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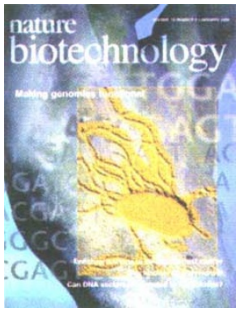
Remune response

To the editor:

I would like to draw your attention to a misprint that appeared in a recent article entitled "Latent HIV needs a knockout punch"[1]. The therapy currently being developed by The Immune Response Corporation, under the trade name Remune, is not a "version of the HIV surface glycoprotein gp120." Rather, it is actually a gp120-depleted inactivated HIV containing all of the other viral structural antigens. This distinction between Remune and the envelope-based therapies is critical because the distinguishing characteristic of Remune is the fact that it can boost immune responses to the multiple conserved core antigens of HIV.



The importance of this kind of immune response has recently been underscored by the work of Walker and colleagues, who have shown that it is the CD4-specific core responses (and not the envelope-specific responses) that are associated with the control of viremia[2]. These authors conclude that *p24*-specific responses "are likely to be important in immunotherapeutic interventions and vaccine development." These findings also support the previously published effects of Remune on viral burden and CD4 cell stabilization[3], and confirm previously published effects on chemokines and tumor necrosis factor levels.

The data are clear that a second type of treatment will be required for the effective long-term control of HIV infection. It is also apparent that the target of such a therapy should be the reservoir of virus, the virus-infected cell. The fact that AIDS is the result of a virus-induced immune suppression, along with the finding that antiviral drugs do not directly impact antiviral immunity, illustrate the need for an HIV-specific immune component in the treatment of HIV infection. It is our hope that HIV core-specific immune-based therapies like Remune will provide that missing piece in the treatment puzzle.

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Furry flasks?

To the editor:

Krensky writes that the human skin xenograft model of Sultan et al.[1] is a "step forward" over other heterochimeric mouse models because it, as opposed to others, has a physiologic human microenvironment, i.e., the skin. This distinction may apply to those models that are constructed by intraperitoneal or intravenous injection of human cells into immunodeficient mice[2,3]. We write to correct the misleading impression that it is also true for the SCID-hu mouse model[4].

The SCID-hu model is created by surgical implantation of small fragments of human fetal tissues into the immunodeficient C.B-17 *scid/scid* mouse. Human organ systems are found to grow in the mouse while maintaining the anatomical architecture and function of their counterparts found in humans. Most importantly, organ-specific, cell-cell interactions are conserved in a manner that is difficult to reproduce in tissue culture. This model has been used to evaluate a number of physiologic and pathophysiologic events that are otherwise difficult to study in humans, including:

1. Human thymopoiesis. The conjoint "Thy/Liv" organ implant comprises fragments of human fetal liver and human fetal thymus and has been shown to support long-term T lymphopoiesis[5]. Functionally competent, mature human T cells develop from uncommitted progenitor cells in the grafts. Selection of the T-cell repertoire is influenced by human major histocompatibility complex molecules expressed on thymic epithelial cells and dendritic cells[6], indicating that physiological interactions are maintained between developing human T cells and the surrounding human thymic microenvironment. Among all heterochimeric models, the Thy/Liv implant is uniquely appropriate for the analysis of a question raised by Krensky: the effects of anti-LFA3 on T-cell development in the human thymus.

2. Multilineage human hematopoiesis. In the SCID-hu bone model, constructed by subcutaneous implantation of whole human fetal long bone, long-term multilineage human hematopoiesis is maintained in the human marrow[7]. Interactions between human hematopoietic cells and the human stromal microenvironment are likely to play important roles in regulating this hematopoietic activity.

3. Cancer cell growth and metastasis in vivo. Intravenous injection of a variety of human cancer cell lines that are incapable of growth within or metastasis to murine organs results in efficient and species-specific tumor formation in transplanted human organs in SCID-hu mice[8]. These observations underscore the importance of interactions with human tissue microenvironments in cancer cell growth and metastasis, which can be uniquely investigated by this model.

The limitations of the SCID-hu models are the same as those manifested by the skin xenograft model of Sultan et al. In each case, the human organs are exposed to murine-derived nutrients, hormones, cytokines, rare elements, and vitamins; therefore, constituents necessary for human cell physiology may be lacking. Conversely, murine cells move into the human grafts and may alter their function. Indeed, human T cells generated in SCID-hu mice become tolerant of murine antigens expressed on infiltrated murine dendritic cells. Murine cells that infiltrate into the human skin grafts in the model of Sultan et al. may likewise alter the observed inflammatory processes. It should be presumed that these cross-species interactions occur in any heterochimeric model. Appropriate controls must therefore be put into place to ensure that they do not adversely or artifactually impact interpretation of experimental results.

Given such controls, heterochimeric mouse models provide preclinical in vivo systems in which to explore important questions of human physiology and pathophysiology. We agree with Krensky that those with intact human microenvironments are "far more than furry flasks" and are most likely to provide meaningful data.

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