Loop mobility and secondary structures in parasite-specific inserts are important for function of the *Plasmodium falciparum* S-Adenosyl Methionine Decarboxylase/ Ornithine Decarboxylase

S.Roux, L.Birkholtz, **A.I.Louw**

Department of Biochemistry, School of Biological Sciences, Faculty of Natural and Agricultural Science, University of Pretoria, Pretoria 0002

Malaria is one of the major public health and economical priorities in South Africa. The polyamines putrescine, spermidine and spermine are essential for the proliferation and differentiation of most eukaryotic cells. Inhibition of the polyamine pathway is known to have antitumor and antiparasitic effects. Ornithine decarboxylase (ODC) and S-adenosylmethionine decarboxylase (AdoMetDC) are the rate-limiting enzymes in the polyamine pathway. Usually they are individually regulated on the transcriptional, translational and post-translational level. In the malaria parasite *Plasmodium falciparum*, these enzymes are part of a singly expressed polypeptide. The bifunctional AdoMetDC/ODC protein contains six inserted regions compared to other homologous proteins. These inserts are species-specific, hydrophilic, low complexity-containing segments forming non-globular domains.

To understand the molecular mechanisms of protein inserts in this protein complex, it is necessary to obtain information about their internal structure and interactions. Previous deletion mutagenesis of the inserts in their respective domains rendered the specific decarboxylase inactive and affected the activity of the neighboring decarboxylase. From these studies it were shown that the parasite-specific inserts mediate physical interactions between the domains.

The size of the deletions is possibly responsible for the incorrect folding of the protein that causes the decrease in activity. This study focused on the introduction of point mutations to disrupt the *Plasmodia* conserved α-helices and deletion of conserved β-plates in the inserts, to define the possible interaction areas. These secondary structures proved to be important for the activity of both the protein domains. It was also shown that mobility of a short insert is essential for dimerization of the ODC domain thereby initiating heterotetrameric complex formation.