CellPress

Opinion

Discovering New Transmission-Blocking Antimalarial Compounds: Challenges and Opportunities

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The ability to target human–mosquito parasite transmission challenges global malaria elimination. However, it is not obvious what a transmission-blocking drug will look like; should it target only parasite transmission stages; be combined with a partner drug killing the pathogenic asexual stages; or kill both the sexual and asexual blood stages, preferably displaying polypharmacology? The development of transmission-blocking antimalarials requires objective analyses of the current strategies. Here, pertinent issues and questions regarding the target candidate profile of a transmission-blocking compound, and its role in malaria elimination strategies, are highlighted and novel perspectives proposed. The essential role of a test cascade that integrates screening and validation strategies to identify next-generation transmission-blocking antimalarials is emphasised.

Malaria: From Control to Elimination

The unsustainable cost of controlling malaria has led to concerted global efforts to **eliminate** (see Glossary) and eventually **eradicate** the disease, resulting in a 37% global decline in malaria incidence since 2000. However, despite this tremendous success, 3.2 billion humans remain at risk and, in 2015, an estimated 214 million cases of malaria resulted in 438 000 deaths [1]. One of the main contributing factors is the sustained transmission of the causative *Plasmodium* parasites between humans through *Anopheles* mosquito vectors. The ability to block transmission relies on: identifying (and treating) asymptomatic or semi-immune human hosts carrying transmissible forms of the parasite and representing major reservoirs of continued infection [2]; eliminating mosquito vectors through multiple and integrated strategies [3]; and eliminating the parasite pool in patients with malaria, which, in the absence of a vaccine, still relies solely on chemotherapy and prophylaxis to prevent new or re-infection [4]. Chemotherapeutics are under threat due to resistance against current antimalarial drugs.

Parasite **population bottlenecks** appear in transition phases of the *Plasmodium* life cycle, during which parasites are transmitted between the vector and human hosts [5]. Prevention of **sporozoite** transmission from the mosquito has thus far relied entirely on vector control and on measures to prevent mosquito bites [5]. By contrast, the transmission of **gametocytes** (the intra-erythrocytic sexual stages) to the mosquito is potentially more amenable to direct intervention, because it is easily targetable within the human blood compartment.

However, targeting gametocytes remains challenging since vast gaps exist in our knowledge of the biology of the sexual stages of *Plasmodium.* Gametocytes are highly specialised cells, very

Trends

Global efforts to eliminate and/or eradicate malaria are targeting all stages of parasite development. Disrupting the transmission of parasites from humans to mosquitoes is an attractive target that is amenable to chemotherapeutic intervention.

Screening compounds that kill gametocytes is performed against a poorly understood biological background of the target cells.

A smart screening strategy that introduces a range of biologically informative and clinically important assays early in the pipeline maximises the confidence in the identification of lead compounds.

Knowledge gaps and questions regarding the identification, characterisation, and optimal profile of transmission-blocking drugs are highlighted and novel perspectives proposed.

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different to the asexual pathogenic stages [6]. In *Plasmodium vivax*, gametocytes require only a slightly longer time to develop than that required for asexual stages to complete their multiplication cycle. By contrast, gametocytes of *Plasmodium falciparum* reach maturity in a uniquely long period of 10–12 days compared with the 48-h asexual cycle. In this species, major morphological differences distinguish the asexual parasites from gametocytes, from whose elongated shape *P. falciparum* derives its name. Five distinct morphological and biochemical stages of gametocyte development (stages I–V) are conventionally identified [7], with immature stage I–IV gametocytes sequestering in tissues (e.g., bone marrow) during development and only mature stage V gametocytes circulating in the blood stream, where they can be transmitted to mosquitoes [8]. After the stochastic, epigenetically driven [9–12] gametocyte conversion rate of approximately 1% of the asexual population [6], the immature stage I–III gametocytes are to some extent biochemically more aligned to asexual parasites than their stage V partners [8], whose metabolism effectively decreases to only retain household activities, such as ATP production and redox maintenance [13]. This raises unique issues in the identification of drugs active on *P. falciparum* gametocytes, and specifically on the mature stage V forms, compared, for instance, to those of *P. vivax*, in which drugs against the asexual stages are also more often active against gametocytes. Thus, here we focus on strategies to target the transmission stages of *P. falciparum.*

Currently, only artesunate, artemether, methylene blue, and primaquine are active against gametocytes, with primaquine the only approved gametocytocidal drug. The use of these compounds is threatened by emerging resistance to artemisinin derivatives and toxicity concerns in the case of primaquine, which causes haemolysis in glucose-6-phosphate dehydrogenase-deficient individuals [14]. Here, we argue that the discovery of new transmission-blocking antimalarials should be strategically driven by how such compounds will ultimately be deployed (Figure 1, Key Figure). We highlight pertinent discussion points and knowledge gaps in the identification, characterisation, and classification of a transmission-blocking drug. We also propose novel perspectives and expert opinions to guide the way towards achieving the goal of identifying transmission-blocking antimalarials.

Targeting Transmission to Eliminate Malaria: What Role Will Transmission-Blocking Antimalarials Need to Fulfil?

Four challenges associated with antimalarial drugs relevant to a malaria eradication agenda have previously been outlined: (i) blocking disease transmission by targeting sexual blood-stage development in humans; (ii) elimination of liver stages, including preventing and/or eliminating relapse from hypnozoites; (iii) developing chemical entities that overcome cross-resistance; and (iv) targeting vulnerable populations [5,15,16]. However, a provocative challenge to the above could be to prioritise blocking transmission as a primary objective, since this could provide an over-arching solution to achieve malaria elimination.

Of particular interest is the role that **transmission-blocking** compounds will need to fulfil (Figure 1). Dual-active compounds (i.e., single compounds that target both asexual blood stages and mature gametocytes equipotently) provide the possibility to consolidate several antimalarial **target candidate profiles** (TCPs) into a single **target product profile** (TPP) [5,15,16], but with increased risk of resistance development (Box 1). Combinations of more than one entity, one with asexual blood-stage activity and one with transmission-blocking ability, could decrease the risk of developing resistance, but are associated with increased development costs and pharmacological complexities. Lastly, the use of a 'transmission-blocking only' compound as a 'chemical vaccine' to prevent transmission holds promise and could be useful to eliminate the vast gametocyte reservoir in asymptomatic individuals within whole populations in a **mass drug administration** (MDA) scenario [17] or in targeted delivery to gametocyte carriers in a mass test and treat scenario, if carriers could be

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