that express HVEM. As predicted, Vγ9Vδ2 T cells proliferated to a greater extent in the presence of antibodies that blocked BTLA-HVEM interactions. Finally, upon careful examination of patient-derived lymph node samples, Vγ9Vδ2 T cells from within these cancerous lymph nodes were found to proliferate to a significantly greater extent when stimulated in the presence of blocking antibodies directed against either BTLA or HVEM.

The major contribution of this work is its demonstration for the first time that BTLA-HVEM interactions can significantly inhibit the activation and proliferation of Vγ9Vδ2 T cells. However, the findings from this report also allow one to pose several important questions—particularly when one considers the dynamic nature of the expression of both BTLA and HVEM and the correspondingly complex interactions that may occur between these 2 molecules in vivo. Several interesting questions stand out in this regard. What, for example, is the significance of the findings that the expression of BTLA varies depending on the developmental status of Vγ9Vδ2 T cells where naive Vγ9Vδ2 T cells express higher levels of BTLA when compared with more differentiated, antigen-experienced Vγ9Vδ2 T cells? In a related point, what is the significance of the findings that BTLA-HVEM interactions can diminish the transition of Vγ9Vδ2 T cells from less differentiated (naive and central memory) to more differentiated effector phenotypes? In this regard, does the BTLA-HVEM interaction actually regulate Vγ9Vδ2 T-cell differentiation? If this is indeed the case, could this provide insight into the mechanisms by which tumor cells—particularly those that express HVEM—might escape from antitumor immunosurveillance provided by Vγ9Vδ2 T cells? In addition, because HVEM itself is expressed on a wide variety of cell types, including γδ T cells themselves, just which cells in the tumor microenvironment are expressing functionally relevant HVEM that interacts with BTLA on Vγ9Vδ2 T cells? These and related questions can surely be addressed in future studies.

To date, the therapeutic potential of human γδ T cells still remains largely unrealized. Beginning with the early pioneering attempts to exploit the antitumor properties of endogenous human γδ T cells in patients with hematolymphoid malignancies,10 to more recent efforts targeting a broader spectrum of tumors,6 clinical responses although clearly evident, have been modest at best. The findings of this current report provide a strong rationale for moving forward with more intensive studies designed to understand how the blockade of the BTLA-HVEM inhibitory pathway might potentiate the in vivo antitumor activity of human γδ T cells. Such efforts could soon enough lead to the design of exciting new clinical trials—provided the appropriate clinical-grade antibodies can be developed in a timely and economically feasible manner.

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Comment on Chou et al, page 1062

Ideal donors, imperfect results in sickle cell disease

Alexis A. Thompson1 ANN AND ROBERT H. LURIE CHILDREN’S HOSPITAL OF CHICAGO

In this issue of Blood, Chou et al report findings from an observational study ofalloimmunization in patients with sickle cell disease (SCD) receiving blood transfusions from ethnically matched donors.1

A n impressive array of Rh allelic variants in African Americans is provided, some of which were associated with clinically significant delayed transfusion reaction (DTR). Of the 182 patients who were transfused in this single institution study, 80 developed alloantibodies. The investigators sought to characterize factors associated with alloimmunization in sickle cell patients, who are of African descent and who were transfused with antigen-matched blood predominantly from African-American donors. They described the antigen specificity of antibodies identified, including extensive high-resolution Rh genotyping. Clinical events, such as DTR, were described in relationship to total red blood cell exposure and RHD and RHCE genotypes. The authors report rates of alloimmunization of 58% and 15% among patients on chronic transfusions and episodic transfusions, respectively. Rates of sensitization to C, E, and Kell in particular were still high, despite extended matching for these antigens.

It is estimated that more than half of all children and 90% of adults with SCD have received ≥1 transfusion in their lifetime.2 Acute or episodic transfusions can relieve severe symptomatic anemia or improve
oxygen-carrying capacity, and chronic transfusions are effective in both primary stroke prevention in children with abnormal transcranial Doppler cerebral blood flow velocities and secondary stroke prophylaxis following overt cerebrovascular events. Even as the indications for transfusions continue to expand, serious hazards of transfusions such as alloimmunization can create almost insurmountable challenges for some patients. Strategies to avoid or manage this risk are desperately needed.

Studies have demonstrated that antibodies against C, E, and Kell antigens account for >50% of alloantibodies identified in patients with SCD and that extended antigen matching to include C, E, and Kell can decrease the development of new antibodies in this population by 40% to 90%. Although academic medical centers are more likely to provide extended antigen matching, a recent North American survey indicated two-thirds of institutions continue to only match for ABO and D in nonalloimmunized patients with SCD. There are also significant global variations in transfusion practices in SCD.

To date, this is the largest cohort of SCD patients who have been supported over an extended period almost exclusively with blood collected from self-identified African-American donors. Ethnic disparity has often been cited as the major contributor to allo sensitization in SCD throughout Europe and North America, where the donor population is predominantly nonblack. Diversity of the blood supply in an increasingly global, multiethnic nation is important, whether planning for national disasters or insuring safe and adequate resources for routine procedures. African Americans, in particular, continue to be underrepresented in community blood donation programs. Strategies to enhance matching by focused recruitment of African-American blood donors or establishing directed donor programs for children with SCD have long been advocated as potential solutions to this very serious transfusion-related complication.

The incorporation of DNA-based methods into standard transfusion practices for determining RBC genotype is becoming more feasible, particularly for polymorphic antigens in most blood group systems. The Rh system, however, has been a notable exception, primarily due to its complexities as demonstrated by Chou et al. The wide diversity of Rh variants among their patients (and presumably their donors) suggests that additional or alternate approaches may be needed to improve matching and reduce alloimmunization.

The authors identify a very relevant concern for hemato logists and for patients with sickle cell disease. Racial differences alone do not explain the increased propensity of patients with SCD to develop allo- and autoantibodies. Patients with hemoglobinopathies and most non-European ethnic groups are among the populations that pose exceptional challenges in blood banking as identified by the 2007 National Heart, Lung, and Blood Institute Working Group on Transfusions Epidemiology and Recipient Outcomes Research and in whom more research is needed. The paper by Chou et al provides some very critical insights to a problem for which as yet there does not appear to be an easy solution.

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Hemoglobin disorders: a look to the future

David G. Nathan123 1DNA-FARBER CANCER INSTITUTE, 2BOSTON CHILDREN’S HOSPITAL, AND 3HARVARD MEDICAL SCHOOL

In this issue of Blood, Locatelli et al compare the results of histocompatible family donor bone marrow and cord blood transplants (BMT and CBT) for severe β thalassemia (SBT) and sickle cell disease (SCD) as experienced by the Eurocord and European Blood and Marrow Transplantation group and collaborating centers in the United States, Hong Kong, and Israel between 1994 and 2005.1 Obviously, many changes in medical care and particularly MHC typing occurred over that decade, so this retrospective represents a moving target, but some firm points can be made for which we are indebted to this excellent group.

In 1984, Thomas and Storb and their colleagues reported on the first 4 patients with SBT who were treated with histocompatible BMT in Seattle.2 Two years later, Johnson and Billings and their associates reported a successful transplant of a child
Ideal donors, imperfect results in sickle cell disease

Alexis A. Thompson