

rabbit  $\beta_2$ -m (2) and tryptophan in Rab 12 kD (1). The possibility that the assignment of tryptophan results from a typographical error in figure 2 of Brinckerhoff *et al.* (1) is suggested by the misquoted assignment in that figure of tryptophan, instead of tyrosine, at the same position of human  $\beta_2$ -m, the only sequence to which Rab 12 kD is compared.

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*Response:* Roth *et al.* object to the fact that we did not cite their work in our paper. We are unaware of any data that enable one to determine whether an ex vivo rat meso-appendix model more closely approximates in vivo sequestration of human parasitized erythrocytes than does the in vitro binding of parasitized erythrocytes to melanoma cells or cultured human endothelial cells. We described the results of in vitro assays because these are the assays used in our laboratory. We encourage investigators who use other assays to confirm, refute, or expand upon our findings using their models.

With specific reference to thrombospondin (TSP), the molecular basis of its interactions with bound infected erythrocytes (IRBC) and with the leukocyte differentiation antigen CD36 is unknown, and there is not an unambiguous single explanation for all of the available data. However, it is clear from previously published reports (1) that TSP alone is insufficient to support cytoadherence to cells in vitro. Preliminary data from our laboratory (2) suggest that CD36 and TSP bind to independent ligand(s) on IRBC. We have been unable to perform studies comparing the affinity of CD36 with that of TSP because, although we have confirmed that immobilized TSP will bind IRBC, we have been unable, using the methods described in our paper, to detect binding of iodinated TSP to IRBC.

We, like Roth *et al.*, continue to have open minds regarding the relative importance of CD36, thrombospondin, intercellular adhesion molecule 1 (3), and other receptors in cytoadherence and sequestration.

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## Malaria Red Cell Cytoadherence

In their report on the identification of a malaria sequestration receptor, Ockenhouse *et al.* (1) allude to in vitro correlates used to study cytoadherence of *Plasmodium falciparum*-infected erythrocytes. They do not discuss the ex vivo perfusion of the rat mesentery microcirculation, the only method that detects adherence to venular endothelium and the only method with which investigators have studied the cytoadherence phenomenon under flow conditions and physiological wall shear stress (2). The venules are the site of true in vivo cytoadherence and microcirculatory occlusion. This approach deserves at least as much attention as cytoadherence to melanoma cells, which are actually not very relevant to in vivo conditions. With the use of the microcirculatory assay, we have found that both soluble thrombospondin (TSP) and antibodies to thrombospondin have a profound inhibitory effect on cytoadherence of *P. falciparum*-infected red cells to venular endothelium (3). However, reversibility with these agents has not been attempted, so it is misleading to say (as the authors do) that "neither TSP nor antibodies to TSP have been reported to reverse cytoadherence." Nevertheless, the fact that cytoadherence is blocked with these agents is sufficient evidence that TSP is an important factor in the cytoadherence process. Moreover, Ockenhouse *et al.* compare activity of soluble glycoprotein IV (GPIV) to that of TSP in inhibition assays on a weight basis. This comparison is unwise when the molecular weights differ by a factor of 4 to 5 (TSP is a

450-kD protein, as compared with 88 kD for GPIV); what is really needed is an estimate of relative affinities. This can best be obtained by a comparison in the same system under the same conditions of ionic composition and strength and, of course, equimolar concentrations. Until this comparison is made, one should have an open mind about the relative affinities of GPIV and TSP. Finally, recent studies have shown that TSP and GPIV bind to each other (4), hence demonstrating that identifying a receptor does not exclude other proteins (such as TSP) from playing a "binding" role between endothelium receptors and the red cells. It is likely, therefore, that a final picture of malaria red cell cytoadherence will involve a scheme in which both proteins (and perhaps others) play an important role.

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# Science

## Malaria red cell cytoadherence

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