Host-directed therapies for infectious diseases: current status, recent progress, and future prospects

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Despite extensive global efforts in the fight against killer infectious diseases, they still cause one in four deaths worldwide and are important causes of long-term functional disability arising from tissue damage. The continuing epidemics of tuberculosis, HIV, malaria, and influenza, and the emergence of novel zoonotic pathogens represent major clinical management challenges worldwide. Newer approaches to improving treatment outcomes are needed to reduce the high morbidity and mortality caused by infectious diseases. Recent insights into pathogen–host interactions, pathogenesis, inflammatory pathways, and the host's innate and acquired immune responses are leading to identification and development of a wide range of host-directed therapies with different mechanisms of action. Host-directed therapeutic strategies are now becoming viable adjuncts to standard antimicrobial treatment. Host-directed therapies include commonly used drugs for non-communicable diseases with good safety profiles, immunomodulatory agents, biologics (eg monoclonal antibodies), nutritional products, and cellular therapy using the patient's own immune or bone marrow mesenchymal stromal cells. We discuss clinically relevant examples of progress in identifying host-directed therapies as adjunct treatment options for bacterial, viral, and parasitic infectious diseases.

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Introduction

Infectious diseases are leading causes of morbidity and mortality worldwide.[1] In high-income countries, mortality from respiratory tract infections remains high despite access to quality health services and availability of antibiotic therapy.[1] The intermittent emergence of new zoonotic pathogens and the increasing incidence of treatment-resistant infections draws attention to the limits of the current antimicrobial treatment portfolio and the urgent need for alternative management strategies.

In evolutionary terms, host–pathogen interactions are dependent on the microbe surviving without causing harm to the host. The host's innate and adaptive immune surveillance mechanisms govern whether the infection will be contained or progress to clinical disease with either recovery or death. Several host factors affect antimicrobial treatment outcome and are responsible for progression of disease after infection, poor treatment response, tissue damage, long-term functional disability, and increased mortality. These factors include immune dysregulation from any cause (aberrant or excess host inflammatory response to infection, stress, immunosuppressive drugs, poor living conditions, socioeconomic factors, micronutrient deficiencies, HIV, malnutrition, and alcohol or substance misuse) and comorbidity with non-communicable diseases such as diabetes, cancer, smoking, and chronic obstructive pulmonary disease.[1]

During the past 4 years, a renaissance of scientific research strategies targeting host factors, rather than pathogen components directly, has opened up novel treatment approaches termed host-directed therapies. A host-directed therapy is any product that can augment host defence mechanisms or modulate excessive inflammation, or both, leading to improved clinical treatment outcomes as shown by reduced morbidity, mortality, and end-organ damage, and long-term functional recovery. A range of host-directed therapies have been identified with different mechanisms of action (figure 1), and they are now regarded as viable adjuncts to standard antimicrobial treatment. Host-directed therapies can improve host cellular responses to pathogens, target disease-causing virulence factors (figure 2), and activate innate and adaptive immune responses and immunological memory (figure 3).[2]

Key messages

- Despite the availability of antimicrobial drugs, infectious diseases are leading causes of morbidity and mortality worldwide.
- The widespread emergence of antimicrobial resistance calls for novel interventions in addition to new antimicrobial development.
- A range of host factors are responsible for development of disease, poor treatment response, and increased mortality. These include immune dysregulation from any cause and comorbidity with non-communicable diseases such as diabetes, cancer, smoking, and chronic obstructive pulmonary disease.
- During the past 4 years, a renaissance of scientific research strategies targeting host factors—rather than pathogen components directly—is leading to development of a wide range of host-directed therapies that target and modify biological pathways to achieve a positive clinical treatment outcome.
- Host-directed therapies can augment host cellular responses to pathogens, target disease-causing virulence factors, activate innate and adaptive protective immune responses, or modulate excessive inflammation, leading to reduced morbidity, mortality, and end-organ damage.
- Host-directed therapies include commonly used, safe, and cheap drugs for non-communicable diseases; biologics; nutritional products; and cellular therapy, using the patient's own immune or mesenchymal stromal cells.
- The broad spectrum efficacy of host-directed therapies could also be useful for treatment of infectious diseases with epidemic potential, which are associated with high mortality.
- Host-directed therapies have the additional unique benefit of preventing or reducing the development of antibiotic resistance.

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See Online for appendix

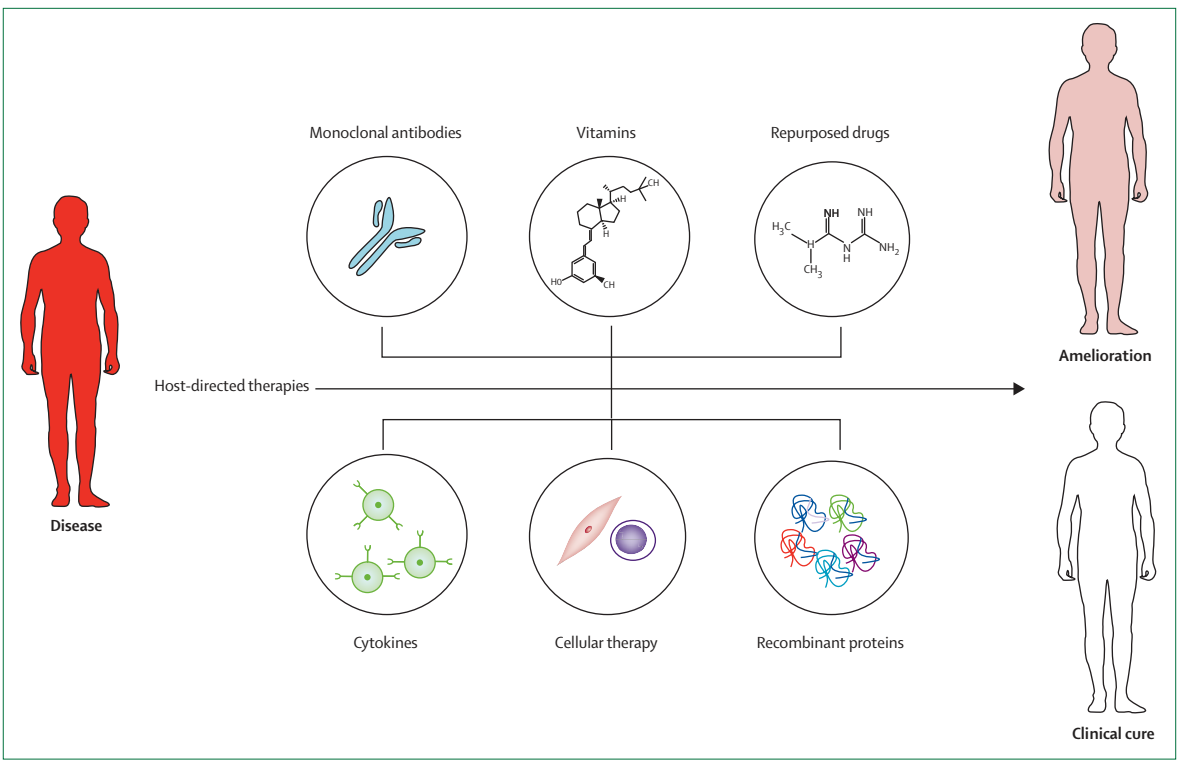

***Figure 1*: The main types of host-directed therapies**
Host-directed therapies focus on ameliorating the severity of disease and improving treatment outcomes. Host-directed therapies constitute a range of therapeutic agents such as repurposed drugs, small molecules, synthetic nucleic acids, biologics (such as monoclonal antibodies), cytokines, cellular therapy, recombinant proteins, and micronutrients.

Examples of host-directed therapies include commonly used and affordable drugs for non-communicable diseases with good safety profiles, immunomodulatory agents, biologics, nutritional products, and cellular therapy using the patient's own immune or mesenchymal stromals cells (table 1). See appendix for discussion of potential host factors for targets of host-directed therapy against infectious disease.

Studies of host-directed therapies also enable new insights into underlying mechanisms of pathogenesis, inflammatory pathways, and the host's innate and acquired immune responses. In this Review we discuss clinically relevant examples of progress in identification of candidate host-directed therapies as adjunct treatment options for bacterial, viral, and parasitic infectious diseases.

Bacterial infections

Tuberculosis is the most common cause of death from an infectious disease worldwide.[89] Since the declaration of tuberculosis as a global emergency in 1993 by WHO, there has been a major focus on development of new drugs that target *Mycobacterium tuberculosis*, the causative pathogen. For decades, the notion that *M tuberculosis* is the sole cause of the continuing worldwide tuberculosis pandemic has led to a focus on treatment of patients with tuberculosis with WHO-recommended combination antituberculosis antibiotic therapy. This focus still thrives, although there are about 2 billion people in the world with latent tuberculosis infection who do not develop active disease.[89] Furthermore, the substantial decline in tuberculosis in Europe and North America in the first half of the 19th century occurred well before the antibiotic era. In 2014, an estimated 1·5 million people died of tuberculosis and there were an estimated 450 000 cases of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis,[89] suggesting that host factors have an important role in achieving anti-*M tuberculosis* immune responses. *M tuberculosis* is largely intracellular in nature, and intact T-cell responses (T-helper-1 [Th1] CD4 cytotoxic lymphocytes, CD8 cytotoxic lymphocytes, and natural killer T cells) and interferon-γ production are needed to restrict *M tuberculosis* growth.[90] Pulmonary tissue pathology, substantial tissue destruction, and subdued protective anti-*M tuberculosis* immune responses are noted in patients with tuberculosis who are predominantly affected by tumour necrosis factor (TNF)-α-mediated inflammation.[91]

Improving treatment for both drug-sensitive and MDR tuberculosis is a high priority. Few new anti-*M tuberculosis* drugs are in clinical assessment and some have substantial safety concerns. Furthermore, resistance is

likely to develop against new tuberculosis drugs. The greatest clinical needs for tuberculosis treatment are interventions that could reduce the lengthy duration of tuberculosis therapy (currently 6 months in patients with drug-sensitive tuberculosis and 18–24 months in patients with MDR or XDR tuberculosis), thus improving patient compliance and reducing long-term toxicity; invigorate immune responses to eradicate or contain *M tuberculosis*; dampen excessive inflammation and repair tissue damage to prevent long-term pulmonary damage and functional disability; and reduce the high mortality from MDR and XDR tuberculosis.

There is an expanding portfolio of host-directed therapies for use as adjunct treatments to tuberculosis therapy for improving treatment outcomes, shortening the duration of therapy, and reducing lung pathology and long-term functional disability for drug-sensitive and drug-resistant tuberculosis (table 2).[91,133] Other host-directed therapies may decrease local inflammatory tissue pathology, including that caused by tuberculosis-associated immune reconstitution inflammatory syndrome. Examples of host-directed therapies currently being developed are cellular therapy using the patient's own bone marrow-derived mesenchymal stromal cells;[133] repurposing commonly used drugs for diabetes, epilepsy, peptic ulcers, hypercholesterolaemia, asthma, cancer, and arthritis; micronutrients and other immune-modulators; antimicrobial peptide inducers and checkpoint inhibitors; specific immune-based therapies; and therapeutic vaccines. Multinational consortia have been established to take these therapies forward in controlled clinical trials.

Streptococcus pneumoniae is a Gram-positive bacterium that remains a major cause of childhood and adult morbidity and mortality worldwide,[134] despite the availability of effective antibiotic therapy. It is largely associated with community-acquired pneumonia, and often causes invasive pneumococcal disease, affecting any organ in the body.[135] Both cell-mediated and humoral immune responses operate in preventing disease in human beings.[136] The pathogenesis of pneumonia is associated with overt inflammatory responses that eventually cause lung damage and death.[137] Thus, several adjunctive host-directed interventions are being investigated.

The use of corticosteroids in pneumonia remains controversial, and data to support the use of corticosteroids in cases of community-acquired pneumonia are limited. In a prospective randomised clinical study of 785 patients with community-acquired pneumonia, prednisolone led to overall improved survival after treatment, concomitant with slightly shorter hospital stay and reduced need for mechanical ventilators, compared with placebo.[3] Corticosteroids can also prevent hearing loss and other neurological sequelae in bacterial meningitis.[138]

Although the clinical use of macrolide antibiotics specifically targets the causative bacteria, macrolides might have an additional host-directed effect in treating community-acquired pneumonia. Preclinical assessment of azithromycin in mice after secondary *S pneumoniae* infection following primary exposure to influenza A virus potentiated anti-inflammatory effects marked by reduction in neutrophil influx, and promoted dampening of immunopathological outcome in the lungs.[21] Retrospective and prospective studies[22–27] have shown that macrolide-containing antibiotic regimens decrease mortality in patients with community-acquired pneumonia, although other studies[28–30] have shown no significant benefit from these regimens. Addition of a macrolide to a fluoroquinolone seems to provide some improvement in

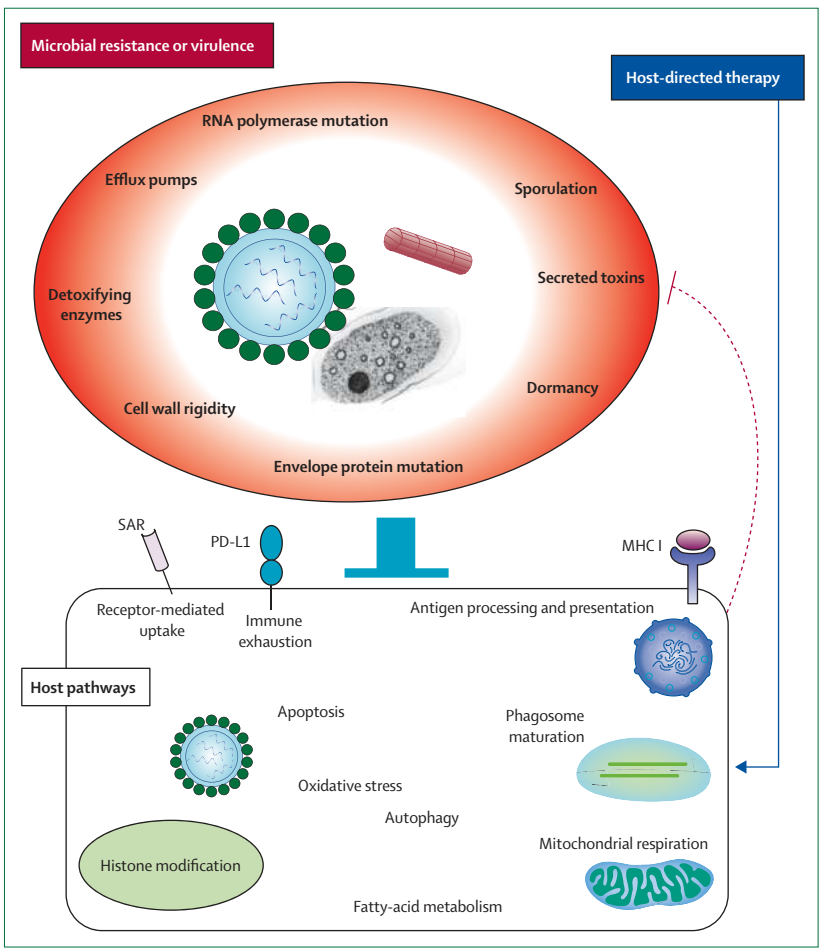

***Figure 2*: Host-directed therapies as a means to counteract antimicrobial resistance**
Pathogens develop resistance to antimicrobial therapy via various factors, including modification of cell-surface proteins and intracellular enzymes (bacteria and parasites), modification of envelope proteins (viruses), secretion of toxins (bacteria and parasites), sporulation and dormancy (bacteria, viruses, and fungi), activation of efflux pumps (bacteria, fungi, and parasites), and decreased permeability of cell wall (bacteria and fungi). These virulence factors impede cellular functions (solid blockade), which are required to successfully eradicate the pathogen. Host-directed therapies can counter these mechanisms by targeting impaired intracellular processes in affected host cells (blue arrow), by mechanisms such as activation of autophagy and apoptosis, induction of oxidative and nitrosative stress, and increased antigen processing and presentation, which in turn trigger necessary adaptive immune responses. Novel host-directed therapeutic strategies target host surface receptors, such as programmed death-ligand 1 (PD-L1; involved in immune exhaustion) and sialic acid-containing receptor (SAR; enhances entry of pathogens into host cells). Histone modification is done by targeting genes involved in pathogen replication and induction of apoptosis, autophagy, and antigen processing and presentation. Fatty-acid metabolism might have a role in maintenance of memory CD8 cytotoxic T-lymphocyte pools in the host. Responses induced by host-directed therapies might counteract microbial virulence factors (dotted blockade), in addition to neutralising tissue damage.

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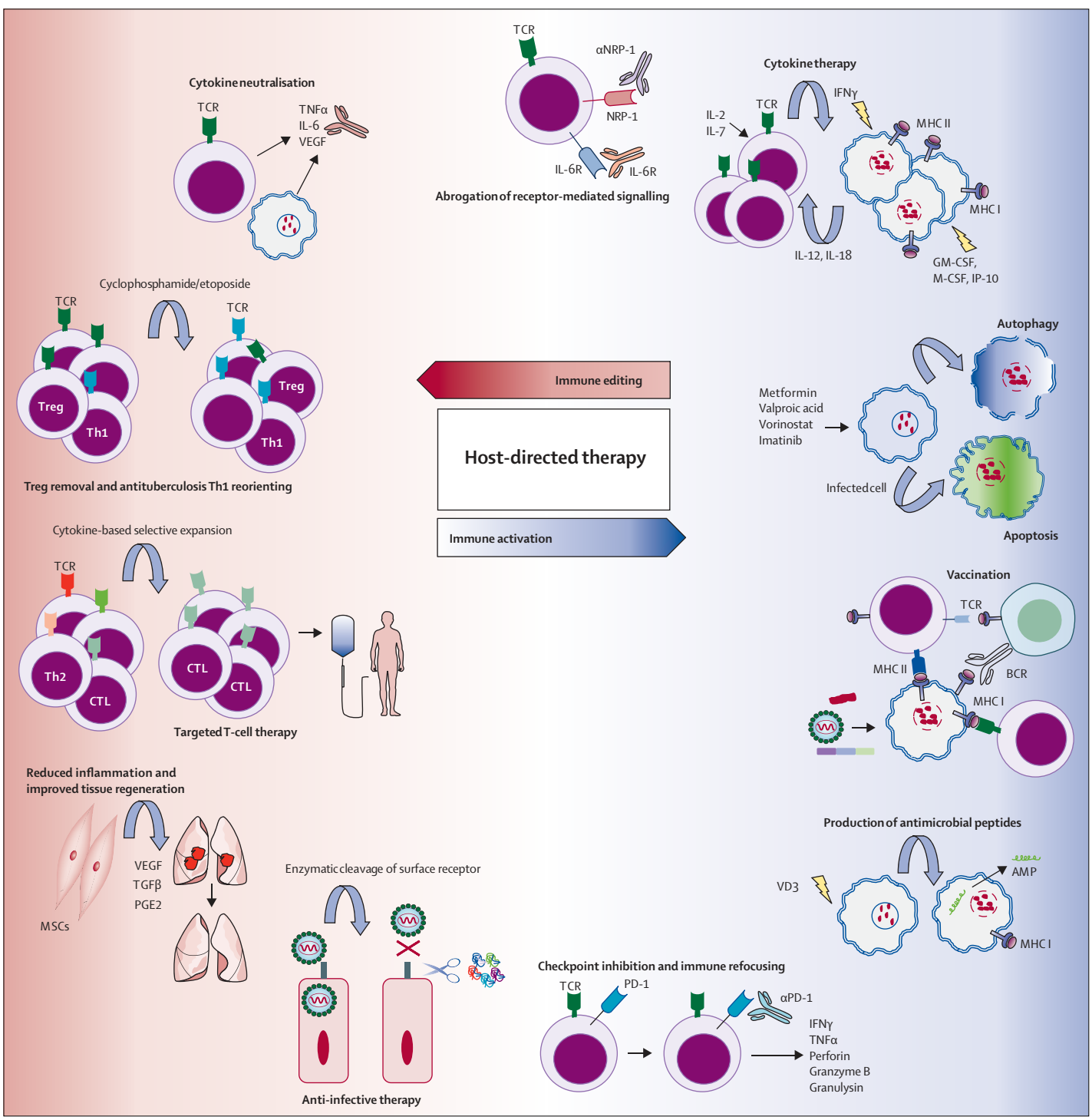
survival,[31] suggesting a host-directed effect. Analyses in patients with community-acquired pneumonia with bacteraemia of all causes[32] or community-acquired pneumonia with severe sepsis[24] showed that benefit specific to macrolides was not only restricted to pneumococcal bacteraemia but was also shown for Gram-negative bacterial infections.[24,32] Findings suggest that macrolides provide benefit mainly to patients with more severe illness.[4,22,24,26,27]

The use of non-steroidal anti-inflammatory drugs (NSAIDs) for the treatment of pneumonia in people has yielded conflicting results.[5,6] A study investigating the



effects of ibuprofen in patients with sepsis (50% had pneumonia) showed some improvement in gas exchange,[7] albeit without any effect on mortality.[139]

Statins (3-hydroxyl-3-methyl-glutaryl-CoA reductase inhibitors) might have a role as adjunct treatment of community-acquired pneumonia via their pleiotropic anti-inflammatory, anti-oxidative, and immunomodulatory effects; however, their effects need to be defined in randomised controlled trials. Observational studies of patients on statins before development of pneumonia or other infection were less likely to develop sepsis, die from sepsis, or have complications leading to intensive care unit admission.[8–19] No study has examined the addition of statins as an adjunctive therapy once pneumonia has developed.

Oral hypoglycaemic agents, such as glitazones, may have anti-inflammatory effects similar to corticosteroids in patients with community-acquired pneumonia, and glyburide has been associated with significantly lower mortality in patients with severe melioidosis than in patients without diabetes or patients taking other diabetes agents.[140] These findings warrant clinical investigation to establish whether oral hypoglycaemic agents are potential host-directed therapies for severe community-acquired pneumonia.

Helicobacter pylori has emerged as a major human pathogen because of its role in gastric cancer (classified as a type 1 carcinogen)[141] and gastric ulcers. More than 50% of the world's population is infected with the pathogen, which has co-evolved with human beings for almost 60 000 years.[142] Raised concentrations of interleukin 1β and TNFα in the gut of individuals with *H pylori* infection have been postulated as risk factors for inflammatory tissue transformation and damage, and carcinogenesis.[33] Efforts to develop host-directed therapies against *H pylori* infection have focused on neutralisation of these pro-inflammatory cytokines with monoclonal antibodies (eg, anti-interleukin 1β, gevokizumab, anti-TNFα, and adalimumab) during the course of antibiotic treatment to clear the infection.[33] Vitamin D3 also has potential for use as a host-directed therapy for *H pylori* infection. In a preclinical study[34] with a gastric epithelial cell line (GES-1) infected with *H pylori*, vitamin D3 supplement augmented killing of intracellular bacteria via induction of cathelicidin and β-defensin 4.

Bordetella pertussis remains an important cause of morbidity and mortality. Antibiotics do not substantially affect the course of whooping cough disease unless treatment is started early after symptom onset. Many patients develop long-term pulmonary damage. Immunotherapy with antipertussis toxin antibodies might confer protection against more severe forms of whooping cough. Halperin and colleagues[36] investigated the use of multiple doses of intravenous antipertussis immunoglobulin in 25 infants with pertussis infection and noted an increase in serum antipertussis antibody titres, a decline in lymphocytosis, and a reduction in paroxysmal coughing compared with baseline; however, findings from more recent studies[37] of antipertussis immunoglobulin were not promising. Manipulation of the sphingosine-1-phosphate signalling pathway, involved in several immunological processes including lymphocyte trafficking, might have therapeutic benefits in reversing the pathological outcome in pertussis disease (appendix).[35]

The number of infections with antibiotic-resistant *Neisseria gonorrhoeae* is increasing worldwide. The histone deacetylase inhibitor sulforaphane, which induces expression of antimicrobial peptides (eg, secretory leucocyte protease inhibitor and β-defensin 2), has been shown to augment the activity of antibiotics against multidrug-resistant *N gonorrhoeae*, thus showing potential as a host-directed therapy.[39,40] Supernatants from human endocervical carcinoma cells pre-treated with sulforaphane potentiated better bacterial killing in combination with sublethal doses of ciprofloxacin and cefixime[40] compared with antibiotics alone.[39] Furthermore, sulforaphane treatment in *N gonorrhoeae*-infected female mice resulted in better control of bacterial load and reduced inflammation.[39] Treatment of cervical cells with sulforaphane in combination with antibiotic therapy might reduce the amount of antibiotic needed to eradicate *N gonorrhoeae*.[40] See appendix for discussion of host-directed therapies for bacterial sepsis.

Viral infections

HIV targets and infects human CCR5-positive T cells[143] and causes AIDS, impeding CD4 T-cell-mediated responses to a wide range of microbes.[144] In 2014,

Figure 3: **Possible biological pathways and mechanisms for host-directed interventions against infectious diseases**

Pharmacological activation of autophagy or apoptosis, or both, drives improved intracellular killing of pathogens and enhanced antigen presentation. Activation and recruitment of antigen-presenting cells (ie, dendritic cells and macrophages) via therapy with the pro-inflammatory cytokines interferon γ (IFNγ), granulocyte-macrophage colony-stimulating factor (GM-CSF), and IFNγ-induced protein (IP-10), among others, could amplify the antimicrobial immune response. Several anticancer drugs (ie, cisplatin, gemcitabine, and paclitaxel) can potentiate antigen-specific CD8 cytotoxic T-lymphocyte (CTL) responses in patients by inducing production of interleukin (IL) 12, tumour necrosis factor α (TNFα), and IL 6. Immune checkpoint inhibition by blocking the programmed cell death 1 (PD-1)/programmed death-ligand 1 (PD-L1) pathway activates antigen-specific T cells. In-vitro selection and expansion of pathogen-specific autologous T-cell subsets (antigen-specific CD4 T cells and CD8 CTLs) can allow for reinfusion into the patient after confirmation of activity. Blockade of cell surface-bound signalling molecules, such as the receptors for IL 6 and neuropilin 1 (NRP-1), may potentiate specific T-cell responses. Removal of excess inflammatory cytokines by use of monoclonal antibodies, or depletion of regulatory T cells (Treg) with cytotoxic agents (eg, cyclophosphamide and etoposide) dampens destructive inflammation in the target organs, and might re-orientate *Mycobacterium tuberculosis*-targeted immune responses (T-helper-1 [Th1] and CD8 CTLs). Histone deacetylase inhibitors, valproic acid, and vorinostat, might reprogramme non-productive Th2 cells to antigen-specific Th1 cells. Infusion of autologous mesenchymal stromal cells (MSCs) could neutralise the local cytokine milieu, promote tissue repair, and orchestrate antigen-specific T-cell responses, in multidrug-resistant tuberculosis. Host-cell surface receptors used by pathogens for entry could be targeted by host-directed therapies. AMP=antimicrobial peptide. BCR=B-cell receptor. M-CSF=macrophage colony-stimulating factor. PGE2=prostaglandin E2. TCR=T-cell receptor. TGF=transforming growth factor. TGFβ=TGF β. VD3=vitamin D3. VEGF=vascular endothelial growth factor.

	Examples of host-directed therapy	Mechanism of action	Developmental stage
Bacterial infections			
Mycobacterium tuberculosis			
Repurposed drug*	Imatinib, verapamil, metformin, ibuprofen	Modulation of inflammation and activation of intracellular antimicrobial defences	Preclinical/clinical (early phase)
Cytokine therapy*	Interleukin 2, GM-CSF, interferon γ, interleukin 12 (early stage)	Induction of pro-inflammatory cell signalling	Clinical (late phase)
Monoclonal antibody*	Anti-TNFα, anti-interleukin 6, anti-VEGF	Reduction of tissue-destructive inflammation by cytokine neutralisation	Preclinical/clinical (early phase)
Monoclonal antibody*	Anti-PD-1, anti-LAG3, anti-CTLA-4	Activation and mobilisation of antigen-specific T cells by immune checkpoint inhibition	Preclinical
Vitamin*	Vitamin D3	Activation and augmentation of intracellular antimicrobial defences (via interferon γ and interleukin-15 signalling)	Clinical (late phase)
Cellular therapy*	Autologous mesenchymal stromal cells, T cells	Neutralisation of tissue-destructive inflammation, enhancement of organ repair, and potentiation of antigen-specific immune responses	Clinical (early phase)
Streptococcus pneumoniae			
Repurposed drug[3]	Prednisone	Reduction of tissue-destructive inflammation by activating the glucocorticoid pathway	Clinical (late phase; also in current practice)
Repurposed drug[4–19]	Ibuprofen, statins, indometacin, aspirin	Reduction of tissue-destructive inflammation by inhibiting prostaglandin release via cyclooxygenase inhibition, regulation of MHC molecules	Clinical (late phase)
Repurposed drug[20]	Glibenclamide	An oral hypoglycaemic agent that modulates voltage-gated calcium channels, leading to immunomodulatory effects	Clinical (early phase)
Antibiotic[4,21–32]	Azithromycin, erythromycin	Reduces local tissue inflammation through anti-inflammatory activities	Clinical (current practice)
Helicobacter pylori			
Monoclonal antibody[33]	Anti-interleukin 1β, anti-TNFα (late stage)	Reduction of tissue-destructive inflammation by cytokine neutralisation	Preclinical
Vitamin[34]	Vitamin D3	Activation and augmentation of intracellular antimicrobial defences (via interferon γ and interleukin-15 signalling)	Preclinical
Bordetella pertussis			
Repurposed drug[35]	Fingolimod	Activates the sphingosine-1-phosphate pathway to improve antigen-specific lymphocyte responses, as well as reduced hyper-inflammation	Preclinical
Monoclonal antibody[36–38]	Antipertussis toxin antibodies	Reduces toxin load via infusion of intravenous immunoglobulins	Clinical (in current practice)
Neisseria gonorrhoeae			
Repurposed drug[39,40]	Sulforaphane	Increased histone acetylation to enhance gene transcription	Preclinical
Recombinant protein[39,40]	Secretory leucocyte protease inhibitor, β-defensin 2	Host-derived antimicrobial peptides with bactericidal effects	Preclinical
Viral infections			
HIV			
Repurposed drug[41–43]	Valproic acid, vorinostat	Reactivation of latent HIV infection and making new viral progeny susceptible to ART and immune attack by enhancing gene transcription	Clinical (early phase)
Monoclonal antibody[44–46]	Anti-PD-1	Activation and mobilisation of antigen-specific T cells via immune checkpoint blockade	Preclinical
Cellular therapy[47]	MSCs	Reduction of destructive inflammation and enhancement of tissue regeneration and organ repair	Not yet tested in HIV infection
Epstein-Barr virus			
Cellular therapy[48–51]	CD19 CAR (for Epstein-Barr virus [EBV] B-cell lymphoma), in-vitro-expanded EBV-specific CD8 CTLs	Depletion of viral reservoirs to deter progression to lymphoma	Clinical (mid phase)
Cytomegalovirus			
Monoclonal antibody[52]	Viral envelope protein-targeted IgG	Neutralises virus and reduces viral load	In clinical use
Cellular therapy[49–51,53,54]	In-vitro-expanded cytomegalovirus-specific CD8 CTLs	Depletion of viral reservoirs to avoid fulminant viraemia in immunocompromised individuals	In clinical use
Adenovirus			
Cellular therapy[49–51,55]	In-vitro-expanded adenovirus-specific CD8 CTLs	Depletion of viral reservoirs to avoid fulminant viraemia in immunocompromised individuals	In clinical use
Hepatitis C virus			
Repurposed drug[56–59]	Miravirsen (SPC3649)	Antisense RNA targeting miR-122 for modulation of fatty acid metabolism to reduce viral burden in host cells	Clinical (early phase)
Monoclonal antibody[60]	Anti-PD-1	Activation and mobilisation of antigen-specific T cells via immune checkpoint blockade	Clinical (early phase)
Cytokine therapy[61]	Pegylated interferon α and β	Potentiation of pro-inflammatory antiviral immune response	In clinical use

(Table 1 continues on next page)

	Examples of host-directed therapy	Mechanism of action	Developmental stage
(Continued from previous page)			
Influenza viruses			
Repurposed drug[62–65]	Metformin	Induction of autophagy and improved antigen processing and presentation; improves maintenance of memory CD8 CTLs	Preclinical
Repurposed drug[62–65]	Glitazones (PPAR-γ), fibrates (PPAR-α)	Pleiotropic effects, including blockade of angiogenesis and pro-inflammatory signalling	Preclinical
Repurposed drug[62–65]	Sartans	Angiotensin-II-receptor blocker that reduce inflammation and allow tissue remodelling	Clinical (mid-late phase)
Repurposed drug[62–65]	Atorvastatin	Angiotensin-converting enzyme blocker that reduces pro-inflammatory signalling and improves tissue repair	Clinical (mid-late phase)
Recombinant protein[66,67]	Sialidase fusion peptide DAS181	Reduces infectivity of influenza viruses by cleaving surface receptors on host epithelia	Clinical (early phase)
Ebola virus			
Repurposed drug[68,69]	Irbesartan	Angiotensin-II-receptor blockers that reduce inflammation and allow tissue remodelling	Clinical (early phase)
Repurposed drug[68,69]	Atorvastatin	Angiotensin-converting enzyme blocker that reduces pro-inflammatory signalling and improves tissue repair	Clinical (early phase)
Cytokine therapy[70]	Pegylated interferon α and β	Potentiation of pro-inflammatory antiviral immune response	Clinical (early phase)
Monoclonal antibody[71]	ZMAb	Antibody neutralises virus and reduces viral load	Preclinical
Recombinant protein[72]	rNAPc2	Blocks blood coagulation to reduce vasculopathy; also reduces release of pro-inflammatory cytokines	Preclinical
Dengue virus			
Repurposed drug[73]	Lovastatin	Angiotensin-converting enzyme inhibitor that reduces pro-inflammatory signalling and improves tissue repair	Preclinical
Repurposed drug[73,74]	Dasatinib	Tyrosine kinase inhibitor that inhibits viral replication via blockade of host proto-oncogene kinase (Fyn)	Preclinical
Repurposed drug[73,74]	Ciclosporin	Cyclophilin inhibitor that reduces viral replication via blockade of host cyclophilin A	Preclinical
Cytokine therapy[75]	Pegylated interferon α and β, interferon γ	Potentiation of pro-inflammatory antiviral immune response	Not yet tested in dengue fever
Recombinant protein[72]	rNAPc2	Blocks blood coagulation to reduce vasculopathy; also reduces release of pro-inflammatory cytokines	Preclinical
Middle East respiratory syndrome coronavirus (MERS-CoV)			
Repurposed drug[76,77]	Sitagliptin, vildagliptin	Incretin-based inhibitors or blockers of host DPP-4 surface receptors that inhibit virus entry into host cells	Preclinical
Monoclonal antibody[76,78]	Anti-interleukin 17A, anti-interleukin 23	Cytokine neutralisation of tissue-destructive inflammation	Not yet tested in MERS-CoV disease
Parasitic diseases			
Malaria			
Repurposed drug[79]	Desferrioxamine	Ferrochelatase inhibitor reduces *Plasmodium sp* replication in erythrocytes	Preclinical
Recombinant protein[80,81]	IDR-1018	Innate defence regulator peptide enables balanced cytokine release, which allows for pathogen killing without excessive inflammation	Preclinical
Leishmaniasis			
Repurposed drug[82]	Imiquimod, resiquimod	TLR agonist that induces B-cell activation and pro-inflammatory cytokine signalling	In clinical use
Cytokine therapy[83]	Interferon γ, interleukin 2, interleukin 12 (early stage)	Induction of pro-inflammatory immune responses and intracellular antimicrobial activity	Not yet tested in leishmaniasis
Monoclonal antibody[84]	Anti-TNFα (late stage)	Cytokine neutralisation reduces tissue-destructive inflammation	Not yet tested in leishmaniasis

(Table 1 continues on next page)

co-infection with HIV accounted for 12% of the 1·5 million deaths from tuberculosis worldwide.[89] Although HIV-reactive CD8 cytotoxic T lymphocytes and antibodies are present in individuals with HIV infection, the protective role of CD8 T cells and humoral immune responses are rather limited when CD4 T-cell numbers are low.[144] Moreover, expression of programmed cell death protein 1 (PD-1) by circulating HIV-specific CD8 cytotoxic T lymphocytes isolated from patients with AIDS compromises their responsiveness to antigenic stimuli because of cellular exhaustion.[44] Antiretroviral therapy (ART) promotes immune reconstitution (increase in CD4 T-cell numbers) in individuals undergoing treatment, in addition to reducing viral load[145] and restoring a diverse T-cell receptor repertoire. This immune reconstitution, however, does not purge latent viral reservoirs in the host, nor sustain HIV-specific CD8 cytotoxic T-lymphocyte repertoires.[145] Immune reconstitution inflammatory syndrome is an important clinical manifestation in patients with HIV–tuberculosis co-infection early after initiation of ART.[146] Overt Th1-mediated immune responses result in pro-inflammatory cytokine storms (of

	Examples of host-directed therapy	Mechanism of action	Developmental stage
(Continued from previous page)			
African trypanosomiasis			
Cytokine therapy[85,86]	Interferon γ, interleukin 2, TNFα (early stage)	Induction of pro-inflammatory immune responses and intracellular antimicrobial activity	Preclinical
Monoclonal antibody[85,86]	Anti-TNFα (late stage)	Cytokine neutralisation to reduce tissue-destructive inflammation	Not yet tested in trypanosomiasis
Recombinant protein or cytokine therapy[85,86]	Interferon-γ-induced apolipoprotein 1	Cytokine-induced protein that can directly engage and kill trypanosomes	Preclinical
Cellular therapy[85,86]	MSCs (late stage)	Neutralisation of tissue-destructive inflammation and enhancement of organ repair	Not yet tested in trypanosomiasis
Schistosomiasis			
Cytokine therapy[87]	Interleukin 2, interferon γ (early stage)	Induction of pro-inflammatory immune responses and intracellular antimicrobial activity	Not yet tested in schistosomiasis
Recombinant protein[88]	Peroxiredoxin (as adjuvant to vaccine candidate)	Regulation of hydrogen peroxide concentrations in the host; induction of antigen-specific B-cell responses	Preclinical
Cellular therapy[51]	In-vitro-expanded schistosoma-specific CD8 CTLs	Potentiation of parasite-specific cellular immune responses to deter progression to clinical disease	Not yet tested in schistosomiasis

GM-CSF=granulocyte-macrophage colony-stimulating factor. TNFα=tumour necrosis factor α. VEGF=vascular endothelial growth factor. LAG3=lymphocyte-activation gene 3. CTLA-4=cytotoxic-T-lymphocyte-associated antigen 4. MSCs=mesenchymal stromal cells. ART=antiretroviral therapy. PD-1=programmed cell death 1. CAR=chimeric antigen receptor. CTLs=cytotoxic T lymphocytes. miR-122=microRNA 122. PPAR=peroxisome proliferator-activated receptor. rNAPc2=recombinant nematode anticoagulant protein c2. DPP-4=dipeptidyl peptidase 4. TLR=Toll-like receptor. *See table 2 for more details.

Table 1: **Developmental pipeline of host-directed therapies for infectious diseases**

which interleukin 6 is an important component[147]) and hyperactivation of immune cells, mediating extensive tissue damage. At present, repurposing of histone deacetylase inhibitors—eg, vorinostat, panobinostat, and valproic acid—has shown promise as host-directed therapy for improved clinical management of HIV/AIDS. These clinically approved drugs are able to reactivate latent virus reservoirs in the host and expose new virus progeny to ART as well as immune attack.[148] The encouraging results of early-phase clinical trials of histone deacetylase inhibitor treatment of latent HIV infection could revolutionise ART.[148] Since PD-1 expression on HIV-specific CD8 cytotoxic T lymphocytes is a barrier to effective antiviral immune responses in patients with AIDS,[44] timely blockade of the PD-1/programmed death-ligand 1 (PD-L1) pathway could be a viable option to pursue.[45] In-vitro blockade of PD-L1 has already been shown to improve anti-HIV CD8 cytotoxic T-lymphocyte responses, marked by increased proliferation and production of cytokines and cytotoxic molecules.[149] Faster recovery of immune competence in lymphopenic hosts has been seen in HIV-positive patients after treatment with recombinant interleukin 7.[150]

Epstein-Barr virus (EBV) is a human herpesvirus, which is ubiquitous and remains largely latent in nature; at least 95% of the world's population is infected with the virus. EBV has tropism for B cells. It causes a wide range of clinical syndromes, from self-limited infectious mononucleosis to lymphoproliferative syndromes and B-cell lymphomas. Chimeric antigen receptors designed against the B-cell surface antigen CD19 are currently approved for eliminating latent viral reservoirs in the patient to decrease chances of developing B-cell lymphomas.[48] This approach is also feasible for patients with EBV-associated B-cell lymphoma. Alternatively, transfer of EBV-specific CD8 cytotoxic T lymphocytes initially isolated from patients, and cultured and expanded ex vivo, has been clinically tested with much success.[49,50] Not only CD8, but also CD4 T-cell responses have been shown to mediate control of EBV-infected cells. Interleukin 21, produced by CD4 T cells, has been shown to be involved in the EBV nuclear antigen 2 (EBNA-2)-independent expression of latent membrane protein 1 (LMP-1) in EBV-carrying type 2 cells.[151]

Cytomegalovirus is another ubiquitous human herpesvirus that infects the lungs, eyes, CNS, and gastrointestinal tract, but can cause serious disease in adults and children. In particular, patients who have recently undergone haemopoietic stem-cell transplantation (HSCT) are at increased risk of developing clinical cytomegalovirus disease[53] associated with the cytomegalovirus status of the donor and the recipient of of HSCT. Immune control is largely attributed to antigen-specific CD8 cytotoxic T lymphocytes, although cell activation is noticeably subdued after HSCT as a result of immunosuppressive therapy.[53] For host-directed therapies, transfer of autologous or allogeneic antigen-specific CD8 cytotoxic T lymphocytes has been investigated, mainly in HSCT settings.[49,50] The timing of this strategy is crucial to avoid cytomegalovirus-associated immune reconstitution inflammatory syndrome.

Hepatitis C virus (HCV) causes at least 3% of liver diseases worldwide, and is the leading cause of liver cirrhosis and hepatocellular carcinoma.[152] Acute and chronic stages of HCV infection of the liver promote T-cell exhaustion, which, as in HIV infection, is characterised by PD-1 expression on virus-specific CD4 and CD8 cytotoxic T lymphocytes.[153] Another immune checkpoint, cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), is also expressed on exhausted T cells and reduces the immune reactivity of anti-HCV effector T cells to virus-infected

	Class or type	Mechanism of action	Host effect	Developmental stage for tuberculosis
Mitochondrial respiration and fatty acid oxidation				
Metformin[92-94]	Biguanide	Interrupts the mitochondrial respiratory chain and induces ROS production; increases mitochondrial biogenesis and respiration	Enhanced killing of intracellular *Mycobacterium tuberculosis* via ROS production; improved control of bacterial burden and reduced lung pathology in mice; enhanced T-cell responses; might improve maintenance of memory CD8 T cells via increased FAO; promotes generation of CD8 T-cell memory against tumour engraftment in experimental TRAF6-deficient mice by restoring FAO, possibly via AMPK activation; increases mitochondrial biogenesis and hence respiration in rabbit renal proximal tubular cells	Preclinical
Niraparib[95]	PARP inhibitor	Inhibition of PARP-1 and PARP-2 activity, and impairs repair of DNA single strand breaks	Restores mitochondrial respiratory function in human myotubes, also by improved FAO; might promote maintenance of antituberculosis memory CD8 T cells	Preclinical
Interleukin 15[96,97]	Cytokine	Involved in maintenance and possibly proliferation of CD8 T cells	Increases mitochondrial mass and FAO in memory CD8 T cells to prolong survival in experimental mice	Preclinical
Arachidonic acid metabolism				
Aspirin[98]	NSAID	Increased lipoxin A4 production to reduce TNFα levels and achieve eicosanoid balance during chronic inflammation	Dampening of TNFα-induced hyperinflammation to aid tissue repair and control burden of *M tuberculosis*	Preclinical
Zileuton[99]	Leukotriene synthesis inhibitor	Blocks leukotriene production by disrupting lipooxygenase activity; promotes prostaglandin production via cyclooxygenase activation	Increases PGE2 levels and augments interleukin-1β-mediated immune control of tuberculosis in mice; promotes reduced lung *M tuberculosis* burden and pathology	Preclinical
Ibuprofen[100,101]	NSAID	Blocks production of prostaglandins possibly by inhibiting cyclooxygenase activity	Reduces lung pathology and mycobacterial burden in a highly susceptible mouse model of tuberculosis	Clinical (early phase)
Corticosteroid metabolism				
Prednisone[102]	Glucocorticoid receptor antagonist	Forms a complex with glucocorticoid receptor and triggers transcription of several important host genes (ie, iNOS, cyclooxygenase-2, collagenase)	Use in patients with community-acquired pneumonia showed improved survival; results in patients with tuberculosis require further validation	Clinical (mid-late phase)
Histone acetylation				
Valproic acid and vorinostat[41,103]	Histone deacetylase inhibitor	Acetylation of lysine residues on histones to promote DNA unwinding and gene transcription	Valproic acid and vorinostat can activate latent HIV reservoirs and increase ART efficacy as well as CD8 T-cell activity; both drugs can improve efficacy of isoniazid and rifampicin against intracellular *M tuberculosis*	Preclinical
Phenylbutyrate[104,105]	Histone deacetylase inhibitor	Acetylation of lysine residues on histones to promote DNA unwinding and gene transcription	Augments vitamin D3 activity, cathelicidin production, and MAPK signalling to kill intracellular *M tuberculosis*	Clinical (early phase)
Host cell cytotoxicity				
Cyclophosphamide[106,107]	Alkylating agent	CYP450 metabolism of cyclophosphamide produces chemical species that can alkylate DNA guanine to reduce cell proliferation. Cells highly expressing ALDH are resistant to cyclophosphamide	Abrogation of regulatory T-cell responses, and potentiation of RCC vaccine candidate efficacy in clinical trials, with induction of CD8 T-cell responses; might increase efficacy of the BCG vaccine	Not yet tested in tuberculosis
Etoposide[108,109]	Topoisomerase inhibitor	Blockade of DNA topoisomerase II to prevent re-ligation of nascent DNA strands	Depletion of pathogenic inflammatory T cells in influenza-induced HLH	Preclinical
Modulation of ion efflux channels				
Verapamil[110]	Calcium-channel blocker	Modulation of voltage-gated calcium-channel activity for maintenance of cellular ionic homeostasis	Improves efficacy of conventional and novel antituberculosis drugs in *M tuberculosis*-infected mice	Preclinical
Carbamazepine[111]	Sodium-channel blocker	Anticonvulsant; acts via voltage-gated sodium-channel downmodulation and activation of GABA receptors for reduced sensitivity to neuropathic pain. Activates AMPK to induce autophagy	Shown to induce inositol depletion-dependent autophagic killing of intracellular *M tuberculosis* in macrophages; augments reduced lung pathology and improved immune responses in the mouse model of tuberculosis	Preclinical
Statins[112,113]	Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme reductase	Block biosynthesis of endogenous cholesterol	Simvastatin can reduce *M tuberculosis* CFUs (human macrophages and mice)	Preclinical
Inhibition of tyrosine kinases				
Imatinib mesylate[114]	Inhibitor of BCR-ABL tyrosine kinase	Induces apoptotic death of cancerous B cells, and cells expressing related kinases	Reduces CFU load and pathology in lungs of *M tuberculosis*-infected mice; induces myelopoiesis	Preclinical (about to enter early phase clinical trials)

(Table 2 continues on next page)

	Class or type	Mechanism of action	Host effect	Developmental stage for tuberculosis
(Continued from previous page)				
Innate immune defences				
Vitamin D3[115,116]	Vitamin	Induces cathelicidin production, improves antigen processing and presentation, augments response to interferon-γ signalling	Kills intracellular *M tuberculosis* and improves T-cell responses	Clinical (late phase)
Immune activation				
GM-CSF, interleukin 2, and interferon γ[117]	Cytokine	Contribute to proliferation and activation of macrophages, dendritic cells, monocytes, T cells	Variable results but with a generally positive outcome following treatment, coupled with reduction in sputum AFB	Clinical (mid-late phase)
Immune checkpoint inhibition				
Ipilimumab (anti-CTLA-4)[118,119]	Monoclonal antibody	Blockade of CTLA-4 to undo T-cell exhaustion; restores interleukin-2 secretion and signalling	CTLA-4 inhibition in melanoma increases CD8 T-cell activity and tumour regression; might improve CD8 T-cell activity against *M tuberculosis*-infected cells	Preclinical
Nivolumab or pembrolizumab (anti-PD-1)[120-122]	Monoclonal antibody	Blockade of PD-1 to restore lymphocyte functionality. Also, PD-L1 blockade on the surface of APCs contributes to T-cell activation	PD-1 blockade potentiates in-vitro killing of *M tuberculosis*-infected macrophages by CD4 T cells in an interferon-γ-dependent manner and prevents apoptosis of T cells; downregulation of PD-1 on CD4 T cells is commensurate with antituberculosis treatment	Preclinical
Anti-Tim3[123,124]	Monoclonal antibody	Modulation of Tim3–Gal9 interaction to induce targeted T-cell responses	*M tuberculosis*-infected human CD14 monocytes shown to have reduced Tim3 expression with extent of tuberculosis disease in patients; Tim3–Gal9 interaction induces interleukin-1β-driven immune control of *M tuberculosis* infection in vitro	Preclinical
Anti-LAG3[125,126]	Monoclonal antibody	Blockade of LAG3 to abrogate regulatory T-cell interaction with activated effector CD4 and CD8 T cells	Blockade of LAG3 can potentiate targeted CD8 CTL responses in patients with solid tumours. In tuberculosis, low LAG3 expression may be reflective of successful containment of tuberculosis infection	Preclinical
Cytokine neutralisation				
Adalimumab (anti-TNFα)[127]	Monoclonal antibody	Removal of excess TNFα from tissue and circulation	Successfully used salvage therapy in a patient with severe pulmonary tuberculosis	Clinical (compassionate use)
Siltuximab (anti-interleukin 6)[128,129]	Monoclonal antibody	Removal of excess interleukin 6 from tissue and circulation	Effective against arthritis and Castleman's disease; used prospectively in patients with HIV/tuberculosis co-infection may reduce mortality from tuberculosis-associated IRIS	Preclinical
Angiogenesis inhibition				
Bevacizumab (anti-VEGF)[130,131]	Monoclonal antibody	Blockade of VEGF-induced neovascularisation in tissue	Disrupts neovascularisation within lung granulomas in a rabbit model of tuberculosis; improves small-molecule penetration into granulomas and increases air supply, might therefore improve antituberculosis drug efficacy	Preclinical
Reduction of inflammation and improved tissue regeneration				
BM-MSCs[132]	Cell-based therapy	BM-MSCs can reduce destructive inflammation, regenerate tissue, and restore positive modulation of immune responses, secretion of soluble factors, and activation of regulatory T cells	Autologous MSC reinfusion in a phase 1 trial in Belarus of patients with multidrug-resistant tuberculosis was safe and reconstituted anti-*M tuberculosis* T cell responses; a phase 1 study is underway in Durban, South Africa	Clinical (early phase)

ROS=reactive oxygen species. FAO=fatty acid oxidation. TRAF6=tumour necrosis factor receptor-associated factor 6. AMPK=5′ adenosine monophosphate-activated protein kinase. PARP=poly (ADP-ribose) polymerase. NSAID=non-steroidal anti-inflammatory drug. TNFα=tumour necrosis factor α. PGE2=prostaglandin E2. iNOS=inducible nitric oxide synthase. ART=antiretroviral therapy. MAPK=mitogen-activated protein kinase. CYP450=cytochrome P450. ALDH=aldehyde dehydrogenase. RCC=renal cell carcinoma. HLH=haemophagocytic lymphohistiocytosis. GABA=γ-aminobutyric acid. CFUs=colony forming units. GM-CSF=granulocyte-macrophage colony-stimulating factor. AFB=acid-fast bacilli. CTLA-4=cytotoxic-T-lymphocyte-associated antigen 4. PD-1=programmed cell death 1. PD-L1=programmed death-ligand 1. APCs=antigen-presenting cells. Tim3=T-cell immunoglobulin and mucin-domain containing-3. Gal9=galectin 9. LAG3=lymphocyte-activation gene 3. IRIS=immune reconstitution inflammatory syndrome. VEGF=vascular endothelial growth factor. BM-MSCs=bone marrow-derived mesenchymal stromal cells. BCR-ABL=breakpoint cluster-Abelson tyrosine kinase.

***Table 2*: Developmental pipeline of host-directed therapies for adjunct treatment of drug-sensitive and drug-resistant tuberculosis, by host pathway**

tissue in patients.[154] The current first-line treatment for HCV infection is a combination regimen of direct-acting antiviral drugs, which mandatorily includes the nucleotide analogue sofosbuvir.[155] Despite their high efficacy, the high financial cost of direct-acting antiviral drugs is a barrier to provision of HCV treatment.

The anti-PD-1 monoclonal antibody nivolumab has been shown to induce productive clinical responses in patients with HCV infection, marked by pronounced viral load reduction.[60] No adverse side-effects were noted, although some important observations were reported. In one patient receiving nivolumab only, a transient, grade 4 rise in alanine transaminase concentration was concomitant with maximum HCV viral load reduction (4·55 log IU/mL) 22 days after treatment. Another patient, who also had diabetes

mellitus and was receiving metformin treatment, had an increase in blood glucose concentrations, requiring insulin therapy. Anti-PD-1 therapy has been used for treatment of melanoma and other solid cancers,[156] including HCV-induced hepatocellular carcinoma in combination with anti-CTLA-4 (NCT01658878). HCV-infected hepatocytes secrete newly formed viruses bound to apolipoprotein B (apoB),[157] thus making increased apoB expression a risk factor for infection and progression to active hepatitis, and a potential target for host-directed therapy. MicroRNA-122 (miR-122) is highly expressed in the liver and has an important role in fatty-acid metabolism. Notably, increased levels of circulating miR-122 in serum samples from patients with HCV infection (genotypes 1 and 3) qualifies it as a disease biomarker and target for host-directed therapy.[56] A phase 2 clinical trial of miravirsen (SPC3649; Santaris Pharma, Hørsholm Municipality, Denmark), an antisense oligonucleotide targeting miR-122, in patients with chronic HCV infection, has recently been completed (NCT01200420), and previous preclinical assessment showed promising antiviral effects.[57]

Influenza virus has caused several pandemics with millions of deaths worldwide. Many patients with influenza succumb to extensive lung pathology or secondary bacterial pneumonia, and resistance to current neuraminidase inhibitors presents a major hurdle to management of future pandemics. Immunosuppressive treatment with etoposide to dampen the cytokine storm-induced lung pathology was clinically beneficial in patients with severe influenza infection.[108,109] DAS181 (fludase; Ansun Biopharma, San Diego, CA, USA) is a sialidase fusion peptide that cleaves off the sialic acid residues on host epithelial cell-surface receptors. Following approval by the US Food and Drug Administration (FDA), DAS181 has been used in two HSCT recipients with parainfluenza infection; the first patient died whereas the second recovered.[66] Clinical benefit and reduction of viral load has been reported from a phase 2 clinical trial of DAS181 in patients with pneumonia caused by either influenza B or the 2009 H1N1 pandemic strain.[67] Several immunomodulatory drugs,[62,63] statins,[62] angiotensin-II-receptor blockers, angiotensin-converting enzyme inhibitors, peroxisome proliferator-activated receptor γ (PPARγ) and PPARα agonists (glitazones and fibrates, respectively), and adenosine monophosphate-activated kinase agonists (eg, metformin) have been suggested to modify the host response to severe influenza to improve survival,[62] since these interventions have been shown to reduce mortality in mice infected with influenza virus. In an observational study of more than 3000 patients admitted to hospital with laboratory-confirmed influenza, statins reduced the number of deaths in hospital and within 30 days of discharge by 41%.[64] An observational study showed that inpatient treatment with angiotensin-II-receptor blockers, angiotensin-converting enzyme inhibitors, and statins reduced 30-day pneumonia mortality by 53%, 42%, and 32%, respectively.[158]

In the 2014–15 epidemic of Ebola virus disease, this disease caused more than 28 639 cases and 11 316 deaths in three west African countries.[159] Clinical trials of experimental antiviral agents, antibody preparations, and vaccines were completed. The clinical success of treating patients with Ebola virus infection with convalescent plasma from individuals who survived the 1976 and 1995 disease outbreaks in the Democratic Republic of the Congo prompted use of this strategy in the 2014 Ebola outbreak in west Africa.[160] Although this intervention provided some survival benefit, acute kidney or lung injury were reported; however, these adverse effects could not be directly attributed to convalescent plasma transfusion.[160]

New treatment strategies targeting host factors in Ebola virus disease are in development. Recombinant nematode anticoagulant protein c2 (rNAPc2), an anticoagulant with FDA approval for treatment of thrombosis, has shown promising preclinical data in Ebola virus-infected monkeys,[72] although no clinical trials are currently listed. Endothelial dysfunction causes the fluid and electrolyte imbalances seen in patients with Ebola virus infection; in-vitro studies have shown that statins and angiotensin-II-receptor blockers preserve or restore endothelial barrier integrity.[62,68] These drugs could be considered for treating the host response in these patients. In Sierra Leone, about 100 patients with Ebola virus infection were treated with this combination, and reports suggest substantial extension of survival.[69]

Dengue virus belongs to the genus of flaviviruses, which also includes yellow fever virus, West Nile virus, tick-borne encephalitis virus, and Zika virus; all are arthropod-transmitted infections.[161] Four different serotypes of dengue virus exist, and infection with one serotype does not protect against the other. Dengue virus infection can lead to establishment of severe haemorrhagic disease, and in some cases leads to shock syndrome, which is fatal.[162] As a host-directed therapy, lovastatin, a known modulator of cholesterol metabolism, was shown to inhibit replication of dengue virus in A549 human epithelial cells.[73] Other repurposed drugs have also been clinically tested: ivermectin, dasatinib, and ciclosporin.[73] Additionally, use of type 1 interferon (α or β) and interferon γ has shown promising results in animal models (non-human primates).[75] rNAPc2 could also be useful in managing vasculopathy during dengue haemorrhagic fever or shock syndrome, but this approach requires clinical investigation.

Middle East respiratory syndrome coronavirus (MERS-CoV) was first isolated in June, 2012, in Jeddah, Saudi Arabia, from a patient who died of severe respiratory infection and multiorgan failure.[78] MERS-CoV is associated with high mortality in patents with co-morbidities and there are no effective anti-MERS-CoV antiviral agents or therapeutics. The lung pathology seen

in patients with MERS probably represents the end result of a fine balance of host immune and MERS-CoV interactions. In-vitro laboratory investigation identified the membrane-bound form of dipeptidyl peptidase 4 to be the cardinal host-cell receptor for virus entry.[76] Pneumonia is a common feature in patients with MERS and the high mortality caused by MERS-CoV is attributable to acute lung injury or development of acute respiratory distress syndrome (ARDS). ARDS is associated with leaky alveolar–capillary interfaces with pulmonary oedema, hypoxia, polymorphonuclear leucocytes or lymphocytic cellular infiltrates, and an aberrant immune response, with upregulation of pro-inflammatory cytokines, including interferon γ, which results in further tissue damage and deterioration of lung function. Analysis of serum and bronchoalveolar lavage fluid samples from patients who died from MERS-CoV infection showed non-productive inflammatory immune responses and induction of interleukin 6 and interleukin 17A.[76] Patients with acute lung injury or ARDS died from the disease. Blockade of the pro-inflammatory cytokines interleukin 17A and interleukin 6 during severe disease might be useful as adjunct therapy and needs to be assessed in clinical trials. Additionally, reinfusion of bone marrow mesenchymal stem cells might also help ameliorate lung pathology in critically ill patients.[78] Potential host-directed therapies to improve treatment outcomes of MERS are shown in table 1.

Parasitic diseases

Plasmodium falciparum malaria kills up to 1 million people worldwide every year. Individuals with *P falciparum* infection often develop severe clinical symptoms such as brain damage and multiple organ failure. Up to 25% of cases of severe clinical malaria are fatal even with access to the best health care, partly because the parasite triggers inflammation that damages vital organs. Case fatality rates for severe malaria remain high even in the best clinical settings because antimalarial drugs act against the parasite without alleviating life-threatening inflammation.[163] Drug resistance now threatens efficacy of artemisinin-based therapies.[164]

Ferrochelatase, an enzyme important for haem biosynthesis in human erythrocytes, has been reported to be instrumental in parasite survival. Human erythrocytes deficient for ferrochelatase (from patients with erythropoietic protoporphyria) are more resistant to *P falciparum* growth, and pharmacological inhibition of host ferrochelatase in vitro abrogated parasite replication in healthy human erythrocytes.[79] Desferrioxamine is a potent inhibitor of ferrochetalase,[165] and could be considered for repurposing in human malaria.

Excess TNFα production is involved in the pathogenesis of severe malaria.[166] In a clinical study that included 20 Gambian children in malaria-associated coma, treatment with an anti-TNFα antibody reduced parasite load in a dose-dependent manner and had noteworthy antipyrogenic effects.[167] The use of anti-TNFα drugs (eg, adalimumab, etanercept) in severe malaria need to be further investigated in clincial trials.

A small synthetic peptide known as innate defence regulator (IDR)-1018 seems to have broad therapeutic potential, including in-vivo activity in murine models by enhancement of wound healing and protection against *Staphylococcus aureus*, multidrug-resistant *M tuberculosis*, herpes simplex virus, and inflammatory disorders, including cerebral malaria.[80] Recent studies of the *Plasmodium berghei* ANKA model of experimental cerebral malaria showed that IDR peptides prevented CNS inflammation and protected mice from experimental cerebral malaria, improving survival.[81] IDR peptides enhance the beneficial aspects of the initial immune response, while dampening harmful tissue damage by downregulating the secretion of pro-inflammatory cytokines including TNFα and interleukin 1β. Co-administration of IDR-1018 with standard first-line antimalarial drugs (pyrimethamine and chloroquine) increased survival in infected mice. Thus, IDR peptides could serve as adjunctive host-directed therapy for severe disease in combination with antimalarial treatment.[80,81]

Leishmania spp cause a range of clinical disease including cutaneous, mucocutaneous, and visceral involvement.[168] Like most intracellular pathogens, *Leishmania* spp parasites are difficult to kill because their localisation protects against immune responses and chemotherapy. Drug treatments have limited efficacy, have to be used for lengthy periods of time, and the systemic side-effects sometimes outweigh any clinical benefits. Thus, successful treatment of diseases caused by intracellular pathogens might need combination therapies and effective delivery systems. Imiquimod and resiquimod are currently used for treatment of leishmaniasis; both trigger Toll-like receptor (TLR)-7-mediated innate immune responses, inducing production of interleukin 6, type 1 interferons, and TNFα,[82] and thus act in a host-directed manner. Overproduction of TNFα in *Leishmania braziliensis* infection contributes to mucosal tissue damage, consequently leading to development of mucocutaneous leishmaniasis.[84] In this case, a combination of antileishmanial drugs and anti-TNFα (adalimumab) during active *L braziliensis* infection might yield a clinical response. In preclinical studies, delivery of nanocapsulated doxorubicin (in a formulation that included chondroitin sulfate) to hamsters increased killing of leishmanial promastigotes via augmentation of Th1-mediated immune responses via induction of interferon γ, TNFα, and interleukin 2 release in addition to direct antiparasitic activity.[83] Sequential chemoimmunotherapy, with a single low dose of liposomal amphotericin B and a novel T-cell-epitope-enriched DNA vaccine candidate (LEISHDNAVAX; Mologen AG, Germany) was tested as host-directed therapy. The vaccine candidate boosted the efficacy of a single suboptimal dose of liposomal amphotericin B in C57BL/6 mice.[169] Polyhexanide is a cationic polymer, which is able to directly

kill *Leishmania major* and to enhance host-directed killing by improving the delivery of immunomodulatory nucleic acids. Polyhexanide spontaneously binds CpG ODN (short synthetic oligodeoxynucleotides comprising cytosine triphosphate [C] and guanine triphosphate [G] residues in sequential order), forming stable nanopolyplexes that enhanced uptake of CpG ODN, potentiated antimicrobial killing, and reduced host-cell toxicity of polyhexanide.[170] These findings warrant further investigation.

Trypanosoma spp cause human trypanosomiasis, two important vector-borne diseases: human African trypanosomiasis (also known as sleeping sickness; caused by *Trypanosoma brucei gambiense* and *T brucei rhodesiense*) and Chagas disease (caused by *Trypanosoma cruzi*).[171] Severe pathology in patients with human African trypanosomiasis can lead to fatal meningoencephalopathy and in many cases coma.[172] In Chagas disease, patients are prone to infectious myocarditis or meningoencephalitis, or both, which are often life-threatening, and progressive damage of the autonomic nervous system occurs with organ enlargement and failure.[171]

In mouse models of *T brucei* infections, equilibrium between early onset of Th1 responses (interferon γ, TNFα) and late Th2 responses (interleukin 4, interleukin 10) can control parasitaemia and associated pathology.[85] Additionally, interferon-γ-driven nitric oxide, MHC-I antigen processing and presentation, and CD8 cytotoxic T-lymphocyte activation have a role in eliminating parasite reservoirs in macrophages.[85] In human beings, cytokine analysis of cerebrospinal fluid specimens showed that patients with late-stage human African trypanosomiasis have raised levels of pro-inflammatory cytokines, including TNFα, interleukin 6, interleukin 8, monocyte chemotactic protein 1 (MCP-1; also known as CCL2), and macrophage inflammatory protein (MIP)-1α, among others.[85] This destructive inflammation might be amenable to cellular therapy in late-stage human African trypanosomiasis, whereas immunostimulatory treatment with vitamin D3, interferon γ, and interleukin 2 could be useful at early stages. Interferon-γ-induced apolipoprotein 1 is a known host factor with antitrypanosomal activity. Thus, activating the immune system at an early stage with interferon γ could help control burden of parasitaemia via different effector mechanisms. Since the immune response profile in Chagas disease is similar to that in human African trypanosomiasis,[171] host-directed therapies relevant to human African trypanosomiasis might also benefit patients with *T cruzi* infection, in addition to antiparasitic therapy.

Schistosomiasis affects more than 250 million people in 78 countries,[173] and is caused by the trematode parasites of the genus *Schistosoma*. Major clinical manifestations arise from pathology due to granulomatous reaction around the ova in all major organs of the body, especially the urinary and gastrointestinal tracts.[173] The anti-schistosomal immune response milieu mainly consists of Th1 cytokines (interferon γ, TNFα, interleukin 12p40) and interleukin 17. Interleukin 6 and interleukin 1β also seem to have an important role early after infection with *Schistosoma* spp cercariae.[87] In interleukin-10-deficient mice repeatedly infected with *Schistosoma mansoni*, CD4 T-cell activity was more pronounced, targeted, and efficient, upon exposure to schistosoma antigen preparation.[174] This finding, if extrapolated to human beings, would suggest that multiple exposures to *S mansoni* might reduce T-cell responsiveness in an interleukin-10-dependent manner and hence, weaken productive cellular immune responses. Use of interleukin 2 and interferon γ might help to recover T-cell responses in patients in endemic countries. Notably, the use of Th2 cytokines such as interleukin 25 and interleukin 33 in a mixture with schistosomal glyceraldehyde-3-phosphate dehydrogenase and peroxi-redoxin in a post-exposure vaccination attempt resulted in immense reduction of migrating cercariae in *S mansoni*-infected mice.[88]

Search strategy and selection criteria

We searched PubMed, the Cochrane Library, Embase, and Google Scholar for articles published in English between Nov 15, 2000, and Jan 15, 2016, with the terms "infectious diseases", "parasitic diseases" and combined with the terms "host", "host-directed therapy", "host-directed treatment", "adjunct therapy", "adjunct treatment", "immunotherapy", "cellular therapy", "repurposed drugs", "therapeutic advances", "treatment", "treatment regimens", "trials", "clinical trials", and "animal models". We also found publications from searches of websites of manufacturers of anti-infective drugs and immune-based therapies. We also reviewed studies (published between Nov 15, 2000, and Jan 15, 2016) cited by articles identified by this search strategy and selected those we identified as relevant. Selected review articles are cited to provide readers with more details and references than this Review can accommodate.

Conclusions

Host-directed therapies targeting host immune and inflammatory pathways to enhance immune responses and alleviate immunopathology could benefit treatment outcomes in a range of bacterial, viral, and parasitic diseases. The variability in the potential of adjunct host-directed therapies to deliver clinically meaningful benefit for each pathogen demands definition. This definition will in part depend on how effective the standard antimicrobial therapy is, and whether tissue damage or other events represent therapeutic targets that otherwise are not addressed by conventional treatment. The focus on host-directed therapeutic strategies across various infectious diseases will require more investment for multidisciplinary research collaborations between academic and industrial partners to develop and take forward the assessment of host-directed therapies.

Contributors
AZ, MM, and MR developed the first drafts of the manuscript, and the draft of the revisions. All authors contributed to the writing of subsequent and final drafts.

Declaration of interests
We declare no competing interests.

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