EM studies of cytochrome bc_1 to elucidate inhibitor binding

Rachel Johnson, University of Leeds

Kangsa Amporndanai[2], Colin Fishwick[1], Samar Hasnain[2], Svetlana Antonyuk[2], Stephen Muench[1]

[1]University of Leeds, UK. [2]University of Liverpool, UK.

Parasitic protozoa are responsible for causing a wide range of devastating diseases. Diseases such as malaria, leishmaniasis, toxoplasmosis and sleeping sickness are a significant global burden with over ~500 million people affected each year. Malaria is caused by the protozoan parasite *Plasmodium falciparum* (*P. falciparum*) and predominately affects people in the developing world. However, resistance is emerging to all current treatments therefore there is an urgent need to develop new medicines. Cytochrome bc_1 is an established anti-parasitic drug target with a number of crystal structures which are bound to highly potent inhibitors. However, the design of compounds which are more selective to the parasitic targets over the model bovine system has been hindered by a lack of structural information of the parasite-derived protein. Elucidating structural information using X-ray crystallography requires large quantities of protein which cannot be obtained from the host parasite therefore alternative strategies, such as Electron Microscopy (EM), are needed. As high-resolution structures are routinely being solved, EM could be used as a tool in drug discovery. In this project, cryo-EM has been used in a proof of principle approach to solve four structures of bovine bc_1 in the absence and presence of three different inhibitors (GSK932121, SCR0911 and JAG021) to ~4 Å resolution. The resolutions attained have enabled the inhibitors to be unambiguously positioned in the density thereby showing that cryo-EM could be used on the parasitic-derived protein.