PATENT

LIH383: novel positive regulator of the opioid system modulator

Opioid peptides are small proteins that act as neuromodulators by interacting with four 'classical' opioid receptors located on the surface of central nervous system (CNS) cells. They thereby mediate pain relief and emotions such as euphoria, anxiety, stress and depression. Previous research by the Immuno-Pharmacology and Interactomics group of the LIH Department of Infection and Immunity (DII) identified the atypical chemokine receptor ACKR3 as a novel previously unknown opioid receptor in the brain.

ACKR3 binds to a variety of naturally-secreted opioids, enkephalins, nociceptins and dynorphins, but does not trigger the typical molecular signalling events that result in painkilling or tranquillising effects. Instead, ACKR3 acts as a scavenger that sequestrates the secreted opioid peptides, thereby reducing the levels that can bind to traditional receptors and dampening their analgesic and antianxiety activity. ACKR3 is therefore a negative regulator of the opioid system with dual chemokine-opioid 'scavenging' activity and high drug targeting potential.

Meet the experts

Dr Andy Chevigné

› **Head of the Immuno-Pharmacology and Interactomics group**, Department of Infection and Immunity (DII)

› Deputy Head of Academic affairs of DII and Lecturer at the Faculty of Biomedical Sciences and Preclinical Studies at ULiège

› **45** peer-reviewed articles (e.g. Nature Communications, JACI)

› Inventor of **3** patents

› Co-awarded **Galien prize of Pharmacology 2019**

› **PhD**, Centre for Protein Engineering (ULiège) and the Laboratory of Applied Genetics (Free University Brussels, ULB); **MSc Biochemistry**, University of Liège (Belgium)

Dr Martyna Szpakowska

› **Co-supervisor** of Immuno-Pharmacology and Interactomics group with Andy Chevigné

› **22** peer-reviewed pharmacology and GPCRs articles and book chapters

› Co-inventor of **3** patents

› Member of ERNEST and ONCORNET2.0 European networks

› Co-awarded **Galien prize of Pharmacology 2019**

› **PhD in Molecular Pharmacology**, GIGA Research Centre at ULiège and Luxembourg Institute of Health (LIH); **MSc Biomolecular sciences**, Vrije Universiteit Brussel (VUB) (Belgium)

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TECHNOLOGY SUMMARY

LIH383 is a novel highly potent and specific negative modulator of ACKR3, developed by Dr Andy Chevigné, Head of Immuno-Pharmacology and Interactomics, and Dr Martyna Szpakowska.
It is an octapeptide (short chain of eight amino acids) with high selectivity and subnanomolar affinity for ACKR3. It was engineered by introducing a series of mutations to adrenorphin. Compared with other natural opioid ligands, its sequence (FGGFMRRK) confers it maximum specificity and affinity for ACKR3 and minimum selectivity and affinity for other opioid receptors.
LIH383 therefore binds to and blocks ACKR3, thereby modulating the availability of opioid peptides that can bind to classical opioid receptors in the brain and potentiating their natural painkilling and antidepressant properties. LIH383 is therefore a positive regulator of the opioid system.

In a nutshell, LIH383 presents the following advantages:

› Subnanomolar potency
› High selectivity for ACKR3
› Short chain (8 amino acids)
› Easy to synthesise/customise

Unmet clinical need addressed

Despite their effectiveness, opioid prescription drugs against severe pain — including morphine, oxycodone and fentanyl — frequently lead to several side-effects, such as tolerance, dependence and respiratory disorders. Therefore, there is an urgent need to find new means to modulate the opioid system by developing drugs with novel mechanisms of action and fewer complications, particularly given the current public health crisis ("opioid crisis") linked to the growing abuse of and addiction to synthetic opioids. As a new regulator of the opioid system, LIH383 holds promising potential as the precursor of a novel class of opioid drugs against chronic pain, stress, anxiety, depression, but also metastatic cancers, since ACKR3 also binds chemokines (involved in tumour initiation and metastasis) and is expressed abundantly in glioblastoma and breast cancer.

APPLICATIONS

› Therapeutic agent
› Detection ACKR3 - imaging
› Pharmacological tool
› Targeted delivery of drugs/toxins to cancer cells
› Neuromodulator pain-stress-anxiety

Advantages and benefits for partners and investors

› Novel molecule that modulates the opioid system in an innovative way means priority access to future breakthrough research and high-potential clinical applications;
› Molecule already tested in ex-vivo models, which sets the basis for successful in-vivo testing;
› Experienced team of world-class researchers ensures the rigour and quality of scientific results during further development stages;
› Dedicated Business Development Office ensures maximised scientific, economic and societal value of the patent and the successful transfer of future applications to the clinic or market.

NEXT STEPS

› Perform further in vivo experiments;
› Continue the development of the second generation of LIH383;
› Finalise partnerships, funding and technical aspects;
› Further investigate possible side effects of the manipulation of ACKR3 on both the opioid and chemokine systems (e.g. pain, stress, addiction and immunity);
› Tested LIH383 in glioblastoma multiforme.

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