Harrison S. Weisinger[1], James A. Armitage[2,3], Andrew J. Sinclair[1], Algis J. Vingrys[3], Peta L. Burns[2] & Richard S. Weisinger[2]
[1]Department of Food Science, Royal Melbourne Institute of Technology University Melbourne, Victoria, Australia
[2]Howard Florey Institute of Experimental Physiology and Medicine and
[3]Department of Optometry and Vision Sciences, University of Melbourne, Parkville, Victoria, Australia
Email: harrison.weisinger@rmit.edu.au

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Countering the 'counterattack' hypothesis

To the editor—In this issue, O'Connell *et al.* suggest that Fas ligand (FasL) mediates immune privilege by protecting tumors or tissues from immune attack, but we maintain that there is no convincing evidence of this. We would also like to re-emphasize our views of FasL: contrary to the suggestion of O'Connell and colleagues, we do not regard FasL as "solely a mediator of inflammation", but instead, find that Fas and its ligand are involved in target cell killing and immune cell homeostasis, especially as mediators of activation induced cell death in T-cells[2]. Although there can be differences of opinion, there are a number of important studies omitted from this commentary crucial to the interpretation of evidence supporting the 'FasL counterattack' hypothesis[1].

We caution against any dismissal of concerns about scientific methods and reagents[1]. Faulty reagents have been and continue to be a significant source of error[2]. The antibodies used in many studies have been clearly shown to lack specificity[3]. This is especially the case for the monoclonal antibody mAb33 from Transduction Labs, which stains CD95L-transfected and untransfected cells to a similar extent, labels tissue sections that lack CD95L mRNA and stains a protein by 2D-electrophoresis with a different mobility than FasL. A similar lack of specificity has been observed for both the C-20 and N-20 antibodies from Santa Cruz Biotechnology. The validity of functional assays, especially those using Jurkat cell death, have been challenged by others[4].

Well-controlled work in experimental animals clearly indicates that engineered expression of FasL on tumors or transplanted tissues actually results in accelerated rejection, rather than immune privilege[2,5]. Though FasL-mediated inflammation can be abrogated through a variety of means, animal studies simply do not demonstrate that conferring FasL expression to a tumor or a tissue grants it immune privilege. In fact, one promising new use for FasL is to induce inflammation and immunity[6,7].

Clinical data is used to support the case that FasL expression by tumors correlates with disease progression and or with poor prognosis[1]. Several studies omitted from the analysis in this issue[1] are inconsistent with this hypothesis[8,9].

Although mounting experimental evidence has indicated that FasL does not play a role in immune privilege in the testis[10], many still support the possibility of FasL-mediated immune privilege in the eye. A team lead by Caspi recently found that neither lack of Fas nor lack of FasL on ocular tissue alters eye pathology in a model of experimental autoimmune uveitis[11]. Also, if FasL expression in the eye was critical for the maintenance of immune privilege, patients with autoimmune lymphoproliferative syndrome, who cannot signal through Fas, would be expected to have ocular immune dysfunction, but they do not (J. Puck, pers. comm. and ref. 12). Thus, reports of FasL-mediated immune privilege in the eye do not appear to have clinical corroboration.

Thus, if one takes into account all of the experimental data, one may conclude that the body of evidence supporting a role for FasL in immune privilege is lacking. Thomas Huxley once lamented: "The great tragedy of science—The slaying of an original, beautiful hypothesis by an ugly fact."

Nicholas P. Restifo
National Cancer Institute
National Institutes of Health
Bethesda, Maryland
email: restifo@nih.gov

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