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Structural biology: A powerful tool to gain insight into the biology of the malaria parasite, Plasmodium falciparum

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Plasmodium falciparum is responsible for the vast majority of malaria cases and deaths, especially in sub-Saharan Africa. Progress towards malaria elimination is hampered by the lack of an effective vaccine, the rapid development of drug-resistant parasites and insecticide-resistant Anopheles mosquito vectors, and insufficient knowledge of the biology of the parasite, in particular of the proteome and gene regulation. The array of sophisticated structural biology techniques available at ESRF and ILL provides a powerful tool to study critically important P. falciparum proteins and their interactions within the parasite. Two potential therapeutic target proteins are currently being investigated: Erythrocyte Binding Antigen, EBA-181, which is required for the invasion of erythrocytes, and PfMyb2, a DNA-binding protein and putative transcription factor.

Biophysical characterization of the RIII–V regions of EBA-181 (EBA-181945–1097) revealed an intrinsically disordered structure. Characterization of the protein at atomic resolution using nuclear magnetic resonance (NMR) spectroscopy showed that it is essentially a statistical coil with several turn motifs but it does not possess transiently populated secondary structures commonly seen in intrinsically disordered proteins that fold via specific, pre-formed molecular recognition elements. Small-angle synchrotron X-ray and neutron scattering experiments confirmed the overall shape of the molecule and suggested also the binding region with its macromolecular receptor.

PfMyb2 localises to the nucleus as demonstrated by an indirect immunofluorescence assay. Gene knockout studies implied that the gene is essential for parasite survival. The N-terminal DNA-binding domains of PfMyb2 were expressed as recombinant his-tagged proteins from a pET-15 vector construct and electrophoretic mobility shift assays (EMSAs) revealed binding to a consensus DNA sequence. To improve solubility of the recombinant PfMyb2, four smaller sections of the DNA binding domains of the gene have been amplified and cloned into pETM-11, a kanamycin-resistant vector, to allow for the production of deuterated protein for structural studies on the PfMyb2-DNA complex.

Envisaged future studies will focus on the role of structural biology in a malaria drug development pipeline. The interaction of lead anti-malarial compounds with their target proteins will provide valuable information to guide optimisation of the lead compounds.

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