A Quantitative Systems Pharmacology Model of Alzheimer’s Disease Pathology and Treatment Modalities

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Background and Objectives

• Alzheimer’s disease (AD) is a progressive neurodegenerative brain disease that gradually destroys memory and cognitive skills.
• AD is the most common cause of dementia among older adults. An AD-affected brain is shown to have accumulation of abnormal protein clumps (plaques) and tangled fibers (neurofibrillary tangles).1
• Our objective was to develop a comprehensive quantitative systems pharmacology (QSP) model of (AD) pathologies to assess the impact of investigational treatments in support of drug development in this progressive neurodegenerative disease with a high unmet medical need.

Methodology

The comprehensive QSP model based on ordinary differential equations (ODE) includes the two defining features of AD pathology: Aβ production and aggregation to form dense plaques, and tau hyperphosphorylation, aggregation, spreading, and formation of neurofibrillary tangles (NFTs).1 Detailed features of the model include:

• Regulated Aβ40 and Aβ42 production and secretion, including BACE1 and γ-secretase activity
• Aβ monomer aggregation into oligomers, fibrils, and plaques with mixed Aβ42 / Aβ40 composition
• Aβ clearance by protein degradation, receptor-mediated uptake, phagocytosis, active and passive transport
• Peripheral production of Aβ
• Tau production, hyperphosphorylation, aggregation, NFT formation, and extracellular spreading
• Hypothesized regulation of tau pathology by Aβ
• Active and passive transport of soluble Aβ and tau species between brain interstitial fluid (ISF), cerebrospinal fluid (CSF), and plasma
• Representation of both Aβ42 carrier and non-carrier status
• Antibody PK and binding to Aβ or tau species and consequent impact on Aβ or tau pathology

Software: SimBiology® (R2017b), a MATLAB® based application was used for the implementation of the model. Calibration and Qualification: Initial conditions and parameters were informed by literature and in-house preclinical and clinical data. Biomarkers and endpoints were compared to clinical data. Qualification was informed by Rosa’s Model Qualification Method.5

Biomarkers and Endpoints: (a) Fluid biomarkers (Aβ and Tau), (b) AβPET SUVR, (c) Fluid biomarkers (Aβ and Tau), (d) Tau PET SUVR

Therapies/Interventions: (a) Aβ targeting agents: solanezumab, crenezumab, aducanumab, and gantenerumab. (b) Tau targeting agents (anti-tau antibody)

Key Assumptions and Limitations: Neuronal cell population and protein production is assumed to be constant. Brain ISF is modeled as a single well-mixed compartment. The model does not attempt to translate biomarker dynamics to cognitive endpoints at this stage.

Results

Antibody PK and PD Calibration Insights

Figure 2 Model fitted versus observed plasma concentration-time profiles a. crenezumab3-6; b. aducanumab

Figure 3 Model fitted/predicted versus observed percent change in Aβ PET SUVR a. gantenerumab7-8; b and c. aducanumab

Figure 4 Simulated profiles of target neutralization in brain (interstitial fluid volume = 242 mL) after administration of solanezumab, crenezumab, aducanumab, and gantenerumab at their clinical doses as flat dosing a. unbound Aβ monomers; b. unbound Aβ oligomers; c. unbound Aβ plaques.

Figure 5 Patient phenotype-based model calibrated and simulated a. change in Aβ SUVR in brain upon treatment with plaque targeting antibody; b. percent change in tau SUVR over 12 months.10

Figure 6 Model slightly overpredicts effect at 18 months; likely reflects the slightly lower reduction in Aβ PET observed in aducanumab Ph 3 vs 1b (due to lower cumulative dose)

Conclusions

✓ A calibrated AD QSP model incorporating a detailed representation of Aβ and tau production, aggregation, transport and clearance was developed. The model facilitates a quantitative assessment of the effects of several therapeutic agents in development on biomarker dynamics via in-silico predictions.

✓ The model provides a platform to quantitatively evaluate drug delivery and target engagement in the brain and CSF. The model can be leveraged to evaluate the disease from a mechanistic perspective as it progresses longitudinally.

References

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