

INTRODUCTION

Microglial inflammatory state contributes to Alzheimer's Disease development. Tau and amyloid influence the microglial state, while inflammatory mediators exacerbate the markers on pathology in neurons. Immunotherapy targeting microglial receptors (TREM2) is investigated for treatment of AD and tauopathy. The goal of this work was to apply QSP (Quantitative Systems Pharmacology) modeling **1**) to describe the interaction between inflammatory mediators and tau pathology and **2**) to simulate effects TREM2-targeting therapy on neuronal and inflammatory markers.

MODEL DESCRIPTION

Fig. 1. Model scheme

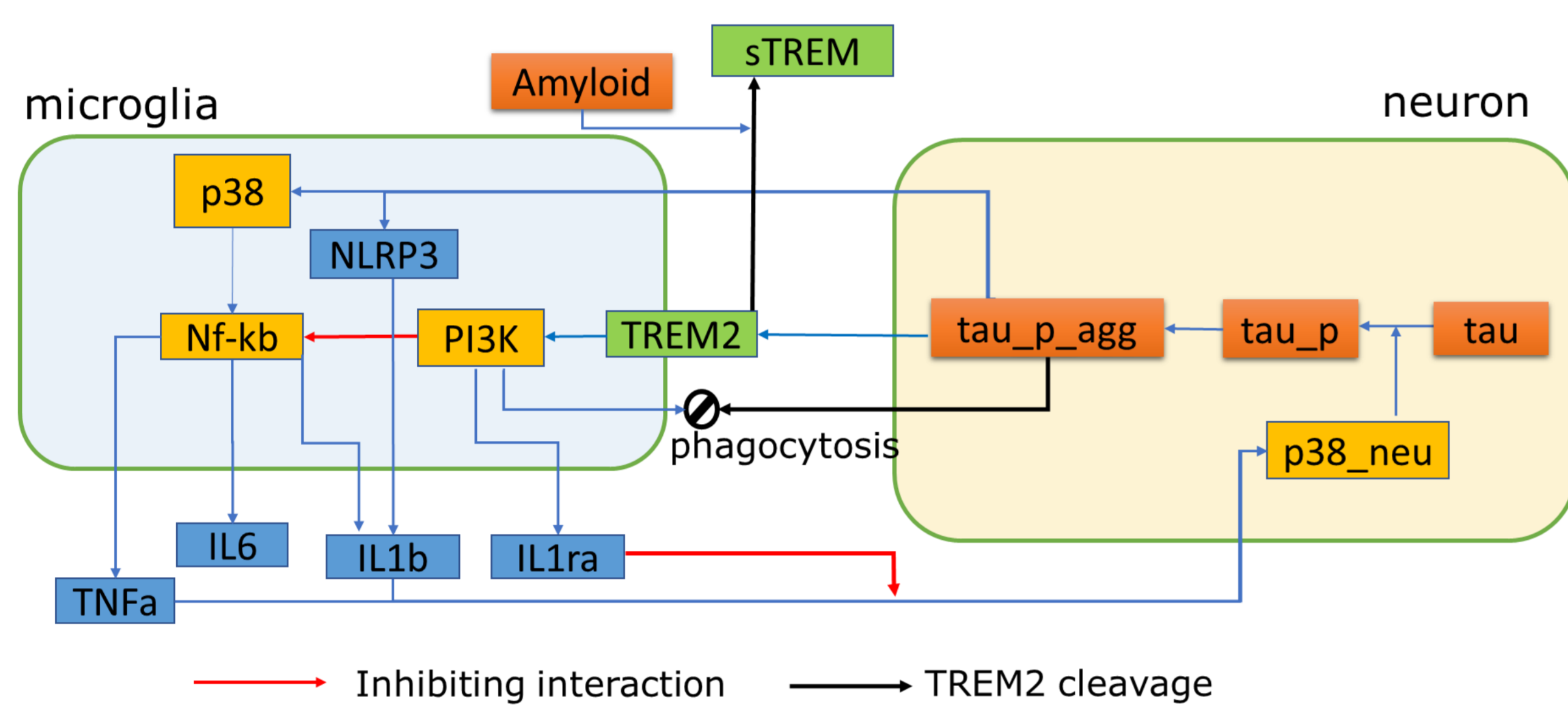
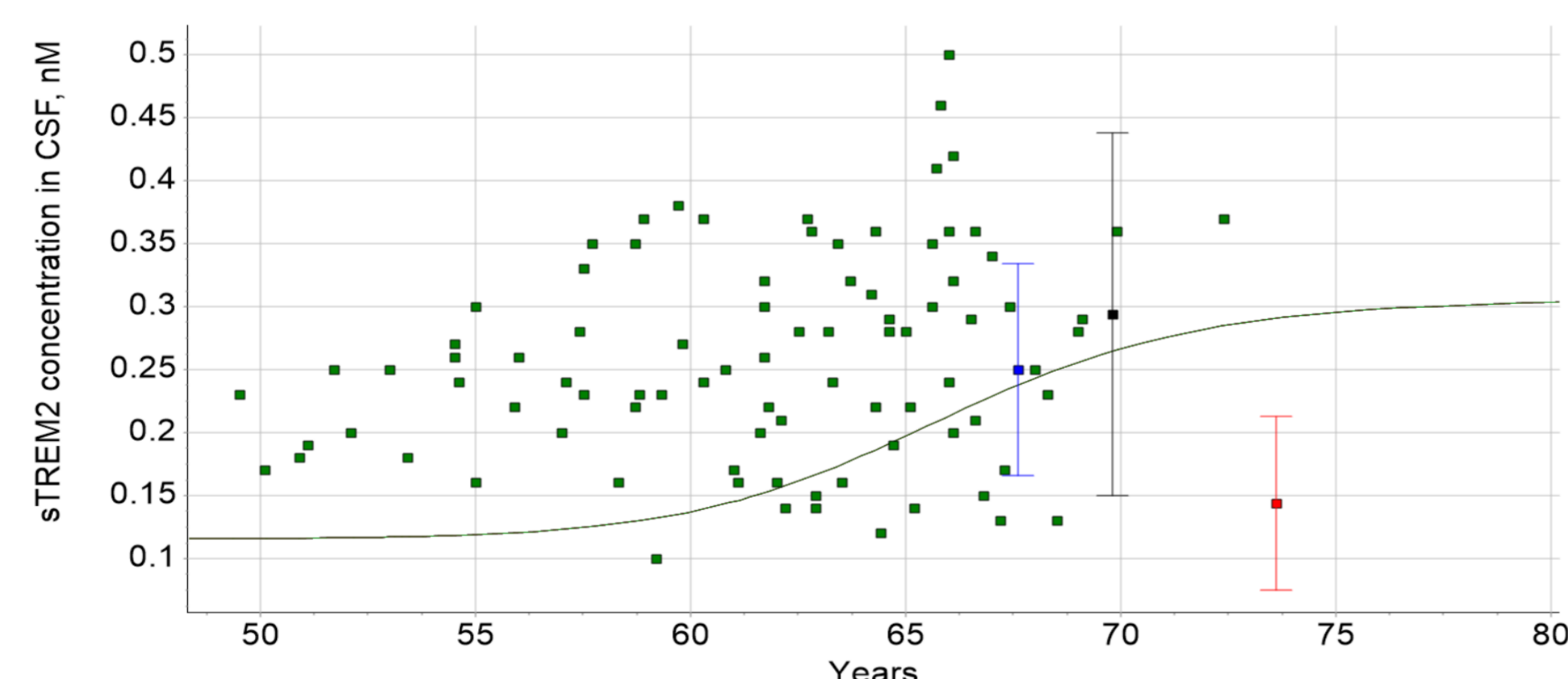


Fig. 2. Workflow of QSP model generation

- Calibration of amyloid influence on data from AD patients
- Calibration of model on cytokines, tau aggregation on tau transgenic mouse data with and without KO TREM2
- Calibration of TREM2 effect on anti-inflammatory signaling on ALOO2c treatment data
- Simulation of effect of TREM2 immunotherapy in tau transgenic mice

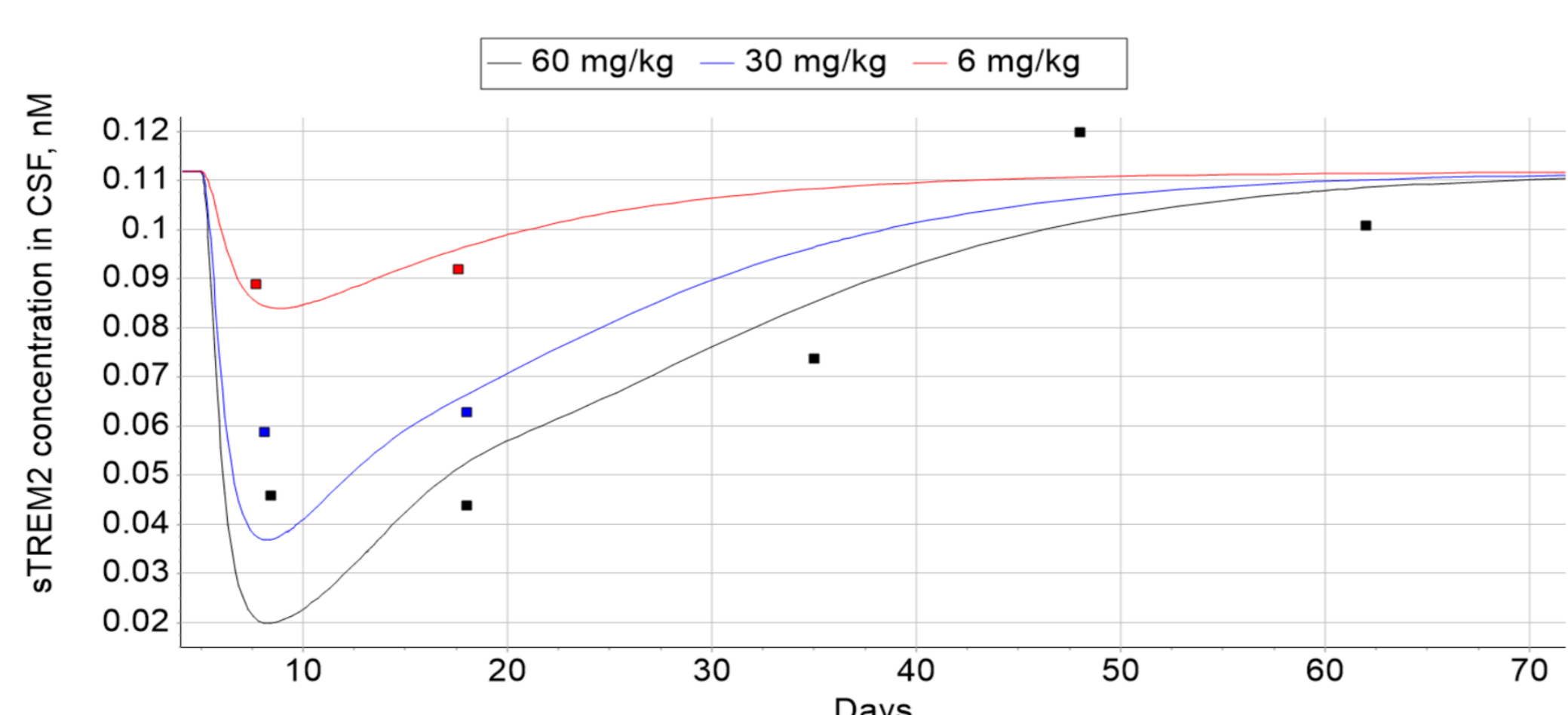
STREM2 IN ALZHEIMER DISEASE

Fig. 3. Calibration of sTREM2 PD in CSF of people with Alzheimer disease, where green points – validation data [PMID: 32573951].



STREM2 WITH ALOO2c

Fig. 4. Calibration of sTREM2 PD in CSF of healthy people for ALOO2c treatment (single injection at t=5) [1].

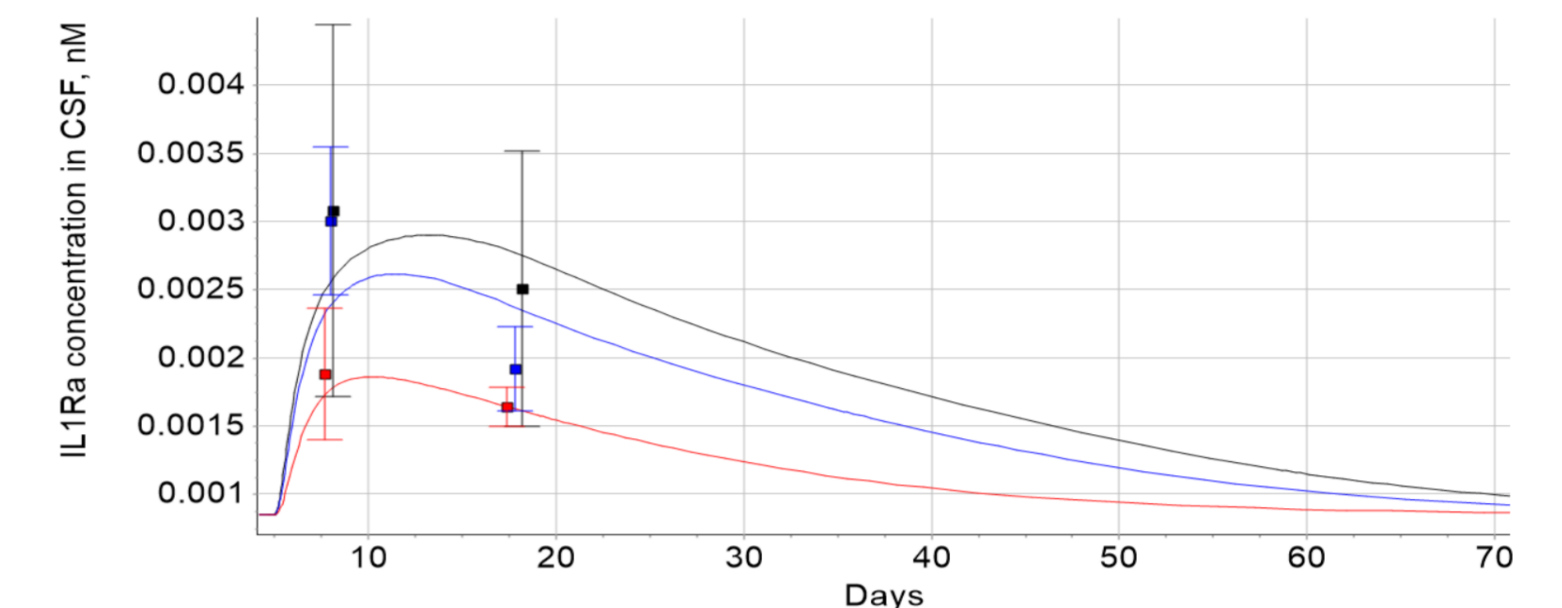


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IL1RA WITH ALOO2c

Fig. 5. Calibration of IL1Ra PD in CSF of healthy people for ALOO2c treatment (single injection at t=5) [1].



TREM2 IN INFLAMMATION AND TAU PATHOLOGY

Fig. 6. Calibration of microglial p38 and caspase 1 levels in tau transgenic mouse model [2] [PMID: 31748742].

- In our model transgenic mouse has increased for 100 times level of aggregated tau in comparison with WT mouse
- Levels of microglial p38 and caspase 1 in WT mouse were chosen as baselines
- The differences between TG and WT mice are defined by the tau aggregation rate and three parameters - $k_{\text{tau_p_agg_P2X7}}$, $k_{\text{trd_syk_tau_agg}}$, $K_{\text{m_tau_TREM}}$

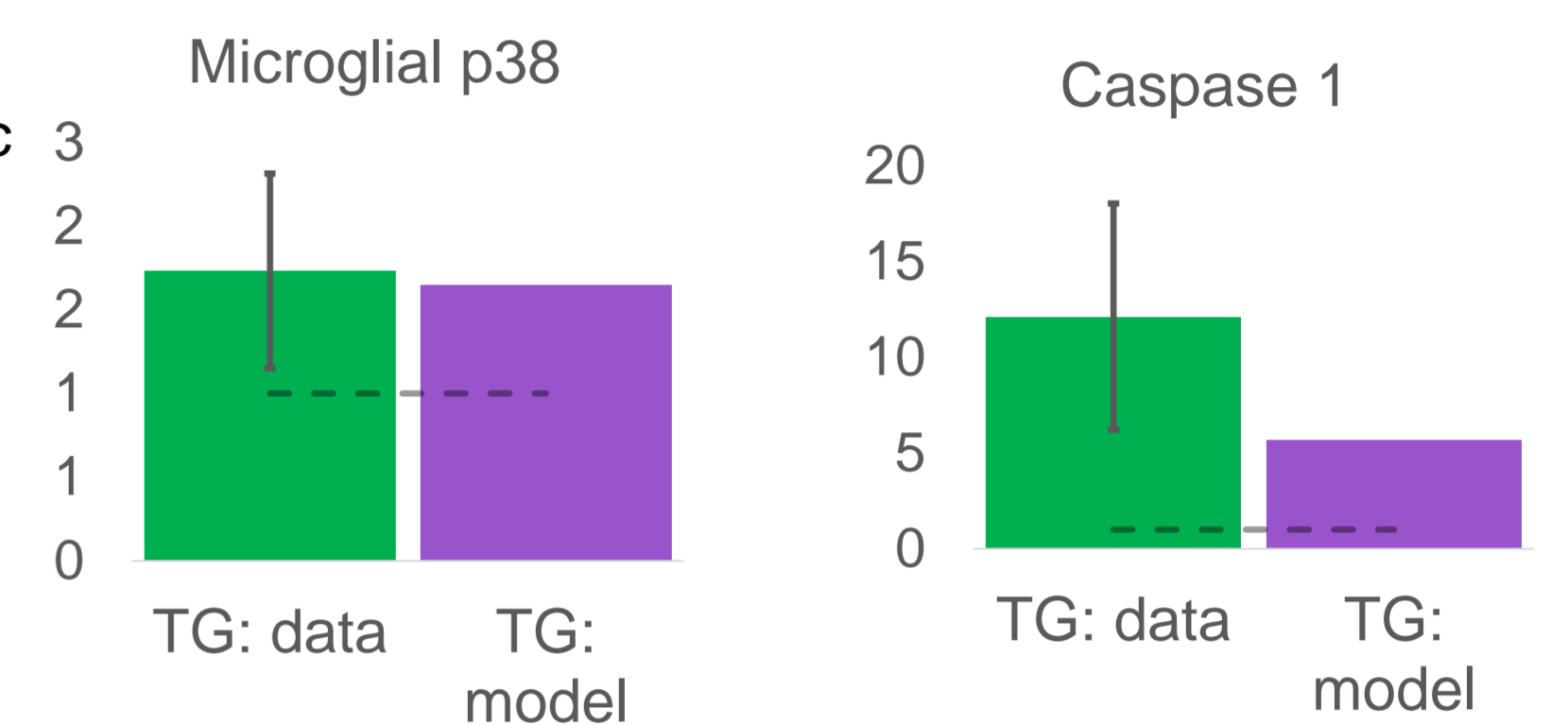
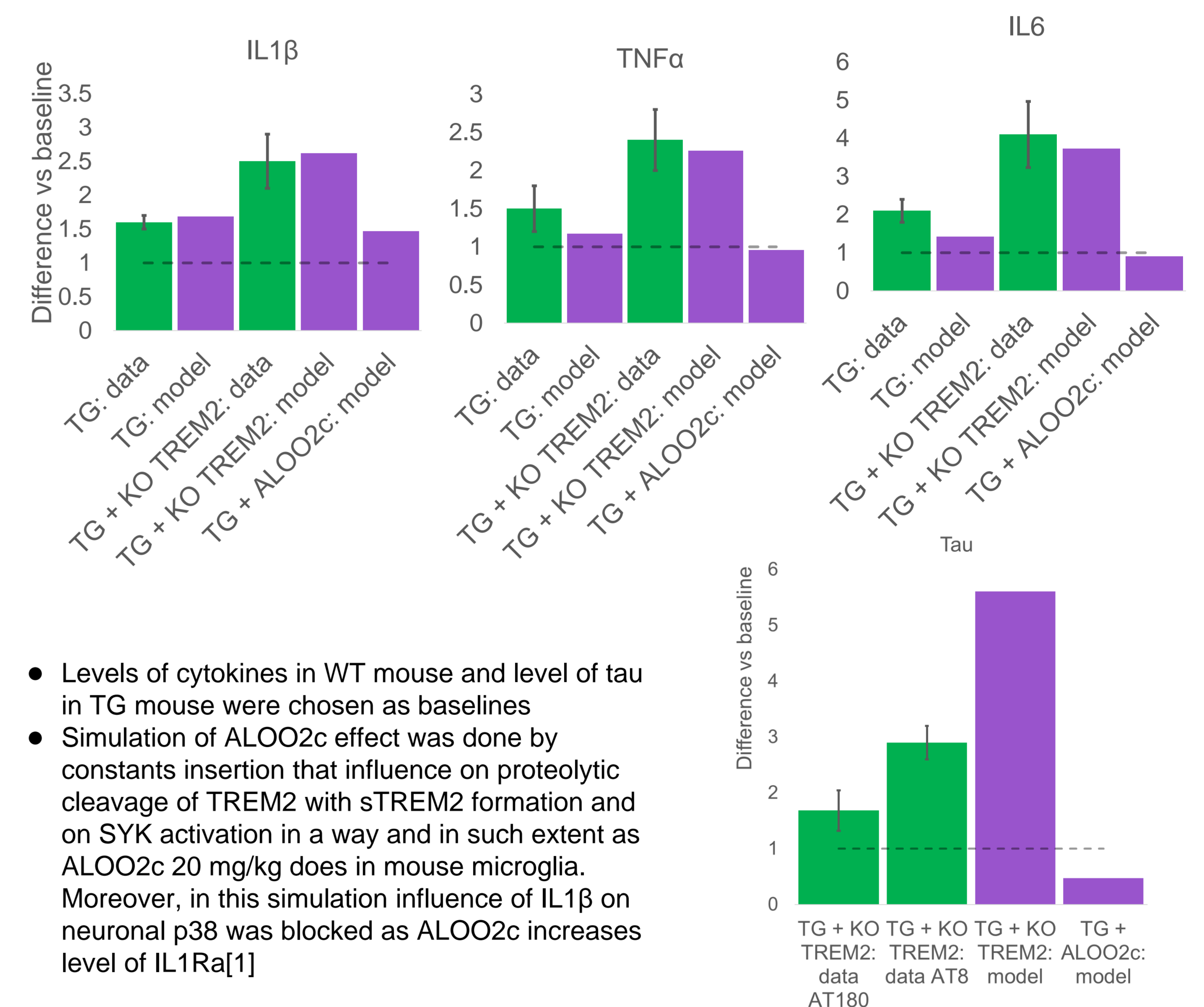


Fig. 7. Calibration and simulation of cytokines and phosphorylated tau level changes in tau transgenic mouse model with knockout TREM2 and with ALOO2c [PMID: 26364736].



- Levels of cytokines in WT mouse and level of tau in TG mouse were chosen as baselines
- Simulation of ALOO2c effect was done by constants insertion that influence on proteolytic cleavage of TREM2 with sTREM2 formation and on SYK activation in a way and in such extent as ALOO2c 20 mg/kg does in mouse microglia. Moreover, in this simulation influence of IL1β on neuronal p38 was blocked as ALOO2c increases level of IL1Ra[1]

CONCLUSIONS

- The current QSP models correctly describe inflammatory response of microglia to stimulation by aggregated tau influence in accordance with mice data, increase of sTREM2 in CSF connected with early stage of AD in human and TREM signaling activation by ALOO2 antibody reduces the IL-1β in CSF in correspondence with the data
- It describes that tau aggregation influences NLRP3, p38 activity and inflammatory cytokine level and that TREM2 overexpression suppresses the microglial inflammatory response, which subsequently improve tau aggregation in 2 times via attenuation of tau kinase activity.
- Nevertheless, our model overestimates influence of TREM2 on tau level, which suggests that another way of its level regulation exists, so this investigation should be continued.

REFERENCES

- Ward, Michael, et al. "A Phase 1 Study of AL002 in Healthy Volunteers (P5-3.004)." (2022)
- Perea, J. R., Garcia, E., Vallés-Saiz, L., Cuadros, R., Hernández, F., Bolós, M., & #38; Avila, J. (2022). p38 activation occurs mainly in microglia in the P301S Tauopathy mouse model. Scientific Reports 2022 12:1, 1–11, 12(1).

* More than 10 sources were used to collect cellular data for calibration