HIV Research in the SCID Mouse: Biosafety Considerations

The SCID (homozygous for severe combined immunodeficiency) mouse engrafted with human cells is a valuable animal model for studies of infection by the human immunodeficiency virus (HIV). Although the guidelines of the National Institutes of Health (NIH) and the Centers for Disease Control (CDC) indicate that biosafety level BSL2 is appropriate for HIV experiments in animals, until now HIV studies in the SCID mouse have been conducted with containment facilities and practices that meet or exceed BSL3.

The National Institute of Allergy and Infectious Diseases (NIAID) sponsored a workshop to review biosafety considerations associated with HIV research in the SCID mouse. Workshop participants included researchers and biosafety specialists and administrators from institutions with SCID mouse facilities, institutions planning SCID mouse facilities, NIH, CDC, and the Food and Drug Administration. A detailed document describing the meeting will be published in the December issue of the *American Society for Microbiology News*.

After a careful review of published and unpublished experimental results, workshop participants agreed unanimously that HIV research in the C.B-17 *scid/scid* mouse does not pose a risk from aerosols and can be conducted safely in BSL2 facilities (a current CDC recommendation) with BSL3 practices. However, BSL2 animal facilities should incorporate design features that prevent escape of HIV-infected animals.

The workshop recommended that studies likely to generate HIV pseudotypes be conducted under BSL3 conditions until evaluation of such potential pseudotypes is possible. *Scid* alleles are being introduced into mouse backgrounds other than C.B-17, and HIV infection of these mice reconstituted with human cells may produce HIV pseudotypes. Furthermore, any research in which HIV is purposely coinfected with mouse amphotropic or xenotropic retroviruses or with human lymphocytotropic viruses such as Epstein-Barr virus and cytomegalovirus may also produce HIV pseudotypes.

There is little to distinguish the biohazards of HIV research in the engrafted SCID mouse from other research with infectious HIV. For all HIV research, careful consideration should be given to minimize risks and to plan procedures that will be used when accidents happen.

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Pseudotypes in HIV-Infected Mice

Paolo Lusso *et al.* (*1*) confirm the well-known fact (*2*) that retroviruses, including the human immunodeficiency virus (HIV), can generate pseudotypes with other enveloped viruses. In particular, they show that a human T leukemic cell line can acquire xenotropic murine leukemia viruses (X-MuLV) after passage through splenectomized, irradiated, and antiasialo–GM1-treated *nu/nu* mice. When the cell line was infected with HIV in vitro, pseudotypes formed between HIV and X-MuLV (*1*). The authors suggest their finding may make data gathered from HIV-infected mice irrelevant.

The critical question is whether and to what extent the possible creation of viral pseudotypes limits the utility of small animal models for HIV. We offer our views based on our work with SCID-hu mice.

Lusso *et al.* "presume" that HIV will directly interreact with X-MuLV within C.B-17 *scid/scid* mice (*3*) that have been either engrafted with human lymphoid organs (SCID-hu) (*4*) or injected with mature human peripheral blood cells (hu-PBL-SCID) (*5*). We have no evidence that this occurs, but the possibility cannot be ruled out. The issue is how frequently it occurs and with what effects. Proof that one can intentionally induce the phenomenon in the laboratory may not be relevant to its significance in vivo.

If such pseudotypes occur in vivo, we do not believe they would compromise the conclusions of our published work. (*6*). We reported that AZT suppressed infection by HIV in the SCID-hu mouse when given 24 hours *before* infection (*6*). The formation of pseudotypes between HIV and X-MuLV should have no impact on the conclusions of this study. Moreover, given the data found in the previous literature (*2*), we assumed that pseudotypes might form in HIV-infected SCID-hu mice and accordingly designed experiments to control for this possibility. The controls have shown that amphotropic pseudotypes did not form in the HIV-infected SCID-hu mouse (that is, mouse spleen cells were not infected (*6*, figure 1); CD4-negative human cells (for instance, in connective tissue) were also uninfected in SCID-hu mice that were viremic with HIV. In other words, pseudotypes did not form between amphotropic or X-MuLV and HIV in SCID-hu mice with a frequency that was high enough to change the interpretation of published experimental data.

Lusso *et al.* suggest that pseudotype formation can account for the absence of certain "characteristic hematologic findings" of human HIV infection in the "SCID-hu/HIV-1 model," namely polyclonal B-lymphocytic activation with hypergammaglobulinemia and CD8+ T-lymphocytic activation. They go on to say that reports of hypogammaglobulinemia in SCID-hu mice may be the result of B cell infection by pseudotyped HIV and that the absence of graft-versus-host (GvH) disease in such animals may result from human T cell suppression by X-MuLV.

The SCID-hu mouse model should not be confused with the hu-PBL-SCID models. These reconstruction approaches are different in design, purpose, and results. Human hematolymphoid organs have been implanted into the SCID-hu mouse in such a way as to circumvent GvH disease (*4*). It has been demonstrated that these mice can be infected with HIV (*7*) and that they can be used to rapidly screen antiviral compounds for efficacy (*6*). It has not been reported that they become hypogammaglobulinemic after infection. It is true that GvH disease has not been initiated by the human T cells within them. These cells were, however, activated by mitogens and by anti-CD3 antibodies when they were removed from the peripheral circulation and tested in vitro (*8*). Our observations suggest that the human T cells have developed selective tolerance during differentiation in the SCID; they are not consistent with generalized viral immunosuppression.

The second SCID model, the "hu-PBL-SCID mouse," was constructed by injection of mature human peripheral blood lymphocytes into SCID mice (*5*). There is no documentation in this system of the development of hypogammaglobulinemia after