Peer-to-peer: reply to the Editor

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Evaluation of manuscripts for potential publication by a scientific journal involves several sequential steps of scrutiny. By far the most crucial step is the editorial decision on whether the submitted study merits close examination by external experts or whether it is turned down, that is, returned to the authors without comment. As is outlined in the Editorial in the April 2001 issue of *Nature Immunology*, Nature journals, including *Nature Immunology*, do so without soliciting the opinion of members of an editorial board. This guarantees "editorial freedom" in the thumbs-up or thumbs-down decision, rather than editors "being told" by an established group of scientists which manuscript is interesting and timely and which is not. Naturally, in cases of uncertainty, expert advice is sought. However, this is not standard procedure and the editorial staff of Nature journals takes on this responsibility in the hope that their unbiased critique will guarantee unrestricted access to peer review of potentially interesting, innovative and well executed studies. The Nature journals have to be congratulated for this policy, although it does place ample pressure on the editorial staff to meet their aspired standard for scientific publication.

This editorial policy, albeit guided by the best intentions, is not without limitations. What immediately comes to mind is the enormous effort required of a handful of internal editors to keep up with the relevant literature, not only within a single area of research but, in the case of *Nature Immunology*, embracing the highly diverse field of immunology in its entirety. This work, which is routinely delegated by other journals to their respective editorial boards, comes on top of all other editorial duties. Obviously, weeding out studies of minor impact from numerous excellent ones for external peer review requires broad knowledge in a given field of research, including background information, that goes beyond reading the title and abstract. A lack of such knowledge can lead to the admission of studies for further processing that should have never made it pass the editorial desk. For instance, I recently happened to inspect a study submitted to one of the Nature journals that stood out for its dashing title and abstract but, in essence, discussed findings that have already been published in a similar form elsewhere. Such errors can be corrected externally if sent to experts with enough time on their hands to thoroughly uncover these shortcomings. However, by passing the first and crucial hurdle in the review process, such manuscripts stand a good chance of publication because the comments by the referees are open for discussion. This may be taken to suggest that the style of data presentation comes first, well before an open and expert discussion of the submitted findings. In addition to articles of inadequate quality slipping through, the pre-peer review policy of Nature journals makes publication of manuscripts portraying alternative and nonmainstream concepts more difficult. Eventually, as an additional safeguard for quality control, Nature journals may favor (deliberately or unintentionally) manuscripts from highly regarded institutions or, alternatively, may encourage manuscript submission by esteemed laboratories. This, of course, would very much resemble the old system of employing a board of external editors, which the current policy seeks to avoid.

I am certain that the publishing policy of Nature journals was implemented in good faith, for unbiased publication of top-quality articles, and I extend my best wishes to the editorial staff in their efforts to maintain balanced research communication. However, with or without the help of external experts, the initial editorial "thumbs-up or thumbs-down" decision remains a difficult step in the publication process and perhaps invitations to corresponding authors to participate in the editorial decision-making could help to improve quality control.

Vascular targeting and antigen presentation

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The activation of macrophages, dendritic cells and other APCs depends on antigen binding to membrane surface receptors followed by internalization, intracellular processing and presentation. Several recent studies have focused on antigen targeting to APCs[1–3]. Two different approaches have been explored. In one approach, specific ligand-receptor pairs such as gp96-CD91[3] and OmpA-TLR2[1] were used for antigen targeting. In another approach, selective stimulation with soluble factors was used: monocytes were targeted by switching-on IL-6–dependent differentiation into macrophages[2]. The latter strategy seems to recapitulate steps that occur when monocytes cross the vascular endothelium. These findings suggest that it is possible to target APCs as a strategy for augmenting or suppressing the immune response.

Although the approaches described above use classical APCs, other cell types—such as those that form blood vessels—may also be used. The advantages of targeting endothelial cells have not been fully appreciated, even though the antigen-presenting function of endothelial cells is well documented[4–8]. Indeed, it may be possible to modulate the immune response by exploiting the molecular diversity of the vascular endothelium for the purposes of cell-specific targeting[9–13].

Several groups have shown that liver sinusoidal endothelial cells constitutively express the molecules necessary for antigen presentation (CD54, CD80, CD86, MHC class I and II and CD40) and can present antigens to $CD4^+$ and $CD8^+$ T lymphocytes[8,14,15]. Because endothelial cells are readily accessible from the circulation, they are well positioned to present processed antigens to circulating lymphocytes. Indeed, endothelial cells may contribute to hepatic immune surveillance by activating effector T cells. Interestingly, naïve T cells activated by sinusoidal endothelial cells do not differentiate into effector T cells, but instead show a cytokine profile and a functional phenotype consistent with the induction of tolerance[8,14,15].

Other data show that systemic targeting of