UNIVERSITY OF LIVERPOOL

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Propofol Derivatives for the Management of Chronic Pain

New chemical entities based on propofol derivatives which have potential applications for the long-term management of chronic pain.

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IP Status

Patent application submitted, Patented

Seeking

Commercial partner, Licensing, Development partner

About **University of Liverpool**

By facilitating access to our expertise, facilities and networks, the University of Liverpool offers the means to transform ideas into creative solutions, improved performance, new technologies, strategies, applications, products or skills.

Background

Chronic pain is a major health problem, which affects 1.5 billion people worldwide. Chronic pain affects ~20% of the European population and is commoner in women, older people, and those in poorer economic classes. Treatment of chronic pain is difficult, and there is currently no single treatment that works for all conditions. Furthermore, existing products are not particularly efficacious and have a great deal of unwanted side effects including sedation and the risk of addiction. Current treatments are only effective in around 40% of patients, who tend to struggle to maintain the balance between adequate pain relief and the adverse effects. Common ways of treating chronic pain include:

- Anticonvulsants e.g. Carbamazepine and Gabapentin. These medications can be very helpful for some kinds of nerve type pain (such as burning, shooting pain), but side effects include sedation and weight gain.
- Opioids e.g. Morphine. When used appropriately, opioids may be very effective in controlling certain types of chronic pain such as cancer pain, however they are less effective or require higher doses in nerve-type pain. Frequent side effects include constipation, sedation and nausea. Key issues are tolerence often leading to hyperanalgesia and physical dependence leading to addiction and misuse.
- Antidepressants e.g. tricyclic antidepressants. Some of the older categories of antidepressants have some use in controlling pain, but again the most common side effect is sedation.
- Nonsteroidal Anti-inflammatory Drugs (NSAIDs) e.g. Ibuprofen and COX II Inhibitors; can be very effective for acute muscular and bone pain as well as some types of chronic pain syndromes, however when taken for an extended period of time or in large quantities, they are associated with potentially serious renal, gastrointestinal, and cardiovascular side effects.
- Acetaminophen is easily obtained over-the-counter, however, care should be taken not to take more than 4g in 24 hours; otherwise, several liver failure may occur.

The majority of existing drugs target either the GABAA receptor or mediators of inflammation for the treatment of chronic pain and all of the existing products have unpleasant side effects. On top of that they also have efficacy problems. The Liverpool team believe the solution is to target the glycine receptors, thereby avoiding sedation and addiction problems.

Tech Overview

A team at the University of Liverpool have been investigating propofol derivatives as a target for modulation of α-1 Glycine receptors in the spinal cord to restore the natural anti-nociceptive spinal signalling which is often suppressed in conditions associated with chronic pain. Whilst the parent compound propofol is a recognised modulator of α-1 Glycine receptors, it is also a profound agonist of GABAa receptors resulting in dose dependant sedation and anaesthesia. Derivatives of propofol however have been developed and extensively screened by the Liverpool team, leading to lead compounds with more selectivity for the α-1 Glycine receptor switching the

pharmacodynamic profile heavily towards analgesia minimising the risk of untoward sedative side effects, a common issue faced with most current centrally acting analgesics.The lead compound, LT-01-25, is now ready for pre-clinical studies.

Benefits

Key findings generated to date have demonstrated that LT-01-025 has:

- 30,000 times more selective for α-1 Glycine receptors over GABAa receptors (= analgesia without sedation)
- 80% oral bioavailability in rodents with > 180 min half-life,
- no organ toxicity at 30 x therapeutic doses in rodents,
- proof of concept demonstrated in 3 different rodent pain models (2 species),
- simple, scalable manufacturing process from the relatively inexpensive starting material (propofol).

Opportunity

The University of Liverpool is looking to out-licence a range of new chemical entities based on derivates of propofol which have potential applications as ‘first in class’ centrally acting oral therapies for the long-term management of chronic pain in both humans and animals. Commercial partners are actively being sought in both the human and veterinary sector.

Patents

- Patents have been filed covering new chemical entities for the treatment of chronic pain, WO 2015/097475,