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Title:

Host-Directed Therapies for tackling Multi-Drug Resistant TB – learning from the Pasteur-Bechamp debates

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40 WORD SUMMARY

Reflecting upon the historical Pasteur–Bechamp debates on the role of the ‘microbe’ versus the ‘host internal milieu’ in disease causation, we describe the case for parallel investments into a range of adjunct host-directed therapies for improving TB treatment outcomes.

Abstract (150 words)

Tuberculosis (TB) remains a global emergency causing an estimated 1.5 million deaths annually. For several decades the major focus of TB treatment has been on antibiotic development targeting *Mycobacterium tuberculosis* (*M.tb*). The lengthy TB treatment duration and poor treatment outcomes associated with multi-drug resistant TB (MDR-TB) are of major concern. The sparse new TB drug pipeline and widespread emergence of MDR-TB signal an urgent need for more innovative interventions to improve treatment outcomes. Building on the historical Pasteur-Bechamp debates on the role of the 'microbe' versus the 'host internal milieu' in disease causation, we make the case for parallel investments into host-directed therapies (HDTs). A range of potential HDTs are now available which require evaluation in randomized controlled clinical trials as adjunct therapies for shortening the duration of TB therapy and improving treatment outcomes for drug-susceptible TB and MDR-TB. Funder initiatives that may enable further research into HDTs are described.

Tuberculosis (TB) remains a global emergency causing an estimated 1.5 million deaths annually.¹ For several decades the major focus of TB treatment has been on antibiotic development targeting *Mycobacterium tuberculosis* (*M.tb*). The lengthy TB treatment duration and poor treatment outcomes associated with Multi-drug resistant TB (MDR-TB), and co-morbidity of TB with HIV are also of major concern. In May 2014, the World Health Assembly adopted the World Health Organization (WHO) post-2015 global TB strategy, which aims to reduce global TB incidence by 90% before 2035.² Given the special challenges of TB in countries with low levels of the disease, WHO in collaboration with the European Respiratory Society, and with experts from low-incidence countries has developed an eight-point framework adapted from the post-2015 global TB strategy to target pre-elimination and, ultimately, elimination.³

Every year, progress being made towards achieving global TB control targets is reflected upon by the global TB community on World TB Day March 24th.⁴⁻⁶ The TB community have been re-assured by WHO Annual Global TB reports over the past decade showing a steady decline of TB rates worldwide. Further optimism for achieving the Millennium Development Goal's TB control targets came from a number of potentially important developments, including: introduction of a new rapid diagnostic test, the GeneXpert MTB/RIF assay⁷ and its widespread rollout; new drugs entering phase II and III trials, including PA-824⁸; fast-track approval by regulatory authorities of two new TB drugs, bedaquiline and delamanid⁹; and the expanding TB vaccine pipeline.¹⁰

However progress towards achieving WHO global TB control targets in appears to have slowed down over the past 2 years. The 2014 annual WHO Report¹ shows reversal in previous downward trends of estimated global TB case load. Half a million more cases of TB globally in 2013 than previously estimated brought the total number of TB cases to 9 million. Alarming, each year, 3 million people with TB are still being 'missed' by health systems and approximately 1.5 million people die from TB. MDR-TB and extensively drug-resistant TB (XDR-TB) continue to spread relentlessly in Eastern Europe, Asia and Africa, with an estimated 480,000 new MDR-TB cases in 2013 alone.¹ The actual case load of drug-susceptible and drug-resistant TB may be higher than current estimates as indicated by national surveys¹¹ and autopsy studies.¹²⁻¹⁴ These are due to programmatic weaknesses of laboratory and diagnostic infrastructures, case detection, recording and reporting systems. Furthermore, lack of resources coupled with other operational challenges contribute to the low cure rates for MDR-TB¹⁵⁻¹⁷ despite the use of TB drug treatment regimens recommended by WHO.¹

Further disappointment came from the long awaited results of the flouroquinolone trials¹⁸⁻²⁰ which failed to demonstrate any usefulness of moxifloxacin or ofloxacin in reducing the duration of TB

therapy from six to four months. The TB new drug and vaccines developmental pipeline remains slim.²¹ Despite two decades of investment into development of new diagnostics, drugs, treatment regimens and vaccines,^{22,23} we are still faced with a global TB emergency. This worrying status quo indicates that prevailing approaches to preventing, diagnosing, treating and managing TB requires critical appraisal by scientists, healthcare workers, funders, advocacy groups and governments. The time has now come for a radical re-think to effect a game change in facilitating progress towards achieving improved treatment outcomes and for achieving aims of the WHO end TB strategy.²⁴

Ever since the declaration of TB as a global emergency in 1993 by the WHO, a major focus has been on developing new drugs, diagnostics and vaccines which target *Mycobacterium tuberculosis* (*M.tb*) - the microorganism central to pathogenesis of TB. For over two decades, funders, pharmaceutical companies, scientists, advocates and policy makers have focused on eradication of *M.tb* via antibiotic therapy, a concept that *M.tb* is the main cause of the ongoing global TB pandemic. This thinking is in line with Louis Pasteur's (1822-1895) 'Germ Theory of disease causation,' which gained widespread acceptance starting in the mid-19th century.²⁵ This focus continues till today despite the fact that there are two billion people in the world infected with *M.tb* who do not develop active TB disease,²⁶ and that the dramatic decline of TB in much of Europe and North America in the first half of the 20th century occurred well before the discovery of anti-TB drugs.²⁷⁻³⁰

In contrast to Pasteur's theory, Pierre Jacques Antoine Béchamp (1816-1908) proposed an alternate theory of disease causation - a host-pathogen relationship that promoted the concept that it was not the microorganism that caused disease, but it was the human body's 'internal milieu' or 'terrain' that was critical to development of disease after infection by the microorganism.²⁵ Claude Bernard, a renowned physiologist from the same era, tried for years to convince Pasteur of the importance and validity of Béchamp's theory but failed to do so. Prior to his death, Pasteur finally acknowledged the 'terrain' theory saying, "*Béchamp avait raison, le microbe n'est rien. Le terrain est tout.*" ("*Bechamp was right- The microbe is nothing. The terrain is everything*").¹⁶ It is well known that a wide range of 'host factors' alter the human body's 'internal milieu' (terrain) and are responsible for increased susceptibility to developing active TB disease, poor treatment response and for increased mortality from TB.²⁷⁻³⁰ These include: immune-dysregulation from any cause (including stress, poor living conditions, socio-economic factors, micronutrient deficiencies, HIV), malnutrition, aberrant or excess host inflammatory response to infection, alcohol and substance abuse, co-morbidities with non-communicable diseases such as diabetes, smoking and chronic obstructive airways disease, pneumoconiosis, all of which are important drivers of the global TB pandemic.

An important component of the WHO post-2015 global End TB strategy²⁴ is ‘research’. It is now important that in addition to the current investments into development of new diagnostics, drugs, biomarkers and vaccines, a major investment is made into research on development of therapies which target a range of “host factors” involved in TB immuno-pathogenesis, increased susceptibility to developing TB disease, and development of excess inflammatory responses which result in tissue damage and end organ dysfunction. Host-directed therapies (HDTs)³¹⁻³⁶ constitute a diverse range of immunological, biological and drug interventions which modulate anti-*M.tb* protective innate and adaptive immunity, reduce excess inflammation, repair or prevent tissue damage or enhance the effectiveness of TB drug therapy by modulating host factors. The use of HDTs as adjunct to standard anti-TB therapy could also reduce the duration of therapy, and result in improved treatment outcomes for drug sensitive and drug resistant TB, and may decrease relapse rates.

A wide range of HDTs³¹⁻³⁶ targeting the ‘host terrain’ are now being investigated for use as adjunct to current TB drug treatment regimens. These include: ‘repurposing’ commonly used drugs for diabetes, epilepsy, peptic ulcers, hypercholesterolemia, asthma, cancer and arthritis which have shown promise *in vitro* and in animal models; immunomodulatory agents, use of Vitamin D and phenyl butyrate, heat killed environmental mycobacteria; and ‘cellular therapy’ using the patient’s own bone marrow derived stromal cells. Selected list of HDTs under evaluation or ready for evaluation in clinical trials are listed in **Table 1**. These need serious consideration by scientists, pharma, governments and the global community.

All these have potential to alter the ‘host terrain’ in favour of the host, and will require development and further evaluation in randomized controlled clinical trials. Importantly, the uptake of any research findings into policy and their effective translation into programmatic implementation into health services needs to be innovatively addressed through more meaningful engagement of scientists, healthcare workers and end users (patients and governments) in high TB burden countries. A persisting bugbear of current basic science and clinical trials research being conducted in low resourced, high TB endemic countries is that much of frontline research is dominated and driven by researchers from high income, developed country institutions without full and equitable engagement of those from developing countries.³⁷⁻⁴⁰ This discrepancy needs to be seriously addressed and redressed through mechanisms which will ensure equitable and fair partnerships and must now be a priority for all funding agencies and research consortia.

Several recent developments provide further hope for taking forward evaluation of adjunct HDTs in randomized clinical trials and improving current status quo of TB treatment and control efforts. The formation of the Host-Directed Therapies Network (HDT-NET)⁴¹ consortium, which held their

inaugural symposium in Cape Town, South Africa on April 7, 2015 hosted by the South African Medical Research Council. Our network is all inclusive and open to any interested group, and will be extended to include Eastern Europe, Asia and South American country partners. Currently it comprises partners from 19 African and 11 European countries. HDT-NET aims to evaluate through randomized controlled clinical trials (RCTs) a range of adjunct HDTs for potentially: (a) Shortening the duration of treatment for drug-susceptible TB (DS-TB) multi-/extensively-drug resistant TB (MDR-/XDR-TB); (b) Improving treatment outcomes (mortality/morbidity) for MDR-/XDR-TB patients; and for specific clinical conditions associated with tissue injury such as HIV co-infected individuals with DS-TB and MDR/XDR-TB, miliary TB and TB meningitis; (c) Preventing recurrence of TB; (d) Improving treatment outcome of TB- and/or HIV- positive individuals with co-morbidities, such as NCDs (e.g. diabetes) and any cancers. This will create a more holistic approach for high quality care and to regain the upper hand in the fight against TB.

Critically, this initiative is committed to developing and maintaining high quality clinical trials and laboratory infrastructure at all partner sites irrespective of current capabilities. This will include staffing, infrastructure, facilities for cell culture, immunology, mycobacteriology and drug sensitivity testing, diagnostics, data entry/storage, protocol harmonization, communication, biobanking, end user involvement, ethics, continuing professional development, and networking with other trials consortia. Central to its ethos is twinning of research closely to capacity development and training with an aim to develop and nurture high caliber cadre of African and other developing country researchers (scientists, health and laboratory personnel), who will be suitably empowered to take active independent leadership of high quality, locally relevant research. A range of postdoctoral fellows, PhDs, Masters, Diploma students will be mentored in close alignment with the design, development and conduct of clinical trials. The Africa-Europe HDT-NET consortium will allow for access to a broader range of multidisciplinary expertise for research, training and supervision, and will enable broader knowledge and resource acquisition to support trials of other poverty-related diseases to be hosted in each country.

Several funder initiatives also provide hope for trialing HDTs and aligning research with capacity development and training: 1) The German Ministry for Science and Education to fund five Research Networks for Health Innovations under African Leadership with 8 million Euros per year;⁴² 2) The National Institutes of Health, USA partners with high TB burden country governments to co-fund Regional Prospective Observational Research for Tuberculosis (RePORT)⁴³ and 3). The European and Developing Countries Clinical Trials Partnership (EDCTP2) launched formally in Cape Town in December, 2014.⁴⁴ There are unique opportunities for tackling the TB epidemic through

development of equitable north-south clinical trials research and training partnerships.^{45,46} Other funders such as the Wellcome Trust,⁴⁷ the UK Medical Research Council,⁴⁸ NIH Fogarty⁴⁹ and other initiatives are also aligning to build developing country-led development of internationally competitive researchers. Since a large range of HDTs require to be evaluated in randomized clinical trials over the next decade, the time is now ripe for these funders to harness and pool resources for better coordination of national and regional research programs and to reduce fragmentation and duplication and achieve optimal deliverables.

All these funder initiatives can only succeed if close engagement of developing country scientists, healthcare workers, patient groups, governments and policy makers in order to facilitate timely translation of research findings into policy and practice and for trained scientists to secure better careers. We are of the firm belief that it is only through empowerment of the younger generation scientific and healthcare leaders of the future to conduct the best quality science and to think more collaboratively beyond individual agendas, that the current status quo can be changed significantly. The conduct of a numerous clinical trials using a whole range of HDTs trial will allow for basic science studies to be conducted on biological samples obtained from a large cohort of patients from wide geographical areas so that the specific mechanisms of action of HDTs, their value in TB management can be defined. Understanding the specific mechanisms by which these drugs act and the relationship of these mechanisms to *M.tb* pathogenesis will be important in selecting appropriate adjunct host-directed therapy. Investments into newer scientific research should be aligned with parallel international efforts at improving social and living conditions through policy and adequate social protection programmes which address health inequalities more generally. Only then will significant progress be made in achieving WHO post-2015 End TB strategy goals, and gains in achieving TB control will be enhanced and sustained.

DECLARATION AND AUTHOR CONTRIBUTIONS:

All authors listed under the Host-Directed Therapies Network (HDT-NET) consortium contributed to the ideation, concept, development and editing of content of this article. Professors Alimuddin Zumla and Markus Maeurer take responsibility for the final material.

CONFLICTS OF INTEREST

All authors are partners in the newly formed “Host-Directed Therapies Network” (HDT-NET) consortium and have an interest in TB research. All authors declare no conflicts of interest.

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Table 1: Host-directed therapies (compiled from references 31-36)

| HDT TARGETED EFFECT AND HDT GROUPINGS | GENERIC PRODUCT GROUP | EXAMPLES OF POTENTIAL HDT | MODE OF ACTION |
|--|--|--|--|
| Repurposing commonly used drugs for reduction of excess or tissue damaging inflammation and/or for modulation of innate and adaptive immune responses | Non-steroidal anti-inflammatory drugs[^] (Analgesics and arthritis) | Ibuprofen | Inhibits prostaglandin production via cyclooxygenase (COX) inhibition. Reduces lung pathology, tissue inflammation and <i>M. tb</i> burden in mouse models. |
| | Biguanides[^] (Diabetes drugs) | Metformin | Inhibits mitochondrial glycerophosphate dehydrogenase. Inhibits <i>M. tuberculosis</i> growth by enhancing macrophage autophagy by promoting phagolysosome fusion and increasing mitochondrial ROS production. In mice infected with <i>M. tb</i> , metformin improves pulmonary pathology and reduces bacterial load. |
| | Tetracycline* (Antibacterial antibiotic) | Doxycycline | Matrix metalloproteinase inhibitor which prevents degradation of collagen and other structural proteins in lung tissue |
| | Statins* (Cholesterol lowering drugs) | Simvastatin Rosuvastatin | Inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase and agonists of peroxisome proliferator activated receptor- γ . Statins reduce the formation of lipid droplets by mycobacteria and reduce survival of <i>M. tb</i> in macrophages by inducing autophagy and maturation of the phagosome |
| | Phosphodiesterase inhibitors* (Vascular and Anti-inflammatory agents) | Sildenafil (Viagra) Cilostazol (Pletal) | Modulation of host cyclic nucleotide phosphodiesterase (PDE). In mice cilostazol plus sildenafil accelerates the clearance of <i>M.tb</i> bacilli from the lungs. |
| | Protein kinase inhibitors* (Used for chronic myelogenous leukemia) | Imatinib (Gleevec) | Direct pharmacological effect on macrophage function, promoting acidification and maturation of phagosomes. In mouse models reduces intracellular <i>M. tb</i> survival <i>in vitro</i> . Also increases neutrophil and monocyte numbers contributing to anti- <i>M.tb</i> host immune response |
| Cellular therapy for reduction of excess or tissue damaging inflammation and modulation of immune responses | Bone-marrow derived stromal cells[^] | Patient's own bone marrow derived stromal cells (MSCs) | MSCs produce prostaglandin E2 (PGE2) that decreases unproductive inflammation by limiting excess of type I – interferon production and decreased <i>M.tb</i> proliferation. They could modulate deleterious inflammation and may have tissue-repairing effects. Phase 2 trial underway. |
| Heat killed environmental saprophytic mycobacteria for modulation of immune responses | Environmental mycobacteria[^] | <i>M.vaccae</i>, <i>M. indicus pranii</i> (<i>M.w</i>), and <i>M. manresensis</i> | Heat killed environmental mycobacteria induce regulatory T lymphocytes and promote macrophage effects. <i>M.vaccae</i> enhances Th1 and switch off the Th2 response. Being evaluated for both treatment and prevention of TB. |

[^] under evaluation *ready for evaluation