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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	

Table 2

The pipeline of antimalarials

Late preclinical	Human volunteers [a]	Patient exploratory[b]	Patient confirmatory
SAR121 (SAR 441121); Sanofi	P218 Janssen, Biotec Thailand	Artefenomel (OZ439)/Ferroquine; Sanofi	Tafenoquine; GSK/MMV GSK/US Army
AN13762; Anacor	SJ733 (SJ557733); Rutgers U., NIH, St Jude Children's Research Hospital, USA	KAF156/Lumefantrine; Novartis	Dihydroartemisinin-piperaquine dispersible; Alfasigma/Pierre Fabre
UCT943; U. of Cape Town, South Africa	ACT-451840 Actelion	Cipargamin (KAE609) Novartis	Co-trimoxazole; ITM Antwerp
NPC1161B; Mississippi U., USA	CDRI 9778 Ipca Labs.	DSM265; Takeda; UTSW	Artemisinin-naphthoquine; Kunming Pharma Co
MK4815; MSD	N-tert butyl Isoquine; LSTM/GSK	Methylene Blue/ amodiaquine; Heidelberg U., Germany	Sulfadoxine–pyrimethamine+ Amodiaquine dispersible; S Kant Healthcare Ltd.
M5717; Merck KGaA		SAR97276; Sanofi	
MMV253; Zydus Cadila		Artemisone HKUST	
SC83288; Heidelberg U., Germany		AQ13; Immtech Pharmaceuticals Inc	
DM1157; DesignMedix		Sevuparin; Dilaforette AB MMV048 (MMV390048); U. of Cape Town, South Africa	

[a] May include experimentally infected volunteers.
[b] Testing molecules as monotherapy or combination. GSK, GlaxoSmithKline; MMV, Medicines for Malaria Venture; U., University; ITM, Institute of Tropical Medicine; UTSW, U. Southwestern, Dallas, USA; MSD is known as Merck & Co in the USA; LSTM, Liverpool School of Tropical Medicine; HKUST, Hong Kong University of Science and Technology. Names between brackets are synonyms. Data adapted from www.mmv.org.

[21,22]) which is in phase II trials in combination with ferroquine, in a collaboration between MMV and Sanofi. A third-generation compound in this series is also in development. It was shown that artefenomel is active against the major artemisinin-resistant strains *in vitro* [23] with good confirmation of this in patients as well [24].

The second way to find new starting points is to rationally design molecules based on known or proposed targets. MMV's poster child for this is DSM265 [25,26], discovered in a collaboration led by the University of Texas Southwestern, which is a selective inhibitor of the parasite enzyme dihydro-orotate dehydrogenase (DHODH), currently in phase IIa trials. A second example is the PfDHFR inhibitor P218 [27], which is fully active against all the pyrimethamine-resistant strains, and is currently in phase I.

Originally MMV had designated TCP1 to refer to fast killers of blood schizonticides, and TCP2 to refer to long-acting molecules [28]. However, as new compounds were evaluated the criteria have been reset to the effect that *all* compounds must be fast-acting, and must maintain plasma concentrations above the MIC for at least a week, and so the TCP2 category has been retired (Table 1; [14••]).

Anti-relapse compounds: TCP3

All of MMV's blood-stage families of compounds are tested initially against multiple strains of the two species of *Plasmodium* that most frequently infect humans, and so from early on we also know if they are active against *P. vivax*, in addition to *P. falciparum*. Generally speaking, the phenotypic screening hits are equipotent against both species, however there are exceptions, as for *Plasmodium* DHODH inhibitors, which have less activity in patients with *P. vivax*. Moreover, three additional *Plasmodium* species are known to infect humans.

The other activity that is needed in an ideal medicine is a capacity to kill the dormant stages, or *P. vivax* hypnozoites. The current treatment for this is a 14 day course of primaquine, which was originally worked out in the 1950s. In 2017, with MMV's partner GlaxoSmithKline the next generation compound, tafenoquine [29] completed phase III studies and has been submitted to the US FDA (Food and Drug Administration) for review. Approvals by stringent regulatory authorities such as the US FDA and the Australian Therapeutic Goods Administration pave the way for approval in disease-endemic countries, and also for the process of gaining inclusion in WHO (World Health Organization) guidelines.

For a next generation TCP3 compounds the requirements are not easy to meet: we need a compound that is as effective as tafenoquine, works via a different mechanisms (if ever tafenoquine resistance should come up), and be safer. For tafenoquine comes with the risk of

inducing hemolysis in patients with G6PD (glucose-6-phosphate dehydrogenase) deficiency. The challenge is to discover a molecule that does not present this risk, without introducing any new ones. To discover new molecules we fortunately have now cellular assays to screen for dormant *P. vivax* forms in human hepatocytes, assays that have become available over the last two years [30•].

Chemoprotection, killing liver schizonts: TCP4

As mentioned above there is a renewed interest in using medicines to protect populations. The current gold standard for chemoprotection is atovaquone-proguanil, which kills liver schizonts (the dividing parasites in that organ), but this has the concern that it must be given once daily. The liver stages are an attractive target for protection, because this is where malaria infection takes off, with few parasites (in sharp contrast to the 10^{12} blood-stage parasites that a symptomatic patient may carry). Our search for new classes of molecules actually starts with the blood-stage hits (TCP1) where we find that around half of our scaffolds have liver schizont activity as well as blood-stage activity. Examples of these are DSM265, KAF156 and P218, where the ability to protect the liver has been shown *in vitro* and *in vivo* and, for the first two molecules, also in patients. However, most excitement in this area currently comes from observations in the HIV field, where properly formulated injectable chemoprotectants provide protection for several months. Such a protection duration could be useful in malaria, where one or two injections would protect for the rainy season, and with four injections per year a high level of protection could even be obtained in the hyper-endemic, equatorial regions.

Transmission blocking, targeting the gametocyte: TCP5, or the insect vector: TCP6

The key to bringing down the prevalence and incidence of malaria is to block the transmission cycle, both from mosquito to human and also from human to mosquito. Blocking from human to mosquito can be achieved by killing the (asymptomatic) gametocytes, or sexual stages, since these are the only forms which are transmitted. The standard of care here is low-dose (0.25 mg/kg) primaquine, given as a single dose. Obviously useful would be new classes of molecules with that activity, but also those that have dual TCP1 and gametocyte killing activity. Although primaquine is on the WHO treatment guidelines for combination with ACTs, this is still not rolled out, presumably because of the complication of adding an extra tablet, supply chain issues and perhaps the absence of an immediate benefit to the individual patient. The next generation therapies should be simpler than combining four molecules, if at all possible. Currently all of MMV's pipeline is screened for gametocidal molecules. MMV's partners, too, carry out primary screens on TCP5 activity, but we have so far not found any compounds that kill gametocytes without activity on the blood stages.

The other approach in this area, TCP6, is taken from the veterinary world. Some compounds are given orally to kill ticks and fleas feeding on animals; key examples are the avermectins such as ivermectin, and the isoxazolines such as fluralaner and sarolaner. Such compounds could in theory also be given to humans to kill mosquitoes that feed on them, to prevent transmission, provided adequate safety data were available.

Ivermectin has long been given to patients to kill roundworm infections and also lice, and current clinical data suggest that it may be possible to give a high dose for three days that would block transmission [31,32]. Note that to impact malaria transmission ivermectin does not need to kill the mosquitoes quickly — when ivermectin plasma concentrations drop the drug merely shortens the blood-feeding insect's lifespan [33], but this will prevent completion of the lengthy process of the development of infectious sporozoites. Such a drug could be added to SMC, (in children up to 10 years old), once adequate safety data are available. Wider use in the general population, specifically women above the age of 12 would be precluded until sufficient data had been obtained in first trimester pregnancy. The problem here is that women who are most at risk are those who are unaware that they may be pregnant. With its partners, the IVCC (Innovative Vector Control Consortium), MMV is starting to look for additional examples of compounds with this kind of activity, since these are also needed for toxic sugar bait traps.

Conclusions

The last ten years have seen an explosion in new molecules in the malaria pipeline. Phenotypic screening has led to new compounds for development and also an entirely new collection of druggable targets. Working with its partners MMV has been able to define the characteristics of the ideal molecules, but also set up international open access platforms for gathering and documenting data [34]. One key aspect here is that we always need to be able to compare and contrast molecules on an equal footing, to be able to decide which are the best ones to move forward. The current roll-out of products, treatments and protection teaches us a lot about how to develop better medicines. The development of controlled human infection models [35] then helps us to further prioritise these, providing human data early in development. It is an exciting time to be in malaria drug discovery and development.

Conflict of interest statement

Nothing declared.

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