Application of the target-mediated drug disposition approach within a minimal PBPK model to investigate pharmacokinetics of therapeutic proteins

Eric P.M. Grist, Iain Gardner, Manoranjenni Chetty, Krishna K. Machavaram
Simcyp Limited, Sheffield, UK
e.grist@simcyp.com

Simcyp Ltd, Blades Enterprise Centre, John St, Sheffield, S2 4SU, UK

Background

Drugs such as therapeutic proteins which bind with high affinity to pharmacologic targets often exhibit a decrease in the volume of distribution and clearance (CL) as the dose is increased. Mager and Jusko (2001) [1] developed a general pharmacokinetic model for describing such ‘Target Mediated Drug Disposition’ (TMDD), as shown schematically in Figure 1. This phenomenon is particularly important for therapeutic proteins because they bind with high affinity to the target receptor and the drug-target complex is prone to degradation once internalised within the cell. Gribbinsky et al (2008) [2] provided an equivalent Quasi-Equilibrium (QE) approximation to this model for when $k_{on}$ and $k_{off} \gg k_{deg}$ in which $k_{off} k_{on}$ is given by an equilibrium dissociation constant $K_d$.

![TMDD Model](image)

**Figure 1. Schematic diagram of the TMDD model proposed by Mager and Jusko 2001 [1]**

**Objectives**

We demonstrate how an equivalent dynamic representation to the target mediated drug disposition (TMDD) model proposed by Mager and Jusko [1] can be achieved through ‘embedding’ the TMDD model within the systemic compartment of the minimal-PBPK model with single adjusting compartment (SAC) employed in the Simcyp simulator[3] as shown in Figure 2.

**Results**

A comparison of the PK profiles generated by the minimal-PBPK with embedded TMDD model with those of the separate TMDD model confirmed that both representations produced equivalent output. The plasma concentration profiles with TMDD and SAC operative gave good matches to the published clinical data for Erythropoietin [4] for doses ranging from 0.0625 to 3.125 microg/kg as shown in Figure 3 (A) below.

![PK Profiles](image)

**Figure 3. Profiles generated by the MPBP with embedded TMDD (QE) model, parameterized for EPO at doses from 0.0625 to 3.125 microg/kg as in Woo et al (2007), illustrating the significance of TMDD on plasma and tissue concentrations with time. Vertical Scale: Logarithmic Base 10. Systemic (or central) compartment with superimposed EPO data obtained by Woo et al (2007) [4] (circles): (A) with TMDD and (B) without TMDD. Respective tissue (or SAC) compartment profiles are shown in (C) with TMDD and (D) without TMDD.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
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<tbody>
<tr>
<td>$R_{max}$</td>
<td>Total binding capacity in blood 0.000136 [microM]</td>
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<tr>
<td>$k_{pt}$</td>
<td>Rate constant of non-specific tissue binding 0.0359 [per h]</td>
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<tr>
<td>$k_{ct}$</td>
<td>Rate constant of non-specific tissue distribution 0.1151 [per h]</td>
</tr>
<tr>
<td>$k_{deg}$</td>
<td>Rate constant of DR internalisation and degradation 0.2216 [per h]</td>
</tr>
<tr>
<td>$K_d$</td>
<td>Apparent zero order production of free receptors 0.0000586 [microM per h]</td>
</tr>
<tr>
<td>$K_e$</td>
<td>Equilibrium dissociation constant 0.00002 [microM]</td>
</tr>
<tr>
<td>$k_{deg}$</td>
<td>Degradation rate of free receptors 0.8974 [per h]</td>
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**Table 1. Parameter values used in simulations. All parameter values as reported in Woo et al (2007) [4] except for those * asterisked.**

Conclusions

This study demonstrates that the minimal-PBPK model with SAC as used within the Simcyp simulator can be parameterized for therapeutic proteins to be dynamically equivalent to the TMDD model of Mager and Jusko (2001) [1]. Hence the minimal-PBPK model within the Simcyp simulator can be employed to explore the influence of key TMDD parameters (such as $R_{max}$, $K_d$ and affinity of binding to target) on compound disposition. In addition inclusion of the single adjusting compartment allows distribution into tissues other than the liver to be accounted for. The systems approach adopted here will enable semi-mechanistic modelling of many therapeutic proteins.

References