Protocol for expediting drug targets search in S . Typhi through subtractive genomics and the identification of lead-based novel small molecules

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Abstract

Typhoid fever is transmitted by ingestion of polluted water, contaminated food, and stool of typhoid-infected individuals, mostly in developing countries with poor hygienic environments. To find novel therapeutic targets and inhibitors, the complete genomes of eight *Salmonella* Typhi strains were primarily subjected to the EDGAR tool to predict the core genome (n=3207). Human non-homology (n=2450) was followed by essential genes identification (n=37). The STRING database predicted maximum protein-protein interactions, followed by cellular localization. The virulent/immunogenic ability of predicted genes were checked to differentiate drug and vaccine targets. Furthermore, the 3D models of the identified putative proteins encoded by the respective genes were constructed and subjected to druggability analyses where only "highly druggable" proteins were selected for molecular docking and simulation analyses. The putative targets include ATP-dependent CLP protease proteolytic subunit, Imidazole glycerol phosphate synthase hisH, 7,8-dihydropteroate synthase folP and 2,3-bisphosphoglycerate-independent phosphoglycerate mutase gpmI. A ZINC drug-like library (n=12000) was screened against each identified targets and top hits were selected based on H-bonds, RMSD and energy scores. Finally, the ADMET properties for novel inhibitors ZINC19340748, ZINC09319798, ZINC00494142, ZINC32918650 were optimized followed by binding free energy (MM/PBSA) calculation for ligand-receptor complexes. The findings of this work are expected to aid in expediting the identification of novel protein targets and inhibitors in combating typhoid Salmonellosis, in addition to the already existing therapies.

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