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SDZ-HSV-863: A human monoclonal antibody to HSV-1 and HSV-2 (gD-Ib) which attenuates acute infection, neurogenic cutaneous lesion formation and the establishment of viral latency.

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SDZ-HSV-863 is a fully human IgG1 monoclonal antibody which reacts with glycoprotein D of HSV-1 and HSV-2. The antibody is effective to protect mice from lethal primary infections produced by HSV-1 (i.p.) or HSV-2 (footpad) using virus challenges ranging from 10 x LD_{50} to 10,000LD_{50} and is active if administered prophylactically (prior to infection) or therapeutically, although activity decreases with time after infection. Good prophylaxis is seen in the range of 2-5mg/kg. This antibody is also active to prevent the establishment of virus latency in sensory ganglia T_{13}-L_5, (ED_{50} ~ 2.0μg/kg) and can prevent the eruption of HSV zosteriform cutaneous lesions in mice at similar doses. SDZ-HSV-863 is specific for the group Ib determinant of gD as shown by competition studies with murine mAb's specific for different gD epitopes. Consistent with this specificity, SDZ-HSV-863 does not block virus adsorption but is very active in virus neutralization and ADCC assays (IC_{50}/ED_{50} ~ 0.3μg/ml), and shows little or no variation among isolates, as may be expected from the conservation of gD group I epitope and the known difficulty to produce group I mar variants, which was confirmed in our studies ($\ll 1/10^8$). SDZ-HSV-863 has a half-life of 17-21 days in Rhesus monkeys and exhibits no toxic effects at very high doses. The combined characteristics of this antibody suggest that it may be a safe and effective reagent for prophylaxis and therapy of HSV diseases in man.

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Phosphorylation of Herpes Simplex Virus (HSV) Thymidine Kinase (TK)–Specific Nucleosides: Effects of Protein-Binding, Exogenous Thymidine (dT), and The *De Novo* Pathway (*dn*p). R.J. Wanklin, B.A. Rennie, D.M. Lyster, H. Dougan, S.L. Sacks. University of BC and TRIUMF, Vancouver, BC.

To further understand the impact of extracellular environments upon the activities of intracellularly-active nucleoside antivirals, we determined the effects of protein binding, exogenous dT, and *dn*p upon the uptake (and phosphorylation) of 1-ß-D-arabinofuranosyl-*E*-5-(2-[^{125}I]-iodovinyl)uracil (^{125}IVaU) into HSV-1-infected cells. ^{125}IVaU was 80% protein bound by ultrafiltration. Plasma equilibrated with ^{125}IVaU was mixed with Medium 199 (Ratio 1:1) and exposed to HSV-1-infected fibroblasts at 37° C. Exposure to diluted plasma for 1 h reduced uptake of ^{125}IVaU by 86.5 to 93.4%. Extending exposure to 4 h increased absolute incorporation of ^{125}IVaU by 64.8%, but did not increase the proportion of ^{125}IVaU incorporated. As has been described for other nucleosides, exogenous dT inhibited the uptake of ^{125}IVaU into HSV-1-infected cells by 35.8% at a concentration of 3.9 μM. Exponential reductions in HSV-selective uptake were seen over the range of added dT up to at least 1 mM. Similar results were found with HSV-2, demonstrating that dT inhibited monophosphorylation. Natural dT monophosphate formation by the *dn*p was then studied using an inhibitor, 5-fluoro-2'-deoxyuridine (5FU). At concentrations ≥ 10 nM, 5FU reduced ^{125}IVaU uptake into HSV-1-infected cells, secondary to toxicity. However, uptake into infected cells preincubated with 5FU (1 nM) was increased 31.7%. 5FU-induced increases in ^{125}IVaU uptake were reduced by exogenous dT. The extracellular environment can alter the activity of antiviral nucleosides which require phosphorylation and/or intracellular transport for activation. Protein-binding, levels of dT in areas of infected tissue, and factors which may influence the *dn*p are 3 areas worthy of consideration.