THE UNIVERSITY OF BRITISH COLUMBIA
Department of Biochemistry & Molecular Biology
Faculty of Medicine

THE UNIVERSITY OF BRITISH COLUMBIA
Department of Cellular & Physiological Sciences
Faculty of Medicine

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THE CENTRE FOR BLOOD RESEARCH

Department of Biochemistry & Molecular Biology, Department of Cellular & Physiological Sciences, and Centre for Blood Research

INVITES YOU TO A SEMINAR ON

Thursday, March 28 @ 12:30PM – 1:30PM | LSC 3

"Structural Studies of Macrophage Immune Effectors Using Cryo-EM"

Dr. James Whisstock

Professor, Biochemistry & Molecular Biology, Monash University
Laureate Fellow, Australian Research Council
Director, ARC Centre of Excellence in Advanced Molecular Imaging
Scientific Head, EMBL Australia

Macrophage Expressed Gene-1 (MPEG-1; also termed Perforin-2) is an endosomal / phagolysosomal perforin-like protein that is conserved across the metazoan kingdom and that functions within the phagolysosome to damage engulfed microbes. Like the Membrane Attack Complex and perforin, MPEG-1 has been postulated to form pores in target membranes, however, its mode of action remains to be established. We used single particle cryo-Electron Microscopy to determine the 2.4 Å structure of a hexadecameric assembly of MPEG-1 that displays the expected features of a soluble pre-pore complex. We further discovered that the MPEG-1 pre-pore-like assemblies can be induced to perforate membranes through mild acidification, such as would occur within maturing phagolysosomes. We next solved the 3.6 Å cryo-EM structure of MPEG-1 in complex with liposomes. Remarkably these data revealed that a C-terminal Multi-vesicular body of 12 kDa (MVB12)-associated b-prism (MABP) domain interacts with target membranes in a mode that positions the pore forming machinery of MPEG-1 to point away from the bound membrane. This unexpected mechanism of membrane interaction raises the intriguing possibility that MPEG-1 may be able to remain bound to the phagolysosome membrane while simultaneously forming pores in engulfed bacterial targets.

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