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Antivirals

P-223 - Celgosivir (MX-3253) resistance profile using bovine viral diarrhoea virus

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Celgosivir (CEL) is an orally bioavailable imino sugar in phase II development for the treatment of chronic hepatitis C virus (HCV) infections. CEL is rapidly metabolized in vivo and in cell-based assays to castanospermine (CST) which is a potent inhibitor of the glycoprotein processing enzyme alpha-glucosidase I. CEL inhibits flavi- and pestivirus replication in vitro and in vivo and shows synergy when combined with interferon alfa and/or ribavirin. Promising safety and efficacy results in clinical studies support further clinical development of this novel agent. The present study evaluated the potential for the development of resistance to CEL and CST using a non-cytopathic bovine viral diarrhoea virus (BVDV) in vitro infection model. BVDV was serially passaged up to 15 times in the presence of increasing concentrations of CEL or CST in an attempt to induce CEL or CST resistant variants. BVDV samples from each serial passage were characterized for their sensitivity to CEL and CST. Passage of the pe515 strain of BVDV up to 15 times in presence of CEL or CST failed to produce resistant mutants. The potency of CEL or CST against passaged BVDV was within 2 to 3-fold of the unpassaged virus. Flavi- and pestivirus including HCV, rely heavily on the host enzyme-mediated glycosylation process for their replication and these results suggest that the emergence of resistance to CEL or CST during human therapy is unlikely to occur.