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Top-down and bottom-up modeling in system pharmacology to understand clinical efficacy: An example with NRTIs of HIV-1

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ABSTRACT

A major aim of Systems Pharmacology is to understand clinically relevant mechanisms of action (MOA) of drugs and to use this knowledge in order to optimize therapy. To enable this mission it is necessary to obtain knowledge on how in vitro testable insights translate into *clinical* efficacy. Mathematical modeling and data integration are essential components to achieve this goal.

Two modeling philosophies are prevalent, each of which in isolation is not sufficient to achieve the above described: In a 'top-down' approach, a minimal pharmacokinetic–pharmacodynamic (PK–PD) model is derived from- and fitted to available clinical data. This model may lack interpretability in terms of mechanisms and may only be predictive for scenarios already covered by the data used to derive it. A 'bottom-up' approach builds on mechanistic insights derived from in vitro/ex vivo experiments, which can be conducted under controlled conditions, but may not be fully representative for the in vivo/*clinical* situation.

In this work, we employ both approaches side-by-side to predict the *clinical* potency (IC_{50} values) of the nucleoside reverse transcriptase inhibitors (NRTIs) lamivudine, emtricitabine and tenofovir. In the 'top-down' approach, this requires to establish the dynamic link between the intracellularly active NRTI-triphosphates (which exert the effect) and plasma prodrug PK and to subsequently link this composite PK model to viral kinetics. The 'bottom-up' approach assesses inhibition of reverse transcriptase-mediated viral DNA polymerization by the intracellular, active NRTI-triphosphates, which has to be brought into the context of target cell infection. By using entirely disparate sets of data to derive and parameterize the respective models, our approach serves as a means to assess the clinical relevance of the 'bottom-up' approach.

We obtain very good *qualitative* and *quantitative* agreement between 'top-down' vs. 'bottom-up' predicted IC_{50} values, arguing for the validity of the 'bottom-up' approach. We noted, however, that the 'top-down' approach is strongly dependent on the sparse and noisy intracellular pharmacokinetic data. All in all, our work provides confidence that we can translate in vitro parameters into measures of clinical efficacy using the 'bottom-up' approach. This may allow to infer the potency of various NRTIs in inhibiting e.g. mutant viruses, to distinguish sources of interaction of NRTI combinations and to assess the efficacy of different NRTIs for repurposing, e.g. for pre-exposure prophylaxis.

1. Introduction

The clinical efficacy of many drugs is not well understood, partly due to a knowledge gap between pre-clinical and clinical science, and a lack of 'translational models' that can fill this gap (Visser et al., 2013). 'Systems Pharmacology' aims to overcome this apparent gap by integrating pre-clinical knowledge and methods from Systems Biology with clinical pharmacology. The ultimate goal is to understand the *clinically* relevant mechanisms of action of drugs and to use this knowledge to optimize therapy in a way that achieves maximum effect and minimal toxicity in a given individual (Sorger et al., 2011).

Understanding the clinical efficacy of drugs represents a formidable task of reducing the vast complexity of intra- & inter-cellular and systemic crosstalk to a minimal set of important processes that alter a compound's efficacy. Typically two approaches are used in this context, which we will refer to as the 'top-down' vs. the 'bottom up' approach. The former utilizes clinical data, which is notoriously difficult and expensive to obtain and aims to fit a minimal model to the data that can approximate the behavior of the underlying complex system sufficiently well. By fitting a minimal model, this approach may lack interpretability in terms of molecular & physiological processes and may only be predictive in treatment/disease scenarios that are somehow already covered by the data used to generate the 'top-down' model.

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The 'bottom-up' approach on the other hand builds on pre-clinical experiments, which can be conducted under controlled conditions, but at the same time may not be fully representative for the in vivo/*clinical* situation. Critical tasks are validation and the integration of dynamic processes that may occur on various time scales (Schmidt et al., 2011). The 'bottom-up' approach will eventually yield a valid molecular mechanism of action (MMOA) model, allowing to forecast therapeutic scenarios not yet tested clinically. In the MMOA model, one can typically assess the compounds efficacy to inhibit a target process based on target-site concentrations. 'Top-down' approaches require a wealth of clinical data to be able to achieve the same goal: if plasma, target-site pharmacokinetics, drug response profiles and a (semi-) mechanistic model of the disease process is available, one may be able to predict a compounds potency/IC_{50} based on target-site concentrations in terms of target process inhibition. However, this is usually only possible after a complete pharmacokinetics model has been established that links drug administration, plasma pharmacokinetics and drug concentrations at the target site. Obviously, the inability to conduct particular experiments clinically also constraints the insights derived from such a model. However, a 'top-down' model could be used to validate a 'bottom-up' approach that, if valid, may answer many of these questions.

Within this work we assess the clinical validity of a MMOA model (von Kleist et al., 2012) for the class of nucleoside reverse transcriptase inhibitors (NRTIs) of HIV-1. NRTIs are used as backbone components in virtually all combinations therapies (highly active antiretroviral therapy, HAART) against HIV-1. They are nucleoside analogs, which are administered as prodrugs and, after entering HIV target cells (Stevenson, 2003), undergo sequential phosphorylation to form the active triphosphate moiety (NRTI-TP) (Jordheim et al., 2013). The intracellular NRTI-TP competes with endogenous deoxynucleoside triphosphate (dNTP) for incorporation into nascent viral DNA during reverse transcription, effectively halting the process once incorporated. If the virus does not succeed to reverse-transcribe its genome, the virus will eventually be cleared intracellularly, before hijacking the cell to produce new viral particles. Consequently, the developed MMOA model (von Kleist et al., 2012) will be used to compute the extent of inhibition of reverse transcription & host cell infection based on NRTI-TP and its endogenous competitor (dNTP) concentrations present within target cells (see Fig. 1, left).

Because the pharmacokinetics of active NRTI-TP are poorly predicted by the pharmacokinetics of the parent compound (NRTI) in the blood plasma (Sharma et al., 2004; Bazzoli et al., 2010), for any 'top-down' approach it is necessary to establish the dynamic link between the plasma NRTI and intracellular NRTI-TP concentrations. This link, however, has only been established in very few cases (von Kleist and Huisinga, 2009; Hurwitz et al., 2007; Duwal et al., 2012). Furthermore, in order to predict the compounds' efficacy, intracellular NRTI-TP concentrations need to be linked to clinically observed viral dynamics after monotherapy (see Fig. 1, right). We will attempt the 'top-down' approach for the NRTIs, emtricitabine (FTC), lamivudine (3TC) & tenofovir disoproxil

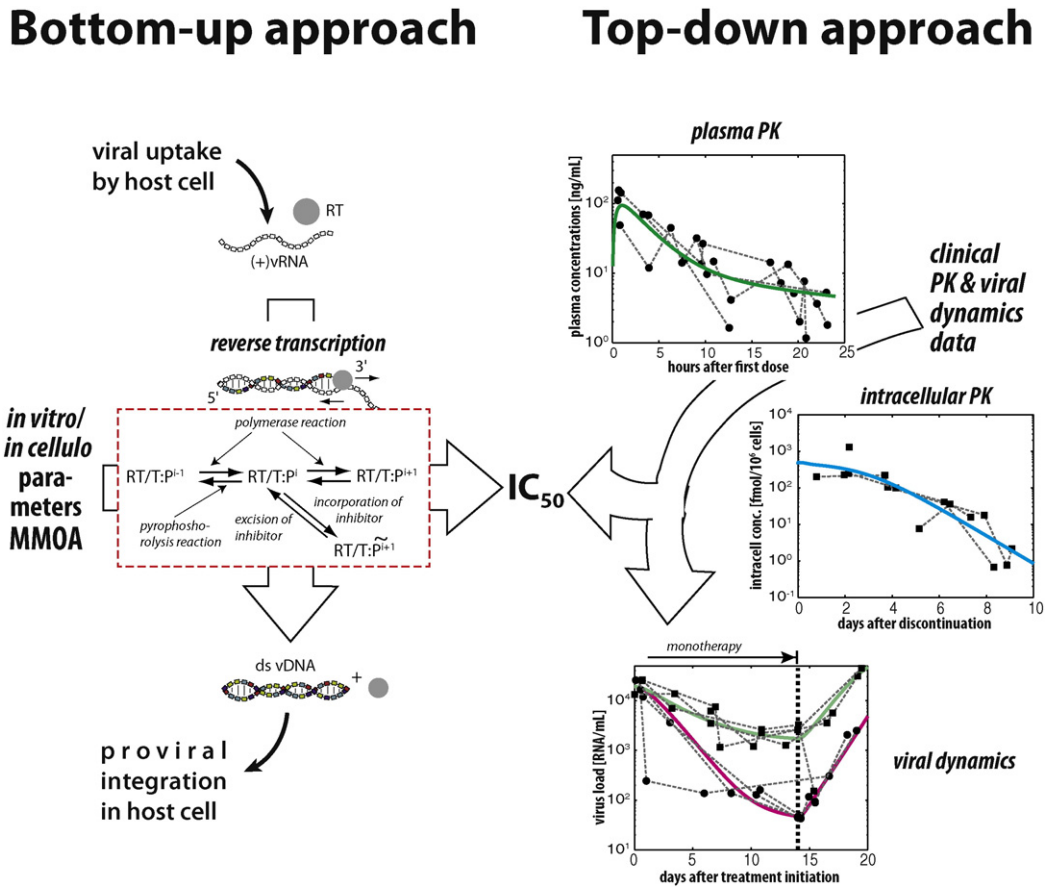

Fig. 1. Schematic of the two approaches used in this article to infer in vivo drug potency. We use two modeling strategies to infer the NRTI-TP concentration that inhibits target cell infection by 50% (IC_{50}). In the 'bottom-up' approach (left) we explicitly model inhibition of reverse transcription by NRTI-TP and take in vitro kinetic parameters, as well as ex vivo physiological parameters as input. The central box depicts the types of reactions that occur during RT-induced DNA polymerization. A reverse transcriptase bound template:primer complex $RT/T:P^i$ can undergo four basic reactions: (i) The primer may be shortened by one nucleotide during the exonuclease reaction $RT/T:P^i \rightarrow RT/T:P^{i-1}$. (ii) The primer may be extended by one base during the polymerase reaction $RT/T:P^i \rightarrow RT/T:P^{i+1}$, (iii) the NRTI-TP may be incorporated and the primer blocked $RT/T:P^i \rightarrow RT/T:\tilde{P}^{i+1}$. In addition (iv) an incorporated NRTI may be excised from the blocked primer $RT/T:\tilde{P}^{i+1} \rightarrow RT/T:P^i$. In the 'top-down' approach (right) we use pharmacokinetic (PK) data (plasma NRTI and intracellular NRTI-TP concentrations) to successively build and validate a composite PK model that links oral pro-drug administration to intracellularly active NRTI-TP. The composite PK model is then linked to an established HIV-1 dynamics model (von Kleist et al., 2010, 2011) and used to predict clinically observed, mono-therapy induced viral dynamics via fitting an Emax model.