Poster Presentation

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Structure-based drug design against Trypanosoma brucei methionyl-tRNA synthetase

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Infection by the protozoan parasite Trypanosoma brucei causes human African trypanosomiasis, commonly known as sleeping sickness. The disease is fatal without treatment; yet, current therapeutic options for the disease are inadequate due to toxicity, difficulty in administration and emerging resistance. Therefore, methionyl-tRNA synthetase of T. brucei (TbMetRS) is targeted for the development of new antitrypanosomal drugs. We have recently completed a high-throughput screening campaign against TbMetRS using a 364,131 compounds library in The Scripps Research Institute Molecular Screening Center. Here we outline our strategy to integrate the power of crystal structures with high-throughput screening in a drug discovery project. We applied the rapid crystal soaking procedure to obtain structures of TbMetRS in complex with inhibitors reported earlier[1] to approximately 70 high-throughput screening hits. This resulted in more than 20 crystal structures of TbMetRS•hit complexes. These hits cover a large diversity of chemical structures with IC50 values between 200 nM and 10 µM. Based on the solved structures and existing knowledge drawn from other in-house inhibitors, the IC50 value of the most promising hit has been improved. Further development of the compounds into potent TbMetRS inhibitors with desirable pharmacokinetic properties is on-going and will continue to benefit from information derived from crystal structures.

[1] *Koh, C. Y., Kim, J. E., Shibata, S., et al, E. & Hol, W. G. (2012). Structure 20, 1681-1691.*

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