



## SEMINAR SERIES 2025

11 February, 10:00 AM AEDT

### Prof. Isabelle Rouiller

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Professor Isabelle Rouiller is the Deputy Director and University of Melbourne Node Leader of CCEMMP. A pioneer in the field of cryo-electron microscopy (cryo-EM), she has applied this technique for over 20 years to study macromolecular complexes critical to health and disease. She graduated as a Biochemical Engineer from INSA Lyon in 1994 and obtained her PhD in 1998 for studying the assembly of African Swine Fever Virus at the Institute for Animal Health in the UK. She pursued postdoctoral training in single-particle cryo-EM and electron tomography at The Scripps Research Institute and The Burnham Institute in San Diego, USA. She then established Canada's first cryo-EM facility while building her independent research program at McGill University. In 2017, she relocated to The University of Melbourne, where she is the Head of the Cryo-EM Laboratory for Studies of Molecular Machines, focusing on understanding protein function in health and disease. Her laboratory explores the molecular mechanisms of proteins involved in membrane fusion, including the HIV Env glycoprotein and OPA1/Drp1 GTPases; the potential ion channel TACAN; and the AAA ATPase p97 (also known as VCP, as preferred by patients with gene mutations). Today's seminar will focus on her groundbreaking work on VCP.



### Unravelling VCP Dynamics: Structural Insights into Cellular Homeostasis and DNA Repair

Maintaining cellular homeostasis is crucial for survival, requiring the degradation of damaged proteins and organelles and the regulation of diverse cellular processes. VCP (p97), a conserved ATP-dependent protein remodeler, plays a pivotal role in these processes, including protein degradation, cell cycle regulation, DNA repair, and stress response. Dysfunction in VCP has been linked to various neurodegenerative disorders and has been identified as a therapeutic target for cancer treatment and infectious diseases. In this seminar, Prof. Rouiller will explore the impact of a disease-associated mutation on VCP dynamics. She will introduce a novel cryo-EM-based image analysis method to characterize continuous conformational changes and demonstrate its application in analysing VCP's substrate-binding domain in both wild-type and mutant forms. Additionally, she will present recent findings on VCP's interactions with UBX family cofactors, key regulators defined by their Ubiquitin Regulatory X domain that direct VCP to a range of cellular functions. The seminar will conclude with insights into the mycobacterial DNA-Ku Non-Homologous End Joining (NHEJ) synapsis complex. NHEJ serves as the sole mechanism for repairing double-strand breaks (DSBs) in Mycobacterium tuberculosis during dormancy in host macrophages, and this system provides a robust model for studying how VCP homologs disassemble Ku during DNA repair. This research not only deepens our understanding of the molecular mechanisms underlying VCP function but also demonstrates the power of combining structural and biochemical approaches to tackle complex biological questions.