PDI-Trans: a promising target for transmission blocking in malaria

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Malaria continues to be an important global challenge, with 241 million cases and 619 thousand deaths in 2021. Though there is a newly licensed anti-malarial vaccine, it has a modest efficacy (30-50%). Resistance markers against frontline antimalarial drugs have been identified in South-East Asia and Africa. More novel antimalarials need to be developed and characterised. Transmission locking interventions (TBI) target the bottleneck sexual stages of the *Plasmodium spp.* either in the human host (gametocytes) or the mosquito vector.

A putative transmission blocking target is PDI-Trans, a protein disulphide isomerase (PDI) expressed on the surface of the male gamete during fertilisation. Homologues of the protein are found in all *Plasmodium* species. Previous work has found that in transgenic lines lacking PDI-Trans, the male gamete showed abnormal fertilisation, a lack of gamete fusion, and no transmission [1].

Known PDI inhibitors were put through a series of three different screening assays to check for anti-transmission ability, examining: 1) inhibition of recombinant PDI-Trans reductase ability; 2) inhibition in fertilisation 24 hours post gamete activation; and 3) the 'gold standard' standard membrane feeding assay (SMFA), examining establishment of parasitic oocysts within the mosquito midgut.

Repurposed PDI inhibitors were able to successfully inhibit transmission and further development of the sexual stages of *Plasmodium berghei*, with significant (>90%) reduction of transmission to mosquitoes observed when gametocytes are exposed to five specific repurposed PDI-inhibitors that are previously unexamined for anti-malarial efficacy.

Targeting PDI-Trans prevents transmission of malaria from the vertebrate host to the mosquito vector and represents a promising target for novel TBIs.

References:

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