91

Evaluation of Anti-AIDS Drugs in Conventional Mice Implanted with a Permeable Membrane (Hollow Fiber) Device Containing Human T Cells Infected with HIV. **L. B. Allen[1], D. C. Quenelle[1], B. A. Taylor[1], B. J. Bowdon[1], K. Keith[1], A.D. Brazier[1], W. M. Shannon[1] and K. E. Dunleavy[2]. [1]Southern Research Institute, Birmingham, AL 35255. [2]W.R. Grace & Co.-Conn., Lexington, MA 02173.**

Permselective membrane devices (hollow fibers, HF) have been developed for the treatment of diabetes by implantation of insulin secreting, xenogeneic pancreatic islet cells. These devices function through selective diffusion across the membrane of essential, small molecular weight nutrients and cell products but prevent the passage of larger molecular weight molecules associated with the immune system. We used modified versions of these hollow fibers to develop a model for evaluating potential anti-AIDS drugs in conventional mice. In these studies, CD4+, CEM cells are infected with HIV (strain RF-II) at a multiplicity of infection (m.o.i.) of 0.001. The cells are placed into the HFs and implanted into the peritoneal cavity of outbred Swiss mice. In development of this model, we have evaluated the growth of CEM cells placed in HFs and either cultured *in vitro* or implanted in Swiss mice. We have also evaluated the cells in HFs for development of infection with HIV *in vitro* and *in vivo*. Further, we have evaluated the antiviral activity of azidothymidine (AZT) both *in vitro* and *in vivo*. For the *in vitro* studies the HFs are filled and placed in cryotubes in 1 ml of RPMI 1640 + 10% FBS. AZT inhibits virus in this HF system at levels similar to those observed in the standard microtiter plate assay using an MTT dye-conversion/viability assay. For the *in vivo* drug evaluation, AZT (~135 and 96 mg/kg/day) was administered to the mice in the drinking water. The CEM cells were infected with HIV as in the *in vitro* assay, placed into HFs, and implanted intraperitoneally in outbred Swiss mice. The HFs were removed on day 6 and the cells and media were placed in microtiter plates for observations of cell morphology and virus-induced cytopathic effect (CPE). The cell viability was measured using the MTT dye conversion assay. Further, samples of cells and supernatant were collected and analyzed for p24 antigen and RT activity. AZT treatment significantly increased CEM cell viability over the untreated virus control group and significantly reduced the levels of HIV p24 antigen and HIV RT activity. This study was supported in part by Public Health Service contract NO1-AI-05086 from the National Institutes of Health and by Southern Research Institute.

92

***In Vitro* and *In Vivo* Enhancement of ddI Activity against Rauscher Murine Leukemia Virus (RMuLV) by Ribavirin,** **D. C. Quenelle, L. B. Allen, L. Westbrook, B. A. Taylor, M. N. Prichard, A. D. Brazier, M. G. Hollingshead, and W. M. Shannon. Southern Research Institute, Birmingham, AL 35255**

The *in vitro* and *in vivo* combination studies were evaluated by the three-dimensional technique of Prichard and Shipman (Antiviral Res. 14:181-206, 1990). The *in vitro* antiviral activity was evaluated in feral mouse embryo (SC-1) cells that were grown in 6-well culture plates. Triplicate wells were inoculated with 0.5 ml of RMuLV and 2.0 ml of drug solution. On day 3 post-inoculation, the cultures were irradiated with ultraviolet light and XC cells were added. On day 3 post UV irradiation, the cultures were fixed with 10% formalin and stained with 0.1% crystal violet. Virus-induced plaques were counted with the aid of a dissection microscope. Activity was measured as the percent reduction in the number of plaques in the drug-treated samples compared to those in the virus controls. In addition, supernatants were collected from the wells at day 3 and titrated for the amount of virus present to assess reductions in virus titer. Combinations of ddI and ribavirin significantly increased both plaque reduction and titer reduction over that observed with either drug alone. For the animal study, male NIH Swiss mice (16 - 18 g) were used. Groups of uninfected mice were treated with diluent (saline) or with drugs (alone and in combination) to evaluate toxicity. For antiviral evaluation, 870 PFU of RMuLV was administered i.v. in a volume of 0.1 ml per mouse. The drugs were administered s.c. three times per day (days 0 - 20). Three doses (total) of ddI (600, 400 or 200 mg/kg/day) were administered alone and in combination with 3 doses of ribavirin (120, 90 or 60 mg/kg/day). Ribavirin was also evaluated alone. On day 21, the mice were bled and spleens were collected and weighed. The serum was titrated for RMuLV. Combinations of the drugs did not appreciably increase the reduction of virus-induced splenomegaly observed with these two drugs when tested alone. However, combinations of the drugs markedly enhanced the reduction of virus titer in the serum. The greatest reductions were observed with combinations of the drugs at their two highest concentrations. These data suggest that ddI + ribavirin combinations are synergistic against RMuLV *in vivo*. This work was supported in part by Public Health Service contract NO1-AI-05086 from the National Institutes of Health.