

Clinical trial simulation and hypothesis testing using amyloid pathology longitudinal translational model

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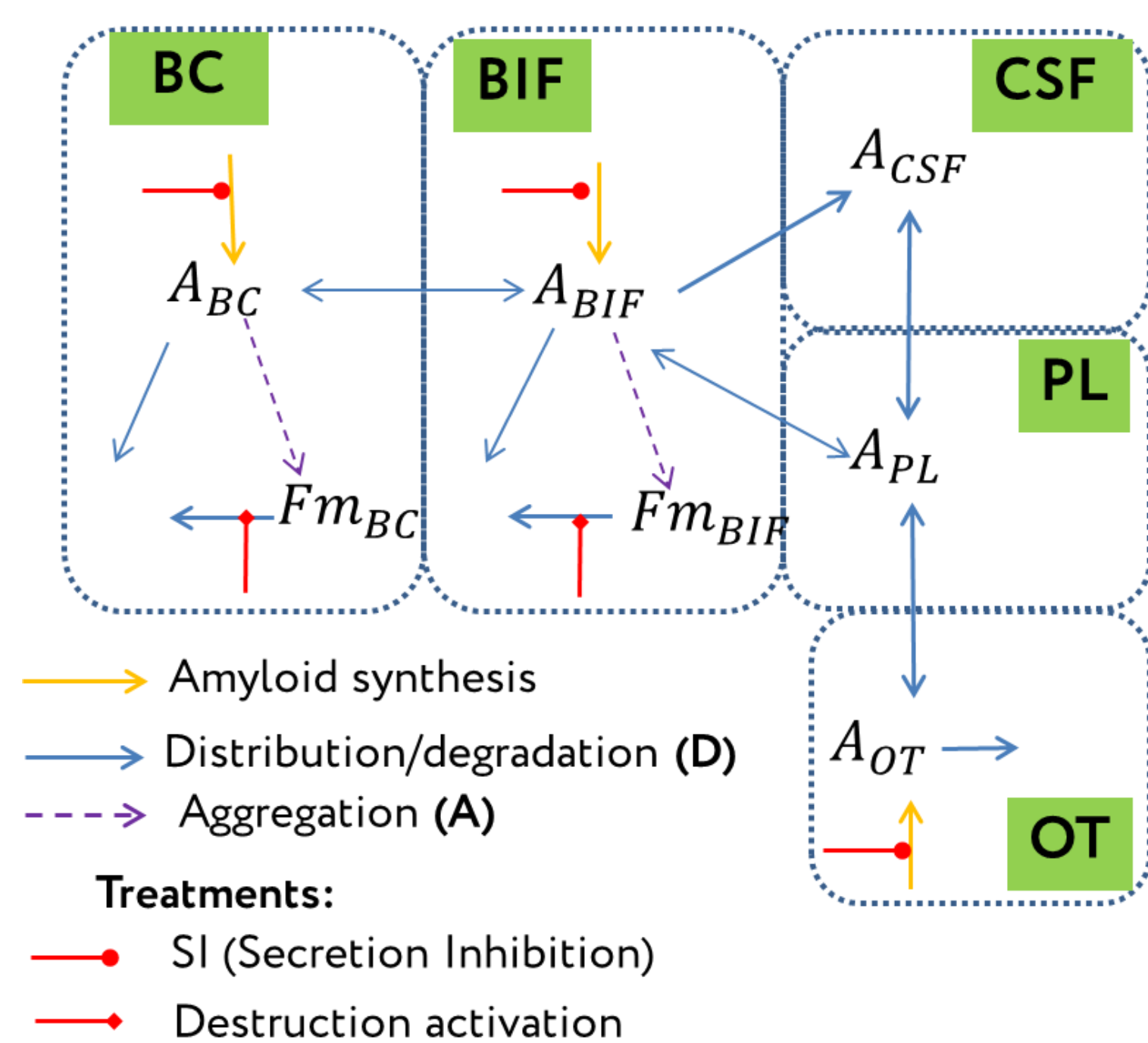
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INTRODUCTION

QSP model describing amyloid secretion, distribution and aggregation was developed earlier. It successfully describes multiple of data on monkey, human, mice. It allows description of longitudinal amyloid progression. Here we apply it for simulation of clinical trial results and amyloid toxicity hypothesis testing.

METHODS

Amyloid pathology model



Fm_{BIF} - insoluble Ab40(42)

Longitudinal progression model

- Progression during 20 years starting at ~ 60.
- Healthy and AD populations have the same baseline (and parameters) before 60 years.
- Healthy and AD populations may have different **prog** and **Ai**.

$$P_i = P_{i0} \cdot (1 + A_i \cdot \text{Age\_dep})$$

$$\text{Age\_dep} = 1 - \frac{1}{1 + K_{in} \cdot \exp((\text{prog} \cdot (t - t_{decline})))}$$

Fig. 1. Scheme of model of Ab distribution and aggregation

D-model: Ab time profiles in brain, CSF and plasma of 129/SVE mouse after administration of 125I-labeled Ab and oral administration of Avagacestat, steady-state values in CSF, PL, BR for human and mice, SILK data for human, Semagacestat PD data

A-model: Measured concentrations in BR, CSF, PL for AD, healthy at different ages, validation on PET data

Cognitive toxicity model

- Ab42 soluble was chosen as the key toxic specie;
- There are no irreversible changes in the system;
- Empirical choice of parameters for Adas-cog score: gradual change from 8 to approximately 35 (Rosenberg et al 2013) during overall disease progression.

Table 1. The list of hypotheses of Ab toxicity

Toxicity of amyloid	Ab is obligatory	#	Description
Proportional	No	H 1.1	$\text{tox}(Ab_{42}) = k_{dr} \cdot (\text{Asoluble}_{BR}^{42} - \text{base\_health})$, $\text{base\_health}=1 \text{ nM}$
	Yes	H 2.1	Same as 1.1, but takes into account decrease of cognition for the low Ab_{42} levels [Puzzo et al]
Threshold (prion type)	No	H 1.2	$\text{tox}(Ab_{42}) = k_{thr} \cdot (t - t_{st})$ if $\text{Asoluble}_{BR}^{42} > \text{base\_health}$
	Yes	H 2.2	Same as 1.2, 2 but takes into account decrease of cognition for the low Ab_{42} levels
Proportional and threshold	No	H 1.3	combination of two influences: Ab is driver of disease, and after achieving threshold independent growth is added to Ab toxicity.

RESULTS

Amyloid pathology model performance

Fig. 2. Model calibration (examples)

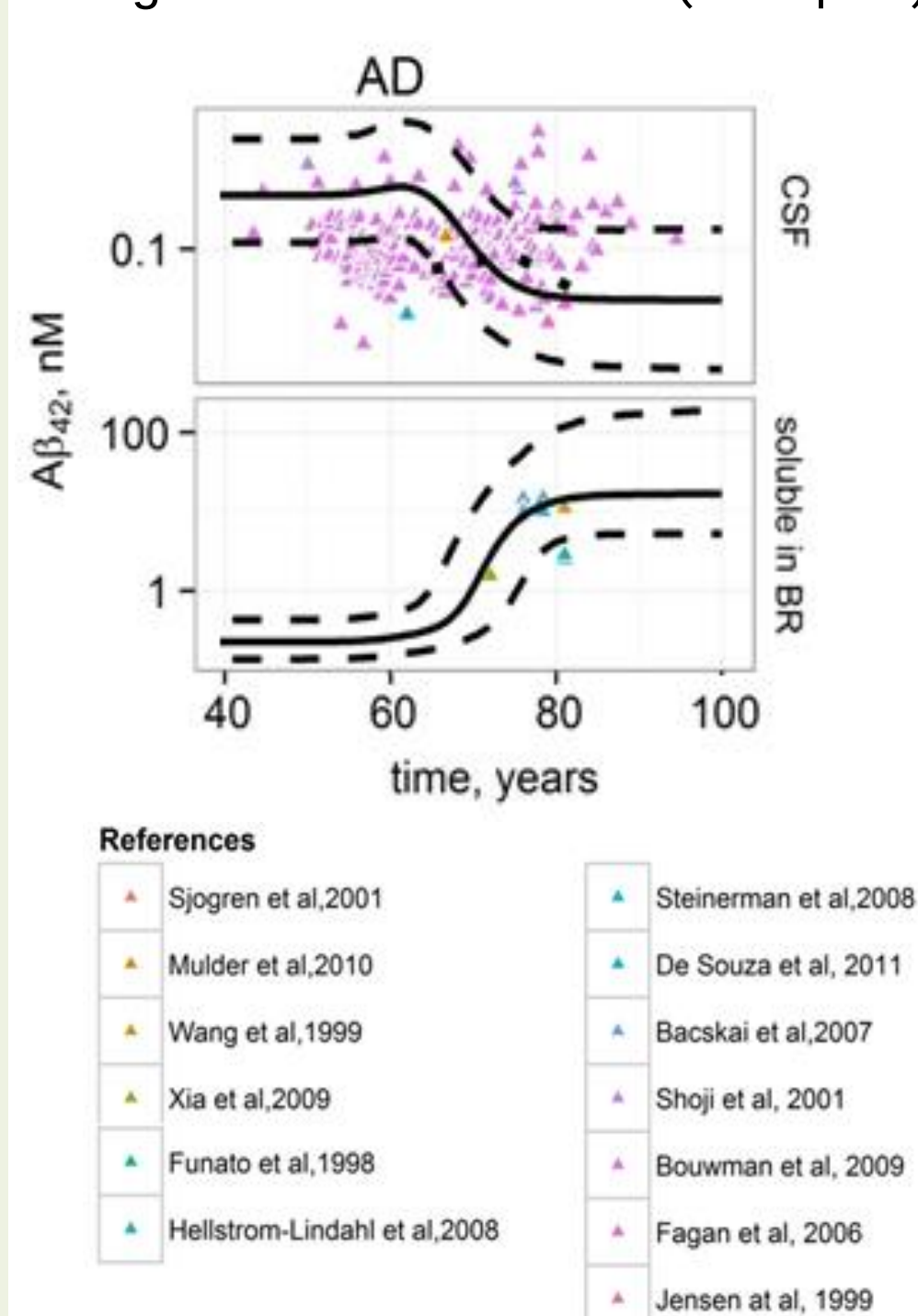


Fig. 3. Model validation

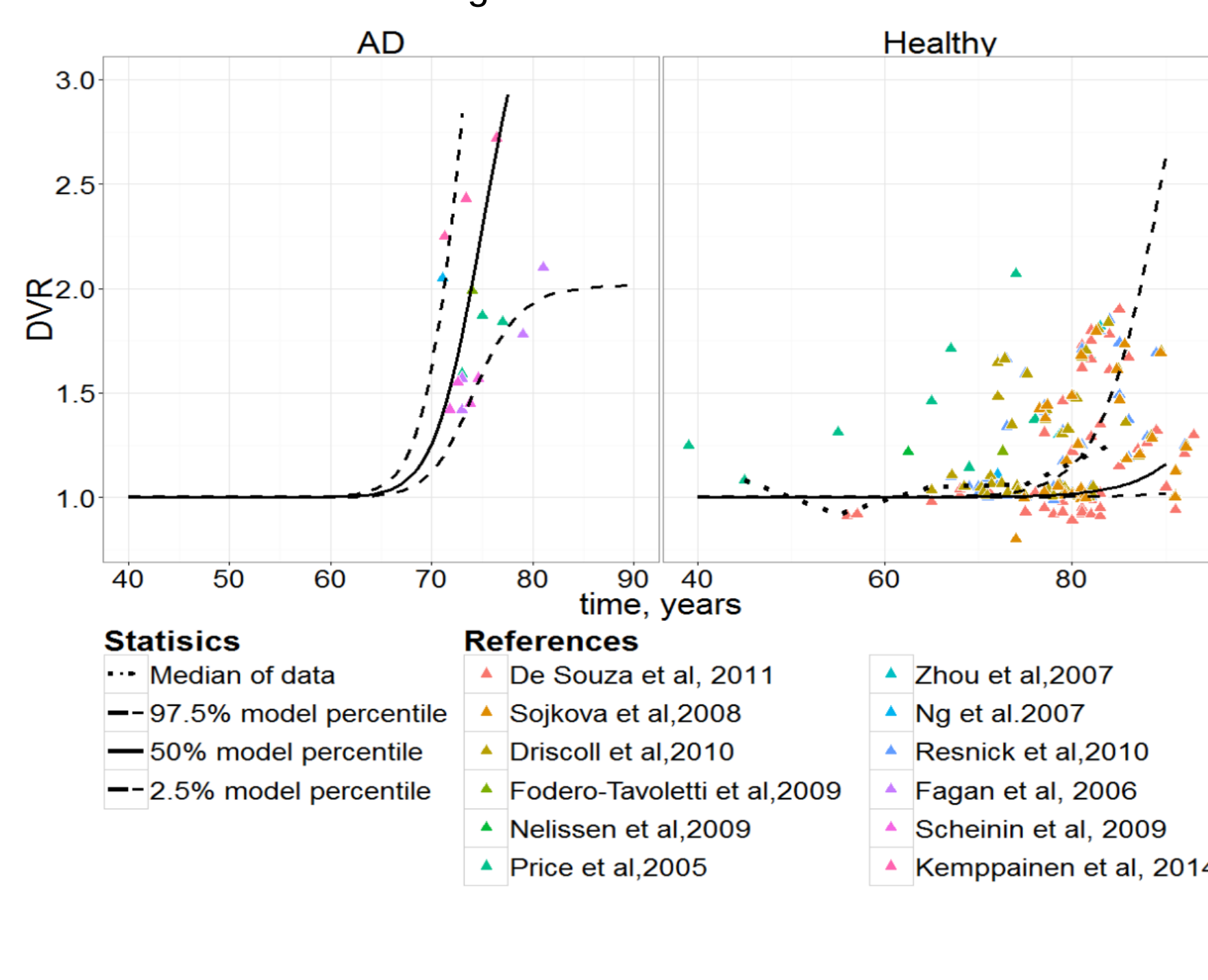


Fig. 4. Simulations of Adas-cog dynamics under different hypotheses and different treatments

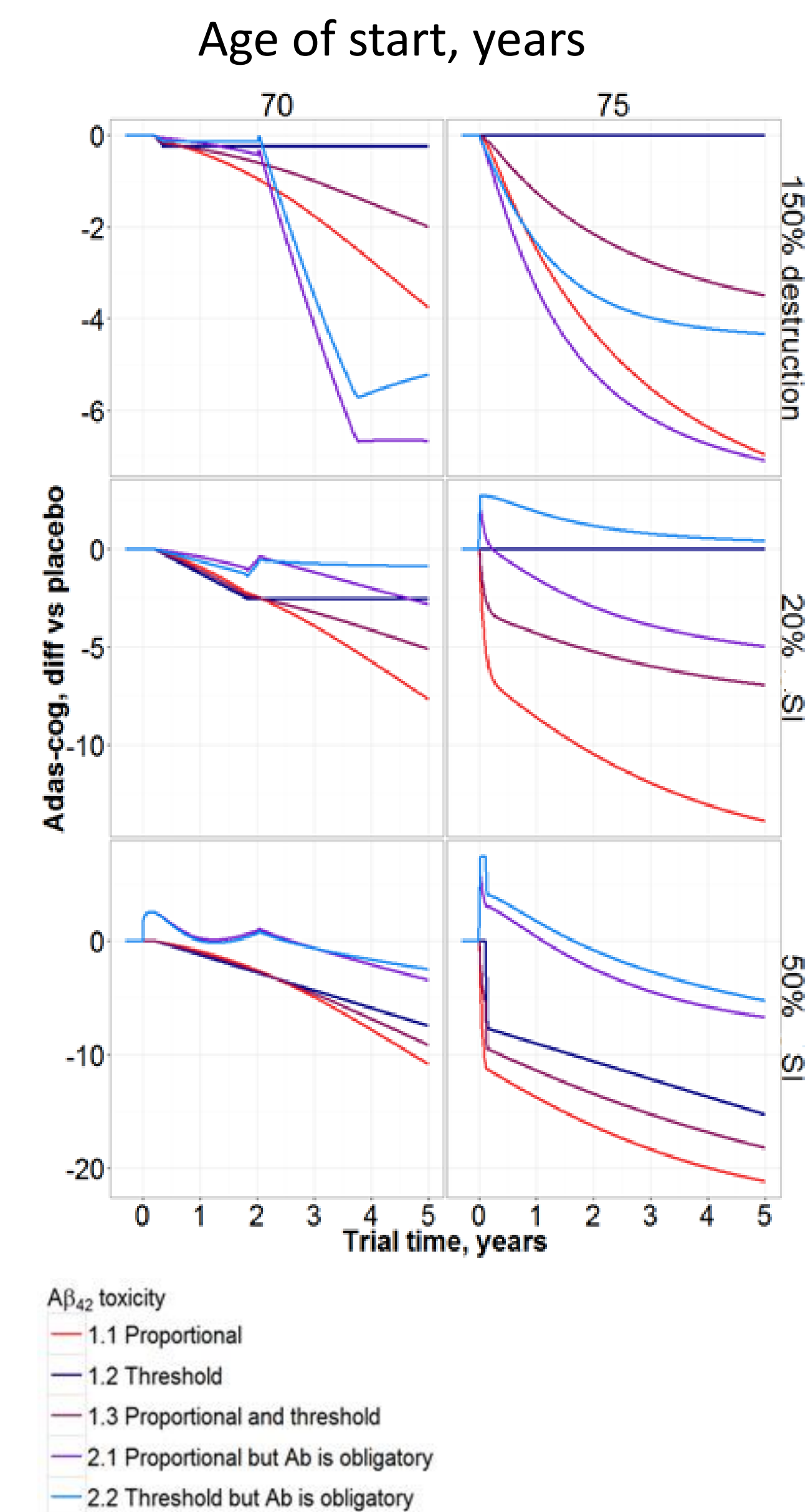


Fig. 5. Simulations of Adas-cog, Ab42 in CSF and DVR under hypothesis 2.1

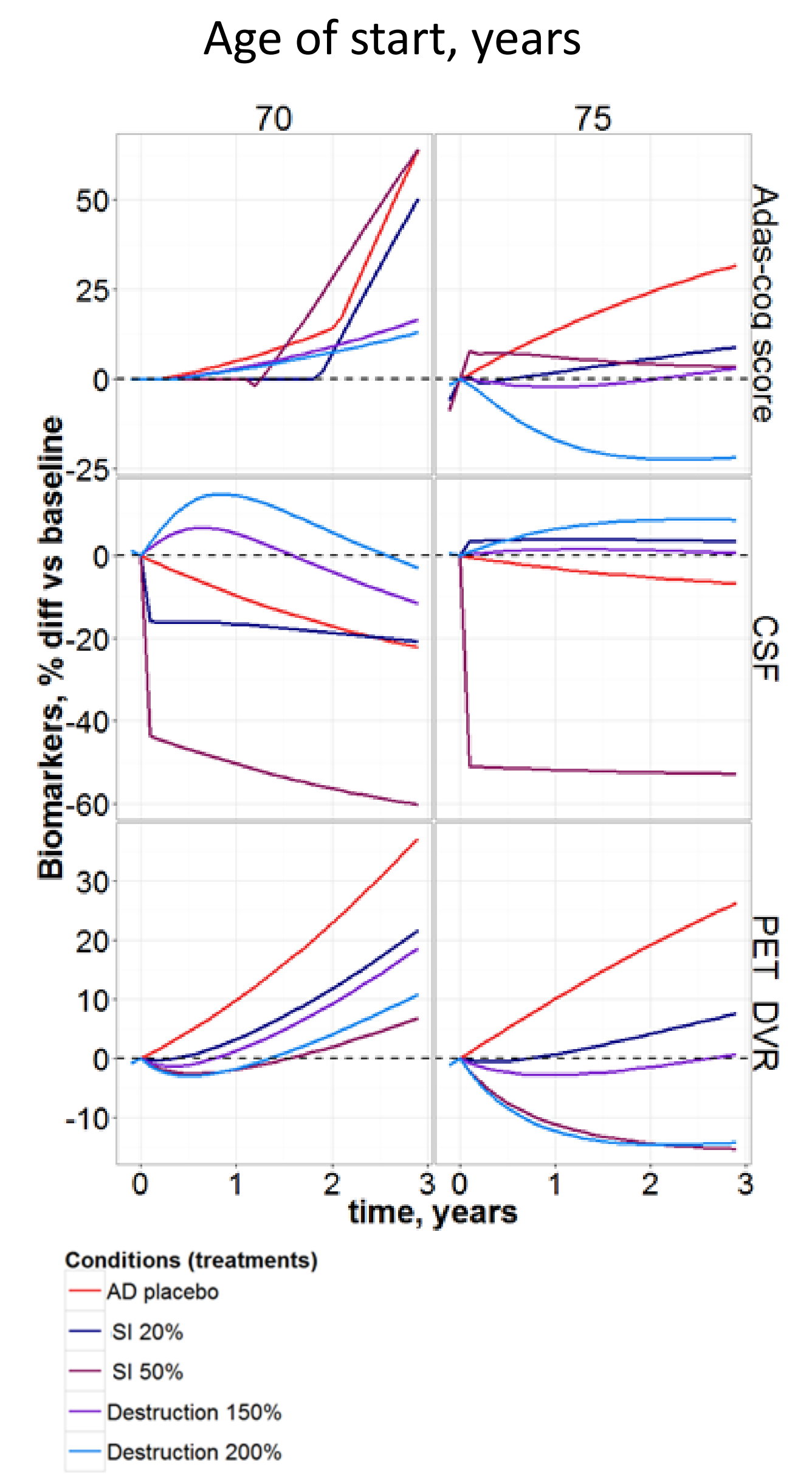


Fig. 6 Validation of H 2.1 on Phase 2 trial data for **avagacestat** (Coric 2012).

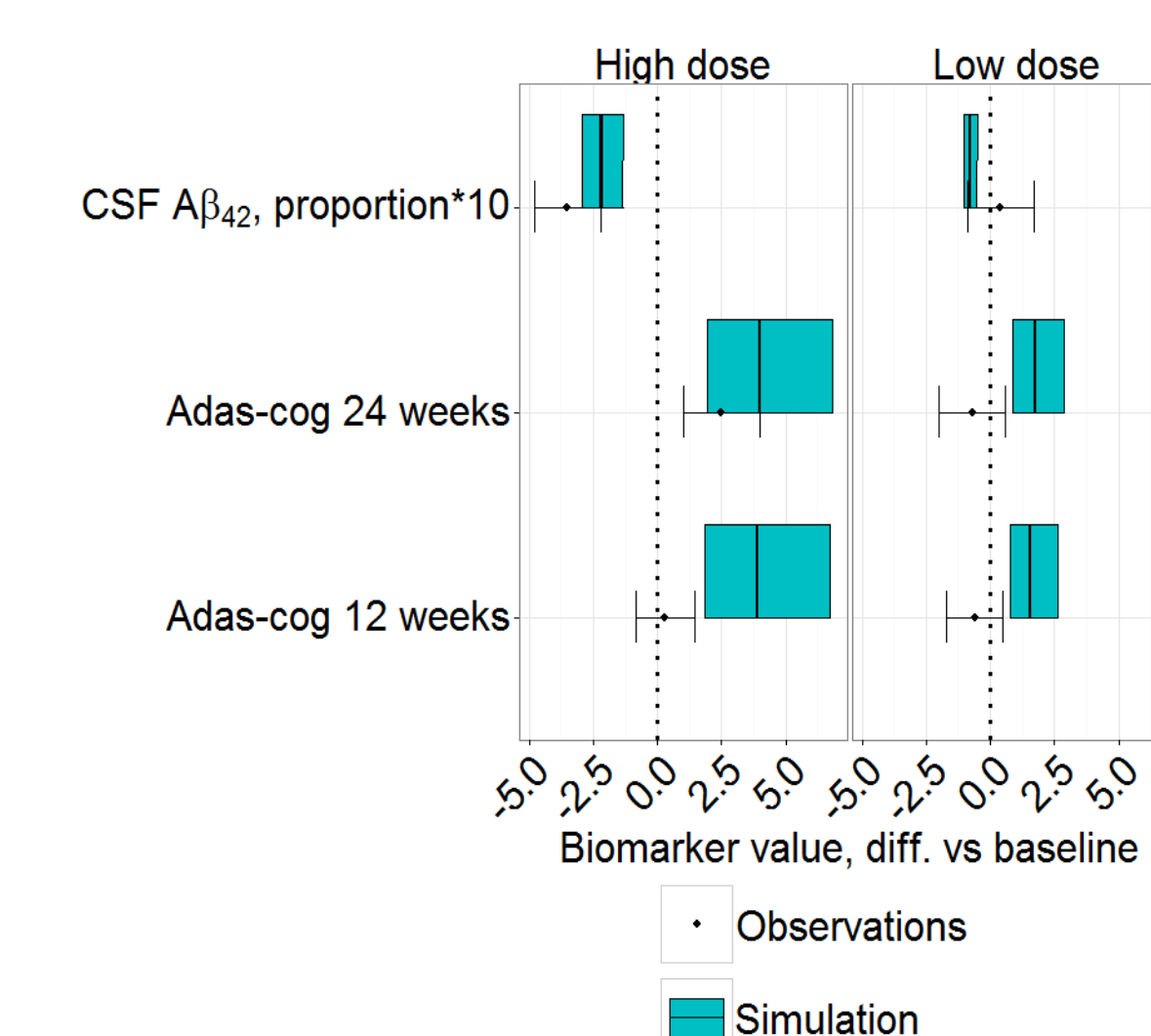
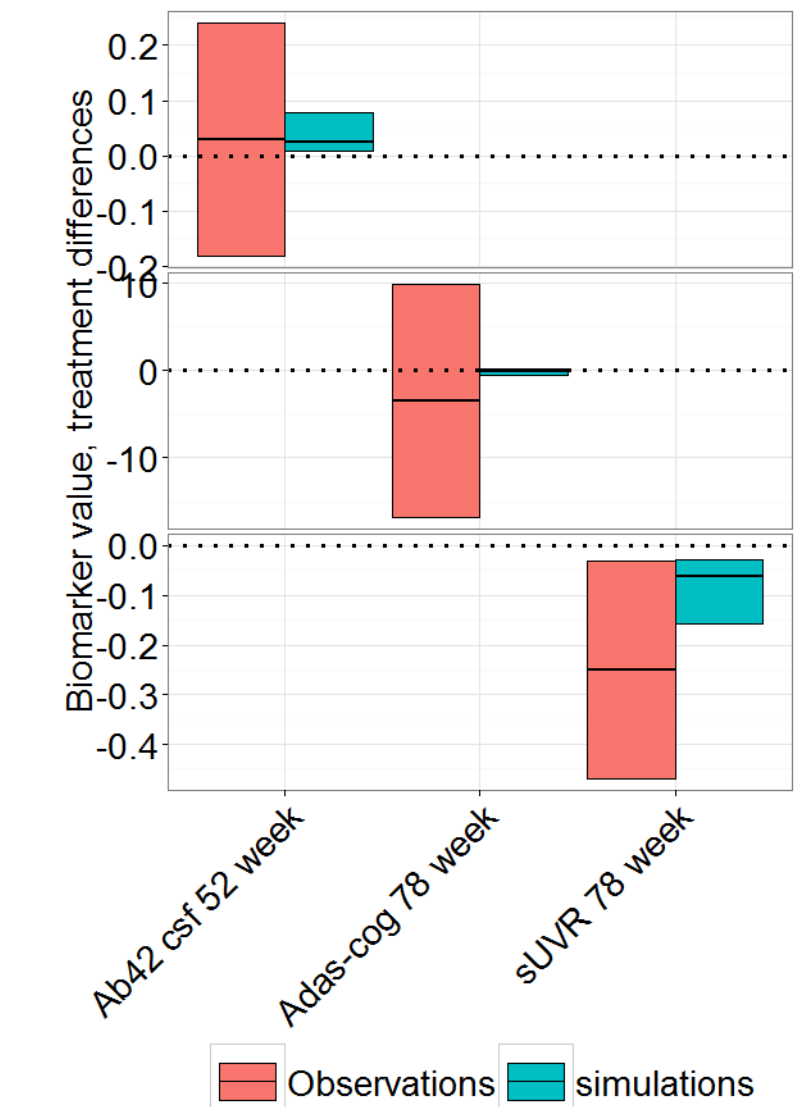


Fig. 7. Validation of H 2.1 on Phase 2 data for **bapineuzumab** (Rinne 2010).



CONCLUSIONS

- Only several designs may be used for legible confirming or rejection of the corresponding hypothesis
- For the threshold hypotheses no positive effect would be seen unless inhibition is high enough to overcome the toxic threshold (50 % inhibition)
- No negative effect predicted at destruction activation for any of the hypotheses
- Model predictions under hypothesis of proportional toxicity (and negative effect of high secretion inhibition) are successfully validated on CT results for two different therapies.

REFERENCES

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CONTACTS

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