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Blue Skies research is essential for ending the Tuberculosis pandemic and advancing a personalized medicine approach for holistic management of Respiratory Tract infections.

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ABSTRACT

Objectives: Investments into 'Blue Skies' fundamental TB research in low- and middle-income countries (LMICs) have not been forthcoming. We highlight why blue skies research will be essential for achieving global TB control and eradicating TB.

Methods: We review the historical background to early TB discovery research and give examples of where investments into basic science and fundamental 'blue skies research' are delivering novel data and approaches to advance diagnosis, management and holistic care for patients with active and latent TB infection.

Findings: The COVID-19 pandemic has shown that making available adequate funding for priority investments into 'Blue skies research' to delineate scientific understanding of a new infectious diseases threat to global health security can lead to rapid development and rollout of new diagnostic platforms, treatments, and vaccines. Several advances in new TB diagnostics, new treatments and vaccine development are underpinned by basic science research.

Conclusions: Blue Skies research is required to pave the way for a personalized medicine approach for management of TB and other Respiratory Tract Infections and preventing long-term functional disability. Transfer of skills and resources by wealthier nations is required to empower researchers in LMICs countries to engage in and lead Blue Skies research.

BLUE SKIES RESEARCH

"Blue Skies" research refers to curiosity driven fundamental basic laboratory-based research for discovering new knowledge (Linden B, 2008). It provides freedom and flexibility to carry out research which can add new knowledge, challenge scientific thinking, and overcome conventional established dogma. Importantly it

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may also yield novel insights and observations not envisaged at the outset, pointing to new fields of study. Scientific breakthroughs can occur by serendipity or chance observations, which present themselves either spontaneously or in research performed with a different purpose but has widespread applications. For example, in 1997 John Walker and Paul Boyer were awarded the Nobel prize for discovery of enzymatic process of synthesis of Adenosine Triphosphate (ATP). It was only in 2012 that this finding from blue skies research became beneficial in discovery and FDA approval of a mycobacterial ATP inhibitor Bedaquiline (Zhang AT, et al, 2019), a novel new drug for treatment of drug resistant TB (DR-TB). This was the first ever new drug developed for TB in over four decades and it has transformed the treatment of MDR-TB (Nasiri MJ et al, 2022).). With *Mycobacterium tuberculosis* (*M.tb*) developing resistance to Bedaquiline and other new TB drugs Delamanid and Pretomanid, novel ways of treating MDR-TB, including host-directed therapies (Zumla A, et al, 2015; 2016; 2020) and phage treatment (Guerrero-Bustamante CA, et al, 2021) remain a priority.

TUBERCULOSIS RESEARCH – HISTORICAL OVERVIEW

To understand why TB remains a global emergency and has not attracted political, scientific and funder attention despite being a global emergency a historical overview is appropriate. At the turn of the 20th century, TB was rampant in the USA and Europe and it was one of the top causes of death. John Bunyan (1628–1688), an English Christian writer, had described TB as "The Captain among these men of death" when TB rates in London had reached a phenomenal 1000 per 100 000 population per year, far more than current rates of TB in TB endemic countries (Zumla A, 2011; Zumla & Grange, 2010). Tuberculosis was known in Victorian Britain as the White Plague due to the loss of skin colour seen in London TB patients. During the 19th century TB continued to ravage Europe and USA and it was one of the top causes of death. In 1901 the UK government set up a Royal Commission to answer fundamental questions regarding TB with a view to controlling the TB epidemic. The high death toll began to slowly fall in Europe in the first half of the 20th century, as better housing, nutrition, and economic status improved. In the second half of the 20th century, political attention and appropriate financial investments into research advanced research rapidly between 1940s and 1960s leading to discovery of the first TB drug streptomycin. In 1948 the British Medical Research Council (MRC) conducted the world's first randomized controlled trial (RCT) of Streptomycin, and in the ensuing decade TB treatment progressed with the discovery of other TB drugs with other mechanisms of action, resulting in introduction of the short-course TB combination chemotherapy. By mid-1980, TB was considered conquered in the UK and National Health Service (NHS) TB services were scaled down considerably, and TB research activities declined globally. In addition, the high hopes for achieving global TB control provided by the TB drug discoveries did not materialize due to inadequate resources to roll out TB treatments in high TB burden countries, the advent of HIV/AIDS epidemic and emergence of TB drug resistance (Grange J et al, 2010). This aptly demonstrates the negative consequences of winding down TB research programmes after early signs of successes.

JUSTIFICATION FOR PRIORITY BLUE SKIES RESEARCH ON TUBERCULOSIS

Tuberculosis today continues to be a global emergency and is responsible for an estimated 1.5 million deaths annually worldwide (WHO,2021). Over one billion people have latent TB infection (LTBI) which may re-activate in their lifetime. Millions of adults and children with active TB and drug resistant TB remain undiagnosed and untreated. In 2020, only 50% of patients with MDR-TB who received WHO-recommended treatment regimens were cured (WHO, 2021). Even when diagnosed and treated many patients do not lead normal lives and continue to suffer from functional disability due to long-term lung damage (Zumla A et al, 2020;). These long-term consequences are similar for all infectious causes of respiratory tract infections including COVID-19 and these sequelae have been attributed to late diagnosis, and aberrant and ineffective immune responses (Maeurer M et al, 2021). Since the advent of the coronavirus disease 2019 (COVID-19) pandemic, the global TB mortality rate is rising due to neglect of health services, making TB detection, treatment, prevention and control even more challenging (Ntoumi et al, 2022). Whilst achieving an end to the global TB epidemic will require revamping and optimization of existing interventions, and addressing the wider social determinants underlying the pandemic, there are many shortcomings of existing interventions.

The COVID-19 pandemic has shown that making available adequate funding for priority investments into 'Blue skies research' to delineate scientific understanding of a new infectious disease threat to global health security can lead to rapid development and rollout of new diagnostic platforms, treatments and vaccines. One of the key messages from numerous WHO, STOP-TB Partnership and other global public health expert advisory groups over the past 2 decades have been that increased investment to accelerate TB research and development and bring new diagnostics, biomarkers, transcriptomic blood gene signatures, therapeutics, and vaccines to clinical practice would bring an end the TB pandemic (Mulenga H et al, 2022; Chaisson & Harrington, 2009;Marais B et al, 2010; Raviglione et al., 2012; Reid et al., 2019; Reid MJ et al 2019; Zumla A et al, 2016; Tiberi S et al, 2018; Vjecha MJ et al, 2018; WHO, 2018; WHO, 2021). Adult and paediatric TB research has always been chronically underfunded and the need for more investments into development of new and more patient friendly transformative diagnostics to cover all causes of RTIs, better treatment regimens, preventive vaccines and more recently call for a more precision and personalized medicine and approach to management of RTIs to effect holistic management outcomes (Kumar K et al, 2021; Lange C et al, 2020; Rao M et al, 2019; Nicolau I et al, 2012; McKenna L et al, 2022; Grundner C, 2018; Gebreselassie N et al 2019).

ADVANCING BLUE SKIES RESEARCH IN HIGH TB ENDEMIC COUNTRIES

Investments into fundamental TB research in LMICs have not been forthcoming and the scanty blue skies research appears restricted to 'for-profit pharma' or a privileged few academic institutions in wealthier nations. It may be that in high TB endemic areas, the benefits of investing into blue skies research and fundamental basic science discoveries may not be immediately visible or applicable and thus usually does not attract national government and funder investments. Most of the basic science developmental research leading to recent advances in new TB drugs and diagnostics have been driven by for-profit pharma from wealthier nations outside high TB endemic regions. Important innovations such as GeneXpert and Whole genome sequencing (WGS) platforms for rapidly detecting *M.tb* resistance genes have rapidly progressed from being research tools to a clinical application (Walzl G et al, 2018; WHO, 2021; Hamada et al, 2021; Satta G et al, 2018; Meehan et al, 2019).

Despite these encouraging developments, the required funder investments for conduct of blue skies research by local researchers in high TB endemic countries have not been forthcoming. Only a select few privileged groups with specific limited grant funding have been able to conduct basic science research in Africa. When

generic grant calls become available, reviewers and national research organisations usually appear not to give high priority for conduct of blue skies research in developing countries. Grant applications are usually rejected on basis of anticipated immediate impact need deliverables, poor understanding of the long-term benefits of proposed basic science research, and personal uninformed comments made by reviewers of the likelihood of novel interventions being of benefit health services. Furthermore, the cost of new innovations is high and thus are perceived as not affordable or implementable in developing countries. This has developed the status quo that most funder investments and grant based research activities in high TB endemic countries are focussed on clinical trials research evaluating new TB tools and drug regimens discovered in wealthier nations, or on implementation and operational research (Zumla et al, 2015b; Nyirenda T et al, 2021). This status quo and the mindset of funders, grant funding bodies' and their reviewers, and other stakeholders is now unacceptable and needs to change.

Unique opportunities now arise with the growing portfolio of trained scientists, clinical trials networks and high quality research capable laboratories in LMICs (Nyirenda T et al, 2021; Zumla et al, 2015b). These now provides the required infrastructures, and conducive atmosphere for the younger generation scientists to take forward their research instincts, think out of the box, and lead their own blue skies basic science research guided by their own local experiences.

NEW TB VACCINES DEVELOPMENT

Blue skies research during the COVID-19 pandemic led to rapid development of a range of effective COVID-19 vaccines within a year of the appearance of the novel SARS-CoV-2 and re-awakened hope that a new TB vaccine is possible from application of blue skies research technological advances (Fan & Lowrie, 2021). Development of a new universally effective TB vaccine is a major research priority, and it is increasingly becoming clear that eradicating TB will be dependent on developing an effective vaccine (Braziet & Mcshane, 2020; Gong et al 2022; Kaufmann S. 2021; Jeyananthan et al. 2022;). No new TB vaccine has yet been approved for use since the discovery of the century old Bacille Calmette-Guérin (BCG) vaccine which has not had a major impact on global TB control, although it has saved many lives since its first rollout (Dockrell & Smith, 2017). Whilst the past decade has seen novel vaccine approaches based on current knowledge of immunity to TB, efforts to develop TB vaccines such as viral vector vaccines, subunit vaccines, attenuated live mycobacterial vaccines, and killed or attenuated whole cell vaccines have not yet been successful. The principal barriers to developing a TB vaccine is the lack of understanding of the pathogenesis of *M.tb* and host protective innate and adaptive immune mechanisms which eliminate *M.tb* or keep it at bay it in its latent form (Domaszewska T et al 2021; Kanaparthi KJ et al, 2022; Zumla et al, 2011; Maeurer et al, 2018). Blue skies research underpins all current vaccine development efforts. Advances in molecular genetics, viral vectors and adjuvants have facilitated TB vaccine development (Brazier & McShane, 2020; Garcia J et al, 2021; Gong et al, 2022; Jeyanathan M et al, 2022). According to the report released by WHO, there are 14 TB vaccine candidates in clinical trials (WHO 2021).

The first proof of concept of the protective effect of mRNA vaccination against TB in mice was published in 2004 one of the first proofs of concept for RNA vaccines (Xu T et al, 2004; Fan & Lowrie, 2021). This concept was successfully used for the rapid development of the COVID-19 mRNA vaccines and this novel and successful advance needs to be exploited for development of TB vaccines (Fan & Lowrie, 2021). The rapid development and deployment of mRNA and adenovirus-vectored vaccines against COVID-19 have still not achieved global COVID-19 vaccine equity. Immunizing people at risk for COVID-19 in the world's low- and middle-income countries (LMICs) still relies on the availability of vaccines produced and scaled through traditional and new technology approaches in wealthier countries. Developing expertise in LMICs for application of multiple vaccine technologies and producing low cost, easily transported and administered vaccines is important, rather than relying on any one individual platform (Hotez & Botazzo, 2022).

Further innovations in bioinformatics, immunoinformatic, synthetic technologies, new materials, and transgenic animal models are facilitating research on peptide-based vaccines for TB. Bioinformatics now make it possible to predict and design a peptide-based vaccine with computers and peptide-based vaccines have several advantages including faster production, stability during transportation, storage, and delivery, in addition to lower cost, and fewer side effects (Gong et al, 2022). However additional research is required to identify suitable antigens, their immunogenicity, antigenicity, protective efficiency, toxicity, mode of delivery and duration of protection.

HOST-DRECTED THERAPIES FOR TUBERCULOSIS MANAGEMENT

Ever since TB was declared a global emergency, TB control activities have focussed on eradicating the *M.tb* the microbiological cause of TB. The global TB community has repeatedly emphasized the need for development of new TB drugs. This mindset needs to change, with more comprehensive investments for holistic care, targeting both *M.tb* and the host. Whilst drug treatment usually provides microbiological cure for respiratory tract infections such as TB, other bacterial, viral and fungal infections, many patients continue to have ill health after cure. They continue to suffer from long-term functional disability and reduced quality of life due to permanent lung damage. These sequelae arise from excessive and aberrant host immune and inflammatory responses to *M.tb* resulting in extensive tissue destruction (Menzies NA et al, 2021; Allwood BW et al, 2021; Frank DJ et al, 2019; Rao et al 2021; Maeurer M et al, 2021; Shaw et al., 2021; Zumla et al., 2017). For more holistic treatment of TB a range of Host-Directed Therapies (HDTs) with various mechanisms of action to enhance immune responses or reduce excessive inflammation, are being considered for use as adjunct therapy in addition to anti-TB drug treatment regimens. These might act synergistically with TB drug regimens and could decrease the duration of treatment and prevent long term disability. Opportunities for conduct of blue skies research for LMICs researchers arise from the need to evaluate the effect and modes of actions of a whole range of commonly used drugs as HDTs for adjunct TB treatment (Zumla and Maeurer, 2015). Cellular therapy using Human mesenchymal stromal cells (MSCs) could modulate host innate and adaptive immune cells and their potent antimicrobial effects against the major classes of human pathogens (bacteria, viruses, fungi, and parasites) across a wide range of infection models have been described. Data from several human phase 1/2 trials show MSCs to be safe and well tolerated (Maeurer, Wang et al 2021). Production of standardized, affordable, clinical-grade MSCs from umbilical cords and other sources is required to pave the way for phase 3 efficacy trials. Immune profiling could also inform optimisation of endotype-specific HDTs.

TRANSCRIPTOMICS, EPIGENETICS AND METABOLOMICS RESEARCH

Convention has it that **h**uman TB pathogenesis is expressed clinically as a continuum from asymptomatic LTBI, subclinical to different pulmonary and extra pulmonary forms of active TB disease. Transcriptomics and epigenetics are also current areas of blue

skies research being conducted for TB diagnosis, predicting response to TB treatment and progression of LTBI to active disease (Mulenga Walzl et al, 2021; Cox H et al, 2022;). Recent data indicate that TB is not a monomorphic disease, and host responses to *M.tb* infection constitute a range of clinical disease presentations, pathologies and spectrum of immunological and molecular pathways (endotypes) (Dinardo AR et al, 2022;. Different endotypes may benefit from personalized TB treatment regimens. Metabolomics methodologies may aid in identifying new TB drugs, elucidation of their mechanisms of action and metabolic TB biosignatures could inform clinical care, adverse effects of toxic TB drugs, and facilitate metabolism-informed treatment Planck & Rhee, 2021; (Phouc Long et al, 2022; DiNardo et al., 2022; Sakallioglu et al., 2021; Wu et al, 2022). Thus these insights and novel therapeutic approaches will help study disease diversity and guide development of precision medicine approaches.

PERSONALISED AND PRECISION MEDICINE FOR TUBERCULOSIS

The diagnosis and treatment of patients with active TB disease follows standard WHO recommended protocols aim to simplify uniform approaches that will achieve the best overall outcomes. One of the major challenges is that of providing care to people with drug resistant TB in terms of standardised programmatic responses. These do not take into account variation of infecting *M.tb* genotype strains, host susceptibility factors, immune responses, TB drugs pharmacokinetics, and the duration of treatment needed to achieve cure and relapse rates. Given the poor global management outcomes of patients with MDR-TB, the current 'one-size-fits-all' approach DR-TB TB treatment is now being replaced in lieu of ongoing advances which bring forth new approaches to achieve unique personalized data-driven treatments where management is individualised to the genotypic and phenotypic data of patients (Mahomed S et al, 2019; Lange et al 2020). Whilst this may seem a low priority for low resourced high TB endemic settings it provides an achievable vision for taking forward better person-centred care. Anti TB drug treatment response varies between patients and populations partly due to genetic variations (Petros et al, 2016)). Blue Skies research in local population in high TB endemic countries would provide newer insights for the development of new drugs and predict treatment outcome. For instance, black African population are characterized by extensive genetic diversity, population substructure, less linkage disequilibrium, and more genetic adaptation evolved in response to diverse climates, diets, and exposure to infectious disease (Campbell & Tishkoff, 2008). The high levels of genetic and phenotypic diversity in African ancestries provides opportunities to study disease susceptibility genes, identify new therapeutic targets and predict treatment response. Personalized medicine where appropriate dosages tailored to the individual patient based on their predicted response would maximize the safety and efficacy of anti-TB drugs and prevent further development of drug resistance.

Over the past decade the field of blue skies research has experienced a revolution in several areas which could unravel the mechanistic understanding of the basic principles of pathogen-host interactions. Advancing these may lead to novel interventions and more holistic approaches for the care of persons with respiratory tract infections, and prevent long term pulmonary complications.There is consensus that for MDR-TB management outcomes to improve, an integrated, personalised medicine, patient-centred approach to holistic care would be ideal. This could be achieved by defining unique host–pathogen profiles; optimal TB drug treatment regimens, maximise effectiveness and minimise toxicity by using pharmacogenetics and therapeutic drug monitoring and adding any relevant adjuvant HDTs to prevent excessive inflammation and enhance protective immune responses. Whilst for profit industry have their own funding, only a few academic researchers have managed to obtain grants to conduct Blue Skies research on TB transcriptomics, metabolomics and HDTs, and that too with time limited funding with no sustainability of activities after grant funding ends.

CONCLUSIONS

The COVID-19 pandemic has shown that making available adequate funding for priority investments into 'Blue Skies' research to delineate scientific understanding of a new infectious diseases threat to global health security can lead to rapid development and rollout of new diagnostic platforms, treatments, and vaccines. Since LMICs now have extensive research capable infrastructures and personnel resource, the time is now ripe for transfer of skills and resources by wealthier nations to enable local researchers in high-TB endemic countries to fully engage them in discovery basic science research.

We also make a case for advancing basic science research in developing countries focused on a personalized medicine approach for management of Respiratory Tract infections and for alleviating or preventing their long-term complications. There is a great need for funders and their reviewers to get on top of frontline visionary research concepts and take the risk of funding Blue Skies research to stimulate out of the box thinking which may result in breakthroughs to facilitate TB eradication efforts. The ideal way forward would be to take advantage of current large multidisciplinary consortia and networks and provide adequate flexible funding (for expanding breadth and depth of research based on results) sustained over a longer period. This will require a step up change in the status quo from funding agencies and their reviewers. Wealthier more indutrialized countries should create research funding specifically for insitutions in LMICs countries without dominance of institutions in western countries. We need a "Global Fund" for research in LMICs. This should be in equitable partnerships with LMICs researchers who should obtain commitment from their governments to sustain the research long term. This will facilitate novel deliverables arising from new scientific breakthroughs to be made available at well-functioning points of care in high TB endmic areas.

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Declaration of Competing Interest

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