All mycobacteria are inventive, but some are more Daedalean than others

Geluk, A.

DOI: 10.1111/imr.12970

Immunological Reviews WILEY

INTRODUCTION

All mycobacteria are inventive, but some are more Daedalean than others

Annemieke Geluk

Department of Infectious Diseases, Leiden University Medical Center, Leiden, The Netherlands

Correspondence: Annemieke Geluk, Department of Infectious Diseases, Leiden University Medical Center, The Netherlands.
Email: ageluk@lumc.nl

Funding information
The author is supported by grants of the Leprosy Research Initiative (LRI), the Turing Foundation, the QM Gastmann-Wichers Foundation, and EDCTP.

1 | INTRODUCTION

Since the end of 2019, when the world was struck by the COVID-19 pandemic,[1,2] discussions regarding immunology seem not to be restricted to lecture halls and laboratories anymore, but have moved beyond the scientific community into public society. Popular talk shows and social media platforms nowadays not sporadically contain (non-scientific) conversations about herd immunity, neutralizing antibodies, the R-number, T cell cross-reactivity, rapid tests, host-directed therapy (chloroquine), and, of course, vaccines. With respect to the latter, the post-COVID-19 laymen attention focuses, besides on availability, on vaccine composition, regimen, trials, boosters, and efficacy, topics that, not too long ago, were considered far from appealing topics of conversation by non-scientist. To pull us out of the economically and socially devastating restrictions imposed on society by this global pandemic, the hope of the public is now directed on the new anti-COVID-19 vaccines that are currently being rolled out in many countries across the world.

Taken this present-day extent of public attention for immunology into consideration, it should have become common knowledge by now that long-term investments in research of immunology (inseparably linked with vaccinology) of infectious diseases, including those caused by pathogenic mycobacteria, have provided vital contributions to the current capability to develop and produce COVID-19 vaccines in <1 year.

Still, development of better diagnostics and improved vaccines has been relatively slow despite their protracted impact on the health of humans and animals as well as global economies. This controversy is reflecting the unpropitious funding situation of this research domain, which is quite disproportional with the number of casualties particularly in the case of tuberculosis (TB), a respiratory disease that, before 2020, has been more lethal than any other disease from a single infectious agent.[3] However, in contrast to COVID-19, which has severely hit Europe and the USA as well, mycobacterial diseases mostly affect individuals in low- and middle-income countries (LMICs).

This volume of Immunological Reviews comprises papers that encompass (recent) findings on the immunology of mycobacterial diseases caused by *Mycobacterium tuberculosis* (*Mtb*), *M leprae*, *M ulcerans*, *M avium*, *M absessus*, *M bovis*, and *M avium* subspecies *paratuberculosis*, as well as immunity induced by the vaccine strain *M bovis* Bacillus Calmette-Guérin (BCG), thereby illustrating the progress made in basic research on Immunity to Mycobacteria.

This includes the role that classical and more recently discovered (T) cells play in these intriguing host-pathogen interactions as well as potential application thereof within vaccination strategies and as correlates of protection and disease in diagnostics. To unravel mechanisms of disease various "omics" technologies have contributed, leading to new insights regarding (prospective) diagnostics for[4-8] as well as immune mechanisms of mycobacterial diseases.[9,10]

In addition, it addresses the plethora of sophisticated survival strategies including manipulation of phagosome maturation, autophagy, mitochondrial activity, antigen presentation, and metabolic pathways that these mycobacteria can employ to evade the hosts' immune systems.

2 | TUBERCULOSIS

Despite the discovery of effective antibiotic treatments and neonatal BCG vaccination in endemic areas, tuberculosis (TB) has historically

This article introduces a part of a series of reviews covering Immunity to Mycobacteria appearing in Volume 301 of *Immunological Reviews*.

caused more deaths than any other single human infectious disease worldwide, even surpassing HIV/AIDS and malaria as the leading cause of death.[11] Globally, an estimated 10.0 million people fell ill with TB in 2019 and 1.4 million deaths (including 208 000 among HIV-positive people) were attributed to this disease representing more than 3800 deaths per day.[11] It is estimated that about 1,7 billion people (23% of the world's population) are latently infected with *Mtb* and thus at risk of developing active TB disease sometime during their lifetime.[12] Moreover, multidrug-resistant tuberculosis (MDR-TB) represents a major obstacle to effective care and prevention worldwide. Furthermore, the large gap (2.9 million) between the number of newly diagnosed patients reported and the estimated 10 million active TB cases, which is due to a combination of under-reporting of detected cases and under-diagnosis (if people with TB cannot access health care or are not diagnosed when they do),[13] calls for better diagnostic tests. Of note is also the One Health aspect of this disease, as in LMICs, a significant number of human TB cases are actually caused by *M bovis* infection.[14-16]

Since vaccines, in general, represent an extremely efficient way to reduce disease burden by preventing disease or even infection,[17] multiple research projects have focused on new vaccines and vaccination strategies to prevent TB as alternative to or combined with BCG.[18-21] In order to develop new vaccines, detailed insight into the complex events of host immunity against mycobacteria has been deemed necessary for decades.[22,23] At the basis of such efforts lies the search for what substantiates the optimal protective, non-pathogenic T cell response.[24-26] This involves a growing number of T cells that contribute to either enhancing or suppressing protective immunity and recognize antigens involved in various stages of infection and disease.[21,27,28] A dominant role is reserved for CD4 T cells as clear from depletion of this subset or transduction of HLA class II in animal models and supported by the fact that patients with HIV infection who have reduced CD4 T cell counts are more susceptible to primary *Mtb* infection, reinfection and reactivation.[27,29-31]

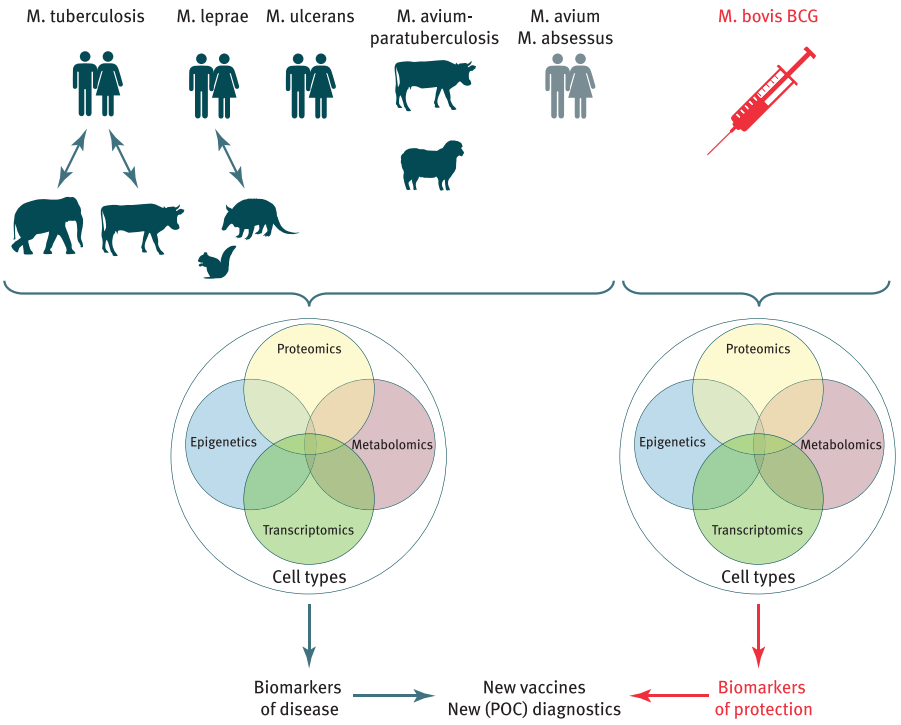
In this issue, Morgan and colleagues (IMR-2021-001.R1) provide a holistic view on the role of classical, HLA class II-restricted CD4 T cells in *Mtb* infection. From this perspective, they compare the presence of various classical CD4 T cell subsets (classified using proteomics in functional signatures according to extensive cell surface expression as well as cytokine production), that have been identified to have importance for *Mtb*-specific immunity in either latent infection, active TB, severe TB, after BCG-vaccination, or environmental exposure (eg, by non-tuberculous mycobacteria). This involves a detailed subdivision into memory phenotypes and helper T cell phenotypes like Th1, Th2, Th17, and the heterogeneous Th1*, a distinct hybrid Th1/Th17 population.[32] Besides CD4 T cells, they discuss their antigenic targets which identified, for example, using epitope megapools[33] (4,000 ORFs of the *Mtb* genome) as universal tool to measure HLA class II-restricted CD4 T cells across different disease states. Jointly, CD4 activation markers, the epitopes they recognize, and proteins they secrete as well as transcriptomic and metabolomic markers are promising correlates of protection, although they may vary in different populations.

On the other hand, Ruibal and colleagues (IMR-2020-074.R1), inspired by the limited success of vaccines against TB based on classical T and B cells, embark on the non-classical path and convincingly argue on the value of donor-unrestricted T-cells (DURTs) as targets for novel vaccines against TB. The attractiveness of these DURTS lies in the fact that they recognize antigenic ligands via genetically conserved antigen presentation molecules such that their application avoids. The attractiveness of such an approach is that DURTs, in contrast to classical T cells which are activated via highly polymorphic HLA class I and II molecules, can respond to the same ligands across diverse human populations. This not only provides advantages for vaccination but also for correlates of protection. In their contribution, they describe several populations of T cells categorized under DURTS such as HLA-E-restricted T cells,[34,35] CD1-restricted T cells, mucosal-associated invariant T-cells (MAITs), and TCR γδ T cells. Besides DURTS, they discuss NK cells and innate lymphoid cells (ILCs) and the gain of targeting these cells with vaccines against *Mtb*. It needs to be assessed in future studies how, combined with classical immune responses, these unconventional subsets have potential to contribute essential, additional protective immunity against TB, leprosy, and NTM infections.

The role of yet another T cell subset is scrutinized in the review by Verma and colleagues (IMR-2020-082.R2) who discuss regulatory T cells (Tregs)[36] in the context of homeostasis. But also the potential role of Tregs in tipping the (Th-Treg) balance based on studies in humans and animal models of *Mtb* that suggest Tregs cannot only help reduce tissue-damaging inflammation, but also have immunosuppressive functions that interfere with protective responses against this mycobacterium. Additionally, they describe immune mechanisms in the often difficult to treat infections with non-tuberculous mycobacteria (NTM) such as *M avium* and *M absessus* the prevalence of which is increasing at an alarming rate.[37]

From a completely different angle, Kilinç and colleagues (IMR-2020-087) believe in prospective use of host-directed therapy (HDT) to tackle the problems encountered in mycobacterial infections, namely the multiple counter-strategies that mycobacteria have ingeniously developed to persist and survive inside host cells. This has been investigated substantially already for the cunning tactics that *Mtb* utilizes,[38,39] but receives warranted attention for NTM as well in this review for which they included all relevant studies of the past 20 years. In their review, they include not only Mtb infection but also discuss what is known or assumed about NTM, particularly *M avium* infections.

On yet another angle of approach, Laval and colleagues (IMR-2020-071.R1) have chosen to investigate the effect of macrophage fatty acid metabolism on host immunity to *Mtb*. By integrating findings from immunological and microbiological studies, they introduce the new concept that lipid droplet formation in *Mtb*-infected macrophages, besides allowing the bacterium to produce energy and build the lipid-rich cell wall, may also benefit the host. This pro-host mechanism by preventing *Mtb's* access to host fatty acids while limiting the flux of fatty acids through β-oxidation. Key in the metabolic adaptation of macrophages to *Mtb* infection leading to cytoplasmic accumulation of FAs which potentiates their anti-mycobacterial responses and forces the intracellular pathogen to shift into fat-saving, survival mode.



3 | BCG

Despite years of intensive research, Bacille Calmette-Guerin (BCG) remains the only licensed vaccine against TB. The 100-year-old vaccine protects against childhood TB, but is not unanimously effective in adult pulmonary TB. Several vaccine trials using BCG have, however, established its protective effect against leprosy[40] and NTM.[41] It has also become clear that BCG can modulate the innate immune system leading to protection against unrelated pathogens through a mechanism referred to as trained immunity.[42] These heterologous benefits of BCG may even prove relevant in vaccination strategies to prevent COVID-19.

To optimally utilize and improve upon the BCG vaccine in new vaccine strategies such as BCG re-vaccination[17] or new administration routes,[43] Ahmed and colleagues (IMR-2021-007) unravel what is known about protective immune responses elicited by BCG against TB and other mycobacterial ailments including factors that may be responsible for the variable efficacy of BCG such as host and environment. In view of the current COVID-19 pandemic, these authors also involve the debate on potential protective responses against SARS-CoV-2 induced by BCG vaccination.[44,45]

As opposed of addressing protection against TB disease, Foster and colleagues (IMR-2020-084.R1) focus on BCG-induced protection against *Mtb* infection. They review evidence from observational and BCG re-vaccination studies, including limitations and variation in protection as well as possible underlying mechanisms such as antibody-mediated protection and innate immune mechanisms, particularly histone modifications at the promoter and enhancer regions of pro-inflammatory genes the hallmark of BCG-induced trained immunity.

4 | PARATUBERCULOSIS

Paratuberculosis, like bovine TB, is a mycobacterial disease of ruminants caused by *Mycobacterium avium* subspecies *paratuberculosis* (MAP) which has a considerable impact on livestock health, welfare, and production.[46] MAP causes a granulomatous chronic intestinal infection also known as Johne's disease, impacting cattle, sheep, goat, and deer industries globally. Although there are at least three vaccines, vaccinated animals can still shed MAP thereby maintaining transmission[47] and disease detection still relies heavily on dated methods. De Silva (IMR-2020-086.R2) describes potential suitable biomarkers and the immunological mechanisms they represent, focusing on the resilience phenotype. Since MAP is an enteric pathogen, she argues that vaccination inducing mucosal immunity should be prioritized. In this process, the ease of application and access to mucosal surfaces will determine the most practical and efficient vaccine.

5 | LEPROSY

After TB, leprosy, caused by *M leprae*, ranks second in the order of severe human mycobacterial diseases. In contrast to *Mtb*, it is not very contagious, requiring frequent and intense contact c. It predominantly affects the skin and peripheral nerves reflecting the optimal growth temperature of this mycobacterium. Although leprosy is known to humans for many centuries, its immunopathology still represents a complex scientific challenge to clinicians as well as immunologists.[48] Characteristic for leprosy is its unique disease spectrum,

in susceptible individuals, reflecting the vast inter-individual variability in clinical manifestations, whereas it shares issues on the lack of sensitive diagnostics for early disease and infection with other mycobacterial diseases.

Based on extensive immunological expertise in leprosy, particularly regarding animal models, Adams (IMR-2020-085.R1) presents a historic overview identifying key immunological aspects of the immune response against *M leprae* based on different animal models (mostly mice, non-human primates, and armadillos) that have been used for leprosy research compelled by the inability to culture this mycobacterium in vitro. The generation of various knockout mice has not only provided more insights into which immunoregulatory mechanisms lead to susceptibility or protection, but also provide well-defined models for different parts of the disease spectrum including leprosy reactions which are difficult to study in humans. Since an additional advantage of animal models is that dose, time, and site of infection are known, the genetically altered mice represent useful tools for assessment of new (chemoprophylactic) treatment regimens, vaccines, and diagnostics.

Van Hooij and Geluk (IMR-2021-003) aim to identify phase-specific biomarkers to improve leprosy diagnostics by assessing studies published about the role of various cell subtypes associated with *M leprae* infection and the various disease states in which leprosy occurs in humans. Taking the alleged route *M leprae* follows in the host, this leads them to conclude that the innate immune system is dominant in the initiation of nerve damage, an early disease manifestation, whereas the adaptive immune system further aggravates nerve damage and determines the type of leprosy. Application of biomarkers associated with different forms of leprosy will improve leprosy diagnosis and treatment.

A different view on the maneuvers of *M leprae* to evade protective host immunity is provided by Oliveira and colleagues (IMR-2021-002.R2). Driven by the findings that genetic variations in enzymes related to central metabolism and mitophagic process, such as HIF-1α, FAMIN, PRKN, and LRRK2, are associated with leprosy, they focus on mitochondria as target of suppression of host defense. It is presumed that Mleprae reduces the generation of oxidative stress concomitantly lowering inflammasome activation and other pertinent mitochondrial signaling involved in innate immunity. These insights generate options for new drugs that block mitochondrial deactivation.

6 | BURULI ULCER

Buruli ulcer (BU) represents a neglected tropical skin disease manifesting as chronic wounds that can leave victims with major, life-long deformity and disability. The causative agent, *M ulcerans*, possesses a unique trait as, in contrast to other pathogenic mycobacteria, it produces mycolactone, a diffusible lipid factor with unique cytotoxic and immunomodulatory properties.[49] An additional divergence compared to TB and leprosy is that epidemiologic and genetic analyses argue against human-to-human transmission. BCG is the only vaccine available that has been studied for BU prevention, but only conferred short-lasting protection.[50] DeMangel (IMR-2020-083.R1), completes this issue with a comprehensive review on the immunosuppressive properties of mycolactone including blockade of Sec61, the host receptor mediating the immunomodulatory effects of mycolactone and thereby the virulence of *M ulcerans*.

Finally, Fevereiro and colleagues (IMR-2020-088.R1) elegantly review the most recent data on "Buruli ulceromics", that is, omics-based studies on Buruli ulcer including GWAS to depict the mechanism of *M ulcerans* infection. They describe the resemblance with and differences from host immune responses in other mycobacterioses. As has been shown for TB and leprosy, application of omics-based research provides promising options for Buruli ulcer research which are required to render this disease truly negligible.

7 | CONCLUSION

Together, this volume provides a wide-ranging update on current views of immunological mechanisms involved in mycobacterial infection and disease which display potential for translational research regarding development of vaccines, drugs, and diagnostics. The comprised reviews will hopefully instigate innovative research activities aimed at developing novel therapeutic strategies for mycobacterial disease in humans and animals that are as inventive as their causative agents.

CONFLICT OF INTEREST

The author declares no conflict of interest.

REFERENCES

1. Huang C, Wang Y, Li X et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395:497-506.
2. Fauci AS, Lane HC, Redfield RR. Covid-19 - Navigating the Uncharted. *N Engl J Med*. 2020;382:1268-1269.
3. Frick M. Funding for tuberculosis research-an urgent crisis of political will, human rights, and global solidarity. *Int J Infect Dis*. 2017;56:21-24.
4. Zak DE, Penn-Nicholson A, Scriba TJ et al. A blood RNA signature for tuberculosis disease risk: a prospective cohort study. *Lancet*. 2016; 387(10035):2312–2322.
5. Penn-Nicholson A, Mbandi SK, Thompson E et al. RISK6, a 6-gene transcriptomic signature of TB disease risk, diagnosis and treatment response. *Sci Rep*. 2020;10:8629.
6. Tio-Coma M, van Hooij A, Bobosha K et al. Whole blood RNA signatures in leprosy patients identify reversal reactions before clinical onset: a prospective, multicenter study. *Sci Rep*. 2019;9:17931.
7. Mayboroda OA, van Hooij A, Derks R et al. Exploratory urinary metabolomics of type 1 leprosy reactions. *Int J Infect Dis*. 2016;45:46-52.
8. Weiner J, Maertzdorf J, Sutherland JS et al. Metabolite changes in blood predict the onset of tuberculosis. *Nat Commun*. 2018;9:5208.
9. Teles RMB, Lu J, Tio-Coma M et al. Identification of a systemic interferon-gamma inducible antimicrobial gene signature in leprosy patients undergoing reversal reaction. *PLoS Negl Trop Dis*. 2019;13:e0007764.
10. Geluk A, van Meijgaarden KE, Wilson L et al. Longitudinal immune responses and gene expression profiles in type 1 leprosy reactions. *J Clin Immunol*. 2014;34:245-255.

11. WHO. Global tuberculosis report. 2020. http://www.who.int/tb/publications/global_report/en/
12. Houben RM, Dodd PJ. The global burden of latent tuberculosis infection: a re-estimation using mathematical modelling. *PLoS Med*. 2016;13:e1002152.
13. Denkinger CM, Dolinger D, Schito M et al. Target product profile of a molecular drug-susceptibility test for use in microscopy centers. *J Infect Dis*. 2015;211(Suppl 2):S39-49.
14. Cosivi O, Grange JM, Daborn CJ et al. Zoonotic tuberculosis due to *Mycobacterium bovis* in developing countries. *Emerg Infect Dis*. 1998;4:59-70.
15. Torres-Gonzalez P, Cervera-Hernandez ME, Martinez-Gamboa A et al. Human tuberculosis caused by *Mycobacterium bovis*: a retrospective comparison with *Mycobacterium tuberculosis* in a Mexican tertiary care centre, 2000–2015. *BMC Infect Dis*. 2016;16:657.
16. Muller B, Dürr S, Alonso S et al. Zoonotic *Mycobacterium bovis*-induced tuberculosis in humans. *Emerg Infect Dis*. 2013;19:899-908.
17. Nemes E, Geldenhuys H, Rozot V et al. Prevention of *M tuberculosis* infection with H4:IC31 vaccine or BCG revaccination. *N Engl J Med*. 2018;379:138-149.
18. Kaufmann SHE, Dockrell HM, Drager N et al. TBVAC2020: advancing tuberculosis vaccines from discovery to clinical development. *Front Immunol*. 2017;8:1203.
19. Ottenhoff TH, Kaufmann SH. Vaccines against tuberculosis: where are we and where do we need to go? *PLoS Pathog*. 2012;8:e1002607.
20. Van Der Meeren O, Hatherill M, Nduba V et al. Phase 2b controlled trial of M72/AS01E vaccine to prevent tuberculosis. *N Engl J Med*. 2018;379:1621-1634.
21. Geluk A, van Meijgaarden KE, Joosten SA, Commandeur S, Ottenhoff TH. Innovative strategies to identify *M tuberculosis* antigens and epitopes using genome-wide analyses. *Front Immunol*. 2014;5:256.
22. Ottenhoff TH, Haanen JB, Geluk A et al. Regulation of mycobacterial heat-shock protein-reactive T cells by HLA class II molecules: lessons from leprosy. *Immunol Rev*. 1991;121:171-191.
23. Cooper AM. Cell-mediated immune responses in tuberculosis. *Annu Rev Immunol*. 2009;27:393-422.
24. Petruccioli E, Scriba TJ, Petrone L et al. Correlates of tuberculosis risk: predictive biomarkers for progression to active tuberculosis. *Eur Respir J*. 2016;48:1751-1763.
25. Ottenhoff TH, Ellner JJ, Kaufmann SH. Ten challenges for TB biomarkers. *Tuberculosis*. 2012;92(Suppl 1):S17-S20.
26. Chegou NN, Sutherland JS, Malherbe S et al. Diagnostic performance of a seven-marker serum protein biosignature for the diagnosis of active TB disease in African primary healthcare clinic attendees with signs and symptoms suggestive of TB. *Thorax*. 2016;71:785-794.
27. Geluk A, van den Eeden SJF, van Meijgaarden K et al. A multistage-polyepitope vaccine protects against *Mycobacterium tuberculosis* infection in HLA-DR3 transgenic mice. *Vaccine*. 2012;30:7513-7521.
28. Coppola M, van Meijgaarden KE, Franken KLMC et al. New genome-wide algorithm identifies novel in-vivo expressed *Mycobacterium tuberculosis* antigens inducing human T-cell responses with classical and unconventional cytokine profiles. *Sci. Rep*. 2016;6:37793.
29. Ottenhoff TH, De BT, van Dissel JT, Verreck FA. Human deficiencies in type-1 cytokine receptors reveal the essential role of type-1 cytokines in immunity to intracellular bacteria. *Adv Exp Med Biol*. 2003;531:279-294.
30. Ottenhoff TH. New pathways of protective and pathological host defense to mycobacteria. *Trends Microbiol*. 2012;20:419-428.
31. Selwyn PA, Hartel D, Lewis VA et al. A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. *N Engl J Med*. 1989;320:545-550.
32. Acosta-Rodriguez EV, Rivino L, Geginat J et al. Surface phenotype and antigenic specificity of human interleukin 17-producing T helper memory cells. *Nat Immunol*. 2007;8:639-646.
33. Dan JM, Lindestam Arlehamn CS, Weiskopf D et al. A cytokine-independent approach to identify antigen-specific human germinal center T follicular helper cells and rare antigen-specific CD4+ T cells in blood. *J Immunol*. 2016;197:983–993.
34. Joosten SA, van Meijgaarden KE, van Weeren PC et al. *Mycobacterium tuberculosis* peptides presented by HLA-E molecules are targets for human CD8 T-cells with cytotoxic as well as regulatory activity. *PLoS Pathog*. 2010;6:e1000782.
35. Lampen MH, Hassan C, Sluijter M et al. Alternative peptide repertoire of HLA-E reveals a binding motif that is strikingly similar to HLA-A2. *Mol Immunol*. 2012;53:126-131.
36. Savage ND, de Boer T, Walburg KV et al. Human anti-inflammatory macrophages induce Foxp3+ GITR+ CD25+ regulatory T cells, which suppress via membrane-bound TGFbeta-1. *J Immunol*. 2008;181:2220-2226.
37. Wu ML, Aziz DB, Dartois V, Dick T. NTM drug discovery: status, gaps and the way forward. *Drug Discov Today*. 2018;23:1502-1519.
38. Korbee CJ, Heemskerk MT, Kocev D et al. Combined chemical genetics and data-driven bioinformatics approach identifies receptor tyrosine kinase inhibitors as host-directed antimicrobials. *Nat Commun*. 2018;9:358.
39. Kuijl C, Savage NDL, Marsman M et al. Intracellular bacterial growth is controlled by a kinase network around PKB/AKT1. *Nature*. 2007;450:725-730.
40. Merle CS, Cunha SS, Rodrigues LC. BCG vaccination and leprosy protection: review of current evidence and status of BCG in leprosy control. *Expert Rev Vaccines*. 2010;9:209-222.
41. Zimmermann P, Finn A, Curtis N. Does BCG vaccination protect against nontuberculous mycobacterial infection? A systematic review and meta-analysis. *J Infect Dis*. 2018;218:679-687.
42. Netea MG, Quintin J, van der Meer JW. Trained immunity: a memory for innate host defense. *Cell Host Microbe*. 2011;9:355-361.
43. Vierboom MPM, Dijkman K, Sombroek CC et al. Stronger induction of trained immunity by mucosal BCG or MTBVAC vaccination compared to standard intradermal vaccination. *Cell Rep Med*. 2021;2:100185.
44. Lindestam Arlehamn CS, Sette A, Peters B. Lack of evidence for BCG vaccine protection from severe COVID-19. *Proc Natl Acad Sci USA*. 2020;117:25203-25204.
45. Moorlag SJCFM, van Deuren RC, van Werkhoven CH et al. Safety and COVID-19 symptoms in individuals recently vaccinated with BCG: a retrospective cohort study. *Cell Rep Med*. 2020;1:100073.
46. Wright K, Plain K, Purdie A, Saunders BM, de Silva K. Biomarkers for detecting resilience against mycobacterial disease in animals. *Infect Immun*. 2019;88:1–23.
47. Juste RA, Geijo MV, Elguezabal N, Sevilla IA, Alonso-Hearn M, Garrido JM. Paratuberculosis vaccination specific and non-specific effects on cattle lifespan. *Vaccine*. 2021;39:1631-1641.
48. Lockwood DN, Saunderson P. Nerve damage in Leprosy: a continuing challenge for scientists, clinicians and service providers. *Int Health*. 2012;4:77-85.
49. Walsh DS, Portaels F, Meyers WM. Recent advances in leprosy and Buruli ulcer (*Mycobacterium ulcerans* infection). *Curr Opin Infect Dis*. 2010;23:445-455.
50. Phillips RO, Phanzu DM, Beissner M et al. Effectiveness of routine BCG vaccination on buruli ulcer disease: a case-control study in the Democratic Republic of Congo, Ghana and Togo. *PLoS Negl Trop Dis*. 2015;9:e3457.

How to cite this article: Geluk A. All mycobacteria are inventive, but some are more Daedalean than others. *Immunol Rev*. 2021;301:5–9. https://doi.org/10.1111/imr.12970