TARGETING CHAGAS DISEASE USING FRAGMENT-BASED LEAD DISCOVERY: VALIDATION AND SCREENING OF FPPS ENZYME

Opassi, G.;[a] Nordström, H.;[a,b] Lundin, A.;[c] Napolitano, V.;[d] Magari, F.;[e] Dzusz, T.;[a] Klebe, G.;[e] Jahnke, W.;[f] Danielson, U. H.[a,b]

[a]Department of Chemistry - BMC, Uppsala University, Husargatan, 752 37 Uppsala, Sweden; [b]SciLifeLab, Husargatan 3, 752 37 Uppsala, Sweden; [c]Biothema AB, Handens stationsväg 17, 136 40 Handen, Sweden; [d]Małopolskie Centrum Biotechnologii, Jagiellonian University, Gronostajowa 7A, 30-387 Kraków, Poland; [e]Institut für Pharmazeutische Chemie, Phillips-Universität Marburg, Marbacher Weg 6, 35037 Marburg, Germany; [f]Novartis Pharma AG, Center for Proteomic Chemistry, Institutes for Biomedical Research, Novartis Campus, Fabrikstrasse 2, 4056 Basel, Switzerland.

E-mail of the presenting author: giulia.opassi@kemi.uu.se

Fragment-based lead discovery (FBDL) is one of the most efficient approaches when comes to the exploration of the available chemical space. The restricted molecular weight of fragment molecules (< 300 Da) allows a superior sampling of the chemical space using libraries containing few but structurally diverse compounds. Principal requirement for screening fragment libraries is the use of sensitive biophysical methods for the identification of hit compounds which interact with the target. The weak affinity that typically fragments have for the target of interest is actually one of the major challenges in this approach. A successful screening therefore implies the use of very sensitive methods, high quality preparations of the target protein and an extensive understanding of its physicochemical properties under various conditions. Here we described a Surface Plasmon Resonance (SPR) biosensor-based driven fragment-based discovery of novel leads targeting farnesyl pyrophosphate synthase (FPPS) from *Trypanosoma Cruzi*, causative agent of the neglected infectious tropical disease known as Chagas Disease. A panel of orthogonal biophysical methods have been initially applied to confirm folding, structural homogeneity and thermal stability of the produced enzyme. A real time luminescence-based enzymatic assay for pyrophosphate detection was developed and used to confirm FPPS activity. A 90 fragments library was screened using SPR against FPPS from both human and *Trypanosoma*, resulting in the identification of few selective hits. The study resulted in the validation of FPPS from *Trypanosoma Cruzi* as a suitable target for FBDL and in the identification of weak but selective hits for the parasitic enzyme.