TB - the urgent need to tackle a new scourge

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Recent reports from India highlighting a new strain of totally-drug resistant tuberculosis-(TB) have brought the disease known in the 19th Century as the 'White Plague' back to public consciousness. Despite success in treating the disease in the latter half of the 20th Century, TB remains one of the most significant global health challenges.

At least 30 million individuals worldwide will have died from tuberculosis (TB) in the last decade of the 20th Century. In the UK, the steady decline in TB cases over the whole of the last century halted in the mid 1980s, and there has been alarming signs of increased numbers of cases in certain communities.

The situation is compounded by the AIDS epidemic and by the emergence of Mycobacterium tuberculosis strains that are multi-drug resistant (MDR) and extensively-drug resistant (XDR). A recent report in India has highlighted the transition to totally-drug resistant TB (TDR-TB), virtually all the drugs that would normally be used to treat TB are no longer a viable option. It could be argued that, with the emergence of these deadly TB cases, M. tuberculosis is the single most important infectious agent affecting mankind on a global scale.

All bacteria have cells that, like plants, are enclosed in a cell wall. This protects the organism from its immediate environment and, fortuitously, presents an important target for drugs, like penicillin, that can be used to treat bacterial infections. However, M. tuberculosis has a distinctive cell wall that differs in composition from that of other bacteria. Although, there are drugs that affect the unique M. tuberculosis cell wall, the current treatment for tuberculosis lasts 6 months and is potentially toxic to patients who often cease treatment early. Moreover, the efficacy of treatment is threatened by the emergence of MDR, XDR, and TDR strains of M. tuberculosis. There is a great need for new and better drugs to treat TB.

Our goal at the University of Birmingham is to develop lead compounds, which will act on novel mechanisms not utilised by currently available drugs, and therefore are active against MDR, XDR, and TDR-TB strains. Selected hits will be further examined using extensive biochemistry and structural biology studies, which will allow us to identify new targets, unravel their corresponding mode of action, and will lead to the development of corresponding novel enzymatic assays. Since, TB drugs are never administered as single agents, any new inhibitor identified will be evaluated in combination with existing TB drugs. The proposed studies will deliver invaluable, detailed information both on the bacterium and on the host cell, providing not only potential compound scaffolds, but also urgently needed novel targets.

In summary, to overcome the problem of MDR, XDR, and TDR-TB, there is a strong need to identify and validate new classes of drug targets that have not been previously exploited. As a result, the studies at the University of Birmingham fulfill a clear need to extend our understanding of the bacterial physiology of the tubercle bacillus, in the hope of priming novel therapeutic approaches to this ancient human adversary.

Professor Gurdyal Besra
School of Biosciences

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