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Pipeline Report - Neuronal alpha 7 nicotinic receptors: Candidates for the treatment of Alzheimers disease and Schizophrenia

Description: Neuronal alpha 7 nicotinic receptor (a7nAChR) ligands represent an emerging class of drug for the treatment of various CNS disorders associated with cognitive dysfunction. This report describes the proof of concept supporting the development of this class and analyzes the various different pharmacological approaches.

The report evaluates the a7nAChR pipeline. Preclinical and clinical stages candidates are identified and experimental data surrounding their development described and analyzed. In addition the companies developing these candidates are profiled.

a7nAChRs are selectively expressed in the brain, particularly in regions implicated in cognitive function and especially Alzheimer's disease and schizophrenia.

A large body of evidence supports the development of a7nAChR ligands for the treatment of Alzheimer's disease. Nicotinic agonists support neuronal survival through a7nAChRs and may therefore counter the neurodegenerative activity of beta amyloid. In addition to being involved in neural cell death or survival, a7nAChRs is also associated with learning and memory. Receptor agonists enhance LTP, an electrophysiological correlate of memory. In animal models of Alzheimer's disease a7nAChR agonists have also been shown to improve memory. Most compelling are recent clinical data demonstrating improved cognition in patients treated with MEM 3454.

Preclinical and clinical data also exist to suggest that a7nAChR ligands have a role in the treatment of schizophrenia. In particular, schizophrenia is associated with defective inhibitory pathways and hence gating. a7nAChR stimulation enhances inhibitory GABAergic pathways. Most recently GTS-21 has been shown to improve RBANS score in a phase 2 study of schizophrenia patients.

Although the a7nAChR is primarily associated with CNS function it is required for cholinergic inhibition of macrophage TNF release and thus mediates the anti-inflammatory effect of vagal stimulation.

A number of pharmacological options exist for the development of a7nAChR ligands. Most promising are partial agonists and allosteric modulators. Not enough information exists yet to support the development of antagonists. Allosteric modulators are most promising for the treatment of schizophrenia. Partial agonists and allosteric modulators may both be of use in the treatment of Alzheimer's disease although allosteric modulators may have less impact as endogenous acetylcholine levels drop with neurodegeneration.

CoMentis leads the a7nAChR development field with GTS-21. The molecule has demonstrated efficacy in schizophrenia providing proof of concept for the approach. The eventual success of GTS-21 may be negatively impacted by its dosing requirements. Memory Pharmaceuticals is more likely to succeed with MEM 3454 which has the developmental support of Roche.

Six phase 1 candidates have been described, most of which are stated or are assumed to be partial agonists. In contrast Targacept's TC-5619 is a full agonist with the interesting and potentially competitive advantage of having antipsychotic activity.

At least 8 preclinical stage programs have been reported. Of note NeuroSearch are developing a first in class positive allosteric modulator of the a7-nAChR, a mechanism of action that may offer advantages in certain circumstances over the rest of the pipeline. Pfizer have a compound in development which combines both modulation and agonist activity.

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