

MS16.P56*Acta Cryst.* (2011) **A67**, C307**Structural basis for inhibiting human tankyrases**

Mohit Narwal, Lari Lehtiö, *Pharmaceutical Sciences, Department of Biosciences, Åbo Akademi University, Turku (Finland)*. E-mail: Mohit.Narwal@abo.fi

Poly (ADP-ribose) polymerases (PARPs) are enzymes that catalyze a covalent post-translational modification of proteins. PARPs attach ADP-ribose units from NAD⁺ to glutamate and lysine residues of the target molecule or to the growing chain of poly (ADP-ribose). These enzymes are involved in important cellular functions like DNA damage detection and repair, transcriptional regulation, intracellular trafficking, chromatin modification and cell death.

Tankyrases form a subfamily of human PARPs. They are also known as TRF1 (telomeric repeat binding factor)-interacting ankyrin related ADP ribose polymerases 1 & 2 [1]. Tankyrases are multidomain proteins having four distinct characteristics domains: HPS domain with an unknown function, 24 ankyrin repeats involved in the protein-protein interactions, SAM (sterile-alpha motif) domain required for multimerization of tankyrase and a C-terminal PARP domain catalyzing poly(ADP-ribose) polymerization.

Tankyrases are potential drug targets for cancer and therefore efforts are ongoing within industry and academia to find potent inhibitors for it. The most evident benefits for inhibiting tankyrase are due to its functions Wnt signaling and in telomere homeostasis. Both of these are frequently misregulated in cancers leading to excessive Wnt signaling and subsequently accumulation of β -catenin, and elongated telomeres of cancer cells. Recently potent inhibitors for tankyrase were reported providing basis for development of drugs against tankyrases [2], [3].

We present a crystal structure of tankyrase 2 in complex with a highly potent and selective inhibitor. Most PARP inhibitors utilize the binding site of nicotinamide of NAD⁺. This is the first reported experimental complex structure of a PARP inhibitor not occupying that site. The structure reveals the plasticity of the NAD⁺ binding loop and it will create new strategies for inhibitor development for PARPs and especially for tankyrases.

[1] S. Smith, I. Gariat, A. Schmitt, T. de Lange, *Science* **1998**, *282*, 1484-1487. [2] S.-M.A. Huang, Y.M. Mishina, S. Liu, A. Cheung, F. Stegmeier, G.A. Michaud, O. Charlat, E. Willelte, Y. Zhang, S. Wiessner, M. Hild, X. Shi, C.J. Wilson, C. Mickanin, V. Myer, A. Fazal, R. Tomlinson, F. Serluca, W. Shao, H. Cheng, et al *Nature* **2009**, *461*, 614-620. [3] B. Chen, M.E. Dodge, W. Tang, J. Lu, Z. Ma, C.-W. Fan, S. Wei, W. Hao, J. Kilgore, N.S. Williams, M.G Roth, J.F. Amatruda, C. Chen & L. Lum, *Nat. Chem. Biol.* **2009**, *5*, 100-107.

Keywords: cancer, inhibitor, crystallography

MS16.P57*Acta Cryst.* (2011) **A67**, C307**“Crystal structure of the CBS domain pair of human CNNM4 transporter”**

June Ereño, Inmaculada Gómez-García, Iker Oyenarte, Luis Alfonso Martínez-Cruz, *Structural Biology Unit, CIC Biogune, Ed. 800 Technology Park of Bizkaia 48160-Derio, Bizkaia (Spain)*. E-mail: jereno@cicbiogune.es.

This work describes the crystal structure of the CBS-pair regulatory domain of the human ancient domain protein 4 (ACDP4), also known as CNNM4 [2]. ACDP proteins represent the least-studied members of the eight different types of magnesium transporters that have been identified in mammals to date [1]. In humans the ACDP family includes four members: CNNM1-4 [6]. CNNM1 acts as a cytosolic

copper chaperone and has been associated with urofacial syndrome; CNNM2, encoding a basolateral protein required for renal Mg²⁺ handling is mutated in dominant Hypomagnesemia. Interestingly, mutations in the CNNM4 gene have clinical consequences that are limited to retinal function and biomineralization and are considered to be the cause of Jalili syndrome, which consists of autosomal recessive cone-rod dystrophy and amelogenesis imperfecta [3], [4], [5]. The truncated protein was overexpressed, purified and crystallized in the orthorhombic space group C222. The crystals diffracted X-rays to 3.6 Å resolution using synchrotron radiation.

[1] S. Ferrè, J.G. Hoenderop, R.J. Bindels. *Curr Opin Nephrol Hypertens.* **2011**, *20* (2), 169-176. [2] I. Gómez García, I. Oyenarte, L.A. Martínez-Cruz. *Acta Crystallogr Sect F Struct Biol Cryst Commun.* **2011**, *1;67* (Pt 3), 349-353. [3] I.K. Jalili. *Eye (Lond)* **2010** *24*(11), 1659-1668. [4] D.A. Parry, A.J. Mighell, W. El-Sayed, R.C. Shore, I.K. Jalili, H. Dollfus, A. Bloch-Zupan, R. Carlos, I.M. Carr, L.M. Downey, K.M. Blain, D.C. Mansfield, M. Shahrabi, M. Heidari, P. Aref, M. Abbasi, M. Michaelides, A.T. Moore, J. Kirkham, C.F. Inglehearn. *Am J Hum Genet.* **2009**, *84*(2), 266-273. [5] B. Polok, P. Escher, A. Ambresin, E. Chouery, S. Bolay, I. Meunier, F. Nan, C. Hamel, F.L. Munier, B. Thilo, A. Mégarbané, D.F. Schorderet. *Am J Hum Genet.* **2009**, *84*(2), 259-265. [6] G.A. Quamme. *Am J Physiol Cell Physiol.* **2010**, *298*(3), C407-C429.

Keywords: ion transporter, CBS domain, Jalili syndrome

MS16.P58*Acta Cryst.* (2011) **A67**, C307-C308**Structural studies of aspergillus fumigatus UDP-galactopyranose mutase**

Karin E. van Straaten, David A. R. Sanders, *Department of Chemistry, University of Saskatchewan, Saskatoon, S7N 5C9, (Canada)*. E-mail: kev138@mail.usask.ca

Drug resistant pathogens are a serious health problem, creating an urgent need for alternative antibiotics and antibiotic drug targets. One such target is UDP-galactopyranose mutase (UGM). UGM is a flavoprotein that catalyzes the interconversion of UDP-galactopyranose (UDP-Galp) to UDP-galactofuranose (UDP-Galf); a precursor for the construction of Galf containing oligosaccharides. Galf is an essential component of the cell wall in bacteria, fungi and the cell surface matrix of protozoan parasites and appears to be essential for survival and virulence. Gene knock-out studies using *Mycobacterium smegmatis* (a model for *M. tuberculosis*) revealed that UGM is essential for the survival of the bacteria. A recent study in the protozoan parasite *Leishmania major* has shown that a UGM-- strain is attenuated towards virulence [1]. The *L.major* knock-out strain is deficient in Galf-containing lipophosphoglycans (LPG) and expresses truncated glycoinositol-phospholipids (GIPLs). Furthermore, mice inoculated with the UGM- mutant didn't develop lesion and are completely avirulent, indicating the importance of UGM for pathogenic survival and proliferation in mammals [1]. Work has also been done on *A. niger* and *A. nidulans* showing that Galf is important in *Aspergillus*. Deletion of the UGM gene dramatically attenuates virulence in *Aspergillus*. Since Galf is unique and UGM is not found in humans UGM is an interesting target for novel structure based drug design.

We are focusing on UGMs from eukaryotic pathogens from the fungus *Aspergillus fumigatus* (causes acute pneumonia and aspergillosis) and the protozoan parasite *L. major* (causes leishmaniasis). The eukaryotic enzymes share 51% sequence identity, but share only about 18% amino acid sequence identity to the prokaryotic UGMs [2]. We have solved the structure of *L. major* UGM (LmUGM) and used this structure to solve the *Aspergillus fumigatus* UGM (AfUGM) structure with and without substrate UDPgalp and inhibitor UDP. Despite low sequence identity with known prokaryotic UGMs the overall fold