A novel design to identify small molecules to target antimicrobials

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Technology

Too few antibiotics are in the pipeline to tackle the global crisis of drug resistance, which is responsible for the rise of almost untreatable infections around the world, the World Health Organization warns. Among the alarming diseases that are increasing and spreading is bacterial multi-drug resistant is mycobacterium tuberculosis (Mtb), which requires treatment lasting between nine and 24 months. There are 250,000 deaths a year from drug-resistant Mtb and only 52% of patients globally are successfully treated. Yet, only two new Mtb antibiotics have reached the market in 70 years. Among of the major challenges in reaching this goal are the long and expensive drug discovery processes.

Dr. Akabayov and his team developed a novel fragment-based screening with NMR and virtual screening (FBVS) to select small molecules (NCE) that target the bacterial small RNA region of bacterial ribosome, named bacterial peptidyl transferase center (PTC). Over 900 molecules were selected out of 230 million compound libraries, for additional FBVS based on structural motif identified in them. The inhibition effect of 10 compounds was experimentally further examined, out of which two molecules possessed superior inhibition of the ribosome. The docking data collected was used subsequently for establishing machine learning design principles for drug-sized molecules, with increased binding efficiency to the ribosomal PTC.

Advantages

- FBVS approach combines tools from different disciplines in drug development that bypasses many of the limitations of current drug discovery high-throughput screening in terms of costs and time.
- FBVS enable the isolation of inhibitors against targeted pathways that cannot be adapted for HTS and therefore considered as “undruggable” targets in potentially any biochemical pathway.

Applications

- Two lead compounds for treating active Tuberculosis.
- This platform can be used to identify molecules for different applications

Patent

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