Haemolytic peptides directed against the malarial blood stages of *Plasmodium falciparum*

Marina Rautenbach[1] and Heinrich C. Hoppe[2]

[1]Department of Biochemistry, University of Stellenbosch, South Africa; mra@sun.ac.za
[2]Division of Pharmacology, University of Cape Town Medical School, South Africa; hhoppe@uctgsh1.uct.ac.za

Malaria affects more than 300 million people in third world countries per year, causing the annual death of at least one million children in Africa. Of particular concern is malaria caused by *Plasmodium falciparum*, of which a large number of strains are drug resistant [1]. The search for new drugs led us to investigate a number of peptides with known antimicrobial and haemolytic activity. Bilayer membranes are the primary targets of these peptides and their interaction with the cell membrane induces a permeability change followed by cell lysis [2]. Such a mechanism of action makes it difficult for organisms to develop resistance, but this non-selectivity is also highly problematic for systemic routes of drug administration. However, we found that the haemolytic activity is beneficial in killing the blood stages of the malaria parasite *P. falciparum*. Erythrocytes infected with the trophozoite stage were particularly vulnerable to lysis.

It is known the malaria parasite alters the protein [3] and lipid composition [4] of the host erythrocyte membrane, which makes the infected cell a possible target. We found that that three of the heamolytic peptides were at least ten times more active against the trophozoite blood stage of the parasite (IC_{50} of 0.5-5 mM), than against uninfected erythrocytes. However, the highly haemolytic peptide from bee-venom, melittin, showed only a three times higher specificity. Also, two highly antimicrobial peptides, but non-haemolytic peptides from *Xenopus laevis*, were virtually inactive. We therefore conclude some haemolytic peptides may be very promising lead compounds for designing a magic bullet against *P. falciparum* infected erythrocytes.

[1] Macreadie I, Ginsburg H, Sirawaraporn W and Tilley L. Antimalarial drug development and new targets. Parasitol Today 2000, 16, 438-444

[2] Oren Z, Shai Y. Mode of action of linear amphipathic α-helical antimicrobial peptides. Eur J Biochem 1996, 237, 303-310

[3] Haldar K, Holder AA. Export of parasite proteins to the erythrocyte in *Plasmodium falciparum*-infected cells. Semin Cell Biol 1993, 4, 354-353

[4] Haldar K. Lipid transport in Plasmodium. Infect Agents Dis 1992, 1, 254-262.