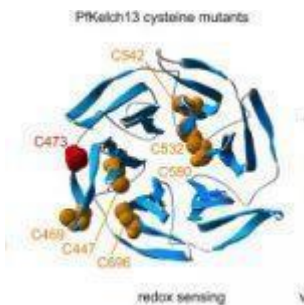


# Resistance to key antimalarial drug?



Endoperoxide artemisinin and its several derivatives are significant role players in the treatment of malaria and are recommended as first-line drugs for artemisinin-based combination therapies by the World Health Organization. Delayed *parasite clearance* was found to be associated with reduced drug susceptibility of the ring stage as well as mutations in *PFKELCH13*, which encodes a kelch domain-containing protein on chromosome 13. PfKelch13 belongs to the top 5% of most conserved proteins in *Plasmodium* and comprises an N-terminal apicomplexan-specific region followed by a CCC domain, a *BTB domain*, and a six bladed kelch β-propeller domain. It has now become evident that mutations in PfKelch13 mutations remain a significant problem in our battle to eliminate malaria, an infectious disease that poses a significant problem to global health systems, especially in the developing world.

In a recent study, Schumann, et al., made use of selection-linked integration (SLI) in combination with *glmS* ribozyme-tagging and established a *purification* protocol for recombinant PfKelch13 to study the relevance of the abundance, conformational stability, and redox state of PfKelch13 for the artemisinin susceptibility in *P. falciparum*.

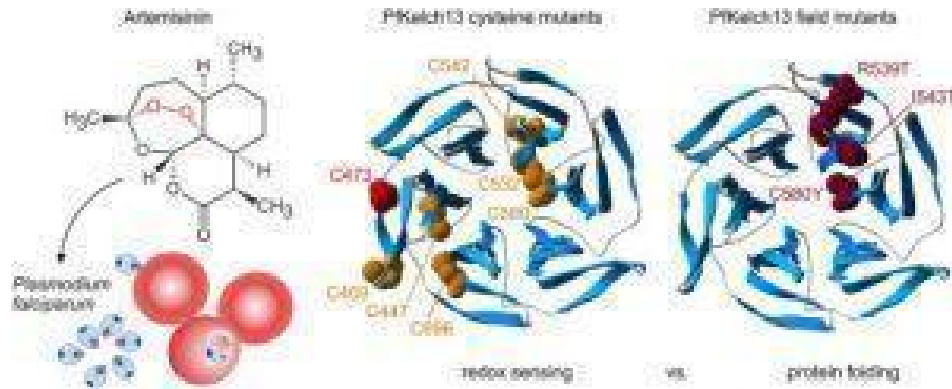


Figure 1: Schumann, et al., addressed the relevance of the redox and folding properties of the Keap1 homologue PfKelch13 for the artemisinin susceptibility of the malaria parasite *Plasmodium falciparum* (Schumann, et al., 2021).

In short, the researchers reported the down-regulation of PfKelch13 which results in ring-stage survival rates of up to 40% and that common field mutations have a destabilizing effect on the folding properties of PfKelch13. In addition, they reported that PfKelch13 exists in at least two different forms and established a protocol for the production of recombinant PfKelch13.

In their own words:

*“In summary, in contrast to residues C469, C532, and C580, the surface-exposed thiol group of residue C473 appears to be essential. However, not the redox properties but impaired folding of PfKelch13, resulting in a decreased PfKelch13 abundance, alters the artemisinin susceptibility and is the central parameter for mutant selection.”*

**Journal article: Schumann, et al., 2021. [Protein abundance and folding rather than the redox state of Kelch13 determine the artemisinin susceptibility of Plasmodium falciparum](#). *Redox Biology*.**

Summary by Stefan Botha