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

Vidya Ramakrishnan[1,*], Christina Friedrich[2,*], Colleen Witt[2], Meghan Pryor[2], Michael Dolton[1], Jasi Atwal[1], Kristin Wildsmith[1], Katherine Kudrycki[2], Robert Sheehan[2], Seung-Hye Lee[1], Hans Peter Grimm[3], Roxana Aldea[3], Norman Mazer[3], Carsten Hofmann[3], Ronald Gieschke[3], Reina Fuji[1], Saroja Ramanujan[1], Angelica Quartino[1], Jin Yan Jin[1]

[1]Genentech, Inc., South San Francisco, CA, USA; [2]Rosa & Co., LLC., San Carlos, CA, USA; [3]Hoffmann-La Roche Ltd., Basel, Switzerland. *VR and CF are co-first authors.

Genentech
A Member of the Roche Group

ROSA

Background and Objectives

- Alzheimer's disease (AD) is a progressive neurodegenerative brain disease that gradually destroys memory and cognitive skills[1].
- AD is the most common cause of dementia among older adults. An AD afflicted 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 ApoE4 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.[2]

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

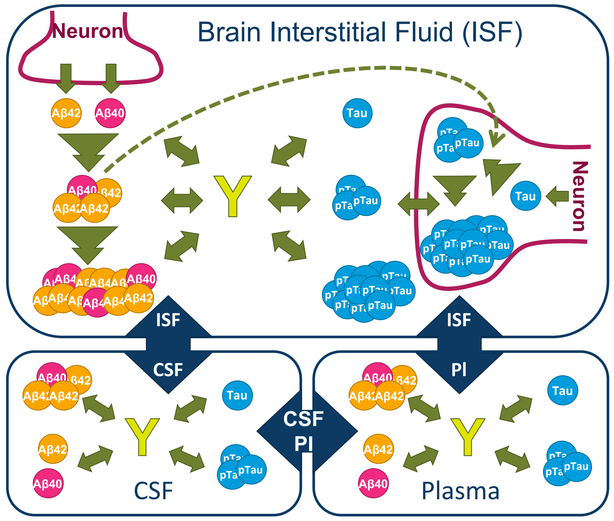


Figure 1 Overview of the AD QSP Model Schematic depicting major scope components and pathways.

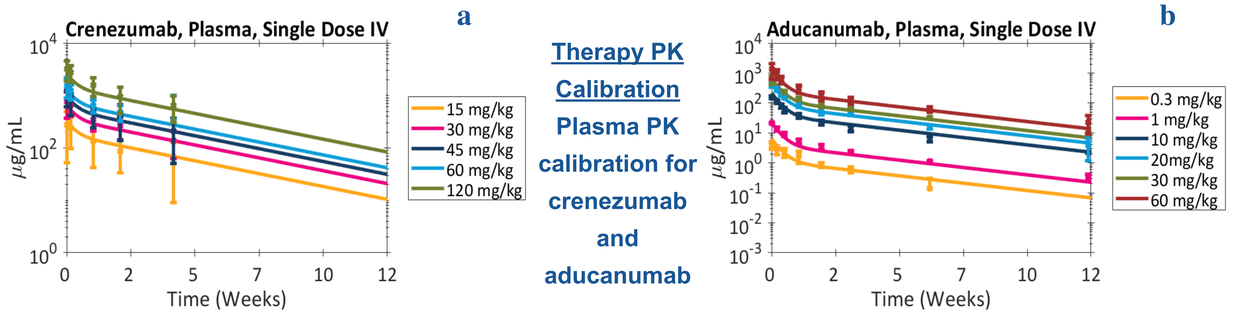
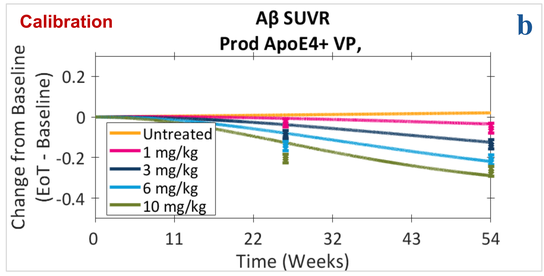
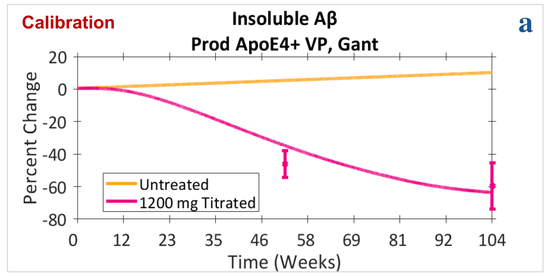


Figure 2 Model fitted versus observed plasma concentration-time profiles **a.** crenezumab[3-5]; **b.** aducanumab[6]





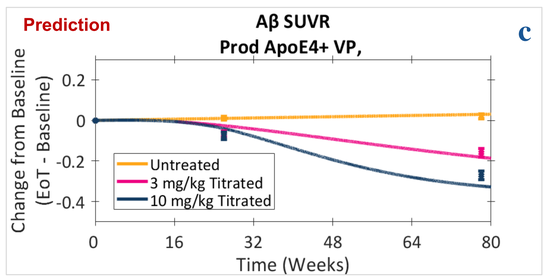


Figure 3 Model fitted/predicted versus observed percent change in Aβ PET SUVR **a.** gantenerumab[7-8]; **b and c.** aducanumab[6,9]

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)

Target Neutralization in ISF

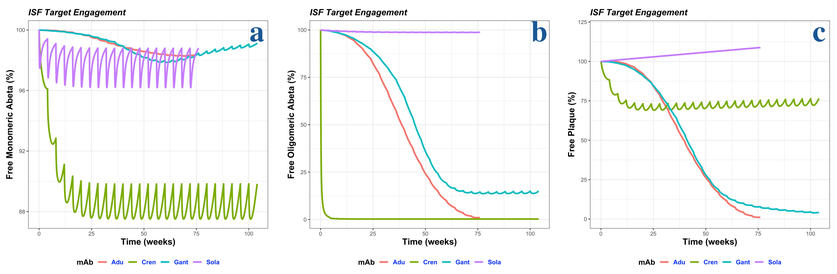


Figure 4 Simulated profiles of target neutralization in brain (interstitial fluid volume = 242 ml) after administration of solanezumab, crenezumab, aducanumab, and gantenerumab at their clinical doses as flat dosing **a.** unbound Aβ monomers; **b.** unbound Aβ oligomers; **c.** unbound Aβ plaques.

Patient Phenotypes

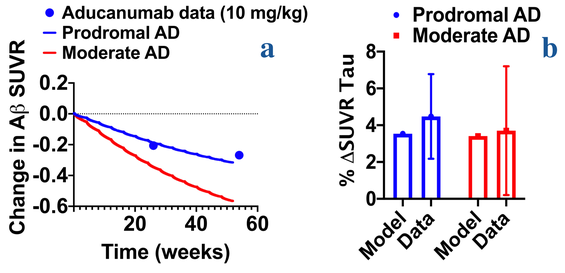


Figure 5 Patient phenotype-based model calibrated and simulated **a.** change in Aβ SUVR in brain upon treatment with plaque targeting antibody[6]; **b.** percent change in tau SUVR over 12 months[10].

The most abundant data for Aβ and tau come from post-mortem brains from deceased moderate to severe (mod/sev) AD patients. A prodromal AD phenotype was then developed representing an earlier version of the same AD patient. In addition, the model includes patients with different ApoE4 carrier status.

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

1. Masters CL, *et al.* Alzheimer's disease. *Nature Reviews Disease Primers* 1 15056 (2015)
2. Friedrich CM. A model qualification method for mechanistic physiological QSP models to support model-informed drug development. *CPT:PSP* 5 43-53. (2016)
3. Cummings JL, *et al.* ABBY: A phase 2 randomized trial of crenezumab in mild to moderate Alzheimer disease. *Neurology* 90 e1889-97. (2018)
4. Salloway SS, *et al.* Amyloid positron emission tomography and cerebrospinal fluid results from a crenezumab anti-amyloid-beta antibody double-blind, placebo-controlled, randomized phase II study in mild-to-moderate Alzheimer's disease (BLAZE). *Alzheimer's Research & Therapy* 10 96. (2018)
5. https://clinicaltrials.gov/ct2/show/NCT02353598 accessed 31 March 2019
6. Sevigny J, *et al.* The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. *Nature* 537 50-6. (2016)
7. Ostrowitzki S, *et al.* A phase III randomized trial of gantenerumab in prodromal Alzheimer's disease. *Alzheimer's Research & Therapy* 9 95. (2017)
8. Klein G, *et al.* Gantenerumab reduces amyloid-β plaques in patients with prodromal to moderate Alzheimer's disease: a PET substudy interim analysis. *Alzheimer's Research & Therapy* 11 101. (2019)
9. Haeberlein SB, *et al.* EMERGE and ENGAGE Topline Results: Two Phase 3 Studies to Evaluate Aducanumab in Patients With Early Alzheimer's Disease. *CTAD* San Diego CA USA. (2019)
10. Sanabria-Bohorquez S, *et al.* Evaluation of [18F]GTP1 (Genentech tau probe 1) Extent and Load for assessing tau burden in Alzheimer's disease. Presented at HAI, 16-18 January 2019, Miami, FL, USA.