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SCID mice engrafted with HIV-infected human T4-lymphocytes as an *in vivo* model for the evaluation of anti-HIV drugs

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SCID (severe combined immune deficiency) mice fail to reject transplanted allogeneic tumors. Two human T4-lymphocyte cell lines, MOLT-4 and CEM, which are highly susceptible to the cytopathic effect of human immunodeficiency virus (HIV) and simian immunodeficiency virus (SIV), were adapted to *in vivo* growth by 2 serial subcutaneous (s.c.) passages in nu/nu mice. Upon s.c. injection of 10^7 to 10^8 MOLT-4 or CEM cells in SCID mice, tumors appeared 3 to 4 weeks later at the site of injection. Further serial passage did not increase the tumorigenicity of the human T4 cells. When MOLT-4 and CEM cells, isolated from the tumors that had developed in the SCID mice, were examined for their susceptibility to HIV-1 and SIV *in vitro*, both MOLT-4 and CEM cells had remained highly susceptible to the cytopathic effects of HIV-1 and SIV. Following inoculation of mock-infected MOLT-4 cells in SCID mice, tumors appeared within 20 to 26 days in all mice. In contrast, only 40% of the mice that had been inoculated with SIV-infected MOLT-4 cells, developed tumors and these tumors appeared later than 30 days after inoculation of the SIV-infected cells. This SCID/T4 model is now being used to assess the *in vivo* efficacy of 9-(2-phosphonylmethoxyethyl)-2,6-diaminopurine (PMEDAP).

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The Suppression of p24 Antigenemia in the HIV-1 Xenotransplanted Nude Mouse by Azidothymidine. N. T. Wetherall, J. Zhou, S. Armstrong, and D. C. Montefiori. Department of Pathology, Vanderbilt University School of Medicine, Nashville, TN 37232-2561.

Murine models of HIV-1 disease are needed for the evaluation of candidate anti-HIV agents *in vivo*. On approach towards a functional model is undergoing development in our laboratory, and the results of our early studies have recently been published. This model utilizes the "nude" mouse which is well recognized as an animal model system to assay candidate antineoplastic agents. Through the transplantation of HIV-1 challenged CCRF-CEM cells into irradiated nude mice, we have demonstrated that HIV-1 p24 gag antigenemia is produced and maintained for a nine week period. To investigate whether AZT has any effect upon serum p24 levels, we administered varying does of AZT^1 prophylactically (.25 to 2.0 mg/day/mouse p. o.) to groups of nude mice bearing human CEM cell transplants. The animals were challenged with 10^5 TCID50 units of HIV by injection of the 0.1 ml inoculum directly into the palpable mass. After 3-4 weeks of treatment the mice were sacrificed. Serum p24 levels and excised CEM cell HIV antigen expression (by IFA) were measured. The levels of these HIV indicators were significantly reduced in the AZT treated animals. To assay for other AZT effects in the nude mice, levels of AZT as high as 8 mg/day/mouse did not exhibit any mortality, morbidity, or antineoplastic effects over a 35 day period, suggesting that the inhibition of HIV is due solely to the presence of AZT. Our results indicate that this model of HIV disease can potentially be used to evaluate anti-HIV agents *in vivo* This work was supported by USAMRDC Contract No DAMD 17-88-C-8071.