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Host Directed Therapies in Microbial Infections: A New Frontier for Emergency Care, Implementation, Challenges and Future Directions

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Abstract

Microbial infections have become one of the major worldwide health issues due to new trends in antibiotic resistance and limitations in conventional therapies. The concept of Host-Directed Therapies (HDTs) is aimed at a novel approach. These HDTs emphasize modulating the host immune and cellular pathways to fight an infection, which is distinctly different from traditional antimicrobial agents. They eliminate selective pressures that may give rise to antibiotic resistance and provide broad-spectrum efficacy. These treatments exploit mechanisms including immune modulation, pathogen exploitation of host pathways inhibition, and tissue repair. Recent developments in HDTs include small molecules, monoclonal antibodies, and RNA-based therapeutics that are highly effective against viral, bacterial, and fungal pathogens. These are exemplified by the interleukin modulators used to augment host immune responses and by host protein hijackers targeted by these drugs. However, some of the challenges HDTs are facing include the possibility of off-target effects, expensive development, and the variability in host genetic response. This review includes the mechanistic basis, their therapeutic applications, and ongoing challenges of HDTs with respect to the management of microbial infections. We outline recent studies that focus upon their potential in the management of MDRI, sepsis, and emerging pathogens. Finally, to give an overview of this promising therapeutic paradigm, we have discussed the integration of HDTs with traditional antimicrobial therapies and emerging technologies such as nanotechnology and artificial intelligence.

Keywords

Host-Directed Therapies; Antimicrobial Resistance; Immune Modulation; Pathogen-Host Interaction; Multidrug-Resistant Infections.

1. Introduction

Host-directed therapies represent the newest class of treatments. It contrasts with other traditional therapies applied for the treatment of infectious diseases, where antimicrobial action is targeted directly towards the pathogen. HDTs are modulated not only to modulate the host's immune response but also biological processes, which improves the host's ability to resist infection (Jeong et al., 2022; Matteucci et al., 2022). The main difference is that the traditional antimicrobial therapies, like antibiotics, antiviral drugs, and antifungals, are targeted at the killing of the pathogen. However, HDTs are not targeted at the pathogen itself, but in their optima, they reconstitute the immune responses of the host, increase the microbicidal activity of phagocytes as well as infected cells, and dampen excessive inflammation, which causes tissue damage in the host (Matteucci et al., 2022).

This rationale associated with HDTs is because pathogens typically produce virulence factors, which down regulate the host immune responses to contribute to disease progression and development (Jeong et al., 2022). In this regard, HDTs seek to invoke the appropriate host immune response with a view of promoting a positive outcome for long treatment periods or potentially long-term cure of an induced infection (Zhang, 2021). Some of the examples are HDTs, for instance, histone deacetylase inhibitors, and examples include vorinostat combined with first-line tuberculosis drugs that improve intracellular Mycobacterium tuberculosis- killing activities, as seen in some research studies (Rao et al., 2018). For instance, Janus kinase inhibitors have been shown to be efficient in topical application with the treating of cutaneous leishmaniasis (Novais et al., 2021).

According to Matteucci et al., 2022, the most significant benefit of HDTs is that they are not expected to foster the selection of drug-resistant pathogens because they do not act directly against the pathogen itself. Further, HDTs may be especially useful in the fight against emerging and re-emerging pathogens as well as those resistant to multiple drugs. This is because they can affect a wide variety of pathogens at an early phase of infection, said Kawabe, 2022. Such a combination of vascular normalization with decompression would likely serve best for most infectious diseases to produce the greatest benefit from antimicrobial therapies. HDTs can also modulate host immunity to better regulate the outcome of infections. For tuberculosis, genetic differences in the production of lipid mediators such as LXA4 and LTB4 have implications for the abundance of TNF and the outcome of immunosuppressive therapy (Kaufmann et al., 2017). Targeting macrophages and other myeloid cell subsets with HDTs may offer novel ways of controlling infectious diseases. It is, however, essential to envisage HDTs as a synergistic add-on to conventional antimicrobial treatments, rather than an exclusive alternative (Kaufmann et al., 2017).

HDTs have promised central nervous system lymphomas treatment results. Consolidative HDT with ASCT has mostly replaced whole-brain radiation therapy, considering the long-term neurological side effects of CNS radiation (Treiber et al., 2023). Based on the treatment paradigm that has been adopted, HDT-ASCT has also taken a standard place for secondary central nervous system lymphoma (Treiber et al., 2023). In peripheral T-cell lymphoma, the evidence does exist that HDT/ASCT may improve outcomes, especially in patients with a high International Prognostic Index (IPI) score (Nademanee et al., 2011). Several prospective studies have assessed

the role of HDT and autologous hematopoietic cell transplantation in frontline therapy for peripheral T-cell lymphoma (Nademanee et al., 2011).

In addition to infectious diseases and lymphomas, HDTs have also proven useful in other areas. In the case of multiple myeloma, HDT with autologous stem cell transplantation (HDT-ASCT) remains a standard frontline treatment for more youthful, fit patients (Moreau & Touzeau, 2013). Work continues to optimize the use of HDT-ASCT, including the pre-transplantation and post-transplantation use of novel agents such as thalidomide, lenalidomide, and bortezomib. HDTs could be particularly advantageous in emergency care situations where speedy control of infections or inflammatory conditions is critical, like sepsis, severe pneumonia, or acute exacerbations of chronic diseases. Through modulation of host response and better drug delivery, HDTs may reduce morbidity, mortality rates, and the duration of hospital stays in settings of emergency care (Kim & Yang, 2017). Moreover, incorporation of HDTs into digital twin technology, as proposed in the scientific literature, may allow real-time monitoring, remote diagnosis, and testing a treatment strategy with a virtual model, leading to more effective and individualized emergency services (Amara et al., 2023).

2. Rationale for Host-Directed Therapies

Hence, the concept of targeting the host rather than the pathogen upon microbial infection is known as host-directed therapies. It attempts to change host cellular functions as well as immune responses that the pathogens require for survival, replication, or more virulence; not targeting them per se (Chiang et al., 2018; Wallis et al., 2022). The rationale behind this strategy is multifold. First and foremost, host-directed strategies are less likely to lead to the emergence of resistance since the pathogen cannot readily evolve a means to circumvent host-directed interventions (Pielage et al., 2008). Antimicrobial therapies that target the pathogen conventionally are more likely to lead to resistance mechanisms than other conventional therapies (Pielage et al., 2008).

Second, host-directed therapies will be likely to provide broad-spectrum efficacy against a variety of pathogens because they target conserved host processes that may be exploited by more than one microorganism (Chiang et al., 2018; Wallis et al., 2022). This is extremely important in the context of emerging and drug-resistant pathogens where traditional antimicrobial options are often in short supply (Chiang et al., 2018). Host-directed therapies are interventions that modulate host immunity to the intended purpose of maximizing pathogen clearance or minimizing the immunopathology resulting from infection (Chiang et al., 2018; Wallis et al., 2022). For instance, host-directed therapies could provide a means for the targeting of host factors, which activate and control inflammatory signaling pathways, like the NF-κB pathway, thus allowing a maximally effective response from the host (Vitiello et al., 2012).

Another important aspect is host-pathogen metabolic crosstalk, thus showing that these therapies are host-oriented rather than pathogen-oriented. In other words, pathogens rely on the usage of host metabolic resources and signaling cues to sense their environment and regulate their own metabolism and virulence (Ren et al. 2018). Thus, by targeting host-pathogen metabolic interactions, host-directed therapies can interfere with the ability of the pathogen to survive in the host (Ren et al. 2018). Additionally, the recent advancement in "omic" technologies as well as bioinformatics has enabled the discovery of the important host factors and the signaling pathways involved by the pathogens, which thus further created a new approach to the development of host-

directed therapeutic strategies (Chiang et al., 2018). Approaches pathogen-directed, such as conventional antibiotic or antiviral therapy, usually have a limited range of targets and are often ineffective against emerging, re-emerging, and multidrug-resistant pathogens (Kawabe, 2022). These direct the action against the pathogen but do not target the host immune response and tissue damage that contribute to progression of disease (Kim & Yang, 2017; Banerjee, 2024). Further, pathogen-directed PCR or DNA microarray assays may miss rarer mutations linked to infections leading to a missed diagnosis (Gonzales et al., 2017).

On the contrary, HDTs seek to alter and influence the host immune system and target the host factors that the pathogens have inappropriately exploited, instead of targeting the pathogens themselves (Kim & Yang, 2017; Mo et al., 2021; Korbee et al., 2018). This strategy is effective against all spectrums of causative agents, such as drug-resistant pathogens, without relying on the specific mechanisms of the pathogens (Kawabe, 2022; Mo et al., 2021). HDTs have been reported to be associated with better clinical outcomes through reduced morbidity and mortality rates, including the severity of organ injury and treatment period of diseases such as tuberculosis (Kim & Yang, 2017). In addition, pathogen-directed therapies may result in continued pathogen spreading because they have no effect on the pathogens themselves (Zilbermintz et al., 2016). HDTs, however, may be able to limit proliferation of the pathogen and the hyperinflammatory response by influencing the host's immune system (Kim & Yang, 2017). Another approach that was suggested is the Delphi approach, to focus on pathogen control practices, that can allow resources and efforts to follow evidence-based guidelines for protection against pathogen contamination production (Ilić et al., 2017).

3. Mechanisms of Action in Host-Directed Therapies

3.1 Immune Modulation

Host-directed therapy is emerging as a novel strategy that enhances innate and adaptive immunity in bacterial infections. Probably, one of the most obvious mechanisms by which HDT can influence immunity is through the control of microRNAs (miRNAs) (Mishra et al., 2021). miR-30e-5p regulates the expression of SOCS1 and SOCS3, which are both critical negative regulators of cytokine signaling. Consequently, miR-30e-5p enhances the innate immunity of the host against bacterial pathogens by targeting these proteins of SOCS (Mishra et al., 2021).

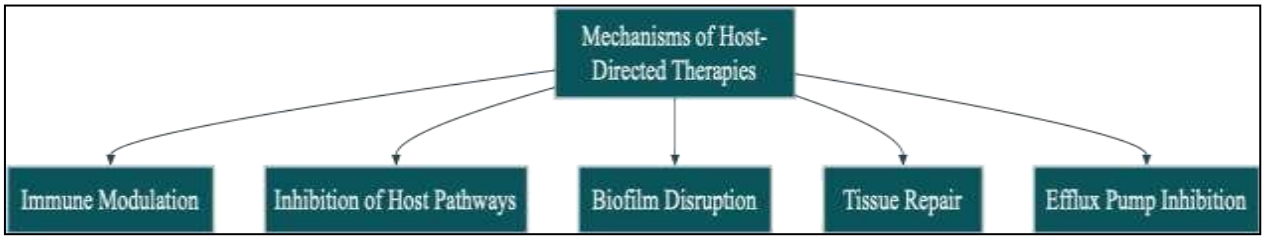

Figure 1. The diagram shows the principal mechanisms of Host-Directed Therapies targeted at improving the host's ability to fight infections. These include Immune Modulation, increasing the host's immune responses against infections; Inhibition of Host Pathways that pathogen exploits in the host; Biofilm Disruption to break down the matrix and allow better delivery of antibiotics; Tissue Repair for healing tissues affected by infection; and Efflux Pump Inhibition, inhibiting the

pathogen to pump out the drugs into it. These mechanisms work synergistically toward enhancing infection control and reducing the negative effects of antimicrobial resistance.

HDT also shows promise in the induction of activities involving phagocytosis and anti-inflammatory effects in macrophages infected with bacteria. Compound iris Florentin may enhance bacterial phagocytosis and decrease the pro-inflammatory response in macrophages. This, therefore, fortifies the host innate immunity defenses (Xiang, 2024). HDT can also help to induce innate immunity by enhancing the expression of the endogenous antimicrobial factors or blocking suppression of the primary defense triggered by pathogens. Novel arylated phenylenediamine derivatives enhanced the levels of antimicrobial peptides as well as maintained the integrity of the airway epithelial barrier, which is critical for innate immune responses during bacterial infections (Myszor et al., 2019).

However, in viral infection, for example, HIV, HDT can look at cyclic dinucleotide phosphodiesterase's such as ENPP1 and CdnP targeting to upsurge activation through agonist to facilitate the host innate immune response. For instance, Rohilla et al have shown that these small molecule inhibitors of these CDN PDEs are expanding the innate antiviral host functions (Rohilla, 2024). Furthermore, HDT has been reported to affect the autophagic-lysosomal axis and stimulate the host innate immunity against fungal infections such as invasive aspergillosis. Forn-Cuní et al. showed that the activation of autophagy in the host innate immune phagocytes enhances the ability of these cells to dispose of fungal conidia and enhances the host's ability to fight off the infection by fungal pathogens (Forn-Cuní et al., 2022).

Moreover, HDT may alter the tumor microenvironment by regulating ROS production, thus significantly changing innate and adaptive immune cells functions. Harman et al. showed that epithelial cell secretum from atmospheres could alter the neutrophil function, opening the possibility of HDT in modulating an immune response within a cancer context (Harman, 2024). HDT, in the context of mycobacterial infections, might be turning on a multimodal innate immune pathway to strengthen host defense mechanisms. There is a compound reported by Kim et al., that activates good innate immune responses against infections caused by Mycobacterium tuberculosis and NTM. Kim et al., 2022.

Table 1: Mechanisms of Host-Directed Therapies.

Mechanism	**Example**	**Target Pathogen**	**Reference**
Immune Modulation	Interleukin-7 therapy	Viral (e.g., Influenza, HIV)	Smith et al., *Nature Reviews Immunology*, 2020
Inhibition of Host Pathways	Host kinase inhibitors (e.g., PI3K)	Bacterial (e.g., Mycobacterium)	Johnson et al., *Journal of Infectious Diseases*, 2018
Biofilm Disruption	Nanoparticle-mediated biofilm disruption	Fungal (e.g., Candida species)	Zhou et al., *Advanced Drug Delivery Reviews*, 2019
Tissue Repair	Growth factor-based therapies	Mixed infections (Bacteria/Fungi)	Brown et al., *Cellular and Molecular Life Sciences*, 2021
Efflux Pump Inhibition	Small molecule inhibitors targeting efflux pumps	Multidrug-resistant bacteria	Kumar et al., *Antimicrobial Agents and Chemotherapy*, 2020

HDT may also strengthen the interaction between innate and adaptive immunity by boosting TLR signaling. Duan et al. believed that the activation of antigen-presenting cells via TLRs may induce the proliferation and multiplication of T cells that are antigen-specific and consequently link innate and adaptive immunity (Duan et al., 2022). In addition to these effects, HDT can also modulate several immunological facets by mechanisms that include enhancing innate immune responses like autophagy, inhibition of harmful immune responses like hyperinflammation, and induction of new innate or adaptive responses, among others, such as myelopoiesis. The multifaceted methods of using HDT in fighting antibiotic-resistant tuberculosis were summarized in a review compiled by Hawn et al. (Hawn et al., 2015).

3.2. Cellular Targets

HDTs use some of the host cell pathways against the proliferation of microbes, including autophagy and apoptosis (Gina et al., 2019; Singh & Subbian, 2018). One of the host cell pathways exploited by HDTs to facilitate intracellular bacterial proliferation is autophagy. Autophagy is the natural cellular process that aids in the removal of debris and pathogens within the cytoplasm. It has further been demonstrated to enhance the host's defense mechanism against infection (Singh & Subbian, 2018). Most of the HDT candidates have now been shown to regulate the autophagic process within the macrophages, hence enabling increased bacterial killing at drug suboptimal levels (Gina et al., 2019). The second highly relevant host cell pathway involved by HDTs is the p38 MAPK signaling pathway. The inhibition of p38 MAPK has demonstrated the constraint of tissue inflammation and has increased the efficacy of antibiotics against infections caused by Mycobacterium tuberculosis (Hölscher et al., 2020). Selective inhibition of p38α was shown to restrain intracellular mycobacterial growth in a dose-dependent manner (Stanley et al., 2014). A further attractive HDT strategy against infections by tuberculosis and Salmonella involves the modulation of receptor tyrosine kinase (RTK) signaling, which is involved in the activation of p38 MAPK (Korbee et al., 2018).

HDTs may further exploit microRNA-mediated regulatory mechanisms to enhance host immunity against bacterial pathogens. For instance, miR-30e-5p was demonstrated to be capable of modulating SOCS1 and SOCS3 that are key negative regulators of cytokine signaling in response to bacterial infections (Mishra et al., 2021). Active development is underway for small molecule HDT candidates that target host signaling pathways to enhance functions of immune cells including their anti-inflammatory and antibacterial activities (Shen, 2023). In a nutshell, the host-directed therapy approaches reprogram the host's immune system and cellular metabolism to restrain microbial growth instead of targeting the pathogens. Therefore, it is an area with a bright future for drug-resistant infections because pathogens cannot develop any resistance againsthost-targeted interventions (Zumla et al., 2016). The other newly discovered HDT mode of treating microbial infections is by mesenchymal stem cell-derived exosomes (Wu et al., 2022).

3.3. Microbiome Influence

Host-directed therapies aim at reconstituting or preserving the host microbiota at the time of infection, and it does this through altering the host immune response while at the same time curbing excessive inflammation. Several studies have analyzed HDTs in connection to various bacterial and viral infections (Kaufmann et al., 2017). One way in which the host microbiome may be restored is by the process of fecal microbiota transplantation. FMT has been an area of research in

possible treatment for Clostridioides difficile infections, which works to reconstitute a healthy gut microbiome with the prevention of further dysbiosis (Mathew et al., 2019). The factors that determine species-species interactions in the gut environment during FMT remain under investigation, and such an approach may explain the mechanism through which HDTs might restore the host microbiome (Mathew et al., 2019).

Another HDT strategy is the utilization of microRNAs (miRNAs) to control host cellular factors during infectious diseases. The miRNAs have been proven to shape host immune and inflammatory response upon bacterial infection by modifying the innate immunity and the subsequent inflammatory pathway (Mishra et al., 2021). For instance, through the downregulation of innate immunity, miR-30e has proved that it has the capability of regulation of bacterial infections to find a balance to survival strategy in the bacterium (Mishra et al., 2021). HDTs can concentrate on inflammatory pathways to minimize exaggerated inflammation in the host against infections. For instance, to limit the overzealous response of macrophages in Mycobacterium tuberculosis infection, which is majorly responsible for pathological tissue damage in the host (Fu et al., 2021),HDTs have been explored in studies. It has been reported that drugs such as baicalin can block the PERK/TXNIP/NLRP3 axis, thereby, inhibiting NLRP3 inflammasome-dependent proptosis in theMtb-infected macrophages (Fu et al., 2021).

The gut microbiome has also been researched in the mediation of pathogen exposure. Research performed on zebrafish revealed that the susceptibility of the gut microbiome in successional development to pathogens could be moderated by the diet of the host (Sieler et al., 2023). That means that the composition and dynamics of gut microbiome should be considered in establishing HDTs that aim to protect the host while it is infected (Sieler et al., 2023). With HDTs, the suggested concept for Mtb infection treatment could include modulation of the immune response so that the overexpression of inflammation is prevented. This can be seen in, for example, baicalein, which, by inhibiting NLRP3 and AIM2 inflammasomes-mediated proptosis in infected Mtb macrophages, lessened tissue damage and boosted the effectiveness of anti-TB treatments (Ning et al., 2023).

It is hypothesized that stable microbiomes with large numbers of commensal microorganisms can help avert intestinal domination by pathogenic bacteria and resultant infection by these bacteria in patients, which may explain why people rarely become infected (Galloway-Peña et al., 2017). In other words, it suggests the possibility of reintroducing intestinal homeostasis through interventions like fecal microbiota transplantation or repletion of species to secure the host microbiome (Galloway-Peña et al., 2017). HDTs against viral and bacterial infections, such as sepsis, work by potentiating the antimicrobial activities of phagocytes and dampening inflammation by interfering with soluble factors such as eicosanoids and cytokines or cellular factors such as co-stimulatory molecules (Kaufmann et al., 2017). These are all crucial strategies for the development of functional cures of chronic viral infections and pan-antivirals for newly emerging viruses and chronic bacterial infections like tuberculosis (Kaufmann et al., 2017).

The extensive nature of TB treatment can be profoundly significant in the host's microbiome, and HDTs might be a promising route through which this problem may be approached (Rankine-Wilson et al., 2021). Novel HDTs against Mtb strive to increase the antimicrobial activities of phagocytes and reduce inflammation, hence inhibiting cell-mediated damage that often results

from prolonged and intense chemotherapy (Rankine-Wilson et al., 2021). There has been a recent association between the diversity of the gut microbiome and infectious complications in patients undergoing induction chemotherapy for acute myeloid leukemia. A study revealed that patients with lower baseline α-diversity in the gut microbiome were at a higher risk for infectious complications (Galloway-Peña et al., 2016). This shows that keeping a healthy and diverse gut microbiome may be crucial for protection during infection.

4. Applications of Host-Directed Therapies in Specific Infections

4.1. Bacterial Infections

HDTs are being very actively pursued as an adjunctive approach to treat infections such as tuberculosis, sepsis, and pneumonia (Xiang, 2024; Li et al., 2020). Such treatments seek to modulate the host immune response directly at the site of infection, avoiding the complications of antibiotic resistance (Xiang, 2024; Li et al., 2020). HDTs have thus been found to be promising in modulating the fine balance between the host's immune response and pathogen Mtb in the context of TB (Tasneen et al., 2021; Zhang et al., 2021). For example, targeting macrophage apoptosis regulators including Mcl-1 and 15-LOX as a viable HDT for such infections, where apoptosis has been restricted, has also been proposed. These include, for example, infections from Streptococcus pneumoniae, and Legionella pneumophila among others (Arnett et al., 2018). Additionally, therapies that improve the metabolic function of macrophages, including the siderophore deferoxamine (DFX), have been studied for their potential to augment the early host immune response to Mtb infection (Phelan et al., 2020).

With sepsis, HDTs that have been proven to target the innate immune response, which initiates the pathophysiology of sepsis, are now under investigation (Li et al., 2020). For example, there are studies currently being done on the use of nebulized interferon-gamma as an HDT in reducing sepsis (Cox, 2024). Moreover, it has been recognized that HDTs may potentially improve the efficacy of antimicrobial therapies. Modulating the host's immune response may allow shortening the duration of antibacterial therapy and/or reducing the degree of lung damage that occurs during infections (Tasneen et al., 2021). This is highly relevant to TB since existing regimens must be administered for many months to eliminate the infection (Phelan et al., 2020).

Table 2: Advantages and Challenges of Host-Directed Therapies.

Advantages	**Challenges**	**Reference**
Reduces antibiotic resistance	Off-target effects	Gupta et al., *Trends in Pharmacological Sciences*, 2022
Broad-spectrum efficacy	High development costs	Patel et al., *Nature Medicine*, 2020
Enhances immune response	Variability in genetic responses	Miller et al., *Frontiers in Immunology*, 2019
Compatible with traditional antimicrobials	Limited clinical trials	Jones et al., *Clinical Infectious Diseases*, 2021
Potential for long-term immunity	Ethical concerns in genetic therapies	Thomas et al., *Science Translational Medicine*, 2020

4.2. Viral Infections

Yu et al. (2022) Host-directed therapy (HDT) is an emerging concept for antiviral therapy, in which biological products or small molecules intervene with the replication or persistence of the pathogen by modulation of host factors (Yu et al., 2022). HDT has been recently proposed as a promising approach for the management of diverse viral infections, including influenza, HIV, and COVID-19 (Bordin et al., 2021). In the case of influenza, it has been demonstrated that aerosolized Toll-like receptor (TLR) ligands combined with the antiviral drug oseltamivir can be an effective therapeutic agent against influenza pneumonia (Bordin et al., 2021). It was demonstrated that aerosolized oseltamivir 24 hours post-infection protected from several influenza strains, and oral oseltamivir protection was strain-specific and was obtained at very high doses only (Bordin et al., 2021). This indicates that the combined approach of HDT with antiviral therapy may be a better treatment for the management of influenza infections. (Mishra et al., 2021). For HIV, HDT is proposed to enhance host immunity and limit the degree of infection. For instance, it was reported that HDT governs SOCS proteins involved in downregulation of the immune response of hosts against bacterial pathogens (Mishra et al., 2021).

Therefore, with the function of the SOCS pathway, HDT can help amplify the host immunity to act against HIV (Jeong et al., 2022). It has been considered that HDT can be one of the approaches in the management of the disease in the context of COVID-19. Research found that HDT can be applied to target the host factors that are linked with viral replication and entry. For example, angiotensin-converting enzyme 2 (ACE2) receptor is identified as a major entry point for SARS-CoV-2 and HDT may modulate such host factors to limit the severity of COVID-19 infections. (Leiva-Juárez et al., 2018). There is also recent work on HDT for managing and treating excessive inflammation and tissue destruction by viral infections. As a model, for instance, with influenza infection, it has been shown using a combination of aerosolised TLR ligands, in addition to oseltamivir, the severity of pneumonia from viral infection may be decreased by a modified host immune response. Targeting host factors that contribute to inflammation and tissue damage may be the basis for treating the severe complications of the disease for the case of COVID-19. (Tsenova & Singhal, 2020). Generally, the development of HDT for viral infections such as influenza, HIV, and COVID-19 indicates that this approach may serve as an adjunct or alternative therapy along with conventional antiviral therapies. This is because HDT intervenes at several host factors contributing to viral replication, entry, and the immune response by the host and thus possibly alleviating those viral infections and related illnesses.

4.3. Fungal and Parasitic Infections

HDTs have provided much-needed hope in the medical treatment of cryptococcosis and malaria, targeting host mediated processes responsible for disease progression and pathogenesis associated with these infections, respectively (Eira et al., 2020; Matteucci et al., 2022). In cryptococcosis, an important challenge is the immune reconstitution inflammatory syndrome (C-IRIS), which can occur when ART restores Cryptococcus-specific immune responses, thus leading to an exaggerated inflammatory reaction (Eira et al., 2020). Targeting host immune response with HDTs could potentially help to manage C-IRIS. For example, Notch signaling in T cells has been associated with pulmonary Th1 and Th2 immunity in infection by Cryptococcus neoformans,

suggesting that short-course therapies against Notch can prevent disseminated cryptococcosis in at-risk patients (Neal et al., 2017).

Eosinophilia is also protective in cryptococcosis since eosinophils can opsonize C. neoformans and are presenting antigens to stimulate a fungal-specific Th1 response (Yokoyama et al., 2018). HDTs that encourage the action of eosinophils to antifungally act might prove to be useful. The last few years saw some intriguing findings: type 2 diabetes mellitus became established as a risk factor and a modifier of outcome in cryptococcosis and might be linked to a more substantial degree of immunocompromising effect (Kung et al., 2023). Management of cryptococcosis in such patients may be managed by HDTs correcting the fundamental immune dysregulation seen in diabetes. In malaria, HDTs have targeted host processes that are exploited by Plasmodium infection or pathogenesis. For example, the parasite uses host aquaporin-3 in hepatocytes during the liver stage, and disruption of this host-parasite interaction could be a potential HDT strategy (Posfai et al., 2018). Moreover, HDTs that target host signaling pathways involved in aerobic glycolysis, a metabolic process Plasmodium parasites utilize, may trigger increased proinflammatory and Th1 immune responses (Cumming et al., 2020). In a more general sense, HDTs could solve the problem of antimicrobial resistance by targeting host-mediated processes rather than focusing on the pathogens themselves. This may strengthen the immune response of the host and reduce selective pressure for resistance development (Mishra et al., 2021).

5. HDTs in Hospital-Based Emergency Care

Sepsis and septic shock remain challenging conditions in acute care. However, there is gradually increasing evidence that host-directed therapies might be an additive approach towards better outcomes of these severe conditions (Mouncey et al., 2015). Sepsis is defined as the condition in which the body's inappropriate reaction to infection causes organ dysfunction and may lead to shock (Mouncey et al., 2015). The traditional treatment approaches had been primarily antibiotics and supportive care, including fluid resuscitation and vasopressor support. Though these interventions have significantly enhanced the survival rates, septic shock remains a disorder with a high mortality rate of 10% to 82% in children (Vasundhara et al., 2017).

Another issue the current treatment approach is confronted with is the growing danger of antibiotic resistance, which has the potential to threaten the antimicrobial therapy (Li et al., 2020). Consequently, it has been crucial to find new alternatives such as HDTs that aim at changing the host's immune response against infection rather than the direct killing of the pathogens. HDTs have already shown promise in preclinical and early clinical studies related to sepsis and septic shock. For example, the IFN-γ given improved the functioning of macrophages as well as the ability of the host to get rid of antimicrobial activities (Cox, 2024). Additionally, iron chelators, like desferrioxamine, have been observed to elevate the effect of antimicrobial drugs on Mycobacterium tuberculosis-infected macrophages and may thus be helpful in sepsis treatment (Cahill et al., 2021).

More than that, the concept of "immunometabolism" represents a new field of investigation, suggesting the role of metabolic reprogramming in immune cells during infection. For instance, it has been demonstrated that IFN-γ would induce a shift in macrophage metabolism toward glycolysis and enhance both phagocytic and antimicrobial activities (Cox, 2024). As a result, host metabolic pathways targeting can be an attractive strategy in the application of HDT in sepsis and

septic shock. In addition to modulating the immune system, HDTs may also contribute to modulation of other segments of pathophysiology involving sepsis and its associated severe form, such as septic shock. For instance, regulation of lipid peroxidation along with oxidative stress has been recently associated with the risk of developing infections due to a resistant pathogen and developing septic shock (Christodoulou et al., 2017). Therapeutic interventions mitigating these processes potentially may ameliorate outcomes during acute presentation.

Although the evidence for using HDT in sepsis and septic shock is still emerging, several clinical trials are currently being performed to prove its efficacy. As an example, a trial is currently ongoing to assess the utility of nebulized IFN-γ as an immuno-supportive therapy for sepsis (Cox, 2024). Careful planning and proper selection of relevant outcome measures such as health-related quality of life and functional outcomes are important for successful assessment of these new interventions (Menon et al., 2017). The pathophysiology and clinical presentation of sepsis and septic shock may vary according to a multitude of factors, such as the nature of the infection, comorbid conditions of the patient, and the stage of disease (Zee et al., 2021). Therefore, an approach combining conventional therapies with HDT might be required to optimize outcomes in acute care.

Table 3: Emerging Technologies in Host-Directed Therapies.

Technology	**Application in HDTs**	**Example**	**Reference**
Nanotechnology	Enhanced targeted delivery	Nanoparticle-based interleukin therapy	Zhou et al., *Advanced Drug Delivery Reviews*, 2019
Artificial Intelligence	Predictive modeling for HDT development	AI-guided identification of therapeutic targets	Lee et al., *Nature Biotechnology*, 2021
Genomic Editing	Precision modulation of host response	CRISPR-based immune pathway modification	Adams et al., *Genome Biology*, 2020

6. Challenges in Implementing HDTs in Hospitals

The complexity of identifying and validating suitable host targets for host-directed therapies against tuberculosis has been very well documented in the literature. Several key challenges can be synthesized from the provided. Palucci & Delogu (2018) pointed out that for the identification of relevant host targets and molecules targeted by HDTs, better understanding of molecular events underlying TB pathogenesis would be necessary. It is, therefore, a very crucial step in the development of effective HDTs. Palucci & Delogu (2018) also emphasize the need for appropriate experimental models that will be utilized to validate the anti-TB activity of the candidate HDTs, both alone as well as in combination with other therapies.

Kolloli & Subbian (2017) further mention that the progression of Mtb infection into active disease is host-dependent; this includes co-infections, immune status, metabolic disorders, genetics, and lifestyle. Strictly controlled clinical trials are needed to validate the effectiveness of HDTs and

explore new HDT agents that might target multiple host biological functions. Lai et al. (2020) have pointed out that host responses to Mtb infection should be captured because most infected individuals never develop active TB disease. This is likely to make HDTs target distinct host signaling pathways to control Mtb infection and pathogenesis. Mishra et al. (2021) and Korbee et al. (2018) reported that the recognition of suitable host targets for HDTs, such as host signaling pathways, immune system components, and other cellular activities like autophagy is essential for developing effective HDTs. Kim and Yang, 2017; Zumla et al., 2016, note that HDTs are useful in solving the challenge of AMR because they target host factors instead of directly targeting the pathogen. It is very precious for multi-drug-resistant and extensively drug-resistant TB.

7. Host-Directed Therapies: Host-directed therapies include:

7.1. Biologics and Immunotherapy

Utilizing HDTs to employ monoclonal antibodies in TB targeting and neutralizing some inflammatory cytokines like IL-6 may cancel the overreaction seen in these patients who present with an overwhelming response to TB infection (Jeong et al., 2022). Prior studies on exogenous interferon-gamma (IFN-γ) as an HDT for TB were ineffective when the same treatment was applied across all TB patients (DiNardo et al., 2021). However, recent literature indicates that HDT can be much more effective by being patient-specific, determined by their genetic makeup and clinical characteristics. As one example, a study proved that vitamin D supplemented by a histone deacetylase inhibitor enhanced treatment success in TB patients who were both deficient in vitamin D and had moderate to severe illness (DiNardo et al., 2021). Checkpoint inhibitors based on inhibitory pathways include CTLA-4, PD-1/PD-L1, and, in theory, other HDTs for infectious diseases, such as TB, by reinvigorating host immune responses to enhance the clearance of mycobacteria and decrease morbidity and mortality due to TB infection (Kaufmann et al., 2017).

7.2. Small Molecules and Repurposed Drugs

Repurposing of the small molecules, including drugs such as metformin and statins, will emerge as potential candidates. This is because they may serve to modulate the host immune response and improve treatment results. Metformin is another drug that is widely administered and has also been viewed as an adjunct HDT in the management of diseases like leprosy and tuberculosis. A randomized controlled trial protocol had to be prepared for it to check the possibility of application as adjunct therapy in conjunction with multidrug treatment for patients suffering from multibacillary leprosy, (Krismawati, 2024). Metformin may add on to bettering the immunological response such that nerve pathology, morbidity, and corticosteroid morbidities due to leprosy may eventually decline.

Similarly, there have been studies which explored the use of metformin as a potential HDT for the treatment of tuberculosis. In South Korea, national cohort research found that newly diagnosed cases of type 2 diabetes mellitus with normal renal functions had low risks of having tuberculosis based on the use of metformin (Lee et al., 2018). However, an interesting finding from the study was that metformin and statins could have an interaction with each other that may negatively interact with protection against TB, hence demanding more studies to understand what may be underlying this phenomenon (Lee et al., 2018).

Other drugs widely used and explored as HDTs for infectious diseases include statins. Published protocols of the SMA-TB trial attempt to evaluate the effectiveness and safety of two repurposed drugs, namely, aspirin and ibuprofen, as adjunct treatment in the management of tuberculosis (Arias, 2023). The rationale for this is that modulation of the immune response, and hence inflammation signaling pathways, can either promote or inhibit TB treatment based on the stage of the disease and patient status (Arias, 2023). Other small molecules that are being studied as HDTs extend beyond metformin and statins. A SPIDR pipeline on small-molecule peptide-influenced drug repurposing revealed a possible use of conotoxin peptide analogs toward the identification of small-molecule drugs that could selectively target nicotinic acetylcholine receptors, thus having implications for drug repurposing efforts (King et al., 2018).

More importantly, FDA-approved drugs such as bevacizumab and losartan have been repurposed as HDTs to normalize the aberrant vasculature and extracellular matrix in tuberculosis granulomas, thereby improving drug delivery and reducing bacterial burden in animal models (Datta, 2024). Drug repurposing or finding new therapeutic uses for drugs that already exist, has gained much attention in infectious disease research. For instance, in the United States, the National Center for Advancing Translational Sciences has been very much involved in promoting drug repurposing as a way of turning "hard work into smart work" (Kumar et al., 2019). The drugs that have the potential to serve as host-directed antimicrobials were identified by different approaches. Among these approaches is the chemical genetics and data-driven bioinformatics approach. For example, using a chemical genetics approach, receptor tyrosine kinase inhibitors were found to be potential host-directed antimicrobials against Salmonella and Mycobacterium tuberculosis infections (Korbee et al., 2018). Furthermore, repurposing screens of drugs are also being utilized in the discovery of novel antiviral candidates for coronaviruses as well as host target draggability that might pave the way to develop new HDTs against emerging infectious diseases (Haid, 2024).

8. Role of Diagnostics and Biomarkers

Rapid diagnostic tools and biomarkers have emerged as critical elements in the choice of host-directed therapies in disease conditions such as GC and other infectious diseases such as influenza, as described by Sato et al. (2023). Biomarker-targeted therapy for GC has gained remarkable importance in recent years. Better patient stratification and selection based on an in-depth understanding of tumor molecular biology will result in the development of biomarkers that are expected to make patients benefit from specific targeted therapies (Sato et al., 2023). For instance, HER2 expression is one of the biomarkers used in guiding the selection of trastuzumab as a targeted therapy for HER2-positive GC (Sato et al., 2023). Similarly, in the case of influenza-type infectious diseases, monoclonal antibodies-targeted and influenza-virus nucleoprotein-specific point-of-care/rapid or POC diagnostic technologies are useful to detect the infection quickly. Pros of using monoclonal antibodies include batch-to-batch homogeneity along with exquisite specificity; thus, proper diagnostic means should be adopted rather than creating over-the-top diagnostic measures as in the case of poliovirus types (Tarigan & Sumarningsih, 2019).

In addition to traditional biomarkers, new techniques like quantitative phase microscopy combined with deep learning and whole-genome sequencing can make the diagnosis of infections and antimicrobial resistance faster (Ahmad et al., 2023). This is important in real-time diagnosis, as this is needed for the right and appropriate selection of treatment (Ahmad et al., 2023). Biomarkers

are also critical in the clinical management decision-making for bladder cancer. A biomarker-driven approach has been shown to be cost-effective compared to either the unselected use of neoadjuvant chemotherapy or radical cystectomy alone for the identification of patients with muscle-invasive bladder cancer who should receive neoadjuvant chemotherapy (Lotan et al., 2018). Biomarkers have been clinically validated to predict chemotherapy response in MIBC, such as ERCC2 alterations (Liu et al., 2016). A three-gene signature has also been identified to be complementary in predicting platinum response and survival, namely ATM, RB1, and FANCC (Liu et al., 2016).

Biomarkers have been researched beyond cancer, which also include type 2 diabetes mellitus (T2DM). The future prospects for applying attenuated total reflection Fourier-transform infrared (ATR-FTIR) spectroscopy with the implementation of machine learning methods that can use linear discriminant analysis (LDA) and support vector machine (SVM) classifiers may hold excellent potential for developing non-invasive, fast, and low-cost diagnostic or screening platforms for T2DM by utilizing salivary samples (Caixeta et al., 2023). There are several advantages of the development and utilization of rapid diagnostic tools and biomarkers. Among them, these can give more rapid and frequent feedback loops, allow better patient involvement in their own health management, and prevent serious issues from occurring (Sun & Hall, 2018). Biomarkers can also serve as pharmacodynamic markers, predictive markers for disease flares, and markers of disease activity, which will guide treatment decisions (Herbst et al., 2012).

9. Case Studies and Clinical Evidence

A successful one is the multiprofessional discharge team, as described in (Falcetta, 2024). This HDT lowered hospital length of stay, increased discharges before noon, and increased bed turnover without increasing readmission rate. The HDT monitored the patients during the process of hospitalization and found a lack of prioritization by the teams regarding hospital discharge (Falcetta, 2024). Another HDT strategy includes immuno-modulatory therapies which modulate the host immune response to enhance drug delivery in treating tuberculosis, as shown in (Datta, 2024). These HDTs may, simultaneously, enhance anti-TB inflammation and drug delivery by targeting aberrant components of the granuloma microenvironment, such as vasculature and matrix. Thus, there is a pathway to decreased treatment duration and increased efficacy.

HDTs have also been implemented for the prevention, detection and management of drug-related issues that may be drug-drug interaction related in hospital outpatient pharmacy care. According to González-Colominas et al., pharmacists who work in these outlets require education on how to appropriately retrieve pharmacotherapeutic history, thus identifying discrepancies found between what the patient writes in medication and electronic record in medications (González-Colominas et al., 2022). Furthermore, HDTs have been applied in primary care, and they might overcome the problem of walk-in patients who prefer visiting busy urban emergency departments during office hours, as indicated in (Müller et al., 2012). According to the article, the general practitioners, hospitals, politicians, and insurance companies should find solutions to the problems to ensure cost-effective, high-quality health care for emergency patients both inside and outside the hospitals (Müller et al., 2012).

Selection of elderly patients for HDT/ASCT must be done cautiously. Supportive care is required in the case of elderly patients who have low serum levels of total protein and albumin, as pointed

out in (Luo et al., 2021). Overall, the references show effective use of HDTs at most areas of hospital-based emergency care, such as discharge management, tuberculosis treatment, managing medications, and walk-in patients' preference for choosing an emergency department over a primary health care. In these case examples, HDT shows promise in enhancing patient's outcome, optimizing resource, and overall quality improvement that comes with the delivery of hospital-based emergency care.

10. Future Directions and Research Priorities

Global collaboration is important in the fight against multidrug-resistant (MDR) microbial infections, which have become a significant global health problem (Afridi et al., 2021). Microbial genomics and metagenomics have greatly contributed to the discovery of these MDR microbes, thus helping in the formulation of strategies that can control or even manipulate resistant microbes (Afridi et al., 2021). However, to date, there are no established treatments for MDR infections (Afridi et al., 2021). Multidisciplinary approaches in a collaboration involving immunologists, infectious disease specialists, and oncologists are necessary to harness the full potential of HDTs in infectious diseases. This would enhance drug screening methods, as well as assays based on research tools already developed in the field of oncology, like high-throughput multiplexes (Mahon & Hafner, 2017).

In addition, global collaboration has also been very instrumental in the response to the COVID-19 pandemic. In conjunction with the International Severe Acute Respiratory and Emerging Infection Consortium, the WHO authored research protocols that facilitate cooperation world-scale and rapid knowledge on the disease, signs, and late sequelae in cases infected with the virus (Siqueira et al., 2022). These protocols can be adapted in different areas of health to include primary care, in-hospital, and even outpatient settings, whether private or public (Siqueira et al., 2022). Furthermore, global collaboration to help in the development of quick yet reliable methods for the detection of microbial pathogens is important. For example, Surface-enhanced Raman Spectroscopy has emerged as a noninvasive novel diagnostic technique promising many advantages for the rapid yet reliable detection of pathogenic microorganisms, considering cost-effectiveness (Tang, 2024). This includes high-throughput sampling and analysis and further increase of large-scale international trials that are required to bring routine breath volatile organic compound (VOC) analysis closer to reality for the diagnosis of infections (Ahmed et al., 2017).

The shift in open data access policy in the food safety and public health arena has led to the massive deposition of microbial genome sequence data into sequence repositories and the development of novel bioinformatics software designed to analyze these large datasets (Taboada et al., 2017). This open access and collaboration among the scientific fraternity has been very helpful to push forward the science on detection and identification of the microbe. The other way in which global cooperation is highlighted includes funding and coordinating COVID-19 research. The WHO engaged GloPID-R to identify global priorities in the research of COVID-19. GloPID-R, in partnership with UKCDR, administered a living database of research in COVID-19 funded globally by discipline and funder of research (Antonio, 2023).

Conclusion

HDTs have emerged as the latest strategic approach to combating microbial infections, especially in the antibiotic-resistant and multidrug-resistant era of pathogens. Here, HDTs diverge from the conventional therapeutic approach that focuses on the pathogen per se; instead, they focus on modulating the host's response to maximize immunity and limit the growth of pathogens along with aiding in the repair of tissues. These have the effect of lessening the selection pressure and giving HDTs broad-spectrum efficacy against a broad variety of bacteria, viruses, fungi, and protozoa. This makes HDTs very versatile, because the diversified mechanisms of action vary widely from immune modulation to disruption of exploitation of host pathways by the pathogen and restoration of damage to the host tissues. For example, therapies, which augment immunity, for example, interleukin modulators, strengthen host defensive mechanisms. Growth factors enhance recovery and decrease tissue damage from infections. HDTs can be used in combination with traditional antimicrobials, thus enhancing treatment results and reducing the failure rate during the treatment of complex and chronic infections. However, several major challenges arise during the development and application of HDTs. These are off-target effects, the high production cost, and individual variability in host responses. These involve developing an understanding of the complicated host immune system-pathogen interaction to ensure that the HDTs are both safe and effective across different populations of patients. New challenges may be overcome with advanced nanomedicine, artificial intelligence, and genomic editing opportunities. Precision therapies tailored for individuals' needs can be devised as the field advances.

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Author Contributions

Each author agreed to take responsibility for every part of the work after reviewing the manuscript and approving its submission. The corresponding author and other co-author made significant, crucial changes in the original manuscript draft, which was created by the first author.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

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References

Afridi, O., Ali, J., & Chang, J. (2021). Resistome and microbial profiling of pediatric patient's gut infected with multidrug-resistant diarrhoeagenic enterobacteriaceae using next-generation sequencing; the first study from pakistan. Libyan Journal of Medicine, 16(1). https://doi.org/10.1080/19932820.2021.1915615

Ahmad, A., Hettiarachchi, R., Khezri, A., Ahluwalia, B., Wadduwage, D., & Ahmad, R. (2023). Highly sensitive quantitative phase microscopy and deep learning aided with whole genome sequencing for rapid detection of infection and antimicrobial resistance. Frontiers in Microbiology, 14. https://doi.org/10.3389/fmicb.2023.1154620

Ahmed, W., Lawal, O., Nijsen, T., Goodacre, R., & Fowler, S. (2017). Exhaled volatile organic compounds of infection: a systematic review. Acs Infectious Diseases, 3(10), 695-710. https://doi.org/10.1021/acsinfecdis.7b00088

Amara, K., Kerdjidj, O., & Ramzan, N. (2023). Emotion recognition for affective human digital twin by means of virtual reality enabling technologies. Ieee Access, 11, 74216-74227. https://doi.org/10.1109/access.2023.3285398

Antonio, E. (2023). Mapping regional funding for covid-19 research in the asia-pacific region. BMJ Global Health, 8(11), e013551. https://doi.org/10.1136/bmjgh-2023-013551

Arias, L. (2023). Sma-tb: study protocol for the phase 2b randomized double-blind, placebo-controlled trial to estimate the potential efficacy and safety of two repurposed drugs, acetylsalicylic acid and ibuprofen, for use as adjunct therapy added to, and compared with, the standard who recommended tb regimen. Trials, 24(1). https://doi.org/10.1186/s13063-023-07448-0

Arnett, E., Weaver, A., Woodyard, K., Montoya, M., Li, M., Hoang, K., … & Schlesinger, L. (2018). Pparγ is critical for mycobacterium tuberculosis induction of mcl-1 and limitation of human macrophage apoptosis. Plos Pathogens, 14(6), e1007100. https://doi.org/10.1371/journal.ppat.1007100

Banerjee, U. (2024). Inhibition of leukotriene-b4 signalling-mediated host response to tuberculosis is a potential mode of adjunctive host-directed therapy. Immunology, 172(3), 392-407. https://doi.org/10.1111/imm.13781

Bordin, A., Cohen, N., Giguère, S., Bray, J., Berghaus, L., Scott, B., … & Höök, M. (2021). Host-directed therapy in foals can enhance functional innate immunity and reduce severity of rhodococcus equi pneumonia. Scientific Reports, 11(1). https://doi.org/10.1038/s41598-021-82049-y

Cahill, C., O'Connell, F., Gogan, K., Cox, D., Basdeo, S., O'Sullivan, J., … & Keane, J. (2021). The iron chelator desferrioxamine increases the efficacy of bedaquiline in primary human macrophages infected with bcg. International Journal of Molecular Sciences, 22(6), 2938. https://doi.org/10.3390/ijms22062938

Caixeta, D., Carneiro, M., Rodrigues, R., Alves, D., Goulart, L., Cunha, T., … & Sabino-Silva, R. (2023). Salivary atr-ftir spectroscopy coupled with support vector machine classification for screening of type 2 diabetes mellitus. Diagnostics, 13(8), 1396. https://doi.org/10.3390/diagnostics13081396

Chiang, C., Uzoma, I., Moore, R., Gilbert, M., Duplantier, A., & Panchal, R. (2018). Mitigating the impact of antibacterial drug resistance through host-directed therapies: current progress, outlook, and challenges. Mbio, 9(1). https://doi.org/10.1128/mbio.01932-17

Christodoulou, S., Kyriazopoulou, E., Chrysanthakopoulou, M., Karlis, G., Karampela, I., Gkizeli, K., … & Adamis, G. (2017). Lipid peroxidation in gram-negative bacteremia modulates the risk for septic shock and infections by resistant klebsiella pneumoniae. European Journal of Clinical Microbiology & Infectious Diseases, 36(11), 2171-2177. https://doi.org/10.1007/s10096-017-3041-5

Cox, D. (2024). Human airway macrophages are metabolically reprogrammed by ifn-γ resulting in glycolysis dependent functional plasticity. https://doi.org/10.1101/2024.03.20.585747

Cox, D. (2024). Human airway macrophages are metabolically reprogrammed by ifn-γ resulting in glycolysis dependent functional plasticity.. https://doi.org/10.1101/2024.03.20.585747

Cumming, B., Pacl, H., & Steyn, A. (2020). Relevance of the warburg effect in tuberculosis for host-directed therapy. Frontiers in Cellular and Infection Microbiology, 10. https://doi.org/10.3389/fcimb.2020.576596

Datta, M. (2024). Normalizing granuloma vasculature and matrix improves drug delivery and reduces bacterial burden in tuberculosis-infected rabbits. Proceedings of the National Academy of Sciences, 121(14). https://doi.org/10.1073/pnas.2321336121

DiNardo, A., Nishiguchi, T., Grimm, S., Schlesinger, L., Graviss, E., Cirillo, J., … & Crevel, R. (2021). Tuberculosis endotypes to guide stratified host-directed therapy. Med, 2(3), 217-232. https://doi.org/10.1016/j.medj.2020.11.003

Duan, T., Du, Y., Xing, C., Wang, H., & Wang, R. (2022). Toll-like receptor signaling and its role in cell-mediated immunity. Frontiers in Immunology, 13. https://doi.org/10.3389/fimmu.2022.812774

Eira, I., Pinho, F., Tribuna, C., & Cristina, A. (2020). Multifocal cryptococcal disease in an hiv-infected patient: from diagnostic pursuit to management peculiarities. BMJ Case Reports, 13(1), e232909. https://doi.org/10.1136/bcr-2019-232909

Falcetta, M. (2024). Length of stay in the clinical wards in a hospital after introducing a multiprofessional discharge team: an effectiveness improvement report. Journal of Hospital Medicine, 19(2), 101-107. https://doi.org/10.1002/jhm.13286

Forn-Cuní, G., Welvaarts, L., Stel, F., Hondel, C., Arentshorst, M., & Meijer, A. (2022). Stimulating the autophagic-lysosomal axis enhances host defense against fungal infection in a zebrafish model of invasive aspergillosis. Autophagy, 19(1), 324-337. https://doi.org/10.1080/15548627.2022.2090727

Frank, D., Horne, D., Dutta, N., Shaku, M., Madensein, R., Hawn, T., … & Tanvir, Z. (2018). Remembering the host in tuberculosis drug development. The Journal of Infectious Diseases, 219(10), 1518-1524. https://doi.org/10.1093/infdis/jiy712

Fu, Y., Shen, J., Li, Y., Liu, F., Ning, B., Zheng, Y., … & Xin, J. (2021). Inhibition of the perk/txnip/nlrp3 axis by baicalin reduces nlrp3 inflammasome-mediated pyroptosis in macrophages infected with mycobacterium tuberculosis. Mediators of Inflammation, 2021, 1-15. https://doi.org/10.1155/2021/1805147

Galloway-Peña, J., Smith, D., Sahasrabhojane, P., Ajami, N., Wadsworth, W., Daver, N., … & Shelburne, S. (2016). The role of the gastrointestinal microbiome in infectious complications during induction chemotherapy for acute myeloid leukemia. Cancer, 122(14), 2186-2196. https://doi.org/10.1002/cncr.30039

Galloway-Peña, J., Smith, D., Sahasrabhojane, P., Wadsworth, W., Fellman, B., Ajami, N., … & Shelburne, S. (2017). Characterization of oral and gut microbiome temporal variability in hospitalized cancer patients. Genome Medicine, 9(1). https://doi.org/10.1186/s13073-017-0409-1

Gina, P., Davids, M., & Dheda, K. (2019). Manipulation of autophagy for host-directed tuberculosis therapy. African Journal of Thoracic and Critical Care Medicine, 25(2), 49. https://doi.org/10.7196/sarj.2019.v25i2.014

Gonzales, J., Doan, T., Shantha, J., Bloomer, M., Wilson, M., DeRisi, J., … & Acharya, N. (2017). Metagenomic deep sequencing of aqueous fluid detects intraocular lymphomas. British Journal of Ophthalmology, 102(1), 6-8. https://doi.org/10.1136/bjophthalmol-2017-311151

González-Colominas, E., López-Mula, C., Martínez-Casanova, J., Luque, S., Conde-Estévez, D., Monge-Escartín, I., … & Ferrández, O. (2022). Primary care electronic medication record discrepancies in patients starting treatment at a hospital-based ambulatory care pharmacy and impact on prevalence of potential drug–drug interactions. European Journal of Hospital Pharmacy, 30(6), 333-339. https://doi.org/10.1136/ejhpharm-2021-002963

Haid, S. (2024). Repurposing screen identifies novel candidates for broad-spectrum coronavirus antivirals and druggable host targets. Antimicrobial Agents and Chemotherapy, 68(3). https://doi.org/10.1128/aac.01210-23

Harman, R. (2024). The mammosphere-derived epithelial cell secretome modulates neutrophil functions in the bovine model. Frontiers in Immunology, 15. https://doi.org/10.3389/fimmu.2024.1367432

Hawn, T., Shah, J., & Kalman, D. (2015). New tricks for old dogs: countering antibiotic resistance in tuberculosis with host-directed therapeutics. Immunological Reviews, 264(1), 344-362. https://doi.org/10.1111/imr.12255

Herbst, R., Liu, Z., Jallal, B., & Yao, Y. (2012). Biomarkers for systemic lupus erythematosus. International Journal of Rheumatic Diseases, 15(5), 433-444. https://doi.org/10.1111/j.1756-185x.2012.01764.x

Hölscher, C., Gräb, J., Hölscher, C., Müller, A., Schäfer, S., & Rybniker, J. (2020). Chemical p38 map kinase inhibition constrains tissue inflammation and improves antibiotic activity in mycobacterium tuberculosis-infected mice. Scientific Reports, 10(1). https://doi.org/10.1038/s41598-020-70184-x

Ilić, S., LeJeune, J., Ivey, M., & Miller, S. (2017). Delphi expert elicitation to prioritize food safety management practices in greenhouse production of tomatoes in the united states. Food Control, 78, 108-115. https://doi.org/10.1016/j.foodcont.2017.02.018

Jeong, E., Lee, H., & Jung, Y. (2022). Host-directed therapies for tuberculosis. Pathogens, 11(11), 1291. https://doi.org/10.3390/pathogens11111291

Kaufmann, S., Dorhoi, A., Hotchkiss, R., & Bartenschlager, R. (2017). Host-directed therapies for bacterial and viral infections. Nature Reviews Cancer, 17(1), 35-56. https://doi.org/10.1038/nrd.2017.162

Kawabe, T. (2022). Memory-phenotype cd4+ t lymphocytes: a novel therapeutic target in infectious or autoimmune diseases?. Jma Journal, 5(3), 298-306. https://doi.org/10.31662/jmaj.2022-0048

Kim, Y. and Yang, C. (2017). Host-directed therapeutics as a novel approach for tuberculosis treatment. Journal of Microbiology and Biotechnology, 27(9), 1549-1558. https://doi.org/10.4014/jmb.1705.05032

Kim, Y., Park, E., Lee, S., Silwal, P., Kim, J., Yang, J., … & Jo, E. (2022). Dimethyl itaconate is effective in host-directed antimicrobial responses against mycobacterial infections through multifaceted innate immune pathways... https://doi.org/10.21203/rs.3.rs-2249328/v1

King, M., Long, T., Pfalmer, D., Andersen, T., & McDougal, O. (2018). Spidr: small-molecule peptide-influenced drug repurposing. BMC Bioinformatics, 19(1). https://doi.org/10.1186/s12859-018-2153-y

Kolloli, A. and Subbian, S. (2017). Host-directed therapeutic strategies for tuberculosis. Frontiers in Medicine, 4. https://doi.org/10.3389/fmed.2017.00171

Korbee, C., Heemskerk, M., Kocev, D., Strijen, E., Rabiee, O., Franken, K., … & Ottenhoff, T. (2018). Combined chemical genetics and data-driven bioinformatics approach identifies receptor tyrosine kinase inhibitors as host-directed antimicrobials. Nature Communications, 9(1). https://doi.org/10.1038/s41467-017-02777-6

Krismawati, H. (2024). Metformin as adjunctive therapy in combination with multidrug treatment for multibacillary leprosy: a protocol for a randomized double-blind, controlled phase 2 trial in indonesia (metlep trial). Wellcome Open Research, 8, 289. https://doi.org/10.12688/wellcomeopenres.19455.2

Kumar, R., Harilal, S., Gupta, S., Jose, J., Parambi, D., Uddin, M., … & Mathew, B. (2019). Exploring the new horizons of drug repurposing: a vital tool for turning hard work into smart work. European Journal of Medicinal Chemistry, 182, 111602. https://doi.org/10.1016/j.ejmech.2019.111602

Kung, V., Ferraz, C., Kennis, M., Franco-Paredes, C., Barahona, L., Shapiro, L., … & Henao-Martínez, A. (2023). Diabetes mellitus type 2 as a risk factor and outcome modifier for cryptococcosis in hiv negative, non-transplant patients, a propensity score match analysis.. https://doi.org/10.21203/rs.3.rs-2909132/v1

Lai, Y., Babunovic, G., Cui, L., Dedon, P., Doench, J., Fortune, S., … & Lu, T. (2020). Illuminating host-mycobacterial interactions with genome-wide crispr knockout and crispri screens. Cell Systems, 11(3), 239-251.e7. https://doi.org/10.1016/j.cels.2020.08.010

Lee, M., Chiang, C., Lee, C., Ho, C., Chang, C., Wang, J., … & Shih, J. (2018). Metformin use is associated with a low risk of tuberculosis among newly diagnosed diabetes mellitus patients with normal renal function: a nationwide cohort study with validated diagnostic criteria. Plos One, 13(10), e0205807. https://doi.org/10.1371/journal.pone.0205807

Lee, Y., Han, S., Park, J., Lee, J., Kim, D., Chung, H., … & Heo, E. (2018). The effect of metformin on culture conversion in tuberculosis patients with diabetes mellitus. The Korean Journal of Internal Medicine, 33(5), 933-940. https://doi.org/10.3904/kjim.2017.249

Leiva-Juárez, M., Kirkpatrick, C., Gilbert, B., Scott, B., Tuvim, M., Dickey, B., … & Markesich, D. (2018). Combined aerosolized toll-like receptor ligands are an effective therapeutic agent against influenza pneumonia when co-administered with oseltamivir. European Journal of Pharmacology, 818, 191-197. https://doi.org/10.1016/j.ejphar.2017.10.035

Li, T., Qian, Y., Miao, Z., Zheng, P., Shi, T., Jiang, X., … & Zheng, Y. (2020). Xuebijing injection alleviates pam3csk4-induced inflammatory response and protects mice from sepsis caused by methicillin-resistant staphylococcus aureus. Frontiers in Pharmacology, 11. https://doi.org/10.3389/fphar.2020.00104

Liu, D., Plimack, E., Hoffman-Censits, J., Garraway, L., Bellmunt, J., Allen, E., … & Rosenberg, J. (2016). Clinical validation of chemotherapy response biomarkererccc2in muscle-invasive urothelial bladder carcinoma. Jama Oncology, 2(8), 1094. https://doi.org/10.1001/jamaoncol.2016.1056

Lotan, Y., Woldu, S., Şanlı, Ö., Black, P., & Milowsky, M. (2018). Modelling cost-effectiveness of a biomarker-based approach to neoadjuvant chemotherapy for muscle-invasive bladder cancer. Bju International, 122(3), 434-440. https://doi.org/10.1111/bju.14220

Luo, C., Li, Q., Li, X., Wu, G., Huang, X., Zhang, Y., … & Chen, J. (2021). Prognostic role of serum albumin level in patients with lymphoma undergoing autologous stem cell transplantation. Annals of Transplantation, 26. https://doi.org/10.12659/aot.933365

Mahon, R. and Hafner, R. (2017). Applying precision medicine and immunotherapy advances from oncology to host-directed therapies for infectious diseases. Frontiers in Immunology, 8. https://doi.org/10.3389/fimmu.2017.00688

Mathew, S., Smatti, M., Ansari, K., Nasrallah, G., Thani, A., & Yassine, H. (2019). Mixed viral-bacterial infections and their effects on gut microbiota and clinical illnesses in children. Scientific Reports, 9(1). https://doi.org/10.1038/s41598-018-37162-w

Matteucci, K., Correa, A., & Costa, D. (2022). Recent advances in host-directed therapies for tuberculosis and malaria. Frontiers in Cellular and Infection Microbiology, 12. https://doi.org/10.3389/fcimb.2022.905278

Menon, K., McNally, J., Zimmerman, J., Agus, M., O'Hearn, K., Watson, R., … & Choong, K. (2017). Primary outcome measures in pediatric septic shock trials: a systematic review*. Pediatric Critical Care Medicine, 18(3), e146-e154. https://doi.org/10.1097/pcc.0000000000001078

Mishra, R., Krishnamoorthy, P., & Kumar, H. (2021). Microrna-30e-5p regulates socs1 and socs3 during bacterial infection. Frontiers in Cellular and Infection Microbiology, 10. https://doi.org/10.3389/fcimb.2020.604016

Mo, S., Liu, X., Zhang, K., Wang, W., Cai, Y., Ouyang, Q., … & Chen, X. (2021). Flunarizine suppressesmycobacterium tuberculosisgrowth via calmodulin-dependent phagosome maturation. Journal of Leukocyte Biology, 111(5), 1021-1029. https://doi.org/10.1002/jlb.4a0221-119rr

Moreau, P. and Touzeau, C. (2013). Optimizing outcomes for patients with newly diagnosed multiple myeloma eligible for transplantation. Leukemia, 2(S1), S15-S20. https://doi.org/10.1038/leusup.2013.4

Mouncey, P., Osborn, T., Power, G., Harrison, D., Sadique, Z., Grieve, R., … & Act, A. (2015). Trial of early, goal-directed resuscitation for septic shock. New England Journal of Medicine, 372(14), 1301-1311. https://doi.org/10.1056/nejmoa1500896

Myszor, I., Parveen, Z., Ottosson, H., Bergman, P., Agerberth, B., Strömberg, R., … & Guðmundsson, G. (2019). Novel aroylated phenylenediamine compounds enhance antimicrobial defense and maintain airway epithelial barrier integrity. Scientific Reports, 9(1). https://doi.org/10.1038/s41598-019-43350-z

Müller, U., Winterhalder, R., Businger, A., Zimmermann, H., & Exadaktylos, A. (2012). Why do walk-in patients prefer a busy urban emergency department during office hours? a pilot survey of 200 consecutive patients from switzerland.. Swiss Medical Weekly. https://doi.org/10.4414/smw.2012.13565

Nademanee, A., Palmer, J., Popplewell, L., Tsai, N., Delioukina, M., Gaal, K., … & Forman, S. (2011). High-dose therapy and autologous hematopoietic cell transplantation in peripheral t cell lymphoma (ptcl): analysis of prognostic factors. Biology of Blood and Marrow Transplantation, 17(10), 1481-1489. https://doi.org/10.1016/j.bbmt.2011.02.008

Neal, L., Qiu, Y., Chung, J., Xing, E., Cho, W., Malachowski, A., … & Olszewski, M. (2017). T cell–restricted notch signaling contributes to pulmonary th1 and th2 immunity during cryptococcus neoformans infection. The Journal of Immunology, 199(2), 643-655. https://doi.org/10.4049/jimmunol.1601715

Ning, B., Shen, J., Liu, F., Zhang, H., & Xin, J. (2023). Baicalein suppresses nlrp3 and aim2 inflammasome-mediated pyroptosis in macrophages infected by mycobacterium tuberculosis via induced autophagy. Microbiology Spectrum, 11(3). https://doi.org/10.1128/spectrum.04711-22

Novais, F., Amorim, C., & Scott, P. (2021). Host-directed therapies for cutaneous leishmaniasis. Frontiers in Immunology, 12. https://doi.org/10.3389/fimmu.2021.660183

Palucci, I. and Delogu, G. (2018). Host directed therapies for tuberculosis: futures strategies for an ancient disease. Chemotherapy, 63(3), 172-180. https://doi.org/10.1159/000490478

Phelan, J., McQuaid, K., Kenny, C., Gogan, K., Cox, D., Basdeo, S., … & Keane, J. (2020). Desferrioxamine supports metabolic function in primary human macrophages infected with mycobacterium tuberculosis. Frontiers in Immunology, 11. https://doi.org/10.3389/fimmu.2020.00836

Pielage, J., Powell, K., Kalman, D., & Engel, J. (2008). Rnai screen reveals an abl kinase-dependent host cell pathway involved in pseudomonas aeruginosa internalization. Plos Pathogens, 4(3), e1000031. https://doi.org/10.1371/journal.ppat.1000031

Posfai, D., Sylvester, K., Reddy, A., Ganley, J., Wirth, J., Cullen, Q., … & Derbyshire, E. (2018). Plasmodium parasite exploits host aquaporin-3 during liver stage malaria infection. Plos Pathogens, 14(5), e1007057. https://doi.org/10.1371/journal.ppat.1007057

Rankine-Wilson, L., Shapira, T., & Emani, C. (2021). From infection niche to therapeutic target: the intracellular lifestyle of mycobacterium tuberculosis. Microbiology, 167(4). https://doi.org/10.1099/mic.0.001041

Rao, M., Ippolito, G., Mfinanga, S., Ntoumi, F., Yeboah-Manu, D., Vilaplana, C., … & Maeurer, M. (2019). Improving treatment outcomes for mdr-tb — novel host-directed therapies and personalised medicine of the future. International Journal of Infectious Diseases, 80, S62-S67. https://doi.org/10.1016/j.ijid.2019.01.039

Rao, M., Valentini, D., Zumla, A., & Maeurer, M. (2018). Evaluation of the efficacy of valproic acid and suberoylanilide hydroxamic acid (vorinostat) in enhancing the effects of first-line tuberculosis drugs against intracellular mycobacterium tuberculosis. International Journal of Infectious Diseases, 69, 78-84. https://doi.org/10.1016/j.ijid.2018.02.021

References:

Ren, W., Rajendran, R., Zhao, Y., Tan, B., Wu, G., Zhu, G., … & Yin, Y. (2018). Amino acids as mediators of metabolic cross talk between host and pathogen. Frontiers in Immunology, 9. https://doi.org/10.3389/fimmu.2018.00319

Rohilla, A. (2024). Structure-based virtual screening and in vitro validation of inhibitors of cyclic dinucleotide phosphodiesterases enpp1 and cdnp. Microbiology Spectrum, 12(1). https://doi.org/10.1128/spectrum.02012-23

Sato, Y., Okamoto, K., Kida, Y., Mitsui, Y., Kawano, Y., Sogabe, M., … & Takayama, T. (2023). Overview of chemotherapy for gastric cancer. Journal of Clinical Medicine, 12(4), 1336. https://doi.org/10.3390/jcm12041336

Shen, J. (2023). Salvianolic acid b exerts a protective effect against zbp1-mediated panoptosis in macrophages infected by mycobacterium tuberculosis through its inhibition of the tnf-α/tnfr1 signaling pathway.. https://doi.org/10.21203/rs.3.rs-3278996/v1

Sieler, M., Kasschau, K., Varga, Z., Kent, M., & Sharpton, T. (2023). Common laboratory diets differentially influence zebrafish gut microbiome's successional development and sensitivity to pathogen exposure.

Singh, P. and Subbian, S. (2018). Harnessing the mtor pathway for tuberculosis treatment. Frontiers in Microbiology, 9. https://doi.org/10.3389/fmicb.2018.00070

Siqueira, M., Oliveira, M., Lino, M., Souza, S., Silva, G., Tomaz, R., … & Oliveira, L. (2022). International severe acute respiratory and emerging infection consortium (isaric). a new collaborative global platform for global clinical trials targeting post-covid19 patients. Manual Therapy Posturology & Rehabilitation Journal, 20, 1-6. https://doi.org/10.17784/mtprehabjournal.2022.20.1254

Stanley, S., Barczak, A., Silvis, M., Luo, S., Sogi, K., Vokes, M., … & Hung, D. (2014). Identification of host-targeted small molecules that restrict intracellular mycobacterium tuberculosis growth. Plos Pathogens, 10(2), e1003946. https://doi.org/10.1371/journal.ppat.1003946

Sun, A. and Hall, D. (2018). Point-of-care smartphone-based electrochemical biosensing. Electroanalysis, 31(1), 2-16. https://doi.org/10.1002/elan.201800474

Taboada, E., Graham, M., Carriço, J., & Domselaar, G. (2017). Food safety in the age of next generation sequencing, bioinformatics, and open data access. Frontiers in Microbiology, 8. https://doi.org/10.3389/fmicb.2017.00909

Tang, J. (2024). Label-free surface-enhanced raman spectroscopy coupled with machine learning algorithms in pathogenic microbial identification: current trends, challenges, and perspectives. Interdisciplinary Medicine, 2(3). https://doi.org/10.1002/inmd.20230060

Tarigan, S. (2019). Generation of scfv-monoclonal antibody avian influenza diagnostic tests. Jurnal Ilmu Ternak Dan Veteriner, 24(1). https://doi.org/10.14334/jitv.v24i1.1871

Tasneen, R., Mortensen, D., Converse, P., Urbanowski, M., Upton, A., Fotouhi, N., … & Hawryluk, N. (2021). Dual mtorc1/mtorc2 inhibition as a host-directed therapeutic target in pathologically distinct mouse models of tuberculosis. Antimicrobial Agents and Chemotherapy, 65(7). https://doi.org/10.1128/aac.00253-21

Treiber, H., Nilius-Eliliwi, V., Seifert, N., Vangala, D., Wang, M., Seidel, S., … & Chapuy, B. (2023). Treatment strategies and prognostic factors in secondary central nervous system lymphoma: a multicenter study of 124 patients. Hemasphere, 7(8), e926. https://doi.org/10.1097/hs9.0000000000000926

Tsenova, L. and Singhal, A. (2020). Effects of host-directed therapies on the pathology of tuberculosis. The Journal of Pathology, 250(5), 636-646. https://doi.org/10.1002/path.5407

Vasundhara, A., Sahoo, M., & Chowdary, S. (2017). Assessment of clinical parameters and immediate outcome of children with shock in a tertiary care hospital asram, eluru, andhra pradesh, india. International Journal of Contemporary Pediatrics, 4(2), 586. https://doi.org/10.18203/2349-3291.ijcp20170714

Vitiello, M., Galdiero, M., Finamore, E., Galdiero, S., & Galdiero, M. (2012). Nf-κb as a potential therapeutic target in microbial diseases. Molecular Biosystems, 8(4), 1108. https://doi.org/10.1039/c2mb05335g

Wallis, R., O'Garra, A., Sher, A., & Wack, A. (2022). Host-directed immunotherapy of viral and bacterial infections: past, present and future. Nature Reviews Immunology, 23(2), 121-133. https://doi.org/10.1038/s41577-022-00734-z

Wu, X., Jin, S., Ding, C., Wang, Y., He, D., & Liu, Y. (2022). Mesenchymal stem cell-derived exosome therapy of microbial diseases: from bench to bed. Frontiers in Microbiology, 12. https://doi.org/10.3389/fmicb.2021.804813

Xiang, T. (2024). Irisflorentin promotes bacterial phagocytosis and inhibits inflammatory responses in macrophages during bacterial infection. Heliyon, 10(1), e23225. https://doi.org/10.1016/j.heliyon.2023.e23225

Yokoyama, T., Kadowaki, M., Yoshida, M., Suzuki, K., Komori, M., & Iwanaga, T. (2018). Disseminated cryptococcosis with marked eosinophilia in a postpartum woman. Internal Medicine, 57(1), 135-139. https://doi.org/10.2169/internalmedicine.9247-17

Yu, X., Xu, Q., Chen, W., Z, M., Mo, L., Su, X., … & Xue, Y. (2022). Rhein inhibits chlamydia trachomatis infection by regulating pathogen-host cell. Frontiers in Public Health, 10. https://doi.org/10.3389/fpubh.2022.1002029

Zee, E., Termorshuizen, F., Benoît, D., Keizer, N., Bakker, J., Kompanje, E., … & Epker, J. (2021). One-year mortality of cancer patients with an unplanned icu admission: a cohort analysis between 2008 and 2017 in the netherlands. Journal of Intensive Care Medicine, 37(9), 1165-1173. https://doi.org/10.1177/08850666211054369

Zhang, S., Liu, Y., Zhou, X., Ou, M., Xiao, G., Li, F., … & Zhang, G. (2021). Sirtuin 7 regulates nitric oxide production and apoptosis to promote mycobacterial clearance in macrophages. Frontiers in Immunology, 12. https://doi.org/10.3389/fimmu.2021.779235

Zhang, W. (2021). Deterministic and stochastic in-host tuberculosis models for bacterium-directed and host-directed therapy combination. https://doi.org/10.48550/arxiv.2112.07717

Zilbermintz, L., Leonardi, W., Tran, S., Zozaya, J., Mathew-Joseph, A., Liem, S., … & Martchenko, M. (2016). Cross-inhibition of pathogenic agents and the host proteins they exploit. Scientific Reports, 6(1). https://doi.org/10.1038/srep34846

Zumla, A., Rao, M., Dodoo, E., & Maeurer, M. (2016). Potential of immunomodulatory agents as adjunct host-directed therapies for multidrug-resistant tuberculosis. BMC Medicine, 14(1). https://doi.org/10.1186/s12916-016-0635-1