



ARTICLE

Quantitative systems pharmacology model of the amyloid pathway in Alzheimer's disease: Insights into the therapeutic mechanisms of clinical candidates

Vidya Ramakrishnan¹  | Christina Friedrich² | Colleen Witt² | Robert Sheehan² | Meghan Pryor² | Jasvinder K. Atwal¹ | Kristin Wildsmith¹ | Katherine Kudrycki² | Seung-Hye Lee¹ | Norman Mazer³ | Carsten Hofmann³ | Reina N. Fuji¹ | Jin Y. Jin¹  | Saroja Ramanujan¹ | Michael Dolton⁴ | Angelica Quartino¹

¹Genentech, Inc., South San Francisco, California, USA

²Rosa & Co., LLC., San Carlos, California, USA

³F. Hoffmann-La Roche Ltd, Basel, Switzerland

⁴Roche Products Australia Pty Ltd, New South Wales, Sydney, Australia

Correspondence

Vidya Ramakrishnan, Genentech, Inc., 1 DNA Way, Mailstop 258A, South San Francisco, CA 94080, USA.

Email: ramakrishnan.vidya@gene.com

Abstract

Despite considerable investment into potential therapeutic approaches for Alzheimer's disease (AD), currently approved treatment options are limited. Predictive modeling using quantitative systems pharmacology (QSP) can be used to guide the design of clinical trials in AD. This study developed a QSP model representing amyloid beta (A β) pathophysiology in AD. The model included mechanisms of A β monomer production and aggregation to form insoluble fibrils and plaques; the transport of soluble species between the compartments of brain, cerebrospinal fluid (CSF), and plasma; and the pharmacokinetics, transport, and binding of monoclonal antibodies to targets in the three compartments. Ordinary differential equations were used to describe these processes quantitatively. The model components were calibrated to data from the literature and internal studies, including quantitative data supporting the underlying AD biology and clinical data from clinical trials for anti-A β monoclonal antibodies (mAbs) aducanumab, crenezumab, gantenerumab, and solanezumab. The model was developed for an apolipoprotein E (APOE) $\epsilon 4$ allele carrier and tested for an APOE $\epsilon 4$ noncarrier. Results indicate that the model is consistent with data on clinical A β accumulation in untreated individuals and those treated with monoclonal antibodies, capturing increases in A β load accurately. This model may be used to investigate additional AD mechanisms and their impact on biomarkers, as well as predict A β load at different dose levels for mAbs with known targets and binding affinities. This model may facilitate the design of scientifically enriched and efficient clinical trials by enabling a priori prediction of biomarker dynamics in the brain and CSF.

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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Designing clinical trials for Alzheimer's disease (AD) is challenging. Quantitative systems pharmacology modeling supports the design of scientifically informed clinical trials.

WHAT QUESTION DID THIS STUDY ADDRESS?

How to leverage the data from prior clinical studies and known pathophysiology of AD quantitatively to understand disease and biomarker dynamics.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The model enables simulation of target engagement and biomarker dynamics upon treatment. The study confirmed that documented mechanistic differences between apolipoprotein E $\epsilon 4$ carriers and noncarriers can account for their different amyloid plaque progression rates. The study demonstrated that clearance of antibody-bound plaque is not sufficient to account for the clinical efficacy of aducanumab and suggested a hypothesized mechanism of plaque clearance due to microglial activation that is scientifically grounded and dynamically consistent with clinical results.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

The model provides a platform to test competing mechanisms targeting the A β pathway and alternate biological mechanisms to assess the impact on biomarkers, providing a priori information to design efficient clinical studies.

INTRODUCTION

Alzheimer's disease (AD) is a chronic and progressive neurodegenerative disease associated with decline in memory and cognitive function.¹ Current estimates suggest that between 15% and 20% of people above the age of 60 years have mild cognitive impairment, and up to 15% of these individuals will progress to dementia within a year.² The projected worldwide burden of AD could be over 100 million by 2050. The known pathophysiology of AD includes the aggregation and accumulation of amyloid beta (A β) into oligomers and plaques, and the aggregation of the microtubule-associated protein tau into neurofibrillary tangles in the brain.¹ Both A β and tau are biomarkers for AD diagnosis and have been targets for drug development.³

Despite considerable investment, currently, four drugs are approved by the US Food and Drug Administration (FDA) to treat symptoms of AD; however, they do not halt or significantly slow disease progression, with over 100 having negative results in clinical trials.^{1,4} In June 2021, the FDA granted accelerated approval to aducanumab, a monoclonal antibody (mAb) targeting A β , as the first disease-modifying therapeutic for the treatment of AD based on reduction of A β plaque in the brain and the reasonable likelihood to predict a clinical benefit.⁵ Aducanumab was the first drug approved for AD since 2003.⁵

Clinical trials in AD have been facing setbacks due to a lack of effect on the primary and secondary clinical end

points that assess cognitive and functional progression in participants.⁴ Numerous challenges contribute to this lack of therapeutic progress in the field. Large sample sizes are required for AD trials due to the heterogeneous responses observed in participants.⁶ Issues with participant dropout or death can be a problem due to the long duration of trials needed to evaluate cognitive improvements adequately.⁶ Dose-ranging studies are not easily feasible, and failed trials lead to questions about drug dosing and efficacy.⁷ The right choice of clinical trial participants is a factor in clinical trial success as well. Considering that AD pathologic manifestation begins much earlier than symptom onset, a key challenge in early stages of the disease is identification of participants who could benefit from treatment.⁶

Biomarkers can play a key role in clinical trial success too. The accelerated approval of aducanumab was based on the drug's effect on the surrogate biomarker end points of dose- and time-dependent reduction in the level of amyloid plaque in the brain.⁵ This emphasizes the considerable role that biomarkers can play in closing the gap between drug effect and potential clinical benefit. Identifying the mechanisms of disease progression and drug effect in the brain via noninvasive, easy-to-measure, blood-based biomarkers would be ideal. Better methods to assess adequate concentrations of the drug available in the brain are also needed.

Predictive modeling provides one approach to support drug development in the face of these issues. Quantitative

systems pharmacology (QSP) modeling aims to quantitatively assess drug pharmacology and downstream biology, including disease pathophysiology, in tandem.⁸ Given the biological complexity of AD, QSP modeling is well-suited for applications to guide clinical drug development. QSP modeling enables target identification and benchmarking of similarities and differences in dynamics of A β or tau biomarkers at different states of aggregation. It allows for representation of virtual patients based on targeted biological elements and enables simulation of clinical trial scenarios. A priori predictions of biomarker dynamics in difficult-to-measure regions, such as the brain and cerebrospinal fluid (CSF), can be made. QSP also provides a model to test various target- and treatment-related hypotheses, leading to insights and guidance for drug development. More recently, QSP models representing A β dynamics in AD have been published in the literature and highlight the strength of the approach to understand disease progression and A β biomarker dynamics in AD.^{9,10} Our work is uniquely distinguished from the prior work on two key aspects: (1) this work characterizes the dynamics of different biomarker species (A β 40 and 42 specifically) in detail. This enables a biologically plausible hypothesis-driven approach to understand the differences in the mode of action of the mAbs targeting the A β pathway, thereby enabling quantitative benchmarking; and (2) the work incorporates and enables evaluation of the

mechanistic differences based on the stage of the disease and the *APOE* ϵ 4 carrier status, enabling future exploration based on virtual patients with a specific phenotype.

Here, we present the development of a QSP model for AD and investigate its predictive capability using data from clinical trials of novel therapeutic agents targeting aggregated A β . The current model is solely focused on the A β component of AD pathology, considering that A β pathology precedes tau pathology and cognitive impairment,¹¹ without incorporating tau pathology or cognitive functionality. Our goal is to create a model that can support the development of clinical trials by allowing researchers to predict A β dynamics in the brain prior to participant enrollment.

METHODS

The AD QSP model was developed as a set of ordinary differential equations (ODEs; available in the Supplementary Material) implemented in MATLAB SimBiology version 2017B. The ODEs represent key pathophysiological and therapeutic pathways in three compartments: the brain, CSF, and plasma (Figure 1 depicts a schematic overview). The model tracks the insoluble and soluble biomarkers across these compartments, including production of A β in the brain and plasma, aggregation of A β in the brain,

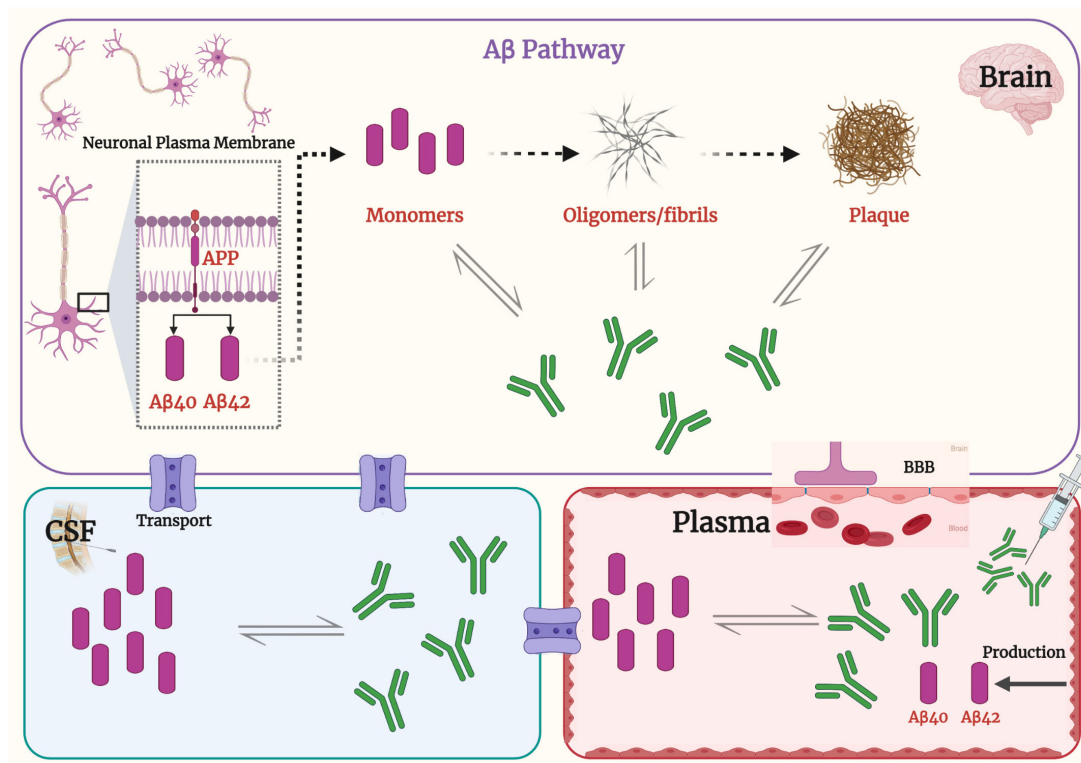


FIGURE 1 Key pathways for amyloid transport. A β , amyloid beta; APP, amyloid precursor protein; BBB, blood–brain barrier; CSF, cerebrospinal fluid

and the transport of soluble A β from the brain to the CSF and plasma. A β monomer production and secretion are regulated by β -secretase 1 (BACE1) and γ -secretase.¹² A β 40 and A β 42 are produced and tracked separately and exhibit different behaviors, including higher aggregation and slower clearance rates for A β 42.^{13,14}

The temporal scope of the model focuses on the ~20-year progression duration during which A β aggregation in the brain exhibits constant linear growth (i.e., the upward slope of the characteristic S curve).¹¹ Aggregation is modeled as progressing from monomers (assumed to be 10-mers) to fibrils to plaque. A β 42 monomers aggregate at a higher rate than A β 40, forming oligomers that contain a mix of species with relatively more A β 42 than A β 40.¹⁵ Once the aggregated species have formed, their A β 42 and A β 40 content is not tracked separately, and further aggregation to higher-order species is assumed to be driven by the species that form them. To facilitate comparison with clinical data, the quantitative assessment of the total A β burden, measured clinically as the standard uptake value ratio (SUVR) from positron emission tomography (PET) imaging, is calculated in the model assuming a linearly proportional relationship between the insoluble A β (fibril plus plaque) mass and SUVR. Soluble A β

species are transported across the blood–brain-barrier by active transport or from brain interstitial fluid to CSF by bulk flow. A β monomers are also produced peripherally. All A β production, aggregation, transport, and clearance process parameters were informed by mechanistic data (Table 1).^{16–26}

States of A β aggregation in the three compartments were calibrated simultaneously to match available clinical data for untreated participants and participants undergoing treatment with the A β -targeting mAbs solanezumab,²⁷ crenezumab,²⁶ aducanumab,²⁸ and gantenerumab.^{21,29} A β -targeting mAbs in the model can be configured to bind to any form of A β , including monomers, oligomers, fibrils, and plaque. The binding affinity for each form is mAb-specific, with solanezumab binding strongly to monomers only; crenezumab binding strongly to oligomers, moderately to monomers, and weakly to fibrils and plaques; and aducanumab and gantenerumab binding strongly to fibrils, plaque, and oligomers, and weakly to monomers (Table 2).^{28,30–33}

Following subcutaneous or intravenous dosing with an mAb, the model follows mAb transport into the CSF and brain via passive diffusion. The pharmacokinetics (PK) of the mAb is described by a target-mediated drug

TABLE 1 A β 42 biomarker and A β SUVR values for normal, prodromal, and moderate-to-severe individuals used to guide virtual patient development. Values are mean \pm standard deviation unless otherwise specified

Stage	Cognitive impairment	A β 42	A β	References
		CSF pg/ml	PET SUVR (PiB tracer) ^a	
Normal healthy	None	206 \pm 55 ¹⁶ Median = 111 (25–1060) ¹⁷ 563.3 \pm 191.0 ¹⁸	<1.42 ¹⁹ (determined as cutoff for A β +) Typical range 1.17–1.37 ¹⁹	Shaw et al. ¹⁶ Jack et al. ¹⁹ Mehta et al. ¹⁷ Maruyama et al. ¹⁸
Prodromal	Early mild/mild	\leq 192 ²⁰ 146 \pm 38 ¹⁶ 539.5 \pm 149.6 ¹⁸ (focus on intra-study values for trend)	1.65 ²¹ Rate of increase of 0.043 in SUVR (-3%)/year ^{22–24} Rate of increase 1.3%/year ²⁵	Steenland et al. ²⁰ Shaw et al. ¹⁶ Ostrowitzki et al. ²¹ Villemagne et al. ²² Villemagne et al. ²³ Villain et al. ²⁴ Maruyama et al. ¹⁸ Landau et al. ²⁵
AD	Dementia	144 \pm 41 ¹⁶ Median = 38 (25–325) ¹⁶ 397.6 \pm 164.1 ¹⁸	-1.8–2.0 (mild to moderate AD) ²⁶ -2.2 and greater (severe) ²² Rate of increase slows in late stages ^{22–24}	Shaw et al. ¹⁶ Salloway et al. ²⁶ Villemagne et al. ²² Villemagne et al. ²³ Villain et al. ²⁴ Mehta et al. ¹⁷ Maruyama et al. ¹⁸

Abbreviations: A β , amyloid beta; AD, Alzheimer's disease; CSF, cerebrospinal fluid; PET, positron emission tomography; PiB, Pittsburgh Compound B; SUVR, standard uptake value ratio.

^aCortical SUVR with cerebellar cortex reference region.

mAb	K_D monomers	K_D oligomers	K_D fibril/plaque	References
Crenezumab	3–5 nM ³⁰	0.4–0.6 nM ³⁰	50 nM ^a	Ultsch et al. ³⁰
Gantenerumab	17 nM	1.2 nM	0.6 nM	Bohrmann et al. ³¹
Solanezumab	10 pM ^b	0	0	Crespi et al. ³²
Aducanumab	>1 μ M	0.1 nM	0.1 nM	Sevigny et al. ²⁸

Abbreviations: A β , amyloid beta; K_D , equilibrium dissociation constant; mAb, monoclonal antibody.

^aAssumption used because crenezumab binds plaque poorly relative to oligomers.³³

^bEstimated from Crespi et al.³²

TABLE 2 Antibody (mAb) dissociation constants for A β monomers, oligomers, fibrils, and plaque

Parameter	<i>APOE</i> $\epsilon 4+$ VP value	<i>APOE</i> $\epsilon 4-$ VP value	References
BACE1 K_m (μ M)	7.760	8.438	Stockley et al. ³⁸
BACE1 V_{max} (μ M/h)	0.455	0.253	Stockley et al. ³⁸
A $\beta 40$ astrocyte receptor clearance fraction	0.100	0.200	Deane et al. ³⁹
A $\beta 42$ astrocyte receptor clearance fraction	0.117	0.235	Deane et al. ³⁹
A $\beta 40$ brain to CSF clearance fraction	0.301	0.602	Deane et al. ³⁹
A $\beta 42$ brain to CSF clearance fraction	0.353	0.707	Deane et al. ³⁹
A $\beta 40$ brain to plasma active clearance fraction	0.349	0.698	Deane et al. ³⁹
A $\beta 42$ brain to plasma active clearance fraction	0.246	0.492	Deane et al. ³⁹

TABLE 3 Mechanistic differences in *APOE* $\epsilon 4$ carriers and noncarriers in the literature

Note: Clearance fraction parameters are expressed in terms of the fraction of clearance attributed to each pathway for the *APOE* $\epsilon 4+$ VP. Fractions add up to >1 for *APOE* $\epsilon 4-$ VP, indicating that the total clearance is expected to increase. A $\beta 40$ and A $\beta 42$ refer to A β monomers.

Abbreviations: A β , amyloid beta; *APOE*, apolipoprotein E; BACE1, beta-secretase 1; CSF, cerebrospinal fluid; K_m , enzyme concentration at half of V_{max} ; V_{max} , maximum rate of reaction; VP, virtual patient.

disposition model based on its binding to A β . It then predicts brain target engagement based on target concentrations, mAb concentrations, and mAb binding properties for A β monomers, oligomers, and fibrils/plaque. Once bound to a target, the mAbs are assumed to inhibit further aggregation. The implementation of aducanumab and gantenerumab required an additional assumption of microglial activation and clearance of plaque, as further discussed in the Results below. For more specific details about model calibration and implementation, see the Supplemental Methods.

QSP modeling is useful for investigating the system-level effects of mechanistic differences between drugs or individual variability. One well-documented difference between individuals with AD is in the *APOE* gene.³⁴ To date, *APOE* remains the gene with the strongest impact on risk in non-familial sporadic AD.³⁴ In addition to its role in lipid metabolism,³⁵ *APOE* also mediates active transport of A β across the blood–brain barrier³⁶ and regulates

A β uptake into astrocytes.³⁷ The *APOE* gene is polymorphic, with three major alleles that encode three protein isoforms: epsilon 2 (*APOE* $\epsilon 2$), epsilon 3 (*APOE* $\epsilon 3$), and epsilon 4 (*APOE* $\epsilon 4$).³⁵ The $\epsilon 4$ isoform is associated with increased risk of AD, whereas $\epsilon 2$ appears to be protective, and $\epsilon 3$ is considered “neutral.” The impact of *APOE* $\epsilon 4$ expression on rates of A β production and clearance has been reported in the literature.^{38,39}

The model was initially developed to represent the most typical individual with AD, an *APOE* $\epsilon 4$ carrier.¹ As a way of validating the QSP model’s representation of biology, we tested whether implementing observed differences between carriers and noncarriers in the model would produce the differences in A β aggregation rates that have been observed. Toward this goal, a second virtual patient was created that represented an *APOE* $\epsilon 4$ noncarrier. Mechanistic differences between *APOE* $\epsilon 4$ carriers and noncarriers have been identified and implemented as parameter differences in the model, as summarized in Table 3.^{38,39}

RESULTS

The AD model integrates known characteristics of AD into a single mechanistic framework. A β species concentrations in the brain, CSF, and plasma are consistent with data and are dynamically maintained. A β plaque in the brain increases at a rate that is consistent with clinical progression data. The model is also able to reproduce clinical responses to A β -targeting antibodies, as further described below. Only parameters relevant to mAb treatment, such as binding rates for different A β species, were changed to produce appropriate responses to all treatments.

Pharmacokinetics

Prior PK models were adapted into the QSP model to recapitulate the dynamics of mAb concentrations in the plasma and CSF. The mAb transport across the compartments was described using first-order processes. A peripheral compartment was included to capture the distribution of the mAb to other compartments. The model described the plasma PK of the different mAbs at various dosing ranges and dosing frequencies well. The calibration results are represented in [Figure 2a–c](#) and [Figure S1A](#).

Clinical trial data from phase II and phase III studies of crenezumab were used for calibration of the CSF PK. The model described the data, which suggested that the CSF steady-state mAb concentrations are generally between 0.2% and 0.3% of plasma concentration.^{40,41} The calibrated model was used to simulate the CSF and brain PKs of other mAbs ([Figure 2d–f](#) and [Figure S1B](#)).

Pharmacodynamic biomarkers

Plasma and CSF

The half-life of A β in plasma is ~ 3 h.⁴² It was estimated that 40% of A β in plasma was derived from effluxed A β from the brain⁴³ and the remainder was produced in the periphery. Calibration of plasma A β with mAb treatment using the crenezumab studies produced a model that adequately characterizes the biomarker dynamics of soluble A β 40 and A β 42 in plasma for crenezumab ([Figure 2g](#) and [Figure S1C](#)).

The predominant mechanism of A β clearance in the CSF was implemented as efflux to plasma. It has been shown that enzymatic degradation activity is present in CSF but is greatly reduced in prodromal AD.⁴⁴ Therefore, we assumed that the contribution to clearance via

enzymatic degradation was negligible as compared with efflux. The reported absolute concentrations of A β in CSF are highly variable⁴⁰ and hence the data calibration was performed using percent changes in the levels of the soluble biomarkers ([Figure 2h](#) and [Figure S1D](#)). The model was used to predict the percent change in A β in CSF with solanezumab treatment and the predictions are consistent with the data ([Figure 2i](#)).

Brain predictions

The model was used to simulate and benchmark the effect of mAb administration on the dynamics of A β states in the brain ([Figure 2j–l](#)). The simulations were in accordance with the relative specificities of the mAbs for the various A β aggregation states and the predicted consequences of target engagement on state dynamics. The model suggests that the plaque-targeting antibodies, gantenerumab and aducanumab, reduce plaque in the brain to below 10% of the initial concentrations by the end of the treatment duration ([Figure 2l](#); dose and duration based on phase III clinical trials). As A β plaque reduces, the oligomeric A β species also reduce as a consequence ([Figure 2k](#)). Consistent with clinical data, the model indicates that crenezumab, which primarily targets the oligomeric state, reduces the oligomeric A β and slows plaque growth ([Figure 2k](#)), but has minimal effect on existing A β plaque burden ([Figure 2l](#)). The A β -monomer-targeting antibody solanezumab binds the monomeric state, and simulations show no effect on oligomers or plaque at its clinical dose.

PET imaging

The calibration of PET imaging-based biomarker data included florbetapir SUVR data from the crenezumab phase III CREAD (NCT02670083) and CREAD2 (NCT03114657) trials, and the aducanumab phase I trial (NCT01677572).²⁸ The data from these studies represented SUVR change from baseline. The model calibrations are shown in [Figure 3](#). According to the model, crenezumab ([Figure 3b](#)) inhibits nascent plaque formation but does not produce a significant decrease in total plaque. Aducanumab produces a dose-dependent decrease in total plaque ([Figure 3a](#)). The model slightly underpredicts the early reduction in SUVR but captures the response at a later timepoint.

The calibrated model was then used to predict the SUVR change from baseline upon administration of the phase III titration dose of aducanumab. The model predictions qualitatively capture the observed data from

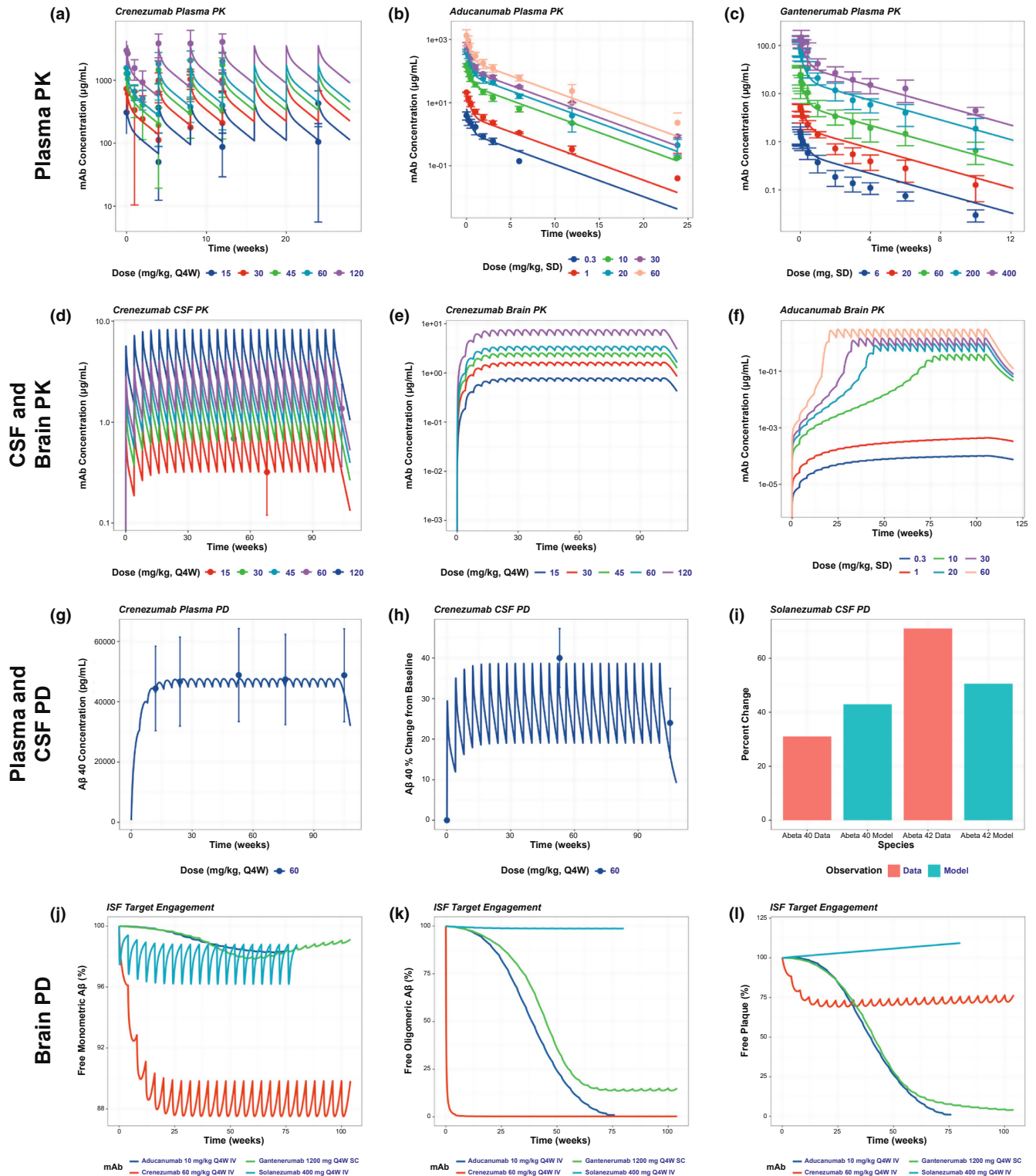


FIGURE 2 Calibration and simulation results for plasma PK (a–c), CSF and brain PK (d–f), plasma and CSF PD (g–i), and brain PD (j–l). A β , amyloid beta; CSF, cerebrospinal fluid; ISF, interstitial fluid; IV, intravenous; mAb, monoclonal antibody; PD, pharmacodynamic; PK, pharmacokinetic; Q4W, every 4 weeks; SC, subcutaneous; SD, standard deviation

the phase III studies (EMERGE: NCT02484547) as seen visually in Figure 3c. Similarly, the model was also used to predict the percent change in A β burden with

gantenerumab treatment. The decrease in insoluble A β states compared well with the reported decrease in absolute Centiloids.²⁹

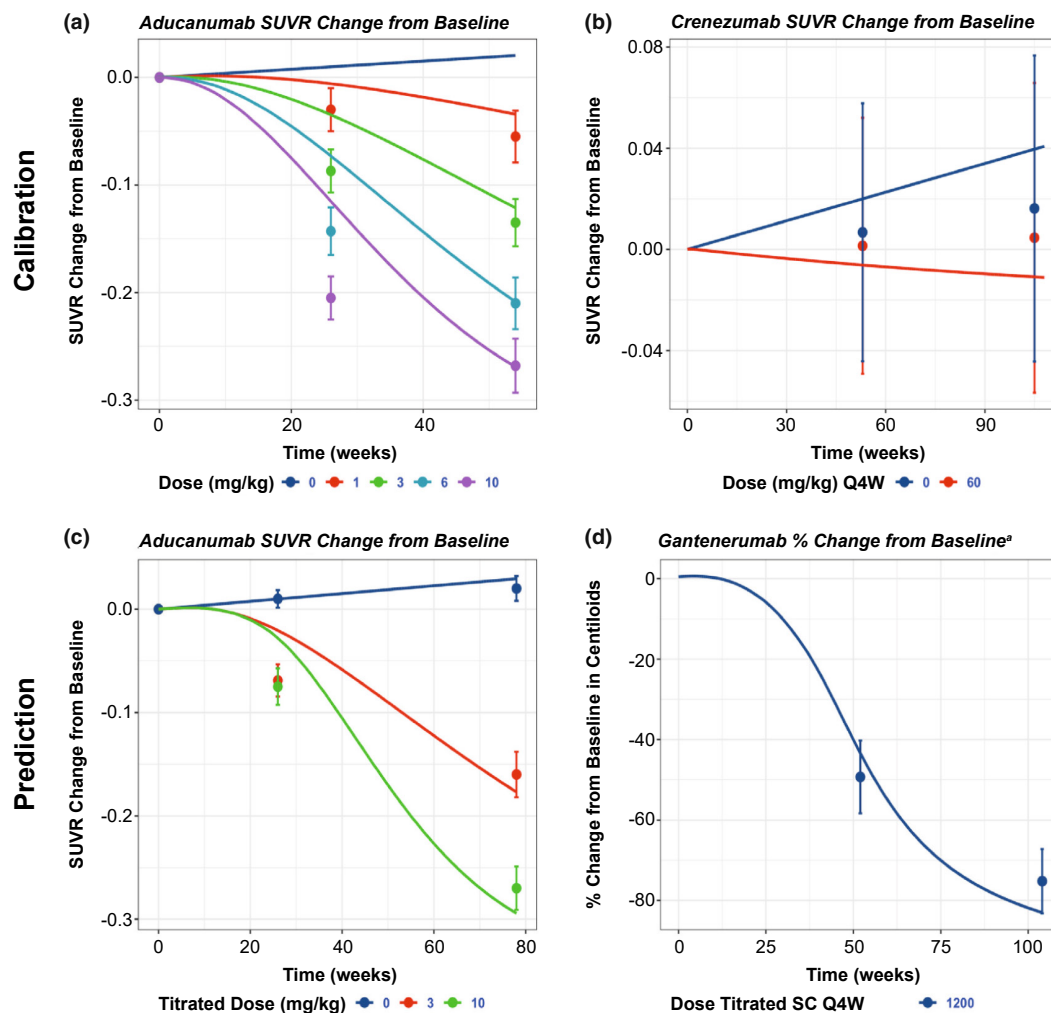


FIGURE 3 Model calibrations (a, b) and predictions (c, d) overlaid on observed clinical data of changes in A β PET SUVR upon treatment with candidate mAbs: aducanumab phase Ib PRIME study (a), crenezumab phase III CREAD and CREAD2 (b), aducanumab phase III EMERGE study (c), and gantenerumab phase III SCarlet RoAD and Marguerite RoAD (d). A β , amyloid beta; mAb, monoclonal antibody; PET, positron emission tomography; Q4W, every 4 weeks; SUVR, standard uptake value ratio. ^aReported in Centiloids

Investigation of plaque clearance by plaque-binding IgG1 antibodies

The mechanism of plaque clearance is a key element in evaluating and predicting mAb treatment efficacy. In the model, it is assumed that endogenous plaque clearance in absence of treatment is negligible. However, mAb binding to plaque allows for the recruitment and activation of microglia, which are capable of clearing plaque. The model implementation of the plaque-binding mAbs aducanumab and gantenerumab assumed that microglia would clear sections of plaque directly bound to the mAb via phagocytosis following a direct interaction between the bound mAb and fragment crystallizable (Fc) receptors. However, initial model simulations did not agree with published data following aducanumab treatment (Figure S2). Aducanumab treatment resulted in a fast initial clearance of plaque during the first year of treatment, which began

to level off during the second year.^{28,45} Model simulations suggested that the reported level of plaque clearance could not be achieved by the presumed mechanism of clearing only antibody-bound plaque. Given the estimated concentration of mAb in the brain and the known binding affinity of the mAb, only a small amount of plaque would be bound to the mAb at a given time. This assumption would lead to linear rather than exponential clearance dynamics, as demonstrated in initial simulations. Varying the clearance rate for mAb bound to plaque did not eliminate this discrepancy as the model could match either the 1-year data point or the 2-year data point, but not both.

The rate of plaque clearance following aducanumab treatment appears to suggest first-order clearance of all plaque (Figure 3a). This effect is consistent across multiple doses of the drug and cannot be achieved under the assumption that only plaque directly bound to the mAb is being cleared by the newly activated microglia. To account

for the discrepancy between the simulations and data, a new term was added to incorporate microglia activation in the presence of therapeutic antibodies. This effect is more pronounced in IgG1 antibodies, which are known to be relatively more activating compared with other IgG isotypes.⁴⁶ Once microglia were activated in the model, the microglia were capable of clearing any plaque, independent of specific mAb binding. This mechanism still results in a small lag in achieving the ultimate clearance rate until mAb levels in the brain reach steady-state, but the final result is a first-order clearance of all plaque. Updated simulations qualitatively describe the clinical data for plaque clearance following treatment with IgG1 antibodies, such as aducanumab (Figure 3a).

Creation of an *APOE* $\epsilon 4$ noncarrier virtual patient

The *APOE* $\epsilon 4$ noncarrier virtual patient was developed by implementing mechanistic differences between *APOE* $\epsilon 4$ carriers and noncarriers (Table 3).^{38,39} Decreased A β 42 production and increased clearance in the *APOE* $\epsilon 4$ noncarrier compared with the carrier caused a decrease in the A β 42:40 ratio, decreased aggregation rate, and slower plaque progression (SUVR; Figure 4) for the *APOE* $\epsilon 4$ noncarrier in the model, consistent with clinical reports of earlier amyloid deposition in *APOE* $\epsilon 4$ carriers.⁴⁷ The model's prediction of the appropriately reduced progression rate in the noncarrier as a result of the mechanistic differences between carriers and noncarriers was a useful

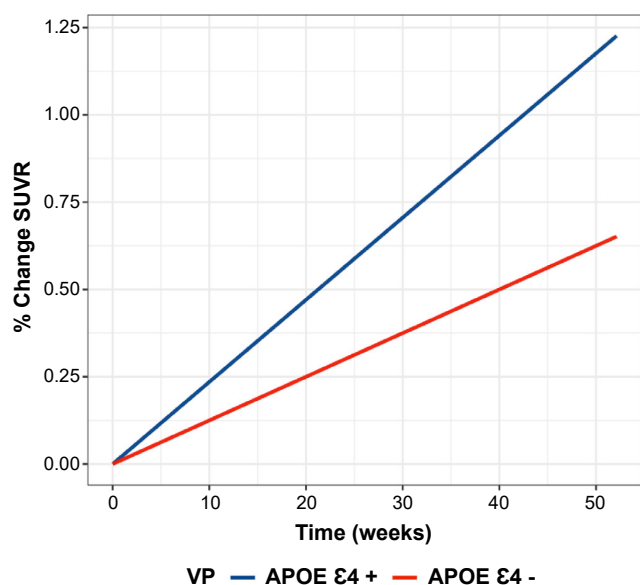


FIGURE 4 *APOE* $\epsilon 4$ carrier and noncarrier predictions for A β SUVR. A β , amyloid beta; *APOE*, apolipoprotein E; SUVR, standard uptake value ratio; VP, virtual patient

validation that plaque progression mechanisms are appropriately captured in the model.

DISCUSSION

A major value of using QSP to research a complex process, such as the pathology that underlies AD, is the ability to query the collective effects on the system that arise from numerous mechanistic factors acting in concert. We used QSP modeling to simulate A β dynamics in individuals with AD. The model was calibrated using virtual patients experiencing A β progression who possess the *APOE* $\epsilon 4$ gene. We introduced treatment effect using four A β -targeting mAbs to calibrate/assess change in A β in the brain, CSF, and plasma. The model was then tested using virtual patients who did not have the *APOE* $\epsilon 4$ gene. The model was able to recapitulate untreated and treated outcomes and biomarker dynamics.

The results of the brain prediction analysis confirmed that the target states, binding affinity, and the antibody concentrations determine biomarker dynamics. The model can be leveraged to predict A β burden or SUVR at different dose levels for mAbs with different binding specificities. The profile of the mAb's binding properties and unique specificities for A β states (i.e., monomer vs. oligomer vs. plaque) can lead to potentially different mechanisms of action with varied outcomes in both *APOE* subpopulations.

The brain PK simulations for plaque-targeting mAbs suggested that steady-state PK concentrations are achieved only when plaque and mAb binding reach an equilibrium, due to the presence of large amounts of accumulated plaque in the AD brain that acts as a sink for mAb binding. This process takes time due to the excess of plaque relative to mAb concentration in the brain at the beginning. The time taken to achieve this equilibrium is dependent on the dose administered, with higher doses reaching equilibrium sooner than lower doses. At the clinical doses, the model simulations suggest that aducanumab binding aggregated A β takes about 4–5 times longer to achieve equilibrium in contrast to crenezumab binding to oligomers.

Modeling of PET imaging biomarker data suggested that clearance of plaque is not proportional to mAb-bound plaque alone. Modeling indicated that the clearance of unbound plaque is necessary to explain the observed clinical decrease in SUVR following aducanumab and gantenerumab treatment. This is supported by biological evidence for microglial activation by plaque-targeting antibodies. There are a number of potential hypotheses to explain how mAb in the brain leads to a decrease in plaque burden. There is strong evidence that the isotype backbone of the mAb influences

the strength of the glial response to treatment.⁴⁸ Both aducanumab and gantenerumab are IgG1 antibodies, which, compared with other isotypes, are known to bind Fc receptors with higher affinity and elicit more robust activation of microglia and other innate immune cells. Therefore, clearance of plaque by microglia-mediated phagocytosis would be more efficient with treatments that use antibodies of the IgG1 isotype. Indeed, this appears to be supported by the observation that high doses of both aducanumab and gantenerumab in clinical trials were associated with a significant risk of amyloid-related imaging abnormalities, believed to be a consequence of high glial activation.⁴⁹ A more detailed and mechanistic representation of microglia should be capable of producing an even greater match to the data, as modeling an initial burst of activation and recruitment of microglia following brain penetration by the mAb could explain the strong initial response as mAb levels are still reaching equilibrium. This lack of detail is a current limitation of the model and highlights a potential opportunity to further expand the model to include microglial activation mechanisms.

APOE $\epsilon 4$ carriers and noncarriers can have different responses to therapeutic treatments as well.⁵⁰ Implementation of mechanistic differences between *APOE* $\epsilon 4$ carriers and noncarriers led to a greater A β aggregation in carriers than noncarriers, providing an important validation for the model. Our simulation results indicate that the model may be leveraged to predict potential differences in carrier versus noncarrier progression of A β accumulation and a subsequent effect on response to therapeutic treatments, especially on their amyloid-lowering capabilities.

The current model has been used to compare and benchmark A β -targeting therapies and suggests that agents targeting insoluble forms, specifically fibrils and plaque, are more effective in reducing the A β burden in the brain in comparison with therapies that primarily target soluble forms of A β (monomers and oligomers). The binding affinity to the diverse A β species can determine the relative clearance of the different forms of A β . However, the activation of downstream processes as a consequence of binding and clearance of A β also play a major role in the totality of effect on A β burden. It is imperative to understand the downstream effect of A β engagement to understand its effects on A β clearance and, further, on the efficacy markers, cognition, and function. This model lays a foundation to explore similar downstream processes. The model is a useful platform for hypothesis testing of newer therapies targeting the A β pathway, or for assessing the impact of improved brain uptake technologies, and is positioned to leverage incoming data from very recent A β -targeting

agents, such as donanemab and lecanemab, not used in model development, to improve the model calibration and predictions.

A key feature of the QSP model is its flexibility to include additional mechanisms and pathways to the structure. This can be implemented in two ways: including diverse additional pathways (e.g., tau pathway) with the known connections of these pathways to the A β pathway and extending mechanistic details to already existent pathways (e.g., microglial plaque clearance and endogenous plaque clearance). In addition to the *APOE* $\epsilon 4$ non-carrier virtual population example, other extensions of the virtual population could include representation of individuals with autosomal-dominant AD, individuals with more progressed moderate AD, and more. The model serves as a backbone to implement and evaluate several such disease mechanisms and their potential impact on biomarker dynamics.

The model facilitates the design of more informative and efficient clinical trials by enabling a priori prediction of biomarker dynamics and target engagement in the brain (Figure 2j–l). Model validation extends the value of the model beyond that of a predictive tool. Our results show that mechanistic models can be used to examine the systemic implications of mechanistic perturbations and diversity more generally. The manifestation of pathology is rarely the result of a single factor, but rather the collective result of many factors working in concert. For example, *APOE* $\epsilon 4$ noncarrier simulations that matched observation were achieved by implementing numerous contributing factors simultaneously. QSP modeling allows the query into emergent behaviors that are simply not manifested when the components are reduced in isolation. Our work illustrates that a systems approach can reveal insights that may otherwise be unrealized when using reductionist approaches alone.

AUTHOR CONTRIBUTIONS

V.R., C.F., C.W., R.S., M.P., J.A., K.W., K.K., S.-H.L., N.M., C.H., R.N.F., J.Y.J., S.R., M.D., and A.Q. wrote the manuscript. V.R., C.F., C.W., R.S., M.P., J.A., K.W., K.K., S.-H.L., N.M., C.H., R.N.F., J.Y.J., S.R., M.D., and A.Q. designed the research. V.R., C.F., C.W., R.S., M.P., and K.K. performed the research. V.R., C.F., C.W., R.S., M.P., J.A., K.W., K.K., S.-H.L., N.M., M.D., and A.Q. analyzed the data. V.R., C.F., C.W., R.S., M.P., J.A., K.W., K.K., S.-H.L., N.M., M.D., and A.Q. contributed new reagents/analytical tools.

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CONFLICT OF INTEREST

V.R., J.A., S.-H.L., R.F., S.R., and J.Y.J. are full-time employees of Genentech, Inc. and may own company stock/stock options. C.F., C.W., R.S., and K.K. are current employees of Rosa & Co. LLC and may own company stock/stock options. M.P. is a former full-time employee of Rosa & Co. LLC. M.D. is a former full-time employee of Genentech, Inc. and is a current full-time employee of Roche Products Australia Pty Ltd. and may own company stock/stock options. N.M. and C.H. are current employees of F. Hoffmann-La Roche Ltd. and may own company stock/stock options. A.Q. and K.W. are former full-time employees of Genentech, Inc.

ORCID

Vidya Ramakrishnan  <https://orcid.org/0000-0001-7726-6278>

Jin Y. Jin  <https://orcid.org/0000-0002-3627-0323>

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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