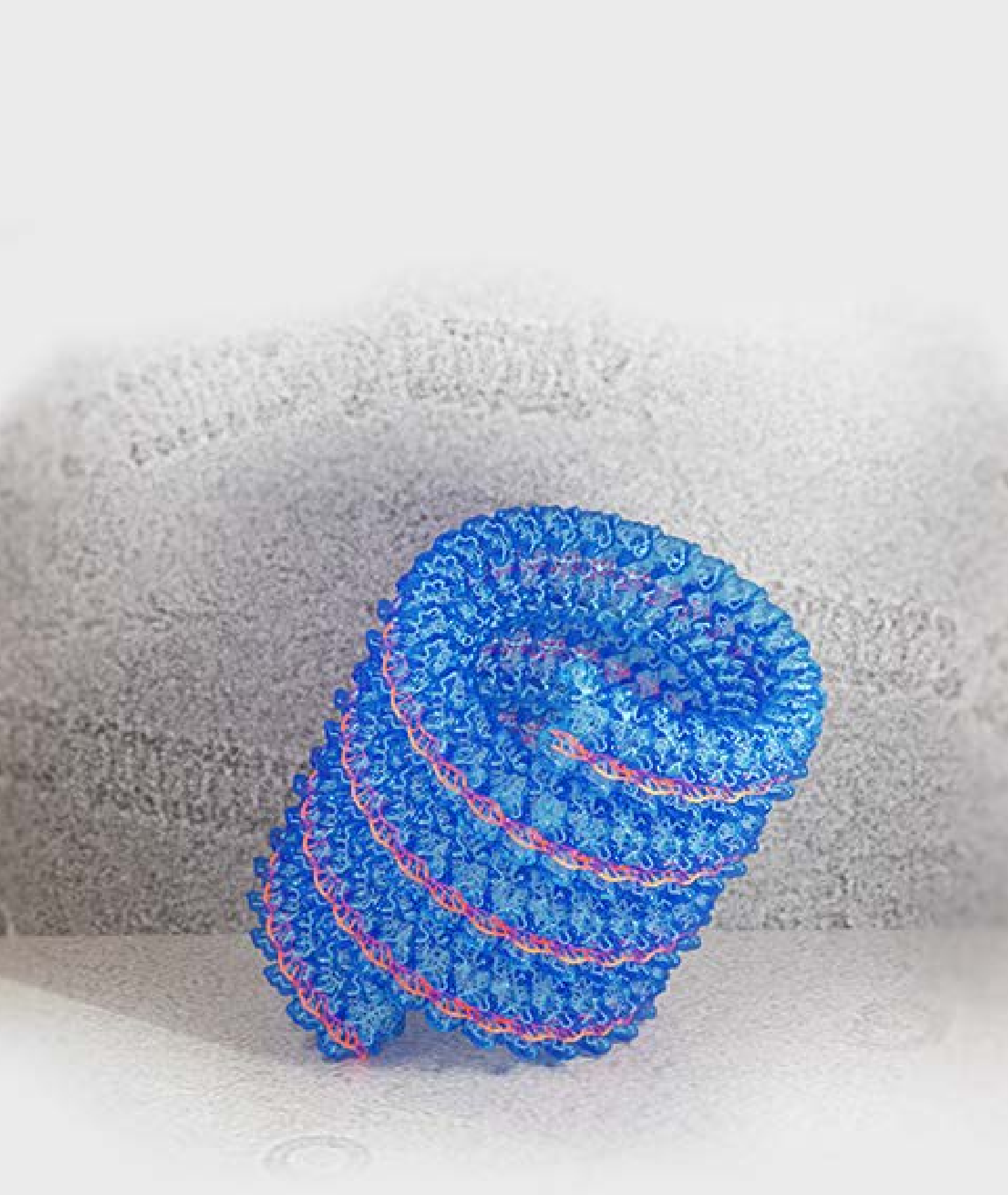
Centre for Cryo-electron Microscopy of Membrane Proteins

May 2023

ANNUAL REPORT

Year 2 (2022/2023)



From the UoW node (PDB 7UJL). Newing TP, Brewster JL, Fitschen LJ, Bouwer JC, Johnston NP, Yu H, Tolun G. Redβ177 annealase structure reveals details of oligomerization and λ Red-mediated homologous DNA recombination. Nat Commun. 2022 Sep 26;13(1):5649.
https://doi.org/10.1038/s41467-022-33090-6 ***Image credit: Dr Sarah Piper***

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Table of Contents (cont.)

On the cover: From the Monash node, Dr Sarah Piper's "In Bloom", NHMRC Biennial Science to Art competition posted on NHMRC instagram page (March 22, 2023) . The calcitonin family of receptors are involved in a range of detrimental diseases such as migraine. Here we see the molecular surface representation of the CGRP receptor (green), which interacts closely with an activity-modifying protein (purple). The front half of the receptor, looking like a flower, represents a symbol for the "blooming" drug discovery research in the area of understanding the function of these receptors and their role in migraine.

Image credit: Dr Sarah Piper

Centre Overview

Centre Overview

The Centre for Cryo-electron Microscopy of Membrane Proteins (CCeMMP) is funded by the Australian Government through the Australian Research Council (ARC) Industrial Translation Research Program (ITRP). The Centre is an academic-industry partnership supported by the Industrial Transformation Training Centre arm of the scheme. Our core academic partners are Monash University (Administering Institution), The University of Melbourne, the Walter and Eliza Hall Institute of Medical Research (WEHI), and the University of Wollongong. Key goals of the Centre include training industry-ready, world-class graduates in cryo-electron microscopy (cryo-EM) of membrane proteins, and providing leadership and innovation in the application of cryo-EM to advance industrial expansion in structure-enhanced drug design. Expected outcomes include world-first structural biology knowledge and techniques, and the generation of next-generation cryo-EM researchers with entrepreneurial and technical skills desired by industry.

Vision

The Centre will provide a world-leading workforce that can advance Australia's biotechnological capability and to build strong linkages with the drug discovery and development industries. Our Centre will train industry-ready, world class graduates in cryo-EM of membrane proteins. The Centre's graduates and research results will enable tomorrow's industrial expansion in structure-enhanced drug design.

Director's Report

Patrick Sexton, ARC CCeMMP Director

I am delighted to summarise the 2nd year of operation of the Centre, through to the end of April 2023. This was an exciting year for us as we progressively moved to more "in-person" activities across the different Nodes.

Research Success: Our Centre members continue to provide leadership in the application of cryo-EM, and the study of membrane proteins of therapeutic importance, including via publications in leading scientific journals, such as Nature, Nat Chem Biol, Nat Commun, Commun Biol, Cell Reports, Nuc Acids Res and major reviews in Chem Rev and Endoc Rev. Our members have also released 10 novel structures into the PDB and EMDB databases. Centre researchers have also been active in presenting their research at important local and international conferences, and to academic institutions and industry. Particular congratulations to our members and affiliates who have been successful in securing national and international competitive grant funding in an increasingly difficult funding environment, and also to those who received career fellowships and industry funding. We also tip our hat to the Centre members who received awards over the last 12 months. These many successes are highlighted in the current report.

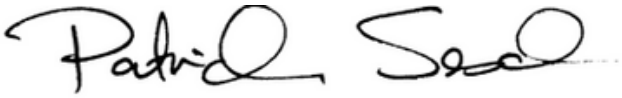
Comings and Goings: Our Centre Manager, Dr. Jackie How, has been on maternity leave for much of year 2, following the birth of her daughter, Mia. Dr. Tracie Pierce has filled the role of interim Centre Manager during this time. We also saw a change of leadership at our University of Wollongong Node, with Prof. Antoine van Oijen stepping down from his role as Node Leader, coinciding with his departure from his position as inaugural Director of the Molecular Horizons Institute that houses the cryo-EM facilities of the University of Wollongong Node. Stepping into the Node Leader role, and replacing Antoine on the Centre Executive committee is Assoc. Professor Gökhan Tolun. We thank Antoine for his many contributions to the original funding application for the Centre, to the development of the Wollongong Node and as an important member of the Centre Executive. We welcome Gökhan as the new Node Leader and are excited to work with him to develop the Centre over the coming years. Finally, our inaugural Centre student representative, Jack Tovey, completed his term in January 2023 and is replaced by Qinghao Ou. We thank Jack for his contributions in his role and look forward to working with Qinghao.

Ins and Outs: We were delighted to enter into a new Project Agreement with our Partner Organisation, Novo Nordisk, who are funding research into the structure and pharmacology of metabolic targets. However, we were sad to see the departure of Catalyst Therapeutics Pty Ltd from the Centre, after Centre researchers and Catalyst were unable to reach an agreement on projects.

Director's Report (cont.)

External Engagement: The Centre convened an embedded satellite meeting on "Cryo-EM of Membrane Proteins" within the high-profile Lorne Proteins 2023 meeting in February 2023, which brought together leading international and national scientists working in the field. Centre members were also active contributors to many cryo-EM workshops that were organised by different facilities across Australia. Our monthly seminar series continued with an excellent line up of speakers and we kept our stakeholders updated on our activities with our quarterly newsletters.

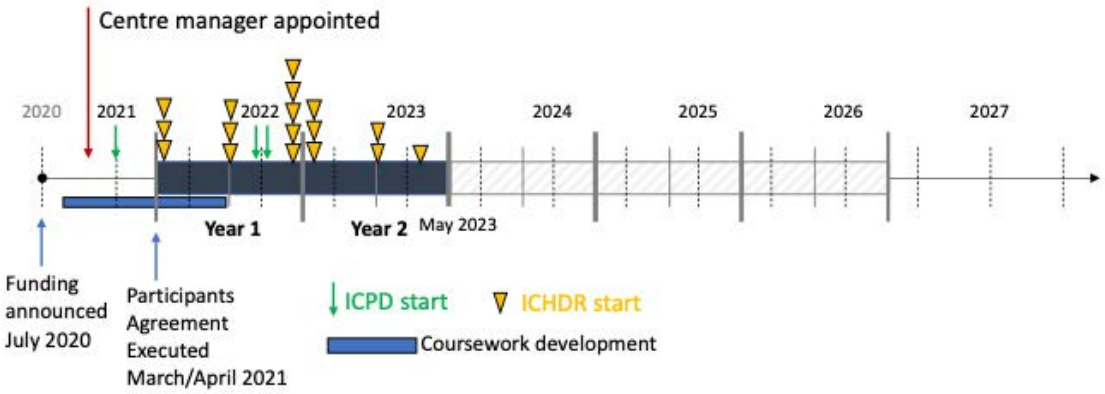
Overall, it was another strong year for the Centre, and we are looking forward to further growth and strong research outcomes in the coming year.



Patrick Sexton
ARC CCeMMP Director

CCeMMP Snapshot

Centre Operational Timeline



Current Partners

4 Academic Institutions

10 Industry Partners

4 Education Partners

MONASH University

THE UNIVERSITY OF MELBOURNE

bio21 institute

MOLECULAR HORIZONS

UNIVERSITY OF WOLLONGONG AUSTRALIA

WEHI brighter together

astex pharmaceuticals

AstraZeneca

Boehringer Ingelheim

Dimerix

novo nordisk

Pfizer

sanofi

Genentech A Member of the Roche Group

SERVIER

ThermoFisher SCIENTIFIC The world leader in serving science

LabArchives

Clarivate

MASSIVE

FB RICE

IP The IP Navigators

Key Data

24 Publications

10 Structures published

$24M New funding leveraged

6 Awards to members

22 Academic presentations

4 Industry presentations

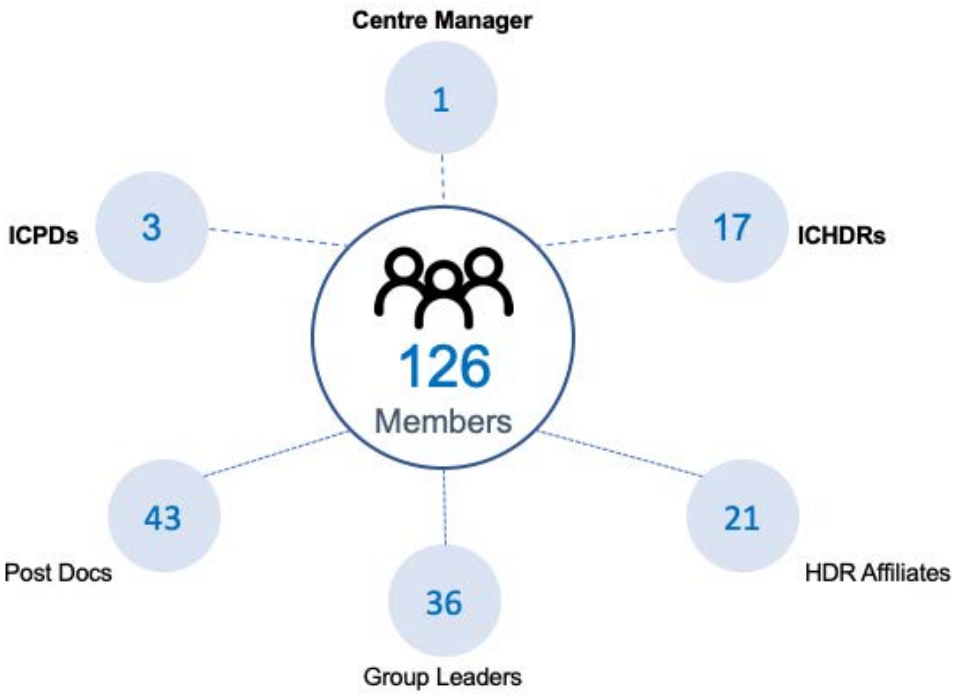
2 Career Fellowships

58 Conference presentations

6 Conference presentation awards

32 Local meeting presentations

Our People



Expanding CCeMMP Membership

As part of its strategic plan the Centre is reaching out to scientists, outside of the founding academic institutions, who are involved in cryo-EM and membrane protein research to provide opportunities for them to become members or affiliates of the Centre. Of course, we continue to actively seek inclusion of new staff and students from within our existing Nodes, as part of the Centre.

Some of our new members are familiar faces/names who have presented or participated in our Research Symposiums, our CCeMMP seminar series and/or our satellite meeting on Cryo-EM of membrane proteins at the recent Lorne Proteins 2023 meeting.

We have welcomed 8 new affiliate members from around the country and 10 new affiliates/members from within our nodes, not including our new ICHDRs.

- Dr. Emily Furlong (Group Leader), Australian National University
- Dr. Joe Brock (Group Leader), Australian National University
- Prof Renae Ryan (Group Leader), The University of Sydney
- Dr Alastair Stewart (Group Leader), Victor Chang Cardiac Research Institute
- Prof Megan O'Mara (Group Leader), The University of Queensland
- Dr Yan Jiang (PostDoc), The University of Sydney
- Alex Williams (Student Affiliate), Australian National University
- Alice (Jeeeun) Shin (Student Affiliate), Australian National University
- Somavally Dalvi (Student Affiliate), University of Melbourne
- Doulin Shepherd (Student Affiliate), University of Melbourne
- Bindusmita Paul (Student Affiliate), University of Melbourne
- Elaine (Ye) Jiang (Student Affiliate), Monash University
- Ruohua Gao (Student Affiliate), Monash University
- Michaela Kaoullas (Student Affiliate), Monash University
- Kieran Deane-Alder (Student Affiliate), Monash University
- Felix Bennetts (Student Affiliate), Monash University
- Muhammad Zahir Siddiqui (Student Affiliate), University of Wollongong
- Jhonnatan Reales-Gonzalez (Student Affiliate), University of Wollongong
- Susovan Das (Student Affiliate), Walter and Eliza Hall Institute of Medical Research

From the Monash Node, "Atomic jewellery" -- Runner Up, NHMRC Biennial awards; Science to Art, Dr. Sarah Piper, March 29, 2023. In this 'ball and stick' model, we see the structure of GLP-1 receptor (white), an important drug target for diabetes and obesity, with a small molecule bound (blue). The atoms and bonds are rendered using Blender3D to give it a shiny look similar to pearls on a string.

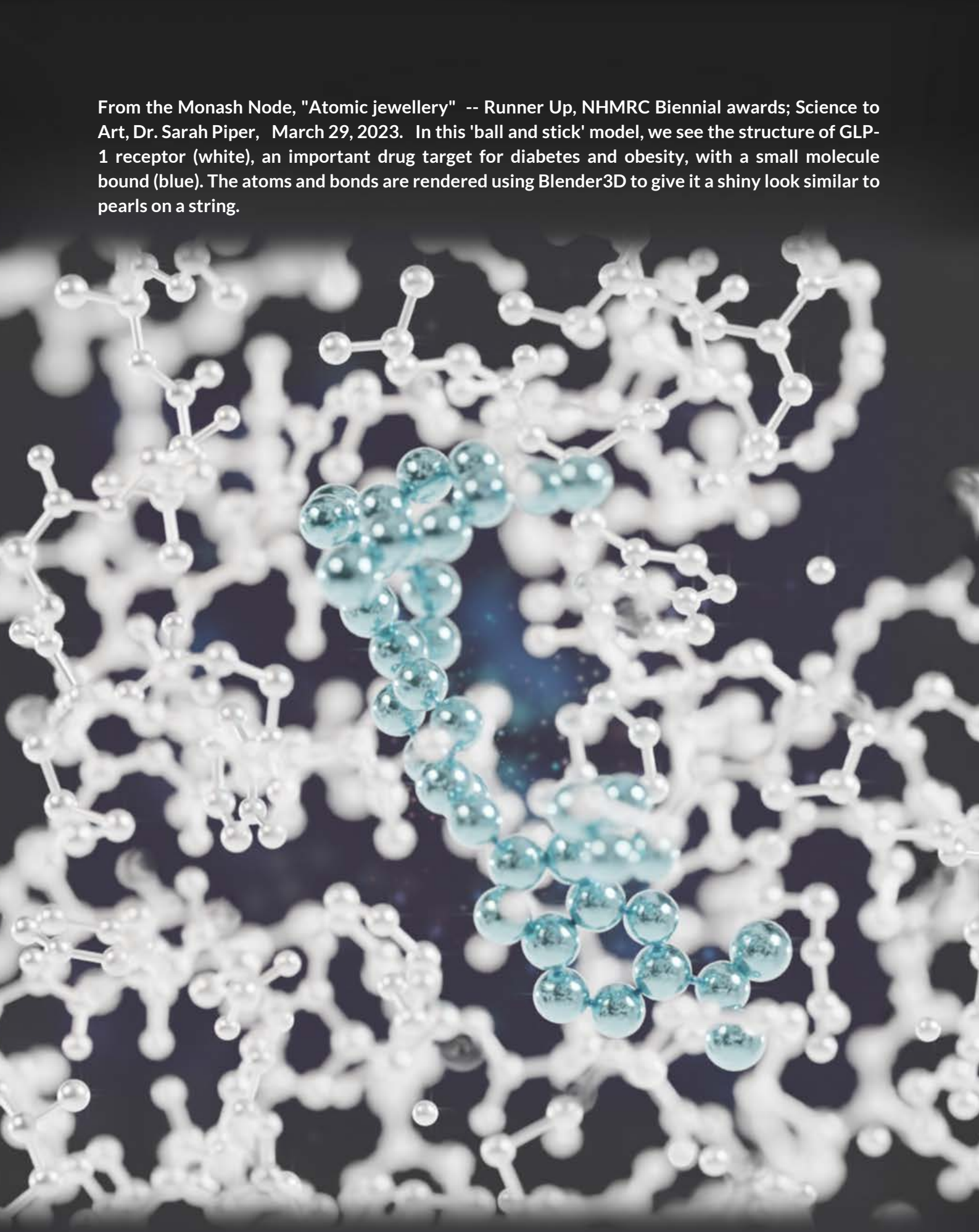


Image credit: Dr Sarah Piper

Education and Training

Education Overview

The CCeMMP Doctoral training program is a 4-year degree, inclusive of specialist training in cryo-EM of membrane proteins (3 x practical rotations in year 1), an experiential, embedded, industry placement and a series of vocational workshops and advanced coursework.

ICHDR Recruitment

In year 2 we welcomed 6 new ICHDRs, bringing the number of students enrolled in the Centre's HDR program to 17. Details on the new students and their projects are outlined below.

Our ICHDRs

Ania Beyger

Ania is a PhD candidate in Prof. Chris Langmead's laboratory at the Monash node. Her project will investigate the structure and pharmacology of CXCR3, a GPCR implicated in a number of diseases, including cancer and auto-immunity. Her project is in collaboration with industry partner Servier. Ania completed her Master's degree in Medicinal Chemistry (University of Glasgow) where she utilised computational methods for docking and SAR studies; this started her fascination with the structure-directed drug discovery process. Outside of the lab, she can be found exploring the great outdoors; hiking, camping and surfing.

Mayada Mazher

Mayada is a PhD candidate in Associate Prof. Isabelle Rouiller's laboratory at the University of Melbourne/Bio21 node. Her PhD will investigate the role of TACAN membrane protein as a mechanosensitive ion channel in chronic pain using cryo EM, electrophysiology and NMR. Mayada grew up in Cairo, Egypt and completed her MSc at The American University in Cairo. Mayada is enchanted by structural biology and protein biochemistry. In her free time, she loves acrylic painting and listening to music.

Inamur Rahman

Inam is a PhD candidate under the supervision of Associate Prof. Isabelle Rouiller at the University of Melbourne/Bio21 node. In his PhD, he will use single particle cryo-EM, mass-spectrometry and electron-tomography combined with sub-tomogram averaging to investigate the role of the envelope glycoprotein of HIV-1 in viral entry and its inhibition with antibodies. Inam completed his Master's degree in biotechnology at the Interdisciplinary Biotechnology Unit, Aligarh Muslim University, Aligarh, India. In his free time, he likes to play various outdoor and indoor games and explore new places.

Bhavika Rana

Bhavika is a PhD candidate at the Monash University Node under the supervision Dr. David Thal and Dr. Celine Valant. She will be working on understanding ligand selectivity of muscarinic acetylcholine receptors (mAChRs) using cryo-EM. Her research could open up new insights in comprehending how different types of ligands bind to and activate mAChRs. Other than scrutinizing mAChRs, Bhavika likes to explore art and music, and she loves to travel.

David Safadi

David is a PhD candidate in Distinguished Prof. David Adams' laboratory at the University of Wollongong Node. His project will involve investigating the structure and function of the GABA(B) receptor upon the binding of analgesic peptides. David first became fascinated about structure-function relationships in protein - particularly from a drug-design standpoint - during his undergraduate at the University of Wollongong, where he majored in medicinal chemistry. Outside of research, he enjoys discovering new music, playing sports, and video games.

Xiaomin Wang

Xiaomin is a PhD candidate in Dr. Shabih Shakeel's laboratory based at the WEHI node. Her PhD will investigate the structural basis for neuropilin-1 interaction with SARS-CoV-2 using advanced technology such as cryo-EM. Xiaomin grew up in Lanzhou, China and completed her MSc at The King Mongkut's University of Technology Thonburi (KMUTT) in Thailand. As a big fan of movies, Xiaomin can't help imagining 3D Cryo-EM movies to visualize the dynamics of structures at near-atomic resolution under native physiological conditions. She also loves to go everywhere and explore the world.

Rotational Training

The Centre ICHDRs undertake ~5 months of intensive hands-on training through three practical rotations that provide an introduction to and core skills in biochemical approaches to study membrane proteins, cryo-EM preparation and imaging, and data processing for 3D map reconstruction and protein modelling. The biochemistry rotation is Node specific, focussing on the classes of membrane proteins that their thesis projects will use. The Theory and Operation of Cryo-EM instruments, and Data Processing and Analysis rotations are delivered as integrated units across all four Nodes. Students learn from trainers within the Centre, Dr. Matthew Belousoff, Dr. Sarah Piper, Dr. Rachel Johnson, Dr. Cindy Zhang (Monash University Node), A/Prof. Isabelle Rouiller, Dr. Debnath Ghosal, Dr. Sepideh Valimehr (University of Melbourne Node), Dr. Isabelle Lucet, Dr. Josh Hardy (WEHI Node) and Dr. James Bouwer (University of Wollongong Node) and external instructors, Dr. Lingbo Yu (Thermo Fisher Scientific), Jay van Schyndel (Monash MASSIVE facility) and Prof. Rado Danev (University of Tokyo). The "Cryo-EM" training is presented as a hybrid of local practical training and Zoom (University of Wollongong) and in-person (Monash University, University of Melbourne and WEHI) lectures and workshops with hands on training at individual Nodes supported by local ICPDs in between the lectures/workshops.

Advanced technical training in CryoEM

The Process of Drug Discovery

Drug discovery scientists in academia and industry must appreciate how different facets of discovery science are integrated into the discovery pipeline. The Centre, in collaboration with the Drug Discovery Biology Theme at the Monash Node delivers advanced coursework that provides an in-depth understanding of the different stages of the drug discovery process, including target validation, drug screening methods, computational modelling, drug design and physicochemical optimisation, preclinical development, clinical development, and pharmacoepidemiology. The unit concludes with students designing their own drug discovery program. Centre students join PhD students in the Drug Discovery Biology Theme at the Monash Node for this unit.

EduWeek 2022

We were excited to begin the roll out of our professional development series in 2022 after this had been deferred in Year 1 due to the lingering impact of Covid for in-person meetings. The majority of the activities were held during what we are calling "EduWeek". These sessions were held in-person with all ICHDRs of the Centre attending. Many of the sessions were also open to other members of the Centre, and were well attended and highly valued by everyone. EduWeek 2022 included sessions on the application of competitive intelligence tools (delivered by our Educational Partner Organisation, Clarivate Analytics), various sessions on science communication, encompassing basics of structure graphics and communicating research in STEM, as well as an introduction to peer review training for journal articles. Importantly, EduWeek also included a leadership workshop titled "Leading in an age of inclusion".

Centre ICHDRs at EduWeek 2022

Leading in the age of inclusion

Leading in the Age of Inclusion

This workshop, as presented by an energetic Dr Jennifer Whelan, focused on diversity, and the lack thereof, at higher levels of academic institutions. Discussing ideas of diversity and intersectionality, not only in the theoretical but with examples of how paradigm shifts can better support diverse workforces, as drawn from her own experience in both academic and commercial spheres. The use of data driven findings set this apart from other presentations on the need for diversity.

Competitive intelligence tools (Clarivate Analytics)

- Workshop 1: Drug discovery and target druggability (Drug Research Advisor)
- Workshop 2: Competitive landscape and commercial assessment (Cortellis Competitive Intelligence)

The workshops were focused on two Clarivate analytic tools designed to support life science innovation and drug development, from early-stage research all the way through to commercialisation. To maximise attendance, we offered this as a hybrid session. These workshops were also opened up to participants outside of the Centre.

Communicating Your Research in STEM

Communicating your research in STEM

This workshop was facilitated by Dr. Graham Philips (Host of ABC Catalyst), Suzanne Lyons (former radio science journalist) and Peter Spinks (former journalist, The Age & New Scientist), who brought their breadth of experience in science communication to Centre members. This workshop was set apart from other STEM Communication workshops by its emphasis on less common avenues of communication. Dr Graham Phillips, highlighted the use of video, radio and social media to better communicate research to non-scientific audiences, by drawing on modern trends in narrative structure and film language, non-verbal communication patterns nearly everyone is fluent in, to make complex scientific findings concise and digestible without the need for lengthy argon-heavy explanations.

Basics of generating structure graphics

Basics of Generating Structure Graphics

This workshop focussed on commonly used software for manipulating and displaying structural data. The workshop was facilitated by the Centre's Executive Manager for Science Communications, Dr. Sarah Piper.

Peer Review Training

This workshop, facilitated by our Centre Director, Patrick Sexton, provided an overview of journal peer review processes, peer review ethics, how to assess manuscripts and the features of good peer review

Peer review training

Other Workshops

ARC CCeMMP Interactive Workshop

Dr. Raymond Shrijver (Thermo Fisher Scientific) facilitated an interactive discussion: *"Optimization of the Single Particle Analysis pipeline, from vitrification to the microscope to a structure"* on September 2nd, 2022. Raymond has vast experience in the application of Single Particle Analysis (SPA) within the pharmaceutical industry and has been instrumental in the progress that Thermo Fisher Scientific is making to accelerate the time from sample to structure. Assisted by Dr. Matt Belousoff (Monash University ICPD), Raymond chaired an interactive forum on behalf of the ARC CCeMMP. The discussions were aided by local experts from the Monash Institute of Pharmaceutical Sciences (MIPS), the Walter and Eliza Hall Institute of Medical Research (WEHI), the Monash Biomedical Discovery Institute (BDI) and the Bio21 Institute to workshop both practical considerations and technological improvements to relieve some of the major bottlenecks experienced in the application of SPA. This was an intimate, in-person, session with a focus on collaborative discussion with local colleagues who have years of experience in various aspects of this technique.

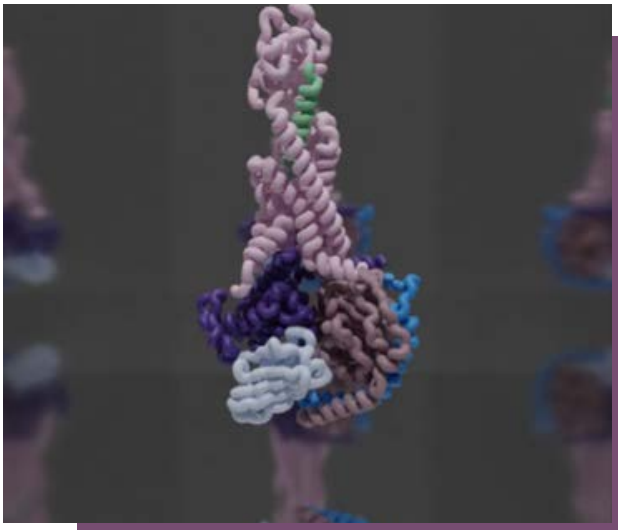
CCeMMP Interactive workshop, Sept 2022

Blender3D Workshop: Making Atoms Visible:

In February 2023 we held a two-day Blender3D workshop led by Brady Johnston, biochemist and Blender-in-Science expert. The small workshop was organised by Dr Sarah Piper for a limited number of experienced users within each of the Nodes as a trial for a larger workshop to be held later in the year in association with the planned 2023 EduWeek.

We appreciate Brady for coming all the way from Perth to teach the group how to use Blender3D, and thanks to all participants for sharing their amazing outputs.

Blender3D Workshop, Feb 2023



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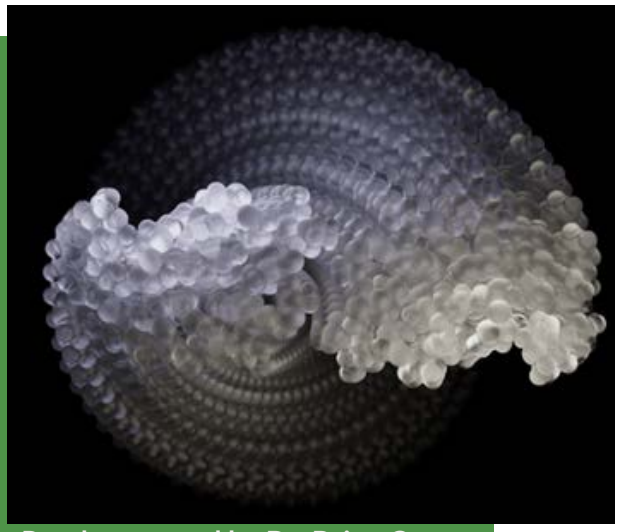

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Research

Research Overview

The Centre has three major program areas that address Key Objectives of the ARC Industrial Transformation Training Centre Scheme. These key objectives and activities against the three program areas are described below.

Centre objectives:

- Key objective 1. Industry-ready, world-class graduates with critical and highly-sort after expertise in the application of cryo-EM to drug discovery.
- Key objective 2. Innovation in membrane protein cryo-EM that advances robustness, resolution and cycle times that will be internationally leading.
- Key objective 3. Solution of novel membrane protein structures that are relevant to drug development.
- Key objective 4. Advancement of Australian biotechnological capacity and improved linkages with major pharmaceutical partners.

Research Programs

Program area 1. Advanced training in single particle cryo-EM of membrane proteins

Details of the bespoke 4-year Doctoral Training Program were outlined in the Year 1 report (KO1; core ITTC subprogram objective).

In 2022, five ICHDRs completed the three technical rotations (biochemistry; microscopy; data processing and structure determination) comprising ~5 months of intensive hands-on training in the core disciplines for the field. A further two students completed the microscopy and data processing and structure determination rotations due to timing of their commencement and will complete the remaining (biochemistry) modules in 2023.

Outside of the core ICHDR training, Centre members were actively involved in delivery of national cryo-EM training workshops run through:-

(i) Ramaciotti Centre for Cryo-Electron Microscopy (Monash University; 28 national and international participants), August 22-26, 2022 [ARC ICPD Dr. Matthew Belousoff contributed to planning and delivery of the course; two other CCeMMP members contributed to coursework delivery].

(ii) a workshop on Single Particle Cryo-EM through the Bio21 Ian Holmes Imaging Centre (ARC CCeMMP University of Melbourne Node; 8 national participants), October 19-21, 2022. This latter was organised by the local ICPD, Dr. Sepideh Valimehr, and included presentations from two other CCeMMP members.

(iii) CCeMMP member James Bouwer (University of Wollongong) presented a Masterclass on "Imaging at 200keV on mid-range instruments", August 30, 2022 at Monash University, to an audience of >50 participants, including other members of CCeMMP.

Single Particle Cryo-EM workshop, Bio21 Ian Holmes Imaging Centre

Program area 2. Innovative research for implementation of cryo-EM in membrane protein structure-based drug design.

Academic and academic-industry partnered research across membrane protein targets to deliver on KO2, KO3 and KO4 of the Centre (aligned to the core objective of the ITTC subprogram). We have included reference to publications formally published in 2022 or which were deposited into a publicly accessible pre-print server during 2022.

Theme 1: Technological advancements

Subproject 1. Integrated methods to study membrane protein dynamics

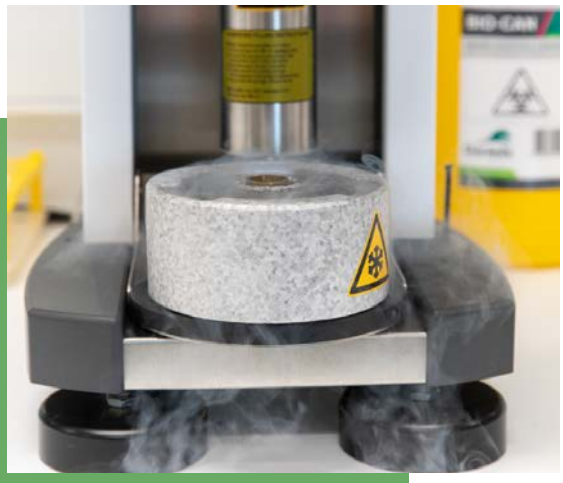
To understand membrane protein conformational dynamics and mechanism of drug action, ARC CCeMMP researchers have been using integrated approaches that describe the intrinsic conformational dynamics of membrane proteins and how these are influenced in a ligand-specific (natural ligands and/or drugs), including conformational variance information that can be directly extracted from cryo-EM data. A major tool used in the Centre is the 3D Variance Analysis algorithm in the software platform CryoSPARC and this continues to provide critical information not captured in static proteins subclasses. This has been applied to new research on G protein-coupled receptors (GPCRs) and to research on interleukin signalling complex dynamics with multiple publications arising (e.g. Cao et al, Science 2022; Piper et al, Nat Commun 2022; Deganutti et al, Nat Commun 2022; Cary et al, Nat Chem Biol 2022; Cary et al, Structure in press; Cao et al, Nat Chem Biol in revision; Metcalfe et al, bioRxiv 2022), and has also been used with complementary molecular dynamics simulations to probe longer time-scale events (e.g. Deganutti et al, Nat Commun 2022; Piper et al, Nat Commun 2022; Metcalfe et al, bioRxiv 2022). The importance of dynamics in membrane protein cryo-EM has also been discussed in major reviews authored by CCeMMP researchers (Piper et al, Chem Rev 2022; Cary et al, Endocrine Rev 2022; Lu et al, Int J Mol Sci 2022). In unpublished work, CCeMMP researchers are also expanding the integrated application of hydrogen-deuterium exchange-mass spectrometry (continuous and pulsed) to interrogate differential and sequential conformational changes upon membrane protein engagement with different ligands that further supports understanding of protein structure derived from cryo-EM. Centre researchers continue to assess new algorithms to analyses conformational information within cryo-EM data, including CryoDRGN, a neural network for continuous heterogeneous reconstruction developed at MIT, and 3DFlex (cryoSPARC), as well as new graphical tools for visualisation of 3D variance data (e.g. "Wiggle").

Subproject 2. Structural utility of 200kV cryo-EM

With the expense of the higher end 300kV instruments and limited access in some instances, CCeMMP researchers are investigating the structural resolutions that can be achieved with 200kV imaging on membrane protein samples of differing complexity (yield, dynamics, heterogeneity), and also how this can support commercial and academic drug discovery and development at lower cost. Our researchers have demonstrated a routine ability to achieve resolutions suitable for many structural questions, including identification of drug binding (Cao et al, Science 2022; Perlaza-Jimenez et al, Micro Spect 2022; Cary et al, Structure in press) and are using the data to develop processes that prioritise the best samples for more expensive, higher resolution, 300kV imaging.

Subproject 3. General advances in cryo-EM

Work is continuing on development of new cryo-EM sample preparation devices (noted in the Year 1 report), and this joint program between WEHI (New Medicines & Advanced Technologies) and Monash (Monash Industry Team Initiative) continues to provide training opportunities for students to develop ways to improve the device. A second iteration has provided a simpler design and a two-fold speed increase; this is now in the testing phase. CCeMMP researchers have also developed an improved approach for rapid measurement of ice-thickness in cryo-EM, which is important for understanding distribution of particles in vitrified ice and also for selection of optimal areas on grids for cryo-EM imaging (Brown & Hanssen, Commun Biol 2022). Centre members are also applying cryo-EM to soluble and peripheral membrane proteins (Paudel et al, Nuc Acids Res 2022; Newing et al, Nat Commun 2022; Perlaza-Jimenez et al, Micro Spect 2022; Newing et al, bioRxiv 2022; Kaplan et al, bioRxiv 2022).



Theme 2. Cell surface receptors (GPCRs)

GPCRs are a major membrane protein family studied by many researchers within the Centre. Of note, while we have divided the research into subproject areas, in many instances publications and collaborative partnerships cross over between subprojects. As such, outputs may appear in more than one subproject research update.

Subproject 1. Understanding receptor activation and transducer coupling

We have continued to determine structures of different agonist-receptor complexes to support understanding of how individual ligands control efficacy and selectivity. Within this subproject area are collaborative projects with our Industry partners Novo Nordisk, Boehringer Ingelheim, Sanofi, AstraZeneca and Dimerix. In addition to determination of novel ligand-receptor complexes (e.g. Cary et al, Nat Chem Biol 2022; Piper et al, Nat Commun 2022; Deganutti et al, Nat Commun 2022; Cao et al, Science 2022; Cao et al, Nat Chem Biol in revision, with Sanofi collaborators), we have been exploring the relationship between constitutive activity at different receptor subtypes, and different transducer proteins, and stability of agonist-receptor complexes to support structure determination as part of our collaborations with AstraZeneca and Boehringer Ingelheim.

Our structural work is also informing (and being informed by) in vitro and in vivo studies on the mechanism and consequences of GPCR activation. Exemplars of these studies include correlative work on ligand-binding kinetics and receptor signalling at the GLP-1 receptor (Zhao et al, Biochem Pharmacol 2022), where we have previously solved equivalent agonist-receptor complexes, and extension to structural determination of the secretin-secretin receptor complexes that use the structural data to support understanding of how changes to the activation domain of the secretin peptide control agonism. In other work, researchers investigated relationships of expression and activation to classification of muscarinic receptor ligands (Jiang et al, BJP) and consequences of muscarinic receptor activation in the context of prion disease (Dwomoh et al, Sci Signal 2022).

Subproject 2. Molecular mechanism for biased agonism

Understanding efficacy and biased agonism (the ability of individual ligands acting at the same receptor to generate different profiles of transducer and regulatory protein binding and activation) remains a major area of research within Theme 2. This has been a productive area of research in 2022 with multiple papers exploring the structure and function of GPCRs in complex with different agonist ligands (e.g. Cary et al Structure in press; Cary et al, Nat Chem Biol 2022; Cao et al, Science 2022; Deganutti et al, Nat Commun 2022; Piper et al, Nat Commun 2022; Zhao et al, Biochem Pharmacol 2022; Reviews, Cary et al, Endocrine Rev 2022; Lu et al, Int J Mol Sci 2022; Trinh et al, Pur Signal 2022). Within this subproject area, we have active industry collaborations with Boehringer Ingelheim, Servier, Novo Nordisk and Septerna.

Subproject 3. Allosteric and bitopic regulation of GPCRs

We are continuing our pharmacological and structural research across two fronts:-

(i) small molecule modulation of receptors, with new work on muscarinic structures (collaboration with Karuna Therapeutics; manuscript under review) and pharmacology (Jiang et al, Brit J Pharmacol 2022), as well as collaborative research with Astex Pharmaceuticals investigating the structural basis for allosteric ligand action at cholecystokinin receptors.

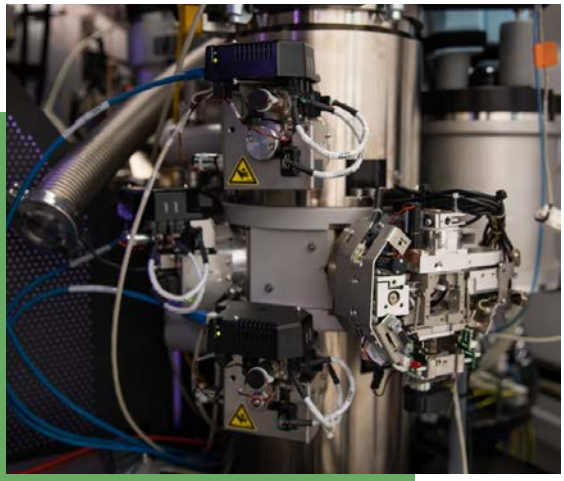
(ii) protein-protein modulation of receptors by other GPCRs and by accessory proteins (Cao et al, Science 2022; Cao et al, Nat Chem Biol in revision; Gregory & Jorg, Purinergic Signal 2022); collaborative projects with Dimerix and Novo Nordisk.

Subproject 4. Inhibitor-bound GPCR structures

While cryo-EM has become the primary method for structure determination of GPCRs in complex with agonist ligands, the application of cryo-EM to inactive, inhibitor-bound, receptors is more challenging. We have been investigating methods for generation of novel receptor constructs that can potentially improve particle alignment and resolution. This includes correlative assessment of chimeric receptors and the ability of software such as AlphaFold to predict optimal constructs. These constructs are now being investigated via pharmacological and biochemical approaches before extending this to identify how different constructs behave in cryo-EM imaging. We have a collaboration with Pfizer in this research area.

Subproject 5. Orphan receptor structures

Work has progressed well on the collaborative projects with our industry partners AstraZeneca and Boehringer Ingelheim. Multiple constructs have been generated and the ability of receptor constructs to potentially form a transducer bound complex with different G proteins has been performed. In parallel, pharmacological evaluation of the extent of constitutive activity for each construct with different G proteins is being assessed. In one of the projects, stable complex formation of the target orphan GPCR has been achieved with promising preliminary results on cryo-EM imaging.



Theme 3. Other membrane proteins

Subproject 1. Applying cryo-EM to understand receptor tyrosine kinase structure and function

Work is continuing on the development of methodology to express and purify the full-length membrane receptor tyrosine pseudokinase, EphA10. To help generate tools that can facilitate our structural studies, we have initially focused on establishing a robust expression system to produce truncated constructs of the ectodomain and intracellular domains of EphA10 and successfully used these to generate nanobodies (collaboration with the Centre for Biologics Therapies) and screen for small molecule inhibitors. We are now in the process of validating those tools via biochemical/biophysical and cell-based approaches before extending our studies to the full-length protein.

Subproject 2. Structural and functional studies of potassium ion channels linked to epilepsy

A new project on the Kv7.3 ion channel has commenced. The cytosolic coiled-coil domain 'helix D' within the Kv7 family plays an important role in tetramer formation but is not resolved in cryo-EM structures of Kv7 ion channels. In order to study this Kv7 structural component and discern its role in functional tetramer formation, and investigate the impact of a novel Kv7.3 mutation in that region, Helix-D will be expressed as a fusion protein with MBP, similar to previous studies. Attempts will be made to crystallise this domain with and without the novel point mutation to determine their structures via the cryo-EM modality Micro-ED.

Subproject 3. Cryo-EM on membrane proteins involved in chronic pain

Progress was made on assays to assess G protein interaction (and activation) with the target receptor. These assays will inform the most appropriate G proteins to use in complex formation prior to expression and purification for cryo-EM imaging.

Other projects

Centre researchers have applied cryo-EM to examine the structure and dynamics of interleukin 11 signalling complex, revealing dynamics of the gp130 extracellular domains mechanisms of cytokine variant inhibition (Metcalfe et al, bioRxiv 2022). They have applied cryo-EM to characterise the binding site of bovine antibodies on the envelope glycoprotein (Env) of the human immunodeficiency virus (HIV) (Heydari et al, Cell Rep Med 2022). Centre researchers are also involved in a range of academic collaborative projects on structure of various additional membrane proteins. An exemplar is recent work on bacterial secretion systems that revealed stoichiometric protein-phospholipid assembly (Kreida et al, Structure, in press). A new project has also commenced that will study the interaction of the single-pass membrane protein, neuropilin-1, with SARS-CoV-2 virus.

Program area 3. Joint research projects with industry partners and embedded industrial training

Industry-partnered research to deliver on KO4 of the Centre (aligned to the core objective of the ITTC subprogram).

The Centre continues its active engagement with Industry, both through our founding and new partner organisations and via other industry partnerships. This includes commencement of projects in 2022 with our partners Boehringer Ingelheim, Pfizer, Dimerix and Servier coinciding with the enrolment and completion of rotational training for newly appointed ICPDs and recruitment of staff to funded projects. We also established new project funding with our existing PO, Novo Nordisk. The Centre was visited by investigators from Industry including Dr. Laurent Vuillard (Servier) and Dr. Raymond Schrijver (Thermo Fisher Scientific).

We currently have multiple collaborative projects with our industry partners (detailed below), inclusive of regular joint meetings that provide important experiential training for the project participants.

Investigation of factors driving resolution of receptor structures and interactions with low affinity ligands. Dedicated project members: 1xICHDR, 1xICPD; additional support from the Monash ARC ICPD [monthly joint meetings].

Investigation of molecular mechanisms for biased agonism at incretin receptors. Structure determination for orphan receptors. Dedicated project members: 2xICHDR, 2xICPD – projects commenced in 2022; additional support from the Monash ARC ICPD [monthly joint meetings].

Methods for orphan receptor structure determination. Dedicated project members: 1xICHDR; additional support from the Monash ARC ICPD [monthly joint meetings].

Methods for determination of inhibitor-bound structure determination. Dedicated project members: 1xICHDR – project commenced in 2022; additional support from the Monash ARC ICPD [monthly joint meetings]

Structure and allosteric regulation across GPCR oligomers. Dedicated project members: 1xICHDR project commenced in 2022; additional support from the Monash ARC ICPD [monthly joint meetings].

New project commenced in 2022. Structure and pharmacology of peptide obesity therapeutics. Dedicated project members: 2xICPDs; additional support from the Monash ICPD [minimally monthly joint meetings, additional ad hoc meetings].

Structural mechanisms for activation and inhibition of Chemokine receptors. 1xICHDR project commenced in 2022 [monthly meetings].

The Centre continues its broad partnership with Thermo Fisher Scientific in the areas of innovations in cryo-EM, improving workflows for drug discovery and implementation of training in cryo-EM.

High Performance Computing

The Centre has partnered with Monash Massive M3 to purchase new HPC dedicated to Centre researchers. The new infrastructure comprising six NVIDIA A10 equipped GPU compute nodes was delivered to Monash in January 2023 and became operational in April 2023. The Centre is also partnering with Monash Massive for a second procurement in 2023 that is focused on large scale data storage.

Externally Highlighted Research

- Microscopy Australia – Research Outcomes and Impact 2022; Structural Studies for Better Obesity Drugs highlighting Cao et al., Science, 2022.

- Thermo Fisher Scientific highlighted the work of Zhang et al., "Evolving cryo-EM structural approaches for GPCR drug discovery, Structure, 2021". The article highlighted the application of 200kV EM to resolve drug binding to GPCRs. “Researchers at Monash University have been able to successfully determine the structure of GPCR to 3.2 A resolution on a 200 kV Glacios Cryo-TEM”.

Engagement

External facing events

1 Symposium

1 Satellite meeting

14 CCeMMP seminars

1 SP cryo-EM optimization workshop

2 Professional workshops

Internal events

2 Competitive intelligence workshops

1 Blender3D workshop

1 Peer review training

1 Research communication

1 Basics of structure graphics

1 Leading in an age of inclusion

4 Newsletters

CCeMMP members and affiliates at CCeMMP Satellite meeting, Lorne Proteins, Feb 2023

Industry Engagement

Servier Visit

Dr. Laurent Villuard visited the Monash University and WEHI Nodes (May 9th – 13th 2022), participating in discussions on project opportunities and research capability.

Boehringer Ingelheim Visit

Early February 2023, the Monash Node hosted two visitors from Boehringer Ingelheim Pharma GmbH (BI) in Biberach, Germany. Dr. Rebecca Ebenhoch and Dr. Dietmar Weichert are core members of the BI-CCeMMP-MIPS collaboration and have been working closely with the team at MIPS (ICHDRs Dongju Lee and Qinghao Ou; Postdocs Elita Yulianta and Fabian Bumbak).

Boehringer Ingelheim mentoring session

During their visit to MIPS, Rebecca and Dietmar participated in project meetings with their local collaborators, as well as taking the opportunity to attend academic group meetings, including the Wootten/Sexton group's monthly laboratory meeting and their fortnightly cryo-EM subgroup meeting. They participated in general discussions on GPCR biochemistry and cryo-EM data processing giving postdocs and students a chance to exchange of ideas and experiences with our partners. The visit also included a detailed discussion on sample preparation, cryo-EM data acquisition, and data processing, led by Monash ICPD, Matt Belousoff. Rebecca and Dietmar also gave generously of their time to provide an opportunistic in-person mentoring session for local CCeMMP members and affiliates to learn about working in industry (with a focus on large pharma).

Thermo Fisher Scientific Visit

Dr. Raymond Schrijver from Thermo Fisher Scientific (The Netherlands) visited the Centre in August 31-September 2, 2022. Raymond is a member of our Science and Industry Advisory Committee and brought his Industry experience to the SIAC's review of the Centre.

Dr. Schrijver also ran an interactive discussion workshop "Optimization of the single particle analysis pipeline, from vitrification to the microscope to a structure workshop" (Sept 2, 2022). Assisted by ICPD Dr Matt Belousoff, Raymond chaired an interactive forum with discussions aided by local experts (from MIPS, WEHI, BDI and Bio21), they explored the practical considerations and technological improvements to relieve some of the major bottlenecks experienced in the application of SPA.

Astex

Dr. Nazanin Mohebali presented at the Astex Pharmaceuticals Scientific Advisory Board meeting, 6 October 2022. "Membrane mimetic systems and their effect on the structure resolution, confirmation and dynamics of G protein-coupled receptors."

AstraZeneca

Prof. Patrick Sexton visited our Partner Organisation, AstraZeneca (Cambridge, UK), August 2022. Prof. Sexton delivered a seminar *"Application of cryo-EM to understanding of ligand binding and activation of class B peptide hormone GPCRs."* He also participated in a round-table workshop on pharmacology and cryo-EM of GPCRs.

Septerna

Prof. Patrick Sexton visited our industry collaborator, Septerna, April 6th-7th, 2023 and delivered a seminar, *"Intersecting structural biology and pharmacology to advance understanding of GPCR agonist action".*

Miscellaneous

- Dr. Natalie Diepenhorst - webinar, Australian Cardiovascular Alliance (ACvA) Industry Insights for Academia, 25 March, 2022, online. Panel speaker on the strengths of industry/academia collaborations.

- Prof. Patrick Sexton delivered a briefing (online) to Novo Holdings, Denmark, 1 November, 2022 on Cryo-EM and GPCR drug discovery.

Staff Transitions to Industry

Dr. Rachel Johnson was recruited by OMass Therapeutics (Oxford, UK) in October 2022.
Dr. Thomas Coudrat was recruited by CSIRO (Victoria) in January 2023.
Dr Jodi Brewster is now a Senior Research Scientist at Teva Pharmaceuticals, April 2023

Academic and Public Engagement

CCeMMP Seminar Series

In Year 2 of operation, the Centre continued its seminar series centred around the advancement of research on cryo-EM and membranes proteins. Speakers were selected and invited by the CCeMMP Seminar Subcommittee. The scheduled monthly seminars are open to the scientific and public communities and highlight leading researchers in the field. The seminars are routinely recorded and posted on our webpage. Since our last annual report, we have had 11 speakers in the regular program, and 3 special seminars.

Dr. Raphael Trenker , University of California (San Francisco) - Cryo-EM structures of the active HER2/HER3 receptor complex reveal dynamics at the dimerization interface induced by binding of a single ligand
(May 10, 2022)

Dr. Beatriz Herguedas, BIFI Institue, Spain - *Structural studies of heteromeric AMPA Glutamate receptors*
(Special Seminar; June 7, 2022)

Assistant Prof. Jianping Wu , Westlake University, China - *Structural elucidation of CatSper by CryoEM*
(June 14, 2022)

Assistant Prof. Natalie Zeytuni , McGill University, Canada - Structural insights into the cytotoxic peptides ATP-driven exporter essential to pathogenicity of drug resistant Staphylococcal aureus by hybrid approaches
(July 12, 2022)

Associate Prof. Megan Maher , University of Melbourne - *Structural insights into manganese transport across membranes*
(Aug 9, 2022)

Prof. Stefan Raunser, Max Plank Institute, Germany- *Bringing life into frozen proteins to elucidate their molecular mechanisms*
(Special Seminar; Sept 6, 2022)

Dr. David Thal, Monash University - *The Ups and Downs of Structure -Based Drug Discovery*
(Sept 13, 2022)

Dr. Matthew Doyle, University of Sydney - *Protein folding within the bacterial outer membrane*
(Oct 11, 2022)

Dr. Slavica Jonic, Sorbonne Université - *DeepHEMNMA approach for analysing continuous conformational heterogeneity*
(Extra Seminar; Nov 4, 2022)

Associate Prof. Michael Landsberg, University of Queensland - *Using Cryo-EM to understand structure, function and evolution of a bacterial toxin family*
(Nov 8, 2022)

Assistant Prof. Kliment Verba, University of California (San Francisco) - *Using the power of cryo-EM to uncover principles of kinase signaling at the membrane*
(Dec 13, 2022)

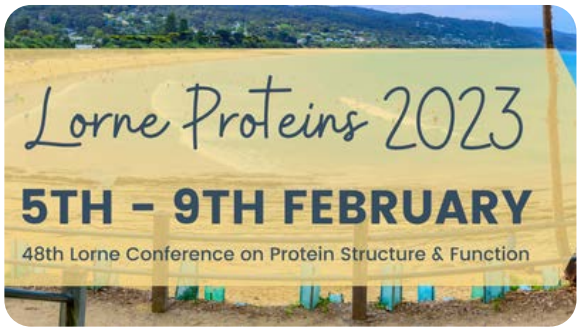
Prof. Eva Nogales, University of California (Berkeley) - *Structural insights into the regulation of the gene silencer PRC2*
(Feb 14, 2023)

Dr. Evan O'Brien, Stanford University - *Cryo-EM as a tool to characterize & exploit allostery in GPCRs*
(Mar 14, 2023)

Associate Prof. Michael Griffin, University of Melbourne - *Structures of the interleukin 11 signalling complex*
(Apr 18, 2023)

CCeMMP Satellite Meeting (conjoint with the Lorne Proteins 2023)

The ARC CCeMMP was proud to host an embedded Satellite Meeting at the International Lorne Proteins 2023 conference on Tuesday 7th February 2023. The meeting brought together experts in cryo-EM of membrane proteins to discuss recent progress within this rapidly advancing field, including 7 field leading international speakers.



CCeMMP Embedded Session

Topics ranged from proteins involved in lipid modification and transporter proteins, neurotransmitter receptors, endocytic caveolins, GPCRs, assembly of beta-barrel proteins, and red blood cell membrane scaffolds. Although some some satellite meeting sessions ran parallel to the main conference, the room was overflowing with attendees and there were many engaging questions from the audience.

Invited Speakers

- Radu Aricescu (MRC Laboratory of Molecular Biology)
- Gira Bhabha (New York University)
- Filippo Mancia (Columbia University)
- Melanie Ohi (University of Michigan)
- Denise Wootten (Monash Institute of Pharmaceutical Sciences)
- Matt Doyle (University of Sydney)
- Yan Jiang (University of Sydney)

Poster session

Selected speakers

- Jesse Mobbs (Monash University)
- Oliver Clarke (Columbia University)
- Rosemary Cater (Columbia University)
- Sarah Piper (Monash University)
- Shu-Sin Chng (National University of Singapore)
- Sulin Li (University of Queensland)
- Tyler Chang (Monash University)

Meeting awards

Meeting Awards

CCeMMP meeting Poster Prize Awardee: Theodore Nettleton (Monash University) "Structure of the pituitary adenylate cyclase-activating polypeptide 1 receptor bound to its secondary signal transducer Gq".

Speakers and organising committee

Organising Committee

- Joshua Hardy (Chair, WEHI),
- Renae Ryan (USyd),
- Shabih Shakeel (WEHI),
- Nazanin Mohebali (Monash),
- Sepideh Valimehr (Bio21/UniMelb),
- Patrick Sexton (Monash).

The ARC CCeMMP would like to acknowledge the generous support provided for the satellite meeting from the Lorne Proteins 2023 meeting, Monash Institute of Pharmaceutical Sciences and our industry partners AstraZeneca, Boehringer Ingelheim, Novo Nordisk, and Thermo Fisher Scientific.

CCeMMP Research Symposium

The Centre held its second (first in-person) research symposium on September 1st, 2022 at the Bio 21 Institute of the University of Melbourne Node. It was a pleasure to *finally* see people in the auditorium, having discussions around posters during tea breaks and lunch, as well as people enjoying the VR setup.

Posters in the auditorium, Bio21

Organising Committee

The meeting was organised entirely by a committee comprising Centre HDR students and Postdoctoral fellows from different Nodes; Dr. Cindy Zhang, Dongju Lee, Dr. Fabian Bumbak, Dr. Aidan Grosas and Haitian Chen, who did an amazing job across all facets of organisation, from venue, catering, poster boards, and prize committees to program design and execution. Indeed, they have set a very high benchmark for all future symposiums.

The symposium included 8 invited speakers, 20 posters and was attended by 129 registrants from across the country. Our morning and afternoon session chairs were Dr Katrina Black and Dr Emily Furlong and our opening and closing keynote Chairs were Prof Patrick Sexton and Dr Cindy Zhang.

Session Chairs

We began the day with our opening keynote speaker Dr. Raymond Schrijver (Thermo Fisher Scientific, The Netherlands) who spoke on *"Impact of advances in cryo-EM for drug discovery"*. We also heard from Dr Gökhan Tolun (University of Wollongong), *"Cryo-EM structure of phage **λ** annealase Red**β** provides insights into its molecular mechanisms and evolution, half a century after its discovery"*; Dr Sarah Piper (Monash University), *"Dynamic drug targets: using cryo-EM data and MD simulations to create realistic 3D animations of class B1 GPCR activation"*; Dr Debnath Ghosal (The University of Melbourne), *"Understanding architecture, assembly, and regulation of bacterial toxin delivery systems by electron cryomoragphy"*; Dr Hamish Brown (The University of Melbourne), *"Measurelce: accessible ice thickness measurement for single particle cryogenic transmission electron microscopy"*; Dr Rachel Johnson (Monash University), *"Applications of cryo-EM for drug discovery programs: from conformational dynamics to inactive state structures"*; and Dr Rhys Grinter (Monash University), *"Energy extraction from air: structural basis of atmospheric hydrogen"*. The final speaker was the lead researcher on a recent manuscript in Nature that achieved an Altmetric score of 1827 in just two months since publication. Our closing keynote speaker (and our only zoom session for the day!) was Prof Rado Danev (University of Tokyo) who spoke on *"Optimising cryo-EM for GPCRs and first steps in cryo-tomography"*.

Most popular oral presentation

The audience voted Dr. Gökhan Tolun as the most popular oral presentation. Gökhan received a certificate of recognition, a 3D printed model of choice and 2D print of choice.

VR set up

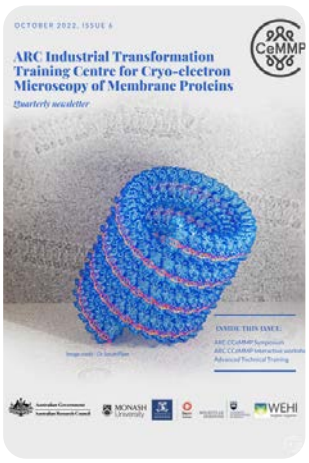
Dr Aidan Grosas closed the symposium and presented the Oral and Poster prizes. We are grateful to our industry partner, Thermo Fisher Scientific, for sponsoring the Poster Prizes; the winner was Yi Zeng, a PhD student from the Victor Chang Cardiac Research Institute. Yi received a certificate of recognition, $250 AUD and a 3D printed model of choice. ICHDR student MariaKatarina Lambourne from the University of Wollongong was Runner Up and received a 2D print of choice.

ThermoFisher SCIENTIFIC
The world leader in serving science

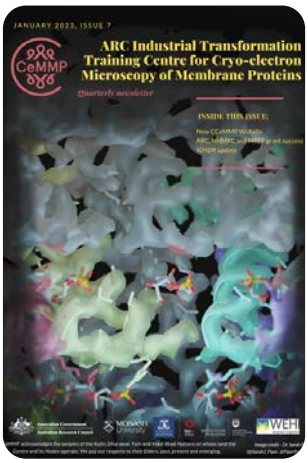
Newsletters

We continued our quarterly newsletters that keep our members and stakeholders abreast of current research and achievements of the Centre. All Newsletters can be accessed via the Centre website.

July 2022



October 2022



January 2023

April 2023

Charcot-Marie-Tooth Australia

Dr Winnie Tan and Dr Shabih Shakeel hosted a visit at WEHI on October 7th, 2022 for 6 people with lived experience of Charcot-Marie-Tooth in conjunction with a philanthropic partner, Charcot-Marie-Tooth Australia.

Dr. Winnie Tan - lay research presentation, Charcot-Marie-Tooth National Conference, 24 September 2022, online. Investigating MORC2 mutations in the Charcot-Marie-Tooth neuromuscular disease.

Charcot-Marie-Tooth Australia visit WEHI.

Media Engagement

CCeMMP Members in the News

Gökhan Tolun and Jodi Brewster

- Media Release: https://www.uow.edu.au/media/2022/researchers-at-uows-molecular-horizons-unlock-structure-of-a-protein-from-bacteria-killing-virus.php
- RADIO: https://www.abc.net.au/illawarra/programs/drive/drive/14068276 (38:40 mins)
- NEWS: https://www.miragenews.com/researchers-at-uows-molecular-horizons-unlock-867272/

Digital & Social Media

Youtube

27.3K views

330 subscribers

LinkedIn

184 connections

207 followers

Eventbrite

114 followers

Twitter

177K impressions

612 followers

337 retweets

1536 likes

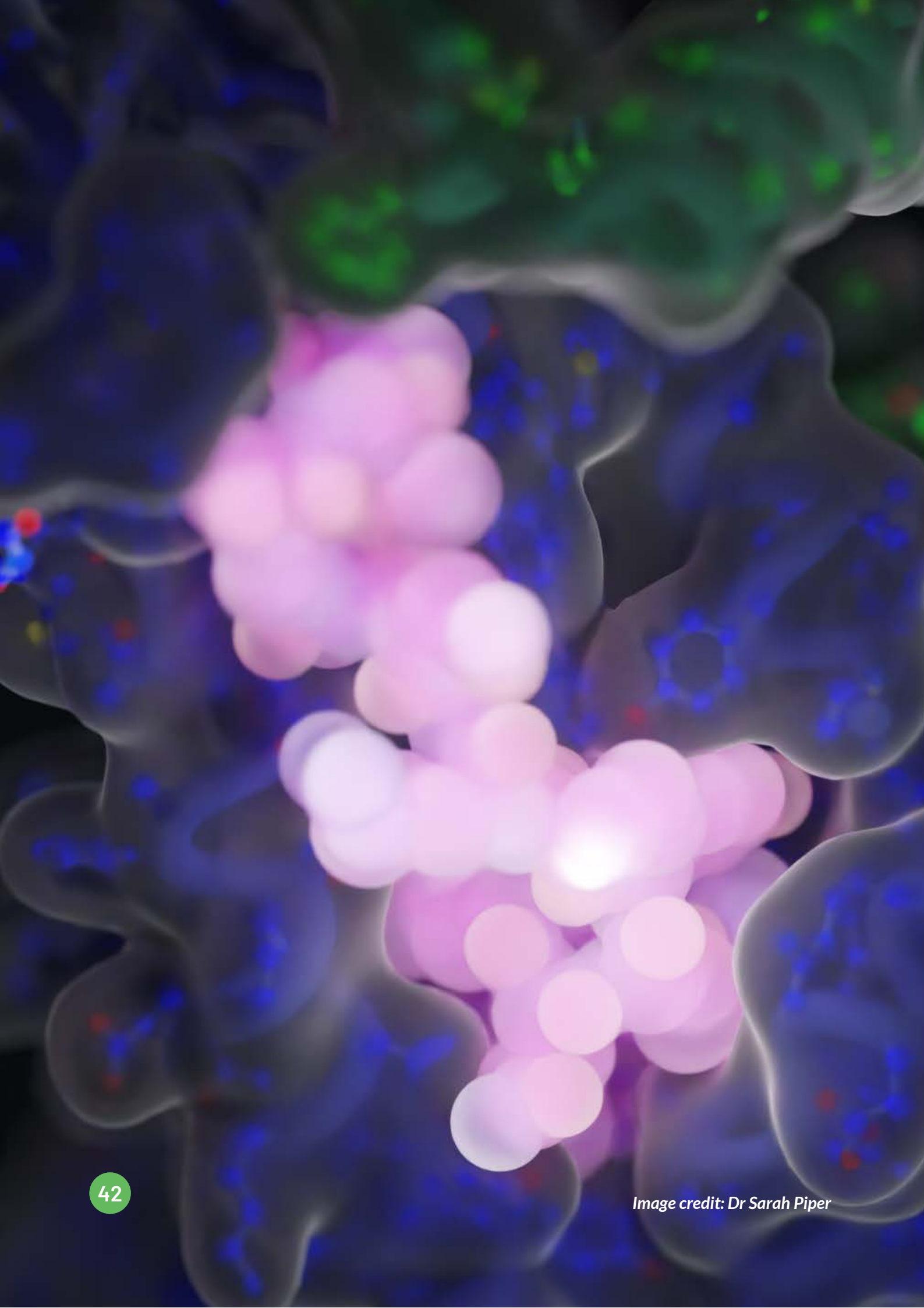
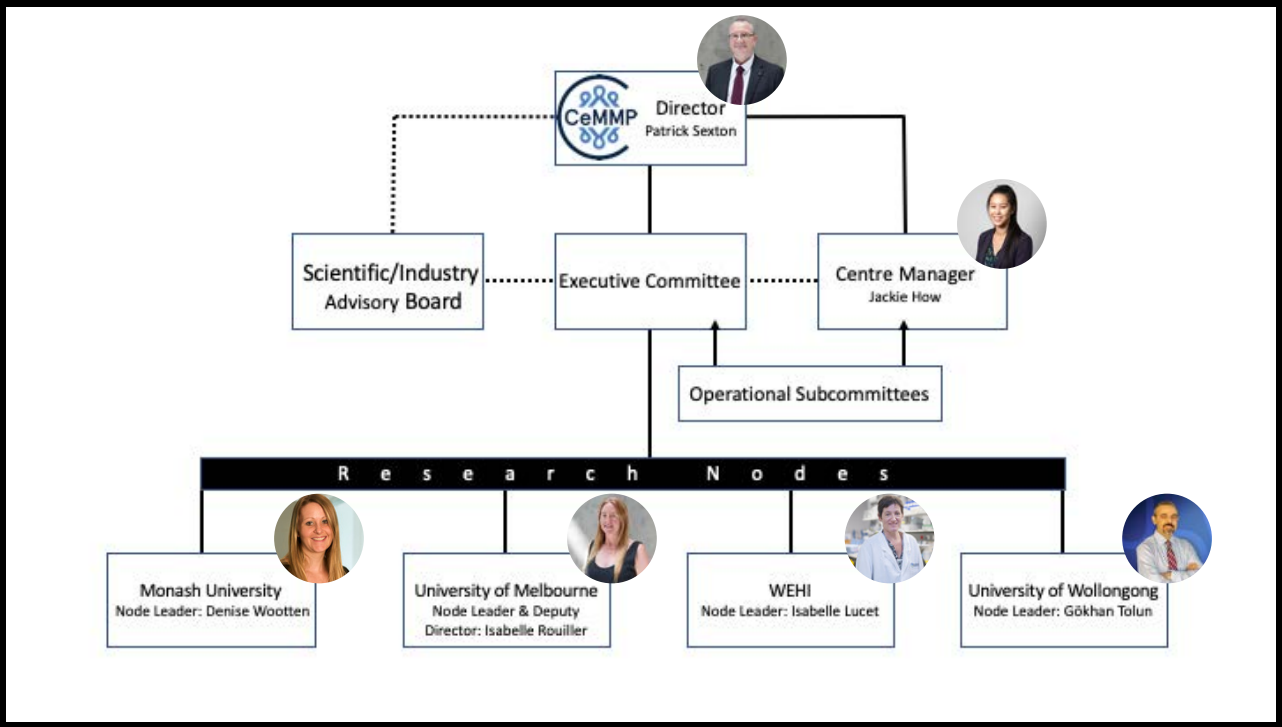
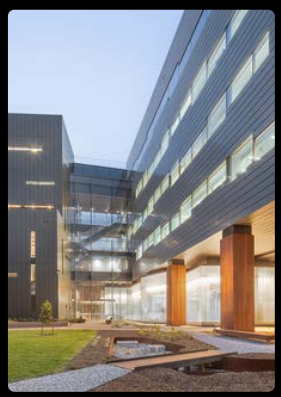


Image credit: Dr Sarah Piper

Governance


Director
Patrick Sexton
Scientific/Industry Advisory Board
Executive Committee
Centre Manager
Jackie How
Operational Subcommittees
Research Nodes
Monash University
Node Leader: Denise Wootten
University of Melbourne
Node Leader & Deputy Director: Isabelle Rouiller
WEHI
Node Leader: Isabelle Lucet
University of Wollongong
Node Leader: Gökhan Tolun



Changes to Governance

Centre Manager

The Centre Manager Dr. Jackie How has taken maternity leave (September 2022 – September 2023). The interim Centre Manager is Dr. Tracie Pierce. Dr. Pierce is an experienced research scientist who has worked both within academia and at the interface between academia and industry.

Executive Committee

Prof. van Oijen stepped down as Node Leader, University of Wollongong, coinciding with his resignation from the role of Director of the Molecular Horizons Institute. A. Prof. Gökhan Tolun has been appointed as the new Node Leader. Prof. van Oijen remains an active member of the Centre and provides corporate knowledge and advice to the new Node leader. Mr. Jack Tovey (Monash Node based ICHDR) will complete his 12-month term as the ICHDR representative at the end of January 2023. Mr. Qinghao Ou (Monash Node) was elected as the new ICHDR representative by a ballot of the current ICHDR cohort

Graduate Research Committee

The Coursework and Training subcommittee and the Graduate Research recruitment subcommittee were consolidated into a single Graduate Research committee (see below).

Science & Industry Advisory Committee:Centre Review

The Centre Operations were reviewed by the SIAC on August 31st 2022. The Committee noted that the Centre was active and productive in many areas but that there was a corresponding high administrative load. They recommended looking to consolidating some of the committees, particularly those whose initial roles were focused on establishment of the core framework for Centre operation.

Building on this recommendation, the Coursework and Training subcommittee and the Graduate Research recruitment subcommittee have been merged into a new single "Graduate Research Committee". This coincides with completion of the design and implementation of the major coursework and training components for the Centre ICHDRs and near completion of the recruitment of the 20 originally funded ICHDR places. The composition of the new committee is as follows:

- Prof. Denise Wootten (Chair, Monash)
- Centre Manager (Dr. Tracie Pierce, secretariat)
- Node representatives: Dr Sepideh Valimehr (Bio21/UoM), Dr Matthew Belousoff (Monash), Dr Aidan Grosas (UoW), Dr Josh Hardy (WEHI)
- Student representative: Mr Qinghao Ou

The SIAC also noted that the current operational and strategic plan was very ambitious for a Centre with only a single administrative staff member, noting that while achievements to date were impressive, some of the ambitions were on a scale more consistent with large Centres with 4-7 administrative staff. The Centre has tried to distribute workload to support operational and strategic planning through engagement of Centre members in its subcommittees and is looking to increase the pool of people who can support these roles through expansion of Centre membership. Nonetheless, it is likely that some of the planned activities of the Centre will be constrained by resourcing, with consequent impact on timing and implementation. To address this, the Centre will undertake an internal review of its planning every 6 months to determine if activities are realistically achievable.

SIAC Review Aug, 2022


PDB: 8FLQ
Human PTH1R in complex with PTH(1-34) and Gs
Image Credit Dr Sarah Piper

Performance

ACCESS TO
13
CRYO-ELECTRON MICROSCOPES

RUN
7
DAYS PER WEEK

UP TO
24
HOURS PER DAY

IMAGE DATA
13
TERABYTES PER DAY

Many thanks go to the trainers and managers, at each of our facilities, who maintain the smooth operation of all these instruments and enable the advanced training for our CCeMMP students.

Key Performance Measures

24 Publications

10 Structures published

$24M New funding leveraged

6 Awards to members

22 Academic presentations

4 Industry presentations

2 Career Fellowships

58 Conference presentations

6 Conference presentation awards

32 Local meeting presentations

Industry Related Performance Measures

2 Research Co-publications

4 Industry presentations

7 ICHDR partnered Research projects

7 Project Agreements

8 Industry funded postdocs

4 Visits from Industry Partner investigators

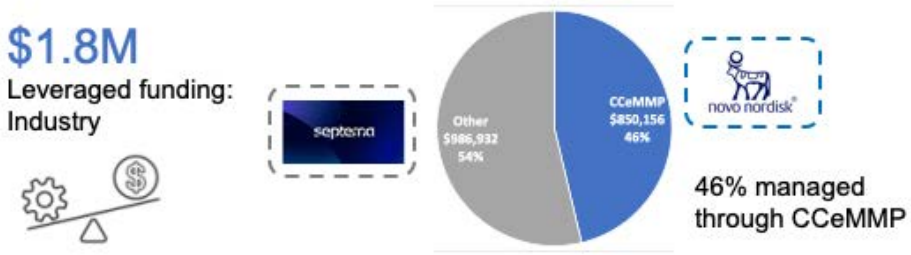
1 New spin-out company

3 Researchers transitioning to industry

Structures Published in Publicly Accessible Databases (PDB & EMD)

- Bacteriophage Lambda Red-Beta N-terminal domain helical assembly in complex with dsDNA [PDB: 7UJL, EMD-26566]
- Horse spleen apoferritin [EMD-25619]
- PAC1R-PACAP27-Gs complex [PDB: 8E3X, EMD-27872]
- VPAC1R-PACAP27-Gs complex [PDB: 8E3Y, EMD-27873]
- VPAC1R-VIP-Gs complex [PDB: 8E3Z, EMD-27874]
- PTH1R in complex with PTH(1-34) and Gs [PDB: 8FLQ, EMD-29283]
- PTH1R in complex with PTHrP and Gs [PDB: 8FLR, EMD-29284]
- PTH1R in complex with Abaloparatide and Gs [PDB: 8FLS, EMD-29285]
- PTH1R in complex with M-PTH(1-14) and Gs [PDB: 8FLT, EMD-29286]
- PTH1R in complex with LA-PTH and Gs [PDB: 8FLU, EMD-29287]
- GLP-1R in complex with Ex4-D-Aa and Gs [PDB: 7S1M, EMD-24805]
- 50S ribosomal subunit for Staphylococcus aureus [PDB: 7TTU, EMD-26124]
- 50S ribosomal subunit for Staphylococcus aureus [PDB: 7TTW, EMD-26125]

Leveraged Research Funding



Funding

Major funding

Alzheimer's Drug Discovery Foundation, Parker MW, Development of small molecule inhibitors of a microglia receptor as treatments for Alzheimer's disease.

Australia-India Strategic Research Fund (AISRF) Grant, Ghosal D, Das Dibyendu. SARS-CoV-2 entry: Exploring structural dynamics and therapeutic landscape.

ARC Centre of Excellence in Quantum Biotechnology, CE230100021, Ooi L, van Oijen A; Centre Director: Bowen W; Administering Organisation: The Univ of Queensland; CIs - UQ: Fish A, Mark A, Rowan A, Rubinsztein-Dunlop H, Stow J; Flinders Univ: Coote M; Univ of Melbourne: Hall L, Hinde E, Hollenberg L, Cao K-A, Simpson D; Univ of Wollongong: Ooi L, van Oijen A; Univ of Technology, Sydney: Jin D, Kabakova I, Reimers J, Zhou J; Other participating organisations: Olympus Australia Pty Ltd, IBM Corp., Genieus Genomics Pty Ltd, Q-CTRL Pty Ltd, Intelligent Imaging Innovations, Inc., Elemental Instruments Pty Ltd, Orica Australia Pty Ltd, Silanna Semiconductor Pty Ltd, Protein Evolution Ltd., Defence Science & Technology Group, CSIRO, Dept of Environment & Science, MIT, UC Berkeley, Univ of Ulm, CNRS, Univ of Victoria (Canada), Univ of Exeter (UK), Univ of Surrey, UC Irvine, Univ of Glasgow (UK), Univ of Michigan, Medical Univ of Innsbruck, Delft Univ of Technology (Netherlands), Univ of Stuttgart, Johns Hopkins Univ.

ARC Discovery Project 2023, DP230100769, Burns B, Duggin I, & Ghosal D, Asgard archaea: the first eukaryotic cells?

ARC Discovery Project 2023, DP230102422, Griffin M, Hanssen E, Putoczki T, How do cytokine receptors transmit signals?

ARC Discovery Project 2023, DP230101981, Ooi L, Phenotyping hippocampal DCX+ cells to unravel human adult neurogenesis.

ARC Discovery Project 2023, DP230101148, Parker MW, All in the family: understanding a new class of bacterial toxins.

ARC Discovery Project 2023, DP230102776, Wootten D, Belousoff M & Josephs T, Structure and dynamics of class B1 G protein coupled receptors.

ARC Discovery Project 2023, DP230102777, Wootten D, Hutchinson D, The physiological importance of GLP-1R and GIPR dimerization.

ARC Linkage Infrastructure, Equipment and Facility 2023, LE 230100099, Hanssen E, Ghosal D, McFadden G, Rouiller I, Parker M, Ivanova E, Wootten D, Belousoff M, Lucet I, Czabotar P, Bouwer J, Cryo correlative Focused Ion Beam, a new frontier in structural biology.

CUREator grant (MRFF), Griffin M, Advancing a new target identified for inflammatory bowel disease.

CUREator Grant (MRFF), Langmead C, Stewart G, [Phrenix Therapeutics]. New approaches to improve cognition.

Dementia Australia Research Foundation Faye Williams Innovation Grant. Parker MW, Crack P, Hermans S, Gooi J. A new approach to tackle Alzheimer's disease.

MRFF 2021 Genomics Health Futures Mission Stream 1, 2016760, Vandenberg J, Ng CA, Cox C, Wu K, Waters S, Adams DJ, Palmer E, High throughput functional genomics assays for ion channelopathies.

MRFF funding, Czabotar P, Lessene G, Komander D, Pellegrini M, Sleebs B and Call M (WEHI), Charman S (MIPS). Development of COVID-19 antivirals.

MRFF. MRFCTI000025; 2021 mRNA Clinical Trial Enabling Infrastructure. Purcell D, Lewin S, Caruso F, McAuley J, Wheatley AK, Londrigan S, Wang L, Mackenzie J, Anderson D, Williamson D, Corbin VDA, Jacobs J, Rouiller I, Dolcetti R, Godfrey D, McMahon JH. RNA powered antiviral antibodies. NHMRC Development Grant, Wootten D, Stewart G, Development of novel GPR52 agonists for the treatment of schizophrenia.

NHMRC Ideas Grant, ID:2020780, Ralph S, Tilley L, Hanssen E, Cobbolt S, Does finite slowing of feeding cause artemisinin resistance in malaria?

NHMRC Ideas Grant, ID:202167, Poole D, Valant C, Carbone S, Mobbs J. Harnessing endogenous opioids to treat gut motility disorders and pain.

The Michael J Fox Foundation, Ooi L, Single cell metabolomics on Parkinson's disease to understand how changes in lipids and metabolites affect disease onset and progression.

USA Department of Defense, Ooi L, Investigation of ion channel function in motor neurone disease and test novel therapeutics.

Small Grants (<$100,000)

Australian Dental Research Foundation (ADRF) Grant, Paul B, Ye X, Veith P, Ghosal D, Characterisation of the structure and dynamics of oral polymicrobial biofilms using confocal microscopy and cryo-electron tomography.

Australian Society for Medical Research (ASMR) Early Career Researcher Small Grant 2022, Tan W, Harnessing cryo-electron microscopy to study epigenetic regulation associated with the Charcot-Marie-Tooth (CMT) neuromuscular disorder.

Charcot-Marie-Tooth Australia Research Grant, Tan W, Understanding how MORC2 mutations contribute to Charcot-Marie-Tooth disease.

Monash Commercialisation Incubator Program, Riddy D, Wootten D, Sexton P, Stupple P. In vivo assessment of novel small compound series with potential future utility for treatment of obesity.
MRIF grant, Stewart G, GPR52 modulators for the treatment of cognitive impairments associated with schizophrenia.

Career Fellowships

Dr. Shabih Shakeel

Dr. Shabih Shakeel - NHMRC EL2 Investigator Grant. Capturing atomic snapshots to visualise epigenetic silencing machinery for identification of novel therapeutic targets.

Dr. Cindy (Xin) Zhang - ARC DECRA 2023. Cryo-electron microscopy determination of G protein-coupled receptor states.

Dr. Cindy (Xin) Zhang

Awards

Prof. Patrick Sexton

Prof. Patrick Sexton - Gordon Hammes Lectureship Award from the American Chemical Society.

Dr. Alastair Stewart - NHMRC Peter Doherty Investigator Grant Award (Emerging Leadership), 2022 Research Excellence Awards. Structure-function relationships in drug transport and inhibition of membrane proteins.

Dr. Alastair Stewart

Dr. Cindy (Xin) Zhang

Dr. Cindy (Xin) Zhang -- Mollie Holman Medal 2022, Understanding structure and activation of GLP1R.

Conference Awards

Dr. Fabian Bumbak, Best Early Career Oral Presentation Award at ANZMAG, 2022 Dec 5, Dynamics of neurotensin receptor 1 (NTS1) allostery and signaling bias.

Dr. Fabian Bumbak

Dr. Bronte Johnstone

Dr. Bronte Johnstone, Oral presentation award at SCANZ Crystal-Lite ECR Meeting, 2022 May 20, Bacterial competition between prominent gut microbial species is mediated by a bacterial toxin with a novel structural fold.

Lucy Fitschen, Poster Presentation Award at 27th Australian Conference on Microscopy and Microanalysis, 2023 Jan 29 - Feb 2, Towards the cryo-EM structure of the bacteriophage lambda EATR Complex.

Lucy Fitschen

Dr. Alice Shin

Dr. Alice Shin, Presentation Award Runner Up at ANU Research School of Biology HDR Conference, 2023 April 5, Structural investigation pathogenic yeast Candida albicans multi-drug efflux ABC transporter (CalbCDR1) using Cryo-EM.

Jessica Lu, Poster Presentation Award at Lorne Proteins, 2023 Feb 5-9, Characterisation of the transducer coupling profiles of PAC1 receptor splice isoforms.

Jessica Lu

MariaKatarina Lambourne

MariaKatarina Lambourne, Best Poster Runner Up at ARC CCeMMP Symposium, 2022, Sept 1 . The cryo-EM structure of the Erf annealase provides insights into its molecular mechanisms and evolution.

Other Achievements

Prof Patrick Sexton and Prof Arthur Christopoulos have been included in the list of the world's most influential researchers as 2022 Clarivate analytics Highly Cited Researchers in two separate categories 'Pharmacology & Toxicology' and 'Biology & Biochemistry'

Dr. Natalie Diepenhorst -Advancing Women's Success Award 2023, $10,000 in research funding and professional coaching.

Prof. Arthur Christopoulos

Prof. Patrick Sexton

Dr. Natalie Diepenhorst

Of the world's population of scientists and social scientists, Highly Cited Researchers™ are 1 in 1,000.

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Academic Promotions

- A/Prof. Karen Gregory promoted to Level D
- Dr. Josh Hardy promoted to Level B
- Prof. Lezanne Ooi promoted to Level E
- Dr. Lisanne Spenkelink promoted to Level B1.
- A/Prof. Gökhan Tolun promoted to Level D
- Prof. Denise Wootten promoted to Level E

A/Prof. Karen Gregory

Dr. Josh Hardy

Prof. Lezanne Ooi

Dr. Lisanne Spenkelink

A/Prof. Gökhan Tolun

Prof. Denise Wootten

Conference Presentations

International Conference Presentation (invited)

Dr. Jodi Brewster - Discover BMB 2023, 25-28 Mar 2023, Seattle, USA. Structures and kinetics of Thermotoga maritima MetY reveal insights into the predominant route for methionine biosynthesis in bacteria. *Herbert Tabor Early Career Investigator Award.

A/Prof. Karen Gregory – 96th Annual Meeting of the Japanese Pharmacological Society, 30 Nov - 3 Dec 2022, Yokohama, Japan. Fine-tuning glutamate receptor activity with allosteric modulators for psychiatric and neurodegenerative disorders.

Prof. Eric Hanssen - Queenstown Research Week 2022, 30 Aug 2022, Queenstown, NZ. Cryo-electron microscopy at the Bio21 Ian Holmes Imaging Centre.

A/Prof. Lezanne Ooi - International Society of Neurochemistry - Asia Pacific Society for Neurochemistry Meeting 2022, 29 Aug 2022, Honolulu, USA. Disparate phenotypes of microglia in Alzheimer's Disease in vitro.

A/Prof. Lezanne Ooi - 3rd Annual Meeting of Aisa Pacific Association for Neural Transplantation and Repair, 14 Oct 2022, Hobart, Australia. Reversing early phenotypes of neurodegeneration in Alzheimer's disease iPSC-derived neurons.

Prof. Patrick Sexton - RegPep24 2022, 3 Aug 2022, Stirling, Scotland. Understanding the structure, ligand-binding and function of family B G Protein-coupled receptors.

Prof. Patrick Sexton - ENDO Annual Conference 2022, 12 Jun 2022, Atlanta, USA. Structure and dynamics of calcitonin family receptor.

Prof. Patrick Sexton - 27th American Peptide Symposium 2022, 16 Jun 2022, Whistler, Canada. Structure and dynamics of class B peptide hormone G protein-coupled receptors.

Prof. Patrick Sexton - 11th Conference of the International Chemical Biology Society 2022, 4-7 Dec 2022, Brisbane, Australia. Harnessing cryo-EM to probe G protein-coupled receptor structure and function.

4GPCRnet 2022

Dr. Shabih Shakeel - 2022 Joint Congress of ABA, APPA and Taiwan Biophysics Society, 22-26 Jun 2022, Tainan, Taiwan. Structures of protein complexes involved in Fanconi anemia DNA repair.

Prof. Antoine van Oijen - Gordon Research Conference Single Molecule Approaches to Biology 2022, 7 Jul 2022, Barcelona, Spain. Single-molecule studies of DNA replication.

Prof. Denise Wootten - 4GPCRnet 2022, 26-29 Sept 2022, Leipzig, Germany. Mechanistic insights into class B1 GPCR signalling and allostery.

International Conference Presentation (selected oral presentation)

Dr. Brian Cary - 4GPCRnet 2022, 26-29 Sept 2022, Leipzig, Germany. Structural and functional diversity among agonist-bound states of the GLP-1 receptor.

A/Prof. Karen Gregory - Dr. GPCR Summit 2022, 10-16 Oct 2022, online. Fine-tuning glutamate receptor activity with allosteric modulators for neurodegenerative and psychiatric disorders.

Dr. Aidan Grosas - International Conference on the Lens 2022, 6 Dec 2022, Hawaii, USA. Structural, functional, and mechanistic basis for the oligomerisation of the major eye lens protein βB2-crystallin.

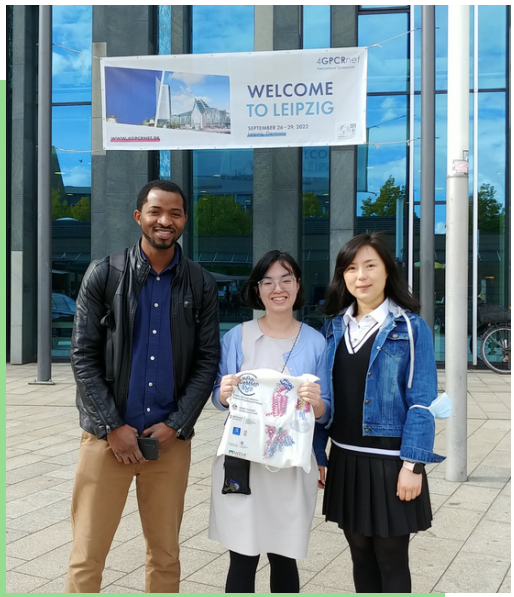
Dr. Sepideh Valimehr - Gordon Research Seminar on 3-D Electron Microscopy 2022, 18-19 Jun 2022, Barcelona, Spain. Conformation and dynamics of the AAA ATPase p97.

International Conference Presentation (posters)

Dr. Natalie Diepenhorst - EMBO Workshop 'In situ structural biology: from cryo-EM to multi-scale modelling', 8-11 Feb 2023, online/Heidelberg, Germany. CryoEM to enable drug discovery at orphan G protein-coupled receptor GPR88.

Jessica Lu - 2nd IRN iGPCRnet Meeting 2022, 30 Sept - 1 Oct 2022, Würzburg, Germany. Characterisation of the transducer coupling profiles of PAC1 receptor splice isoforms.

Jessica Lu - 4GPCRnet 2022, 26-29 Sept 2022, Leipzig, Germany. Characterisation of the transducer coupling profiles of PAC1 receptor splice isoforms.



4GPCRnet 2022

Dr. Sarah Piper - 4GPCRnet 2022, 26-29 Sept 2022, Leipzig, Germany. Dynamic drug targets: Using Cryo-EM data and MD simulations to create realistic 3D animations of class B1 GPCR activation.

Dr. Sepideh Valimehr - Gordon Research Conference on 3-D Electron Microscopy 2022, 19-24 Jun 2022, Barcelona, Spain. Technical advances in 2DEM to study biological structures across scales.

Dr. Sepideh Valimehr, Dr. Mohsen Kazemi, A/Prof. Isabelle Rouiller - Gordon Research Conference on 3-D Electron Microscopy 2022, 19-24 Jun 2022, Barcelona, Spain. The impact of the disease-associated mutant on the dynamic & conformation of the AAA+ ATPase p97.

Dr. Cindy Zhang - 4GPCRnet 2022, 26-29 Sept 2022, Leipzig, Germany. Structural insights into GLP-1R activation and allosteric modulation by non-peptidic ligands.

National Conference Presentation (invited)

Dr. Alisa Glukova -14th Australian Peptide Conference, 8-13 May 2022, Gold Coast. Understanding ligand binding to GPCR using cryo-EM.

A/Prof. Michael Griffin - ComBio, 27-30 Sept 2022, Melbourne. Structures of the interleukin 11 signalling complex reveal dynamics of GP130 extracellular domains and a surprising inhibitory mechanism of a cytokine variant.

Dr. Aidan Grosas - 13th ACT Mass Spectrometry Symposium, 24 Nov 2022, Canberra. Using native ion-mobility mass spectrometry coupled to SEC to elucidate the oligomerisation pathway of the eye lens protein betaB2-crystallin.

Prof. Chris Langmead - RACI National Congress, 3-8 Jul 2022, Brisbane. Cryo-EM-enabled orphan GPCR drug discovery.

Yao Lu - Neurotherapeutics Symposium, 26 Oct 2022, Melbourne. Using cryo-EM to enable novel CNS drug discovery.

Yao Lu - Dr. GPCR Symposium on 'Recent Advances in Understanding Challenging GPCRs', 24 Mar 2023. Molecular and structural characterisation of GPR52, a novel target for schizophrenia.

MariaKatarina Lambourne, Dr. Jodi Brewster, Lucy Fitschen, A/Prof. Gökhan Tolun - Australian Society for Microbiology Conference, 11-14 Jul 2022, Sydney. Half a century after their discovery, cryo-EM structures of Red**β** and Erf annealases provide insights into their evolution & molecular mechanisms.

A/Prof. Lezanne Ooi - 40th Annual Scientific Meeting of the Australian Neuroscience Society, 5-7 Dec 2022, Melbourne. Disease mechanisms and drug discovery in ALS stem cell models: past, present and future.

Dr. Lisanne Spenkelink - Bugs by the Beach, 9 Dec 2022, Wollongong. E. coli DNA replication does not require ATP.

27th Australian Conference on Microscopy and Microanalysis

Dr. David Thal - ComBio, 27-30 Sept 2022, Melboourne. Two for one: the clinical candidate xanomeline displays a dual orthosteric and allosteric binding profile at the M4 muscarinic acetylcholine receptor.

A/Prof. Gökhan Tolun - 27th Australian Conference on Microscopy and Microanalysis, 29 Jan-2 Feb 2023, Perth. A half a century long wait is over: Cryo-EM structure of Red**β**177 provides insights into the evolution and molecular mechanisms of single strand annealing homologous DNA recombination.

Prof. Denise Wootten - 4th Immunometabolism Symposium, 15 Jul 2022, Melbourne. Harnessing cryo-EM to probe the structure and function of GPCRs involved in metabolic functions and disease.

Prof. Denise Wootten - Innovation2Translation Symposium, 19 May, 2022 Melbourne. Harnessing cryo-EM to probe G protein-coupled receptor structure and function - application to GPCR drug discovery and development.

Prof. Denise Wootten - Melbourne Protein Group Symposium, 22 Jul 2022, Melbourne. Structure and dynamics of class B peptide hormone G protein-coupled receptors.

National Conference Presentation (selected oral presentation)

Dr. James Bouwer - eResearch Australasia Conference, 20-22 Oct 2022, Brisbane. Managing big-data and processing in cryogenic cryo-electron microscopy.

Dr. Fabian Bumbak* - ANZMAG, 4-8 Dec 2022, Marysville. Dynamics of neurotensin receptor 1 (NTS1) allostery and signaling bias. *Best Early Career Oral Presentation Award

A/Prof. Karen Gregory - ASCEPT-APSA, 29 Nov-2 Dec 2022, Perth. Fine-tuning glutamate receptor activity with allosteric inhibitors for neurodegenerative and psychiatric disorders.

CCeMMP Embedded Satelite Meeting, Lorne Proteins 2023

Dr. Bronte Johnstone* - SCANZ Crystal-Lite, 19-20 May 2022, Melbourne. Bacterial competition between prominent gut microbial species is mediated by a bacterial toxin with a novel structural fold. *Oral Presentation Award

Dr. Jesse Mobbs - ASCEPT-APSA, 29 Nov-2 Dec 2022, Perth. Cryo-EM structure of the human P2X1 purinoceptor for use in male contraception.

Dr. Jesse Mobbs - Lorne Proteins CCeMMP Satellite Session, 7 Feb 2023, Lorne. Cryo-EM structures of human arachidonate 12S-Lipoxygenase (12-LOX) bound to endogenous and exogenous inhibitors.

Dr. Sarah Piper - Lorne Proteins CCeMMP Satellite Session, 7 Feb 2023, Lorne. The role of functional disulphide bonds in G protein-coupled receptors using integrative structural approaches.

CCeMMP Embedded Satelite Meeting, Lorne Proteins 2023

Dr. Lisanne Spenkelink - Australian Society for Biophysics Meeting, 20-23 Nov 2022, Hobart. Single-molecule genotyping of thousands of variants.

Dr. Winnie Tan - SCANZ Crystal-Lite, 19-20 May 2022, Melbourne. Mechanism of inhibition and activation of MORC2 ATPase.

Dr. Sepideh Valimehr - SCANZ Crystal-Lite, 19-20 May 2022, Melbourne. Structure and dynamic studies of the AAA+ ATPase p97.

National Conference Presentation (posters)

Joydeep Baral, A/Prof. Isabelle Rouiller - ComBio, 26-30 Sept 2022, Melbourne. Structure-function insight into the two-component DNA repair system of Mycobacterium tuberculosis.

Dr. Jason Cao - Lorne Proteins, 5-7 Feb 2023, Lorne. Toward a structural understanding of amylin receptor phenotype: implications for therapeutic development for obesity.

Dr. Brian Cary - SCANZ-Crystal Lite, 19-20 May 2022, Melbourne. Prolonged signaling of backbone-modified glucagon-like peptide-1 analogues with diverse receptor trafficking.

Poster session Australian Conference on Microscopy & Microanalysis

Lucy Fitschen - 27th Australian Conference on Microscopy and Microanalysis, 29 Jan - 2 Feb 2023, Perth. Towards the cryo-EM structure of the bacteriophage lambda EATR complex.

Dr. Mohsen Kazemi, A/Prof. Isabelle Rouiller - ComBio, 27-30 Sept 2022, Melbourne. ENRICH: a fast method to improve the quality of flexible macromolecular reconstructions.

Jessica Lu - Lorne Proteins, 5-7 Feb 2023, Lorne. Characterisation of the transducer coupling profiles of PAC1 receptor splice isoforms. *Poster Presentation Award

Yao Lu - Lorne Proteins, 5-7 Feb 2023, Lorne. Agonist-mediated GPR52 trafficking and their binding pocket revealed by cryo-EM.

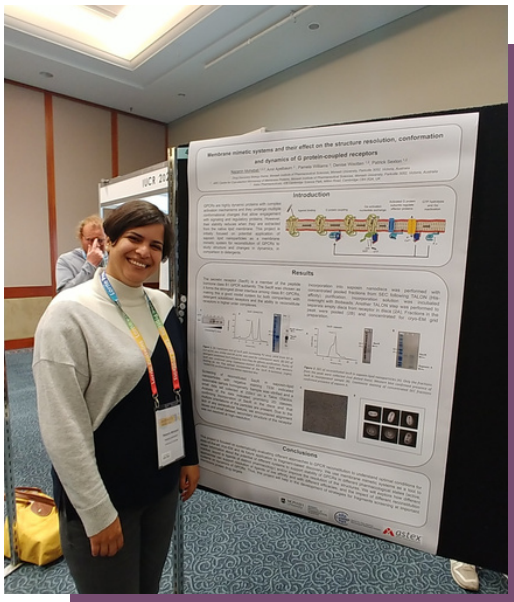
Yao Lu - ComBio, 27-30 Sept 2022, Melbourne. Agonist-mediated GPR52 trafficking and their binding pocket revealed by cryo-EM.

Dr. Mehdi Matak, Dr. Sepideh Valimehr, Dr. Mohsen Kazemi, A/Prof. Isabelle Rouiller - ComBio, 27-30 Sept 2022, Melbourne. Structural and functional characterisation of AAA+ ATPase p97 protein homologs from malaria parasite.

Jordan Nicholls - 27th Australian Conference on Microscopy and Microanalysis, 29 Jan - 2 Feb 2023, Perth. A ball with BALF2: Characterisation of an essential epsterin-barr virus annealase.

Isabella Russell - Lorne Proteins, 5-7 Feb 2023, Lorne. Stabilisation Methods for the Parathyroid Receptor 1 and its Constitutively Active Mutants.

Jack Tovey - Lorne Proteins, 5-7 Feb 2023, Lorne. A Structural Investigation into the Allosteric Regulation of the Cholecystokinin Type 1 Receptor.



Poster session Lorne Proteins, 2023

Academic Presentations

Dr. James Bouwer - Masterclass, Monash University, Parkville, 30 Aug 2022. Imaging at 200keV on mid-range instruments.

Dr. Wessel Burger - PhD submission seminar, Monash University, Parkville, 10 Jun 2022. Mechanisms of Allosteric Modulation at the Muscarinic Acetylcholine Receptors.

A/Prof. Karen Gregory - led panel discussion with Dr. Matt Belousoff, Prof. Chris Langmead, Dr. Sarah Piper, Monash University, Parkville, 6 Apr 2023. Expert views on cryo-EM.

Dr. Aidan Grosas - School of Science, Western Sydney University, Sydney, 21 Oct 2022. More than meets the eye - the oligomerisation of lens crystallin proteins.

Dr. Tracy Josephs - Monash University, 23 Mar 2022. A pharmacogenomic and structural-dynamic approach to inform autosomal dominant hypocalcaemia treatment.

Coventry 2022

Prof. Chris Langmead - Monash Biomedicine Discovery Institute Seminar Series, Monash University, Jun 7 2022. Orphan GPCRs as novel targets in neuropsychiatry.

Jessica Lu - University of Leeds, Leeds, UK 5 Oct 2022. Optimisation of the protein purification of the PAC1 receptor splice isoforms in complex with Gs.

Prof. Megan Maher - CCeMMP Seminar Series, 9 Aug 2022, online. Structural insights into manganese transport across membranes.

Prof. Lezanne Ooi - MIPS Neuro Tea and Talk, Monash University, 16 Jun 2022. Neuronal excitability changes and early phenotypes of neurodegeneration.

Prof. Lezanne Ooi - Japan Society for the Promotion of Science, online, 24 Nov 2022. Lipid alterations and an increased susceptibility to ferroptosis in Alzheimer's disease neurons.

Dr. Sarah Piper – Coventry University, Coventry, UK, 4 Oct 2022. Dynamic drug targets: Using cryoEM and MD simulations to understand peptide binding and selectivity of VPAC receptors.

Dr. Sarah Piper - Australia Biochemistry Lunch Seminar 'Making Futures',online, 14 Nov 2022. Dynamic drug targets: using cryo-EM data and MD simulations to create realistic 3D animations of GPCR complexes.

Dr. Sarah Piper - Osnabrück University, Osnabrück, Germany, 10 Oct 2022. Using CryoEM, MD simulations and 3D animations to understand GPCR activation.

Prof. Patrick Sexton - Department of Chemistry, Monash University, Clayton, 7 Nov 2022. Using cryo-EM to interrogate peptide hormone GPCR structure and dynamics.

Prof. Patrick Sexton - University of Glasgow, Glasgow, Scotland, 1 Aug 2022. Structural insight into ligand binding and activation of class B peptide hormone GPCRs.

Prof. Patrick Sexton - Tianjin University, China, online, 17 Jan 2023. Understanding structure and activation of amylin and calcitonin receptors.

Dr. Alastair Stewart - Max Planck Institute for Multidisciplinary Sciences, Göttingen, Germany, 21 Apr 2023. Bacterial ATP synthases.

Dr. Alastair Stewart - ANU Research School of Biology, ANU, Canberra, 30 Mar 2023. How we think APT synthase works.

Dr. David Thal - CCeMMP Seminar series, online, 13 Sept 2022. The ups and downs of structure-based drug discovery.

Prof. Antoine van Oijen - University of Melbourne Physics Colloquium, University of Melbourne, 7 Jun 2022. Biophysics at the nanoscale, one molecule at a time.

Dr. Cindy (Xin) Zhang - MRC Laboratory of Molecular Biology, Cambridge, UK, 3 Oct 2022. Structural insights into GLP-1R activation and allosteric modulation by non-peptidic ligands.

Coventry University October 2022

Dr. Cindy (Xin) Zhang - Coventry University, Coventry, UK, 4 Oct 2022. Structural insights into GLP-1R activation and allosteric modulation by non-peptidic ligands.

Academic Presentations (oral presentation at local meetings)

Dr. Jason Cao - Peptide Users Group Winter Symposium, 17 Jun 2022, online. Toward a structural understanding of amylin receptor phenotype: implications for therapeutic development for obesity.

Cameron Fairweather - 10th Annual DDB Student Symposium, Monash University, 9 Sept 2022, Parkville. Investigating the structural dynamics and signaling of amylin receptors.

Lucy Fitschen - Bugs by the Beach, 9 Dec 2022, Wollongong. Towards the cryo-EM structure of phage **λ** EATR complex.

Marialena Georgopoulou - Graduate Research Conference, University of Melbourne, 4 Oct 2022, Parkville. Structural studies of cell signalling receptors.

Dr. Aidan Grosas - 4th Proteostasis and Disease Symposium, 22 Nov 2022, Wollongong. Structural, functional, and mechanistic basis for the oligomerisation of the major eye lens protein **β**B2-crystallin.

Dr. Rachel Johnson - ARC CCeMMP Annual Research Symposium, 1 Sept 2022, Melbourne. Applications of cryo-EM for drug discovery programs: from conformational dynamics to inactive state structures.

Riya Joseph - Graduate Research Conference, University of Melbourne, 4 Oct 2022, Parkville. Structural studies of cholesterol-dependent cytolysins-like proteins.

Jordan Nicholls - Bugs by the Beach, 9 Dec 2022, Wollongong. Structural characterisation of BALF2 annealase by cryo-EM.

Dr. Sarah Piper - ARC CCeMMP Annual Research Symposium, 1 Sept 2022, Melbourne. Using Cryo-EM data and MD simulations to create realistic 3D animations of class B1 GPCR activation.

Isabella Russell - 10th Annual DDB Student Symposium, Monash University, 9 Sept 2022, Parkville. The mysterious life of receptors.

A/Prof. Gokhan Tolun* - ARC CCeMMP Research Symposium, 1 Sept 2022, Melbourne. Cryo-EM structure of phage **λ** annealase Red**β** provides insights into its molecular mechanisms and evolution, half a century after its discovery. *Best Oral Presentation

Jack Tovey - 10th Annual DDB Student Symposium, Monash University, 9 Sept 2022, Parkville. EM for AM: Cryo-electron microscopy for the discovery and development of allosteric modulators.

Maleesha Ubhayarathna - 10th Annual DDB Student Symposium, Monash University, 9 Sept 2022, Parkville. Elucidating pharmacologically relevant ligands at the 5-HT2CR in the treatment of substance use disorders.

Academic Presentations (poster presentation at local meetings)

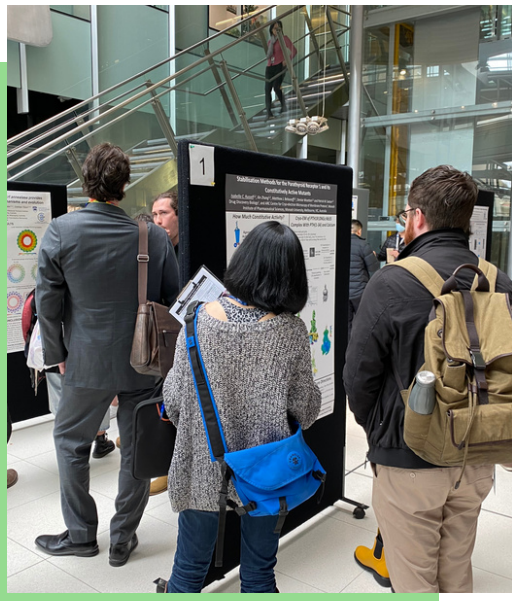
Joydeep Baral, A/Prof. Isabelle Rouiller - ARC CCeMMP Research Symposium, 1 Sept 2022, Melbourne. Structure-function insight into the two-component DNA repair system of Mycobacterium tuberculosis.

Dr. Wessel Burger - ARC CCeMMP Research Symposium, 1 Sept 2022, Melbourne. Structure of xanomeline bound M4 muscarinic acetylcholine reveals an unexpected dual orthosteric and allosteric binding profile.

Dr. Jason Cao - ARC CCeMMP Research Symposium, 1 Sept 2022, Melbourne. Toward a structural understanding of amylin receptor phenotype: implications for therapeutic development for obesity.

Dr. Brian Cary - ARC CCeMMP Research Symposium, 1 Sept 2022, Melbourne. Prolonged signaling of backbone-modified glucagon-like peptide-1 analogues with diverse receptor trafficking.

HaiTian Chen - ARC CCeMMP Research Symposium, 1 Sept 2022, Melbourne. Application of cryo-EM to understand the molecular structure and signal transduction of the Ephrin Receptor Pseudokinase EphA10.



ARC CCeMMP Research Symposium, September 2022

HaiTian Chen - Melbourne Protein Group Student Symposium, 21 Jul 2022, Melbourne. Application of cryo-EM to understand the molecular structure and signal transduction of the ephrin receptor pseudokinase EphA10.

Lucy Fitschen - ARC CCeMMP Research Symposium, 1 Sept 2022, Melbourne. Towards the cryo-EM structure of bacteriophage **λ** EATR complex.

Dr. Mohsen Kazemi, A/Prof. Isabelle Rouiller, Prof. Megan Maher - ARC CCeMMP Research Symposium, 1 Sept 2022, Melbourne. Understanding the structural basis of manganese transport by streptococcus pneumoniae.

MariaKatarina Lambourne* - ARC CCeMMP Research Symposium, 1 Sept 2022, Melbourne. The cryo-EM structure of the Erf annealase provides insights into its molecular mechanisms and evolution. *Best Poster Runner Up

Dongju Lee - 10th Annual DDB Student Symposium, Monash University, 9 Sept 2022, Parkville. Towards structural understanding of GPR151.

Jessica Lu - ARC CCeMMP Research Symposium, 1 Sept 2022, Melbourne. Characterisation of the transducer coupling profiles of PAC1 receptor splice isoforms.

Bhanu Mantri, A/Prof. Gökhan Tolun - ARC CCeMMP Research Symposium, 1 Sept 2022, Melbourne. A preliminary cryo-EM map of human herpes virus 8 ORF6 illustrates the overall structural similarity with herpes simplex virus 1 ICP8 single-stranged annealing homologous recombination protein.

Dr. Nazanin Mohebali - ARC CCeMMP Research Symposium, 1 Sept 2022, Melbourne. Membrane mimetic systems and their effect on structure resolution, conformation and dynamics of GPCRs.

Theodore Nettleton - ARC CCeMMP Research Symposium, 1 Sept 2022, Melbourne. Structure of the pituitary adenylate cyclase activating polypeptide 1 receptor in the apo-state and bound to non-canonical signal transducers.

Jordan Nicholls - ARC CCeMMP Research Symposium, 1 Sept 2022, Melbourne. Characterisation of the essential epstein-barr virus annealase BALF2.

Qinghao Ou - ARC CCeMMP Research Symposium, 1 Sept 2022, Melbourne. Investigating the structure of GIPR/GLP-1R co-agonists in complex with GIPR-G**α**s and GLP-1R-G**α**s.

Qinghao Ou - 10th Annual DDB Student Symposium, Monash University, 9 Sept 2022, Parkville. Investigating the structure of GIPR/GLP-1R co-agonists in complex with GIPR-G**α**s and GLP-1R-G**α**s.

Isabella Russell - ARC CCeMMP Research Symposium, 1 Sept 2022, Melbourne. Stabilisation methods for the parathyroid receptor 1 and its constitutively active mutants.

Isabella Russell - 17th Annual Graduate Research Symposium 2 Nov 2022, Parkville. Stabilisation methods for the parathyroid receptor 1 and its constitutively active mutants.

Publications

1. Brown, HG, Hanssen, E. MeasureIce: accessible on-the-fly measurement of ice thickness in cryo-electron microscopy. Commun Bio, 5:817 (2022). https://doi.org/10.1038/s42003-022-03698-x

2. Bumbak F, Pons M, Inoue A, Paniagua JC, Yan F, Wu H, Robson SA, Bathgate R, Scott DJ, Gooley PR, Ziarek JJ. Ligands selectively tune the local and global motions of neurotensin receptor 1 (NTS1). Cell Reports, 42(1):112015, 2023. https://doi.org/10.1016/j.celrep.2023.112015

3. Cary BP, Zhang X, Cao J, Johnson RM, Piper SJ, Gerrard EJ, Wootten D, Sexton PM. New insights into the structure and function of class B1 GPCRs, Endocr Rev, 44(3):492-517, 2023. https://doi.org/10.1210/endrev/bnac033

4. Dwomoh L, Rossi M, Scarpa M, Khajehali E, Molloy C, Herzyk P, Bottrill AR, Sexton PM, Christopoulos A, Conn PJ, Lindsley CW, Bradley SJ, Tobin AB. M1 muscarinic receptor activation reduces the molecular pathology and slows the progression of prion-mediated neurodegenerative disease. Sci Signal, 15(760), 2021. https://doi.org/10.1126/scisignal.abm3720

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Structures Solved Year 2

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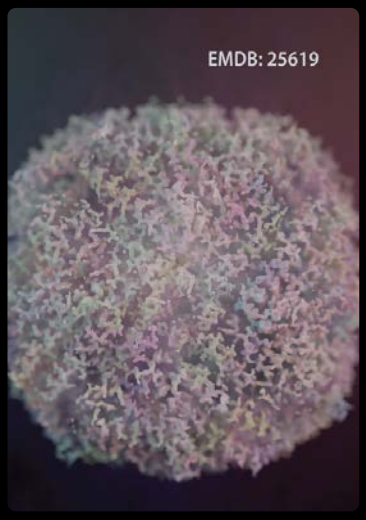
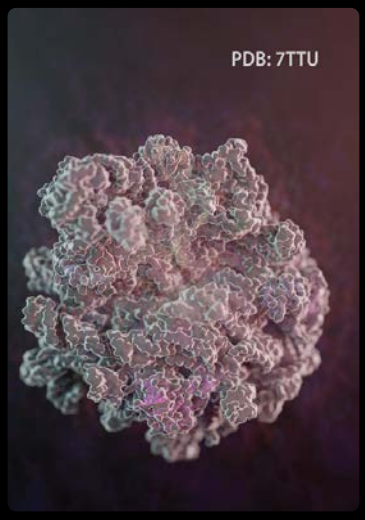
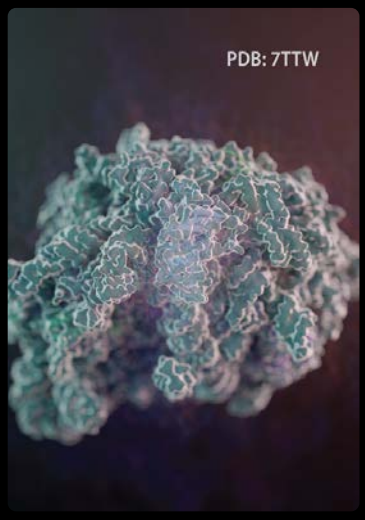
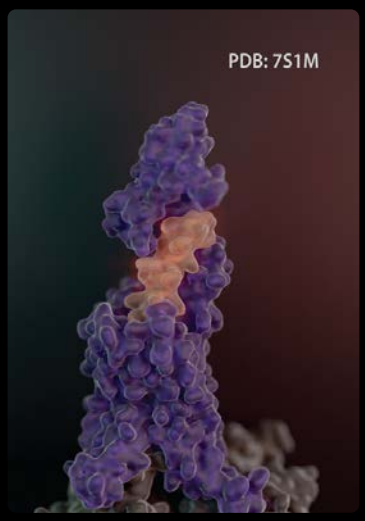
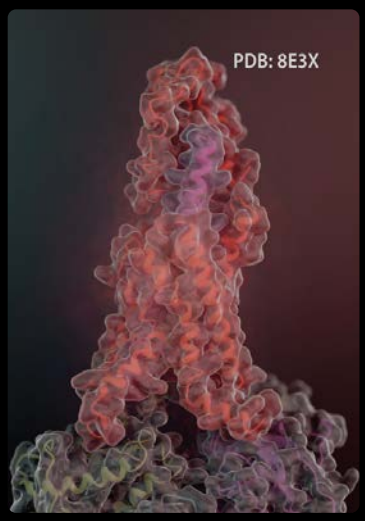
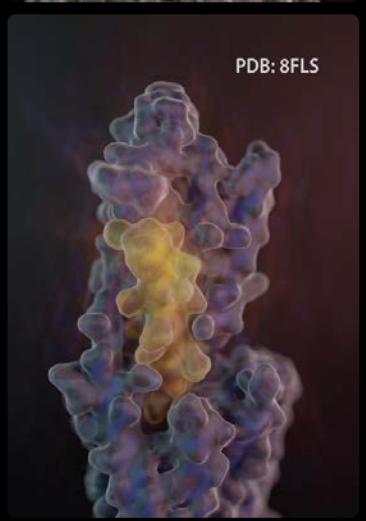


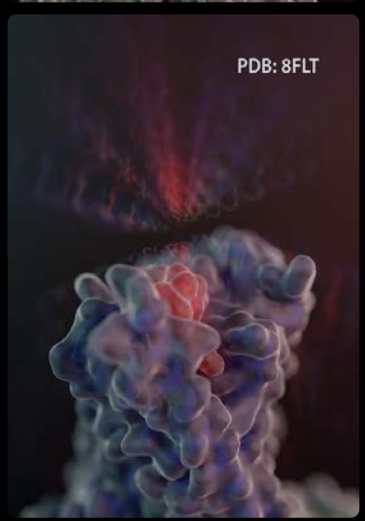


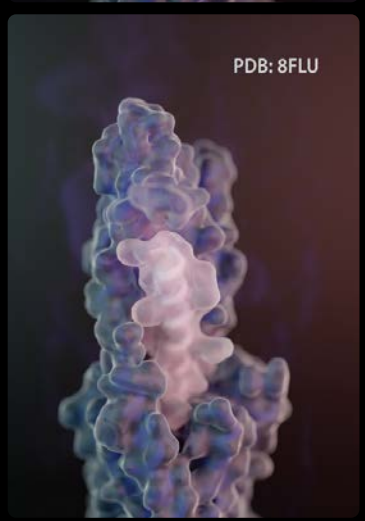




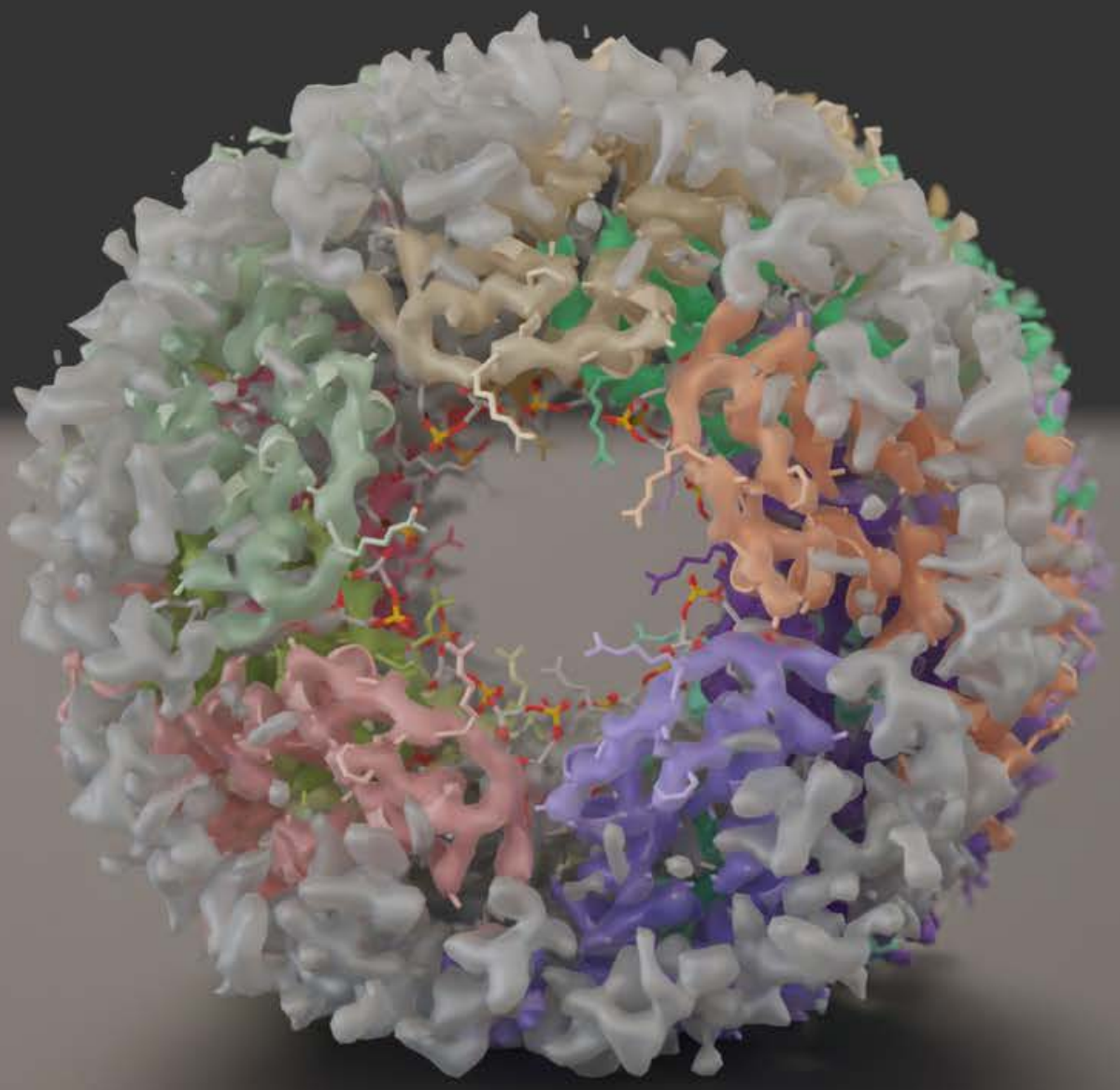








From the UoM/Bio21 node, an extracellular filament structure (~3A) where each of the monomers are membrane proteins and processed before incorporation into the filament. Kreida S, Narita A, Johnson MD, Tocheva EI, Das A, Ghosal, D, Jensen GJ. Cryo-EM structure of the Agrobacterium tumefaciens type IV secretion system-associated T-pilus reveals stoichiometric protein-phospholipid assembly. bioRxiv. doi: https://doi.org/10.1101/2022.09.25.509369. Accepted in Structure.



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