Unrelated donors are more commonly used than siblings for allogenic stem cell transplantation. However, despite almost 20 million donors and cords available worldwide, only two-thirds of the white population, and less of smaller ethnic minorities, can find a donor fully compatible for HLA-A, -B, -C, and -DRB1 loci, — such is the enormous population diversity at these loci. For the patients without such a match, clinicians struggle to pick the best possible donor among those who are mismatched. In this issue, Spellman et al. [1] evaluated an algorithm established by Elsner et al. [2] to estimate the allogenic reaction potential between mismatched individuals. The HistoCheck program is available online at http://www.histochek.de and can be used by anyone to calculate a dissimilarity score between two individuals mismatched for one HLA molecule [3]. The analysis used the National Marrow Donor Program transplantation outcome database previously reported by Lee et al. [4], and single locus mismatched pairs were scored by the HistoCheck algorithm. With the exception of neutrophil engraftment in a subset analysis, no association was found between the dissimilarity score and transplantation outcome. What is the lesson from this study? The principles used to calculate the dissimilarity score seem sound: the first is the functional relevance of mismatched amino acid residues within the HLA molecule. Amino acids that anchor the antigenic peptide or bind to the T cell antigen receptor score higher than others. The second principle assumes that disparities between amino acids that are structurally “similar,” as defined by Risler et al. [5], are better tolerated immunologically than dissimilar ones. By the Risler criteria, tyrosine and phenylalanine that differ only for a hydroxyl group have a score of 4 (similar), whereas tyrosine and serine that differ for an aromatic hydrocarbon have a score of 45 in a scale of 100 (less similar). The message of this article is that the “similarity” between the mismatched amino acids is not good for the patients after all. Other groups have investigated how to seek out “permissive” mismatches, and the greatest advance in the field has been made by Kawase, Morishima, and collaborators from the Japan National Donor Program (JMDP) [6-8]. Subsequent work from Marino et al. [9] is largely confirmatory of the main JMDP findings using a predominantly white population for study. Through a series of publications, the Japanese investigators provided convincing data that mismatch for certain specific amino acids in positions that function as peptide binding residues at HLA-A and -C, and killer cell immunoglobulin-like receptor (KIR) binding residues at HLA-C are responsible for graft rejection, graft-versus-host disease (GVHD), prevention of leukemia relapse, and, overall mortality. The Japanese data are consistent with the principle adopted by Elsner that amino acid disparities for antigenic peptide binding sites in the HLA molecule can be the cause of alloreactivity, however, do not support a significant role for TCR binding sites and extend prior data from related mismatched transplantations on the relevance of KIR binding sites. As understanding the relationship between HLA structure and function evolves, it is likely that additional HLA polymorphisms will gain relevance in transplantation. Doubts were raised against the Elsner assumption that disparity for similar amino acids has less relevance to alloreactivity. In the studies by the JMDP, mismatches for tyrosine versus phenylalanine in position 9 of HLA-A or position 99 of HLA-C (classified similar by the HistoCheck with a score of 4) were associated with a 1.7 hazard of severe acute GVHD compared to match. Mismatch for tyrosine versus serine in position 9 of HLA-A (classified less similar by HistoCheck with a score of 45) were also associated with a 1.7 hazard of severe acute GVHD. Asparagine and serine differ only slightly in their side chain (HistoCheck score 7), however, such disparity in position 77 at HLA-C, the KIR2DL binding site, was associated with graft rejection, GVHD, and protection from leukemia relapse. These observations indicate that even subtle differences in the structure of donor and recipient HLA molecules at binding sites for peptide, KIR ligands, and possibly TCR may elicit alloreactivity.
Second Stem Cell Transplants for Multiple Myeloma. If at once you don’t succeed, should we really try, try again?

Sergio Giralt

In this edition of Biology of Blood and Marrow Transplantation, Jimenez-Zepeda et al. [1] explore the role of a second autologous stem cell transplant (ASCT) as salvage therapy for patients with multiple myeloma. Although all the pitfalls and caveats regarding retrospective reviews apply to this analysis (ie, selection bias, uncertain denominator, patient and treatment heterogeneity, etc.), we can learn from this 17-year single institutional experience.

Salvage high-dose therapy with ASCT improved responses to induction therapy in most patients. Complete remission rates increased from 0% to 7.7%; very good partial response rates increased from 12.5% to 39.7% with partial remission or greater rates increasing from 86.2% to 97.4%. The median time to relapse after transplant was 19 months, and treatment-related deaths occurred in 2.6% of patients. As reported by others, remission duration after the first autograft predicts response and remission duration after a second autograft. Patients relapsing within 24 months of their initial autograft had a median progression-free survival of 9.8 months, whereas patients whose remission duration lasted more than 2 years had a progression-free survival of 17.3 months. Looking at these data, it is important to note that these patients were selected based on their response to re-induction therapy. In contrast, more than 20 years ago, Jagannath et al. [2] reported on 21 patients who were resistant to standard melphalan-prednisone and vincristine, Adriamycin, dexamethasone and received high-dose therapy with bone marrow support. Five toxic deaths occurred in these patients with refractory relapsed myeloma and the remission duration was approximately 7 months. Thus, this strategy is not optimally effective in multiply relapsed and refractory patients.

The report of Jimenez-Pineda et al. [1] confirms previous reports of the use of high-dose therapy with ASCT as consolidation therapy for patients relapsing after primary therapy. Response rates of greater than 75% are routinely reported, but with few patients achieving a complete remission. Remission durations of 12 to 18 months are usually reported with a fraction of patients having long-term disease control. In all reports, chemosensitivity as well as duration of myeloma