

For immediate release

Press Release

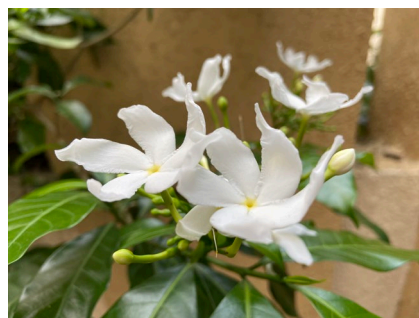
Luxembourg, June 3rd 2021

New Study Further Advances the Treatment of Chronic Pain

LIH and RTI International put forward the mode of action of natural painkiller conolidine, and develop new molecule with enhanced pharmacological properties

Building on their previous findings, scientists from the Immuno-Pharmacology and Interactomics group at the Department of Infection and Immunity of the Luxembourg Institute of Health (LIH), in collaboration with the Center for Drug Discovery at RTI International (RTI), a nonprofit research institute, have demonstrated that conolidine, a natural painkiller derived from the pinwheel flower and traditionally used in Chinese medicine, interacts with the newly identified opioid receptor ACKR3/CXCR7 that regulates opioid peptides naturally produced in the brain. The researchers also developed a synthetic analogue of conolidine, RTI-5152-12, which displays an even greater activity on the receptor. These findings, which were published on June 3rd in the prestigious international journal 'Signal Transduction and Targeted Therapy' (Nature publishing group), further advance the understanding of pain regulation and open alternative therapeutic avenues for the treatment of chronic pain.

Opioid peptides are small proteins that mediate pain relief and emotions, including euphoria, anxiety, stress and depression, by interacting with four classical receptors (“molecular switches”) in the brain. Dr Andy Chevigné, Head of Immuno-Pharmacology and Interactomics, and his team had previously identified the chemokine receptor ACKR3 as a novel fifth atypical opioid receptor, with high affinity for various natural opioids ([Nature Communications, Meyrath et al. 2020](#)). ACKR3 functions as a ‘scavenger’ that ‘traps’ the secreted opioids and prevents them from binding to the classical receptors, thereby dampening their analgesic activity and acting as a regulator of the opioid system.



In the current study, the researchers identified ACKR3 as the most responsive target for conolidine, an alkaloid with analgesic properties, by screening over 240 receptors for their ability to be activated or inhibited by this molecule.

“We confirmed that conolidine binds to the newly identified opioid receptor ACKR3, while showing no affinity for the other four classical opioid receptors. By doing so, conolidine blocks ACKR3 and prevents it from trapping the naturally secreted opioids, which in turn increases their availability for interacting with classical receptors. We believe that this molecular mechanism is at the basis of the beneficial effects of this traditionally used

medicine on pain relief”, said Dr Martyna Szpakowska, first author of the publication and scientist within the LIH Immuno-Pharmacology and Interactomics group.

In parallel to characterising the interaction between conolidine and ACKR3, the two teams went a step further. The scientists developed a modified variant of conolidine — which they called “RTI-5152-12” — which exclusively binds to ACKR3 with an even higher affinity. Like LIH383, a patented compound previously developed by Dr. Andy Chevigné and his team, RTI-5152-12 is postulated to increase the levels of opioid peptides that bind to classical opioid receptors in the brain, resulting in heightened painkilling activity. The LIH-RTI research teams established a collaboration agreement and filed a joint patent application in December 2020.

“The discovery of ACKR3 as a target of conolidine further emphasises the role of this newly discovered receptor in modulating the opioid system and, consequently, in regulating our perception of pain”, said Dr. Chevigné, corresponding author of the publication and leader of the LIH Immuno-Pharmacology and Interactomics group.

“Our findings could also mean that conolidine, and potentially also its synthetic analogues, could carry new hope for the treatment of chronic pain and depression, particularly given the fact that conolidine was reported to trigger fewer of the detrimental side-effects — namely addiction, tolerance and respiratory problems — associated with commonly used opioid drugs like morphine and fentanyl”.

“Our work could therefore set the basis for the development of a new class of drugs with alternative mechanism of action, thereby contributing to tackling the public health crisis linked to the increasing misuse of and addiction to opioid drugs”, says Dr. Ojas Namjoshi, co-corresponding author of the publication and lead scientist on the study at RTI.

“Once again, we have built on the findings of our excellent fundamental research and translated them into applications with the potential of tangibly improving clinical outcomes for patients”, said Prof Markus Ollert, Director of the LIH Department of Infection and Immunity. “We are grateful to the Luxembourg National Research Fund, the Ministry of Higher Education and Research and the European Commission for the generous support”.

Funding and research teams

This study was supported by funds from the Luxembourg Institute of Health (LIH), the Luxembourg National Research Fund (Pathfinder “LIH383”, INTER/FWO “Nanokine” grant 15/10358798, INTER/FNRS grants 20/15084569, PoC “Megakine” 19/14209621, PRIDE 11012546 “NextImmune” and 14254520 “I2TRON”), F.R.S.-FNRS-Télévie (grants 7.4593.19, 7.4529.19 and 7.8504.20) and by RTI International Internal Research and Development Funds (awarded to O. Namjoshi). M. Meyrath and C. Palmer are Luxembourg National Research Fund PhD fellows (grants AFR-3004509 and AFR-14616593). C. Palmer is part of the Marie Skłodowska-Curie Actions - Innovative Training Networks ONCORNET2.0 “ONCOgenic Receptor Network of Excellence and Training” (MSCA-ITN-2020-ETN). The authors wish to thank Manuel Counson for technical assistance in binding competition experiments.

The study was performed in close collaboration with the Center for Drug Discovery of RTI International (USA).

About the Luxembourg Institute of Health: Research dedicated to life

The Luxembourg Institute of Health (LIH) is a public research organization at the forefront of biomedical sciences. With its strong expertise in population health, oncology, infection and immunity as well as storage and handling of biological samples, its research activities impact on people's health. At LIH, devoted scientists investigate disease mechanisms to develop new diagnostics, innovative therapies and effective tools to implement personalized medicine.

About the Department of Infection and Immunity

LIH's Department of Infection and Immunity is a basic clinical-translational research entity aiming at understanding the complex mechanisms of infectious and inflammatory disease processes to enable new ways to diagnose, prevent and cure human diseases. Building on a highly interdisciplinary research environment, the research strategy of the Department of Infection and Immunity focuses on experimental discovery and validation, bridging to clinical application and technology development to address major unsolved medical needs in the areas of immune-mediated inflammation (such as in allergy, asthma, autoimmunity), cancer and infectious diseases (COVID-19, AIDS, influenza, measles and rubella virus infection, amongst others).

About RTI International

RTI International is an independent, nonprofit research institute dedicated to improving the human condition. Clients rely on us to answer questions that demand an objective and multidisciplinary approach—one that integrates expertise across the social and laboratory sciences, engineering, and international development. We believe in the promise of science, and we are inspired every day to deliver on that promise for the good of people, communities, and businesses around the world. For more information, visit www.rti.org.

Scientific contacts:

Dr Andy Chevigné
Group Leader, Immuno-Pharmacology and Interactomics
Department of Infection and Immunity
Luxembourg Institute of Health
E-mail: andy.chevigne@lih.lu

Dr Ojas Namjoshi
Research Scientist, Center for Drug Discovery
RTI International
E-mail: onamjoshi@rti.org

Dr Martyna Szpakowska
Scientist, Immuno-Pharmacology and Interactomics
Department of Infection and Immunity
Luxembourg Institute of Health
E-mail: martyna.szpakowska@lih.lu

Press relations:

Arnaud D'Agostini

Head of Marketing and Communication
Luxembourg Institute of Health
Tel: +352 26970-524
E-mail: arnaud.dagostini@lih.lu