Identification of inhibitors of the unique trypanothione metabolism to fight parasitic neglected diseases

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- This line of research aims at identifying novel compounds endowed with inhibitory activity towards the trypanosomatidal NADPH-dependent flavoenzyme trypanothione reductase (TR) and other enzymes of the unique trypanothione metabolism, essential for the redox metabolism of Trypanosomatids.
- Trypanosomatids are causative agents of a series of vector-borne neglected diseases as leishmaniasis, Chagas disease and human African trypanosomiases, affecting millions of people worldwide and leading to death more than 100,000 humans per year, comprehensively.
- TR is an ideal drug target, being a unique and essential enzyme, exclusively present in the parasitic family of Trypanosomatidae and absent in mammals. TR is highly conserved in all the trypanosomatidal species and selectivity over the human homologous glutathione reductase can be achieved on the basis of the sequence diversity and the different dimension and charge of the active site.
- Thus far, vaccines are unavailable while a limited number of drugs are accessible for the treatment of these life-threatening conditions; all of these display an insufficient efficacy, poor safety and inadequate pharmacokinetic profiles. In this framework our research aims at discovering family-specific, rather than species-specific, novel compounds, by targeting TR.
- Via both a high-throughput and a rational design approach, together with the use of biophysical assays and especially of X-ray crystallography, new active molecules are identified, paving the way for the design and synthesis of new potent broad spectrum inhibitors, effective over the different parasitic trypanosomatidal species.
- In collaboration with the pharmaceutical company IRBM (Pomezia, Rome) an HTS assay has been set up: 3097 compounds were assayed against TbTR and a novel hit series of spiro-containing derivatives has been identified. Among these, Compound 1 activity has been validated through SPR and demonstrated activity against LiTR also, while the solution of the crystal structure in complex with TbTR revealed the structural basis of inhibition.
- Starting from LeishBox, a 192-molecule set of best antileishmanial compound identified by GlaxoSmithKline (GSK) HTS (based on 1.8 million compounds, which were used to build up also a HATBox and a ChagasBox), specific competitive inhibitors of LiTR have been identified through SPR and kinetic experiments. Structural information was obtained via docking predictions; a preliminary model of the crystal structure of compound A1/7 in complex with TbTR was obtained, which confirmed the mechanism of inhibition. Interestingly, compound A1/7 is contained in all GSK boxes, so it has been used, in collaboration with the medicinal chemistry group of Prof. Giuseppe Campiani (University of Siena, Italy), to rationally generate derivatives, which are being tested, in order to yield a single inhibitor for TR from all sources.

References:
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