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TUBERCULOSIS

Old dogs and new tricks

Tuberculosis, an infectious lung disease that is most commonly caused by *Mycobacterium tuberculosis*, claims between 1.6 and 2 million lives each year. Furthermore, multidrug-resistant strains are becoming increasingly prevalent, in part because the current long drug regimens, involving a cocktail of antimicrobial agents for up to 9 months, are associated with poor patient compliance. Two papers published in *Science* — one focusing on a new class of drug and the other on a new combination of established antimicrobials — now highlight avenues that might help address these treatment challenges.

In the first paper, reported by the New Medicines for Tuberculosis Consortium, the researchers investigated the activity of sulphur-containing heterocyclic compounds against *M. tuberculosis*. Benzothiazinones (BTZs) were identified as showing potent and specific activity against mycobacteria in various *in vitro* assays. The compound BTZ038 inhibited the growth of *M. tuberculosis* more potently than existing tuberculosis drugs and, importantly, was equally effective against all clinical isolates of *M. tuberculosis* tested, including multidrug-resistant and extensively drug-resistant strains. In a mouse model of chronic tuberculosis, 4 weeks of treatment with the *S* enantiomer of BTZ038 significantly reduced the bacterial burden in lungs and spleen, with no adverse effects.

To determine the target of BTZs, the authors carried out genetic and biochemical characterizations of *Mycobacterium* mutants that were resistant to the compounds. This analysis revealed that BTZs inhibit decaprenylphosphoryl-β-D-ribose 2′-epimerase, an enzyme involved in the production of an essential mycobacterial cell wall component, arabinan, and thereby promote cell lysis. These findings suggest that further development of BTZs or other compounds that target this enzyme might lead to much-needed novel drugs with the potential to combat drug-resistant tuberculosis.

The second paper describes an approach to render *M. tuberculosis* susceptible to β-lactams. This class of antibiotic, of which penicillin is the canonical example, is not effective against tuberculosis because *M. tuberculosis* expresses a highly active β-lactamase, which rapidly hydrolyses β-lactams. However, by delivering the β-lactam meropenem with the β-lactamase inhibitor clavulanate, the investigators were able to circumvent this mycobacterium defence mechanism, achieving sterilization of *in vitro* cultures within 14 days.

Importantly, this drug combination inhibited the growth of *M. tuberculosis* in an *in vitro* model of the 'persistent state' of the disease — in which non-replicative mycobacteria form a reservoir of disease within a population and thereby necessitate long treatment regimens. Furthermore, the two drugs together also inhibited the growth of drug-susceptible and drug-resistant strains with equal efficacy. As both meropenem and clavulanate are already FDA-approved drugs, their combined use in the treatment of tuberculosis is an attractive and realistic goal.

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ORIGINAL RESEARCH PAPERS Makarov, V. *et al.* Benzothiazinones kill *Mycobacterium tuberculosis* by blocking arabinan synthesis. *Science*, 19 Mar 2009 (doi: 10.1126/science.1171583) | Hugonnet, J.- E. *et al.* Meropenem–clavulanate is effective against extensively drug-resistant *Mycobacterium tuberculosis*. *Science* **323**, 1215–1218 (2009)