New intervention strategy for tuberculosis: blocking multiple essential targets

Mycobacterium tuberculosis is the causative agent of tuberculosis (TB), a disease responsible for almost 1.3 million deaths per year. In recent years, different classes of drug resistant ***M. tuberculosis*** strains have emerged, making the discovery of novel anti-TB drugs a major global priority. This awareness has resulted in several new initiatives to find new (classes of) antimicrobial compounds. One of these initiatives is NM4TB, a consortium containing two noTBsec members, which discovered the benzothiazinones as promising new antimycobacterial compounds. A major disadvantage of most existing and new TB compounds is that they target a single molecule, which significantly increases the chance that resistant strains will emerge. In this project, we will address this problem by identifying compounds that target multiple type VII secretion (T7S) systems. T7S systems are used by ***M. tuberculosis*** to secrete proteins across the cell envelope to the cell surface or into the host environment. Interestingly, this bacterium has several different T7S systems, three of which are essential for viability or virulence. We predict that, by blocking multiple T7S systems with a single compound, we will considerably reduce the development of drug resistance. To target T7S systems, we will use two complementary approaches to identify: (i) secretion blockers based on secretion activity assays and (ii) compounds designed to target specific T7S components. As proof of principle, we have already successfully used the first approach to identify two different classes of compounds that block T7S systems. Importantly, one of these compounds significantly reduced mycobacterial growth ***in vivo***. For the second approach we will exploit the detailed knowledge of T7S systems that has been recently generated within the consortium, including structures of several crucial druggable components. To increase the activities of our secretion-blocking compounds, we will also identify compounds that act synergistically with them from libraries of antibiotics and other FDA-approved drugs. Subsequently (combinations of) compounds will be tested ***in vivo*** in a high throughput animal model for activity, toxicity and resistance development. Together, these experiments will identify molecules inhibiting T7S secretion. These will be used to test the concept that by inactivating multiple essential targets, the emergence of drug resistance is reduced.

Keywords: tuberculosis, secretion, ESX, multi-target, synergistic

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