

Oral Session II

Herpesvirus Infections I

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Preclinical Evaluation of a Phosphorothioate Oligonucleotide with Potent Antiviral Activity against Human Cytomegalovirus. *K.P. Anderson, R.F. Azad, V.B. Driver, H. Zhang, P. Cossum, J. Leeds, and D. Kornbrust. ISIS Pharmaceuticals, 2292 Faraday Ave., Carlsbad CA 92008 USA,*

ISIS 2922 is a phosphorothioate oligonucleotide complementary to mRNA encoding regulatory proteins of immediate early region 2 (IE2) of human cytomegalovirus (HCMV). ISIS 2922 exhibits potent and specific antiviral activity in several cell culture assays for HCMV replication. (Azad et al., 1993. *Antimicrob. Agents Chemother.* 67:4409). The potential of ISIS 2922 for use as an intravitreal therapeutic for HCMV retinitis is currently under investigation. ISIS 2922 inhibited plaque formation by all of a panel of clinical HCMV isolates and was equally effective in inhibiting replication of HCMV strains which were sensitive or resistant to ganciclovir and foscarnet. ISIS 2922 treatment in combination with ganciclovir or foscarnet resulted in additive inhibition of HCMV replication. AZT and ddC did not interfere with the antiviral activity of ISIS 2922. Following intravitreal administration in rabbits, ISIS 2922 was cleared relatively slowly from the vitreous ($t_{1/2}$ = 3 days). Intact oligonucleotide accumulated in the retina for 5 days after dosing, with clearance comparable to that of vitreous thereafter. The antiviral activity of ISIS 2922 against clinical HCMV isolates and in combination with available antiviral drugs, and the biodistribution properties of ISIS 2922 following intravitreal administration in rabbits demonstrate the potential of ISIS 2922 as an intravitreal therapeutic for HCMV retinitis.