

ORIGINAL ARTICLE

MODELS OF HLA-DPB1 PERMISSIVENESS AND UNRELATED DONOR HEMATOPOIETIC CELL TRANSPLANTATION

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ABSTRACT

In current allo-HCT practice, a fully HLA-matched sibling donor is the best donor associated with improved transplant outcomes. When a matched sibling donor is unavailable, the second best available donor option is a matched unrelated donor (MUD), either HLA 8/8 or HLA 10/10. One notable characteristic in the MUD setting is that HLA-DPB1 mismatches are present in around 80/85% of unrelated donor/recipient pairs. This unique feature has an additional layer of complexity as these HLA-DPB1 incompatibilities may be further divided into permissive and non-permissive mismatches by two biological-driven permissiveness models, namely T-cell epitope (TCE) and DP expression. In the current review article, we described the basics of T-cell allorecognition, the unique HLA-DPB1 immunogenetics, the early conflicting results regarding HLA-DPB1 mismatching in allo-HCT, the development and the clinical impact of T-cell epitope and Expression models, the new indirect allorecognition algorithm of HLA-DPB1 permissiveness (PIRCHE model), the role of HLA-DPB1 in nonmalignant disease setting, and future perspectives on HLA-DPB1 permissiveness.

Keywords: HLA-DP beta-Chains. Hematopoietic Stem Cell Transplantation. Unrelated Donors.

INTRODUCTION

Allogeneic hematopoietic cell transplantation (allo-HCT) is a highly complex curative treatment for patients with malignant and nonmalignant diseases^{1,2}. While several patient, donor, and transplant characteristics influence the HCT prognosis, the Human Leukocyte Antigen (HLA) genetic disparity between patient/donor pairs is a critical factor affecting HCT outcomes³. The HLA gene complex is highly polymorphic and located in the short arm of chromosome 6. It contains several genes with immu-

nological functions, and the classical histocompatibility genes include HLA-A, -B, and -C in class I and HLA-DRB1, -DQB1, and -DPB1 in class II⁴.

A major immunological feature of HSCT is the potent allorecognition of HLA mismatched proteins via T-cell receptors. Allorecognition occurs when T cells from one individual recognize and react to foreign HLA molecules from another individual⁵. This vigorous alloimmune response occurs bidirectionally in Host-versus-Graft (HvG) and Graft-versus-Host (GvH) directions⁶. In the HvG allorecognition, the

patient T-cell recognizes HLA-mismatched proteins expressed in donor cells. In turn, the donor T-cell recognizes HLA mismatches in the patient's cells in the GvH direction. Moreover, T-cell allorecognition may occur from three distinct pathways: direct, indirect, and semi-direct⁵. In direct T-cell allorecognition, T-cells recognize an intact allogeneic HLA molecule expressed by a distinct individual (Figure 1A). Indirect allorecognition occurs when T-cells recognize a self-HLA molecule presenting an allogeneic peptide derived from the foreign HLA molecule (Figure 1B). The semi-direct pathway has been described in solid organ transplantation but has not been investigated in the allo-HCT⁵.

In the allo-HCT context, HvG and GvH alloreactivities lead to immune graft rejection and acute and chronic graft-versus-host disease (GVHD)⁶. The GvH alloreactivity may also be beneficial by mediating relapse control via the graft-versus-leukemia (GvL) effect⁷. Therefore, to minimize the deleterious T-cell allorecognition following allo-HCT, the best donor option is a 12/12 HLA-matched sibling⁸; however, depending on the patient's age and ethnicity, a fully matched sibling is available for only 13% to 51% of patients⁹. For the remaining patients, the second-best option is an 8/8 matched unrelated donor (MUD)¹⁰. However, selecting the best MUD can be challenging, as it is influenced by the unique characteristics of HLA-DPB1 immunogenetics¹¹.

HLA-DPB1 IMMUNOGENETICS

HLA-DPB1 is a classical transplantation antigen capable of eliciting GVH allorecognition¹². Due to its unique exon 2 polymorphism, with six hypervariable regions (A, B, C, D, E, and F) and differential expression in 3'-untranslated region (rs9277534 marker), the HLA-DPB1 locus presents distinct immunogenetic features compared to other classical histocompatibility genes^{13,14}.

The HLA-DPB1 gene is located 400 Mb away from the HLA-DRB1/DQB1 genes and is separated by a recombination hotspot¹⁵. This results in a significant variation in the HLA-DPB1 locus, leading to extensive mismatching in 80-85% of MUD^{16,17} and 5-10% of HLA-matched siblings¹⁸⁻²⁰. Moreover, the HLA-DPB1 antigens exhibit differential expression levels based on the single nucleotide polymorphism rs9277534 (G/A) in the 3' untranslated region¹⁴. Previous studies have demonstrated that HLA-DPB1 antigens associated with the rs9277534G variant have higher surface expression than those associated with the rs9277534A variant (Figure 2). Low-expression *HLA-DPB1* alleles include *02:01, *02:02,

*04:01, *04:02, *17:01, 23:01, 24:01, 30:01, 31:01, 39:01, 40:01, 41:01, while high-expression *HLA-DPB1* alleles include *01:01, *03:01, *05:01, *06:01, *09:01, *10:01, *11:01, *13:01, *14:01, *15:01, *16:01, *18:01, *19:01, and *20:01²¹.

Importantly, the two validated models of HLA-DPB1 permissiveness, T-cell epitope (TCE)¹⁶ and HLA-DP expression²², have been translated into clinical practice based on HLA-DPB1's exon 2 polymorphism and rs9277534G/A expression marker, respectively.

"EARLY ERA" OF HLA-DPB1 MISMATCHING

The impact of HLA-DPB1 mismatching was also assessed in the early era of bone marrow transplantation, showing controversial results. In 1993, Petersdorf et al. evaluated 129 patients who underwent bone marrow transplantation from 10/10 MUD and found no association between HLA-DPB1 mismatching and acute GVHD²³. In a follow-up study, the Seattle group reassessed the role of HLA-DPB1 mismatching in a cohort of 205 patients receiving 10/10 MUD allo-HCT. Compared to the HLA-DPB1 match group, only two HLA-DPB1 mismatches were associated with increased odds of grade III/IV acute GVHD²⁴. In this cohort, the survival was similar among the groups with and without HLA-DPB1 mismatches²⁴.

In 2002, a French group studied the impact of DP incompatibilities in 57 unrelated donor/recipient pairs matched for HLA-A, B, C, DRB1, DQB1, and DRB3/4/5. It was observed that two HLA-DPB1 mismatches were significantly severe acute GVHD and poor survival²⁵. In 2003, the Anthony Nolan group studied 143 patients who underwent T-cell depleted 10/10 MUD allo-HCT. This study showed that the absence of DPB1 mismatches led to a lower risk of acute GVHD, albeit with a higher relapse risk²⁶. In a subsequent study, the same group confirmed these findings with a larger group of 423 patients undergoing T-cell depleted allo-HCT with 10/10 MUD, demonstrating that HLA-DPB1 matching was significantly associated with an increased risk of disease relapse²⁷.

A multicenter study from the International Histocompatibility Working Group with 5929 recipient/MUD pairs who underwent allo-HCT between 1984 and 2005 revealed that HLA-DPB1 mismatching increased the risk of GVHD but decreased the risk of relapse without affecting overall survival¹⁷. The multicenter study by Lee et al., which included 3857 MUD transplants, also found no association between HLA-DPB1 mismatching and decreased overall survival²⁸. Therefore, the National Marrow Donor Program (NMDP) guideline for unrelated donor selection pub-

lished in 2008 did not include HLA-DPB1 matching as a selection criterion due to the lack of association between HLA-DPB1 disparities and poorer survival²⁹.

As most HLA-8/8 or HLA-10/10 MUD have HLA-DPB1 mismatches^{16,17}, there was a need to distinguish clinically tolerable HLA-DP incompatibilities (permissive mismatches) from those associated with poorer outcomes (non-permissive mismatches). As novel evidence highlighting how the unique HLA-DPB1 immunogenetics differentially impact allo-HCT became available, it has led to the development of two biological-driven permissiveness models, namely TCE¹⁶ and Expression²², and the translation of these models into the clinical MUD allo-HCT practice³⁰. Notably, these "intelligent" HLA-DP mismatch permissive algorithms provided a new reassessment of the role of HLA-DPB1 mismatching in allo-HCT with unrelated donors.

TCE PERMISSIVENESS MODEL

In 2001, Fleischhauer et al. reported a case of allograft rejection in a patient with chronic myeloid leukemia³¹. The patient received a transplant from a donor who was 10/10 matched, with only one HLA-DPB1*09:01 mismatch in the HvG direction. Remarkably, it was found that HLA-DPB1*0901-specific CD4+ T-cell clones with cytotoxic activity were present during the onset of graft rejection³¹.

A milestone study led by Zino et al. has classified HLA-DPB1 alleles into three distinct immunogenicity groups based on the T-cell epitope reactivity patterns of two alloreactive HLA-DPB1*0901-specific T-cell clones³². The three HLA-DPB1 allele groups were divided in high immunogenicity (TCE1: HLA-DPB1*0901, *1001, *1701), intermediate immunogenicity (TCE2: HLA-DPB1 *0301, *1401, *4501) and low immunogenicity (TCE3: most other HLA-DPB1 alleles)³². Furthermore, the authors developed an algorithm for HLA-DPB1 mismatch permissiveness based on direct T-cell allorecognition. In this model, HLA-DPB1 mismatches are classified as permissive if they share the same immunogenicity group. Conversely, if the HLA-DPB1 mismatches have different immunogenicity groups, they are classified as non-permissive. Nonpermissive mismatches are further categorized as GvH or HvG, depending on whether the patient or the donor has the higher immunogenicity TCE group. Indeed, a retrospective evaluation of 118 MUD transplants revealed that the predicted nonpermissive HLA-DPB1 mismatches were significantly related to increased risks of grade II to IV acute GVHD and transplantation-related mortality³². In an Italian Registry study with 621 adult patients who re-

ceived unrelated allo-HCT, Crocchiolo et al. proposed a new TCE model, considering the HLA-DPB1*02:01 as a separate immunogenicity group³³. The TCE4 model also revealed that there was an association between nonpermissive HLA-DP mismatching and a higher risk of nonrelapse mortality as well as inferior overall survival³³.

Under the auspices of the International Histocompatibility Working Group in HCT, Fleischhauer et al. led a validation of the TCE model in a cohort of 5428 HLA 10/10 MUD transplants¹⁶. In the 10/10 setting, the study revealed that nonpermissive mismatches were associated with a higher incidence of severe aGvHD, increased non-relapse mortality, and inferior overall mortality when compared with permissive mismatches¹⁶. In a multicenter study conducted by the NMDP, Pidala et al. aimed to validate the TCE model in an independent cohort of 4710 HLA 8/8 matched cases. The study confirmed that nonpermissive HLA-DPB1 allele mismatch was associated with poorer survival outcomes than permissive HLA-DPB1 mismatches³⁴.

Although the clinical impact of TCE permissiveness was validated, only 72 HLA-DPB1 alleles had a defined TCE group, limiting the early practical application of this algorithm. Thus, Crivello et al. developed a "functional distance" score based on site-directed mutagenesis and its impact on T cell alloreactivity to overcome this limitation³⁵. It was shown that "functional distance" scores ≤ 0.59 , 0.6-1.99, and ≥ 2 were highly correlated with TCE groups 1, 2, and 3, respectively³⁵. With this new approach, all HLA-DPB1 alleles can now be readily classified into the three TCE groups. Later, Arrieta-Bolaños et al. carried out a validation study of the "functional distance" TCE groups in a multicenter study with 2730 patients with malignancies³⁶. Similar to the previous TCE version, they observed that nonpermissive HLA-DPB1 mismatches were significantly associated with poorer overall survival, increased transplant-related mortality, and higher incidence of acute and chronic GVHD³⁶.

A recent study by the Center for International Blood and Marrow Transplant Research, conducted by Arrieta-Bolaños et al., divided a cohort of 2216 TCE3 permissive mismatches into two sub-groups: 930 "core" (DPB1*02:01, 04:01, 04:02, and 23:01) and 1286 "non-core" (other TCE3 alleles)³⁷. The study aimed to test the hypothesis that TCE3 DPB1 alleles with immunopeptidome overlap would be less immunogenic. The study found that "core" permissive mismatches had significantly lower grade II-IV acute GVHD and transplant-related mortality when compared to nonpermissive mismatches. In contrast, "non-core"

permissive mismatches had similar outcomes than nonpermissive mismatches³⁷.

HLA-DP EXPRESSION MODEL

Petersdorf et al. conducted a landmark study assessing the role of *rs9277534* expression marker in 1441 recipients of transplants from HLA-10/10 MUD with only one HLA-DPB1 mismatch³⁸. They found that when the donor carried a low-expression HLA-DPB1 mismatch, the risk of grade II-IV acute GVHD was significantly higher in patients with high-expression HLA-DPB1 mismatches compared to those with low-expression HLA-DPB1 mismatches³⁸.

In 2018, Morishima et al. proposed the DP2/DP5 model, which included 19 common DPB1 alleles found either in the DP2 (*rs9277534A*) or DP5 (*rs9277534G*) evolutionary clade in the Japanese population³⁹. This study revealed that grade 2-4 aGVHD risks were significantly higher in the DP5 (high expression) group than in the DP2 (low expression) group. It was also observed that within the TCE permissive mismatch group, DP5 (high expression) patients had an increasing incidence of acute GVHD when compared to the DP2 (low expression) recipients³⁹. Later, Lorentino et al. replicated and validated the association of *rs9277534A/G* expression and DP2/DP5 models with higher risks of acute GVHD in 422 Italian patients with malignancies who had undergone MUD allo-HCT⁴⁰.

More recently, an International Histocompatibility Working Group in HCT study led by Petersdorf et al. aimed to confirm the impact of the expression model in acute GVHD in an independent cohort of 11318 HLA-10/10 unrelated donor/recipient pairs²². Among these pairs, 2047 were HLA-12/12, 5880 had one HLA-DPB1 mismatch (HLA-11/12), and 3391 had two HLA-DPB1 mismatches (HLA-10/12). As previously shown in other studies, patients with high-expression HLA-DPB1 mismatches had a significantly increased risk of grades II to IV and severe acute GVHD compared to those with low-expression HLA-DP mismatches²². This independent finding validated the clinical significance of the expression model in the MUD allo-HCT scenario.

Most recently, Ruggeri et al. hypothesized that a combination of TCE and Expression models, named TCE-permissive and high-expression HLA-DPB1 mismatches (TPHE), could act synergically to improve allo-HCT outcomes⁴¹. This contemporary registry study, which included 6627 8/8 MUD/patient pairs, found that TPHE mismatches had better relapse-free survival than non-TPHE mismatches and HLA-DPB1

mismatches. Further, compared to TPHE, non-TPHE mismatches showed poorer overall survival⁴¹. These findings suggest that applying the TPHE model could enhance MUD selection, especially for patients with high-risk malignant diseases. In this sense, a public web application called Expression of HLA-DP Assessment Tool (<https://dpb1-tce-expression.nmdp.org/>) was released to optimize the combined use of TCE and Expression models in unrelated donor selection (Figure 3)⁴².

PREDICTED INDIRECTLY RECOGNIZABLE HLA EPITOPES (PIRCHE) MODEL

A new algorithm called Predicted Indirectly Recognizable HLA Epitopes (PIRCHE) has been developed to evaluate HLA permissiveness as an *in silico* measure of indirect alloreactivity⁴³. In the 10/10 HLA MUD scenario, the patient's HLA-DP-mismatched peptides are presented by shared HLA-A, -B, and -C (PIRCHE I) or shared HLA-DR and -DQ (PIRCHE II) (Figure 4).

In 2014, Thus et al. performed the first study applying the PIRCHE model in the MUD allo-HCT setting, using a cohort of 88 patients receiving 10/10 unrelated donor allo-HCT⁴⁴. Interestingly, this study found that patients with PIRCHE I or II have a higher risk of developing acute GVHD compared to those without any PIRCHE. In addition, considering only patients with TCE HLA-DPB1 permissive mismatches, it was shown that patients with PIRCHE I had a higher risk of acute GVHD when compared to those with no PIRCHE I. This initial evidence suggested that the PIRCHE model could refine the TCE permissive mismatches⁴⁴.

A recent study conducted by Buhler et al. examined the impact of PIRCHE I and II scores in a group of 909 recipient/MUD pairs⁴⁵. The study revealed that GvH PIRCHE I was not associated with any outcomes, while GvH PIRCHE II significantly increased the risks of grade II-IV acute GVHD and lowered the risk of relapse. Thus, the authors suggested that prioritizing HLA-DPB1 mismatches with no PIRCHE II for patients with low relapse burden could help reduce the risks of acute GVHD⁴⁵.

Zou et al. investigated the impact of molecular mismatch approaches, including PIRCHE scores, in 1514 patients with malignancies receiving allo-HCT from unrelated donors matched at HLA-A, -B, -C, -DRB1/3/4/5, and -DQB1⁴⁶. The MD Anderson group found that high PIRCHE I and II scores in the GvH direction were significantly associated with an increased risk of grade 2-4 acute GVHD and higher

non-relapse mortality, although with a concomitant reduced risk of disease relapse⁴⁶.

Despite promising data, the PIRCHE model has not been included as a formal criterion in current NMDP guidelines for selecting unrelated donors³⁰.

HLA-DPB1 MISMATCHING AND PERMISSIVENESS IN NONMALIGNANT DISORDERS

The role of HLA-DPB1 mismatching and permissiveness models in MUD allo-HCT for nonmalignant disorders has been poorly reported. Few studies have been conducted in this setting, showing conflicting evidence.

Horan et al. conducted a large retrospective registry study with a cohort of 663 patients with various non-malignant disorders. The study demonstrated that HLA-DPB1 mismatching did not impact clinical outcomes following MUD transplantation⁴⁷. Similarly, the Japanese Marrow Donor Program evaluated the effect of HLA-DPB1 mismatching in 101 10/10 HLA-matched pairs and 69 9/10 single-allele mismatched pairs in 2011. The study also found that HLA-DPB1 mismatching did not predict any outcome following unrelated donor allo-HCT⁴⁸. However, it's worth noting that TCE permissiveness was not assessed in these two retrospective registry studies^{47,48}.

In contrast, Fleischhauer et al. evaluated the role of TCE permissiveness in 72 patients with beta-thalassemia major who received 10/10 MUD⁴⁹. The study revealed that TCE non-permissive mismatches in the HvG direction were associated with higher risks of graft rejection and lower thalassemia-free survival⁴⁹. More recently, Lima et al. studied 106 patients who underwent 10/10 MUD allo-HCT with in vivo T-cell depletion for nonmalignant disorders, mainly acquired and inherited bone marrow failure⁵⁰. This single-center study also found that the presence of

TCE non-permissive HvG disparities significantly increased the incidence of graft rejection⁵⁰. Furthermore, the impact of HLA-DP expression model on MUD allo-HCT for non-malignant diseases remains unclear.

Thus, further studies are required to confirm the clinical significance of HLA-DPB1 mismatching and TCE/Expression permissiveness after MUD allo-HCT for nonmalignant diseases.

CONCLUSION

In current allo-HCT practice with calcineurin inhibitor-based GVHD prophylaxis, the MUD allo-HCT survival outcomes are similar to those of HLA-matched sibling donors (8). Applying HLA-DPB1 permissive models may greatly enhance MUD selection and improve transplant outcomes, particularly when combined with HLA-A, -B, -C, -DRB1 matching and younger donor age³⁰.

The "intelligent" use of HLA-DPB1 (mis)matching, based on the patient's unique needs, may provide a tailored-based MUD selection, thereby optimizing allo-HCT results. For instance, if disease relapse is a major concern, as for high-risk Acute Leukemia patients, the MUD search should prioritize TPHE mismatches to increase the likelihood of the GvL effect, thereby improving relapse control and relapse-free survival⁴¹. In turn, if avoiding acute GVHD is the major goal, as for patients with nonmalignant disorders, the MUD search should first prioritize HLA-DPB1 matching and, when unavailable, a core permissive mismatch³⁷.

Further investigation is clearly warranted to examine the impact of HLA-DPB1 permissive mismatch models on MUD allo-HCT with innovative GVHD prophylaxis approaches, such as post-transplantation cyclophosphamide and abatacept^{51,52}.

FIGURE 1: Pathways of T-cell allorecognition. A Direct allorecognition. B Indirect allorecognition.

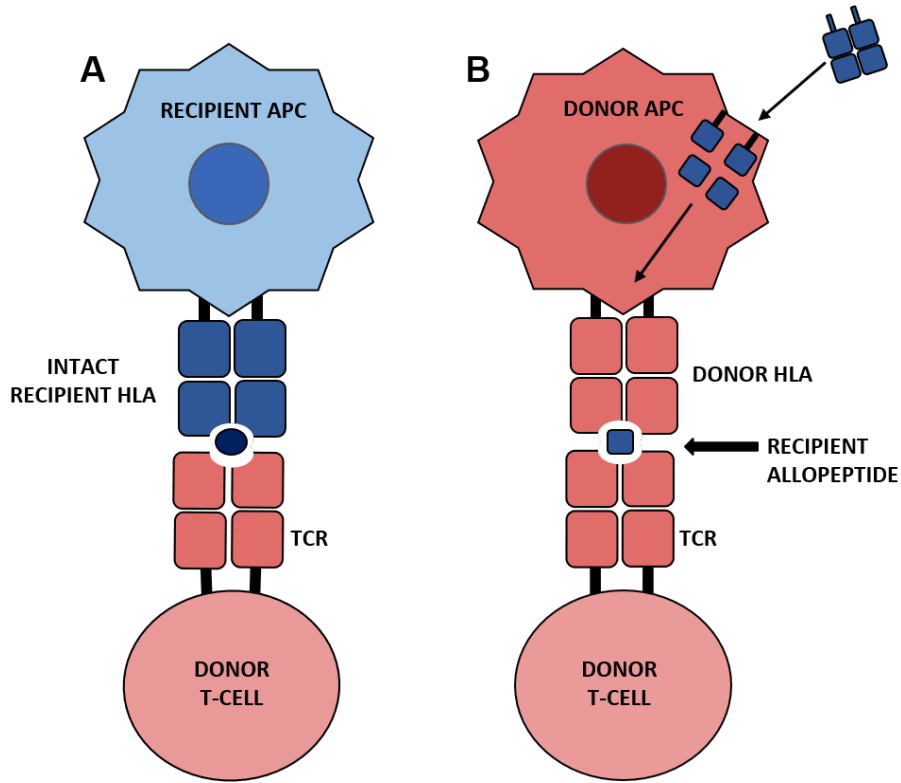


FIGURE 2: HLA-DPB1 expression variants.

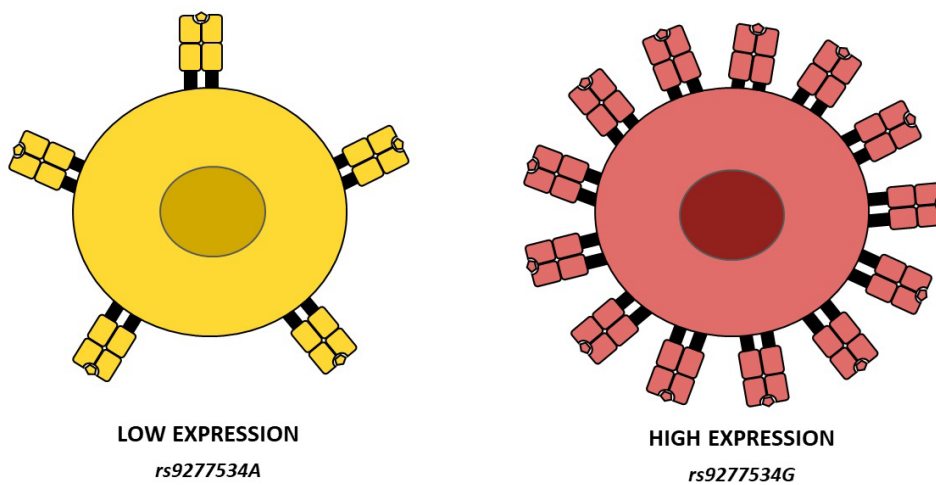


FIGURE 3: Expression of HLA-DP Assessment Tool (<https://dpb1-tce-expression.nmdp.org/>).

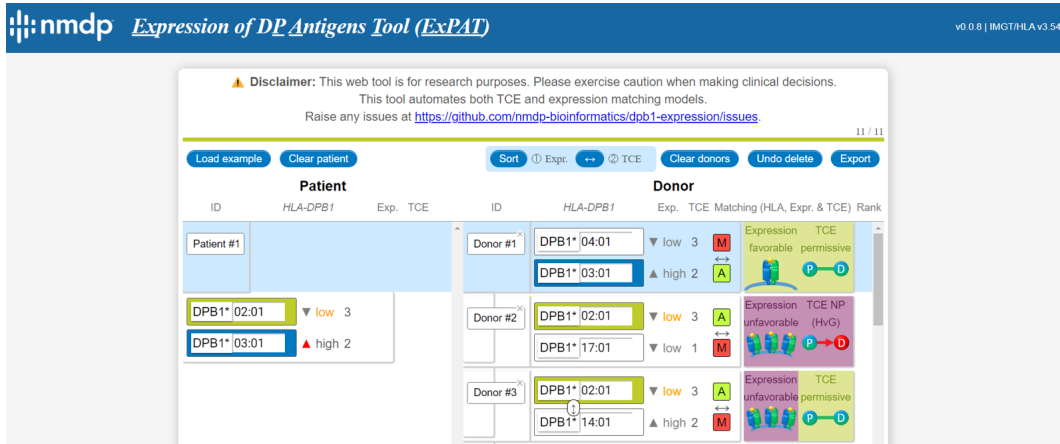
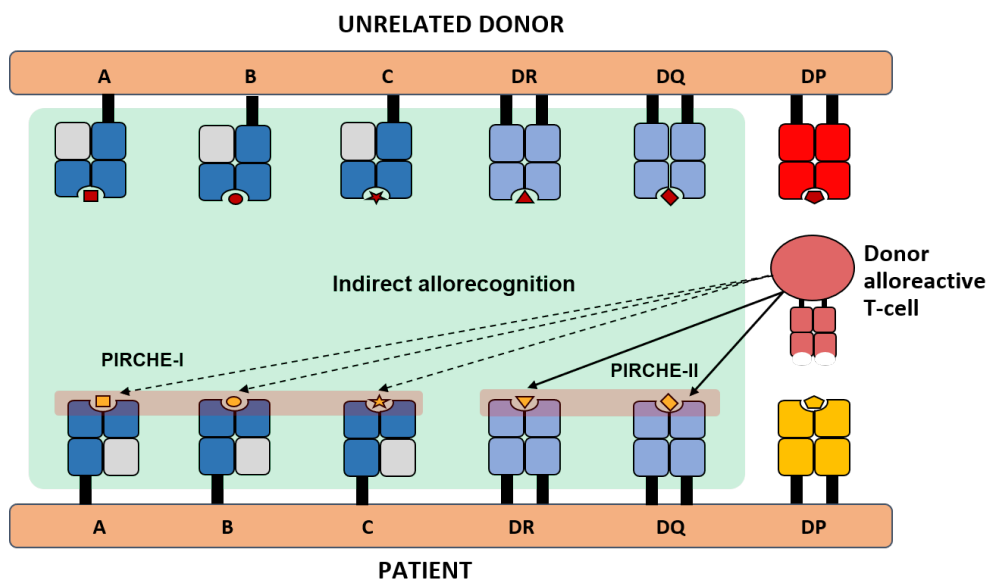


FIGURE 4: The Predicted Indirect Recognizable Human Leukocyte Antigen (PIRCHE) Algorithm.



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