

A GLOBAL pandemic of tuberculosis (TB) has afflicted mankind for many centuries. TB is a debilitating and chronic disease caused when *Mycobacterium tuberculosis* (Mtb) is spread by coughing, sneezing or even talking. It is mistakenly considered by most to be a disease of the past, yet currently it kills approximately 2 million people every year. It infects one-third of the world's population and at any given time up to 13 million people globally will be suffering from an active TB infection.

The problem is a growing threat because of an inadequate drug regime, lasting for 6 months, based on drugs discovered over 40 years ago. This has caused patient non-compliance, which in addition to an epidemiological co-existence between HIV/AIDS sufferers and the inadequacies of healthcare in the developing world, has resulted in rampant multiple drug resistance.

To control this problem we need new tools, of which the most important are new drugs. There are significant barriers to overcome. Although much information about Mtb has been gained over the last decade, including the complete sequencing of its genome, it is not understood how this relates towards developing new, faster-acting TB drugs. The drug discovery process is also complex and expensive. It takes between 10 and 20 years to deliver a new drug to the clinic from an initial scientific concept, and can cost in excess of £400 million. Owing to rigorous safety evaluation and the scientific complexities associated with Mtb, this means that only a tiny percentage of new compounds identified in the early stages will ever make it to the clinic.

Given the high risks and costs involved, the ultimate question is: who really should be funding TB drug discovery? There is an insufficient commercial market for new TB drugs as 94% of cases are in the developing world where drugs must be delivered at low cost. Understandably, this may prove very unattractive to the pharmaceutical industry.

The strategy being adopted to address this issue is the integration of academic institutions, not-for-profit organizations and governments into a working partnership. Some pharmaceutical companies have also even begun to integrate their efforts in this way over the last decade. In the USA, Johnson & Johnson, GlaxoSmithKline and Bayer have led the way in partnership with the Global Alliance for TB Drug Development (GATB).

So what is the state of TB drug discovery in the UK? Britain was once a leader in finding new antibiotics, notably with the discovery and development of the very first antibiotic, penicillin, and there is no doubt that we should be making a significant contribution. To this end, UK scientists researching new treatments for TB have formed TB Drug

Macrophage engulfing TB bacteria. Science Photo Library

TB is no longer just a disease of the past — it is a very worrying problem of the present. What measures are in place to increase UK research capacity for TB drug discovery?

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Discovery UK (TBD-UK). The initiative aims to align its expertise and form partnerships with like-minded scientists working on drugs for other diseases such as cancer and obesity. Funded by the Medical Research Council, over the next two years TBD-UK aims to identify mechanisms by which new drugs can be developed. It will specifically involve bringing microbiologists, biochemists, geneticists, organic chemists, medicinal chemists, process chemists, X-ray crystallographers, molecular modellers and clinicians to identify routes to combine their diverse skills and increase their capacity for TB drug discovery. Already this approach has led to the identification of a new class of anti-TB agent, the 2-aminothiazolecarboxylates, by combining integrated medicinal chemistry expertise with that of those involved in the development of the fluoroquinolones and their clinical evaluation. More are on the way!

TBD-UK aims to work with government, not-for-profit organizations such as GATB, charities and industry in order to maximize the UK's research potential in the search for new TB drugs. Embracing such a multidisciplinary strategy is the only way to make sure that the UK makes a full contribution to the overall global effort to eradicate TB.

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FURTHER READING

Al-Balas, Q, Anthony, N.G., Al-Jaidi, B., Alnimir, A., Abbott, G. & others (2009). Identification of 2-aminothiazole-4-carboxylate derivatives active against *Mycobacterium tuberculosis* H37Rv and the β -Ketoacyl-ACP Synthase mtfABH. *PLoS ONE* 4, e5617. doi:10.1371/journal.pone.0005617

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COMMENT

TB – strength in numbers