Cholinergic neurotransmission has long been implicated in processes of attention, cognition, and learning and memory. The α7 acetylcholine nicotinic receptor (α7 nACHR) is a promising drug target for diseases involving cognitive impairment such as Alzheimer’s and schizophrenia. α7 nACHR positive allosteric modulators (α7 PAMs) are a novel class of drugs offering advantages over α7 full/partial agonists. In contrast to α7 agonists, α7 PAMs do not activate α7 nACHRs by themselves and do not desensitize them. Instead, α7 PAMs work via amplification of responses induced by intrinsic agonist which preserves spatio-temporal signalling patterns.

1. **BNC375 is a potent and efficacious α7 nACHR positive allosteric modulator.**

   
   ![Figure 1. α7 nACHR-mediated current traces obtained from stably expressing GH4C1 cells on a Dynaflow® II system. Concentration-response (left, 300nM-10 μM) and a representative trace of potentiation by BNC375 at 3 μM (middle). Application of ACh/PAM+AcH = 250μM (blue bar). Right, Concentration-response showing potentiation of peak current and area under curve (AUC) by BNC375. Fit parameters for peak potentiation: EC₅₀ = 1.9 μM, n₉ = 1.62, E_max = 1572%. AUC: EC₅₀ = 1.3 μM, n₉ = 1.6, E_max = 2616%.](image1)

2. **Effects of BNC375 on ACh concentration-response curve**

   - EC₅₀: 14.5 μM, n₉ = 1.6
   - EC₅₀: 12.2 μM, n₉ = 1.62
   - EC₅₀: 127.7 μM, n₉ = 1.76

   ![Figure 2. 2 μM BNC375 (EC₅₀) shifts ACh concentration-responses to the left and upward direction showing potentiation at both sub-threshold and saturating agonist concentrations (300 nM to 2.5 μM ACh).](image2)

3. **Kinetics of α7 nACHR-mediated currents and re-activation of desensitized receptors compared between BNC375 and a classical type II α7 PAM PNU-120596**

   - BNC375
   - PNU-120596
   - EC₅₀ ACh
   - PAM
   - SCALED
   - SUPERIMPOSED

   ![Figure 3. Kinetics of α7 nACHR-mediated currents after pre-incubation with either BNC375 or a ‘classical’ type II PAM PNU-120596 using 2 seconds application of ACh-PAM (blue bar) (upper row). Note that BNC375 has much more subtle effects on kinetic parameters of α7 currents as evidenced by the scaled traces (upper right), namely, no slowing activation and de-activation, and, especially, difference in kinetics of desensitization. Effect of the compound on re-activation of desensitized α7 nACHRs (lower row). α7 receptors were desensitized with a high ACh concentration (1 mM) after which either BNC375 or PNU-120596 was applied with ACh still present. Note that PNU-120596 re-activates desensitized receptors (induces the current) and BNC375 does not. Overall, taking into account effects of desensitization and re-activation of α7 nACHRs, the kinetic profile of BNC375 is consistent with type I α7 nACHR PAMs.](image3)

4. **BNC375 demonstrates in vivo cognition enhancing properties in rodent behavioral models**

   ![Figure 4. Behavioural tests in classical rodent cognition models show that BNC375 reverses scopolamine-induced impairment of spontaneous alternation score in T-maze Continuous Alternation Task (T-CAT) (upper, mice), or recognition index in the novel object recognition test (NOR) (lower, rats). See METHODS for details. T-CAT is used for assessment of working memory and NOR for episodic memory. Note that therapeutic window for BNC375 is 0.1-10 μg/kg p.o. and that BNC375 matches performance of Donepezil.](image4)

**CONCLUSIONS**

- **BNC375 is an α7 nACHR PAM**
- **Effective across a wide range of agonist concentrations (from subthreshold to saturating).**
- **Favourable type I-like kinetics mainly affecting the peak α7 current with little effect on current desensitization.**
- **Demonstrates efficacy in animal models of episodic and working memory with a broad therapeutic window (100 fold).**
- **Matches performance of Donepezil.**
- **BNC375 is Biomimics’ clinical candidate for Alzheimer’s disease entering into IND enabling studies.**

(Also see BNC announcement from 14/12/2013)


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