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The antimalarial pipeline

Rob Hooft van Huijsduijnen and Timothy NC Wells

Over the past decade, new high-throughput phenotypic assays with malaria parasites have been developed, and these were used to screen millions of compounds. This effort, as well as improving older chemical scaffolds and optimising compounds against both known and new drug targets has resulted in the discovery of exciting new pipeline drug candidates that are now being evaluated in a number of clinical trials. In addition, the pitfalls and opportunities from this experience has led to a better definition of the optimal target compound and product profiles for new antimalarials, including medicines that treat uncomplicated or severe malaria, provide chemoprevention, or stop disease transmission, covering all stages of the parasite. An important decision element is how to combine these new molecules with existing ones in today's dynamic resistance landscape.

Address
Medicines for Malaria Venture, 20 route de Pre-Bois, 1215 Geneva, Switzerland

Corresponding author: Wells, Timothy NC (Wells)

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Deploying today's medicines for maximum impact

Uncomplicated malaria

The complete set of antimalarial medicines includes molecules that differ widely in the extent to which they are used, mostly associated with regional differences in pathogen resistance, and access. Except for severe malaria these medicines are administered as combinations, whose components are chosen on the basis of local resistance and other factors. When allocating resources for the development of new chemical entities it is worth discussing where the opportunities lie in further deploying the current portfolio of malaria drugs. Over the last two decades there has been a tremendous development in the deployment of artemisinin combination therapies (ACTs), which are administered orally for non-severe malaria. An estimated 409 million treatment courses of ACTs were procured in 2016, an increase from 311 million in 2015 [1]. There are now six ACTs approved by stringent regulatory authorities, or prequalified by the World Health Organisation (WHO): artemether-lumefantrine, amodiaquine-artesunate, mefloquine-artesunate, dihydroartemisinin-piperaquine, artesunate-sulfadoxine/pyrimethamine and pyronaridine-artesunate (Only two of these, artemether-lumefantrine and pyronaridine-artesunate have specific child-friendly formulations). Resistance against three of artemisinin's partner drugs (amodiaquine [2], mefloquine [3] and piperaquine [4,5]) has been described clinically. Artemisinin resistance has been described as well; in 2008 there were reports of parasites which, although killed by artesunate, required curative treatments that were twice as long (six days; [6]). So far, there are no reports of any more severe artemisinin-resistance phenotypes. Thus, the field is left with the situation where, for the moment, there are always ACTs that are fully active, but the partner drugs are at risk. Strategies to further protect ACTs which are currently being tested clinically include triple therapies, that is, an artemisinin plus *two* partner drugs [7], or using two three-day courses of different, approved ACTs [8]. These approaches, if clinically validated, may also contribute to eliminate malaria in the Greater Mekong Subregion, which historically has been one of the epicentres of resistance generation.

Severe malaria

The second indication to consider is severe malaria. This is an area where the peculiarities of neglected disease can be best illustrated. The clinical data from the Aquamat [9] and Seaquamat [10] trials have demonstrated the superiority of artesunate injections over quinine. Artesunate has the other major advantage that it can be given either intramuscularly or as suppositories. Artesunate injections were prequalified by the WHO in 2010, and since then over 100 million vials of artesunate for injection have been distributed, providing improved therapy for 20–30 million children globally. Recently artesunate suppositories have been WHO-prequalified for use in what is called 'pre-referral treatment' — '*bringing emergency treatment closer to severely ill children with malaria in rural areas where injectable treatment is not possible for several hours*' [11].

Chemoprevention

The third area is the use of medicines to protect the general population: disease prevention. For many viral pathogens and a few bacteria this is successfully achieved by vaccines. However, a malaria vaccine is a problematic prospect.

Travellers all have the option to take chemoprevention, and this has raised the question as to whether a chemoprevention strategy can be used in African populations. In

the Sahel (the region south of the Sahara desert), a monthly regimen of three doses of amodiaquine and a single dose of sulphadoxine–pyrimethamine is given each month during the rainy season to children up to 5 years old, and this has resulted in spectacular reductions in morbidity and mortality in these countries. Some countries such as Senegal have begun to extend this seasonal malaria chemoprevention (SMC) protection to include children up to the age of 10 years old. This approach is now being used by half of the children in the Sahel, and the speed at which the program has taken off underlines that from the country's perspective the impact justifies the investment in time and energy.

This approach could be expanded in three directions: First, to increase coverage to older children, as pioneered in Senegal. This approach is however limited by the safety data in early pregnancy, which precludes women who might be pregnant in the first trimester, when they would be unaware of their pregnancy status. Second, other agents could be added to the regimen. Trials are ongoing to test azithromycin [12], which would help reduce malaria, but also have an effect on other pathogens. From a malaria perspective, the addition of transmission-blocking agents such as low-dose primaquine or endectocides such as a higher-dose ivermectin could change SMC from a control to an elimination tool when used in MDA (mass drug administration) campaigns, a transition that comes with even higher safety requirements. Finally, of course, there is a need for new chemopreventive regimens that could be used south of the Equator, since the scientific consensus is that sulphadoxine–pyrimethamine plus amodiaquine will not work in that region, even though the data supporting this are somewhat limited.

Beyond SMC, MDA and use in travellers, chemoprevention is also used for IPTp (intermittent preventive treatment in pregnancy). This is a rather special case, due to (even higher) safety concerns with medicine use for the foetus, which is to be balanced against the enhanced risks of malaria during pregnancy.

Work on chemoprotection raises the question as to whether injectable drugs could be a useful path forwards. In HIV protection, injectable formulations are advancing rapidly in the clinic [13]. For malaria, current chemoprotective drugs provide either one day of protection, in the case of atovoquone-proguanil, or a week's protection, in the case of mefloquine, so moving to once-a-month or once-a-quarter would be a major boon.

Looking for new molecules — defining target candidate profiles

Learning from these successes we can then describe the types of molecules that will form the basis of new medicines. In each treatment, to protect against resistance, there will most likely be more than one active drug, and so it is important to distinguish between the target candidate profiles (TCPs, which describe the individual molecules) and the target product profiles (TPPs, which describe the product), their formulation, and so on. These TCPs and TPPs have recently been redefined and described [14••]. How these TCPs are used to compose TPPs is summarised in Table 1.

Blood schizonticides: TCP1

The majority of the antimalarial portfolio molecules (Table 2; [15••]) in early development through to clinical phase IIb are active against blood schizonts, the *Plasmodium* parasite stage that is responsible for the symptoms and patient deaths from malaria. The ideal type of molecule here is one that kills quickly, and also is capable of maintaining a plasma concentration above the Minimal Inhibitory Concentration (MIC; [16••]) — where killing exceeds growth — for eight days.

The screening cascades developed over the last decade, starting with an assay directly against the parasite, have been probed by almost seven million compounds, and this has led to a whole new generation of compounds, and many new targets [17], all discovered in the last decade. The most advanced are KAE609 [18] and KAF156 [19] which are in development with Novartis, and MMV048 (MMV390048; [20]) which originated from a collaboration between MMV (Medicines for Malaria Venture) and the University of Cape Town (Table 2). KAE609 targets the sodium channel PfATP4, which was a previously largely overlooked target, and MMV048, which targets PfPI 4-kinase, again a somewhat overlooked kinase target.

New molecules also come from two other paradigms: The classical optimisation of existing scaffolds is still important. Starting from the active moiety of artesunate, an artemisinin endoperoxide, a coalition between the Nebraska, Monash and Basel Universities has developed a series of fully synthetic replacements. The first was arterolane (OZ277) which is marketed in India and currently going through phase III trials in Africa with Sun Pharmaceuticals. The second is artefenomel (OZ439;

Table 1

Combining molecules with different Target Compound Profiles (TCPs) for medicines with Target Product Profile (TPPs) 1 or 2; after [14••]. The (X) signifies that TCP1 compounds are only to be included as part of a TPP2 after use in TPP1, further establishing safety

	TPP1: Treating patients	TPP2: Chemo-protection
TCP1: Targeting the asexual blood stage	X	(X)
TCP3: Anti-relapse molecules	X	
TCP4: Targeting liver schizonts		X
TCP5 and 6: Transmission blocking	X	