PBMCs. Rather, exposure to photodepletion-preserved Tregs was necessary and sufficient to induce the conversion of CD4+CD25−Foxp3−T cells to CD4+CD25+Foxp3+ Tregs. Cell-cell contact involving CTLA4 expressed on Tregs proved to be a critical initiating event leading to IL-10 secretion, which supported this conversion.

As with many studies involving GVHD, this one also focuses on the effector arm of the immune response. An important unanswered question in this study, however, is whether TH9402-sensitized photopheresis also affects the other half of this equation, which is the afferent sensitization of donor T cells at the level of antigen presentation. Dendritic cells (DCs) are a heterogeneous group of highly potent, bone marrow--derived, antigen-presenting cells (APCs) that direct the balance of peripheral tolerance and T-cell sensitization. Important remaining unknowns therefore include the extent to which this and other forms of ECP may alter the number and function of circulating DCs, how ECP affects donor DC cross-presentation of host antigens to donor T cells, whether effects on circulating DCs translate to effects in GVHD target organs and tissues, and whether the consequences of ECP vary between different DC subsets and maturation states.

Among other putative mechanisms, for example, photodepletion-preserved DCs may mediate the observed increase in Foxp3+ Tregs through an indoleamine 2,3-dioxygenase (IDO) mechanism, as IDO-expressing conventional DCs can significantly expand Tregs in autologous or HLA-matched human systems. One could speculate that a similar mechanism supports the beneficial effects on experimental GVHD in mice when mouse DCs increase IDO after exposure to histone deacetylase inhibitors. Harnessing the graft-versus-tumor (GVT) effect of the transplant, by restricting graft alloreactivity to antigens unique to the tumor and not shared with normal host tissues (thereby reducing GVHD), remains one of the overarching goals in the field. Although the current report does not yet provide data regarding relapse in treated patients with chronic GVHD, mouse models suggest that Tregs can help maintain protection against GVHD without compromising GVT. Investigators still have much to learn about the complete immunosuppressive mechanisms underlying ECP, although altered function of DCs and other APCs likely plays a critical role. For a complication like treatment-refractory GVHD, the field of allo-genetic HSCT eagerly awaits more detailed and long-term results of the incipient clinical trial informed by the careful laboratory–based investigations undertaken by Basten and colleagues.

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REFERENCES

LYMPHOID NEOPLASIA

Comment on Harvey et al, page 4874

Taking childhood leukemia personally

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The concept of biologic unity and the feasibility of “one–fits–all” treatment strategies has become outdated for most malignancies and certainly for acute lymphoblastic leukemia (ALL) of childhood. Conventionally defined malignant diseases represent a collection of molecularly distinct entities with characteristic features that define their response to treatment as well as their prognosis. Clinically significant heterogeneity of childhood ALL became apparent when disparity in treatment responses and differences in the cytogenetic makeup of leukemia cells were identified. Even today, with molecular subtyping of leukemias, these seemingly archaic features remain important components of the individual risk stratification of modern treatment protocols that allow us to successfully individualize treatment according to risk. The concept of risk–adapted therapy has been one of the cornerstones in achieving the current 80% cure rates of childhood ALL in developed countries. This is all very well, unless you belong to the 20% of patients who eventually relapse or show treatment resistance. Furthermore, identifying those children who would be cured with a less intensive regimen with less acute and long-term side effects is difficult yet equally important.

The advent of mRNA expression and genomic high-resolution DNA analyses has revolutionized the technical potential to define the functional genetic composition of malignant cells. Various studies of expression arrays have defined previously undetectable subgroups of childhood ALL patients with different risk levels. However, mRNA expression analyses are prone to preanalytical changes, which is also reflected by different expression analyses identifying different components of risk signatures. The more robust genomic DNA analyses by array–comparative genomic hybridization, single nucleotide polymorphism arrays, or deep sequencing have therefore proved to be most useful to complement.
expression studies in finding correlations between genetic lesions and prognostic biomarkers and, more importantly, in finding functionally critical drivers of leukemogenesis. 5–7 In this issue of Blood, Harvey and co-workers now confirm that children with B-precursor ALL, who have been classified as high risk on the basis of the simple clinical National Cancer Institute criteria age and high white blood cells at the time of diagnosis, can be subdivided into subgroups by a combination of mRNA expression analyses and assessment of genomic DNA copy number aberrations. 8 Two of these subgroups coincided with known cytogenetically defined risk groups. Two other subgroups were remarkable in that they identified patients with an excellent prognosis of 4-year event-free survival (EFS) of >90% or a particularly bad prognosis of 4-year EFS of ~30%. The favorable subgroup was defined by the high expression of 4 outlier genes and ERG deletions. The unfavorable group was characterized by (1) high expression of 4 genes and (2) DNA deletions, rearrangements, and mutations of another 6 gene loci including CRLF, RAG, JAK2, and IKZF1 (thus confirming the prognostic significance of these genes and a BCR-ABL–like expression signature in pediatric ALL5,6,9–12 and also confirming the power of combined mRNA expression and DNA analyses in determining individual risk profiles). Although the definition of the subgroups represents a remarkable success, critical questions remain. The first relates to the influence of therapy on the risk profile. This is well illustrated by the case of pediatric T-ALL, where the favorable impact of activating NOTCH1 mutations depends on the subtypes of the different treatment protocols. 13–15 While the role of CRLF has been documented in both Childhood Oncology Group8,16 and Berlin–Frankfurt–Munster protocols, 11 the general role of the other changes in different treatment protocols still requires testing. A second issue relates to the small size of the subgroups of a disease that is already rare. Tailoring and testing treatment concepts in the context of such a personalized medicinal approach will require studies that are designed on a wide international scale: this will challenge the different cultures that underlie medicine in general, and the organization of clinical studies including different regulatory agencies in particular. Finally, while it is helpful to define very–high-risk groups in pediatric ALL, identifying druggable pathways of high–risk ALL and developing logical new treatments for this most difficult group of patients will be essential.

In this issue, Harvey and colleagues state that they will focus on identifying hitherto unidentified altered kinases that may contribute to the BCR-ABL–like expression profile of high-risk childhood ALL that may also represent new targets for therapeutic intervention. Alternatively, one may want to look at the potential of epigenetic strategies to reverse the block in B-cell differentiation in this group of patients. In any case, finding new options for the unfortunate 20% of children with ALL is what future patient generations will expect from us.

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Comment on Gunay–Ayyun et al, page 4990

Filling a void in Gray Platelets

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The Gray Platelet Syndrome (GPS) is the paradigm of clinical α-granule deficiency. Yet, its description had been limited to case reports. Gunay–Ayyun et al now provide the first comprehensive study of GPS and assign the causative gene to a locus on chromosome 3.1

1 In 1971, Raccuglia described a patient with thrombocytopenia whose platelets included a high percentage of large cells that were nearly devoid of granules, rendering them gray upon Wright staining. He termed the disorder the Gray Platelet Syndrome. The sine qua non of GPS is the identification by electron microscopy of a large number of empty

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