disrupting IL-6 signaling might have context-dependent implications. As is typically the case in research, more work will be needed to resolve certain questions, such as why IL-6 treatment causes reduced CLL cell numbers in mice and how it enhances sensitivity of TLR7-activated CLL cells to cytotoxic agents. In particular, focused examination of the IL-6 context dependency reported here may help to reconcile the complex and sometimes contradictory reports regarding IL-6 in CLL: for example, the cause and importance of IL-6 secretion by CLL cells themselves, as well as the observation that high serum levels of IL-6 correlate with more aggressive disease.10 Hopefully, the data provided by Li et al move us closer to being able to manipulate the CLL microenvironment to the benefit of our patients.

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

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LYMPHOID NEOPLASIA

Evolution: IMiDs to PPMs, revolution in DLBCL?

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In this issue of Blood, Hagner et al provide preclinical evidence that CC-122 might be active in both major molecular subtypes of diffuse large B-cell lymphoma (DLBCL).1

The development and evolution of immunomodulatory drugs (IMiDs) is one of the most fascinating drug development stories in cancer medicine.2 This history began with their use as an antiemetic drug used in pregnancy and was abruptly halted because of the association with severe birth defects. Their testing in multiple myeloma was stimulated by their antiangiogenic effects and led to a new active class of drugs in multiple myeloma. Their utility in other hematologic malignancies continues to evolve with demonstrated activity in molecularly defined subtypes of DLBCL. After years of evolution driven by chemistry, preclinical work, and clinical experience, the next family member of the thalidomide analogs, CC-122, emerges with features that differentiate it from IMiDs, giving rise to a new class of drugs: pleiotropic pathway modifiers (PPMs; see figure). Novel properties make CC-122 potentially active in a subtype of DLBCL in which its predecessor, lenalidomide, has limited activity.

There are 2 subtypes of DLBCL: activated B-cell-like (ABC) and germinal center B-cell-like (GCB) subtypes.3 The former is characterized by tonic B-cell receptor

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BCR signaling and a significantly worse clinical outcome. Recognition of molecular subtypes of DLBCL, because of their different biology and pathogenesis, play an important role in the selection of therapy. Lenalidomide, as a single agent, demonstrates significant activity in relapsed and refractory DLBCL. However, the activity of lenalidomide alone or in combination with rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP) appears to be confined primarily to ABC DLBCL. The activity of lenalidomide in ABC DLBCL has 2 postulated mechanisms: inhibition of the nuclear factor κB pathway downstream of BCR signaling and upregulation of the interferon death pathway. Although the first pathway is particularly important for ABC DLBCL because of tonic BCR/MYD88 signaling, the second effect appears to be able to potentially impact both GCB and ABC DLBCL. In this regard, Hagner et al demonstrated that in contrast to the IMiD lenalidomide, the PPM CC-122 has significant activity in preclinical models of both GCB and ABC DLBCL. Similar to IMiDs, the PPM CC-122 also binds to CRBN, which in turn affects ubiquitination of Aiolos and Ikaros by the Cullin 4 RING E3 ubiquitin ligase complex, leading to their subsequent proteasomal degradation. The studies of DLBCL tumor tissue from patients exposed to CC-122 from the ongoing clinical trial are particularly revealing and confirm that this in vitro mechanism occurs in the clinic. In turn, degradation of Aiolos and Ikaros leads to a direct antitumor effect mediated through the interferon pathway.

Important questions remain. First, this mechanism does not address why the IMiDs and PPMs have a different impact on GCB DLBCL despite that both target CRBN. Hagner et al nicely outlined potential hypotheses behind this observation, including the role of different metabolites (see figure); however, further studies are needed. Second, as the name of class indicates, the effect of CC-122 is pleiotropic; hence, other potential mechanisms for its activity in DLBCL can, and likely do, exist. Furthermore, like their cousins, the PPMs also have immunomodulatory effects and impact the nonimmune environment as well. These effects are difficult to reproduce in preclinical models.

The demonstration of preclinical activity of the PPM CC-122 in GCB DLBCL is important. Although GCB DLBCL is associated with superior outcomes, ~15% to 20% of the patients will develop disease relapse with 24 months postdiagnosis when treated with R-CHOP. Once relapsed, DLBCL has a poor outcome regardless of molecular subtype, with the majority of these patients dying of the disease. Approximately a quarter of relapsing GCB DLBCL patients (3% to 5%
THROMBOSIS AND HEMOSTASIS

Comment on Ciciliano et al, page 817

Physiochemical artifacts in FeCl₃ thrombosis models

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In this issue of Blood, Ciciliano et al demonstrate that thrombus formation in ferric chloride (FeCl₃) thrombosis models relies on physiochemical, rather than biological, mechanisms.¹

The FeCl₃ model is the most widely used animal model of thrombosis, but its mechanism remains a source of debate. It was originally assumed that thrombus formation was initiated through the generation of reactive oxygen species, leading to denudation of endothelial cells, and subsequent exposure of the prothrombotic subendothelium. This assumption has been called into question by careful light and electron microscopy studies showing that red blood cells (RBCs), rather than platelets, are the first blood cells to adhere to FeCl₃-treated endothelial cells,² and evidence of platelet adhesion and aggregation independent of collagen and fibrinogen receptors.³ Ciciliano et al provide evidence that initial blood cell adhesion is an artifact of ferric ions leaking into the bloodstream leading to flocculation.

Flocculation is a separation strategy in the chemical industry to remove suspended solids or soluble impurities from fluids using metal salts or charged polymers. The mechanism of flocculation relies on charge suppression and entrainment. FeCl₃ is one of the more common “coagulants” used, for instance, in water treatment to remove solids. The hydrated form of the ferric ion, Fe(H₂O)₆³⁺, is positively

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