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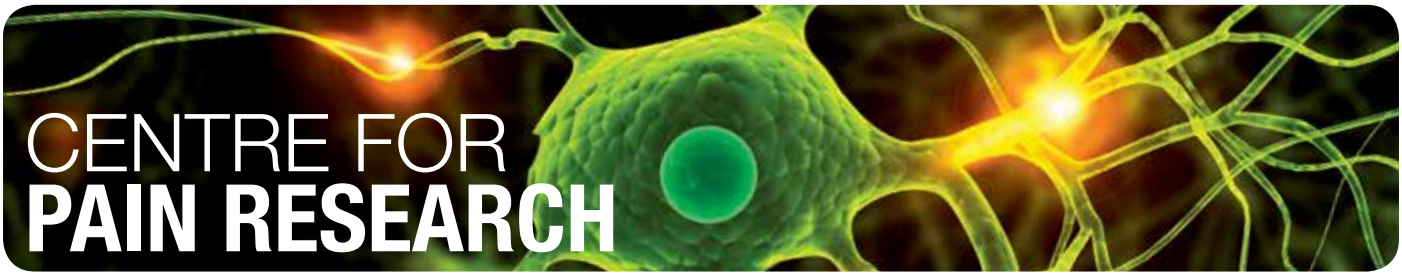
For scientists



CENTRE FOR PAIN RESEARCH

The vision of IMB's Centre for Pain Research (CPR) is to discover and develop new molecules for treating pain in humans. Specifically, we focus on pain that is difficult to manage, such as neuropathic, diabetic, chemotherapy and cancer pain. CPR researchers use advanced technologies to accelerate discovery and optimisation of analgesic small molecules, peptides, and natural products. We also examine their characterisation in disease and pathway-specific models of analgesic efficacy.

WHAT IS PAIN?

Pain is an unpleasant warning sign of tissue damage. It is usually transient in nature but can progress to chronic states that are challenging to treat.

One in five Australians, and one in three Australians over the age of 65, suffer from chronic pain, which remains one of the most under-recognised and under-treated medical problems.

The economic cost of treating chronic pain in Australia exceeds $34 billion per year, which is more than the cost of treating cancer, stroke, and diabetes. Many types of chronic pain (e.g. neuropathic pain) are poorly treated by current-generation analgesics ('painkillers') due to lack of efficacy and/or dose-limiting side effects. New classes of analgesics are required to better manage acute and chronic pain.

Our aim is to understand the mechanisms underlying the origins and transmission of pain, and to use this knowledge to produce more effective analgesics and improve quality of life for all Australians living with pain.

OBJECTIVES

- Develop a diverse repertoire of pharmacologically-characterised new molecules active in different pain pathways
- Improve our understanding of the molecular mechanisms underlying modality- and disease-specific pain pathways
- Isolate and characterise new research tools to delineate pain mechanisms and identify novel pain targets
- Develop and characterise new models of analgesic efficacy
- Identify new translational opportunities with industry partners
- Provide outstanding training and leadership in multidisciplinary pain research.

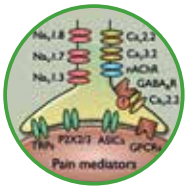
IMB PAIN RESEARCH

Discovery of novel analgesics

CPR uses a broad and comprehensive panel of assays for pain targets, addressing aspects of pain initiation and transmission using state-of-the-art screening technologies. Using unique compounds and libraries derived from natural products and venoms, these technologies place our research at the cutting edge of analgesic drug discovery.

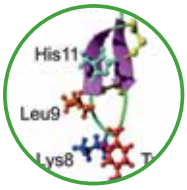
Structure-function

CPR uses advanced NMR and X-ray crystallographic approaches to obtain accurate three-dimensional structure of molecules and precisely position the residues contributing to affinity. This knowledge will be used to rationally optimise for target specificity, and, in parallel, will engineer out off-target liabilities to improve the therapeutic window of drug leads.



Analgesic efficacy models

CPR directly assesses analgesic efficacy of novel compounds in the pain pathway and clinically relevant disease models of pain. These approaches provide information to enable translation of our discoveries to the clinic by identifying preferred candidate molecules through to suitable patient populations, dosing routes, and strategies to minimise side effects in people living with pain.



Lead optimisation and development

Molecules showing significant analgesic efficacy in disease models of pain will be chemically modified to maximise storage and enzyme stability, ease of synthesis, and plasma half-life *in vivo*, without compromising therapeutic index, efficacy or safety.

INVESTIGATORS

- Richard Lewis (CPR Director)
- Paul Alewood
- Rob Capon
- Matt Cooper
- David Craik
- David Fairlie
- Glenn King
- Mark Smythe
- Rohan Teasdale
- Irina Vetter

COLLABORATORS

(Non-funding)

- Maree Smith (IMB Adjunct)
- Peter Cabot (UQ School of Pharmacy)
- Joe Lynch (QBI)
- Johan Rosengren, Walter Thomas (UQ SBMS)

EXTERNAL COLLABORATORS

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- Nigel Bunnett, Bill Charman, Joseph Nicolazzo (Monash Institute of Pharmaceutical Sciences)
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- MacDonald Christie (University of Sydney)
- Arthur Christopoulos (Monash University)
- Michael Cousins (Pain Australia)
- Julia Fleming, Paul Gray (Royal Brisbane and Women's Hospital)
- Janet Hardy, John Hooper (Mater Research)
- David Julius (University of California, San Francisco, US)
- Michael Nitabach (Yale University, US)
- Steven Petrou (The Florey Institute)
- Christian Vaughan (Royal North Shore Hospital)
- John Wood (University College London)
- Katharina Zimmermann (University of Erlangen-Nuremberg, Germany)

COLLABORATORS

(Funding)

- National Health and Medical Research Council
- Australian Research Council
- Boehringer Ingelheim
- Janssen
- Alchemia

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CENTRE FOR PAIN RESEARCH

PROFESSOR MATT COOPER

Professor Matt Cooper aims to develop completely new and orthogonal approaches to pain therapeutics by focusing on neuroinflammation in the area of burns pain and fibromyalgia; areas in which there is a paucity of effective treatments.

The majority of research efforts towards a new treatment for neuroinflammatory pain focus on blocking or attenuating neurotransmission, ignoring the immunological component. This may be particularly important in burns pain and fibromyalgia (chronic, widespread pain and a heighted sensitivity to pressure). Direct data to support the use of current treatments such as paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs) in fibromyalgia are limited.

In a population survey of 1800 patients with rheumatic diseases, including fibromyalgia, 60% reported preferring NSAIDs to paracetamol and 14% preferred paracetamol to NSAIDs. Any decision to advise NSAIDs or paracetamol needs to take account of patient preference, comorbidities, and adverse effects.

The discovery of the 'inflammasomes' in the late 1990's has opened up new targets for drug discovery in this area. The pro-inflammatory cytokine interleukin-1β (IL-1β) plays a key role in acute and chronic inflammation. It causes potent mechanical and thermal hyperalgesia in peripheral tissues, and increased expression of IL-1β in the spinal cord and injured nerve is seen in several models of inflammatory and neuropathic pain.

Our team has developed a potent (IC_{50} 7nM), orally active inhibitor of NLRP3 inflammasome activation, which has been shown to be involved in different types of neuroinflammatory pain. These new drug leads can also help unravel the role of inflammasomes in pain, including neuropathic, central and peripheral inflammatory pain.

RESEARCH APPROACHES

Professor Cooper's research is at the interface of pain and inflammation research. Research capacity is comprised of:

- medicinal and synthetic chemists working on drug design discovery and development
- biologists/biochemists working on pathway elucidation, characterisation, target identification
- high-throughput cell impendence screening of ion channels
- high-throughput functional FLIPR screening.

KEY ACHIEVEMENTS

Professor Cooper completed his PhD in 1995 and spent 13 years in the UK, firstly at the University of Cambridge, and then in start-ups and biotechnology companies. He returned to Australia as a NHMRC Australia Fellow at the University of Queensland, where he is currently driving new antibiotic and bacterial diagnostic R&D. He was founder and Managing Director of Cambridge Medical Innovations (part of Alere Inc.) and Chief Scientific Officer and co-founder of Akubio. He has published more than 140 scientific articles, 2 books, 20 patents, and has helped launch many medical technology products on the market today.