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# Kinase Inhibition as a Therapeutic Approach for *P. falciparum Malaria*

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## Editorial

Malaria caused by parasitic protists of the genus *Plasmodium* remains a widespread, life-threatening infectious disease in the developing countries of the world [1]. Of the five *Plasmodium* species, *P. falciparum* is the most virulent and responsible for the most severe form of malaria. There are few known drugs that have been effective in the treatment of malaria, a problem that is complicated further by the development of resistance to existing antimalarials. Artemisinins have been one of the most effective antimalarials. As a result, artemisinin-based combination therapy, which involves the combination of artemisinin and a long acting antimalarial with a varied mechanism of action, has largely replaced monotherapy. Some of the agents used in combination with artemisinin have included amodiaquine, mefloquine and lumifantrine. In recent years, resistance to artemisinin has also been observed, necessitating the development of novel antimalarials targeting varied processes in the malarial life cycle.

The *P. falciparum* kinases play a role in the sexual and asexual phase of the malarial life cycle and provide novel targets that could be pursued in the development of antimalarials [2,3]. Interestingly, one of the mechanisms of action for artemisinin involves inhibition of *Plasmodium falciparum* phosphatidylinositol-e3-kinase (*Pf*PI3K), and an increase in levels of *Pf*PI3K with a C580Y mutation has been observed in resistant strains [4].

The *P. falciparum* kinome contains fewer than 100 kinases and includes kinase families that are observed in the human kinome such as casein kinase 1(PfCK1), aurora kinases (*PfArk1, PfArk2, PfArk3*), cyclin dependent kinases (*Pf*crk-3, *Pf*crk-4, *Pf*PK5) and glycogen synthase kinase 3(*Pf*GSK3) [2,3]. The *P. falciparum* kinome also includes kinases with no counterparts in the human kinome. These include the calcium-dependent protein kinases (*Pf*CDPK1, *Pf*CDPK2, *Pf*CDPK4, *Pf*CDPK5), *P. falciparum* protein kinase 7(*Pf*PK7) and the *P. falciparum* FIKK kinases.

The human kinome has been extensively explored in the development of anticancer agents and kinase inhibitors have been very successful in the clinic based on their role in cancer cell proliferation, angiogenesis and metastasis [5]. Approved anticancer agents, sunitinib and sorafenib are multi-targeted kinase inhibitors that have shown synergistic effects in the clinic and delayed incidence of resistance due to multiple kinase inhibition in cancer cells. Perhaps a similar approach could be applied to antimalarials. Multi-targeted inhibitors of *P. falciparum* kinases designed to inhibit various stages in the parasite life cycle could possibly delay the emergence of resistance associated with known antimalarials.

High-throughput screenings with compound libraries have yielded multiple antimalarial hits that closely resemble known anticancer kinase inhibitors [2,3]. For example, anticancer agents sorafenib, imatinib, dasatinib and nilotinib have all demonstrated potent antimalarial effects and are being further evaluated against malarial kinases [6]. Diverse chemical scaffolds have demonstrated inhibition of malarial kinases such as *Pf*CK1, *Pf*PK5, *Pf*GSK3, *Pf*CDPK1, *Pf*CDPK2, *Pf*CDPK4, *Pf*CDPK5 and *Pf*PK7. These molecules are being further developed to improve potency and selectivity against target malarial kinases. The members of the malarial kinome exhibit certain structural differences compared to the human kinases that could be exploited in the design of selective *P. falciparum* kinase inhibitors. Crystal structures have been solved for the kinases *Pf*PK7, *Pf*PK5 and *Pf*CDPK2 and homology models have been generated for *Pf*CDPKs and *Pf*GSK3 that have guided the development of potent and selective inhibitors [2,7]. For example, a thieno [2,3-*d*] pyridine derivative has been identified as selective *Pf*GSK3 inhibitor by optimally substituting the heterocyclic scaffold to preferentially interact with a methionine residue and a small hydrophobic pocket in *Pf*GSK3 versus *h*GSK3 [7].

Atypical kinases include a small amino acid as the gatekeeper residue in the ATP-binding site while the gatekeeper residues of human kinases are larger. For example, *Pf*CDPK1 has a threonine gatekeeper residue while *Pf*CDPK4 has a serine gatekeeper residue. This structural difference has been exploited in the development of several atypical kinase inhibitors targeting various members of the CDPK family. A bumped kinase inhibitor, compound 1294 is a potent and selective *Pf*CDPK4 inhibitor [8]. Bumped kinase inhibitors are ATP-competitive and include large lipophilic substitutions that can be accommodated in the ATP pocket of atypical kinases owing to the smaller gatekeeper residues, which thereby confer selectivity for plasmodial kinases compared to human kinases. Compound 1294 has a long half-life and is orally bioavailable in mouse models.

Current antimalarials used in therapy target the asexual phase of the malarial lifecycle [2,3]. The kinase *Pf*CDPK4 is involved in male gametocyte exflagellation required for the formation of infectious sporozoites during the sexual phase of the malarial life cycle [8]. In the quest for new antimalarials, the *Pf*CDPK4 inhibitor, compound 1294 is noteworthy as it provides a novel mechanism for antimalarial action by preventing the transmission of parasites from mosquitoes to humans.

Imidazopyridine derivatives have been identified as potent and selective inhibitors of *Pf*CDPK1 with nanomolar antiplasmodial potencies in cells and moderate efficacies in murine *Plasmodium berghei* models [9]. The moderate *in vivo* efficacy was explained based on differences in parasite biology in murine *P. berghei* versus human *P. falciparum*. The human *P. falciparum* kinome has additional kinases compared to the *P. berghei* kinome. Perhaps, the imidazopyridine derivatives could inhibit additional kinases in the *P. falciparum* kinome that are not found in *P. berghei.*

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Inhibitors of *P. falciparum* kinases provide several unique approaches for further investigation as novel curative agents, transmission blockers, and potential multi-targeted agents in the treatment of malaria. Diverse inhibitor scaffolds have been identified against *P. falciparum* kinases with demonstrated efficacies in enzymatic, cellular and animal models. These molecules have proved useful as probes to better understand the role of malarial kinases in the malarial life cycle and their potential as effective antimalarials. Current research focuses on the development of *P. falciparum* kinase inhibitors with improved potency, plasmodial selectivity and translatable clinical data.

## References

1. WHO (2014) World Malaria Report. Geneva. World Health Organization.
2. Lucet IS, Tobin A, Drewry D, Wilks AF, Doerig C (2012) Plasmodium kinases as targets for new-generation antimalarials. Future Med Chem 4: 2295-2310.
3. Derbyshire ER, Zuzarte-Luis V, Magalhaes AD, Kato N, Sanschagrin PC, et al. (2014) Chemical interrogation of the malaria kinome. Chembiochem 15: 1920-1930.
4. Pandharkar T, Liu H, Estiu G, Stahelin RV, Rizk SS, et al. (2015) A molecular mechanism of artemisinin resistance in Plasmodium falciparum malaria. Nature 520: 683-687.
5. Ghose A, Herbertz T, Pippin D, Salvino J, Mallamo J (2008) Knowledge Based Prediction of Ligand Binding Modes and Rational Inhibitor Design for Kinase Drug Discovery. J Med Chem 51: 5149-5171.
6. Ishiyama A, Iwatsuki M, Hokari R, Sawa M, Omura S, et al. (2015) Antimalarial activity of kinase inhibitor, nilotinib, in vitro and in vivo. J Antibiot (Tokyo) 68: 469-472.
7. Masch A, Kunick C (2015) Selective inhibitors of Plasmodium falciparum glycogen synthase-3 (PfGSK-3): New antimalarial agents? Biochim Biophys Acta 1854: 1644-1649.
8. Ojo KK, Eastman RT, Vidadala R, Zhang Z, Rivas KL, et al. (2014) A specific inhibitor of PfCDPK4 blocks malaria transmission: chemical-genetic validation. J Infect Dis 209: 275-284.
9. Chapman TM, Osborne SA, Wallace C, Birchall K, Bouloc N, et al. (2014) Optimization of an imidazopyridazine series of inhibitors of Plasmodium falciparum calcium-dependent protein kinase 1 (PfCDPK1). J Med Chem 57: 3570-3587.