blood and lymphatic vessel integrity to organ development (eg, brain, kidney, and lung) and tumor metastasis. To the extent that efforts to treat thrombotic events by targeting CLEC-2 continue, these additional aspects of CLEC-2 biology must be taken into account.

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REFERENCES

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Comment on Flynn et al, page 4085

Syk and tired of current chronic GVHD therapies

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In this issue of Blood, Flynn et al\(^1\) provide key data that lend further support to the development of clinical trials of spleen tyrosine kinase (Syk) inhibition for more effective chronic graft-versus-host disease (cGVHD) treatment.

Treatment of cGVHD with medications such as corticosteroids and calcineurin inhibitors is often insufficient or toxic and causes immunosuppression that can increase malignancy relapse. As illustrated by Flynn et al\(^1\) in this issue of Blood, an improved understanding of cGVHD biology and the availability of targeted therapies may help solve these obstacles. Flynn and colleagues have identified Syk signaling in murine allogeneic B cells as a mediator of cGVHD, including the devastating complication of bronchiolitis obliterans. Targeting of Syk during established chronic lung GVHD was effective using either conditional genetic ablation or pharmacologic tyrosine kinase inhibitor (TKI) therapy. Syk inhibition was also effective at inducing apoptosis of human cGVHD B cells.

Previously, inhibition of the Syk signaling pathway with fostamatinib prevented experimental murine acute GVHD more effectively than cyclosporine therapy.\(^2\) Importantly, fostamatinib inhibited myeloid-derived antigen-presenting cells (APCs) and T cells (including inhibition of migratory function) yet preserved T-cell cytolytic effects against lymphoma and viral challenge. Fostamatinib was also previously evaluated in a cGVHD model that was somewhat different from the multiple models used by Flynn et al; in this prior study, fostamatinib reduction of skin and lung disease was again primarily attributed to modulation of APC and T-cell function.\(^3\) The experiments by Flynn et al place a new emphasis on the role of B cells in Syk-driven cGVHD as (1) recipients of Syk-deficient donor T cells developed cGVHD, (2) recipients of Syk-deficient marrow had limited B-cell reconstitution and avoidance of cGVHD, and (3) conditional in vivo deletion of Syk-expressing marrow-derived cells (or in vivo therapy with fostamatinib) was effective against established pulmonary cGVHD.

The work of Flynn et al is also instructive because of the multiple experimental models of cGVHD that were evaluated. Although control of cGVHD cutaneous manifestations was incomplete and variable between the models, fostamatinib was relatively consistent in terms of its ability to modulate some of the immunologic end points associated with cGVHD biology. This type of diversity in modeling may help in the design of clinical trials, both with respect to types of cGVHD patients to accrue and immune end points to monitor as potential surrogates for drug activity. The inclusion of well-annotated human samples in this investigation is an advantageous feature that may assist in the more effective screening of promising agents, especially as the number of cGVHD patients and clinical trials are relatively scarce. Indeed, as exemplified in the current work, new efforts in cGVHD drug development...
will benefit from an integrated multicenter cooperation between all stakeholders in the experimental modeling and clinical trial realms.  

Clinical trials of small-molecule inhibitors of Syk that have advanced to phase 2 studies in autoimmune disease have focused on fostamatinib, which is a relatively nonspecific TKI compared with other agents that have only recently entered the drug-development pipeline; of note, fostamatinib can exacerbate hypertension, which may be due to VEGFR2 inhibition (see the recent review of Syk inhibitors by Lucas and Tan5). Narrowing the specificity of Syk inhibitor therapy could ultimately improve safety, although therapeutic effects of TKI therapy are sometimes mediated through multiple targets.

Syk inhibitor therapy with fostamatinib can be considered in the context of a growing list of agents known to modulate B-cell–mediated cGVHD. Most recently, the US Food and Drug Administration–approved Bruton tyrosine kinase (Btk) inhibitor ibrutinib was effective against murine cGVHD.6 As Flynn et al propose, the combination of Syk plus Btk inhibition may represent a powerful approach to inhibit B cells during cGVHD. Although Syk lies upstream of BTK in the B-cell signaling cascade, nonoverlapping pathways predict that combination therapy will consolidate inhibitory effects and prevent the emergence of drug resistance. Alternatively, B-cell depletion with rituximab has been used to treat cGVHD7; the relatively limited success of rituximab therapy may in part be due to the existence of memory-type plasma cells that survive depleting strategies.8 Because Syk signaling contributes to long-term memory antibody responses,9 Syk inhibition would predictably represent a more potent therapy of cGVHD relative to B-cell depletion approaches; such potency could be further augmented by any beneficial off-target effects and on-target inhibition of Syk-expressing APC and T-cell populations.

Syk inhibition can not only spare an allogeneic cytolytic graft–versus-leukemia effect2 but also directly mediate antitumor effects against multiple hematologic malignancies (potentially including chronic lymphocytic leukemia, non–Hodgkin lymphoma, acute lymphoblastic leukemia, posttransplant lymphoproliferative disorder, myeloproliferative disorders, and acute myeloid leukemia; see the review by Krisenko and Geahlen10). As such, Syk inhibitor therapy represents a novel approach to treat cGVHD (including B-cell–driven manifestations as described by Flynn et al) while also treating the underlying malignancy (see figure).

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REFERENCES
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