

Predicting Affinity & Dose for an Antibody Inhibiting Target Dimerization

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Abstract

Objective : Predict dose & affinity (Kd) of a therapeutic antibody (Ab) to achieve a prescribed efficacy in humans when target is a receptor that dimerizes to signal.

Method : Develop a mechanistic PK/PD model that incorporates target binding and dimerization.

Results :

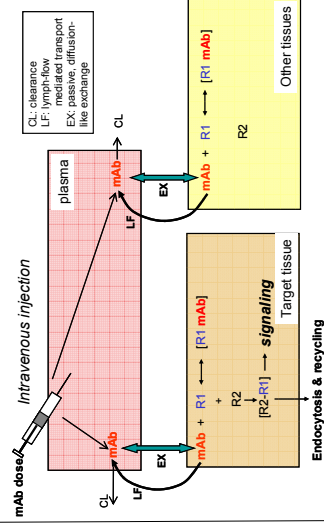
- Dose required for 95% efficacy at current Ab affinity.
- Importance of target receptor (R1) levels in tissues other than target tissue on efficacy results.
- Influence of dimerization receptor (R2) expression levels in target tissue on efficacy results.

Background

- Disease progression driven by dimerization + activation of 2 cell surface receptors (R1 and R2).
- Ab blocks heterodimerization of receptors.
- Efficacy 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

Model diagram

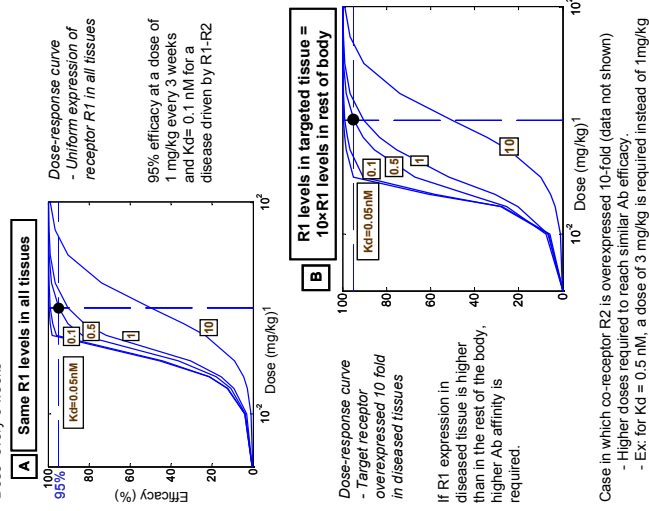


Model diagram : mAb is injected and distributed to tissue. It binds to the target receptor R1. In targeted tissue only, R1 binds to R2 to lead to abnormal signaling. The complex R1-R2 is endocytosed and recycled.

- Model structure : set of ODE's written in Matlab
- Model output: amounts of Ab, receptors, and bound species as a function of time
- Clearance from the plasma compartment based upon the 21-day half life typical of this IgG isotype.

Results

Dose every 3 weeks



Case in which co-receptor R2 is overexpressed 10-fold (data not shown)
 - Higher doses required to reach similar Ab efficacy.
 - Ex: for Kd = 0.5 nM, a dose of 3 mg/kg is required instead of 1 mg/kg

Conclusion

An Ab PK/PD model was developed to predict the affinity and doses required to achieve desired efficacy in humans.

- At Kd = 0.5 nM, the model predicts 95% efficacy achieved at 1mg/kg.
- Target receptor (R1) levels in other tissues more important at smaller dose (<0.5nM) or higher affinity (Kd<0.1nM)
 Ex: High affinity Ab (Kd=0.05nM) yields 95% efficacy at:
 - 0.08mg/kg when R1 10X less expressed in other tissues
 - 0.2mg/kg when R1 levels same in all tissues
- In patients with 10 fold R2 overexpression, a 3x larger dose required to achieve 95% efficacy

Future directions

- Investigate other endpoints for efficacy
- Incorporate more dimerization partners in the model
- Incorporate signaling molecules downstream of receptor dimer, possibly the whole pathway.