spots” truly exist for lymphocyte extravasations, and future investigation will be needed to resolve this issue. Additionally, Bajenoff and Germain recently reported that the remodeling of the conduit system that allows efficient delivery of soluble antigens from the periphery to FDC accompanies B-cell follicle development. It remains to be determined what role, if any, LTαβ expression by B cell may contribute to this process.15

Finally, the observation presented in this report also poses the possibility that a similar paradigm may exist to accomplish LN resolution following viral clearance. As mRNA levels of LTα and LTβ diminish after day 4 after LCMV infection, there is a concomitant decrease in the number of B cells in the LN.13

Understanding molecular and cellular identities involved in the restoration of LN architecture and lymphocyte homeostasis following viral insults will add to our knowledge base in understanding the complex communication network regulating immune responses in vivo. The current work by Kumar et al furthers our understanding in a rapidly evolving cutting-edge field and highlights the symbiotic relationship between anatomy and function in immunobiology.1

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

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comment on chen et al, page 4778

hitting the sweet spot for lymphoma

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Anyone who has ever played a racket sport, baseball, cricket, and/or golf can attest to experiencing the “sweet spot”—that place where the least jolt is felt on contact. In this issue of Blood, Chen et al show how sugar–decorated liposomes can be used to deliver doxorubicin in a targeted manner to malignant B cells, thus limiting the systemic jolt of this potent cytotoxic agent.1

As envisioned by scientists as far back as the 1800s, the ideal chemical therapy would possess exquisite selectivity, thereby restricting, if not eliminating, collateral cellular damage (eg, Ehrlich’s “magic bullet”). In cancer therapeutics, selectivity has been achieved to varying degrees of success by employing mAb, with (eg, gemtuzumab ozogami-
Taken together, the restricted expression of CD22, its inherent high endocytic property(s), and the specificity of receptor/ligand interactions conferred by cognate glycans, support the potential use of the described liposome-based CD22-targeted chemotherapy of B-cell lymphomas. However, some caveats bear mention in contemplating this approach clinically. The authors use a sialoside construct containing a specific biphenylcarboxyl modification that increases affinity of the glycan to CD22. At the same time, however, this modification increases affinity to another sialic, Sn (Siglec-1), expressed on macrophages. Uptake by macrophages increases clearance of the liposomes (thereby attenuating potency). There is also the real possibility that competing uptake by Sn could induce adverse effects secondary to tissue macrophage cytotoxicity. In this regard, the authors show that a different biphenyl modification (ie, biphenylacetyl) that binds poorly to Sn displays reduced clearance in vivo, but these constructs also have reduced affinity for CD22. More critically, glycosidases that cleave sialic acid linkages (ie, sialidases) are present in serum and on the surfaces of cells, including lymphocytes and granulocytes. Desialylation of the cognate glycan would result in loss of selective targeting to CD22 and yield coincident liposomal uptake by asialoglycoprotein receptors (eg, in hepatocytes and macrophages), with resultant delivery of the chemotherapeutic agent to bystander cells. Despite these considerations, the results presented are both novel and provocative in suggesting that a cognate glycans-based approach exploiting the lectin function of CD22 could be an option to antibody-mediated chemotherapy targeting of B-cell malignancies. The Chen et al report certainly provides persuasive logic to broadening the potential applications of their approach. Notably, the well-known myeloid antigen CD33 is also a Siglec (it is Siglec-3), which raises the possibility that myeloid leukemias could also be subject to a cognate glycan–based liposomal chemotherapy approach (eg, using liposomes containing daunorubicin and/or cytosine arabinoside). Thus, for hematologic malignancies, the promise of selective delivery of cytotoxic agents with improved therapeutic efficacy and minimal systemic effects may just well be realized by, literally, hitting with an expanded sweet spot.

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LYMPHOID NEOPLASIA

Comment on Schafer et al, page 4798

MILL: exploring the methyleome

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In this issue of Blood, Schafer and colleagues report their findings on MLL-r infant ALL.1 They examined global promoter methylation in infants and found hypermethylation in cases with MLL-r ALL compared with both the normal and non-MLL-r ALL cases. When treating MLL-r cell lines with decitabine, they observed a reexpression of silenced genes and a cytotoxic effect. This may open up the next treatment options for a disease entity with a dismal prognosis.

Hardly any other gene in cancer medicine is involved in as many different chromosomal translocations as the mixed lineage leukemia (MLL) gene. It has thus far been possible to identify more than 60 different genes dispersed throughout the genome and to cytogenetically characterize another 35 loci that are involved in MLL translocations.2 Around 10% of acute leukemia (AML and ALL) patients carry MLL aberrations. These patients have been shown to exhibit a distinct gene expression signature.3 In acute lymphoblastic leukemia (ALL), MLL aberrations are usually associated with an adverse prognosis in all age

Infant ALL has a unique genetic background with approximately 80% of patients carrying MLL aberrations (data according to Jansen et al4).
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