a sustained immune response after vaccination and could help improve future vaccination strategies. For approaches of adoptive immunotherapy, this subpopulation may be an effective tool for treating viral infections with Th1 cells. Adoptive T-cell therapy using targeted ex vivo isolation of this unique cell population may be advantageous for sustained therapeutic protection.

The characterization of a quiescent T-cell population that survives chemotherapy and is able to mount functional active T-cell responses also has implications for current immunotherapy approaches against malignancies. Bispecific T-cell engagers recruit endogenous T cells and direct them against leukemia. This treatment relies on the activation and Th1 effector function of those T cells that survive chemotherapy. The generation of genetically modified T-cell therapies from patient samples during chemotherapy relies on quiescent cells. CD161-expressing memory T cells with superior survival and functional attributes would be ideal candidates. Obviously, this cell population is going to be an exciting and important topic of basic and future clinical research.

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

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DOI 10.1182/blood-2016-11-751891 © 2017 by The American Society of Hematology

Comment on Martin et al, page 791

Major vs minor histocompatibility antigens

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In this issue of Blood, Martin et al found that the number of minor histocompatibility antigen mismatches doubles in unrelated vs sibling HLA-matched transplants, but has less impact on graft-versus-host disease (GVHD) than mismatching at HLA-DP. Minor histocompatibility antigens are small peptides that are found on the cell surface in association with class I or class II major histocompatibility complex (MHC) molecules. Minor histocompatibility antigens correspond to polymorphic structures and are therefore instrumental in the molecular definition of self to the immune system. Single
amino acid differences are detectable by T cells that can become immunoreactive and cause GVHD in the context of HLA-matched allogeneic stem cell transplantation. Although >100 minor histocompatibility antigens have been identified and sequenced, few data are available on the global role of minor histocompatibility antigen disparities on the development of GVHD. In particular, the total number of minor histocompatibility antigen mismatches important in the prediction of GVHD. Alternatively, is a constrained number of minor histocompatibility antigens responsible for most of the GVHD observed? Does the dogma of MHC-mismatching predominance over minor histocompatibility antigen mismatching in terms of immunoreactivity still hold as we learn more about minor histocompatibility antigens?

Martin et al have used a genomic approach to answer these questions. Genome sequencing of donor and recipient allowed identification of coding single nucleotide polymorphisms (SNPs), likely to correspond to minor histocompatibility antigens, a number of coding SNPs, likely to correspond to minor histocompatibility antigens that is commensurate with the objectives of the study.

Based on population genetics, matched unrelated donors are expected to harbor greater differences in minor histocompatibility antigen repertoire than sibling transplants. Here the authors found that the use of unrelated donors implies a twofold increase in magnitude of genome-wide minor histocompatibility antigen disparity. How important is a doubling in the number of minor histocompatibility antigen discrepancies on GVHD occurrence? No significant difference in acute or chronic GVHD occurrence could be found with this increase. In contrast, mismatching at the single HLA-DP locus generated a clear increase in GVHD. These results immediately suggest that mismatching at a single HLA locus is more important than mismatching at half of all minor histocompatibility antigen loci. Consistent with this, the total number of unshared minor histocompatibility antigens (presented by HLA class I and II allotypes) between 2 MHC-identical subjects is inferior to 100, whereas each HLA allele can present around 5000 different peptides. Hence, mismatching for a single HLA allele could lead to the presentation of thousands of nonself MHC-peptide complexes, an order of magnitude over the total number of unshared minor histocompatibility antigens. These findings therefore emphasize the crucial need for stringent HLA matching, particularly in the setting of unrelated transplants.

In the context of HLA-identical sibling donor transplantation, Martin et al found that an increase in minor histocompatibility antigen disparity increased severe (grade III-IV) and stage 2-4 gut GVHD. However, SNP mismatching did not correlate with chronic GVHD. Nevertheless, the ~60% of grade II-IV acute GVHD and ~40% chronic GVHD observed in sibling HLA-matched pairs should be attributable to minor histocompatibility antigen mismatching. This suggests that anti-minor histocompatibility antigen immune response can become saturated. It also underlines the role of a select subset of peptides with greater immunogenicity: immunodominant minor histocompatibility antigens. The recent observation that MHC class I-associated peptides are not randomly distributed across the genome, but rather originate from a restricted fraction of the exome, suggests some form of hierarchy in minor histocompatibility antigen development. It will be useful to determine whether the increased number of SNPs identified in unrelated donors reflect genomic polymorphisms that are less likely to be expressed by MHC molecules or are less immunogenic.

The insights gained on minor histocompatibility antigens and their clinical impact are also highly encouraging for the development of therapeutic approaches. Indeed, the current publication suggests that minor histocompatibility antigens represent particularly appealing targets in order to eliminate leukemia and other cancer cells without causing GVHD. In addition, recent technological developments in proteogenomics have allowed the identification of minor histocompatibility antigens that are preferentially expressed on hematopoietic cancer cells over epithelial cells, and can be used for T-cell immunization. The multiple strategies that have become available to study minor histocompatibility antigen biology, investigate their role in GVHD and graft-versus-leukemia activity, and intervene clinically have overcome the obstacles to minor histocompatibility antigen usage in the fight against cancer. It is about time that minors are not minor anymore.

Conflict-of-interest disclosure: D.C.R. has been a consultant for Novartis, Paladin, and Fate Therapeutics and has received research support from Kiadis Pharma. C.P. is inventor on a patent filed by the Université de Montréal on minor histocompatibility antigen usage.

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DOI 10.1182/blood-2016-12-754515

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