Prediction of Human Drug-Drug Interactions

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Patients suffering from complex diseases (infectious diseases, oncology) or several conditions (co-morbidities) require combination therapies of different drugs. Combining different drugs will potentially lead to drug-drug interactions, influencing the efficacy and safety of the treatment. Development of novel drugs that are intended to be used in combination should consider drug-drug interactions as early as possible. Even with limited data, drug-drug interactions in humans can be predicted using model-informed drug discovery and development (MID3). The concept to utilize and integrate data from *in vitro* combination experiments combined with preclinical *in vivo* data on the exposure-response relationships of the drugs in combination through a computational model-informed approach, is introduced here with tuberculosis as case study.

Some diseases require combination therapy for efficacious and safe therapy. For example tuberculosis requires treatment with at least three different antibiotics to prevent resistance development of the pathogen against one or more of the antibiotics. Combination therapy inherently has the risk of interactions between the individual drugs, so called drug-drug interactions or DDIs. The same holds for patients with different diseases (comorbidities) that require treatment with different drugs at the same time.

Drug-drug interactions between drugs that are intended to be used in combination should be considered as early as possible in drug development [1]. The prediction of DDIs from preclinical data will improve the ability to predict the total efficacy of the combination in relation to the drugs in monotherapy, as well as compared to expected additivity, i.e., the sum of all effects from the drugs when given alone. Drug-drug interactions that result in less efficacy in the combination than in a combination with one less drug should be avoided. However, combinations that result in an efficacy less than the expected additivity, but still result in more efficacy than when one drug is omitted, can be considered. Drug-drug interactions can relate to both pharmacokinetic (PK) interactions, i.e., one drug (the perpetrator) impacting the absorption, distribution, metabolism, or excretion of another drug (the victim), or pharmacodynamic (PD) interactions, i.e., the perpetrator impacting the potency or efficacy of the victim drug.

Regulatory guidelines on the investigation of DDIs are brief about the use of *in vitro* data. An innovative approach in the field, model-informed drug discovery and development (MID3) is a promising way of integrating prior information [2][3][4]. Knowledge on the relevant mechanisms of, e.g., metabolism combined with *in vitro* data can be leveraged to decide on suitable combinations of drugs without extensive experimentation [5][6]. Both *in vitro* studies as well as animal experiments can be utilized to assess the potential for PK DDIs [7]. *In vitro* studies make use of metabolically active hepatocytes or cells overexpressing drug transporters to determine the PK interaction potential of a new drug [8]. When studying DDIs in preclinical species, for example mice[9] or zebrafish [10], the between-species differences in transporters or enzymes should be taken into account [11].

Pharmacokinetic DDIs mostly impact drug clearance by the induction or inhibition of metabolic enzymes like those from the cytochrome P450 (CYP) family and, to some extent, ATP-binding cassette (ABC) transporters and transport proteins. Such an interaction by the perpetrator drug will greatly enhance or reduce the exposure of the victim drug. An example from tuberculosis therapy is the fact that rifampicin induces bedaquiline clearance 5-fold, and should therefore not be combined for therapy[12]. Because bedaquiline has a very long terminal half-life, potential DDIs are difficult to identify using traditional methods, whereas properly designed experiments and quantitative modeling are necessary to elucidate such interactions [13].

Drug distribution can also be impacted because of the induction or inhibition of drug transporters like the permeability glycoprotein (P-gp), which is present on the canalicular membrane and blood-brain barrier, among others. Physiology based pharmacokinetic modeling (PBPK) can be very successful to predict metabolic DDIs, and specific DDI studies can be assisted by modeling and simulations [14].

Some anti-tuberculosis drugs are reported to be substrates for different hepatic enzymes or known to be inducers or inhibitors of metabolic enzymes. Rifampicin is well known as a CYP3A4 modulator [15][16], as well as an inducer of P-gp [17]. Additionally, even though the effect of clofazimine on CYP3A4 and P-gp is still unclear, clofazimine has been shown to delay the time taken to reach C_{max} of rifampicin [18]. Horita et al. studied the effects of anti-TB and antiretroviral drugs on CYP3A4 and P-gp, and they found that clofazimine exhibits weak inductive effects on CYP3A4 [19]. Furthermore, the co-administration of bedaquiline and clofazimine has been reported to increase the risk of QT prolongation potentially resulting in cardiac adverse events [20][21]. As described above, these potential DDIs can be predicted from *in vitro* data through, for example, *in vitro-in vivo* scaling [22] or

PBPK [23]. A transcription/translation model and a PBPK model have been developed to predict rifampicin-induced DDIs with reasonable accuracy [24].

In contrast to PK interactions, due to clearly defined processes of absorption, distribution, metabolism, and excretion, PD interactions are harder to investigate and quantify. This is because, since a clinical DDI study has to study the drugs both alone and in combination, the number of arms in the study will substantially increase when studying three or more interacting drugs. The Greco model [25], which is derived from Loewe additivity, was developed to assess PD interactions. However, such a model suffers from being limited to interactions between only two drugs. On the other hand, the general pharmacodynamic interaction (GPDI) model overcomes this limitation, in addition to being flexible to different drug interaction data without requiring knowledge on the modes of action of the studied drugs [26]. The GPDI model-based approach proposes a PD interaction to be quantifiable, as multidirectional shifts in drug efficacy (E_{max}) or potency (EC_{50}) and explicates the drugs' role as victim, perpetrator or even both at the same time. The GPDI model has been utilized along with the multistate tuberculosis pharmacometric (MTP) model [27] to develop a model-informed preclinical approach for the prediction of PD interactions [28]. The MTP-GPDI model has been further employed to successfully evaluate and quantify the PD interactions of anti-TB drug combinations in mice [29]. Furthermore, it has been demonstrated that the GPDI model outperforms conventional methods in the evaluation of PD interactions for TB drugs [30].

It is clear that the need for a combination therapy of TB could potentially result in DDIs in the clinic. It is therefore essential to quantitatively understand the DDIs, both PK- and PD-interactions, as early as possible in drug development. Utilizing data from *in vitro* combination experiments combined with preclinical *in vivo* data on the exposure-response relationships of the drugs in combination and early clinical data, will inform on which combinations of drugs at which doses are efficacious and safe for patients. This quantitative integration of data and translation to the clinic is possible through the MID3 model-informed framework.

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Keywords

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