

CDPME kinase - A target for structure-based inhibitor design against microbial diseases

Tanja Sgraja, Nicola Ramsden and William N. Hunter

Division of Biological Chemistry and Molecular Microbiology,

Wellcome Trust Biocentre, University of Dundee, Dow Street, DD1 5EH Dundee, UK

t.sgraja@dundee.ac.uk

The enzyme diphosphocytidyl-2C-methyl-D-erythritol (CDPME) kinase participates in the biosynthesis of isoprenoids in the non-mevalonate pathway which is also known as the DOXP (1-deoxy-D-xylulose 5-phosphate) or MEP (2C-methyl-D-erythritol 4-phosphate) pathway. The isoprenoids are precursors for sterols, dolichols, triperpenes and ubiquinones which contribute to many biological functions including electron transport in respiration or hormone-based signalling. The non-mevalonate pathway is present in most eubacteria and some parasites like *Plasmodium*, but lacking in mammals[1]. The CDPME kinase catalyses the transfer of the γ -phosphate of ATP to the erythritol moiety of CDPME forming CDPME-2-phosphate and ADP. The crystal structure of the *E. coli* CDPME kinase in complex with ATP analogue and CDPME was determined to a resolution of 2.0 Å. The purine moiety of ATP is bound in the uncommon *syn* orientation in the active site[2].

For the discovery and design of novel inhibitors, the databases ACD (Available Chemical Directory), SCD (Screening Compounds Directory) and NCI (National Cancer Institute Database) which are part of the Integrated Scientific Information System (ISIS) were searched for cytosine and adenine analogues with the programme MDL@ISIS/Base. The ISIS Databases contains more than 3 millions compounds. The search was restricted by applying a few filter criteria. More than 200 cytosine and 2000 adenine derivatives were docked into the corresponding binding sites with the program FlexX[3] and ranked with XScore[4]. Several compounds were selected using the Sybyl interface. In the future, we plan to co-crystallise these compounds with the CDPME kinase and determine their binding affinities by kinetic measurements. As the *E. coli* CDPME kinase is very difficult to crystallise, the CDPME kinase of *T. maritima* and *A. aeolicus* were purified and crystallisation screens performed recently.

References

- [1] Eisenreich et al., *Cell Mol Life Sci*, 2004, **61**, 1401.
- [2] Millau et al., *PNAS*, 2002, **100**, 9173.
- [3] Rarey et al., *J Mol Biol*, 1996, **261**, 470.
- [4] Wang et al., *J Mol Model*, 1998, **4**, 379.