of a concentration effect is not unexpected, as the analytical method used measures only the antibody that has not bound to the target epitope. Additionally, saturation of anti-RhD binding sites was observed at all MonoRho doses except 300 μg.

Analyzing elimination rates rather than half-lives generates the same results, when both variables are log transformed.

The results of the ANOVA that we have performed rule out the possibility that the observed effect of the FCGR2A polymorphism was due to a linkage disequilibrium between FCGR2A and FCGR3A polymorphisms.

Thus, in our study the FCGR2A polymorphism had a statistically significant influence on the clearance of RhD-positive erythrocytes mediated by the monoclonal immunoglobulin G1 (IgG1) antibody MonoRho. However, there was no effect on the clinically more important end point of RhD sensitization. An effect of FCGR2A polymorphism on the clinical response to another IgG1 monoclonal antibody, rituximab, has been reported,2 while others have not seen such an effect.3-5

These observations are consistent with an independent effect of FCGR2A polymorphisms on antibody-mediated effector mechanisms. This effect may vary according to the monoclonal antibody, the effector mechanisms involved, the disease, and the end point of the study. Nevertheless, the possibility of a linkage disequilibrium with genes other than FCGR3A cannot be ruled out.

Further investigations are needed to clarify the effect of FcγR polymorphisms on the response to antibody therapies. In clinical trials, statistical tests such as analysis of variance or logistic regression should be used to test for effects of both polymorphisms, taking linkage disequilibrium into account. Clinical trials should be complemented with laboratory studies, which may help to unravel the different mechanisms and have important implications for the treatment of many diseases with monoclonal antibodies.

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To the editor:

Up against the wall

In the January issue of Blood, Day and colleagues published an article claiming that macrovascular thrombosis is driven by tissue factor (TF) derived primarily from the blood vessel wall.1 In this study, the authors compared TF activity measurable in a homogenized carotid vessel with relatively unperturbed, intact, isolated blood fractions and concluded that the vessel wall “drives” thrombosis. As TF within the vessel wall is spatially separated from the lumen, it is likely that much, if not all, of the activity being assayed as the “vessel-wall fraction” never comes into contact with flowing blood during a thrombotic episode. Hence, the thrombus-driving TF activity coming from the vessel wall is likely grossly overestimated. Using this rationale, the authors should have concluded that the brain (very rich in TF) drives thrombosis, and that the blood vessel is irrelevant. Moreover, the use of isolated blood fractions is likely to lead to underestimation of the ability of these fractions to either recruit or expose decrypted TF. Whereas the authors do recognize that they are measuring active TF, they apparently ignore the commonly held view that circulating TF is likely cryptic. Comparisons of vessel-wall activity and blood activity using equal volumes ignore the ability of flow to convectively deliver TF to the injured site from a larger pool. Thus, the comparisons of vessel-wall TF activity to TF activities from the blood are improper, and the conclusion that vessel-wall TF “drives” thrombosis is unwarranted.

Furthermore, the in vivo experiments, using a harsh combination of laser and Rose Bengal to induce continuous injury for 60 minutes (based on cited reference no. 31),1 do not support the conclusion that vessel-wall TF “drives” thrombosis. It is clear that vessel-wall TF has a role in the initiation of thrombosis. Thus, it may be more difficult to initiate a successful vessel-wall injury in a mouse that has low levels of TF in the vessel wall. Moreover, the long duration of the injury makes it difficult to conceive what events may be occurring in the blood over the 30 to 45 minutes prior to occlusion.

In their introduction, Day and colleagues summarized a report by Giesen et al2 and stated that “a small amount of TF is detectable in the blood and is capable of supporting clot formation in vitro.”1(p192) The cited article, however, actually measured ex vivo thrombus formation, not in vitro clot formation. In their discussion, the authors stated that the experiments of Himber et al3 did not establish a cause-and-effect relationship between leukocyte-TF expression and thrombus growth. However, Himber et al3 observed that the addition of an anti-TF antibody abrogated thrombus growth as measured by fibrin accretion in a silastic jugular-jugular shunt.

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References
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