The use of physiologically-based pharmacokinetic modeling in the design of pH-dependent target binding antibodies

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Introduction and Objectives

A known limitation of biologic therapies is the inability to deliver high doses to patients due to cost of goods, patient convenience, and other factors
It is also known that increasing target affinity does not always increase potency beyond a certain limit.
Reducing the binding affinity of therapeutic proteins to their target within acidic endosomal space is a strategy to increase the half-life and in vivo potency of these drugs [1,2].
However, identification of the optimum affinity to associate at plasma pH and dissociate at endosomal pH poses a challenge since this is likely to depend on various factors including target levels, turnover rates, achievable plasma affinity, etc.
A trial-and-error approach to the design of these molecules is likely to be resource-intensive due to protein engineering needs.

The aim of the study was to investigate if physiologically-based pharmacokinetic (PBPK) modeling can be used to help design high potency pH-dependent recycling antibodies.

Specific objectives of the work included:

- Could existing physiologically-based models of antibody drugs be modified to describe pH-dependent processes in detail?

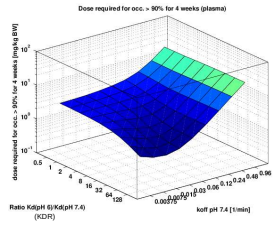
- Could the modified models be used to predict the in vivo disposition of an unmodified and modified antibody, described in literature?

- Assess what limitations exist in translating in vitro data to in vivo disposition predictions for such molecules.

Results: The relationship between affinity and target blocking potency is complex

A non-monotonic relationship exists between KDR and affinity

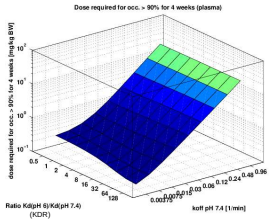
Soluble target, plasma conc.: 10 nM



The increase in potency over an optimum affinity non-pH binding antibody is ~75% (4-fold lower dose) at KDR~100 and k_{off} (pH7.4)= 0.015 min^{-1}

The optimal KDR depends on the level of soluble target

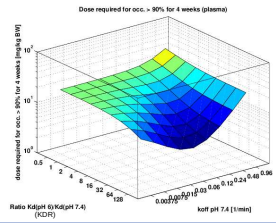
For lower target levels (1 nM), the increase in potency due to pH binding is less pronounced



Soluble target, plasma conc.: 1 nM

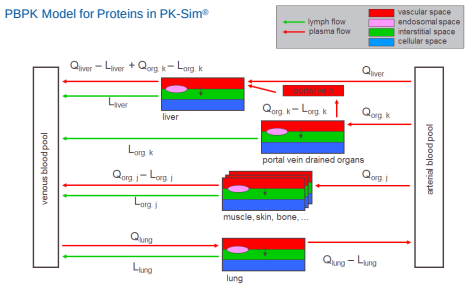
Same for a membrane bound target (IL-6R)

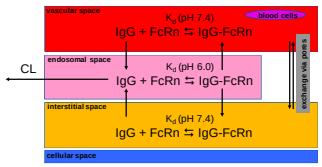
Membrane bound target



A similar bell-shaped affinity potency relationship exists for membrane-bound targets also

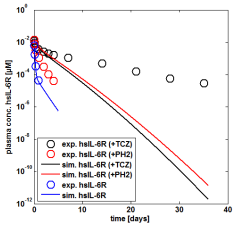
Description of the mathematical model

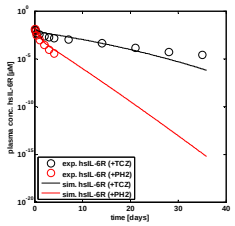




- The pharmacokinetic data [2] of pH-dependent binding variants of tocilizumab (TCZ), an antibody against the IL-6 receptor (IL-6R), was predicted in this case study.
- For experiments with soluble target (hsIL-6R) in wild-type mice the standard PK-Sim® [3] model for proteins was extended by hsIL-6R binding in interstitial space (pH 7.4) and endosomal space of vascular endothelium (assumed pH 6). For experiments with effective membrane bound IL-6R (transgenic mice & cynomolgus) the standard PK-Sim® mouse & monkey models for proteins were extended by membrane-bound and endosomal IL-6R in tissue cells.
- The processes of biosynthesis, endocytosis & recycling were introduced.

Results: The in vitro affinities do not adequately predict in vivo PKPD for this combination of data and model





- The reported Kd values were used to predict in vivo behaviour (left): adequate description was NOT achieved
- Changing the in vivo affinities by 4-fold (right) resulted in an acceptable description of observed data in [2]

Discussion and Conclusions

The relationship between the KDR and KDs at individual pH for antibodies is complex; mathematical modelling can help in identifying this "sweet spot" since it is a complex function of "system properties" - antigen load, turnover rate, other competing ligands, etc.

- A prediction of the PK of antibodies with pH dependent target binding based on BIAcore binding assays and PBPK modeling was not possible. Potential reasons for this include limitations of in vitro measurements, measurements at pH 6 do not reflect physiologic conditions (exact pH of endosomal space not known but levels below pH 6.0 are reasonable).
- The structure of the PBPK model may neglect potentially relevant biological and physico-chemical processes and properties.
- In spite of these limitations, mathematical modelling provides a useful tool for design of new biologic modalities such as pH-dependent binding antibodies.

[1] C.S. Sarkar et al., Nat. Biotechnol. 20, 908-913 (2002);
[2] T. Igawa et al., Nat. Biotechnol. 28, 1203-1207 (2010)
[3] S. Willmann et al., Biosilico. 1, 121-124 (2003)

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