**2.9**

## R3487/MEM 3454, a novel nicotinic alpha 7 receptor partial agonist, improves attention and working memory performance in cynomolgus macaques

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The nicotinic alpha 7 (nic $\alpha_7$) receptor plays an important role in cognitive function, and selective nic $\alpha_7$ agonists have been proposed as novel therapeutic agents for treating cognitive impairments associated with schizophrenia (CIAS) and Alzheimer's disease (AD). R3487 / MEM3454 (R3487) is a novel nic $\alpha_7$ receptor partial agonist with 5-$HT_3$ antagonist properties that is being developed for the treatment of both CIAS and AD. R3487 exhibits pro-cognitive effects in rodents, healthy volunteers and, more recently, in a Phase IIa AD population. In attempt to further understand the cognitive enhancing and antidepressant-like effects of R3487 and to improve on translatability between preclinical and clinical studies, additional characterization was conducted using nonhuman primate (NHP) efficacy methods. Following acute administration, R3487 (0.3–10 mg/kg, p.o.) was studied in the NHP object retrieval model of attention (response inhibition) in which the compound improved percent-correct first reaches in the difficult trials with a minimally effective dose (MED) of 1.0 mg/kg. In addition to improving attentional measures, R3487 (0.1–10 mg/kg, p.o.) was assessed in the delayed match to sample (DMTS) NHP model of working memory. In this procedure, R3487 (MED, 1.0 mg/kg) significantly improved accuracy in the long delay of this task, similar to effects observed with the non-selective nicotinic agonist, nicotine. In both the object retrieval and DMTS procedures, R3487 exhibited a characteristic inverted U-shaped dose-response function that is often reported with nicotinic agonists. In addition to further assessing the effects of R3487 for cognitive improvements, R3487 was also evaluated in the differential reinforcement of low-rate (DRL) behavior model to examine potential antidepressant-like properties. Unlike nicotine (0.03–0.3 mg/kg), which increased the number of reinforcers obtained (MED, 0.1 mg/kg, i.m.), R3487 (0.3–10 mg/kg, p.o.) did not exhibit this effect at the doses tested. Similarly, the nicotinic $\alpha4\beta2/\alpha_7$ agonist, varenicline (0.03–0.3 mg/kg, p.o.), had no effect on reinforcers obtained in the DRL procedure. Overall, the data from these studies indicate that R3487 improves attention and working memory function in line with clinical data suggesting that the NHP models may be useful in advancing drug discovery efforts.

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**2.10**

## Characterization of JNJ-1930942, a novel positive allosteric modulator of the $\alpha_7$ nicotinic acetylcholine receptor

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The $\alpha_7$ nicotinic acetylcholine receptor ($\alpha_7$ nAChR) is a therapeutic target for the treatment of cognitive deficits associated with schizophrenia, Alzheimer's disease, Parkinson's disease and ADHD. Activation of these receptors with $\alpha_7$ agonists improves sensory gating and memory and attention in animal models, and early clinical trials have shown a beneficial effect on cognitive function in schizophrenia and Alzheimer's disease patients. Here, we describe the novel highly selective $\alpha_7$ nAChR positive allosteric modulator (PAM), JNJ-1930942. This compound enhances choline-evoked rise in intracellular $Ca^{2+}$ in the GH4C1 cell line stably transfected with cloned human α7 nAChRs. JNJ-1930942 does not act on α4β2, α3β4 nAChRs nor on the related 5-$HT_3$ channel. Electrophysiological assessment in the GH4C1 cell line shows that JNJ-1930942 increases the peak and net charge response to choline, acetylcholine and PNU-282987. The potentiation is obtained mainly by affecting the receptor desensitisation characteristics, leaving activation and deactivation kinetics as well as recovery from desensitisation fairly unchanged. The choline efficacy is increased over its full concentration response range and its potency is increased more than ten-fold. The potentiating effect is α7 channel-dependent, since it is blocked by the α7 antagonist methyllycaconitine. Moreover, in hippocampal slices, JNJ-1930942 enhances in a dose dependent manner neurotransmission at hippocampal synapses and facilitates the induction of long term potentiation of electrically evoked synaptic responses in the dentate gyrus. Hence, with these properties, JNJ1930492 is able to improve a genetically based auditory gating deficit in DBA/2 mice. These results support the potential of an $\alpha_7$ nAChR PAM as a pharmacotherapy for cognitive dysfunction.

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**2.11**

## Profile of A-716096, a novel thiazolylidine positive allosteric modulator of the α7 nicotinic acetylcholine receptor

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Targeting α7 neuronal nicotinic receptors (α7 nAChRs) via selective α7 NNR agonism has potential to treat cognitive deficits of schizophrenia and Alzheimer's disease. An alternative approach is modulation of α7 NNR function to enhance effects of the endogenous neurotransmitter acetylcholine via positive allosteric modulators (PAMs). Structurally distinct small molecules continue to be identified as viable tools to explore this novel pharmacology.

In this study, we described the properties of a thiazolylidene analog, A-716096, to elucidate biochemical neurotransmitter release, electrophysiological activity and behavioral effects *in vivo*. A-716096 was found to potentiate ACh-evoked α7 nAChR currents in oocytes expressing rat or human α7 nAChRs, but did not potentiate other nAChR subtypes (hα4β2 and hα3β4) in FLIPR-based $Ca^{2+}$ influx assays. A-716096 enhanced agonist-evoked phospho-ERK in PC12 cells as well as α7 nAChR-evoked [$^3$H] NE release in SH-SY5Y cells. Like other α7 PAMs (NS1738, TQS and PNU-120596), A-716096 did not displace the binding of either [$^3$H] MLA or [$^3$H] A-585539 to rat cortical membranes. Co- or pre-application of A-716096 amplified choline-evoked α7-like current responses in hippocampal CA1 slices and enhanced synaptic inhibitory activity in dentate gyrus in electrophysiological studies. Consistent with *in vitro* data, *in vivo* administration of A-716096 in mice increased dose-dependently phosphorylation of the downstream signaling protein, CREB. *In vivo* evoked-potential EEG recordings revealed that A-716096 improved sensory gating in DBA2 mice, a strain that exhibits natural deficits on this pre-attention measure. Taken together, these results demonstrate that A-716096 is a valuable tool compound with which to further study mechanism of action and other physiological effects of PAMs including modulation of synaptic effects and signaling mechanisms critical for learning and memory.

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**2.12**

### 2,2-Dimethylcyclopropyl-benzamides: Novel positive allosteric modulators of α7 nAChRs

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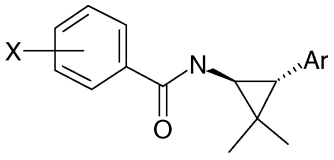
Activation of $\alpha_7$ nicotinic acetylcholine receptor (nAChR-$\alpha_7$) has been shown by pre-clinical and clinical evidence to improve cognitive function and a number of partial or full agonists are in advanced clinical trials, among them GTS-21, EVP-6124, AZD-0328 and R34787/MEM3454. Positive allosteric modulators of this ion channel offer the option of enhancing the endogenous signal of acetylcholine while avoiding the rapid desensitization and long-lasting deactivation caused by agonists. A prototypic agent in this class is PNU-120596. The identification and early optimization of a novel series of 2,2-dimethylcyclopropyl-benzamides as positive modulators of the nAChR-$\alpha_7$ channel is described.

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**2.13**

### *In vitro* and *in vivo* characterization of PheTQS, a novel α7 nAChR positive allosteric modulator

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PheTQS ((3aR, 4S, 9bS)-4-(4-methylphenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-sulfonamide, WO2004098600) facilitated nicotine (10 μM)-evoked responses in GH4C1 cells stably expressing human α7 nAChRs with a $pEC_{50} = 7.4 \pm 0.2$ and exhibited >30-fold selectivity vs. the 5-$HT_3$ receptor and α4β2 and α1, α3-containing nAChRs. PheTQS also facilitated ACh (300 μM)-evoked currents in rat cultured hippocampal neurons with a $pEC_{50} = 7.0 \pm 0.2$ to a maximum of 6191±955% of control response charge, but did not activate the receptor in the absence of ACh at up to 3 μM. Bath application of PheTQS (1 μM) mediated an MLA-sensitive potentiation of currents evoked by local ejection of ACh (1 mM) onto CA1 stratum radiatum interneurons in rat hippocampal slices. PheTQS exhibited good brain exposure following oral administration (Brain $C_{max}$ = 1540 ng/g, 10 mg/kg p.o.) but had no affect on activity measures up to 32 mg/kg in the rat. PheTQS (30 mg/kg, p.o.) elicited a significant increase in extracellular levels of dopamine in the prefrontal cortex and significantly increased c-Fos immunoreactivity in the central nucleus of the amygdala and the shell of the nucleus accumbens. PheTQS (10 mg/kg, i.v.) enhanced auditory gating in anaesthetised DBA2 mice and this effect was abolished by prior administration of α-bungarotoxin (1.25 nmol, i.c.v.). PheTQS (10 and 30 mg/kg, p.o.) attenuated deficits in pre-pulse inhibition in isolation-reared rats and significantly improved performance in a rat novel object recognition task. Thus, PheTQS is a selective α7 nAChR positive allosteric modulator which exhibits efficacy in rodent sensory gating and cognition models suggesting potential therapeutic utility in psychiatric disorders.

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**2.14**

### Dual allosteric modulators of neuronal nicotinic-acetylcholine and GABAA receptors

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We have designed a molecule that incorporates selective negative allosteric modulation of $GABA_A$ α5 receptors and positive modulation of α7 neuronal nicotinic receptors (nAChRs). This molecule termed 2-228 represents the first known compound with putative cognition enhancing properties derived from simultaneous modulation of both $GABA_A$ and nAChRs. The research goal is to develop a positive allosteric modulator of α7 nAChRs that