superfamily. By generating a panel of activating or inhibitory anti-CD277 monoclonal antibodies (mAbs), Harly and coworkers uncovered that certain activating anti-CD277 mAbs induced a selective and exclusive activating or inhibitory anti-CD277 monoclonal superfamily. By generating a panel of activating or inhibitory anti-CD277 mAbs, Harly and coworkers developed other inhibitory anti-CD277 mAbs that specifically blocked the activation and proliferation of Vγ9Vδ2 T cells in response to phosphoantigens and n-BP. Moreover, the recognition of Vγ9Vδ2-susceptible lymphoma cells was also strongly inhibited by the blocking anti-CD277 mAbs. A series of elegant experiments then addressed the question of how the CD277 molecule contributes to the phosphoantigen-mediated γδ T-cell activation. To this end, they specifically knocked down the expression of different isoforms of the CD277 molecule and found out that the membrane mobility of CD277 was drastically influenced by phosphoantigens through the intracellular part of one particular isoform. Together with additional experiments, the results of this study suggest that activating anti-CD277 mAbs and phosphoantigens modify the CD277 molecule in such a way that the γδ T-cell receptor is triggered on coculture with CD277-expressing cells. It appears that agonistic anti-CD277 mAbs induce changes in the membrane mobility of the CD277 molecules that are somehow sensed by the Vγ9Vδ2 T-cell receptor (see figure panel A). In the case of phosphoantigens generated in tumor cells, particularly after treatment with n-BP, the presented data are in line with the assumption that the intracellularly generated phosphoantigens (ie, IPP) act through the intracytoplasmic domain of one CD277 isoform to induce a membrane reorganization of the CD277 molecule (see figure panel B).

The studies of Harly et al have undeniably discerned a pivotal role of the CD277 molecule for the activation of human Vγ9Vδ2 T cells. This notwithstanding, several issues require further analysis. Most importantly, it is presently unknown how the Vγ9Vδ2 T cells recognize the phosphoantigen (or anti-CD277 mAb)–induced changes of the CD277 surface molecule. The possibility of direct interaction of the Vγ9Vδ2 T-cell receptor with the modified CD277 molecule appears unlikely on the basis of preliminary experiments mentioned in their report.1 It is also possible that modified CD277 molecule might recruit additional molecules that are then sensed by the Vγ9Vδ2 T-cell receptor. In any case, the key role of CD277 for activation of Vγ9Vδ2 T cells described by Harly et al also provides an explanation as to why murine cells cannot act as presenting cells for phosphoantigen–reactive human Vγ9Vδ2 T cells: there is no CD277 ortholog in rodents.

Apart from providing novel insights into the mechanisms of phosphoantigen–dependent γδ T-cell activation, this study also opens new translational aspects. Agonistic anti-CD277 mAbs might be useful reagents to boost the antitumor and antilymphoma/leukemia efficacy of human Vγ9Vδ2 T cells. Considering that this population comprises up to 5% of all blood T cells, new strategies targeting the immunotherapeutic potential of Vγ9Vδ2 T cells might thus have major clinical implications.

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

**REFERENCES**


**LYMPHOID NEOPLASIA**

Comment on Perry et al, page 2290

**A promising new biologic prognostic model in diffuse large B-cell lymphoma**

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In this issue of *Blood*, Perry et al show that immunohistochemical markers for the cell–of-origin and the microenvironment in diffuse large B-cell lymphoma delineate 2 groups with markedly different survival.1

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoma in all countries and its frequency varies from 35% to 60% of non-Hodgkin lymphomas. In the World Health Organization classification, DLBCL is clinically, biologically, and pathologically heterogeneous because it includes over 20 entities, subtypes, and variants.2 Nevertheless, the 2 most common (~ 85%) subtypes of DLBCL are: (1) those with a germinal center B-cell (GCB) origin and (2) those with a non–GCB origin, most of which have activated B-cell (ABC) phenotype. The non-GCB subtype has a more aggressive clinical course than the GCB subtype.3,4

For optimal patient management, an accurate diagnosis is mandatory. For the next 5 or more years, there is agreement among senior academic lymphoma pathologists that immunohistochemistry–based markers will continue to be most valuable in making an accurate diagnosis. Immunostaining is widely available to most pathologists in the developed world, as well as in large hospitals in big cities in the developing world.

Several papers published in the past decade on the clinical utility of separating DLBCL of GCB subtype from the non-GCB/ABC subtype have yielded conflicting survival results, especially since the addition of rituximab to
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Zebrafish lead the way in control of vascular permeability

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In this issue of Blood, Hoeppner et al create an extremely valuable model of vascular permeability that is amenable to high throughput chemical screening as well as genetic analysis.1
A promising new biologic prognostic model in diffuse large B-cell lymphoma

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