WHY DO AMYLOID-MODULATING CLINCIAL TRIALS FAIL IN ALZHEIMER'S DISEASE? A CRITICAL ANALYSIS USING QUANTITATIVE SYSTEMS PHARMACOLOGY.

Hugo Geerts[1], Athan Spiros[2]

[1] In Silico Biosciences, [2] In Silico Biosciences

In Silico Biosciences, Berwyn, PA

Methodological Question Being Addressed. Performing an analysis of failed amyloid modulation trials in Alzheimer's Disease using an innovative modeling approach to learn from previous mistakes and providing recommendations for improved clinical trial design.

Background. The discovery of genetic mutations in the amyloid pathway in familial AD patients had led to the amyloid hypothesis and generated high hopes of curing AD by reducing amyloid levels. However, sofar no clinical trial has successfully improved cognitive readout, despite evidence of substantial reduction of amyloid levels.

Methods. We applied an ADAS-Cog calibrated mechanism-based computer model (Quantitative Systems Pharmacology or QSP) to the documented biology of different forms (Aβ40 and Aβ42) of the beta-amyloid peptide, constrained the parameters by predicting three independent clinical datasets and applied the model to the reported pharmacodynamic effect of β-amyloid levels of ongoing and past amyloid modulating trials.

Results. We provide evidence that the beneficial effect of short form Aβ peptides on glutamate neurotransmission for a low dose-range is absolutely necessary for explaining (1) the absolute ADAS-Cog values for MCI Aβ- and Aβ+ subjects, (2) the higher sensitivity of Aβ to scopolamine—induced cognitive deficit in MCI subjects and (3) the absence of an APOE genotype effect on the cognitive trajectory of unmedicated AD patients over 78 weeks.

When simulating clinical trials with BACE-inhibitors, passive amyloid vaccination and Gamma-secretase inhibitors the model predicts a substantial worsening in subjects that start out with low or zero amyloid baseline, but a beneficial effect of maximal 2 points for subjects with a high amyloid baseline. This explains why most experimental interventions work well in transgene mouse models.

Discussion. By modeling the known amyloid biology in a quantitative way, the model suggests that the beneficial effect of amyloid-reducing interventions is highly dependent upon the baseline amyloid level and questions the usefulness of these strategies in prodromal MCI or elderly healthy subjects with low Aβ load.

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