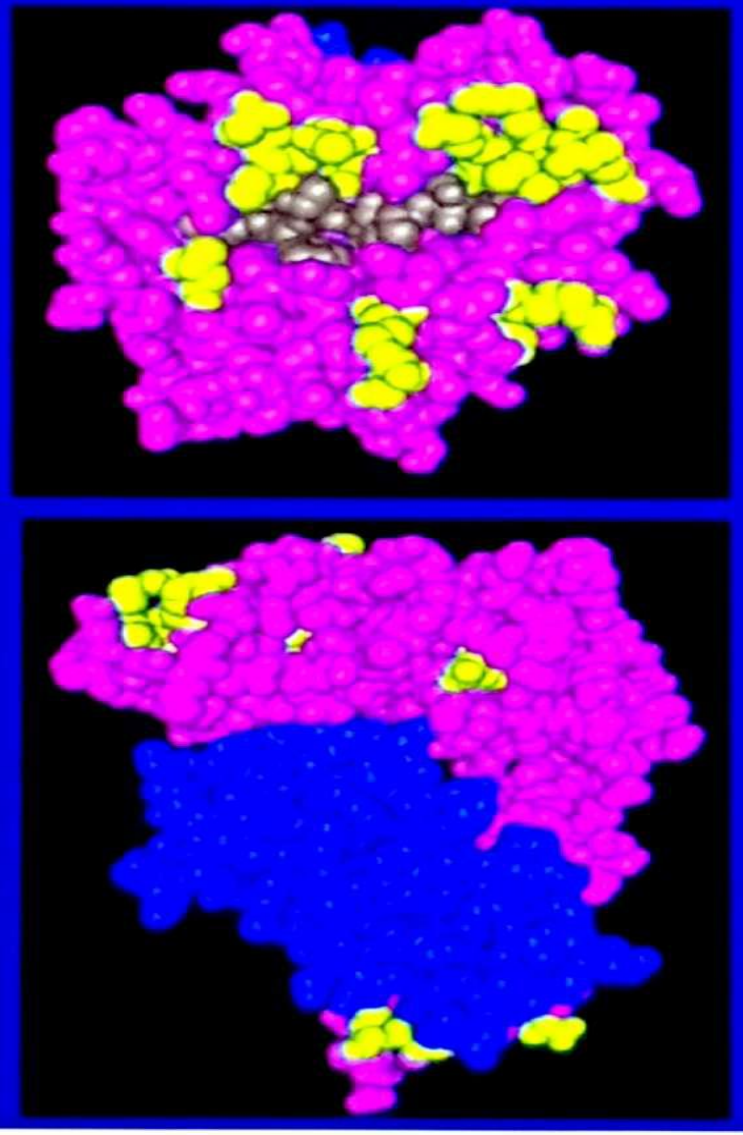
United Network for Organ Sharing Policies

- Mandate use of molecular methods for HLA typing of deceased donors
- Mandate use of a solid-phase assay to identify unacceptable antigens in sensitized candidates

- *These policies help ensure that laboratories are employing the most accurate technologies for determining donor HLA types and the most sensitive and specific methods for assessing a candidate's HLA antibody status*

Is the lack of a match effect in AM patients due to a lower number of antibody epitopes on acceptable mismatches?

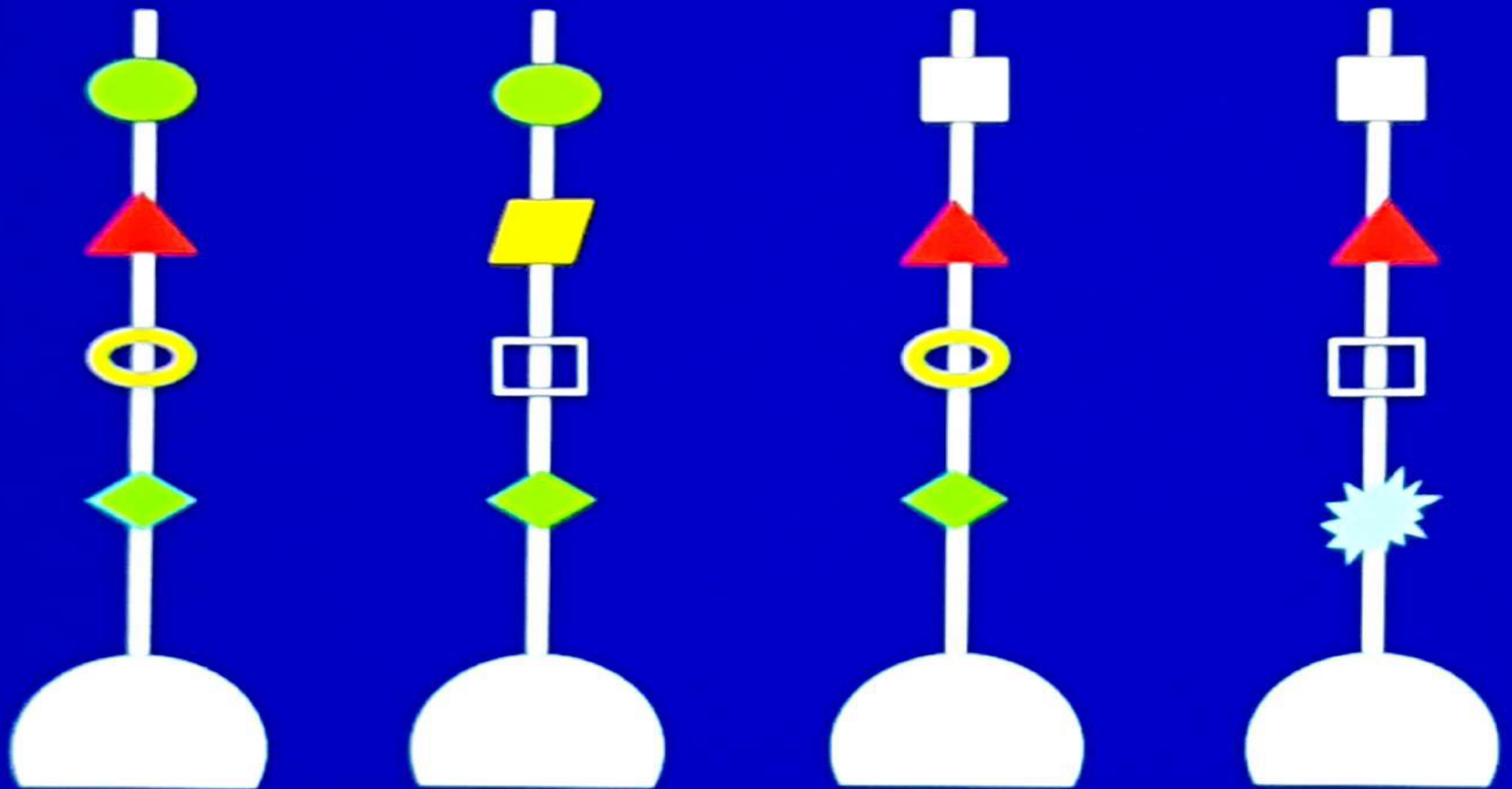
Every HLA allele has many polymorphic positions



All yellow amino acids configurations are potential targets for antibodies.

LUMC

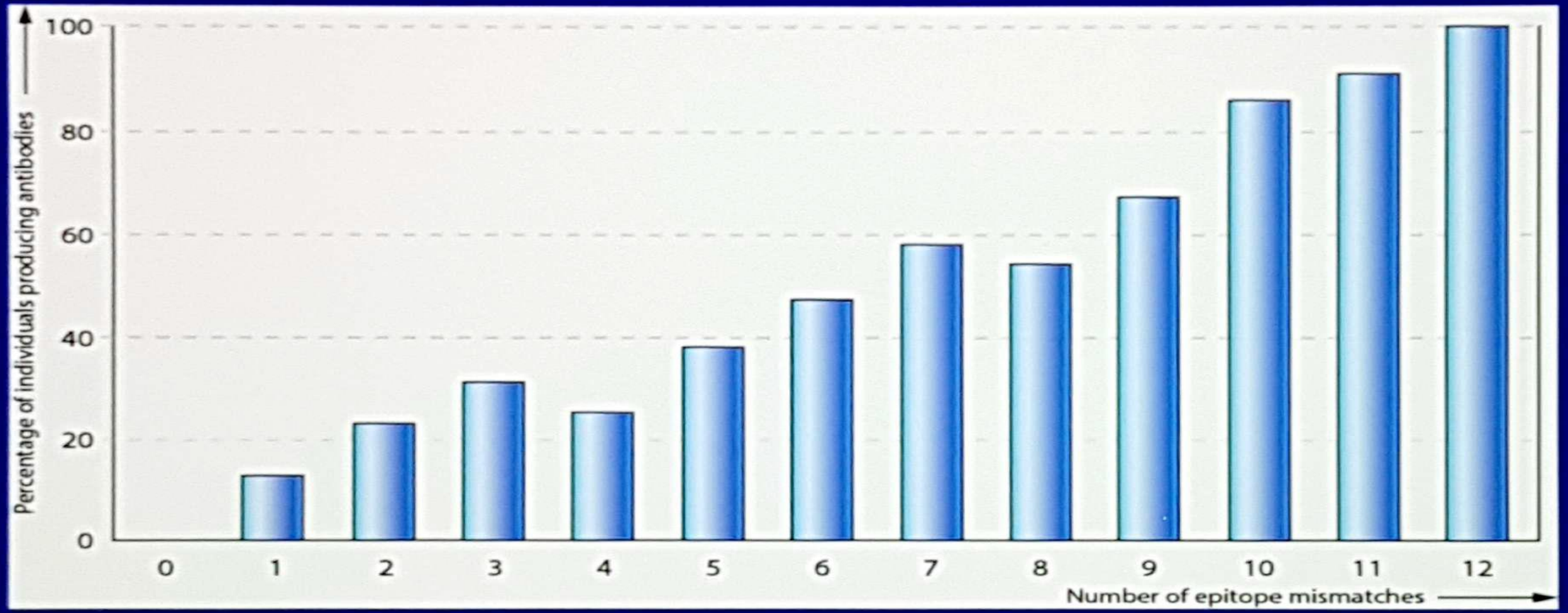
Every HLA antigen carries an unique set of epitopes but the individual epitopes can also be present on other HLA antigens



Patient HLA **HLA antigen 1** **HLA antigen 2** **HLA antigen 3**

Tambur & Claas 2015

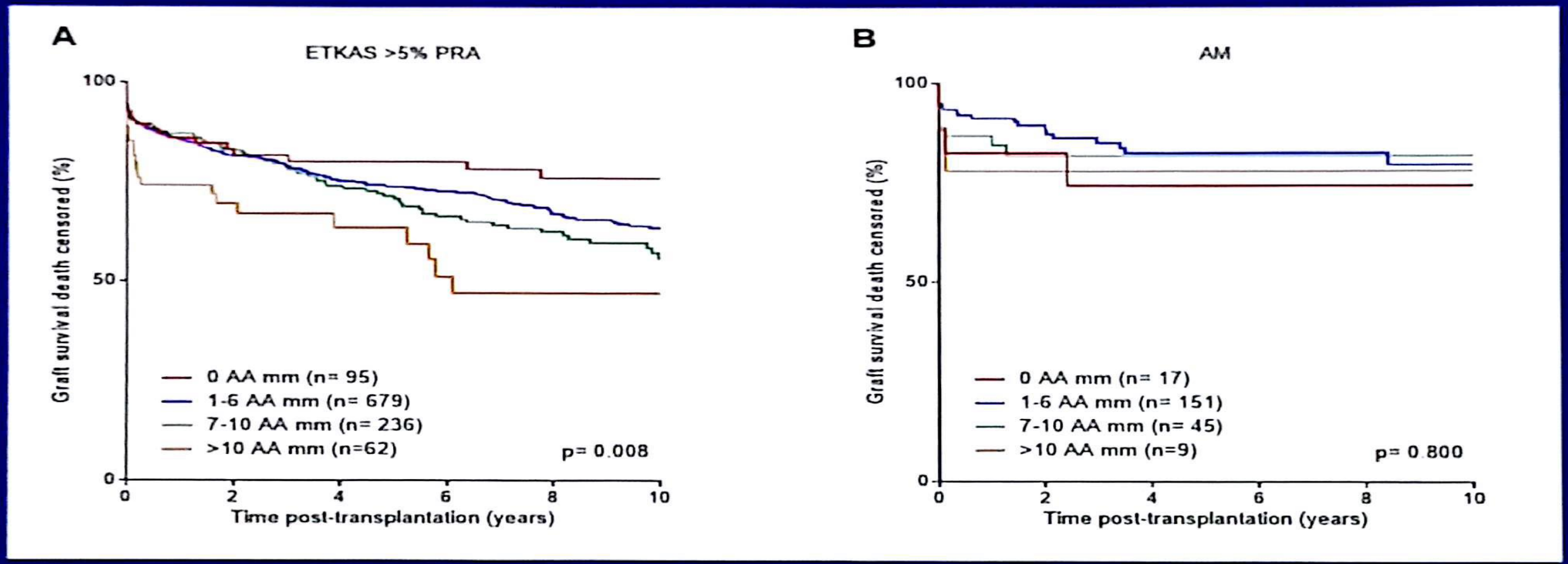
The number of foreign "epitopes" on an HLA mismatch predicts antibody production after renal allograft rejection



Antibody detection in CDC

Dankers et al., Transplantation 2005

No effect of epitope matching in acceptable mismatch transplants.



Immunized single HLA antigen mismatched retransplants

Heidt et al. 2018