







## OPEN LETTER

# Intervening along the spectrum of tuberculosis: meeting report from the World TB Day nanosymposium in the Institute of Infectious Disease and Molecular Medicine at the University of Cape Town [version 1; peer review: 1 approved]

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**v1** **First published:** 12 Jun 2019, 3:1491  
<https://doi.org/10.12688/gatesopenres.13035.1>  
**Second version:** 30 Jul 2019, 3:1491  
<https://doi.org/10.12688/gatesopenres.13035.2>  
**Third version:** 12 Nov 2019, 3:1491  
<https://doi.org/10.12688/gatesopenres.13035.3>  
**Latest published:** 28 May 2020, 3:1491  
<https://doi.org/10.12688/gatesopenres.13035.4>

## Abstract

Tuberculosis, caused by the highly infectious *Mycobacterium tuberculosis*, remains a leading cause of death worldwide, with an estimated 1.6 million associated deaths reported in 2017. In South Africa, an estimated 322,000 people were infected with TB in 2017, and a quarter of them lost their lives due to the disease. Bacille Calmette-Guérin remains the only effective vaccine against disseminated TB, but its inability to confer complete protection against pulmonary TB in adolescents and adults calls for an urgent need to develop new and better vaccines. There is also a need to identify markers of disease protection and develop novel drugs. On March

## Open Peer Review

Reviewer Status  

Invited Reviewers

25<sup>th</sup> 2019, the Institute of Infectious Disease and Molecular Medicine at the University of Cape Town hosted the second annual World TB Day nanosymposium. The theme of the nanosymposium was “Intervening across the spectrum of TB II” and the goal was to commemorate World TB Day by showcasing research insights shared by early-career scientists and researchers in the field. The speakers spoke on four broad topics: identification of novel drug targets, development of host-directed drug therapies, transmission of tuberculosis and immunology of TB/HIV co-infections. Assistant Professor Bryan Bryson gave a highly interesting keynote address that showcased the application of engineering tools to answer fundamental biological questions, particularly in the context of tuberculosis.

## Keywords

Tuberculosis, TB/HIV co-infections, Host directed Therapies, transmission, new tools

### version 4

(revision)  
28 May 2020

### version 3

(revision)  
12 Nov 2019

### version 2

(revision)  
30 Jul 2019

### version 1

12 Jun 2019

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**Competing interests:** No competing interests were disclosed.

**Grant information:** The work is supported by PravaTB EDCTP2 programme European Union (grant number RIA2017T-2004) to RG, Wellcome Trust (grant number 211360/Z/18/Z), NRF Thuthuka Grant (117721), MRC (SA) SIR grant and Robert Bosch Stiftung Fellowship to SH, Faculty Research Committee (FRC): Start up emerging researcher award to MC, MRC (SA), the NRF and the Carnegie Corporation of New York under the Developing the Emerging Academic Leaders (DEAL) scheme, MIT Biological Engineering and Ragon Institute of MGH, MIT and Harvard to BB, Global Health Innovative Technology (GHIT) Fund- Japan (GHIT-RFP-TRP-2016-001) to SPP, NRF and NRF Innovative (grant number 98963 and 95984) PhD Scholarship UCT/CSIR PhD Scholarship to KN, Bill & Melinda Gates Foundation (grant number OPP1210776), Wellcome Trust (grant number 206751/Z/17/Z), MRC (SA) SIR grant, the NRF (SA), MRC (SA) Capacity Development Grant to MJM. NRF CSUR (Grant Number 116260), NRF Incentive grant For Rated Researchers (IFRR) (Grant Number 119071) and SA MRC Capacity Development Grant to HH. *The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.*

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**How to cite this article:** Hadebe S, Chengalroyen M, Guler R *et al.* **Intervening along the spectrum of tuberculosis: meeting report from the World TB Day nanosymposium in the Institute of Infectious Disease and Molecular Medicine at the University of Cape Town** [version 1; peer review: 1 approved] Gates Open Research 2019, 3:1491 <https://doi.org/10.12688/gatesopenres.13035.1>

**First published:** 12 Jun 2019, 3:1491 <https://doi.org/10.12688/gatesopenres.13035.1>

## Disclaimer

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Tuberculosis (TB) is a debilitating communicable disease affecting millions of people worldwide, with the highest incidence and mortality rates in Southern Africa. In 2017 an estimated 1.6 million people died of TB worldwide, making it a leading cause of death due to a single infectious agent<sup>1</sup>. TB is transmitted through airborne inhalation of *Mycobacterium tuberculosis* (Mtb) that seeds in alveolar spaces in the lungs. Interestingly, almost one-third of the world population that is exposed to Mtb infection is able to control the infection and remain asymptomatic, otherwise known as latently infected<sup>2</sup>. However, 5–10% of these latently infected individuals progress to active TB and manifest symptoms of the disease<sup>2</sup>. More recently, the situation has been made more complex by the emergence of drug-resistant bacteria and co-infections with the human immunodeficiency virus (HIV). In 2017, the WHO estimated that there were 160,000 new cases of multi-drug resistant TB (MDR-TB) worldwide and approximately 5–10% of these patients progressed to extremely-drug resistant TB (XDR-TB)<sup>1</sup>. This underpins an urgent need to develop better and efficacious vaccines than the currently available Bacille Calmette-Guérin (BCG) and to develop novel drugs for tuberculosis.

## Identifying new drug targets

Mtb has a sophisticated metabolic repertoire: it is able generate its own nutrients, but it can also scavenge for some nutrients from the host<sup>3</sup>. Studies have shown that Mtb is able to synthesise essential amino acids such as L-arginine and tryptophan, where deletion of these key metabolites restricts Mtb growth in culture and renders it more susceptible to host immune pressure reducing its survival<sup>4,5</sup>. Dr Melissa Chengalroyen, a postdoctoral research fellow in the Molecular Mycobacteriology Research Unit, under the directorship/supervision of Prof Valerie Mizrahi, opened the morning session and spoke about the key elements required for Mtb survival and how Mtb sequesters these elements to evade host-recognition by non-conventional T cells. She then described a complex *de novo* riboflavin metabolic pathway and different tools to create Mtb mutants lacking key enzymes involved in this pathway to facilitate understanding of each step in the pathway. Her study showed that not all the enzymes involved in the riboflavin pathway are essential—some play redundant roles, while others are absolutely necessary for Mtb survival, and these may hold promise as new candidate drug targets for TB or play an essential role in alerting non-restricted T cell immune arm for faster clearance of the bacteria.

The second speaker in the morning session was Dr Kehilwe Nakedi, a postdoctoral research fellow in the laboratory of Prof Jonathan Blackburn. Her research project was aimed at identifying novel substrates for mycobacterial protein kinase G (PknG) using a mass spectrometry-based phosphoproteomics approach to elucidate the mechanisms mycobacteria interferes with the host signalling during LTBI. She identified 3164 phosphopeptides with high confidence using label-free data analysis<sup>6</sup>. Moreover, she identified 63 host phosphopeptides that were phosphorylated in macrophages infected with *M. bovis* BCG

only and not those infected with the mutant lacking PknG. Further analysis of the data revealed that these substrates phosphorylated in the presence of PknG play a key role in regulating actin polymerisation and cytoskeleton integrity<sup>6</sup>. This work suggest that pathogenic mycobacteria survives inside the host macrophages during early tuberculosis infection through interfering with the host's cytoskeletal dynamics mediated by PknG.

## Development of host-directed drug therapies

Although the currently available TB treatment regimens are effective at killing the bacteria, the emergence of drug resistance and the long duration of treatment threaten their long-term efficacy. This underpins an urgent need to develop new anti-TB drugs and exploration of other treatment strategies to control the disease. One such strategy is to develop host-directed drug therapies (HDTs) with the aim of boosting the host's innate ability to fight the infection and also limit the deleterious tissue pathology<sup>7</sup>. Although this field is still in its infancy, it holds a huge potential as adjunctive therapy for tuberculosis in clinical settings with a high disease burden.

Assistant Prof Reto Guler discussed in detail their published pre-clinical data on the use of statins as a potential host-directed therapy for TB in mice<sup>8</sup>. He then spoke about the translation of this work in a proof-of-concept phase IIB, double-blind, randomized, placebo-controlled trial launched in Khayelitsha township and funded by the European & Developing Countries Clinical Trials Partnership ((EDCTP), RIA2017T-2004). The coordinator of this consortium is Reto Guler (University of Cape Town, Division of Immunology). Chief principal investigator of the clinical trial is Friedrich Thienemann (University of Zürich), local PI in Cape Town is Sandra Mukasa (University of Cape Town). Other project partners include Robert J. Wilkinson (Imperial College London), Claudia Schacht (LINQ Management GmbH, Germany), Gunar Günther and Emmanuel Nepolo (University of Namibia). The aim of the clinical trial is to investigate the use of statins to prevent chronic lung inflammation and potentially TB relapse in patients post completion of a standard TB treatment regimen. He also talked about other potential candidates targets for HDTs such as the transcriptional factor BATF2<sup>9</sup> and microRNA-143 and microRNA-365<sup>10</sup>.

Another speaker on this topic was Dr Suraj Parihar, a Senior Research Officer and contributing investigator at CIDRI-Africa in the Institute of Infectious Diseases and Molecular Medicine (IDM). His talk focused mainly on preclinical studies that investigated the efficacy of repurposed drug generally used to reduce blood glucose and cholesterol as HDTs for TB. He found that this drug was able to reduce lung inflammation in pre-clinical *in vitro* and *in vivo* models of TB. He then went on to speak about how growth factors can also be repurposed to enhance the killing ability of human and mouse macrophages. Although some of these studies are still at the pre-clinical stage, they hold a great promise and may pave way for alternative therapies and new clinical trials supported by strong pre-clinical data.

## Transmission of Mtb

Mtb is transmitted through the inhalation of Mtb-containing aerosols from person to person. Transmission of the bacteria is high in places such as schools, churches, mines, hospitals and heavily

congested neighbourhoods of Cape Town such as informal settlements and townships<sup>11,12</sup>. In places with high prevalence of human immunodeficiency virus (HIV), such as Khayelitsha, the rate of new Mtb infections accounts for more than half of TB cases. In 2006, it was reported that as high as 1500/100,000 incidence rates were observed in some of the townships, exceeding that of national average<sup>13</sup>. The rate of transmission and subsequent disease development has been linked with high aerosol bacillary loads. There are many challenges when it comes to measuring Mtb transmission via aerosol such as the low numbers of bacilli that can be captured, contamination by other bacterial or fungal particles in patients and other airborne particulate matter<sup>14</sup>. New aerosol methods for capturing Mtb such as respiratory aerosol sampling chamber (RASC) hold promise in quantifying rate of transmission especially in high endemic areas. The capacity to measure the rate of transmission and the type of bacilli strain circulating becomes even more critical in the era of high antimicrobial resistance<sup>15</sup>.

Dr Anastasia Koch, a Carnegie Developing the Next African Leaders (DEAL) early career fellow, mentored by Prof Helen Cox and Prof Digby Warner, started off her talk by mentioning the potential of whole genome sequencing technology in identifying Mtb genotypes resistant to the first line tuberculosis drugs<sup>16</sup>. She discussed the major differences in genetic diversity observed in broth cultured Mtb populations and those derived directly from sputum, and moreover how simple culturing could result in loss of some of key genotypes. Anastasia then moved on to discussing the importance of getting a sample as close to that being transmitted by an infected person as possible in order to accurately study the strains that are being transmitted and driving disease in a community. She gave an example of how colleagues from the MMRU and the Desmond Tutu HIV Centre, have been able to capture and isolate Mtb strains from RASC bio-aerosols. She was able to culture these samples and compare whole genome of those strains with sputum induced strains. The ability to isolate Mtb from bio-aerosols and combining that with whole genome sequencing could greatly inform our understanding of TB transmission and treatment, particularly of emerging drug or multi-drug resistant strains.

### TB/HIV co-infection

More than 36.7 million people live with HIV/IDS globally and most of these people live in sub-Saharan Africa. In 2017, it was estimated that more than 350 000 people died due to HIV/TB co-infection, making TB a highest contributor to death in people living with HIV<sup>17</sup>. HIV targets and depletes CD4 T cells at later stages of disease, including protective TB specific CD4 T cells<sup>18,19</sup>. Early antiretroviral (ARV) drug treatment is associated with improved outcomes and helps restore CD4 T cell count, including protective TB-specific CD4 T cells. However, there are complications associated with early ARV treatment in people who also are starting TB treatment. Some of these people develop TB-associated immune reconstitution syndrome (TB-IRIS), which can be fatal, unless controlled by host-directed immune suppressants such as corticosteroids<sup>20</sup>.

To set the scene, Mohau Makatsa, a PhD candidate in the laboratory of Prof Wendy Burgers in the Division of Medical Virology, talked about a particular subset of CD4 T helper cells

expressing IL-22, or “Th22 cells”, which are targeted by HIV. He showed how these cells can be stimulated ex-vivo by Mtb antigens and express different surface molecules compared to Th1 cells. There is a similar magnitude of these cells compared to Th1 cells in people with latent TB, but they are depleted in the peripheral blood in active TB disease and HIV co-infection. IL-22 has been shown to be important for the control of Mtb in mice<sup>21</sup>. It is unclear how these cells play a role in the pathogenesis of TB in humans.

Dr Muki Shey, a Senior Research Officer & Wellcome Intermediate Fellow at CIDRI-Africa in the IDM followed and talked about identification of predictive immunological biomarkers associated with mortality in people who died of severe HIV-associated TB (HIV-TB). He detailed a set of immunological markers that were investigated that could be linked to people that died after presenting to hospital with advanced HIV with first diagnosis of TB and starting TB treatment. Identification of markers that can predict mortality in these patients could lead to better management, development of host-directed therapies and improved survival.

### Engineering tools for TB

The international guest speaker at the Nanosymposium was Assistant Prof Bryan Bryson from the Massachusetts Institute of Technology. Bryan spoke about using cutting-edge single cell RNA sequencing technology to dissect activation states of macrophages infected with Mtb. He identified key regulatory proteins that are differentially expressed in granulocyte-macrophage colony-stimulating factor (GM-CSF) versus M-CSF differentiated macrophages. He showed that GM-CSF turns off IL-10 in Mtb infected macrophages. Using the same macrophages stimulated *in vitro*, he showed how he could use parametric stitching of single cell RNA sequencing and align in a multidimensional way these macrophage profiles with non-human primate macrophages. This method allows a greater understanding of macrophage heterogeneity and spatiotemporal localisation within granulomas. He also talked about phagosomics, a new way of measuring phagosome maturation and identifying new genes/proteins associated with phagosome formation during Mtb infection. He also talked about how to build a phagosome de novo, which allows large scale testing of Mtb host stresses such as drugs. This uses tagged Mtb strains in combination with gene expression data to allow for better understanding of phagosome transcriptional changes in the presence of multiple Mtb stresses.

### Way forward

Prof Valerie Mizrahi, the director of the IDM gave the closing speech at the end of the symposium. In her concluding remarks she said, “It’s with incredible passion that people are progressing TB research, and that is because we’re living with it. It’s incumbent on all of us to think about why we’re doing what we’re doing and to remember that at the end of the day, it’s about the TB patients. Ultimately, one of the things we want to do is put ourselves out of business.”

### Conclusion

It is evident from the talks given by the various speakers that a lot of research is being done to combat TB at the IDM in the Faculty of Health Sciences at the University of Cape Town. The



research ranges from the identification of new candidate drug targets, investigating the utility of repurposed drugs as host-directed drug therapies, understanding the transmission of the bacteria in high burden communities, investigating the immunology of TB/HIV co-infection and identification of biomarkers for TB disease progression. An important highlight of this year's World TB Day NanoSymposium is that a bulk of this research is being undertaken and led by early career research; thus, demonstrating the depth and breadth of talented TB researchers at the IDM.

### Data availability

No data are associated with this article.

### Grant information

The work is supported by PravaTB EDCTP2 programme European Union (grant number RIA2017T-2004) to RG, Wellcome Trust (grant number 211360/Z/18/Z), NRF Thuthuka Grant (117721), MRC (SA) SIR grant and Robert Bosch Stiftung Fellowship to SH, Faculty Research Committee (FRC): Start up emerging researcher award to MC, MRC (SA), the NRF and

the Carnegie Corporation of New York under the Developing the Emerging Academic Leaders (DEAL) scheme, MIT Biological Engineering and Ragon Institute of MGH, MIT and Harvard to BB, Global Health Innovative Technology (GHIT) Fund- Japan (GHIT-RFP-TRP-2016-001) to SPP, NRF and NRF Innovative (grant number 98963 and 95984) PhD Scholarship UCT/CSIR PhD Scholarship to KN, Bill & Melinda Gates Foundation (grant number OPP1210776), Wellcome Trust (grant number 206751/Z/17/Z), MRC (SA) SIR grant, the NRF (SA), MRC (SA) Capacity Development Grant to MJM. NRF CSUR (Grant Number 116260), NRF Incentive grant For Rated Researchers (IFRR) (Grant Number 119071) and SA MRC Capacity Development Grant to HN.

*The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.*

### Acknowledgements

The organisers would like to thank URC for Travel Award and IDM Transformation and Education Task Team for supporting this event. We also thank Prof Valerie Mizrahi, Dr Christle De Beer, Nobhongo Gxolo, Andruween Khadalie and Delena Fredericks.

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# Open Peer Review

Current Peer Review Status: 

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## Version 1

Reviewer Report 02 July 2019

<https://doi.org/10.21956/gatesopenres.14148.r27372>

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**Larry S. Schlesinger**

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This Open Letter is a nicely constructed report out of a meeting held in March 2019 around World TB day for the Institute of Infectious Disease and Molecular Medicine at the University of Cape Town in South Africa. The letter consists of a broad overview of relevant areas in tuberculosis (TB) research, brief summaries of the speakers at the meeting and a comment regarding the road forward. The program was by and large for local participants. However, there was participation from KwaZulu Natal, the University College London and MIT/Harvard.

New information is provided that will be of interest to the field. However, the nature of this format necessitated that information was brief and not really detailed so that the reader only gets some insight into the general topics and way forward.

My comments are mostly editorial:

- Page 3, first paragraph after the disclaimer: “Interestingly, almost one-third of the world population that is exposed to Mtb...control infection...latently infected.” Given current thoughts in the field, I would suggest changing the beginning of the sentence to something like: “Realizing the limitations of the TST and IGRA, it has been estimated (or it is assumed) that almost one-third...”
- Page 3, third paragraph: “...mechanisms mycobacteria interferes with” should be “...mechanisms by which mycobacteria interfere with...”
- Page 3, regarding the paragraph about PknG: Has it ever been proven that this enzyme enters the cytosol? It would be important to know regarding its presumed functions.
- The manuscript uses both tuberculosis and TB...should stick with TB once defined.
- Page 3, last sentence paragraph 5: “candidates targets” should be “candidate targets”.
- Page 3, paragraph 6: Is it repurposed drug or drugs? Also which drug is “this drug”?

- Page 4, first paragraph: “capturing Mtb such as respiratory....” Would add “the” after as.
- Page 4, third paragraph: “TB a highest contributor...” Would change “a” to “the”.
- Page 4, 5<sup>th</sup> paragraph: “...after presenting to hospital...” Would add “the” after to.
- Page 4, 6<sup>th</sup> paragraph: “allows” appears twice and should be followed by “for”.

**Is the rationale for the Open Letter provided in sufficient detail?**

Yes

**Does the article adequately reference differing views and opinions?**

Partly

**Are all factual statements correct, and are statements and arguments made adequately supported by citations?**

Yes

**Is the Open Letter written in accessible language?**

Yes

**Where applicable, are recommendations and next steps explained clearly for others to follow?**

Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** TB research, innate immunity, lung cellular immunity

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

Author Response 22 Jul 2019

**Sabelo Hadebe**, Institute of Infectious Diseases and Molecular Medicine (IDM), Cape Town, South Africa

- Page 3, first paragraph after the disclaimer: “Interestingly, almost one-third of the world population that is exposed to Mtb...control infection...latently infected.” Given current thoughts in the field, I would suggest changing the beginning of the sentence to something like: “Realizing the limitations of the TST and IGRA, it has been estimated (or it is assumed) that almost one-third...”.

**Response:** Thank you for this comment, this is absolutely true, we have changed the sentence as suggested.

- Page 3, third paragraph: “...mechanisms mycobacteria interferes with” should be “...mechanisms by which mycobacteria interfere with...”.

**Response:** changed as suggested.

- Page 3, regarding the para graph about PknG: Has it ever been proven that this enzyme enters the cytosol? It would be important to know regarding its presumed functions.



**Response:** The enzyme is predicted to be secreted into the cytosol, but there is no biochemical proof that has definitely shown that it is in the cytosol.

- The manuscript uses both tuberculosis and TB...should stick with TB once defined.

**Response:** changed, Tuberculosis has been used once in Abstract followed by abbreviation TB in brackets, TB is then used throughout.

- Page 3, last sentence paragraph 5: “candidates targets” should be “candidate targets”.

- Page 3, paragraph 6: Is it repurposed drug or drugs? Also which drug is “this drug”?

**Response:** barberine, this has been added in main article now.

- Page 4, first paragraph: “capturing Mtb such as respiratory....” Would add “the” after as.

**Response:** changed as suggested.

- Page 4, third paragraph: “TB a highest contributor...” Would change “a” to “the”.

**Response:** changed as suggested

- Page 4, 5<sup>th</sup> paragraph: “...after presenting to hospital...” Would add “the” after to.

**Response:** changed as suggested.

- Page 4, 6<sup>th</sup> paragraph: “allows” appears twice and should be followed by “for”.

**Response:** changed as suggested.

**Competing Interests:** No competing interests were disclosed.