Statins: a viable candidate for host-directed therapy against infectious diseases

Suraj P. Parihar[1,2,3,4]*, *Reto Guler*[1,2,3] *and Frank Brombacher*[1,2,3]*

Abstract | Statins were first identified over 40 years ago as lipid-lowering drugs and have been remarkably effective in treating cardiovascular diseases. As research advanced, the protective effects of statins were additionally attributed to their anti-inflammatory, antioxidative, anti-thrombotic and immunomodulatory functions rather than lipid-lowering abilities alone. By promoting host defence mechanisms and inhibiting pathological inflammation, statins increase survival in human infectious diseases. At the cellular level, statins inhibit the intermediates of the host mevalonate pathway, thus compromising the immune evasion strategies of pathogens and their survival. Here, we discuss the potential use of statins as an inexpensive and practical alternative or adjunctive host-directed therapy for infectious diseases caused by intracellular pathogens, such as viruses, protozoa, fungi and bacteria.

Low-density lipoproteins
(LDLs). Molecules that transfer lipids (fats) in extracellular fluid for cell receptor-mediated uptake. Increased levels of circulating LDLs are associated with atherosclerosis and an elevated risk of developing heart diseases.

Isoprenoids
15-Carbon farnesyl or 20-carbon geranylgeranyl lipid moieties derived from the cholesterol synthesis pathway. They are important for protein prenylation, which regulates protein–protein and protein–membrane interactions.

Prenylation
A post-translation protein modification that occurs through the addition of an isoprenoid lipid derived from the cholesterol synthesis pathway.

*e-mail: suraj.parihar@uct.ac.za; frank.brombacher@icgeb.org

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In 1976, the first statin, mevastatin, was discovered in Japan by Akira Endo in the culture broth of the fungus *Penicillium citrinum*[1]. Subsequently, it became apparent that the dual role of statins in the clearance of cholesterol from intracellular and extracellular compartments made them highly effective drugs. Statins inhibit 3-hydroxy-3-methyl glutaryl (HMG)-CoA reductase, a rate-limiting enzyme that catalyses the conversion of HMG-CoA into L-mevalonate[1], and thereby inhibit cholesterol biosynthesis[2]. This targeted inhibition of intracellular cholesterol synthesis leads to the upregulation of receptors for low-density lipoproteins (LDLs) on the cell surface, which enhances clearance of cholesterol from circulation[3] (BOX 1). A similar mechanism of action is shown by the recently marketed proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, which also upregulate LDL receptors on hepatocytes to remove LDL from the circulation and may also remove bacterial endotoxins during sepsis[4]. Considering the implication for new treatment strategies, further development of statins and their prescription were prompted worldwide. As a result, statins achieved a total of US$27 billion in revenue in 2009 (REF.[5]) alone. This dropped to $20.5 billion in 2011 owing to the expiration of registered patents. Competition with generic drugs further slumped the statin market to $12.2 billion in revenues in 2018. However, owing to the increasing size of the target population (namely, healthy individuals at low risk of developing cardiovascular disease) and their affordability, the cumulative global sales of statins are estimated to approach $1 trillion by 2020 (REF.[6]).

Large-scale clinical studies have provided indisputable evidence that statins protect against cardiovascular diseases by an astounding 30–35%[7,8]. In addition to lowering cholesterol, statins also inhibit isoprenoids, which are vital in the protein prenylation functions of cells. This inhibition of prenylation accounts for a large part of the anti-inflammatory abilities of statins[7,9]. Specifically, the CARE, LIPID and HPS clinical trials were the first to prompt the fundamental idea that the beneficial effects of statins were not limited to cholesterol reduction alone[7]. Ezetimibe, a non-statin that is equally effective in lowering lipids, was not able to improve endothelial functions in patients with coronary events. By contrast, statins improved endothelial functions in these patients, thereby suggesting a regulatory role of statins beyond cholesterol reduction[10]. Furthermore, statins have pleiotropic cholesterol-independent functions, such as broad-range immunomodulatory[11] and anti-inflammatory properties[12]. For instance, statins increase the activity of endothelial nitric oxide synthase to promote angiogenesis[13]. In addition, statins also induce new bone formation by activating osteoblast cells and show potential for the treatment of osteoporosis[14]. Importantly, the JUPITER trial provided evidence for the prophylactic use of statins in reducing the risk of coronary events. Healthy individuals prophylactically treated with rosuvastatin had reduced levels of cholesterol and C-reactive protein (CRP), and their risk of developing coronary events was diminished by 55%[15].

The recognition of these pleiotropic effects of statins has generated interest in exploring their influence

C-reactive protein
(CRP). A systemic marker of inflammation produced by the liver; elevated levels of CRP are associated with a high risk of heart disease risk.

RAS, RAB, RHO, RAC and RAP
GTP-binding proteins that act as switches to regulate vital cell functions. For example, RAS and RAP regulate cell proliferation, cell differentiation and responses to a stimulus, RAB regulates intracellular vesicular transport, and RHO and RAC regulate the cytoskeleton and cell morphology.

on the outcome of infectious diseases. Cholesterol is an integral contributor to the normal cellular homeostasis in host cells, particularly in the maintenance of cellular membranes and the formation of lipid rafts, as well as in vesicular trafficking and signal transduction[16]. Moreover, cholesterol also contributes to successful invasion by pathogens by acting as a docking site for the internalization, uptake and safe cellular invasion of viruses[17], protozoan parasites[18], fungi[19] and bacteria[20].

The global increase in antibiotic resistance has peaked with dire consequences for public health. Therefore, additional treatment strategies are urgently needed to improve clinical outcomes of infectious diseases. Despite conflicting reports, statins have emerged as a major contender against other repurposed drugs with the potential not only to be used as an alternative treatment where drug resistance has emerged but also to increase the efficacy of standard therapies. Furthermore, statins have the benefit of being safe, well-tolerated and widely used for oral administration and can therefore be quickly implemented. In this Review, we consider the use of statins in the context of infectious diseases by interrogating beneficial as well as detrimental effects in preclinical models of disease. We will focus on mechanistic data, observational studies and randomized controlled trials, which together suggest the clinical potential of statins as a host-directed therapy.

Statins: mode of action

At the proximal end of the mevalonate pathway, statins inhibit HMG-CoA reductase, thereby decreasing the immediate synthesis of mevalonate and cholesterol biosynthesis (FIG. 1). In addition, statins also prevent the synthesis of downstream lipid isoprenoid intermediates such as farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP)[21]. During prenylation, isoprenoids are added to several proteins including G protein subunits like RAS, RAB, RHO, RAC and RAP, which facilitate anchoring to lipid rafts in the cell membrane. This crucial pathway is regulated by feedback mechanisms at multiple levels, including transcriptional, translational and post-translational products by both the sterol and non-sterol arms. The importance of these intermediates has been shown in several studies demonstrating that statins are crucial for apoptosis, angiogenesis, cell secretion, proliferation, growth, inflammation and immunomodulation[22]. Given the pivotal role that G proteins play in cellular functions, it is not surprising that the immune response was modified independently of the lipid-lowering effects of statins. This was evident from our own[23–25] and other studies[26,27], where rescuing metabolic pathways with mevalonate and GGPP could reverse statin-inhibitory effects while treatment with FPP was not effective. This was not surprising considering that statins block isopentenyl pyrophosphate (IPP), which is required by FPP to restore GGPP (FIG. 1) in the mevalonate pathway. This suggests that GGPP plays a primary role in the statin-mediated host-protective effects. Reviews by Jain et al. and Greenwood et al. have discussed this in detail, particularly the statin-mediated inhibition of FPP and GGPP and their effects on prenylation[9], transcription factors and basic cell biology[7] (FIG. 1). Indeed, preclinical studies have contributed substantially to our basic understanding of the mechanisms of how statins mediate host-protective functions beyond the inhibition of HMG-CoA reductase. For instance, RHO proteins activate nuclear factor-κB (NF-κB), a major transcriptional regulator of inflammation. This highlights the excellent potential to identify targets to develop highly specific drugs of clinical relevance for inflammatory conditions. One such example is that the inhibition of RHO by statins exerts direct anti-inflammatory effects. This observation has guided the development of fasudil, a RHO kinase inhibitor[28]. Notably, statins also induce Kruppel-like factor 2 (KLF2) expression, which negatively regulates the pro-inflammatory activation of monocytes by suppressing NF-κB activation, thus decreasing the pathology associated with inflammation[29]. Therefore, the development of statins, which are potent inducers of KLF2, would suppress NF-κB activity and in turn decrease host inflammatory damage.

The cellular effects of statins are variable, and on the basis of their specific chemical properties, they are either hydrophilic or lipophilic in nature. Hydrophilic statins such as rosuvastatin, fluvastatin and pravastatin are administered directly in the active hydroxyl form. However, the new-generation rosuvastatin is much more potent owing to greater lipophilicity and a longer half-life. Lipophilic statins are more likely to enter endothelial cell membranes via passive diffusion. Lipophilic statins, including simvastatin, lovastatin and atorvastatin, need to be administered in lactone (closed ring) and converted to an active hydroxyl form (open ring) by hepatic cells[30].

Statins in infectious diseases

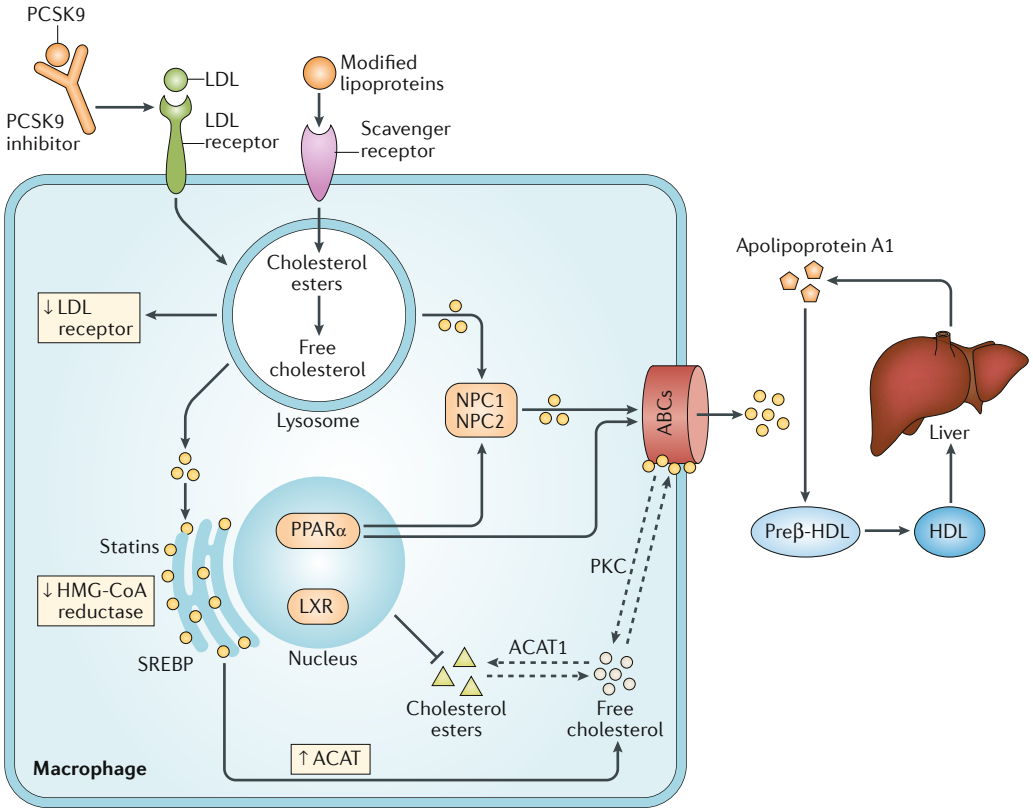
Evidence from preclinical models. Statins are well established as immunomodulators in preclinical studies[11]. The immunomodulatory and anti-inflammatory functions of statins are attributed to their inhibition of protein prenylation[9]. Statins have been shown to affect both T helper 1 (T_H1) cell-type and T_H2 cell-type responses. For instance, the treatment of mouse dendritic cells with simvastatin decreased the induction of T_H1 cell responses, and this was associated with a reduced IFNγ and T-BET signature. Conversely, simvastatin treatment resulted in the increased expression of T_H2 cell-associated mediators, such as IL-4, IL-5, IL-13 and GATA3. Statins have been shown to promote T_H2 cell responses by inducing dendritic cell expression of the chitinase family member YM1 (also known as CHIL3)[31]. This suggests that statins

Author addresses

[1]International Centre for Genetic Engineering and Biotechnology (ICGEB), Cape Town-Component, Cape Town, South Africa.
[2]Institute of Infectious Diseases and Molecular Medicine (IDM), Department of Pathology, Division of Immunology and South African Medical Research Council (SAMRC), Immunology of Infectious Diseases, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa.
[3]Wellcome Centre for Infectious Diseases Research in Africa (CIDRI-Africa) and Institute of Infectious Disease and Molecular Medicine (IDM), Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa.
[4]Division of Medical Microbiology, Department of Pathology, University of Cape Town, Cape Town, South Africa.

Box 1 | **Regulation of cholesterol in extracellular and intracellular compartments**

Scavenger receptors or low-density lipoproteins (LDL) receptors mediate the uptake of cholesterol-enriched lipoproteins from the circulation. Lysosomal hydrolysis releases cholesterol into the cytoplasm, resulting in activation of the sterol regulatory element-binding protein (SREBP) pathway in the endoplasmic reticulum, which suppresses gene expression of 3-hydroxy-3-methyl glutaryl (HMG)-CoA reductase to decrease de novo cholesterol biosynthesis. Transcription factors such as peroxisome proliferator-activated receptor-α (PPARα) and liver X receptor (LXR) trigger the efflux of cholesterol by driving the expression of the genes encoding NPC intracellular cholesterol transporter 1 (NPC1), NPC2 and ATP-binding cassette (ABC) transporters. This decreases the availability of free cholesterol for storage in the form of cholesteryl esters by the action of ACAT enzymes. Free cholesterol is also transported by the action of protein kinase C (PKC) via membrane diffusion. Extracellular cholesterol is then loaded into high-density lipoproteins and transported to the liver for subsequent bile acid synthesis or excreted. This dual mode of statins in driving the clearance of cholesterol has made them highly effective drugs for cardiovascular diseases. In addition, subtilisin/kexin type 9 (PCSK9) inhibitors block the ability of PCSK9 to bind LDL receptors for subsequent lysosomal degradation, thereby increasing the abundance of LDL receptors on the cell surface to clear cholesterol from the circulation.



HDL, high-density lipoprotein.

could be beneficial in controlling infections that are dependent on T_H2 cell responses for resolution, such as helminth infections. Below, we discuss relevant studies that highlight the potential of statins as a host-directed therapeutic in viral, parasitic, fungal and bacterial infectious diseases.

Viral infections. There is compelling evidence that demonstrates the inhibitory effects of statins on viral infections by targeting specific mechanisms of the mevalonate pathway. These mechanisms include rearrangement of the cytoskeleton and cell cycle, inhibition of sterols and augmentation of protein prenylation, which all have downstream effects on the host immune response to infection. Interestingly, statins were also shown to inhibit HIV replication in $CD4^+$ T cells. Here, statins induced an increase in expression of the cyclin-dependent kinase inhibitor p21, which inhibited immune cell activation and proliferation as well as their expression of CC-chemokine receptor 5 (CCR5), a co-receptor that facilitates HIV infection[32]. Furthermore, by inhibiting sterols, statins have also been shown to suppress murine cytomegalovirus (MCMV) loads in multiple organs by increasing type I interferon responses[27]. However, this protective type I interferon response was also shown to decrease antiviral activity of lovastatin in a mouse model of gamma herpesvirus (MHV) infection[33]. Besides sterols, isoprenoid inhibition by statins has been shown to reduce respiratory syncytial virus (RSV) loads owing to the lack of sufficient intermediates of protein prenylation and the associated disease pathogenesis in mice[34]. The latter is due to the decreased production of inflammatory mediators such as CC-chemokine ligand 2 (CCL2), CCL4, CCL5, IL-6 and tumour necrosis

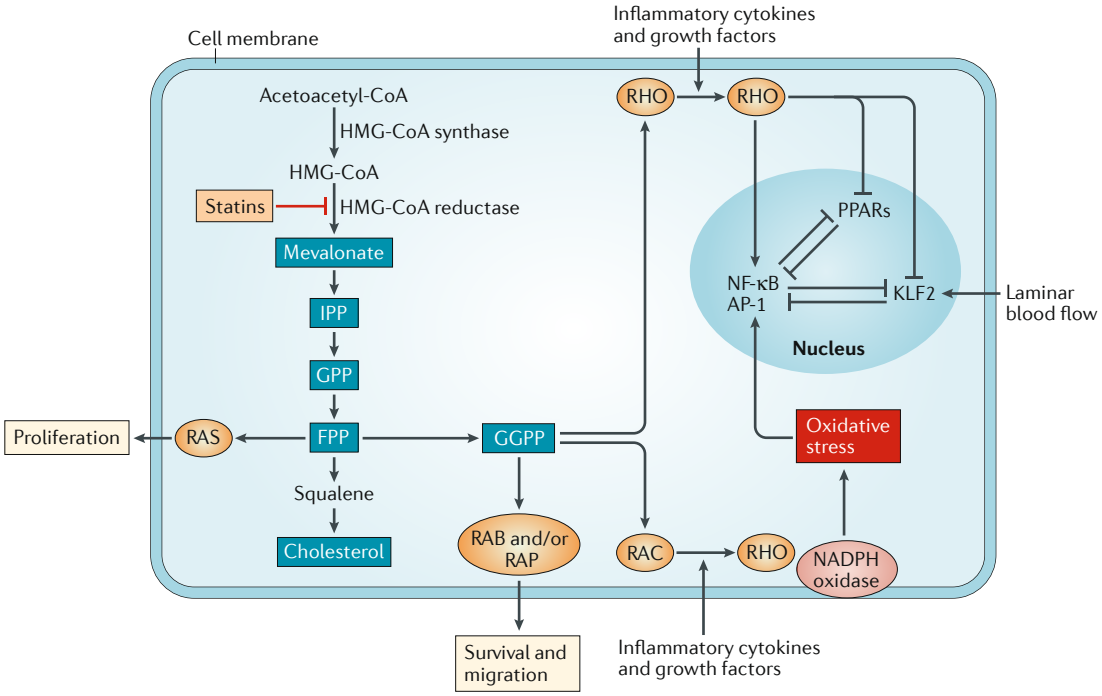


Fig. 1 | **The effect of statins on cellular processes.** Statins inhibit 3-hydroxy-3-methyl glutaryl (HMG)-CoA reductase to prevent the synthesis of mevalonate, which in turn inhibits cholesterol synthesis and isoprenoid production. Statins also inhibit the prenylation pathway (blocking farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP) synthesis) to reduce cell proliferation, survival, secretion and migration. Reduced isoprenoid production also decreases nuclear factor-κB (NF-κB) expression, thereby increasing expression of Kruppel-like factor 2 (KLF2) and inhibiting pro-inflammatory responses. Statins with greater potential to induce KLF2 expression are better able to protect the host from tissue-damaging pro-inflammatory cytokines. In addition, NF-κB also has inhibitory activity on the expression of peroxisome proliferator-activated receptors (PPARs). GPP, geranyl pyrophosphate; IPP, isopentenyl pyrophosphate. Adapted with permission from REF.[7], Springer Nature Limited.

factor (TNF)[35]. The key mechanism by which fluvastatin decreases cytomegalovirus (CMV) loads seems to be attenuation of inflammatory responses by targeting NF-κB activity in human primary endothelial cells[36]. In human peripheral blood mononuclear cells, lovastatin inhibited the replication of dengue virus by partially targeting protein prenylation of the mevalonate pathway[17]. Moreover, in HeLa cells, simvastatin suppressed poliovirus infection by directly targeting viral RNA synthesis[37]. Of interest, statins failed to protect during influenza A virus infection (H3N2 and H1N1) in both BALB/c and C57BL/6 mouse models[38]. Remarkably, a preventive therapeutic approach using a combination of statin and caffeine was more effective at reducing viral replication and associated lung damage owing to the immunomodulatory effects of caffeine in a BALB/c model of H5N1, H3N2 and H1N1 influenza. Furthermore, the treatment proved to be equally as effective as oseltamivir and ribavirin[39]. More recently, simvastatin was shown to be a potent vaccine adjuvant against influenza. By decreasing protein prenylation, statin increased antigen retention, presentation and T cell activation, which completely protected mice and cynomolgus monkeys against influenza HA1 infection[40]. Thus, the approach of manipulating statin-mediated host immunity to viral diseases opens a window for specific targeting of downstream products of the mevalonate pathway. We summarize the effects of statin on the immune response in FIG. 2 and the various mechanisms by which statins control infections with viruses and other pathogens in TABLE 1.

Oseltamivir and ribavirin
Oseltamivir is an antiviral drug used to treat influenza A and influenza B infection through the inhibition of neuraminidase, which is an enzyme that supports viral replication. Ribavirin inhibits viral polymerases and is widely used for the treatment of hepatitis C, respiratory syncytial virus infection and viral haemorrhagic fever. The combination of oseltamivir and ribavirin is used against highly pathogenic H5N1 influenza viruses.

Parasitic infections. Evidence supports the idea that statins play an anti-parasitic role, partly owing to their ability to reduce cholesterol, increase phagocytosis and produce anti-parasitic molecules. Statins also drive cyclooxygenase 2 (COX2; also known as PTGS2) induction and the generation of lipoxins that downregulate inflammation. Intracellular parasites rely on cholesterol to anchor onto the host cell membrane for subsequent internalization. For instance, the simultaneous inhibition of both endogenous cholesterol by mevastatin and exogenous cholesterol by lipid-deficient serum decreased the replication and growth of *Toxoplasma gondii* parasites in parasitophorous vacuoles of fibroblasts[41]. This highlights the importance of LDL receptor-mediated acquisition of cholesterol during pathogenesis. Sterol inhibition was also shown to decrease the intracellular growth of *Leishmania donovani* in human macrophages[42]. During *Leishmania amazonensis* infection, statins increased phagocytosis and nitric oxide production but limited the production of TNF, a tissue-damaging cytokine, in peritoneal macrophages[43]. This macrophage response was associated with an increased survival and decreased footpad swelling in pravastatin-treated BALB/c mice[44]. We were able to show that statin treatment of both BALB/c

	B cell	Monocyte	Endothelial cell	T cell	Peripheral blood mononuclear cell	Dendritic cell	Macrophage
Mouse	↓ IgG1 ↓ IgG2a	↓ CCL2	↓ CCL2 ↑ IL-1 ↑ TNF ↑ ICAM ↑ eNOS	↓ Immune synapse ↓ IFNγ and MHC class II ↓ CCR7 and LFA1 ↓ Proliferation ↓ IL-2 and TNF ↑ IL-4 ↑ IL-5 ↑ IL-10 ↑ TGFβ ↑ IFNγ	No difference in immune response to mitogens	↓ IL-1β ↓ iNOS ↑ TNF and IL-6 ↑ IL-12 ↑ MHC class II	↓ Phagocytosis and CIITA ↓ Migration and MHC class II ↓ NF-κB and MMP9 ↓ CD40, CD80 and CD86 ↑ TNF ↑ IL-12 ↑ COX2 ↑ H_2O_2
Human	↑ Apoptosis ↓ CD80, CD86 and MHC class II ↓ Proliferation ↓ CCL2 and CCL5	↑ CCL2 and IL-1β ↑ TNF and IL-8	↑ eNOS ↓ MHC class II ↓ CIITA ↓ CCL2	↓ Proliferation ↓ Lipid rafts and/or GM1 ↓ CD69 ↑ IFNγ	↑ IFNγ ↑ IL-1β ↑ IL-18 ↓ IL-2, IL-6, IL-8 and IL-10 ↓ IL-1Rα and CCL2 ↓ IL-4, IL-5 and IL-17	↑ TLR2 ↑ TLR4 ↓ Endocytosis and MHC class II ↓ CD40, CD80 and CD86 ↓ IL-6, IL-8 and IL-12 ↓ IL-2Rα and CD71 ↑ MHC class II	↓ MHC class II ↓ MMP9 ↓ TNF

Fig. 2 | **The effect of statins on immune cell populations in mice and in humans.** Statins influence the ability of phagocytic cells such as macrophages, dendritic cells and monocytes to produce cytokines and chemokines[150]. These drugs also affect the ability of lymphocytes to proliferate and release cytokines and chemokines. In addition, endothelial cells increase their expression of adhesion molecules, cytokines and endothelial nitric oxide synthase (eNOS) upon statin treatment. The immunomodulatory properties of statins are due to their ability to influence the immune cells in the context of existing diseases. Most of the cytokines and chemokines depicted in this figure are downregulated in the presence of statins in both mice and humans, reinforcing their overall anti-inflammatory functions[151]. However, statins also augment pro-inflammatory cytokines in an immune cell-specific manner, which may be attributed to the type of statin (hydrophilic versus lipophilic)[134], cell type and response measured ex vivo[152,153]. Recently, statin has been discovered to be a potent vaccine adjuvant that increases antigen presentation and retention, which in turn enhance T cell activation[40]. CCL, CC-chemokine ligand; CCR, CC-chemokine receptor; COX2, cyclooxygenase 2; H_2O_2, hydrogen peroxide; iNOS, inducible nitric oxide synthase; TNF, tumour necrosis factor.

and C57BL/6 mice during *Leishmania major* infection reduced disease severity as well as parasite burden in both footpads and draining popliteal lymph nodes[25]. This was associated with increased production of hydrogen peroxide and phagosomal maturation (as measured by lysosome-associated membrane glycoprotein 3 (LAMP3) positivity) in statin-treated macrophages (FIG. 3). Moreover, topical application of statin on ear lesions reduced swelling and parasite burdens[25]. In addition, parasite burdens were also decreased in draining cervical lymph nodes, suggesting a positive outcome that expands beyond the ear pinna infection site. Hence, host-directed therapy might offer promising innovative approaches in the treatment of skin lesions or infections caused by leishmaniasis, which can result in permanent physical disfiguration and social stigma.

Host-directed therapeutics offer an important adjunctive therapy option to complement current treatment strategies for specific parasitic diseases. This invaluable alternative approach to use statins in a combination of therapies has immense potential. Evidence already suggests a promising outcome for cerebral malaria. Statins administered together with the anti-malarial drugs mefloquine or dihydroartemisinin reduced the mortality of mice infected with *Plasmodium berghei*. This has been associated with decreased neuronal apoptosis[45] and lower production of tissue-damaging cytokines and chemokines (such as IL-13, CCL4, CCL11, CXC-chemokine ligand 2 (CXCL2) and CXCL5)[46]. Increased levels of anti-inflammatory mediators were also beneficial to contain *Trichinella spiralis* infection. Here, statins increased the efficacy of metformin (an anti-diabetic drug) and reduced larval counts in the muscle tissue of infected mice. These protective effects were associated with a marked reduction in host cellular infiltration, COX2 expression and oxidative stress[47]. Moreover, in a study using hypercholesterolemic mice, statins administered with the anti-malarial drug artesunate enhanced protection against schistosomiasis[48]. This was achieved by targeting the structural organization of the worms, thereby rendering them susceptible to artesunate.

Recently, in an experimental model of cryptosporidiosis, atorvastatin decreased the severity of *Cryptosporidium* spp. infection. For this model, mice were immunosuppressed with dexamethasone and represented an immunocompromised host. Moreover, this protective effect was enhanced when atorvastatin was administered with standard nitazoxanide therapy[49]. In another study, simvastatin increased the trypanocide activity of benznidazole therapy, thereby improving

Table 1 | **Mechanisms of statin action against various intracellular pathogens**

Mechanism of statin action	Infectious agents targeted	Refs
Inhibition of sterols, prenylation and isoprenoids	RSV, CMV, gamma herpesvirus, influenza virus (H5N1, H3N2 and H1N1 strains), dengue virus, HIV-1, *T. gondii*, *T. cruzi*, *L. donovani*, *Cryptosporidium* spp., *C. neoformans*, *C. albicans*, *Aspergillus* spp., *F. oxysporum*, *M. tuberculosis*, *M. leprae*, *S. aureus*, *K. pneumoniae*, *C. burnetii*, *R. conorii* and *S. enterica*	17,27,32,34,36,38,39,41, 42,49–51,54,55,66,69–71,77,78
Induction of anti-inflammatory cytokines	RSV, *P. pneumoniae*, *L. amazonensis*, *H. capsulatum*, *C. pneumoniae*, *P. berghei*, *T. spiralis*, *C. albicans*, *S. aureus*, *B. burgdorferi*, *Y. pestis* and *P. aeruginosa*	35,43,46,47,57,80,83,85–87,123
Induction of pro-inflammatory cytokines	*M. tuberculosis*, *L. monocytogenes* and *S. aureus*	24,75,77,79
Modulation of reactive oxygen and nitrogen species	*L. amazonensis*, *L. major*, *C. pneumoniae*, *T. spiralis* and *C. gatti*	25,43,47,81,149
Phagosome maturation	*M. tuberculosis*, *M. leprae*, *L. monocytogenes*, *S. enterica*, *H. pylori*, *L. major* and *C. burnetii*	23–25,67–69,71,155
Autophagy	*M. tuberculosis* and *H. pylori*	23,68
Apoptosis	*C. albicans* and *P. berghei*	56,57
Extracellular traps	*S. aureus* and *C. albicans*	61,62
Modulation of COX2	*T. spiralis* (statins downregulate COX2) and *S. aureus* (statins induce COX2)	47,77
Induction of lipoxin A4	*T. cruzi*	50

B. burgdorferi, *Borreliella burgdorferi*; *C. albicans*, *Candida albicans*; *C. burnetii*, *Coxiella burnetii*; *C. gatti*, *Cryptococcus gatti*; *C. neoformans*, *Cryptococcus neoformans*; *C. pneumoniae*, *Chlamydia pneumoniae*; CMV, cytomegalovirus; COX2, cyclooxygenase 2; *F. oxysporum*, *Fusarium oxysporum*; *H. capsulatum*, *Histoplasma capsulatum*; *H. pylori*, *Helicobacter pylori*; *K. pneumoniae*, *Klebsiella pneumoniae*; *L. amazonensis*, *Leishmania amazonensis*; *L. donovani*, *Leishmania donovani*; *L. major*, *Leishmania major*; *L. monocytogenes*, *Listeria monocytogenes*; *M. leprae*, *Mycobacterium leprae*; *M. tuberculosis*, *Mycobacterium tuberculosis*; *P. aeruginosa*, *Pseudomonas aeruginosa*; *P. berghei*, *Plasmodium berghei*; *P. pneumoniae*, *Pneumococcal pneumoniae*; *R. conorii*, *Rickettsia conorii*; RSV, respiratory syncytial virus; *S. aureus*, *Staphylococcus aureus*; *S. enterica*, *Salmonella enterica*; *T. cruzi*, *Trypanosoma cruzi*; *T. gondii*, *Toxoplasma gondii*; *T. spiralis*, *Trichinella spiralis*; *Y. pestis*, *Yersinia pestis*.

the pathophysiological condition of patients who were infected. Statin therapy induced 15-epi-lipoxin A4 production and prevented *Trypanosoma cruzi*-induced activation of endothelial cells[50]. TABLE 1 highlights some of the cellular mechanisms responsible for the control of parasite growth and survival of the host. In summary, these studies provide compelling evidence that statins, in combination with standard therapies, have pronounced effects on the outcome of infection by reducing the inflammatory responses that are detrimental to the host.

Fungal infections. Studies have reported that the anti-fungal effects of statins are due to their ability to inhibit the sterol arm of mevalonate synthesis, inhibit prenylation, influence host immune responses and increase extracellular traps. Fungal metabolites such as ergosterol (the equivalent of cholesterol), prenylation and dolichol synthesis are required for growth and survival. These metabolites and associated processes have been directly targeted to develop anti-fungal drugs in the past. Thus, the inhibitory action of statins in fungal cultures was not surprising. However, the synergistic and additive effects that statins have in conjunction with the anti-fungal drugs fluconazole and itraconazole, which inhibit the growth of *Candida* spp. and *Cryptococcus neoformans*[51], raise the potential of using statins as an adjunct therapy. Statins have been shown to directly target fungal mitochondrial DNA and inhibit ergosterol synthesis, thereby attenuating the growth of *Candida* spp.[52] and pathogenic *Aspergillus fumigatus*[53]. These statin-mediated inhibitory effects were completely reversed by the supplementation of ergosterol, indicating that statins act through blockade of sterol synthesis in fungi. In mouse candidiasis, pravastatin induced the inhibition of fungal farnesol and consequently increased the survival of *Candida albicans*-infected mice[54].

In a cataract mouse model, topical application of both simvastatin and an iron chelator directly on the cornea inhibited fungal siderophore and ergosterol biosynthesis. Consequently, the growth of *A. fumigatus* and *Fusarium oxysporum* was reduced[55]. As previously mentioned for other infections, statins have been associated with modulating host immune responses to fungi. Apoptosis, a key immune mechanism responsible for the fungistatic effect of drugs on *C. albicans*[56], was shown to be mediated by statins. Moreover, statins were shown to regulate macrophage apoptosis during *Histoplasma capsulatum* infection. This was associated with a decrease in TNF and an increase in IL-10 production[57]. Lovastatin mediates an anti-inflammatory response by augmenting local CCL1 induction. This in turn recruits regulatory T cells, shifting the immune response to favour T_H2 cell-type responses both at the site of infection and in draining lymph nodes[58]. This suggested lovastatin-induced regulatory T cell recruitment was CCL1-dependent. In vitro, statins appear to increase the activity of fluconazole against *C. albicans* by increasing the expression of genes involved in the ergosterol pathway and prenylation, which are responsible for controlling fungal respiration and growth[59]. In another culture system using *Aspergillus* spp., statins were also shown to be fungicidal. However, statins had no added benefit on the activity of the anti-fungal drugs including itraconazole, voriconazole and amphotericin B[60].

Statins are known to induce the formation of extracellular traps[61], a mechanism responsible for killing both yeast and hyphae cells in *C. albicans*-infected human neutrophils[62]. At physiological concentrations, statins were shown to be moderately effective without altering the anti-fungal activity of fluconazole, suggesting that coadministration could be safer[63]. More importantly, results from preclinical studies suggest that statins used in combination with anti-fungal drugs lower the concentration of drugs required to achieve the same efficacy. This has important implications when considering aspects of drug safety and has the potential to reduce the frequency of fungal drug resistance[64]. Though statins require higher concentrations to exhibit anti-fungal properties in vitro, their potential in the topical treatment of dermatophyte infections should not be overlooked. This approach offers a novel avenue

Fluconazole and itraconazole
Fluconazole is anti-fungal drug used to prevent *Candida* spp. infections. Itraconazole is a second-line drug with a wide spectrum against fungal infections.

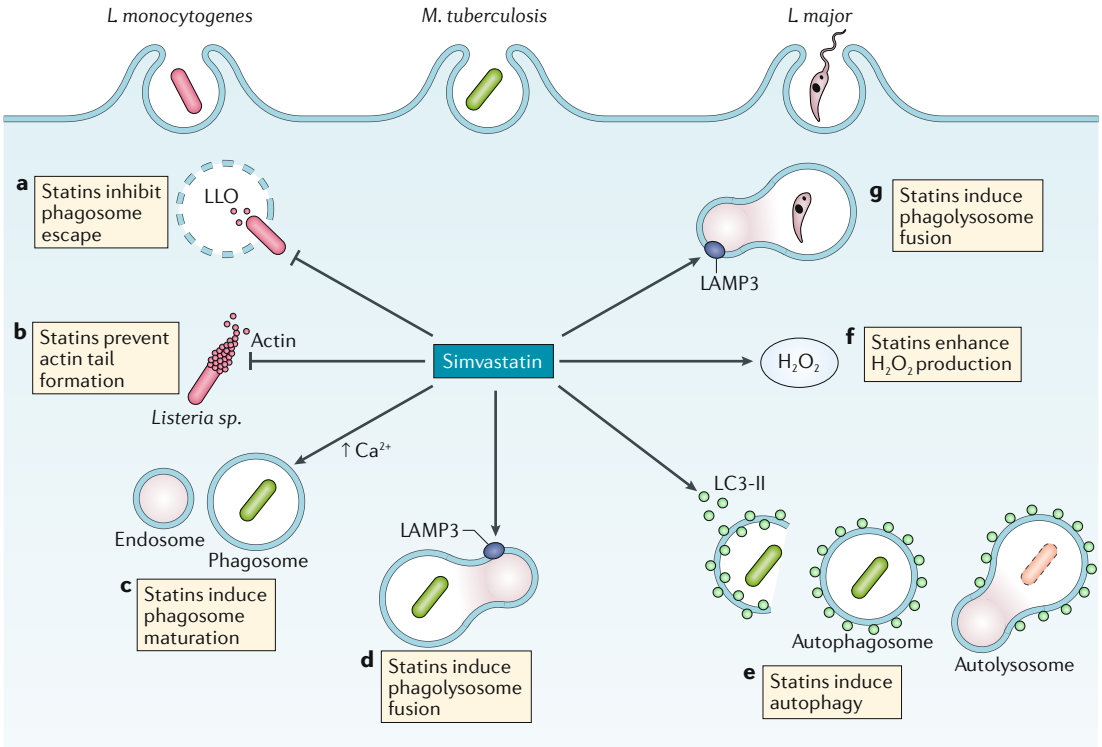


Fig. 3 | **Mechanisms by which statins increase macrophage killing functions to contain the growth of *Listeria monocytogenes*, *Mycobacterium tuberculosis* and *Leishmania major*. a** | Phagosome escape of *Listeria monocytogenes* is prevented by simvastatin in a listeriolysin O (LLO)-dependent manner. **b** | The statin-inhibitory effect on the actin cytoskeleton reduces the ability of cytosolic *L. monocytogenes* to disseminate through actin comet tails. **c** | Statins counter *Mycobacterium tuberculosis*-induced phagosome arrest by inducing the expression of early endosome antigen 1 (EEA1), which might be due to increased Ca^{2+} levels in macrophages. **d** | The increased expression of lysosome-associated membrane glycoprotein 3 (LAMP3) on *M. tuberculosis*-containing phagosomes induces fusion of lysosomes in the presence of statin. **e** | Autophagy is enhanced by simvastatin via the increased expression of light chain 3-II (LC3-II) into the autophagic membrane, facilitating the fusion of autophagosomes with lysosomes required for efficient killing of *M. tuberculosis*. **f** | Hydrogen peroxide (H_2O_2) radical production is enhanced by simvastatin treatment, which decreases *Leishmania major* parasite loads. **g** | Statin-mediated enhanced phagolysosome fusion contributes to killing of *L. major* parasites. Adapted with permission from REF.[154], Springer Nature Limited.

for host-directed therapeutics in the control of fungal colonization and warrants further investigation.

Bacterial infections. Statins exert their antibacterial effects by targeting invasion, virulence factors, biofilm formation and growth. Hennessy et al.[65] recently reviewed the direct effects of statins on bacterial virulence factors and intracellular growth in vitro and in mouse models. Increasing evidence shows that statins might be another avenue for preventing bacterial infections, particularly those associated with immunomodulatory functions, isoprenoids and/or prenylation, cholesterol and/or lipids, phagocytosis, extracellular traps, phagosome maturation and autophagy (FIG. 2; TABLE 1).

There is convincing evidence suggesting that statins increase the capacity of macrophages to kill *Mycobacterium tuberculosis*. An earlier study found that inhibiting cholesterol with a statin decreased the intracellular survival of *Mycobacterium leprae* in macrophages, highlighting the importance of cholesterol in promoting bacterial growth[66]. Furthermore, cholesterol deprivation was associated with phagosome containment of *M. leprae* and increased macrophage killing functions[67]. This could potentially explain the bactericidal effect against *Mycobacterium tuberculosis* variant *bovis* and *M. tuberculosis* in macrophages. Concurrently, we showed that statin-mediated cholesterol inhibition increased maturation of *M. tuberculosis*-containing early endosome antigen 1 $(EEA1)^+$ and $LAMP3^+$ phagosomes, thereby reducing mycobacterial burdens in macrophages. Furthermore, statins induce autophagy (light chain 3-II $(LC3\text{-}II)^+$), a mechanism responsible largely for the attenuation of *M. tuberculosis* growth in both murine model and human macrophages[23] (FIG. 3). These mechanisms were corroborated by a study which found that statin-induced $EEA1^+LAMP1^+$ phagosomes and autophagy indeed attenuated the growth of *Helicobacter pylori* in primary macrophages[68]. The ability of statins to reduce cholesterol levels in $LAMP1^+$ phagosomes is also linked to the decreased growth of other respiratory pathogens such as *Coxiella burnetii*[69] (which causes Q fever) and *Rickettsia conorii*[70] (a plaque-forming bacteria) in mouse fibroblast cells. Notably, calcium plays a critical role in macrophage phagosome maturation during *M. tuberculosis* infection. Indeed, statins increased calcium levels in murine macrophages and macrophages isolated from patients on statin therapy (S.P.P., unpublished

Autophagy
The process of self-digestion, which involves the delivery of cytoplasmic contents such as damaged organelles, misfolded proteins and invading pathogens to the lysosomes for degradation.

Phagosomes
Cellular organelles that are formed by invagination of the cell membrane during endocytosis. Fusion of a phagosome with lysosomes leads to the degradation of its contents.

observations), suggesting an additional mechanism by which statins influence phagosome maturation. Earlier, we showed that statin treatment had the ability to reduce the bacterial burden of *Listeria monocytogenes* in mice. We showed that the decrease in intracellular growth and dissemination in macrophages was through inhibition of cholesterol, which is responsible for bacterial phagosome escape and actin tail formation[24] (FIG. 3). The inhibitory effect of statins on sterols also induced extracellular trap formation, which increased the killing of *Staphylococcus aureus* in human and mouse phagocytes[61]. However, statins also inhibited non-sterol precursors of the mevalonate pathway and promoted localization of the protease cathepsin D on *Salmonella* spp.-containing phagosomes to increase bacterial killing[71]. These studies highlighted the role of statins on phagosome maturation and autophagy pathways, which could eliminate intracellular pathogens. Remarkably, adjunctive therapy of atorvastatin increased the microbicidal efficacy of rifampin and reduced footpad inflammation during *M. leprae* infection in BALB/c mice[67]. Importantly, simvastatin as an adjunctive therapy increased the efficacy of a first-line tuberculosis regimen[72] and reduced tuberculosis treatment in mice by 1 month[73]. Given these data, it is possible that statins could emerge as an adjunctive therapy for tuberculosis.

The mechanism by which statins attenuate bacterial burdens is also associated with immunomodulatory functions. In a model of tuberculosis using heat-killed avirulent *M. tuberculosis*, statins inhibited geranylgeraniol isoprenoids[74], leading to activation of caspase 1 and enhanced production of IL-1β, IL-18 and IFNγ[75]. Moreover, statins inhibit tyrosine phosphorylation to decrease the formation of lipid rafts and activation of γδ T cells upon stimulation with avirulent *M. tuberculosis* antigens[76]. An important observation was that statins exert different effects on the immune response following the phagocytosis of opsonized versus non-opsonized bacteria, which is due to their ability to inhibit the oxidative burst and protein prenylation. For instance, simvastatin inhibited FcγR-mediated phagocytosis of *S. aureus* by disrupting actin reorganization but enhanced TNF and COX2 production in human macrophages[77]. As such, statin-mediated inhibitory effects on actin polymerization, RAC activation, chemotaxis, neutrophil killing function and inflammation increased blood dissemination of *Klebsiella pneumoniae* in mice[78]. Similarly, statin-mediated inhibition of nitric oxide, haem oxygenase 1 and TNF production seem to hamper the ability of dendritic cells to control *L. monocytogenes* infection through an IFNβ-dependent mechanism[79]. Despite the negative regulation of actin polymerization, phagocytosis and oxidative burst, simvastatin increased the pulmonary recruitment of inflammatory cells, which reduced bacterial growth and dissemination of *Chlamydia pneumoniae* in mice[80]. Statins inhibited inflammatory signalling pathways (such as the NF-κB, RHO and RAC pathways) and the production of pro-inflammatory mediators (such as reactive oxygen species, CCL2 and CCL5) in *C. pneumoniae*-infected human macrophages, and this was associated with decreased dissemination of bacteria to smooth muscle cells[81]. Such a profound ability of statins to attenuate key pro-inflammatory responses was apparent in the decreased mortality of mice during lipopolysaccharide (LPS)-induced sepsis[82]. Lovastatin also decreased pathological immune responses during infection with the plague-causing bacterium *Yersinia pestis*, which was associated with inhibition of septicaemia and reduced inflammatory destruction of lungs and spleen tissue[83]. Furthermore, simvastatin decreased chemokine production to reduce neutrophilic infiltration in the lungs without supressing host-protective pro-inflammatory mediators. Despite reduced neutrophil recruitment, statins decreased platelet-activating factor receptor expression on lung epithelia, which reduced bacterial invasion[84]. This study also showed that statins protected resident alveolar macrophages from pneumolysin-induced cell lysis, which enhanced the bacterial clearance of *pneumococcal pneumonia* in mice[85]. By contrast, statins increased production of anti-inflammatory and type 2 cytokines (namely, IL-4, IL-5, IL-13, IL-9 and IL-10) during *Borrelia burgdorferi* infection in mice, and this was associated with lower bacterial burdens[86]. This study also highlighted that the immune-modulating effects of statins are dependent on the type of statin used. In addition to anti-inflammatory effects, anti-thrombotic activities of statins reduced dissemination and enhanced bacterial clearance of *S. aureus* in a mouse model of pneumonia[87]. Here, statin interfered directly with the microdomain lipids of methicillin-resistant *S. aureus* (MRSA), which is the mechanism that conferred susceptibility of drug-resistant strains to antibiotics[88]. This could explain why the topical application of statin decreases biofilm formation, bacterial growth and levels of inflammatory cytokines (namely, IL-6, IL-1β and TNF) in MRSA-infected skin lesions[89]. This suggests that statin-mediated disruption of membrane microdomains with standard antibiotics could offer a new strategy against multidrug-resistant infections.

Thus, evidence suggests that in the majority of bacterial infections, statins possess beneficial antibacterial properties (TABLE 1). Without overlooking the few cases that describe the negative effects above, the apparent advantages of statin treatment appear to substantially outweigh the disadvantages. More importantly, statins limit the extent of tissue damage owing to pro-inflammatory cytokines, which further emphasizes the potential of statins in host-directed therapeutic strategies. Supplementary Table 1 provides a comprehensive summary of statin studies in preclinical models of the infectious diseases.

Statins in human infectious diseases

Substantial efforts have been invested in understanding the role of statins during human infections caused by bacteria, fungi and viruses. Statins have been strongly associated with improved clinical outcomes despite study limitations such as the use of different types of statins and the heterogeneity of the studies[90].

Bacterial infections. The immunomodulatory activity of statins has been extensively investigated in bacteraemia[91–94], pneumonia[95–99] and sepsis[100–104] (Supplementary Table 2). For example, a case–control study found that the use of statins reduced risk of community-acquired

bacteraemia[91]. A prospective cohort study also found statin therapy to be associated with a decrease in mortality and persistent bacteraemia among patients who were infected with *S. aureus*[92]. Similarly, a retrospective study reported that treatment with statins reduced the 30-day in-hospital all-cause mortality. Here, the long-term prior usage of statins increased the survival of patients with bacteraemia[105]. A randomized controlled trial of statin treatment in patients with acute bacterial infection demonstrated reduced production of the inflammatory cytokines IL-6 and TNF[93]. This suggests that statins play a role in limiting the pathology associated with excessive inflammation. However, a systematic review and meta-analysis of studies in which statin demonstrated beneficial effects against bacterial infection showed that once publication bias was taken into account, the described effect was not significant[106]. Recently, PCSK9 inhibitors (a new class of cholesterol-lowering drugs) enhanced survival and decreased inflammatory cytokine response in a mouse model of sepsis[4]. Mechanistically, PCSK9 inhibitors also clear endotoxins by upregulating LDL receptors on hepatocytes, suggesting a pathogenic role for LDL in sepsis. The PCSK9 inhibitors provide mechanistic insight into how statins protect against sepsis[4]. In humans, PCSK9 loss-of-function genetic variants increased LDL clearance, which improved septic shock outcome in patients by decreasing inflammatory cytokine response[4]. Therefore, PCSK9 inhibitors also open a window for reducing LDL cholesterol levels in statin-intolerant, statin-resistant or statin-unresponsive patients.

Besides bacteraemia, a UK-based population study found that statins were associated with a marked reduction in mortality in patients with pneumonia. This reduction in mortality was even more evident among patients with fatal pneumonias[98]. Supporting this observation, a randomized controlled trial from Israel revealed that even the incidence of pneumonia was modestly decreased upon intervention with rosuvastatin[96]. However, a randomized controlled trial showed that the use of simvastatin as an alternative therapy for ventilator-associated pneumonia had an unfavourable outcome of low probability of improvement as determined by the Data and Safety Monitoring Board, and the trial was terminated[95]. In fact, a retrospective analysis from a cohort of intensive care patients in Spain found that statins were associated with increased mortality despite lower infection rates[107]. A large Danish population based study showed that prior use of statin was associated with decreased mortality in patients hospitalized with pneumonia[108]. However, a small Canadian prospective cohort revealed that statins were not associated with reduced mortality in patients with pneumonia upon adjustment for the healthy user effect[99]. In contrast to pneumonia, a study using the large Taiwanese National Health Insurance Database found that higher doses of potent statins were associated with a decrease in sepsis-related mortality[109]. Indeed, a multicentre randomized study showed that atorvastatin therapy decreases baseline levels of IL-6, which was responsible for increased survival among intensive care patients with severe sepsis[100]. Notably, simvastatin reinforces anti-inflammatory functions by inhibiting LPS-induced upregulation of NF-κB in human monocytes to reduce inflammation in both pulmonary and systemic compartments of healthy volunteers[110]. A double-blind randomized controlled trial showed that statins inhibited systemic inflammation by reducing CXCL8, TNF and ICAM expression and improved the respiratory functions in patients with bronchiectasis resulting from infection with *Pseudomonas aeruginosa* by decreasing neutrophil activation[111]. Despite heterogeneity and potential bias, a meta-analysis of observational studies showed that statin use was associated with survival benefits in cases of infection and sepsis; however, this effect was not statistically significant among randomized controlled trials[112]. Another meta-analysis of randomized controlled trials for sepsis in patients who were critically ill suggested that statins were unable to provide consistent survival benefits[113]. In agreement with this, a recent prospective study concluded that prior statin use had no effect in patients who were critically ill and had sepsis[114], indicating that statins were ineffective at the terminal stages of infection. Notably, a retrospective cohort study showed that the coadministration of statins with an angiotensin II receptor blocker and an inhibitor of angiotensin-converting enzyme decreased pneumonia-related 30-day mortality[115,116]. Similarly, statin treatment with an angiotensin II receptor blocker decreased mortality in patients hospitalized with sepsis[117]. These encouraging results demonstrate the potential of statins as an adjunctive therapy.

Importantly, a retrospective study using the large Taiwanese National Health Insurance Database showed that statin use reduced the risk of developing active tuberculosis, depending on the length of statin treatment[118]. Moreover, this cohort revealed that statin use for more than 30 days was associated with reduced incidents of tuberculosis in a dose-dependent manner[119]. Such large studies in different ethnic groups are required to better generalize statin effects on the population at large. Importantly, it still needs to be determined whether statins influence the relapse of tuberculosis in individuals infected with *M. tuberculosis*. This is noteworthy in the context of emerging drug-resistant strains of *M. tuberculosis*, which require treatment for 18–24 months and display high mortality. For example, statins are known to disarm MRSA by directly targeting membrane microdomains, thereby rendering this highly multidrug-resistant bacteria vulnerable to antibiotics[88]. This suggests that statin disassembles the pathogen cell wall and on the other hand modulates the host immune system to control infection. In doing so, it further increases the efficacy of standard therapy when used as an adjunct. Therefore, a randomized controlled trial that focuses on the mechanism by which statins (as an adjunctive therapy) influence the outcome of tuberculosis in patients is of much relevance.

Fungal infections. New evidence has revealed that statins reduce fungal invasion and subsequent human colonization[120–122]. For example, in patients with cystic fibrosis, systemic inflammation was diminished by fluvastatin use, which reduced IL-8 production, a major chemoattract for neutrophils induced by *P. aeruginosa*

and *A. fumigatus*[123]. Furthermore, a retrospective matched-cohort study found that statin use increased survival of patients with candidaemia and reduced the subsequent colonization with *C. albicans* compared with no statin use[120]. By contrast, statins were not able to reduce the risk of invasive mould infection[124]. In addition, some studies reported that statins increased the incidence of common infections and were not associated with improved outcomes of viral influenza, fungal infection[121] and candidaemia-related mortality[122]. The observational nature of these studies makes their findings largely inconclusive; therefore, additional randomized controlled trials in the field of fungal diseases are much warranted. Additionally, statins used in combination with anti-fungal drugs open a new avenue in clinical practice, which may allow for a reduction in the dosage of current anti-fungal drugs. However, preclinical studies reflecting the effect of combination therapy against infective fungal diseases should be conducted before the implementation of statins with established anti-fungal drugs. Furthermore, caution must be taken to avoid potential drug–drug interactions owing to the metabolism using the same cytochrome isoenzymes in the host. Importantly, the efficacy of topical application of statins in treating cutaneous fungal infections would need to be established, as the use of a topical ointment would significantly reduce the risk of adverse effects.

Viral infections. Increasing evidence suggests that statins have the ability to reduce viral infections, such as those caused by HIV, influenza virus and Ebola virus[125–127]. By disrupting prenylation, RHO activity, rearrangement of the actin cytoskeleton[26], coagulation and systemic inflammation[125], statins could potentially reduce HIV-1 infection. In patients chronically infected with HIV, lovastatin inhibited RHO activity, a mechanism that improves HIV-1 prognosis by activating latent virus and reducing viral loads[26]. Antiretroviral (ART) drugs are known to disturb body fat distribution, which results in elevated cholesterol and triglyceride levels[128]. In such cases, statins are administered to patients with HIV[129]. However, a small pilot study showed that at physiological concentrations, statins did not influence mean viral loads or $CD4^+$ T cell counts in patients who were HIV positive[130]. A large randomized controlled trial investigating the effects of atorvastatin on viral loads and immune activation markers in patients with HIV that had not received ART has been completed, but the results have not yet been disclosed (NCT00367458). In cases of viral co-infection, statins were shown to inhibit the progression of cirrhosis in patients co-infected with HIV and hepatitis C virus[131] and to protect against liver failure during co-infection with hepatitis B virus and hepatitis C virus[132].

Another example of potential statin use is treating patients with the deadly Ebola virus. Remarkably, statins coadministered with angiotensin receptor blockers to patients with Ebola substantially decreased mortality from pneumonia or sepsis by restoring endothelial cell function and supporting tissue repair[126]. In addition, a multinational observational study showed that statin intervention was associated with reduced mortality in patients with influenza[133].

How do statins modulate the immune system in human infections?. Statins modulate the human immune system through their effects on various immune cell populations (FIG. 2). In contrast to what has been shown for mice, statins appear to reduce the production of TNF, CCL2 and IL-12 in human immune cells. This discrepancy could be attributed to the use of different statins (hydrophilic or lipophilic) between the two species and variations in the cell type investigated. Furthermore, in human studies, orally administered statins would be a weaker immune activator in the gastrointestinal tract. By contrast, most animal studies involved the injection of statins into peripheral tissues, bypassing the gastrointestinal tract and therefore serving as a stronger activator of immune responses. Importantly, lipophilic but not hydrophilic statins influence a regulatory pathway in monocytes that controls cytokine production and reactive oxygen intermediates as well as induce different pro-inflammatory responses both in vitro and in vivo[134]. Moreover, a unique observation showed that lipophilic but not hydrophilic statins exert strong adjuvanticity, which is essential for boosting adaptive immune responses[40]. In addition, cytokine responses were most consistent with statin treatment studies in mouse models when compared with human studies, where such responses are not robust owing to in vitro assay conditions.

Altogether, the data described in these studies need to be interpreted appropriately, taking into account the importance of such differences in immune response between mice and man and between the cell types. In light of this, whether the mechanisms that have been proposed in animal studies recapitulate what is demonstrated in humans is still an open question. Regardless, it is evident that a host-directed therapeutic approach has the potential to reduce prolonged treatment regimens, reduce long-term tissue damage and therefore reduce the associated side effects of the treatment to potentially increase patient adherence. This further warrants large randomized controlled trials, which adjust for the type of statins used and infection-specific settings, to consider statins as a potential alternative, innovative and adjunctive therapy for infectious diseases. Supplementary Table 2 comprehensively summarizes studies demonstrating the beneficial or detrimental effects of statins in human infectious diseases. Finally, while substantial data exist on the roles of statins in bacterial and viral infections, studies describing the effects of statin treatment in parasitic diseases are lacking. It is possible that the topical application of statin directly on skin lesions, together with anti-parasitic therapy, might be an interesting avenue to pursue as a host-directed strategy.

Factors affecting patient responses to statins

Human polymorphisms. Statins are most effective at a population level, despite considerable variation between individual user responses. The exact mechanisms for these variations are still uncertain; however, genetic differences are most likely a contributing factor. The wide variabilities in statin plasma concentrations and drug-induced responses are linked to single-nucleotide polymorphisms in genes involved in the import, export and metabolism of statins[135]. For instance, patients

expressing polymorphisms in *CYP2C9* and *CYP3A4* that result in reduced enzyme activity are more responsive to the cholesterol-lowering effects of statins[136]. Patients with polymorphisms in *CYP2C9*, which encodes a cytochrome, and *SLCO1B1*, which encodes a solute carrier, are defective for hepatic statin uptake and show high plasma levels of statins following treatment and an elevated risk of myopathy[137]. Another study investigating *SLCO1B1*, which encodes a drug transporter, and *ABCG2*, which accounts for transport function, reported that polymorphisms in these genes were responsible for 90% of the variability in plasma levels of rosuvastatin[138]. Future studies addressing the pharmacogenetics of statins should identify additional mutations and polymorphisms within specific targets that could help to modify individual therapy. This would be an important consideration when comparing both the benefits and the risks associated with statin treatment.

Metabolism of statins. On the basis of their metabolism, statins can be divided into two groups. The first group (simvastatin, lovastatin and atorvastatin) is metabolized by the cytochrome CYP3A4, and the second group (fluvastatin) is metabolized by CYP2C9, which facilitates hepatic statin uptake, and the ATP-binding cassette subfamily G member 2 (ABCG2) export pump. Therefore, drugs that inhibit CYP3A4 and CYP2C9 will increase the potential for complications in combination therapy with statins. The major challenge faced with implementing statins into coadministration treatment strategies would be the possibility of lethal adverse effects owing to drug–drug interactions. For instance, rifampicin suppresses plasma levels of simvastatin and its acid form by 90% in human subjects[139], thus reducing the efficacy of statin. By contrast, despite the muscle injury associated with the use of statins and the lipopeptide antibiotic daptomycin, no synergistic adverse effect was seen when they were coadministered[140]. The second group, which is not metabolized by cytochromes, could be considered for combination therapies, which include drugs targeting the CYP2C9 and/or CYP3A4 cytochromes and anion transporters. For example, drugs such as ketoconazole, amiodarone, cyclosporine, ritonavir and indinavir are potentially used in conjunction with statins[141]. However, administration of statins with the anti-fungal drug itraconazole resulted in rhabdomyolysis and renal failure[142].

Drug–drug interaction. The drug interaction between protease inhibitors (ritonavir and indinavir) and statins among patients with HIV also leads to increased rhabdomyolysis[143]. This offers a challenge to treat dyslipidaemia in patients with HIV owing to the competition between statins and antiretrovirals for cytochrome P450 metabolism. Some comfort can be gained with the use of pitavastatin, which is not dependent on P450 for its metabolism[144]. In agreement, the European AIDS Clinical Society guidelines recommend pravastatin for coadministration in patients with HIV because its metabolism is cytochrome P450-independent. Statins are also recommended to reduce inflammation in patients with HIV[145]. However, a report showed that metabolism-independent mechanisms might contribute to drug–drug interactions, thereby increasing complexity[146]. Therefore, the dose of statin should not exceed the maximum tolerated dose to avoid drug–drug interactions[147]. Nevertheless, statins have been shown to reduce the progression and severity of diseases in combination therapies, as discussed earlier. Complementary results from preclinical[39,45,46,148,149] and clinical studies[115–117,125,126] provide compelling evidence that statins in combination with other therapies increase the efficacy of the standard treatment options and therefore have the potential to improve disease prognosis by modulating host factors. This is critical and highly relevant to public health practices in countries with a high HIV burden, such as South Africa. This is important, as HIV infection eventually leads to the activation of tuberculosis, which further increases the risk of potential drug–drug interactions with the initiation of tuberculosis therapy. Carefully designed clinical studies considering such critical factors as the type of statins used, the dose in combination therapies, the length of treatment and the genetic background of patients are essential to evaluate all the potential limitations.

Challenges and future prospective

Therapeutic approaches that directly target virulence factors of viruses, parasites, fungi and bacteria always pose a risk of encouraging drug-resistant pathogen strains. This is evident in the rise of general microbial resistance, which has created a global public health crisis. The repurposing of existing drugs presents an attractive, alternative strategy to potentially expedite the development of new antimicrobial drugs. Despite the insignificant effect of statins in a few clinical studies, they have been shown, overall, to be effective in decreasing the severity of many infectious diseases. Given their safety record, efficacy and affordability, statins are attractive candidates for host-directed therapy against infectious diseases. However, there are still several key questions that remain. First, we need to identify key metabolites of the mevalonate pathway, which may be directly targeted against different intracellular pathogens. Second, we need to fully understand the chemical properties of statins, as these may affect the outcome of clinical manifestations. Third, following statin treatment, we need to understand the immune correlates that predict increased host survival as a result of reduced disease and tissue pathology. Fourth, we need to improve knowledge of how statins may vary in their affinity to different tissues and/or organs. Fifth, we also need to explore and understand the protective mechanisms of statins, such as their production of oxide radicals and their induction of apoptosis, necrosis, autophagy and phagosome degradation. Finally, caution must be stressed for potential drug–drug interactions, particularly with drugs that are metabolized by the same cytochromes as statins, which were initially tested in the form of small-scale trials. Indeed, the known pleiotropic aspects of statins are indicative of improved public health. We need further studies such as proof-of-concept clinical studies and large randomized controlled trials to confirm the feasibility of statins as a potential candidate for host-directed therapy against infectious diseases.

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1. Endo, A., Kuroda, M. & Tsujita, Y. ML-236A, ML-236B, and ML-236C, new inhibitors of cholesterogenesis produced by penicillium citrinium. *J. Antibiot.* **29**, 1346–1348 (1976).
This is the first paper to identify statins as potent inhibitors of cholesterol synthesis.
2. Istvan, E. S. & Deisenhofer, J. Structural mechanism for statin inhibition of HMG-CoA reductase. *Science* **292**, 1160–1164 (2001).
3. Goldstein, J. L. & Brown, M. S. Regulation of the mevalonate pathway. *Nature* **343**, 425–430 (1990).
4. Walley, K. R. et al. PCSK9 is a critical regulator of the innate immune response and septic shock outcome. *Sci. Transl Med.* **6**, 258ra143 (2014).
5. Market Publishers. *Statins: World Market Outlook 2011–2021* (Visiongain, 2011).
6. Ioannidis, J. P. A. More than a billion people taking statins? Potential implications of the new cardiovascular guidelines. *J. Am. Med. Assoc.* **311**, 463–464 (2014).
7. Jain, M. K. & Ridker, P. M. Anti-inflammatory effects of statins: clinical evidence and basic mechanisms. *Nat. Rev. Drug Discov.* **4**, 977–987 (2005).
8. Brown, M. S. & Goldstein, J. L. Heart attacks: gone with the century? *Science* **272**, 629 (1996).
9. Greenwood, J., Steinman, L. & Zamvil, S. S. Statin therapy and autoimmune disease: from protein prenylation to immunomodulation. *Nat. Rev. Immunol.* **6**, 358–370 (2006).
References 7 and 9 are excellent reviews on the basic mechanisms of statin actions and immunomodulatory functions.
10. Landmesser, U. et al. Simvastatin versus ezetimibe: pleiotropic and lipid-lowering effects on endothelial function in humans. *Circulation* **111**, 2356–2363 (2005).
11. Kwak, B., Mulhaupt, F., Myit, S. & Mach, F. Statins as a newly recognized type of immunomodulator. *Nat. Med.* **6**, 1399–1402 (2000).
This is the first paper to show the inhibitory effect of statins on MHC class II expression and T cell functions.
12. Liao, J. K. & Laufs, U. Pleiotropic effects of statins. *Annu. Rev. Pharmacol. Toxicol.* **45**, 89–118 (2005).
13. Kureishi, Y. et al. The HMG-CoA reductase inhibitor simvastatin activates the protein kinase Akt and promotes angiogenesis in normocholesterolemic animals. *Nat. Med.* **6**, 1004–1010 (2000).
14. Mundy, G. et al. Stimulation of bone formation in vitro and in rodents by statins. *Science* **286**, 1946–1949 (1999).
This is a unique report that shows that statins promote bone formation by increasing BMP2 gene expression and are therefore a potential treatment for osteoporosis.
15. Ridker, P. M. et al. Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial. *Lancet* **373**, 1175–1182 (2009).
16. Maxfield, F. R. & Tabas, I. Role of cholesterol and lipid organization in disease. *Nature* **438**, 612–621 (2005).
17. Rothwell, C. et al. Cholesterol biosynthesis modulation regulates dengue viral replication. *Virology* **389**, 8–19 (2009).
18. Pucadyil, T. J., Tewary, P., Madhubala, R. & Chattopadhyay, A. Cholesterol is required for Leishmania donovani infection: implications in leishmaniasis. *Mol. Biochem. Parasitol.* **133**, 145–152 (2004).
19. Xiong, Q. et al. Cholesterol import by *Aspergillus fumigatus* and its influence on antifungal potency of sterol biosynthesis inhibitors. *Antimicrob. Agents Chemother.* **49**, 518–524 (2005).
20. Gatfield, J. & Pieters, J. Essential role for cholesterol in entry of mycobacteria into macrophages. *Science* **288**, 1647–1650 (2000).
21. Edwards, P. A. & Ericsson, J. Sterols and isoprenoids: signaling molecules derived from the cholesterol biosynthetic pathway. *Annu. Rev. Biochem.* **68**, 157–185 (1999).
22. Demierre, M. F., Higgins, P. D., Gruber, S. B., Hawk, E. & Lippman, S. M. Statins and cancer prevention. *Nat. Rev. Cancer* **5**, 930–942 (2005).
23. Parihar, S. P. et al. Statin therapy reduces the mycobacterium tuberculosis burden in human macrophages and in mice by enhancing autophagy and phagosome maturation. *J. Infect. Dis.* **209**, 754–763 (2014).
This is the first study to demonstrate the underlying mechanisms by which statins control mycobacterial growth in humans and mice.
24. Parihar, S. P. et al. Simvastatin enhances protection against *Listeria monocytogenes* infection in mice by counteracting listeria-induced phagosomal escape. *PLOS ONE* **8**, e75490 (2013).
25. Parihar, S. P., Hartley, M. A., Hurdayal, R., Guler, R. & Brombacher, F. Topical simvastatin as host-directed therapy against severity of cutaneous leishmaniasis in mice. *Sci. Rep.* **6**, 33458 (2016).
26. del Real, G. et al. Statins inhibit HIV-1 infection by down-regulating Rho activity. *J. Exp. Med.* **200**, 541–547 (2004).
This is an important report that shows direct inhibition of HIV-1 by statins in chronically infected patients.
27. Blanc, M. et al. Host defense against viral infection involves interferon mediated down-regulation of sterol biosynthesis. *PLOS Biol.* **9**, e1000598 (2011).
28. Mueller, B. K., Mack, H. & Teusch, N. Rho kinase, a promising drug target for neurological disorders. *Nat. Rev. Drug Discov.* **4**, 387–398 (2005).
29. Das, H. et al. Kruppel-like factor 2 (KLF2) regulates proinflammatory activation of monocytes. *Proc. Natl Acad. Sci. USA* **103**, 6653–6658 (2006).
30. Hamelin, B. A. & Turgeon, J. Hydrophilicity/lipophilicity: relevance for the pharmacology and clinical effects of HMG-CoA reductase inhibitors. *Trends Pharmacol. Sci.* **19**, 26–37 (1998).
This is an excellent review on the pharmacological and pharmacokinetic properties of various statins on the market.
31. Arora, M. et al. Simvastatin promotes Th2-type responses through the induction of the chitinase family member Ym1 in dendritic cells. *Proc. Natl Acad. Sci. USA* **103**, 7777–7782 (2006).
32. Elahi, S., Weiss, R. H. & Merani, S. Atorvastatin restricts HIV replication in $CD4^+$T cells by upregulation of p21. *AIDS* **30**, 171–183 (2016).
33. Lange, P. T. et al. Type I interferon counteracts antiviral effects of statins in the context of gammaherpesvirus infection. *J. Virol.* **90**, 3342–3354 (2016).
34. Gower, T. L. & Graham, B. S. Antiviral activity of lovastatin against respiratory syncytial virus in vivo and in vitro. *Antimicrob. Agents Chemother.* **45**, 1231–1237 (2001).
35. Ravi, L. I. et al. Lovastatin treatment mitigates the pro-inflammatory cytokine response in respiratory syncytial virus infected macrophage cells. *Antiviral Res.* **98**, 332–343 (2013).
36. Potena, L. et al. Hydroxymethyl-glutaryl coenzyme a reductase inhibition limits cytomegalovirus infection in human endothelial cells. *Circulation* **109**, 532–536 (2004).
37. Liu, S., Rodriguez, A. V. & Tosteson, M. T. Role of simvastatin and methyl-beta-cyclodextrin [corrected] on inhibition of poliovirus infection. *Biochem. Biophys. Res. Commun.* **347**, 51–59 (2006).
38. Radigan, K. A. et al. The effect of rosuvastatin in a murine model of influenza A infection. *PLOS ONE* **7**, e35788 (2012).
39. Liu, Z. et al. Evaluation of the efficacy and safety of a statin/caffeine combination against H5N1, H3N2 and H1N1 virus infection in BALB/c mice. *Eur. J. Pharm. Sci.* **38**, 215–223 (2009).
40. Xia, Y. et al. The mevalonate pathway is a druggable target for vaccine adjuvant discovery. *Cell* https://doi.org/10.1016/j.cell.2018.08.070 (2018).
This is the first paper to show that statins can be a potent adjuvant in vaccines against influenza and cancer immunotherapy.
41. Coppens, I., Sinai, A. P. & Joiner, K. A. *Toxoplasma gondii* exploits host low-density lipoprotein receptor-mediated endocytosis for cholesterol acquisition. *J. Cell Biol.* **149**, 167–180 (2000).
42. Dinesh, N., Soumya, N. & Singh, S. Antileishmanial effect of mevastatin is due to interference with sterol metabolism. *Parasitol. Res.* **114**, 3873–3883 (2015).
43. Kuckelhaus, C. S., Kuckelhaus, S. A., Tosta, C. E. & Muniz-Junqueira, M. I. Pravastatin modulates macrophage functions of *Leishmania* (*L.*) *amazonensis*-infected BALB/c mice. *Exp. Parasitol.* **134**, 18–25 (2013).
44. Kuckelhaus, C. S., Kuckelhaus, S. A. & Muniz-Junqueira, M. I. Influence of long-term treatment with pravastatin on the survival, evolution of cutaneous lesion and weight of animals infected by *Leishmania amazonensis*. *Exp. Parasitol.* **127**, 658–664 (2011).
45. Souraud, J. B. et al. Atorvastatin treatment is effective when used in combination with mefloquine in an experimental cerebral malaria murine model. *Malar. J.* **11**, 13 (2012).
46. Dormoi, J. et al. Improvement of the efficacy of dihydroartemisinin with atorvastatin in an experimental cerebral malaria murine model. *Malar. J.* **12**, 302 (2013).
47. Othman, A. A. et al. Atorvastatin and metformin administration modulates experimental Trichinella spiralis infection. *Parasitol. Int.* **65**, 105–112 (2016).
48. Alencar, A. C. et al. Simvastatin and artesunate impact the structural organization of adult *Schistosoma mansoni* in hypercholesterolemic mice. *Exp. Parasitol.* **167**, 115–123 (2016).
References 45, 46, 47 and 48 highlight that statins can be used in combination therapies against parasitic diseases.
49. Madbouly Taha, N., Salah A Yousof, H. A., El-Sayed, S. H., Younis, A. I. & Ismail Negm, M. S. Atorvastatin repurposing for the treatment of cryptosporidiosis in experimentally immunosuppressed mice. *Exp. Parasitol.* **181**, 57–69 (2017).
50. Gonzalez-Herrera, F. et al. Simvastatin attenuates endothelial activation through 15-epi-lipoxin A4 production in murine chronic chagas cardiomyopathy. *Antimicrob. Agents Chemother.* **61**, e02137–16 (2017).
51. Chin, N. X., Weitzman, I. & Della-Latta, P. In vitro activity of fluvastatin, a cholesterol-lowering agent, and synergy with flucanazole and itraconazole against Candida species and *Cryptococcus neoformans*. *Antimicrob. Agents Chemother.* **41**, 850–852 (1997).
52. Wikhe, K., Westermeyer, C. & Macreadie, I. G. Biological consequences of statins in Candida species and possible implications for human health. *Biochem. Soc. Trans.* **35**, 1529–1532 (2007).
53. Macreadie, I. G., Johnson, G., Schlosser, T. & Macreadie, P. I. Growth inhibition of Candida species and *Aspergillus fumigatus* by statins. *FEMS Microbiol. Lett.* **262**, 9–13 (2006).
54. Tashiro, M. et al. Pravastatin inhibits farnesol production in *Candida albicans* and improves survival in a mouse model of systemic candidiasis. *Med. Mycol.* **50**, 353–360 (2012).
55. Leal, S. M. Jr. et al. Targeting iron acquisition blocks infection with the fungal pathogens *Aspergillus fumigatus* and *Fusarium oxysporum*. *PLOS Pathog.* **9**, e1003436 (2013).
56. Gyetvai, A. et al. Lovastatin possesses a fungistatic effect against *Candida albicans*, but does not trigger apoptosis in this opportunistic human pathogen. *FEMS Yeast Res.* **6**, 1140–1148 (2006).
57. Deepe, G. S. Jr & Buesing, W. R. Deciphering the pathways of death of *Histoplasma capsulatum*-infected macrophages: implications for the immunopathogenesis of early infection. *J. Immunol.* **188**, 334–344 (2012).
58. Mira, E. et al. Statins induce regulatory T cell recruitment via a CCL1 dependent pathway. *J. Immunol.* **181**, 3524–3534 (2008).
59. Song, J. L., Lyons, C. N., Holleman, S., Oliver, B. G. & White, T. C. Antifungal activity of fluconazole in combination with lovastatin and their effects on gene expression in the ergosterol and prenylation pathways in *Candida albicans*. *Med. Mycol.* **41**, 417–425 (2003).
60. Qiao, J., Kontoyiannis, D. P., Wan, Z., Li, R. & Liu, W. Antifungal activity of statins against *Aspergillus* species. *Med. Mycol.* **45**, 589–593 (2007).
61. Chow, O. A. et al. Statins enhance formation of phagocyte extracellular traps. *Cell Host Microbe* **8**, 445–454 (2010).
This is an important paper demonstrating that statins promote an extracellular mechanism of killing pathogens.
62. Urban, C. F., Reichard, U., Brinkmann, V. & Zychlinsky, A. Neutrophil extracellular traps capture and kill *Candida albicans* yeast and hyphal forms. *Cell. Microbiol.* **8**, 668–676 (2006).
63. Nash, J. D., Burgess, D. S. & Talbert, R. L. Effect of fluvastatin and pravastatin, HMG-CoA reductase inhibitors, on fluconazole activity against *Candida albicans*. *J. Med. Microbiol.* **51**, 105–109 (2002).
64. Afeltra, J. & Verweij, P. E. Antifungal activity of nonantifungal drugs. *Eur. J. Clin. Microbiol. Infect. Dis.* **22**, 397–407 (2003).
65. Hennessy, E., Adams, C., Reen, F. J. & O'Gara, F. Is there potential for repurposing statins as novel antimicrobials? *Antimicrob. Agents Chemother.* **60**, 5111–5121 (2016).
66. Mattos, K. A. et al. *Mycobacterium leprae* intracellular survival relies on cholesterol accumulation in infected macrophages: a potential target for new drugs for leprosy treatment. *Cell. Microbiol.* **16**, 797–815 (2014).

67. Lobato, L. S. et al. Statins increase rifampin mycobactericidal effect. *Antimicrob. Agents Chemother.* **58**, 5766–5774 (2014).
68. Liao, W. C. et al. Statin decreases *Helicobacter pylori* burden in macrophages by promoting autophagy. *Front. Cell. Infect. Microbiol.* **6**, 203 (2016).
69. Botelho-Nevers, E., Espinosa, L., Raoult, D. & Rolain, J. M. Lovastatin, but not pravastatin, limits in vitro infection due to *Coxiella burnetii*. *J. Antimicrob. Chemother.* **62**, 845–847 (2008).
70. Botelho-Nevers, E., Rolain, J. M., Espinosa, L. & Raoult, D. Statins limit Rickettsia conorii infection in cells. *Int. J. Antimicrob. Agents* **32**, 344–348 (2008).
71. Catron, D. M. et al. *Salmonella enterica* serovar Typhimurium requires nonsterol precursors of the cholesterol biosynthetic pathway for intracellular proliferation. *Infection Immun.* **72**, 1036–1042 (2004).
72. Skerry, C. et al. Simvastatin increases the in vivo activity of the first-line tuberculosis regimen. *J. Antimicrob. Chemother.* **69**, 2453–2457 (2014).
73. Dutta, N. K. et al. Statin adjunctive therapy shortens the duration of TB treatment in mice. *J. Antimicrob. Chemother.* **71**, 1570–1577 (2016).
Using preclinical models, references 72 and 73 show that statins increase the efficacy of anti-tuberculosis drugs and reduce the length of tuberculosis treatment.
74. Montero, M. T., Matilla, J., Gomez-Mampaso, E. & Lasuncion, M. A. Geranylgeraniol regulates negatively caspase-1 autoprocessing: implication in the Th1 response against *Mycobacterium tuberculosis*. *J. Immunol.* **173**, 4936–4944 (2004).
75. Montero, M. T. et al. Hydroxymethylglutaryl-coenzyme A reductase inhibition stimulates caspase-1 activity and Th1-cytokine release in peripheral blood mononuclear cells. *Atherosclerosis* **153**, 303–313 (2000).
76. Lu, H. Z. & Li, B. Q. Effect of HMG-CoA reductase inhibitors on activation of human gammadeltaT cells induced by *Mycobacterium tuberculosis* antigens. *Immunopharmacol. Immunotoxicol.* **31**, 485–491 (2009).
77. Benati, D. et al. Opposite effects of simvastatin on the bactericidal and inflammatory response of macrophages to opsonized *S. aureus*. *J. Leukoc. Biol.* **87**, 433–442 (2010).
78. Fessler, M. B. et al. A role for hydroxy-methylglutaryl coenzyme a reductase in pulmonary inflammation and host defense. *Am. J. Respir. Crit. Care Med.* **171**, 606–615 (2005).
79. Dominguez, P. M., Lopez-Bravo, M., Kalinke, U. & Ardavin, C. Statins inhibit iNOS-mediated microbicidal potential of activated monocyte-derived dendritic cells by an IFN-beta-dependent mechanism. *Eur. J. Immunol.* **41**, 3330–3339 (2011).
80. Erkkila, L. et al. Effect of simvastatin, an established lipid-lowering drug, on pulmonary *Chlamydia pneumoniae* infection in mice. *Antimicrob. Agents Chemother.* **49**, 3959–3962 (2005).
81. Dechend, R. et al. Hydroxymethylglutaryl coenzyme A reductase inhibition reduces *Chlamydia pneumoniae*-induced cell interaction and activation. *Circulation* **108**, 261–265 (2003).
82. Ando, H., Takamura, T., Ota, T., Nagai, Y. & Kobayashi, K. Cerivastatin improves survival of mice with lipopolysaccharide-induced sepsis. *J. Pharmacol. Exp. Ther.* **294**, 1043–1046 (2000).
83. Ayyadurai, S., Lepidi, H., Nappez, C., Raoult, D. & Drancourt, M. Lovastatin protects against experimental plague in mice. *PLOS ONE* **5**, e10928 (2010).
84. Rosch, J. W. et al. Statins protect against fulminant pneumococcal infection and cytolysin toxicity in a mouse model of sickle cell disease. *J. Clin. Invest.* **120**, 627–635 (2010).
This is an important paper showing the mechanism by which statins inhibit pneumococcal infection in mice.
85. Boyd, A. R., Hinojosa, C. A., Rodriguez, P. J. & Orihuela, C. J. Impact of oral simvastatin therapy on acute lung injury in mice during pneumococcal pneumonia. *BMC Microbiol.* **12**, 73 (2012).
86. Van Laar, T. A. et al. Statins reduce spirochetal burden and modulate immune responses in the C3H/HeN mouse model of Lyme disease. *Microbes Infect.* **18**, 430–435 (2016).
87. McDowell, S. A., Ma, Y., Kusano, R. & Akinbi, H. T. Simvastatin is protective during *Staphylococcus aureus* pneumonia. *Curr. Pharm. Biotechnol.* **12**, 1455–1462 (2011).
88. Garcia-Fernandez, E. et al. Membrane microdomain disassembly inhibits MRSA antibiotic resistance. *Cell* **171**, 1354–1367 (2017).
89. Thangamani, S. et al. Exploring simvastatin, an antihyperlipidemic drug, as a potential topical antibacterial agent. *Sci. Rep.* **5**, 16407 (2015).
This is an important report showing that topical application of statin reduces *Staphylococcus* spp. biofilms and the growth of drug-resistant strains in skin lesions.
90. Chopra, V. et al. Is statin use associated with reduced mortality after pneumonia? A systematic review and meta-analysis. *Am. J. Med.* **125**, 1111–1123 (2012).
91. Smit, J. et al. Statin use and risk of community-acquired *Staphylococcus aureus* bacteremia: a population-based case-control study. *Mayo Clin. Proc.* **92**, 1469–1478 (2017).
92. Lopez-Cortes, L. E. et al. Effect of statin therapy in the outcome of bloodstream infections due to *Staphylococcus aureus*: a prospective cohort study. *PLOS ONE* **8**, e82958 (2013).
93. Novack, V. et al. The effects of statin therapy on inflammatory cytokines in patients with bacterial infections: a randomized double-blind placebo controlled clinical trial. *Intensive Care Med.* **35**, 1255–1260 (2009).
94. Kruger, P., Fitzsimmons, K., Cook, D., Jones, M. & Nimmo, G. Statin therapy is associated with fewer deaths in patients with bacteraemia. *Intensive Care Med.* **32**, 75–79 (2006).
This is an important retrospective cohort study demonstrating a reduction in mortality from bacteraemia in patients receiving statin therapy.
95. Papazian, L. et al. Effect of statin therapy on mortality in patients with ventilator-associated pneumonia: a randomized clinical trial. *JAMA* **310**, 1692–1700 (2013).
96. Novack, V. et al. The effect of rosuvastatin on incident pneumonia: results from the JUPITER trial. *CMAJ* **184**, E367–372 (2012).
97. Chalmers, J. D., Singanayagam, A., Murray, M. P. & Hill, A. T. Prior statin use is associated with improved outcomes in community-acquired pneumonia. *Am. J. Med.* **121**, 1002–1007 (2008).
98. Schlienger, R. G., Fedson, D. S., Jick, S. S., Jick, H. & Meier, C. R. Statins and the risk of pneumonia: a population-based, nested case-control study. *Pharmacotherapy* **27**, 325–332 (2007).
99. Majumdar, S. R., McAlister, F. A., Eurich, D. T., Padwal, R. S. & Marrie, T. J. Statins and outcomes in patients admitted to hospital with community acquired pneumonia: population based prospective cohort study. *BMJ* **333**, 999 (2006).
100. Kruger, P. et al. A multicenter randomized trial of atorvastatin therapy in intensive care patients with severe sepsis. *Am. J. Respir. Crit. Care Med.* **187**, 743–750 (2013).
101. Patel, J. M. et al. Randomized double-blind placebo-controlled trial of 40 mg/day of atorvastatin in reducing the severity of sepsis in ward patients (ASEPSIS Trial). *Crit. Care* **16**, R231 (2012).
References 100 and 101 are placebo-controlled clinical trials demonstrating that the use of atorvastatin improves survival and reduces disease severity in sepsis.
102. Dobesh, P. P., Klepser, D. G., McGuire, T. R., Morgan, C. W. & Olsen, K. M. Reduction in mortality associated with statin therapy in patients with severe sepsis. *Pharmacotherapy* **29**, 621–630 (2009).
103. Almog, Y. et al. The effect of statin therapy on infection-related mortality in patients with atherosclerotic diseases. *Crit. Care Med.* **35**, 372–378 (2007).
104. Gupta, R. et al. Statin use and sepsis events [corrected] in patients with chronic kidney disease. *JAMA* **297**, 1455–1464 (2007).
105. Nseir, W., Mograbi, J., Abu-Elheja, O., Bishara, J. & Assy, N. The impact of prior long-term versus short-term statin use on the mortality of bacteraemic patients. *Infection* **40**, 41–48 (2012).
106. Bjorkhem-Bergman, L., Bergman, P., Andersson, J. & Lindh, J. D. Statin treatment and mortality in bacterial infections—a systematic review and meta-analysis. *PLOS ONE* **5**, e10702 (2010).
107. Fernandez, R., De Pedro, V. J. & Artigas, A. Statin therapy prior to ICU admission: protection against infection or a severity marker? *Intensive Care Med.* **32**, 160–164 (2006).
108. Thomsen, R. W. et al. Preadmission use of statins and outcomes after hospitalization with pneumonia: population-based cohort study of 29,900 patients. *Arch. Intern. Med.* **168**, 2081–2087 (2008).
109. Ou, S. Y. et al. Effect of the use of low and high potency statins and sepsis outcomes. *Intensive Care Med.* **40**, 1509–1517 (2014).
110. Shyamsundar, M. et al. Simvastatin decreases lipopolysaccharide-induced pulmonary inflammation in healthy volunteers. *Am. J. Respir. Crit. Care Med.* **179**, 1107–1114 (2009).
This is a double-blind, placebo-controlled study showing that simvastatin reduces pulmonary inflammation even in healthy humans exposed to inhaled LPS.
111. Bedi, P. et al. A randomized controlled trial of atorvastatin in patients with bronchiectasis infected with *Pseudomonas aeruginosa*: a proof of concept study. *Chest* **152**, 368–378 (2017).
112. Wan, Y. D., Sun, T. W., Kan, Q. C., Guan, F. X. & Zhang, S. G. Effect of statin therapy on mortality from infection and sepsis: a meta-analysis of randomized and observational studies. *Crit. Care* **18**, R71 (2014).
113. Thomas, G. et al. Statin therapy in critically-ill patients with severe sepsis: a review and meta-analysis of randomized clinical trials. *Minerva Anestesiol.* **81**, 921–930 (2015).
114. Wiewel, M. A. et al. The host response in critically ill sepsis patients on statin therapy: a prospective observational study. *Ann. Intensive Care* **8**, 9 (2018).
115. Mortensen, E. M. et al. Population-based study of statins, angiotensin II receptor blockers, and angiotensin-converting enzyme inhibitors on pneumonia-related outcomes. *Clin. Infect. Dis.* **55**, 1466–1473 (2012).
116. Mortensen, E. M. et al. Impact of statins and angiotensin-converting enzyme inhibitors on mortality of subjects hospitalised with pneumonia. *Eur. Respir. J.* **31**, 611–617 (2008).
117. Mortensen, E. M. et al. Impact of previous statin and angiotensin II receptor blocker use on mortality in patients hospitalized with sepsis. *Pharmacotherapy* **27**, 1619–1626 (2007).
118. Lai, C. C. et al. Statin treatment is associated with a decreased risk of active tuberculosis: an analysis of a nationally representative cohort. *Thorax* **71**, 646–651 (2016).
119. Su, V. Y. et al. Statin use is associated with a lower risk of TB. *Chest* **152**, 598–606 (2017).
References 118 and 119 clinically demonstrate the beneficial effects of statins against active tuberculosis.
120. Forrest, G. N., Kopack, A. M. & Perencevich, E. N. Statins in candidemia: clinical outcomes from a matched cohort study. *BMC Infect. Dis.* **10**, 152 (2010).
121. Magulick, J. P. et al. The effect of statin therapy on the incidence of infections: a retrospective cohort analysis. *Am. J. Med. Sci.* **347**, 211–216 (2014).
122. Welch, M. L., Liappis, A. P. & Kan, V. L. Candidemia outcomes not improved with statin use. *Med. Mycol.* **51**, 219–222 (2013).
123. Jouneau, S. et al. Anti-inflammatory effect of fluvastatin on IL-8 production induced by *Pseudomonas aeruginosa* and *Aspergillus fumigatus* antigens in cystic fibrosis. *PLOS ONE* **6**, e22655 (2011).
124. Thompson, J. N., Huycke, M. M., Greenfield, R. A., Kurdgelashvili, G. & Gentry, C. A. Case-control study of statin prevention of mould infections. *Mycoses* **54**, e481–485 (2011).
125. Calza, L. et al. Significant decrease in plasma levels of D-dimer, interleukin-8, and interleukin-12 after a 12-month treatment with rosuvastatin in HIV-infected patients under antiretroviral therapy. *AIDS Res. Hum. Retroviruses* **33**, 126–132 (2017).
126. Fedson, D. S., Jacobson, J. R., Rordam, O. M. & Opal, S. M. Treating the host response to ebola virus disease with generic statins and angiotensin receptor blockers. *MBio* **6**, e00716 (2015).
127. Montoya, C. J. et al. Randomized clinical trial of lovastatin in HIV-infected, HAART naive patients (NCT00721305). *J. Infect.* **65**, 549–558 (2012).
128. Penzak, S. R. & Chuck, S. K. Hyperlipidemia associated with HIV protease inhibitor use: pathophysiology, prevalence, risk factors and treatment. *Scand. J. Infect. Dis.* **32**, 111–123 (2000).
129. Feinstein, M. J., Achenbach, C. J., Stone, N. J. & Lloyd-Jones, D. M. A. Systematic review of the usefulness of statin therapy in HIV-infected patients. *Am. J. Cardiol.* **115**, 1760–1766 (2015).
This is an extensive systematic review evaluating 18 clinical trials of statins that shows that pravastatin, rosuvastatin and pitavastatin have the best safety profiles when coadministered with ART in patients infected with HIV.
130. Moncunill, G. et al. Evaluation of the anti-HIV activity of statins. *AIDS* **19**, 1697–1700 (2005).
131. Oliver, N. T., Hartman, C. M., Kramer, J. R. & Chiao, E. Y. Statin drugs decrease progression to

cirrhosis in HIV/hepatitis C virus coinfected individuals. *AIDS* **30**, 2469–2476 (2016).
132. Chang, F. M. et al. Statins decrease the risk of decompensation in hepatitis B virus- and hepatitis C virus-related cirrhosis: a population-based study. *Hepatology* (2017).
133. Vandermeer, M. L. et al. Association between use of statins and mortality among patients hospitalized with laboratory-confirmed influenza virus infections: a multistate study. *J. Infect. Dis.* **205**, 13–19 (2012).
134. Kiener, P. A. et al. Stimulation of inflammatory responses in vitro and in vivo by lipophilic HMG-CoA reductase inhibitors. *Int. Immunopharmacol.* **1**, 105–118 (2001).
135. Gelissen, I. C. & McLachlan, A. J. The pharmacogenomics of statins. *Pharmacol. Res.* **88**, 99–106 (2014).
136. Wang, D., Guo, Y., Wrighton, S. A., Cooke, G. E. & Sadee, W. Intronic polymorphism in CYP3A4 affects hepatic expression and response to statin drugs. *Pharmacogenom. J.* **11**, 274–286 (2011).
137. Group, S. C. et al. SLCO1B1 variants and statin-induced myopathy—a genomewide study. *N. Engl. J. Med.* **359**, 789–799 (2008).
138. DeGorter, M. K. et al. Clinical and pharmacogenetic predictors of circulating atorvastatin and rosuvastatin concentrations in routine clinical care. *Circ. Cardiovasc. Genet.* **6**, 400–408 (2013).
References 136, 137 and 138 identify several polymorphisms associated with the individual variability in responses to statin therapy.
139. Kyrklund, C. et al. Rifampin greatly reduces plasma simvastatin and simvastatin acid concentrations. *Clin. Pharmacol. Ther.* **68**, 592–597 (2000).
140. Golightly, L. K., Barber, G. R., Barron, M. A. & Page, R. L. 2nd. Statins and daptomycin: safety assessment of concurrent use and evaluation of drug interaction liability. *Drug Metabol. Drug Interact.* **28**, 49–58 (2013).
141. Causevic-Ramosevac, A. & Semiz, S. Drug interactions with statins. *Acta Pharm.* **63**, 277–293 (2013).
142. Roques, S., Lytrivi, M., Rusu, D., Devriendt, J. & De Bels, D. Rhabdomyolysis-induced acute renal failure due to itraconazole and simvastatin association. *Drug Metabol. Drug Interact.* **26**, 79–80 (2011).
143. Chauvin, B., Drouot, S., Barrail-Tran, A. & Taburet, A. M. Drug-drug interactions between HMG-CoA reductase inhibitors (statins) and antiviral protease inhibitors. *Clin. Pharmacokinet.* **52**, 815–831 (2013).
This is an excellent review summarizing the drug–drug interactions between statins and antiretroviral treatments.
144. Aberg, J. A. et al. Pitavastatin versus pravastatin in adults with HIV-1 infection and dyslipidaemia (INTREPID): 12 week and 52 week results of a phase 4, multicentre, randomised, double-blind, superiority trial. *Lancet HIV* **4**, e284–e294 (2017).
145. Bernal, E., Marin, I., Masia, M. & Gutierrez, F. Statins in HIV-infected patients: potential beneficial effects and clinical use. *AIDS Rev.* **19**, 59–71 (2017).
146. Li, D. Q. et al. Risk of adverse events among older adults following co-prescription of clarithromycin and statins not metabolized by cytochrome P450 3A4. *CMAJ* **187**, 174–180 (2015).
147. Wiggins, B. S. et al. Recommendations for managing drug-drug interactions with statins and HIV medications. *Am. J. Cardiovasc. Drugs* **17**, 375–389 (2017).
148. Canavese, M. & Crisanti, A. Vascular endothelial growth factor (VEGF) and lovastatin suppress the inflammatory response to *Plasmodium berghei* infection and protect against experimental cerebral malaria. *Pathog. Glob. Health* **109**, 266–274 (2015).
149. Ribeiro, N. Q. et al. Atorvastatin as a promising anticryptococcal agent. *Int. J. Antimicrob. Agents* **49**, 695–702 (2017).
150. Matsumoto, M., Einhaus, D., Gold, E. S. & Aderem, A. Simvastatin augments lipopolysaccharide-induced proinflammatory responses in macrophages by differential regulation of the c-Fos and c-Jun transcription factors. *J. Immunol.* **172**, 7377–7384 (2004).
151. Youssef, S. et al. The HMG-CoA reductase inhibitor, atorvastatin, promotes a Th2 bias and reverses paralysis in central nervous system autoimmune disease. *Nature* **420**, 78–84 (2002).
This is the first paper to show that statins promote T_H2 cell responses and inhibit T_H1 cell-type immunity.
152. Bessler, H., Salman, H., Bergman, M., Straussberg, R. & Djaldetti, M. In vitro effect of statins on cytokine production and mitogen response of human peripheral blood mononuclear cells. *Clin. Immunol.* **117**, 73–77 (2005).
153. Yilmaz, A. et al. Differential effects of statins on relevant functions of human monocyte-derived dendritic cells. *J. Leukoc. Biol.* **79**, 529–538 (2006).
154. Guler, R. & Brombacher, F. Host-directed drug therapy for tuberculosis. *Nat. Chem. Biol.* **11**, 748–751 (2015).
155. Ayyobi, A. F. et al. Small, dense LDL and elevated apolipoprotein B are the common characteristics for the three major lipid phenotypes of familial combined hyperlipidemia. *Arterioscler. Thromb. Vasc. Biol.* **23**, 1289–1294 (2003).

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