that platelet FV plays in promoting thrombin generation at the activated platelet surface. What remains uncertain, however, is whether residual platelet FV levels correlate with the severity of bleeding in severe FV–deficient patients. Although there has been speculation on this correlation, no systematic study has been done. Furthermore, mechanistic studies are needed to investigate some remaining questions. The first relates to the origin of residual platelet FV in these severe FV–deficient patients. Are megakaryocytes able to synthesize a very small amount of FV that is protected in the platelet environment or, alternatively, do megakaryocytes have an extremely efficient system to endocytose most of the FV that is being synthesized? The mechanism responsible for single-donor skewing has heretofore remained elusive. Is it the result of a hematopoietic competitive advantage or an immunologic one? In our experience, which unit would “win” appeared to be random.

Duckers et al underscores the complexity of a seemingly simple deficiency of one clotting factor and reminds us that a balance of multiple components ultimately contribute to the clinical phenotype.

Conflict-of-interest disclosure: The author declares no competing financial interests.

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UCB and atmospheric noise

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In this issue of Blood, Gutman and colleagues demonstrate that single-unit engraftment after double UCB transplantation is not random.

Allogeneic hematopoietic cell transplantation (allo-HCT) is potentially curative therapy for patients with genetic diseases, bone marrow failure, and hematopoietic malignancies. Compared with bone marrow or mobilized peripheral blood, umbilical cord blood (UCB) has a number of benefits including the lack of collection risk to the donor, absence of donor attrition, and rapid availability. At one level, UCB has made allo-HCT available to nearly everyone, because of the unique characteristics of the neonatal immune system, which permits HLA-mismatched transplants with a relatively low risk of graft–versus-host disease.1,2

Widespread application of UCB has been constrained by the small volume of blood in the placenta and umbilical cord. With limiting numbers of mononuclear and progenitor cells, UCB transplantation was historically reserved for children and small adults. In an attempt to overcome the obstacle of cell dose, we and others explored confusion of 2 partially HLA-matched UCB units. With hundreds of such transplantations now performed, the safety and efficacy of “double UCB transplantation” has been established,3–5 resulting in greater overall use of UCB. This approach results in reliable hematopoietic engraftment in patients who would otherwise have an inadequate cell dose from a single UCB unit.3

Notably, in more than 90% of recipients of double UCB transplantation, sustained hematopoiesis is derived from a single UCB unit (M.R.V. and J.E.W., unpublished data, October 2009). This is probably beneficial because long-term “dual donor chimerism” could adversely affect outcome, potentially leading to antibody–mediated hemolysis in the setting of donor–to–donor ABO incompatibility. However, the mechanism responsible for single-donor skewing has heretofore remained elusive. Is it the result of a hematopoietic competitive advantage or an immunologic one? In our experience, which unit would “win” appeared to be random.1,6 Ballen et al contested this by suggesting that it was due to infusion order. Differences in clinical practice might explain this discrepancy in that the Boston investigators separated the timing of the 2 UCB infusions by as much as 6 hours, and the first unit infused was more likely to engraft.4 In contrast, at our center units were infused immediately following one another and in tandem. In this situation, the order of infusion was not associated with which unit ultimately engrafted. We speculated that single-unit engraftment might be the culmination of an immunologic interaction between the 2 units or between the host and the 2 units (much like an in vivo mixed lymphocyte reaction). However, there were no biologic data supporting this assertion.

Thus, predicting the winning unit seemed impossible and more like atmospheric noise due to wildly unpredictable lightening strikes. In this issue of Blood, Gutman and colleagues refute the atmospheric noise theory.7 First, they show evidence that donor T cells from the engrafting UCB unit specifically recognize the nonengrafting unit. CD8+ T cells with a memory phenotype (CD8+CD45RO+/−CCR7−) from the engrafting unit produce interferon-γ (IFN-γ) specifically in response to the rejected unit, but not against cells from a third party. These T cells appear early after transplantation (within the first 40 days) and were not detectable at later time points. As reactions were demonstrable in 9 of 10 evaluable recipients with single-unit engraftment, it would appear that single-unit engraftment is not random. Furthermore, Gutman et al...
also found a lack of IFN-γ production from either unit in 3 of 3 cases of dual-unit engraftment. Last, in the single case of graft rejection, host T cell IFN-γ production against both UCB units was observed.

Perhaps this work raises more questions than it provides answers. For instance, what antigens do the responding T cells recognize? Why does one unit respond first or more robustly? Could it be caused by prenatal factors, for example, tolerance to noninherited maternal alleles and subsequent lack of response by one unit against the other? Whereas Gutman et al have elegantly demonstrated graft-to-graft interactions, they did not describe graft-versus-host reactions. Why was there not a graft-versus-host response, potentially key to graft-versus-leukemia reactions?

Regardless of the more mechanistic questions, there is also the issue of how this new information might be used clinically and to our advantage. For instance, could this assay be used to select the “winning” unit, and if so, why might we want to do this? Transplantation-related mortality is clearly associated with the degree of HLA mismatch. One might imagine engineering a double UCB transplantation in which the larger, more HLA-mismatched unit might result in a transient wave of hematopoietic recovery, followed by long-term engraftment and immune reconstitution from a smaller but more closely HLA-matched unit. In contrast, data also suggest that HLA mismatch might be associated with a lower risk of leukemia relapse. Whether a transient wave of engraftment from a more mismatched unit is sufficient for graft-versus-leukemia remains to be determined, and perhaps long-term engraftment of mismatched units might be desirable in the setting of high-risk leukemia. Regardless of how these data drive further clinical research, Gutman et al have provided the first clue that supports an immune-based graft-versus-graft interaction following double UCB transplantation. Perhaps, it must now be acknowledged that engraftment of a particular unit after double UCB transplantation is not random.

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