Update on HLAMatchmaker: A Molecularly Based Algorithm for Histocompatibility Determination at the Epitope Level

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Introduction

A previous issue of the *ASHI Quarterly* introduced HLAMatchmaker as a matching program that considers the structural basis of epitopes on class I HLA antigens.[1] Each HLA antigen can be viewed as a string of short sequences (triplets) involving polymorphic amino acid residues in antibody-accessible positions; the triplets are considered key elements of epitopes that can induce the formation of specific antibodies.[2-4] The patient's own HLA antigens represent the repertoire of self-triplets to which no antibodies can be made and HLAMatchmaker determines, for each mismatched donor HLA antigen, which triplets in corresponding sequence positions are different. The HLA phenotype of the recipient determines the degree of structural compatibility of a mismatched HLA antigen. For certain HLA phenotypes, a given mismatch has no or few mismatched triplets, while for other phenotypes, the same HLA antigen has many mismatched triplets and is, therefore, structurally highly incompatible.

Triplet Matching in Transplantation

The triplet matching concept has clinical relevance as suggested by an analysis of the UNOS and Eurotransplant kidney transplant databases showing that HLA-A,B-mismatched kidneys that are compatible at the triplet level exhibit almost identical graft survival rates as the zero HLA-A,B antigen mismatches defined by conventional criteria.[5] This beneficial effect of triplet matching applies to both non-sensitized and sensitized patients and also to white and non-white patients. Haririan et al.[6] have also shown that triplet matching can provide useful prognostic information about kidney transplantation in African-Americans. Although the group of Opelz et al. concluded from their analysis of the Collaborative Transplant Database that triplet matching had no significant association with kidney graft survival,[7] their data showed clearly similar five-year graft survivals for the zero-antigen mismatches and groups with zero or few triplet mismatches.[8] Interestingly, in 2003, Opelz et al. published a study showing that mismatching for HLA-DP, especially at the level of structurally-defined DPB epitopes, had an adverse effect on kidney transplant survival.[9] Class I triplet-based matching is also associated with a better prognosis for penetrating keratoplasty and reduces the time on the waiting list for most patients awaiting a corneal transplant.[10] Thus, HLAMatchmaker can be used to increase the number of suitably matched kidney donors.[11]

In view of the importance of HLA antibodies in transplantation, Dankers et al.[12] have shown a strong correlation between the number of mismatched triplets and the degree of humoral sensitization induced by a kidney transplant or developed during pregnancy. In contrast, there seems no significant association between triplet mismatching and cytotoxic T-cell precursor frequencies, an indicator of cellular alloimmune responsiveness.[13]

Triplet-based Serum Analysis

HLAMatchmaker has primarily been used to analyze the reactivity patterns of sera from highly sensitized patients analysis and to identify potential donors with acceptable mismatches. Early studies by Lobashevsky et al.[14] have shown that the number of immunogenic triplet mismatches offers a reliable predictive value for results of flow cytometry crossmatches with high-PRA sera from renal patients. The group of Frans Claas et al. in Leiden has convincingly demonstrated that the primary purpose of serum screening is the identification of acceptable mismatches for highly sensitized patients.[15-18] This approach shortens the waiting time for a suitable kidney donor and leads to excellent graft survivals comparable to those seen with non-sensitized recipients.[15] The application of HLAMatchmaker has enhanced the Acceptable Mismatch program[16] and is now routinely used in Eurotransplant.[18] The cumulative frequencies of self-antigens and acceptable mismatches can be used to calculate a PFD (Probability of Finding a Donor) as an assessment of the transplantability of a sensitized patient.[11]

Other investigators have also reported the usefulness of HLAMatchmaker in the clinical setting. Investigators in Greece demonstrated that patients with rejected transplants had antibodies specific for triplets on donor class I mismatches and they suggested that this information is beneficial in the selection of suitable donors for retransplantation.[19,20] Goodman et al. reported a strong correlation between the number of mismatched triplets and the presence of HLA antibodies detected in Luminex assays with single class I allele beads.[21] A report by Nambiar et al. has validated the potential of HLAMatchmaker in refining and expanding platelet donor selection for refractory, thrombocytopenic patients.[22] Very recently, Valentini et al. applied HLAMatchmaker to the selection of successful kidney transplants for two highly sensitized pediatric patients treated with intravenous immunoglobulin.[23,24]

Structural Aspects of Epitopes on Protein Antigens

Although the triplet version of HLAMatchmaker has proven to be clinically useful, it provides an incomplete description of the structural HLA epitope repertoire. Expanded criteria for epitope definition must be used, including longer sequences, polymorphic residues in discontinuous positions, with consideration of the structural basis of antibody-antigen interactions including contact areas and binding energy, the essence of antigenicity.

A recent report describes the development of a structurally-defined HLA epitope repertoire based on stereochemical modeling of crystallized complexes of antibodies with different protein antigens such as Hen Egg Lysozyme and Horse Cytochrome C.[25] This analysis also considered data in the literature concerning contributions of critical amino acid residues to antigen-antibody binding energy. The results have led to the concept that antigenic proteins have structural epitopes consisting of 15-22 residues that constitute the binding face with alloantibody. Most structural epitopes have one patch of about 2-5 so-called highly energetic residues (sometimes referred to as "hot spots") that dominates the strength and specificity of binding with antibody. The residues of such a functional epitope are about 3 Ångstroms apart from each other and at least one of them is non-self. The remaining residues of a structural epitope provide supplementary interactions that increase the stability of the antigen-antibody complex.[26]

Certain structural epitopes have two energetic residue patches that are about 8-15 Ångstroms apart. The two-patch shape of a functional epitope may also apply to some HLA epitopes. A recent study on triplet-specific human monoclonal antibodies has shown that antibody binding depends on the presence of a critical second contact site shared between the immunizing antigen and the triplet-carrying reactive alleles.[27] For instance, the reactivity of an anti-62QE human monoclonal antibody requires the presence of a glycine residue in position 56. 62QE-carrying alleles are non-reactive if they have 56R. Similarly, the reactivity of two 142MI-specific monoclonals requires the presence of the GTLRG sequence in positions 79-83. These residues are located about 10-15 Ångstroms from these triplets and they appear to serve as critical contact sites for another CDR of the antibody rather than the specificity-determining CDR. Interestingly, 56G and 79GTLRG are self-residues present in the HLA antigens of the antibody producer.

Absorption-elution analyses of allosera[28] and site-directed mutagenesis studies on class I HLA antigens[29-31] have identified additional residues that are critical for antibody-binding to epitope-defining residues. For instance, the Bw6-specific antibody SFR8-B6 recognizes an epitope defined by 75R, 79R and 82R but its reactivity also requires the presence of the 90A residue which is about 10 Å away.[31]

Development of the Eplet Version of HLAMatchmaker

These concepts about functional epitope structure have been applied to the stereochemical modeling of crystallized HLA antigens. Each polymorphic residue on the molecular surface is considered an essential component of a functional epitope that comprises all residues within a radius of 3.0-3.5 Ångstroms. Figure 1 shows the polymorphic residues on three crystallized class I molecules, HLA-A2, HLA-B27 and HLA-Cw3. On the α1 helices of HLA-A and HLA-B antigens, the molecular surface around the bound peptide (see top view) has similar numbers of exposed polymorphic positions but more polymorphic positions are visible on the α2 helices of HLA-A antigens. The α helices of HLA-C antigens have much fewer exposed polymorphic positions.

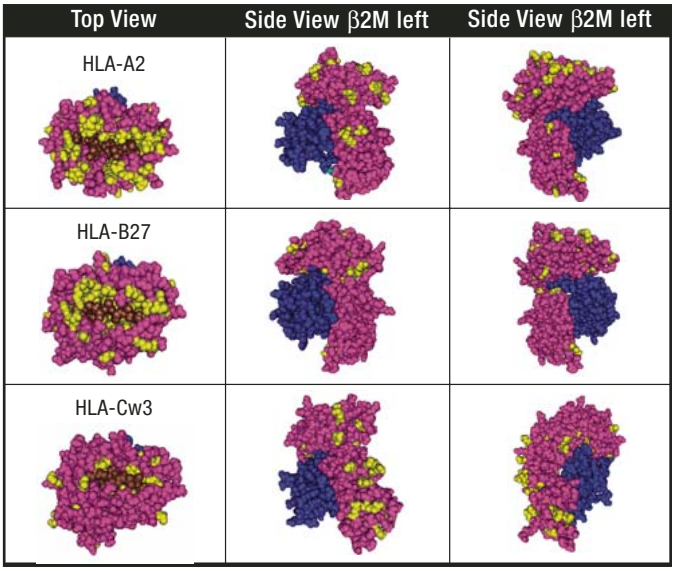


Figure 1
Polymorphic residues on class I molecules controlled by HLA-A, B and C loci

In contrast, HLA-C antigens have more polymorphic positions in the membrane-proximal domain, which become visible upon side viewing. HLA-A antigens also have more surface-exposed polymorphic positions in that region than HLA-B antigens. It should be noted that the sequence positions in the membrane-proximal domain of HLA-B are all monomorphic. Altogether, there are 75 polymorphic positions on class I HLA molecules, and the Cn3D molecular viewer analysis showed a total of 94 distinct residue combinations.[25] A determination of residue compositions yielded more than 500 unique patches. Many patches had overlapping residues and were expressed by the same allele or group of alleles. The term "eplet" is used represent one patch or an overlapping group of patches. This analysis yielded a total of 199 distinct eplets on HLA-A, B, C antigens; 110 are on the α helices, 60 are on the side surface and 29 are in less accessible positions at the bottom and under the peptide-binding groove.

Many eplets represent short linear sequences identical to those referred to as triplets, but others have residues in discontinuous sequence positions that cluster together on the molecular surface. Serologically-defined HLA determinants correspond well to eplets. The eplet version of HLAMatchmaker represents, therefore, a more complete repertoire of structurally-defined HLA epitopes and provides a more detailed assessment of HLA compatibility.

Another recent report describes the class II eplet version of HLAMatchmaker.[32] It considers all transplantation-relevant class II loci and, as Figure 2 shows, includes structural polymorphisms on both α and β chains (DRα is monomorphic). Cn3D viewing of crystalline structural models of class II molecules led to the identification of 44 DRB, 33DQB, 29 DQA, 20 DPB and 9 DPA unique combinations of polymorphic positions. Analysis of their residue compositions resulted in a repertoire of 146 DRB, 74 DQB, 58 DQA, 45 DPB and 19 DPA eplets. In many eplets, the residues are in short linear sequences but many other eplets have discontinuous sequences of residues that cluster on or near the molecular surface. This analysis has also shown that all serologically defined DR and DQ antigens detectable by monospecific antibodies have unique corresponding eplets. Other eplets are present in groups of class II antigens many of which appear cross-reacting. The application of the class II eplet version of HLAMatchmaker permits a ready detection of antibodies not only against epitopes on DRB and DQB but also on DQA, DPB and even DPA alleles. The use of eplets permits a structural assessment of donor-recipient compatibility and facilitates the determination of mismatch acceptability for sensitized patients.

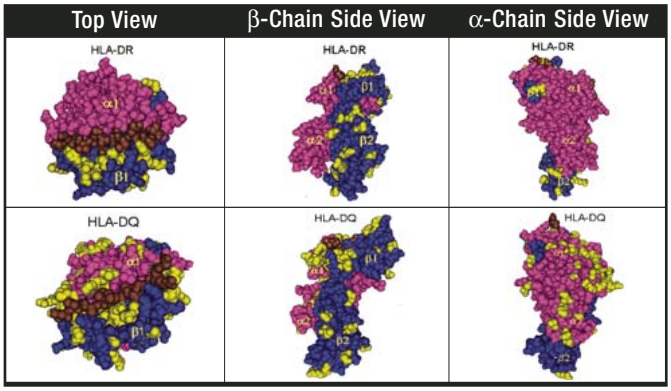


Figure 2
Visualization of polymorphic amino residue positions on HLA-DRB and HLA-DQ molecules. The following crystalline models are shown: DRA1*0101, DRB1*0101 (PDB # 1KG0) and DQA1*0301, DQB1*0302(PDB # 1JK8). Left: top view, middle: β-chain side view, right: α-chain side view

HLAMatchmaker-based Analysis of Antibody Reactivity Patterns with Single HLA Alleles

The application of the eplet version of HLAMatchmaker to the analysis of serum screens in single HLA allele Luminex assays can provide informative data about epitopes reacting with antibodies from highly sensitized patients. Figure 3 shows an example of a highly reactive antibody against HLA-DP; this patient typed as DPB1*0201, (no typing information was available for DPA1). This serum reacted with 17 of 22 DP preparations in the Luminex kit (Tepnel Lifecodes) and their mismatched eplets are shown in the upper part of Figure 3. The following alleles gave negative reactions: DPB1*0201 (self), DPB1*0401, DPB1*0402, DPB1*1801, DPA1*0103 and DPA1*0301. The eplets on these alleles can be considered acceptable mismatches. After recording the negative alleles in HLAMatchmaker, the program removes the acceptable eplets and the resultant antibody reactivity pattern corresponds with the presence of 84DE and 87AV on DPB1 and 51RA and 83RA on DPA1 (Figure 3, lower part). These eplets can be considered unacceptable mismatches. The 84DE and 87AV eplets are in close proximity and this combination probably represents a single epitope. This is consistent with studies by Marshall et al.[33] who described two monoclonal antibodies with specificities towards the 84-87 DEAV sequence. In our experience, about 20% of sera with class II antibodies react with HLA-DP eplets. About 40% of the anti-DPB1 antibodies react with an epitope defined by 84DE and 87DV and this is consistent with the findings by Danny Youngs (reported in a previous issue of the *ASHI Quarterly*[34]) who showed a 43% frequency of antibodies reacting with DEAV in positions 84-87 of DP1.

HLAMatchmaker can also readily determine antibodies against eplets shared between DRB1 and DRB3, -4, -5 alleles and distinguish between antibodies against DQB1 and DQA1 eplets. The analysis of serum screening results should consider high-resolution (four-digit) molecular types of the antibody producer and if possible, the immunizing donor. Also, very helpful is the categorization of HLA-sensitized patients according to the presence of sensitizing tissue: (1) sensitizing tissue is absent, as when a previous transplant has been removed, or a prior transfusion or pregnancy, (2) sensitizing tissue is present and may absorb donor-specific HLA antibodies and (3) the combination of both conditions, 1 and 2.

HLAMatchmaker-based Matching: Avoid Immunogenic Epitopes

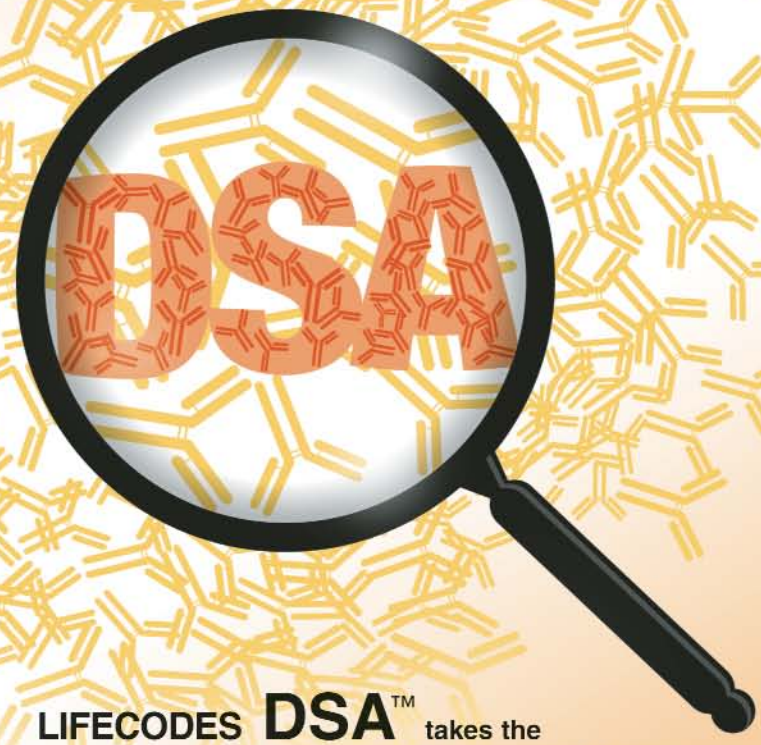
HLAMatchmaker can be considered as algorithm to determine histocompatibility at the epitope rather than antigen level in terms of the humoral alloimmune response. An epitope has two characteristics namely, antigenicity, i.e. the reactivity with antibody, and immunogenicity, i.e. the ability to induce an antibody response. Immunogenicity depends on the structural difference between an immunizing protein and the antibody responder's homologous proteins.[35] Certain structural differences lead to immunodominant epitopes whereas others are associated with low immunogenicity.

The different features of HLA immunogenicity and antigenicity are relevant to the application of structurally-based algorithms for histocompatibility testing.[17,36] HLAMatchmaker can be used as a quantitative tool to determine the degree of a mismatch. For instance, the magnitude of kidney transplant-induced humoral sensitization correlates with the number of mismatched triplets on donor antigens.[12] Moreover, certain HLA antigen mismatches are compatible at the structural level and they are associated with kidney transplant survival rates that are similar to zero-antigen mismatches.[5]

Epitope immunogenicity, as determined by the frequency of a specific antibody response, is important for histocompatibility.[3] High-immunogenicity epitope mismatches should be avoided whereas low-immunogenicity epitopes might be considered permissible mismatches. This information permits an expanded donor selection in platelet transfusions.[22]

There is no structurally-based prediction model for determining epitope immunogenicity. Possible factors include location and

Is it or isn't it donor specific antibody?



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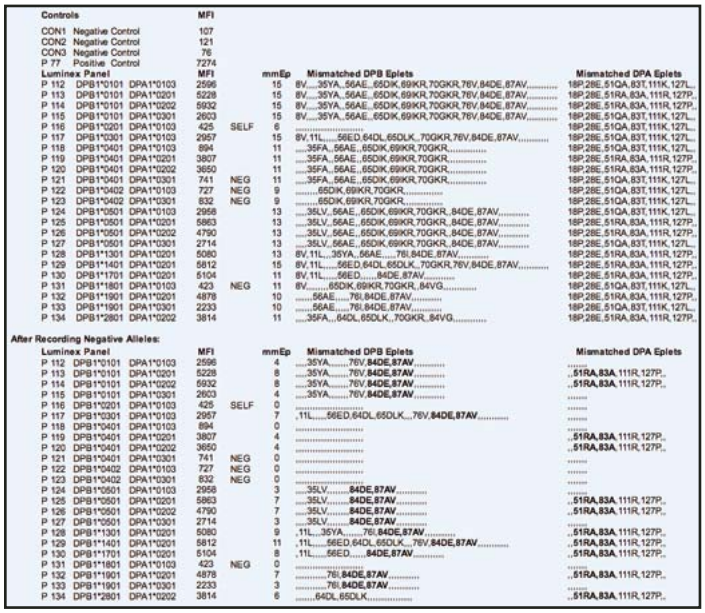
exposure of an epitope on the molecular surface, the relative difference in amino acid residue composition, and the (HLA) genetic make up of the antibody responder. For the latter, the HLA-DR phenotype of the responder has been reported to influence antibody formation to class I mismatches.[37] At present, a practical approach is to collect information about the frequencies of epitope-specific antibody responses in the context of the exposure rate to epitope mismatches.[38]



Controls			MFI			
CON1	Negative Control		107			
CON2	Negative Control		121			
CON3	Negative Control		76			
P 77	Positive Control		7274			
Luminex Panel			MFI		mmEp	Mismatched DPB Eplets
P 112	DPB1*0101	DPA1*0103	2596		15	8V,...35YA,..56AE,..65DIK,69IKR,70GKR,76V,84DE,87AV,.....
P 113	DPB1*0101	DPA1*0201	5228		15	8V,...35YA,..56AE,..65DIK,69IKR,70GKR,76V,84DE,87AV,.....
P 114	DPB1*0101	DPA1*0202	5932		15	8V,...35YA,..56AE,..65DIK,69IKR,70GKR,76V,84DE,87AV,.....
P 115	DPB1*0101	DPA1*0301	2603		15	8V,...35YA,..56AE,..65DIK,69IKR,70GKR,76V,84DE,87AV,.....
P 116	DPB1*0201	DPA1*0103	425	SELF	6	.....
P 117	DPB1*0301	DPA1*0103	2957		15	8V,11L,....56ED,64DL,65DLK,,70GKR,76V,84DE,87AV,.....
P 118	DPB1*0401	DPA1*0103	894		11	....35FA,..56AE,..65DIK,69IKR,70GKR,.....
P 119	DPB1*0401	DPA1*0201	3807		11	....35FA,..56AE,..65DIK,69IKR,70GKR,.....
P 120	DPB1*0401	DPA1*0202	3650		11	....35FA,..56AE,..65DIK,69IKR,70GKR,.....
P 121	DPB1*0401	DPA1*0301	741	NEG	11	....35FA,..56AE,..65DIK,69IKR,70GKR,.....
P 122	DPB1*0402	DPA1*0103	727	NEG	9	.....65DIK,69IKR,70GKR,.....
P 123	DPB1*0402	DPA1*0301	832	NEG	9	.....65DIK,69IKR,70GKR,.....
P 124	DPB1*0501	DPA1*0103	2958		13	....35LV,..56AE,..65DIK,69IKR,70GKR,..84DE,87AV,.....
P 125	DPB1*0501	DPA1*0201	5863		13	....35LV,..56AE,..65DIK,69IKR,70GKR,..84DE,87AV,.....
P 126	DPB1*0501	DPA1*0202	4790		13	....35LV,..56AE,..65DIK,69IKR,70GKR,..84DE,87AV,.....
P 127	DPB1*0501	DPA1*0301	2714		13	....35LV,..56AE,..65DIK,69IKR,70GKR,..84DE,87AV,.....
P 128	DPB1*1301	DPA1*0201	5080		13	8V,11L,...35YA,.56AE,....76I,84DE,.87AV,.....
P 129	DPB1*1401	DPA1*0201	5812		15	8V,11L,....56ED,64DL,65DLK,,70GKR,76V,84DE,87AV,.....
P 130	DPB1*1701	DPA1*0201	5104		11	8V,11L,....56ED,.....84DE,87AV,.....
P 131	DPB1*1801	DPA1*0103	423	NEG	11	8V,.....65DIK,69IKR,70GKR,,84VG,.....
P 132	DPB1*1901	DPA1*0201	4878		10	.....56AE,....76I,84DE,87AV,.....
P 133	DPB1*1901	DPA1*0301	2233		10	.....56AE,....76I,84DE,87AV,.....
P 134	DPB1*2801	DPA1*0202	3814		11	....35FA,..64DL,65DLK,,70GKR,84VG,.....

After Recording Negative Alleles:						
Luminex Panel			MFI		mmEp	Mismatched DPB Eplets
P 112	DPB1*0101	DPA1*0103	2596		4	....35YA,.....76V,84DE,87AV,.....
P 113	DPB1*0101	DPA1*0201	5228		8	....35YA,.....76V,84DE,87AV,.....
P 114	DPB1*0101	DPA1*0202	5932		8	....35YA,.....76V,84DE,87AV,.....
P 115	DPB1*0101	DPA1*0301	2603		4	....35YA,.....76V,84DE,87AV,.....
P 116	DPB1*0201	DPA1*0103	425	SELF	0	.....
P 117	DPB1*0301	DPA1*0103	2957		7	,11L,....56ED,64DL,65DLK,,,76V,84DE,87AV,.....
P 118	DPB1*0401	DPA1*0103	894		0	.....
P 119	DPB1*0401	DPA1*0201	3807		4	.....
P 120	DPB1*0401	DPA1*0202	3650		4	.....
P 121	DPB1*0401	DPA1*0301	741	NEG	0	.....
P 122	DPB1*0402	DPA1*0103	727	NEG	0	.....
P 123	DPB1*0402	DPA1*0301	832	NEG	0	.....
P 124	DPB1*0501	DPA1*0103	2958		3	....35LV,.....84DE,87AV,.....
P 125	DPB1*0501	DPA1*0201	5863		7	....35LV,.....84DE,87AV,.....
P 126	DPB1*0501	DPA1*0202	4790		7	....35LV,.....84DE,87AV,.....
P 127	DPB1*0501	DPA1*0301	2714		3	....35LV,.....84DE,87AV,.....
P 128	DPB1*1301	DPA1*0201	5080		9	,11L,...35YA,.....76I,84DE,87AV,.....
P 129	DPB1*1401	DPA1*0201	5812		11	,11L,....56ED,64DL,65DLK,,,76V,84DE,87AV,.....
P 130	DPB1*1701	DPA1*0201	5104		8	,11L,....56ED,.....84DE,87AV,.....
P 131	DPB1*1801	DPA1*0103	423	NEG	0	.....
P 132	DPB1*1901	DPA1*0201	4878		7	.....76I,84DE,87AV,.....
P 133	DPB1*1901	DPA1*0301	2233		3	.....76I,84DE,87AV,.....
P 134	DPB1*2801	DPA1*0202	3814		6	.....64DL,65DLK,.....

Mismatched DPA Eplets
18P,28E,51QA,83T,111K,127L,..
18P,28E,51QA,83T,111K,127L,..
18P,28E,51RA,83A,111R,127P,..
18P,28E,51RA,83A,111R,127P,..
18P,28E,51QA,83T,111K,127L,..
18P,28E,51QA,83T,111K,127L,..
18P,28E,51QA,83T,111K,127L,..
18P,28E,51RA,83A,111R,127P,..
18P,28E,51QA,83T,111K,127L,..
18P,28E,51QA,83T,111K,127L,..
18P,28E,51QA,83T,111K,127L,..
18P,28E,51RA,83A,111R,127P,..
18P,28E,51RA,83A,111R,127P,..
18P,28E,51RA,83A,111R,127P,..
18P,28E,51RA,83A,111R,127P,..
18P,28E,51RA,83A,111R,127P,..
18P,28E,51QA,83T,111K,127L,..
18P,28E,51QA,83T,111K,127L,..
18P,28E,51RA,83A,111R,127P,..

Mismatched DPA Eplets
.....
..51RA,83A,111R,127P,..
..51RA,83A,111R,127P,..
.....
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..51RA,83A,111R,127P,..
..51RA,83A,111R,127P,..
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..51RA,83A,111R,127P,..
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..51RA,83A,111R,127P,..
.....
..51RA,83A,111R,127P,..

Figure 3

One possibility is to analyze serum screenings on patients with rejected kidney transplants who have undergone allograft nephrectomy. HLAMatchmaker-based analysis reveals restricted antibody specificity patterns against certain structurally-defined epitopes on immunizing donor HLA antigens.[39] A preliminary study conducted under auspices of the 14th International HLA Workshop, has shown differences in immunogeniticity between eplets.[38] Serum screening was limited to lymphocytotoxicity assays and in some instances, antigen-binding assays such as Elisa and Flow beads. Almost no data were available about antibody responses to class II epitopes.

This study will continue as a 15th International HLA Workshop project. All serum screenings will include Luminex assays with single HLA-A, B, C and HLA-DR, DQ and DP alleles so that HLA antibody reactivity patterns can be analyzed in much more precise detail. The goal is to analyze about 200-250 informative allograft nephrectomy cases so that we can obtain reasonable estimates about epitope immunogenicity following kidney transplantation. Laboratories with informative allograft nephrectomy cases are invited to participate in this project. If needed, sera can be tested with Luminex assays in Pittsburgh. For more information, go to the website of the 15th Workshop Project: Determination of Structurally Defined Immunogenic HLA Epitopes (Coordinators: Rene Duquesnoy and Frans Claas) www.15ihiws.org/project.php?n=13. You can also contact Duquesnoy by phone at (412) 860-8083 or via e-mail at Duquesnoyr@upmc.edu.

Eplet versions of HLAMatchmaker and additional programs and tutorials can be downloaded from the Transplant Pathology Internet Service of University of Pittsburgh website: http://tpis.upmc.edu.

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