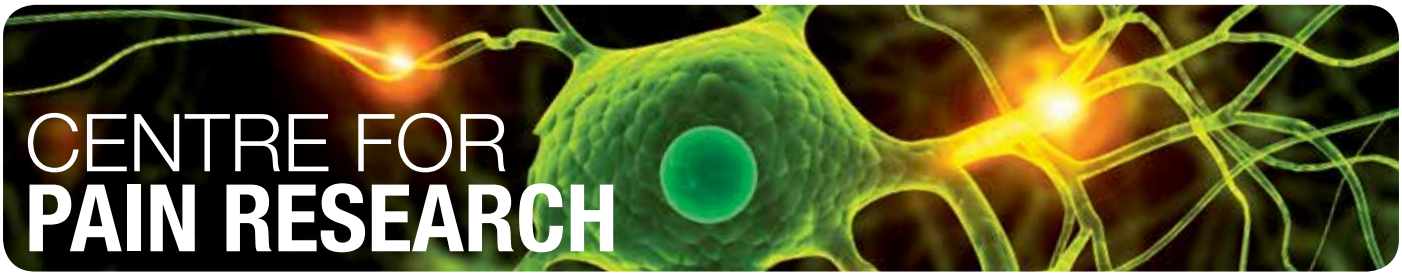
The University Of Queensland AUSTRALIA | IMB

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.

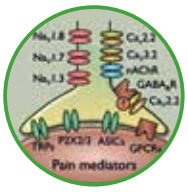
IMB PAIN RESEARCH

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.

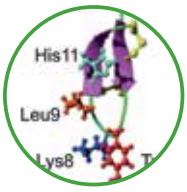
Structure-function

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

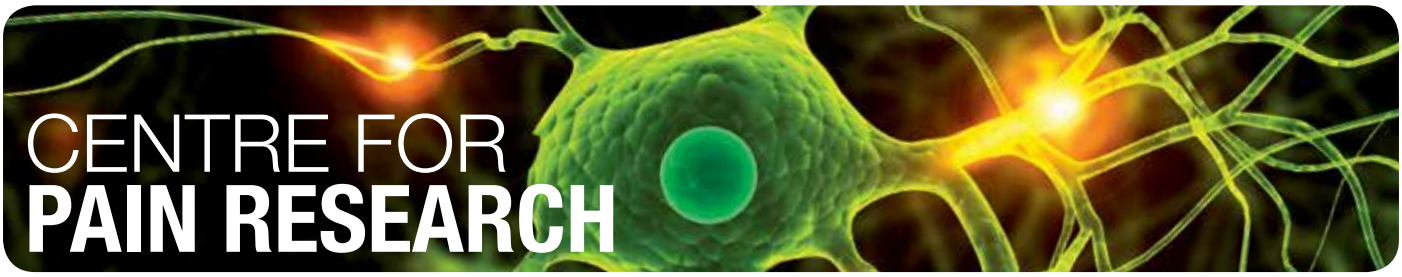
- David Adams (RMIT)
- Stuart Brierley (University of Adelaide)
- Nigel Bunnett, Bill Charman, Joseph Nicolazzo (Monash Institute of Pharmaceutical Sciences)
- Brian Chait (Rockerfeller University, US)
- MacDonald Christie (University of Sydney)
- Arthur Christopoulos (Monash University)
- Michael Cousins (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

Discover more at imb.uq.edu.au



CENTRE FOR PAIN RESEARCH

PROFESSOR ROHAN TEASDALE

The movement of thousands of distinct membrane proteins between the cell surface and intracellular compartments is a critical cellular process. It controls the organisation of cells in tissues and the communication between cells and their environment. This process depends on the regulated sorting and trafficking of proteins within the highly dynamic intracellular endosomal compartments of the cell. Defects in endosomal trafficking are linked to many human diseases including various neurodegenerative diseases, cancers and metabolic diseases.

Associate Professor Teasdale's long-term research program is focused on the discovery and characterisation of novel endosome associated proteins to define their molecular function in endosomal trafficking pathways. He is currently investigating defects in endosomal trafficking associated with intracellular pathogen invasion and various human diseases. His research also aims to understand the sorting signals that control the movement of transmembrane cargo proteins.

RESEARCH APPROACHES

Associate Professor Teasdale's research is at the interface of pain research and cell biology, and draws on the sophisticated infrastructure and resources available at the IMB.

These approaches include:

- molecular cell biology
- endocytosis and intracellular trafficking assays
- advanced microscopy techniques including confocal, superresolution & real-time microscopy
- RNA-interference (RNAi) screens & gene editing approaches (e.g. CrispR)
- maintaining and updating LOCATE: A Protein Subcellular Localisation Database.

KEY PUBLICATIONS

Highlights of Associate Professor Teasdale's research include the discovery and characterisation of novel endosome associated proteins including members of the PX protein family and the retromer protein complex. In addition, his recent research into the characterisation of retromer, a central regulator of early endosome protein trafficking, has provided the first molecular insight into how its function is modified in Parkinson's disease. Selected publications include:

Follett J, Norwood SJ, Hamilton NA, Mohan M, Kovtun O, Tay S, Zhe Y, Wood SA, Mellick GD, Silburn PA, Collins BM, Bugarcic A, **Teasdale RD** (2013) The Vps35 D620N Mutation Linked to Parkinson's Disease Disrupts the Cargo Sorting Function of Retromer. *Traffic* **15**(2): 230-44.

Kerr M, **Teasdale RD** (2014) Live imaging of endosome dynamics. *Seminars In Cell and Developmental Biology* **31**: 11-19.

Teasdale RD, Collins BC (2012) Insights into the PX (phox-homology) domain and SNX (sorting nexin) protein families: structures, functions and roles in disease. *Biochemistry Journal* **441**: 39-59.

Bugarcic A, Zhe Y, Kerr MC, Griffin J, Collins BM, **Teasdale RD** (2011) Vps26A and Vps26B Subunits Define Distinct Retromer Complexes. *Traffic* **12**: 1759-1773.

Ghai R, Bugarcic A, Liu H, Norwood SJ, Skeldal S, Coulson EJ, Li SS, **Teasdale RD**, Collins BM (2013) Structural basis for endosomal trafficking of diverse transmembrane cargos by PX-FERM proteins. *Proceedings of the National Academy of Sciences USA* **110**(8): E643 - E6525.