

**THE UL97 PROTEIN KINASE OF HUMAN CYTOMEGALOVIRUS  
(HCMV) AND HOMOLOGUES IN OTHER HERPESVIRUSES:  
RELEVANCE FOR VIRUS AND HOST**

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The human herpesviruses (HSV-1, HSV-2, VZV, EBV, HCMV, HHV-6A, HHV-6B, HHV-7 and HHV-8) establish latent or persistent infections, with recurrence e.g. during immunosuppression. One of the first antiherpetic compounds, the nucleoside analogue aciclovir (ACV) requires phosphorylation to the triphosphate, the active inhibitor of the viral polymerases. The initial activation of ACV by monophosphorylation is achieved by viral kinases.

HCMV is susceptible to the nucleoside analogues ganciclovir (GCV) and ACV, but the potency of ACV is much lower than against HSV or VZV. GCV is presently the compound of choice for the treatment of HCMV diseases. Biron et al. [1] first reported a GCV-resistant HCMV strain with a phosphorylation-deficient phenotype. In 1992 it has been shown that the protein encoded by the viral ORF UL97 (pUL97) is responsible for monophosphorylation of GCV [2,3]. The 80 kD pUL97-protein shares homologies with protein kinases and bacterial phosphotransferases. Homologues of pUL97 are found in HSV (UL13), VZV (ORF47), EBV (BGLF4), HHV-6 (U69), as well as in the murine CMV (M97). Zimmermann et al. [4] reported that the indolocarbazoles Gö6976, K252a and K252c are specific inhibitors of pUL97. The biological function of pUL97 is still unclear, but the protein is important for efficient replication [5]. Autophosphorylation of pUL97 was observed in different systems [6,7]. pUL97 can partially substitute the function of the HSV UL13 protein [8], which is able to hyperphosphorylate the eukaryotic elongation factor 1delta. Ansari and Emery [9] demonstrated that the pU69 of HHV-6 also autophosphorylates and can confer GCV sensitivity to baculovirus. Most recently, Marschall et al. [10] found that pUL97 interacts with the DNA polymerase processivity factor pUL44 and that the indolocarbazoles NGIC-I and Gö6976 prevent formation of replication centres and the distinct co-localisation between pUL97 and pUL44.

Indolocarbazole protein kinase inhibitors are promising lead compounds for the development of more specific inhibitors of HCMV.

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