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Title: Revealing the Roles of Lipids and Drugs in Mediating Membrane Protein Function

Abstract: Spanning the membranes of the cell, membrane proteins act as biological gatekeepers often working as part of large molecular machines to control the flow of essential biomolecules such as salts, nutrients and even other proteins across these hydrophobic barriers. They comprise approximately 40% of the human proteome and 60% of drug targets, but many aspects of their structural biology are still poorly understood. Membrane proteins remain difficult to study using classical approaches due to their hydrophobic nature and enigmatic interactions with the lipid bilayer. New techniques are therefore required, particularly to help us understand the interactions with small molecules such as lipids and drugs that mediate their function.

Following the discovery that membrane protein complexes could be transferred into the gas phase in their native state, if protected by an appropriate vehicle (such as detergent micelles), native or non-denaturing mass spectrometry has recently emerged as an especially promising technique. Using Q-ToF mass spectrometry we have shown that membrane proteins can be stabilized by specific lipids (Laganowsky *et al.* 2014 Nature 510,172) and that drugs and lipids can affect their conformations (Marcoux *et al.* 2013 PNAS 110, 24, 9704). However, due to the limited spectral resolution these studies have been restricted to exogenous lipids and precluded direct identification of binding partners that have co-purified with the protein.

In order to overcome these issues, we recently reported high-resolution Orbitrap mass spectrometry of membrane protein complexes (Gault *et al.* 2016 Nature Methods 13, 333). The development of this technique and new data on its application will be presented.

Short biography: Dr. Joseph Gault is a postdoctoral researcher and Junior Research Fellow at The Queen's College, Oxford. Following a PhD in top-down mass spectrometry with Dr. Julia Chamot-Rooke (Institut Pasteur & Ecole Polytechnique, Paris, France) he joined Prof. Dame Carol Robinson's group at the University of Oxford to develop high-resolution native mass spectrometry. His current research focuses on understanding the synergistic relationship between membrane proteins and lipids. In particular, how specific membrane protein-lipid interactions regulate substrate transport, and how lipid binding has evolved across different species.