Passive Immunotherapies Targeting Amyloid-β in Alzheimer’s Disease: A Quantitative Systems Pharmacology Perspective

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Abbreviations: Aβ, amyloid-β; AD, Alzheimer's disease; ADCP, antibody-dependent cellular phagocytosis; ARIA-E, amyloid-related imaging abnormalities with edema; APOE, apolipoprotein E; APP, amyloid precursor protein; BACE, beta-secretase; CSF, cerebrospinal fluid; E-R, exposure-response; Fc, fragment crystallizable (Fc); FDA, Food and Drug Administration; IgG, Immunoglobulin G; MIDD, model-informed drug development; ISF, interstitial fluid; ODE, ordinary differential equations; PK, pharmacokinetics; PD, pharmacodynamics; PET, positron emission tomography; PRKCD, Protein kinase C delta type; QSP, quantitative systems pharmacology; SUVR, standardized uptake values ratios; $T_{effs}$ - effector T cells; $T_{regs}$, regulatory T cells; Th, T helper cells.
Abstract

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by amyloid-β (Aβ) protein accumulation in the brain. Passive immunotherapies using monoclonal antibodies for targeting Aβ have shown promise for AD treatment. Indeed, recent US Food and Drug Administration (FDA) approval of aducanumab and lecanemab, alongside positive donanemab Phase III results demonstrated clinical efficacy after decades of failed clinical trials for AD. However, the pharmacological basis distinguishing clinically effective from ineffective therapies remains unclear, impeding development of potent therapeutics. This study aimed to provide a quantitative perspective for effectively targeting Aβ with antibodies. We first reviewed the contradicting results associated with the amyloid hypothesis and the pharmacological basis of Aβ immunotherapy. Subsequently, we developed a quantitative systems pharmacology (QSP) model that describes the non-linear progression of Aβ pathology and the pharmacologic actions of the Aβ-targeting antibodies. Using the QSP model, we analyzed various scenarios for effective passive immunotherapy for AD. The model revealed that binding exclusively to the Aβ monomer has minimal effect on Aβ aggregation and plaque reduction, therefore antibody affinity towards Aβ monomer is unwanted, as it could become a distractive mechanism for plaque reduction. Neither early intervention, high brain penetration, nor increased dose alone could yield significant improvement of clinical efficacy for antibodies targeting solely monomers. Antibodies that bind all Aβ species but lack effector function exhibited moderate effects in plaque reduction. Our model highlights the importance of binding aggregate Aβ
species and incorporating effector functions for efficient and early plaque reduction, guiding the development of more effective therapies for this devastating disease.

**Keywords:** Alzheimer’s disease, Amyloid-β, Therapeutic Antibody, Quantitative Systems Pharmacology (QSP) Disease Progression, Model-Informed Drug Development (MIDD), Pharmacometrics

**Significance Statement**
Despite previous unsuccessful attempts spanning several decades, passive immunotherapies utilizing monoclonal antibodies for targeting amyloid-beta (Aβ) have demonstrated promise with two recent FDA approvals. However, the pharmacological basis that differentiates clinically effective therapies from ineffective ones remains elusive. Our study offers a Quantitative Systems Pharmacology (QSP) perspective, emphasizing the significance of selectively targeting specific Aβ species and importance of antibody effector functions. This perspective sheds light on the development of more effective therapies for this devastating disease.
1. Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disorder and the leading cause of dementia. In the US, 6.5 million people older than 65 have AD, and these statistics are projected to grow to 13.8 million by 2060 in the lack of treatment that could change this course significantly (2022 Alzheimer's disease facts and figures, 2022). The main pathological hallmarks of AD include the formation of intracellular neurofibrillary tangles consisting of microtubule-associated protein tau, and extracellular plaques composed of the Aβ peptide (Knopman et al., 2021). Certain genetic factors are closely associated with AD pathology, including mutations in amyloid precursor protein (APP) gene and presenilin 1 and 2, and polymorphisms in apolipoprotein E (ApoE) (Gandy et al., 2006; Yamazaki et al., 2019). Symptoms include memory impairment, deterioration of language, and visuospatial deficits (Cummings, 2004). It is lifelong, and there is no cure. Prior to 2021, the available treatment options were able to influence disease symptoms, but were unsuccessful in slowing the progression or addressing the causative aspects of AD. Indeed, clinically available therapies for AD, such as cholinesterase inhibitors (donepezil, rivastigmine, galantamine) or non-competitive N-methyl-D-aspartate receptor antagonist (memantine), are medications which are largely used for palliative treatment (Cummings, 2004; Marucci et al., 2021); they do not modify disease progression or slow the rate of cognitive decline. Developing disease modifying (DM) strategies that prevent the formation of, or induce elimination of protein aggregates have peaked the interest of pharmaceutical companies (Eisele et al., 2015), with nearly 100 DM candidates in the drug development pipeline (Cummings et al., 2019). Anti-tau immunotherapies have emerged in recent years (Karran and De
Strooper, 2022), but most of these immunotherapeutic interventions to date are still directed against Aβ (Novak et al., 2018). Treatments that can alter the brain’s immune microenvironment are also found to be a promising therapeutic strategy, which can improve dysfunctional innate and adaptive immunity and prevent neurodegenerative pathology (Spencer and Masliah, 2014; Golde, 2022).

Passive immunotherapy targeting Aβ has emerged as a promising therapeutic approach for AD. In this approach, monoclonal antibodies bind to Aβ species and promote their clearance from the brain. Prior to aducanumab, a controversial, conditional approval in 2021 (U.S. Food and Drug Administration, 2023), and lecanemab, the first Aβ-targeting antibody to be converted from an accelerated to a traditional approval in 2023 (O of the U.S. Food and Drug Administration, 2023), not a single drug was approved by the US Food and Drug Administration (FDA) for AD in two decades, making it the most prominent unmet medical need, lagging behind other indications. However, the difference in pharmacological activity between clinically effective and ineffective therapies remains elusive, which has hindered the development of more potent therapies. This highlights the need for continued research and development in this area to better understand the underlying mechanisms of action and optimize treatment strategies for AD.

The experiences and results from clinical trials of lecanemab (Logovinsky et al., 2016; Swanson et al., 2021; Hayato et al., 2022; McDade et al., 2022; van Dyck et al., 2023a), gantenerumab (Ostrowitzki et al., 2017a; Portron et al., 2020; Salloway et al., 2021; Retout et al., 2022), donanemab (Lowe et al., 2021; Mintun et al., 2021a; Sims et al., 2023), and aducanumab (Sevigny et al., 2016; Budd Haeberlein et al., 2022; Zhu et
al., 2022) trials, as well as the use of pharmacometrics QSP tools, can provide valuable guidance for future anti-Aβ-antibody development programs (Costa and Cauda, 2022; Hayato et al., 2022; Lin et al., 2022; Geerts et al., 2023). The promise of QSP modelling in neuroscience and pharmaceutical industry has been recently highlighted (Nijsen et al., 2018). Several QSP models were developed to predict various aspects of anti-Aβ antibody therapy: explain Aβ kinetics and aducanumab efficacy observed in the clinical trials (Lin et al., 2022); depict production, transport, and aggregation of Aβ, and effect of beta-secretase (BACE) inhibitors and anti-Aβ antibodies (aducanumab, crenezumab, solanezumab, bapineuzumab) on the plaque reduction (Madrasi et al., 2021), Aβ-binding kinetics of crenezumab and solanezumab (Ferl et al., 2020); QSP model which includes Aβ pathophysiology in AD, and depicts pharmacokinetics, transport, and binding of monoclonal antibodies aducanumab, crenezumab, gantenerumab, and solanezumab to amyloid targets, as well as, mechanistic differences between apolipoprotein E ε4 carriers and noncarriers and microglia engagement (Ramakrishnan et al., 2023); most recently, a PBPK/QSP model with detailed pathology evaluated the impact on amyloid biomarker and amyloid-related imaging abnormalities with edema (ARIA-E) adverse effects of aducanumab, bapineuzumab, crenezumab, gantenerumab, lecanemab, and solanezumab (Geerts et al., 2023). These mechanistic models demonstrated the importance of data generated from various fields, biochemistry, biology, pharmacometrics, statistics, pharmaceutical sciences, neurology, with an overarching goal to provide guidance for drug development in AD using model-informed drug development (MIDD). These data involve everything from target and biomarker identification, molecule development, drug delivery techniques, to patient’s clinical
efficacy, disease state and side effects. In our work, we aim to revisit the amyloid hypothesis surrounding AD pathobiology, explain biochemical aggregation cascade of Aβ accumulation, identify current knowledge gaps regarding passive immunotherapies for AD, their pharmacokinetics (PK) and pharmacodynamics (PD), and develop a QSP tool to elucidate the pharmacological basis for effective anti-Aβ immunotherapies, in the hope to improve the development of more potent and effective therapies for AD. In contrast to previously developed mechanistic models of amyloid aggregation, we provide a novel perspective of nonlinear Aβ aggregation in a form of mathematical solution that is in agreement with in-vitro Aβ-aggregation studies. This, embedded in a comprehensive analysis and critical outlook on the hypothesis surrounding AD, as well as anti-Aβ-antibody features needed for successful therapy, can serve as a new perspective for researchers in the field.
2. Alzheimer's Enigma: Pathology, Amyloid Hypothesis, and Contradicting Results

Following the isolation of Aβ peptide by George Glenner in 1984, he and Caine Wong revealed that Aβ was derived from a larger protein called APP, a type I transmembrane protein (Glenner and Wong, 1984). Consequently, it was shown that Aβ generation begins with the cleavage of APP by the enzyme β-secretase (Sinha et al., 1999), which creates C terminal fragment of the APP. This is followed by “cutting” of the remaining membrane-bound protein portion by γ-secretase and release of Aβ (Figure 1). The resulting peptides can differ in length since the enzyme can cleave the protein in many different sites, and results in many different Aβ isoforms (Aβ1-40 and Aβ1-42 being the most prominent ones). These monomers assemble to form soluble oligomers and protofibrils, which aggregate and form insoluble fibrils, and consequently fibrils accumulate into the insoluble Aβ plaques (Figure 1), often surrounded by a halo of soluble species (Hardy and Selkoe, 2002). Defining particular species in the aggregation process is challenging as intermediates appear to be highly heterogeneous, rather than discrete assemblies (Sehlin et al., 2012a; Michaels, Šarić, Curk, et al., 2020). Categories mentioned here are generally recognized as key players in the aggregation mechanism, but their physicochemical characteristics are not uniform, for instance, size of different intermediates are always defined as a range with a certain average (Nilsberth et al., 2001; Sehlin et al., 2012b; Michaels, Šarić, Curk, et al., 2020). The amyloid hypothesis proposes that the accumulation of the Aβ into soluble and insoluble species is the critical process in neurodegeneration which leads to memory loss and impaired cognitive ability in AD patients.
One of the biggest obstacles in developing AD therapies is the fact that the onset of clinical symptoms appears decades after the first pathophysiological changes due to long aggregation process of pathological protein (Hardy and Higgins, 1992; Hardy and Selkoe, 2002). On one hand, this gives us a window of time to intervene in the progression of the disease, but on the other hand, lack of appropriate biomarkers makes it difficult to diagnose patients before the Aβ aggregation has advanced too far. Nevertheless, in vitro Aβ aggregation occurs on a timescale of hours, which allows protein biochemists to conduct mechanistic studies of this process and elucidate the aggregation kinetics. The initial basis of Aβ aggregation was building fibrils from monomers through specific intermediate stages. Then, once oligomers were proven to be highly cytotoxic, more attention was drawn to the interplay between these species and fibrils. From the biochemical point of view, in vitro Aβ aggregation kinetics is characterized by classical time-dependent sigmoidal curve, where lag phase represents a slow process of primary nucleation, followed by exponential growth. Initially, this fast growth was considered to be a result of fibril elongation and fragmentation, where fibrils have the ability to fragment into smaller units once they reach a certain threshold size. However, this traditional, homogeneous, slow nucleation from oligomer to fibril was not able to fit kinetic data on fibril growth using a sophisticated model. It was shown that the rapid phase of fibril formation process largely relies on monomer concentration, which is not the case for simple fibril fragmentation (Cohen et al., 2013). Cohen and authors proposed a mechanism that is currently accepted, which includes additional step of nucleation, a process that is both, fibril- and monomer-dependent. Oligomers, which are
formed by slow, primary nucleation, start elongating and eventually form insoluble fibrils. When a critical amount of fibrils is formed, they serve as catalytic surface producing toxic oligomers from free monomers, that attach to fibrils and convert to the form able to elongate further to protofibrils and fibrils. This process is described as secondary nucleation analog to the same process in crystallization, and opposed to homogeneous primary nucleation that is only monomer dependent and takes place in the solution (Cohen et al., 2013). Secondary nucleation dominates inefficient primary nucleation once critical amount of fibrils is formed. This theory is supported by the change in oligomer concentration during the aggregation time (Michaels, Šarić, Curk, et al., 2020). It is further extended with the hypothesis that toxic oligomer formation in secondary nucleation includes a step of structural conversion from unproductive oligomeric intermediates, which show slow aggregation to productive ones which form higher species more rapidly (Dear et al., 2020). Such complexity of the aggregation process and the interplay between multiple Aβ species makes it difficult to determine the optimal target for anti-Aβ antibody therapy. Indeed, one of the reasons for this may include ineffective mechanisms of action due to targeting monomeric or fibrillar Aβ, instead of soluble Aβ oligomers or protofibrils shown as the most neurotoxic species. Those soluble species are demonstrated as the promising targets due to their effect on synapses in memory-related brain regions (Nilsberth et al., 2001; O’Nuallain et al., 2010; Goure et al., 2014) and the fact that protofibrils are internalized by microglia (brain-resident macrophages) to a greater extent than monomers (Gouwens et al., 2016). Importantly, fibrils and plaques, on the other hand, are related to synaptic disfunction (Le et al., 2001; Meyer-Luehmann et al., 2008; Spires-Jones and Hyman,
2014). So, even though soluble species are thought to be the most harmful, neurotoxicity of fibrils vs oligomers/protofibrils is still a source of ongoing debate. Instead of counting pros and cons for polarized opinions on this matter, all the data can be interpreted in the context of current aggregation kinetics hypothesis which highlights secondary nucleation as a critical step in fibril formation. In light of drug development, the most important part of this hypothesis is the fact that fibrils act as catalysts, and are the actual source of toxic oligomers and protofibrils that speed-up further fibrillation in a positive feedback manner (Cohen et al., 2013). Contrary to the belief that fibrils, as the endpoint of aggregation, are inert and less harmful, they serve as a link between the aggregation pathway perpetrators and have an essential role in the propagation process.

Despite the established role of Aβ in AD, up until recently, there was no solid evidence of clinical improvement with anti-Aβ passive immunotherapies in AD patients. This is in part due to the lack of understanding of these complicated aggregation processes. Even if the amyloid theory is incomplete, misinterpreted or not entirely correct (Makin, 2018), there may be other factors that contribute to the lack of significant clinical improvement with anti-Aβ therapies. These factors might be suboptimal drug exposure at the site of target expression (lack of medicines entering the clinic, which exploit receptor-mediated transcytosis to pass the blood-brain barrier), inadequate time of drug administration, or unselected patient population (e.g., antibodies being administered too late in the disease progression when the damage in trial participants could not be reversed). Another explanation for lack of clinical efficacy is the fact that there are other pathological brain processes, which are key disease mediators of Aβ
plaque and neurofibrillary tangle pathology. Indeed, dysregulated immune response in the brain microenvironment is increasingly being recognized as an important factor in AD pathogenesis (Gendelman and Mosley, 2015; Heneka et al., 2015; Cisbani and Rivest, 2021; Chen and Dm, 2022). Together with oxidative stress, neuroinflammation plays a significant role in the pathogenesis of AD; it is mainly localized at the sites of Aβ plaques, leading to increased proinflammatory cytokines, complement components, and proteases (Leng and Edison, 2021). At early stages and throughout the disease, T cells and reactive microglia orchestrate neuroinflammatory responses and propagate neurodegeneration. On one side, neuroprotective microglia (M2 phenotype) are responsible for Aβ plaque clearing and maintaining neuronal survival, on the other, inflammatory microglia (M1 phenotype) can elicit tau pathogenesis and accelerate neurotoxicity; though it seems there is a continuum of phenotypes between the two extremes (Gendelman and Mosley, 2015; Tang and Le, 2016). Recent study indicates that dense-core plaques containing Aβ peptides do not form spontaneously, but rather are formed by microglia. This was compared to the assembly of mycobacterial granulomas, the defining histopathological features of tuberculosis (Lemke and Huang, 2022). The plaques are surrounded by activated astrocytes (glial cells) and microglia, the primary source of inflammatory components. Self-antigens, such as Aβ species, may also prompt autoreactive effector T cells (Teffs), which further induce proinflammatory response and impair brain immune homeostasis (Machhi et al., 2021). An increased infiltration of T-cells in AD patients was observed in cerebrospinal fluid (CSF) and brain parenchyma (Togo et al., 2002; Gate et al., 2020). This, and many other examples highlight the importance of disrupted innate and adaptive immune response.
system in disease pathogenesis (Gendelman and Mosley, 2015; Heneka et al., 2015; Machhi et al., 2021; Chen and Dm, 2022) thus emerging as an opportunity for therapeutic development (Jordan et al., 2020; Machhi et al., 2020). One example includes ex-vivo expanded and enhanced regulatory T cells (T\(_\text{regs}\)), which suppress microglia-mediated neuroinflammation via contact-mediated mechanism (Faridar et al., 2020), making it a potential cell-based therapeutic avenue for AD (Saleh et al., 2022).

An additional mechanism which was explored for therapeutic gain is the progression of AD pathology influenced by transcellular propagation of protein aggregation, which is the basis of prion disease. The prion model predicts patterns of neuronal vulnerability and network involvement based on the conformation of pathological proteins. This creates avenues for new therapeutic approaches, such as immunotherapy to block transcellular propagation for instance, or novel diagnostic tools to detect early stages of the disease(Stopschinski and Diamond, 2017). Interestingly, a recent study analyzed the \textit{in-vivo} spatiotemporal distribution of A\(_\beta\) in AD and concluded that A\(_\beta\) accumulation begins in all brain regions around the same time and that heterogeneous regional carrying capacities primarily cause its spatiotemporal distribution for the aggregated protein rather than the long-term distribution from seed regions (Whittington et al., 2018).
3. Passive Aβ Immunotherapy: Learning from Failures

Over the last few decades, attempts were directed at altering Aβ deposition by either inducing humoral immunity to fibrillar Aβ or prompting passive immunity by administering anti-Aβ antibodies. Active immunization with Aβ₁₋₄₂ peptide (AN1792) led to antigen-specific T cell responses, but AN1792 clinical trial has been ceased due to unexpected meningoencephalitis and death, both associated with the vaccine (Gilman et al., 2005). Recently, Aβ synthetic peptide vaccine (UB-311) was developed to stimulate an immune response of T-helper (Th) type 2 instead of Th type 1 proinflammatory response, which can circumvent cross-reactivity with comparable endogenous antigens. UB-311 exhibited a safe profile and generated Aβ antibodies in 96% of subjects in a Phase 2 trial in patients with mild-to-moderate AD (Wang et al., 2017). It is hypothesized that UB-311 can break self-tolerance and limit the possibility of developing a similar T cell-mediated reaction as seen following AN1792 vaccination.

Therapeutic interventions were continuously investigated over the years; nevertheless, a substantial struggle remains to find viable targets within this complex disease framework that can modify disease progression in AD. Seven anti-Aβ immunoglobulin G (IgG) antibodies have been evaluated as passive immunotherapy for clearing aggregated Aβ. These antibodies all entered late-phase clinical trials for treating patients at early stages of AD, including solanezumab, crenezumab, bapineuzumab, gantenerumab, donanemab, lecanemab, and aducanumab (Zhu et al., 2022; Perneczky et al., 2023). On June 7th, 2021, the US FDA provided conditional approval of aducanumab. Aducanumab binds Aβ oligomer and plaque, with negligible
affinity to monomer (Arndt et al., 2018), and once bound it activates antibody-dependent cellular phagocytosis (ADCP) (Sevigny et al., 2016). Two phase III clinical trials EMERGE (NCT02484547) and ENGAGE (NCT02477800) with aducanumab showed a dose-dependent reduction of Aβ plaque in the brain (U.S. Food and Drug Administration, 2021). Aβ standardized uptake values ratios (SUVR) was used as longitudinal biomarker in aducanumab trials, and FDA performed exposure-response (E-R) analyses to quantify the relationship between aducanumab longitudinal exposure and responses (SUVR for Aβ as well as other clinical endpoints). This work supported an evident E-R relationship: SUVR reduction over time increases with increased aducanumab exposure (Zhu et al., 2022; Wang, 2023). The approval has prompted further development of other anti-Aβ antibodies. Consequent approval of lecanemab followed (O of the U.S. Food and Drug Administration, 2023; van Dyck et al., 2023b), significant clinical success of donanemab (Sims et al., 2023), and failure of solanezumab (Honig et al., 2018a; Sperling et al., 2023; Lilly Provides Update on A4 Study of Solanezumab for Preclinical Alzheimer’s Disease | Eli Lilly and Company, 2023) and gantenerumab (Ostrowitzki et al., 2017b; Salloway et al., 2021). So the question poses itself: what differentiates effective vs non-effective anti-Aβ antibodies? The selectivity of Aβ-directed immunotherapies might be critical. Solanezumab, for example, exclusively targets Aβ monomers while most of the other antibodies target higher Aβ species (Zhao et al., 2017; Honig et al., 2018b; Salloway et al., 2021). The exact role of different Aβ species in AD pathology is still being studied, and it is not yet clear which Aβ species relate to the pathology the most, and as such which one should be effectively targeted, as discussed in section 2. Mounting evidence has shown that
oligomers and protofibrils are more toxic than insoluble fibrils or monomers as they enable neurotoxicity and jeopardize synaptic functionality (Walsh et al., 1997; Nilsberth et al., 2001; Lublin and Gandy, 2010; O’Nuallain et al., 2010). Non-fibrillar oligomers cause oxidative stress, membrane permeabilization, mitochondrial dysfunction, and activation of proinflammatory response (Haass and Selkoe, 2007). The ratio of Aβ oligomer to plaque density largely separates demented from non-demented patients (Esparza et al., 2013). Finding methods for specifically detecting oligomers but not the larger aggregates may enable effective diagnostic and therapeutic interventions for AD (Aprile et al., 2020). Despite great efforts, this has not been accomplished yet. As opposed to other amyloid systems such as α-synuclein in Parkinson’s disease, Aβ oligomers are challenging to separate, purify or even detect in vitro due to their poor stability and high dissociation (k_{off}) rate (Michaels, Šarić, Curk, et al., 2020). Consequently, even the definition of oligomer species is vague and varies in different literature sources when taking into account different parameters such as size, growth-rate, structure and biological activity as parameters (Linse, 2017; Dear et al., 2020). Most of the in vitro studies trying to target these species use operational definitions regarding their chromatography or sedimentation behavior, both related to molecular weight (Nilsberth et al., 2001; Johansson et al., 2006). Either approach takes a range of particle sizes with an average as a common value sometimes without specifying if they are dimers, tetramers, further aggregates or (most likely) mixture of these (Michaels, Šarić, Curk, et al., 2020). Another obstacle in differentiating between Aβ species are structural differences on the way to Aβ plaques that include many conformational changes which are actual rate-limiting steps of the process (Dear et al., 2020; Michaels,
Šarić, Curk, et al., 2020) and are likely to affect epitope exposure. To optimize Aβ therapy, a more mechanistic and thorough understanding of the anti-Aβ antibodies, their binding to specific Aβ targets, PK behavior, and pharmacologic effects in the context of Aβ levels and turnover is needed. In this work, we create a mathematical framework that depicts a non-linear progression of the disease which we believe is a more physiologically relevant manner of aggregation. We then explore the pharmacological basis and differences among these anti-Aβ-targeting antibodies, underlying their therapeutic potential and limitations.
4. A QSP Perspective of Passive Aβ Immunotherapy

4.1 Caveats of “Sink Hypothesis” and Implications of Antibody Design

The process of Aβ accumulation from monomer, dimer, tetramer, and further oligomers (Figure 1) is a relatively reversible process. More specifically, the oligomer to monomer dissociation rate constant, $k_{\text{off}}$, was shown to be $73 \text{ s}^{-1}$ (Fawzi et al., 2010). However, due to the slow process of dissociation from the plaque back to smaller species (assumed 1000-fold slower (Madrasi et al., 2021)), it may be presumed that it is largely a one-directional process.

Given that the endogenous plaque turnover is extremely slow, we believe that one rate limiting step for the whole process is the removal of the Aβ plaque/aggregated Aβ plaque-antibody complex, or some other higher order Aβ species (protofibril, fibril), rather than the monomer. If the antibody largely targets the monomer, like in the case of solanezumab, according to the “sink hypothesis”, this will affect monomer equilibration between the brain and the blood, plaque will begin disintegrating towards oligomers and monomers, causing the decrease in the level of Aβ plaque in the brain without the need for entering the brain. Even if a high percentage of neutralization (95% or 99%) is achieved, it may not be sufficient to prompt plaque disintegration, since the reversibility of this process is very low. In the case of monomer-antibody binding, distraction toward other species would also be undesirable and would hinder the totality of this process.

There is evidence against the sink hypothesis, as BACE inhibitors, which inhibit the production of smaller Aβ species in the periphery and prevent the production of new Aβ plaques, do not prompt plaque disintegration (Panza et al., 2018). More than 50 mg/kg of antibody with subnanomolar potency for monomer is needed to maintain less than 40% of the free monomer from the baseline, as shown in a recent modelling study.
(Madrasi et al., 2021). Additionally, Aβ monomer is a small molecule (0.85 nm) (Nag et al., 2011) with a high production rate, fast turnover, and ultimately large concentration in the brain, making it challenging to neutralize 100% of the monomers with Ab. Therefore, Aβ monomer may not be an ideal target for AD therapy.

The efficacy of Aβ-targeted immunotherapies can also depend on the target epitope of the antibodies. Anti-Aβ antibodies have different affinities towards different forms of Aβ species have different affinities for different antibodies (Supp. Table 1), and it is rare that an antibody binds exclusively to one species, since the particular epitope might be exposed in the other species as well (Goure et al., 2014). This multiple binding can reduce the amount of antibody available for neutralizing the most toxic Aβ species, such as soluble oligomer or protofibril, as previously discussed in Section 3.

When an antibody binds to the aggregated Aβ plaque, it may not be sufficient to achieve therapeutic benefit without an effector function. This is because the antibody may not be able to clear the plaque by itself. One important mechanism of antibody-mediated clearance of Aβ plaques is ADCP, which involves the uptake and degradation of the antibody-bound plaques by microglia and other phagocytic cells in the brain. ADCP is facilitated by the fragment crystallizable (Fc) region of the antibody, which binds to Fc receptors on the surface of the phagocytic cells. This binding triggers a signaling cascade that leads to the engulfment and clearance of the antibody-bound plaque by the phagocytic cell. It should be noted, that in clinical trials anti-Aβ mAbs with effector function were shown to induce vasogenic edema/microhemorrhage associated with amyloid-related imaging abnormalities (ARIA) especially in ApoE4 carriers that are likely related to binding onto vascular amyloid (Sperling et al., 2012; Brashear et al.,
2018; Avgerinos et al., 2021). Despite this fact, ADCP is an effective mechanism for Aβ plaque clearance in animal models and in in vitro studies (Bard et al., 2000; Sevigny et al., 2016). Increasing attempts to keep/enhance Fc function, but circumvent neuroinflammation are underway (Crehan et al., 2020). Most of the antibodies under clinical development are IgG1. The strong effector function of IgG1 might trigger neuroinflammation and ARIAs (Kapur et al., 2014), as observed with aducanumab, donanemab, bapineuzumab (Sperling et al., 2012; Mintun et al., 2021b; Salloway et al., 2022). On the other hand, crenezumab, an antibody containing IgG4 backbone, was designed to exert reduced effector function on microglia, but two large Phase III clinical trials in early AD were terminated due to an interim analysis that suggested that treatment would not slow cognitive decline in patients with prodromal to mild AD (Ostrowitzki et al., 2022). This suggests that the interplay between antibody epitope specificity and effector function warrants a thorough analysis. In summary, active removal of Aβ plaques through ADCP is an important mechanism for achieving therapeutic benefit with Aβ-targeting immunotherapy.

4.2. QSP model structure

Using a quantitative mass-balance approach for the Aβ species and their interaction with therapeutic antibodies, we aim to provide a mechanistic analysis of the AD pathobiology and Aβ immunotherapy. This approach can evaluate the potential for neutralization of Aβ species by anti-Aβ antibodies in the brain, based on the target production/elimination, aggregation rates, and Aβ binding selectivity. We consider the following anatomical sites of action: brain, vascular, and peripheral tissues. As previously mentioned, Aβ monomers aggregate and form soluble Aβ oligomers in all
tissue sites. Nevertheless, the plaque formation from the soluble oligomer is limited only to the brain interstitial fluid (ISF). In this scenario, the CSF is not of utmost importance for what occurs in the brain; to demonstrate our points, we focused on the brain compartment/site of action.

This QSP model (Figure 2) aimed to capture Aβ aggregation and explore the feasibility of “sink hypothesis” and role of antibody effector function. The model was constructed using a system of ordinary differential equations (ODEs) and calibrated to observed standard uptake value ratio (SUVR) values, which were obtained from the literature (Insel et al., 2021). This modeling approach allowed for the exploration of various scenarios and hypotheses related to the dynamics of Aβ aggregation and the potential effects of immunotherapy. The results of the simulations could help to inform the development of more effective treatments for AD and other related conditions. The SUVR, PK and PD data was digitized using WebPlot Digitizer (https://automeris.io/WebPlotDigitizer/). Pharmacokinetic parameters were calculated using Phoenix® WinNonlin® version 8.3, Certara USA, Inc., NJ. The modeling and simulation was implemented in R using the mrgsolve package (Baron, 2022).

Model structure (Figure 2) includes vascular compartment which is directly connected to the brain, and peripheral compartment representing all tissues other than the circulation. Main assumptions in our model are:

1. Forward formation is a nonlinear process. It has been established that the Aβ aggregation process is a complex nonlinear kinetic process, where the aggregating species can act simultaneously as the reactants, intermediates, products, and catalysts of the aggregation cascade (Ōsawa and Asakura, 1975; Ferrone et al., 1985; Ruschak...
and Miranker, 2007; Knowles et al., 2009; Cohen et al., 2011, 2013; Michaels et al., 2018; Törnquist et al., 2018; Michaels, Šarić, Meisl, et al., 2020). This cascade is a low-efficiency process, where only a small amount of monomer participates in the aggregation. Mainly the beginning of this long-lasting process is driven by the soluble species, however, it is not proportionally correlated to the soluble species. Hence, the model tries to reflect the complex, nonlinear nature of the Aβ aggregation process, which is characterized by low efficiency and limited reversibility.

(2) Brain is assumed to be the main site of action, since insoluble Aβ species only appear in the brain.

The ODEs in our model describes the nonlinear assembly of Aβ species and their concentration in the brain over time:

1) Monomer (T)

\[
\frac{d(T)}{dt} = k_{syn}T - \frac{R_{max}TT * T}{K_{dTT} + T} + k_{off}TT * TT - k_eT * T
\]

2) Dimer (TT)

\[
\frac{d(TT)}{dt} = \frac{R_{max}TT * T}{K_{dTT} + T} - k_{off}TT * TT - \frac{R_{max}TTT * TT}{K_{dTTT} + TT} + k_{off}TTT * TTT
\]

3) Tetramer (TTT)

\[
\frac{d(TTT)}{dt} = \frac{R_{max}TTT * TT}{K_{dTTT} + TT} - k_{off}TTT * TTT - \frac{R_{max}O * TTT}{K_{dO} + TTT} + k_{off}O * O
\]

4) Oligomer (O)
\[
\frac{d(O)}{dt} = \frac{R_{max}O \cdot TTT}{K_dO + TTT} - k_{off}O \cdot O - \frac{R_{max}P \cdot O}{K_dP + O} + k_{off}P \cdot P
\]

5) Protofibril (P)

\[
\frac{d(P)}{dt} = \frac{R_{max}P \cdot O}{K_dP + O} - k_{off}P \cdot P - \frac{R_{max}F \cdot P}{K_dF + P} + k_{off}F \cdot F
\]

6) Fibril (F)

\[
\frac{d(F)}{dt} = \frac{R_{max}F \cdot P}{K_dF + P} - k_{off}F \cdot F - \frac{R_{max}A \cdot F}{K_dA + F} + k_{off}A \cdot A
\]

7) Aggregated plaque (A)

\[
\frac{d(A)}{dt} = \frac{R_{max}A \cdot F}{K_dA + F} - k_{off}A \cdot A
\]

where \(R_{max}\) is the maximum rate of Aβ species formation; \(K_d\) is the constant equal to the concentration of Aβ species at which the \(R_{max}\) is at half of its maximum value. \(k_{off}\) is the first-order rate constant for the Aβ species dissociation. Parameter values and ordinary differential equations for specific simulated scenarios are part of Supplemental Data and Supplemental Tables.

4.3. Model Calibration

4.3.1. AD Natural Trajectory

Calibrating the model using Aβ PET SUVR values from the clinic allows us to ensure that the model can capture dynamics of Aβ accumulation in the brain. Parameter values for calibration are included in Supp. Table 2. Our predicted, Aβ increase over 50 years (20 years prior to and 30 years after first clinical symptom) was able to capture the
observed PET SUVR values (Insel et al., 2021). As shown in Figure 3, the model is able to capture the AD disease trajectory through nonlinear assembly of Aβ species.
4.3.2. PK/PD of Anti-Aβ Antibodies

After calibration of the natural history, we validated the model using available data from clinical trials of anti-Aβ antibodies. This involves comparing the predicted outcomes from our model to the observed outcomes in the clinical trials, such as changes in amyloid PET SUVR levels. Molecular weight (Supp. Table 3), PK (Supp. Table 4) and appropriate doses were incorporated to the model to recapitulate the dynamics of antibody concentrations in the central and peripheral compartment. The plasma PK of the observed data for aducanumab (Ferrero et al., 2016), bapineuzumab (Black et al., 2010), crenezumab (Yoshida et al., 2020), gantenerumab (Portron et al., 2020), lecanemab (Logovinsky et al., 2016), and solanezumab (Uenaka et al., 2012) at various dosing ranges and dosing frequencies was well captured by developed models (PK modelling was performed in Phoenix® WinNonlin® version 8.3, Certara USA, Inc., NJ). Aducanumab and lecanemab PK calibration results are presented in Figure 4, panels, A and C, respectively, whereas plots for remaining antibodies are part of Supplemental Materials (Supp. Fig. 1, 2, 3, 4). To capture PD endpoint of clinically tested antibodies PET SUVR data (Supp. Table 5) from clinical trials on aducanumab (Biogen, 2021; Haeberlein et al., 2023), bapineuzumab (Liu et al., 2015; Brody et al., 2016), crenezumab (Ostrowitzki et al., 2022), gantenerumab (Ostrowitzki et al., 2017a), lecanemab (Swanson et al., 2021), solanezumab (Doody et al., 2014a; Sperling et al., 2023; Lilly Provides Update on A4 Study of Solanezumab for Preclinical Alzheimer's Disease | Eli Lilly and Company, 2023) was compared to the simulated data at the same dose/dosing regimen, and at the same time point as the observed clinical data. Antibody affinities towards specific Aβ species (K_d values) were taken from the literature.
(Geerts et al., 2023). The PD calibration with aducanumab and lecanemab is presented in Figure 4, panels B and D, respectively. Panel E in the Figure 4 demonstrates satisfactory correlation between the clinical and simulated reduction in the PET SUVR values following different anti- Aβ-antibody therapy. PK/PD calibration for gantenerumab, bapineuzumab, crenezumab and solanezumab is part of Supplemental Materials (Supp. Fig. 1, 2, 3, 4).

Overall, calibrating and validating our model using clinical data allows us to ensure its accuracy and relevance to the real-world scenario of AD and anti-Aβ antibody therapy.

4.4. Unveiling the Crucial Role of Effector Function and Aβ Species Selectivity

To highlight the most important aspects of Aβ immunotherapy, we explored 4 different scenarios using the model. Intervention was introduced two decades before clinical signs and symptoms appeared, but when Aβ pathology already exists. Model parameters are included in Supp. Table 6. First scenario represents a hypothetical Drug A that binds solely to the soluble Aβ monomer. The aim was to investigate whether neutralization of the monomer in the periphery has any effect on disease progression. Similarly to the clinical results with solanezumab that failed to improve disease progression, cognition or functional ability (Doody et al., 2014a; Sperling et al., 2023; Lilly Provides Update on A4 Study of Solanezumab for Preclinical Alzheimer’s Disease | Eli Lilly and Company, 2023), the hypothetical Drug A demonstrated no improvement in disease progression over a period of 50 years from disease onset (Figure 5, Panel A). Of note, a 100-fold higher dose and more frequent dosing regimen did not decrease disease progression either (Figure 5 Panel B).
For a hypothetical Drug B, the aim was to investigate a scenario where it would bind all soluble and insoluble species (from monomers to plaques). This scenario resulted in a mild reduction of disease progression measured by PET SUVR (Figure 5, Panel C).

In the third scenario, a hypothetical Drug C binds oligomer, protofibril, fibril and aggregated plaque (Figure 5, Panel D). Similar effect for Drug B and Drug C means that most of the effect comes from binding to insoluble species, and binding smaller, soluble species does not contribute to PET SUVR reduction as much. These simulation results led us to believe that antibody binding to the monomer may be a “distraction”. Both hypothetical Drug B and C were designed without the antibody effector function.

In the final scenario, we explored the effect of a hypothetical Drug D designed with an effector function, which conferred a significant reduction in the disease progression (Figure 5 Panel D). These results suggest that for efficient, early plaque removal, antibody effector function is a requirement and that binding to Aβ monomer is an ineffective and distracting mechanism of action.

These results are consistent with recent clinical observations: IgG1 antibodies (like aducanumab and bapinezumab) have an activating Fc domain that elicits microglial response, which is responsible for reducing Aβ deposits (Hladky and Barrand, 2014), whereas IgG4 (like crenezumab) does not. On one hand, effector function is necessary for efficient plaque clearance, but on the other, it can lead to toxic side effects like ARIA-E. Therefore, optimizing the effector function of anti-Aβ-antibody therapy is crucial in order to maximize its therapeutic potential while minimizing the risk of adverse effects. This can be achieved through careful design and engineering of the therapeutic antibody, considering factors such as antibody’s affinity for Aβ, its Fc receptor binding
properties, and its ability to engage and activate immune cells. Additionally, dosing regimens and administration routes can also play a role in optimizing the effector function of passive immunotherapy.
5. Outlook

This study provides an overview of the field and our perspective surrounding the challenges of the amyloid hypothesis, the pharmacological basis of anti-Aβ passive immunotherapy, and the factors that contribute to the efficacy of the immunotherapies for AD. The study highlights the importance of effector functions in achieving early and efficient plaque reduction and suggests that antibodies targeting higher-order Aβ species, such as protofibrils and fibrils, rather than solely targeting the monomer may be more effective (Figure 5).

Our simulations demonstrated that even with the higher brain exposure of antibodies targeting monomer (designed to exploit the "sink hypothesis"), it would not be sufficient to neutralize 100% of the monomer in the body (Figure 5, Panel B). Antibody binding to the Aβ monomer may have a distractive effect and further increase in the dose/dosing regimen of monomer-targeting antibodies would not influence plaque reduction. This is confirmed in the solanezumab secondary prevention trial (Sperling et al., 2023; Lilly Provides Update on A4 Study of Solanezumab for Preclinical Alzheimer’s Disease | Eli Lilly and Company, 2023). In the solanezumab secondary prevention trial, more than 1,100 individuals between 65 and 85 years of age with PET-imaging evidence of amyloid plaque accumulation in the brain but with no clinical impairment were enrolled. Solanezumab did not slow down the cognitive decline nor did it improve the clearance of the brain amyloid plaque (Sperling et al., 2023; Lilly Provides Update on A4 Study of Solanezumab for Preclinical Alzheimer’s Disease | Eli Lilly and Company, 2023). This finding is consistent with the clinical results from solanezumab trials (Doody et al., 2014b; Honig et al., 2018b; Salloway et al., 2021) and supports the
idea that efforts should be focused on targeting other intermediate or higher order accumulated Aβ species rather than solely targeting Aβ monomer species,

Targeting oligomers and protofibrils with antibodies has emerged as a promising approach for the treatment of AD. By binding to and sequestering these toxic species, antibodies may prevent their accumulation and subsequent neurotoxicity. The success of lecanemab and aducanumab, which target protofibrils and oligomers/fibrils/plaque respectively, highlights the potential of this approach (Ono and Tsuji, 2020). This is not unusual considering the initial mechanism of Aβ aggregation (continuous primary nucleation, and high oligomer $k_{\text{off}}$ rate blocking the fibril formation). As disease progresses, initial rise in the amount of fibrils further speeds-up the process, secondary nucleation overtakes and leads to increased build-up of plaques. With such mechanistic route, it may be expected that inhibition of the secondary nucleation process is the key to successful treatment (Michaels, Šarić, Meisl, et al., 2020; Chia et al., 2023). As this process involves fibrils (catalyst) and oligomers (including protofibrils according to definitions given by Linse et. al (Linse et al., 2022)), it seems that monoclonal antibodies that bind these species have higher chance of slowing down the disease progression, as demonstrated by aducanumab and lecanemab. Recent pre-clinical research shows great potential for oligomer (Linse et al., 2022) or fibril-binding (Cohen et al., 2015) inhibitors which prevent secondary nucleation, as both insoluble plaque and toxic oligomers are involved in the process. However, even though both fibril and oligomer binding prevents further fibril/plaque formation and subsequent increase in toxicity (as fibrils generate new toxic oligomers), these species are not equally interesting as targets. Once the disease reaches a point where certain amount of fibrils is
accumulated, higher drug dose is needed for its’ neutralization. On the other hand, the amount of oligomer and protofibril population is shown to be ~ 1% of total Aβ mass concentration (Michaels, Šarić, Curk, et al., 2020), which (together with direct sequestering their toxicity) makes these species preferable targets for therapeutic intervention. To consider this further, it is important to revisit current understanding about the differences between oligomers and protofibrils.

Even though distinct steps in secondary nucleation process are elusive, there are firm evidence that fibrils act as catalysts on which surface, soluble species (could be monomers, or smaller oligomers) change their conformation faster and adopt uniform structure which allow facilitated elongation, making a new branch of fibril. Once fibril detaches, it propagates plague formation (Cohen et al., 2013). According to the model that successfully captures in-vitro aggregation data, oligomers have very high dissociation rate, higher than the rate of conversion to fibrils (Michaels, Šarić, Curk, et al., 2020). Secondary nucleation becomes more efficient when oligomer become inert, and transform into a conformation suitable for fibril growth. This conversion is labeled in biophysical literature as “fibrillar oligomers” or growth-competent oligomers (Dear et al., 2020). In a broad sense, protofibrils are a type of oligomers (based on their solubility and size), but they also structurally resemble fibrils (Walsh et al., 1997). Since oligomers and protofibrils are difficult to isolate and characterize in a structural sense (as intermediate species), conformational differences between proposed “nonfibrillar” and “fibrillar” intermediates are unknown. It has been suggested that the conformational changes leading to the formation of β-sheet structures may involve the transformation of disordered monomer assemblies into a more stable structure (Riek, 2017). Kinetic
models based on *in-vitro* studies show that size is not the crucial parameter for transforming "nonfibril" oligomer to the one that elongates easily and becomes insoluble fibril. What is more important for directing the process to aggregate formation seems to be the structural change (Dear *et al.*, 2020). Therefore, targeting specific Aβ species with drugs that can stabilize their structure or prevent their further aggregation may be a promising approach for treating AD (as demonstrated with Drug C).

We also highlighted the antibody effector function (Drug D) as an important aspect for the success of Aβ immunotherapy (Figure 5, Panel D). The effector function of anti- Aβ antibodies, which includes their ability to recruit microglia and remove Aβ plaques, has been shown to play a crucial role in the success of these antibodies. Therefore, the innate immunity in neurodegenerative diseases should be taken into consideration while developing Aβ immunotherapy and balancing their phagocytic activity towards Aβ may be a promising therapeutic strategy. However, the ability of microglia to clear Aβ is impaired during advanced neurodegeneration. Even though microglia have an "activated" phenotype in AD, they are unable to uptake Aβ plaque to prevent the neurodegeneration in AD (Fu *et al.*, 2014). In addition to microglia, other cells in the innate immune system, such as monocytes, macrophages, and dendritic cells, also play important roles in the clearance of Aβ. These cells express receptors for immunoglobulins, including Fc gamma receptors (FcγRs), which can mediate phagocytosis of antibody bound Aβ. Thus, selection of antibodies with appropriate effector functions, such as binding to FcγRs and activating the innate immune system, can enhance the efficacy of Aβ immunotherapy.
Network-based blood gene expression analysis demonstrated dysregulated FcγR-mediated phagocytosis in patients with AD (Park et al., 2020). Protein kinase C delta type (PRKCD) is also associated with neurodegeneration induced by Aβ. Blood-based gene co-expression network analysis identified PRKCD in the FcγR-mediated phagocytosis pathway as being significantly associated with cognitive function and CSF biomarkers in AD patients, thus implicating the peripheral innate immune system in the pathophysiology of AD (Park et al., 2020). This is where an early intervention (prior to manifestation of AD symptoms), or even a combination therapy with agents that induce immune tolerance or restore brain microenvironment to a neurotrophic one might be needed. Early intervention, on the other hand is closely correlated with identification of a disease biomarker. Novel research directed at identifying biomarkers for AD are underway, with one example being neuroinflammation positron emission tomography imaging through translocator protein (TSPO) tracers (Zhou et al., 2021).

CSF also has an important role in maintaining brain homeostasis. Recent studies have revealed new pathways and functions of the CSF, including its role in immune surveillance and the potential for rejuvenation of the ageing brain, serving as a nutrient source and a waste removal system. Recent studies report that CSF circulates into the skull channels and enters the bone marrow as well, thereby participating in the immune surveillance. The discovery of channels linking the skull bone marrow and the meninges, through which bone marrow-derived immune cells can travel and reach the brain (Pulous et al., 2022) provides an opportunity to modulate the immune system through these pathways (Bakoyiannis, 2022). It has been postulated that young CSF had rejuvenating power, where fibroblast growth factor 17 was highlighted as a key
target to restore oligodendrocyte function in the ageing brain (Iram et al., 2022). Collectively, the CSF serves multiple critical functions in the brain, including maintaining homeostasis, immune surveillance, and providing a means to measure AD biomarkers. Further research into the role and functions of the CSF may lead to new insights into the pathophysiology of AD and discovery of more effective diagnostic tools and treatments.

Another challenge in drug development for AD is translation from preclinical animal models to humans. Development of humanized mice models that better reflect human hematopoiesis, natural immunity, neurobiology, and molecular pathways may help to overcome some of these challenges and improve the translation of therapies to the clinic (Dash et al., 2021). Furthermore, recent advances in the understanding of Aβ-antibody interactions and the development of Aβ-targeting biologics may offer new therapeutic approaches for AD and other diseases. It is interesting to note that a recent study identified two peptides from the SARS-CoV-2 proteome that self-assemble into amyloid formations and are toxic to neurons, similar to the aggregated amyloid proteins/peptides in AD. This discovery may provide new insights into the mechanisms of amyloid formation and toxicity in the brain, and could potentially lead to the development of new therapies for both AD and COVID-19 (Charnley et al., 2022).
6. Conclusions

Our study offers a comprehensive and quantitative outlook on the amyloid pathology in Alzheimer's disease (AD) and the therapeutic approach of Aβ passive immunotherapy. By employing multidisciplinary methods and utilizing QSP modeling and simulation techniques, we have made significant strides in comprehending the intricate non-linear progression of the disease and unraveling the key determinants influencing the efficacy of Aβ passive immunotherapy. Our findings emphasize the critical role of antibody specificity in targeting specific Aβ species and shed light on the intrinsic characteristics of antibodies, including their effector function. These valuable insights hold the potential to inform the development of more potent and efficacious Aβ immunotherapy strategies.
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Footnotes

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Authorship Contributions

Participated in research design: Marković M., Milošević J., Wang W., and Cao Y.

Conducted experiments: Marković M.

Performed data analysis: Marković M., Cao Y.

Wrote or contributed to the writing of the manuscript: Marković M., Milošević J., Wang W., Cao Y.

Conflicts of interest

Wang W. is an employee of Janssen Research and Development LLC, The Pharmaceutical Company of Johnson and Johnson. Cao Y. is a consultant for Janssen Research and Development LLC, The Pharmaceutical Company of Johnson and Johnson. All other authors declared no competing interests for this work.

This article contains no datasets generated or analyzed during the current study.
Legend for figures

**Figure 1.** Mapping the AD Aβ aggregation pathway and targeted anti-Aβ therapeutics (small molecules and antibodies) aligned with distinct stages of the pathway.

**Figure 2.** Model Structure depicting peripheral and central compartments (CMT) connected to the brain CMT. Monomer-specific antibody (Drug A) shown in blue, while oligomer, protofibril, fibril, or plaque-specific antibody (Drug C, D) depicted in pink.

**Figure 3** Model calibration with Aβ PET SUVR trajectory profile derived from literature (Insel et al., 2021). Shaded region represents the mean and 95% prediction interval (2.5th and 97.5th percentiles).

**Figure 4** Simulation results for Aducanumab PK (Panel A) and PD (Panel B). Our model used the initial doses without taking into account the titration regimen. The low dose was titrated to 3 mg/kg (ApoE ε4+) or 6 mg/kg (ApoE ε4-) and a high dose titrated to 6 mg/kg (ApoE ε4+) or 10 mg/kg (ApoE ε4-) prior to protocol amendments, and titrated to 10 mg/kg after protocol amendments (Budd Haeberlein et al., 2022). Lecanemab PK (Panel C) and PD (Middle Right Panel). Comparison of simulated and observed changes in PET SUVR with different antibodies at corresponding timepoints (Panel D).
**Figure 5** QSP-evaluated scenario in panels A and B: hypothetical antibody, Drug A, preferentially binds to monomers (A). Increasing the dose (100-fold) or more frequent dosing of Drug A does not result in continuous decrease of monomer concentration (B). Scenario in panel C: hypothetical antibody, Drug B, prefers binding to all soluble and insoluble species. Scenario in Panel D: hypothetical antibodies, Drug C and Drug D, preferentially bind to oligomers, protofibrils, fibrils, and plaques. Drug D includes antibody effector function.
Figure 5

A

Amyloid PET SUVR

Time (years)

Drug A

Predicted

B

Monomer concentration (nM)

Time (year)

Drug A 30,000mg Q2W

Drug A 30,000mg Q4W

Drug A 300mg Q4W

C

Amyloid PET SUVR

Time (years)

Drug B

Predicted

D

Amyloid PET SUVR

Time (years)

Drug C

Drug D

Predicted
Supplemental material for:

Passive Immunotherapies Targeting Amyloid-β in Alzheimer's Disease: A Quantitative Systems Pharmacology Perspective

Molecular Pharmacology  MOLPHARM-MR-2023-000726

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Supplemental Data

The ordinary differential equations (ODE) used in Drug A scenario, where a drug binds the Aβ monomer alone are as follows:

Mass of the Drug A in the Central compartment:
\[
\frac{d(CENT)}{dt} = -\frac{CENT}{Vc} \cdot CL - CENT \cdot kcp + kpc \cdot PER
\]

Mass of Drug A in the Peripheral compartment:
\[
\frac{d(PER)}{dt} = CENT \cdot kcp - kpc \cdot PER
\]

Drug A concentration in the brain compartment:
\[
\frac{d(D)}{dt} = -\frac{CENT}{Vc} \cdot kpT - konDT \cdot D \cdot T + koff DT \cdot DT - kbp \cdot D
\]

Monomer-drug A complex in the brain:
\[
\frac{d(DT)}{dt} = konDT \cdot D \cdot T - koff DT \cdot DT - keD \cdot DT
\]

Monomer concentration in the brain:
\[
\frac{d(T)}{dt} = ksynT - \frac{RmaxTT \cdot T}{KdT T + T} + koff TT \cdot T T - konDT \cdot D \cdot T + koff DT \cdot DT - keT \cdot T
\]

Dimer concentration in the brain:
\[
\frac{d(TT)}{dt} = \frac{RmaxTT \cdot T}{KdTT + T} - koff TT \cdot T T - \frac{RmaxTTT \cdot TT}{KdTT + TT} + koff TTT \cdot TTT
\]

Tetramer concentration in the brain:
\[
\frac{d(TTT)}{dt} = \frac{RmaxTTT \cdot TT}{KdTT + TT} - koff TTT \cdot TTT - \frac{RmaxO \cdot TTT}{KdO + TTT} + koff O \cdot O
\]

Oligomer concentration in the brain:
\[
\frac{d(O)}{dt} = \frac{R_{maxO} \cdot TTT}{KdO + TTT} - k_{off}O \cdot O - \frac{R_{maxP} \cdot O}{KdP + O} + k_{off}P \cdot P
\]

Protofibril concentration in the brain:

\[
\frac{d(P)}{dt} = \frac{R_{maxP} \cdot O}{KdP + O} - k_{off}P \cdot P - \frac{R_{maxF} \cdot P}{KdF + P} + k_{off}F \cdot F
\]

Fibril concentration in the brain:

\[
\frac{d(F)}{dt} = \frac{R_{maxF} \cdot P}{KdF + P} - k_{off}F \cdot F - \frac{R_{maxA} \cdot F}{KdA + F} + k_{off}A \cdot A
\]

Aggregated plaque concentration in the brain:

\[
\frac{d(A)}{dt} = \frac{R_{maxA} \cdot F}{KdA + F} - k_{off}A \cdot A
\]

The ODEs used in Drug B scenario are similar to Drug A, but with additional ODEs for drug binding to all amyloid species, not just the monomer:

Mass of the Drug B in the Central compartment:

\[
\frac{d(\text{CENT})}{dt} = -\frac{\text{CENT}}{Vc} \cdot CL - \text{CENT} \cdot kcp + kpc \cdot \text{PER}
\]

Mass of Drug B in the Peripheral compartment:

\[
\frac{d(\text{PER})}{dt} = \text{CENT} \cdot kcp - kpc \cdot \text{PER}
\]
Drug B concentration in the brain compartment:

\[
\frac{d(D)}{dt} = -\frac{CENT}{Vc} \cdot kpb - konDT \cdot D \cdot T + koffDT \cdot DT - kbp \cdot D - konDTT \cdot D \cdot TT \\
+ koffDTT \cdot DTT - konDTTT \cdot D \cdot TTT + koffDTTT \cdot DTTT - konDO \cdot D \\
* O + koffDO \cdot DO - konDP \cdot D \cdot P + koffDP \cdot DP - konDF \cdot D \cdot F \\
+ koffDF \cdot DF - konDA \cdot D \cdot A + koffDA \cdot DA
\]

Monomer-Drug B complex in the brain:

\[
\frac{d(DT)}{dt} = konDT \cdot D \cdot T - koffDT \cdot DT - keD \cdot DT
\]

Monomer concentration in the brain:

\[
\frac{d(T)}{dt} = ksynT - \frac{RmaxTT \cdot T}{KdT + T} + koffTT \cdot TT - konDT \cdot D \cdot T + koffDT \cdot DT - keT \cdot T
\]

Dimer concentration in the brain:

\[
\frac{d(TT)}{dt} = \frac{RmaxTT \cdot T}{KdT + T} - koffTT \cdot TT - \frac{RmaxTTT \cdot TT}{KdTTT + TT} + koffTTT \cdot TTT - konDTT \cdot D \\
* TT + koffDTT \cdot DTT
\]

Tetramer concentration in the brain:

\[
\frac{d(TTT)}{dt} = \frac{RmaxTTT \cdot TTT}{KdTTT + TT} - koffTTT \cdot TTT - \frac{RmaxO \cdot TTT}{KdO + TTT} + koffTTT \cdot TTT \\
- konDTTT \cdot D \cdot TTT + koffDTTT \cdot DTTT
\]

Oligomer concentration in the brain:
\[
\frac{d(O)}{dt} = \frac{R_{maxO} \cdot TTT}{KdO + TTT} - \frac{\text{koff} \cdot O}{KdP + O} + \frac{R_{maxP} \cdot O}{KdP + O} \]

**Protocollagen concentration in the brain:**

\[
\frac{d(P)}{dt} = \frac{R_{maxP} \cdot O}{KdP + O} - \frac{\text{koff} \cdot P}{KdF + P} + \frac{R_{maxF} \cdot P}{KdF + P} \]

**Fibril concentration in the brain:**

\[
\frac{d(F)}{dt} = \frac{R_{maxF} \cdot P}{KdF + P} - \frac{\text{koff} \cdot F}{KdA + F} + \frac{R_{maxA} \cdot P}{KdF + P} \]

**Aggregated plaque concentration in the brain:**

\[
\frac{d(A)}{dt} = \frac{R_{maxA} \cdot P}{KdF + P} - \frac{\text{koff} \cdot A}{KdA + F} + \frac{R_{maxA} \cdot P}{KdA + F} \]

**Concentration of Drug B complex with dimer:**

\[
\frac{d(DT)}{dt} = k_{on} \cdot D \cdot TTT - k_{off} \cdot DTT \cdot TT
\]

**Concentration of Drug B complex with tetramer:**

\[
\frac{d(DTTT)}{dt} = k_{on} \cdot D \cdot TTT - k_{off} \cdot DO \cdot DO
\]
Concentration of Drug B complex with oligomer:

\[
\frac{d(\text{DO})}{dt} = k_{on}DO \times D \times O - k_{off}DO \times DO
\]

Concentration of Drug B complex with protofibril:

\[
\frac{d(\text{DP})}{dt} = k_{on}DP \times D \times P - k_{off}DP \times DP
\]

Concentration of Drug B complex with fibril:

\[
\frac{d(\text{DF})}{dt} = k_{on}DF \times D \times F - k_{off}DF \times DF
\]

Concentration of Drug B complex with aggregated plaque:

\[
\frac{d(\text{DA})}{dt} = k_{on}DA \times D \times A - k_{off}DA \times DA
\]

The ODEs used for model building of Drug C are similar to those for Drug B, but without drug binding to the monomer, dimer, tetramer, oligomer.

Mass of the Drug C in the Central compartment:

\[
\frac{d(\text{CENT})}{dt} = -\frac{CENT}{V_c} \times CL - CENT \times k_{cp} + k_{pc} \times PER
\]

Mass of Drug C in the Peripheral compartment:

\[
\frac{d(\text{PER})}{dt} = CENT \times k_{cp} - k_{pc} \times PER
\]

Drug C concentration in the brain compartment:
\[
\frac{d(D)}{dt} = -\frac{CENT}{V_c} \cdot kpb - kbp \cdot D - konDP \cdot D \cdot P + koffDP \cdot DP - konDF \cdot D \cdot F + koffDF \cdot DF - konDA \cdot D \cdot A + koffDA \cdot DA
\]

Monomer concentration in the brain:
\[
\frac{d(T)}{dt} = ksynT - \frac{RmaxTT \cdot T}{KdTT + T} + koffTT \cdot TT - keT \cdot T
\]

Dimer concentration in the brain:
\[
\frac{d(TT)}{dt} = \frac{RmaxTT \cdot T}{KdTT + T} - koffTT \cdot TT - \frac{RmaxTTT \cdot TT}{KdTTT + TT} + koffTTT \cdot TTT
\]

Tetramer concentration in the brain:
\[
\frac{d(TTT)}{dt} = \frac{RmaxTTT \cdot TT}{KdTTT + TT} - koffTTT \cdot TTT - \frac{RmaxO \cdot TTT}{KdO + TTT} + koffO \cdot O
\]

Oligomer concentration in the brain:
\[
\frac{d(O)}{dt} = \frac{RmaxO \cdot TTT}{KdO + TTT} - koffO \cdot O - \frac{RmaxP \cdot O}{KdP + O} + koffP \cdot P
\]

Protofibril concentration in the brain:
\[
\frac{d(P)}{dt} = \frac{RmaxP \cdot O}{KdP + O} - koffP \cdot P - \frac{RmaxF \cdot P}{KdF + P} + koffF \cdot F - konDP \cdot D \cdot P + koffDP
\]

Fibril concentration in the brain:
\[
\frac{d(F)}{dt} = \frac{RmaxF \cdot P}{KdF + P} - koffF \cdot F - \frac{RmaxA \cdot F}{KdA + F} + koffA \cdot A - konDF \cdot D \cdot F + koffDF
\]
Aggregated plaque concentration in the brain:

\[
\frac{d(A)}{dt} = \frac{R_{max} A \cdot F}{K_d A + F} - k_{off} A \cdot A - k_{on} D \cdot A + k_{off} D \cdot A
\]

Concentration of Drug C complex with protofibril:

\[
\frac{d(DP)}{dt} = k_{on} D \cdot P - k_{off} D \cdot P
\]

Concentration of Drug C complex with fibril:

\[
\frac{d(DF)}{dt} = k_{on} D \cdot F - k_{off} D \cdot F
\]

Concentration of Drug C complex with aggregated plaque:

\[
\frac{d(DA)}{dt} = k_{on} D \cdot A - k_{off} D \cdot A
\]

The ODEs used for model building of Drug D also include an effector function:

Mass of the Drug D in the Central compartment:

\[
\frac{d(CENT)}{dt} = -\frac{CENT}{V_c} \cdot C_L - CENT \cdot k_c p + k_c p \cdot P_E R
\]

Mass of Drug D in the Peripheral compartment:

\[
\frac{d(PER)}{dt} = CENT \cdot k_c p - k_c p \cdot P_E R
\]

Drug D concentration in the brain compartment:
\[
\frac{d(D)}{dt} = - \frac{CENT}{V_c} * kpb - kbp * D - konDP * D * P + koffDP * DP - konDF * D * F \\
+ koffDF * DF - konDA * D * A + koffDA * DA
\]

Monomer concentration in the brain:
\[
\frac{d(T)}{dt} = k_{synT} - \frac{R_{maxTT} * T}{KdT + T} + koffTT * TT - keT * T
\]

Dimer concentration in the brain:
\[
\frac{d(TT)}{dt} = \frac{R_{maxTT} * T}{KdT + T} - koffTT * TT - \frac{R_{maxTTT} * TT}{KdTTT + TT} + koffTTT * TTT
\]

Tetramer concentration in the brain:
\[
\frac{d(TTT)}{dt} = \frac{R_{maxTTT} * TT}{KdTTT + TT} - koffTTT * TTT - \frac{R_{maxO} * TTT}{KdO + TTT} + koffO * O
\]

Oligomer concentration in the brain:
\[
\frac{d(O)}{dt} = \frac{R_{maxO} * TTT}{KdO + TTT} - koffO * O - \frac{R_{maxP} * O}{KdP + O} + koffP * P
\]

Protofibril concentration in the brain:
\[
\frac{d(P)}{dt} = \frac{R_{maxP} * O}{KdP + O} - koffP * P - \frac{R_{maxF} * P}{KdF + P} + koffF * F - konDP * D * P + koffDP
\]

Fibril concentration in the brain:
\[
\frac{d(F)}{dt} = \frac{R_{maxF} * P}{KdF + P} - koffF * F - \frac{R_{maxA} * F}{KdA + F} + koffA * A - konDF * D * F + koffDF
\]
Aggregated plaque concentration in the brain:

\[
\frac{d(A)}{dt} = \frac{R_{max}A \cdot F}{KdA + F} - koffA \cdot A - konDA \cdot D \cdot A + koffDA \cdot DA
\]

Concentration of Drug D complex with protofibril:

\[
\frac{d(DP)}{dt} = konDP \cdot D \cdot P - koffDP \cdot DP - keDP \cdot DP
\]

Concentration of Drug D complex with fibril:

\[
\frac{d(DF)}{dt} = konDF \cdot D \cdot F - koffDF \cdot DF - keDF \cdot DF
\]

Concentration of Drug D complex with aggregated plaque:

\[
\frac{d(DA)}{dt} = konDA \cdot D \cdot A - koffDA \cdot DA - keDA \cdot DA
\]
### Table 1. Antibody affinity towards different amyloid species

<table>
<thead>
<tr>
<th>Amyloid species</th>
<th>Parameter name</th>
<th>Aducanumab</th>
<th>Bapineuzumab</th>
<th>Crenezumab</th>
<th>Gantenerumab</th>
<th>Lecanemab</th>
<th>Solanezumab</th>
</tr>
</thead>
</table>

*a* assumed same as fibril  

*b* assumed same as plaque
Table 2. Physiological parameters and parameters for non-linear amyloid aggregation cascade

<table>
<thead>
<tr>
<th>Definition</th>
<th>Value</th>
<th>Unit</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_0$ Monomer initial state</td>
<td>0.75</td>
<td>nM</td>
<td>[5]</td>
</tr>
<tr>
<td>$TT_0$ Dimer initial state</td>
<td>1</td>
<td>nM*</td>
<td>Assumed</td>
</tr>
<tr>
<td>$TTT_0$ Tetramer initial state</td>
<td>1</td>
<td>nM*</td>
<td>Assumed</td>
</tr>
<tr>
<td>$O_0$ Oligomer initial state</td>
<td>1</td>
<td>nM*</td>
<td>Assumed</td>
</tr>
<tr>
<td>$P_0$ Protofibril initial state</td>
<td>1</td>
<td>nM*</td>
<td>Assumed</td>
</tr>
<tr>
<td>$F_0$ Fibril initial state</td>
<td>1</td>
<td>nM*</td>
<td>Assumed</td>
</tr>
<tr>
<td>$A_0$ Plaque initial state</td>
<td>1</td>
<td>nM*</td>
<td>Assumed</td>
</tr>
<tr>
<td>$k_eT$ Monomer elimination rate</td>
<td>0.05</td>
<td>1/h</td>
<td>[6]</td>
</tr>
<tr>
<td>$k_{syn}T$ Monomer synthesis rate</td>
<td>$k_{syn} = T_0 \cdot k_eT = 0.0375$</td>
<td>1/h</td>
<td>Calculated</td>
</tr>
<tr>
<td>$R_{max}T$ the maximum rate achieved by the system</td>
<td>0.00002</td>
<td>nM/h</td>
<td>Optimized using natural disease progression</td>
</tr>
<tr>
<td>$K_dT$ the constant equal to $A\beta$ species at which the $R_{max}$ is at half-maximum</td>
<td>0.05</td>
<td>nM</td>
<td>Optimized using natural disease progression</td>
</tr>
<tr>
<td>$k_{offTT}$ the first-order rate constant for the $A\beta$ dimer dissociation</td>
<td>0.000005</td>
<td>1/h</td>
<td>Assumed</td>
</tr>
<tr>
<td>$k_{offTTT}$ the first-order rate constant for the $A\beta$ tetramer dissociation</td>
<td>$0.1 \cdot k_{offTT}$</td>
<td>1/h</td>
<td>Assumed</td>
</tr>
<tr>
<td>$k_{offO}$ the first-order rate constant for the $A\beta$ oligomer dissociation</td>
<td>$0.1 \cdot k_{offTTT}$</td>
<td>1/h</td>
<td>Assumed</td>
</tr>
<tr>
<td>$k_{offP}$ the first-order rate constant for the $A\beta$ protofibril dissociation</td>
<td>$0.1 \cdot k_{offO}$</td>
<td>1/h</td>
<td>Assumed</td>
</tr>
<tr>
<td>$k_{offF}$ the first-order rate constant for the $A\beta$ fibril dissociation</td>
<td>$0.1 \cdot k_{offP}$</td>
<td>1/h</td>
<td>Assumed</td>
</tr>
<tr>
<td>$k_{offA}$ the first-order rate constant for the $A\beta$ aggregate dissociation</td>
<td>$0.1 \cdot k_{offA}$</td>
<td>1/h</td>
<td>Assumed</td>
</tr>
<tr>
<td>$Y$ $R_{max\ higher\ species} = Y \cdot R_{max\ lower\ species}$</td>
<td>0.675</td>
<td>Unitless</td>
<td>Optimized using natural disease progression</td>
</tr>
<tr>
<td>$Z$ $K_{d\ higher\ species} = Z \cdot K_{d\ lower\ species}$</td>
<td>1</td>
<td>Unitless</td>
<td>Optimized using natural disease progression</td>
</tr>
</tbody>
</table>
*Initial concentrations were assumed to be 1 nM due to high variability in literature sources [7–9], as well as in initial values used in previously developer QSP models [2,5,10]. If more data becomes available, adjusting the Y and Z can be used to re-calibrate the model further.

**Table 3.** Antibody molecular weight used to calculate dose

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Molecular weight (g/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aducanumab</td>
<td>145912.34</td>
</tr>
<tr>
<td>Bapineuzumab</td>
<td>145871.99</td>
</tr>
<tr>
<td>Crenezumab</td>
<td>144884.91</td>
</tr>
<tr>
<td>Gantenerumab</td>
<td>146274.65</td>
</tr>
<tr>
<td>Lecanemab</td>
<td>147181.62</td>
</tr>
<tr>
<td>Solanezumab</td>
<td>144082.24</td>
</tr>
</tbody>
</table>

**Table 4.** PK parameters used in model validation

<table>
<thead>
<tr>
<th>Antibody</th>
<th>References for the clinical PK data used</th>
<th>CL, Clearance (L/h)</th>
<th>Vc, Central Volume (L)</th>
<th>Vp, Peripheral Volume (L)</th>
<th>Optimized against plasma data (Phoenix WinNonlin™)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aducanumab</td>
<td>[11]</td>
<td>0.035</td>
<td>6.3</td>
<td>10.5</td>
<td></td>
</tr>
<tr>
<td>Bapineuzumab</td>
<td>[12]</td>
<td>0.018</td>
<td>8.6</td>
<td>6.2</td>
<td></td>
</tr>
<tr>
<td>Crenezumab</td>
<td>[13]</td>
<td>14.71</td>
<td>1.54</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>Gantenerumab</td>
<td>[14]</td>
<td>0.029</td>
<td>14.8</td>
<td>5.3</td>
<td></td>
</tr>
<tr>
<td>Lecanemab</td>
<td>[15]</td>
<td>0.002</td>
<td>2.5</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Solanezumab</td>
<td>[16]</td>
<td>0.009</td>
<td>3.0</td>
<td>4.4</td>
<td></td>
</tr>
</tbody>
</table>

**Table 5.** PD endpoint used in model validation

<table>
<thead>
<tr>
<th>Antibody</th>
<th>References for the clinical PET SUVR data</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aducanumab</td>
<td>[17–19]</td>
<td>relative to baseline</td>
</tr>
<tr>
<td>Bapineuzumab</td>
<td>[20,21]</td>
<td>relative to baseline</td>
</tr>
<tr>
<td>Crenezumab</td>
<td>[22]</td>
<td>relative to baseline</td>
</tr>
<tr>
<td>Gantenerumab</td>
<td>[23]</td>
<td>relative to baseline</td>
</tr>
<tr>
<td>Lecanemab</td>
<td>[24]</td>
<td>relative to baseline</td>
</tr>
<tr>
<td>Solanezumab</td>
<td>[25,26]</td>
<td>relative to baseline</td>
</tr>
</tbody>
</table>
Table 6. Parameters used in the simulation of Drug A, B, C and D scenario

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Drug</th>
<th>Value</th>
<th>Unit</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>kpb</td>
<td>Plasma to brain distribution rate</td>
<td>A-D</td>
<td>1</td>
<td>1/h</td>
<td>Assumed</td>
</tr>
<tr>
<td>kbp</td>
<td>brain to plasma distribution rate</td>
<td></td>
<td>kpb*1000</td>
<td>1/h</td>
<td>to account for the exposure of 0.1 % of total antibody in the brain [27]</td>
</tr>
<tr>
<td>keDO</td>
<td>Constant of antibody-oligomer elimination through ADCP</td>
<td>D</td>
<td>0.000001</td>
<td>1/h</td>
<td>Manually adjusted</td>
</tr>
<tr>
<td>keDP</td>
<td>Constant of antibody-protofibril elimination through ADCP</td>
<td>D</td>
<td>0.000001</td>
<td>1/h</td>
<td>Manually adjusted</td>
</tr>
<tr>
<td>keDF</td>
<td>Constant of antibody-fibril elimination through ADCP</td>
<td>D</td>
<td>0.000001</td>
<td></td>
<td>Manually adjusted</td>
</tr>
<tr>
<td>keDA</td>
<td>Constant of antibody-plaque elimination through ADCP</td>
<td>D</td>
<td>0.000001</td>
<td></td>
<td>Manually adjusted</td>
</tr>
<tr>
<td>konDT</td>
<td>Drug-monomer binding rate constant</td>
<td>A, B</td>
<td>3.96</td>
<td>1/nM*h</td>
<td>[5]</td>
</tr>
<tr>
<td>konDTT</td>
<td>Drug-dimer binding rate constant</td>
<td>B</td>
<td>0.001</td>
<td>1/nM*h</td>
<td>Assumed for hypothetical drug</td>
</tr>
<tr>
<td>konDTTT</td>
<td>Drug-tetramer binding rate constant</td>
<td>B</td>
<td>0.001</td>
<td>1/nM*h</td>
<td>Assumed for hypothetical drug</td>
</tr>
<tr>
<td>konDO</td>
<td>Drug-oligomer binding rate constant</td>
<td>B-D</td>
<td>0.001</td>
<td>1/nM*h</td>
<td>Assumed for hypothetical drug</td>
</tr>
</tbody>
</table>
Volume of brain interstitial fluid was assumed to be constant for all cases 0.25 L. This is derived from the fact that 15-20 % of 1130cm^3 (1.13 L) for women, and slightly higher for men is ~0.25 L [28,29].
Supplemental Figures

PK/PD relationship of 4 remaining antibodies used for model validation is presented in Supplementary Figures 1-4:

**Supp. Fig. 1.** Observed vs. Predicted values for Gantenerumab PK (left panel) and changes in the amyloid PET SUVR (right panel).

**Supp. Fig. 2.** Observed vs. Predicted values for Bapineuzumab PK (left panel) and changes in the amyloid PET SUVR (right panel).
Supp. Fig. 3. Observed vs. Predicted values for Crenezumab PK (left panel) and changes in the amyloid PET SUVR (right panel).

Supp. Fig. 4. Observed dose/weight-normalized solanezumab concentration (after single doses of 0.5, 1.5, 4 and 10 mg/kg) vs. Predicted (1 mg/kg dose) values for PK (left panel) and changes in the amyloid PET SUVR (right panel).
References for supplementary materials


