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Use of Fluorescent Tracking Dye PKH26 to Follow the Fate of HIV-Infected Human PBMC in SCID Mice: An *In Vivo* Model for AIDS Drug Development. PAUL L. BLACK, DENNIS D. BROUD, OWEN L. WOOD, GARY P. GOLDBERG, and MICHAEL A. USSERY. U.S.F.D.A., Rockville, Maryland, USA.

In order to validate a murine model of HIV infection for use in AIDS drug development, we injected adult human peripheral blood mononuclear cells (PBMC) IP into female SCID mice. Human lymphocytes were readily detectable in the peritoneal cavities of all such SCID mice for at least 6 weeks after injection. CD4/CD8 ratios in human CD3+ lymphocytes found in the peritoneums of SCID mice declined even in the absence of HIV infection. Human cells were also detectable in circulation in most mice, but at much lower levels (≤10%). Low percentages (≤2%) of human lymphocytes were also detected in the spleens. Additionally, we utilized the lipophilic, fluorescent dye PKH-26 to track the fate of human PBMC injected into SCID mice. PKH-26 is stably incorporated into the membranes of human PBMC, and prelabeled human PBMC were detected in SCID mice for at least 6 weeks after injection. The dye also permitted easy visualization of concentrations of human PBMC in lymph nodes in the inguinal area near the femoral artery and in the peritoneum between the liver and the spleen. These findings prove that human lymphocytes do survive in SCID mice after IP injection. Further experiments have shown that SCID mice reconstituted with human PBMC can be infected with HIV. HIV was readily detected (by quantitative co-culture with human PBMC blasts) in splenocytes and in peritoneal cells 2-3 weeks after infection. Preliminary results also indicate that oral AZT treatment initiated in drinking water 24 hr before HIV infection did not prevent the establishment of HIV infection. These results suggest the utility of HIV-infected SCID mice as *in vivo* model for AIDS drug development.

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HIV-Infected Hu-PBMC-SCID Mice as a Model for Antiviral Drug Development. Michael A. Ussery, Dennis D. Broud, Owen L. Wood, and Paul L. Black. Division of Antiviral Drug Products, FDA, Rockville, MD.

Adult human blood peripheral mononuclear cells (PBMC) were injected intraperitoneally (i.p.) into female 5-7 wk old SCID mice as part of a program to validate murine animal models for use in AIDS drug development. Two weeks later, the mice were infected i.p. with 10^3 $TCID_{50}$ HIV-1 9320 (AZT sensitive isolate A018, D.Richman). At two and half weeks postinfection, the extent of infection in blood cells, splenocytes, and peritoneal cells was assayed by quantitative coculture with human PBMC blasts. A relatively low percentage of peritoneal cells were infected with HIV in 2/5 animals. HIV infected cells were detected in the spleens of 1/5 animals, but not in any blood samples. Preliminary results from animals treated continuously with AZT at 1 mg/ml in the drinking water beginning 1 day before infection surprisingly revealed 3/4 animals with up to a 100-fold higher level of HIV-infected cells in their peritoneums. Splenocytes from all 4 animals were HIV positive while again none of the blood cultures was positive for HIV infected cells. Quantitative viral cocultures, quantitative p24 assays, and AZT drug levels were also performed on cell-free plasma and peritoneal wash fluid and will be presented. Additional compounds from different chemical classes will be examined in the model in the validation process.