Host-directed immunotherapy of viral and bacterial infections: past, present and future

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Abstract | The advent of COVID-19 and the persistent threat of infectious diseases such as tuberculosis, malaria, influenza and HIV/AIDS remind us of the marked impact that infections continue to have on public health. Some of the most effective protective measures are vaccines but these have been difficult to develop for some of these infectious diseases even after decades of research. The development of drugs and immunotherapies acting directly against the pathogen can be equally challenging, and such pathogen-directed therapeutics have the potential disadvantage of selecting for resistance. An alternative approach is provided by host-directed therapies, which interfere with host cellular processes required for pathogen survival or replication, or target the host immune response to infection (immunotherapies) to either augment immunity or ameliorate immunopathology. Here, we provide a historical perspective of host-directed immunotherapeutic interventions for viral and bacterial infections and then focus on SARS-CoV-2 and Mycobacterium tuberculosis, two major human pathogens of the current era, to indicate the key lessons learned and discuss candidate immunotherapeutic approaches, with a focus on drugs currently in clinical trials.

Infectious disease immunotherapies are broadly defined as host-directed interventions that modify aspects of intracellular, innate or adaptive immune responses to microbial pathogens to promote the anti-pathogen immune response or to prevent immunopathology. Renewed interest in this area of research is being driven by the growing global burden of drug-resistant pathogens and, with the exception of the ongoing COVID-19 pandemic, by the declining involvement of the pharmaceutical industry in antimicrobial research and development. Although the emergence of drug resistance can be countered in some cases by the use of drug combinations, for example for HIV-1 infection, host-directed immunotherapies should, in principle, remain fully effective against microorganisms with high-level antimicrobial drug resistance. Furthermore, immunotherapies hold promise for those cases where drugs are not available against the pathogen, as is the case for many viral infections such as hepatitis B, or where sterile cure is not achieved by drug treatment such as in people living with HIV-1. Moreover, in the case of tuberculosis (TB), where poorly tolerated antimicrobial drugs need to be delivered for many months, leading to poor compliance, host-directed therapies administered on their own or adjunctively may contribute to shorter and more effective treatment. In contrast to antimicrobial drugs, resistance to host-directed therapies is unlikely to be a major problem, particularly for those that target multiple cellular mechanisms essential for microbial pathogenesis. Thus, the potential of immunotherapies to ameliorate pathology, prevent permanent functional impairment and improve long-term survival from infectious disease should be key to their adoption into clinical practice, spurred on by the striking successes achieved during the past decade with cancer immunotherapies.

Here, we examine the use and promise of host-directed immunotherapies in viral and bacterial infectious disease (key approaches summarized in Box 1), first from a general historical perspective (Fig. 1), then focusing on two major killers in infectious disease — COVID-19, caused by SARS-CoV-2 infection, and TB, caused by Mycobacterium tuberculosis infection — with emphasis on drugs currently in clinical trials, and finally indicating the key issues that need to be addressed in future studies. We do not discuss passive immunotherapies or therapeutic vaccines owing to space considerations.

Historical perspectives

The largest relevant body of historical clinical experience comes from clinical trials of immunotherapies for influenza, viral hepatitis, TB and HIV/AIDS. These studies generally fall into two categories: cytokine-based therapies for augmenting immunity to eradicate infection and strategies for ameliorating pathology to prevent permanent tissue injury. In the past 20 years, animal studies and clinical trials have helped to identify circumstances in which cytokine therapy can be beneficial and have also contributed to current thinking regarding optimal timing of these interventions (Fig. 1). Similarly, studies of corticosteroids, showing both benefits and limitations, have guided subsequent research targeting specific pathogenic mechanisms responsible for tissue destruction.

Cytokine-based strategies to augment immunity. Historically, most immunotherapeutic interventions to improve antiviral immunity have been applied in the setting of chronic infections such as viral hepatitis and HIV/AIDS. Acute viral infections may leave only a short time-window for enhancing the immune response; the practical challenges for rapid diagnosis and therapeutic intervention have historically limited clinical research in this setting, although these now seem to have substantial promise.

An early example of the development of cytokine-based therapies to augment the host antiviral response was the use of type I interferons (Fig. 1). Although the first studies demonstrating their ability to induce an antiviral state in cells were carried out in the late 1950s, randomized controlled trials of the use of interferons to treat viral infections...
Box 1 | Key approaches to host-directed immunotherapy for infectious disease

**Augmenting immunity**
- Recombinant cytokines (for example, interferon treatment of chronic hepatitis C)
- Cytokine administration by RNA or DNA application (experimental)
- Macrophage-targeting strategies (for example, tyrosine kinase inhibitors and mechanistic target of rapamycin (mTOR) inhibitors in tuberculosis)
- Cell-based immunotherapies (for example, CAR T cells in HIV-1; not discussed here)
- Passive infusion of anti-pathogen antibodies (used for COVID-19 and respiratory syncytial virus infection; for example; not discussed here)
- Vaccination (all infectious diseases; not discussed here)

**Ameliorating immunopathology**
- Anti-cytokine antibodies (for example, IL-6 receptor blockade in COVID-19; anti-tumour necrosis factor treatment of paradoxical reactions to antitubercular therapy in tuberculous meningitis)
- Cytokine modulators (for example, Janus kinase (JAK) inhibitors in COVID-19; phosphodiesterase inhibitors such as CC-11050 in tuberculosis; high-dose corticosteroids)
- DNAse treatment or elastase inhibitors for removal of neutrophil extracellular traps (COVID-19)
- Complement inhibitors (COVID-19)
- Anticoagulants (COVID-19)
- Anti-oxidants (for example, N-acetylcysteine in tuberculosis)
- Anti-inflammatory drugs (for example, statins and cyclooxygenase 2 inhibitors in tuberculosis)

awaited their production to pharmaceutical standards in the late 1980s. These trials ultimately showed that polyethylene glycol (PEG)-conjugated IFNa (to increase plasma clearance at 1 or 2 months after treatment)21. However, the historical experience indicates that interferons may be poorly tolerated, including flu-like symptoms, bone marrow depression, neuropsychiatric disorders and autoimmune syndromes. More recently, IFNa has also been tested with some success in HCV infection7, but with the introduction during the past decade of antiviral regimens for HCV7, including oral inhibitors of NS3/4A, NS5A and NS5B, the era of interferon-based treatment of this virus was brought to a close7.

Furthermore, interferon administration has not been successful as a therapeutic for other chronic viral infections such as hepatitis B virus (HBV) and HIV/AIDS8,9. Indeed, in the case of HIV/AIDS, host-derived type I interferons may cause pathology in the chronic phase10,11. Similarly, influenza virus infections are not routinely treated with interferons. Although there is general agreement that prophylaxis and early treatment with type I or type III interferons are effective against influenza, preclinical studies show that the therapeutic treatment window is small in terms of dosage and timing, particularly for type I interferons12,13. Treatment later during severe influenza may lead to enhanced inflammation and impaired epithelial repair14,15. These early conclusions regarding the feasibility of interferon-based immunotherapies have recently been reiterated in the case of COVID-19, for which therapeutic success also seems to depend strongly on the timing of administration. Thus, the historical experience indicates that interferons may be an effective treatment for viral infections if given early, but that clinical administration late in persistent or chronic viral infection is successful only in some cases and may be poorly tolerated.

Much has also been learnt from clinical trials examining the therapeutic potential of IL-2, which is required for T cell proliferation, in individuals with HIV-1 infection (FIG. 1). Twenty-five therapeutic trials of IL-2 in HIV-1 infection were published between 1998 and 2009, including six studies with a total of 6,565 participants reporting mortality as an end point. A meta-analysis of these studies concluded that periodic IL-2 infusion combined with antiretroviral therapy (ART) increased the CD4+ T cell count but simultaneously increased the risk of high-grade adverse events (including gastrointestinal disorders, psychiatric disorders and deep venous thrombosis) without reducing mortality or the incidence of opportunistic infection16. It has been speculated that the absence of protection was due to the expansion of regulatory (FOXP3+) T cells17. The studies also prompted a reassessment of CD4+ T cell enumeration for measuring the success of immunotherapeutic drug development in HIV/AIDS.

Pro-inflammatory cytokines, such as IL-2 and IFNγ, have also been studied for their ability to increase immunity to mycobacterial infection often together with antibacterial drug therapy, mostly with limited success18. The proliferation of M. tuberculosis-specific T cells producing IFNγ depends on local production of IL-2, and adjunctive therapies using IL-2 to augment the immune response in TB were first considered in small trials conducted in the late 1990s and early 2000s19. However, a randomized, placebo-controlled trial of adjunctive recombinant IL-2 immunotherapy in patients with TB reported in 2003 failed to show statistically significant improvement in bacterial clearance at 1 or 2 months after treatment20. The most likely explanation is that IL-2 supports the proliferation not only of IFNγ-producing effector T cells but also of regulatory T cells that dampen the protective response21 although, in one preclinical study in non-human primates, some protection against TB pathology was observed despite the dual expansion of both T cell subsets in response to treatment with the cytokine22.

IFNγ is essential for the full activation of macrophages, which is crucial for controlling M. tuberculosis growth23,24. In patients with Mendelian susceptibility to mycobacterial disease, which is associated with IFNγ deficiency resulting from IL-12Rβ1 mutation, adjunctive treatment with IFNγ and antibiotics has proven efficacious25. These observations led to several therapeutic trials of adjunctive IFNγ in patients without apparent defects in interferon production or action, with the goals of accelerating eradication of M. tuberculosis infection and preventing relapse. However, the initial positive findings of safety and efficacy for IFNγ in a 1997 pilot study26 failed to be confirmed by larger, more definitive trials (summarized in REF.26). The most rigorous trial of IFNγ therapy in TB compared the use of aerosolized IFNγ to placebo in 80 patients with multidrug-resistant TB, all of whom also received therapy with second-line drugs. The study was halted in 2003 because of a trend towards increased mortality in the experimental arm, without evidence of clinical or microbiological benefit. The study findings were never published but appear...
in an online supplement to an inconclusive subsequent trial. It has since been reported that most IFNγ-induced genes are already maximally upregulated in the lung in TB and that aerosolized IFNγ therefore has little additional effect. Thus, two historical lessons are apparent regarding immunotherapy of viral or mycobacterial infections. In patients with chronic infections who do not have distinct defects in cytokine production or signalling, therapy with interferons or IL-2 risks causing immunopathology with mixed microbiological benefit. By contrast, at least in preclinical models, a potential benefit was demonstrated for cytokine treatment of early infection. The pleiotropic effects of these potent immunostimulators and insufficient knowledge of how to limit their effects in terms of timing, space and target cells are likely to explain the mixed success of these approaches in the clinic. Future developments should factor in the multitude and dynamic nature of cytokine effects and find more precise ways to target these.

**Strategies to ameliorate immunopathology.** Immune activation aimed at pathogen elimination can cause significant collateral tissue damage in acute infection. For example, in both HCV and HBV infection, the immune response can lead to liver cirrhosis, hepatic failure and malignancy. In pulmonary TB, IFNγ production contributes to lung necrosis, cavitation, fibrosis and bronchiectasis, and studies in experimental models show that high-level induction of type I interferon-inducible genes can lead to myeloid cell-mediated tissue necrosis and release of neutrophil extracellular traps (NETs) in TB. In humans, these permanent effects impair lung function and reduce long-term survival despite microbiological cure.

Historically, corticosteroids have been the most successful therapeutics for the treatment of infection-related immunopathology. Corticosteroids have dose-dependent anti-inflammatory and immunosuppressive effects on nearly all immune cells, reducing the production of pro-inflammatory cytokines and inhibiting cellular microbicidal responses. Although corticosteroids can increase the risk of acquiring many bacterial, fungal and viral infections, including TB, multiple randomized controlled trials of the use of adjunctive corticosteroids together with drug therapies against *M. tuberculosis* were started in the 1950s. A systematic review in 1997 and a formal meta-analysis in 2013 concluded that corticosteroids conferred a survival advantage in patients with central nervous system and pericardial TB, and that they hastened the resolution of pulmonary abnormalities but did not affect end-of-treatment outcomes. More recent studies indicate that corticosteroids are also effective in treating or preventing immune reconstitution inflammatory syndrome in patients with both HIV/AIDS and TB, which most often manifests as a clinical worsening shortly after patients start combined TB therapy and ART. Based

**Timeline of key developments in host-directed immunotherapeutic interventions for infectious disease.** Indicated are the time of discovery or first description for corticosteroids, interferons, IL-2, IL-6 receptor antagonists and Janus kinase (JAK) inhibitors, together with their successful uses in humans as immunotherapies for the indicated non-infectious and infectious diseases. Asterisks indicate that therapies that were ultimately adopted into routine clinical use are also effective in treating or preventing immune reconstitution inflammatory syndrome in patients with both HIV/AIDS and TB, which most often manifests as a clinical worsening shortly after patients start combined TB therapy and ART. Based

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**Fig. 1** | **Timeline of key developments in host-directed immunotherapeutic interventions for infectious disease.** Indicated are the time of discovery or first description for corticosteroids, interferons, IL-2, IL-6 receptor antagonists and Janus kinase (JAK) inhibitors, together with their successful uses in humans as immunotherapies for the indicated non-infectious and infectious diseases. Asterisks indicate that therapies that were ultimately adopted into routine clinical use are also effective in treating or preventing immune reconstitution inflammatory syndrome in patients with both HIV/AIDS and TB, which most often manifests as a clinical worsening shortly after patients start combined TB therapy and ART. Based
on a meta-regression analysis of 12 trials carried out in 2014 (REFS 51–53), high-dose adjunctive corticosteroids also seem to accelerate the conversion of sputum culture from positive to negative in patients with TB. This apparent indirect antimicrobial effect of high-dose corticosteroids has been attributed to impaired integrity of granulomas, with resulting improved lesional penetration of anti-TB drugs. This process also likely allows a return of aerobic metabolism and replication to previously semi-dormant bacilli owing to the return of oxygen and nutrients to central regions of the granuloma, which increases their susceptibility to anti-TB drugs. In addition, multiple randomized controlled trials carried out in the 1990s found that early adjunctive treatment with corticosteroids substantially improves oxygenation and survival in patients with pneumonia caused by the fungus Pneumocystis jirovecii, particularly in patients with HIV/AIDS who are not yet on ART, in other words, those with the most profound immune dysregulation54–56.

Severe influenza is also characterized by cytokine excess57 but, in contrast to TB, retrospective studies of the use of corticosteroids in severe influenza have shown no benefit58. Indeed, two meta-analyses of mainly retrospective series found that they increased mortality risk59,60. As severe influenza is often accompanied by secondary bacterial infections, it is possible that the deleterious effects of corticosteroids on mucosal defences account for their increased mortality risk58. Agents with greater specificity that are currently under investigation to control the hyperinflammatory response in severe influenza include non-steroidal anti-inflammatory drugs, statins, macrolides (antibiotics with additional anti-inflammatory effects), antibodies to complement factor C5a and N-acetylcysteine (a non-prescription medicine used to prevent death owing to hepatic necrosis after paracetamol acetaminophen poisoning) (reviewed in REF 61).

In summary, historical studies have shown a potentially important role for corticosteroids in reducing infectious immunopathology although, in some circumstances, more specific anti-inflammatory adjunctive treatments are warranted. At the same time, the use of cytokines to augment immunity during chronic infection has been limited by their exacerbation of immunopathology; immune induction seemed to be most promising during early viral infection although its use was limited by practical measures of prompt detection and intervention. How can the lessons learnt from these historical investigations be applied to current approaches? We discuss these questions in the context of COVID-19 and TB, currently two of the most deadly viral and bacterial diseases, respectively.

**Current approaches to COVID-19**

The extraordinary global impact of COVID-19 has placed it at the focus of extensive original research and critical review62–64 and provides an opportunity to examine current thinking regarding the immunotherapeutic approaches that have evolved across a wide spectrum of infectious and non-infectious diseases. The current view of SARS-CoV-2 pathogenesis in humans is that it can be divided into two phases: an early phase characterized by high-level viral replication and reduced or absent immune responsiveness, and a second phase in which this balance is reversed. Both phases can be targeted by immunotherapeutic strategies — to augment immunity in the first phase or reduce immunopathology in the second (FIG. 2). Two major lessons from the historic experiences outlined above were rapidly translated into treatment design: first, that the therapeutic window for antiviral immune intervention may be small and early; and second, that cytokines can be harmful as well as beneficial and, therefore, that cytokine responses might need to be inhibited in order to reduce immunopathology.

**Interferon-based strategies to augment immunity.** Building on the historical knowledge of the antiviral effect of interferons in HCV and influenza, and based on retrospective studies showing that type I interferon is essential for protection against SARS-CoV-2 (REFS 65,66), the therapeutic use of type I interferon in early SARS-CoV-2 infection was rapidly proposed in the early stages of the ongoing pandemic67 although other studies showed that interferon levels strongly correlate with COVID-19 disease severity68–71. Thus, the timing of the interferon response seems to be a crucial factor69 as has been shown for influenza and, more recently, in preclinical studies of severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and COVID-19 (REFS 65,66). A retrospective multicohort study published early in the pandemic suggested that the likelihood of survival was increased by early IFNa treatment (within 5 days of hospitalization), whereas it was reduced if interferon therapy was started later72, findings that are reminiscent of earlier data obtained from patients with MERS73. Several prospective studies of hospitalized patients with COVID-19 followed, showing that the effects of interferon therapy relate to the timing of intervention and severity of illness. In the WHO Solidarity trial, in which hospitalized patients at different stages of disease were randomly assigned to receive subcutaneous IFNβ1a or other repurposed drugs, IFNβ1a tended to slightly increase mortality risk in patients requiring supplemental oxygen therapy compared with controls, suggesting that these patients were too advanced in the course of disease to benefit from interferon treatment74. However, a small randomized controlled trial in a similar population of hospitalized patients with COVID-19 found that treatment with aerosolized IFNβ1a led to more rapid recovery compared with placebo75. In another randomized controlled trial of 127 hospitalized patients, only 13% of whom required supplemental oxygen, the addition of IFNβ1b plus ribavirin to lopinavir–ritonavir ART yielded a shorter time to resolution of symptoms76. Lastly, in a trial of 60 outpatients with COVID-19, none of whom required supplemental oxygen, a single dose of PEG–IFNa increased the likelihood of having undetectable virus by day 7 of infection77. Together with results from hamster and mouse infection models78,79, these studies suggested greater clinical and virological benefit when interferon treatment is started early in the course of SARS-CoV-2 infection.

The assumption is that, in early treatment, the antiviral effects of interferons contribute to protection, whereas later in infection, interferon treatment may enhance immunopathology47,71 (FIG. 3). The cellular specificity of interferon receptors may also be a significant factor. The receptor for type I interferon is ubiquitous, allowing for effects on immune cells to drive inflammation and immunopathology, particularly late in infection75. By contrast, the receptor for type III interferon is mainly expressed on epithelial cells; IFNA therefore lacks some of the immunopathogenic potential of type I interferons and has been proposed as the interferon treatment of choice80. Although it is generally less pro-inflammatory, IFNβ impaired epithelial repair when administered late in respiratory infection, which suggests that its use should also be restricted to early intervention in COVID-19 (REFS 81,82). Further trials using subtypes of the IFNα, IFNβ or IFNλ families are under way to bring more clarity to this complex issue83.
Strategies to ameliorate immunopathology.

Corticosteroid treatment leads to clear improvement in seriously ill patients with COVID-19 (REF 78) (Fig. 1). In one trial, corticosteroids reduced the risk of death from 41% to 29% in patients receiving invasive mechanical ventilation and from 26% to 23% in those receiving oxygen without mechanical ventilation 79. No benefit was found for patients not receiving respiratory support at randomization. The basis for this distinct difference from influenza — in which corticosteroids were ineffective at preventing immunopathology and were harmful in patients with severe disease — is uncertain but may relate to the markedly lower frequency of secondary bacterial infections in COVID-19, which in turn may be linked to SARS-CoV-2 inducing high levels of IL-6, a cytokine that has strong pro-inflammatory but also potent antibacterial effects.

One of the defining features of severe COVID-19 is a high-level cytokine response that contributes to immunopathology, although the absolute cytokine levels are only a fraction of those in other potentially lethal syndromes unrelated to COVID-19 (REF 80). How to control the virus-induced hyperinflammatory response has remained an open question despite ongoing trials in severe influenza, and the issue is now receiving increased attention as a result of the COVID-19 pandemic. Several anti-cytokine approaches are currently being studied. In particular, IL-6 was targeted early in the pandemic based on the use of anti-IL-6 therapy in immune-mediated inflammatory diseases, such as rheumatoid arthritis 81, and on the successful therapy experience in hyperinflammatory complications associated with CAR T cell therapy 82 (Fig. 1). Two classes of anti-IL-6 reagents have been studied, targeting either the IL-6 receptor (tocilizumab and sarilumab) or IL-6 itself (siltuximab). Tocilizumab has had the most extensive evaluation in COVID-19. Although an early study (COVACTA) found no benefit 83, two others (RECOVERY and REMAP-CAP) found that IL-6 receptor blockade improved the clinical outcomes of COVID-19, including progression to invasive mechanical ventilation and death 84–86. The contrary findings of these studies may be due to the concomitant use of corticosteroids, which were given more often and earlier.

**Fig. 2 | Host-directed immunotherapeutic intervention points for severe COVID-19.** If the initial interferon and inflammatory responses are insufficient to control SARS-CoV-2 infection, the inflammatory cascade may persist and become hyperactivated. This can lead to monocyte and neutrophil infiltration into the lung, high local and systemic levels of cytokines, tissue damage in the lung, formation of neutrophil extracellular traps (NETosis), complement hyperactivation, coagulation, and the formation of microthrombi. Immunotherapeutic interventions aim to improve virus control early in infection (indicated in green) or to limit immune-mediated tissue damage owing to uncontrolled inflammation (indicated in red). JAK, Janus kinase.
in RECOVERY and REMAP-CAP. It seems that the two treatments target complementary inflammatory pathways and that the benefit of IL-6 blockade becomes more evident when corticosteroids are co-administered. Therapies that block signalling by granulocyte–macrophage colony stimulating factor (GM-CSF), IL-1 or other cytokines are also being tested for COVID-19. Early reports of treatment with the IL-1 receptor antagonist anakinra and with antibodies to GM-CSF indicate improved outcomes but larger-scale trials are necessary to demonstrate this conclusively. As all of these cytokines are potent immunomodulators with pleiotropic functions, understanding their effects in severe COVID-19 and learning from this which patient groups may benefit the most from cytokine-directed therapies are of crucial importance. For example, GM-CSF has been shown to improve the outcome of influenza infection in animal models by improving alveolar epithelial repair and, therefore, clinical trials have been carried out either adding or blocking GM-CSF.

Cytokine-mediated signalling can alternatively be blocked further downstream by pharmacological inhibition. Inhibitors of the Janus kinases (JAKs) that signal downstream of many cytokine receptors were originally developed for use in patients with chronic inflammatory conditions such as rheumatoid arthritis and inflammatory bowel diseases (FIG. 1). As orally bioavailable small molecules, they presented an attractive alternative to large molecule therapeutics requiring injection such as anti-tumour necrosis factor (TNF) agents. The combination of baricitinib (a JAK inhibitor) plus remdesivir (a direct antiviral) has been shown to shorten recovery time and reduce mortality in patients with COVID-19 compared with remdesivir alone. A similar trial of the JAK inhibitor tofacitinib in patients with COVID-19 found improved survival despite a relatively small sample size. How much of this effect is due to the blockade of multiple cytokine signalling pathways or to apparent direct antiviral activity is not yet clear. For practical reasons, these oral therapies are more likely to be suitable for widespread use than intravenous application of monoclonal antibodies and should therefore continue to be investigated as a priority. Similarly, two small studies of the serotonin reuptake inhibitor fluvoxamine found that it prevented clinical deterioration in patients with early COVID-19 (REFS 96, 97). Fluvoxamine dampens pro-inflammatory cytokine production, but the relationship of this effect to the clinical findings in COVID-19 is uncertain.

**Novel strategies for immunotherapy.** Excessive coagulation and thrombosis are found together with hyperinflammation in severe COVID-19 (REF 101). Endothelial dysfunction and damage, coagulopathy, and excessive complement activation combine with inflammation to cause thrombotic complications that likely contribute to the acute respiratory distress syndrome. Although...
the above-mentioned anti-inflammatory interventions can contribute to alleviating this pathogenic process, additional therapies, including antithrombotic drugs, such as heparin, garadacimab, nafamost mesylate and tissue-type plasminogen activator, and inhibitors of the complement cascade, such as the C5 inhibitors eculizumab and ravulizumab and the inhibitor of C3 cleavage AMY-101, may synergize with anti-inflammatory treatment.

Another unmet therapeutic need — with some analogies to post-TB lung disease, as discussed below — is for ‘Long COVID’, which is characterized by persistent fatigue, anhedonia, muscle weakness, concentration deficits, anxiety or even depression, myalgia and arthralgia. As the underlying mechanisms of Long COVID are unclear, no immunotherapeutic strategies have been developed so far, but persistent inflammation and the prothrombotic state often found in these patients will likely require anti-inflammatory and antithrombotic therapy similar to that described above for acute COVID-19. Neutrophil activation and release of NETs (NETosis) have also been observed in patients with COVID-19, and several clinical trials are under way (among others, ClinicalTrials.gov: NCT04402944, NCT04355364, NCT044432987, NCT04359654, NCT04445285 and NCT04402970) to confirm initial observations of the beneficial effects of dissolving NETs by treatment with DNase.

In summary, greater success has been achieved so far in ameliorating the immunopathology of severe COVID-19 using cytokine and signalling pathway inhibitors than in boosting immunity as the latter must occur early during infection, when the pathogen burden is low, to be successful. The same themes are evident in studies of TB as described below.

**Current approaches to TB**

As is the case for COVID-19, it is convenient to categorize host-directed immunotherapies for TB on the basis of their original intended use: either to ameliorate immunopathology or to augment immune control of the bacteria, although therapeutic interventions affecting one of these processes may have unanticipated effects on the other (Fig. 4). With few exceptions, the agents that have entered testing so far are re-purposed drugs that were originally approved for other wide-ranging indications, most of which are unrelated to the treatment of infectious disease. This strategy reflects the economic reality that TB case numbers in North America and Europe are insufficient to support the costs of development and licensing of new drugs for TB. In most clinical trials, these host-directed therapies are administered adjunctly with standard antibiotics targeting *M. tuberculosis*, either for rifampin-resistant or rifampin-resistant infection. In some cases, alternative antibiotics, such as rifabutin, have been used to avoid deleterious pharmacokinetic interactions between drugs.

**Strategies to modulate the effects of interferons.** The role of interferon signalling in *M. tuberculosis* infection and disease is complex. As in COVID-19, interferon is a key element in the early protective antimycobacterial response but, in the case of TB, type II interferon (IFNy) rather than type I or type III interferons seems to have a dominant role. Unlike in COVID-19, immune success in TB is most often non-sterilizing, resulting in containment of a latent infection rather than eradication of *M. tuberculosis*, and active tuberculosis most often results from progression of latent infection. In such cases, interferon signalling is detrimental, promoting the formation of lung cavities in which bacilli replicate to high numbers, thereby facilitating aerosol transmission. Indeed, the lack of genetic diversity in major *M. tuberculosis* antigens has been interpreted as evidence of an evolutionary strategy to provoke a host immune response. Patients with TB and advanced AIDS, in whom interferon...
responses are reduced or absent, often lack radiographic evidence of lung disease, have reduced numbers of bacilli in sputum and are less likely to transmit M. tuberculosis infection.37,118

Additional data from patients and experimental infection models also show that type I interferon signalling has a major role in TB pathogenesis and exacerbation53–56,116–125. For example, antibody to type I interferon receptor (IFNAR1) blocks disease progression in infected TB-susceptible mice, even when applied 7 days after infection14. However, in genetically resistant mice infected with a lab strain of M. tuberculosis, an absence of IFNα signalling resulted in either an increased or unchanged bacterial load54,122,126,127, which highlights the complexities of interferon responses in different host genetic backgrounds16 and, possibly, the pleiotropic effects of interferons in the immune system. Human data support this complexity, also documenting situations in which type I interferon seems to be protective rather than disease promoting. For example, several clinical case reports have described improved clinical symptoms and decreased bacterial burden after co-administration of IFNα together with antimycobacterial chemotherapy. It is imperative to better understand the circumstances in which type I interferons induce exacerbation of TB rather than protection from disease and the mechanisms underlying these effects. Several mechanisms have been proposed for the pathogenic effects, including pulmonary recruitment of a pathogen-permissive monocyte and/or macrophage population based on findings in a model of TB exacerbated by intranasal treatment with poly(I:C)15, induction of the immunoregulatory cytokine IL-10, and suppression of IL-12 [REFS16,128] (a major inducer of IFNγ synthesis) and/or IL-1 production by myeloid subsets37,118 (FIG. 3). IL-1 was reported to promote host resistance and mycobacterial control through the induction of eicosanoids that limit excessive type I interferon production (discussed later)15. Type I interferon signalling was also shown to trigger immunopathology in TB-susceptible mice by modulating lung phagocyte dynamics, with increased migration of inflammatory monocytes and neutrophils to the lung, and increased death of alveolar macrophages15. In TB-susceptible mice, type I interferon induces neutrophil-mediated lung inflammation and NETosis and promotes both bacterial growth and disease severity17, and blockade of IFNAR1 signalling or depletion of neutrophils in these mice abrogated lung pathology18,19. More recently, a role for autocrine or paracrine signalling by macrophage-derived type I interferon in the death of M. tuberculosis-infected macrophages in vitro has also been shown20.

Further knowledge of the pathways of type I interferon-driven lung pathology and disease in vivo may lead to the discovery of small-molecule inhibitors amenable for the development of affordable host-directed therapies20. In this regard, the JAK inhibitor tofacitinib has been studied in mouse models of TB. During early or latent M. tuberculosis infection, tofacitinib reduces host containment of infection and promotes bacterial replication in the lungs21. During late or active infection, tofacitinib reduces the production of pro-inflammatory mediators and enhances the effects of antmycobacterial chemotherapy21. These observations of a two-phase response, in which interferons might switch from augmenting immunity to mediating immunopathology, are very similar to those in SARS-CoV-2 infection.

**Novel strategies to ameliorate immunopathology.** Oxidative stress is a major sequela of M. tuberculosis infection that contributes to necrotic tissue damage as well as bacterial spread, in part through lipid peroxidation-induced damage to host cell membranes. As such, it is a logical target for host-directed therapy to ameliorate immunopathology. N-acetylcysteine, which functions by restoring cellular levels of the reduced form of glutathione, a major anti-oxidant that protects cells from oxidative damage, has been shown to reduce lung pathology and M. tuberculosis bacterial burden in several animal model studies and to inhibit tolerance to the antibiotic isoniazid in vitro31. It is currently being tested in three clinical trials for its effects in patients with TB [TABLE 1]. In separate work, ferrostatin, a radical-trapping anti-oxidant that inhibits lipid peroxidation-induced membrane damage and cell death, has been shown to reduce pulmonary necrosis and bacterial burden in mice infected with M. tuberculosis32.

Eicosanoids, which are lipid mediators derived from the catabolism of arachidonic acid, have been shown in vivo and in vitro to have an important role in regulating M. tuberculosis infection; products of the cyclooxygenase pathway (for example, prostaglandins) limit acute infection and disease, whereas products of the lipoxygenase pathway (for example, lipoxins) promote infection and disease. The pathogenic effects of type I interferon on M. tuberculosis infection seem to be caused, in part, by modulation of these pathways, and experimental administration of either prostaglandin E2 or a clinically approved 5-lipoxygenase inhibitor protected mice against the disease-promoting effects of type I interferon33. Other studies, by contrast, have noted that prostaglandins have disease-promoting effects in late infection, which suggests that cyclooxygenase 2 inhibitors, such as aspirin, might be effective in TB therapy. Trials testing the effects of aspirin on tuberculosis meningitis in adults have yielded encouraging results but the benefit in terms of preventing strokes may be due to anti-platelet effects33,134. One trial of aspirin in children with tuberculosis meningitis showed no benefit33. Additional clinical studies using newer-generation, more-selective cyclooxygenase 2 inhibitors for both drug-sensitive and drug-resistant M. tuberculosis strains are in progress [TABLE 1].

Another class of anti-inflammatory drugs currently undergoing clinical trials in patients with TB are the statins [TABLE 1]. These HMG-CoA reductase inhibitors, which are widely used to reduce the risk of cardiovascular disease, function by lowering lipid levels but also have immunomodulatory activity. In the mouse model of TB, statins accelerate the clearance of mycobacteria and facilitate shortening of treatment136,137. Interestingly, statins can also promote bacterial control by reducing macrophage lipids that promote the growth of M. tuberculosis and by enhancing phagosome–lysosome fusion.

Even after mycobacterial cure, most patients with TB are left with bronchiectasis and fibrosis, permanent conditions that impair lung function and have profound long-term health consequences associated with excess mortality risk138–142. Addressing these long-term effects has become a major focus for studies of adjunctive host-directed therapies for TB. Phosphodiesterase inhibitors can inhibit pro-inflammatory cytokine production by preventing the degradation of cAMP. Several such inhibitors have shown promise in animal models of TB. Perhaps the best studied is CC-11050, which, when used adjunctively with the antibiotic isoniazid in mice and rabbits, ameliorated pulmonary pathology and decreased M. tuberculosis bacterial load in the lung to a greater extent than isoniazid alone140,141. In patients given CC-11050 as an adjunct for the first 112 days of rifabutin-substituted standard TB treatment, the results suggested that CC-11050 may interrupt mechanisms responsible for the
irreversible loss of lung function\textsuperscript{145}. A trial of CC-11050 in patients with rifampin-resistant TB is currently under way\textsuperscript{139} (Table 1).

**Strategies to augment immunity**: The induction of phagosome acidification and autophagy in *M. tuberculosis*-infected macrophages are important effector mechanisms of host resistance to infection and, accordingly, have become major targets of host-directed immunotherapeutic approaches for this pathogen. Unlike strategies to augment immunity in COVID-19, none of the agents for TB is a cytokine-based therapy. Tyrosine kinase inhibitors are one class of drugs that promote the macrophage phagocytic response. For example, in preclinical studies in *M. tuberculosis*-infected macrophages and mice, low doses of the tyrosine kinase inhibitor imatinib (an anticancer agent) were shown to reduce mycobacterial viability by promoting phagosome–lysosome fusion as well as increasing myelopoiesis\textsuperscript{146,147}. This approach is currently being assessed in a phase I clinical trial (Table 1). Inhibitors of mechanistic target of rapamycin (mTOR) are a second group of agents thought to promote macrophage-mediated control of *M. tuberculosis*, in this case through the induction of autophagy\textsuperscript{111}. In addition, mTOR inhibitors have been described to have anti-inflammatory and anti-fibrotic effects that could have a role in reducing immunopathology\textsuperscript{164,165}. In a recent trial, the mTOR inhibitor everolimus had similar effects to CC-11050 on the recovery of lung function in patients with TB\textsuperscript{146}. The AMPK activator metformin, which also inhibits mTOR, has been shown to promote macrophage control of *M. tuberculosis*, an effect associated with the induction of autophagy and reactive oxygen species, and to reduce pulmonary immune pathology, accelerate the resolution of lung fibrosis and enhance the efficacy of conventional antimicrobials in *M. tuberculosis*-infected mice\textsuperscript{150}. Multiple studies in patients with diabetes found that metformin reduced the risk of TB compared with other diabetes treatments\textsuperscript{151–153} and improved outcomes in persons with diabetes and TB\textsuperscript{154,155,156}. These findings do not seem to be due to superior glucose control. One recently reported phase II trial of metformin in TB found enhanced resolution of lung cavities but no effect on sputum culture conversion\textsuperscript{156}. Other trials of metformin in patients with TB and without diabetes are presently under way (Table 1).

Given the markedly increased risk of TB caused by loss of CD4\textsuperscript{+} T cells\textsuperscript{157}, enhancing T cell function would seem to be an obvious approach for host-directed therapy of TB. However, several studies involving PD1 blockade or deficiency in mice and rhesus monkeys and in a 3D in vitro granuloma model concur that checkpoint inhibition through PD1 markedly increases rather than decreases TB susceptibility\textsuperscript{158–160}. These findings are consistent with a growing number of case reports of TB reactivation in patients with cancer who are treated with checkpoint inhibitors\textsuperscript{158–160}. In experimental models, the exacerbation of TB resulting from PD1 blockade was associated with increased granulomatous inflammation as well as increased production of TNF and IFNγ and increased caspase 1 activity. Similarly, absence of cyclophilin in T cells, which directly increases T cell activity independently of checkpoint receptors, did not reduce bacterial burden but increased mortality in mouse models of TB\textsuperscript{161}.

Together, these observations highlight the potential negative consequences of interventions designed to augment T cell function in TB. Nonetheless, they should not discourage the investigation of other checkpoint-inhibition strategies that might have a therapeutic rather than a disease-promoting outcome.

**The future of infection immunotherapy**

Several themes have emerged from past and recent studies of infection immunotherapy. First, across a wide range of infecting

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**Table 1 | Ongoing clinical trials of host-directed immunotherapies for tuberculosis**

| Immunotherapy | Mechanism | Trial acronym | Patient population | Main end points | Clinical trial number |
|---------------|-----------|---------------|-------------------|-----------------|----------------------|
| CC-11050      | Phosphodiesterase inhibitor; inhibits cytokine production | DRTB-HDT | Rifampin-resistant TB | Sputum culture conversion and lung function | Horizon 2020: project 847465 |
| N-acetylcysteine (NAC) | Restores reduced form of glutathione; anti-oxidant | NAC-TB sub-study of TB-SEQUEL | Rifampin-susceptible TB | Sputum culture conversion and lung function | ClinicalTrials.gov: NCT03702738 |
| | NAC-TB | Rifampin-susceptible TB | Durable cure, drug-induced liver injury, lung function | EDCTP: RIA2019AMR-2647 |
| | NAC-Trial | Rifampin-resistant TB | Adverse drug reactions | PACTR: 202007736854169 |
| Metformin | AMPK activator; inhibits mTOR | METHOD | HIV-1-infected plus rifampin-susceptible TB | Sputum culture conversion and lung function | ClinicalTrials.gov: NCT04930744 |
| | DRTB-HDT | Rifampin-resistant TB | Sputum culture conversion and lung function | Horizon 2020: project 847465 |
| Statins | Lipid-lowering and anti-inflammatory | STAT-TB | Rifampin-susceptible TB | Safety and pharmacokinetics | ClinicalTrials.gov: NCT03828177 |
| | ATOR-TUB | Rifampin-susceptible TB | Sputum culture conversion | ClinicalTrials.gov: NCT04721795 |
| | Statin-TB | Post-TB treatment | PET-CT glycolytic activity | ClinicalTrials.gov: NCT04147286 |
| Imatinib | Tyrosine kinase inhibitor | IMPACT-TB | Healthy volunteers | Pharmacokinetics, myeloid cell numbers, whole blood mycobacterial activity | ClinicalTrials.gov: NCT03891901 |
| Cyclooxygenase inhibitors | Inhibit prostaglandin synthesis | SMA-TB | Adult TB | Composite symptom score | ClinicalTrials.gov: NCT04575519 |

EDCTP: European & Developing Countries Clinical Trials Partnership; mTOR, mechanistic target of rapamycin; PACTR, Pan-African Clinical Trials Registry; PET-CT, positron emission tomography-computed tomography; TB, tuberculosis.
organisms, there has been greater success in reducing immunopathology than in boosting immunity. This, in part, is a reflection of the importance of the timing of intervention as the ‘early’ phase of an acute infection, where enhancing anti-pathogen responses holds promise, may be over by the time of symptom onset. There may, however, be unexplored opportunities for early cytokine therapy of latent TB infection, for example, in household contacts of TB index cases. The potential advantage of using immunotherapy to augment immunity in this setting is that knowledge of microbial drug susceptibility would not be required; in addition, the low pathogen burden may decrease the risk of inducing immunopathology.

Factors other than cytokines have become recognized as important in modulating the host response. It has also become apparent that there is sizeable individual-to-individual variation in the response to pathogens such as *M. tuberculosis* and SARS-CoV-2. Therefore, the success of any host-directed therapy may depend heavily on both knowledge of disease as well as baseline parameters for each patient receiving treatment. Endotypes, which are defined as distinct molecular profiles based on metabolism, epigenetics, transcription or immune function, have been proposed to guide the application of personalized immunotherapies. However, specific endotypes remain to be defined for most infections, even for those with ostensibly similar clinical phenotypes. A particular challenge exists for diseases of global public health impact such as TB and now COVID-19, for which individualized therapies are considered impractical. Nevertheless, it will nonetheless will require that public health programs begin to include post-TB morbidity and mortality in estimates of the benefit of new therapies. The remarkable success of vaccines against tuberculosis and SARS-CoV-2 is also poorly understood. The wide diversity of outcomes has long been known for influenza but is now particularly apparent for SARS-CoV-2 infection as the virus spreads through an immunologically naive population.

Improved immunotherapies for COVID-19 will depend on a better understanding of the mechanisms of immunopathology and of the highly dynamic nature of the course of infection. Interventions with greater specificity may be possible, for example preserving the beneficial effects of IL-6 on epithelial repair and B cell responses while minimizing its pro-inflammatory signals. As several members of the IL-6 family have similar effects on immune responses, inhibition of additional family members, such as Oncostatin M, which has been implicated in driving excessive inflammation in COVID-19, or specific targeting of the receptor chain gp130 that is used by most IL-6 family members may be considered. Similarly, the mixed effects of a broad-range JAK inhibitor, such as baricitinib, may be improved by more specific inhibition of TYK2, which blocks signals downstream of type I interferon receptor chain gp130 that is used by most IL-6 family members may be considered. Thus, the invention field of immunometabolism may reveal new insights and approaches to achieve this dual therapeutic aim.

Finally, a compelling cost–benefit analysis must be advanced if immunotherapies are to become part of a new standard of care as either adjunctive or stand-alone therapies. This is particularly true for biotherapeutics such as cytokines and antibodies, which are typically substantially more expensive to produce at large scale than antimicrobial drugs. The remarkable success of mRNA-mediated delivery of vaccine antigens may stimulate similar methods for immunotherapy such as the delivery of cytokine-encoding genes. In the case of TB, one may estimate that the added recovery of lung function afforded by treatment with CC-11050 could be quite favourable in terms of cost per disability-adjusted life year, but it nonetheless will require that public health programs begin to include post-TB morbidity and mortality in estimates of national and global health burdens. Similar cost–benefit and ‘quality of life’ analyses will be required for patients with Long COVID. Combining host-directed therapies for TB with new antimicrobial regimens and adjusting treatment duration based on a simple measure at diagnosis is a strategy that could add substantial value both to patients and health programmes and promote uptake of these new therapies.

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