Structures of Thymidine kinase from *Herpes simplex* virus type 1 in complex with new substrates

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Infections of *Herpes simplex* virus type 1 (HSV1) are associated with oral-facial infections, skin infections, and genital infections. During the past decade, potent agents against herpes virus infections have been found. The action of these agents is based on the difference between viral thymidine kinase (TK) and human TK. Thymidine kinase (TK, EC 2.7.1.21) is the key enzyme in the pyrimidine salvage pathway and catalyzes the phosphorylation of thymidine (dT) to thymidine monophosphate (dTMP) in the presence of Mg²⁺ and ATP. HSV1 TK exhibits a broad substrate diversity in contrast to the cellular isoenzyme, accepting pyrimidine as well as purine with different sugar analogs. These compounds are selectively activated through phosphorylation by HSV1 TK to finally act as inhibitors of polymerases as well as DNA chain terminators. The increasing clinical use of acyclovir and ganciclovir has been associated with the emergence of drug-resistance, mainly linked to TK mutations decreasing the activation efficiency of the prodrug into the active drug and more rarely linked to alteration of viral DNA polymerase mutations leading to a decreased drug inhibition. Several structures of TKHSV1 in complex with natural substrates and substrate-analogs are known to date (Wild et al., 1997; Champness et al. 1998). Three crystal structures of the *Herpes simplex* virus type 1 thymidine kinase in complex with new substrates have been determined by X-ray crystallography at resolutions between 1.7 Å and 2.4 Å. Data were collected on beamlines X11 and BW7B. The spacegroup of all crystals was C222₁ with cell dimensions of a=114 Å, b=118 Å, c=108 Å. All data were of good quality with R_sym ranging from 5.0 to 6.8, completeness of 99 % and multiplicities of 3.9 to 4.1.

References
