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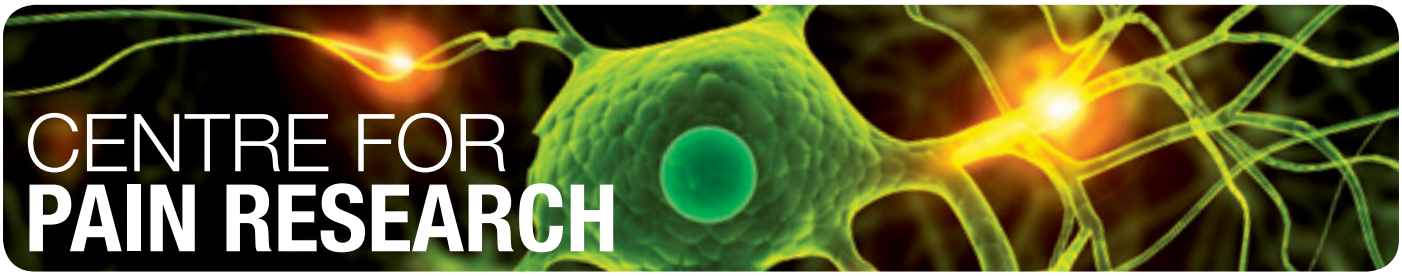
For scientists



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.

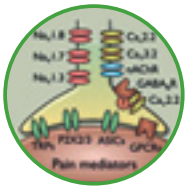
IMB PAIN RESEARCH

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.

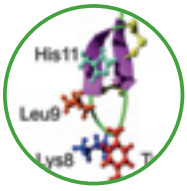
Structure-function

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

(Funding)

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

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CENTRE FOR PAIN RESEARCH

DR IRINA VETTER
(CPR DEPUTY DIRECTOR)

Dr Irina Vetter's internationally renowned research focuses on the neuropharmacology of pain. She aims to improve our current knowledge on pain signaling pathways through understanding the mechanisms of somatosensation, animal models of pain, toxinology and natural product drug discovery. Dr Vetter's research has a translational focus that crosses the fields of pharmacology and drug discovery to identify new toxins and repurpose old drugs to provide new avenues for targeted pain treatments.

RESEARCH APPROACHES

Dr Vetter's research is at the interface of pain research and toxinology, and draws on the sophisticated infrastructure and resources available at IMB.

These approaches include:

- disease- and pathway-specific in *vivo* pain pathway characterisation
- analgesic efficacy profiling in clinically relevant models of pain
- *ex vivo* recordings from the murine skin-saphenous nerve preparation
- high-content imaging of sensory neurons
- high-throughput electrophysiology of ion channels
- high-throughput functional FLIPR screening.

KEY PUBLICATIONS

Dr Vetter has established a number of disease- and pathway-specific animal models of pain that have provided significant insight into the pathophysiological mechanisms underlying these conditions as well as putative treatment approaches. Highlights include identifying $Na_v1.6$ as a pain target in peripheral sensory nerve endings, charactersing the pathophysiological basis of ciguatoxin-induced cold allodynia, and identification of highly selective venom peptides active at important pain targets. Selected publications relevant to pain are provided below.

1. Deuis JR, Zimmermann K, Romanovsky AA, Possani LD, Cabot PJ, Lewis RJ, **Vetter I**. An animal model of oxaliplatin-induced cold allodynia reveals a crucial role for $Na_v1.6$ in peripheral pain pathways. *Pain*. 2013 Sep;154(9):1749-57.
2. **Vetter I**, Hein A, Sattler S, Hessler S, Touska F, Bressan E, Parra A, Hager U, Leffler A, Boukalova S, Nissen M, Lewis RJ, Belmonte C, Alzheimer C, Huth T, Vlachova V, Rehh PW, Zimmermann K. Amplified Cold Transduction in Native Nociceptors by M-Channel Inhibition. *J Neurosci*. 2013 Oct 16;33(42):16627-41.
3. **Vetter I**, Touska F, Hess A, Hinsbey R, Sattler S, Lampert A, Sergejeva M, Namer B, Sharov A, Collins L, Eberhardt M, Engel M, Cabot PJ, Wood J, Vlachova V, Reeh P, Lewis R, Zimmermann K. Ciguatoxins activate specific cold pain pathways to elicit burning pain from cooling. *EMBO J*; 2012 Oct 3;31(19):3795-808.
4. Deuis JR, Lim YL, Rodrigues de Sousa S, Lewis RJ, Alewood PF, Cabot PJ, **Vetter I**. Analgesic effects of clinically used compounds in novel mouse models of polyneuropathy induced by oxaliplatin and cisplatin. *Neuro Oncol*. 2014 Apr 8. [Epub ahead of print]
5. Dantas de Araujo A, Mobli M, Brierley SM, Castro J, Harrington AM, **Vetter I**, Dekan Z, Muttenthaler M, Wan JJ, Lewis RJ, King GF, Alewood PF. Selenoether oxytocin analogues have analgesic properties in a mouse model of chronic abdominal pain. *Nat Commun*. 2014 Jan 30;5:3165.