a clinically relevant immune response to FVIII. This competition-based ELISA may therefore be of interest for evaluating the immunogenicity of novel FVIII concentrates in a well-standardized and sensitive manner. It may also help in identifying the poorly characterized noninhibitory antibodies suspected of accelerating the clearance of FVIII. Given that FVIII is at a low concentration in plasma (0.1-0.2 nM), such antibodies should have a high affinity for making complexes with FVIII.

The ability of this novel assay to detect early anti-FVIII antibody development may also have useful clinical applications for optimizing inhibitor eradication because the success rate of immune tolerance induction is higher when treatment is started early after inhibitor detection and when inhibitor titer is low. Similarly, this novel assay may be useful for the follow-up of patients with mild/moderate hemophilia A, in whom the spreading of an immune response from the allogeneic FVIII to the patient’s self FVIII can transform the patients’ bleeding phenotype into that of severe hemophilia A. In such patients, the detection of an initial immune response to allogeneic FVIII may allow their therapy to be adapted to prevent the development of an autoimmune response to self FVIII.

Prospective clinical studies will thus be needed to investigate the opportunities provided by this novel approach of inhibitor detection.

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**HLA mismatching in transplantation**

**Effie W. Petersdorf**

**Fred Hutchinson Cancer Research Center**

In this issue of *Blood*, Morishima et al report on the risks of acute and chronic graft-versus-host disease (GVHD), relapse, and mortality associated with mismatching for HLA-A, -B, -C, -DRB1, -DQB1, and -DPB1 loci after unrelated donor transplantation for Japanese patients.1 In such cases, the detection of an initial immune response to allogeneic FVIII may allow their therapy to be adapted to prevent the development of an autoimmune response to self FVIII.

Prospective clinical studies will thus be needed to investigate the opportunities provided by this novel approach of inhibitor detection.

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LA matching between a transplant donor and recipient remains the most robust predictive factor for outcome after hematopoietic cell transplantation from unrelated donors.2-4 The presence of recipient HLA-A, -B, -C, or -DRB1 differences not shared by the donor is associated with higher risks of GVHD, increased morbidity, and increased mortality compared with complete matching, whereas the presence of donor disparity not shared by the recipient increases the risk of graft failure. For this reason, current pretransplant donor selection strategies include the use of molecular methods to ascertain donor-recipient matching for allelic subtypes at each HLA locus and to limit the total mismatches to the least possible number.

Early on in the unrelated transplant experience, preliminary observations suggested that risks associated with HLA mismatching were not necessarily equivalent across all HLA loci. In other words, depending on the mismatched locus, risks could differ. Early data suggested that HLA mismatching for the class I locus HLA-A, -B, or -C may be associated with different risks than mismatching for the class II locus HLA-DRB1 or -DQB1.1 As the unrelated donor transplant experience matured, registry data from the United States and Japan confirmed the negative impact of HLA disparity on GVHD and mortality,4,5 and furthermore suggested that mismatching at HLA-DQB1 was better tolerated in general than mismatching at any other HLA locus.

Until recently, the clinical significance of the third classical class II locus, HLA-DPB1, has remained ill defined. Because of the weak linkage disequilibrium between HLA-DR, -DQ, and -DP, the vast majority of otherwise HLA-matched transplant pairs are mismatched for 1 or both HLA-DPB1 alleles. The limited number of HLA-DPB1-mismatched transplants precluded definitive retrospective examination of this locus until recently. Like HLA-DRB1 and -DQB1, HLA-DPB1 mismatching is associated with higher incidence of acute GVHD; however, HLA-DPB1 mismatching is also associated with lower recurrence of disease after transplantation, and this favorable graft-versus-leukemia (GVL) effect can in part balance the deleterious effects of severe GVHD on mortality.6

It is in this context that the current analysis by the Japan Marrow Donor Program takes on new meaning. Morishima et al1 mounted a large-scale effort to retype all HLA loci to ensure that modern nomenclature could be applied to each patient’s and donor’s HLA assignment and to accurately define donor-recipient allele matching. By using an exceedingly large transplant population of
7898 Japanese patients who received a T-replete marrow transplant from a Japanese donor facilitated by the Japan Marrow Donor Program, the authors measured risks associated with mismatching at each HLA locus and the impact of multilocus mismatching on outcomes. The six major findings were that (1) grade 3 to 4 acute GVHD is increased with mismatching at HLA-A, -B, -C, or -DPB1; (2) chronic GVHD is increased with mismatching at HLA-C; (3) relapse is lower with mismatching at HLA-C or -DPB1; (4) GVL effects stemming from HLA-DPB1 mismatching are independent of chronic GVHD; (5) acute GVHD and mortality are lower with mismatching at HLA-C or -DPB1; and (6) deleterious effects of multilocus mismatching are synergistic.

These new data highlight the importance of locus-specific differences in clinical risks. In particular, the data may help explain why some patients who develop acute GVHD soon after transplantation do not experience chronic GVHD. Avoidance of any HLA disparity is a priority, however, in the absence of matched donors, limiting the number of HLA mismatches to a single locus (DRB1-DQB1 considered as one locus) will help lower risks overall.

The study confirms and extends the observation of GVL effects associated with HLA-DPB1 mismatching, but importantly shows the pivotal role of HLA-DPB1 in GVHD-independent relapse. The potential for leveraging these effects of HLA-DPB1, particularly in high-risk patients, may provide avenues for targeting disease recurrence in the future.

One of the major challenges in deciphering the role of specific HLA mismatches is the ethnogeographic distribution of alleles and haplotypes worldwide. In a recent analysis of Japanese unrelated donor transplant pairs, 3 major HLA-B haplotypes were observed among Japanese transplant populations compared with a much greater extent of allele and haplotypic diversity observed among Northern European-white transplant pairs. These population-based genotype differences contribute to the richness of side-by-side comparisons of transplant outcomes as a means to further understanding the nature of HLA diversity and its biological implications.

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Effie W. Petersdorf