EFFECTS OF ANTI-AMYLOID TREATMENT ON TAU BIOMARKERS AND FUNCTIONAL OUTCOME. A MECHANISTIC QUANTITATIVE SYSTEMS PHARMACOLOGY STUDY

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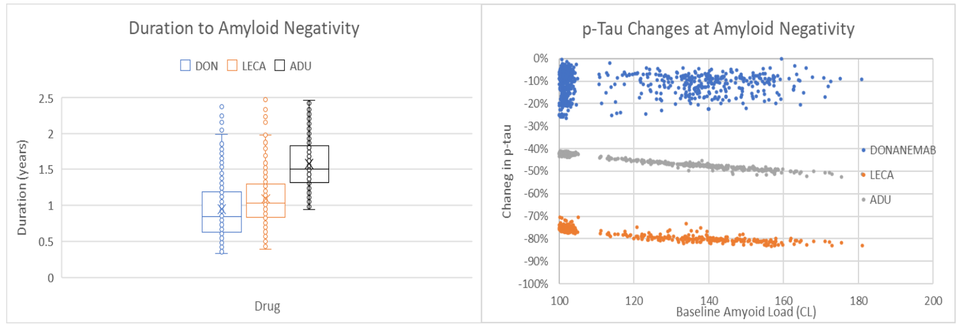
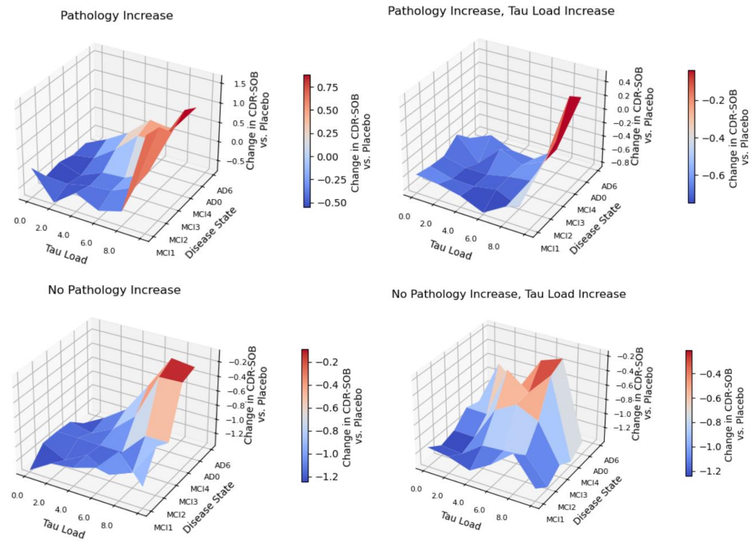
Background

- Major unaddressed issues in clinical practice
  - Identifying accessible fluid biomarker to determine time for reaching amyloid negativity to know when to stop treatment
  - Understanding impact of disease state on functional outcome
  - Understanding impact of baseline tau load on functional outcome
- We use a combination of a mechanistic QSP Model of amyloid aggregation with a computational neuroscience model, calibrated on functional scales with symptomatic treatments
- Abeta monomers affect glutamate and a7 nAChR, oligomers affect AMPA, gK and GABA; Tau oligomers affect voltage-gated K+ and Na+ channels

Simulated P-Tau Changes at Amyloid Negativity

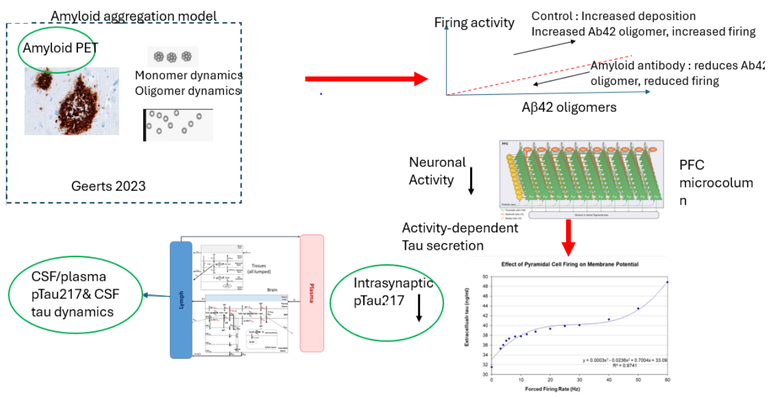


Disease State and Tau Load on CDR-SOB

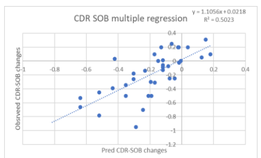


Surface plots demonstrating the effect of baseline disease state (referred to as MCI1 to AD6) and baseline tau load (0.8) on the functional improvement in CDR-SOB from baseline relative to the placebo values (negative values mean a slower worsening with treatment). Blue colors are associated with treatment being more favorable than placebo while the inverse is true for red colors. Most of the blue colors are situated in the lower left, suggesting that amyloid antibodies have a better functional outcome in baseline conditions of lower pathology and tau load, despite the same change in amyloid biomarkers, for 4 different progression scenarios.

Amyloid-Tau QSP Model



CDR-SOB : Simulated Abeta versus Clinical Changes



34 observations
7 antibodies

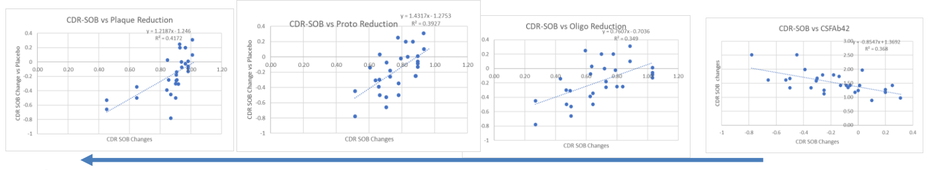
Multiple Regression
R^2=0.50

Plaques*
R^2=0.41

Protofibrils
R^2=0.39

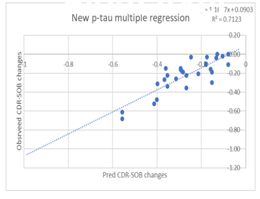
Oligomers
R^2=0.35

Monomers*
R^2=0.37



Aggregation

Plasma p-tau : Simulated Abeta vs Measured



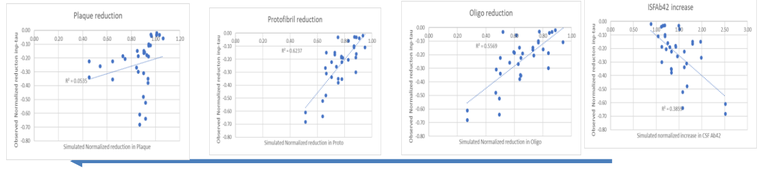
32 observations
7 antibodies
Plaques
R^2=0.05

Multiple Regression
R^2=0.71

Protofibrils*
R^2=0.62

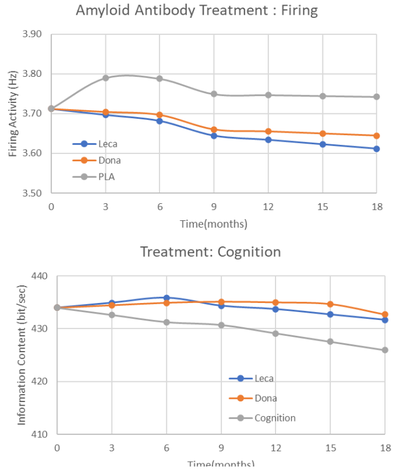
Oligomers*
R^2=0.56

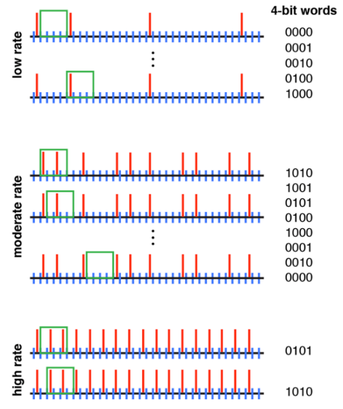
Monomers*
R^2=0.39



Aggregation

Opposite Effects on Neuronal Firing and Cognition





Discussion

- We derive an antibody-specific threshold of change for plasma p-tau to indicate timing of amyloid negativity
- Model recapitulates the observed hyperactivity on amyloid hotspots, explains effects of amyloid antibodies on neuronal firing and levels of plasma p-tau
- The Model generates a biological hypothesis on why
  - Difference of treatment versus placebo decreases with more advanced disease pathology.
  - Difference of treatment versus placebo decreases with higher baseline tau pathology.

References

- Geerts et al 2018 Alzheimers Res Ther.;10(1):14
- Geerts et al 2020 Alzheimers Dement.16(6):862-872
- Geerts et al 2023, CPT:PSP 12, 444
- Pontecorvo et al 2022 AMA Neurol.;79(12):1250-1259
- Mc Dade et al 2022 Alzheimers Res Ther. Dec 21;14(1):191
- Nisenbaum 2023 Alzheimers Dement. doi: 10.1002/alz.12919