

Title: Predicting Affinity and Dose for an Antibody Inhibiting Target Dimerization

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Objectives:

The present study aims to predict the dose and affinity (K_D) of a therapeutic antibody (Ab) required to achieve a prescribed efficacy in humans. We consider the case for which the disease progression is driven by the dimerization and activation of 2 cell surface receptors (R1 and R2). The Ab blocks heterodimerization of the receptors. In this study, efficacy is defined as the decrease in the number of R1-R2 dimers in the diseased tissue relative to the number of R1-R2 dimers without treatment.

Methods:

A 3-compartment PK/PD model was developed to predict the amounts Ab, receptors, and bound species as a function of time following *i.v.* injection in a human (Figure 1). We assumed bi-directional distribution of the Ab between plasma and interstitium via passive exchange across the vascular endothelium. In addition, we included convective transport of the Ab from the interstitium to the plasma via lymph flow. Clearance from the plasma compartment was based upon the 21-day half-life typical of this IgG isotype. We also included Ab-receptor binding and receptor dimerization. The latter occurs in various tissues; however, it is linked to abnormal signaling only in the diseased tissue. Therefore, dimerization was only considered in the diseased tissue.

The model was formulated as a system of ordinary differential equations and solved with MATLAB (v.7.1, The Mathworks, Natick, MA).

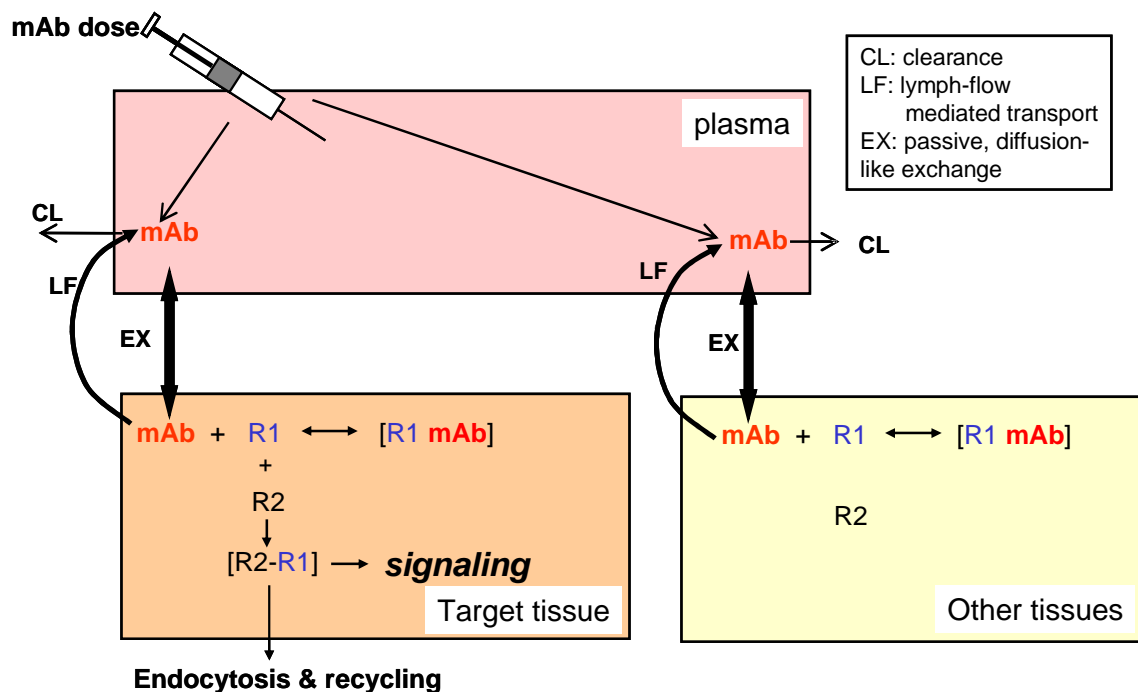


Figure 1. Model schematic.

Results:

We used the model to explore Ab efficacy in various biological contexts and simulated dose-response curves for doses ranging from 0.001 to 100 mg/kg administered regularly every 3 weeks.

First, we assumed uniform expression of receptor R1 in all tissues. The model predicts 95% efficacy at a dose of 1 mg/kg every 3 weeks and $K_D = 0.5$ nM (Figure 2A) for a disease driven by R1-R2. Lower doses require higher Ab affinity, particularly if R1 expression in diseased tissue is higher than in the rest of the body (Figure 2B).

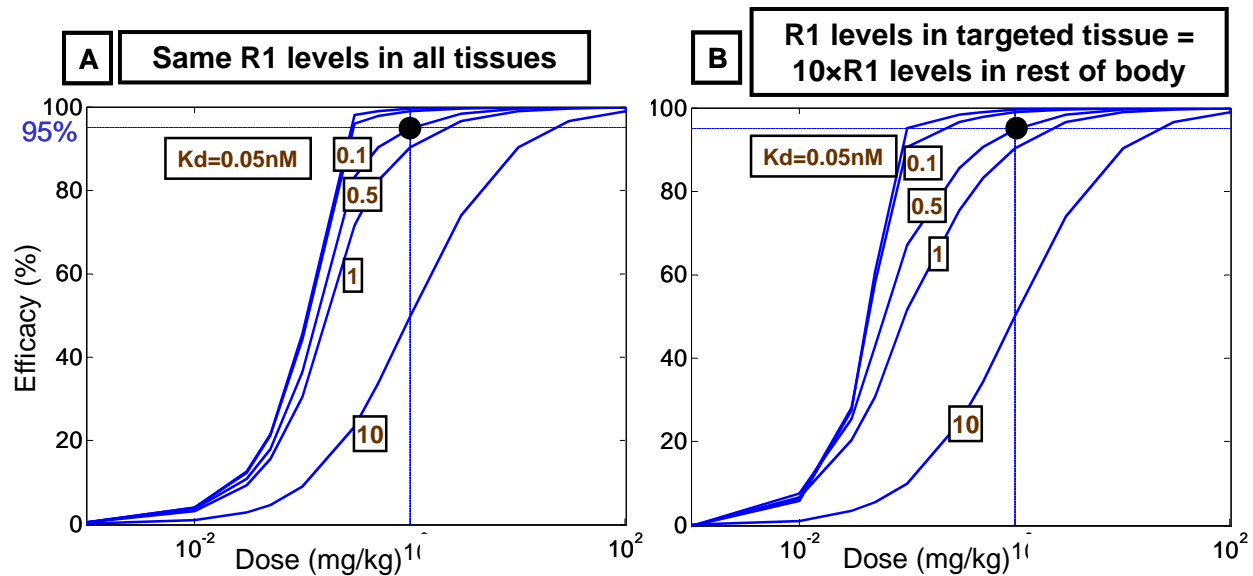


Figure 2: Dose-response curves for the case in which (A) the target receptor R1 is expressed at the same level in diseased tissues as in other tissues and (B) the target receptor is overexpressed 10-fold in the diseased tissue.

We also considered the case in which the co-receptor R2 is overexpressed 10-fold. For this case, higher doses are required to reach similar Ab efficacy. For example, for $K_D = 0.5$ nM, a dose of 3 mg/kg is required instead of 1 mg/kg (data not shown).

Conclusions:

An Ab PK/PD model was developed to predict the affinity and doses required to achieve desired efficacy in humans. At $K_D = 0.5$ nM, the model predicts that a dose of 1 mg/kg is required to obtain 95% efficacy. The receptor expression level in normal tissues is more critical at smaller doses (< 0.5 mg/kg) or higher affinities ($K_D \leq 0.1$ nM). For example, an Ab with $K_D = 0.05$ nM yields 95% efficacy, at a dose of 0.08 mg/kg when R1 expression is 10-fold less in normal tissue as compared to a dose of 0.2 mg/kg when R1 expression is the same in all tissues. In patients with 10-fold R2 overexpression, a 3-fold larger dose is required to achieve 95% efficacy.