Structure-guided design of pan inhibitors of metallo-p-lactamases

The fight against infectious diseases is one of the greatest public health challenges, especially with the emergence of pan-drug resistant carbapenemase-producing Gram-negative bacteria. In particular, the pandemic NDM-1 and other plasmid-borne metallo-ß-lactamases (MBLs) disseminating worldwide in Gram-negative organisms threaten to take medicine back to the pre-antibiotic era as the treatment options remaining for infections caused by these “superbugs” are very limited.
The aim of the present proposal is to combine complementary approaches (microbiology, biochemistry, structural biology, molecular modelling and chemical synthesis) to gain vital insights into structure-function relationship of MBLs, in order to better understand substrate specificities, to determine key residues involved in carbapenem recognition and hydrolysis, to foresee the impact of mutations on the hydrolysis profile, and finally to develop an efficient MBL pan inhibitor.
In-depth biochemical characterization of broad-profile MBLs and co-crystallization of these enzymes with various ligands will provide crucial information for the development of efficient inhibitors that could serve as leads in drug discovery. Site directed mutagenesis will be used to confirm the role of key amino-acid residues in the active sites of the enzymes. With the increasing prevalence of MBLs, new variants will be described, with likely modified hydrolysis properties, which will provide further information on the role of different active site residues. Recently, a novel MBL inhibitor capable of efficiently inhibiting NDM-1 (sub-micromolar IC50) was identified by Partners 1 and 3, using a combined approach of docking and pharmacophore-based virtual screening of focused ligand libraries. We will take advantage of this discovery and use two strategies to obtain an MBL pan inhibitor: i) structure- and function-guided optimization of the previously identified inhibitor in order to ensure efficient inhibition of most or all MBLs, using the data gathered during this project; ii) identification of new pan inhibitors of MBLs using a consensus pharmacophore common to all clinically-relevant MBLs.
Our results will advance the development of pan inhibitors of MBLs that, used in combination with ß-lactams, will protect the ß-lactam antibiotics from degradation by these MBLs.

Keywords: Cla558carhapenemase5,metall0-heta-lactama5e5, X-ray Cry5tallography,hlOChemi5try, mutagenesis, pan inhibitors design, docking, pharmacophore models, focused virtual ligand libraries, organic synthesis, mechanistic enzymology

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