Title: **Advancement of Host-Directed Therapies for Tuberculosis**

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INTRODUCTION

Despite the availability of effective anti-TB antibiotics for the past half century, TB remains an important global health problem causing an estimated 9 million active TB cases and 1.5 million deaths annually (***Link 3***). The high mortality rate and widespread emergence of multi-drug resistant TB (MDR-TB) and a very thin new TB drug pipeline[2] signal an urgent need for new TB therapeutic strategies that could address the many unmet clinical needs. Health services globally face major barriers to achieving optimal TB treatment outcomes using current WHO recommended TB drug treatment regimens. These include: the relentless spread of multidrug-/extensively drug- resistant TB (MDR-/XDR-TB); complex and toxic treatment regimens for MDR-TB; HIV-co-infection; pharmacokinetic interactions between TB drugs and anti-retroviral drugs; relapse following cure; 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 airways disease. Another fundamental problem is the long duration of TB drug treatment (six months for drug sensitive TB and at least 18 months for drug resistant TB) to achieve a cure. This is due to *M.tb* achieving a dormant state which renders non-replicating *M.tb* phenotypically resistant to classes of anti-TB drugs that target *M.tb* replication for their action. For the past 60 years efforts at developing new treatment have focused on development of new TB drugs and regimens which target *M.tb* but not the host response or *M.tb*-host interactions resulting in tissue damage. However, recently attention has focused on investigating a range of adjunct treatment interventions which aim to target the host response, known as 'Host Directed Therapies' (HDTs). We highlight the rationale for HDTs, the current portfolio of HDTs, their possible mechanisms of action and the urgent need for their evaluation in clinical trials, is discussed.

RATIONALE FOR HDTS

HDTs aim to augment anti-*M.tb* protective immune mechanisms and/or directly reduce the excess inflammation, prevent end organ tissue damage, repair damaged tissues, preserve lung function, and

enhance the effectiveness of TB drug therapy by eliminating *M.tb*. HDTs may also have additional advantages for patients with TB/HIV co-infection since HDTs will have no interaction with ARVs with TB or acquired drug resistance, and may reduce development of IRIS and death. It is also hoped that by using these HDTs as adjunct to anti-TB chemotherapy, the combination could lead to fulfilling the unmet clinical needs by reducing the duration of therapy, and achieving better treatment outcomes, lowering the risk of developing further drug resistance and decreasing relapse or re-infection.

Development of HDTs for TB[3] and are focused on two general approaches: a) Modulating host inflammatory pathways to reduce aberrant or excessive inflammation and lung tissue destruction, b) Augmenting components of the host innate and adaptive immune effector mechanisms. A range of interventions with immunomodulatory effects are under investigation for use as HDTs (Supplementary online **Table 1**) for adjunct TB treatment. These include 'Repurposed' commonly used drugs for arthritis, lowering cholesterol, diabetes, antibiotics, epilepsy and cancer with no direct anti-*M.tb* activity; other products with immune-modulatory effects such as micronutrients and environmental mycobacteria; 'Cellular therapy' with mesenchymal stromal cells derived from patient's own bone marrow to reduce damaging inflammation, regenerating damaged tissues and inducing anti-*M.tb* immune responses; Therapeutic vaccines; Immunosuppressive drugs which re-activate dormant *M.tb* bacilli by changing metabolic state, thus increasing *M.tb* susceptibility to anti-TB drugs; Products targeting pathology due to both *M.tb* and HIV.

HDTs READY FOR 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-morbid with other diseases (see Supplementary information S1 (table).

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 maturation of phagosome. The cancer drug Imatinib (Gleeeac-a tyrosine kinase inhibitor) activates autophagy and inhibits *M.tb* replication in macrophages by enhancing macrophage apoptosis and acidification.

Other drugs which require further evaluation in animal or tissue models before entering human clinical trials, and their mechanisms of action are listed in **Supplementary Table 1**:

Cell based therapies. Mesenchymal stromal cells (MSCs) derived from the patient's own bone marrow may have the potential to modulate aberrant immune responses through their anti-inflammatory and tissue-repairing effects. MSCs exposed to a pro-inflammatory environment, such as high TNF-alpha levels in lungs, produce prostaglandin E2 (PGE2) limiting excess of type I – interferon production which is linked to disease exacerbation and increased *M.tb* proliferation. Adjunct therapy using MSCs derived from the patient's own bone marrow and expanded *ex vivo* before re-infusion, is currently being trialed to improve management outcomes in both HIV-infected and uninfected individuals with MDR-

TB. Infusion of MSCs in a phase 1 trial in Belarus patients with MDR-TB/XDR-TB was found to be safe, and a phase 2 trial is underway in Durban, South Africa. Adjunct cellular therapy using autologous MSCs could be useful as for treatment of a range of inflammatory disorders including TB pericarditis, IRIS and miliary TB.

CLINICAL TRIALS EVALUATION PLANS FOR HDTs

Since the repurposed drug are have well-defined safety and pharmacokinetic profiles their individual evaluations through randomized controlled clinical trials are required to define their effectiveness in all forms of clinical TB, TB/HIV co-infected patients and TB co-morbidities with other communicable diseases and non-communicable diseases. The main aims would be to evaluate their effects on reducing duration of TB chemotherapy for both drug sensitive TB and MDR-TB, and on improving treatment outcomes (morbidity, mortality, relapse, lung function, and long term sequelae), inducing protective immune responses, reducing inflammation, and on tissue repair/regeneration. These trials will also allow for biomarkers of the effects of HDTs to be developed and validated.

Phase 2b/phase 3 trials using several repurposed drugs (metformin, doxycycline, statins, NSAIDS) are currently being planned. Trials are underway for improved treatment outcomes for TB-IRIS with vitamin D with phenylbutryrate (***Link 6***), and with NSAIDS (***Link 7***). A multiple-arm, multiple-stage (MAMS), trial design would facilitate multiple evaluations for preparations from similar groups of HDTS such as re-purposed drugs. Since a large numbers of trials, trials sites and patient cohorts are required to evaluate HDTs a multi-disciplinary, multi-country consortium with close engagement of end users and stakeholders will be required to take forward evaluations of HDTs. At a stakeholders meeting held on 7th April, 2015 in Cape Town (***Link 8***) held under the auspices of the SA-MRC the AFRICA- EUROPE HDT-NET consortium of 29 African and 11 European country partners (***Link 9***) was launched. The multi-country, multidisciplinary consortium aim to conduct a range of RCTrials (some using the 'MAMS' trial designs to allow for quicker exclusion or inclusion of adjunct therapies) of several 'repurposed' drugs (***Link 10***). Central to the ethos of HDT-NET is to produce a high calibre cadre of African researchers (scientists, health and laboratory personnel) who will be suitably empowered to take leadership and conduct of high quality research and clinical trials.

OUTLOOK

A whole range of HDTs with the potential to meet unmet clinical needs for treatment of drug sensitive and drug resistant TB are becoming available. Further pre-clinical and clinical optimization studies are required for the large numbers of drugs which show promise for being repurposed as HDTs for adjunct TB therapy. Current funder and pharma focus on new TB drug development needs to be complimented by further research which should focus on discovery of HDTs which can overcome the ability of *M.tb* to arrest the normal progress of phagosome maturation.[4] This should include new anti-*M.tb* agents that are regulators of cellular processes such as growth and proliferation, glucose metabolism, apoptosis, and autophagy and restrict *M.tb* growth in macrophages include kinase modulators, G-protein coupled receptor modulators, ion channel inhibitors, membrane transport proteins, and anti-inflammatory drugs.[5] Closer collaborations between funders, drug developers, basic science, translational clinical research and clinical trials researchers are required to identify other candidates for HDTs from existing drugs and newer adjunct therapies. Increased donor funding into development and evaluation of novel therapeutic strategies using a range of HDTs are urgently required.

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LINKS TO WEBSITES

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SUPPLEMENTARY INFORMATION

Title: **Advancement and Genesis of Host-Directed Therapies for Tuberculosis**

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Supplemental table: attached