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MINI-REVIEW

Monoclonal antibody therapy efficacy can be boosted by combinations with other treatments: Predictions using an integrated Alzheimer's Disease Platform

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Abstract

For many years, clinical research in Alzheimer's disease (AD) has focused on attempts to identify the most explicit biomarker, namely amyloid beta. Unfortunately, the numerous therapies that have been developed have failed in clinical practice. AD arises as a consequence of multiple factors, and as such it requires a more mechanistic analytical approach than statistical modeling. Quantitative systems pharmacology modeling is a valuable tool for drug development. It utilizes in vitro data for the calibration of parameters, embeds them into physiologically based structures, and explores translation between animals and humans. Such an approach allows for a quantitative study of the dynamics of the interactions between multiple factors or variables. Here, we present an overview of the quantitative translational model in AD, which embraces current preclinical and clinical data. The previously published description of amyloid physiology has been updated and joined with a model for tau pathology and multiple intraneuronal processes responsible for cellular transport, metabolism, or proteostasis. In addition, several hypotheses regarding the best correlates of cognitive deterioration have been validated using clinical data. Here, the amyloid hypothesis was unable to predict the aducanumab clinical trial data, whereas simulations of cognitive impairment coupled with tau seeding or neuronal breakdown (expressed as caspase activity) matched the data. A satisfactory validation of the data from multiple preclinical and clinical studies was followed by an attempt to predict the results of combinatorial treatment with targeted immunotherapy and activation of autophagy using rapamycin. The combination is predicted to yield better efficacy than immunotherapy alone.

PATHOLOGY AND BIOMARKERS OF AD

Alzheimer's disease (AD), is a neurodegenerative disorder that invariably leads to complete cognitive deterioration.[1]

Hypotheses on the pathological mechanisms of AD are mostly based on amyloid β (Aβ) plaques and neurofibrillary tangles (NFTs) found postmortem in brain tissues.[2] These findings are then associated with numerous in vivo markers (Table 1), as measured by brain positron emission

TABLE 1 Clinical biomarkers of AD[3–5]

Marker	Trend	Comments
Aβ1-42 (CSF)	↓	Correlates with amyloid SUVR
t-tau (CSF)	↑	Correlates with amyloid SUVR
p-tau (CSF)	↑	Correlates with amyloid SUVR
p-tau/Aβ1-42 (CSF)	↑	Predicts disease progression (conversion from MCI to AD)
Amyloid PET (SUVR)	↑	Most often used as marker in clinical trials
Tau PET (SUVR)	↑	Correlates with amyloid and cognitive impairment

Abbreviations: AD, Alzheimer's disease; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; PET, positron emission tomography; p-tau, phosphorylated tau; SUVR, standardized uptake volume ratio; t-tau, total tau.

tomography (PET) tracers or in the cerebrospinal fluid (CSF). Images of the PET tracer uptake intensity in specific brain regions emulates postmortem stereological findings.[3,4] These intensities have been correlated with CSF markers and cognitive impairment.[5]

Various mechanisms that connect amyloid and tau accumulation in neurons include the activation of kinases,[6] calcium dysregulation,[7] and inhibition of protein transport and degradation.[8]

The landscape of current therapeutic options for AD is limited. Standard cholinomimetic therapy can mitigate some symptoms in the early or mild stages of the disease, the underlying synaptic degeneration is not alleviated, and the disease progresses along its normal trajectory.

Amyloid targeting therapy

Tremendous efforts have been undertaken during the last couple of decades to develop disease-modifying therapies[9] that would allow patients to escape the progressive cognitive decline. In this regard, Aβ, the first marker discovered historically and most observable in the course of disease, has been at the center of drug research for a long time.

One treatment approach has resulted in the development of a large class of treatments aimed at inhibiting amyloid production. These drugs are inhibitors of gamma- and beta-secretase (GSi and BACEi). However, because gamma secretase is an enzyme with multiple substrates, the GSi class causes multiple side effects and fails to demonstrate any efficacy at moderate stages of the disease.[10] Similarly, BACEi failed in clinical trials; they were tested at earlier stages of the disease and should have prevented toxic amyloid oligomerization. Overall, no positive clinical efficacy has been observed with these inhibitors; moreover, BACEi verubecestat treatment worsened clinical outcomes in the high-dose group.[11] This is in line with the observed positive role of picomolar Aβ in long-term potentiation.[12]

As an alternative, the specific blockade of toxic protein forms by monoclonal antibodies has been explored. Unfortunately, several monoclonal antibodies have also failed in clinical trials due to insufficient efficacy even in presymptomatic stages.[9]

Agents, such as solanezumab, gantenerumab, and crenezumab, all failed in patients with presymptomatic autosomal dominant AD,[9] although target engagement and biomarker efficacy (e.g., amyloid reduction) was achieved. Indeed, a significant proportion of patients moved from A+ to A- (amyloid PET negative) during aducanumab treatment, but efficacy, as assessed by meeting clinical end points and statistical significance, were modest at best.[13]

TAU PATHOLOGY

Because targeting amyloid is no longer considered to be the best option, other hypotheses and mechanisms have emerged in AD research. Targeting tau pathology may be a better approach, as tau markers are more reliably correlated with cognitive symptoms.[5] Analogous to anti-amyloid treatments, targeting tau demonstrated encouraging results in preclinical studies. However, inhibition of key drivers of tau pathology, for example, kinases GSK3β or CDK5p25, may lead to a variety of side effects, because these kinases are signaling nodes that are particularly important for cell function (memory) and metabolism. Specific targeting of seeding forms of pathological tau, for example, oligomers or NFTs, is problematic because they accumulate intracellularly, and the concentration of therapeutic antibodies in the brain may not saturate targets.

MODELING IN AD

The multifactorial nature of AD and its irreversibility pose a critical challenge for disease prevention requiring early intervention. The long duration required for AD clinical trials is one of the reasons for the slow progress in clinical development. Large datasets have been used to develop regression models predicting disease progression and variability from baseline covariates.[14] The probabilistic event-based model describes the sequence of disease stages as

determined by abnormalities in the CSF and in imaging markers.[15] Statistical models based on population data, correlations, or exploratory analyses of interactions between biomarkers and clinical scores are useful for specifying trends, but they give us only a superficial representation, lacking any insight into intrinsic mechanisms. "Higher-dimensional" structures require mechanistic and dynamic descriptions that embrace different types of quantitative data. Quantitative systems pharmacology (QSP) modeling is a valuable tool for embedding diverse types of information into one integrated structure of differential equations. It can facilitate research on the pathogenesis of disease and mechanistic drivers, allow for exploration of populations at risk, and evaluate markers for early diagnosis. Finally, it can speed up the process of target selection or testing combinations of treatments.

Clinical trial failures suggest that focusing on one target may not be a reliable way to achieve success. Accordingly, modeling only specific biological pathways is insufficient for the sensible prediction of treatment efficacy or for reconstructing disease pathogenesis. Integration of different modules into one platform step by step would allow for broader and deeper understanding.

DEVELOPMENT OF A TRANSLATIONAL QSP MODEL

Due to the popularity of targeting amyloid and availability of quantitative data, QSP modeling for AD begins with a description of amyloid-related processes.[16] The published platform describes amyloid production, degradation, and distribution from brain cells to extracellular fluid, CSF, and plasma.

Inhibition of Aβ secretion has been realistically predicted.[16] The model has been retrospectively validated on results published before 2015 and has been used to test several amyloid-related cognitive impairment hypotheses. Under the model assumptions of reversibility of decline, only plaque clearance by immunotherapy might improve cognition within a 2-year trial. Although this has been partially confirmed by the latest data released from the aducanumab trial, the efficacy is far from providing a reliable option to patients.

The QSP amyloid platform has been updated by the inclusion of a detailed description of processing (BACE), hetero-oligomerization ($A\beta_{40}$ vs. $A\beta_{42}$), and amyloid clearance by glia.

To explore potential tau-targeting treatments, a similar tau platform has been developed. It describes a set of processes analogous to the amyloid model[16]: namely production of tau in the brain, its distribution to the extracellular space and the CSF, and aggregation. Aggregation is regulated by post-translational tau modifications, such as phosphorylation and truncation. The Tau multisite phosphorylation model[17] enables the calculation of the probability of phosphorylation of specific sites by different kinases.

An essential feature of the tau model is that it captures the regional Braak stages. The Braak classification describes six stages of spatial tau distribution, which can be classified into three groups: Braak I–II (or entorhinal), Braak III–IV (or limbic), and Braak V–VI (or isocortical).[2] In contrast to amyloid pathology, tau pathology embraces cortical regions only in the final stages of the disease.[2] The model captures tau spatial-temporal dynamics within three regions (compartments), with tau oligomer transmission among them.

The key idea is that the transmission hubs, entorhinal cortex and hippocampal region, are more vulnerable to tau pathology. It should be noted that this is a simplification of the structural model, because there are other sources of heterogeneity between the cortical and subcortical regions. Nevertheless, it appears to be reasonable because higher synaptic activity in the hubs leads to a higher risk of excitotoxicity, calpain, and kinase activation. This stimulation boosts in tau oligomerization through phosphorylation and truncation, qualitatively similar to the higher flux of tau oligomers from the cortical to subcortical regions.

NEURON HOMEOSTASIS PLATFORM

The mechanisms of interaction between amyloid and tau pathologies have been reconstructed in a new submodel that focuses on intraneuronal processes and addresses the following questions:

1. What are the mechanisms connecting the accumulation of amyloid and tau?
2. Can we find common upstream processes that drive both pathologies and could therefore be AD drivers or early biomarkers?
3. Can these processes be directly connected to neurodegeneration and used as correlates of clinical effects?
4. Can these basic processes become targets for monotherapy or combination therapy with anti-tau or anti-amyloid therapy?

A literature analysis of biomarkers (excluding amyloid and tau) in early AD and biomarkers of intraneuronal lesions in preclinical models was performed. It revealed several essential pathways and allowed for the construction of a simplified model that combines information about the mutual regulation between lipid metabolism, the autophagic-lysosomal system (ALS), calpain, caspases, sphingolipid metabolism, and the microtubule transport. This model is referred to as the neuron homeostasis (NH) model. To avoid redundancy

and complexity, only specific hubs were selected to represent the interactions between key nodes. The choice was based on the regulation of amyloid and tau-related processes (e.g., proteasome and calpain) and the availability of data on their changes, or the application as potential treatment targets (e.g., lipids and mTOR) in mouse models of AD and in humans. Lipids, sphingolipids, and the volumes of autophagic vesicles are dynamic variables because quantitative data are available for these. For the other elements, their relative activation is calculated as function:

$$X_i = \frac{\sum \mathrm{ka}_i^j \cdot A^j}{k_i^{\mathrm{base}} + \sum \mathrm{ka}_i^j \cdot A^j + \sum \mathrm{ka}_i^k \cdot I^k}, \quad (1)$$

In this generalized equation, A^j is an activator of the considered node X_i (e.g., S1P for the proteasome), I^j is an inhibitor of the considered node (e.g., PHF tau for the proteasome); ka_i^j and ka_i^k are parameters defining the sensitivities of node X_i to activator A^j and inhibitor I^k, respectively; in some cases, $\mathrm{ka}_i^j(\mathrm{ka}_i^k)$ can be replaced by $1/IC50_i^j$, where $\mathrm{IC50}_i^j$ could be obtained from the corresponding concentration-dependence data, if available. Therefore, the baseline activation level is below 1 (or equal to 1) in the healthy state, depending on the choice of k_i^{base} and tends to a maximum of 1 (or declines from 1) with increasing activator (inhibitor) concentrations during disease progression. The NH model was calibrated using in vivo baseline values (sphingolipids, lipids, and volumes of ALS vesicles) and by using in vitro data on various metabolic perturbations (pathway activation or inhibition).

After calibration, the NH model became central to the combined amyloid and tau platform (Figure 1). It contains processes that govern the post-translational modification and degradation of proteins. For example, the proteasomal system and autophagy are the main pathways of degradation of the amyloid precursor, bCTF, tau, and protein oligomers, but can be inhibited by them.[18] Hyperphosphorylated tau disrupts microtubules, leading to an inhibition of the autophagic system. Amyloid and tau through oxidative stress led to the activation of stress-response kinases[19] (e.g., p53), which activate caspases.

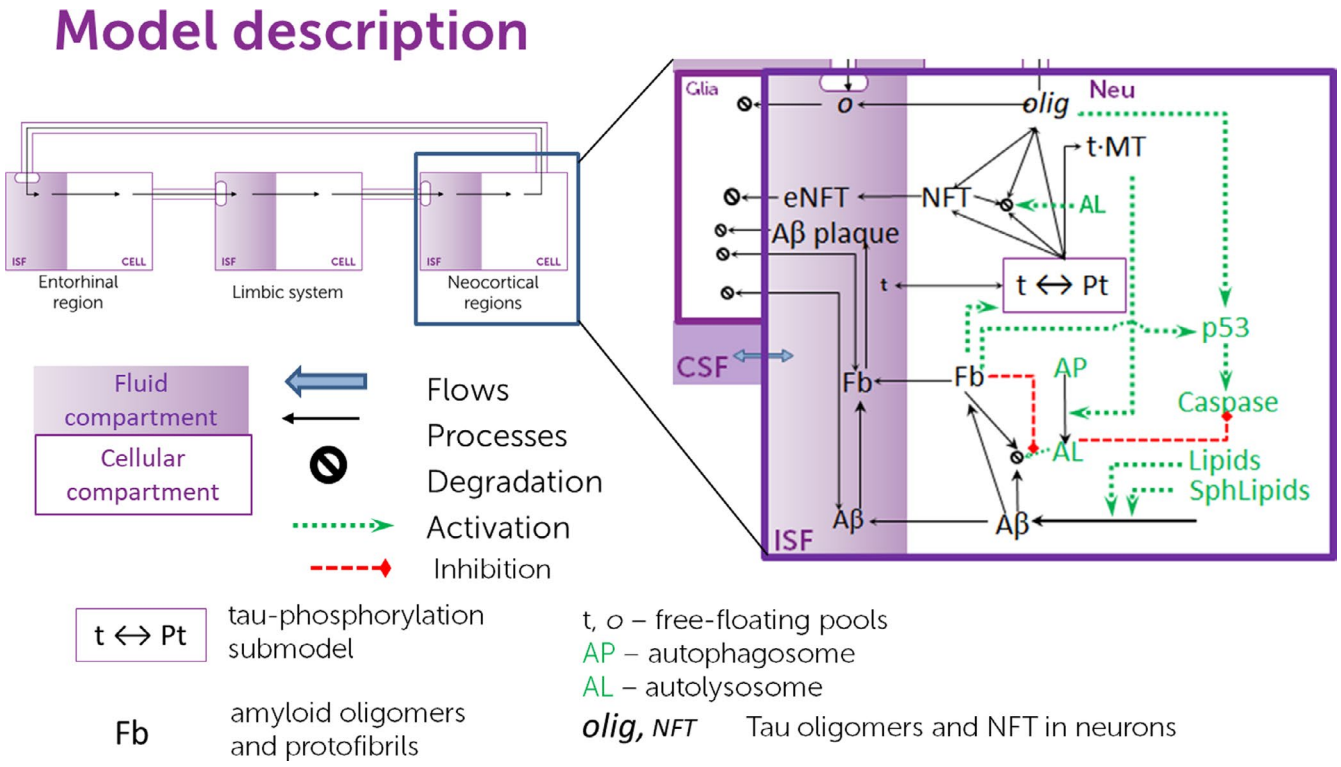

FIGURE 1 Sketch of the integrated platform. The model describes three brain regions (left hand side), with arrows denoting the distribution of tau oligomers through the connectome. Right hand side: intracellular aggregation of amyloid beta (Aβ) to oligomers and protofibrils (Fb), and tau (t) to oligomers and neurofibrillary tangles (NFTs), and secretion into the interstitial fluid (ISF). Tau-processes and amyloid interact in neurons through the autophagic-lysosomal system (ALS). Amyloid and tau oligomers and NFTs degrade in autolysosomes (ALs). Tau bound to microtubules (t-MTs) supports the transport of vesicles and ALS functioning (autophagosome AP transformation to autolysosome [AL] after fusion with lysosome [omitted]), whereas tau phosphorylation and aggregation compete with this function. Amyloid oligomers may activate tau phosphorylation. In addition, amyloid oligomers disrupt autolysosome membranes, inhibiting protein degradation. Lipids and sphingolipids participate in the regulation of amyloid production. Caspase activity is sensitive to the stress-response (p53) and the activity of ALS. Amyloid plaques mature from protofibrils (Fb) in the extracellular space. Amyloid and tau species undergo uptake by glial cells or can be cleared to the cerebrospinal fluid (CSF) via bulk flow or to the plasma PL (not shown). Additional regulation by calcium and calpain is omitted

Functional autophagic systems can antagonize caspase activation, and their dysfunction may lead to the activation of caspases. Interactions between the most widely explored therapeutic targets (amyloid and tau) and intracellular pathways may contribute to disease progression or therapy efficacy.

DISEASE DRIVERS

One interesting application of the NH platform is for sensitivity analysis of potential disease drivers, that is, mechanisms launching the breakdown of cell metabolism and proteostasis, depending on age. Potential age-dependent drivers were selected for analysis based on the following criteria: (1) they represent different cellular pathways, (2) they are not likely to be downstream of tau and Aβ (inferred from data on transgenic mice), and (3) their divergence from healthy values has been detected in the early stages of AD. For example, we found data on the rise of p53 in AD versus control (CTRL), or reduced expression of synaptic proteins, such as SNAREs. These drivers, which are assumed to depend on age, were combined in different ways, and simulations of disease progression were performed for each driver combination. The simulated differences for AD versus CTRL for multiple biomarkers were compared with the data, and the top 100 combinations were selected to choose the most probable disease driver mechanisms.

Second, we can test hypotheses on the leading mediators of cognitive impairment, that is, connect the modeled intracellular processes to clinical symptoms. Soluble amyloid as a hypothetical mediator was considered and tested in detail in ref. 16. Using the integrated platform, at least three hypotheses on mediators can be considered: (1) amyloid oligomers (Fb) provoke cognitive impairment, (2) impairment is proportional to tau oligomers (*olig*; see Figure 1) because the tau seeding activity[20] correlates with Mini-Mental State Examination (MMSE) and is detected even in the absence of insoluble tau, and (3) impairment is proportional to the breakdown of general cell processes, expressed through the rise of caspase activity.[21] In the reconstructed network, all of these processes interact, but nevertheless may arise independently from each other due to age-dependent drivers of pathology. Cognitive impairment can be described through a simple function (linear or saturation law), for example, for tau:

$$\mathrm{MMSE} = \mathrm{MMSE0} - \frac{\mathrm{Eff}_{\mathrm{tau}}^{\mathrm{MMSE}} \cdot \mathrm{olig}}{\mathrm{olig} + \mathrm{EC50}_{\mathrm{tau}}^{\mathrm{MMSE}}}, \qquad (2)$$

where MMSE corresponds to Mini-Mental Score Examination data, and the parameters MMSE0, $\mathrm{Eff}_{\mathrm{tau}}^{\mathrm{MMSE}}$, and $\mathrm{EC50}_{\mathrm{tau}}^{\mathrm{MMSE}}$ are chosen to satisfy available disease progression and aducanumab placebo data.

THERAPY ASSESSMENT AND INVESTIGATION OF MECHANISM

This platform was verified using multiple AD biomarker data: amyloid and tau dynamics in mice and humans (see examples in Figure S1 and Figure S2), including biochemical postmortem data on the concentrations of amyloid and tau in the brain and CSF data; the differences between AD and healthy for the appearance of tau in the CSF, ALS disruption, lipid accumulation, and caspase and calpain activation.

The calibrated model was validated using treatment data. As a general strategy, pharmacokinetic (PK) models were fitted to the PK-data and drug half-maximal inhibitory concentration values were taken from the literature, and then long-term pharmacodynamic data were used for validation. The model correctly predicted the limited efficacy of verubecestat on tau pathology, despite significant target engagement (Figure S3). The model has also simulated preclinical data on calpain inhibition, ALS activation (rapamycin), proteasome activation, and acyl-CoA cholesterol acyltransferase inhibition in several types of mouse AD models. For example, the clearance of insoluble tau by rapamycin treatment in the P301S mouse[22] was captured by the model (Figure 2a). The higher efficacy of shorter (6 weeks) treatment in the data may not be statistically reliable and is not confirmed by stereological studies from the same paper.

Immunotherapies were modeled according to their assumed mechanisms using in vitro data. Blocking tau seeding in the tau preclinical model R34[23] attenuated pathology (Figure 2b). Aducanumab reduced soluble and insoluble amyloid in a dose-dependent manner in accordance with the data for Tg2576[13] (Figure S4). Data for soluble amyloid were not available for humans, but amyloid reduction was reproduced satisfactorily (Figure 2c).

MMSE data from the aducanumab trial[13] were used to test the cognitive impairment hypotheses formulated above. All 3 hypotheses similarly described a 2-year reduction in cognition (Figure 2d). However, predictions for treatment efficacy differ between the hypotheses, demonstrating the inconsistency of the amyloid hypothesis with the data. Although amyloid contributes to tau and caspase build-up in the model, they have independent sources of activation and their reduction is less sensitive to anti-amyloid treatment. Interestingly, this level of sensitivity allows for correct prediction of MMSE. However, these two hypotheses cannot be distinguished unless they are compared with the expected data from tau targeting

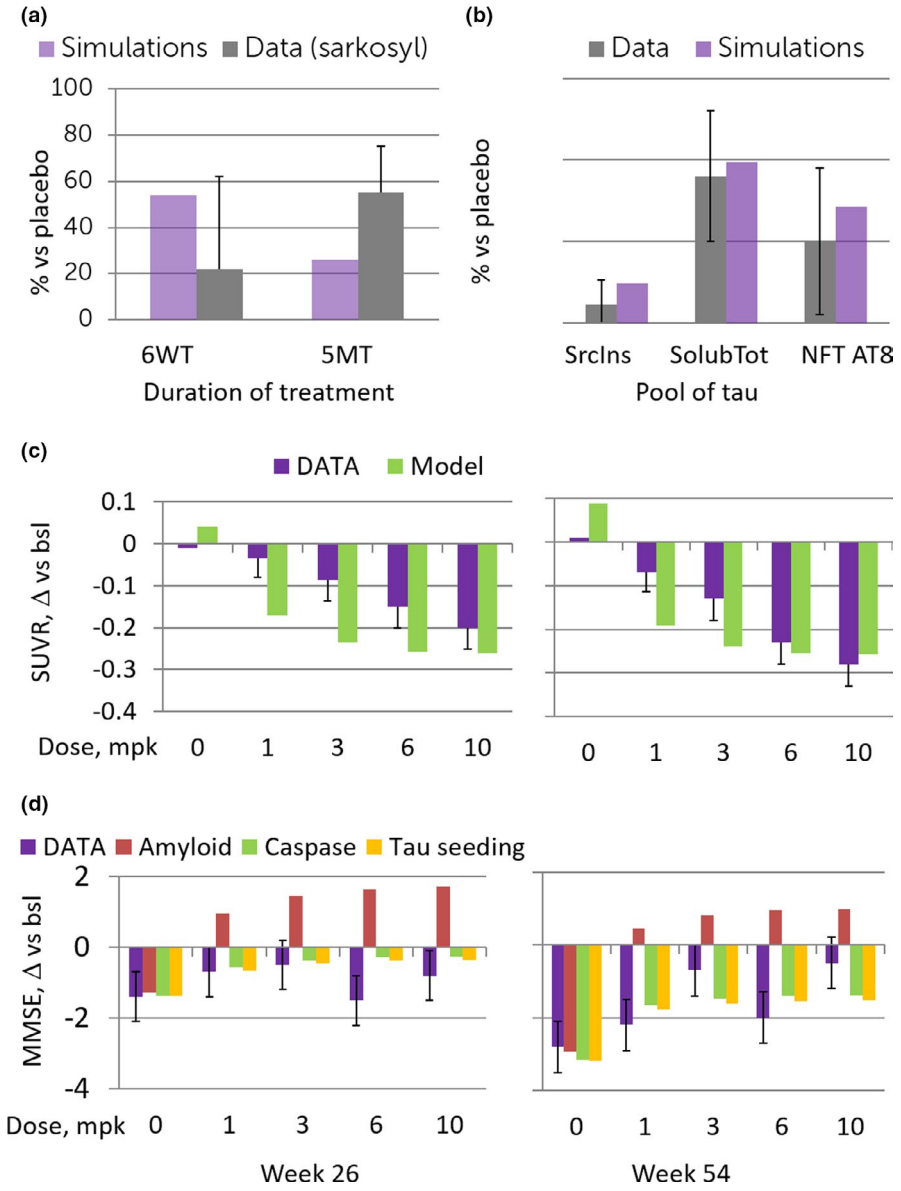

FIGURE 2 Simulations in tau preclinical models and reproduction of aducanumab clinical data. (a) Clearance of sarcosyl extracted tau at two rapamycin dosing regimens in P301S mouse (data from ref. 22): 5MT - 5 months treatment, 6WT - 6 weeks treatment. (b) Prevention of tau pathology in R34 mouse using antibody DC8E8 (data from ref. 23); SrcIns – sarcosyl insoluble tau, SolubTot – total soluble tau, neurofibrillary tangle (NFT) AT8 – tau NFT recognized by AT8 antibody. (c) Model validation on aducanumab data[13] for standardized uptake volume ratio (SUVR); SUVR is calculated as linear function of the mass of fibrils, see details in ref. 17. (d) Prediction of changes in Mini-Mental State Examination (MMSE) from baseline based on the three hypotheses. Parameters for the hypotheses were adjusted to describe placebo data from MMSE = 24 (baseline) during the next 54 weeks. MT, microtubule

trials. The model did not capture the nonmonotonic dose-dependence of amyloid reduction for aducanumab. We searched for nonmonotonic dose-dependence among the different model variables and found it for $A\beta_{42}$ protofibrils (Figure S5). This can be explained by the inhibition of existing plaque growth and a redirection of monomers to form new oligomers. We assume that at a higher dosage (10 mg) of aducanumab, this effect is outweighed by a lower concentration of protofibrils that are free from antibodies and by reduction of other pathology mediators. In this case, amyloid toxicity can explain MMSE, at least partially, and any mechanistic model of toxicity should consider several mediators.

COMBINATION OF TREATMENTS

Because the platform has been validated successfully using both preclinical data for rapamycin and preclinical and clinical data for aducanumab, we assumed that it could be used to reasonably predict the effect of combinations. We tested three types of monotherapies (aducanumab, DC8E8,

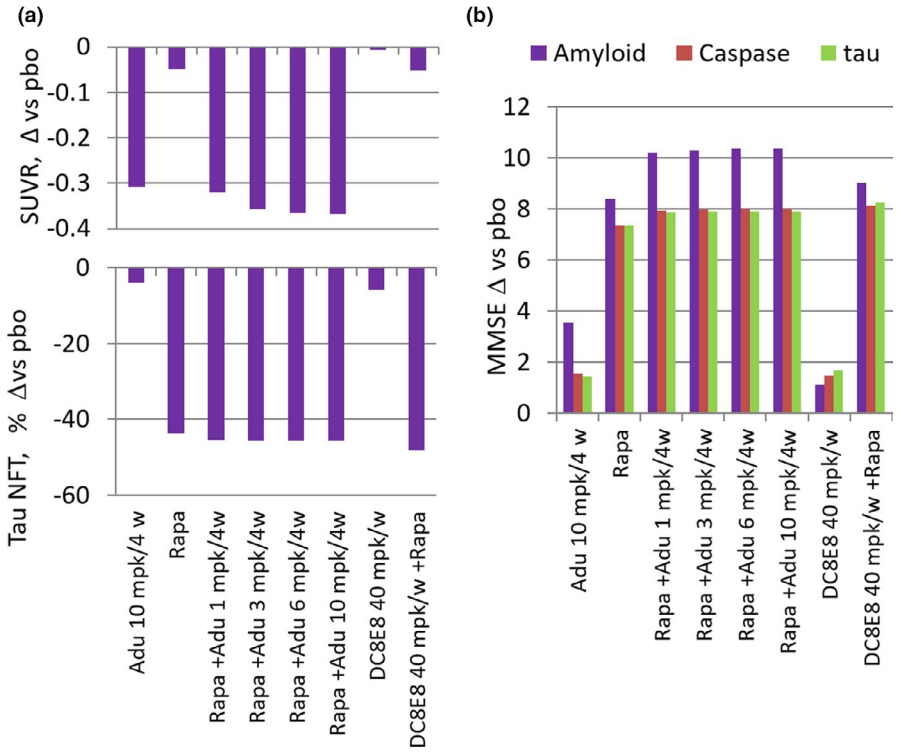

FIGURE 3 Model predictions for different therapies (shown on x-axes): (a) amyloid standardized uptake volume ratio (SUVR; calculated as a linear function of fibril mass) and neurofibrillary tangle (NFT; fibrillar tau); (b) Mini-Mental State Examination (MMSE) predictions based on the different hypotheses. Baseline and duration (54 weeks) correspond to simulations of aducanumab trial (SUVR 1.4, MMSE = 24 at baseline, assumed Braak stage III–IV at baseline). Predictions for different drivers of impairment are denoted by color

and rapamycin) and several composite regimens using the model.

The predicted effect of rapamycin on amyloid reduction was similar to that seen for aducanumab (Figure 3a). According to the predictions, rapamycin attenuated tau more efficiently than a tau antibody. Such a discrepancy between preclinical results (Figure 2b) and the predictions in humans can be explained by the more advanced tau stage in humans at the moment of intervention. The onset of therapy in the human model simulations corresponds to Braak stage III, where there is already a significant accumulation of tau in the hippocampus. The antibody concentration in the brain may not saturate the potential seeds and reduce NFT growth at this stage. However, the combination of immunotherapy with rapamycin increased the effect of immunotherapy, providing almost complete recovery, independent of the hypotheses (Figure 3b). Importantly, efficacy is improved even for the lowest dosages of amyloid targeting antibody, which is critical for avoiding the risk of vasogenic edema. The tremendous predicted reduction of amyloid standard uptake value ratio (SUVR) may be the consequence of linearity of SUVR dependence from amyloid fibril mass, as derived in the previous model version[16] and probably, a logarithmic relationship[24] would yield more reliable prediction. However, large improvements in MMSE can be overpredicted due to the skipped effect of the irreversible downstream degenerative mechanisms in the model (e.g., brain atrophy).

Of course, before testing any combinations, each monotherapy should be approved, including rapamycin. Although there are no clinical data to support the treatment of AD with rapamycin, it is assumed that potential side effects would be acceptable if AD disease progression could be attenuated,[25] and clinical studies to assess the rapamycin effect in AD are already planned.

Finally, other therapeutic combinations with immunotherapy can be tested using the platform, including lipid metabolism modifications, kinase inhibition, and proteasome activation. These combinations may have a synergetic effect on key drivers and reduced side effects due to dose reductions and an optimized schedule.

CONCLUSION

Here, we present the first translational model describing tau and amyloid pathology in humans and mice Accordingly, this is the first attempt to apply QSP to translate and combine the results of preclinical studies to project quantitative clinical

simulations. Because monotherapies have failed in clinical trials so far, a combinatorial approach may be required.

The simulation platform, with some modifications, could be applied to other neurodegenerative disorders, specified by protein misfolding and aggregation, such as Parkinson's disease and Lewy body dementia.

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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