ABSTRACT

Title: **Studies on the structure & function of *Pf*HAM1, an atypical nucleotide cleansing protein of the human malignant malaria parasite**
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Index Number: **175/18/Life Sc./26**

Around 247 million cases and 619,000 deaths occurred worldwide in the year 2022 owing to malaria, which lurks around to be recognised as a global public health menace. The prevalence of *P. vivax* and *P. falciparum* is astounding, with the malignant nature of *P. falciparum*. The growth of antimalarial resistance, mainly in Southeast Asia, due to antimalarial overuse and inadequate malaria medicine therapy highlights the urgent need to create more potent and effective antimalarial medications. The DNA of the parasite is constantly under stress by endogenous and exogenous factors. Throughout its intricate life cycle, *Plasmodium falciparum's* DNA sustains unusually high levels of genotoxic damage in both the human host and the vector. The presence of non-canonical nucleotides in the nucleotide precursor pool is a typical cause of endogenous DNA damage that lowers DNA replication fidelity. These aberrant nucleotides have the potential to cause mispairing, which substantially raises the mutation rate and results in transition and transversion mutations if they are incorporated into the growing DNA. Such non-canonical dNTPs may be recognised and hydrolysed to stop DNA deterioration and aid DNA repair mechanisms. This thesis thoroughly describes the *P. falciparum* ortholog of ITPase (*Pf*HAM1), an evolutionarily conserved inosine/xanthosine triphosphate pyrophosphohydrolase. This enzyme transforms non-canonical (d)/ITP and XTP nucleotides into the appropriate monophosphate forms and pyrophosphate. The protein's biophysical, biochemical and genetic analysis was investigated in detail. Also, the first X-ray crystallographic structure of the homodimeric *Pf*HAM1 protein with its critical residues for substrate recognition and metal binding is revealed here. This detailed study of the protein's structure and function will contribute to a better understanding of its role in non-canonical nucleotidic surveillance in the parasite and its overall function in parasite biology.

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30/01/24
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