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Host-directed therapy for the treatment of tuberculosis: rewiring the host to recover control

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CHAPTER 7

Summarizing Discussion

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Introduction

Tuberculosis (TB) remains a persistent global health challenge, responsible for significant morbidity and mortality despite advances in diagnosis and treatment [519]. *Mycobacterium tuberculosis* (*Mtb*), the causative agent, has developed sophisticated mechanisms to evade immune detection and persist within host cells, leading to a complex interplay with the immune system [520]. While the host immune response is essential for pathogen clearance, excessive inflammation can contribute to disease pathology, exacerbating tissue damage and impairing lung function [520].

The current standard of care for TB involves prolonged combinations of antibiotics, typically lasting six to nine months, and is effective in eradicating drug-susceptible *Mtb* infections. However, these regimens are associated with significant side effects, low adherence rates, and the increasing emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) *Mtb* strains [519]. Additionally, treating latent TB, an asymptomatic condition affecting approximately 25% of the global population [29], remains challenging due to the lack of reliable diagnostics and the potential for reactivation, particularly in immunocompromised individuals [28]. The only licensed vaccine, i.e. the attenuated strain of *Mycobacterium bovis*, Bacille Calmette-Guérin (BCG), provides inconsistent protection and fails to prevent pulmonary TB in adults [36]. Thus, *Mtb* has proven resilient despite efforts to control and eradicate it, which is additionally complicated by the increased emergence of TB comorbidities, such as HIV and diabetes mellitus, that are risk factors for more severe disease as well as latent TB reactivation [519].

Given the urgent need for innovative TB treatment strategies that circumvent these limitations, host-directed therapy (HDT) has emerged as a promising alternative. Unlike conventional antitubercular drugs that directly target *Mtb*, HDT typically involves small molecules and biological agents that modulate the host immune response to enhance pathogen clearance while minimizing collateral tissue damage. This approach, which can be combined with existing antibiotic treatment, holds the potential for shorter treatment durations, improved adherence, and a reduced likelihood of resistance development. HDT interventions can target multiple aspects of host immunity [235], including:

- Inflammation modulation: Reducing excessive inflammatory responses that contribute to lung pathology while maintaining sufficient immune activation for bacterial clearance.
- T-cell activation: Enhancing the function and inhibiting exhaustion of CD4+ and CD8+ T cells, particularly through responses that produce IFN-γ, IL-17 and TNF-α, key cytokines for *Mtb* control.

- Mycobacterial killing: Stimulating macrophage functions such as autophagy, phagolysosomal maturation, and reactive oxygen/nitrogen species (ROS/RNS) production to enhance intracellular pathogen clearance.

The aim of this thesis was to identify and validate novel HDT candidates and to investigate their mechanisms of action against *Mtb*. To achieve this, a multidisciplinary approach was employed, integrating chemical-genetic screening, computational modelling, and *in vitro* and *in vivo* validation. The findings presented not only reveal novel HDT leads but also provide mechanistic insights into host-pathogen interactions, offering new therapeutic targets for adjunctive TB treatment. In the following discussion, the findings described in this thesis and potential implications for the advancement of TB treatment will be discussed.

An Intracellular Screening Platform For HDT Discovery

The identification of HDT candidates requires screening platforms that capture the complexity of host-pathogen interactions while enabling high-throughput applications. Traditional assays such as colony-forming unit (CFU) enumeration, bioluminescence-based bacterial quantification, and automated microscopy have contributed significantly to intracellular infection research but pose limitations for large-scale screening efforts [521]. CFU assays, the gold standard in TB research, require prolonged incubation periods due to the slow proliferation of *Mtb*, delaying readouts for weeks. Bioluminescence-based approaches provide more rapid bacterial quantification but only offer single-parameter readouts without the resolution to assess bacterial load at the single-cell level. Automated microscopy-based screens enable high-content phenotypic analysis but generate large datasets requiring intensive computational resources and custom analysis pipelines, limiting accessibility.

To address these challenges, a novel flow cytometry-based screening assay was developed that enables the rapid and precise quantification of bacterial loads, infection rates, as well as host cell toxicity (Chapter 2). This platform employs engineered fluorescent *Mtb*, but also other pathogens such as *Salmonella enterica* serovar Typhimurium (*Stm*) strains, which allows for high-resolution assessment of intracellular bacterial burden within 24–72 hours, a significant improvement over traditional CFU-based methods. The assay was applied to medium-scale chemical (up to 1,200 compounds) and siRNA (1,000 siRNA pools) screens, demonstrating its utility in identifying novel HDT candidates.

The MelJuSo cell line was selected as the host system due to its intrinsic phagocytic capacity [522], reproducibility, and high transfectability. Unlike primary macrophages,

which pose donor variability and scalability challenges, or THP-1 cells, which require differentiation steps that alter intracellular signalling [523], MelJuSo cells provide a stable and consistent infection model. Gating strategies allowed the differentiation between infected and uninfected cells, ensuring precise quantification of bacterial burden.

The translational value of this platform was validated through studies showing comparable HDT effects in primary macrophages, regardless of pro-inflammatory or anti-inflammatory polarization status. Additionally, the high transfectability of MelJuSo cells facilitated efficient small interfering RNA (siRNA)-mediated gene silencing, supporting investigations into host factors essential for intracellular bacterial survival. However, a limiting factor of this tool is that it primarily identifies HDT leads that promote bacterial killing, thereby overlooking compounds that exert their effects through immune modulation or other indirect mechanisms.

Despite this limitation, the successful application of this system in large-scale compound and siRNA screens in this thesis underscores its value in HDT discovery. This assay contributed to the identification of Receptor Tyrosine Kinase (RTK) inhibitors (Chapter 2), the optimized AKT1/PKB inhibitor 97i (Chapter 3), and several autophagy-modulating compounds with high host-mediated efficacy against intracellular *Mtb* (Chapters 4 and 5). Future integration with immune-modulating readouts, transcriptomic profiling, or CRISPR-based functional genomics could further refine the HDT screening strategy.

In Silico Models For HDT Discovery

The integration of machine learning (ML) into drug discovery has revolutionized therapeutic development that offers enhanced efficiency over traditional wet-lab methods [524]. In Chapter 2, we employed a Predictive Clustering Trees (PCT)-based model to predict and rank HDT candidates from the PubChem repository. This approach uses inferred target profiles rather than single-target specificity and it facilitated the identification of numerous new multi-target compounds with host-modulating potential. This *in silico* model greatly improved our identification success rates since they increased by a factor of 5 and 3.5 for *Mtb* and *Stm*, respectively compared to random screening (Chapter 2). Compared to conventional structure-activity relationship (SAR) methods, this biology driven prediction model is both scalable and adaptable, with applications extending beyond tuberculosis (TB) drug discovery.

A key advantage of using a target profile-based approach is its ability to identify multi-target drugs, which offer distinct benefits over single-target drugs [525]. Single-target

drugs, while highly specific, may lead to the development of resistance as pathogens evolve to bypass a single molecular target. In contrast, multi-target drugs simultaneously modulate multiple proteins and pathways and have already been demonstrated to be effective in other infectious diseases and cancer therapies [526]. Furthermore, many diseases, including TB, involve complex host-pathogen interactions that cannot be effectively addressed by single-target interventions alone. Given the complexity of TB pathogenesis and the intricate host-pathogen interactions involved, multi-target therapeutics seem a particularly attractive strategy for HDT. By using target profiles, the PCT-based model facilitates the discovery of compounds that influence multiple host pathways, potentially leading to more robust and durable therapeutic effects [526].

However, the PCT-based model presents certain limitations. Its dependence on predefined functional annotations and curated datasets can introduce biases and limit the discovery of novel mechanisms of action. For instance, the majority of compounds identified in this study were inhibitors of tyrosine kinases (TKs) (Chapter 2), suggesting that the model was skewed towards predicting this class of inhibitors. While this strongly implicates TKs as critical regulators of TB pathogenesis, it also indicates a bias in the model's output, potentially overlooking other relevant druggable targets. The predictive power of the model is also dependent upon the quality and completeness of available datasets, potentially leading to false positives and false negatives. Additionally, the inherent trade-off between sensitivity and specificity requires a lot of attentions as an overly permissive model may predict inactive compounds, while an overly restrictive model could exclude promising candidates [527].

Over the past decade, significant advancements in ML have transformed computational drug discovery. New deep learning techniques have demonstrated superior performance in predicting drug-target interactions and molecular properties through their ability to capture intricate chemical and biological relationships [524, 528]. Compared to the PCT-based model utilized in this study, these modern ML techniques offer greater flexibility, improved accuracy, and an enhanced capacity to uncover novel drug candidates as demonstrated for the ML driven discovery of Halicin [41]. However, they also present challenges related to interpretability, computational cost, and the requirement for extensive training data [529].

Looking ahead, future iterations of our *in silico* model could benefit from hybrid ML models that integrate rule-based decision trees with deep learning architectures [530]. Such models could combine the interpretability of traditional methods with the predictive power of advanced algorithms. Additionally, incorporating multi-omics datasets, including transcriptomics and proteomics, could further refine predictions

by including a broad spectrum of host-pathogen interactions. By continually evolving computational approaches, the field of ML-driven drug discovery will continue to accelerate the identification of promising HDT candidates, ultimately enhancing therapeutic strategies against TB and other infectious diseases.

The Primary Human Macrophage Model – Advantages and Limitations

Macrophages (Mϕs) are central to the immune response against *Mtb*, shaping both pathogen control and disease progression. Within TB granulomas, a dynamic and specialized microenvironment, multiple immune cell types, including dendritic cells and T cells, coordinate the host response to infection. Among these, alveolar macrophages (AMϕs) and interstitial macrophages (IMϕs) assume diverse functional states that influence bacterial containment and disease progression (Chapter 1). Their phenotypic plasticity is driven by local cytokine signals, metabolic cues, and cellular interactions, ultimately determining whether the granuloma acts as a site of bacterial restriction or a reservoir for persistent infection [100, 101].

In this thesis, novel HDTs and host-pathogen interactions were investigated using primary human Mϕs polarized into distinct functional states: Mϕ1 (GM-CSF-derived macrophages and Mϕ2 (M-CSF-derived macrophages). Cytokine concentrations were selected to be within the physiological range in plasma so that the findings reflect biologically meaningful responses rather than artifacts of excessive stimulation [245]. The Mϕ1–Mϕ2 paradigm, originally proposed in 2000 [531], mirrors T helper (Th) cell nomenclature, that is T helper 1 (Th1) and T helper 2 (Th2), yet increasing evidence suggests that AMϕs and IMϕs do not fit entirely and precisely into these classifications [96, 532, 533]. Nevertheless, IMϕs exhibit glycolytic metabolism, aligning with Mϕ1-like characteristics, whereas AMϕs rely on fatty acid oxidation, resembling an Mϕ2-like state [96, 534]. Additionally, AMϕs exhibit a dampened inflammatory response, which is linked to their Nrf2-associated antioxidant pathway [532, 535].

Mouse studies further indicate that AMϕs and IMϕs display distinct cytokine responsiveness. AMϕs require GM-CSF for their development [536, 537], whereas IMϕs express higher levels of M-CSF receptors and are more sensitive to M-CSF [538]. In steady-state conditions, M-CSF is continuously present, supporting Mϕ survival, while GM-CSF levels increase upon inflammation, promoting a strong pro-inflammatory response [539]. Notably, while *in vitro* cytokine stimulation of monocytes produces distinct polarization states, the *in vivo* differentiation of resident tissue macrophages (RTMϕs), including AMϕs and IMϕs, remains less well understood [245, 540]. Interestingly, while the consensus is that AMϕ are *Mtb* permissive [96], recent

evidence shows that AMϕ are capable of restricting *Mtb* after the development of adaptive immune responses, further illustrating that context has a major yet poorly understood impact on the cellular response [541-543].

Mouse bone marrow-derived Mϕs (BMDMϕs) are commonly used in Mϕ activation and metabolism studies, but their relevance to human Mϕs is not fully understood. Species-specific metabolic differences have been observed, particularly in response to IL-4 and lipopolysaccharide (LPS) stimulation [544, 545]. Unlike murine Mϕ2s, human Mϕ2s do not exhibit a significant increase in oxidative metabolism or switch from oxidative phosphorylation (OxPhos) to fatty acid oxidation (FAO). Additionally, human Mϕ2s do not undergo a shift to glycolysis in response to LPS, whereas mouse BMDMϕs do [545]. Human Mϕ1s display higher metabolic flux than Mϕ2s, but both subsets increased their glycolysis driven ATP production upon activation with *Mtb* lysate to a larger extent [546]. This did, however, not indicate a metabolic shift from glycolysis to OxPhos in Mϕ2s, reinforcing that murine Mϕ metabolism cannot always be extrapolated to humans. These findings highlight the importance of using human Mϕ for HDT research.

To further validate the relevance of the *in vitro* human Mϕ model, *ex vivo* non-human primate (NHP) AMϕs were employed as an additional relevant model system (Chapter 3, Chapter 4). Given that NHPs are evolutionarily closer to humans than rodents, their use provides an intermediate validation step before clinical translation. NHP-derived AMϕs were isolated via bronchoalveolar lavage (BAL) from *Macaca mulatta* (rhesus macaques) and enriched for AMϕs. Notably, HDT candidates that showed efficacy in human Mϕs also demonstrated HDT activity in NHP AMϕs, reinforcing the relevance of the *in vitro* human Mϕ model. These findings bridge the gap between *in vitro* human models and *in vivo* applications, ensuring that promising HDT candidates advance with a higher likelihood of translational success.

A key strength of the *in vitro* human Mϕ model is its ability to dissect the functional roles of Mϕ polarization in TB. By testing HDT candidates in Mϕs with distinct inflammatory states, this thesis enhances the translatability of identified compounds. However, the Mϕ1–Mϕ2 framework oversimplifies Mϕ heterogeneity, as Mϕ phenotypes exist along a continuum rather than discrete categories, as mentioned above [547, 548]. Moreover, granuloma-associated factors, including hypoxia, lipid metabolism, and immune interactions, may influence Mϕ responses in ways not fully captured by *in vitro* models. Future research integrating single-cell RNA sequencing, advanced imaging, and 3D granuloma models will be essential for increasing our understanding of Mϕ diversity in TB as well as the relevance of polarization models within the broader context of TB immunopathology.

Key Findings described in this thesis

Tyrosine Kinases as Regulators of Mtb intracellular survival and HDT Targets

The ability of *Mtb* to persist within host cells relies on its capacity to manipulate key cellular signalling pathways, evade immune recognition, and manipulate host defences (Chapter 1). While early studies demonstrated that the ESX-1 secretion system disrupts phagosomal integrity [120], more recent findings have revealed that *Mtb* utilizes a diverse arsenal of both ESX-1 dependent and ESX-1 independent bacterial effectors to reprogram host cell responses [549]. Among the host factors affected by these bacterial effectors, we have identified RTKs as key regulators of intracellular bacterial survival, presenting an interesting target for HDT (Chapter 2).

Tyrosine Kinases (TKs) play a fundamental role in signal transduction by mediating cellular processes such as proliferation, differentiation, and survival in response to extracellular stimuli, including growth factors, cytokines, and hormones. RTKs play a critical role in fine-tuning Mϕ immune functions, inflammation resolution, and tissue homeostasis. Mϕs express RTKs from at least three primary families, Platelet-Derived Growth Factor Receptors (PDGFR), TAM (Tyro3, Axl, Mer), and the RON/MET superfamily [550]. Each of these receptor groups governs distinct Mϕ functions, including development, apoptotic cell clearance, and immune suppression [550]. CSF1R, a member of the PDGFR family, is essential for Mϕ differentiation and survival, and its activation by M-CSF *in vitro* promotes an Mϕ2 phenotype that is associated with reduced antimicrobial activity [551]. Notably, CSF1R positive Mϕs have been found to be abundant in TB granulomas, suggesting a role in bacterial persistence [552]. Conversely, GM-CSF signalling, which lacks intrinsic TK activity but is associated with the non-receptor tyrosine kinase Jak2, drives a more bactericidal Mϕ phenotype, and Mϕs with higher GM-CSF levels exhibit enhanced intracellular *Mtb* control [553]. While the TAM (Tyro3, Axl, Mer) and MET family RTKs are known to suppress inflammation and promote apoptotic cell clearance, their precise role in *Mtb* infection remains unclear [554, 555].

Using the intracellular screening platform described earlier, a library of pharmaceutically active drugs was screened and four compounds that significantly reduced intracellular *Mtb* burden through RTK inhibition RTKs were identified (Chapter 2). Leveraging machine learning-based predictive modelling, additional HDT candidates were identified, and three more RTK inhibitors were validated to enhance bacterial control without compromising host cell viability (Chapter 2). Moreover, an unbiased siRNA screen targeting the human kinome, independently confirmed the role

of RTK signalling in *Mtb* survival, reinforcing the therapeutic potential of RTK inhibition in TB (Chapter 2).

Several RTK inhibitors have been identified as potential HDT agents. Previous studies demonstrated that Abl1, Abl2, and other imatinib-sensitive kinases facilitate *Mtb* entry and intracellular persistence, reversed by Imatinib treatment [160, 309, 556]. RTK inhibition through Gefitinib, an approved EGFR inhibitor, enhances Mϕ bacterial clearance by inducing autophagy and increasing pro-inflammatory responses, with efficacy confirmed in both *in vitro* and murine TB models [162, 557]. Similarly, inhibition of CSF1R signalling shifts Mϕs toward a pro-inflammatory state, which may enhance intracellular *Mtb* killing [552]. Targeting the VEGF Receptor with Pazopanib has been shown to reduce *Mtb* burden by limiting granuloma vascularization and potentially modulating Mϕ metabolism [191]. In addition, Nilotinib, a PDGFR and KIT inhibitor, improves bacterial clearance in *Mtb*-infected Mϕs and mouse models [558].

In this thesis, we have extended the repertoire of RTK inhibitors as HDT for TB with the identification of Tyrphostin AG 494, SU6656, SB216763, GW5074, AT9283, ENMD-2076 and Dovitinib, with the latter three having been more extensive validated (Chapter 2). While RTK inhibition certainly represents a promising HDT strategy, challenges remain. RTKs are critical for normal cellular function, are widely distributed, and systemic inhibition is known to cause on-target toxicity [559]. Furthermore, kinase redundancy allows alternative signalling pathways to compensate for RTK blockade, which could reduce therapeutic efficacy, as has been observed in cancer treatment [560]. Future studies should also explore the interaction between RTK inhibitors and first-line TB antibiotics, particularly in the context of granuloma-associated drug penetration and immune modulation.

Lysosomal Targeting and Degradation

AMϕs are the first line of cellular defence in the lungs, ingesting inhaled *Mtb* via phagocytosis. As explained in Chapter 1, this process is initiated by a broad array of pattern recognition receptors (PRRs) on the Mϕ surface that bind *Mtb*'s pathogen-associated molecular patterns (PAMPs) [107, 108] (Chapter 1). These receptor-ligand interactions activate signalling cascades, mediated among others by TKs discussed earlier. As a result, the actin cytoskeleton is remodelled and membrane extensions (pseudopods) around the bacterium formed, engulfing it into an intracellular vacuole called the phagosome [110]. In an effective immune response, this phagosome matures by sequentially acquiring early endosomal markers (Rab5, EEA1), late endosomal markers (Rab7), and ultimately fuses with lysosomes to form a phagolysosome [112, 115]. The interior pH of the phagosome drops from neutral to acidic (circa 5.0) via the vacuolar-type ATPases (V-ATPase) proton pump, creating an

environment that activates lysosomal hydrolytic enzymes and promotes the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) [114]. However, *Mtb* has evolved ways to subvert this process [442].

Given *Mtb*'s manipulation of the phagosomal maturation process, it naturally represents an interesting target for HDT. One approach is to override the phagosome maturation block imposed by *Mtb*. HDT that promote phagolysosomal fusion or acidification can tip the balance in favour of the host. For example, activating Transcription factor EB (TFEB), the master regulator of lysosomal biogenesis, has emerged as a promising strategy [561]. TFEB activation increases the formation of lysosomes and expression of hydrolases, essentially "arming" Mϕs with more bactericidal organelles [561]. Notably, a subset of *Mtb* permissive monocytes was shown to display poor lysosomal function and lower amounts of nuclear TFEB than *Mtb*-restrictive cells, further supporting the importance of this response [543]. The TK inhibitors Imatinib and Nilotinib, described before, were shown to enhance the lysosomal response via TFEB nuclear translocation, effectively reducing *Mtb* burden [543].

This thesis identified several HDT candidates that modulate lysosomal function. Specifically, the kinase inhibitor 97i (Chapter 3), the diphenylbutylpiperidine-class antipsychotic drugs Fluspirilene and in particular Pimozide (Chapter 4), as well as Tamoxifen (Chapter 5), a selective estrogen receptor modulator, were all found to enhance the lysosomal response via TFEB nuclear translocation. As a result, these HDT candidates increased the localization of *Mtb* within lysosomes. However, the mechanistic studies in this thesis were predominantly conducted in Mϕ2, which rapidly acidify lysosomes for efficient hydrolysis and recycling, aligning with their homeostatic function [562]. In contrast, Mϕ1 exhibit delayed phagosome maturation but sustain ROS production, prioritizing bactericidal activity and antigen presentation [562, 563]. A limitation of the work in this thesis is that the mechanistic work was primarily performed in Mϕ2 for practical reasons. This experimental bias toward Mϕ2 may have led to an overestimation of lysosomal activity's role in *Mtb* clearance, while underappreciating the contribution of ROS-mediated killing. Future studies should investigate these HDT candidates in not only a broader subset of Mϕ populations, but also other immune cells such as neutrophils to increase our understanding of their mechanism of action.

Regulation of TFEB nuclear translocation is subject to multiple signalling pathways, and a more detailed understanding of these interactions could improve HDT strategies. PKCα and PKCδ inhibit TFEB phosphorylation by GSK3, thereby promoting TFEB activation and nuclear translocation [564]. Conversely, the kinase Akt phosphorylates

TFEB at S467, preventing nuclear translocation and thereby impairing lysosomal activation [565]. Additionally, the nuclear receptor peroxisome proliferator-activated receptor (PPAR), nuclear receptor subfamily 1, group D, member 1 (NR1D1), IFN-γ, Immunity related GTPase M (IRGM), tripartite motif family proteins (TRIMs), and Nuclear receptor corepressor (NCoR1) also mediate the nuclear translocation of TFEB [561].

TFEB nuclear translocation induced by H-89 and 97i can be readily explained since both inhibit Akt1 (Chapter 3), a negative regulator of TFEB [565]. Although not studied in this thesis, TFEB activation by Pimozide might be explained by Akt inhibition as well since Pimozide mediated reduction of phosphorylated Akt has been observed in multiple studies [326, 566]. This agrees with the observation that the impact of Fluspirilene on TFEB activation as well as on lysosomal activity is less clear (Chapter 4), since Fluspirilene lacks the capacity to inhibit Akt [567]. The nuclear translocation of TFEB induced by Tamoxifen (Chapter 5), might be explained by recent findings that Tamoxifen facilitates the release of calcium from lysosomes, which then activates phosphatases like calcineurin that dephosphorylate TFEB, leading to its nuclear translocation [568]. It would be interesting to validate these observations from breast cancer cell lines in primary Mϕs in the context of *Mtb* infection, since its relevance in this context remains unexplored. Additionally, Calcium/Calmodulin dependent protein kinase type 2 (CaMKII) that is also activated by the release of calcium [569], might play a role as well since its importance in intracellular *Mtb* survival has been demonstrated both via cell intrinsic regulation as well as via the HDT candidate Flunarizine [570, 571]. Given the vital role of calcium signalling in immune regulation and inflammatory responses, it would be important to investigate whether Tamoxifen's effect on TFEB activation extends beyond lysosomal biogenesis to other Mϕ functions.

While inducing lysosomal biogenesis is one strategy, enhancing phagosomal delivery to the lysosome represents another. This thesis corroborates previous findings that Pimozide inhibits STAT5 activation (Chapter 4) [572] and further demonstrates that Fluspirilene exerts a similar effect, an observation consistent with their structural similarity. STAT5 is a transcription factor activated by cytokines such as GM-CSF, which *Mtb* can exploit to establish a permissive intracellular niche. Inhibition of STAT5 by both Pimozide and Fluspirilene was associated with reduced accumulation of the suppressor protein CISH on *Mtb*-containing phagosomes (Chapter 4). Since CISH contributes to the inhibition of phagosome maturation [573], its reduction effectively relieves this blockade, thereby promoting phagosomal acidification and fusion with lysosomes. In conclusion, targeting the lysosomal degradation pathway through HDT represents a promising approach to combating *Mtb* infection and this thesis demonstrated that it can be achieved through various mechanisms of action.

Autophagy in Bacterial Clearance

Autophagy is an intracellular degradation pathway that plays a critical role in maintaining cellular homeostasis and controlling intracellular infections. In the context of *Mtb*, Mϕs utilize autophagy to degrade intracellular bacteria serving as an essential component of host defence, also known as xenophagy [123]. The process involves the sequestration of cytosolic components, including pathogen-containing vacuoles or cytosol-invading pathogens, within double-membraned autophagosomes that ultimately fuse with lysosomes, leading to bacterial destruction (Chapter 1).

Autophagy is tightly controlled by metabolic and immune signalling pathways. The mechanistic target of rapamycin (mTOR) is a central inhibitor of autophagy under nutrient-rich conditions, whereas AMP-activated protein kinase (AMPK) activation suppresses mTOR and stimulates the Unc-51-like autophagy-activating kinase 1 (ULK1) complex to initiate autophagy [574]. Pharmacological agents, such as rapamycin (an mTOR inhibitor) and metformin (an AMPK activator), have been shown to enhance autophagic flux and restrict *Mtb* survival in infected Mϕs [131, 575]. Despite the protective role of autophagy, *Mtb* has evolved mechanisms to evade autophagy-mediated killing. Virulent *Mtb* strains actively inhibit autophagy induction by secreting factors that elicit or perturb autophagy signalling. The ESX-1 secretion system, which includes ESAT-6, disrupts phagosomal membranes, inducing xenophagy as a second line of defence but part of the *Mtb* bacteria are able to escape from the resulting autophagic vesicles [576]. In addition, *Mtb* phosphatases, such as PtpA, and kinases interfere with host signalling pathways to block autophagosome formation [577].

LC3-associated phagocytosis (LAP) is a non-canonical autophagy pathway that facilitates host defence against intracellular pathogens [578]. Unlike classical autophagy, LAP involves the recruitment of LC3 to single-membrane phagosomes, a process activated by PRRs such as Toll-like receptors (TLRs), Fcγ receptors, and dectin-1 [577]. LAP requires Rubicon and NOX2-dependent ROS production to recruit autophagy-related genes (ATGs) to the phagosomal membrane for LC3 conjugation [579]. Despite its similarities to autophagy, LAP appears to be functionally distinct, primarily serving to enhance phagosome maturation, regulate inflammation, and promote antigen presentation [580].

Species-specific differences in LAP efficiency have been reported, with murine Mϕs exhibiting significantly higher proportions of LC3-positive phagosomes (~40–80%) compared to human cells (~5–10%) [580, 581]. This discrepancy may contribute to differences in host susceptibility and presents a challenge for translating murine findings to human infections. Recent studies indicate that in human Mϕs, LC3 recruitment to *Mtb*-containing vacuoles (MCVs) is frequent (~70% of MCVs) but largely

ineffective in bacterial clearance [582]. Notably, approximately 40% of LC3-positive MCVs later lose LC3 signal, suggesting that *Mtb* can actively evade LAP-mediated targeting [576]. Interestingly, LC3 recruitment appears to be influenced by bacterial burden rather than time-dependent mechanisms, implying that enhancing LAP efficiency could represent a therapeutic opportunity.

This thesis identified several HDT candidates that modulate autophagy; 97i (Chapter 3), Fluspirilene and Pimozide (Chapter 4) as well as Tamoxifen (Chapter 5). The autophagy inducing effect of these HDT leads might very well be explained by their translocation of TFEB, which regulates besides lysosomal biogenesis also autophagy [583]. This however does not explain the observations upon 97i treatment, since H-89 also induced TFEB nuclear translocation while protective autophagy, that is *Mtb* targeting autophagy, seemed comparable to the control (Chapter 3). It would be interesting to investigate whether the kinases targeted additionally by 97i might play a role in inducing protective autophagy. Indeed, 97i treatment reduced *in situ* CAMK1 activity (Chapter 3) which is known to induce autophagy in an AMPK and Akt independent manner [584, 585].

Pimozide and Fluspirilene have emerged as potent inducers of autophagy in multiple screening studies and experimental models [586]. This was first identified in an unbiased high-throughput screen for autophagy inducers, in which they induced autophagic flux without causing toxicity [317]. Their chemical structure, a biphenyl piperidine scaffold, appears particularly favourable for autophagy induction, as other drugs sharing this motif (for example trifluoperazine) also stimulate autophagy [587]. Subsequent studies confirmed that Pimozide and Fluspirilene stimulate autophagy in various cell types, including neuronal cells and cancer cell lines, and does so largely independent of the canonical mTOR pathway [339]. Pimozide and Fluspirilene were found to disrupt intracellular calcium homeostasis, leading to the inactivation of calpain proteases. Calpains normally impair autophagy by cleaving the essential autophagy protein ATG5. By lowering cytosolic calcium levels, Pimozide and Fluspirilene prevent this cleavage, preserving the ATG12–ATG5 complex and thereby enhancing autophagic flux [339, 588]. Additionally, Pimozide's autophagy activation has been associated with activation of the energy-sensor kinase AMPK and phosphorylation of ULK1, suggesting an mTOR-independent, AMPK-mediated mechanism [339, 589]. Lastly, as lysosomotropic drugs, Pimozide and Fluspirilene accumulate in lysosomes, potentially disrupting their function and triggering compensatory autophagy and lysosomal biogenesis via TFEB activation [590].

Beyond the well-established activation of TFEB and subsequent enhancement of lysosomal biogenesis (Chapter 5), Tamoxifen modulates several additional pathways

that converge on autophagy. These effects are primarily attributed to immunomodulatory mechanisms that are independent of estrogen receptor (ER) signalling (chapter 5). Notably, Tamoxifen activates AMPK and inhibits mTOR, thereby promoting autophagy in an mTOR-dependent manner [591]. This mechanism contrasts with that observed for diphenylbutylpiperidine-class HDTs (Chapter 4), where AMPK activation does not suppress mTOR. Concurrently, Tamoxifen is known to impact sphingolipid metabolism by inhibiting acid sphingomyelinase (ASM), which disrupts the conversion of sphingomyelin to ceramide in lysosomes [592, 593]. Ceramide, a bioactive lipid, contributes to autophagosome formation by activating the c-Jun N-terminal kinase (JNK) pathway, leading to Bcl-2 phosphorylation and the release of Beclin-1, a key initiator of autophagy [594, 595]. While ceramide also binds LC3 on autolysosomes to facilitate autophagic degradation, its accumulation can potentially destabilize lysosomal membranes and trigger cytotoxicity [596]. The balance between these effects may be context- and cell-type dependent. Thus, Tamoxifen simultaneously engages the TFEB pathway, AMPK/mTORC1 signalling, and ceramide-associated autophagy, creating a robust, multi-faceted regulation of the important host defence mechanism autophagy. Further delineation of these pathways and how they impact *Mtb*'s intracellular survival, will enhance our understanding and may help the development of structurally related analogues with improved specificity and reduced off-target effects.

Taken together, autophagy and its non-canonical variant LAP represent a critical arm of the host's defence against intracellular pathogens such as *Mtb* and this thesis identified several HDT that demonstrate promising capacity to restore or enhance autophagic responses. The mechanistic diversity of these HDTs reflects the complexity of autophagy regulation and underscores the importance of context-specific modulation. Compounds such as 97i, Pimozide, Fluspirilene, and Tamoxifen exert their effects through distinct as well as overlapping signalling pathways, providing complementary strategies to overcome *Mtb*'s intracellular persistence. Enhancing autophagy thus remains a viable approach for HDT against *Mtb*. Further mechanistic dissection of HDT candidates, including their impact on protective versus non-protective autophagy, is needed to be able to fully harness their therapeutic potential.

The Oxidative Response

ROS and RNS are critical components of the innate immune response, particularly within Mϕs, where they serve as antimicrobial agents. Upon phagocytosing pathogens, Mϕs initiate a respiratory burst, producing ROS such as superoxide anions, hydrogen peroxide and hydroxyl radicals using the NADPH oxidase complex (NOX) [597]. These reactive molecules damage microbial DNA, proteins, and lipids, ultimately leading to

pathogen death [597]. Additionally, inducible nitric oxide synthase (iNOS) and nitric oxide synthase 2 (NOS2) catalyze the production of high quantities of nitric oxide from L-arginine although this seems to more relevant in murine Mϕs than in human Mϕs [598, 599]. Collectively, these species impose oxidative stress that *Mtb* must counteract to survive inside the Mϕ. Importantly, even if ROS/RNS do not directly lyse *Mtb*, it contributes significantly to bacterial control by inducing a state of dormancy or increasing susceptibility to other immune mechanisms [600]. Furthermore, high phagosomal ROS has been linked to triggering apoptosis of infected Mϕs, which may serve as an additional defence mechanism by depriving *Mtb* of its intracellular niche and promoting clearance as well as antigen presentation through efferocytosis by surrounding phagocytes [601]. However, an overabundance of ROS can shift cell death toward necrosis or necroptosis, leading to tissue damage and facilitating bacterial dissemination [602]. This dual role underscores the importance of a finely tuned oxidative response in the host defence against *Mtb*.

To persist within the hostile environment of Mϕs, *Mtb* has evolved multiple mechanisms to detoxify ROS and RNS and to manipulate host immune responses. These include detoxifying enzymes, production of antioxidant molecules, RNS neutralizing enzymes, and a proteasome to remove oxidatively damaged proteins [601]. Additionally, *Mtb* manipulates the host cells by secreting factors that among others suppress expression of genes involved in the oxidative and nitrosative response but also prevent proper NOX2 assembly on the phagosome, thereby also interfering with LAP [601, 603]. Given the central role of ROS and RNS in mycobacterial killing, HDT strategies seek to either enhance ROS/RNS-mediated bacterial clearance or modulate oxidative stress to prevent excessive inflammation and tissue damage. Several approaches have been explored. Mϕ1 produce more ROS than Mϕ2 and therapies that promote Mϕ1 polarization, such as IL-1β therapy, have been shown to improve TB outcomes in animal models by upregulating iNOS and boosting ROS production, although enhanced IL-1 responses lead to severe inflammation and tissue damage [562, 604]. Other examples are Bazedoxifene and soluble CD157, an innate cell expressed protein, that reduced intracellular *Mtb* survival by stimulating ROS/RNS [168, 169]. Conversely, therapies that reduce excessive inflammation can indirectly improve bacterial killing by preventing tissue necrosis which *Mtb* exploits to spread. For example, antioxidants, such as N-acetyl-cysteine (NAC) [605] and Nicotinamide [170], can mitigate excessive ROS levels, preventing Mϕ necroptosis and tissue pathology while preserving antimicrobial function. Lastly, Aspirin and Ibuprofen are being investigated in a clinical trial as HDT adjuncts to standard TB therapy, aiming to limit neutrophil-driven pathology without compromising bacterial clearance [606].

Interestingly, this thesis describes HDT candidates that decrease the oxidative response (97i and H-89, Chapter 3) as well as increase ROS production (Pimozide, Chapter 4), while all reduced intracellular *Mtb* survival. H-89, a PKA and PKB (Akt) inhibitor, and its derivative 97i, both reduced ROS production in Mϕ1 as well as Mϕ2 (Chapter 3). Akt knockdown in RAW 264.7 Mϕs reduced cellular ROS levels, but interestingly also increased *Mtb* survival [607]. It is however unclear whether this reflects a difference in *Mtb* survival or in *Mtb* uptake and single-gene knockdown does not fully capture the kinase target profile of H-89 and 97i (Chapter 3). Of note, both H-89 and 97i skewed Mϕ1 and Mϕ2 metabolism more towards glycolysis. This observation is unexpected, as glycolysis is often linked to increased ROS production. One possible explanation is that the reduction in oxidative phosphorylation caused by H-89 and 97i treatment leads to decreased mitochondrial ROS production, which might outweigh the glycolysis-associated ROS increase [562]. However, further investigation is required to confirm this hypothesis. Pimozide, on the other hand, increased ROS production and this could be partially reversed by the addition of the antioxidant NAC (Chapter 4). Interestingly, the addition of NAC, but also of the NOS inhibitor L-NMMA, during Pimozide treatment of *Mtb* infected Mϕs partially abrogated the efficacy of Pimozide. This suggests iNOS/NOS2 mediated nitric oxide production despite evidence that this seems less relevant in human Mϕs [598]. It would be interesting to further investigate whether the oxidative stress induced by Pimozide, is at least partially responsible for the AMPK dependent activation of autophagy [608]. A limitation of the mechanistic investigational work is that it was performed in Mϕ2s only, which as described earlier, lack a strong oxidative response in the phagosome [562]. Future work should investigate whether Mϕ polarization plays a role in Pimozide induced ROS/RNS production.

Although targeting ROS/RNS pathways seems promising, it is not without its challenges. Direct augmentation of ROS/RNS in patients is challenging due to potential host toxicity. Also, many findings on ROS/RNS mechanisms have been derived from murine models, while the differential expression of NOS2 in murine versus human Mϕs raises concerns about the translational applicability of findings from murine models. Nevertheless, HDT approaches that selectively enhance Mϕ oxidative activity while preventing excessive tissue damage could provide a valuable adjunct to antibiotic therapy.

Targeting Epigenetics to Remodel The Macrophage

Among the many HDT targets, histone deacetylases (HDACs) have gained increasing attention due to their pivotal role in epigenetic regulation and immune modulation. HDACs are a class of enzymes that regulate gene expression by removing acetyl groups

from histone and non-histone proteins. This process leads to chromatin condensation and transcriptional repression, impacting key cellular pathways, and is balanced by histone acetylases (HATs) that counteract this process by adding acetyl groups [447]. HDACs are divided into four classes: Class I (HDAC1, 2, 3, and 8), class II (class IIa HDAC4, 5, 7, and 9; class IIb HDAC6 and 10), class III (SIRT1-7), and class IV (HDAC11) [448]. HDACs shape the cellular response [449, 450, 512, 609], and *Mtb* has been shown to alter HDAC expression to promote intracellular bacterial survival [454-456]. These recent findings, as well as the findings described in Chapter 6 in this thesis, suggest that HDACs and their regulation play an important role in the response to *Mtb* and HDAC inhibition (HDACi) can enhance anti-mycobacterial immunity. Thus, HDACs are a promising target for HDT against TB.

For instance, *Mtb* drives HDAC1-mediated suppression of IL-12 transcription which hampers polarization towards a pro-inflammatory phenotype, whereas *Mtb* also downregulates sirtuin deacetylase 1 (SIRT1) thereby impairing autophagy and enhancing NF-κB-driven inflammation [194, 455]. This dual effect creates an immunological paradox where the host experiences both inadequate antimicrobial responses and excessive inflammation, contributing to *Mtb* survival. The inhibition of specific HDACs can modulate immune responses in a beneficial manner. Blocking HDAC1 restores IL-12 production, thereby promoting a robust Th1 response [455]. Similarly, pharmacological activation of SIRT1 enhances autophagy and phagolysosomal fusion, critical processes for intracellular *Mtb* clearance [194]. Furthermore, HDAC6 and HDAC9 have been implicated in Mϕ differentiation and TLR responses, highlighting the broader role of HDACs in immune regulation [610]. The interplay between HDACs, cytokine signalling, and Mϕ polarization underscores the importance of precise therapeutic targeting to avoid unintended immunosuppressive effects.

Given HDAC regulatory roles in immune function as well as their regulation by *Mtb* infection, HDAC inhibitors have been investigated as potential adjunct therapies for TB. Several HDAC inhibitors have demonstrated efficacy in reducing *Mtb* burden in Mϕs, for example suberoylanilide hydroxamic acid (SAHA), a class I and II HDAC inhibitor also known as Vorinostat [611]. SAHA is thought to exert its effects by restoring pro-inflammatory cytokine responses, enhancing IL-1β production while suppressing IL-10, which shifts Mϕs towards a bactericidal state. HDACi using SAHA also promotes glycolysis, which is associated with enhanced antimicrobial activity in infected Mϕs [611]. Additionally, HDACi using Trichostatin A (TSA) facilitates the acetylation of key autophagy regulators, improving bacterial clearance mechanisms [483]. Beyond direct immunomodulation, certain HDAC inhibitors also exhibit intrinsic antimycobacterial properties. For instance, the selective HDAC3 inhibitor RGFP966 has been shown to

inhibit *Mtb* growth in Mϕs and in cell free bacterial cultures, suggesting that some HDACi compounds may have dual host-pathogen targeting effects [192].

In our human Mϕ model, HDAC3, HDAC5, HDAC7, HDAC10, and HDAC11 were found to be differently regulated during *Mtb* infection (Chapter 6). Since HDAC5 and HDAC7 are part of the class IIa HDACs (HDAC4, 5, 7, and 9), a more refined approach to HDAC inhibition as HDT was taken by evaluating class IIa inhibitors (TMP195 and TMP269) compared to TSA, a class I and II inhibitor [460] (Chapter 6). These selective inhibitors might reduce the risk that comes with broad immunosuppression associated with pan-HDAC inhibitors. Selective inhibition of class IIa HDACs indeed demonstrated promising effects in reducing *Mtb* burden in both *in vitro* as well as in an *in vivo* zebrafish embryo model, but so did TSA (Chapter 6). Importantly, TMP195 still lacked toxicity in the zebrafish embryo model at a concentration of 10 µM, while the concentration of TSA had to be reduced to 30 nM to prevent toxic effects. Interestingly, in response to *Mtb* infection of macrophages a decrease in the secretion of pro-inflammatory cytokines and chemokines was found (Chapter 6), which seems paradoxical to other findings that show Mϕ1 polarization upon TMP195 treatment [612]. It raises the question whether the improved bacterial control by these Mϕs results in a reduced cytokine response, similar to what has been found for LPS induced responses in the context of TMP195 treatment in an acute kidney injury model [613]. If so, these inhibitors could hold the potential to drive a more bactericidal Mϕ while preventing an excessive immune response. Further research is needed to determine whether class IIa HDAC inhibition does create a distinct Mϕ phenotype that balances bactericidal activity with controlled inflammation.

One of the primary advantages of using HDAC inhibitors as HDTs is their potential to enhance the efficacy of existing TB antibiotics. Preclinical studies have indicated that combining HDAC inhibitors with first-line TB drugs, such as rifampicin and isoniazid, results in improved bacterial clearance [196]. This synergy may result from HDACi-induced changes in Mϕ function, which enhance intracellular drug penetration and retention, making HDACi-based therapies particularly relevant for treating drug-resistant TB [614]. Additionally, HDAC inhibitors can alter Mϕ metabolism, increasing glycolytic flux and ROS production, which enhances bactericidal activity [610]. The synergistic potential of HDACi is strongly illustrated in the randomized clinical trial that evaluated Phenylbutyrate (PBA), a class I and class IIa HDAC inhibitor, with or without vitamin D3 alongside standard TB treatment, where PBA together with vitamin D significantly accelerated sputum culture conversion [214]. Lastly, HDACi has demonstrated the potential to not only synergize with existing TB antibiotics, but also with other HDT such as kinase inhibitors as demonstrated in Chapter 6 of this thesis.

While HDAC inhibitors hold promise for TB treatment, several challenges must be addressed before their clinical implementation. Broad-spectrum HDAC inhibitors may lead to unintended immunosuppressive effects, requiring selective inhibitors that target the mechanisms of choice while preserving beneficial immune functions. Additionally, many HDAC inhibitors repurposed from oncology may require dose optimization or alternative delivery systems, such as inhalable formulations, to ensure efficacy and safety in TB treatment [615, 616]. The success of HDAC inhibitors may also depend on the timing of administration relative to TB progression, as different stages of infection correspond with distinct immune landscapes. Given the growing understanding of HDACs in metabolic regulation, research should uncover how HDAC inhibitors impact Mϕ bioenergetics and long-term immune memory to determine how they will shape durable immunity against TB. Despite these challenges, findings in this thesis demonstrate that class-specific HDAC inhibition effectively reduces *Mtb* burden while maintaining low toxicity (Chapter 6). Future research should explore *in vivo* efficacy, combination therapies with existing HDT or antibiotics, and the potential role of HDACi in shaping durable immunity against TB.

Comparative Insights: *Mtb* Versus Other Intracellular Pathogens

Mtb shares elements of its intracellular lifestyle with other (facultative) intracellular bacteria, such as *Salmonella enterica*, *Listeria monocytogenes*, *Brucella spp*., and *Legionella pneumophila*, but also non-tuberculous mycobacteria (NTM), indicating there is potential in reevaluating current treatment paradigms. Given that *Mtb* is the most extensively studied model for HDTs, examining the extent to which these strategies can be repurposed across other pathogens is of considerable translational interest.

Salmonella, like Mtb, manipulates host phagosome maturation and evades xenophagy, making it a plausible candidate for HDT cross-application. Indeed, several HDT have been identified that besides their potential to treat TB, also reduce intracellular Stm survival (Chapter 2, 3, 4 and 5). Both pathogens establish modified vacuolar niches, Mtb via phagosome arrest and Salmonella via formation of a Salmonella-containing vacuole (SCV). Mtb's use of PI3P hydrolysis and Rab7 exclusion mechanistically resembles to Salmonella's deployment of SPI-2 effectors, for example SifA and SipC, that uncouple Rab7 from vesicle tethering complexes [617]. Importantly, Salmonella's reliance on host Akt1 signalling to block phagosome maturation can be exploited as shown by treatment with H-89 and 97i (Chapter 3). However, a notable difference is Salmonella's differential sensitivity to phagosomal pH. While Mtb arrests acidification, Salmonella requires moderate acidification [618], pH of circa 5.5, to induce its virulence gene expression. HDTs that enhance phagosome acidification may

therefore be expected to exhibit opposing effects, beneficial against Mtb but potentially enhancing Salmonella virulence. Supporting this, there was limited overlap between the HDT hits identified in Mtb and Salmonella screens, with RTK inhibitors demonstrating specificity for Mtb (Chapter 2). In contrast, Pimozide, Fluspirilene, and Tamoxifen showed strong HDT activity against Salmonella (Chapters 4 and 5), likely due to their broad and multifaceted target profiles.

Unlike Mtb, Listeria adopts an entirely cytosolic lifestyle, escaping from the phagosome shortly after uptake thus completely avoiding the phagolysosomal killing pathway [617]. This fundamental difference diminishes the applicability of HDTs that target phagosome maturation arrest, such as those modulating Rab GTPase activity or PI3P-dependent trafficking. However, both pathogens must contend with autophagic clearance. *Mtb* employs ESX-1 secretion effectors to inhibit autophagy initiation, whereas *Listeria* camouflages itself with ActA and InlK to evade ubiquitin tagging and adapter protein recruitment [619]. Thus, HDTs that broadly enhance autophagic flux, for example through mTOR inhibition or AMPK activation, may be efficacious.

Brucella, the causative agent of Brucellosis [620], shares *Mtb*'s slow replication and chronic intracellular persistence. Both evade phagolysosomal fusion, though Brucella diverts its vacuole to the endoplasmic reticulum (ER) using VirB type IV secretion system effectors and modifies the vacuole's identity [617]. While *Mtb* is vulnerable to autophagy, Brucella paradoxically benefits from certain autophagy proteins to support its niche and facilitate egress [621]. This duality signals caution, HDTs that stimulate autophagy might support or hinder infection depending on the pathway targeted. Brucella also suppresses host immune activation through secreted effectors that target host Myeloid differentiation primary response 88 (MyD88) signalling, blocking downstream Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation [621]. This dampens pro-inflammatory cytokines such as TNF-α and IL-12 and promotes an M2-like macrophage phenotype characterized by IL-10 production [622]. Similar to *Mtb*, HDTs with immunomodulatory functions may therefore provide therapeutic benefit by restoring host antimicrobial activity.

Legionella, which causes Legionnaires' Disease [623], redirect the vacuoles in which they reside after phagocytosis, toward ER-Golgi pathways to entirely bypass lysosomal fusion [624]. However, through the autophagy pathway, Legionella-containing vacuoles could still be targeted for lysosomal degradation [625]. *Legionella*'s strategy of autophagy suppression via RavZ, which irreversibly cleaves LC3, indicates that HDT that aim at restoring xenophagy could be beneficial [626]. HDAC inhibitors, which can upregulate autophagy-related genes, may help bypass such blocks, as evidenced by the role of HDAC6 in suppressing autophagy mediated protection against Legionella

[627]. Indeed, a large compound screen on intracellular *Legionella* survival revealed hits that modulate autophagy, but also Akt1 inhibitors indicating an overlap in druggable targets [628]. Interestingly, although calcineurin inhibitors also emerged in these screens, their role in *Legionella* survival remains uncertain [628].

Lastly, NTM, including *Mycobacterium avium* (*Mav*) and *Mycobacterium abscessus* (*Mab*), pose increasing clinical challenges, particularly in immunocompromised individuals and patients with pre-existing lung conditions [21]. Like *Mtb*, NTM are capable of persisting within Mϕs by interfering with phagosome maturation, although the exact molecular mechanisms and host-pathogen dynamics differ [629]. Species from the *Mav* complex, responsible for the majority of NTM related infections [630], reside in a membrane-bound vacuole that shares early endosomal markers but resists phagolysosomal fusion [631]. While less is known about NTM and their interaction with autophagy, they exhibit resistance to canonical xenophagy, suggesting overlap with *Mtb* in terms of host manipulation [631]. HDTs enhancing autophagic flux or restoring lysosomal acidification, such as compounds that inhibit mTOR or modulate calcium (suspected targets of 97i, Pimozide, Fluspirilene and Tamoxifen), may thus hold therapeutic promise. Additionally, the class of Phenothiazines that includes Trifluorperazine, identified in this thesis as HDT lead for *Mtb* (Chapter 2), has been shown to reduce intracellular *Mav* survival by among others increasing the Mϕ oxidative response [632]. However, other direct evidence is limited, and species-specific variability indicates a need for caution with extrapolation from *Mtb*-focused studies [235]. *Mab*, by contrast, exhibits greater virulence and intrinsic drug resistance [629].

Collectively, these comparative insights highlight the importance of tailoring HDT strategies to pathogen-specific intracellular niches and immune evasion mechanisms. While *Mtb* provides a robust model for identifying and characterizing HDTs, translating these findings to other pathogens, especially NTMs, requires consideration of their unique replication dynamics, host modulation strategies, and intracellular localization. Nevertheless, by demonstrating the cross-species potential of the HDT leads identified and validated in Chapter 3, 4, and 5, this thesis provides evidence that HDT can be employed against a variety of pathogens. In particular mechanistically diverse HDTs that engage conserved host pathways, such as autophagy and the oxidative response, may offer the broadest therapeutic potential and shorten therapeutic development timelines.

Drug Repurposing In HDT For TB - Opportunities And Challenges

In this thesis, several approved drugs were identified as HDT candidates, i.e. Pimozide and Fluspirilene (Chapter 4), Amiodarone (Chapter 4, [633]), Tamoxifen (Chapter 5),

while others are currently in clinical trials such as Dovitinib (phase 3) and AT9283 and ENMD-2076 (phase 2) (Chapter 2). Repurposing existing drugs for HDT offers significant advantages over traditional drug development. De novo drug discovery is time-intensive and costly, often requiring 10 to 15 years and up to billions of dollars [634]. In contrast, repurposed drugs bypass many early-stage barriers, as they already possess established pharmacokinetic, safety, and toxicity profiles, reducing both cost and regulatory hurdles [635]. This makes drug repurposing a particularly attractive strategy for TB, where urgent solutions are needed to improve treatment efficacy and reduce disease burden.

Several drugs originally developed for non-infectious diseases have demonstrated HDT potential against *Mtb*. For example, metformin, an AMP-activated protein kinase (AMPK) activator, enhances host metabolic responses, promoting antimicrobial immunity in TB while having a well-characterized safety profile [636]. Similarly, statins, widely used for cholesterol reduction, have been shown to modulate Mϕ activation, leading to reduced lung pathology and improved immune control of TB [637]. Given their pre-existing clinical approval, such drugs can be rapidly integrated into TB treatment regimens, particularly in high-burden, resource-limited settings, where cost-effective interventions are critical.

Despite these advantages, several challenges must be addressed before repurposed HDTs can be widely implemented. A primary concern is the limited availability of robust clinical data confirming their efficacy in *Mtb* infection, particularly in the context of comorbidities such as HIV and diabetes. While preclinical studies provide encouraging results, many repurposed drugs have yet to undergo large-scale randomized controlled trials (RCTs) to establish clinical efficacy and safety (Chapter 1). Tamoxifen, being widely used in oncology, has a known safety profile and is generally well-tolerated long-term [638]. In TB, it could potentially be used for a shorter term, for example 1-2 months adjunctive therapy. Pimozide and Fluspirilene have more pronounced central nervous system related side effects [639, 640], however, TB patients might tolerate a low dose for a limited time. Of note, Fluspirilene is formulated as a long-acting injection, but has been phased out from clinical practice and information is relatively scarce [641]. Alternatively, they might be considered in desperate cases of XDR-TB under close monitoring on compassionate grounds [642].

Another challenge is drug-drug interactions, particularly when repurposed HDTs are combined with standard TB antibiotics. While a start for the evaluation of potential synergistic or antagonistic effects was done for the HDT candidate and Rifampicin or Isoniazid (Chapter 3, 4 and 5), more work is needed to ensure that host-directed interventions do not compromise antimicrobial efficacy or drug safety. Additionally,

regulatory and financial barriers limit investment in TB-specific drug repurposing. Since many repurposed drugs are generic compounds, pharmaceutical companies may lack financial incentives to fund their development, leading to gaps in funding and research efforts [643]. Patient-specific variability presents an additional challenge, as genetic polymorphisms, immune status, *Mtb* strain heterogeneity, and coexisting infections (e.g., HIV, diabetes) are expected to significantly influence HDT efficacy [644, 645]. Biomarker-driven approaches may be necessary to identify patient subgroups most likely to benefit from repurposed treatments.

Drug repurposing presents a viable, cost-effective alternative to traditional TB drug development. However, careful consideration of clinical validation, safety, regulatory challenges, and patient variability is crucial for successful integration into TB treatment paradigms. With targeted investment and translational research, repurposed HDTs have the potential to significantly improve TB outcomes and global disease control efforts.

Concluding Remarks

TB remains one of the most complex and challenging infectious diseases of our time, with its causative agent, *Mtb*, demonstrating a remarkable capacity to persist within host cells and evade immune elimination. This thesis set out to explore and validate novel HDT strategies that harness the host's immune machinery to enhance intracellular bacterial clearance. By employing a multidisciplinary framework that integrated chemical-genetic screening, computational prediction, and functional validation across human and non-human primate *in vitro* systems and *in vivo* zebrafish embryo models, this work uncovered multiple promising HDT candidates and elucidated host pathways that can be therapeutically used to combat *Mtb* infection

Among the most noticeable insights emerging from this research is the identification of RTKs as key regulators of intracellular *Mtb* survival. Several RTK inhibitors, discovered through phenotypic screening and reinforced by machine learning-driven prioritization, demonstrated robust host-mediated control of *Mtb* in Mϕs. These findings expand the repertoire of known HDT targets and underscore the therapeutic relevance of modulating host signalling pathways. Furthermore, the convergence of multiple HDT candidates, such as 97i, Pimozide, Fluspirilene and Tamoxifen, on pathways regulating lysosomal biogenesis and autophagy underscores the centrality of these processes in host-mediated pathogen restriction. Notably, this thesis demonstrates that unrelated compounds, though structurally and functionally diverse, can converge mechanistically on TFEB-mediated lysosomal activation and autophagy induction, providing a robust starting point for rational HDT design.

Despite these advances, several limitations must be acknowledged. Mechanistic investigations were predominantly performed in Mϕ2, potentially overestimating the contribution of lysosomal pathways while underrepresenting oxidative stress, RNS, and other characteristic of Mϕ1. Additionally, while non-human primate AMϕs yielded translationally relevant data, the absence of complex granuloma models prevented assessment of HDT efficacy within spatially organized immune environments marked by hypoxia, cellular heterogeneity, and limited drug penetration.

Future studies should prioritize the integration of physiologically relevant 3D granuloma models, single-cell transcriptomics, and multiplexed imaging approaches to better capture the complexity of *Mtb* infection. Mechanistic dissection of HDT candidates, particularly their impact on protective versus non-protective autophagy, Mϕ metabolism, and plasticity, remains essential for informed compound optimization. On the computational front, future iterations of machine learning tools could incorporate deep learning architectures and multi-omics datasets to enhance prediction accuracy and generalizability across diverse host-pathogen contexts.

Beyond TB, the strategies and platforms developed in this thesis have broader implications. Several HDT candidates identified here, inducers of the lysosomal and autophagic response, may be repurposed against other intracellular pathogens such as *Stm*, which share elements of immune evasion mechanisms. Furthermore, understanding the key host factors of pathogen control may enable the design of personalized immunotherapies for TB patients with comorbidities such as HIV or diabetes, where immune dysfunction complicates treatment outcomes. Given that HDTs modulate host pathways rather than directly targeting pathogens, their application in the context of co-infections does however require careful consideration. Therapeutic modulation of the host response may benefit against one pathogen, while inadvertently impairing immune control of another.

In conclusion, this thesis presents a compelling case for HDT as a transformative adjunctive strategy in TB treatment. By targeting host pathways rather than microbial targets, HDT offers a multifaceted approach to reducing treatment duration, minimizing therapeutic resistance development, and improving outcomes in vulnerable populations. Continued investment in investigating mechanisms of action, as well as translational validation and generating clinical evidence, will be critical to unlock the full therapeutic potential of HDT in the ongoing global effort to eliminate TB.

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