## Oral Session 5: Herpesvirsues and Poxviruses

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### Role of Angiogenesis and Wound Repair Factors in the Acceleration of Allograft Rejection by Cytomegalovirus

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### 33
### Design, Synthesis and Evaluation of Novel Anti-VZV BCNAs

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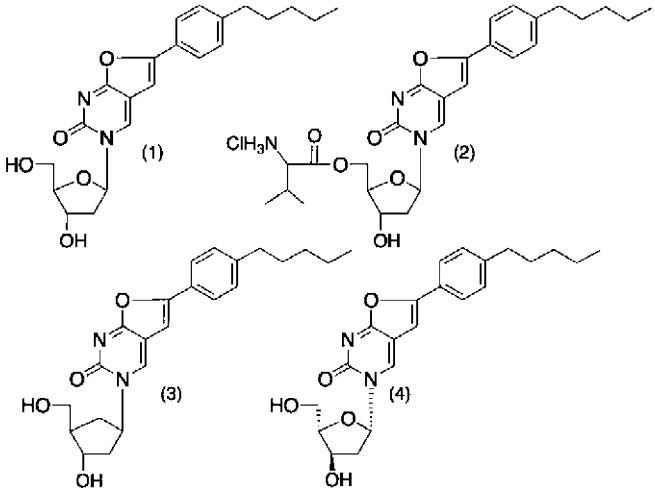
The bicyclic nucleoside analogues (BCNAs) are a family of exquisitely selective anti-VZV agents developed in our laboratories. The lead compound Cf1743 (**1**) has recently entered phase 1 clinical trials as its 5′-valyl ProDrug (FV100) (**2**). We herein report modifications in the sugar region of the lead (McGuigan et al., 2007). In particular, we describe the design, synthesis and evaluation of the carbocyclic analogue of (**1**) and also the L-enantiomer of (**1**), compounds **3** and **4**, respectively. Besides antiviral data, we will present VZV TK inhibition data and also molecular modelling studies of key agents with the VZV-encoded nucleoside kinase.




#### Reference

McGuigan, C., et al., 2007. J. Antimicrob. Chemother. 60, 1316–1330.

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### Maribavir Inhibits the Replication of Human Herpesvirus 6 and the Activity of the U69 Protein Kinase

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Infections with the B variant of human herpesvirus 6 (HHV-6) are self-limiting and occur in almost all children very early in life. In immunocompromised hosts, reactivation of either the A or B variant can cause serious disease, particularly those receiving hematopoietic cell transplants. Drugs with improved efficacy and good toxicity profiles are needed to treat these infections in transplant patients. We reported previously that maribavir (MBV) was a poor inhibitor of HHV-6 replication. This lack of activity was difficult to explain since MBV was a good inhibitor of human cytomegalovirus (HCMV) replication, and the UL97 protein kinase targeted by this drug in HCMV was conserved in HHV-6 (U69). Recent results from our laboratory suggested that the inactivation of the RB tumor suppressor by UL97 was an important function and that this did not occur in the presence of MBV. This result was consistent with the reduced activity of MBV against HCMV in dividing cells where the stimulation of the cell cycle by RB was less important. We reasoned that the poor activity observed with MBV against HHV6 might reflect the fact that the assays were conducted in rapidly dividing lymphocytes. To test this hypothesis, the activity of MBV was reevaluated against the GS strain of HHV-6A in HSB-2 cells with reduced serum to slow the growth of the lymphocytes. Under these conditions, MBV exhibited increased activity with $EC_{50}$ values of approximately 15 μM, while the $EC_{50}$ values for the cidofovir controls were unaffected. To confirm these results, we developed a surrogate assay for activity of the U69 protein kinase based on its kinase-dependent inhibition of nuclear aggregation. In this assay, MBV proved to be a good inhibitor of U69 activity and suggested that this kinase was also targeted by the drug. These results suggest that MBV is a good inhibitor of HHV-6 replication and the target of the drug is likely the U69 protein kinase. We conclude that the spectrum of activity of MBV includes Epstein-Barr virus, HCMV, and HHV-6 and may be useful in the treatment of these infections.

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### Antiviral Potency of ST-246 on the Production of Enveloped Orthopoxviruses and Characterization of ST-246 Resistant Vaccinia, Cowpox and Camelpox Viruses

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ST-246 is a highly potent and orally bioavailable anti-orthopoxviral molecule that targets the F13L protein of vaccinia virus (VACV). Its in vitro antiviral effect against VACV,