

Mechanistic model of amyloid beta ($A\beta$) and anti- $A\beta$ mAb dynamics

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Objectives: Our goal was to develop a mechanistic mathematical model capable of predicting neutralization of multiple $A\beta$ species in the brain, cerebrospinal fluid (CSF) and plasma during the course of Alzheimer's disease therapy with anti- $A\beta$ monoclonal antibodies (mAbs) that possess varying PK/PD properties.

Methods: We utilized physiological and biochemical values from the literature and internal experiments and studies, including *in vitro* crenezumab Biacore affinity data ($K_D=5$ nM for monomeric $A\beta$, 0.5 nM for oligomeric $A\beta$), to develop a model structure and estimate values for model parameters. Within the model structure we include mechanisms that describe mAb binding to soluble and insoluble $A\beta$ species, efflux rates of $A\beta$ and the mAb- $A\beta$ complex from brain to CSF, degradation rates of $A\beta$ and the mAb- $A\beta$ complex within the brain and transport of $A\beta$ across the blood brain barrier. Specifically, we consider scenarios in which the soluble $A\beta$ pool is entirely composed of monomeric $A\beta$ and scenarios in which the soluble $A\beta$ pool is entirely composed of oligomeric $A\beta$ and the impact that binding to insoluble $A\beta$ may have on binding kinetics to each soluble species. Results generated under these scenarios are supported by further extending the model to dynamically simulate the interconversion of soluble monomeric and oligomeric $A\beta$ species. The model is evaluated by its ability to

recapitulate the observed plasma PK/PD data from solanezumab [1] and crenezumab [2] clinical studies.

Results: The model was able to describe the observed plasma PK/PD data following estimation of the baseline plasma $A\beta$, plasma $A\beta$ clearance, PK and K_D parameters. The estimated *in vivo* mAb/ $A\beta$ binding affinity for crenezumab is consistent with the *in vitro* K_D value (5.7 vs. 5 nM). The impact on the neutralization of soluble $A\beta$ in brain given the affinity of the mAb to insoluble $A\beta$ pool is also demonstrated, where, during the first 12 months of treatment, the insoluble $A\beta$ pool acts as a significant sink for mAb at affinities significantly greater than 5 nM.

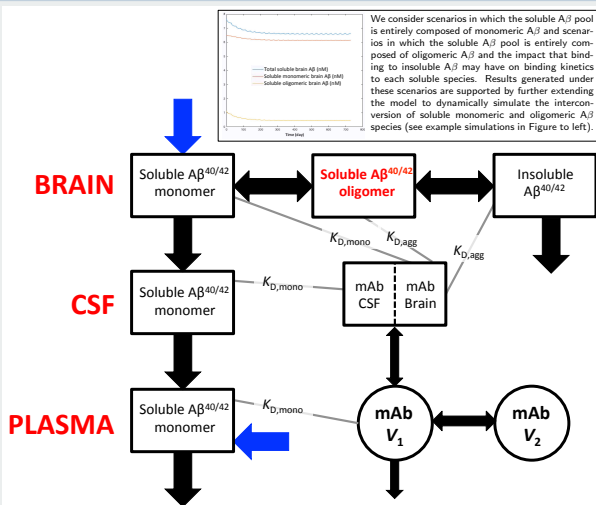
Conclusions: Our model generated predictions that yield insight into neutralization of soluble and insoluble $A\beta$ species in brain during anti- $A\beta$ mAb therapy. We also developed hypotheses regarding mechanisms such as the potentially significant impact of mAb binding to insoluble $A\beta$ pools in the brain on overall mAb/ $A\beta$ dynamics.

References

- [1] Uenaka, K. *et al.* Clin Neuropharmacol 2012.
- [2] Boxer, AL. *et al.* Alzheimers Dement 2010.

MODEL DEVELOPMENT

Key structural components of model



Key issues addressed by mechanistic model

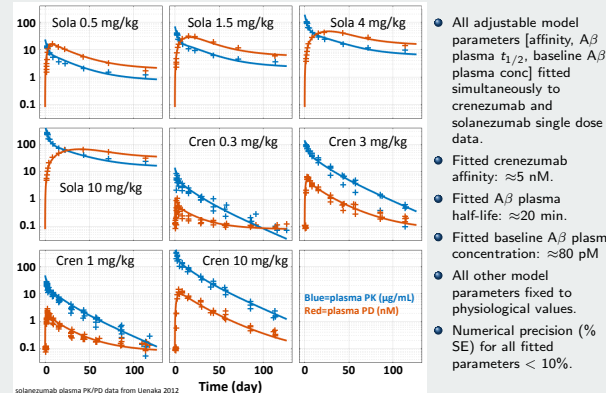
- 1 Drug / $A\beta$ binding kinetics and subsequent concentration-time profiles in brain, CSF and plasma.
- 2 Impact of insoluble $A\beta$ pool in brain on target engagement profiles.
- 3 Explicit representation of monomeric and oligomeric $A\beta$.
- 4 Note that only key model elements are depicted in this high-level schematic, e.g., transport of proteins from brain to plasma via the BBB, degradation of proteins in brain, intercompartment kinetics of mAb- $A\beta$ complex are all included in full model.

Key model parameters

Parameter	Units	Definition
$K_{D,mono}$	nM	Binding affinity of mAb for soluble monomeric $A\beta$
$K_{D,oligo}$	nM	Binding affinity of mAb for soluble oligomeric $A\beta$
$K_{D,insol}$	nM	Binding affinity of mAb for insoluble plaque $A\beta$
R_{brain}	nanomole/day	Synthesis rate of $A\beta$ in the brain (derived)
R_{periph}	nanomole/day	Synthesis rate of $A\beta$ in non-brain tissues (derived)
τ_{brain}	dimensionless	Plasma to brain mAb concentration ratio at steady state
$C_{brain,mono}$	nanomole/mL	Baseline monomeric $A\beta$ concentration in brain
$C_{brain,oligo}$	nanomole/mL	Baseline oligomeric $A\beta$ concentration in brain

Table: Subset of most critical model parameters.

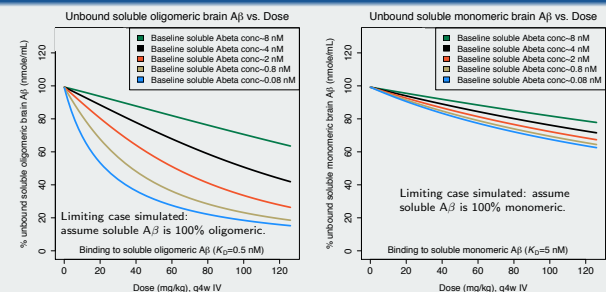
Model fitted to plasma PK and PD



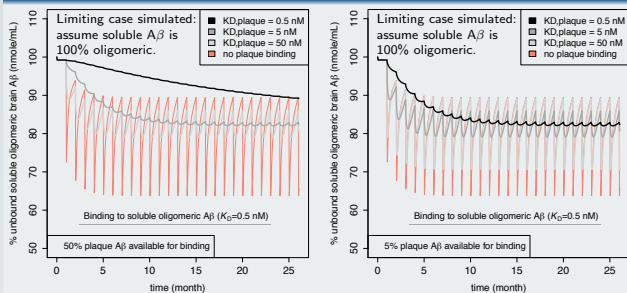
Model fitted to plasma PK/PD data gives confidence in model's ability to describe *in vivo* mAb/ $A\beta$ binding profiles.

MODEL APPLICATIONS

Simulate $A\beta$ neutralization in brain



Impact of plaque on oligomeric $A\beta$ neutralization in brain



CONCLUSIONS

- *in vivo* estimated K_D for crenezumab binding to soluble monomeric $A\beta$ (≈ 5 nM) consistent with *in vitro* estimates. Compare to much higher *in vitro* affinity of crenezumab for soluble oligomeric $A\beta$ (≈ 0.5 nM).
- Simulations suggest that once binding to plaque has reached steady state, neutralization of soluble $A\beta$ is strongly dependent not only on K_D , but our assumptions of baseline target concentration and synthesis rate.
- Simulations suggest that concentration of insoluble $A\beta$ available for binding may impact time to steady state target neutralization for both soluble and insoluble $A\beta$.