A New Paradigm

HLA epitope based donor/recipient mismatch assessment

FDA Workshop, ABMR in Kidney Transplantation

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Relevant Financial Relationship Disclosure Statement

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Consultant for Astellas, GSK, Novartis and Vitaeris

AND

My presentation does not include discussion of off-label or investigational use of drugs

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RENAL HOMOTRANSPLANTATION IN IDENTICAL TWINS*

JOSEPH E. MURRAY, JOHN P. MERRILL AND J. HARTWELL HARRISON

Surg. Forum VI: 432–436, 1955

Personalized Immunosuppression

TARGETING HLA MISMATCHING

Amos
Bodmer
Ceppellini
Dausset
Kissmeyer-Nielsen
Payne
Terasaki
van Rood

60 yrs of HLA Transplant Science

N Engl J Med (**1968**) 279:501
Lancet (**1969**) 1:790
Lancet (**1971**) 1:609
N Engl J Med (**1974**) 290:979
Lancet (**1975**) 1:240
Lancet (**1975**) 2:1126
Lancet (**1978**) 1:575
Lancet (**1978**) 1:1278
Lancet (**1980**) 2:282
N Engl J Med (**1980**) 303:850
N Engl J Med (**1984**) 311:358
Lancet (**1988**) 2:61
N Engl J Med (**1988**) 318:1289
Lancet (**1991**) 338:461
N Engl J Med (**1991**) 324:1032
N Engl J Med (**1992**) 327:834
N Engl J Med (**1994**) 331:765
N Engl J Med (**1995**) 333:333
N Engl J Med (**1999**) 341:1440
N Engl J Med (**2000**) 343:1078
N Engl J Med (**2004**) 350:545

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Personalized Immunosuppression

HLA MISMATCHING – BEYOND WHOLE HLA MOLECULES

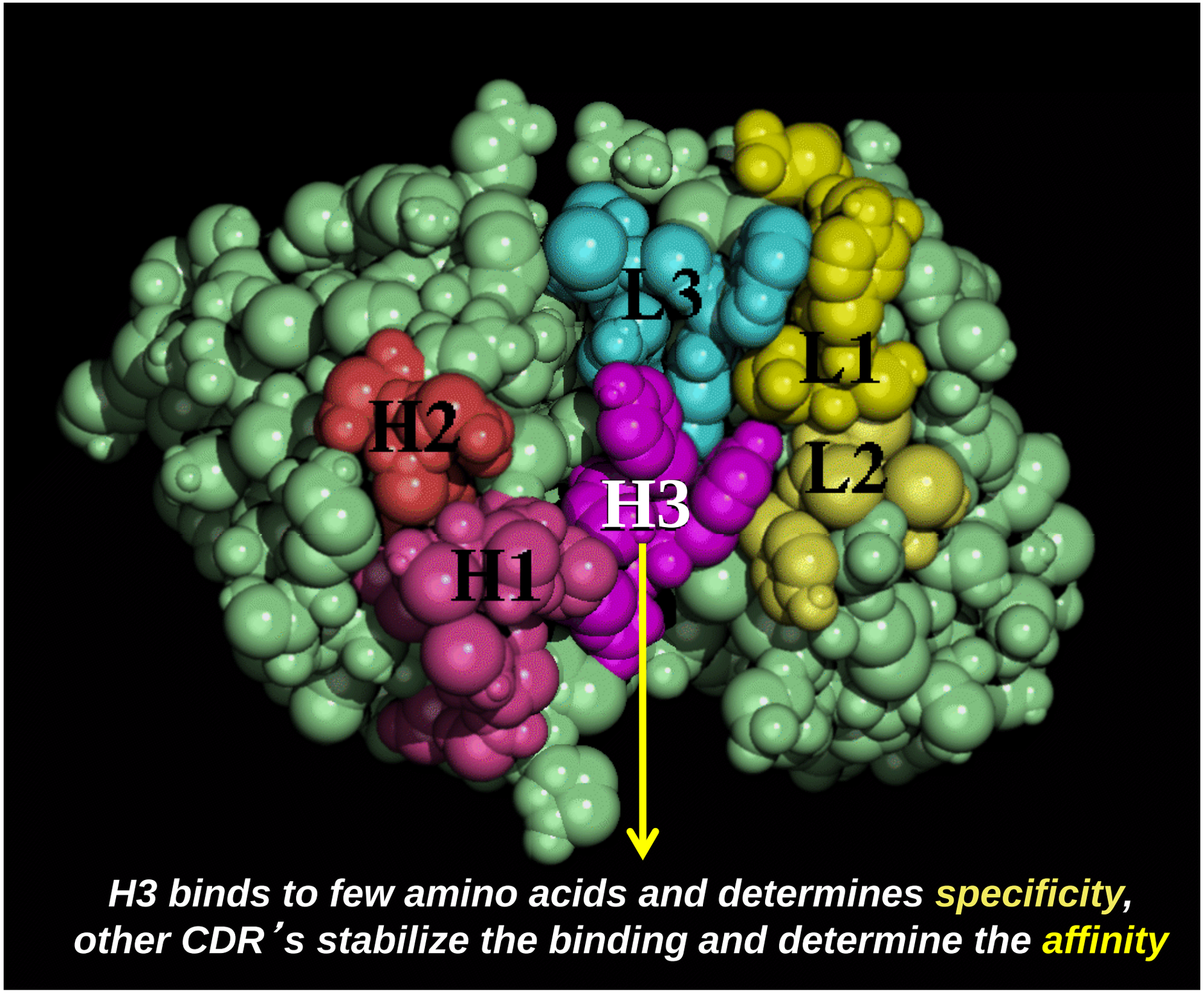
"We must now prepare for the second phase in which more sophisticated measures of HLA compatibility should be developed for more accurate prediction of outcome"

Mickey, Kreisler, Albert, Tanaka, Terasaki

Tissue Antigens (1971) 1:57

Six contact sites determine the reactivity between antibody and antigen

(complementarity determining regions (CDR)

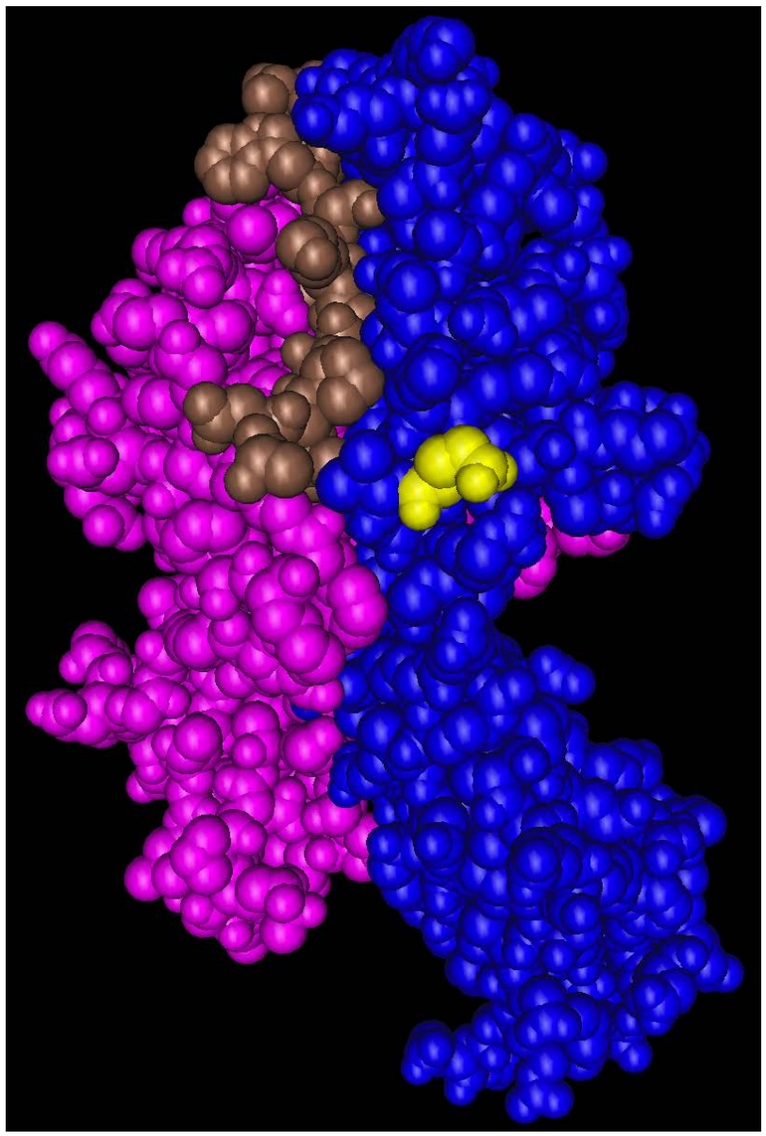


Antibody-reactive epitope determination with HLAMatchmaker and its clinical applications

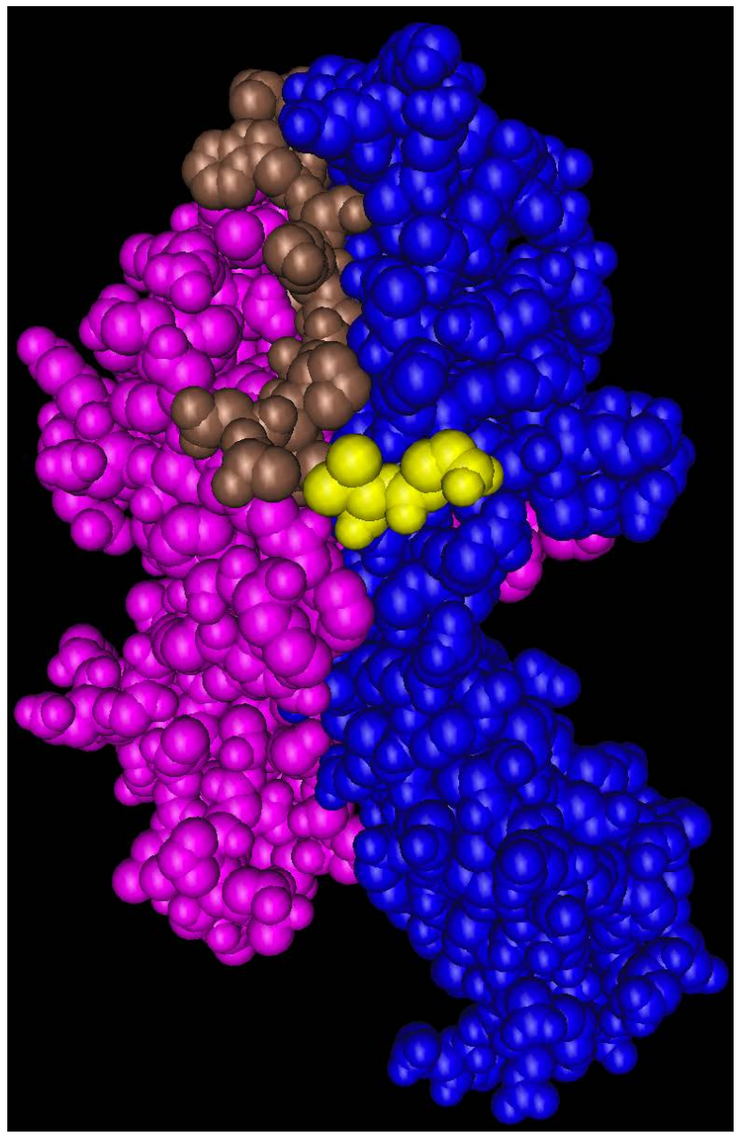
R. J. Duquesnoy

Tissue Antigens (2011) 77:525

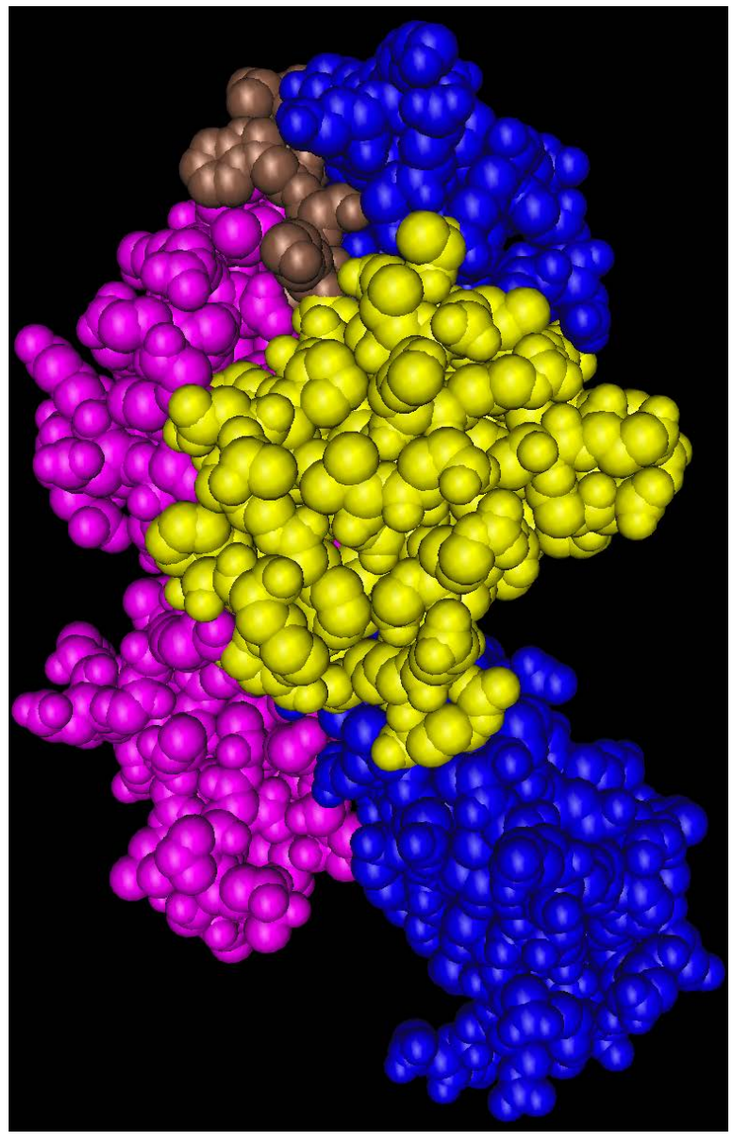
Polymorphic amino acid



Functional Epitope (H3 CDR)
(3Å radius – “Eplet”)



Structural Epitope
(15Å radius)



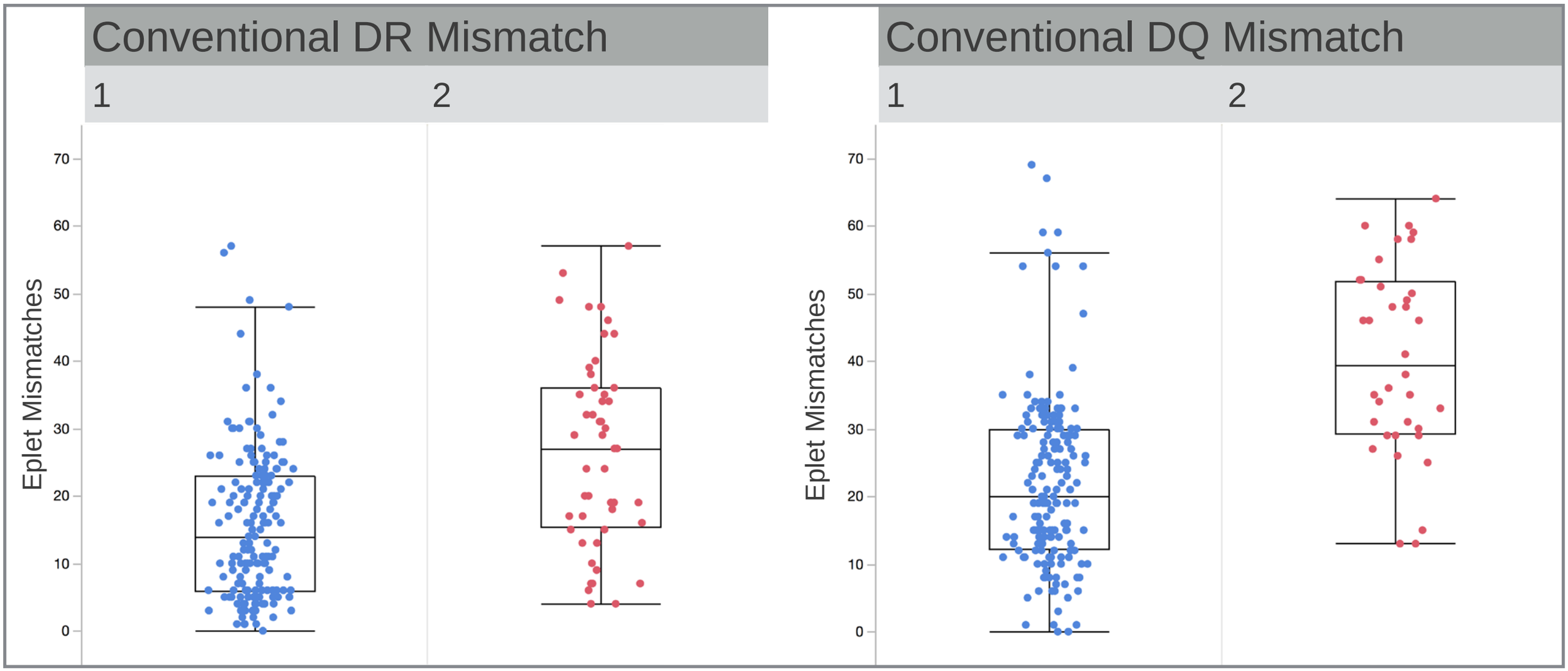
HLAMatchmaker Eplet Mismatch Assessment

Most Accurate with 4-digit HLA Typing data

Patient HLA	Donor HLA	mmEp	Mismatched Donor Eplets
DRB1*1101	DRB1*0405	11	, ,12VKH,14HEH, , ,32FYH,34HQ, , ,57SA, ,67LR,71QRA, , , ,96YL,98EN, ,120N, , , ,180LT, ,
DRB1*1302	DRB1*1119	1	, , , , , , , , , , ,67IR, , , , , , , , , , , ,
DRB3*0101	DRB3*0202	-	, ,
DRB3*0202	DRB4*0101	19	4Q,18L,12AKC,14CEH,16HLW,26WN,32IYN, ,41YNL,48YQ, , ,67LR,71RRA, ,81YV,85VV,96QM,98KN,
DQB1*0301	DQB1*0301	-	, ,
DQB1*0301	DQB1*0302	7	,14GM, ,26L, ,45GV,46GVY, , ,57PA, , , , , , , , , , , ,167RG, ,185I, , ,
DQA1*0103	DQA1*0302	13	, , ,25YS,34HE,41ER, ,47EQL,48LF,50LF,52FRR,56RR, , , ,75IVR,80IRS, , , , , ,160DD, ,175E,187T
DQA1*0505	DQA1*0505	-	, ,
DPB1*0301	DPB1*0201	-	, , , , , , , , , , , ,
DPB1*0201	DPB1*2301	3	, , , , , ,55AA,56AE, , , , , ,
DPA1*0103	DPA1*0103	-	, , , , , , ,
DPA1*0103	DPA1*0103	-	, , , , , , ,

CONTEXT (Donor – Recipient relatedness)

Conventional Whole Molecule HLA MM vs. Range of Eplet MM



Wiebe et al., Transplantation (2016) 100:2048-2052

Eplet MM is an Independent Predictor for *de novo* Class II DSA

Model	HLA Loci	Predictors	Odds Ratio (per unit change)	p value
Clinical Predictors	HLA-DR	Non-Adherence	6.0 (2.1-17.0)	p<0.001
		HLA-DR Eplet Mismatch Load	1.06 (1.03-1.10)	p<0.001
		Clinical Rejection Preceding *dn* DSA	2.6 (1.5-4.6)	p<0.001
	HLA-DQ	Non-Adherence	8.5 (3.6-20.0)	p<0.001
		HLA-DQ Eplet Mismatch Load	1.04 (1.0-1.02)	p<0.001
		Younger Age	1.03 (1.0-1.10)	p<0.01

* Odds ratios with 95% Confidence Intervals

Wiebe et al., AJT (2013) 13:3114-3122

Immunogenicity: Electrostatic Potentials of HLA Epitopes

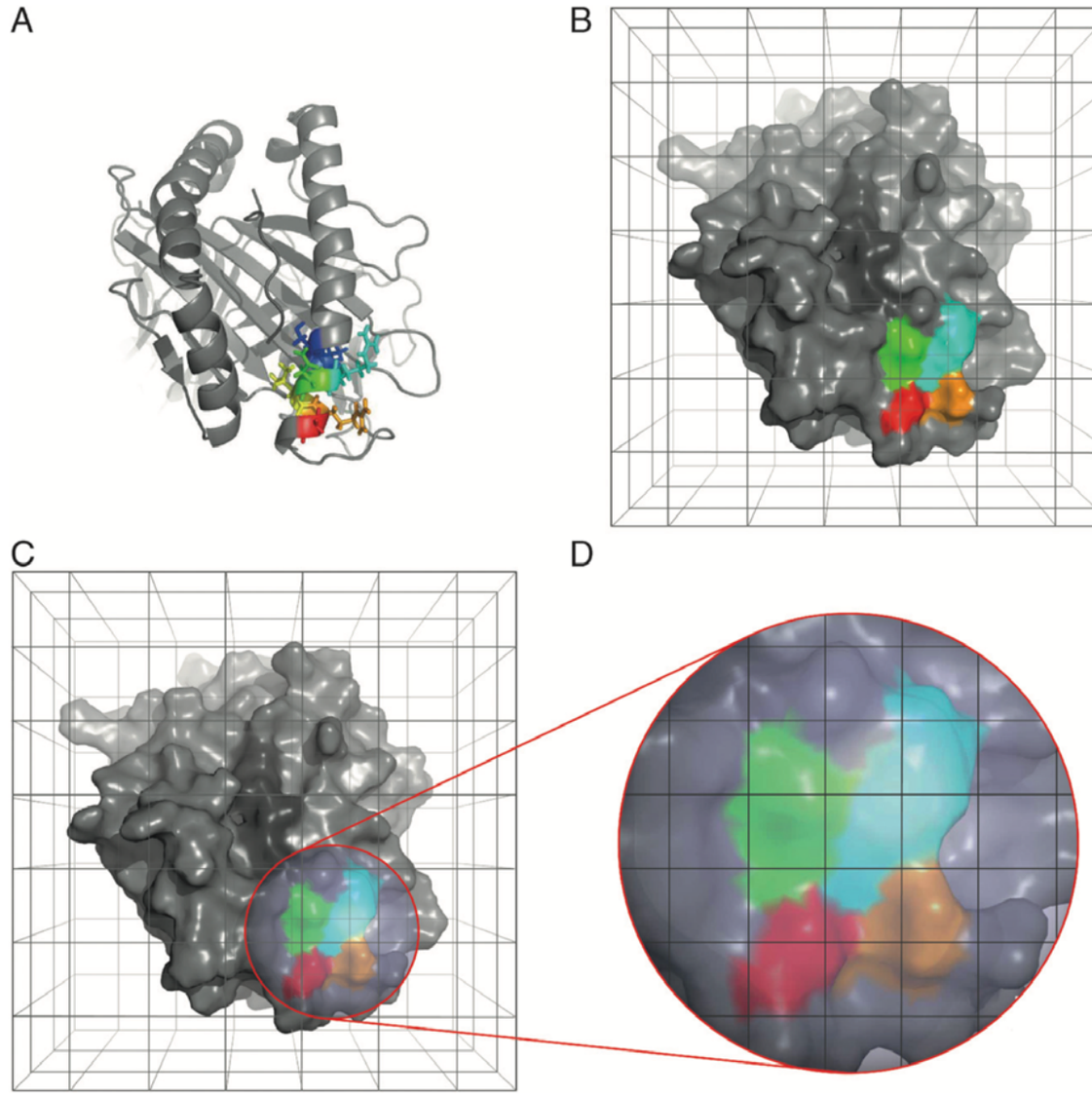


FIGURE 1. Schematic representation of the method used to quantitate the surface electrostatic potential of the Bw4 and Bw6 epitopes expressed on HLA class I molecules. The HLA class I molecule is depicted in gray and the Bw4 or Bw6 epitope is highlighted in color. A, Atomic resolution 3-dimensional structural models of common HLA-A and HLA-B alleles that express the Bw4 or Bw6 epitope were created. B, The electrostatic potential in the 3-dimensional space around each HLA class I model was calculated by solving the linearized Poisson-Boltzmann equation, as implemented in APBS, for a cubic grid with sides of 353 points spaced 0.33Å apart. C and D, To enable selective electrostatic potential comparison of the Bw4 and Bw6 epitopes, a virtual sphere of interest (10Å in radius) was created to encompass the canonical Bw4/Bw6 motif. Quantitative comparisons of the electrostatic potential of the Bw4/Bw6 epitope were made for each HLA allele by comparing electrostatic potential at analogous grid points within the sphere of interest.

Mallon et al. Transplantation (2015) 99:2

Predicting Class II DSA development <u>after</u> Graft Loss

Mismatch evaluation methods appear equivalent

Amino Acid Mismatch

Eplet Mismatch

Electrostatic Mismatch

Variable	Odds ratio (95% CI) on developing HLA donor-specific antibodies (MFI > 2000) OR (95% CI)	p-value
HLA-DRB1/3/4/5		
AMS (per 10 AA MM)	5.42 (2.23, 15.01)	**<0.001**
Dual agent immunosuppression	0.05 (0.01, 0.21)	**<0.001**
Time on the waiting list (per year)	1.00 (0.83, 1.19)	0.96
EpMS (per 10 eplet MM)	6.30 (2.30, 19.30)	**<0.001**
Dual agent immunosuppression	0.06 (0.01, 0.23)	**<0.001**
Time on the waiting list (per year)	0.98 (0.82, 1.17)	0.83
EMS (per 10 units)	2.77 (1.52, 5.52)	**0.002**
Dual agent immunosuppression	0.06 (0.01, 0.24)	**<0.001**
Time on the waiting list (per year)	0.94 (0.79, 1.11)	0.50
HLA-DQ		
AMS (per 10 AA MM)	1.79 (1.19, 2.71)	**0.005**
Dual agent immunosuppression	0.18 (0.01, 1.10)	0.12
Time on the waiting list (per year)	0.91 (0.70, 1.15)	0.43
EpMS (per 10 eplet MM)	1.99 (1.20, 3.47)	**0.011**
Dual agent immunosuppression	0.17 (0.01, 1.00)	0.10
Time on the waiting list (per year)	0.91 (0.71, 1.15)	0.45
EMS (per 10 units)	1.46 (1.14, 1.90)	**0.003**
Dual agent immunosuppression	0.17 (0.01, 1.01)	0.11
Time on the waiting list (per year)	0.89 (0.69, 1.14)	0.37

Kosmoliaptsis et al. AJT (2016) 16:2139

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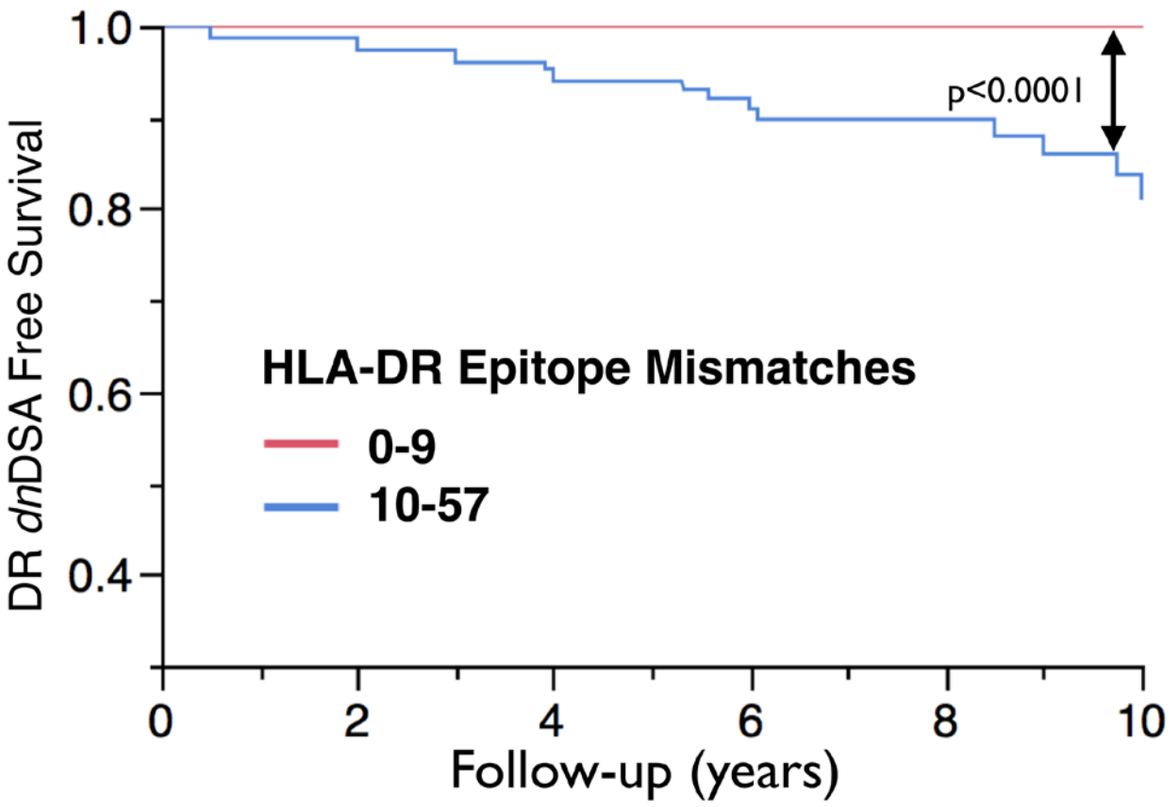
Personalized Immunosuppression

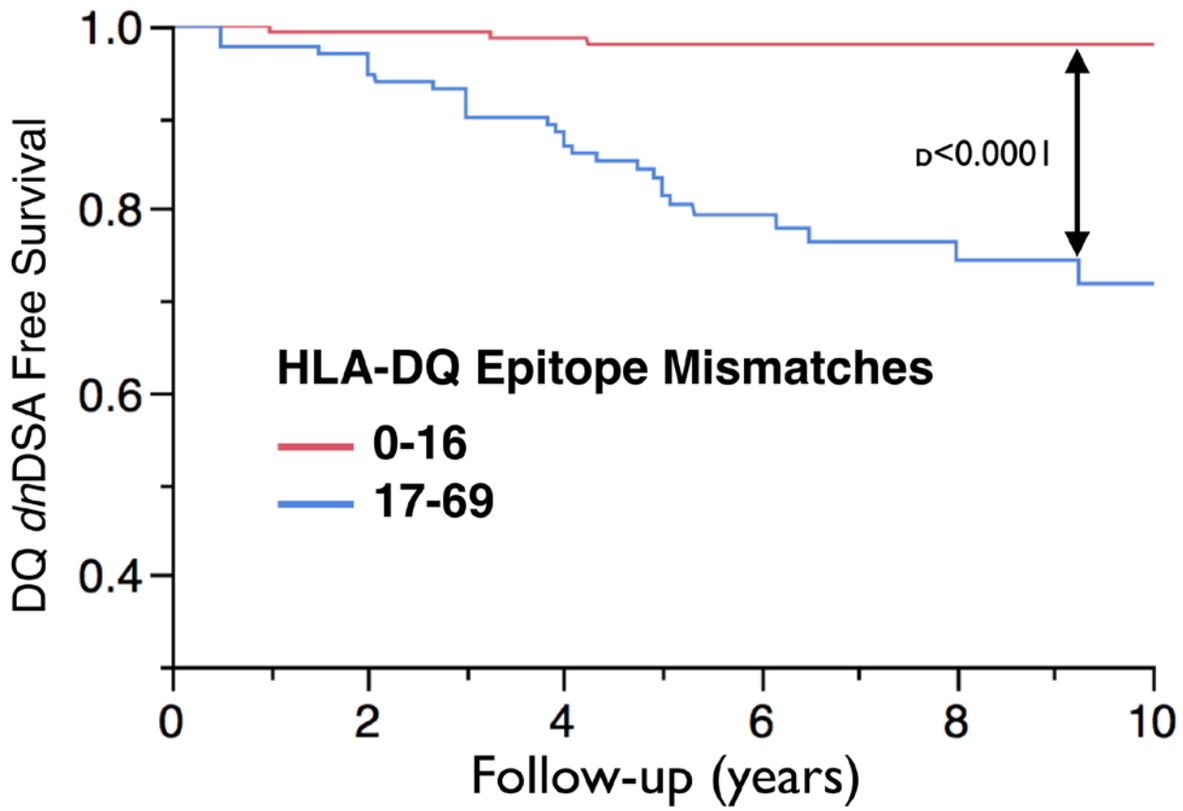
HLA MISMATCHING – EPLET MM LOAD FOR RISK ASSESSMENT

Optimal HLA Eplet MM thresholds predictive of *de novo* DSA (ROC analysis)

HLA DR



HLA DQ



Wiebe et al., AJT (2013) 13:3114-3122

HLA-DR and -DQ Eplet Mismatches and Transplant Glomerulopathy: A Nested Case–Control Study

R. Sapir-Pichhadze[1,2,3,*,†] K. Tinckam[1,4], K. Quach[1,5], A.G. Logan[1,2,3], A. Laupacis[2,6], R. John[4], J. Beyene[2,6,7] and S.J. Kim[1,2,3,8]

American Journal of Transplantation 2015; 15: 137–148

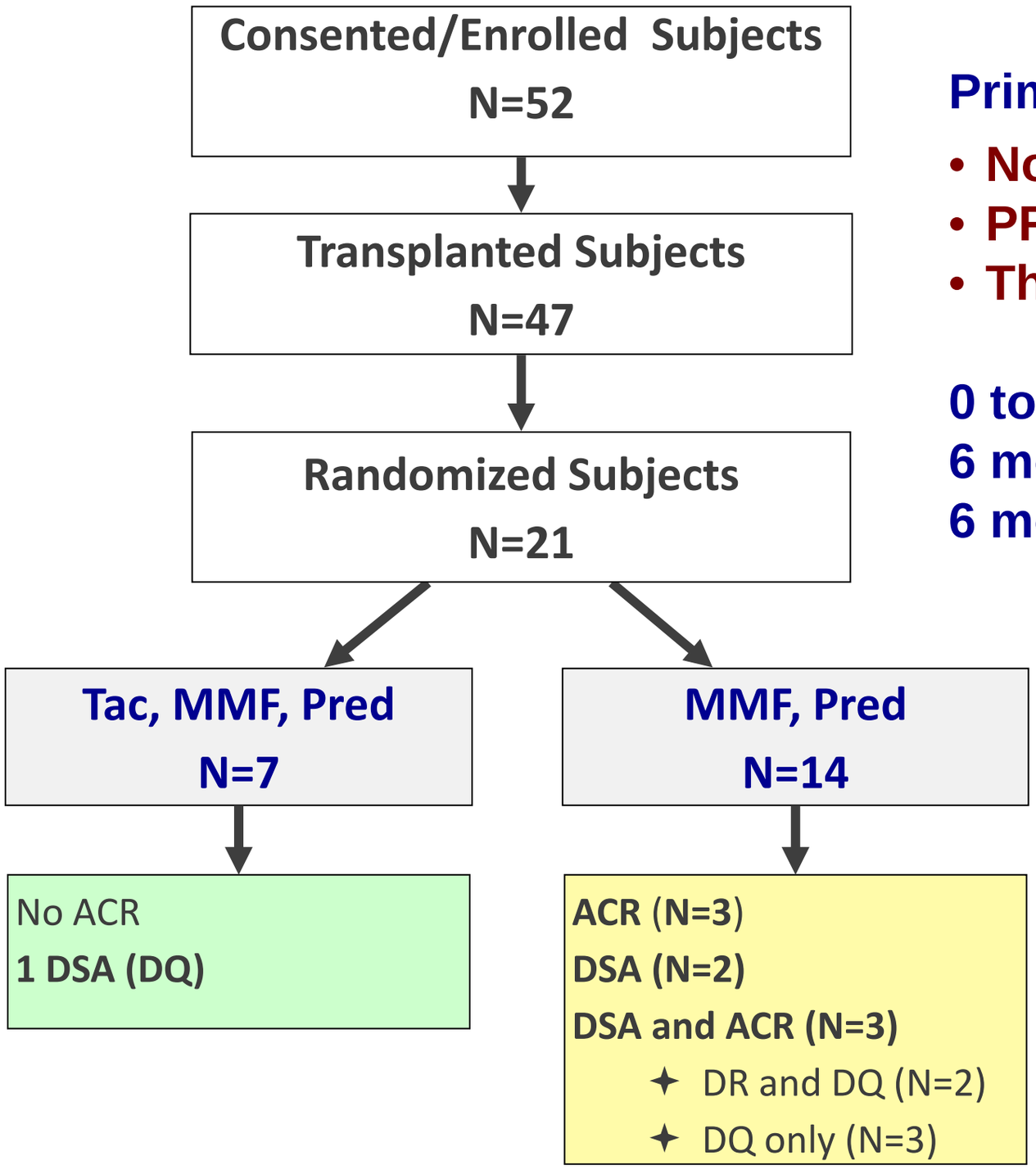
Odds Ratio of Developing TG based upon Total Eplet Threshold

	Univariate	Multivariate **
DR + DQ ≥36	2.01[1.01-4.01]	3.21 [1.26-7.56]
DQ ≥18	1.50 [0.75,3.00] NS	2.42 [1.03,5.70]
DR ≥15	2.44 [1.16,5.12]	3.64 [1.42,9.37]

** Model includes Eplet exposure, recipient age, sex, peak PRA, race, induction and donor type.

Tacrolimus withdrawal in *Immune Quiescent* Kidney Transplant Recipients (CTOT-09)

University of Manitoba



Primary Living Donor Transplants

- No DSA
- PRA <30%
- Thymo, Tacrolimus, MMF, Prednisone

0 to 6 mo course: No Acute Rejection
6 mo Protocol Biopsy: Normal Histology
6 mo Antibody Screen: No DSA

Tacrolimus tapered over 3 months

Trial Halted by DSMB

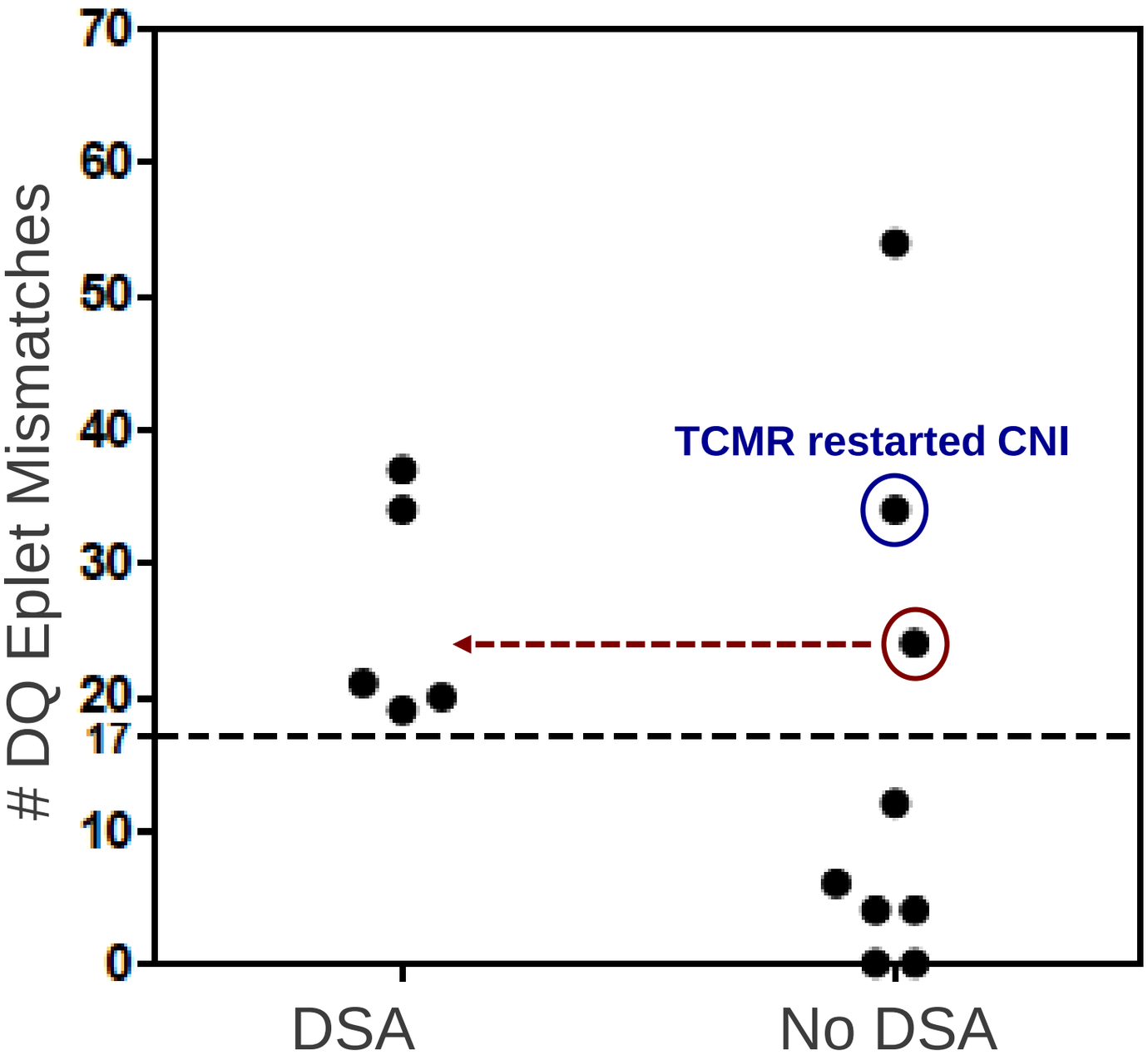
Quiescence ≠ Low Risk to Minimize

NIH National Institute of Allergy and Infectious Diseases

CTOT Clinical Trials in Organ Transplantation

Hricik et al., JASN (2015) 26:3114-22

Tacrolimus withdrawal in *Immune Quiescent* Kidney Transplant Recipients (CTOT-09)



***De novo DQ* DSA associated with high Eplet MM load (≥ 17)**

5/8 in Tac withdrawal

(P=0.0310)

6/8 in longer follow-up

(P=0.0096)

National Institute of Allergy and Infectious Diseases

Hricik et al., JASN (2015) 26:3114-22

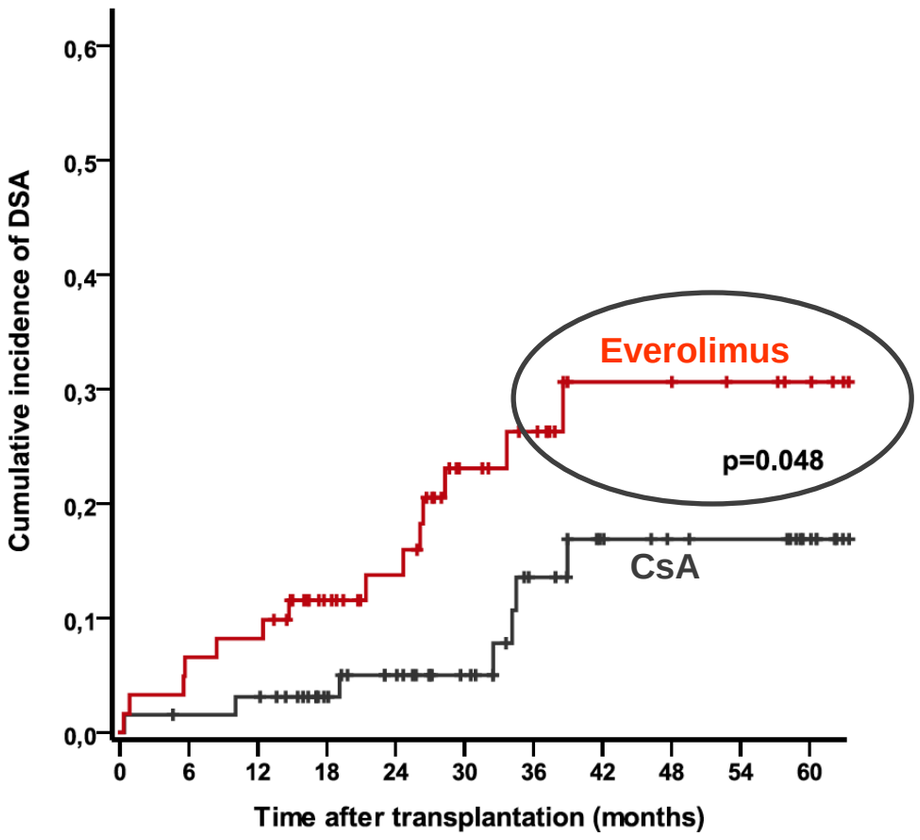
Donor-Specific HLA Antibodies in a Cohort Comparing Everolimus with Cyclosporine After Kidney Transplantation

L. Liefeldt[a,†,*], S. Brakemeier[a,†], P. Glander[a], J. Waiser[a], N. Lachmann[b], C. Schönemann[b], B. Zukunft[a], P. Illigens[a], D. Schmidt[a], K. Wu[a,c], B. Rudolph[c], H.-H. Neumayer[a] and K. Budde[a]

AJT (2012) 12:1192-1198

Anti-CD25 Induction + CsA + MMF + Pred

Patients switched from CsA to Everolimus at 3.0 to 4.5 months post-transplant have an increased incidence of *de novo* DSA and ABMR



DR *dn*DSA n=6

DQ *dn*DSA n=24,

DQ eplet MM 14.3 vs. 7.4, p<0.0001

AJT 2016 Vol 16, S3, 203–404

Abstract #279 R. Snanoudj et al.

Predictive Patterns of Early Medication Adherence in Renal Transplantation

Thomas E. Nevins,[1,4] William N. Robiner,[2] and William Thomas[3]

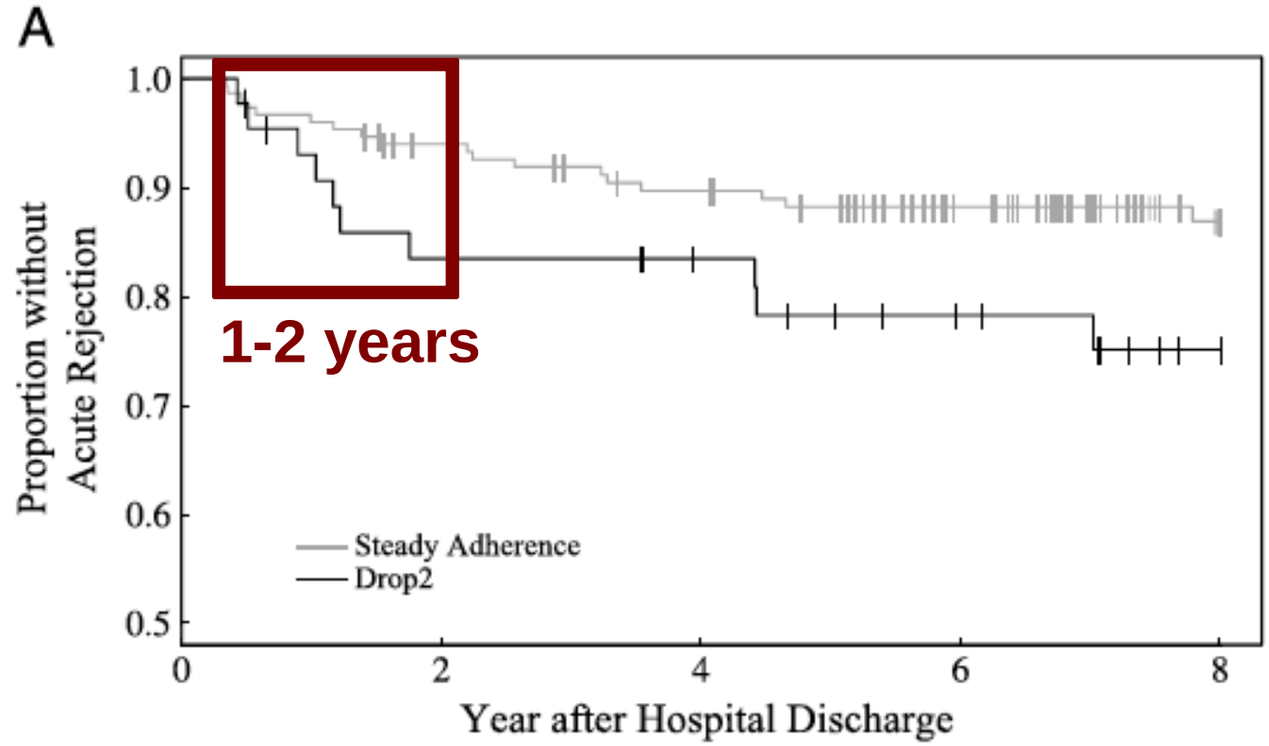
MEMS
(Medication Event Monitoring System)

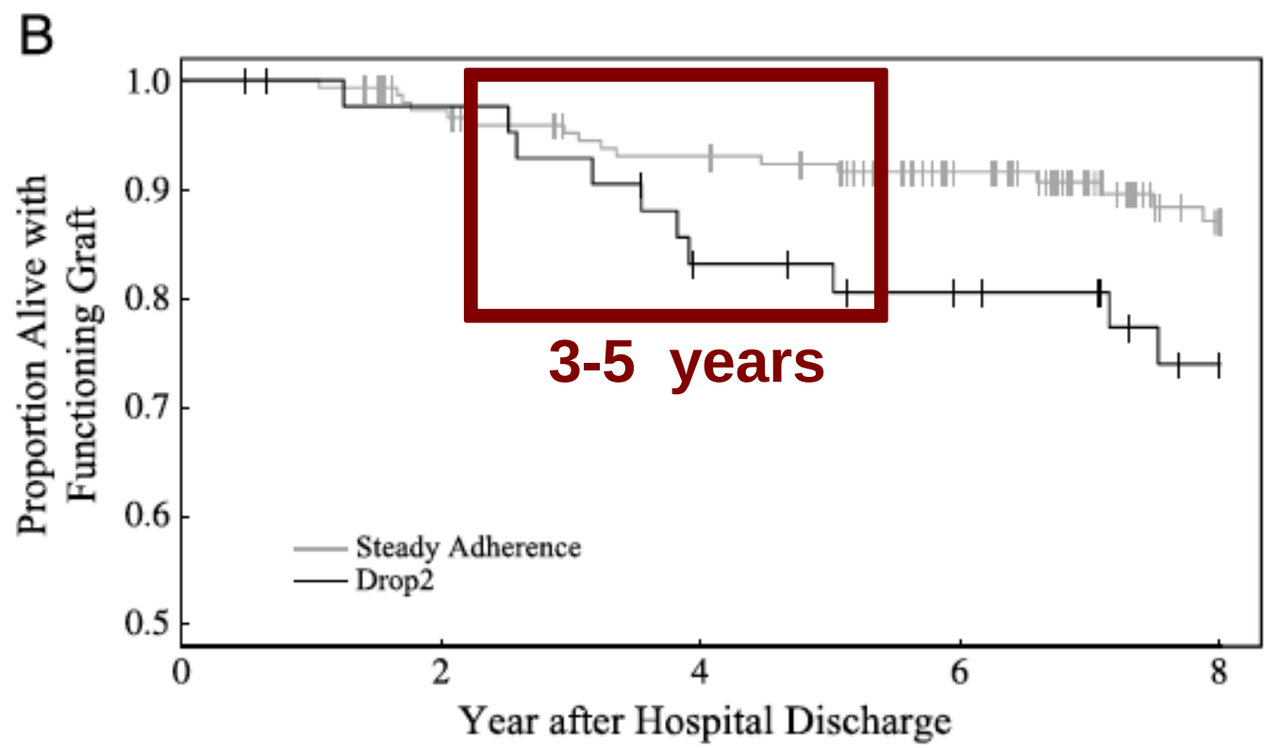
195 patients

- **44 (22.6%)** decreased adherence by 7% or more in **month 2** post tx

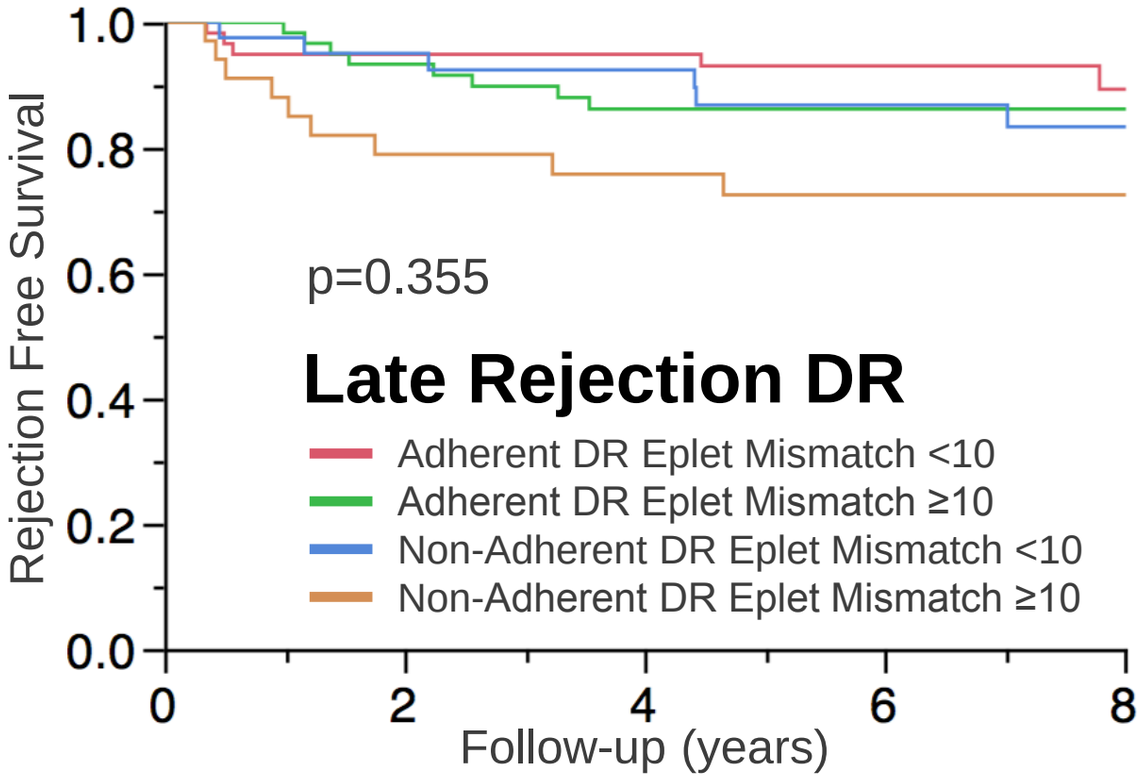
  → **Late Acute Rejection**
  → **Early Graft Loss**

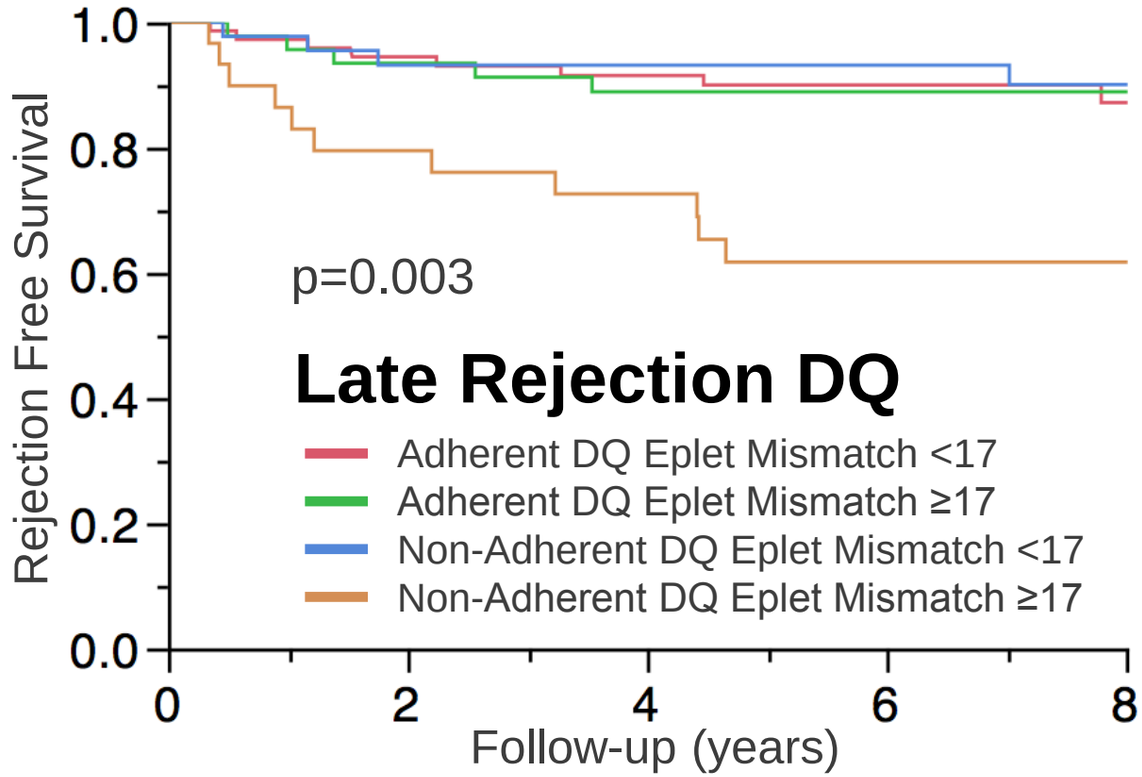
Transplantation (2014) 98:878-884





Synergy of Non-Adherence and Eplet MM Load





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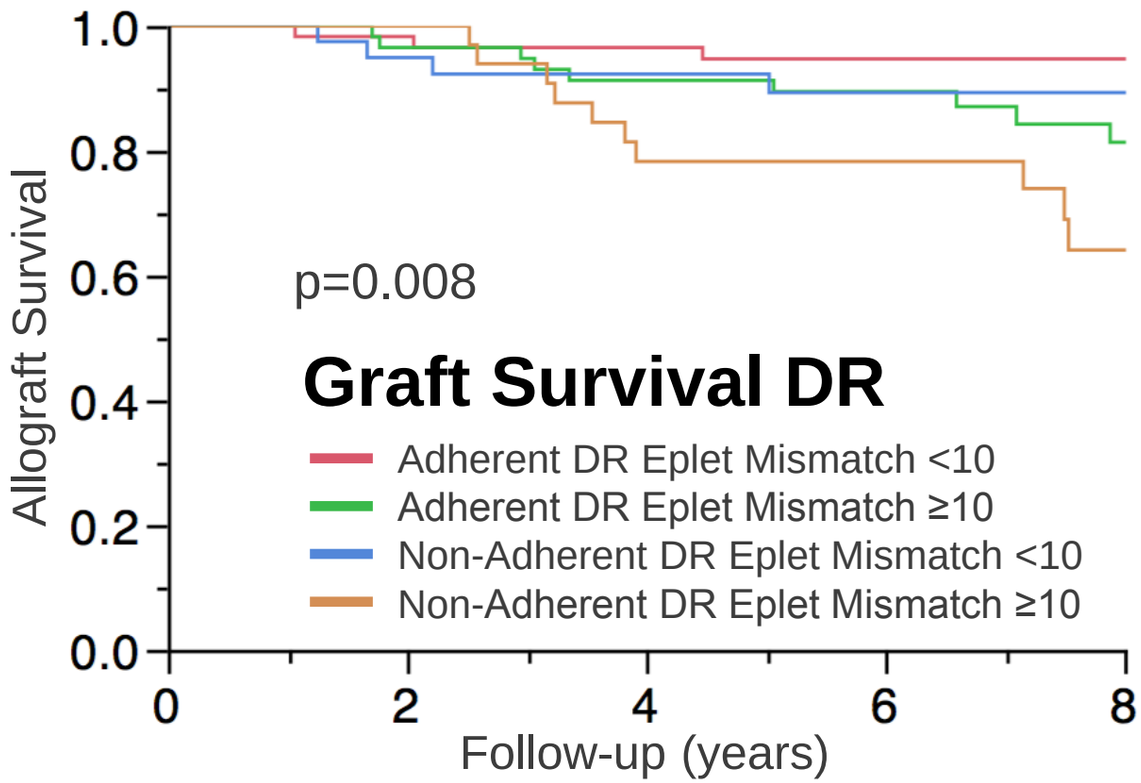

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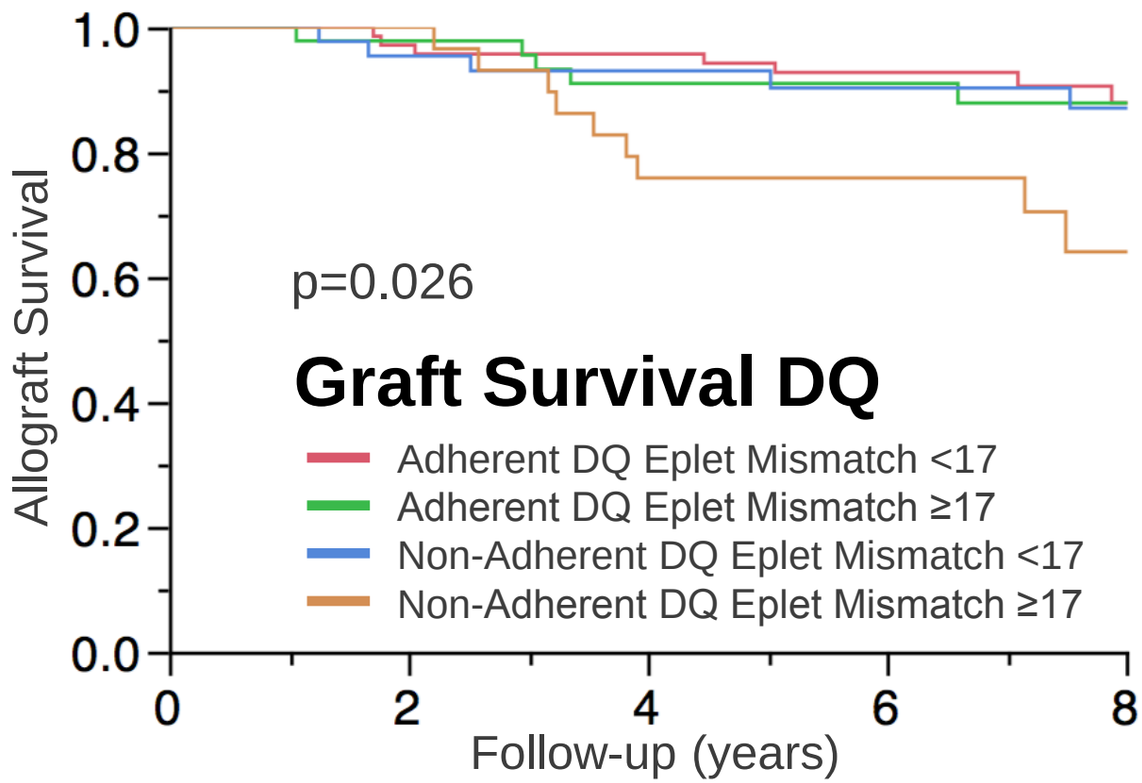
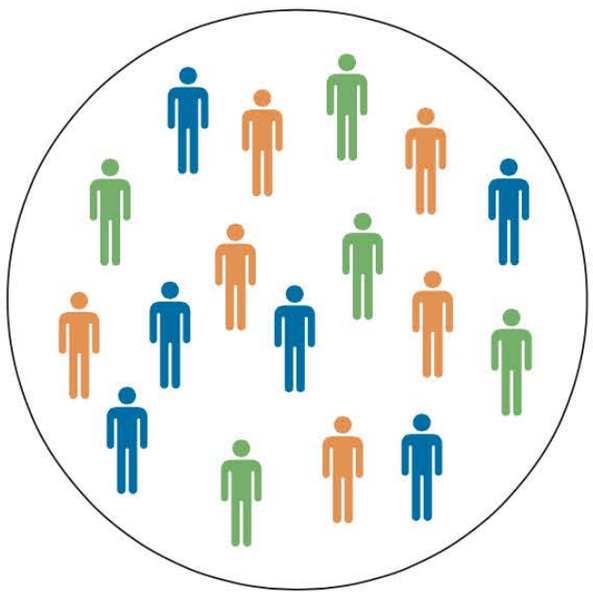
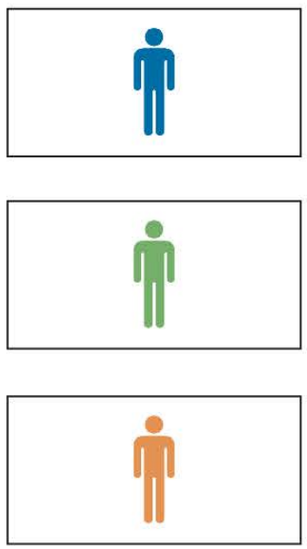
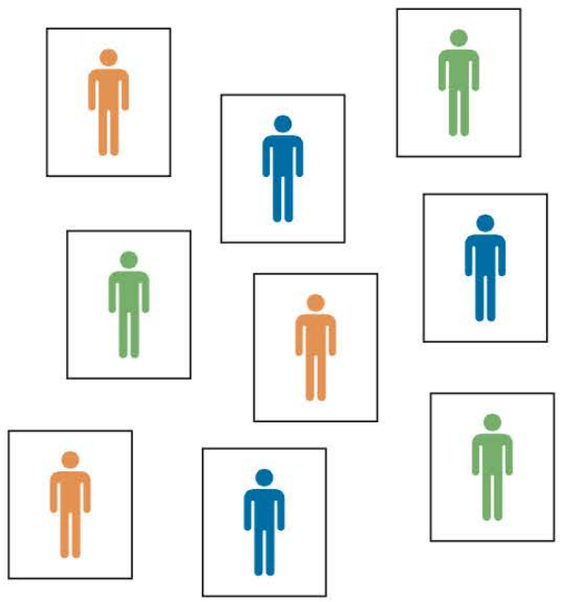


Wiebe et al., AJT (2015) 15:2197-2202

JCD Willis and GM Lord, Nature Rev Immunol (2015) 15: 323-329

Empirical medicine	Stratified medicine	Personalized medicine
		
HLA Mismatch	**DR or DQ Eplet MM Load Electrostatic MM**	**DR or DQ Immunogenic Epitopes**
Low Allocation Points (2 points – 0 DR MM)	**Low (both)** Allocation Points Minimization ???	**Immunodominant** Avoid or Low Priority
Same Treatment for All	**High (either)** Avoid Minimization	Avoid Minimization

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