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Animal Models of Herpes Family Viral Retinitis

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A major problem in the development of antiviral drugs for CMV retinitis is the lack of a suitable animal model. Drug dosing is based on animal infection by other viruses in other organ systems and human serum levels. A suitable animal model of retinal infection would thus be useful. In order to study both systemic and intravitreal therapy for retinitis due to herpes viruses, we developed a non-lethal herpes retinitis model. We inoculated 10,000 PFU of PH strain of HSV-I onto the posterior retinal surface using a transvitreal surgical approach in 33 Dutch pigmented rabbit eyes. The animals were followed with fundus photography, ophthalmoscopy and histology and immunocytochemistry for up to 42 days after inoculation. All inoculated eyes developed a focal area of retinitis that shared many similarities to HCMV retinitis in humans. The retinitis was initially well circumscribed and accompanied by variable retinal hemorrhage. The lesion enlarged in a predictable fashion and was histologically characterized by the presence of viral inclusions, retinal necrosis and inflammation. 33% of animals developed retinitis in the fellow eye. Encephalitis was present histologically in 73% of the animals. HCMV was also injected onto the retinal surface of rabbits to produce a similar model. A clinical isolate, passaged to high titer as well as AD 169 strain (10^5 PFU per cc were used. The latter strain did produce a focal area of vitritis over the retinal surface but no evidence of viral retinitis was detected histologically. We have used the herpetic model of retinitis to study the duration of intravitreal antiviral effect of HPMPC injections. 100 mcg of HPMPC has a duration of action of 30 days; approximately an order of magnitude larger than is seen with ganciclovir in this model. The focal herpetic retinitis model appears to be useful for testing antiviral drugs that have activity against Herpes Simplex. We are unable to produce histological or clinical evidence of infectious retinitis in the rabbit using HCMV.

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Stereoselective Synthesis of Novel Antiviral Nucleoside Analogues

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Recent strategies to antiviral agents have focused on the design of novel nucleoside analogues, particularly the series of hetero-2',3'-dideoxynucleoside analogues. The absolute configuration of active analogues requires their synthesis from novel precursors. This presentation will focus on new routes to several important members of hetero-2',3'-dideoxynucleoside analogues.