

## Structural epitope matching for HLA-alloimmunized thrombocytopenic patients: a new strategy to provide more effective platelet transfusion support?

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**BACKGROUND:** During the past three decades, HLA matching for platelet (PLT) transfusion of refractory thrombocytopenic patients has been based on serologic cross-reactivity between HLA-A and HLA-B antigens. Although many blood banks are using this matching strategy, the general experience is that such matched PLT transfusions are often ineffective.

**STUDY DESIGN AND METHODS:** This report describes a new HLA matching algorithm that considers structurally defined epitopes recognized by antibodies. HLAMatchmaker is a computer program that determines histocompatibility at the amino acid level initially designed as triplets (i.e., linear sequences of three residues in molecular surface-exposed positions) but now updated as eplets representing patches of antibody-accessible polymorphic residues surrounded by residues within a 3-Å radius. The eplet version of HLAMatchmaker is also useful in the analysis of HLA antibody reactivity patterns of alloimmunized patients so that acceptable mismatches can be identified.

**CONCLUSION:** An HLA epitope-based matching protocol is proposed that may permit a more effective PLT transfusion management of refractory patients. This protocol includes high-resolution HLA-A, -B, and -C typing of patients and donors, serum screening to identify acceptable mismatches, and the identification of suitable donors in a donor database that incorporates HLAMatchmaker as a search engine. HLAMatchmaker programs can be downloaded from the Web site <http://tpis.upmc.edu/tpis/HLAMatchmaker/>.

Alloimmunization against HLA Class I antigens has remained the major cause of refractoriness of thrombocytopenic patients to random-donor platelet (PLT) transfusions. Yankee and coworkers<sup>1</sup> first demonstrated in 1969 that alloimmunized patients can be successfully transfused with PLTs from HLA-identical donors. Duquesnoy together with Glenn Rodey and Richard Aster at the Milwaukee Blood Center applied the concept of serological cross-reactivity between HLA-A and HLA-B antigens to increase the number of potential donors.<sup>2</sup> Although after 30 years, the so-called B1X, B1U, B2X, etc., match categories are still widely implemented by apheresis PLT transfusion services, this matching strategy is often enough ineffective.<sup>3</sup> Because alloimmunization-induced refractoriness is caused by antibodies, several investigators have applied different PLT cross-matching methods to select compatible PLTs mostly from the local inventory of the blood bank.<sup>4-7</sup> This approach will also detect antibody reactivity against PLT-specific antigens but their specificity is difficult to determine in the presence of HLA antibodies. Another approach is to avoid PLTs with HLA antigens reacting specifically with the patient's antibodies.<sup>8</sup>

Obviously, the combination of matching for compatible antigens and the application of mismatch

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**ABBREVIATION:** CREG = cross-reactive group.

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acceptability determined by serum screening for HLA antibodies offers the best approach for an HLA-based PLT transfusion support of refractory patients. An important consideration is that HLA antigens have multiple epitopes that can be recognized by specific antibodies. During the 1980s, the description of epitope repertoire was based on serologic cross-reactivity between HLA antigens and antibody specificities against so-called private and public determinants.<sup>9</sup> Serum screening of highly sensitized patients shows often restricted antibody specificity patterns against high-frequency public determinants.<sup>10-12</sup> Elucidation of the stereochemical structure of the HLA molecule and determinations of amino acid sequences of HLA antigens made it possible to learn more about the structural basis of private and public determinants. This has led to many studies showing correlations between antibody specificity patterns and the presence of polymorphic amino acid residues on reactive HLA antigens. This concept was also applied to the analysis of serum samples from alloimmunized thrombocytopenic patients.<sup>13</sup>

### STRUCTURALLY BASED HLA MATCHING

Matching at the single polymorphic residue level yielded, however, limited success.<sup>14</sup> HLAMatchmaker represents an alternative structurally based matching algorithm that originally considered linear sequences of three amino acids (triplets) in antibody-accessible positions on HLA molecules; they can be considered key elements of epitopes that can induce the formation of specific antibodies.<sup>15,16</sup> 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 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 and for other phenotypes, the same HLA antigen has many mismatched triplets and is therefore structurally highly incompatible.

The triplet matching concept has clinical relevance as indicated by a large database analysis that showed that HLA-A,B-mismatched kidneys that are compatible at the triplet level have practically the same graft survival rates as the zero HLA-A,B antigen mismatches defined by conventional criteria.<sup>17</sup> This beneficial effect of triplet matching applies to both nonsensitized and sensitized patients and also to white and nonwhite patients. Thus, HLAMatchmaker can be used to increase the number of suitably matched kidney donors.<sup>18</sup> An investigation at the National Institutes of Health Clinical Center has validated the potential of HLAMatchmaker in refining and expanding

PLT donor selection for refractory, thrombocytopenic patients.<sup>19</sup> Another study has also shown that triplet matching benefits PLT transfusions and makes better use of a limited donor pool.<sup>20</sup>

HLAMatchmaker is also useful in the analysis of serum reactivity patterns with HLA panels.<sup>21,22</sup> The group of Frans Claas<sup>23-25</sup> in Leiden University Medical Center has demonstrated that the primary purpose of serum screening is the identification of acceptable mismatches for highly sensitized patients. This approach increases donor availability and leads to excellent graft survivals comparable to those seen with nonsensitized recipients.<sup>23</sup> The application of HLAMatchmaker has enhanced the Acceptable Mismatch program<sup>26</sup> and is now routinely used in Eurotransplant.<sup>25</sup> 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.<sup>18</sup>

### DEVELOPMENT OF THE EPLET VERSION OF HLAMATCHMAKER

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 must be used including longer sequences and polymorphic residues in discontinuous positions and they should consider 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.<sup>27</sup> This analysis considers the concept that antigenic proteins have functional epitopes consisting of amino acid residues that are about 3 Å apart from each other and at least one of them is nonself. There are 75 polymorphic positions on the surface of Class I HLA molecules, and a molecular viewer analysis has yielded a total of 199 so-called "eplets" on HLA-A, -B, and -C antigens.<sup>27</sup> Another report describes the Class II eplet version of HLAMatchmaker.<sup>28</sup> These computer programs can be downloaded from the Web site <http://tpis.upmc.edu/tpis/HLAMatchmaker/>.

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.

### LIMITATIONS OF THE CROSS-REACTIVITY BASED HLA MATCH GRADE SYSTEM FOR MANAGING REFRACTORY PATIENTS

The so-called Duquesnoy match grade system described in the AABB *Technical Manual*<sup>29</sup> has three shortcomings that can be readily solved with HLA-Matchmaker. The first one deals with groups of cross-reacting antigens that are used to assign the B1X, B1UX, B2X, etc., match grades. As an example, HLA-A2, HLA-A23, HLA-A24, HLA-A68, and HLA-A69 form the so-called A2 cross-reactive group (CREG) because they share a public epitope that corresponds to an eplet defined by 127K, that is, a lysine residue in the polymorphic position 127.<sup>30</sup> Accordingly, A23 and A24 are B1X mismatches for A2. As shown in Table 1, these antigens have, however, considerable differences in their eplet makeup. For instance, A\*2301 and A\*2402 have the 79RI, 80IL, and 82LR eplets, which correspond to Bw4. (In the eplet notation system, a number indicates the sequence position of the polymorphic amino acid residue and the polymorphic residues within a 3-Å radius; residues are listed with the standard single-letter code.) Early studies had shown that Bw4 incompatibility may adversely affect PLT transfusion responses of refractory patients.<sup>31</sup> The HLA type of the patient determines the acceptability of the Bw4-associated eplets on A\*2301 and A\*2402. These eplets would be unacceptable for a patient who types as HLA-A2,A3;B7,B8 but acceptable for a patient who types as HLA-A2,A25;B7,B8 because A25 has the 79RI, 80IL, and 82LR eplets. For the latter, acceptability of A\*2301 and A\*2402 would be overruled if the patient has antibodies against other eplets on these alleles such as 9S, 62EE, 65GKA, and others shown in Table 1, because each one has the potential of inducing specific antibodies. Similarly, A2, A68, and A69 are considered as a short A2 CREG (they uniquely share 142MT) but they have eplet differences in positions 9, 62, 65, etc. The degree of eplet matching depends on the HLA type of the patient and HLA-Matchmaker can readily determine this.

The second limitation deals with the A, B1U, and B2U match groups, which are based on identity of serologically defined antigens and assume homozygosity for one or both loci. Molecular typing at the high-resolution or four-digit level has revealed additional subtypes (alleles) with amino acid sequence differences. Several of them involve antibody-accessible positions on the surface of the HLA molecule, and Table 2 shows examples of eplet differences between alleles. For instance, A\*0203 has four eplet differences with A\*0201, including 149TAH, which is also found on A25-, A26-, and A34-associated alleles. A\*0203 would be a mismatch for patients who type for A\*0201 and all other HLA-A antigens except A25, A26, and A34. Table 2 also shows that subtypes of antigens like A24, A30, B27, and B55 are not always matched at the epitope level.

TABLE 1. Eplet compositions of common alleles in the A2 cross-reactive group\*

A*0201	9FT	11SV	14RR	30D	35RME	41A	44RM	46RME	56G	62GET	65RKAT	66KAHT	71HST
A*2301	9ST	11SV	14RR	30D	35RME	41A	44RM	46RME	56G	62EE†	65GKAT	66KAHT	71HST
A*2402	9ST	11SV	14RR	30D	35RME	41A	44RM	46RME	56G	62EE†	65GKAT	66KAHT	71HST
A*6801	9YT	11SV	14RR	30D	35RME	41A	44RM	46RME	56G	62RNT†	65RNAT	66NAQT	71QST
A*6901	9YT	11SV	14RR	30D	35RME	41A	44RM	46RME	56G	62RNT†	65RNAT	66NAQT	71QST
A*0201	73TD†	76VDT†	79GT†	80TR†	90A	105S	107W†	109F	113YH†	116Y†	127K‡	131R	142MT†
A*2301	73TN†	76ENI†	79RI†	80IL†	90A	105S	107G†	109F	113YH†	116Y†	127K‡	131R	142MI†
A*2402	73TN†	76ENI†	79RI†	80IL†	90A	105S	107G†	109F	113YH†	116Y†	127K‡	131R	142MI†
A*6801	73TD†	76VDT†	79GT†	80TR†	90A	105S	107G†	109F	113YH†	116D†	127K‡	131R	142MT†
A*6901	73TD†	76VDT†	79GT†	80TR†	90A	105S	107W†	109F	113YH†	116Y†	127K‡	131R	142MT†
A*0201	144KH†	145HAA†	149AAH†	150AHV†	158A	161E	163TW†	166EW	177ET	180Q	184A†	193AV†	
A*2301	144QR†	145RAA†	149AAP†	150ARV†	158A	161E	163TG†	166DG	177ET	180Q	184P†	193PI†	
A*2402	144KR†	145RAA†	149AAH†	150AHV†	158A	161E	163TG†	166DG	177ET	180Q	184P†	193PI†	
A*6801	144KH†	145HAA†	149AAH†	150AHV†	158A	161E	163TW†	166EW	177ET	180Q	184A†	193AV†	
A*6901	144KH†	145HAA†	149AAH†	150AHV†	158A	161E	163TW†	166EW	177ET	180Q	184A†	193AV†	

\* The standard amino acid code is used to show the polymorphic residues in each eplet.

† Eplet differences between alleles.

‡ The 127K eplet represents the public epitope shared by the members of the A2 CREG.

**TABLE 2. Examples of eplet differences between allelic subtypes of HLA antigens**

A*0201	9F	145HAA	149AAH	150AHV	151HV				
A*0203	9F	145HTA	149TAH	150AHE	151HE				
A*0205	9Y	145HAA	149AAH	150AHV	151HV				
A*2402	163TG	166DG							
A*2403	163TW	166EW							
A*3001	66NAQ	71QS	73TD	76VDT	150ARW	151RW			
A*3002	66NAH	71HS	73TN	76ENT	150ARR	151RR			
B*2702	73TN	76ENI	79RI	80IL	82LR	113YH	116D	150ARV	151RV
B*2705	73TD	76EDT	79RT	80TL	82LR	113YH	116D	150ARV	151RV
B*2706	73TS	76EST	79RT	80TL	82LR	113YD	116Y	150ARE	151RE
B*2708	73TS	76ESN	79RN	80NR	82RG	113YH	116D	150ARV	151RV
B*5501	150ARE	151RE							
B*5502	150ARV	151RV							

**TABLE 3. Proposed HLA epitope-based matching protocol for PLT transfusion management of alloimmunization-induced refractoriness**

- A. Refractory patients
  1. Perform HLA-A, -B, and -C typing of patients and donors by DNA methods at the high-resolution (four-digit allele) level.
  2. Screen patient serum samples with HLA-typed panel:
    - a. Complement-dependent methods: direct and/or antiglobulin-augmented lymphocytotoxicity;
    - b. Antigen-binding assays such as Luminex, flow cytometry, and ELISA preferably with single HLA Class I alleles;
    - c. HLAMatchmaker-based analysis of serum reactivity pattern to identify acceptable mismatches.
  3. Conduct a PLT donor search:
    - a. Establish a computerized PLT donor registry that incorporates an HLAMatchmaker-based search engine;
    - b. Enter the HLA type of the patient and the nonreactive mismatched alleles in this database and the computer will generate a list of donors with matches and acceptable mismatches at the eplet level;
    - c. No need for PLT cross-match testing for HLA incompatibility.
  4. Evaluate the outcome of the PLT transfusion, if increment is low then:
    - a. Determine whether serum reactivity patterns have improperly been interpreted in terms of HLA mismatch acceptability;
    - b. Look for antibodies against PLT-specific antigens and blood groups or autoimmune phenomena and drug reactions;
    - c. Consider clinical conditions such as coagulopathy, infection, and hepatosplenomegaly.
- B. Prevention or delay of HLA alloimmunization
  1. HLAMatchmaker-based selection of apheresis PLTs with minimal numbers of mismatched eplets:
    - a. From existing inventories of stored PLTs;
    - b. Do a computer search for compatible PLT donor;
    - c. Avoid immunogenic eplets.
  2. Leukoreduction of PLT preparations before transfusion.

The third shortcoming of the CREG-based matching is that it considers only HLA-A and HLA-B antigens. The reason for excluding HLA-C is based on an early report that this locus plays no role in PLT transfusion responses.<sup>32</sup> Moreover, it was believed that HLA-C antigens have low expression on PLTs.<sup>33</sup> In those days HLA-C typing was done with serologic methods using inadequate typing sera defining a small number of HLA-C antigens. At present, complete HLA-C typing can be achieved with DNA-based methods. Recent studies have suggested that HLA-C matching might be necessary for the PLT transfusion support of some alloimmunized patients.<sup>34</sup> This could best be done by HLA-C typing at the DNA level and by

considering the structural basis of HLA-C epitopes. HLA-C alleles have a repertoire of more than 40 eplets. Certain eplets like 1C and 6K on Cw\*0102 and 14W on Cw\*0401, correspond to serologically defined antigens whereas many other eplets such as 21H on Cw\*0202, Cw\*0303, Cw\*0304, and Cw\*1502 are shared between two or more alleles and may represent public epitopes. HLAMatchmaker can determine HLA-C compatibility by comparing eplet strings of donor and recipient alleles. In our experience, serum screening with single-allele Luminex beads has shown HLA-C eplet-specific antibodies in HLA-sensitized patients.

### PROPOSAL FOR AN HLA EPIPEptide MATCHING SYSTEM FOR PLT TRANSFUSIONS OF REFRACTORY PATIENTS

HLAMatchmaker can readily overcome the shortcomings of the CREG matching system because it provides a better assessment of histocompatibility. This algorithm considers HLA matching at the epitope level and applies the concept that HLA antibodies are specific for epitopes that can be structurally defined as eplets. Moreover, HLAMatchmaker can be used in the analysis of serum reactivity with HLA panels to determine the acceptability of HLA mismatches for alloimmunized patients.

Table 3 represents an outline of a proposed HLA epitope-based matching protocol for PLT transfusion support of thrombocytopenic patients. All patients and donors should be typed for HLA-A, -B, and -C by DNA-based methods at the high-resolution (i.e., four-digit allele) level because it permits a more accurate determi-

nation of HLA epitope repertoires. Often enough, HLA typing is only available at the serological or two-digit DNA level. In such cases, the most likely four-digit types could be estimated from allele frequencies in populations of individuals with the same racial or ethnic background. The HLA-Matchmaker programs incorporate this approach.

Each patient suspected with HLA alloimmunization-induced refractoriness should be serum screened for HLA antibodies. The best approach is to use a combination of a complement-dependent method such as the direct and/or antiglobulin-augmented lymphocytotoxicity together with an antigen-binding assay such as Luminex, flow cytometry, and enzyme-linked immunosorbent assay (ELISA). Single HLA allele panels especially in the Luminex assays will generate the most informative reactivity patterns. The primary goal of a serum screen is to identify the acceptable HLA mismatches because this information offers a window of opportunity of finding more suitable donors for a refractory patient. The HLA-Matchmaker-based analysis of serum reactivity patterns can determine which alleles have eplets that do not react with the patient's antibodies and these can be considered acceptable mismatches. The program will also identify additional alleles not used in the panel but which can be considered as acceptable mismatches. Conversely, HLA-Matchmaker can also identify antibody-reactive eplets and all such eplet-carrying alleles are unacceptable mismatches.

The identification of suitable donors can be readily done with a donor database that incorporates HLA-Matchmaker as a search engine. Entering the patient's HLA type and the mismatched alleles that do not react with the patient's serum sample will generate a list of donors with matches and acceptable mismatches. Such donors do not need to be tested by labor-intensive PLT cross-matching for HLA incompatibilities. It is possible that insufficient numbers of donors are available for patients with uncommon HLA types and extremely high serum reactivity with the HLA panel. In such cases, the search could be extended to alleles with one or few mismatched eplets especially those with low immunogenicity. A few reports describe preliminary data about the relative immunogenicity of eplets (and triplets)<sup>16,35,36</sup> but more studies are needed to obtain more complete information.

Although HLA-Matchmaker is an epitope-based program for histocompatibility, it should be noted that donor match groups are presented as HLA alleles and are therefore easy to use in the practical setting. The success of any PLT transfusion depends on the resulting increment and the correction of the bleeding problem. Cases with low increments might be due to unrecognized HLA-related problems relative to serum screening results and erroneous interpretations of antibody reactivity patterns.

With this improved HLA matching system, it would be easier to recognize other immunologic causes of low increment such as antibodies against PLT-specific antigens, autoimmune reactivity, and drug reactions. Nonimmune clinical conditions such as coagulopathy, sepsis, and hepatosplenomegaly are of course also frequent causes of low increments.

## PREVENTION OR DELAY OF HLA ALLOIMMUNIZATION

The frequency of immune refractoriness has declined during the past decade largely due to the application of leukoreduction to PLT preparations and red cells before transfusion.<sup>37,38</sup> Nevertheless, significant proportions of thrombocytopenic patients become refractory due to HLA alloimmunization. The latter problem can be minimized by providing long-term transfusion support with PLTs from HLA-matched apheresis donors. This strategy is impractical because not many such donors are available for most patients. Another approach is to apply HLA-Matchmaker to identify donors with fewest possible epitope mismatches. The demonstration by the Leiden group of a strong correlation between the number of mismatched triplets and the degree of antibody sensitization induced by a kidney transplant or developed during pregnancy is relevant.<sup>39</sup> This concept could be applied to the selection of inventoried PLTs with no or few eplet mismatches or, better yet, recruiting appropriately matched apheresis donors.

## CONCLUDING REMARKS

The serologic cross-reacting antigen matching system introduced in 1977 should be replaced by a system that incorporates modern concepts of epitope reactivity with antibody. The proposed HLA epitope matching protocol is expected to benefit PLT transfusion outcome and increase the number of compatible donors for refractory patients. Three reports have provided evidence of the usefulness of HLA-Matchmaker in selecting PLT donors.<sup>19,20,36</sup> A prospective study at the National Blood Services in the United Kingdom is under way to evaluate the clinical efficacy of HLA epitope-matched PLT transfusions in aplastic anemia patients.

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