

the use of UCB makes possible a better chance of cure and lower rates of GVHD. Reed et al (*Blood*. 2003;101:351-357) recently reported on their successful banking initiative of sibling donor UCB for children with hematologic disorders, despite the challenges associated with remote-site collections. Further studies are indicated to determine the impact of HLA disparity on related-donor UCB transplantation outcomes.

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### Platelet message and microarrays

Platelets are anucleate, and until the late 1980s it was thought that circulating platelets have little residual RNA message. But in 1988 Newman et al (*J Clin Invest*. 1988; 82:739-743) showed that one can use RT-PCR to amplify platelet-specific messages from purified peripheral blood platelets. Since then, numerous laboratories have taken advantage of this observation to clone and identify mutations and determine relative levels of platelet-specific messages. In time, it has been assumed that platelets are actually a rich source of platelet message. With the more recent development of microarrays and related approaches for widespread transcript analysis, one can envision an even greater use of circulating platelet RNA. One might expect to more fully define the genes representative of late megakaryocyte development. Perhaps these approaches would define gene products whose expression levels correlate with an increased risk of thrombotic or other clinical states.

The manuscript by Gnatenko and colleagues (page 2285) represents an early use of such a strategy, and not only provides exciting new information but also grounds expectation in reality. Platelets are not a rich source of message. First, the vast majority of messages actually are derived from the mitochondria. Second, even with taking extra steps to ensure purity, the top 3 messages determined by microarray were white cell or red cell messages. On the plus side, the study clearly defined the relative abun-

dance of a number of platelet-specific genes, including the demonstration that chemokines such as PF4, PBP, and RANTES are among the most abundant messages, pointing to the importance of platelets in both thrombosis and inflammation. Also, 2 previously unrecognized messages for neurogranin, a protein kinase C substrate, and clusterin, a complement lysis inhibitor, are present in platelets. It is hoped that with further technical improvements, additional insights and clinical usage can come from analysis of this ready source of megakaryocyte/platelet message.

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### Cytologic subtypes of grade 3 follicular lymphoma

Histologic grading of follicular lymphoma poses a dilemma. On one hand, there are data to support the notion that histologic grade (no matter what system of grading is used) correlates to some extent with clinical outcome. Furthermore, those patients with the highest grade of follicular lymphoma (follicular large-cell lymphoma by the Working Formulation, or follicular lymphoma grade 3 by the REAL and WHO classifications) show favorable response rates more akin to those seen in diffuse large-cell lymphoma when treated with anthracycline-based multiagent chemotherapy regimens. On the other hand, there is poor consensus on exactly which grading criteria should be used and poor interobserver reproducibility of grading on a case-by-case basis. This dilemma is inherent in any system that attempts to establish discrete groups using what amounts to a continuous variable (in this case the number of large cells within neoplastic follicles).

Since the Rappaport classification was published more than 40 years ago, grading has been a part of follicular lymphoma diagnosis. Until the recent publication of the WHO classification of hematopoietic neoplasms, however, no single grading scheme was officially sanctioned by a widely used classification system. The WHO officially

recommends utilizing the grading system of Mann and Berard, in which grade is assigned based upon the quantification of large transformed lymphocytes (centroblasts) within neoplastic follicles per high power microscopic field (0.159 mm<sup>2</sup>) based on a formal count of 10 fields. When using this grading system, 2 patterns may be encountered: follicular lymphoma with sufficient centroblasts to warrant a grade 3 designation but with many residual small cells; and follicular lymphoma with monotonous sheets of centroblasts. The WHO classification recognizes this histologic dichotomy and assigns a grade of "3a" to the former case and "3b" to the latter. This distinction makes intuitive sense to many, since grade 3a cases would be assumed to overlap significantly with low-grade follicular lymphoma with respect to treatment response and outcome. Potential biologic differences between grades 3a and 3b have been evaluated in previous studies, but this grading system has never been formally evaluated for clinical relevance.

The article by Hans et al (page 2363) is the first to formally (albeit retrospectively) analyze differences in clinical outcome between follicular lymphoma grades 3a and 3b by WHO criteria. The authors conclude that the 3a-3b distinction does not correlate with response to treatment or with clinical outcome. But the presence and extent of a diffuse large-cell component does correlate with behavior of the disease. The latter finding appears to justify the WHO-sanctioned practice of rendering a separate diagnosis of diffuse large B-cell lymphoma in such cases.

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### Photochemical pathogen reduction: improved safety for the blood supply?

Safety of the blood supply depends on an increasingly intense donor-screening process and a series of serologic or nucleic acid-based tests for HIV1/2, HTLV1/II, hepatitis B, hepatitis C, and syphilis. There are,

however, no tests for myriad other disease agents that could threaten the blood supply, including bacteria, malaria, babesiosis, Chagas disease, and emerging agents such as West Nile virus. Pathogen reduction (PR) technology is a new approach that places a PR compound in the donor blood bag ready to be activated after blood collection. Several technologies are separately being developed for platelets, red cells, and plasma. The common approach taken by the various methodologies is to disrupt pathogen DNA or RNA polymerase activity and interfere with pathogen nucleic acid replication and, thus, disease transmission. The key is for the PR technology to prevent pathogen transmission but preserve functional activity of transfused cells and plasma proteins.

van Rhenen and colleagues (page 2426) report on the first randomized double-blind clinical trial in European patients using one such technology. Their system exposes bags

of buffy-coat-prepared platelets containing a synthetic psoralen compound (amotosalen) to UVA light. Once photoactivated, the amotosalen intercalates and crosslinks pathogen nucleic acid bases, preventing replication. van Rhenen's protocol randomized thrombocytopenic oncology patients to receive either untreated control (n = 51 patients; 256 transfusions) or photochemically treated (PCT; n = 52 patients; 311 transfusions) platelet products. The estimated effect of PCT treatment on the mean 1-hour post-transfusion corrected count increment (CCI), one primary endpoint, was a decrease of 1800 ( $P = .11$ ) in the platelet count. The mean 24-hour CCI for the PCT arm, however, was 3200 lower than that for the control arm ( $P = .02$ ). Blinded, clinically assessed bleeding events were equivalent between the 2 groups, speaking to preservation of platelet hemostatic function. There were no reported differences in adverse events between the 2 groups.

While data from this first reported clinical trial are very promising, more data on in vivo platelet function would be useful. Further, any long-term adverse effects on recipients exposed to platelets treated by the amotosalen and UVA light procedure remain to be determined. Clearly, this paper presages the future focus on PR methods for ensuring the safety of the blood supply from known, as well as emerging, pathogens. This study reports on buffy-coat-prepared platelets, a technology used widely in Europe but not in the United States, where platelets are prepared by apheresis or from whole blood as platelet-rich plasma. Studies on these products and future reports on red cell PR systems are awaited. At least in the US for the short term, PR technology might be used in addition to, not in lieu of, existing blood screening maneuvers. The important role to be played by PR in the future remains to be defined.

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