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Long-lasting Therapeutics for Chronic & Acute Pain

A proprietary multiprotease botulinum neurotoxin derivative with durable analgesic effects

Request an introduction

Reference: ODY01

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IP Status

Patented

Seeking

Development partner, Licensing, Commercial partner

About **Dublin City University**

Dublin City University (DCU) aims to transform lives and societies through education, research and innovation. Research and Innovation at DCU stems from the academic excellence of its four faculties coupled with a passion for translating knowledge into innovations for economic or societal benefit.

Background

Chronic pain is a major health problem that affects millions of people worldwide but current treatments are often ineffective, addictive, or have severe side effects. Thus, new and safer therapies are needed. The sensation of pain usually begins with the activation of peripheral neurons called nociceptors that send electrical signals to the central nervous system and ultimately to the brain where they are interpreted as pain.

The sensitivity of nociceptors for activation can be modulated by intracellular membrane trafficking, which increases their expression of pain-signalling proteins (e.g. ion channels and receptors) and causes them to release pro-algesic neurotransmitters such as the calcitonin-gene-related peptide (CGRP). These processes of nociceptor sensitisation are attractive targets for therapeutic interventions. They can be inhibited by botulinum neurotoxins (BoNTs), bacterial neurotoxins that enter neurons and release inside an enzymatic domain (known as the light chain [LC]) that cleave one or more proteins called SNAREs (soluble N-ethylmaleimide-sensitive factor attachment protein receptors) that are essential for membrane fusion.

There are several serotypes, designated BoNT/A through to G and BoNT/X, but to date only BoNT/A (BOTOX®) has been approved for clinical treatment of pain. The serotypes vary in their duration of action, receptor specificity and in the target and degree of protein cleavage.

BoNT/A shows a moderate ability to inhibit the exocytosis of CGRP, leading to its use as a preventative migraine treatment. However, studies show that the inhibitory effect of BoNT/A is incomplete at high concentrations Ca2+, such as when stimulated by capsaicin. This is thought to be because BoNT/A's cleavage of 9 C-Terminal residues from the SNAP25 SNARE protein only partially impairs its activity.

By contrast, BoNT/E protease removes 26 residues from the C-terminus of SNAP-25; thereby, it more effectively disrupts the function of this SNARE protein so that capsaicin is unable to elicit membrane fusion. Unfortunately, sensory neurons are resistant to intoxication with BoNT/E and the /E LC has a much shorter half-life than its counterpart from /A.

Tech Overview

By combining the BoNT/A serotype with the LC of BoNT/E, a novel chimera, "**LC/E-BoNT/A**" combines BoNT/A's long-duration and ability to act on sensory neurons with BoNT/E's higher degree of protein cleavage. This leads to more effective disablement of SNAP-25 and an enhanced potential to alleviate chronic and acute pain.

LC/E-BoNT/A is an engineered recombinant chimera of BoNT/A and the proteolytic LC domain of /E, creating a multi-protease BoNT derivative. LC/E-BoNT/A reduces the upregulation of transducers on the cell membrane and persistently inhibits the release of neuropeptides from sensory neurons, even those stimulated at high concentrations of capsaicin.

LC/E-BoNT/A has been tested in pre-clinical animal models of neuropathic and inflammatory pain, both by the university and by an independent research laboratory, and has shown significant and long-lasting antinociceptive effects:

- LC/E-BoNT/A has been proven safe and non-toxic in rat models at higher doses than BoNT/A.
- When tested in a rat spared nerve injury (SNI) model, a single intra-plantar (IPL) injection of LC/E-BoNT/A alleviated for ~2 weeks mechanical and cold hyper-sensitivities, in a dose-dependent manner. The highest non-paralytic dose (75 U/Kg, IPL) proved significantly more efficacious than BoNT/A (15 U/Kg, IPL) or repeated systemic pregabalin (10 mg/Kg, intraperitoneal), a clinically-used pain modulator (Figure 1).[1]
- LC/E-BoNT/A injected into the whisker pad of rats inhibited the nocifensive behaviour (grooming, freezing, and reduced mobility) induced by activating TRPV1 with capsaicin, injected at various days thereafter (Figure 2).[2]

References:

1. A novel therapeutic with two SNAP-25 inactivating proteases shows long-lasting anti-hyperalgesic activity in a rat model of neuropathic pain, Wang J. et al., 2017.

2. Botulinum Neurotoxin Chimeras Suppress Stimulation by Capsaicin of Rat Trigeminal Sensory Neurons In Vivo and In Vitro. Antoniazzi C. et al., 2022.

Benefits

LC/E-BoNT/A offers several advantages over existing solutions for chronic pain, such as:

- Long-lasting anti-nociceptive effects with a single application.
    - Superior performance to BoNT/A and pregabalin in SNI tests.
    - Comparable relief to the opioid buprenorphine applied just before the capsaicin challenges.
- Delivered locally, reducing the risk of systemic side effects or addiction.
- Can be used prophylactically or post-injury.
- Proprietary with extensive patent coverage.

Applications

The LC/E-BoNT/A chimera has the potential to be developed as a novel class of biopharmaceutical for the treatment of painful conditions, such as neuropathic pain, migraine, inflammatory pain, cancer pain, or post-surgical pain.

Opportunity

The inventors seek partners interested in licensing or co-developing the technology. They are also open to collaboration with researchers or clinicians who want to test the technology in different models or settings.

Patents

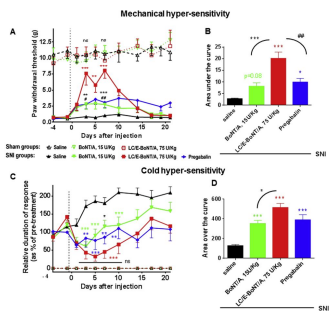
- US 9,216,210 B2 and 17 European patents granted under EP3087089B1 in AT/BE/DK/FI/FR/DE/Gr/IE/IT/NL/NO/PT/ES/SE/CH/GB. Chinese patent pending
- US divisional patent: US 10,457,927 B2
- A second patent family was filed in 2021 and is currently in the PCT phase.

Appendix 1

Figure 1

Effects of LC/E-BoNT/A on mechanical (A, B) and cold (C, D) hyper-sensitivity following SNI surgery: comparison with BoNT/A and pregabalin.

Analyses were performed on data from days 3–10 post injection. Behavioural time courses were analysed by repeated measures ANOVA with time and experimental group as factors. For both mechanical and cold responses there was a significant main effect of group (F (6, 56) = 38.9, _p_ < 0.001; F (6, 59) = 34.6, _p_ < 0.001 respectively). Bonferroni *post hoc* tests revealed a significant attenuation of mechanical hyper-sensitivity associated with SNI by LC/E-BoNT/A on days 3, 5 and 7 post injection, such that SNI animals treated with the toxin did not differ from sham controls on days 3 and 7. Withdrawal thresholds were also significantly higher in the SNI + LC/E-BoNT/A group than in either the BoNT/A or pregabalin-treated SNI groups on days 3 and 7. Similarly, LC/E-BoNT/A significantly attenuated SNI-induced cold hyper-sensitivity from days 3–10. BoNT/A and pregabalin also effectively reduced the % duration of nocifensive responding; however, BoNT/A did so to a lesser extent on day 7. The time course data are summarised by area under/over the curve histograms (B, D), where an increase in these area under/over the curve is indicative of reduced sensitivity. SNI groups were only analysed by one-way ANOVA followed by Bonferroni *post hoc* tests. LC/E-BoNT/A- and pregabalin-treated SNI rats showed reduced sensitivity compared with their saline-treated counterparts and BoNT/A-treated SNI rats also showed a trend for reduced sensitivity. However, the effect was significantly greater in the LC/E-BoNT/A group, suggesting an improved anti-hyperalgesic effect of the engineered toxin. Data are presented as means ± SEM; sham groups: n ≥ 6; SNI groups: n ≥ 8. *_p_ < 0.05, **_p_ < 0.01, ***_p_ < 0.001, #_p_ < 0.05, ##_p_ < 0.01; red symbols: SNI + LC/E-BoNT/A vs SNI + saline; green symbols: SNI + BoNT/A vs SNI + saline; blue symbols: SNI + pregabalin vs SNI + saline; black symbols: respective groups vs. SNI + LC/E-BoNT/A; ns: not significant vs. respective sham control.



Appendix 2

Figure 2

LC/E-BoNT/A showed a long-lasting anti-nociceptive effect on acute nocifensive behaviour induced by capsaicin. (A) Weight gained, (B) grooming, as the time each animal spent rubbing the injected facial area with its paws in a 20 min recorded period, (C) locomotor behavior assessed by the measurement of total distance walked, and (D) freezing time evoked by injection of capsaicin (2.5 µg in 20 µL) or vehicle 2 (solvent for capsaicin) into rat right whisker pad, assessed at various days after administration of neurotoxin (75 units/kg) or vehicle 1 (solvent for LC/E-BoNT/A). Data are expressed as mean + SEM (n = 10) and were analyzed by one-way ANOVA followed by Bonferroni's post hoc test. ## p < 0.01, ### p < 0.001 vs. vehicle 1 → vehicle 2 group; * p < 0.05, ** p < 0.01, *** p < 0.001 vs. vehicle 1 → capsaicin group.

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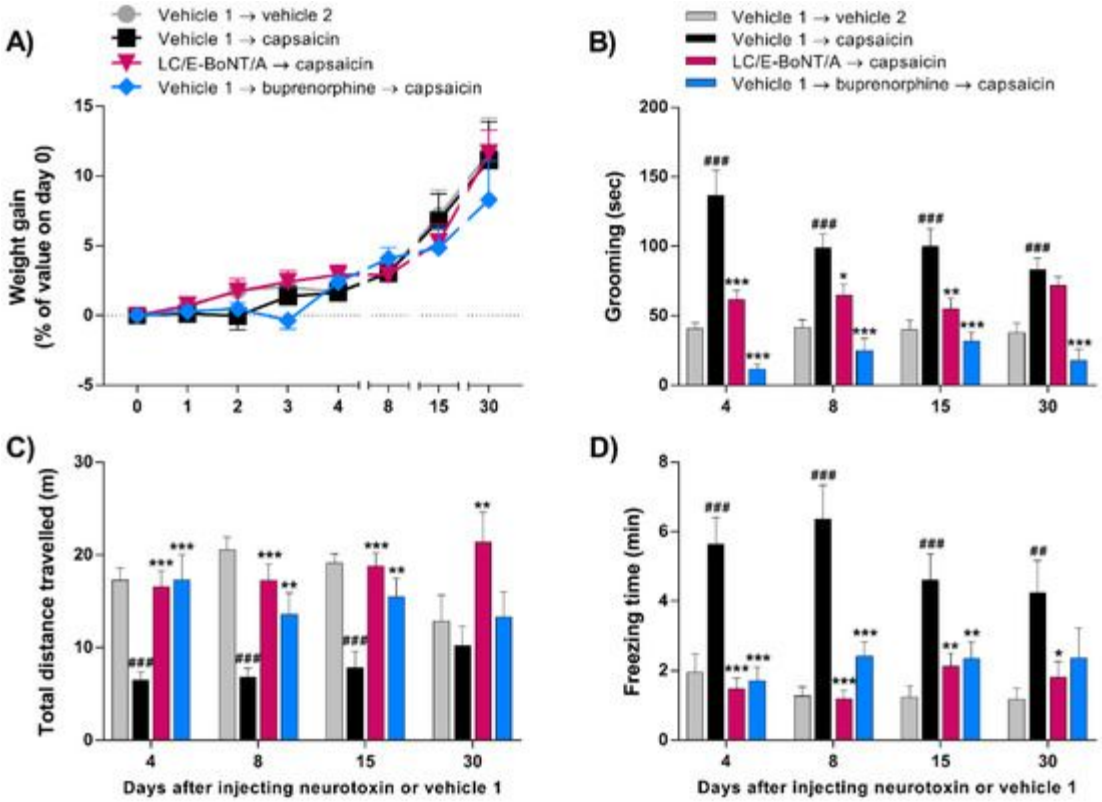

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