Malaria medicines: a glass half full?

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Abstract | Despite substantial scientific progress over the past two decades, malaria remains a worldwide burden that causes hundreds of thousands of deaths every year. New, affordable and safe drugs are required to overcome increasing resistance against artemisinin-based treatments, treat vulnerable populations, interrupt the parasite life cycle by blocking transmission to the vectors, prevent infection and target malaria species that transiently remain dormant in the liver. In this Review, we discuss how the antimalarial drug discovery pipeline has changed over the past 10 years, grouped by the various target compound or product profiles, to assess progress and gaps, and to recommend priorities.

Chemotypes
Families of molecules with similar chemical structures that share biological or therapeutic effects. Many distinct chemotypes may have the same biological activity.

Chemoprotection
In the context of malaria, chemoprotection refers to medicines that prevent healthy individuals from contracting malaria. Such drugs are used by travellers but are also considered for mass eradication campaigns.

Malaria is a human tragedy: by one estimate it may have killed half of all the people who ever lived[1] and currently claims the lives of hundreds of thousands of young children every year[2]. Stark as the numbers are, these figures understate the loss of developmental potential for malaria-endemic countries, the impact on their health-care systems and on their economic growth[3,4]. However, the past decade has seen a renaissance in the research and development for malaria medicines[5–7]. The critical factors at play here are an increased collaboration between academia and industry and a focus on finding new chemotypes by screening directly against the parasite. A call for the eradication of malaria by the Bill and Melinda Gates Foundation in 2007 (REF. 8) identified new priorities, such as transmission blocking and chemoprotection in vulnerable populations[9], and new target candidate profiles[10]. The past decade has seen a transformation of the portfolio of malaria medicines, with a dozen or so new chemical entities entering clinical development and breakthroughs in translational research that have enabled human proof-of-concept experiments to be performed rapidly[11] (FIGS 1,2). Not only have new classes of molecules been discovered, but so have new ways of collaborating and methods to accelerate drug development. However, emerging drug resistance threatens all this success. Artemisinin-based combination therapies (ACTs) are used worldwide as the first line of treatments[12], but patients with resistance to artemisinin and its partner drugs are now being routinely identified in Southeast Asia[13–18]. However optimistic the pipeline appears, there is still a need for new chemical agents, especially to prevent relapse of *Plasmodium vivax* infection and to protect vulnerable populations, especially in early pregnancy. Eradication of malaria will take many decades: the challenge is to continually find innovative ways of targeting the parasite. Paradoxically, the lack of commercial incentives for new malaria medicines has a silver lining: it has created a niche in which academia and industry can continue to work together to pioneer new models of collaboration and openness.

The announcement of the United Nations' Millennium Development Goals[19,20] highlighted the eradication of malaria as a key target. The goal outlined in this announcement is to decrease the incidence of malaria by 2015. In 2000, malaria was responsible for 350 million to 500 million infections and more than 1 million deaths, particularly in children under the age of 5 years and in expectant mothers[21]. Progress in the first decade of the new millennium to reduce these frightening statistics was steady but slow, with 4% year-on-year reductions in deaths driven by the roll out of insecticide-treated bed nets[22] and fixed-dose ACTs[12]. In 2007, the Bill and Melinda Gates Foundation, with the support of the Director General of the WHO (World Health Organization), announced a campaign to drive the eradication of malaria. The advantages of such a call were obvious; the elimination of malaria would have tremendous benefits for public health. However, gains made against malaria are fragile, and whenever a country has decreased its public health focus and funding on malaria control the disease prevalence has climbed dramatically[23].

To eradicate malaria, achievable milestones must be set. The publication of the Global Malaria Action Plan (GMAP) by the WHO[24] set some of those milestones; for example, a tenfold reduction in malaria incidence and deaths by 2030 (compared with 2015). The first GMAP was published in 2008 and covered the period until 2015. More recently, input and consultations are being sought from experts and regions for GMAP2. Both GMAP2 and the Global Technical Strategy for Malaria (co-ordinated by the WHO) will cover the 10 years between 2016 and 2025. All these plans and proposals

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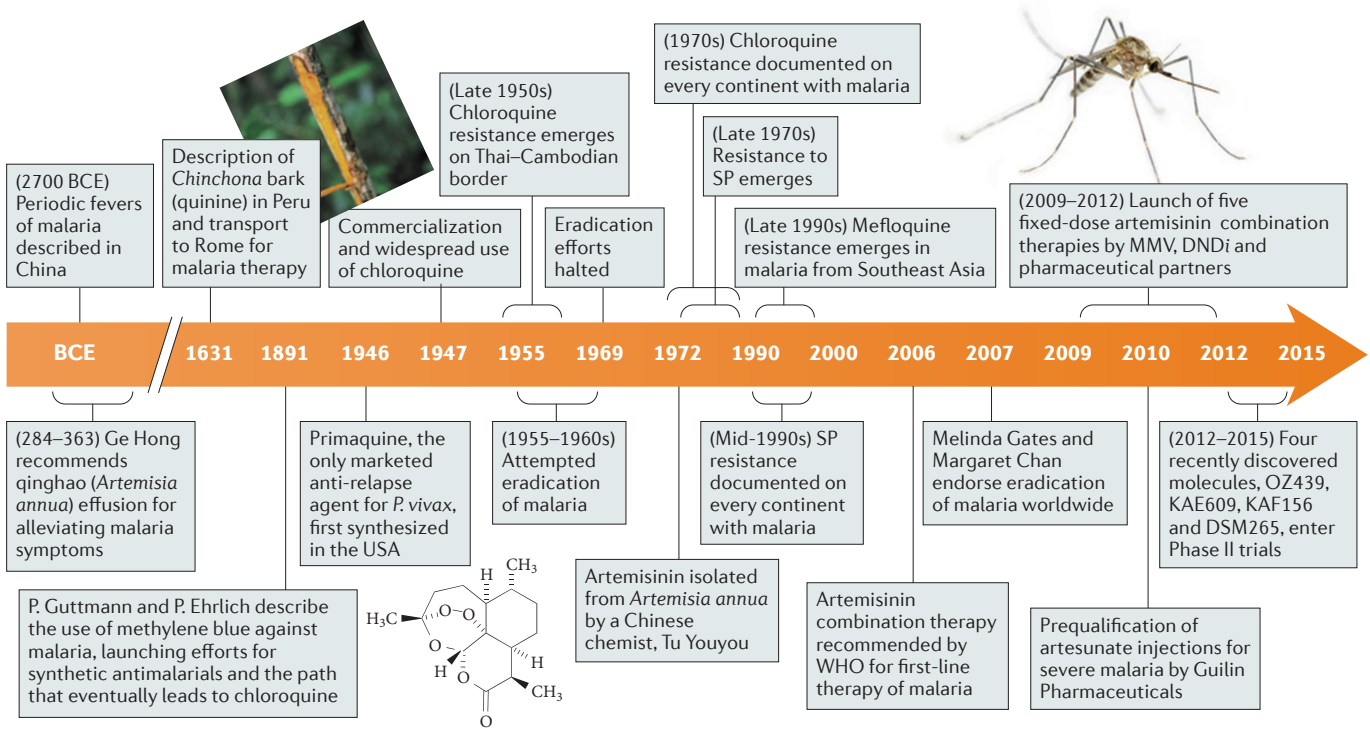

Figure 1 | **Key events in the historical timeline of the discovery of antimalarial therapeutics.** Guided by millennia-old Chinese and South-American ethnobotanical knowledge of medicinal plant extracts that relieve fevers, chemists isolated and described two major classes of antimalarials: the quinines and artemisinins. Inappropriate use of some antimalarials in the mid-twentieth century resulted in the emergence of drug resistance, halting earlier malaria eradication campaigns in the 1960s. Parasite resistance against chloroquine, sulfadoxine–pyrimethamine (SP), amodiaquine and mefloquine is now widespread. Moreover, emergence of resistance in the greater Mekong region in Southeast Asia against the newest antimalarials, artemisinins, and new partner drugs such as piperaquine threatens to reverse recent gains in the battle against malaria. Recently, novel molecules that act on new targets in the parasite have entered clinical development both for the treatment of acute, blood-stage *Plasmodium falciparum* infection and conforming to other malaria-related target compound profiles. DND*i*, Drugs for Neglected Diseases *initiative*; *P. vivax*, *Plasmodium vivax*; MMV, Medicines for Malaria Venture; WHO, World Health Organization. Images (left to right) courtesy of: Worldwide Picture Library/Alamy (bark); Getty Images/iStockphoto Thinkstock Images (mosquito).

call for a transformation of the malaria landscape. That is, even though substantial progress has been made over the past decade with the number of deaths from malaria falling by 4% per year, to achieve a 90% reduction by 2030 we need to accelerate progress to as much as a 10–16% fall each year[24]. As a public health goal, this is audacious and is clearly not a call to business as usual. Along with the widespread deployment of insecticide-treated bed nets, the discovery of new malaria medicines is a key pillar in reducing malaria-associated deaths by this margin Moreover, in the context of malaria eradication, despite considerable progress towards vaccination, no effective vaccines capable of protecting a sufficient proportion of the population to elicit herd immunity are on the horizon (BOX 1).

Since 2000, malaria-associated mortality has been reduced by more than 50%, but emerging drug- and insecticide-resistance continues to pose a major threat[2]. Insecticides continue to be at the front line, both as larvicides and as part of insecticide-treated bed nets. Although tremendous gains have been made as a result of wider distributions of bed nets[22], new classes of insecticides are urgently needed to combat the emergence of resistant mosquito strains. Currently, only pyrethroid is approved for use with bed nets, and resistance among malaria vectors is increasing[25].

Medicines have also had a tremendous impact on reducing malaria-associated mortality, and ACTs have been used to treat hundreds of millions of patients, following the isolation of the active ingredient, artemisinin, by Chinese researchers. Here, the landscape has changed dramatically in the past 5 years, and five types of fixed-dose ACTs have been approved by either Stringent regulatory authorities or prequalified for purchase by the WHO (BOX 2; FIGS 1,2; TABLE 1).

These successes, however, are no grounds for complacency. We need to protect the medicines we have by ensuring correct deployment and continual vigilance to stop the production and distribution of counterfeit medicines. Even with fixed-dose combinations there remains a risk of resistance emerging, and therefore a need for new medicines. New molecules should shorten the duration of treatment and increase compliance, and also prevent the transmission of the parasite back to the insect vector. If the parasite reservoir is going to be eliminated, medicines have to demonstrate a level

Target candidate profiles
A specific set of quantitative criteria that a molecule must be predicted of achieving before it is considered for development. These criteria typically involve biological activity, pharmacokinetics and, in malaria, cost of goods. The target product profile is the definition of the specifications for the final medicine, which, for malaria, may consist of several active molecules.

Herd immunity
Immune protection that occurs when an entire population, including those without immunity themselves, is protected from an infectious disease owing to the high rate of immunity within that population.

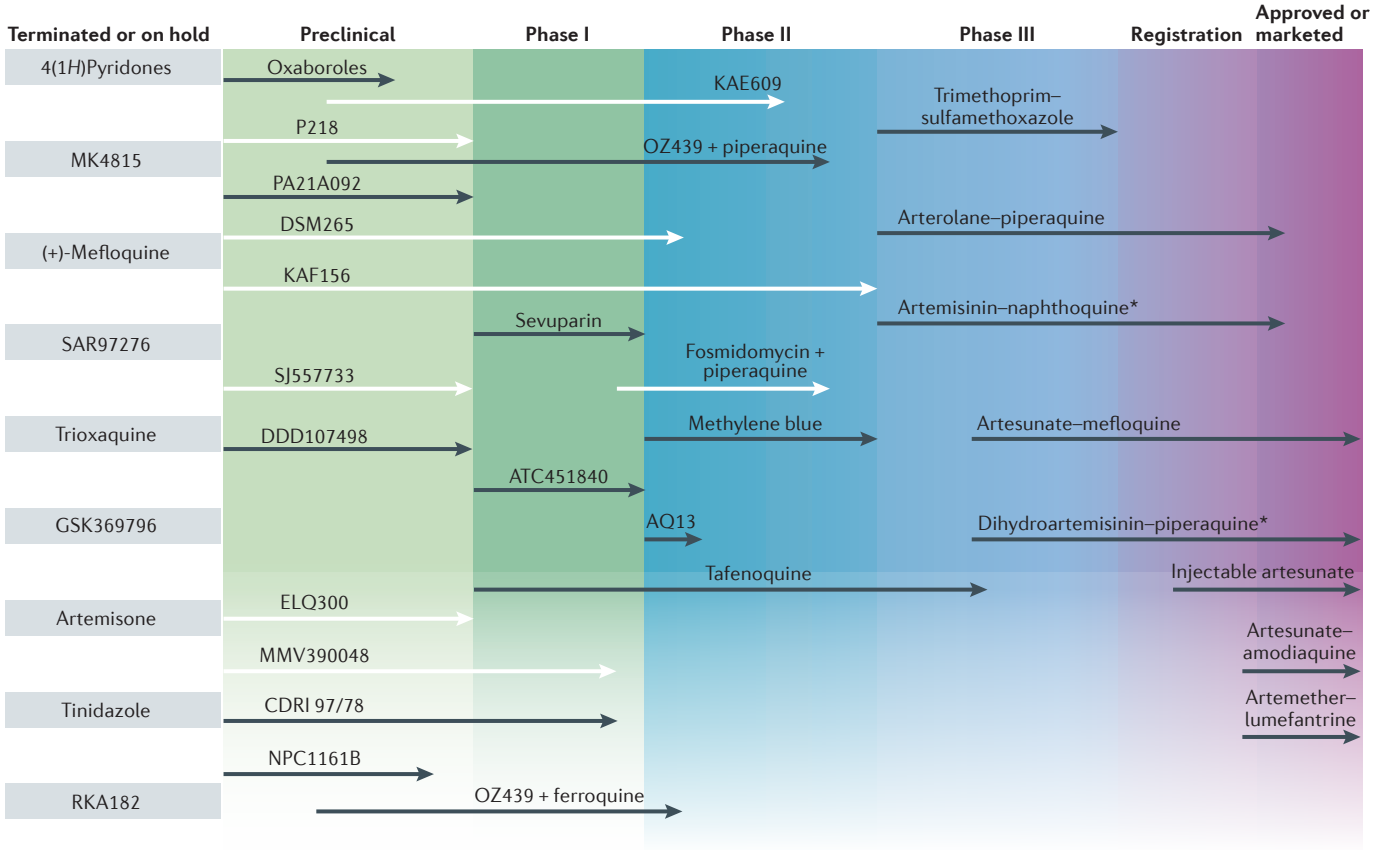

Figure 2 | **Progression of the clinical development of new antimalarial candidates over the past 5 years.** Drug candidates with white arrows have molecularly defined targets. Some molecules have been approved by disease-endemic countries and not by stringent regulatory authorities or prequalified by the WHO (World Health Organization), and these are indicated by asterisks. This local marketing may be due to the fact that either the manufacturing sites have not been inspected to international standards or that the clinical data are still limited, especially in areas of clinical safety. The injectable form of artesunate is marketed as Artesun. The fixed-dose combination (FDC) of artesunate–mefloquine is marketed as ASMQ; the FDC of artesunate–amodiaquine is marketed as ASAQ Winthrop; the FDC of artemether–lumefantrine is Coartem-Dispersible, for which several generic versions have been prequalified; the FDC of dihydroartemisinin–piperaquine is Eurartesim; and the FDC of arterolane–piperaquine (arterolane is the international non-proprietary name (INN) for OZ277) is marketed as Synriam. Two of the newer compounds already have an INN: cipagamin for KAE609 and artefenomel for OZ439. Phase II includes both Phase IIa (tests of compounds in patients as monotherapies) and Phase IIb (tests of compounds in patients as combination therapies). Note that the width of the panels does not reflect the large differences in required time, costs or the probability of success of the individual drug development phases.

Stringent regulatory authorities
Regulatory agencies from the European Union (for example, the European Medicines Agency), the USA (the Food and Drug Administration) and Japan (the Ministry of Health, Labour, and Welfare), all of which are members of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), and other agencies that adhere to the same guidelines, such as in Switzerland, Australia and Canada.

of safety such that they can be given to people who are infected with extremely low levels of parasite and are asymptomatic. New molecules that can either prevent relapses from *P. vivax* or *Plasmodium ovale* infection or that can provide chemoprotection for vulnerable populations, including expectant mothers, are also needed. This need for protection will only increase as the malaria eradication agenda proceeds. People in areas that are currently disease-endemic will have fewer infections, will lose their partial immune protection and will need chemoprotection when entering the remaining disease-endemic areas. In this article, we summarize the discovery of new classes of medicines, illustrated with several case studies, to underline the progress made and also the challenges that remain in treating and preventing malaria.

Eradication requires different types of drugs

In 2007, the global agenda for malaria eradication brought together several themes to describe the perfect medicine for treating malaria, termed the SERCaP (single exposure radical cure and prophylaxis)[8]. However, it soon became clear that no single chemical entity could meet these needs and therefore the ideal medicine would be a combination of two or more ingredients, each of which meets a number of different target candidate profiles[10]. The first question is how to treat malaria with a single exposure to a drug: the current gold standard for treating malaria is a 3-day course of an ACT. Moving to a single exposure would mean that a health worker could directly observe the administration, and this could provide a critical advantage in a malaria eradication campaign. Currently, one major concern in the field

Box 1 | **Malaria vaccine development**

Much of the optimism for malaria eradication has centred on the launch of a vaccine. Developing a vaccine against this pathogen is a tremendous challenge: even after multiple infections, adults in malaria-endemic regions naturally acquire only partial immune protection against the disease[109]. Despite considerable efforts over the past 40 years, there is currently no approved malaria vaccine.

Malaria is a protozoan disease, with active antigenic variation that distinguishes it from the viruses and bacterial toxins that have been highly successful vaccine targets[110]. Until now, there have been no human vaccines developed for any protozoan disease — including Chagas disease, African sleeping sickness, visceral leishmaniasis, cryptosporidiosis and giardiasis — other than malaria. The most advanced malaria vaccine, Mosquirix (the peptide RTS,S and the proprietary AS01 adjuvant, which contains monophosphoryl lipid A and QS-21), was co-developed by GlaxoSmithKline, the PATH Malaria Vaccine Initiative, the Walter Reed Army Institute of Research, USA, and the Bill and Melinda Gates Foundation. Mosquirix provides efficacy against all episodes of malaria with 55% protection in children but only 33% protection in infants[111]. Mosquirix was submitted to the European Medicines Agency (EMA) for scientific opinion under Article 58 in June 2014, with a decision expected in 2015 (Article 58 allows the EMA to provide a scientific opinion even though the vaccine will not be marketed in the European Union). Even Mosquirix's partial protection will save lives in Africa. However, its deployment still faces major hurdles such as affordability, determining which populations will receive the vaccine, and how the three to four doses required will be distributed and implemented in childhood immunization programmes in Africa.

There are currently no other malaria vaccines in late-stage Phase III trials[112]. Alternative strategies of thinking are needed, perhaps a return to more classical whole-organism-based vaccines such as PfSPZ[113], which comprises attenuated *Plasmodium falciparum* sporozoites. This general type of vaccine successfully prevents protozoan disease in veterinary medicine[114]. In the clinical setting, PfSPZ was administered 4–6 times intravenously, which also raises significant issues in terms of production, delivery and costs. Increasing the response to the antigen by simply increasing the power of the adjuvant risks inappropriate immune stimulation[115]. The choice of adjuvant for human use is more restricted than in veterinary practice, and it is not easy to predict human efficacy from animal models[116] (both for antigenicity and adjuvant). Another concern with recombinant antigens and protozoans is that they enable the pathogen to easily reduce its immunogenicity through genetic drift. Even without relying on population-level mutations, protozoans are masters of antigenic variation: *Plasmodium* spp. carry approximately 60 variants of the *var* family of surface protein-encoding genes[117] and switch between these during a single infection to evade host immune response[118]. As a comparison, the genomes of trypanosomes encode ~1,000 variants of their variant surface antigen, and the parasites switch these episodically during infection[119]. Malaria vaccines are species-specific, and almost all vaccines in the clinical pipeline (24 of them) target *P. falciparum* and not *Plasmodium vivax* (the exception is PvDBP)[112]. Many candidates target the pre-erythrocytic stages. However, recently there has been a prioritization of vaccines that would prevent transmission of the parasite. Such vaccines will require new regulatory and clinical development strategies as the benefit would be for the community as a whole rather than for the individual patient.

is that the patient frequently does not take the full course of treatment; for example, if the symptoms are resolved rapidly, the danger is that a mother will save the remainder of the treatment for the next time her child is infected. Exposing parasites to subtherapeutic doses leads to more treatment failures and recrudescence of the original malaria parasites, which then encourages the emergence of resistant strains.

A single-exposure cure places a very high barrier for any new molecule: a hyperparasitaemic patient may carry as many as 1×10^{12} parasites in the circulation. Clinically, an acceptable cure rate would result in >95% of treated patients clearing the initial infection, which can be achieved with currently available ACTs. Even though new molecules would be used in combinations (to protect against the emergence of resistance), each active ingredient should still ideally be capable of killing a large proportion, if not all, of the parasites on its own. Medicines such as artesunate are capable of rapidly killing the parasite, reducing the parasite load by as much as 10,000-fold over a single 48-hour life cycle[26]. Nevertheless, such medicines would need to be active for three or four parasite life cycles to ensure a complete cure[27]. New medicines active against the blood stages would therefore need both a 'fast kill' profile and be able to maintain a plasma concentration above the minimal inhibitory concentration (MIC) for more than 1 week. Longer duration of action could be also useful in some parts of Africa to provide post-treatment protection, in areas where a child can be bitten almost every night. Five years ago, conventional wisdom dictated that the choice was between short-acting and fast killers, such as artemisinin derivatives, or long-acting drugs with relatively slower parasite reduction rates. It is encouraging to note that many of the new generation of antimalarials are both fast-acting and can maintain active plasma concentrations for more than 1 week. This reflects the increased focus on attempting to increase the *in vivo* half-life of compounds in the early stages of the drug discovery process.

Another drug class needed in the ongoing battle against malaria is the chemoprotectants. Chemoprotectants should be safe and effective drugs to prevent infection, particularly in vulnerable populations such as expectant mothers and small children, and all residents in areas where continuous, intense transmission is absent and partial malaria immunity does not develop (also known as seasonal chemoprevention). Until recently, the sulfadoxine–pyrimethamine combination has been used for this purpose, but with the emergence of resistance against this combination[28,29] chemoprevention is threatened[30]. New medicines for chemoprevention are therefore needed, and molecules that have activity against the liver schizont stage of the parasite are good chemoprotectants. However, the vulnerability of the target group means that safety and efficacy of such medicines must be first demonstrated in less vulnerable populations. The goal in this strategy is not so much to design new compounds that are safe for chemoprotection in these populations, but instead to accelerate reproductive and juvenile toxicology studies, including for approved drugs, and deprioritize compounds for which significant concerns are raised.

Requirements for eradication

Eradication requires completely different approaches to simple control. One key intervention is to block the transmission cycle; that is, stopping parasite-carrying humans from infecting the mosquitoes. Only the sexual stages of the parasite survive after being taken up in the blood meal of the mosquito when she feeds. Therefore, a medicine that can selectively kill the sexual stages or prevent the completion of their development in infected mosquitoes would halt malarial transmission. Although it is possible to think of new medicines that only target transmission, many of the new compounds currently in development both block transmission and kill the blood stages.

Prequalified
The WHO (World Health Organization) prequalification process is a formal assessment of diagnostics, medicines and vaccines, including review of the clinical dossier and the manufacturing and stability data, and site visits to manufacturers. This is a centralized procedure to approve products for purchase by specialized agencies of the United Nations.

Box 2 | **New artemisinin-based combinations and recent new product launches**

A child-friendly taste-masked artemether–lumefantrine combination (Coartem-Dispersible) developed by Novartis in collaboration with the Medicines for Malaria Venture (MMV), was approved in 2009 by Swissmedic and more recently by the European Medicines Agency (EMA) and the US Food and Drug Administration. A fixed-dose amodiaquine–artesunate combination (ASAQ-Winthrop), developed by Sanofi in collaboration with the Drugs for Neglected Diseases *initiative* (DND*i*) was prequalified by the WHO (World Health Organization) in 2008. In both cases, more than 250 million courses of treatment have been distributed in the past 4 years at affordable prices: as low as US$0.25-0.50 for the youngest children.

Three other new fixed-dose artemisinin-based combination therapies (ACTs) have also been launched: dihydroartemisinin–piperaquine (Eurartesim), developed by Sigma Tau with MMV and approved by the EMA in 2011 (REF. 120); pyronaridine–artesunate (Pyramax), developed by Shin Poong Pharmaceutical with MMV (which was the first medicine to be given a positive scientific opinion by the EMA under the Article 58 process in 2012); and artesunate–mefloquine, a collaboration led by the DND*i* (the drug is now manufactured by CIPLA), which was prequalified by the WHO in 2012. From a regulatory perspective these are seen as originator combinations, with a complete dossier of clinical trials. Other companies are now able to make generic versions, requiring only good manufacturing practice data and comparative bioequivalence, and several such versions now exist.

The second major transformation has been the availability of new treatments for severe malaria. Clinical studies have demonstrated the superiority of injected artesunate over the classical treatment of injected quinine[121,122]. At the time of the studies, no product existed that was either prequalified by the WHO or approved by a stringent regulatory agency. Guilin Pharmaceuticals achieved prequalification for an injectable artesunate in 2010 (Artesun), and to date 25 million vials have been distributed. After more than a decade of research, two generic manufacturers are producing suppositories of artesunate for re-referral treatment, and these are anticipated to be submitted to the WHO Medicines Prequalification Programme in 2015.

In terms of chemoprotection, non-immune travellers have two main options: atovaquone–proguanil (Malarone), which has the limitations of high cost and daily dosage, and mefloquine, which was discovered at the Walter Reed Army Institute of Research, USA, and has increasingly been under pressure owing to psychiatric side effects[123]. Malarone's high costs are mainly associated with the cost of synthesizing atovaquone, but beginning in 2011 a generic version (marketed by Glenmark) became available at a cost of approximately $3 per day for the adult dose — a 50% cost reduction. The raw materials account for ~25% of this cost, suggesting that there is margin for further cost reduction. Mefloquine is a racemic mixture with significantly different pharmacokinetics and pharmacology between the two enantiomers. It was believed that the binding of (–)-enantiomer to adenosine receptors was responsible for the psychiatric side effects, but a trial with the (+)-enantiomer failed to demonstrate improved safety[124].

In the absence of a fully effective vaccine, chemoprotection in Africa is essential for vulnerable populations, such as expectant mothers and young children. So far, chemoprotection has had to rely on older medicines. There has, however, been substantial progress in the use of the sulfadoxine–pyrimethamine combination to protect pregnant women[125]. Studies in the Sahel region[122,126], where malaria is seasonal, showed that monthly use of sulfadoxine–pyrimethamine plus amodiaquine reduced malaria incidence by 75%[126] at a cost of less than $0.60 per year; this regimen is now being used to protect millions of children[2]. Here, the synergy of academic medicine combined with the engagement of pharmaceutical manufacturers (in this case Guilin Pharmaceuticals, China) was a critical success factor.

Blood stages
Early steps in the asexual, intra-erythrocytic replication cycle include the attachment of the *Plasmodium* spp. merozoites to blood cells, reorientation, irreversible attachment, junction formation, parasitophorous vacuole formation and invasion. The resulting immature trophozoite ring stage progresses into the mature tro-phozoite and schizont stages, which ruptures the blood cell to release new merozoites.

Standard membrane feeding assays
Assays that measure the transmission of *Plasmodium* parasites back to mosquitoes; the insects' uptake of blood gametocytes and their successful mating is measured by counting (post-zygotic) midgut oocysts (the only route to re-infection). These assays involve mosquitoes feeding on human blood or serum through a membrane.

In 2012, the WHO recommended that adding a single dose of primaquine (0.25 mg per kg) to current treatment regimens would help block transmission[31]. The next generation of medicines could have this transmission-blocking component already built in; some of the current candidates do provide partial inhibition of transmission in standard membrane feeding assays. The second requirement is that medicines should be usable in mass screen-and-treat campaigns to remove the parasite even from patients who are asymptomatic. The major difference in such usage of new antimalarials compared with conventional treatment is that these medicines must demonstrate exceptional safety, and therefore larger investments in Phase IV safety studies will be needed.

Treating relapses from *P. vivax* and *P. ovale*

Although 90% of global malaria fatalities are caused by *Plasmodium falciparum*, up to 2.5 billion people are at risk from *P. vivax*, which is mostly prevalent in South America and Asia[32]. *P. vivax* has an additional complication in its life cycle: dormancy. Forms of *P. vivax* can remain dormant in the human host from a few weeks to several years, and then re-emerge and cause a new infection[32]. Radical cure means effectively clearing the body of parasites, including those that are dormant. The target candidate profile for this type of malaria (which we have called TCP3b)[10] is based on finding a molecule better than primaquine. Fourteen days of primaquine treatment is sufficient to completely eradicate *P. vivax* in the body. However, primaquine has an Achilles heel: in patients who are deficient in glucose 6-phosphate 1-dehydrogenase (G6PD), primaquine causes a significant increase in the risk of haemolysis[33]. G6PD deficiency segregates with protection against malaria. New agents will need to be as effective as primaquine but with a shorter regimen and preferably an improved safety profile.

In 2014, the completion of a clinical study of a new 8-aminoquinoline, called tafenoquine, provided a breakthrough in this regard. Tafenoquine was discovered by researchers at the Walter Reed Army Institute of Research, USA, and developed by GlaxoSmithKline with support from the Medicines for Malaria Venture (MMV). The clinical study showed that tafenoquine could have the same therapeutic effect after a single dose as 14 days of primaquine (but the study was not powered to show this statistically)[34,35]. The hope is that tafenoquine will be

Table 1 | **WHO prequalified and/or EMA- or US FDA-approved ACTs**

Drugs	Trade names	Partners and/or initial manufacturer	Formulation	Approval date	Stringent Regulatory Authorities granting approval
Artemether–lumefantrine	Coartem, Coartem-Dispersible, Riamet, Faverid, Amatem, Lonart, AL	Novartis (Coartem, Riamet), MMV/Novartis (Coartem-Dispersible); generic versions of CIPLA, IPCA, Strides and Guilin	Tablet (adult), dispersible flavoured tablets (paediatric)	2001 (adult) and 2009 (paediatric), Swissmedic	Swissmedic, EMA, US FDA, WHO prequalified
Artesunate–amodiaquine*	Coarsucam, ASAQ-Winthrop	Sanofi, DND*i*, MMV	Dispersible tablets for all ages	WHO prequalified and approved in Morocco (2007), a non-stringent regulatory authority (SRA)	WHO prequalified; stringent approval not yet granted
Dihydroartemisinin–piperaquine	Eurartesim, Duo-Cotecxin	Sigma-Tau/MMV (Eurartesim), Beijing Holley-Cotec (Duo-Cotecxin)	Tablet (adult, paediatric), dispersible formulation for children (submission in 2015)	2011, EMA and WHO prequalified	EMA
Pyronaridine–artesunate	Pyramax	Shin Poong Pharmaceutical, University of Iowa, USA, MMV	Tablet (adult), sachet with granules (paediatric; submission in 2014)	2012, EMA (Article 58); WHO prequalified. Approved by the Korean FDA in 2011, and for use in Vietnam and Cambodia in 2014	EMA
Artesunate–mefloquine	ASMQ, Mefliam Plus, Artequin	Farmanguinhos, DND*i*, CIPLA, Mepha	Tablet (adult, paediatric)	2012, WHO prequalified; Artequin (Mepha) originally approved by Portugal's SRA	Stringent approval not yet granted

ACT, artemisinin-based combination therapy; CHMP, Committee for Medicinal Products for Human Use; DND*i*, Drugs for Neglected Diseases *initiative*; EMA, European Medicines Agency; EU, European Union; Farmanguinhos, The Institute of Drug Technology, Brazil; FDA, Food and Drug Administration; MMV, Medicines for Malaria Venture; WHO, World Health Organization. *Fixed-dose combination generics are manufactured by Ajanta, IPCA and Guilin Pharmaceuticals, and co-blistered generics are manufactured by Strides and CIPLA. Information in this table is from REF. 6.

submitted to the regulatory authorities in 2016–2017. However, it still has the haemolytic liabilities of primaquine and will require a point-of-care G6PD diagnostic test; thus, there is room for improvement. New approaches to eliminate the dormant liver stages or hypnozoites require a better understanding of their basic biology. Moreover, the mechanism of action of primaquine is unknown, so the only way to find new drugs is to directly study the effect that compounds have on relapse, as discussed under phenotypic screening below.

Blanket protection: leaving nobody behind

It is an interesting paradox that although many individuals use chemoprophylaxis against malaria as a personal safeguard, this is frequently downplayed as an approach in public health. Recent data on the use of sulfadoxine-pyrimethamine plus amodiaquine in the Sahel region helped bring more perspective in this regard. Monthly administration of chemoprotection for the 4 months of the transmission season is extremely inexpensive — less than US$0.60 per child — and is highly effective[126]. This sets a very high hurdle for a future vaccine in terms of cost effectiveness.

To expand chemoprotection there are three main populations that need to be considered. First, new molecules need to be developed that can be used in eastern Africa, where sulfadoxine–pyrimethamine resistance could limit the usefulness of the sulfadoxine–pyrimethamine plus amodiaquine combination[36]. Second, to protect the entire population, new medicines suitable for use in pregnant women are also a priority, especially because pregnancy increases the risk of malaria infection[37]. However, African women often do not report pregnancy in the first trimester; therefore, any drug that is given to the general population should ideally be known to be safe in pregnancy. To help address this issue, reproductive toxicology evaluation of new medicines should be accelerated. Typically, reproductive toxicology evaluation is performed during the Phase II studies of a new chemical entity. Currently, at MMV this evaluation is being performed in parallel with Phase I studies, but in the future it should be conducted as part of the preclinical work-up. The third and final group that needs protection is the non-immune travellers. Traditionally, these individuals have not been part of the public health agenda. However, as malaria starts to be eliminated from regions of the world, new non-immune populations will begin to emerge, and mobility becomes a major risk factor. One country with this dichotomy is Zambia, where the disease is beginning to be controlled in many parts in the south of the country, but in the north there are areas where malaria incidence in children aged 5 years

Hypnozoites
Latent liver stages of *Plasmodium vivax* and *Plasmodium ovale*, species that are predominant in South and Southeast Asia and South America but only in Ethiopia and Sudan in Africa. Hypnozoites can remain dormant for weeks or even years, and carriers remain symptom-free until a relapse occurs.

and under is greater than 15%[38]. New chemoprotective regimens are needed that can protect workers from the south of Zambia (or even from other essentially malaria-free zones) travelling to the north. As the pipeline of new medicines to treat malaria grows and strengthens, the pressure to increase the focus on new types of chemoprotection will increase.

Strategies for developing new medicines

Improving on existing success: expanding the medicinal arsenal. The gold standard of malaria treatment is the ACT. This is a fixed-dose combination of an artemisinin derivative (artesunate, artemether or dihydroartemisinin) and a 4-aminoquinoline or aminoalcohol, compounds that trace their ancestry back through chloroquine and eventually to quinine (which was first used in Europe in the seventeenth century) (FIG. 3). Given that artemisinin endoperoxides and their derivatives, such as artesunate, are the mainstay of current therapy, these endoperoxides are logically good starting points for drug discovery. However, one of the biggest concerns with artesunate is that the raw material is derived from plants and there is an 18-month lead time between demand for this material and its supply. This lag in demand and supply has sometimes caused catastrophic changes in price: artesunate prices have varied as much as fourfold in the past decade. In 2002, the MMV in collaboration with the University of Nebraska, USA, Monash University, Australia, and the Swiss Tropical Institute (now known as the Swiss Tropical and Public Health Institute) began a collaboration to attempt to make a fully synthetic endoperoxide molecule that was as effective as artesunate and also as affordable as artesunate at its best price ($400 per kg).

Although there has been much progress in simplifying the total synthesis of endoperoxide antimalarials[42–44], we are still a long way from achieving a cost-competitive total synthesis. The result of the initial work was OZ277 (FIG. 4), developed through a partnership between the MMV and Ranbaxy, and subsequently called Rbx11160 or arterolane, the synthesis of which was efficient, with a cost of $800 per kg, less than artesunate at its peak price. The activity of arterolane in clinical studies was in the same order of magnitude of activity as the marketed artemether–lumefantrine combination (Coartem; Novartis)[45]. Ranbaxy continued with the development of arterolane, in partnership with the Department of Science and Technology of the Government of India, combining arterolane with the 4-aminoquinoline piperaquine. A limited Phase III programme has led to the submission and eventual approval of arterolane–piperaquine (under the trade name Synriam) in India in 2013, followed by approval in seven African Nations in 2014, although the medicine has yet to be approved by a stringent regulatory agency or prequalified by the WHO. At 120 Indian Rupees ($2), Synriam is cheaper than many of the marketed ACTs, although the price of these may fall with the anticipated marketing of Sanofi's new, semisynthetic artemisinin. The rapid approval of Synriam based on a single study, and the fact that in the first year the drug was used to treat almost one million patients in India, highlights another issue in malaria drug development: the involvement of local companies can significantly enhance the impact of a medicine.

The original team that developed OZ277 continued with the discovery and development of other new synthetic endoperoxides. At this time the Phase IIa results for OZ277 were available and there were already suggestions that the next-generation compound could solve the issue of artesunate price fluctuations and also have a much longer half-life — with plasma exposures above the MIC for more than 1 week — and therefore could be part of a shorter course of treatment or a single-dose cure. The resultant molecule, OZ439 (also known as artefenomel), has now progressed to Phase IIb combination studies, whereby it is being tested in combination with piperaquine, registered at ClinicalTrials.gov as NCT02083380. The challenges for both OZ439 and OZ277 include the extent to which they can differentiate themselves from their artemisinin heritage. First, artemisinin resistance — or, more correctly, artemisinin insensitivity — is a substantial concern. For example, in patients in western Cambodia there is a clear change in the kinetics of parasite killing but an unclear effect on the half-maximal inhibitory concentration (IC_{50}) for artesunate[46,47]. Analysis of the parasites has suggested that the cause of this insensitivity is in the early ring stages of the parasite[48] and that the *kelch13* gene has a role[16]. The first Phase IIa clinical study of OZ439 showed no strong correlation between *kelch* genotypes and the speed of parasite killing, and the *in vitro* data on the early ring stages confirmed that OZ439 is fully active on artemisinin-resistant strains (J. Möhrle and D. Menard, personal communication); more data from ongoing clinical studies will shed further light on this issue. Additionally, one Achilles heel for artemisinin derivatives is that they have been associated with reproductive toxicology: their actions in the embryonic yolk sac in rats have suggested that there might be a risk of spontaneous abortions in the first trimester[49]. There are no clinical data on the use of OZ277 or OZ439 in pregnancy, but both OZ277 and OZ439 show a safety margin almost a hundred times higher than artemisinin derivatives in preclinical embryo–fetal developmental safety studies.

Improved 4-aminoquinolines are also being pursued. Ferroquine is a good example of such a candidate[39,40] (FIG. 3); it is a ferrocene moiety coupled to a 4-aminoquinoline and could theoretically kill the parasite even faster owing to the capacity of ferrocene to generate parasite-killing radicals[41]. However, improving upon 4-aminoquinolines will be difficult because historical data on 4-aminoquinolines suggest that as monotherapies they kill as fast as artesunate. Ferroquine is being developed by Sanofi in combination with OZ439 (FIG. 4; TABLE 2). All new compounds must be fully active against the existing collection of primary *Plasmodium* strains, and, promisingly, ferroquine is active against chloroquine-, amodiaquine- and mefloquine-resistant strains[39].

The global portfolio of antimalarials contains two other interesting endoperoxides: artemisone (also known as BAY-44-9585)[50], which is a derivative of artesunate at the 10-position and is a potential replacement for

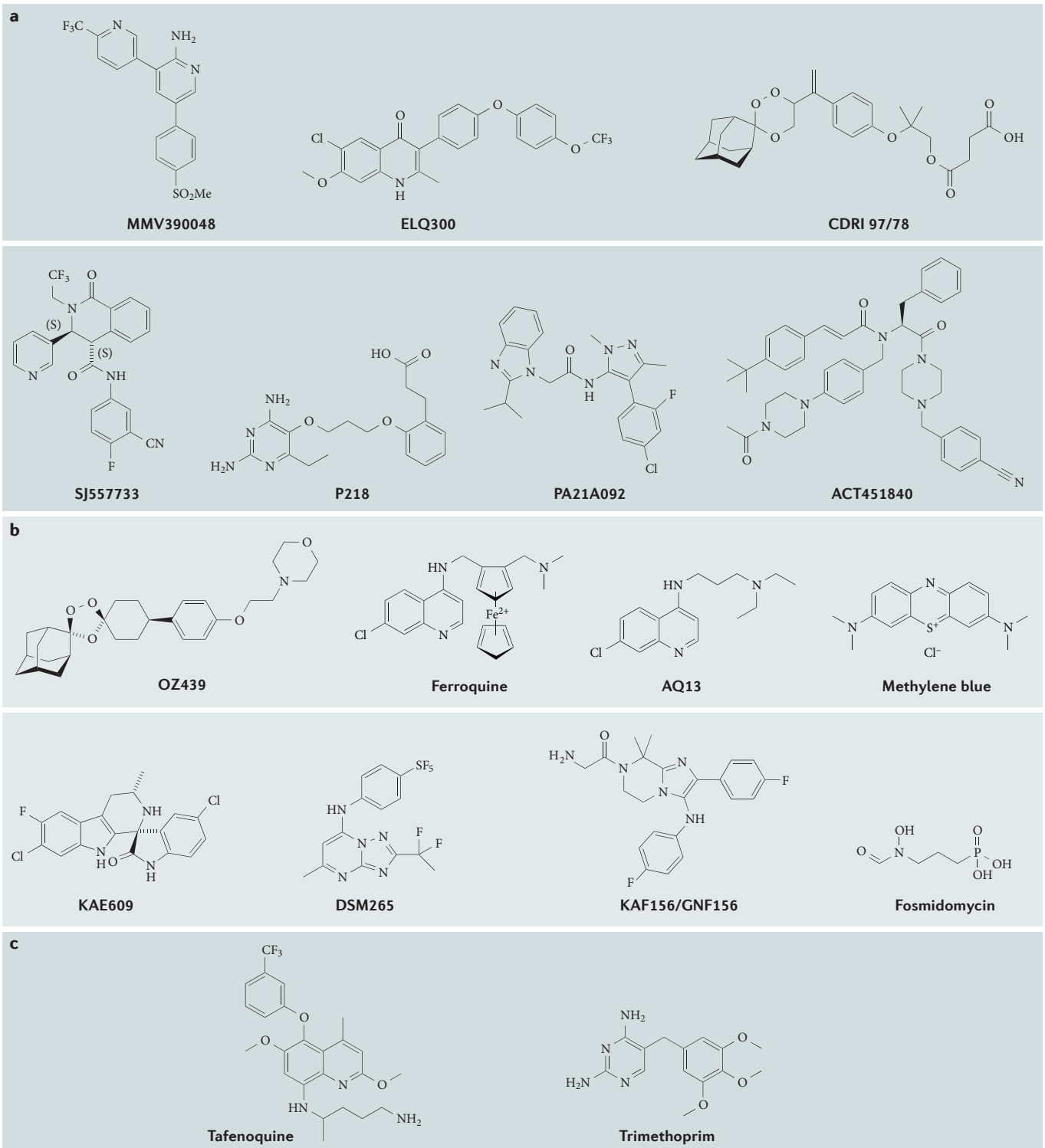

Figure 3 | **Structures of some new experimental antimalarial molecules in clinical trials.** The portfolio presented here represents a chemically diverse set of compounds that are in Phase I (part **a**), Phase II (part **b**) or Phase III (part **c**) clinical trials. These compounds inhibit diverse targets, with a few synthetic trioxolanes (CDRI 97/78, OZ439) that contain the endoperoxide active group found in artemisinin, but are otherwise structurally unrelated. KAE609, SJ557733 and 21A092 are molecules that inhibit a novel *Plasmodium* target, Na^+-ATPase 4; MMV390048 is an inhibitor of phosphatidylinositol 4-kinase. P218 is a selective inhibitor of the *Plasmodium* dihydrofolate reductase. DSM265 is an inhibitor of dihydroorotate dehydrogenase and KAF156 is an inhibitor of the cyclic amine resistance locus. The portfolio also includes molecules discovered more than a decade ago, such as fosmidomycin and tafenoquine. Some compounds, such as methylene blue and trimethoprim, have been registered for other indications, and are being clinically evaluated for malaria.

artesunate, and the tetraxoane TDD E209, the next generation compound following RKA182, which was discovered by researchers at the University of Liverpool, UK[51]. The challenge for both of these newcomers is similar to the new endoperoxides currently in clinical trials: to demonstrate a significant advantage in one of the following: safety, compliance, activity against resistant strains or reduced cost compared with other compounds in development.

The 4-aminoquinoline scaffold is relatively old, and few other compounds have been developed based on this scaffold. AQ13 is one example[52] (FIG. 3; TABLE 2), and many compounds have been proposed to have dual activity or to be used as fusion compounds[53]. Here, caution is advised, as optimizing two activities while retaining safety is not a simple task. The primary issue with all 4-aminoquinolines, even chloroquine, is their potential for prolongation of the cardiac QTc interval, which may be associated with torsades de pointes and cardiac sequelae[54]. Interestingly, it seems that all the 4-aminoquinolines have the potential to prolong the QTc interval, but in a recent review of 16,382 patients taking piperaquine, no drug-related sequelae have been observed, indicating that these compounds are probably among the exceptions to the strong correlation between QTc and torsades de pointes[55].

Better by design: the power of structure to improve a molecule. The classical drug discovery paradigm of the past 20 years, fuelled by the genomic revolution, has been to identify a molecular target, perform experiments that satisfy one's confidence in the role of that target in human disease and then find an inhibitor by high-throughput screening, often combined with three-dimensional structure elucidation[56]. A good example of this process for malaria is the recent development of DSM265, an inhibitor of *Plasmodium* dihydroorotate dehydrogenase[57]. The validation of targets in malaria is always imperfect because it consists of making a gene-deficient parasite and showing a lack of viability. Screening of early-stage compounds against the dihydroorotate dehydrogenase enzyme and the high-resolution crystal structure identified a conformationally induced hydrophobic inhibitor-binding pocket at the end of the nucleotide ring where additional binding interactions could be made[58] (FIG. 4).

DSM265 has an interesting parentage because it was suggested at a meeting between erstwhile competitors: the University of Texas, USA, Harvard University, USA, GlaxoSmithKline and Genzyme. DSM265 was also one of the first molecules to take advantage of the early availability of data from the human experimentally induced infection model. Currently, the Queensland Institute of Medical Research, Australia, is studying the effect of medicines on the speed of parasite reduction in human volunteers with very low level, subclinical infections[59]. In these data and other unpublished observations, parasite reduction rates are similar between volunteers with thousands of parasites per millilitre of blood and patients with thousands of parasites per microlitre of blood for the major classes of antimalarials tested so far. PCR-based parasite detection methods enable monitoring and treatment of the volunteers before they develop malaria symptoms. Another advantage of working with Australian volunteers is that they have no immune protection against the parasite: in that sense they are as naive as children in Africa but are otherwise healthy and robust. We were able to test DSM265 in a challenge cohort only 7 months after the first-in-human (Phase I) study[160], which provided an early readout as to the efficacy and pharmacodynamics in 'real' patients and therefore confidence to select a dose for the upcoming patient studies. This compound began Phase IIa monotherapy studies in Peru in early 2015; Peru, as with many South American and Asian countries, has both *P. falciparum* and *P. vivax* infections.

A renaissance in phenotypic screening. The major breakthrough in hit discovery in the past 7 years came from an unexpected source: phenotypic screening. A minority of compounds currently in clinical testing had molecularly defined targets from the outset. The majority of compounds currently in development are derived from phenotypic screening; in most cases the targets were subsequently identified (FIG. 2). Advances in automation and in image capture and analysis technology have meant that over the period leading up to 2007, the cost of assaying a compound against primary human erythrocytes infected with *P. falciparum* fell almost 100-fold to approximately $1 per data point. Led by collaborations established with the pharmaceutical companies Novartis[60] and GlaxoSmithKline[61], and the hospital-based drug discovery group at the St Jude Children's Research Hospital, USA[62], large compound collections were screened, initially in-house[63] and later at The Eskitis Institute, Australia[64]. A total of ~6 million compounds have been screened to date and, excitingly, more than 25,000 of these have shown half-maximal (IC_{50}) activity at approximately 1 μM or lower against *P. falciparum*. The advantage of the relatively low price of screening is that it was easier to screen all compounds than to triage first, enabling a wide variety of compounds to be tested with, in some cases, structure–activity relationships determined for positive hits. In addition, it was relatively simple to propose a business model in which compounds would be screened and the details of follow-up collaborations discussed only once the initial hit data were available. This model for precompetitive collaboration helped bypass much of the sterile intellectual property discussions that have plagued neglected disease drug discovery (and drug discovery in general) in the previous decade.

The most advanced compound derived from this approach is the spiroindolone KAE609 (also known as cipargamin)[65,66], which was developed in a collaboration between the Novartis Institute for Tropical Diseases in Singapore, its Genome Foundation in San Diego, USA, and the Swiss Tropical and Public Health Institute. The initial singleton hit (FIG. 4) was reasonably active and therefore the main problem in the medicinal chemistry programme was how to improve its *in vivo* half-life without losing activity against the parasite. Knowledge of the target was not essential in the early stages of identifying

Human experimentally induced infection model
A model for malaria in which human volunteers are infected with *Plasmodium* parasites either by injection with infected erythrocytes (or sporozoites) or from the bite of an infected mosquito. Valuable pharmacokinetic and pharmacodynamic information of candidate drugs can thus be obtained at safe, well-monitored parasitaemia levels that are many orders of magnitude below those that induce symptoms.

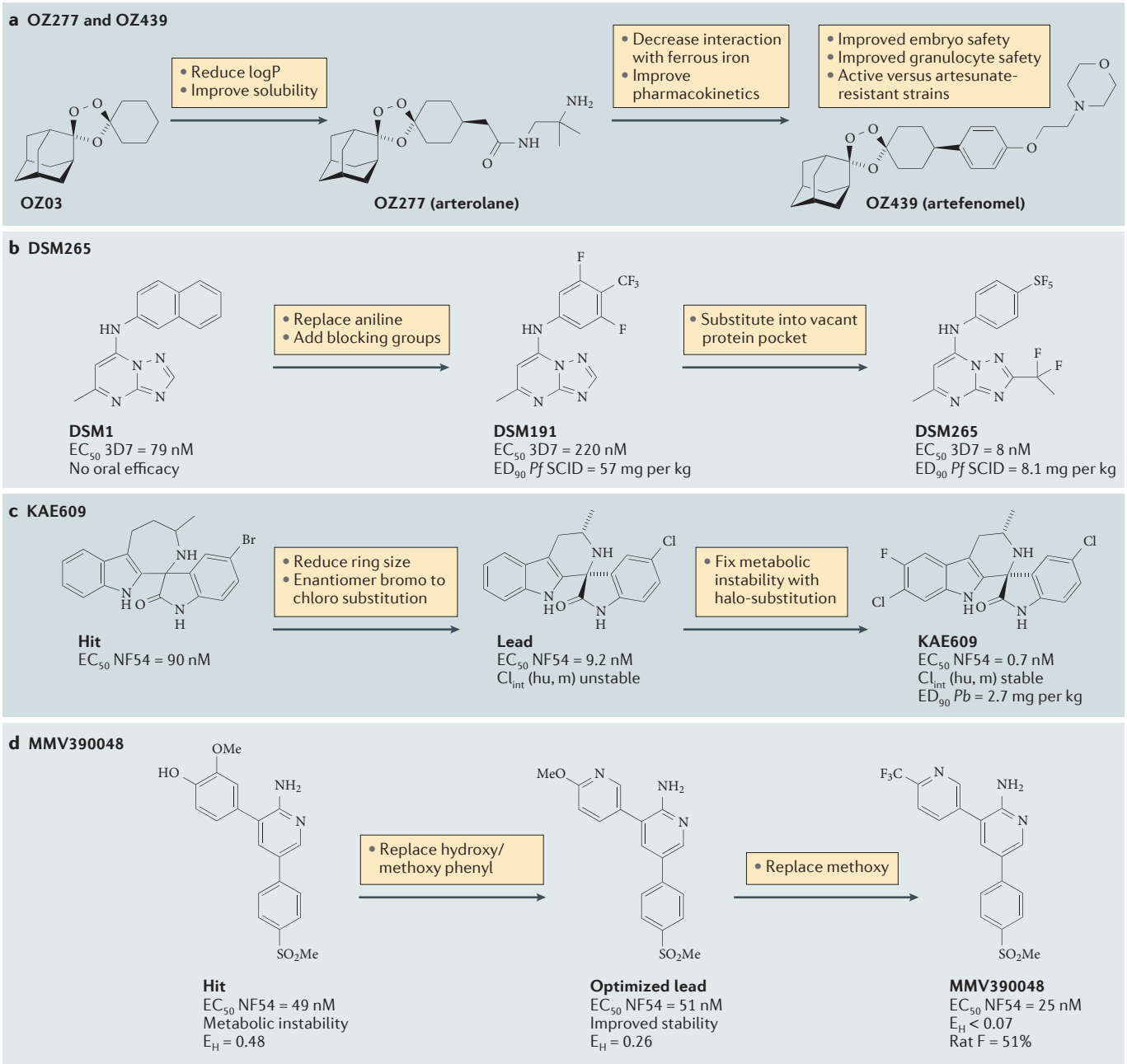

Figure 4 | **Key steps in the design of selected antimalarial compounds. a** | OZ277 (also known as arterolane) and OZ439 (also known as artefenomel) are fully synthetic trioxolanes, identified from a project originally designed to overcome the supply chain uncertainties caused by large fluctuations in the price of artemisinin. They both contain the active endoperoxide moiety but are otherwise structurally unrelated. OZ277 was discovered by a Medicines for Malaria Venture (MMV)-funded project team, and initially developed in a partnership between MMV and Ranbaxy. Development of the combination with piperaquine (Synriam), by Ranbaxy and the Indian Department of Science and Technology, led to its registration in India, and subsequently in several African countries. The original team that developed OZ277 continued with new synthetic endoperoxides, resulting in OZ439. OZ439 has a much longer half-life, with plasma exposures above the minimum inhibitory concentration for more than 1 week after a single administration, compared with a few hours for OZ277 or artesunate. OZ439 could be part of a single-dose cure or a much simplified regimen. Both compounds are much safer than artesunate in preclinical studies of embryo-fetal development, and early clinical data show no significant impact of *kelch* genotypes associated with artemisinin resistance and OZ439's speed of parasite kill (J. Möhrle, personal communication). These early observations need to be confirmed in the ongoing clinical studies. Key steps in the design of DSM265 (part **b**), KAE609 (also known as cipargamin; part **c**) and MMV390048 (part **d**) are also shown. 3D7 and NF54 are *P. falciparum* strains that are used for *in vitro* potency testing. *PfSCID* refers to a model that uses severe combined immunodeficient mice that are engrafted with human erythrocytes infected with human P. *falciparum* parasites. Cl_{int}, intrinsic clearance; EC_{50}, effector concentration for half-maximum response; ED_{90}, dose that eradicates 90% of the target pathogen; E_H, hepatic extraction ratio; F, bioavailability; hu, human; m, mouse; *Pb*, *P. berghei*, a strain that infects mice.

Table 2 | **How has the pipeline progressed over the past 5 years?***

Agent (alternative names)	Class	Comments
Discontinued or on hold		
(+)-Mefloquine (AD-452, RS(+) mefloquine, (+)-erythro-mefloquine)	Quinine, an amine alcohol	• Studies in healthy volunteers showed that the safety of the single enantiomer was similar to that of the racemate and the project was discontinued[124]
Artemisone (BAY-44-9585)	Artemisinin derivative	• Showed promising efficacy for the treatment of uncomplicated falciparum malaria in Phase II trials in Thailand (R. K. Haynes, personal communication), but no further development has been reported • A plan to test it clinically in western Cambodia for activity against artemisinin-insensitive strains (ClinicalTrials.gov identifier: NCT00936767) was withdrawn for operational reasons
N-tert butyl isoquine (GSK369796)	4-aminoquinoline	• Investigated in human volunteers (ClinicalTrials.gov identifier: NCT00675064) but showed evidence of ECG changes and lower-than-expected plasma exposure • GlaxoSmithKline thus returned the project to the Liverpool School of Tropical Medicine, UK, and no further development has been reported
GSK932121	4(1*H*)pyridine	• An electron transport inhibitor related to atovaquone; was tested in human volunteers • The project was terminated based on safety data from a soluble phosphate prodrug of the candidate, and work on other members of this series was also stopped[127] • It was recently suggested that these safety liabilities are associated with GSK932121 binding at the cytochrome bc_1 Q_i site rather than the Q_o site[128]
MK4815 (2-amino-methyl-3,5-di-tert-butylphenol)	Aminocresol	• Characterized[129], but preclinical safety studies in 2010 showed a relatively small safety window, even in higher species • There are no current plans to move to first-in-human studies
SAR97276 (albitiazolium bromide)	Bisthiazolium	• This choline transport inhibitor was discontinued after failing to meet its primary end point in Phase II (Sanofi press release; see Further information)
Tinidazole	Nitroimidazole	• This approved antibiotic for amoebae, giardia and trichomonas infections was found to be ineffective in preventing relapse • This result was in line with previous primate data but contradicted anecdotal reports in patients[130]
Trioxaquine[131] (PA1103, SAR116242)	4-aminoquinoline with a synthetic endoperoxide	• This is a fusion molecule of an endoperoxide and a 4-aminoquinoline that had entered preclinical development in 2007 • Palumed has stopped working on this series for malaria in 2010 owing to a lack of financial support (company website; see Further information)
In development or launched		
AQ13	Aminoquinoline	• In 2006, AQ13 was examined in a single-dose healthy volunteer study[52] • In 2013, a Phase IIa study comparing it with the artemether–lumefantrine combination (ClinicalTrials.gov identifier: NCT01614964) was started, funded by the US FDA's Office of Orphan Product Development, with a completion date of 2015
Arterolane–piperaquine combination (Synriam)	Synthetic endoperoxide plus a 4-aminoquinoline	• Launched in India in 2012 • Current development plans include trials in African children, the development of a paediatric dose strength and discussions on WHO prequalification • By December 2014, Synriam was approved in seven African countries
Artesunate–mefloquine combination	Artemisinin derivative plus a 4-aminoquinoline	• Prequalified as a fixed-dose combination by DND*i* and its Brazilian partner Farmanguinhos in 2012 • Now manufactured by CIPLA Global
CDRI 97/78 (REFS 132–134)	1,2,4 trioxane	• Originally developed by India's Central Drug Research Institute, which recently completed a healthy volunteer study[135] • Has a plasma half-life of 12 hours • Work is ongoing to prepare for a multiple-dose study and test the activity against resistant malaria strains
Dihydroartemisinin–piperaquine combination (Eurartesim)	Artemisinin derivative plus a 4-aminoquinoline	• Recommended for approval by the EMA's CHMP in June 2011, and then by the EMA in Oct 2011
Ferroquine (SSR97193)[39,136]	Ferrocene–4-aminoquinoline	• Developed by the Institut Pasteur in Lille, France; this drug was being developed by Sanofi in a Phase II trial in combination with artesunate (ClinicalTrials.gov identifier: NCT00988507) • This project has since been put on hold, and a new project was started combining ferroquine with OZ439 (artefenomel) • The Phase I drug interaction study is completed and a Phase IIb study is expected to start early in 2015 (Sanofi Form 20-F 2014; see Further information)

Table 2 (cont.) | **How has the pipeline progressed over the past 5 years?***

Agent (alternative names)	Class	Comments
Fosmidomycin	Antibiotic	• Inhibits DXP reductoisomerase, a key enzyme in the non-mevalonate pathway of isoprenoid biosynthesis • A clinical trial of fosmidomycin with clindamycin showed poor efficacy in children younger than 3 years[137] • Subsequent studies have switched to using piperaquine as a partner drug (ClinicalTrials.gov identifier: NCT02198807) with a currently ongoing trial in patients over the age of 5 years
KAE609 (cipargamin, NITD-609)[69,70,138] and KAF156 (GNF156)[79,139]	Spiroindolone (KAE609) and imidazolopiperazine (KAF156)	• Developed by Novartis and still in clinical development • Both have been tested in early Phase II clinical trials as monotherapies
Methylene blue	Phenothiazin dye	• This compound, first proposed for the treatment of malaria more than a century ago[140], is now being prioritized for its potential role as a transmission-blocking compound, to be used in combination with ACTs[141] • A trial is ongoing to evaluate its safety in G6PD-deficient subjects in Thailand versus a single high dose (0.75 mg per kg) of primaquine (ClinicalTrials.gov identifier: NCT01668433)
Pyronaridine–artesunate combination (Pyramax)	Chloroquine analogue plus an artemisinin derivative	• Approved first by the Korean FDA in August 2011, followed by positive scientific opinion from the EMA under Article 58 in Feb 2012, for single use in countries with low malaria endemicity • It was then added to the WHO list of prequalified medicines in May 2012 • Further data have been submitted to the EMA to support multiple use and also to support a paediatric formulation
Compounds that have entered the pipeline since 2012‡		
ACT451840 (REF. 142)	A hydroxy-ethyl-amine scaffold-based peptidomimetic protease inhibitor	• Developed by Actelion • In a recently published Phase I trial it was well tolerated at all doses tested[143]
DF02 (Sevuparin)	Heparin analogue with low anticoagulant activity	• Phase I/II studies failed to meet their primary end point for uncomplicated *P. falciparum* malaria and were prematurely ended • A Phase I trial for severe malaria was completed in 2009, and Dilaforette is planning to continue development for this indication (Karolinska Development press release; see Further information)
GSK369796	Isoquine	• Development is on hold after the first-in-human study (ClinicalTrials.gov identifier: NCT00675064), the only clinical study performed with GSK369796 • Two factors contributed to this decision: first, a drug-related serious adverse event (generalized tonic-clonic seizure accompanied by hypotension and ECG changes (QTc prolongation and T-wave abnormalities)) occurred in one subject during the study approximately 2 hours after oral administration of 2,000 mg GSK369796; the subject recovered fully • Second, lower plasma exposures were observed for GSK369796 compared with other 4-aminoquinolines (based on the literature) and compared with other 4-aminoquinolines at equivalent doses (N. Cammack, personal communication)
NPC1161B	8-aminoquinoline	• Discovered and developed at the University of Mississippi, USA • Basic discovery papers have been published[144,145], and preclinical activity assessments have been completed • The compound has been tested in the huSCID[§] model with G6PD-deficient erythrocytes • NPC1161B was more potent, but the margin for safety in causing haemolysis was not significantly better than that for tafenoquine (L. Walker, personal communication)
RKA182	Tetraoxane	• Initially planned for full preclinical development[146], and a Phase I study was initiated in 2011 • Some safety issues were reported[147], and the compound has been replaced by a new tetraoxane TDD E209

CHMP, Committee for Medicinal Products for Human Use; DNDi, Drugs for Neglected Diseases *initiative*; DXP, 1-deoxy-D-xylulose 5-phosphate; ECG, electrocardiogram; EMA, European Medicines Agency; Farmanguinhos, The Institute of Drug Technology, Brazil; FDA, Food and Drug Administration; G6PD, glucose 6-phosphate 1-dehydrogenase; WHO, World Health Organization.*Among the drugs that were in development in 2009 (REF. 5). ‡See REF. 6 for more details. §huSCID refers to a model that uses severe combined immunodeficient mice that are engrafted with human erythrocytes infected with human *P. falciparum* parasites.

a development candidate: this lack of target information was a major change for many in drug discovery and was seen as an inherently high-risk approach. One of the teams described it as "driving in the dark with the headlights off". Ultimately, the target was discovered to be the Na^+-ATPase 4 ion channel PfATP4 (REF. 67). Interestingly, PfATP4 had been identified as a potential target more than a decade earlier but had not been progressed[68]; biochemists tend to work on the targets that are easiest to assay. KAE609 rapidly progressed through to Phase I[69], and has now completed the first studies in human patients in Thailand[70]. The results are stunning; KAE609 kills even faster than artesunate — something that was rarely imagined to be possible — and also maintains a plasma concentration above the MIC for several days. In addition, the doses used in the clinic were relatively low: 30–75 mg in total. One of the goals of drug discovery in malaria is to formulate new compounds

that are affordable. This does not mean that they have to be cheap on a milligram basis. By weight, KAE609 is 7 times more potent than artesunate, and arguably 40 times more potent than 4-aminoquinolines. As such, KAE609 offers an opportunity not only for a single-dose cure but one that could be even cheaper than current therapy. Novartis hopes that KAE609 can be submitted for approval in 2017 (REF. 71).

Several other chemical series have emerged that also target PfATP4, including PA21A092 from Drexel University, USA[72–74], and SJ557733 (also known as SJ733) from a collaboration between St Jude Children's Research Hospital and Rutgers University, USA[62,75]; both of these series are in preclinical development. Indeed, an analysis of the Malaria Box[63], a collection of 400 publicly available compounds distilled from the original 25,000 hits obtained in the high-throughput screening, showed that 7% of these compounds hit PfATP4 (REF. 76). This phenomenon of frequently hit targets has also been observed in phenotypic screens against tuberculosis, and may reflect the inherent bias of the screening assay format and the chemical libraries tested.

Another candidate that has been developed from a phenotypic hit is MMV390048, which has been progressed by the team led by the University of Cape Town, South Africa (initially identified as compound 15)[77]. Initial screening identified a cluster of four aminopyridines, which were then optimized to produce an early lead (FIG. 4) and further refined to produce MMV390048. The compound progressed to preclinical development and at the same time its target was identified to be lipid phosphatidylinositol 4-kinase (PfPI4K)[78]. This target had previously been identified by the Novartis-led group as the target of one of their molecules that had not progressed into preclinical development[79]. Therefore, PfPI4K is another example of a frequently hit target. MMV390048 has successfully completed the preclinical programme and began Phase I human studies in Cape Town in the first half of 2014. This is another major step in the right direction for antimalarial medicines: it is the first time a new medicine has been taken into human volunteers in Africa, with direct readout of safety in the genetic background of the majority of patients with malaria.

Future directions

A renaissance of new targets. As mentioned above, the phenotypic screening programmes followed by lead optimization and target identification have resulted in new molecular targets. Thus, target prioritization in this case is driven by real life druggability. Seven new targets and several revitalized targets have been identified by these approaches in the past 5 years (TABLE 3). These rediscovered targets are all druggable, by definition, and are often in well-characterized target classes (channels or enzymes)[80]. However, the phenotypic screening data allow priorities to be refined and set by the community, providing new opportunities for structure-based design approaches to groups such as the Structural Genomics Consortium[81]. They can also form the basis of target-based screening initiatives such as the Innovative Medicines Initiative's European Lead Factory[82]. In some cases, we are seeing the same target come up from many independent projects, as described above for PfATP4. However, prioritizing the less commonly hit new targets for target-based screening in the future will be an excellent strategy for improving the chemical diversity of our lead optimization projects.

New players and new diversity. Despite the interest in identifying targets, it can be argued that phenotypic screens of diverse chemotypes will continue to be the principal source of new candidate molecules in malaria. The search for radically new chemotypes is always going to be a high priority but is challenging, as illustrated by the disappointing harvest from large combinatorial libraries used in screening in other therapeutic areas[83,84]. The majority of novel chemotypes will come from two areas. First are natural products, from which many highly innovative but somewhat toxic scaffolds have been identified[85]. As malaria is a disease that has historically been treated by herbal medicinal products, selecting extracts with demonstrable clinical activity could clearly lead to new drugs[86]. Diversity in the natural product space has been facilitated by recent alliances with Japanese pharmaceutical companies, which have been aided by the Global Health Innovative Technology Fund, a product development partnership that was established in 2012 (REFS 87,88). Japanese companies have maintained more of a focus on fungal-derived natural products in recent decades. Second, the use of novel heteroatoms has also contributed to chemical diversity. For example, (boron-containing) oxaboroles have provided clinical candidates for bacterial and trypanosome infections; this chemical family also has activity against malaria[89], although the compounds for this disease are still in the lead optimization stage.

Improved models for early-stage drug development. Another pathway to discover new chemotypes is to change the design of the biological screen. Two of the biological activities needed for the malaria eradication agenda are the ability to block transmission and to kill the dormant liver stages. In neither case can we perfectly reproduce the biology in high-throughput screening formats; however, as a surrogate for blocking transmission the ability of compounds to kill the late-stage gametocytes (stage V) can be tested[90]. For the dormant liver stages, we would need to screen surrogates of surrogates — a mouse parasite (*Plasmodium berghei*) in a non-dormant stage — but at least this means that the screening process can start. What is important is that the investment in the primary biology continues so that screening against primate dormant forms[91], or even human cells infected with *P. vivax*[92], can eventually be performed. Again, new classes of drugs for such stages of malaria parasites would truly be transformative and accelerate the decline of malaria — a change that is urgently needed over the next 20 years.

Ultimately, the challenge in drug discovery and development is to show that a medicine is effective in the human clinical situation. Historical development of anti-infective agents has often relied on the use of experimentally induced human infections[93–95]. In recent years, with the development of highly sensitive PCR-based techniques,

Heteroatoms
In organic chemistry, this term refers to all atoms that are not C or H. In the context of medicinal chemistry, novel heteroatoms refer to atoms not usually found in drugs (which are C, H, O, N, S and halogens).

Gametocytes
Asexually replicating *Plasmodium* parasites in erythrocytes occasionally differentiate into gametocytes. These forms of the parasite are the only forms that can be taken up by mosquitoes, mate and propagate disease.

Table 3 | **Selected recently validated or revived antimalarial targets**

Target	Target name	Key investigative molecules	Clinically validated?	Refs
PfATP4	Na^+-ATPase 4	KAE609, SJ557733, 21A092	Yes	75,79
PfPI4K	Phosphatidylinositol-4 kinase	MMV390048	Yes	78
PfDHFR	Dihydrofolate reductase	P218	Yes	148
PfDXR	DXP reductoisomerase	Fosmidomycin	Yes	149
PfDHODH	Dihydroorotate dehydrogenase	DSM265	Yes	150
PfCYTbc_1	Cytochrome bc_1	Decoquinate, GSK932121, ELQ300	Yes	151,152
PfFP2-3	Falcipain cysteine proteases 2–3	Falcitidin	No	153,154
PfHDAC1	Histone deacetylase	SB939, trichostatin A	No	155–157
PfCHT1,2,4	Aspartic protease plasmepsins I, II, IV	CWHM-117, TCMDC-134674	No	158,159
PfCARL	Cyclic amine resistance locus	KAF156	Yes	60

DXP, 1-deoxy-D-xylulose 5-phosphate.

volunteers can be infected with *P. falciparum*, and the effect of treatment can be studied on the resultant subclinical infection. Volunteers can be infected using biting mosquitoes[96], injection with sporozoites[97] or infected erythrocytes[11,59]. Clearly, sporozoite infection enables the study of the hepatic stages of infection, whereas erythrocytic infection focuses on the blood stages. Studies comparing the kinetics of the response to medicines in these subclinical infections show that the parameters obtained (such as the speed of parasite decline and the MIC) are similar to those obtained clinically. Use of the human experimentally induced infection model provides an early readout on the speed of parasite killing in non-immune individuals and enables an early estimation and assessment of whether the compound could be part of a drug combination that produces sterile cures. This trend will continue: new models are now being developed to study transmission to the mosquito[98] and relapse of dormant forms[99].

Subsequent clinical development of antimalarials must establish efficacy and safety in patients. A survey of recent Phase II–IV clinical trial locations (as listed in ClinicalTrials.gov) shows that most trials take place in Africa ($n = 99$) and Southeast Asia ($n = 30$) (FIG. 5a). Trials in patients from sub-Saharan Africa are important because of their wide genetic diversity[100] and enhanced risk of the occurrence of pharmacogenomic complications[101,102]. However, the distribution of trials within Africa is unbalanced, with virtually all trials taking place in Kenya, Malawi and Burkina Faso (FIG. 5b). This unfortunate situation is due to a combination of regulatory, practical and political barriers. Recently, trial sites have opened up in Uganda, Gabon, Mozambique and the Democratic Republic of Congo, but there is still room for improvement.

Pioneering new ways of working together. It could be said that one of the difficulties of drug discovery in the past 20 years has been the lack of peer review: when projects are solely controlled by one company or university they lack the somewhat painful advantages of the peer-review process. In such an environment of "introvert innovation" (REF. 103), key decisions on moving projects forward are typically taken by small committees that lack insider access to data for the global pipeline, instead being guided by internal drivers such as the company's growth expectations, individual personalities and internal competition with other therapeutic areas. To address this issue, we have instituted rigorous peer review for malaria drug development by having every step of the process reviewed by external experts from academic institutions, pharmaceutical companies, funding agencies, governments and malaria clinicians in the form of the Expert Scientific Advisory Committee. One question going forward is whether such peer review can be realistically achieved for other, more commercially important diseases.

Malaria is a disease with market failure, whereby the cost of developing new medicines, and the relatively low price that can be charged to the patient or health care provider, offers no simple commercial incentive to invest. Many of the world's major pharmaceutical companies have invested in neglected disease research and development. Indeed, some, such as Novartis and GlaxoSmithKline, even have centres of excellence dedicated to them. Historically, however, this work has been justified as part of corporate social responsibility. Nevertheless, there is the other side of the coin. The lack of a large commercial market has meant that malaria and other diseases of neglected populations have been at the forefront of exploring new modes of collaboration between academia and industry or even within the industry. The initial high-throughput screening of compound libraries against the malaria parasite is the first example, with the overwhelming majority of the top 20 pharmaceutical companies now having agreed not just to screen but also to share the results, and many of these are now in the public domain.

Second, the availability of large volumes of screening data has driven biological research. For example, the Malaria Box[63], a collection of 400 compounds that was selected from the 25,000-compound malaria phenotypic screens, has been made freely available and without restriction to 200 groups worldwide. It has been tested on a wide variety of different parasites, including *Cryptosporidium parvum*[104,105], *Toxoplasma*

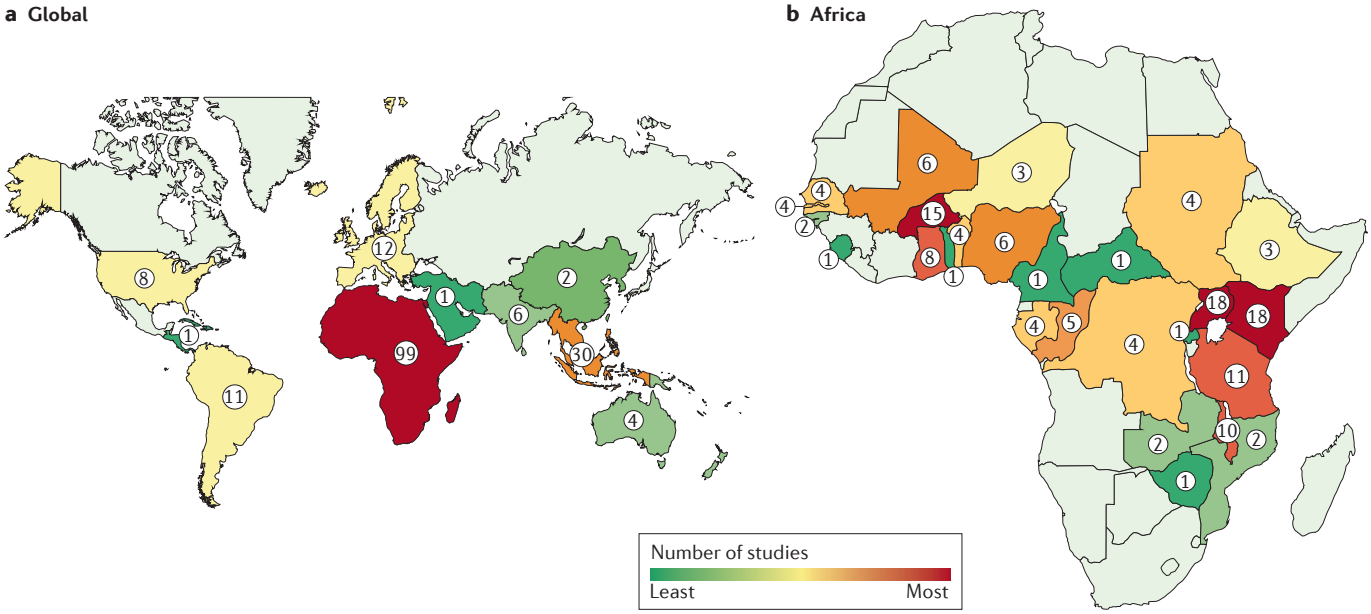

Figure 5 | **Geographical location of clinical Phase II–IV malaria studies from 2010 onwards.** **a** | Worldwide ($n = 160$). **b** | In Africa ($n = 99$). Only malaria trials for new molecules were considered (that is, excluding artemisinin combination therapies). The vast majority of trials were or are conducted in Africa, reflecting the high incidence of the disease in that continent. In addition, several earlier studies have established that sub-Saharan genetic diversity is far greater than that found in other geographical areas, including polymorphisms for genes that affect drug pharmacokinetics. However, within Africa, there is a poor correlation between disease burden and the number of clinical studies; many studies are conducted in Uganda, Kenya, Malawi and Tanzania, whereas very few studies are undertaken elsewhere in Eastern Africa. A similar heterogeneity is seen for West Africa. Source: ClinicalTrials.gov.

gondii, *Entamoeba histolytica*[106], *Trypanosoma cruzi*, *Trypanosoma brucei*, *Leishmania donovani*, *Perkinsus marinus*[107] and *Schistosoma mansoni*[108]. The data from these assays can then be put into the public domain, along with key drug-related parameters such as bioavailability, metabolism and half-lives. What becomes obvious from these types of collaboration networks is the high demand for collections of quality-controlled, validated compounds for biologists to test in their laboratories.

Third, some companies have adopted a different approach to classical partnerships. Both AbbVie and Hoffman-La Roche have allowed their own in-house experts to provide advice on key preclinical development questions to malaria drug developers outside their companies, and have also carried out specific safety and pharmacokinetics experiments on development compounds and donated the results to the projects.

Fourth, academics are finding new ways to collaborate to facilitate the progress of antimalarial drugs. One example is the recently formed Structure-guided Drug Discovery Coalition (see Further information). Funded by the Bill and Melinda Gates Foundation, this group brings effort and funding from structural genomics groups in Canada, the USA and the UK, and links them to experts in chemistry and pharmaceutical drug development to accelerate the translation of structure to drugs. Another example is open-source drug discovery, wherein results are published on the web for all groups to use (Open Source Malaria; see Further information).

Conclusions

The fight against malaria will be a long one; ambitious targets of a 90% reduction in deaths by 2030 have already been proposed by the WHO, indicating that new medicines will be needed for at least another two decades. How urgently we need new medicines depends partly on how good our stewardship of the existing ones is: monotherapies, incorrect dosing and counterfeits still plague malaria treatment. The initial impression from the malaria portfolio is that it is relatively strong and has improved dramatically over the past 5 years. However, it is important to attempt to separate the medicines in the pipeline into the different product types to see the true picture.

First, for blood-stage treatments, there are four molecules currently in Phase II studies, which initially gives the optimistic impression that a new medicine will soon be launched. However, our estimate of the probability of success for each combination is only 34%[10]. In this review, it was calculated that, on average, 18 candidate molecules would be needed for every new blood-stage medicine launched. Based on this and the ten new molecules in the translational part of the portfolio, the pipeline is in good shape to deliver one new candidate medicine. This medicine would be most useful in regions where the current drugs are failing because of resistance. Use of a new medicine in an eradication agenda places increased stringency on safety margins. If these medicines are to be used to treat asymptomatic subjects to

destroy the reservoir of parasites, the risk:benefit ratio needs to be similar to that of a vaccine — a much more difficult goal to achieve — with a consequently lower success rate for drug development. Requiring a single-dose therapy rather than a 3-day regimen also decreases the number of drugs that will be launched but should increase the therapeutic success of those drugs.

Second, for blocking transmission the WHO treatment guidelines recommend low-dose primaquine. The current key challenge here is not discovery but rather making paediatric tablets of low-dose primaquine available. For the future, most of the blood-stage compounds in development show at least partial inhibition of transmission in membrane feeding assays, and therefore it is likely that new combinations will be more effective at blocking transmission than current drugs. The search for new molecules that solely block transmission is therefore less of a priority, although ideally new blood-stage combination therapies should be selected to include transmission-blocking properties.

Third, for prevention of the relapse of *P. vivax*, although the data on tafenoquine are remarkable, there remains the issue of haemolysis in G6PD-deficient subjects. Because there are no new anti-relapse scaffolds in the pipeline, identification of new scaffolds, and indeed new assays, is important, as is investment in a robust diagnostic test for evaluating the G6PD status of patients in the field.

Finally, for chemoprevention, some of the newer molecules, such as KAF156 (also known as GNF156) and DSM265, show interesting preclinical activity against liver schizonts, but this remains to be confirmed in studies in humans. Given that chemoprotection includes protecting expectant mothers, increased resources over the next few years are needed for studies of safety in pregnancy and models that predict this safety.

In summary, although there has been a dramatic improvement in the pipeline of new antimalarial molecules over the past decade, the glass is still rather empty. Attrition in development is a fact of life, and the contents of the glass will tend to evaporate unless they are constantly topped up by the discovery of new molecules. Resistance already exists to the mainstays of therapy: both artemisinin derivatives and the 4-aminoquinoline or aminoalcohol partners. The discovery of new antimalarials is in a race against the spread of such resistance from the Mekong to the major endemic regions of Africa. There has been a massive investment in malaria control in the Mekong region, where the drug resistance has arisen, and this has bought us time in which to develop the next generation of medicines. There is a rich diversity of mechanisms of action among the new medicines entering the pipeline, and all these new compounds are checked for activity against existing clinical isolates and against experimentally produced resistant parasite lines. As much as possible, the pipeline is being protected against future resistance.

Beyond discovering good drugs, there are numerous other obstacles to making the right drug available for the right patient. Keeping the cost down is always a challenge, and the inclusion of price constraints and access clauses into drug discovery grants for malaria is an important first step. Ensuring availability of multiple suppliers is also critical in the long run. Counterfeit drugs remain a problem: they put the lives of patients at risk and also increase the threat of resistance to the active ingredients. More needs to be done to address this issue. There is often too long a gap between the development of the adult dose of new drugs and development of the paediatric version. This gap is being addressed by paediatric ACTs, but early assessment of the correct dose in the paediatric target population is going to be an important challenge over the next decade. Additionally, still too little is known about drug–drug interactions, especially those with drugs for other frequently occurring diseases in the target population (such as HIV and tuberculosis). Deploying new medicines in the areas that most need them is not always straightforward. Review and approval of regulatory files in disease-endemic countries can take several years after approval by a stringent authority. Continued investment is needed in regulatory support, in addition to the development of networks of in-country regulatory authorities, so that the file does not have to be reviewed by every single country on its own.

Against this complex background, the key is to be able to provide the front-line countries with a strong portfolio of new medicines: in a single word, choice. The portfolio of new chemical entities in development against malaria has been transformed in the past decade. One challenge for the next decade will be to ensure that these are registered and rolled out to the countries that need them the most. This objective must be achieved without decreasing investments in drug discovery or the identification of new targets. New classes of medicines are needed to address the more subtle problems such as transmission-blocking and prevention of the relapse of liver-stage parasites. Furthermore, medicines that are safe enough to be used routinely for chemoprevention in vulnerable patient populations are still needed. If we can launch a handful of new classes of medicines over the next decade, without losing the focus in drug discovery, then it may be audacious enough to claim that we have reached, to quote Sir Winston Churchill, "… perhaps, the end of the beginning".

1. Whitfield, J. Portrait of a serial killer: a roundup of the history and biology of the malaria parasite. *Nature* http://dx.doi.org/10.1038/news021001-6 (2002).
2. World Health Organization. *World Malaria Report* (WHO, 2014).
A country-by-country overview of issues and gains made against malaria.
3. Sachs, J. & Malaney, P. The economic and social burden of malaria. *Nature* **415**, 680–685 (2002).
4. Sicuri, E., Vieta, A., Lindner, L., Constenla, D. & Sauboin, C. The economic costs of malaria in children in three sub-Saharan countries: Ghana, Tanzania and Kenya. *Malar. J.* **12**, 307 (2013).
5. Wells, T. N., Alonso, P. L. & Gutteridge, W. E. New medicines to improve control and contribute to the eradication of malaria. *Nature Rev. Drug Discov.* **8**, 879–891 (2009).
6. Anthony, M. P., Burrows, J. N., Duparc, S., Moehrle, J. & Wells, T. N. C. The global pipeline of new medicines for the control and elimination of malaria. *Malar. J.* **11**, 316 (2012).

7. Biamonte, M. A., Wanner, J. & Le Roch, K. G. Recent advances in malaria drug discovery. *Bioorg. Med. Chem. Lett.* **23**, 2829–2843 (2013).
8. Alonso, P. L. *et al.* A research agenda to underpin malaria eradication. *PLoS Med.* **8**, e1000406 (2011).
9. malERA Consultative Group on Drugs. A research agenda for malaria eradication: drugs. *PLoS Med.* **8**, e1000402 (2011).
10. Burrows, J. N., Hooft van Huijsduijnen, R., Möhrle, J. J., Oeuvray, C. & Wells, T. N. C. Designing the next generation of medicines for malaria control and eradication. *Malar. J.* **12**, 187 (2013).
Defines the various target compound and product profiles for the different types of antimalarials and their rationale.
11. Engwerda, C. R., Minigo, G., Amante, F. H. & McCarthy, J. S. Experimentally induced blood stage malaria infection as a tool for clinical research. *Trends Parasitol.* **28**, 515–521 (2012).
Describes a revolutionary translational tool to establish the efficacy and pharmacodynamics of candidate antimalarials in subclinically infected volunteers.
12. Bosman, A. & Mendis, K. N. A major transition in malaria treatment: the adoption and deployment of artemisinin-based combination therapies. *Am. J. Trop. Med. Hyg.* **77** (Suppl. 6), 193–197 (2007).
13. Noedl, H. *et al.* Evidence of artemisinin-resistant malaria in western Cambodia. *N. Engl. J. Med.* **359**, 2619–2620 (2008).
14. Dondorp, A. M. *et al.* Artemisinin resistance in *Plasmodium falciparum* malaria. *N. Engl. J. Med.* **361**, 455–467 (2009).
15. Phyo, A. P. *et al.* Emergence of artemisinin-resistant malaria on the western border of Thailand: a longitudinal study. *Lancet* **379**, 1960–1966 (2012).
16. Ariey, F. *et al.* A molecular marker of artemisinin-resistant *Plasmodium falciparum* malaria. *Nature* **505**, 50–55 (2014).
Describes the discovery of the genetic basis of resistance against artemisinins.
17. Miotto, O. *et al.* Genetic architecture of artemisinin-resistant *Plasmodium falciparum*. *Nature Genet.* **47**, 226–234 (2015).
18. Straimer, J. *et al.* K13-propeller mutations confer artemisinin resistance in *Plasmodium falciparum* clinical isolates. *Science* **347**, 428–431 (2014).
19. Jong-wook, L. Global health improvement and WHO: shaping the future. *Lancet* **362**, 2083–2088 (2003).
20. Owens, S. Malaria and the millennium development goals. *Arch. Dis. Child.* **100** (Suppl. 1), 53–56 (2015).
21. Roll Back Malaria Partnership. Key facts, figures and strategies. *Roll Back Malaria* [online], http://www.rollbackmalaria.org/microsites/gmap/GMAP_Advocacy-ENG-web.pdf (2008).
22. Lengeler, C. Insecticide-treated bed nets and curtains for preventing malaria. *Cochrane Database Syst. Rev.* **2004**, CD000363 (2004).
23. Cohen, J. M. *et al.* Malaria resurgence: a systematic review and assessment of its causes. *Malar. J.* **11**, 122 (2012).
24. Roll Back Malaria Partnership. The global malaria action plan for a malaria-free world. *Roll Back Malaria* [online], http://archiverbm.rollbackmalaria.org/gmap/gmap.pdf (2008).
25. Toe, K. H. *et al.* Increased pyrethroid resistance in malaria vectors and decreased bed net effectiveness, Burkina Faso. *Emerg. Infect. Dis.* **20**, 1691–1696 (2014).
26. Ashley, E. A. *et al.* Spread of artemisinin resistance in *Plasmodium falciparum* malaria. *N. Engl. J. Med.* **371**, 411–423 (2014).
Provides a snapshot of the extent and spread of resistance against artemisinins.
27. Bethell, D. *et al.* Artesunate dose escalation for the treatment of uncomplicated malaria in a region of reported artemisinin resistance: a randomized clinical trial. *PLoS ONE* **6**, e19283 (2011).
28. Gatton, M. L., Martin, L. B. & Cheng, Q. Evolution of resistance to sulfadoxine-pyrimethamine in *Plasmodium falciparum*. *Antimicrob. Agents Chemother.* **48**, 2116–2123 (2004).
Describes the mechanism and spread of resistance to the sulfadoxine–pyrimethamine combination.
29. Vinayak, S. *et al.* Origin and evolution of sulfadoxine resistant *Plasmodium falciparum*. *PLoS Pathog.* **6**, e1000830 (2010).
30. Harrington, W. E., Mutabingwa, T. K., Kabyemela, E., Fried, M. & Duffy, P. E. Intermittent treatment to prevent pregnancy malaria does not confer benefit in an area of widespread drug resistance. *Clin. Infect. Dis.* **53**, 224–230 (2011).
31. Steketee, R. W. & ter Kuile, F. Single low-dose primaquine to reduce malaria transmission. *Lancet Infect. Dis.* **14**, 91–92 (2014).
32. Baird, J. K. Neglect of *Plasmodium vivax* malaria. *Trends Parasitol.* **23**, 533–539 (2007).
Highlights the burden and drug discovery efforts against *P. vivax*.
33. Bolchoz, L. J., Budinsky, R. A., McMillan, D. C. & Jollow, D. J. Primaquine-induced hemolytic anemia: formation and hemotoxicity of the arylhydroxylamine metabolite 6-methoxy-8-hydroxylaminoquinoline. *J. Pharmacol. Exp. Ther.* **297**, 509–515 (2001).
Describes primaquine-induced complications.
34. Llanos-Cuentas, A. *et al.* Tafenoquine plus chloroquine for the treatment and relapse prevention of *Plasmodium vivax* malaria (DETECTIVE): a multicentre, double-blind, randomised, phase 2b dose-selection study. *Lancet* **383**, 1049–1058 (2014).
35. Price, R. N. & Nosten, F. Single-dose radical cure of *Plasmodium vivax*: a step closer. *Lancet* **383**, 1020–1021 (2014).
36. Gesase, S. *et al.* High resistance of *Plasmodium falciparum* to sulphadoxine/pyrimethamine in Northern Tanzania and the emergence of dhps resistance mutation at codon 581. *PLoS ONE* **4**, e4569 (2009).
37. Adam, I., Khamis, A. H. & Elbashir, M. I. Prevalence and risk factors for *Plasmodium falciparum* malaria in pregnant women of eastern Sudan. *Malar. J.* **4**, 18 (2005).
38. Masaninga, F. *et al.* Review of the malaria epidemiology and trends in Zambia. *Asian Pac. J. Trop. Biomed.* **3**, 89–94 (2013).
39. Biot, C. *et al.* The antimalarial ferroquine: from bench to clinic. *Parasite* **18**, 207–214 (2011).
40. Supan, C. *et al.* Pharmacokinetics of ferroquine, a novel 4-aminoquinoline, in asymptomatic carriers of *Plasmodium falciparum* infections. *Antimicrob. Agents Chemother.* **56**, 3165–3173 (2012).
41. Chavain, N. *et al.* Investigation of the redox behavior of ferroquine, a new antimalarial. *Mol. Pharm.* **5**, 710–716 (2008).
42. Zhu, C. & Cook, S. P. A concise synthesis of (+)-artemisinin. *J. Am. Chem. Soc.* **134**, 13577–13579 (2012).
43. Kopetzki, D., Levesque, F. & Seeberger, P. H. A continuous-flow process for the synthesis of artemisinin. *Chemistry* **19**, 5450–5456 (2013).
44. Levesque, F. & Seeberger, P. H. Continuous-flow synthesis of the anti-malaria drug artemisinin. *Angew. Chem. Int. Ed. Engl.* **51**, 1706–1709 (2012).
45. Valecha, N. *et al.* Arterolane maleate plus piperaquine phosphate for treatment of uncomplicated *Plasmodium falciparum* malaria: a comparative, multicenter, randomized clinical trial. *Clin. Infect. Dis.* **55**, 663–671 (2012).
46. Noedl, H. The need for new antimalarial drugs less prone to resistance. *Curr. Pharm. Design* **19**, 266–269 (2013).
47. Dondorp, A. M. *et al.* Artemisinin resistance: current status and scenarios for containment. *Nature Rev. Microbiol.* **8**, 272–280 (2010).
48. Witkowski, B. *et al.* Reduced artemisinin susceptibility of *Plasmodium falciparum* ring stages in western Cambodia. *Antimicrob. Agents Chemother.* **57**, 914–923 (2013).
49. White, T. E., Bushdid, P. B., Ritter, S., Laffan, S. B. & Clark, R. L. Artesunate-induced depletion of embryonic erythroblasts precedes embryolethality and teratogenicity *in vivo*. *Birth Defects Res. B Dev. Reprod. Toxicol.* **77**, 413–429 (2006).
50. Nagelschmitz, J. *et al.* First assessment in humans of the safety, tolerability, pharmacokinetics, and *ex vivo* pharmacodynamic antimalarial activity of the new artemisinin derivative artemisone. *Antimicrob. Agents Chemother.* **52**, 3085–3091 (2008).
51. O'Neill, P. M. *et al.* Identification of a 1,2,4,5-tetraoxane antimalarial drug-development candidate (RKA 182) with superior properties to the semisynthetic artemisinins. *Angew. Chem. Int. Ed. Engl.* **49**, 5693–5697 (2010).
52. Mzayek, F. *et al.* Randomized dose-ranging controlled trial of AQ-13, a candidate antimalarial, and chloroquine in healthy volunteers. *PLoS Clin. Trials* **2**, e6 (2007).
53. Thelingwani, R., Bonn, B., Chibale, K. & Masimirembwa, C. Physicochemical and drug metabolism characterization of a series of 4-aminoquinoline-3-hydroxypyridin-4-one hybrid molecules with antimalarial activity. *Expert Opin. Drug Metab. Toxicol.* **10**, 1313–1324 (2014).
54. van Noord, C., Eijgelsheim, M. & Stricker, B. H. Drug- and non-drug-associated QT interval prolongation. *Br. J. Clin. Pharmacol.* **70**, 16–23 (2010).
55. Zani, B., Gathu, M., Donegan, S., Olliaro, P. L. & Sinclair, D. Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria. *Cochrane Database Syst. Rev.* **1**, CD010927 (2014).
56. Wells, T. N. C. Is the tide turning for new malaria medicines? *Science* **329**, 1153–1154 (2010).
57. Coteron, J. M. *et al.* Structure-guided lead optimization of triazolopyrimidine-ring substituents identifies potent *Plasmodium falciparum* dihydroorotate dehydrogenase inhibitors with clinical candidate potential. *J. Med. Chem.* **54**, 5540–5561 (2011).
58. Deng, X. *et al.* Structural plasticity of malaria dihydroorotate dehydrogenase allows selective binding of diverse chemical scaffolds. *J. Biol. Chem.* **284**, 26999–27009 (2009).
59. McCarthy, J. S. *et al.* A pilot randomised trial of induced blood-stage *Plasmodium falciparum* infections in healthy volunteers for testing efficacy of new antimalarial drugs. *PLoS ONE* **6**, e21914 (2011).
60. Meister, S. *et al.* Imaging of *Plasmodium* liver stages to drive next-generation antimalarial drug discovery. *Science* **334**, 1372–1377 (2011).
61. Gamo, F. J. *et al.* Thousands of chemical starting points for antimalarial lead identification. *Nature* **465**, 305–310 (2010).
Describes how access to nearly 2 million compounds from GlaxoSmithKline resulted in the discovery of thousands of new inhibitors against *Plasmodium* spp.
62. Guiguemde, W. A. *et al.* Chemical genetics of *Plasmodium falciparum*. *Nature* **465**, 311–315 (2010).
63. Spangenberg, T. *et al.* The open access malaria box: a drug discovery catalyst for neglected diseases. *LoS ONE* **8**, e62906 (2013).
64. Avery, V. M. *et al.* Screening and hit evaluation of a chemical library against blood-stage *Plasmodium falciparum*. *Malar. J.* **13**, 190 (2014).
65. Rottmann, M. *et al.* Spiroindolones, a potent compound class for the treatment of malaria. *Science* **329**, 1175–1180 (2010).
66. Yeung, B. K. *et al.* Spirotetrahydro β-carbolines (spiroindolones): a new class of potent and orally efficacious compounds for the treatment of malaria. *J. Med. Chem.* **53**, 5155–5164 (2010).
67. Spillman, N. J. *et al.* Na^+ regulation in the malaria parasite *Plasmodium falciparum* involves the cation ATPase PfATP4 and is a target of the spiroindolone antimalarials. *Cell Host Microbe* **13**, 227–237 (2013).
68. Krishna, S. *et al.* Expression and functional characterization of a *Plasmodium falciparum* Ca^{2+}-ATPase (PfATP4) belonging to a subclass unique to apicomplexan organisms. *J. Biol. Chem.* **276**, 10782–10787 (2001).
69. Leong, F. J. *et al.* A first-in-human randomized, double-blind, placebo-controlled, single- and multiple-ascending oral dose study of novel antimalarial spiroindolone KAE609 (cipargamin), to assess the safety, tolerability and pharmacokinetics in healthy adult volunteers. *Antimicrob. Agents Chemother.* **58**, 6209–6214 (2014).
Describes the Phase I study of KAE609.
70. White, N. J. *et al.* Spiroindolone KAE609 for falciparum and vivax malaria. *N. Engl. J. Med.* **371**, 403–410 (2014).
71. Cully, M. Trial watch: next-generation antimalarial from phenotypic screen shows clinical promise. *Nature Rev. Drug Discov.* **13**, 717 (2014).
72. Flannery, E. L., Chatterjee, A. K. & Winzeler, E. A. Antimalarial drug discovery — approaches and progress towards new medicines. *Nature Rev. Microbiol.* **11**, 849–862 (2013).
73. Das, S. *et al.* in *The Annual Symposium of the Institute for Molecular Medicine & Infectious Disease* Abstract B11, 46 (Drexel Univ. College of Medicine, 2014).
74. Vaidya, A. B. *et al.* Pyrazoleamide compounds are potent antimalarials that target Na^+ homeostasis in intraerythrocytic *Plasmodium falciparum*. *Nature Commun.* **5**, 5521 (2014).

75. Jimenez-Diaz, M. B. *et al.* (+)-SJ733, a clinical candidate for malaria that acts through ATP4 to induce rapid host-mediated clearance of *Plasmodium*. *Proc. Natl Acad. Sci. USA* **111**, E5455–E5462 (2014).
76. Lehane, A. M., Ridgway, M. C., Baker, E. & Kirk, K. Diverse chemotypes disrupt ion homeostasis in the malaria parasite. *Mol. Microbiol.* **94**, 327–339 (2014).
77. Younis, Y. *et al.* 3,5-diaryl-2-aminopyridines as a novel class of orally active antimalarials demonstrating single dose cure in mice and clinical candidate potential. *J. Med. Chem.* **55**, 3479–3487 (2012).
78. Ghidelli-Disse, S. *et al.* Identification of *Plasmodium* PI4 kinase as target of MMV390048 by chemoproteomics. *Malar. J.* **13**, S21 (2014).
79. McNamara, C. W. *et al.* Targeting *Plasmodium* PI(4)K to eliminate malaria. *Nature* **504**, 248–253 (2013). **Describes the discovery of PfATP4 as an antimalarial drug target.**
80. Overington, J. P., Al-Lazikani, B. & Hopkins, A. L. How many drug targets are there? *Nature Rev. Drug Discov.* **5**, 993–996 (2006).
81. Gileadi, O. *et al.* The scientific impact of the Structural Genomics Consortium: a protein family and ligand-centered approach to medically-relevant human proteins. *J. Struct. Funct. Genom.* **8**, 107–119 (2007).
82. Mullard, A. European lead factory opens for business. *Nature Rev. Drug Discov.* **12**, 173–175 (2013).
83. Carroll, J. Will combinatorial chemistry keep its promise? *Biotechnol. Healthc.* **2**, 26–32 (2005).
84. Geysen, H. M., Schoenen, F., Wagner, D. & Wagner, R. Combinatorial compound libraries for drug discovery: an ongoing challenge. *Nature Rev. Drug Discov.* **2**, 222–230 (2003).
85. Wells, T. N. Natural products as starting points for future anti-malarial therapies: going back to our roots? *Malar. J.* **10** (Suppl. 1), 3 (2011).
86. Wells, T. N. Discovering and developing new medicines for malaria control and elimination. *Infect. Disord. Drug Targets* **13**, 292–302 (2013).
87. Holmes, D. The GHIT fund shows its cards. *Nature Rev. Drug Discov.* **12**, 894 (2013).
88. Slingsby, B. T. & Kurokawa, K. The Global Health Innovative Technology (GHIT) Fund: financing medical innovations for neglected populations. *Lancet Glob. Health* **1**, e184–e185 (2013).
89. Zhang, Y. K. *et al.* Synthesis and structure–activity relationships of novel benzoxaboroles as a new class of antimalarial agents. *Bioorg. Med. Chem. Lett.* **21**, 644–651 (2011).
90. Duffy, S. & Avery, V. M. Identification of inhibitors of *Plasmodium falciparum* gametocyte development. *Malar. J.* **12**, 408 (2013).
91. Dembele, L. *et al.* Persistence and activation of malaria hypnozoites in long-term primary hepatocyte cultures. *Nature Med.* **20**, 307–312 (2014).
92. March, S. *et al.* A microscale human liver platform that supports the hepatic stages of *Plasmodium falciparum* and *vivax*. *Cell Host Microbe* **14**, 104–115 (2013).
93. Hayden, F. G. Experimental human influenza: observations from studies of influenza antivirals. *Antivir. Ther.* **17**, 133–141 (2012).
94. Atmar, R. L. *et al.* Norwalk virus shedding after experimental human infection. *Emerg. Infect. Dis.* **14**, 1553–1557 (2008).
95. Cordey, S. *et al.* Rhinovirus genome evolution during experimental human infection. *PLoS ONE* **5**, e10588 (2010).
96. Spring, M., Polhemus, M. & Ockenhouse, C. Controlled human malaria infection. *J. Infect. Dis.* **209** (Suppl. 2), 40–45 (2014).
97. Epstein, J. E. *et al.* Live attenuated malaria vaccine designed to protect through hepatic $CD8^+$ T cell immunity. *Science* **334**, 475–480 (2011).
98. Bousema, T. *et al.* Mosquito feeding assays to determine the infectiousness of naturally infected *Plasmodium falciparum* gametocyte carriers. *PLoS ONE* **7**, e42821 (2012).
99. Price, R. N., Baird, J. K. & Hay, S. I. *The Epidemiology of* Plasmodium vivax*: History, Hiatus and Hubris* (eds. Rollinson, D. & Stothard, R.) (Elsevier, 2012).
100. Campbell, M. C. & Tishkoff, S. A. African genetic diversity: implications for human demographic history, modern human origins, and complex disease mapping. *Annu. Rev. Genom. Hum. Genet.* **9**, 403–433 (2008).
101. Ma, Q. & Lu, A. Y. Pharmacogenetics, pharmacogenomics, and individualized medicine. *Pharmacol. Rev.* **63**, 437–459 (2011).
102. Pang, T. Impact of pharmacogenomics on neglected diseases of the developing world. *Am. J. Pharmacogenomics* **3**, 393–398 (2003).
103. Schuhmacher, A., Germann, P. G., Trill, H. & Gassmann, O. Models for open innovation in the pharmaceutical industry. *Drug Discov. Today* **18**, 1133–1137 (2013).
104. Murphy, R. C. *et al.* Discovery of potent and selective inhibitors of calcium-dependent protein kinase 1 (CDPK1) from *C. parvum* and *T. gondii*. *ACS Med. Chem. Lett.* **1**, 331–335 (2010).
105. Bessoff, K. *et al.* Identification of *Cryptosporidium parvum* active chemical series by repurposing the open access malaria box. *Antimicrob. Agents Chemother.* **58**, 2731–2739 (2014).
106. Boyom, F. F. *et al.* Repurposing the open access malaria box to discover potent inhibitors of *Toxoplasma gondii* and *Entamoeba histolytica*. *Antimicrob. Agents Chemother.* **58**, 5848–5854 (2014).
107. Aleman Resto, Y. & Fernandez Robledo, J. A. Identification of MMV malaria box inhibitors of *Perkinsus marinus* using an ATP-based bioluminescence assay. *PLoS ONE* **9**, e111051 (2014).
108. Ingram-Sieber, K. *et al.* Orally active antischistosomal early leads identified from the open access malaria box. *PLoS Negl. Trop. Dis.* **8**, e2610 (2014).
109. Doolan, D. L., Dobano, C. & Baird, J. K. Acquired immunity to malaria. *Clin. Microbiol. Rev.* **22**, 13–36 (2009).
110. Rappuoli, R. & Aderem, A. A. 2020 vision for vaccines against HIV, tuberculosis and malaria. *Nature* **473**, 463–469 (2011).
111. RTS,S Clinical Trials Partnership. Efficacy and safety of the RTS,S/AS01 malaria vaccine during 18 months after vaccination: a phase 3 randomized, controlled trial in children and young infants at 11 African sites. *PLoS Med.* **11**, e1001685 (2014).
112. World Health Organization. Global malaria vaccine pipeline. *WHO* [online], http://www.who.int/vaccine_research/links/Rainbow/en/index.html (2014).
113. Seder, R. A. *et al.* Protection against malaria by intravenous immunization with a nonreplicating sporozoite vaccine. *Science* **341**, 1359–1365 (2013).
114. McAllister, M. M. Successful vaccines for naturally occurring protozoal diseases of animals should guide human vaccine research. A review of protozoal vaccines and their designs. *Parasitology* **141**, 624–640 (2014).
115. Petrovsky, N. & Aguilar, J. C. Vaccine adjuvants: current state and future trends. *Immunol. Cell Biol.* **82**, 488–496 (2004).
116. Alving, C. R., Peachman, K. K., Rao, M. & Reed, S. G. Adjuvants for human vaccines. *Curr. Opin. Immunol.* **24**, 310–315 (2012).
117. Kyes, S. A., Kraemer, S. M. & Smith, J. D. Antigenic variation in *Plasmodium falciparum*: gene organization and regulation of the *var* multigene family. *Eukaryot. Cell* **6**, 1511–1520 (2007).
118. Kyes, S. *et al. Plasmodium falciparum var* gene expression is developmentally controlled at the level of RNA polymerase II-mediated transcription initiation. *Mol. Microbiol.* **63**, 1237–1247 (2007).
119. Stockdale, C., Swiderski, M. R., Barry, J. D. & McCulloch, R. Antigenic variation in *Trypanosoma brucei*: joining the DOTs. *PLoS Biol.* **6**, e185 (2008).
120. Ubben, D. & Poll, E. M. MMV in partnership: the Eurartesim® experience. *Malar. J.* **12**, 211 (2013).
121. Dondorp, A. *et al.* Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. *Lancet* **366**, 717–725 (2005).
122. Dondorp, A. M. *et al.* Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial. *Lancet* **376**, 1647–1657 (2010).
123. Ritchie, E. C., Block, J. & Nevin, R. L. Psychiatric side effects of mefloquine: applications to forensic psychiatry. *J. Am. Acad. Psychiatry Law* **41**, 224–235 (2013).
124. Tansley, R. *et al.* A randomized, double-blind, placebo-controlled study to investigate the safety, tolerability, and pharmacokinetics of single enantiomer (+)-mefloquine compared with racemic mefloquine in healthy persons. *Am. J. Trop. Med. Hyg.* **83**, 1195–1201 (2010).
125. Peters, P. J., Thigpen, M. C., Parise, M. E. & Newman, R. D. Safety and toxicity of sulfadoxine/pyrimethamine: implications for malaria prevention in pregnancy using intermittent preventive treatment. *Drug Saf.* **30**, 481–501 (2007).
126. Meremikwu, M. M., Donegan, S., Sinclair, D., Esu, E. & Oringanje, C. Intermittent preventive treatment for malaria in children living in areas with seasonal transmission. *Cochrane Database Syst. Rev.* **2**, CD003756 (2012).
127. Bueno, J. M. *et al.* Exploration of 4(1*H*)-pyridones as a novel family of potent antimalarial inhibitors of the plasmodial cytochrome bc1. *Future Med. Chem.* **4**, 2311–2323 (2012).
128. Capper, M. J. *et al.* Antimalarial 4(1*H*)-pyridones bind to the Qi site of cytochrome bc_1. *Proc. Natl Acad. Sci. USA* **112**, 755–760 (2015).
129. Powles, M. A. *et al.* MK-4815, a potential new oral agent for treatment of malaria. *Antimicrob. Agents Chemother.* **56**, 2414–2419 (2012).
130. Macareo, L. *et al.* Triangular test design to evaluate tinidazole in the prevention of *Plasmodium vivax* relapse. *Malar. J.* **12**, 173 (2013).
131. Bousejra-El Garah, F., Claparols, C., Benoit-Vical, F., Meunier, B. & Robert, A. The antimalarial trioxaquine DU1301 alkylates heme in malaria-infected mice. *Antimicrob. Agents Chemother.* **52**, 2966–2969 (2008).
132. Dwivedi, A. *et al.* Role of type-II pathway in apoptotic cell death induction by photosensitized CDRI-97/78 under ambient exposure of UV-B. *Toxicol. Lett.* **222**, 122–131 (2013).
133. Kushwaha, H. N. *et al.* Intersex effect of lamotrigine on the pharmacokinetic parameters of CDRI-97/78, a novel trioxane antimalarial compound, in rats. *Arzneimittelforschung* **62**, 274–279 (2012).
134. Kushwaha, H. N. *et al.* Effect of carbamazepine on the pharmacokinetic parameters of CDRI-97/78 following coadministration to rats. *Drug Res. (Stuttg.)* **63**, 282–288 (2013).
135. Shafiq, N. *et al.* Single ascending dose safety and pharmacokinetics of CDRI-97/78: first-in-human study of a novel antimalarial drug. *Malar. Res. Treat.* **2014**, 372521 (2014).
136. Mombo-Ngoma, G. *et al.* Phase I randomized dose-ascending placebo-controlled trials of ferroquine — a candidate anti-malarial drug — in adults with asymptomatic *Plasmodium falciparum* infection. *Malar. J.* **10**, 53 (2011).
137. Lanaspa, M. *et al.* Inadequate efficacy of a new formulation of fosmidomycin–clindamycin combination in Mozambican children less than three years old with uncomplicated *Plasmodium falciparum* malaria. *Antimicrob. Agents Chemother.* **56**, 2923–2928 (2012).
138. Lakshminarayana, S. B. *et al.* Pharmacokinetics–pharmacodynamics analysis of spiroindolone analogs and KAE609 in a murine malaria model. *Antimicrob. Agents Chemother.* **59**, 1200–1210 (2014).
139. Kuhen, K. L. *et al.* KAF156 is an antimalarial clinical candidate with potential for use in prophylaxis, treatment and prevention of disease transmission. *Antimicrob. Agents Chemother.* **58**, 5060–5067 (2014).
140. Guttmann, P. & Ehrlich, P. Über die wirkung des methylenblau bei malaria. *Berliner Klinische Wochenschrift* **28**, 953–956 (in German) (1891).
141. Coulibaly, B. *et al.* Efficacy and safety of triple combination therapy with artesunate-amodiaquine-methylene blue for falciparum malaria in children: a randomized controlled trial in Burkina Faso. *J. Infect. Dis.* **211**, 689–687 (2014).
142. Ciana, C. L. *et al.* Novel *in vivo* active anti-malarials based on a hydroxy-ethyl-amine scaffold. *Bioorg. Med. Chem. Lett.* **23**, 658–662 (2013).
143. Bruderer, S. *et al.* First-in-humans study of the safety, tolerability, and pharmacokinetics of ACT-451840, a new chemical entity with antimalarial activity. *Antimicrob. Agents Chemother.* **59**, 935–942 (2015).
144. Nanayakkara, N. P. *et al.* Antiparasitic activities and toxicities of individual enantiomers of the 8-aminoquinoline 8-[(4-amino-1-methylbutyl)amino]-6-methoxy-4-methyl-5-[3,4-dichlorophenoxy] quinoline succinate. *Antimicrob. Agents Chemother.* **52**, 2130–2137 (2008).
145. Marcsisin, S. R. *et al.* Tafenoquine and NPC-1161B require CYP2D metabolism for anti-malarial activity: implications for the 8-aminoquinoline class of anti-malarial compounds. *Malar. J.* **13**, 2 (2014).
146. Marti, F. *et al.* Second generation analogues of RKA182: synthetic tetraoxanes with outstanding *in vitro* and *in vivo* antimalarial activities. *MedChemComm* **2**, 661–665 (2011).

147. Copple, I. M. *et al.* Examination of the cytotoxic and embryotoxic potential and underlying mechanisms of next-generation synthetic trioxolane and tetraoxane antimalarials. *Mol. Med.* **18**, 1045–1055 (2012).
148. Yuthavong, Y. *et al.* Malarial dihydrofolate reductase as a paradigm for drug development against a resistance-compromised target. *Proc. Natl Acad. Sci. USA* **109**, 16823–16828 (2012).
149. Jomaa, H. *et al.* Inhibitors of the nonmevalonate pathway of isoprenoid biosynthesis as antimalarial drugs. *Science* **285**, 1573–1576 (1999).
150. Deng, X. *et al.* Fluorine modulates species selectivity in the triazolopyrimidine class of *Plasmodium falciparum* dihydroorotate dehydrogenase inhibitors. *J. Med. Chem.* **57**, 5381–5394 (2014).
151. da Cruz, F. P. *et al.* Drug screen targeted at *Plasmodium* liver stages identifies a potent multistage antimalarial drug. *J. Infect. Dis.* **205**, 1278–1286 (2012).
152. Nam, T. G. *et al.* A chemical genomic analysis of decoquinate, a *Plasmodium falciparum* cytochrome *b* inhibitor. *ACS Chem. Biol.* **6**, 1214–1222 (2011).
153. Wang, J., Kaiser, M. & Copp, B. R. Investigation of indolglyoxamide and indolacetamide analogues of polyamines as antimalarial and antitrypanosomal agents. *Mar. Drugs* **12**, 3138–3160 (2014).
154. Salas-Sarduy, E. *et al.* Antiparasitic effect of a fraction enriched in tight-binding protease inhibitors isolated from the Caribbean coral *Plexaura homomalla*. *Exp. Parasitol.* **135**, 611–622 (2013).
155. Hansen, F. K. *et al.* Discovery of HDAC inhibitors with potent activity against multiple malaria parasite life cycle stages. *Eur. J. Med. Chem.* **82**, 204–213 (2014).
156. Trenholme, K. *et al.* Lysine acetylation in sexual stage malaria parasites is a target for antimalarial small molecules. *Antimicrob. Agents Chemother.* **58**, 3666–3678 (2014).
157. Sumanadasa, S. D. *et al.* Antimalarial activity of the anticancer histone deacetylase inhibitor SB939. *Antimicrob. Agents Chemother.* **56**, 3849–3856 (2012).
158. Jaudzems, K. *et al.* Plasmepsin inhibitory activity and structure-guided optimization of a potent hydroxyethylamine-based antimalarial hit. *ACS Med. Chem. Lett.* **5**, 373–377 (2014).
159. Meyers, M. J. *et al.* Evaluation of aminohydantoins as a novel class of antimalarial agents. *ACS Med. Chem. Lett.* **5**, 89–93 (2014).
160. McCarthy, J. S. *et al.* A Phase I/Ib study to investigate the safety, tolerability and pharmacokinetic profile of DSM265 in healthy subjects and then its antimalarial activity in induced blood stage *Plasmodium falciparum* infection. *ASTMH Ann. Meeting Abstr.* **675**, 204–205 (2014).

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Competing interests statement
The authors declare competing interests: see Web version for details.

FURTHER INFORMATION
Antimalarials are at the origin of Palumed: http://www.palumed.fr/spip.php?article17
ChEMBL database (malaria data): https://www.ebi.ac.uk/chembl/malaria
ClinicalTrials.gov: https://clinicaltrials.gov
Karolinska Development Press Release (30 May 2014): http://www.karolinskadevelopment.com/?cID=551&pid=758222&did=611901&y=2014&m=05
Open Source Malaria: http://opensourcemalaria.org
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Sanoi Form 20-F 2014: http://en.sanofi.com/Images/38473_Sanofi_20-F_2014.pdf
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