Predicting the Free Target Levels Based on Total drug and Total Target Levels for Monoclonal Antibodies

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Background

- In monoclonal antibody (mAb) development the earliest downstream biomarker is target engagement
- Free soluble target levels often cannot be measured directly, and are therefore predicted by using a target mediated drug disposition (TMDD) model of the drug and total target kinetics
- The accuracy of these predictions has never been systematically assessed across compounds and targets
- We use insights from steady state *Averaged Free target concentration to Initial target concentration Ratio* (AFIR) [1] to evaluate the prediction of free target levels based on total drug and total target levels

Methods

AFIR calculation

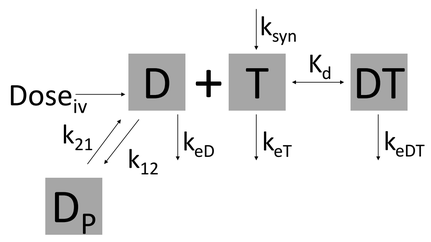

Figure 1: Illustration of a typical TMDD model [2].

- For the TMDD model shown in Figure 1, the average target inhibition at steady state can be estimated by AFIR [1]:

$$AFIR = \frac{T_{avg,ss}}{T_0} = \frac{K_d \cdot T_{acc}}{C_{avg,ss}} = \frac{K_d \cdot (k_{eT}/k_{eDT})}{C_{avg,ss}} = \frac{C_{AFIR}}{C_{avg,ss}} \quad \text{(Equation 1)}$$

- D is drug, T is free target and DT is drug-target complex
- $C_{avg,ss}$ is the average drug concentration at steady state
- K_d is the binding affinity of the drug to its target
- T_{acc} is the fold-accumulation of the total target for large doses at steady state, defined to be $T_{acc} = (k_{eT}/k_{eDT})$, where:
  - k_{eT} is the elimination rate of the free target
  - k_{eDT} is the elimination rate of the complex
- C_{AFIR} is defined to be the "AFIR Concentration" and is given by $C_{AFIR} = K_d \cdot T_{acc}$
  - C_{AFIR} is a lumped parameter that has units of concentration
  - Based on Equation 1, C_{AFIR} can be used to predict the average target inhibition of a drug
  - The accuracy and precision of the C_{AFIR} estimate is assessed in this analysis

Model Fitting

To access the accuracy and precision of C_{AFIR}, the following analysis was performed for four drugs:

1) The PK parameters estimated using the PK observations
2) The PD parameters that were fit were: baseline target $T_0 = k_{syn}/k_{eT}$ steady state target $T_{totss} = k_{syn}/k_{eDT}$, C_{AFIR}, and k_{eDT}. The rate constants were then calculated by: $k_{syn} = T_{totss} \cdot k_{eDT}$, $k_{eT} = k_{syn}/T_0$ and $K_d = C_{AFIR} \cdot k_{eDT}/k_{eT}$.
3) The PK parameters were fixed to the values estimated in step 1 and the values of the lumped PD parameters from step 2 were estimated using two different datasets:
   - PK + total target
   - PK + total target + free target
4) The two C_{AFIR} estimates from step 3 were compared

Data used

The clinical and pre-clinical data used are summarized in Table 1.

Table 1: Compounds used in this study.

Compound	Subjects type	Source
CNTO345	Diseased mice	[3]
Novartis mAb 1	Healthy humans	Novartis
Novartis mAb 2	Healthy monkeys	Novartis
Omalizumab	Diseased humans	[4]

Results

Model fit for CNTO345

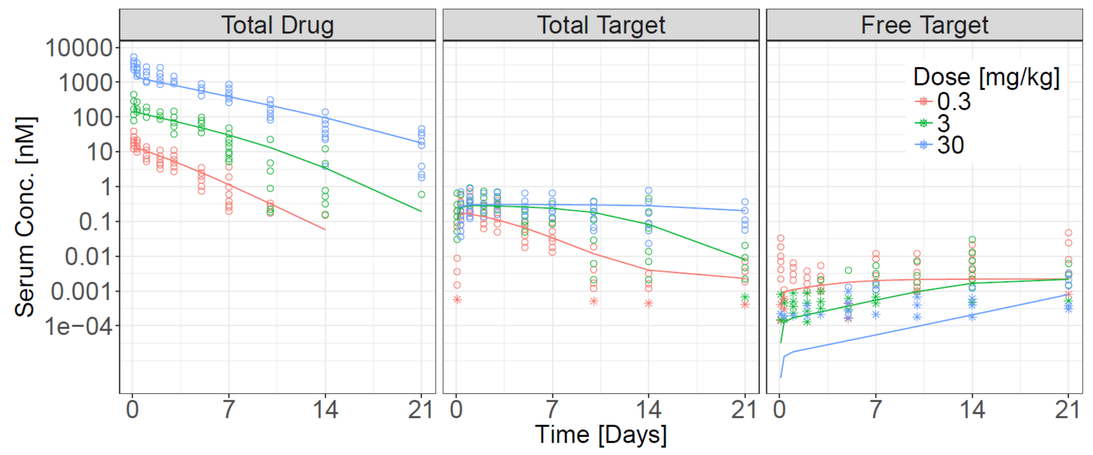

Figure 2: Model fit to CNTO345. The observations were digitized from [3]. The lines correspond to the predictions (using the dataset with PK + total target + free target data), the circles (○) correspond to the observations and asterisks (⋆) correspond to the observations below the limit of quantification.

C_{AFIR} values estimated with and without free target data (step 4)

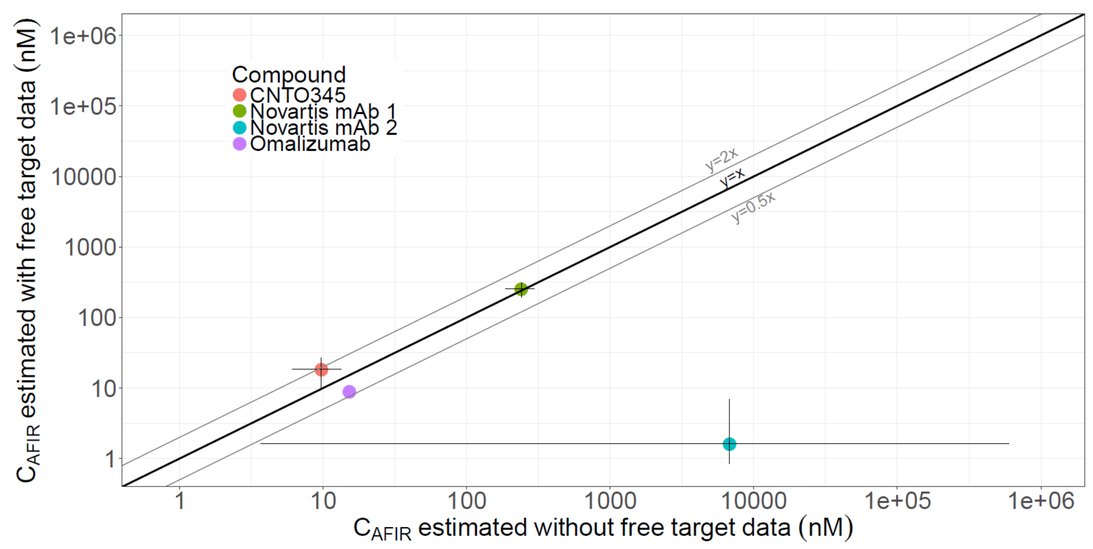

Figure 3: Relationship between the C_{AFIR} values estimated with (y-axis) and without (x-axis) free target data. The circles (●) correspond to the estimated value and the error-bars correspond to the 5th - 95th confidence interval, as calculated from the NONMEM Covariance Matrix (CNTO345), Monolix (Novartis mAb 1) or the log-likelihood profile (Novartis mAb 2). For Novartis mAb 2, the large confidence intervals (100,000-fold) indicate that insufficient data were available to estimate C_{AFIR}.

Conclusions and future work

- For three compounds, the average free target levels were predicted within 2-fold accuracy by using only the total drug and total target data.
- For one compound, the average free target levels could not be accurately predicted by using only the total drug and total target data. This is attributed to the lack of sufficient data: only single dosing data, initial target below limit of quantification and limited follow-up.
- Additional examples are currently being analyzed to assess the predictability of C_{AFIR} without the use of free target data.

References

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Acknowledgments

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