A NOVEL, NON-OPIOID, CONESNAIL PEPTIDE-BASED ANALGESIC AS A THERAPEUTIC ALTERNATIVE FOR THE TREATMENT OF CHRONIC PAIN

INTRODUCTION
Chronic Neuropathic Pain is one of the largest and most unwieldy medical needs, as current therapies (antidepressants and anticonvulsants) are minimally effective and are generally characterized by limited therapeutic outcomes. Therefore, a compelling need for novel therapeutic strategies that not only result in better efficacy but are able to prevent the alterations responsible for chronic pain. A recent study by Xu et al. describes the discovery of a novel non-opioid, Non-Snail Peptide-based analgesic (CSP) which exhibits analgesic and anti-inflammatory effects in various chronic pain models.

Figure 1: CSP analogs concentration response curves on rat and human α2δ2 nAChRs. Xenopus oocytes expressing α2δ2 nAChRs were subjected to two-electrode voltage clamp and K+ values for blocks of acetylcholine induced currents by CSP analogs were determined.

Figure 2: CSP dose-dependent increases paw withdrawal threshold 24 h after administration (A) and reduces the number of inhibiting macrophages after 14 days of CSP treatment (B) in CCI rats [2]. Effects of repeated administration of CSP (14 days) on the reduction in the number of sciatic nerve fibers by CC. *P < 0.01, compared to vehicle [5].

Figure 3: Effect of CSP-4 analog in mechanical hyperalgesia after 1 hour of CSP-4 subcutaneous (s.c.) administration in the rat spared nerve injury model. *P < 0.05, compared to vehicle. n = 6.

Figure 4: Effect of CSP-4 analog in mechanical hyperalgesia after 1 hour of CSP-4 subcutaneous (s.c.) administration in the CFA-induced inflammatory pain model in rats. *P < 0.05, compared to vehicle. n = 6.

Figure 5: Analgesic effects of CSP-7 analog on mechanical allodynia (A) and thermal hyperalgesia (B) after 30 minutes of CSP-7 administration (0.2 μM) in a full-thickness thermal injury model in rats. Thermal burn was elicited in anesthetized rats by placing a pre-heated (100°C) splotch tip on the mid-plantar surface of the left hind paw for 30 seconds. *P < 0.05, n = 8.

CONCLUSIONS
• CSP-4 is a novel, peripherally-acting α2δ2 nAChR agonist for neuropathic pain.
• CSP-4 is efficacious in reducing mechanical and thermal hyperalgesia and allodynia in multiple preclinical models of neuropathic and inflammatory pain demonstrating broad efficacy.
• Preclinical studies suggest that CSP-4 has superior potency when compared to gabapentin and pregabalin (Lyrica®), the most highly prescribed therapy approved for the treatment of neuropathic pain.
• CSP-4 was well tolerated and showed no signs of toxicity when given at doses 2500 fold higher than the therapeutic dose (data not shown) suggesting that the therapeutic index (efficacy over CNS side effects) may be greater for CSP-4 than for currently available therapies.

References: