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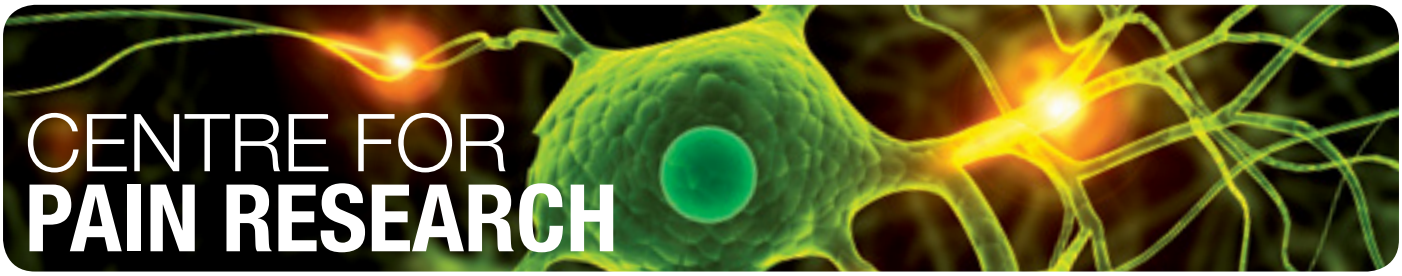
For scientists



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.

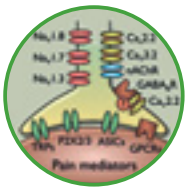
IMB PAIN RESEARCH

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.

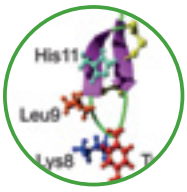
Structure-function

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

PROFESSOR ALEWOOD

Professor Alewood's key strengths centre around his multidisciplinary approach to peptide science. The biological systems he investigates include: ligand-receptor interactions, enzyme-substrate interactions and, over the past 10 years, toxin-ion channel interactions. Within collaborative research programs, his contribution typically involves the design and synthesis of small proteins, peptides and peptidomimetics, in order to elucidate more precisely the molecular details of the interactions. This has led to the identification of new therapeutic lead molecules such as AM336 and Xen2174 for neuropathic pain (with AMRAD and Xenome as commercial partners). His research group is seen as one of the premier groups worldwide in the discovery and the determination of structure-activity relationships of bioactive peptides and proteins.

RESEARCH APPROACHES

Professor Alewood's research group has expertise in high performance chromatography, proteomics, peptide synthesis, nuclear magnetic resonance (NMR) analysis, molecular biology and molecular pharmacology. Professor Alewood is a pioneer in the field of solid phase peptide synthesis, where the chemical approach (in situ neutralization) developed by Steve Kent and himself has been adopted by many researchers in academia, industry (seminal paper cited > 950 times), and in venom-based molecular discovery (> 100 published papers).

Professor Alewood's research approaches include:

- high throughput sequencing by integrating transcriptomics and proteomics
- rapid solid phase peptide synthesis, including high throughput strategies to access cysteine-rich toxins
- probing structure function relationships and using innovative chemistry to develop peptides into drugs with commercial potential.

KEY PUBLICATIONS

Professor Alewood has over 280 peer-reviewed research publications, with 77 publications in the past 5 years. Selected publications relevant to pain include:

Dutertre S, Jin A-H, Vetter I, Hamilton B, Sunagar K, Lavergne V, Dutertre V, Fry BG, Antunes A, Venter DJ, **Alewood PF**, Lewis RJ (2014) Evolution of separate predation- and defence-evoked venoms in carnivorous cone snails. *Nature Communications* **5**: 3521.

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** (2014) Selenoether oxytocin analogues have analgesic properties in a mouse model of chronic abdominal pain. *Nature Communications*. 2014 **5**: 3165.

Akondi KB, Muttenthaler M, Dutertre S, Kaas Q, Craik DJ, Lewis RJ, **Alewood PF** (2014) Discovery, synthesis and development of structure-activity relationships of conotoxins. *Chemical Reviews* **14**(11): 5815–5847.

Jin AH, Dutertre S, Kaas Q, Lavergne V, Kubala P, Lewis RJ, **Alewood PF** (2013) Transcriptomic messiness in the venom duct of Conus miles contributes to conotoxin diversity. *Mol Cell Proteomics* **12**:3824-3833.

Dutertre S, Jin AH, Kaas Q, Jones A, **Alewood PF**, Lewis RJ (2013) Deep venomics reveals the mechanism for expanded peptide diversity in cone snail venom. *Mol Cell Proteomics* **12**: 312-329.

Smith JJ, Hill JM, Little MJ, Nicholson GM, King GF, and **Alewood PF** (2011) Unique scorpion toxin with a putative ancestral fold provides insight into evolution of the inhibitor cystine knot. *Proc Natl Acad Sci* (USA) **108**(26): 10478-83.

Sharpe IA, Gehrmann J, Loughnan ML, Thomas L, Adams DA, Atkins A, Palant, E., Craik, DJ, Adams DF, **Alewood PF**, Lewis, RJ (2001) Two new classes of conopeptides inhibit the α1 adrenoceptor and noradrenaline transporter. *Nature Neuroscience*. **4**: 902-907.