that a sequence read matches multiple locations of the genome.

As made clear in the study by Rowley and colleagues, these data will be invaluable for identifying new mechanistic targets that can be furthered studied in animal or in vitro models (see figure). For clinical studies, the use of genome-wide RNA-seq data will be more challenging. The number of data points generated per sample is enormous and the true importance of these findings in small clinical studies will likely draw comparisons in relevance to early SNP studies with copious false-positive data being generated. However, if used judiciously, these data may be linked to individual genomic data as well as used to identify novel transcripts associated with disease. Subsequent validation and testing using a targeted approach (ie, high-throughput quantitative RT-PCR) in a much larger sample set will reveal the true clinical relevance of these detailed transcript findings. Lastly, as with genome-wide association studies, RNA sequencing in a much larger population will need to be performed before we can establish what is a normal platelet transcript.

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**TRANSPLANTATION**

**Comment on Stevens et al, page 3969**

**HLA matching of CB: it’s complicated**

Marcos de Lima, Marcelo Fernandez-Vina, and Elizabeth J. Shpall  M. D. ANDERSON CANCER CENTER; STANFORD UNIVERSITY

In this issue of *Blood*, Stevens and colleagues report that in single cord blood (CB) transplantations, donor–recipient human leukocyte antigen (HLA) mismatches in the graft–versus-host only (GVH-O) direction produce engraftment and survival comparable to HLA-matched CB units and are significantly better than units mismatched in the rejection-only (R-O) direction.¹

The authors studied the outcomes of 1202 CB transplantations facilitated by the New York Blood Center National Cord Blood Program (median age was 7.2 years). They showed important differences in outcomes in the small subgroups of patients with unidirectional mismatches. GVH-O and R-O mismatches were present in 4.8% and 3.3% of the transplantations, respectively. They describe in detail the GVH-O scenario, where the CB unit is homozygous for one HLA antigen/allele and the recipient is heterozygous at the same locus; matching in one of the alleles only. In contrast, for the R-O situation, the homozygosity occurs in the recipient and the CB unit is heterozygous at the same locus (the HLA mismatch occurs in the rejection direction).

The novel and stimulating results of this study demonstrate that recipients of transplantations with GVH-O mismatches had neutrophil and platelet engraftment rates that were comparable to recipients of transplantations matched in HLA-A, -B, and -DRB1. With the GVH-O mismatches, the time to
engraftment was significantly faster and rate of engraftment higher than transplantations with R-O mismatches. Importantly, patients with hematologic malignancies given GVH-O CB grafts had lower transplantation-related mortality, overall mortality and treatment failure compared with those with one bidirectional mismatch, resulting in outcomes similar to those of matched CB grafts.

Despite the fact that formal documentation of donor engraftment was not available for a significant fraction of patients, R-O mismatches were associated with slower engraftment and higher rejection and relapse rates. Similarly, Petersdorf and coworkers observed higher rejection rates in allogeneic bone marrow transplantation for chronic myelogenous leukemia when the recipient was homozygous at the mismatched HLA class I loci. It would therefore be important to address the chances of presenting allo-antibodies that re-

The described beneficial Killer immunoglobulin-like receptor ligand mismatches occur more often in HLA-B or -C mismatched transplantations and would be manifested more often in the R-O situation. Therefore, natural killer–mediated graft versus leukemia effect could theoretically have a beneficial impact in the R-O vector. Interestingly, Stevens et al identified the opposite effect here, in which there was increased risk for relapse in transplantations with a mismatch in the R-O vector. The impact of a potentially beneficial Killer immunoglobulin–like receptor ligand effect cannot be ruled out here, however, because this study did not evaluate HLA-C and included patients with inherently different susceptibility to this effect.

The lower cell doses of the CB units compared with marrow or peripheral blood likely magnify the R-O direction mismatches—there is no margin for engraftment at these lower doses. It may be that centers are already trying to avoid R-O mismatches; only a small fraction of patients had them in this large retrospective analysis.

Given the caveat that HLA antibodies could have an impact, CB search algorithms in the single CB transplantation setting can be modified to identify unidirectional mismatches. It is now desirable to give priority to GVH-O mismatched units over other mismatches and avoid selecting R-O mismatches, if possible. Whether GVH-O and R-O mismatches will have an impact on double CB transplantations remains to be determined.

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