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Structure of Human dCK Suggests Strategies to Improve Anticancer and Antiviral Therapy. Elisabetta Sabini¹, Stephan Ort², Christian Monnerjahn², Manfred Konrad², Arnon Lavie¹. ¹Univ. of Illinois at Chicago, Dept. of Biochemistry and Molecular Genetics, 900 S. Ashland Ave, Chicago, IL 60607 ²Max Planck Institute for Biophysical Chemistry, Dept. of Molecular Genetics, Am Fassberg 11, D-37077 Göttingen, Germany.

Human deoxycytidine kinase (dCK) phosphorylates the natural deoxyribonucleosides deoxycytidine (dC), deoxyguanosine (dG), and deoxyadenosine (dA) and is an essential enzyme for the phosphorylation of numerous nucleoside analog prodrugs routinely used in cancer and antiviral chemotherapy. For many of these compounds, the phosphorylation step catalysed by dCK is the rate-limiting step in their overall activation pathway. To determine the factors that limit the phosphorylation efficiency of the prodrugs, we solved the crystal structure of dCK to a resolution of 1.6 Å in complex with its physiological substrate deoxycytidine and with the prodrugs AraC and gemcitabine. The structures reveal the determinants of dCK substrate specificity. Especially relevant to new prodrug development is the interaction between Arg128 and the hydrogen-bond acceptor at the sugar 2'-arabinosyl position of AraC and gemcitabine. On the basis of the structures, we designed a catalytically superior dCK variant that could be used in suicide gene-therapy applications.