used on a mouse model that has shown therapeutic fidelity in MM bone disease. CCX721, administered either prophylactically or therapeutically, reduced tumor burden in their model, as demonstrated by a reduction in a monoclonal immunoglobulin biomarker and by green fluorescent protein–tagged cell imaging. Interestingly, the reduction of tumor burden was not due to a direct cytotoxic effect on MM cells, as CCX721 had no effect on the viability of cultured mouse and human MM cell lines, no effect on subcutaneously implanted plasmacytomases and no effect on splenic MM cells in their mice. The effect of CCX721 on MM tumor burden is therefore entirely dependent on the bone marrow microenvironment. Within this environment, the authors demonstrate a marked reduction of osteoclasts and this translates into a reduction in the number osteolytic bone lesions. To suggest potential clinical efficacy in humans, they note that nanomolar concentrations of CCX721 were sufficient to effectively inhibit osteoclastogenesis from normal human mononuclear precursors. These results represent a clear improvement over those seen with other CCL3/MIP-1α inhibitors and use a molecule that is orally bioavailable and whose parent compound is already in clinical trials for inflammatory diseases.

While CCR1 inhibition may seem like an excellent idea in mouse models of diseases, human clinical trials have not been so successful. In the inflammatory diseases, 3 trials of 3 separate CCR1 inhibitors did not show much therapeutic benefit, possibly because of chemokine family cross-talk or low levels of CCR1 inhibition. In MM, Dairaghi and colleagues have shown that exclusive, but potentially reduced tumor burden and osteolysis in vivo in a mouse model, as CCX721 had no effect on the viability of cultured mouse and human MM cell lines, no effect on subcutaneously implanted plasmacytomases and no effect on splenic MM cells in their mice. The effect of CCX721 on MM tumor burden is therefore entirely dependent on the bone marrow microenvironment. Within this environment, the authors demonstrate a marked reduction of osteoclasts and this translates into a reduction in the number osteolytic bone lesions. To suggest potential clinical efficacy in humans, they note that nanomolar concentrations of CCX721 were sufficient to effectively inhibit osteoclastogenesis from normal human mononuclear precursors. These results represent a clear improvement over those seen with other CCL3/MIP-1α inhibitors and use a molecule that is orally bioavailable and whose parent compound is already in clinical trials for inflammatory diseases.

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important adhesion molecules, and thereby the recruitment capabilities of neutrophils.

The mechanism underlying this response remains to be determined. As Ly6G is a GPI-linked protein and therefore cannot directly signal into the cell (see figure), this raises the question as to whether Ly6G associates with other extracellular binding partners that might contribute to its effects on the $\beta_2$ integrins. However, while not fully delineating the mechanism, a number of issues make this an important study. At a technical level, it raises a cautionary note for researchers using anti-Gr-1 or anti-Ly6G to identify neutrophils in vivo to be vigilant in their assessment of potential artifacts associated with their imaging methodology. Secondly, it raises the question as to the existence of as yet- unidentified endogenous ligands that might mediate similar effects to the anti-Ly6G antibody used here. Finally, it reveals a novel function for this poorly understood molecule that, if it could be translated to human biology, may be therapeutically relevant. Ly6G is only present in mice, but human neutrophils express the structurally related molecule CD177, a member of the Ly6/uPAR (urokinase plasminogen activator receptor) family. Interestingly, antibodies against CD177 have been shown to inhibit neutrophil transmigration across an endothelial monolayer, potentially by interfering with an interaction between Ly6G and PECAM-1. While murine Ly6G and human CD177 are unlikely to function identically, the findings from the murine and human systems identify these molecules as worthy of further investigation for their potential as novel therapeutic targets.

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

**REFERENCES**


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**THROMBOSIS & HEMOSTASIS**

Comment on Holzhauer et al, page 1510

**Thrombophilia screening: whom to test?**

Aisha Bruce and M. Patricia Massicotte  UNIVERSITY OF ALBERTA

In this issue of *Blood*, Holzhauer et al have determined a novel method of identifying patients with protein C, protein S, and antithrombin deficiency who are at increased risk of developing venous thromboembolism (VTE; see figure). Children with VTE and their relatives were screened for inherited thrombophilia including proteins C and S and antithrombin deficiency; and Factor (F)V G1691A and FII G20210A. Their study demonstrates that relatives with proteins C and S and antithrombin deficiency are at a significantly higher risk of developing VTE compared with those without inherited thrombophilia.

**Conflict-of-interest disclosure:** The author declares no competing financial interests.
Has Ly6G finally found a job?

Michael J. Hickey