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 ozogamicin) or without (eg, rituximab) toxic conjugates. Although the advent of liposomal particles that carry an encapsulated chemotherapeutic cargo has reduced adverse effects typically associated with the chemotherapeutic agent and commensurately allows for higher drug dose levels, side effects of these agents have generally been attenuated, but not eliminated. Antibody-covered liposomes (immuno-liposomes) incorporating relevant chemotherapeutic agents have been developed to further improve selectivity and, hence, the therapeutic index of encapsulated agents, but these agents are still not without significant toxicities.2

As an alternative to immunoliposomes, the work of Chen et al offers targeted delivery of liposomal doxorubicin to B cells by exploiting the ligand activity of a B cell–specific cell-surface protein, CD22 (also known as Siglec-2).3,4 CD22 is a lectin, that is, a protein that binds carbohydrate structures, that belongs to the family of lectins known as Siglecs that recognize sialylated glycans (sialosides).5 CD22 has specificity for sialic acid in α(2,6)-linkage to galactose.6 Importantly, CD22 displays highly efficient, constitutive endocytosis, which is accelerated by ligation.6 Thus, binding to CD22 by cognate ligands (ie, sialosides) or by mAb would be expected to lead to rapid internalization of the relevant structure(s).7

The authors report that doxorubicin–loaded liposomal nanoparticles incorporating α(2,6)-sialosides show significantly higher cytotoxicity to Daudi cells (a human Burkitt lymphoma cell line) in vitro compared with those using nontargeted doxorubicin–loaded liposomes. In vivo studies using immunocompromised mice injected with Daudi cells showed heightened cytotoxicity when using the sialoside–bearing doxorubicin–liposome preparation, with prolonged survival of tumor–bearing mice. Furthermore, the authors demonstrate that drug–loaded liposomes incorporating sialosides bind to B cells obtained from blood of patients with chronic lymphocytic leukemia, hairy cell leukemia, and marginal zone lymphoma, with binding efficiency correlating with expression of CD22. Notably, in vitro studies show that the capacity of sialoside–bearing drug–loaded liposomes to kill B cells is not proportional to expression of CD22, suggesting that the high efficiency of CD22–mediated drug internalization is sufficient to induce cell death even when surface CD22 levels are relatively low.
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 biphenylcarboxylic modification that increases affinity of the glycan to CD22. At the same time, however, this modification increases affinity to another sialic acid-binding immunoglobulin-like lectin (it is Siglec-3), which raises the 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 glycan-based approach exploiting the lectin function of CD22 could be an option to antibody-mediated chemotherapeutic 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-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 glycan-based approach exploiting the lectin function of CD22 could be an option to antibody-mediated chemotherapeutic 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 chemotherapeutic 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.

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

**REFERENCES**


**LYMPHOID NEOPLASIA**

Comment on Schafer et al, page 4798

**MLL: exploring the methylome**

**Thomas Burmeister** CHARITÉ UNIVERSITÄTSMEDECIN BERLIN

In this issue of Blood, Schafer and colleagues report their findings on MLL-r infant ALL. 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 prospect of new 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. Around 10% of acute leukemia (AML and ALL) patients carry MLL aberrations. These patients have been shown to exhibit a distinct gene expression signature. In acute lymphoblastic leukemia (ALL), MLL aberrations are usually associated with an adverse prognosis in all age groups

![Diagram: Infant ALL has a unique genetic background with approximately 80% of patients carrying MLL aberrations (data according to Jansen et al).](image-url)
Hitting the sweet spot for lymphoma

Robert Sackstein