Quantitative pharmacology approaches to inform treatment strategies against tuberculosis

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Section IV.

Host-directed therapies against tuberculosis
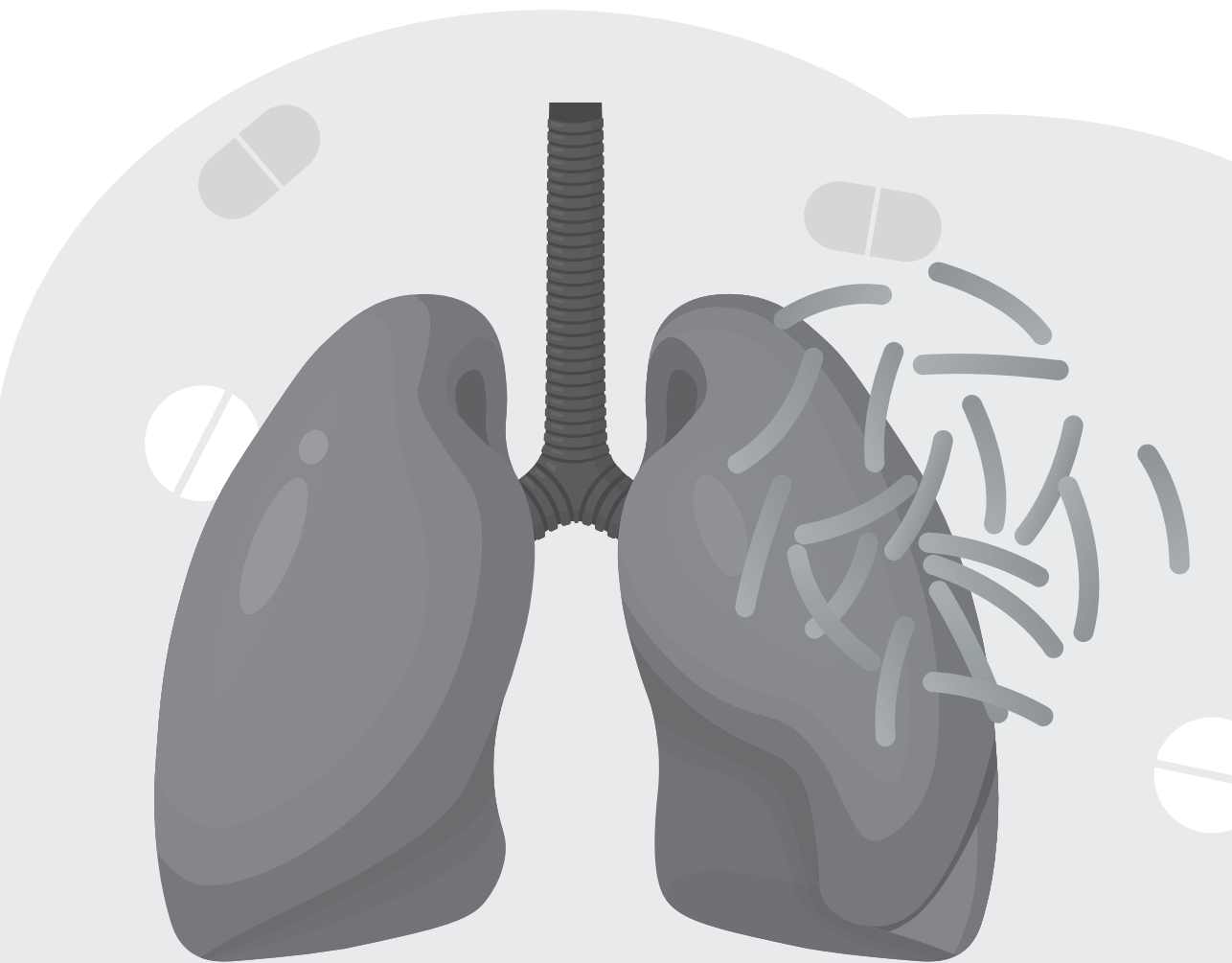
Chapter 7

Host-directed therapies for tuberculosis: quantitative systems pharmacology approaches

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Abstract

Host-directed therapies (HDT) that modulate host-pathogen interactions offer an innovative strategy to combat *Mycobacterium tuberculosis (Mtb) infections.* When combined with tuberculosis antibiotics, HDTs could contribute to improving treatment outcomes, reducing treatment duration, and preventing resistance development. Translation of the interplay of host-pathogen interactions leveraged by HDTs towards therapeutic outcomes in patients is challenging. Quantitative understanding of the multi-faceted nature of the host-pathogen interactions is vital to rationally design HDT strategies. Here, we (1) provide an overview of key Mtb host-pathogen interactions as basis for HDT strategies, and (2) discuss the components and utility of quantitative systems pharmacology (QSP) models to inform HDT strategies. QSP models can be used to identify and optimize treatment targets, to facilitate preclinical to human translation, and to design combination treatment strategies.

Glossary

Autophagy: Autophagy is an intracellular process involving the formation of a phagophore, elongation of the phagophore, autophagosome maturation, and fusion with lysosomes for degradation of the selected cellular material.

AMPK-mTOR pathway: The AMP-activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR) pathway involves complex interplay between various proteins and play a key role in autophagy regulation.

HMG-CoA reductase pathway: HMG-CoA (3-hydroxy-3-methyl-glutaryl-CoA) reductase pathway is involved mainly in regulation of cholesterol synthesis but also known to be involved in regulation of autophagy[1].

Phagocytosis: Phagocytosis is a cellular process involving engulfment of large particles, including bacteria, into the cells.

PK: Pharmacokinetics (PK) describes the concentration-time profile of drugs and is determined by absorption, distribution, metabolism. and elimination processes.

PD: Pharmacodynamics (PD) describes the concentration-effect-time profile of drugs and is determined by drug pharmacology and physiology of the organism[2].

Host-directed therapies: leveraging the host immune system for treatment of tuberculosis

Mycobacterium tuberculosis (Mtb) infections are associated with approximately 1.5-2 million deaths annually worldwide. Two key challenges to successful tuberculosis (TB) treatment are long duration of treatment and emergence of drug resistant strains[3]. In the last decade, host-directed therapy (HDT) strategies have received increasing attention[4-6] to enhance treatment outcomes, shorten treatment durations, and avoid resistance development. HDTs target interactions between the host immune response and the Mtb pathogen, which reduces the likelihood for Mtb to acquire resistance against HDTs. In addition, additive effects of adjunctive HDT treatment with conventional antibiotics on bacterial elimination could help to shorten treatment duration and therefore may avoid development of resistance to conventional antibiotics[7].

The host immune response to Mtb infection is reliant on the cumulative activities of various defense mechanisms such as macrophage activation, phagocytosis (see Glossary), autophagy (see Glossary), antigen presentation, and cytokine and T-lymphocytes production. Genotypic and phenotypic changes in Mtb during infection leading to modulation of the host response allows its survival and virulence in the host[8]. Mechanistic understanding of the multiscale nature of host-pathogen interactions is essential to identify HDT targets, to design and develop new HDT drugs, and to repurpose already marketed drugs as HDT strategy.

A major challenge in the discovery and development of HDTs for TB is the prediction of treatment responses associated with specific pharmacological modulation of an immune response-associated target due to complex systems-level host-drug-pathogen interactions[4]. The translation of systems-level responses to HDT strategies from preclinical models to patients is challenged by inter-species differences in immune responses to Mtb pathogen. Quantitative systems pharmacology (QSP) modelling can serve as a valuable tool to identify relevant HDT targets, and to inform subsequent design of combination drug treatment strategies and dosing schedules[9-11]. The utility of quantitative modelling to improve treatment strategies for TB have been demonstrated for antibiotic therapies[11,12]. However, these approaches have not yet been developed to design HDTs.

Here, we review high-potential host-pathogen interactions of relevance for HDTs. We then outline how QSP modelling approaches can be used to predict optimal HDT strategies with a focus on required model components and the integration

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with available data for application in target selection, inter-species translation, and treatment optimization.

Host-pathogen interactions as basis for host-directed therapy strategies

Several host-pathogen interactions of Mtb involved in its pathogenesis and immune system evasion offer potential targets for design of HDTs[6] **(Figure 7.1)** and are of relevance to capture in QSP modelling approaches.

Induction of autophagy

Autophagy plays an essential role in controlling Mtb infections and has been studied extensively as potential HDT strategy for Mtb[6]. Multiple intertwined pathways affecting glucose and cholesterol metabolism, such as AMPK-mTOR (see glossary) and HMG-CoA reductase pathway (see glossary), are involved in regulation of autophagy **(Figure 7.1)**. AMPK plays a key role in these pathways and therefore in regulation of autophagy. As an evasion mechanism, Mtb inhibits phosphorylation of AMPK protein and inhibits autophagy[13]. Apart from AMPK-mediated autophagy regulation, intracellular cholesterol is also involved in Mtb survival leading to inhibition of autophagosome maturation and autophagosome-lysosome fusion[1]. Thus, autophagy induction through inhibition of mTOR complex 1 (mTORC1) or by inhibition of HMG-CoA reductase represent a potential HDT strategy.

Figure 7.1 The Host-Pathogen interactions as basis for host-directed therapy strategies for the treatment of Mtb infections. Initiation of the host innate immune response occurs shortly after inhalation of aerosols containing Mtb bacteria and Mtb implantation in macrophages. Both resident and activated macrophages stimulate the release of pro-inflammatory cytokines, such as TNF-α and IL-1β, following phagocytosis and autophagy. Antigen presenting cells (macrophages and dendritic cells) that drain into local lymph nodes activate CD4+ and CD8+ T-cell mediated adaptive immune responses. Antigen presenting cells also stimulate the release of IL-12, which helps recruit additional CD4+ T-cells. CD4+ T-cells secrete IFN-γ that stimulate macrophage activation, IL-2, TNF-α, and IL-10 that help balance the pro-inflammatory response by deactivation of macrophages. CD8+ cells have cytotoxic activities. CD4+ T-cell secreted IL-2 drives further proliferation of CD4+ as well as CD8+ T-cells. Autophagic pathways start with parting of a section from endoplasmic reticulum, the phagophore, followed by the elongation of phagophore with engulfment of Mtb, autophagosome formation and maturation, and fusion of the autophagosome with lysosomes. Mtb activates mTORC1 and thus inhibits autophagy, while mTORC1 activates aerobic glycolysis. Intracellular cholesterol inhibits LC3, Ca2+, and LAMP3, and thus inhibits autophagy mediated Mtb killing. Mtb activates HDAC pathway and thus downregulates various genes responsible for innate and adaptive immune response. Potential host-directed therapy strategies are presented in the green text. Figure created with biorender.com.
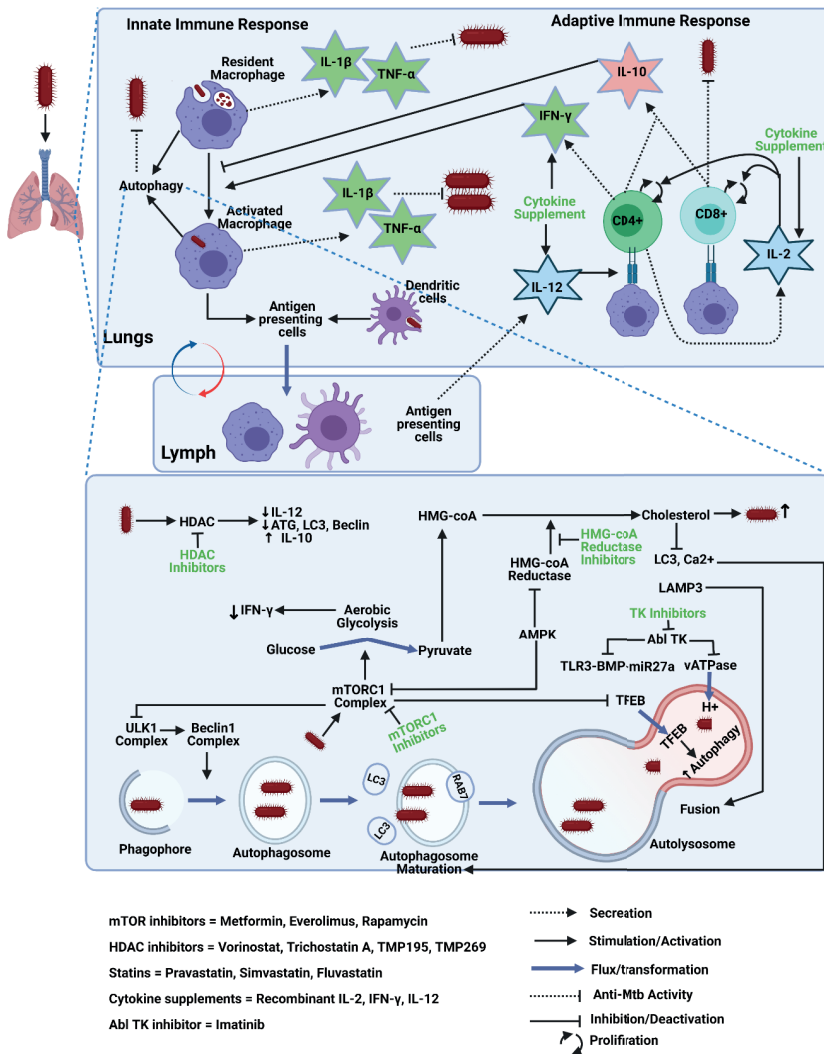
mTORC1 inhibitors

Metformin is the most evaluated mTORC1 inhibitor as potential HDT treatment for Mtb infections. Metformin inhibited the growth of intracellular Mtb in vitro and in mice[13,14]. Multiple reports suggest that metformin adjunctive therapy in diabetic TB patients improved therapy success rate and lowered mortality rate[15,16]. Adjunctive everolimus, an mTOR inhibitor, treatment with rifabutin-substituted standard TB therapy improved lung functions as measured by forced expiratory volume when compared to a control group in a randomized clinical trial[17]. A recent study identified protein kinase inhibitor ibrutinib as a potential mTORC1-mediated autophagy inducer in a mice study[18]. These results provide initial proof-of-concept and justify further evaluations of mTORC1 inhibitors in clinical trials.

HMG-CoA inhibitors

The HMG-CoA reductase pathway has been associated with intracellular cholesterol reduction and autophagy induction. Therapy with HMG-CoA inhibitors, such as simvastatin, pravastatin, and fluvastatin, as adjunctive therapy to conventional anti-TB drugs improved bacterial clearance by the host and improved the efficacy of first-line TB drugs by promoting autophagy in macrophage cell cultures and in mice[19,20]. Several retrospective clinical studies have identified that chronic use of statins reduced the risk of developing TB[21]. On the other hand, a population-based cohort analysis of data from newly diagnosed TB patients recognized no statistically significant difference in hazard ratio between patients who were using statins in addition to standard TB treatment as compared to patients who did not use statins[22]. As chronic use of statins leads to reduced risk of TB, it may be hypothesized that factors such as drug penetration in lungs and drug affinity may play a key role in determining its effectiveness as HDT. Overall, these results highlight the potential of targeting the HMG-CoA reductase pathway as autophagy induction strategy.

Regulation of host epigenetics

Infection with Mtb is associated with alterations of some gene functions important for ensuring immune response. Two key pathways known to be involved in Mtb-induced host epigenetic alterations are histone deacetylases1 (HDAC1) pathway and TLR3-BMP-miR27a pathway both of which can be pharmacologically exploited[23,24].

HDAC inhibitors

Infections with Mtb leads to upregulation of HDAC1, which leads to suppression of IL-12B gene expression leading to suppression of T-cell immunity **(Figure 7.1)**.

Additionally, HDAC1 is known to modulate autophagy associated genes[23]. HDAC inhibitors, such as Trichostatin A, TMP195, and TMP269, reduced bacterial growth in macrophage cell cultures. Vorinostat, an HDAC inhibitor, promoted immune response in macrophage cell cultures[25]. In zebrafish embryos infected with *Mycobacterium marinum* (Mm), HDAC inhibition significantly reduced microbial burden[23]. HDAC inhibition significantly inhibited Mtb growth and showed increased production of key cytokines in mice[26]. These results highlight the potential of exploiting HDAC inhibition as HDT strategy.

Abl Tyrosine Kinase Inhibitors

Protein Abl Tyrosine Kinase (ATK) is involved in entry and survival of Mtb within macrophages through TLR3-BMP-miR27a pathway. ATK also inhibits expression of vATPase pump-relevant genes, and thus inhibits acidification of autolysosomes **(Figure 7.1)**. Pharmacological inhibition of ATK using imatinib improved containment of Mtb within macrophages, induced autophagy, and decreased bacterial load in human macrophage cell cultures and in mice[6,24]. Imatinib also lead to decreased bacterial load in macrophage culture and in mice infected with rifampin-resistant Mm[27]. A clinical study assessing effects of imatinib alone and in combination with conventional anti-TB drugs in drug-resistant- and HIV co-infected- TB patients is ongoing[28]. These data suggest that imatinib may prove effective as HDT towards Mtb.

Modulation of cytokine response

The kinetics of the key cytokines, such as interferon gamma (IFN-γ), tumour necrosis alpha (TNF-α), IL-1β, IL-10, IL-4, IL-12, and IL-2, during Mtb infections have been well studied in humans and in mice. IFN-γ is one of the most important players to the host immune response and its main role is activation of macrophages **(Figure 7.1)**. Both activated and resident macrophage produce pro-inflammatory cytokines, TNF-α and IL-1β, that possess microbicidal properties against Mtb; however activated macrophage-mediated production is much more efficient[29]. Excessive production of pro-inflammatory cytokines, however, can lead to tissue damage in vivo[30]. Anti-inflammatory cytokines, IL-10 and IL-4, are also induced upon macrophage phagocytosis and balance pro-inflammatory cytokines by macrophage deactivation[30]. Excessive production of anti-inflammatory cytokines may result in limiting the immune-mediated microbicidal activities[31]. Thus, the fine balance between the pro- and anti-inflammatory cytokines may determine the overall outcome of the Mtb infection.

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Adjunctive treatment with IFN-y have been evaluated in various clinical studies; however, different patient conditions, routes of administration, and dosing regimen resulted in varying outcomes[31]. Adjunctive treatment with aerosolized IFN-y showed benefits in reducing cavitary lesions and induced negative sputum conversion in TB patients in clinical studies[32]. Thus, modulation of cytokine response may be a useful HDT strategy.

Enhancing t-cell mediated host response

The innate immune reaction plays an important role in the initiation of adaptive immune response by antigen presentation and cytokines production. A few weeks after the initial infection, antigen-presenting cells (APCs) that drain into regional lymph nodes initiate adaptive T-lymphocytes-mediated immune response. Upon antigen presentation, the APCs via major histocompatibility molecules (MHC)-I and II prime CD8+ and CD4+ T-cells to initiate adaptive immune response. Both activated CD4+ and CD8+ T-cells secrete IFN-y, IL-2, IL-17A, and IL-10. Mature dendritic cells secrete IL-12p70 which helps increasing recruitment of additional CD4+ T-cells. IL-2 play a role in further proliferation of T-cells. CD8+ cells have direct microbicidal capabilities through perforin, granzymes, and granulysin or induce apoptosis through Fas/Fas ligand interaction. Adjunctive cytokine supplementation with IL-12 and IL-2 have been evaluated in clinical studies but did not result in significant benefits. However, recombinant human IL-2 supplementation showed significant improvements in negative sputum culture conversion rates and in enhanced X-ray resolution in drug-resistant TB patients[33]. Therefore, the use of recombinant IL-2 supplementation as HDT strategy for TB should be further evaluated.

Design of host-directed therapies using quantitative systems pharmacology modelling

The overall outcome of Mtb disease and treatment is reliant on the integrated results of the molecular and cellular events, and their reflection at tissue, organ, and host level dynamics occurring at different time scales. As such, it can be challenging to predict patient responses to different HDT strategies. Species differences in immune response characteristics make it more challenging to translate the results from preclinical studies to clinical scenarios. Additionally, determination of the effects of treatments and disease progression in specific patient populations, can be challenging, i.e., in patients with weakened immune response or other conditions, patients with specific genotype known to affect certain pharmacology.

QSP modelling can address these hurdles through quantitative integration of host-pathogen interaction mechanisms with PK (see glossary) and PD (see glossary) aspects of HDTs, making it a relevant tool to guide drug discovery and development of HDTs. Development of QSP models for HDTs against TB is the requirement for large amount of mechanistic quantitative data to parametrize the model, which may concern biological system-specific data relating to immunodynamics and pathogen dynamics, as well as drug-specific model related to pharmacokinetics and drug-target interactions. Importantly, once defined, a QSP framework for specific HDT mechanisms is developed, it can be applied as platform model towards different investigational therapeutic agents. Selection of appropriate experimental approaches are important to provide quantitative understanding about components of drug-host-pathogen interactions. Here, we briefly discuss key experimental models that can be of relevance for characterization of HDTs using QSP modelling. Then, we discuss three main components of the QSP framework to evaluate HDTs for Mtb infection, (1) drug PK models, (2) host immune response models, and (3) pathogen dynamic models **(Figure 7.2)**. Lastly, we discuss applications of these models **(Figure 7.3)**.

Experimental approaches to facilitate parameterization of the qsp models

Human-derived macrophage and peripheral blood mononuclear cell cultures are extensively used to screen for the antibiotics but also identify compounds with HDT potential[14,34,35]. The in vitro hollow fiber infection model (HFIM) is commonly used to study the direct effects of antibiotics agents on Mtb, and readily allows to include co-cultures with macrophages. In HFIM, Mtb is cultured in a closed chemostat system with continuous flow of medium, while it allows simulation of concentration-time profiles of underlying PK/PD relationships of antibiotics and HDTs[36]. Several advanced cell culture systems, such as 3D cell cultures, organoids[37], and lung-on-chip[38], have been increasingly used to study host-pathogen interactions. Whilst these approaches are attractive for purposes of quantitative characterization of key mechanisms and phenotypic response profiles to be implemented in QSP models, these systems remain a simplified system that does not include all aspects related to the host immune response.

Adult zebrafish have gained increasing attention as it possess an innate immune system that is highly similar to that of mammals[39,40]. Zebrafish embryos are of interest due to their optical transparency and thus allowing the use of advanced imaging methods. Infection of zebrafish with various mycobacteria leads to

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formation of granuloma structures that are highly similar to those observed in human TB patients; therefore, it has been a successful model to study the progression of TB and the effects of drug treatment[41]. Pharmacological screening of drugs to treat mycobacterial infection at a high throughput level is also possible[42]. Knockdown and overexpression experiments in zebrafish combined with translational QSP modelling would especially provide insights into contribution of certain component to overall immune response and anti-TB effects[43]. Rodents, i.e., mice, rabbits, and guinea-pigs, are commonly used as infection model for Mtb[39]. Even though these models incorporate a full immune system, differences between the human immune response remain and lead to translational challenges[11]. Non-human primates (NHP) have been widely used in immunology and vaccine research. NHP infected with Mtb are of interest in generating HDT-relevant data due to their similarities to humans in basic physiology, immunology, and disease pathology. However, the use of these models has been limited in TB treatment research due to the requirements of scientific and financial resources as well as safety issues due to highly infectious and contagious nature of Mtb[44].

Overall, data collected from a combination of various experimental models, such as in vitro, zebrafish, and mice, can be used to parameterize QSP models. QSP models can link the results from various experimental infection models, enabling predictions in humans.

Components of the qsp modelling framework

A QSP framework for HDTs should contain a combination of model components for PK of the drugs, host immune response, and pathogen dynamics, including their interactions **(Figure 7.2)**. Depending on the type of HDT drug studied, QSP models may be parameterized and adapted in specific ways, e.g., to capture the drug-specific parameters to induce specific immune system effects.

Pharmacokinetics

Consideration of drug concentrations-effect relationships, and therefore PK, is of essential value for design of HDT strategies. Physiologically based PK (PBPK) models describe the concentration profiles in specific tissues of interest and are informed by both drug- and system-specific parameters. PBPK models are of relevance to scale PK between preclinical species and humans in a mechanistic fashion. For TB, PBPK models describing lung exposure are of specific relevance. In the clinical phase, quantifying inter-patient variability in PK is important. Here, population PK models are of relevance, which capture inter-individual variation in underlying

parameters that can be explained by specific patient-specific covariates [45]. It is furthermore helpful that because many HDTs involve repurposed drugs, often PK models are available already to characterize their PK[46,47].

Figure 7.2 Components of the conceptual quantitative systems pharmacology framework to assess HDTs for treatment of Tuberculosis. A QSP framework for HDTs should contain a combination of model components for PK of the drugs, host immune response, and pathogen dynamics, including their interactions. Classical antibiotics and HDTs act by modulating pathogen dynamics and host immune response, respectively. Immune-mediated pathogen killing is dependent on interplay between the host immune response and pathogen evasion mechanisms, i.e., host-pathogen interactions. Key considerations for each model components are listed in green box. Types of studies and data that can be used to inform each model components are presented in purple box. Figure created with biorender.com
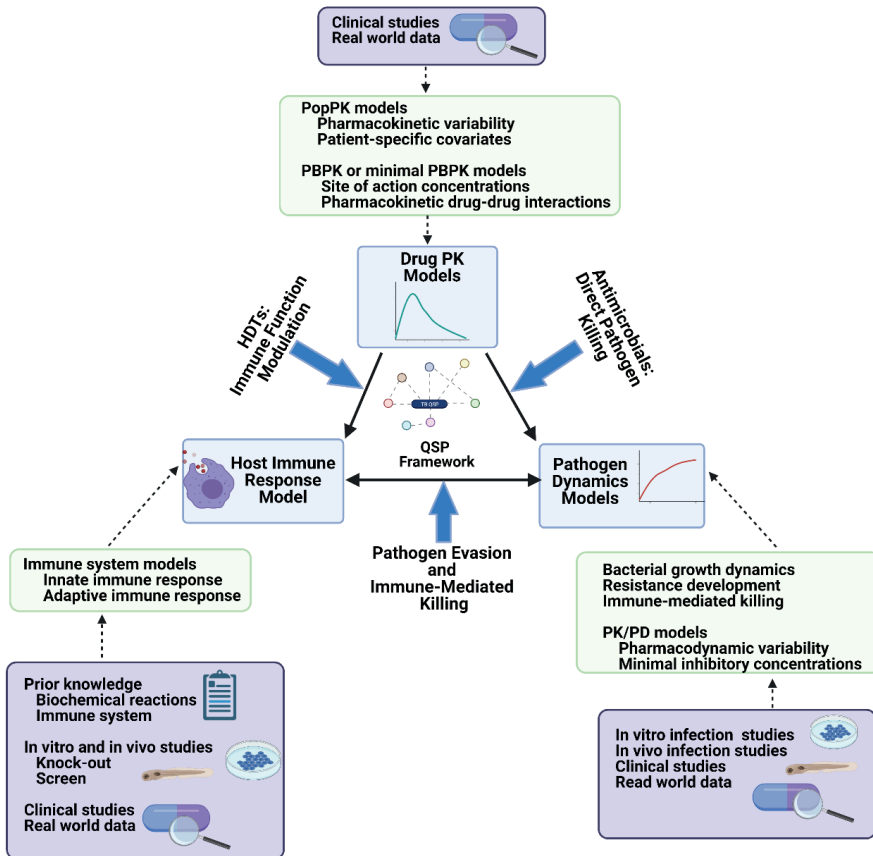
Immunodynamics

Models describing the key immune response components, such as dynamics of macrophage counts, cytokines, and CD4+ and CD8+ lymphocytes are essential for QSP models to study HDTs. Systems biology models describing the host-Mtb interactions within the lungs[48] have been previously developed, and later linked

with lymphatics[49] and blood circulations[50]. The states included in these models were resting-, activated-, and infected-macrophages, cytokines, such as IFN-y, IL-10, and IL-12, dendritic cells, CD4+ lymphocytes, and intra- and extra-cellular Mtb. The key feature of this model was contributions of various immune components on intra- and extra-cellular Mtb. The above-developed model was later expanded to include CD8+ cells dynamics in lungs[51]. The parameters in these models were identified from published human derived or NHP experiments or model fitting to experimental data. These models can be expanded to include key drug targets involved in Mtb HDTs and their downstream effects on functional immune response changes and the quantitative interaction with Mtb.

There are currently no mathematical models available in literature describing HDT-relevant pathways, such as autophagy in Mtb infections; however, components and parameter estimates from single cell systems biology models[52] can be adapted and extended using experimental data. For example, a HDT model containing key biological features of autophagy[52] including HDAC1-related components **(Figure 7.1)** may be developed. The model parameters can be informed using prior data available in literature[52] and data from in vitro experiments[23]. The model may describe dynamics of the phagocytic cells and zebrafish infection with Mm load overtime in HDAC1 inhibitors exposed macrophage cell cultures as compared to controls to estimate the parameters relevant to HDAC1 effect. The simulations from the models may be compared with the experimental outcomes, preferably from different experimental conditions than the original experiments used for parameter estimation. This allows validation of the model structure and parameter estimates. In the above example, the simulations may be validated against data from zebrafish exposed to HDAC1 inhibitors (at various HDAC1 levels) experiments[23]. If multiple targets are affected by certain drugs, i.e., ATK inhibitors (Figure 1), all relevant mechanisms must be captured in such models.

Pathogen dynamics

Models for the dynamics of pathogens include the effect of antibiotic drug on the growth and elimination of Mtb and emergence of treatment resistance. In vitro and in vivo infection studies have enabled our understanding of parameters of Mtb growth rates, bactericidal and bacteriostatic effects of conventional anti-TB drugs[36], and resistance rates of bacteria[12]. The incorporation of immune cell effects on pathogen killing is a key required step to study the effects of HDTs on Mtb treatment. Published host-Mtb interaction models[49] can be updated to include contributions of key HDT components on pathogen killing, as well as pathogen evasion mechanisms. For example, an autophagy model may contain

quantitative relationship between bacterial load, mTOR, and autophagy. This will allow evaluations and predictions of various mTOR inhibitors on Mtb clearance by autophagy.

Applications of the qsp modelling framework

QSP modelling have successfully influenced various decision making at different stages starting from discovery to late-phase in various therapeutic areas[53] and offer potential for the challenges faced in translation and design of HDT strategies against Mtb **(Figure 7.3)**.

Figure 7.3 Applications of the conceptual quantitative systems pharmacology framework to assess host-directed therapies for treatment of Tuberculosis. QSP models can guide TB HDT drug discovery and development at various phases depending on the model attributes. For example, a model developed based on experimental in vitro and/or in vivo data can be useful to study various host-pathogen interactions, to screen for optimal HDT targets, and to guide in vitro and/or in vivo data experimental designs. Upon addition of various translational factors and inter-individual variability components, the models can be useful to design optimal clinical studies, to identify. Figure created with biorender.com.
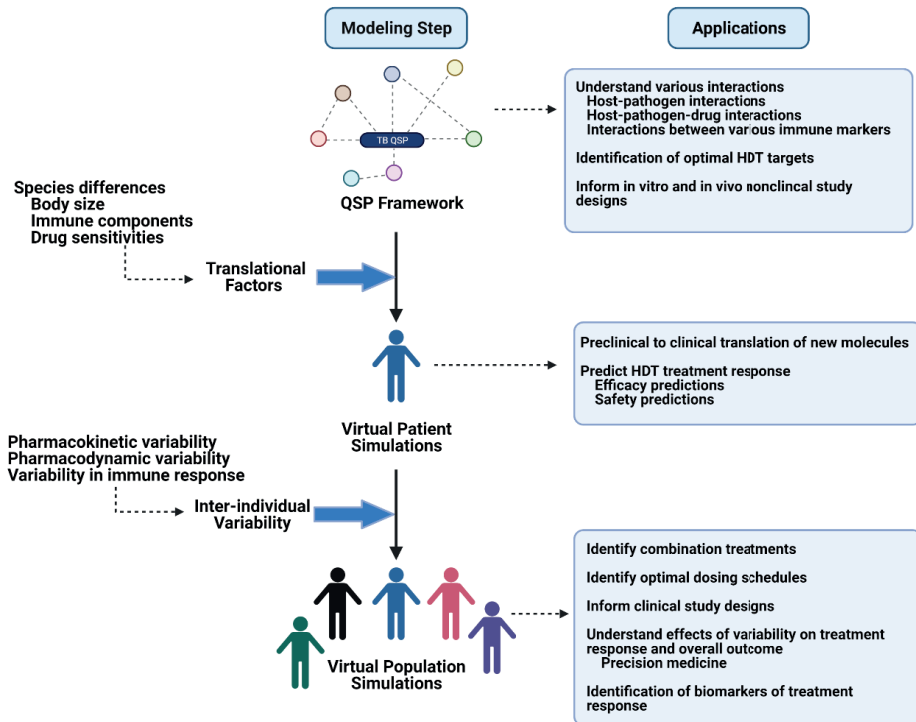
Target identification, drug discovery, and drug repurposing

QSP models integrate various host-pathogen interactions and drug PK/PD components; therefore, they can readily provide assessment of target engagement upon stimulation or inhibition of certain targets at various doses and affinities. This allows evaluations of the iterative process of hypotheses generation, designing new experiments, hypotheses validation and/or generation of new hypotheses. This approach can be applied to evaluate known HDT targets and molecules, to discover new HDT targets, and to discover new HDT molecules. With advances in technologies, applications of combining quantitative modelling and machine learning approaches are being evaluated to screen new virtual drug compounds with optimal characteristics[54]. For example, different ADME properties for a set of virtual compounds were used in a PBPK model combined with tumor dynamics model to simulate tumor size. Machine learning algorithms were then applied to the simulated dataset to identify the combination of ideal drug properties to provide desired outcome. This information may then be applied for lead prioritization[54]. Similar approaches can be applied to repurpose or reposition already marketed drugs using large scale drug-target interactions data[55]. Advanced target screening techniques, i.e., CRISPR-Cas9, can be also considered in combination with QSP models for HDT drug discovery and development in future.

Translational predictions

With increased complexity and innovation in design of new drugs within the last two decades, mechanistic models are increasingly being applied to inform translation of the results across different experimental conditions and species. The systematic incorporation of system-specific parameters not only for various species, but also incorporation of differences between in vitro systems and in vivo models, is crucial to enable translation towards clinical HDT treatment designs39. In some cases, i.e. for scaling from HFIM to humans, such scaling is well studied[36], whilst further studies are needed for the host's immune response components[56]. Consolidating immune-relevant differences between preclinical models and humans[56] may be challenging and resource intensive, as there may be varying strains of models used across different experiments depending on the objectives of the experiments. On the other hand, the shown evolutionary conservation of the metabolic responses to mycobacterial infection in human patients, mice, and zebrafish show that basic disease symptoms such as wasting syndrome are not depending on species or varying strains[57]. Gene expression analysis data across species may be used to inform parameters of expressions of genes responsible for certain immune functions[58]. Such expression data studies can be used to predict metabolism

using whole-genome metabolic network theoretical modelling approach in various organisms[59]. Factors such as severity of infection and sensitivity of drugs to bacterial strains (i.e., Mtb vs. Mm) may also be applied within the QSP framework.

Variability and precision medicine

The presentation and severity of TB is variable amongst patients, and thus treatment responses, especially to HDTs, are variable. Many factors such as age, sex, genotypes, comorbidities play role in determining the outcome of the disease and treatment. PopPK models have evaluated these factors' impact on variability in PK/PD of antibiotics[60] and can be included in QSP simulations. For example, known differences in PK and immune-response components for HIV co-infected TB patients may be incorporated in the framework, enabling extrapolation of results from studies in TB patients to HIV-TB patients[61]. In addition, considering immune-response relevant endotypes is important[62,63]. Technological advances within the last century enabled the generation of large-scale omics data. This data may enable us to better understand the inter-individual variations associated with the parameters of the QSP models. For example, parameters, together with inter-individual variations, describing the expression of baseline state of immune response components within lymph nodes and blood were estimated using data from a flow cytometry analysis of blood leukocytes and genome-wide DNA genotyping from humans[64]. Gene expression analysis of omics datasets from TB patients enabled stratification of the patients into two groups. One of the two groups was characterized by increased gene activity score for inflammatory response and decreased gene activity score for metabolism-relevant pathways, and patients in this group showed slower time to negative TB culture conversion and poor clinical outcome[62,63]. Similarly, gene expression data can be used to include variability in the QSP models and inform outcomes of certain HDT treatment.

Selection of optimal dosing regimens and combination therapies

QSP models are well-suited to efficiently evaluate combination therapies and dosing schedules, which is important to combination treatment strategies of HDTs and classical antibiotics against Mtb. In the field of immune-oncology, such QSP models have been widely applied to design optimal combination treatments of immune-targeting agents[65]. In the TB disease space, a QSP modelling approach for conventional antibiotic Mtb therapy has recently been applied to predict patient outcome with intensive dosing regimen and to explore shorter treatment duration scenarios[12].

Conclusions

HDTs offer a unique treatment strategy to combat Mtb infections but are challenged by complex and multiscale interactions between drug, host, and pathogen. Several key mechanisms are of interest to be exploited as HDTs but are facing challenges in translation towards clinically effective treatment strategies. The combined use of innovative experimental infection models with QSP modelling approaches can address these translational challenges and accelerate the design of novel HDT (combination) treatment strategies towards patients. QSP models supporting HDT design include model components describing biological system specific host-specific immunodynamics, pathogen dynamics and drug-specific models for PK and PK/PD for compounds of interest. Design of QSP models for HDTs relies on the availability of detailed mechanistic knowledge of relevant immunological and pharmacological aspects related to drug-host-pathogen interactions of Mtb infection, with significant knowledge gaps still present. Future work should focus on filling these knowledge gaps, which will require close and prospective coordination with such investigational efforts ensuring the correct data will be collected (see outstanding questions).

References

1. Parihar SP, Guler R, Khutlang R, Lang DM, Hurdayal R, Mhlanga MM, et al. Statin therapy reduces the mycobacterium tuberculosis burden in human macrophages and in mice by enhancing autophagy and phagosome maturation. J Infect Dis. 2014 Mar;209(5):754–63.

2. Jusko W. Foundations of Pharmacodynamic Systems Analysis. In: AAPS Advances in the Pharmaceutical Sciences Series. 2016. p. 161–75.

3. Nahid P, Dorman SE, Alipanah N, Barry PM, Brozek JL, Cattamanchi A, et al. Executive Summary: Official American Thoracic Society/ Centers for Disease Control and Prevention/ Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. Clin Infect Dis. 2016;63(7):853–67.

4. Young C, Walzl G, Du Plessis N. Therapeutic host-directed strategies to improve outcome in tuberculosis. Mucosal Immunol [Internet]. 2020;13(2):190–204. Available from: http://dx.doi.org/10.1038/s41385-019-0226-5

5. Tsenova L, Singhal A. Effects of host-directed therapies on the pathology of tuberculosis. J Pathol. 2020 Apr;250(5):636–46.

6. Kilinç G, Saris A, Ottenhoff THM, Haks MC. Host-directed therapy to combat mycobacterial infections. Immunol Rev. 2021 Feb;

7. Du Preez I, Loots DT. Novel insights into the pharmacometabonomics of first-line tuberculosis drugs relating to metabolism, mechanism of action and drug-resistance. Drug Metab Rev. 2018 Nov;50(4):466–81.

8. Walter ND, De Jong BC, Garcia BJ, Dolganov GM, Worodria W, Byanyima P, et al. Adaptation of Mycobacterium tuberculosis to Impaired Host Immunity in HIV-Infected Patients. J Infect Dis. 2016;214(8):1205–11.

9. van Hasselt JGC, Iyengar R. Systems Pharmacology: Defining the Interactions of Drug Combinations. Annu Rev Pharmacol Toxicol. 2019 Jan;59:21–40.

10. Aulin LBS, de Lange DW, Saleh MAA, van der Graaf PH, Völler S, van Hasselt JGC. Biomarker-Guided Individualization of Antibiotic Therapy. Clin Pharmacol Ther. 2021 Feb;

11. Bartelink IH, Zhang N, Keizer RJ, Strydom N, Converse PJ, Dooley KE, et al. New Paradigm for Translational Modeling to Predict Long-term Tuberculosis Treatment Response. Clin Transl Sci. 2017;10(5):366–79.

12. Fors J, Strydom N, Fox WS, Keizer RJ, Savic RM. Mathematical model and tool to explore shorter multi-drug therapy options for active pulmonary tuberculosis [Internet]. Vol. 16, PLoS Computational Biology. 2020. 1–36 p. Available from: http://dx.doi.org/10.1371/journal.pcbi.1008107

13. Singhal A, Jie L, Kumar P, Hong GS, Leow MKS, Paleja B, et al. Metformin as adjunct antituberculosis therapy. Sci Transl Med. 2014;6(263).

14. Lachmandas E, Eckold C, Böhme J, Koeken VACM, Marzuki MB, Blok B, et al. Metformin Alters Human Host Responses to Mycobacterium tuberculosis in Healthy Subjects. J Infect Dis. 2019 Jun;220(1):139–50.

15. Degner NR, Wang J-Y, Golub JE, Karakousis PC. Metformin Use Reverses the Increased Mortality Associated With Diabetes Mellitus During Tuberculosis Treatment. Clin Infect Dis an Off Publ Infect Dis Soc Am. 2018 Jan;66(2):198–205.

16. Ma Y, Pang Y, Shu W, Liu Y-H, Ge Q-P, Du J, et al. Metformin reduces the relapse rate of tuberculosis patients with diabetes mellitus: experiences from 3-year follow-up. Eur J Clin Microbiol Infect Dis Off Publ Eur Soc Clin Microbiol. 2018 Jul;37(7):1259–63.

17. Wallis RS, Ginindza S, Beattie T, Arjun N, Likoti M, Edward VA, et al. Adjunctive host-directed therapies for pulmonary tuberculosis: a prospective, open-label, phase 2, randomised controlled trial. Lancet Respir Med. 2021 Mar;

18. Hu Y, Wen Z, Liu S, Cai Y, Guo J, Xu Y, et al. Ibrutinib suppresses intracellular mycobacterium tuberculosis growth by inducing macrophage autophagy. J Infect. 2020 Jun;80(6):e19–26.

19. Tahir F, Bin Arif T, Ahmed J, Shah SR, Khalid M. Anti-tuberculous Effects of Statin Therapy: A Review of Literature. Cureus. 2020 Mar;12(3):e7404.

7

20. Dutta NK, Bruiners N, Zimmerman MD, Tan S, Dartois V, Gennaro ML, et al. Adjunctive Host-Directed Therapy With Statins Improves Tuberculosis-Related Outcomes in Mice. J Infect Dis [Internet]. 2020 Mar;221(7):1079—1087. Available from: https://doi.org/10.1093/infdis/jiz517

21. Tahir F, Bin Arif T, Ahmed J, Shah SR, Khalid M. Anti-tuberculous Effects of Statin Therapy: A Review of Literature. Cureus. 2020;12(3).

22. Chen Y-T, Kuo S-C, Chao P-W, Chang Y-Y. Use of lipid-lowering agents is not associated with improved outcomes for tuberculosis patients on standard-course therapy: A population-based cohort study. PLoS One. 2019;14(1):e0210479.

23. Moreira JD, Koch BE V, van Veen S, Walburg K V, Vrieling F, Mara Pinto Dabés Guimarães T, et al. Functional Inhibition of Host Histone Deacetylases (HDACs) Enhances in vitro and in vivo Anti-mycobacterial Activity in Human Macrophages and in Zebrafish. Front Immunol. 2020;11:36.

24. Mahadik K, Prakhar P, Rajmani RS, Singh A, Balaji KN. c-Abl-TWIST1 Epigenetically Dysregulate Inflammatory Responses during Mycobacterial Infection by Co-Regulating Bone Morphogenesis Protein and miR27a. Front Immunol [Internet]. 2018;9:85. Available from: https://www.frontiersin.org/article/10.3389/fimmu.2018.00085

25. Cox DJ, Coleman AM, Gogan KM, Phelan JJ, Ó Maoldomhnaigh C, Dunne PJ, et al. Inhibiting Histone Deacetylases in Human Macrophages Promotes Glycolysis, IL-1β, and T Helper Cell Responses to Mycobacterium tuberculosis. Front Immunol. 2020;11(July):1–15.

26. Wang X, Tang X, Zhou Z, Huang Q. Histone deacetylase 6 inhibitor enhances resistance to Mycobacterium tuberculosis infection through innate and adaptive immunity in mice. Pathog Dis. 2018 Aug;76(6).

27. Napier RJ, Rafi W, Cheruvu M, Powell KR, Zaunbrecher MA, Bornmann W, et al. Imatinib-Sensitive tyrosine kinases regulate mycobacterial pathogenesis and represent therapeutic targets against tuberculosis. Cell Host Microbe [Internet]. 2011;10(5):475–85. Available from: http://dx.doi.org/10.1016/j.chom.2011.09.010

28. Giver CR, Shaw PA, Fletcher H, Kaushal D, Pamela G, Omoyege D, et al. IMPACT-TB*: A Phase II Trial Assessing the Capacity of Low Dose Imatinib to Induce Myelopoiesis and Enhance Host Anti-Microbial Immunity Against Tuberculosis. *Imatinib Mesylate per Oral As a Clinical Therapeutic for TB. Blood [Internet]. 2019 Nov 13;134(Supplement_1):1050. Available from: https://doi.org/10.1182/blood-2019-130275

29. Marino S, Kirschner DE. A Multi-Compartment Hybrid Computational Model Predicts Key Roles for Dendritic Cells in Tuberculosis Infection. Comput (Basel, Switzerland). 2016;4(4).

30. Domingo-Gonzalez R, Prince O, Cooper A, Khader SA. Cytokines and Chemokines in Mycobacterium tuberculosis Infection. Microbiol Spectr. 2016 Oct;4(5).

31. Kolloli A, Subbian S. Host-directed therapeutic strategies for tuberculosis. Front Med. 2017;4(OCT).

32. Koh W-J, Kwon OJ, Suh GY, Chung MP, Kim H, Lee NY, et al. Six-month therapy with aerosolized interferon-gamma for refractory multidrug-resistant pulmonary tuberculosis. J Korean Med Sci. 2004 Apr;19(2):167–71.

33. Zhang R, Xi X, Wang C, Pan Y, Ge C, Zhang L, et al. Therapeutic effects of recombinant human interleukin 2 as adjunctive immunotherapy against tuberculosis: A systematic review and meta-analysis. PLoS One. 2018;13(7):1–14.

34. Van Der Vaart M, Korbee CJ, Lamers GEM, Tengeler AC, Hosseini R, Haks MC, et al. The DNA damage-regulated autophagy modulator DRAM1 links mycobacterial recognition via TLP-MYD88 to authophagic defense. Cell Host Microbe. 2014;15(6):753–67.

35. Korbee CJ, Heemskerk MT, Kocev D, van Strijen E, Rabiee O, Franken KLMC, et al. Combined chemical genetics and data-driven bioinformatics approach identifies receptor tyrosine kinase inhibitors as host-directed antimicrobials. Nat Commun. 2018 Jan;9(1):358.

36. Gumbo T, Pasipanodya JG, Nuermberger E, Romero K, Hanna D. Correlations Between the Hollow Fiber Model of Tuberculosis and Therapeutic Events in Tuberculosis Patients: Learn and Confirm. Clin Infect Dis [Internet]. 2015;61(suppl_1):S18–24. Available from: https://doi.org/10.1093/cid/civ426

37. Tezera LB, Bielecka MK, Chancellor A, Reichmann MT, Shammari B Al, Brace P, et al. Dissection of the host-pathogen interaction in human tuberculosis using a bioengineered 3-dimensional model. Elife. 2017;6:1–19.

38. Thacker V V., Dhar N, Sharma K, Barrile R, Karalis K, McKinney JD. A lung-on-chip model of early m. Tuberculosis infection reveals an essential role for alveolar epithelial cells in controlling bacterial growth. Elife. 2020;9:1–73.

39. Meijer AH. Protection and pathology in TB: learning from the zebrafish model. Semin Immunopathol. 2016;38(2):261–73.

40. H. Meijer A, P. Spaink H. Host-Pathogen Interactions Made Transparent with the Zebrafish Model. Curr Drug Targets. 2011;12(7):1000–17.

41. Johansen MD, Daher W, Roquet-Banères F, Raynaud C, Alcaraz M, Maurer FP, et al. Rifabutin Is Bactericidal against Intracellular and Extracellular Forms of Mycobacterium abscessus. Antimicrob Agents Chemother. 2020 Oct;64(11).

42. Ordas A, Raterink R-J, Cunningham F, Jansen HJ, Wiweger MI, Jong-Raadsen S, et al. Testing tuberculosis drug efficacy in a zebrafish high-throughput translational medicine screen. Antimicrob Agents Chemother. 2015 Feb;59(2):753–62.

43. van Wijk RC, Hu W, Dijkema SM, van den Berg DJ, Liu J, Bahi R, et al. Anti-tuberculosis effect of isoniazid scales accurately from zebrafish to humans. Br J Pharmacol. 2020;177(24):5518–33.

44. Yang H-J, Wang D, Wen X, Weiner DM, Via LE. One Size Fits All? Not in In Vivo Modeling of Tuberculosis Chemotherapeutics. Front Cell Infect Microbiol [Internet]. 2021;11:134. Available from: https://www.frontiersin.org/article/10.3389/fcimb.2021.613149

45. Mehta K, Ravimohan S, Pasipanodya JG, Srivastava S, Modongo C, Zetola NM, et al. Optimizing ethambutol dosing among HIV/tuberculosis co-infected patients: a population pharmacokinetic modelling and simulation study. J Antimicrob Chemother. 2019 Oct;74(10):2994–3002.

46. Hanke N, Türk D, Selzer D, Ishiguro N, Ebner T, Wiebe S, et al. A Comprehensive Whole-Body Physiologically Based Pharmacokinetic Drug–Drug–Gene Interaction Model of Metformin and Cimetidine in Healthy Adults and Renally Impaired Individuals. Clin Pharmacokinet [Internet]. 2020;59(11):1419–31. Available from: https://doi.org/10.1007/s40262-020-00896-w

47. Duong JK, Kumar SS, Kirkpatrick CM, Greenup LC, Arora M, Lee TC, et al. Population pharmacokinetics of metformin in healthy subjects and patients with type 2 diabetes mellitus: simulation of doses according to renal function. Clin Pharmacokinet. 2013 May;52(5):373–84.

48. Wigginton JE, Kirschner D. A Model to Predict Cell-Mediated Immune Regulatory Mechanisms During Human Infection with Mycobacterium tuberculosis . J Immunol. 2001;166(3):1951–67.

49. Marino S, Kirschner DE. The human immune response to Mycobacterium tuberculosis in lung and lymph node. J Theor Biol. 2004;227(4):463–86.

50. Palsson S, Hickling TP, Bradshaw-Pierce EL, Zager M, Jooss K, O'Brien PJ, et al. The development of a fully-integrated immune response model (FIRM) simulator of the immune response through integration of multiple subset models. BMC Syst Biol [Internet]. 2013;7(1):1. Available from: BMC Systems Biology

51. Sud D, Bigbee C, Flynn JL, Kirschner DE. Contribution of CD8 + T Cells to Control of Mycobacterium tuberculosis Infection . J Immunol. 2006;176(7):4296–314.

52. Holczer M, Hajdú B, Lőrincz T, Szarka A, Bánhegyi G, Kapuy O. A double negative feedback loop between MTORC1 and AMPK kinases guarantees precise autophagy induction upon cellular stress. Int J Mol Sci. 2019;20(22).

53. Bradshaw EL, Spilker ME, Zang R, Bansal L, He H, Jones RDO, et al. Applications of Quantitative Systems Pharmacology in Model-Informed Drug Discovery: Perspective on Impact and Opportunities. CPT Pharmacometrics \& Syst Pharmacol [Internet]. 2019;8(11):777–91. Available from: https://ascpt.onlinelibrary.wiley.com/doi/abs/10.1002/psp4.12463

7

54. Chen EP, Bondi RW, Michalski PJ. Model-based Target Pharmacology Assessment (mTPA): An Approach Using PBPK/PD Modeling and Machine Learning to Design Medicinal Chemistry and DMPK Strategies in Early Drug Discovery. J Med Chem. 2021;

55. Zhou Y, Wang F, Tang J, Nussinov R, Cheng F. Artificial intelligence in COVID-19 drug repurposing. Lancet Digit Heal [Internet]. 2020;2(12):e667–76. Available from: http://dx.doi.org/10.1016/S2589-7500(20)30192-8

56. Ernest JP, Strydom N, Wang Q, Zhang N, Nuermberger E, Dartois V, et al. Development of New Tuberculosis Drugs: Translation to Regimen Composition for Drug-Sensitive and Multidrug-Resistant Tuberculosis. Annu Rev Pharmacol Toxicol. 2021;61:495–516.

57. Ding Y, Raterink R-J, Marín-Juez R, Veneman WJ, Egbers K, van den Eeden S, et al. Tuberculosis causes highly conserved metabolic changes in human patients, mycobacteria-infected mice and zebrafish larvae. Sci Rep. 2020 Jul;10(1):11635.

58. Ahmed M, Thirunavukkarasu S, Rosa BA, Thomas KA, Das S, Rangel-Moreno J, et al. Immune correlates of tuberculosis disease and risk translate across species. Sci Transl Med [Internet]. 2020;12(528). Available from: https://stm.sciencemag.org/content/12/528/eaay0233

59. van Steijn L, Verbeek FJ, Spaink HP, Merks RMH. Predicting Metabolism from Gene Expression in an Improved Whole-Genome Metabolic Network Model of Danio rerio. Zebrafish. 2019 Aug;16(4):348–62.

60. McCallum AD, Pertinez HE, Else LJ, Dilly-Penchala S, Chirambo AP, Sheha I, et al. Intrapulmonary Pharmacokinetics of First-line Anti-tuberculosis Drugs in Malawian Patients With Tuberculosis. Clin Infect Dis. 2020;(Mic):1–9.

61. Walker NF, Meintjes G, Wilkinson RJ. HIV-1 and the immune response to TB. Future Virol. 2013 Jan;8(1):57–80.

62. DiNardo AR, Nishiguchi T, Grimm SL, Schlesinger LS, Graviss EA, Cirillo JD, et al. Tuberculosis endotypes to guide stratified host-directed therapy. Med [Internet]. 2021;2(3):217–32. Available from: https://doi.org/10.1016/j.medj.2020.11.003

63. DiNardo AR, Gandhi T, Heyckendorf J, Grimm SL, Rajapakshe K, Nishiguchi T, et al. Gene expression signatures identify biologically and clinically distinct tuberculosis endotypes. medRxiv [Internet]. 2021; Available from: https://www.medrxiv.org/content/early/2021/02/07/2020.05.13.20100776

64. Lazarou G, Chelliah V, Small BG, Walker M, van der Graaf PH, Kierzek AM. Integration of Omics Data Sources to Inform Mechanistic Modeling of Immune-Oncology Therapies: A Tutorial for Clinical Pharmacologists. Clin Pharmacol Ther. 2020;107(4):858–70.

65. Coletti R, Leonardelli L, Parolo S, Marchetti L. A QSP model of prostate cancer immunotherapy to identify effective combination therapies. Sci Rep [Internet]. 2020;10(1):9063. Available from: https://doi.org/10.1038/s41598-020-65590-0

66. Azer K, Kaddi CD, Barrett JS, Bai JPF, McQuade ST, Merrill NJ, et al. History and Future Perspectives on the Discipline of Quantitative Systems Pharmacology Modeling and Its Applications. Front Physiol. 2021;12(March).

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