Associazione Italiana di Immunogenetica e Biologia dei trapianti

GIORNATA DI FORMAZIONE AIBT

in collaborazione con la UOC Coordinamento Trapianti-Laboratorio di Immunologia dei Trapianti della Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano

TOOLS BIOINFORMATICI E RISORSE WEB IN ISTOCOMPATIBILITA'

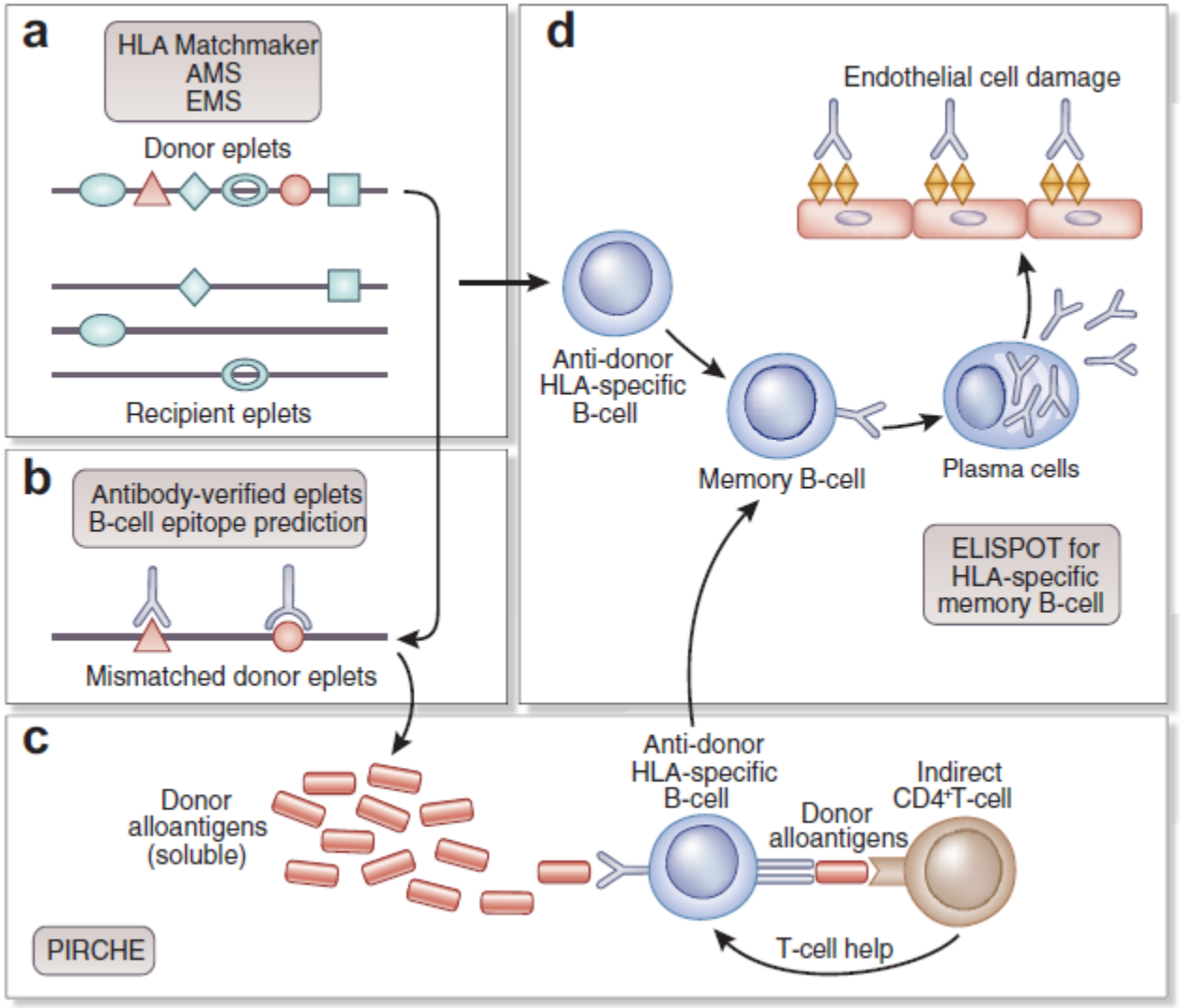
Ospedale Maggiore Policlinico, Via F. Sforza 35

Milano, 17 Settembre 2018

Epitope matching and practical application in kidney transplantation

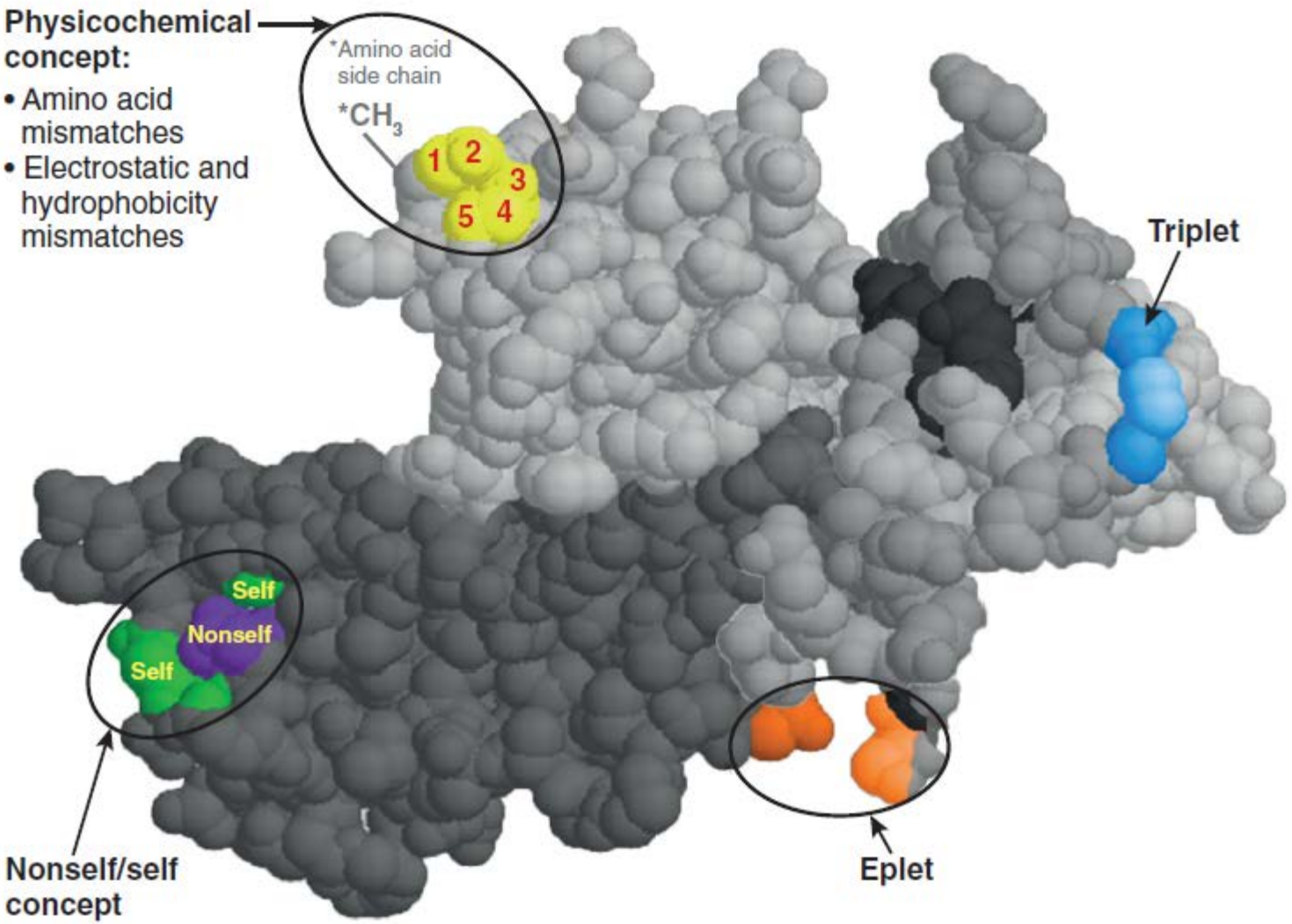
Cristiana Caorsi

Role of B cells in the development of DSA and AMR



[Lim *et al*, KI 2018]

Triplet vs Eplet and more



[Lim *et al*, KI 2018]

American Journal of Transplantation 2017; 17: 3076–3086
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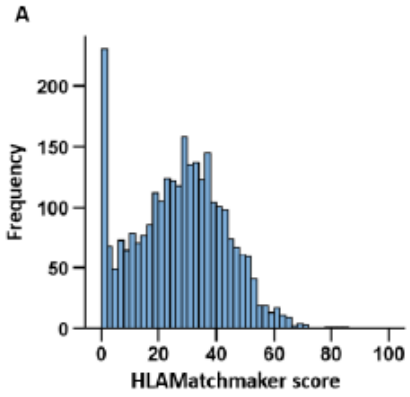
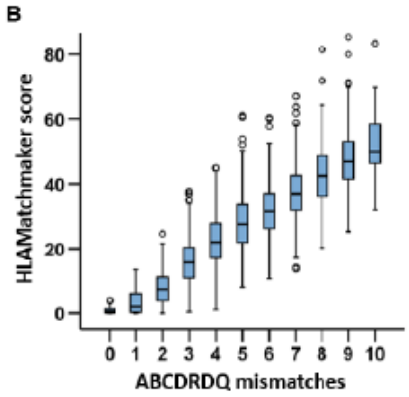
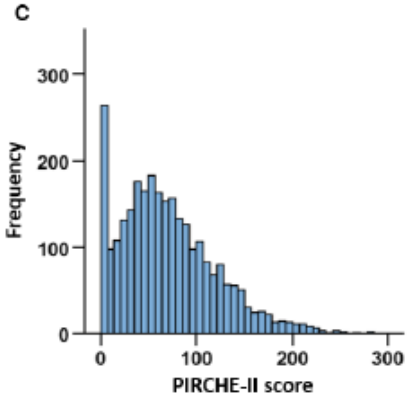
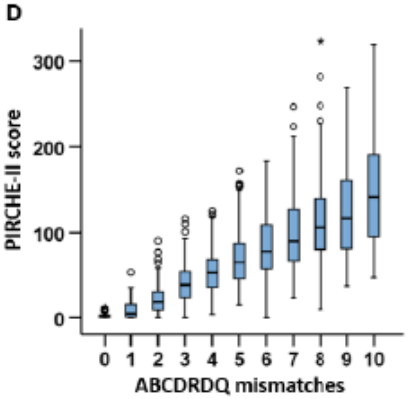
Donor–Recipient Matching Based on Predicted Indirectly Recognizable HLA Epitopes Independently Predicts the Incidence of *De Novo* Donor-Specific HLA Antibodies Following Renal Transplantation

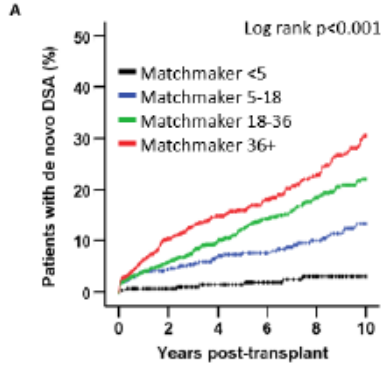
N. Lachmann[1,*], M. Niemann[2], P. Reinke[3,†], K. Budde[3], D. Schmidt[3], F. Halleck[3], A. Pruß[4], C. Schönemann[1], E. Spierings[5] and O. Staeck[3]





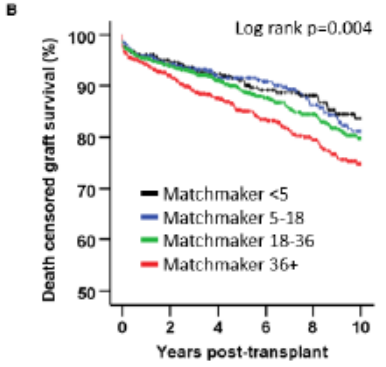






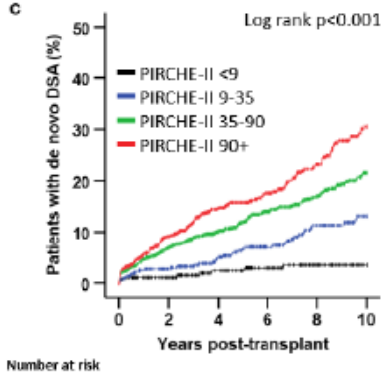
Number at risk

Years post-transplant	0	2	4	6	8	10
Matchmaker <5	323	280	236	193	145	101
Matchmaker 5-18	476	397	326	263	201	150
Matchmaker 18-36	1136	917	683	510	388	249
Matchmaker 36+	852	644	495	371	265	162



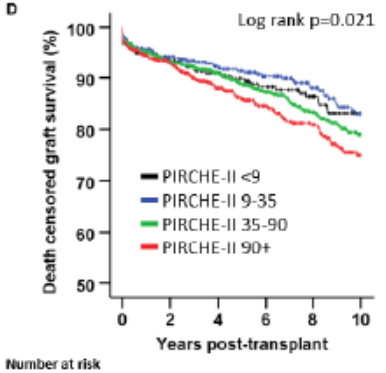
Number at risk

Years post-transplant	0	2	4	6	8	10
Matchmaker <5	323	268	222	179	136	90
Matchmaker 5-18	476	391	320	255	190	138
Matchmaker 18-36	1136	926	703	524	399	250
Matchmaker 36+	852	672	523	388	278	168



Number at risk

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



Number at risk

Years post-transplant	0	2	4	6	8	10
PIRCHE <9	285	234	190	155	116	77
PIRCHE 9-35	446	370	301	238	179	123
PIRCHE 35-90	1222	1001	787	590	450	299
PIRCHE 90+	834	652	490	368	258	147

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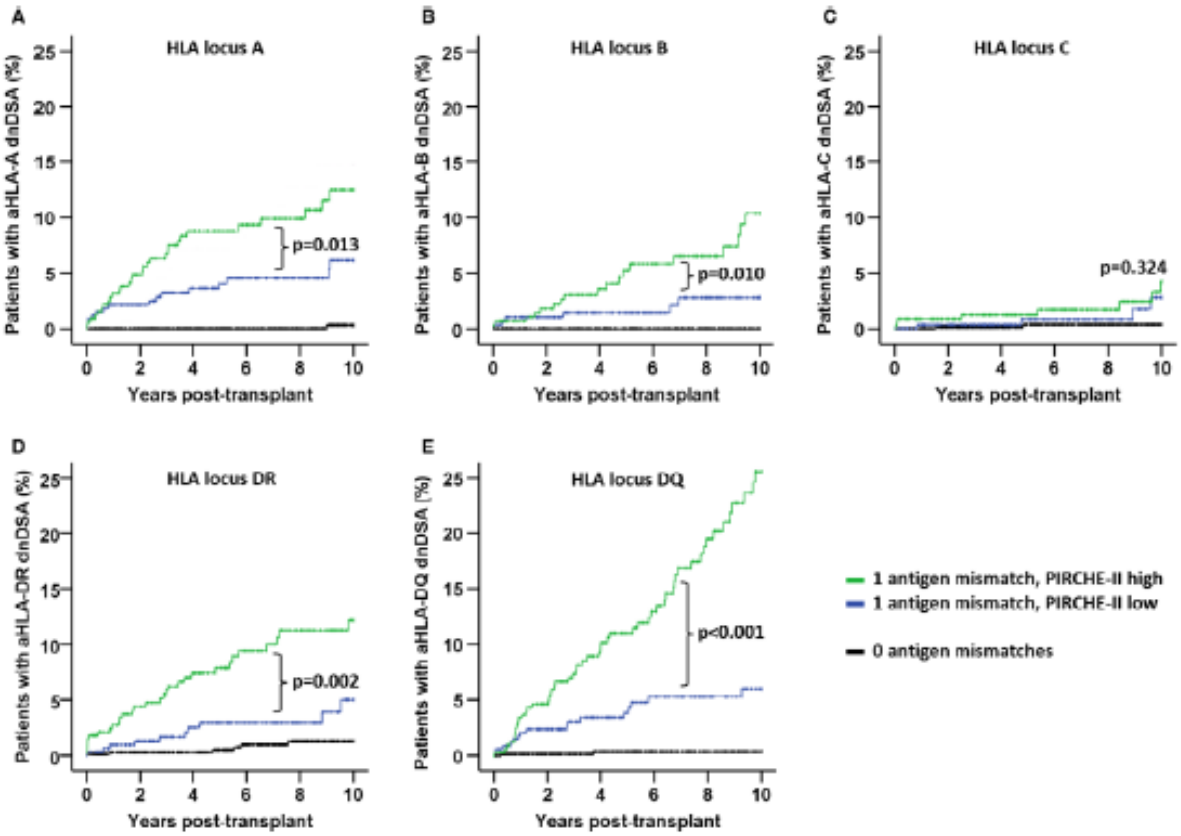

PIRCHE-II Is Related to Graft Failure after Kidney Transplantation

*Kirsten Geneugelijk[1], Matthias Niemann[2], Julia Drylewicz[1], Arjan D. van Zuilen[3], Irma Joosten[4], Wil A. Allebes[4], Arnold van der Meer[4], Luuk B. Hilbrands[5], Marijo C. Baas[5], C. Erik Hack[1], Franka E. van Reekum[3], Marianne C. Verhaar[3], Elena G. Kamburova[1], Michiel L. Bots[6], Marc A. J. Seelen[7], Jan Stephan Sanders[7], Bouke G. Hepkema[8], Annechien J. Lambeck[8], Laura B. Bungener[8], Caroline Roozendaal[8], Marcel G. J. Tilanus[9], Joris Vanderlocht[10], Christian E. Voorter[9], Lotte Wieten[9], Elly M. van Duijnhoven[11], Mariëlle Gelens[11], Maarten H. L. Christiaans[11], Frans J. van Ittersum[12], Azam Nurmohamed[12], Junior N. M. Lardy[13], Wendy Swelsen[13], Karlijn A. van der Pant[14], Nealke C. van der Weerd[14], Ineke J. M. ten Berge[14], Friederike J. Bemelman[14], Andries Hoitsma[15], Paul J. M. van der Boog[16], Johan W. de Fijter[16], Michiel G. H. Betjes[17,18], Sebastiaan Haidt[19], Dave L. Roelen[19], Frans H. Claas[19], Henny G. Otten[1] and Eric Spierings[1]**

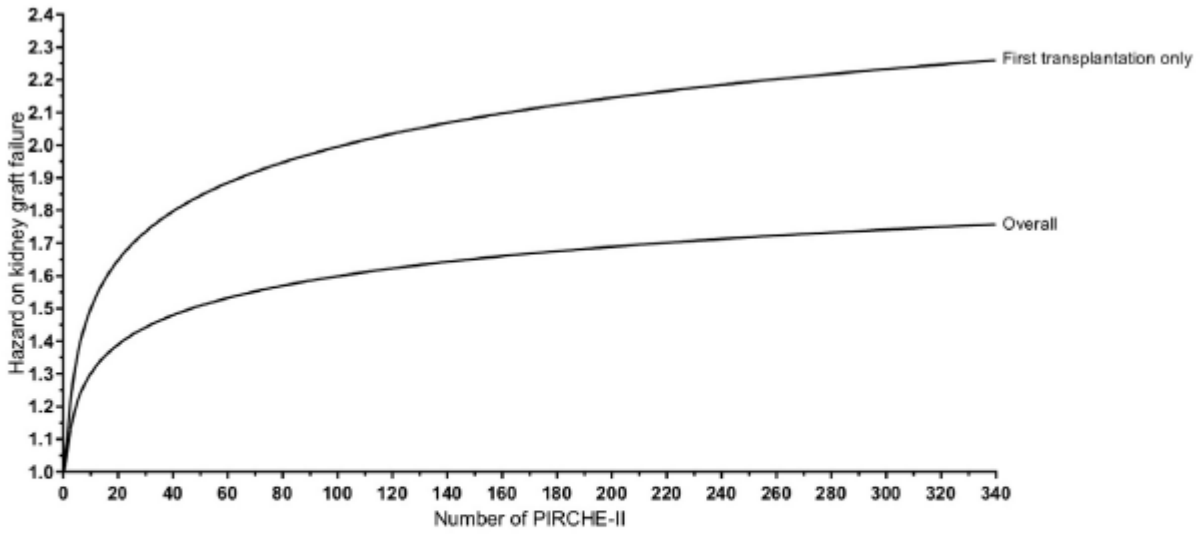

FIGURE 2 | Modeling of the increased hazard on graft failure for each Predicted Indirectly ReCognizable HLA Epitopes presented by recipient HLA class II (PIRCHE-II). Based on the multivariable analyses, the kidney graft failure risk is plotted as a function of the number of PIRCHE-II for both the overall 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*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.

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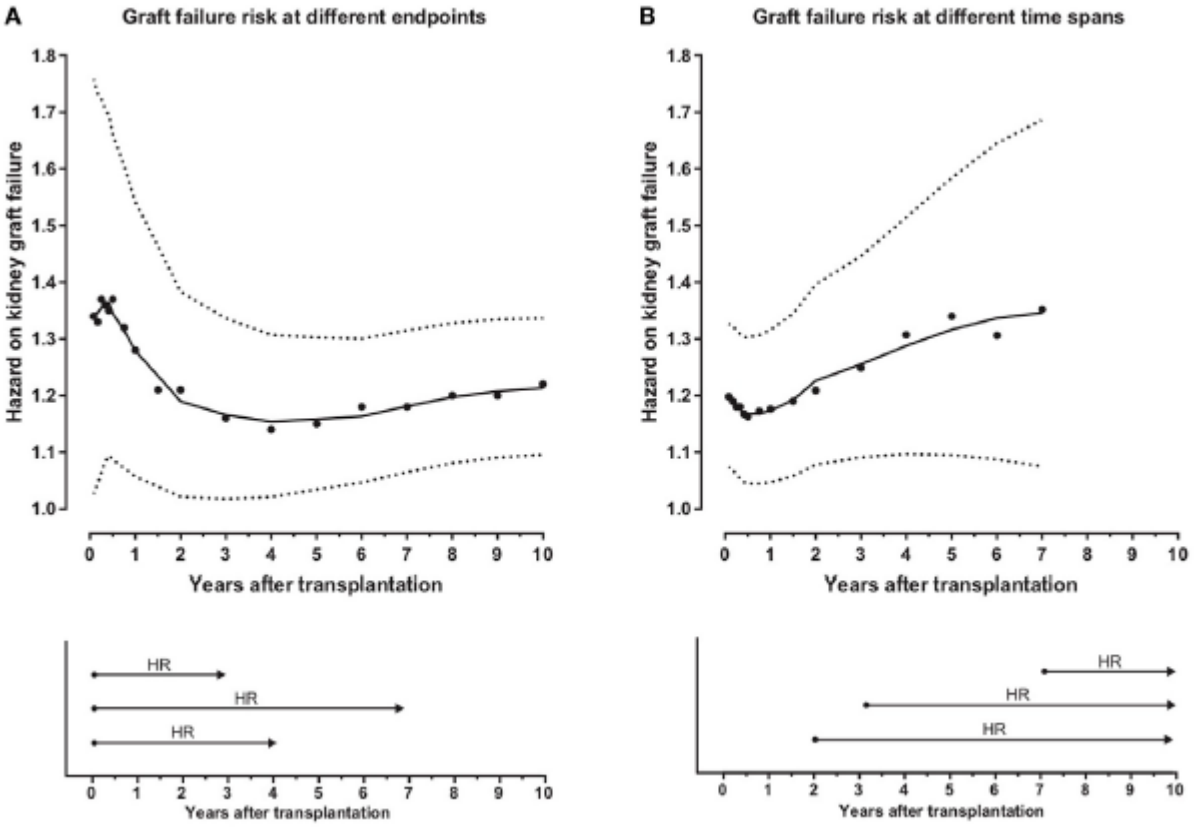
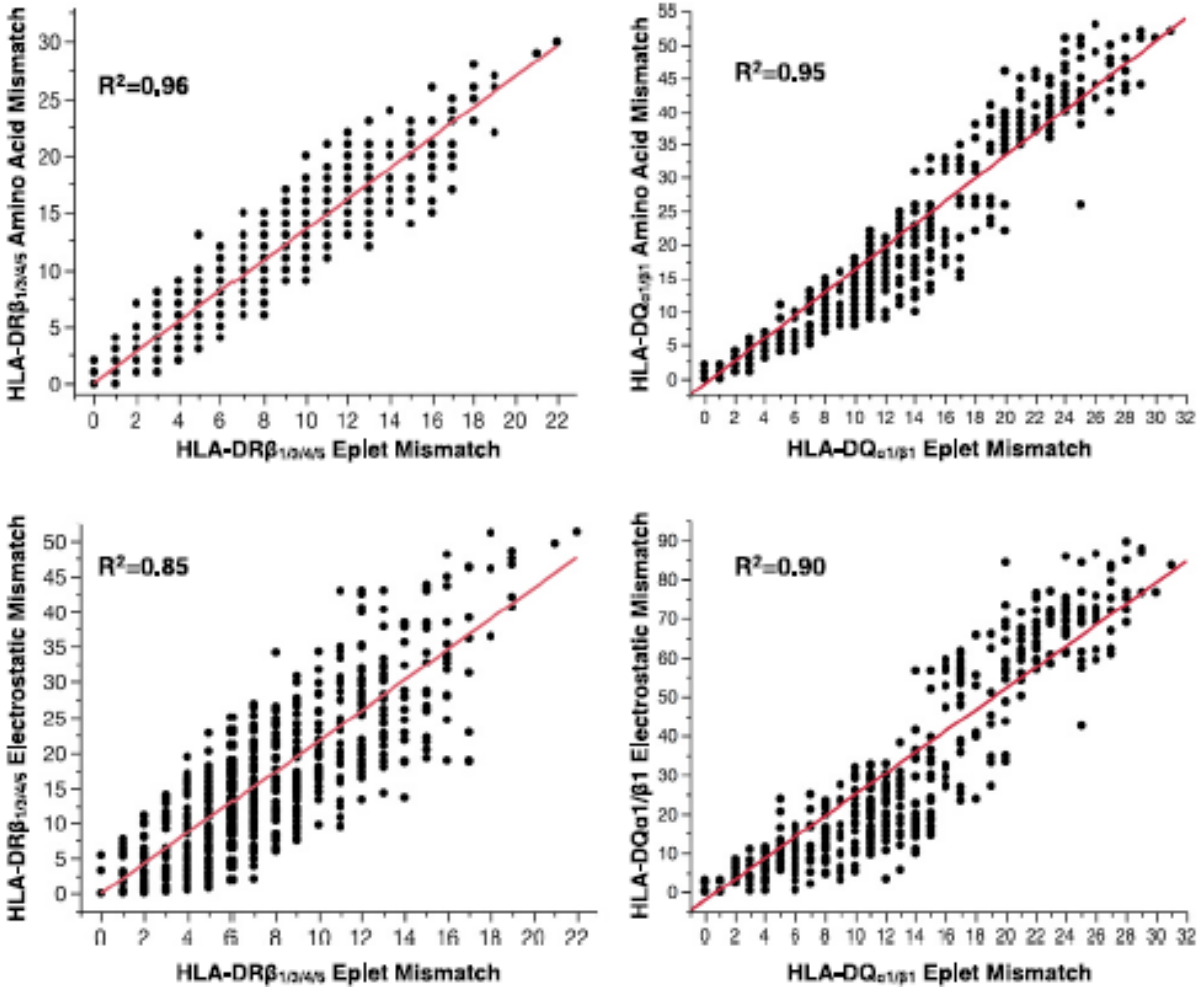


A Comparison of HLA Molecular Mismatch Methods to Determine HLA Immunogenicity

Chris Wiebe, MD,[1,2] Vasilis Kosmoliaptsis, MD, PhD,[3,4] Denish Pochinco,[2] Craig J. Taylor, PhD,[5] and Peter Nickerson, MD[1,2,6]

Background. Antibody-mediated rejection is a major cause of premature graft loss in kidney transplantation. Multiple scoring systems are available to assess the HLA mismatch between donors and recipients at the molecular level; however, their correlation with the development of de novo donor-specific antibody (dnDSA) has not been compared in recipients on active immunosuppression. **Methods.** HLA-DR$\beta_{1/3/4/5}$/DQ$_{\alpha1\beta1}$ molecular mismatch was determined using eplet analysis, amino acid mismatch, and electrostatic mismatch for 596 renal transplant recipients and correlated with HLA-DR/DQ dnDSA development. The molecular mismatch scores were evaluated in multivariate models of posttransplant dnDSA-free survival. **Results.** Eplet mismatch correlated with amino acid mismatch and electrostatic mismatch (R^2 = 0.85-0.96). HLA-DR dnDSA-free survival correlated with HLA-DR eplet mismatch (hazards ratio [HR], 2.50 per 10 eplets mismatched; $P < 0.0001$), amino acid mismatch (HR, 1.49 per 10 amino acids mismatched; $P < 0.0001$), and electrostatic mismatch (HR, 1.23 per 10 units mismatched; $P < 0.0001$). HLA-DQ dnDSA-free survival correlated with HLA-DQ eplet mismatch (HR, 1.98 per 10 eplets mismatched; $P < 0.0001$), amino acid mismatch (HR, 1.24 per 10 amino acids mismatched; $P < 0.0001$), and electrostatic mismatch (HR, 1.14 per 10 units mismatched; $P < 0.0001$). All 3 methods were significant multivariate correlates of dnDSA development after adjustment for recipient age, baseline immunosuppression, and nonadherence. **Conclusions.** HLA molecular mismatch represents a precise method of alloimmune risk assessment for renal transplant patients. The method used to determine the molecular mismatch is likely to be driven by familiarity and ease of use as highly correlated results are produced by each method.

(*Transplantation* 2018;102: 1338–1343)


R²=0.96
HLA-DRβ1/3/4/5 Amino Acid Mismatch
HLA-DRβ1/3/4/5 Eplet Mismatch
R²=0.95
HLA-DQα1/β1 Amino Acid Mismatch
HLA-DQα1/β1 Eplet Mismatch
R²=0.85
HLA-DRβ1/3/4/5 Electrostatic Mismatch
HLA-DRβ1/3/4/5 Eplet Mismatch
R²=0.90
HLA-DQα1/β1 Electrostatic Mismatch
HLA-DQα1/β1 Eplet Mismatch

Utility of epitope or eplet matching in the allocation of donor kidney for transplantation

- **Preventing future allosensitization (e.g. pediatric)**
- **Selecting suitable donor kidney for highly sensitized patients**
- **Identifying acceptable vs. unacceptable immunogenic epitopes (e.g. KPD)**