The Anticipated Clinical Effect of the new Alzheimer drug ANAVEX 2-73 in a Calibrated Quantitative Systems Pharmacology Platform

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Background

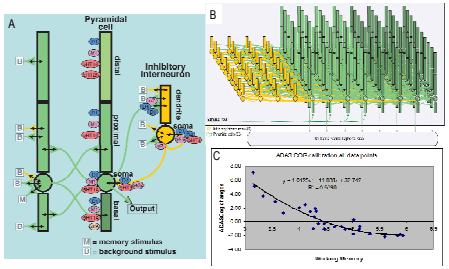
- Cognition enhancing symptomatic R&D programs are still important to Alzheimer's disease
- ANAVEX 2-73 (AV2-73) combines cholinergic and ion channel pharmacology with sigma-1 agonism; can potentially combine symptomatic and neuroprotective properties (Villard 2011, Lahmy 2013)
- Objective: provide guidance for Phase II dose-response of AV2-73 in a calibrated Quantitative Systems Pharmacology model as stand-alone and augmentation with low dose donepezil in mild-to-moderate AD patients
- Utilizing a predictive patent protected QSP Model PCT/US2006/043887, US patent 8,150,629 B2, granted April 30, 2012

AV2-73 Pharmacology

Receptor	Ki (nM)	Ratio vs sigma-1	Endogenous NT (Ki)
Sigma-1	860	1	N/A
M1 mAChR	3320	3.86	8
M2 mAChR	3970	4.62	340
M3 mAChR	5330	6.20	4
M4 mAChR	5190	6.03	6
Na-channels	5080	5.91	N/A
NMDA	7990	9.29	N/A

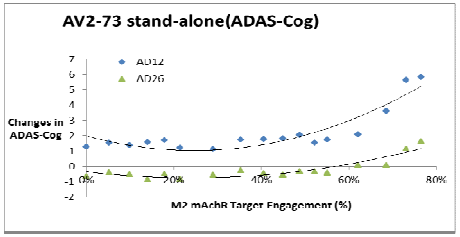
Affinity values of AV2-73 versus different human receptor subtypes. Note the relatively modest affinities of the compound for muscarinic receptors. This will lead to a limited effect on circuit properties, except for the M2 mAChR autoreceptor; blocking this receptor increases presynaptically released Ach.

QSP Model of Alzheimer's Disease



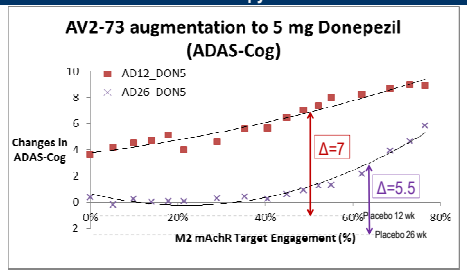
A. Representation of the cortical cognitive model for Alzheimer's disease. The membrane potential that is modulated by the effect of GPCR on the conductance of voltage gated ion-channels is calculated at a time resolution of 0.050 msec. AD pathology is introduced as a lower cholinergic tone and a gradual loss of synapses and neurons over time. B. The network consists of 80 pyramidal cells (green) and 40 inhibitory cells (yellow) with about 10,000 synapses. C. We used a meta-analysis (Ito 2010) of the clinical effect of 28 different drug-dose-time points on ADAS-Cog changes and simulated those historical studies in the QSP model. The correlation between model outcome (positive is worse) and the clinical results suggest that the model captures a substantial amount of variance (Roberts 2012). Note that the cortical network model is calibrated starting from primate electrophysiology data that addresses some of the translational disconnect between rodents and humans on the GABA inhibitory tone (Povysheva 2006).

Anticipated ADAS-Cog Changes with AV2-73 as a stand-alone



Anticipated stand-alone ADAS-Cog response of the cholinergic pharmacology of AV2-73 as a function of M2 tracer 18F-TZTP for mild-to-moderate Alzheimer patients at 12 and 26 weeks. We omitted the Na-channel pharmacology (see further). It is clear that the beneficial effect increases substantially from a target engagement level of 60% and beyond. A maximal effect of 4 points at 12 weeks is likely to be detected clinically.

Anticipated ADAS-Cog Changes with AV2-73 in Augmentation Therapy

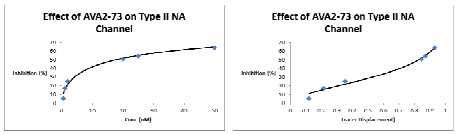


Anticipated ADAS-Cog response of the cholinergic pharmacology AV2-73 with 5 mg donepezil augmentation therapy as a function of M2 tracer 18F-TZTP for mild-to-moderate Alzheimer patients at 12 and 26 weeks. We omitted the Na-channel pharmacology (see further). The beneficial effect increases substantially from a target engagement level of already 40% and beyond. Placebo values for 12 and 26 weeks (broken lines) are derived from Ito 2010. A maximal effect of 4 points at 12 weeks and 3 points at 26 weeks on top of 5 mg donepezil is very likely to be detected clinically.

General Conclusion

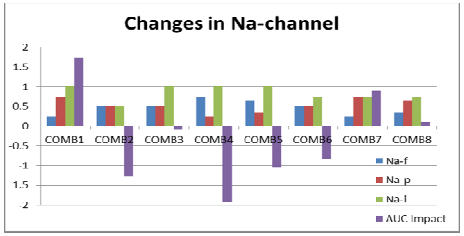
- **Stand-alone therapy AV2-73 provides benefit at target engagement levels >60%: maximal 2-3 points on ADAS-Cog**
- **Augmentation of AV2-73 with 5mg donepezil already at target engagement levels of >40% results in additional effect of 3-4 points on top of stand-alone therapy in mild-to-moderate AD patients**
- **M1 mAChR antagonism can reduce outcome by about 1 point on ADAS-Cog**
- **Na-channel antagonism can reduce effect by 2 points**
- **Including placebo values, this corresponds to a maximal effect of anticipated ADAS-Cog response of 6-7 points at 12 weeks and 4.5-5.5 points at 26 weeks for the combination donepezil / AV2-73 in mild-to-moderate AD patients**

Off-target Na-channel Pharmacology of AV2-73



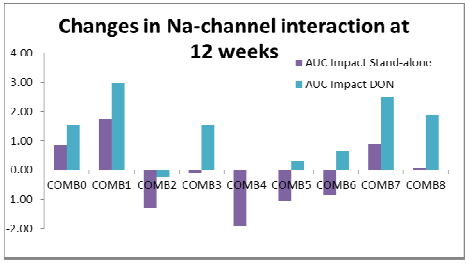
Experimental (blue diamonds) and fitted (line) dose-response of AV2-73 effect on Na-channel inhibition as a function of concentration (left) or target engagement with 18F-TZTP (right). The data suggest that at target engagement of 40% (where the clinical benefit starts), the compound already substantially affects the Na-channel.

Overview of different Na-channel Pharmacology on outcome



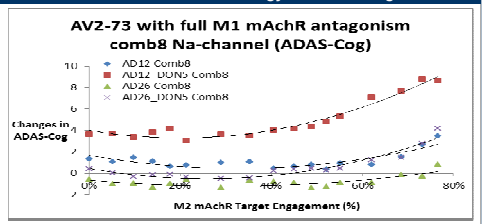
We tested different combinations of the effect of AV2-73 on the Na-channel in the cortical network. For instance, COMB1 is calculated suggesting a 25% weighting factor on the fast Na-channel, a 75% weighting factor on the persistent Na-channel and a 100% weighting factor on the Na-channels located on inhibitory neurons. The Area under the curve (AUC impact) is shown for a stand-alone therapy. The data suggest that inhibition of the fast Na-channel can substantially reduce the outcome. This can be partially rescued by an inhibition of the Na-channel on inhibitory interneurons.

Impact of Na-channel Pharmacology 12 weeks Donepezil (DON) 5 mg Augmentation



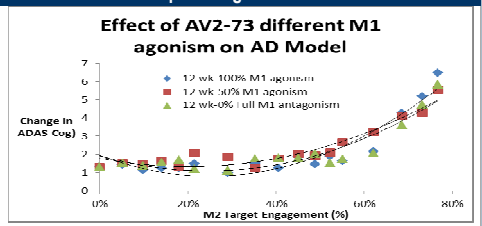
Graphical representation of the effect of different Na-channel weighting factors on the AV2-73 dose-response. Both the complete cholinergic pharmacology and the Na-channel pharmacology are used to predict the outcome in a 12 week trial. COMB0 is the situation without Na-channel pharmacology. The data suggest that adding 5 mg donepezil partially rescues the negative impact of Na-channel inhibition.

Effect of Na-channel Pharmacology on ADAS-Cog outcome



Anticipated effect of AV2-73 on ADAS-Cog in the Alzheimer cognitive model assuming the compound is a full antagonist at the M1 mAChR postsynaptic receptor and has a Na-channel pharmacology with weighting factors Na-f 0.35, Na-p 0.65 and Na-i 0.75. In this case, the augmentation therapy with 5 mg donepezil at 12 and 26 weeks shows a clinical benefit, that starts at target engagement levels above 40%.

Effect of lower partial Agonism at the M1 mAChR



Because the functional effect of AV2-73 at the human M1 mAchR is unclear, we tested different scenarios from a full agonism to a full antagonism. Due to the relatively weak interaction of the drug on this receptor, the effect is small and accounts for less than 1 point on the ADAS-Cog scale for a full antagonist for a 12 week trial in mild-to-moderate AD patients.

Discussion

- Possible synergistic action between presynaptic autoreceptor block by AV2-73 and prolongation of residence time of Ach by donepezil-mediated Acetylcholinesterase block
- This is likely driven by the enhanced desensitization of the $\alpha 4\beta 2$ nAChR that relieves GABA tone in the cortical network
- Positive effect of AV2-73 in presynaptic M2 mAchR-mediated Ach increase dominates negative postsynaptic AV2-73 mediated M1 mAChR block
- Because of the weak interaction of AV2-73 for its cholinergic receptors, minimal functional brain drug concentration for clinical effect is in the high single micromolar range; beneficial clinical effect declines over time as disease progresses
- Study has focused only on symptomatic effects as no sigma-1 effect was implemented or considered

References

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