Systematic in silico analysis of clinically tested drugs for reducing amyloid beta plaque accumulation in Alzheimer's disease

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ABSTRACT

Introduction: Recent clinical trials of Aβ antibodies have established a causative relationship between plaque reduction and positive clinical and functional outcomes. Therefore, Applied Biomath undertook an exercise to quantitatively assess the antibody characteristics that predict Aβ plaque clearance by evaluating the effect of various classes of anti-Aβ therapeutic approaches to better predict potential clinical benefit. We developed a quantitative systems pharmacology (QSP) model using eight different Aβ targeting approaches (aducanumab, lecanemab, crenezumab, solanezumab, bapineuzumab, elenbecestat, verubecestat, and semagacestat).

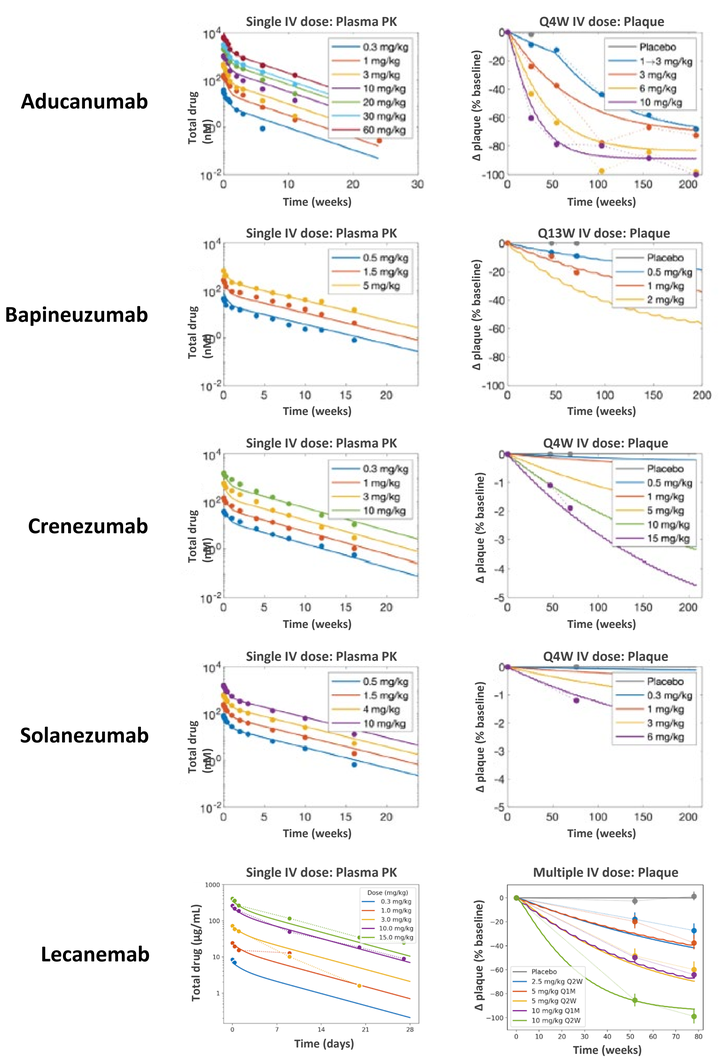
Methods: Ordinary differential equations were used to model the production, transport, and aggregation of Aβ; pharmacology of the drugs; and their impact on plaque.

Results: The calibrated model predicts that endogenous plaque turnover is slow, with an estimated half-life of 2.75 years. The model indicates that binding to plaque and inducing antibody-dependent cellular phagocytosis (ADCP) predicts CNS Aβ plaque reduction. This conclusion is further supported by results from inhibitors of Aβ production (e.g. cleavage and secretase inhibitors), monomer-selective antibodies (e.g. solanezumab), and antibodies with reduced Fc-mediated effector function (e.g. crenezumab) that all show relatively little plaque reduction.

Discussion: A QSP model calibrated to clinical data from investigational drugs with different target species and modalities enables meaningful comparisons between potential therapeutic strategies. The model simulations provide novel insights into clinical results and guidance for future therapeutic development.

MODEL CALIBRATION

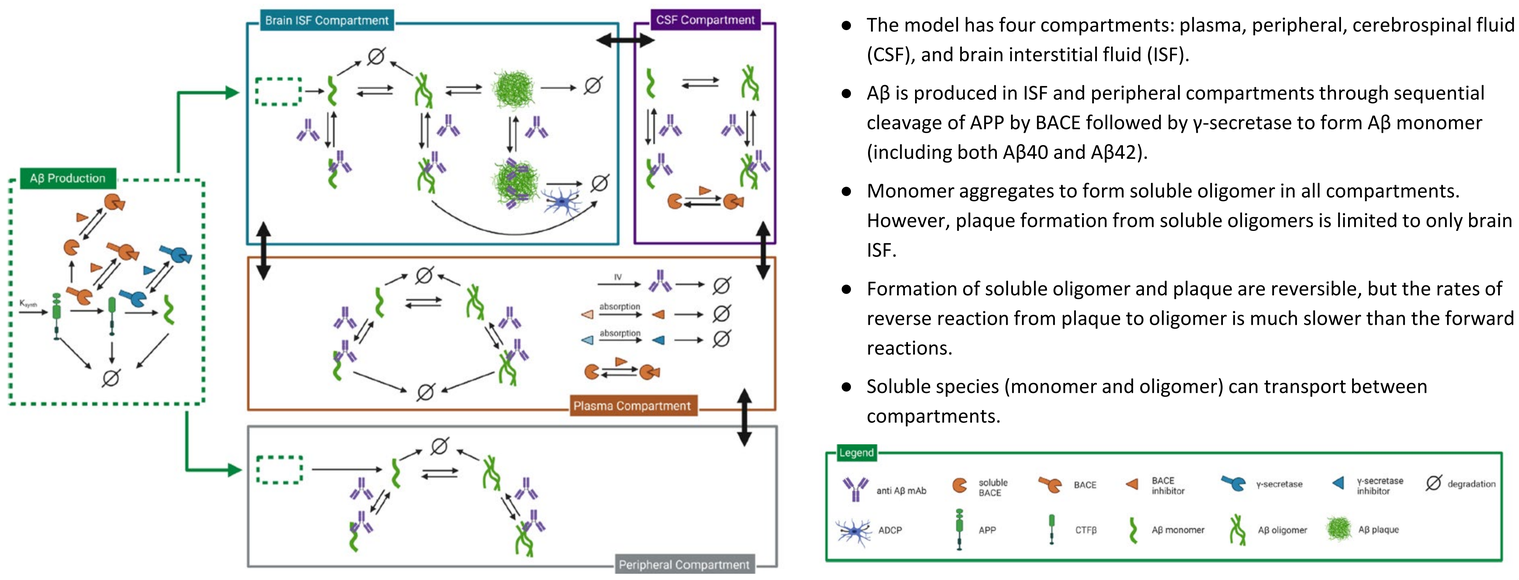
Figure 2. Calibration to clinical PK and amyloid PET data for five anti-Aβ mAbs.



- Differences between mAbs are represented in the model by drug-specific PK parameters and binding affinities to different Aβ species, as well as FcγR, which mediates antibody-dependent cellular phagocytosis (ADCP).
- Literature-derived affinity values were adjusted to fit plaque reduction data.

QSP MODEL DIAGRAM

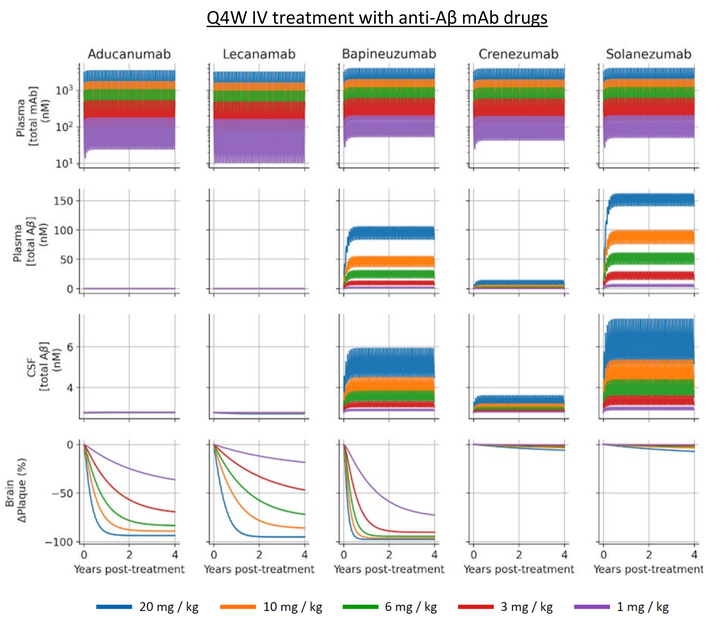
Figure 1. Model diagram.



- The model has four compartments: plasma, peripheral, cerebrospinal fluid (CSF), and brain interstitial fluid (ISF).
- Aβ is produced in ISF and peripheral compartments through sequential cleavage of APP by BACE followed by γ-secretase to form Aβ monomer (including both Aβ40 and Aβ42).
- Monomer aggregates to form soluble oligomer in all compartments. However, plaque formation from soluble oligomers is limited to only brain ISF.
- Formation of soluble oligomer and plaque are reversible, but the rates of reverse reaction from plaque to oligomer is much slower than the forward reactions.
- Soluble species (monomer and oligomer) can transport between compartments.

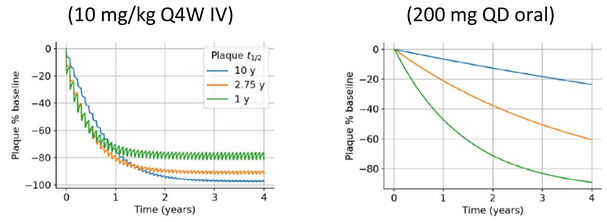
MODEL SIMULATION RESULTS

Figure 3. Simulated biomarker changes for mAbs with different binding profiles at the same doses and interval (Q4W).



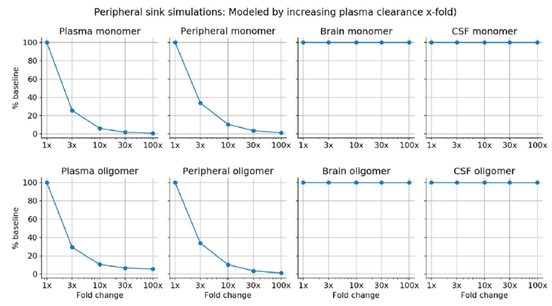
- At the same dose and frequency, the model predicts plaque clearance for bapineuzumab > aducanumab > lecanemab.
- However, due to adverse event limitations (ARIA), bapineuzumab doses tested clinically were significantly lower (0.5-2 mg/kg) and less frequent (Q13W) than aducanumab (Q4W) or lecanemab (Q2W).
- Crenezumab shows minimal plaque reduction, due to weaker FcγR binding and ADCP (IgG4).
- Solanezumab shows minimal plaque reduction as a result of not binding to plaque.
- Slow turnover of endogenous plaque suggests limited plaque reduction is achieved by inhibiting new plaque formation (Figure 3).

Figure 4. Impact of plaque turnover rate on plaque removal



- Plaque $t_{1/2}$ has a large impact on predicted plaque reduction with inhibitors of Aβ synthesis.
- A $t_{1/2}$ of 2.75 years was found to provide the best fit to clinical plaque reduction data across drugs.

Figure 5. Model simulations do not support peripheral sink hypothesis



- Increasing plasma Aβ clearance by up to 100-fold has minimal effect on monomer or oligomer levels in CSF or Brain ISF.
- Consequently, plaque reduction is predicted to be negligible for drugs targeting peripheral Aβ.

CONCLUSIONS

- To provide guidance for clinical development of AD therapies, we developed a single QSP model to analyze treatment effects of anti-Aβ antibodies, BACE, and γ-secretase inhibitors on Aβ monomer, oligomer, and plaque.
- Model calibration to clinical data for eight investigational drugs with a range of mechanisms provides rigorous constraints on model parameters and model structure, and hence a high degree of confidence in model predictions.
- The model provides insights into which drug design properties impact plaque changes in AD. For example, due to the very slow rate of turnover of endogenous plaque, inhibitors of plaque formation are predicted to lead to slow plaque removal and hence have a minimal effect on plaque levels in the brain within the duration of a clinical trial. This may partly explain the lack of clinical efficacy for secretase inhibitors and non-plaque-clearing mAbs (crenezumab and solanezumab).
- The calibrated model can be used to predict biomarker changes for novel therapeutic candidates using preclinical or early clinical data.

Portions of this work were previously published in: Madrasi et al. 2021. Systematic in silico analysis of clinically tested drugs for reducing amyloid-beta plaque accumulation in Alzheimer's disease. Alzheimers Dement. Sep;17(9):1487–1498. Portions of the presented results were supported by funding from Prothena Biosciences, Inc, and by the National Institutes of Health under award number 4R44AG058411-02. The authors declare no competing interests.