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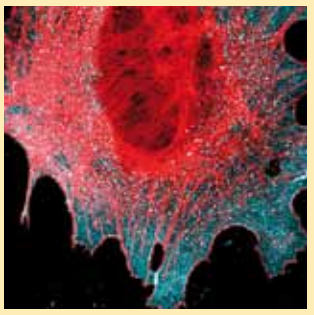
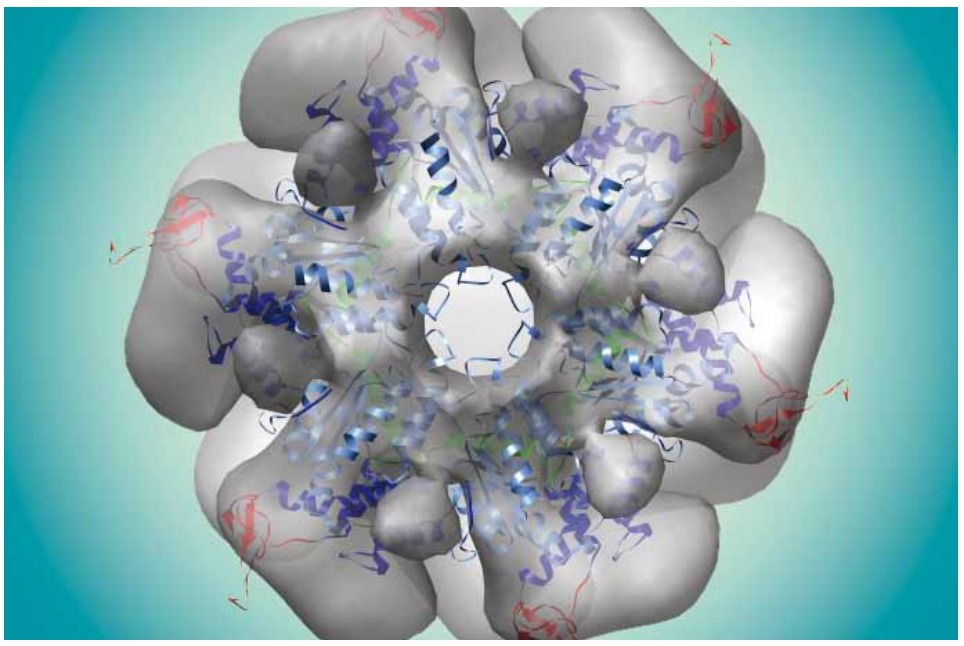
AUSTRALIAN MICROSCOPY & MICROANALYSIS RESEARCH FACILITY



RESEARCH



The structure of the Vps4 protein as determined by cryo-TEM. It has six-fold rotational symmetry, and is 14 nanometres in diameter. Important regions of the protein backbone are highlighted in the form of a ribbon, superimposed on the single-particle density map.

Lightening the impact of HIV and Ebola

AMMRF @ UQ

Understanding protein structure is hugely important if we are to design specific drugs to alter a protein's function. This is exactly what Dr Michael Landsberg and colleagues have been doing at the high-throughput cryo-TEM facility at the University of Queensland.

Dr Landsberg – in conjunction with A/Prof. Ben Hankamer, Rosalba Rothnagel, Dr Parimala Vajjhala from the University of Queensland's Institute for Molecular Bioscience (IMB) and Griffith University's Dr Alan Munn – has taken an important step in the characterisation of a viral infection pathway that may potentially lead to the development of new drugs targeting a broad range of viruses including human immunodeficiency virus (HIV) and Ebola. They have recently solved the 3-D structure of a key control enzyme in the pathway of enveloped virus infection. This is where viruses become wrapped in envelopes of cell membrane and bud off the cell. The potential of this important research has been recognised through its publication in the international journal *Structure* in March 2009.

The enzyme, Vps4, normally controls the budding of small, lipid-enclosed vesicles from cell membranes; these vesicles transport proteins and other important molecules to different destinations. Importantly, a number of viruses, including HIV, Ebola, hepatitis and herpes simplex, appear to hijack this budding pathway to facilitate their own spread.

"There is growing evidence that therapeutic strategies that target Vps4 are able to elicit a protective response against infection by at least some of these viruses," Dr Landsberg said. This process was recently demonstrated by a team of scientists in the USA. They observed that 70% of laboratory mice deficient in Vps4 were able to survive injection with an otherwise lethal dose of Ebola virus. Conversely, a survival rate of less than 20% was observed in normal mice, comparable to human survival rates following outbreaks of the most lethal forms of the virus.

"In order to develop new therapeutics that target Vps4, it is critical that we first know the 3-D structure of the biologically-active form of the enzyme," Dr Landsberg said. "Our study gives some insights into this structure and, in so doing, has identified important regions of the enzyme that are required for it to assemble into its fully functional, biologically active form."

The team used a technique known as single particle analysis to determine the 3-D structure of what they believe is the biologically active form of Vps4. This involves using a transmission electron microscope to record tens of thousands of images of individual protein molecules in different molecular orientations, at high magnification. The images are then combined by computational techniques to obtain a structure of the protein in 3-D.

"The next step now is to build on this research and identify parts of Vps4 that can potentially be targeted by drugs, and in so doing block virus infection. This would be a crucial step in preventing the spread of viruses throughout the body and lessening the impact of diseases such as Ebola and HIV on human populations around the world."

The researchers used instruments at the University of Queensland's Centre for Microscopy and Microanalysis (CMM) extensively throughout the project, including the AMMRF flagship high-throughput cryo-TEM facility.

"The state-of-the-art electron microscopy instrumentation accessible to us through the AMMRF certainly means that we have been able to accomplish research outcomes, such as solving the Vps4 3-D structure, on a far more rapid timescale than would be otherwise possible," Dr Landsberg said.

"Drug discovery is a lengthy process, and any technology that can speed up the research stage is welcome." ■

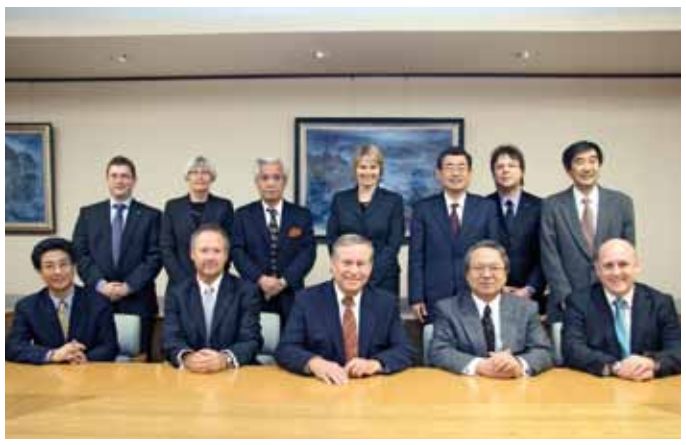
Dr Michael Landsberg at the high-throughput cryo-TEM facility at the CMM, which was used to solve the structure of Vps4.

COMMUNITY

AMMRF and WA Premier talk science in Japan

AMMRF @ UWA

Earlier this year, University of Western Australia Node Director Prof. David Sampson accompanied the Hon. Colin Barnett, MLA, Premier of WA, on his first foray to Japan. A trilateral collaboration exists between the states of WA, Hyogo in Japan and Zhejiang in China, which extends to their major universities. This visit continued to strengthen the collaboration, and the delegation took the opportunity to see first-hand the science and technology infrastructure in the Kobe region. Prof. Sampson was able to advise Premier Barnett as he toured Kobe's impressive Port Island Precinct, dedicated to the biomedical sciences and technology. It houses the Riken Centre for Developmental Biology (CDB) and the Kobe Medical Industry Development Project. The Riken CDB has over 400 staff and extensive microscopy infrastructure centred on live-cell and embryo imaging, which Prof. Sampson took the opportunity to explore in depth. At Kobe University, he briefed the delegation on progress under the Trilateral Collaboration and presented the AMMRF's unique flagship capability in ion microprobes, emphasising the central role played by the State Government in funding core microscopy infrastructure in WA. ■



The Hon. Colin Barnett, MLA, Premier of WA (centre front) and to his right Prof. David Sampson with the WA State Government delegation and officials from Kobe University, including Toshiyuki Nogami, President, Kobe University (to the premier's left).