Building a robust portfolio of new medicines

Malaria is one of the biggest killers of our time. Current estimates from the World Health Organisation (WHO) suggest that more than 250 million people are at risk worldwide[1]. More significantly, almost a million people die each year, of whom more than 700,000 are children under five. One of the ways to combat this disease is by developing new medicines.

By Dr Timothy N.C. Wells

Over the past few years there has been a significant investment in malaria research by not-for profit product development partnerships (PDPs) such as Medicines for Malaria Venture (MMV), Drugs for Neglected Disease initiative and others. This work has been in partnership with several leading pharmaceutical companies, the WHO, the Wellcome Trust and the Bill and Melinda Gates Foundation. As a result, today we have a strong pipeline of new fixed-dose artemisinin combination therapies (ACTs), which are already having a positive impact on health in Africa. More importantly, the pipeline is sustainable and will continue to deliver new medicines in the future that will play a key role in the eventual eradication of the disease.

Malaria – its mode of action and impact on the vulnerable

The majority of the world's malaria is caused by two different species of the parasite family *Plasmodium*. In Africa, where the majority of the deaths occur, the principal form of the parasite is *Plasmodium falciparum*. In Asia and South America, there is second major form, known as *Plasmodium vivax* (**Figure 1**). Both forms are transmitted by mosquitoes, and a number of different mosquito species can carry an infectious bite. The major difference between the two species from the viewpoint of the patient is that the *Plasmodium vivax* infection can come back in the absence of an infectious bite. When an infected mosquito bites, parasites are passed into the host blood stream and infect the liver before finally ending up in the red blood cells (**Figure 2**). The process of passing through the liver is different for the different malaria species, and not fully understood. In *Plasmodium vivax* some of the parasites remain in the liver as a dormant form known as hypnozoites. These hypnozoites can be reactivated without the bite of an infected mosquito, leading patients with *vivax* malaria to suffer another attack of malarial fever. Once in the red blood cells, the parasite goes through a cycle of multiplication which takes 48-72 hours. It is this amplification process which leads to the periodic fevers. Ultimately, if the disease is left untreated, there may be as many as 10^{13} parasites in the body of the patient – with a fever, low blood sugar and massive loss of red blood cells. In cases of severe malaria, the red cells can aggregate in the capillaries of the brain, leading to cerebral malaria and coma[2], and eventually death.

Transmission of malaria from the human host to

References

1 World Malaria Report 2008, World Health Organization, Geneva Switzerland http://www.who.int/malaria/wmr2008/malaria2008.pdf.

2 van der Heyde, HC, Nolan, J, Combes, V, Gramaglia, I, Grau, GE. A unified hypothesis for the genesis of cerebral malaria: sequestration, inflammation and hemostasis leading to microcirculatory dysfunction. Trends in Parasitology. 22(11):503-8, 2006 Nov.

3 Colbourne, MJ. Malaria in Gold Coast students on their return from the United Kingdom. Trans R Soc Top Med Hyg 49: 483-487, 1955.

4 Deloron, P, Chougnet, C. Is immunity to malaria really short-lived? Parasitology Today 8: 375-378 1992.

5 Rogerson, SJ, Mwapasa, V, Meshnick, SR. Malaria in pregnancy: linking immunity and pathogenesis to prevention. American Journal of Tropical Medicine & Hygiene. 77(6 Suppl):14-22, 2007 Dec.

6 Luo, XD, Shen, CC. The chemistry pharmacology and clinical applications of qinghaosu (artemisinin) and its derivatives. Med. Res. Rev. 7 29-52 1987.

7 White, NJ. Antimalarial drug resistance and combination chemotherapy. Philos Trans R Soc Lond B Biol Sci 354: 739-749 1999.

8 Schlitzer, M. ChemMedChem 2: 944-986 2007.

9 Abdulla, S, Sagara, I, Borrmann, S, D'Alessandro, U, Gonzalez, R, Hamel, M, Ogutu, B, Martensson, A, Lyimo, J, Maiga, H, Sasi, P, Nahum, A, Bassat, Q, Juma, E, Otieno, L, Bjorkman, A, Beck, HP, Andriano, K, Cousin, M, Lefevre, G, Ubben, D, Premji, Z. Efficacy and safety of artemether-lumefantrine dispersible tablets compared with crushed commercial tablets in African infants and children with uncomplicated malaria: a randomised, single-blind, multicentre trial. Lancet. 372(9652):1819-27, 2008 Nov 22.

10 www.plos.org/cms/node/208.

Continued on page 19

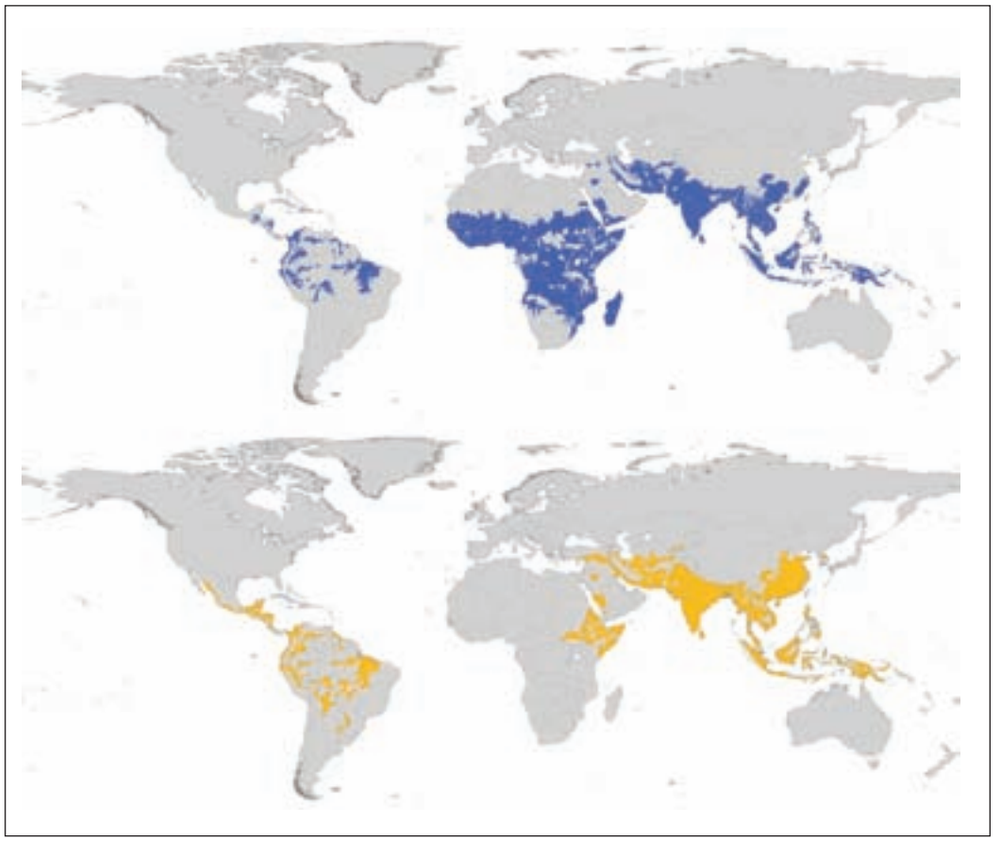

Figure 1: Map of the distribution of malaria cases – for *Plasmodium falciparum* and *Plasmodium vivax*

the vector requires the production of sexual stages of the parasite – gametocytes. During the asexual proliferation of *P. falciparum*, around 1% of the parasites commit to sexual development and become gametocytes. These gametocytes are produced in the human host, but fuse in the gut of the mosquito host to form the next generation of parasites – and the process of reinfection can begin again. To break the cycle of infection therefore, it is important to either stop the gametocytes forming, or to stop infected people being bitten by mosquitoes. This is not a trivial undertaking. In some parts of Africa a child can have many bites every night, at least one of which is from an infected mosquito.

So why do a disproportionate number of infants and expectant mothers die of malaria? For children, it is unfortunately a case of survival of the fittest. In Africa, as soon as the mother's immunity has stopped protecting the child, he is at risk from an infected mosquito. With every attack he survives, his immune system becomes better at defending him. By the age of five, most African children have some immune protection against the disease[3]. Unfortunately, this protection is not for life – it has been argued that Africans who spend a significant time away from a malaria-endemic country become susceptible to the disease if they go back home after a year or two – the immunological clock is reset to some extent[4]. For expectant mothers the story is different. The parasite selectively localises in the placenta, causing an increase in risk not only for the mother, but also for the baby[5].

Effective drugs in the global antimalarial pipeline

The cornerstone of current antimalarial treatment at the moment is the Artemisinin Combination Therapy (ACT). Artemisinin is a natural product, which was first identified by the Chinese, under orders from Mao Zedong[6]. It is a reactive molecule with an internal peroxide bridge, which is the key to biological activity. The high local concentration of free iron (II) in infected red blood cells is able to pass an electron to the artemisinin and generate a highly reactive free radical. This is able to modify local proteins killing the parasite in the process. Artemisinin is very effective as a treatment for malaria, but the concern is that if used on its own,

resistant parasites might be produced. Typically one in 10^{10} parasites makes a resistant strain, and in a fulminant disease a single patient can have a thousand times this level[7]. To avoid resistance, two drugs with completely different mechanisms need to be used. This would lower the possibility of resistance emerging to one in 10^{20}.

The current treatment of choice is a combination of Artemisinin with a 4-aminoquinoline, Lumefantrine. The 4-aminoquinolines are a family of drugs which can trace their pedigree back to quinine (the natural product in the bitter tonic water that goes so well with gin) – and derivatives made dating back to the Second World War[8]. Until recently the two drugs were given as a loose combination for three days (with separate tablets for each drug). The challenge recently has been to develop a tablet that contains both active ingredients – a Fixed-Dose Combination.

The first of these fixed-dose combination treatments is Coartem®, a combination of Artemether (a derivative of Artemisinin) and the 4-aminoquinoline Lumefantrine that was produced by Novartis in 2000. By 2008, Coartem was being used to treat almost 70 million people – and is provided at a cost of close to $1 on average per treatment. By working on manufacturing and supply chain, the ex-factory price has dropped by 60% over five years. One issue with Coartem is the fact that it has to be ground to a powder when given to small children. In addition, the medicine has an extremely bitter taste (the common name for Artemisinin is Wormwood, itself a synonym for bitter). A specific formulation for children was clearly needed and has been developed by MMV in collaboration with Novartis. Coartem®-Dispersible, this new generation of Coartem, is the first new combination medicine from a public-private partnership to be approved by a stringent regulatory authority, Swissmedic. Coartem-D is as effective as Coartem, but disperses rapidly in liquid, and has a pleasant cherry taste – both of which are a major advantage when treating children[9].

A second fixed-dose ACT Coarsucam (Artemisinin and Amodiaquine) was recently produced as part of an innovative partnership between Sanofi-aventis and Drugs for Neglected Diseases Initiative (DNDi). Manufactured in Morocco, the ACT was submitted to the Moroccan authorities for approval[10].

This brings us to two key aspects of development strategy – what regulatory strategy to follow, and which quality standards to uphold. Ideally, a medicine to be used in disease endemic countries should be developed to the same high standards as any medicine destined for use in the west. It should be submitted to a stringent regulatory authority – one that subscribes to the International Commission on Harmonization (ICH)[11]. For medicines developed for use in malaria-endemic countries, there is an additional hurdle – WHO

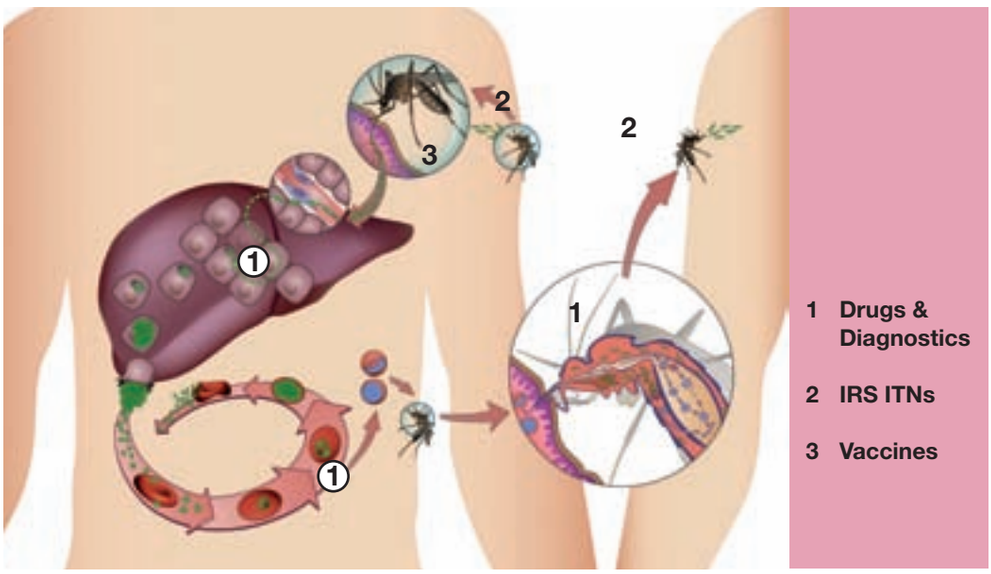

Figure 2: Lifecycle of the malaria parasite showing the initial infection of human liver cells, followed by rapid multiplication in the red blood cells. In later stages, the parasite starts to form gametocytes, or sexual forms of the parasite, which are then taken up into the mosquito host. The key difference between *P. falciparum* and *P. vivax* infection is that *P. vivax* forms hypnozoites or 'sleeping parasites' in the liver. These can be reactivated at any time, leading to a new burst of infection in the absence of a mosquito

Continued from page 18

11 www.ich.org.
12 http://healthtech.who.int/pq/.
13 http://en.sanofi-aventis.com/binaries/081016_coarsucam_who_en_tcm28-22368.pdf.
14 Nosten, F, White, NJ. American Journal of Tropical Medicine & Hygiene. 77(6 Suppl):181-192, 2007 Dec.
15 Bassat, Q. Mulenga, M, Tinto, H, Borrmann, S, Menéndez, C, Nambozi, M, Valéa, I, Nabasumba, C, Sasi, P, Bacchieri, A, Corsi, M, Ubben, D, Talisuna, A, D'Alessandro, U. Dihydroartemesinin-Piperaquine versus Artemether Lumefantrine for treating non-complicated malaria in African children: a randomized open label phase III non inferiority trial in five African countries. PLoS Medicine submitted 2008.
16 Ramharter, M, Kurth, F, Schreier, AC, Nemeth, J, Glasenapp, I, Belard, S, Schlie, M, Kammer, J, Koumba, PK, Cisse, B, Mordmuller, B, Lell, B, Issifou, S, Oeuvray, C, Fleckenstein, L, Kremsner, PG. Fixed-dose pyronaridine-artesunate combination for treatment of uncomplicated falciparum malaria in pediatric patients in Gabon. [Journal Article. Research Support, Non-U.S. Gov't] Journal of Infectious Diseases. 198(6):911-9, 2008 Sep 15.
17 www.dndi.org/cms/public_html/printpage.asp?ArticleId=477&TemplateId=1.
18 www.who.int/medicines/areas/quality_safety/quality_assurance/RAJ2006WHOStability.pdf.
19 www.mmv.org/IMG/pdf/PRODUCT_PROFILE_with_logo.pdf.
20 www.mmv.org/IMG/pdf/mmv07_Glance_reoranized_sept2007.pdf.
21 http://prvinfo.org/files/Biocentury%20-%20Global%20health%20vouchers%202.pdf.

Continued on page 22

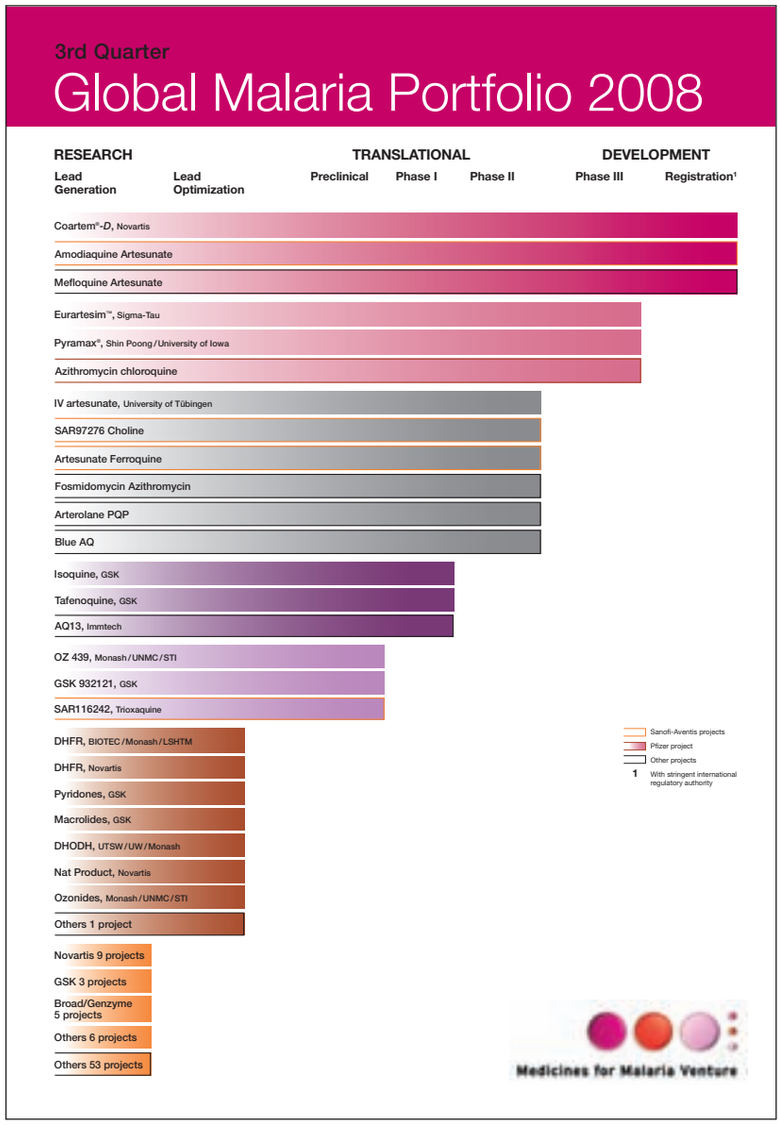

Figure 3: The portfolio of new medicines in development for malaria. For the sake of simplicity only those which are being developed in clinical trials compatible with ICH standards are included. A version of this portfolio is available from MMV's website www.mmv.org and is regularly updated

Prequalification. The WHO has experts who can 'prequalify' medicines for use in UN programmes. Typically, the amount of data in an ICH submission would be enough to also prequalify a medicine[12]. MMV believes that an ideal medicine would be accepted by both groups – ICH and the WHO – which would constitute a seal of approval for a high quality medicine. Coarsucam was recently pre-qualified by the WHO[13]. MMV and DNDi will work together with Sanofi-aventis on gathering data, via implementation studies, on the way Coarsucam is used in the field.

Do we need more fixed-dose ACTs? From the patient's point of view the answer is yes, clearly for reasons of greater choice and availability. In addition to this there is another argument – that several medicines are needed to overcome the potential of resistance[14]. Two important factors are at work here: first, if more varieties of ACTs were available on the ground in disease-endemic countries, there is less chance that resistance will emerge to any one of them; second that the market is still not saturated with high quality products. Even with Novartis producing 70 million treatments of Coartem a year (a number which dwarves both Statins – the largest profit-making commercial medicine) almost 200 million additional treatments are still needed. Currently people in malaria-endemic countries take what they can get. Few have easy access to ACTs, and many end up taking Chloroquine (to which there is already substantial resistance) or even worse unwittingly take fake medicines.

In the global antimalarial pipeline two other fixed-dose ACTs are in development and will be submitted to stringent regulatory authorities in 2009: Eurartesim (a combination of Dihydroartemisinin and Piperaquine phosphate) being developed by MMV and Sigma Tau Pharmaceuticals in Italy[15]; and Pyramax (a combination of Pyronaridine and Artesunate) being developed by MMV and Shin Poong Pharmaceuticals in Korea[16]. In addition, a combination of Mefloquine and Artesunate has been developed for the Brazilian healthcare system by the state-owned pharmaceutical company Farmanguinhos and DNDi. This has so far not been registered with a stringent regulatory authority or with the WHO[17].

On the face of it, once individual drugs used in a combination have already been shown to work in clinical trials, the registration of a combination therapy seems like a fairly simple process. In reality nothing could be further from the truth. First, the active ingredients in ACTs tend to be relatively mature molecules that were discovered more than 35 years ago. This means that although anecdotal evidence exists for their use in man, often safety studies need to be performed to obtain a good toxicological dossier for the combination. Second, the new combinations produced must have the longest possible shelf life, especially under conditions that simulate those found in the tropics, including relatively high temperature and humidity[18]. Unfortunately, the supply chain of antimalarial drugs from the site of production to the patient often means that they can spend a lot of time in government warehouses or central stores – so the longer the shelf life, the more likely the drugs are

Continued from page 19

to be useful. Three years is the current objective[19], in reality, however, achieving such a long shelf life for these combinations has required a lot of work on formulation development.

Partnerships and finance: key ingredients for success

From all the above, it is clear that the discovery and development of antimalarials is not the preserve of any one organisation alone and is best conducted in partnership. From a pharmaceutical viewpoint, the returns from sales of antimalarials are unlikely to be sufficient to cover the costs of development, estimated at more than $40 million not including the cost of material supply and formulation development. This is where PDPs like MMV step in to share the cost. A large part of the PDP financing comes from philanthropic organisations such as the Bill and Melinda Gates Foundation or the Wellcome Trust. Funding also comes from overseas/development aid budgets (eg, currently MMV receives money from the Swiss, British, Irish, Dutch and Spanish governments). In addition, some private donor organisations, such as Exxon Mobil and BHP Billiton[20], have a direct interest in malaria-endemic regions, as do humanitarian organisations such as Médecins sans Frontières which extensively supports DNDi.

In these public-private partnerships, the not-for-profit PDPs provide financial support, an understanding of the field of malaria, expertise with clinical trials in disease-endemic countries and other areas of know-how. The industrial partner provides an understanding of the product, including the manufacturing process, the methods of production and commercialisation of the product to increase awareness, demand and uptake. In addition, the commercial partner brings additional funding: a mixture of direct financing by the partner, and also leveraging support from local and regional government funds. MMV's industrial partners include many of the 'big pharmaceutical' companies, such as Novartis, GlaxoSmithKline and Sanofi-aventis. However, there is also significant interest from middle-tier companies, such as the Italian company Sigma Tau and the Korean company Shin Poong.

The hunt is on for innovative financial mechanisms to fund the research and development of new medicines and this has been recently boosted by changes in the US legislation proposed by Senators Brownback and Brown[21]. They have brought into law the concept of a Priority Review Voucher. Simply put, a pharmaceutical company which develops a new medicine for a tropical disease would, upon its registration, receive a bonus from the FDA. This bonus is a voucher which can then be used to gain priority review of any other commercial product, thus speeding up its approval by several months. This voucher is transferable, and its value has been estimated at several hundreds of millions of dollars. Given that it would only be awarded at the end of development, if discounted cash flow analysis is applied and an allowance is made for the probability of success, then at MMV we estimate that this would reimburse a company for the cost of clinical development of an antimalarial[22]. This is a significant financial incentive for development of new therapeutics in neglected disease by both the large pharmaceutical companies and smaller biotech companies.

Next generation antimalarials: tackling resistance and safety

The challenge for the next generation of molecules in our pipeline of antimalarials is to discover new therapies which protect the world against the emergence of resistance to Artemisinin. There are sporadic reports of patients who do not respond to Artemisinin[23], especially in the Thai-Cambodian border region. To have an effective portfolio then, there has to be a clear priority placed on compounds with new mechanisms of action. At the early stages of the portfolio, we have several such compounds including a new pyridone inhibitor in partnership with GlaxoSmithKline[24], which targets electron transport, and the next generation of a synthetic analog of Artemisinin[25] (**Figure 3**). The new discovery projects being funded are not only looking for new targets but also for ways of overcoming existing resistance. We are currently working in the areas where emerging Artemisinin resistance has been reported to see whether any Artemisinin-resistant parasites would be resistant to the whole class of ozonide-containing compounds. So far we can be optimistic: it would be unusual if a single genetic change would make a parasite resistant to the entire class of compounds; the example of resistance to the 4-aminoquinolines gives us hope that this will not be the case.

MMV's pipeline for early-stage discovery was built with a view to producing one new combination medicine every five years. The new medicine would be scheduled for launch after the current ACTs have been launched (in other words the period 2012-2016). In the area of anti-infectives it has been estimated that every medicine that enters Phase I of clinical development has only a 28% chance of reaching the market[26]. In malaria, since we know that we have to produce a combination

22 Our own estimation of the value of the Priority Review Voucher is based on the real development costs of the product Pyramax (Pyronaridine-Artesunate). Using standard probabilities of success for each clinical phase for an anti-infective medicine, and a commercial cost of capital of 12%, then we estimate that the voucher would repay the investments needed for all of Phase II and Phase III studies, including the CMC costs. For MMV this is a better description of the value, than giving a pure dollar number, given that the voucher is only useful many years after the clinical development is completed.

23 Dondorp, A. Resistance to artemisinin-based malaria treatment regimens: Does it exist? Joint meeting of the Infectious Diseases Society of America and the American Society of Microbiologists, Washington DC, 27 Oct. 27, 2008. Abstract # 3643 2008.

24 Yeates, CL, Batchelor, JF, Capon, EC, Cheesman, NJ, Fry, M, Hudson, AT, Pudney, M, Trimming, H, Woolven, J, Bueno, JM, Chicharro, J, Fernández, E, Fiandor, JM, Gargallo-Viola, D, Gomez de las Heras, F, Herreros, E, León, ML. Synthesis and Structure – Activity Relationships of 4-Pyridones as Potential Antimalarials. Journal of Medicinal Chemistry; 2008; 51(9); 2845-2852.

25 Vennerstrom, JL, Arbe-Barnes, S, Brun, R, Charman, SA, Chiu, FC, Chollet, J, Dong, Y, Dorn, A, Hunziker, D, Matile, H, McIntosh, K, Padmanilayam, M, Santo Tomas, J, Scheurer, C, Scorneaux, B, Tang, Y, Urwyler, H, Wittlin, S, Charman, WN. Identification of an antimalarial synthetic trioxolane drug development candidate. Nature. 430(7002):900-4, 2004 Aug 19.

Continued on page 23

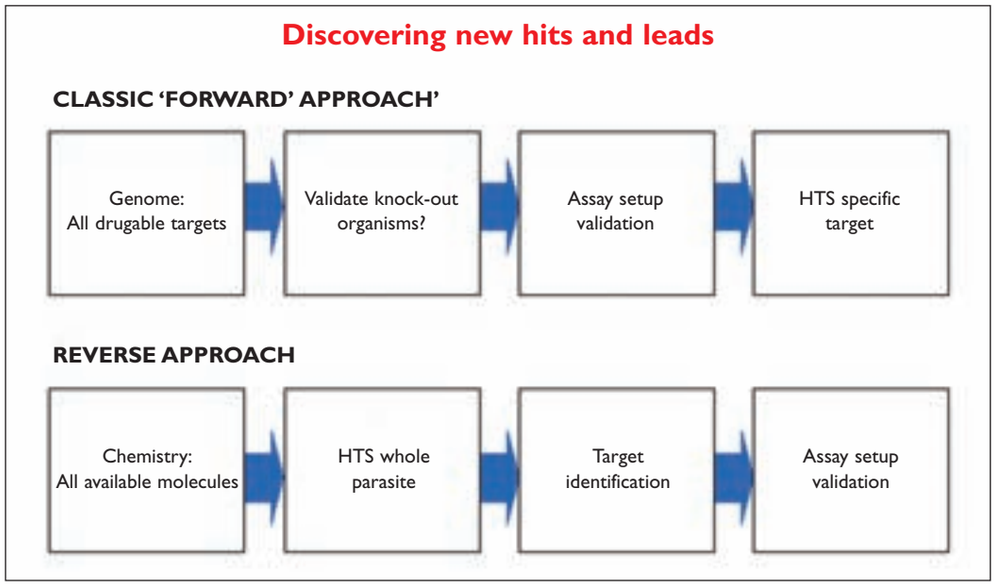

Figure 4: Two approaches to discovery of new hits and leads. The availability of the parasite genomes enables us to select targets for which there is either a strong rationale based on biochemistry, or else where we know that there is a strong probability of success – the ortholog approach. The reverse chemical genetics approach, which in a sense is more classical, requires screening against the whole parasite *in vitro*. Although eventually there will be a need to find the molecular target (probably before clinical studies start), it should be underlined that the molecular basis of many antimalarials is still a subject of active discussion

of at least two active ingredients, then each new product requires that seven new Phase I molecules are tested every five years for malaria. This is a significant challenge given that each individual molecule must have a 90% efficacy against malaria on its own[27].

Efficacy is not the only challenge. In many ways the bigger issue is safety and occurrence of adverse events. Many but not all of the ACTs have been studied in clinical trials involving more than 2,000 people taking the new drug. However, once the products are launched into the public markets in Africa, then the reporting of adverse events falls radically. It is therefore vital that during the clinical trials we garner as much information as possible regarding the safety profiles of the compounds. Safety, more than anything, is to the most important reason to follow ICH guidelines wherever possible.

The search for new drugs: Genomics vs Phenotypic screens

Traditionally, there are two opposing views on how to identify new lead compounds. One is based on identifying molecular targets in the parasite, inhibition of which would lead to its death (**Figure 4**); the other is to screen the whole parasite in a high density format. The first approach has been boosted recently by the availability of the parasite genome from *P. falciparum*[28] as well as *P. vivax*[29]. In the world of human targets (or enzymes), the approach would be to validate as much as possible by knock outs or RNA interference (RNAi) methods. For *P. falciparum* knock-outs are complicated and RNAi machinery does not exist in the parasite[30]. This makes it even more difficult to depend on the validation of a target by genetic methods, and suggests that pharmacological validation is a more important route. One short-cut here is the use of ortholog approaches. Companies have worked for years on human enzymes, and have found inhibitors. Often in the parasite genome there is a similar looking target. By screening the inhibitors found in the 'human' programme then it is often relatively simple to find compounds which are selective for the parasite target[31,32]. This cuts down the numbers of compounds that need to be tested from hundreds of thousands to hundreds.

Using the second approach we have been able to examine the death of the parasite in the red blood cells for a long time – but now we can use these tools to look at large compound collections. The original radioactive assays have been replaced by assays based on image processing, and the format has been changed from the classical 96-well assay to a high content high throughput assay in 1,536-well formats[33]. These assays have been used by Novartis and GSK to screen almost four million compounds. More recently, the academic group at

Continued from page 22

26 The attrition rate of 28% from Phase I to launch for anti-infective medicines comes from the Centre for Medicines Research http://cmr.thomsonreuters.com/. We expect this number to fall over the next 10 years, as the number of medicines targeting unprecedented mechanisms increases.

27 A position paper of the criteria for the selection of partners in a combination therapy against malaria can be found at http://www.mmv.org/article.php3?id_article=27.

28 Gardner, MJ, Hall, N, Fung, E, White, O, Berriman, M, Hyman, RW, Carlton, JM, Pain, A, Nelson, KE, Bowman, S, Paulsen, IT, James, K, Eisen, JA, Rutherford, K, Salzberg, SL, Craig, A, Kyes, S, Chan, MS, Nene, V, Shallom, SJ, Suh, B, Peterson, J, Angiuoli, S, Pertea, M, Allen, J, Selengut, J, Haft, D, Mether, MV, Vaiday, AB, Martin, DM, Fairlamb, AH, Fraunholz, MJ, Roos, DS, Ralph, SA, McFadden, GI, Cummings, LM, Subramanian, GM, Mungall, C, Venter, JC, Carucci, DJ, Hoffman, SL, Newbold, C, Davies, RW, Fraser, CM, Barell, B. Genome sequence of the human malaria parasites *Plasmodium falciparum.* Nature 419 6906 498-511 2002 Oct.

29 Carlton, JM, Adams, JH, Silva, JC, Bidwell, SL, Horenzi, H, Caler, E, Crabtree, J, Angiuoli, SV, Merino, EF, Amedeo, P, Chenq, Q, Coulson, RMR, Crabb, BS, del Portillo, HA, Essien, K, Feldblyum, TV, Fernandez-Bacerra, C, Gilson, PR, Gueye, AH, Guo, X, Kang'a, S, Kooij, TWA, Korsinczky, M, Meyer, EVS, Nene, V, Paulsen, I, White, O, Ralph, SA, Ren, Q, Sargeant, TJ, Salzberg, SL, Stoekert, CJ, Sulivan, SA, Yamamoto, MM, Hoffman, SL, Wortman, JR, Gardner, MJ, Galinski, MR, Barnwell, JW, Fraser Liggett, CM. Comparative genomics of the neglected malaria parasite *Plasmodium vivax.* Nature 455 757-763 2008 October.

Continued on page 24

Continued from page 23

30 *Plasmodium* is haploid for most of its lifecycle, making knock-outs more difficult. The machinery for interference RNA methods has not been conclusively identified in the parasite. More recently, progress has been made using siRNA against potential host targets. Rodriguez, CD, Hannus, M, Prudencio, M, Martin, C, Gonçalves, LA, Portugal, S, Epiphanio, S, Akinc, A, Hadwiger, P, Jahn-Hofmann, K, Röhl, I, Gemert, G-J, Frantich, J-F, Luty, AJF, Sauerwein, R, Mazier, D, Koteliansky, V, Vornlocher, H-P, Echeverin, CJ, Mota, MM. Host Scavenger Receptor SR-BI plays a dual role in the establishment of malaria parasite liver infection. Cell Host & Microbe 4 271-282 2008.

Continued on page 25

the Eskitis Institute in Queensland has independently set up high throughput screening (HTS). MMV hopes to work with partners to expand this technology to consider other aspects of the life cycle of the parasite (**Figure 2**). These will include the gametocyte stages (useful for blocking transmission to other people via the mosquito) and the liver stages (important for preventing the relapses which occur in *P. vivax* infection). In the future we will need drugs which are active against all stages in the parasite life cycle, so the ability to build up a Malaria Life-cycle Fingerprint plays an important part in prioritising which projects to bring forward aggressively.

An integrated approach to malaria control and eradication

At a meeting in Seattle in September 2007, Bill and Melinda Gates called for the eradication of malaria. This call was an appeal to the heart – if no American or European mother should have to face the death of a child through malaria, then why should an African mother[34]? The appeal was also based on the idea that malaria costs African countries some $12 billion a year in lost opportunities and lost working days – too heavy a burden for the continent to handle[35]. The call for eradication was promptly endorsed by the WHO, and has been taken on board as a challenge by most of the malaria community. MMV has revised its vision to include eradication as has the Roll Back Malaria Partnership's Global Malaria Action Plan.

The control, elimination and ultimate eradication of malaria will need a multi-phased approach. The first step is to destroy the habitat of the mosquito (draining stagnant waters, as was done in Europe and the US), and use insecticide spray wherever necessary. The second step is to protect children and expectant mothers from becoming infected, as they are the most vulnerable groups. Here, the role of insecticide treated nets (ITN) is critical as is the role of education to ensure that people spend their nights protected by such nets. Third, we need to work hard to protect all those at risk from being infected. There are two approaches to this: the most obvious is vaccination, and

indeed there is a potent vaccine in Phase III trials at the moment[36] that will seek regulatory approval in 2011, if the trials are successful. However, the wily parasite *Plasmodium* can change its surface antigens to escape immuno-surveillance, and so to date the best vaccines appear to be partial (not everyone gets protected) and time limited (the protection only lasts for a relatively short time). New generations of vaccines are actively being worked on, but we should not forget the possibility and effectiveness of pharmacological protection. Malaria medicines contain drugs with very long half lives, often more than two weeks, and therefore can be given to infants together with vaccinations for other diseases (in other words at two months, three months, and nine months of age). Such intermittent preventive treatment offers pharmacological protection during the early stages of life[37] and also can be used during pregnancy[38], the other particularly vulnerable period.

Taken together, these approaches are important. Indeed, given the inordinate number of deaths from malaria, if each of the above methods could halve this number, we would still be left with an intolerable number of more than 100,000 needless deaths.

The fourth and final step of actually treating all the patients who have malaria with effective medicines is central to eradication. If all patients are treated, there is no-one left to re-infect the mosquitoes, and the cycle of infection is blocked for ever.

A challenging future for antimalarial drug development

A look at the past shows what is needed for the future. For malaria to spread there is a need for infected people, plus mosquitoes, and a failure of the healthcare system to treat all patients before they have a significant number of gametocytes. It is by controlling these three factors that malaria outbreaks no longer occur in the US and Europe, even though there is a regular supply of infected individuals returning home from endemic areas. Malaria is like any other transmissible disease – we have already developed extremely effective and safe medicines – but there is always the possibility that sooner or later resistance will develop against them as they have done with other drugs in the past.

To protect ourselves and the global community in the future, we need a steady pipeline of new products – products as different in their mechanism of action as possible. In addition we have to two extra hurdles not always seen in other therapeutic areas. The medicines must be extremely safe (there is still no accurate reporting of adverse events once they are in use). They must also be cheap. How cheap, is a matter of some debate, although the malaria community has set a target of below $1 for an adult course of treatment. Ideally, if greater uptake is to be achieved, treatment should be as cheap as chloroquine, which sells for less than 15 cents in many parts of the world.

It is clear that the next decade will be challenging for us all as we attempt to rid the world of malaria once and for all.

Acknowledgements

Many thanks to all the team at MMV for their discussions and ideas presented here. Special thanks also go to our Expert Scientific Advisory Committee (ESAC) for the role they have played in shaping the portfolio shown, and for the various partners in the many projects for their enthusiasm and commitment to solving the scourge of malaria. My apologies go to all whose work was not discussed due to space limitations. DDW

Dr Timothy Wells *joined Medicines for Malaria in October 2007 as Chief Scientific Officer with responsibility for the Research and Development Portfolio from basic research through to Registration. Previously he was Senior Executive Vice-President Research at Serono, with responsibilities covering drug innovation and development, from genetics and target validation through testing in volunteers. This included managing an organisation of 800 people throughout Europe and the US. Dr Wells joined Serono in 1998 as the first Head of the Geneva Serono Pharmaceutical Research Institute. Prior to that, he worked for seven years for Glaxo and SmithKline Beecham. Dr Wells' scientific career began with a PhD in Chemistry under the supervision of Sir Alan Fersht, in London; in the founding days of protein engineering, analysing the molecular details of how enzymes work. He moved to Geneva in 1990, and initially worked to pioneer the use of proteins in structure-based design, with several collaborations which led to novel three-dimensional protein structure. His research group in Geneva in the mid-90s moved into cytokine immunology and identified several new chemokines, and their receptors, and pioneered the application of these molecules to a wide range of diseases, from allergy through to HIV infection. As a result he has more than 170 scientific publications, and several patent applications. He is on the Scientific Advisory Board of several Biotechnology funds and University groups. He is married and has four children.*

Continued from page 24

31 Grundner, C, Perrin, D, Hooft van Huijsduijnen, R, Swinnen, D, Gonzalez, J, Gee, CL, Wells, TN, Alber, T. Structural basis for selective inhibition of Mycobacterium tuberculosis protein tyrosine phosphatase PtpB. [Journal Article. Research Support, N.I.H., Extramural. Research Support, Non-U.S. Gov't. Research Support, U.S. Gov't, Non-P.H.S.] Structure. 15(4):499-509, 2007 Apr.

32 Ojo, KK, Gillespie, JR, Riechers, AJ, Napuli, AJ, Verlinde, CL, Buckner, FS, Gelb, MH, Domostoj, MM, Wells, SJ, Scheer, A, Wells, TN, Van Voorhis, WC. Glycogen synthase kinase 3 is a potential drug target for African trypanosomiasis therapy. Antimicrobial Agents & Chemotherapy. 52(10):3710-7, 2008 Oct.

33 Plouffe, D, Brinker, A, McNamara, C, Henson, K, Kato, N, Kuhen, K, Nagle, A, Adrian, F, Matzen, JT, Anderson, P, Nam, TG, Gray, NS, Chatterjee, A, Janes, J, Yan, SF, Trager, R, Caldwell, JS, Schultz, PG, Zhou, Y, Winzeler, EA. In silico activity profiling reveals the mechanism of action of antimalarials discovered in a high-throughput screen. Proc Natl. Acad Sci USA 105(26):9059-64, 2008 Jul 1.

34 Roberts, L, Enserink, M. Did they really say... Eradication Science 318 1544-1545 2007 Nov.

35 Sachs, J, Malaney, P. The economic and social burden of malaria. Nature 415: 680–5 2002.

36 Maire, N, Aponte, JJ, Ross, A, Thompson, R, Alonso, P, Utzinger, J, Tanner, M, Smith, T. Modeling a field trial of the RTS,S/AS02A malaria vaccine. American Journal of Tropical Medicine & Hygiene. 75(2 Suppl):104-10, 2006 Aug. See http://www.malariavaccine.org/files/20080603_VaccineCongress_Singapore_BOTTING.pdf for a review of the current pipeline.

37 Schellenberg, D, Cisse, B, Menendez, C. The IPTi Consortium: research for policy and action. Trends in Parasitology. 22(7):296-300, 2006 Jul.

38 Menendez, C, D'Alessandro, U, ter Kuile, FO. Reducing the burden of malaria in pregnancy by preventive strategies. The Lancet Infectious Diseases. 7(2):126-35, 2007 Feb.