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Ebola Infected SCID Mice as a model for Drug Evaluation

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Primary human outbreaks of the filoviruses Ebola and Marburg cause the most severe viral hemorrhagic fever known, with mortality of 40-90% in sporadic outbreaks. Safe handling of Ebola requires maximum biological containment (BL-4) facilities. Evaluation of antiviral compounds against Ebola virus has been hampered by lack of an adequate small animal model. Efforts to mimic the clinical syndrome have been unsuccessful in rodents. Infection of multiple adult mouse strains (C3H/HeJ, A/J, Beige, CBA/N, SCID-c.d.-17) with Mayinga strain of Ebola produced disease only in the adult SCID mice, where 0.1 to 1000 pfu produces a uniformly lethal infection in animals 4 to 8 weeks old. After infection, virus can be recovered from all major organs (heart, lung, liver, spleen, kidney, brain) by day 5 post infection and reaches peak titer by day 19. Animals die with a mean time to death of 27 days. Initial studies are consistent with a viral wasting disease. The model has been utilized in initial antiviral chemotherapy studies and is useful in evaluating inhibition of virus replication. Although, unlike primates, the SCID mouse model does not mimic the hemorrhagic disease, it is clearly useful during initial drug evaluation.

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Treatment of *Phlebovirus* Infections of Mice by Poly ICLC. J.H. Huffman, R.W. Sidwell, J. Coombs, J. Huggins, and M. Kende. Utah State Univ., Logan, Ut, and U.S. Army Med. Res. Inst. for Infect. Dis., Frederick, MD.

Poly ICLC, an immunomodulating compound prepared by combining poly(I)·(C) with a complex of poly-L-lysine and carboxymethylcellulose, was found to be very efficacious for treatment of Punta Toro virus hepatotropic infection in weaning C57BL/6 mice. Survivor numbers could be increased by a single i.p. injection as late as 48 hr post virus inoculation, even though the mice began dying as early as 72 hr after virus inoculation. The preparation was effective when given either intraperitoneally (i.p.) or subcutaneously (s.c.), but was inactive when given by oral gavage. The preparation was significantly effective at 0.31 mg/kg when given in a single i.p. injection at 24 hr post virus and at 0.625 mg/kg when given at 48 hr post virus. When given 3 times by i.p. injection every other day, beginning 4 hr post virus, the minimum inhibitory concentration was 0.0032 mg/kg/day. A single i.p. injection of 0.1 mg/kg of poly ICLC induced high (approximately 10^3 units/0.1 ml) interferon (IFN) levels in the mouse serum. These high levels were seen at 2, 6, and 12 hr post injection. At 24 hr the level of circulating IFN had dropped to near 10 units/0.1 ml. Although IFN induction correlates well with the antiviral activity in this system, it may not be the only mechanism by which this preparation is active since we have seen other compounds, with greater IFN-inducing ability, that have less protective effects against Punta Toro virus in the same model. (Supported by contract DAMD 17-86-C-6028 from the U.S. Army Medical Research Development Command).