Novel cancer targets in nucleotide metabolism

Juliette Rival, Julian Ludäscher, Emma Scaletti, Geoffrey Masuyer and Pål Stenmark

Stenmark´s group, Department of Biochemistry and Biophysics, University of Stockholm

Our group studies enzymes that are important for clearing oxidative damage from the nucleotide pool which many types of cancer cells exploit for survival. We use X-ray crystallography to study novel cancer targets within these pathways, and analyze their binding to potent inhibitors that are being developed as part of an interdisciplinary research collaboration. One of the objectives of our studies is to investigate the basic function of these proteins and the structural details of their substrate recognition and catalytic mechanisms. The overall goal of our collaborative project is to develop optimized lead compounds and take them all the way to human trials, an ambitious but also achievable goal dependent on the joint efforts of several research groups, spanning from basic science to the clinic.

We have previously solved the crystal structure of several enzymes involved in DNA repair functions, such as MTH1[1], NUDT15[2], or the folate metabolism enzyme MTHFD2[3] with multiple new drug candidates. We have also produced crystal structures which were fundamental to the production of novel inhibitors and mediators of the 8-oxoguanine DNA glycosylase 1 (OGG1) activity [4-5].

My objectives are to produce, purify and crystallize a newly identified cancer target to assist the development of a structure-based drug design pipeline. The goal is to find optimal conditions for crystallization and support the structural determination of the target with a range of small molecule inhibitors, and in preparation for fragment screening.

1. Scaletti, E.R. et al. MutT homologue 1 (MTH1) removes N6-methyl-dATP from the dNTP pool. *J Biol Chem* **295**, 4761-4772 (2020).
2. Zhang, S.M. et al. Development of a chemical probe against NUDT15. *Nat Chem Biol* **16**, 1120-1128 (2020).
3. Bonagas, N. et al. Pharmacological targeting of MTHFD2 suppresses acute myeloid leukemia by inducing thymidine depletion and replication stress. *Nat Cancer.* **3**, 156-172 (2022).
4. Visnes, T. et al. Small-molecule inhibitor of OGG1 suppresses proinflammatory gene expression and inflammation. *Science* **362**, 834-839 (2018).
5. Michel, M. et al. Small-molecule activation of OGG1 increases oxidative DNA damage repair by gaining a new function. *Science* **376**, 1471-1476 (2022)