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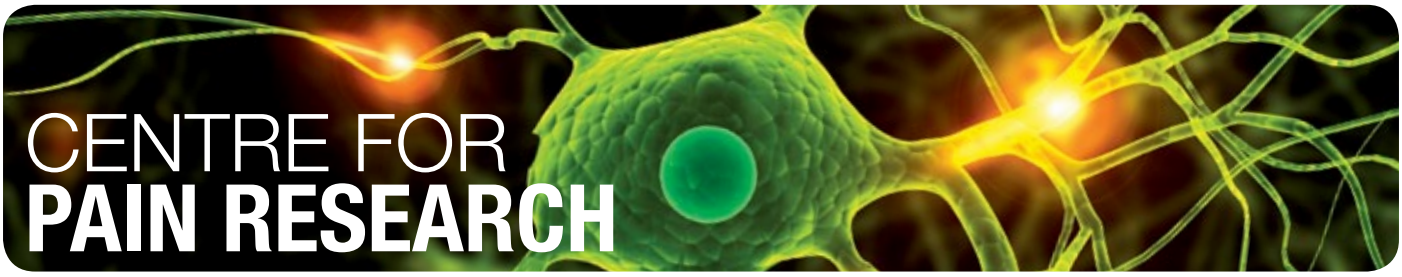
For scientists



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.

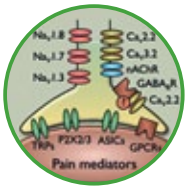
IMB PAIN RESEARCH

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.

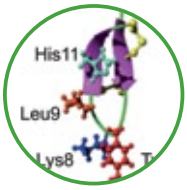
Structure-function

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

- David Adams (RMIT)
- Stuart Brierley (University of Adelaide)
- Nigel Bunnett, Bill Charman, Joseph Nicolazzo (Monash Institute of Pharmaceutical Sciences)
- Brian Chait (Rockerfeller University, US)
- 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

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

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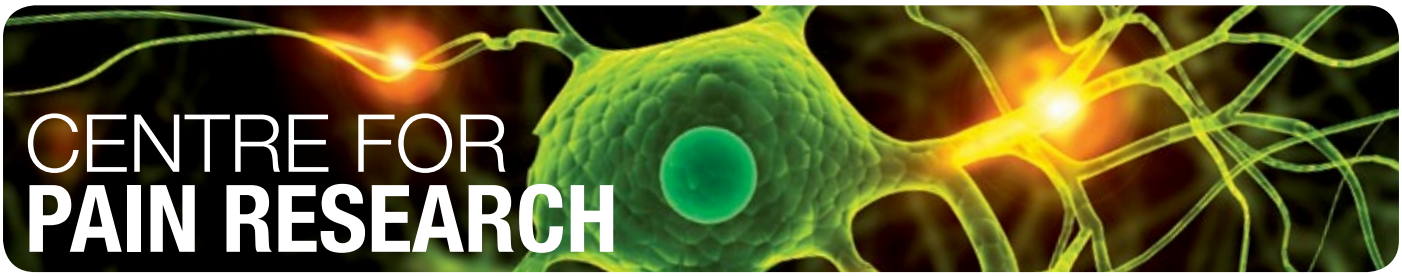

CENTRE FOR PAIN RESEARCH

PROFESSOR DAVID FAIRLIE

Professor David Fairlie is internationally known in drug discovery, medicinal chemistry and pharmacology. He is interested in how GPCRs and ion channels sense their environment, communicate with each other, activate and direct protein signaling networks in cells, and their impact on human health and major diseases. He focuses on understanding the structural basis of ligand interactions with both GPCRs and ion channels, and their subsequent activation.

Professor Fairlie has created novel modulators of inflammatory diseases that act on GPCRs, many of which mediate pain transmission through G protein action on ion channels. He is interested in developing novel methods for downsizing proteins into small molecule modulators of GPCRs and ion channels. His interest in pain research lies in modulating the chronic pain associated with neuroinflammation, inflammatory conditions, cancer, burns, itch and skin conditions.

RESEARCH APPROACHES

Professor Fairlie uses medicinal and biological chemistry for the design and development of treatments that modulate disease and pain. His research uses mechanistic studies to interrogate the molecular mechanisms of drug action in cells and in animal models. The approaches used by Professor Fairlie include:

- pathway- and disease-specific modulation of inflammation and pain in *vivo*
- developing agonists and antagonists of GPCRs (e.g. PAR2, ORL-1, C5aR, C3aR)
- downsizing GPCR and ion channel modulating peptides to peptidomimetics and small molecules
- interrogating and modulating intracellular signaling pathways
- analgesic efficacy in rodent models
- imaging of immune cells, neurons and disease.

KEY PUBLICATIONS

Harrison RS, Ruiz-Gómez G, Hill TA, Chow SY, Shepherd NE, Lohman RJ, Abbenante G, Hoang HN, **Fairlie DP** (2010) Novel helix-constrained nociceptin derivatives are potent agonists and antagonists of ERK phosphorylation and thermal analgesia in mice. *Journal of Medicinal Chemistry* **53**: 8400–8408.

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Reid RC, Yau MK, Singh R, Hamidon JK, Reed AN, Chu P, Suen JY, Stoermer MJ, Blakeney JS, Lim J, Faber JM, **Fairlie DP** (2013) Downsizing a human inflammatory protein to a small molecule with equal potency and functionality. *Nature Communications* **4** (2802): 1-9.

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Blakeney JS, Reid RC, Le GT, **Fairlie DP** (2007) Nonpeptidic ligands for peptide-activated G protein-coupled receptors. *Chemical Reviews* **107**: 2960-3041.

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