CeMMP Centre for Cryo-electron Microscopy of Membrane Proteins

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Dr. Matthew Doyle

Sydney Infectious Diseases Institute,
Sydney Drug Discovery Initiative,
School of Medical Sciences, Faculty of Medicine and Health,
The University of Sydney

Dr Matt Doyle completed his PhD in 2015 at the Research Centre for Infectious Diseases (University of Adelaide) with A/Prof (Hon) Renato Morona. Dr Doyle then spent 6 years in the US conducting fundamental research within the Protein Biogenesis Section with Dr Harris Bernstein (NIDDK/NIH) where he received the NIDDK Director's Award (Individual) (2020) in recognition of the development of a new method to study the function of a potential antibiotic target. In June 2022, Dr Doyle relocated to The University of Sydney to establish a laboratory focused on Bacterial Outer Membrane Biogenesis. Recently, he has contributed a set of papers published in Nature Communications, Molecular Cell, and Cell that combined protein design, in vivo crosslinking, biochemistry, and structural biology techniques to uncover steps in the transmembrane β-barrel folding and autotransporter protein secretion pathways. He argues that this fundamental information is critical for understanding how bacteria cause disease, how better antibiotics can be designed, and how bioprocessing technologies can be improved.

Protein folding within the bacterial outer membrane.

The Gram-negative bacterial outer membrane (OM) is densely packed with β-barrel outer membrane proteins (OMPs) which vary greatly in size (8-36 strands). Despite their structural and functional diversity, almost all newly synthesised OMPs are folded and integrated into the OM by the essential Barrel Assembly Machine (BAM). However, the molecular process of OMP folding by BAM has remained largely a mystery. Major questions include: (1) how are new OMPs recognized by BAM? (2) what are the intermediate stages of OMP folding? (3) what is the energy source for folding? To solve these questions, we tracked protein folding in bacterial culture and observed folding intermediates in native-nanodiscs by CryoEM. Our data leads to unique models of OMP biogenesis including a new idea in which the OM macrostructure can power OMP folding at the molecular level.