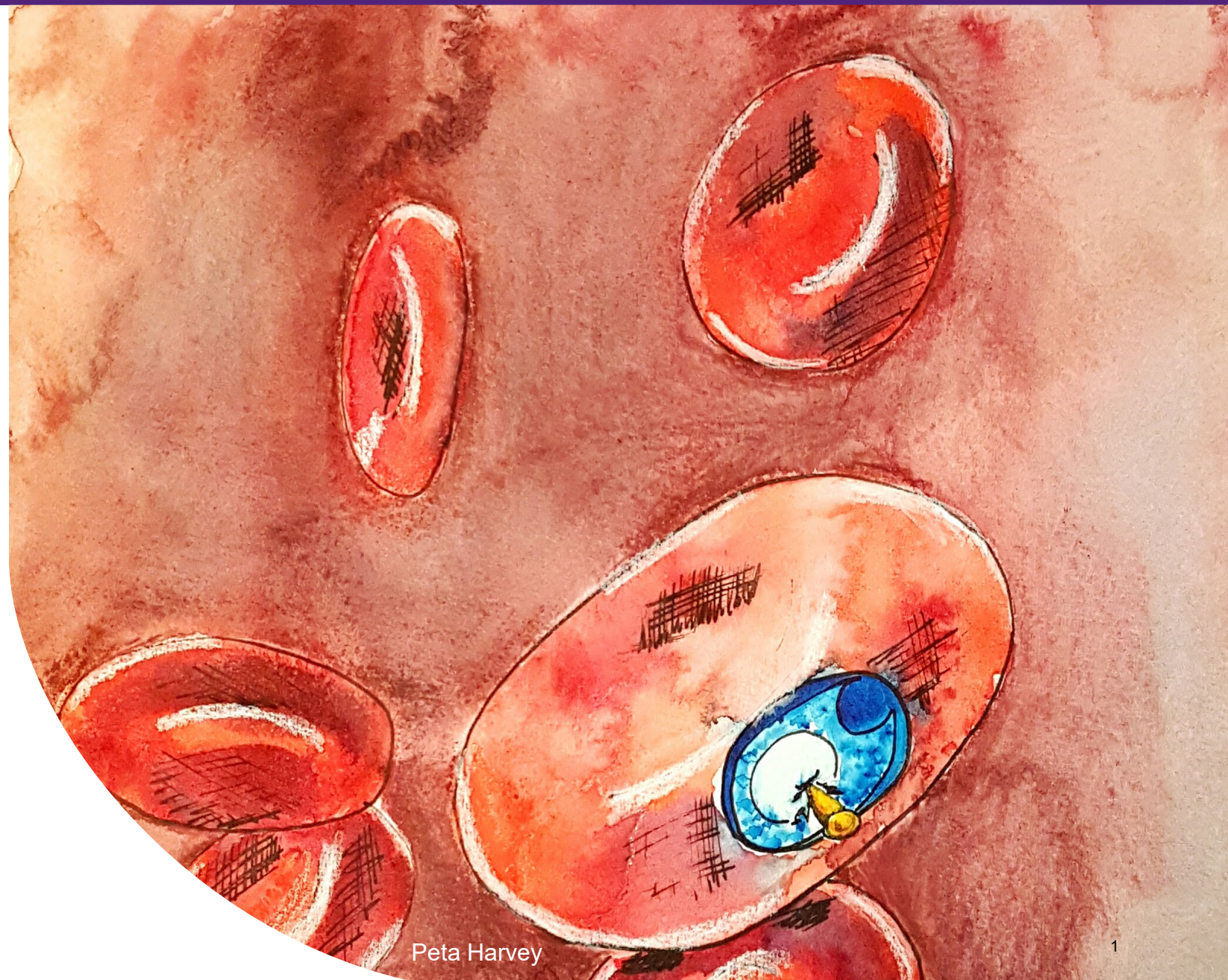
Development of peptide-based antimalarial drugs

Nicole Lawrence

Institute for Molecular Bioscience
The University of Queensland

n.lawrence@imb.uq.edu.au

@NicoleLscientst



Peta Harvey

Malaria: a problem worth solving

- ~ three billion people from > 90 countries are at risk of contracting the disease

- Each year > 200 million people are infected with deadly *Plasmodium falciparum* parasites, and > 400 thousand people die

WHO. World malaria report 2020

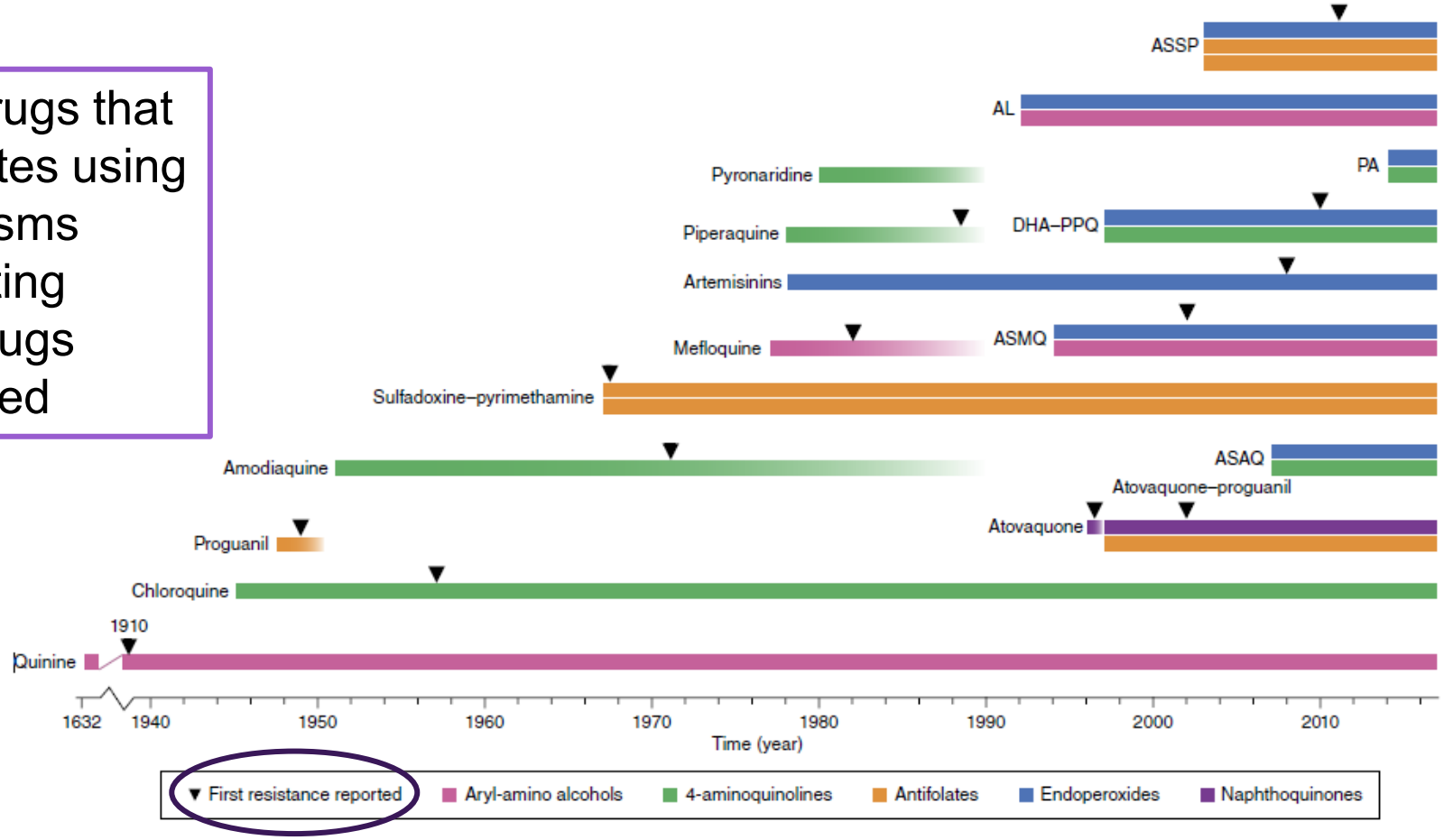
Malaria: the treatment arsenal needs expansion

- control measures including insecticides and use of bed nets have decreased the incidence in many regions
- resurgence of disease due to spread of drug resistant parasites is a major concern
- new classes of antimalarial drugs that act via different mechanisms compared to existing drugs are urgently needed

WHO. World malaria report 2020

Drug resistance (small molecule drugs)

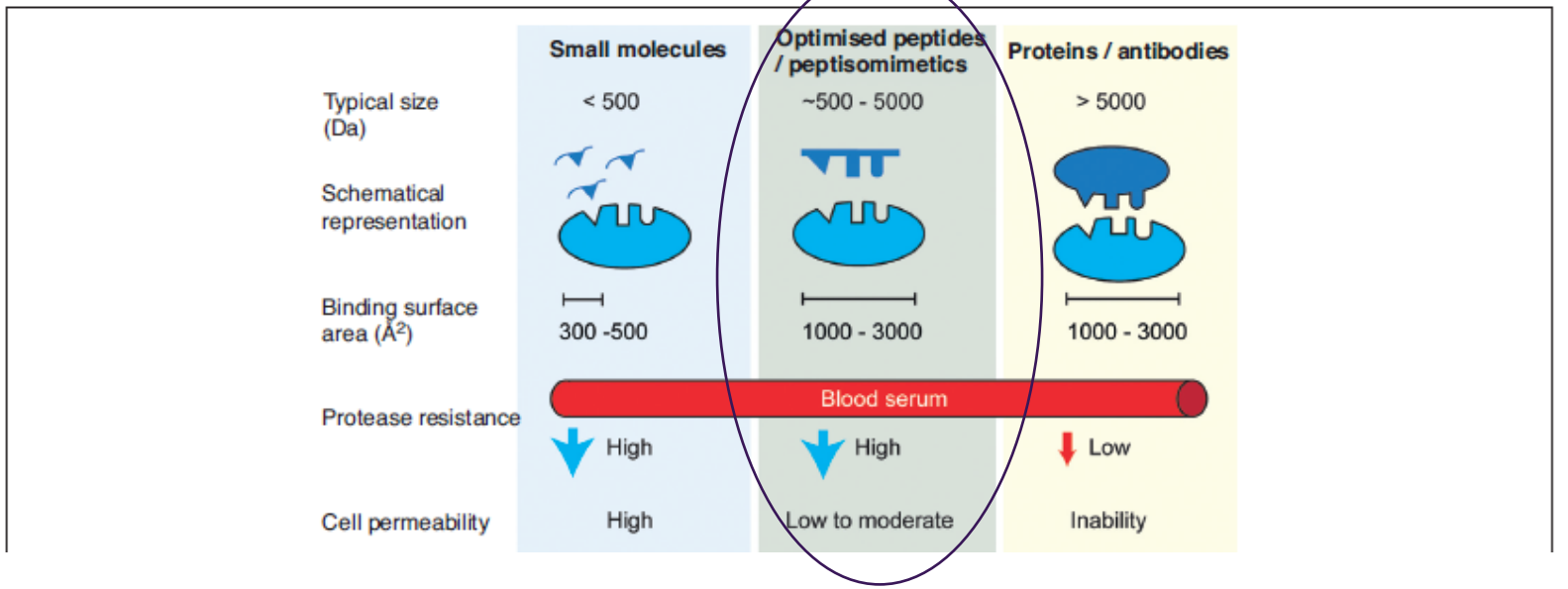
New classes of drugs that kill malaria parasites using different mechanisms compared to existing small molecule drugs are urgently needed

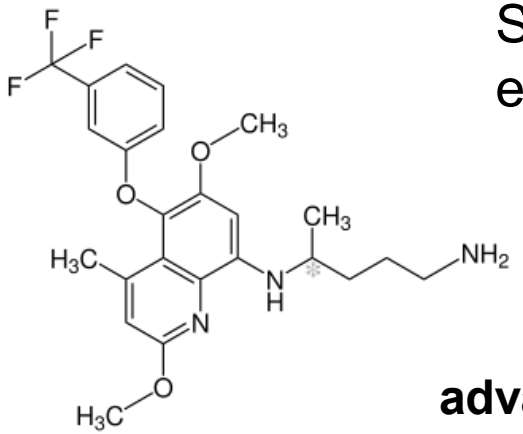


Malaria parasites have developed resistance to every class of small molecule drug that has been developed

Blasco, Leroy, Fidock *Nature Medicine* (2017)

Peptides as a new class of drugs – selective targeting inside cells

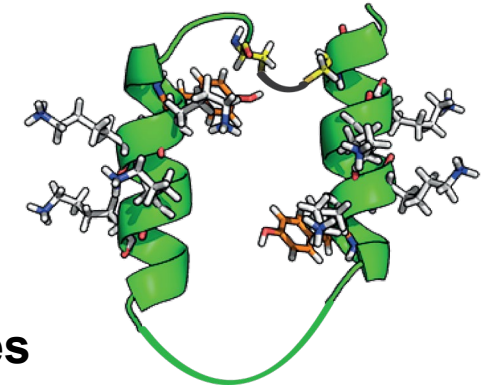




Small molecule
e.g. Tafenoquine

vs

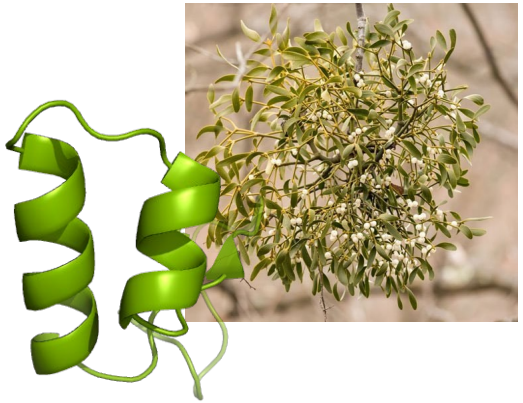
Peptide
e.g. cPF4PD

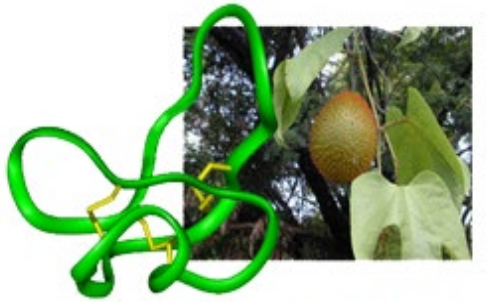
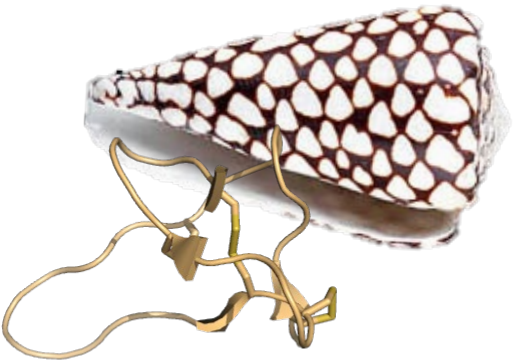
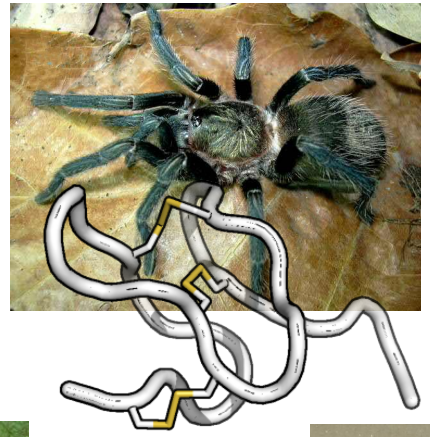


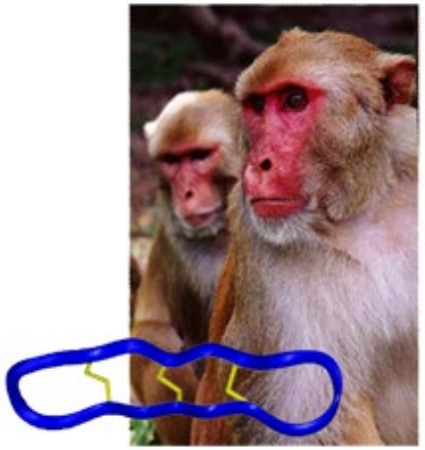
Peptide = chain of amino acids (up to ~50)

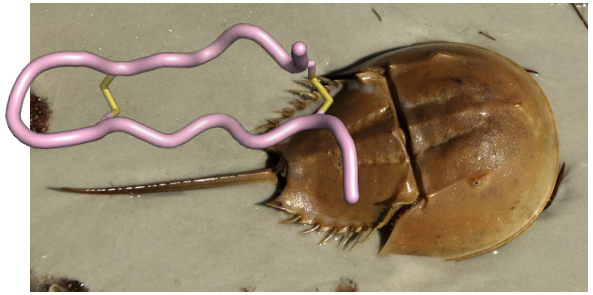
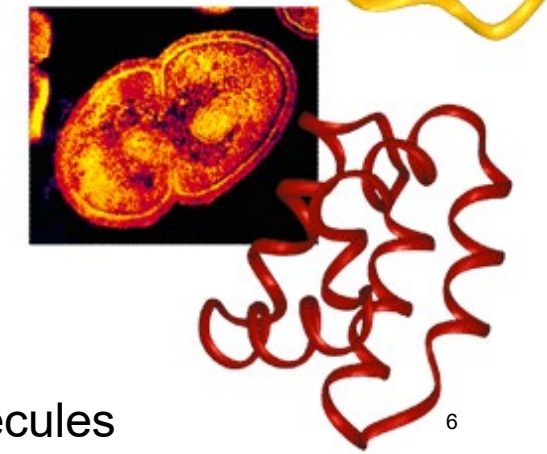
Peptides occupy a privileged space with advantages for development of new therapeutic molecules

Natural defence

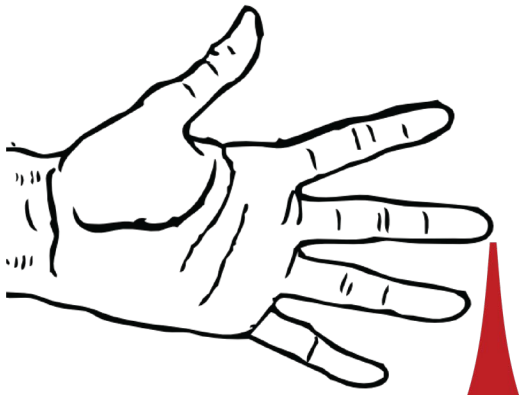



Nature provides a bounty of naturally occurring defence molecules

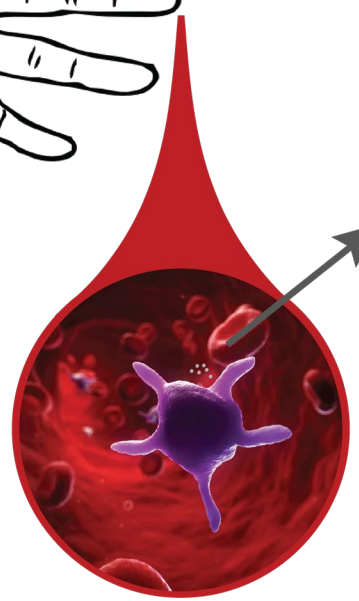
Human defence molecules

Larger, multifunctional and organised into active domains

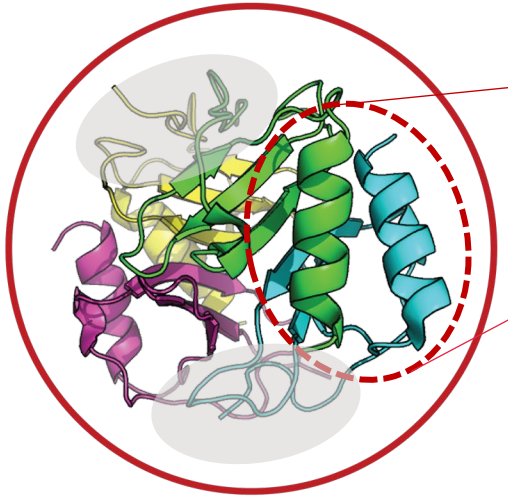
Platelets can kill blood stage malaria parasites



activated platelets



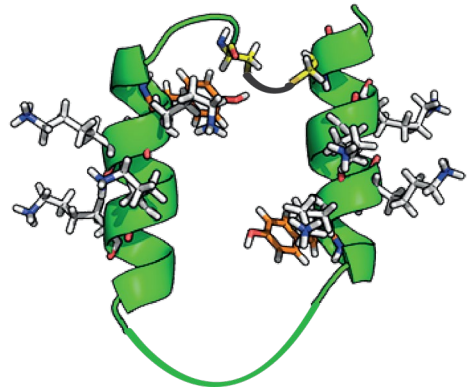
human host defense



platelet factor 4
PF4

antimalarial activity

Peptide drug design

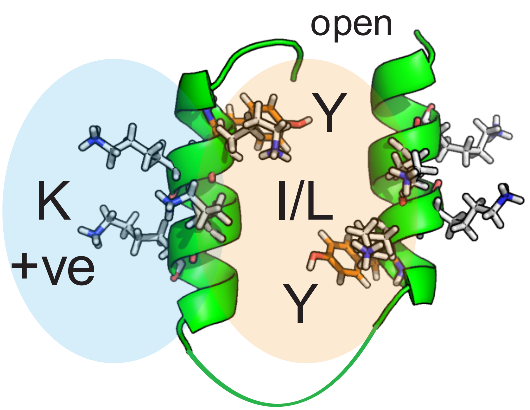


Platelet-derived defence peptide

cPF4PD

McMorran et al. *Science* (2009); McMorran et al. *Science* (2012); Love et al. *Cell Host Microbe* (2012)

Platelet factor 4 (PF4)-derived peptides

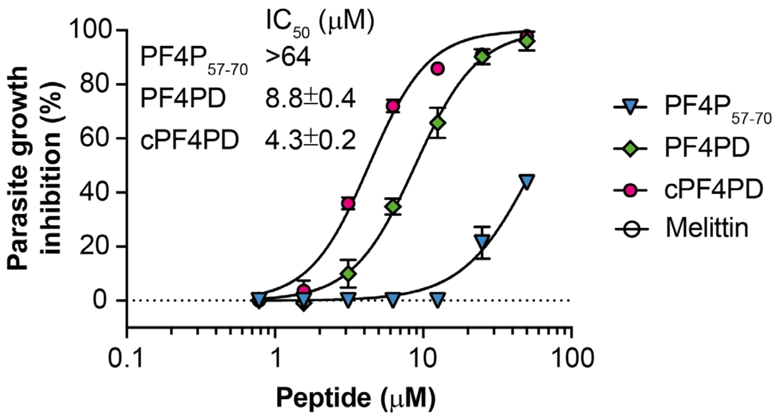


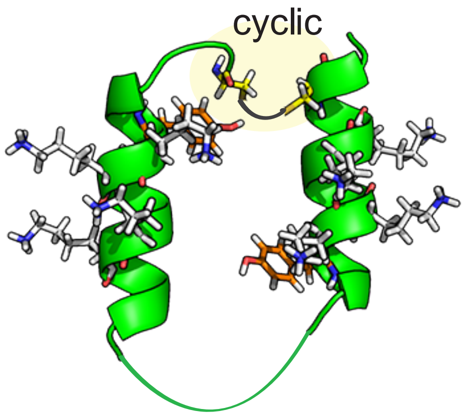
Stable structure

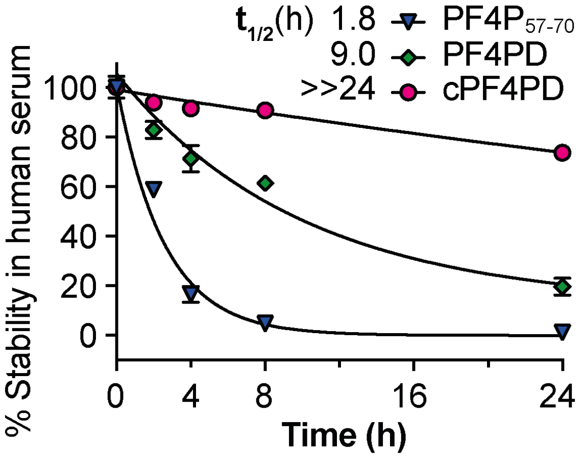
Resistant to breakdown

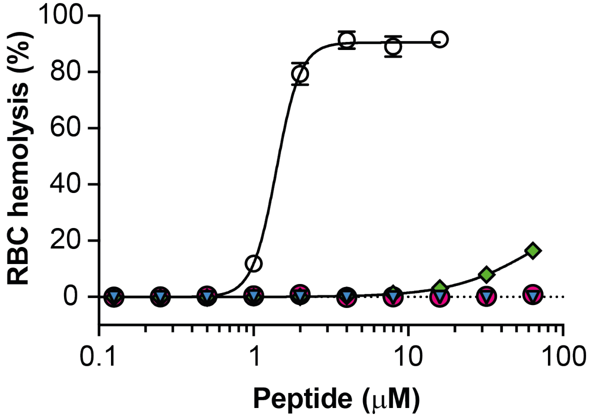
Kill blood stage malaria parasites

Non-toxic to red blood cells



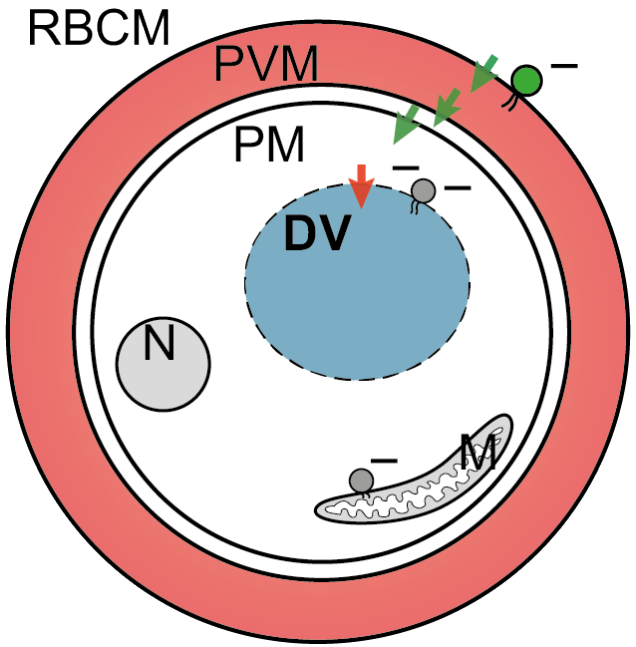


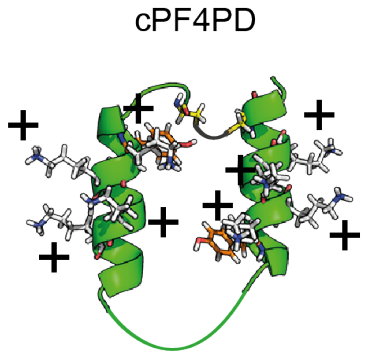


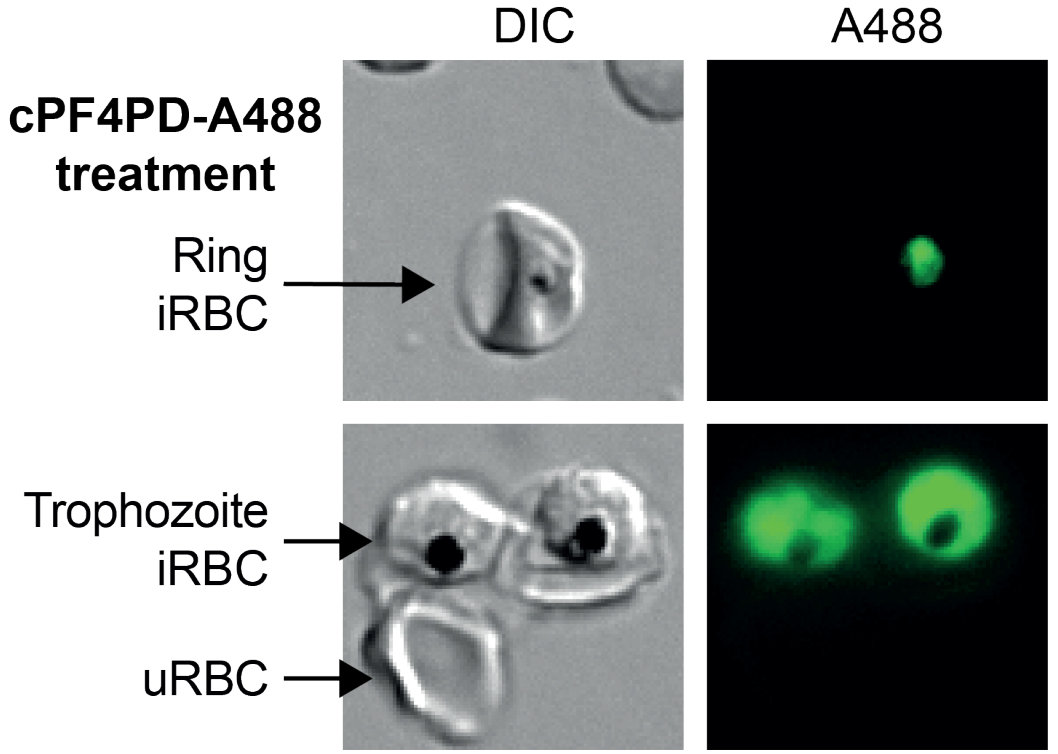


Lawrence et al. *Cell Chem Biol* (2018)

Selective membrane-active mechanism of action



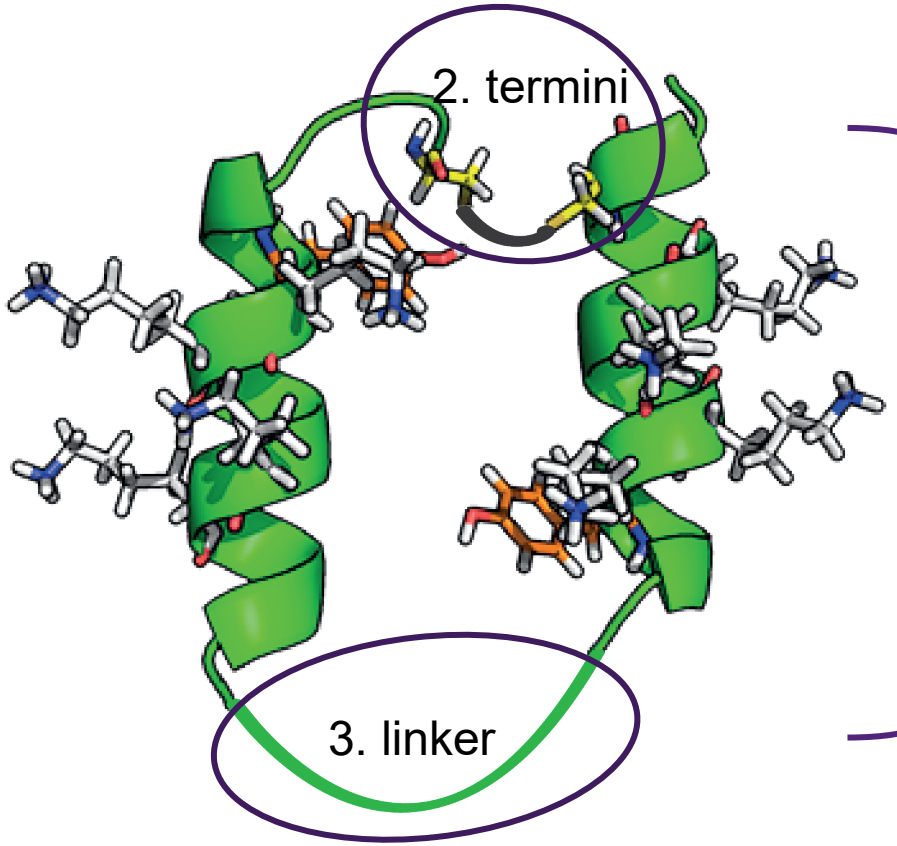


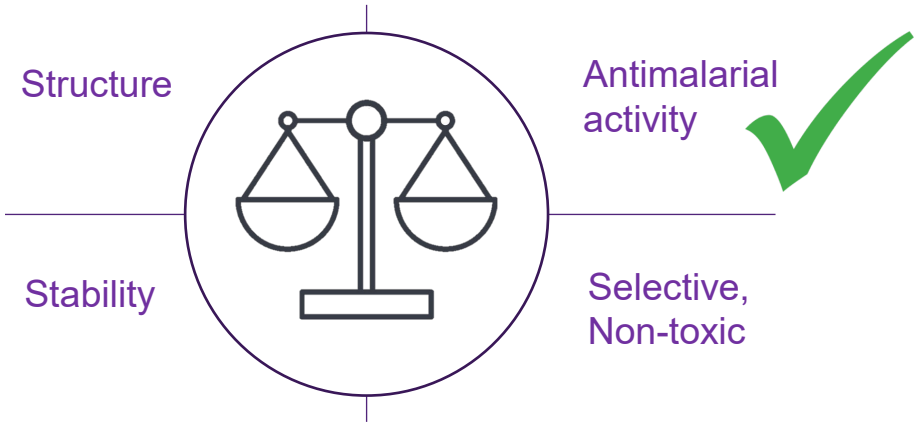


The positively charged peptide recognises the negatively charged surface of infected red blood cells
It crosses the host membrane without damage, enters the parasite and disrupts the digestive vacuole (DV)
The peptide does not enter or harm uninfected cells

Lawrence et al. *Cell Chem Biol* (2018)

Improving potency and drug-like properties of the peptide





1. charged and/or hydrophobic residues

We are working to improve the antimalarial activity of the peptide while maintaining stable structure and non-toxic to healthy cells

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