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Human Monoclonal Anti Cytomegalovirus (CMV) Antibody (MSL-109): Enhancement of In Vitro Foscarnet Induced Inhibition of CMV Replication. M.A. Nokta*, M.D. Tolpin **, P.I. Nadler** and R. B. Pollard*. *Division of Infectious Diseases, The University of Texas Medical Branch, Galveston, Texas and **Sandoz Research Institute, East Hanover, New Jersey, USA.

Human CMV causes serious life threatening diseases among immuno-compromised patients particularly those with AIDS. In this report the effects of a human IgG1 neutralizing monoclonal antibody MSL-109 (Sandoz pharmaceuticals) on CMV replication was examined both alone and in combination with Foscarnet. Human embryonic fibroblasts (MRC-5) were infected with CMV strain AD169 with a multiplicity of infection of 3 plaque forming units/cell for 1 hour. The virus was neutralized for 30 minutes prior to infection at 37°C with serial dilutions of MSL-109 of 0.3 to 10 ug. Dilutions of Foscarnet (50 to 800 uM) were added to CMV infected cells that had been either previously neutralized or not. CMV replication was then determined 5 days postinfection by DNA/DNA probe hybridization using the hyberwix system. Doses of 1 ug of MSL-109 enhanced the foscarnet (50, 100, 200 and 400 uM) mediated inhibition of CMV replication from 17, 41, 75 and 96% to 46, 61, 82 and 98%. Moreover 3 ug of MSL-109 enhanced the inhibitory effects of the above doses of Foscarnet to 66, 81, 92 and 99%. These effects were observed whether the antibody was added back after the 1 hour of adsorption or not, and was also observed in human forskin fibroblasts. The MSL-109 also enhanced the foscarnet induced inhibitory effects of wild type CMV isolates. The doses of MSL-109 used in this study were achievable in AIDS patients receiving .5 mg/kg of MSL-109 every 2 weeks without noticeable side effects. In conclusion, the MSL-109 enhanced the Foscarnet induced antiviral effects in a dose dependent manner, suggesting that the combinations of MSL-109 and Foscarnet may be clinically useful in treatment of CMV disease.

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Mechanisms of inhibition of HIV-1 infectivity by anionic liposomes.

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HIV-1 fusion with anionic liposomes is strongly dependent upon the lipid composition [pure cardiolipin (CL) > phosphatidylinositol (PI) > phosphatidylserine (PS), at neutral pH] and the composition of the medium (e.g. calcium, BSA). Pre-incubation of HIV-1 with CL liposomes or the presence of CL liposomes during infection causes dose-dependent inhibition of viral replication in CD4+ human lymphoblastoid A3.01 and H9 cells (Konopka et al., J.Gen.Virol., 1990, **71**, 2899; J. Virol., 1991, submitted) and in a human monocytic leukemia cell line, THP-1. Here we have investigated the mechanism by which CL liposomes affect the infectivity of HIV-1. Infection was monitored by p24 levels in the supernatant. The presence of PS or PI liposomes during infection, both in the presence of 10% FBS (10 to 100 μM-lipid) or 0.2% FBS (5 or 50 μM-lipid) did not affect p24 production in A3.01 cells. However, pre-incubation of HIV-1 with 50 μM PS liposomes (but not 5 μM) for 2 h or 24 h reduced the infectivity of the virus by 22% and 70%, respectively, after 3 days post-infection. The inhibition for PI liposomes was 46% and 100%, respectively. Pre-incubation of A3.01 cells with CL liposomes (10 to 100 μM-lipid) in the presence of 10% FBS did not cause inhibition of p24 production. In the absence of FBS or in the presence of 0.2% FBS, a cytotoxic effect of CL liposomes (25 to 100 μM) was observed, but CL liposomes were not cytotoxic with 10% serum. In contrast, neither PS nor PI liposomes at 50 μM were toxic both in the absence or presence of 10% FBS. The effect of CL liposomes on virus binding to A3.01 cells was ascertained by measuring cell-associated p24 antigen. The extent of inhibition of binding, under various conditions including incubation at 0°C, was not as extensive as the inhibition of infectivity. Our results suggest that the mechanism of inhibition of binding and infectivity of HIV-1 by anionic liposomes involves the fusion of the liposomes with the virus.