Towards host-directed therapies for tuberculosis

*Alimuddin Zumla[1], Markus Maeurer[2] and the Host-Directed Therapies Network**

The treatment of tuberculosis is based on combinations of drugs that directly target *Mycobacterium tuberculosis*. A new global initiative is now focusing on a complementary approach of developing adjunct host-directed therapies.

Despite the availability of effective antibiotics for tuberculosis (TB) for the past half century, it remains an important global health problem; there are ~9 million active TB cases and ~1.5 million TB-induced deaths per year (see the World Health Organization (WHO) Global Tuberculosis Report in Further information). Health services around the world face major barriers to achieving optimal outcomes from current TB treatment regimens. These barriers include: the spread of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB); complex and toxic treatment regimens for MDR-TB; HIV co-infection; pharmacokinetic interactions between TB drugs and antiretroviral drugs; relapse; permanent damage to lung and other tissues; long-term functional disability; immune reconstitution inflammatory syndrome (IRIS); and co-morbidity with non-communicable diseases such as diabetes and chronic obstructive airway diseases. Another fundamental problem is the long duration of TB drug treatment (6 months for drug-sensitive TB and at least 18 months for drug-resistant TB) to achieve a cure, owing to the presence of dormant *Mycobacterium tuberculosis* bacilli that are phenotypically resistant to current classes of anti-TB drugs, which can only target bacterial replication.

There is therefore an urgent need for new TB treatments. However, the TB drug pipeline is thin[1,2]. For the past 60 years, efforts to develop new treatments have focused on compounds and regimens that target *M. tuberculosis* directly. Recently, however, attention has focused on investigating a range of adjunct treatment interventions known as host-directed therapies (HDTs) that instead target the host response to infection. Here, we highlight the rationale for HDTs, the current portfolio of HDTs and their mechanisms of action, and a consortium-based approach to drive forward their evaluation in clinical trials.

Rationale for HDTs

HDTs aim to augment immune mechanisms against *M. tuberculosis* infection and/or directly reduce excess inflammation, prevent end-organ tissue damage, repair damaged tissues, preserve lung function or enhance the effectiveness of TB drug therapy in eliminating infection. HDTs may also have additional advantages for patients with TB–HIV co-infection, as HDTs may reduce the risk of interaction with antiretroviral drugs and the risk of developing IRIS and death. It is also hoped that combinations of HDTs with anti-TB drug regimens will reduce the duration of therapy, achieve better treatment outcomes, lower the risk of developing further drug resistance and decrease the chances of relapse or re-infection.

The development of HDTs for TB is focused on two general approaches[3]: modulating host inflammatory pathways to reduce aberrant inflammation and lung tissue destruction; and augmenting components of the host's innate and adaptive immune effector mechanisms. A range of interventions that have immunomodulatory effects are under investigation for use as HDTs for adjunct TB treatment (see Supplementary information S1 (table)). These include: 'repurposed' commonly used drugs for other diseases that have no direct activity against *M. tuberculosis*; other products with immune-modulatory effects, such as micronutrients and environmental mycobacteria; mesenchymal stromal cells (MSCs) derived from a patient's own bone marrow; therapeutic vaccines; immunosuppressive agents that re-activate dormant *M. tuberculosis* and thereby increase susceptibility to anti-TB drugs; and products that target pathology associated with both TB and HIV.

HDTs ready for clinical evaluation

Repurposed drugs. Several drugs with potential for repurposing as HDTs already have well-defined safety and pharmacokinetic profiles and are ready to progress to randomized, controlled clinical trials that evaluate their effectiveness in TB, TB–HIV co-infection and TB co-morbidity with other diseases (see Supplementary information S1 (table).

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Vitamin D induces the expression and release of innate antimicrobial peptides such as cathelicidin, and its effects can be enhanced by combining it with the histone deacetylase inhibitor phenylbutyrate. The diabetes drug metformin enhances macrophage autophagy by promoting phagolysosome fusion and increasing mitochondrial production of reactive oxygen species, and also induces expression of AMP-activated protein kinase, leading to reduced TB load and lung pathology. Several non-steroidal anti-inflammatory drugs (NSAIDs) reduce inflammation and tissue pathology, and also have potential to benefit patients who are co-infected with TB and HIV, and those who develop IRIS. The antibacterial drug doxycycline is a matrix metalloproteinase inhibitor that may protect against the degradation of collagen and other structural proteins in lung tissue. Statins such as simvastatin and rosuvastatin have anti-inflammatory effects, and induce autophagy and phagosome maturation. The anticancer kinase inhibitor imatinib interferes with *M. tuberculosis* entry and intracellular survival in host cells and may help to clear *M. tuberculosis* by increasing the number of neutrophils **[OK?]**. Finally, there are several other drugs that require further evaluation in animal or tissue models before entering clinical trials (see Supplementary information S1 (table)).

Cell-based therapies. Patient-derived MSCs may have the potential to modulate aberrant immune responses through their anti-inflammatory and tissue-repairing effects. Adjunct therapy with MSCs is being evaluated in early-stage clinical trials in HIV-infected and non-HIV-infected individuals with MDR-TB, and could be useful in the treatment of a range of associated inflammatory disorders, including TB pericarditis, IRIS and miliary TB.

Plans for clinical evaluation

The main aims of trials of drugs to be repurposed as HDTs will be to evaluate their effects on: the duration of TB chemotherapy for both drug-sensitive TB and MDR-TB; treatment outcomes (including morbidity, mortality, relapse, lung function and long-term sequelae); protective immune responses; inflammation; and tissue repair and regeneration. These trials will also enable biomarkers of the effects of HDTs to be developed and validated.

Trials are under way to assess outcomes in TB-associated IRIS following treatment with vitamin D in combination with phenylbutryrate (NCT01698476), or treatment with an NSAID (NCT02060006). Phase IIb/III trials of several repurposed drugs — including metformin, doxycycline, statins and NSAIDs — are also being planned.

Multiple-arm, multiple-stage (MAMS) trial designs would facilitate efficient evaluations of several regimens including HDTs. In such designs, multiple regimens are simultaneously assessed against a common control group within a single randomized trial. Patient recruitment is discontinued into arms of the trial that are not showing sufficient activity, based on early, pre-planned interim analyses of lack of benefit **[OK?]**.

As a large number of trials, trials sites and patient cohorts is required to evaluate HDTs, a multi-disciplinary, multi-country consortium with a close engagement of end users and stakeholders is needed to take the evaluation of HDTs forward. The Host-Directed Therapies Network (HDT-NET) consortium of 29 African and 11 European country partners was launched under the auspices of the South African Medical Research Council at a stakeholders' meeting held on 7 April 2015 in Cape Town, South Africa (see HDT-NET in Further information). This consortium aims to conduct a number of randomized trials (some using MAMS trial designs, to enable more-rapid exclusion or inclusion of adjunct therapies) of several repurposed drugs. Central to the ethos of the HDT-NET is to develop high-quality clinical trials and laboratory infrastructure at all African partner sites irrespective of current capabilities, as well as a high-calibre cadre of African researchers (including scientists and health and laboratory personnel) who will be suitably empowered to take leadership and conduct of high-quality research and clinical trials.

Outlook

A number of HDTs with the potential to meet unmet clinical needs for the treatment of drug-sensitive and drug-resistant TB have been identified, and several trials have been planned. The development of new TB drugs and evaluation of repurposed drugs needs to be complemented by further research on the discovery of HDTs that can overcome the ability of *M. tuberculosis* to arrest the normal maturation of phagosomes[4]. Such HDTs should include agents that regulate processes such as growth, proliferation, glucose metabolism, apoptosis and autophagy to restrict *M. tuberculosis* growth in macrophages[5]. Finally, increased funding for the development and evaluation of novel therapeutic strategies and biomarkers **[OK?]** using a range of HDTs is urgently required, necessitating a shift from the conventional approach that only new antibiotics and antibiotic treatment regimens will address the unmet clinical needs in the treatment of TB.

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Competing interests statement
The authors declare no competing interests.

FURTHER INFORMATION
ClinicalTrials.gov: http://clinicaltrials.gov/
HDT-NET: http://www.unza-uclms.org/hdt-net
WHO Global Tuberculosis Report 2014: http://www.who.int/tb/publications/global_report/en/

SUPPLEMENTARY INFORMATION
See online article: S1 (table)

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TOC blurb

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Subject categories

Biological sciences / Drug discovery
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Links

NCT01698476
https://clinicaltrials.gov/ct2/show/NCT01698476?term=phenylbutyrate+and+tuberculosis&rank=2

NCT02060006
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