


VIEWPOINT

Can repurposing drugs play a role in malaria control?

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Innovative drug treatments for malaria, optimally with novel targets, are needed to combat the threat of parasite drug resistance. As drug development efforts continue, there may be a role for a host-targeting, repurposed cancer drug administered together with an artemisinin combination therapy that was shown to improve the speed of recovery from a malaria infection.

Reduction in the global burden of malaria has stalled over the past several years. In 2019, there were ~229 million cases in 87 malaria-endemic countries, resulting in an estimated 386,000 fatalities (WHO, 2020). The impact of the ongoing COVID-19 pandemic on malaria control has yet to be determined; however, there is great concern that the diversion of funds, interventions, and supplies will only lead to increased malaria morbidity and mortality (Weiss et al., 2021). Emerging and widespread parasite drug resistance has already complicated malaria control. Resistance to the components of artemisinin combination therapies (ACTs), the worldwide standard treatment for *Plasmodium falciparum* malaria, is a serious concern in Southeast Asia, and the inevitable loss of efficacy of these treatments in Africa must be delayed for as long as possible.

A persistently high burden of disease demands a rethinking of malaria control, including the development of new drug combinations to treat malaria. A potential novel approach to treatment was recently described by Chien et al. (2021). They demonstrated that targeting a host protein with a repurposed cancer drug may serve as an adjunctive treatment to the standard of care, in this case dihydroartemisinin/piperaquine for uncomplicated *P. falciparum* malaria infection. In a small study performed in Vietnam, they found that the addition of the tyrosine kinase inhibitor (TKI) imatinib to the standard of care led to

faster resolution of fevers and parasitemia with no additional adverse events. These results are especially intriguing given the nature of artemisinin resistance, in which, following treatment, parasites remain in the infected host for an extended period of time (WHO, 2020).

Artemisinin and its derivatives are highly potent antimalarial drugs notable for their fast killing of multiple parasite stages. In general, the use of artemisinin is associated with rapid resolution of clinical symptoms and clearance of parasitemia in uncomplicated malaria and decreased mortality in severe disease. For this reason, reports of treatment failures with ACTs in western Cambodia starting over a decade ago alarmed the global health community. Decreased efficacy of artemisinin, likely from earlier extensive use as monotherapy, led to the emergence of resistance to partner drugs. In many areas of the Greater Mekong Subregion (GMS), piperaquine failures are now common, such that guidelines have changed and lumefantrine has increasingly become the partner drug of choice (Hamilton et al., 2019). Resistance to the artemisinin component of ACTs is defined clinically as a delayed parasite clearance time, meaning parasites are still observable after 72 h in peripheral blood by microscopy (WHO, 2020). Currently, >80% of infections in the GMS are noted to have a prolonged parasite clearance half-life and are strongly associated with polymorphisms in the parasite

protein *P. falciparum* Kelch 13 (Pfkelch13; WHO, 2020; Rosenthal, 2021). The dominant GMS Pfkelch13 polymorphism, C580Y, has also emerged independently in Guyana and Papua New Guinea, though with unclear clinical relevance (Mathieu et al., 2020; Miotto et al., 2020). Recent studies from Africa, in particular Rwanda and Uganda, are of great concern, as emergence and expansion of PfKelch13 mutations associated with both in vitro and in vivo resistance was recently reported (Balikagala et al., 2021; Miotto et al., 2020; Rosenthal, 2021). Emergence of clinically relevant artemisinin resistance in Africa and the subsequent inevitable partner drug failure in areas with the heaviest burden of disease would be catastrophic for malaria control (Rosenthal, 2021).

The optimal response to growing ACT failure is hotly debated. To date, there are a limited number of antimalarial agents available with an even fewer number of molecular targets, which makes the idea of a host target so intriguing (Fig. 1). Novel antimalarials, some with new targets, are in the development pipeline but are unlikely to be available within the next 5 yr and are often susceptible to rapidly arising drug resistance. Increasing the duration of ACT usage from 3 to 5 d appears to be effective, but anticipated poor compliance to the extended therapy may exacerbate resistance. Recent studies assessed the potency and safety of triple ACTs (TACT), combining an

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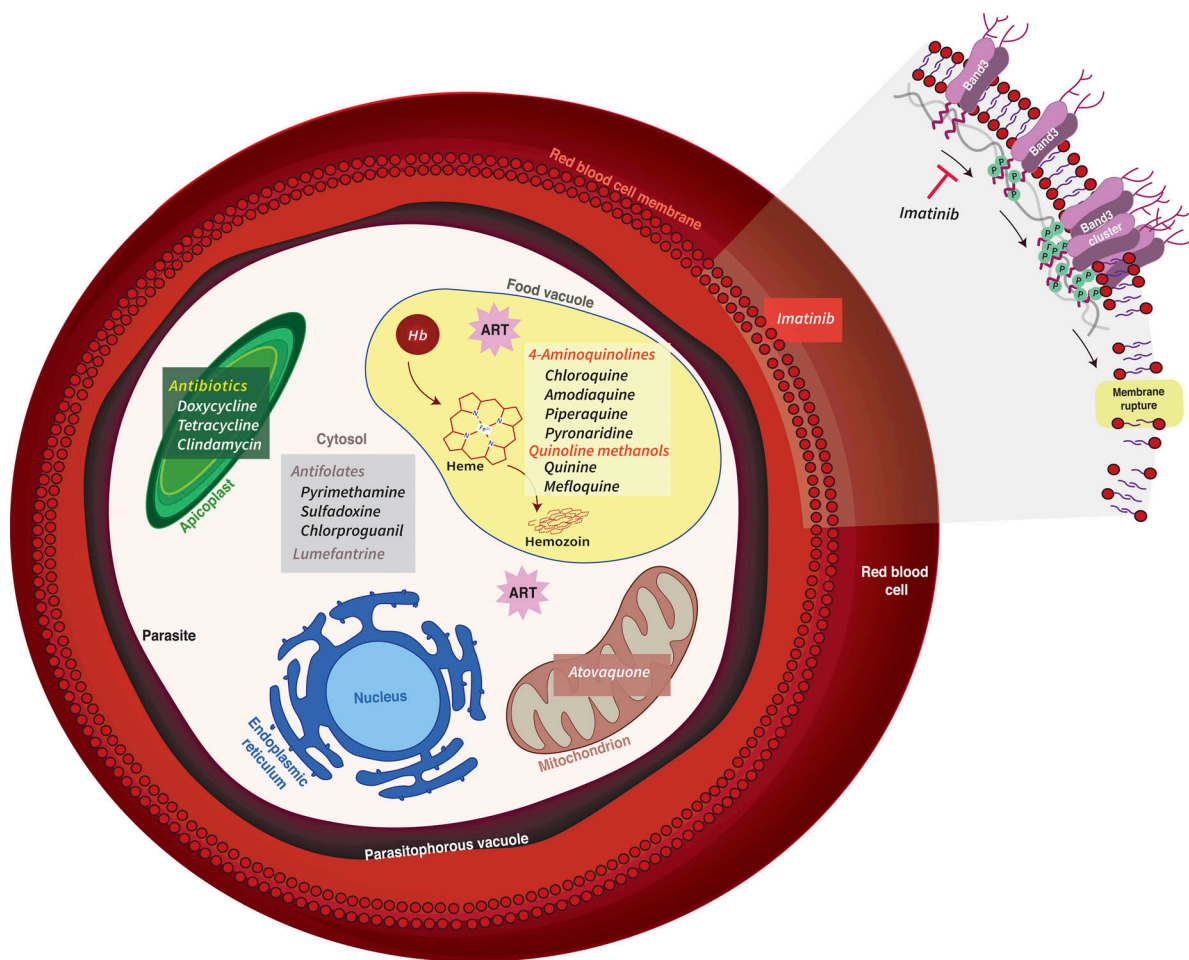


Figure 1. Current antimalarial drugs and putative targets. Many antimalarials such as quinolines have well-defined targets, including the food vacuole where they interfere with hemoglobin digestion or the cyclins that target the parasite apicoplast. The artemisinins cause widespread cellular damage once activated inside the parasite. Imatinib targets a human tyrosine kinase in the host cell that phosphorylates the RBC membrane protein Band 3 as the cell ages and during parasite maturation. When phosphorylation of Band 3 is inhibited by imatinib, Band 3 fails to cluster and the RBC membrane remains resistant to parasite rupture, entrapping the daughter merozoites that would normally infect new RBCs.

ACT with a second partner drug, typically mefloquine or amodiaquine, both of which target the food vacuole but have their own well-documented resistance liabilities (van der Pluijm et al., 2020). Thus, there is great potential benefit for a repurposed, affordable antimalarial with a mechanism independent of the other ACT components as part of a TACT regimen, especially if such a novel agent could forestall the further development and spread of artemisinin resistance.

Repurposing existing drugs has been proposed as an approach to hasten the identification and study of novel therapeutics. However, the reality of the impact of repurposed drugs has been limited to date, and there are potentially many pitfalls while proposing new uses for old drugs (Pessanha de Carvalho et al., 2021; Begley et al., 2021). Antibiotics that target the specialized parasite

organelle of prokaryotic origin, the apicoplast, have been repurposed to be part of second-line malaria treatment options (Biddau and Sheiner, 2019; Pessanha de Carvalho et al., 2021) and chemoprevention but continue to play an important role in malaria control (Fig. 1). The greatest success in drug repurposing for an infectious disease is not pathogen targeting, but host immune response directed. Thalidomide is used to treat a particular complication of leprosy marked by an overactive immune response, termed erythema nodosum leprosum (Begley et al., 2021).

Targeting a host protein would be a unique mechanism of action for an antimalarial drug. Work to define the mechanism of action of host TKI against *P. falciparum* was extensively explored in the laboratory before testing efficacy in the field. The first

TKI approved by the Food and Drug Administration for management of chronic myelogenous leukemia (CML), imatinib, was shown to have activity against *P. falciparum* in vitro (Kesely et al., 2020). TKIs remain the first-line therapy for chronic phase CML with the exception of pregnant women (Hochhaus et al., 2017). Thus, there is widespread experience with these agents, and in general, patients tolerate TKIs for long-term treatment with well-described side effect profiles. Side effects during short-term treatment for falciparum malaria are likely to be minimal but remain to be studied outside an exclusively adult male population (Chien et al., 2021).

Laboratory-based studies revealed that malaria parasites are unable to egress from their host RBC when cultures are treated with TKIs (Pantaleo et al., 2017). Treatment

with imatinib and other TKIs block changes to the host RBC membrane that occur during parasite development, in particular changes to a protein called Band 3, an abundant integral RBC membrane protein that has multiple functions including membrane stabilization. As the RBC ages, Band 3 forms clusters that destabilize the membrane; this process is accelerated under conditions of oxidative damage and during malaria parasite development (Pantaleo et al., 2017; Shimo et al., 2015). Band 3 phosphorylation is required for clustering but is blocked when a host tyrosine kinase (SYK; spleen tyrosine kinase) is inhibited by imatinib (Fig. 1). Previous work has shown that by preventing the phosphorylation of Band 3, the membrane destabilization needed for the mature parasite to egress from the RBC and continue the erythrocytic cycle of infection is blocked. The parasites remain viable but stuck within in the host cell, theoretically prolonging parasite exposure to their own toxic metabolites (Kesely et al., 2020; Pantaleo et al., 2017). When tested in combination, imatinib was shown to be synergistic with artemisinin in vitro (Tsamesidis et al., 2020). In the clinical trial reported by Chien et al. (2021), the faster reduction in parasitemia observed in the dihydroartemisinin/piperaquine plus imatinib arm is potentially meaningful in an area where prolonged clearance time is a harbinger of ACT failure. Though they found only one patient infected with a parasite bearing a PfKelch13 mutation, other parasite factors can lead to prolonged parasite clearance and predate the full emergence of PfKelch13-mediated treatment failure. Parasite resistance to TKIs, on the other hand, are at least theoretically unlikely to emerge, as *P. falciparum* lack their own tyrosine kinases that could serve as an imatinib target.

While this novel therapeutic approach coupled more rapid parasite clearance and faster reduction of fever, many questions must be addressed before imatinib should be considered for more widespread use in

combination with ACTs. Of particular importance is whether the faster parasite clearance or reduction in fever would persist with different ACT dosing and currently recommended regimens using lumefantrine, amodiaquine, or pyronaridine as the partner drug, for example. Safety data from use in CML are well established, yet additional safety data for malaria treatment are needed from larger trials, especially in women and children, the two groups most heavily affected by malaria. Women who have clinical immunity to malaria are known to be at risk of more severe disease during pregnancy-associated malaria. For this reason, intermittent preventative treatment with various antimalarials during pregnancy is known to improve outcomes for both mother and child (Kakuru et al., 2020). Imatinib is associated with increased fetal abnormalities and miscarriage and is not recommended for pregnant or nursing women. Inability to use this agent in women of childbearing age is an important limitation to consider. Similarly, safety in children needs to be considered, as the majority of malaria deaths occur in children under 5 yr of age. Finally, in Africa, where the malaria burden is the highest, host immunity often plays a critical role in parasite clearance, and ACTs generally remain highly effective in the region (Djimé et al., 2003). The benefit of imatinib toward parasite clearance in these populations with varying degrees of immunity needs to be studied.

Malaria is currently a treatable disease, and we must be creative and diligent to assure the availability of new, efficacious therapies. Novel approaches are needed as the threat of drug resistance grows. Imatinib has the advantage of being a novel affordable agent that has a unique mechanism of action. Importantly, as its target is host derived, it should be less likely to fail due to the development of parasite resistance. Malaria researchers will need to study and consider how to use agents such as imatinib that are not treatments on their

own but may enhance the action of current therapy to forestall the emergence and potential spread of additional drug resistant malaria, in a safe and cost-effective manner. The encouraging findings from the field warrant further studies on imatinib and other host-targeting approaches for malaria.

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