

## DEVELOPMENT OF NEW DRUGS FOR CHEMOPROPHYLAXIS OF MALARIA

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**ABSTRACT** • When U.S. troops first encountered drug resistant malaria during the Vietnam war, the United States Army responded by establishing a malaria drug research program. In 1988, the Walter Reed Army Institute of Research developed mefloquine (WR 149240) and halofantrine (WR 171669). Actually, in association with SmithKline Beecham, the WRAIR is developing tafenoquine (WR 238605), an analog of primaquine, which is expected to be effective in both preventing and treating malaria in deployed military personnel. Final phase III studies leading to U.S. Food and Drug Administration approval are planned for 2000. Applied research is also carried out with the association atovaquone-proguanil (Malarone®) or with azithromycin, but also with primaquine, the associations paludrine-dapsone or lapudrine-dapsone, analogs of floxacrine (WR 243251), and a guanyldrazone (WR 182393). The future scientific directions must focus on basic and applied research for a better understanding of the modes of action and mechanisms of resistance to standard and developmental drugs. Using new techniques, the design and synthesis of new drugs would hopefully result in the development of drugs that circumvent the malaria parasites elusive mechanisms of drug resistance.

**KEY WORDS** • Malaria - Mefloquine - Halofantrine - Tafenoquine - Floxacrine - Azithromycin - Guanyldrazone - Malarone.

### LE DEVELOPPEMENT DE NOUVELLES MOLECULES POUR LA CHIMIOPROPHYLAXIE ANTI-PALUDIQUE

**RESUME** • Quand les troupes américaines ont rencontré pour la première fois un paludisme chimiorésistant lors de la guerre du Viêt-Nam, l'armée des Etats-Unis a répondu par la mise en place d'un programme de recherches sur les antipaludiques. En 1988, le Walter Reed Army Institute of Research a développé la méfloquine (WR 149240) et l'halofantrine (WR 171669). En association avec SmithKline Beecham, le WRAIR développe la tafénoquine (WR 238605), analogue de la primaquine, conçue pour être efficace à la fois dans la prévention et le traitement du paludisme chez les personnels militaires déployés. Les dernières études en phase III conduisant à l'autorisation par la Food and Drug Administration (FDA) des Etats-Unis sont prévues pour 2000. Des recherches appliquées sont également conduites avec l'association atovaquone-proguanil (Malarone®) ou avec l'azithromycine, mais aussi avec la primaquine, l'association paludrine-dapsone ou lapudrine-dapsone, des analogues de la floxacrine (WR 243251), et une guanyldrazone (WR 182393). Les directions scientifiques futures se focaliseront sur des recherches fondamentales et appliquées pour mieux comprendre les modes d'action des médicaments classiques et en développement ainsi que les mécanismes de résistance à ces médicaments. Avec de nouvelles techniques, la synthèse de molécules originales devrait aboutir à l'élaboration de médicaments qui échapperont aux mécanismes parasitaires de développement des chimiorésistances.

**MOTS-CLES** • Malaria - Méfloquine - Halofantrine - Tafénoquine - Floxacrine - Azithromycine - Guanyldrazone - Malarone.

Malaria has plagued military campaigns since recorded history. Resistance to current antimalarial drugs is increasing at an alarming rate and is now present in many areas where military personnel may be deployed.

Military personnel, as well as tourists and consultants are recurrently at increased risk of malaria related disease and death. The Walter Reed Army Institute of Research (WRAIR) through the Military Infectious Disease Research Program (MIDRP) at the United States Army Medical Research and Materiel Command (USAMRMC) currently serves as a lead agency for the development of new antimalarial drugs. Since there is no profit motive and very little pri-

vate sector interest, the scientific and financial burdens of drug discovery have fallen almost entirely on the WRAIR program. While this program has been touted as one of the most successful in the world, the current products are a dividend from research that occurred over ten years ago. At that time, more resources were available and the program evaluated thousands of compounds per year. The drug discovery process design is long and complex, and our immediate concern is for the next generation of antimalarial drugs for our future deployments. If we expect to continue to protect deployed soldiers from this serious and fatal disease, we must maintain the required critical mass of multi-disciplinary investigators and resources focused on the objective of discovering and developing new antimalarial drugs.

When U.S. troops first encountered drug resistant malaria during the Vietnam conflict, the United States Army responded by establishing a malaria drug research program to address this new military threat. The mission of this program would be to develop new prophylactic and therapeutic

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tic drugs for military use. Using a multi-disciplinary approach with combined in-house and contract research this program was coordinated through the Division of Experimental Therapeutics at the Walter Reed Army Institute of Research in Washington, DC. Beginning in 1985, the advanced development was to be managed by the US Army Medical Material Development Activity (USAMMDA) at Fort Detrick, Maryland. The Army recognized that there was little economic incentive for private pharmaceutical firms to undertake antimalarial drug discovery activities. This program assumed responsibility as the lead federal agency for antimalarial drug development and was fully expected to maintain the expertise and laboratory capability to manage an experimental compound from the chemist's bench through clinical trials and on to Food and Drug Administration registration.

In response to the emergence of chloroquine resistance, the US Department of Defense (DOD) invented and developed mefloquine (WR149240) with Hoffman LaRoche as the co-development partner. Licensed in the USA in 1988, mefloquine (Lariam®) remains the malaria prophylaxis of choice for US soldiers and travelers. Resistance to mefloquine has been documented in Indochina, East Africa and sporadic cases are occurring in West Africa. In combination with artesunate, it is the only effective treatment available for multidrug-resistant malaria in Southeast Asia. Growing controversies over neurological side effects, though, are appearing in the literature from journal articles to traveler's magazines and resulting legal ramifications threaten global availability. As the «herd mentality» of mefloquine associated psychoses continues to gain momentum, it will certainly affect operational compliance and readiness. As these and other reports of drug resistance continue to evolve, the need for a replacement drug for weekly prophylaxis will continue to escalate.

Halofantrine (WR171669) was developed as a backup drug for mefloquine in a collaborative effort between the US Army and SmithKline Beecham. Halfan® is US Food and Drug Administration (FDA) approved and marketed in many areas of the world. However, its usefulness is limited by possible cross-resistance with mefloquine, cardiac toxicity, and poor absorption. In simian models, there is apparent synergy with halofantrine and WRAIR's new 8-aminoquinoline drug (tafenoquine) for radical cure of *vivax*-like relapsing malarias. The main metabolite of halofantrine appears to be less toxic and equally efficacious against multidrug *falciparum* malaria strains. While halofantrine will continue to be a clinical effective in treatment, the likelihood of its use in prophylaxis will be limited to the development of the metabolite.

As a result of the intensive effort by the WRAIR, tafenoquine (WR238605) is being developed with SmithKline Beecham as a co-development partner. Tafenoquine is expected to be effective in both preventing and treating malaria in deployed military personnel. Final phase III studies leading to FDA approval are planned for 2000. In phase II trials, the drug was used in operational deployments in Thailand and found to last for weeks, such

that three pre-deployment doses could provide protection for up to 30 days without the need for further doses with similar protective efficacy as a short-acting efficacious malaria vaccine. For longer periods of malaria exposure during military deployments, the drug can be given in a convenient weekly regimen. Animal and *in vitro* studies designed to evaluate gametocytocidal and sporontocidal activities suggest a potential role in transmission blocking. This opportunity has significant public health implications for endemic countries, but also has operational utility for shutting down malaria epidemics where military deployments might occur in areas of intense transmission.

Through cooperative agreements with the US DOD, Glaxo Wellcome Pharmaceuticals has filed for a US New Drug Application with the FDA for Malarone®. This drug is a fixed dose combination of atovaquone and proguanil, which acts against blood stages of malaria. It has been shown to be highly effective in the treatment of uncomplicated multi-drug resistant *falciparum* malaria and as a daily chemo-suppressive agent. Early malaria pre-clinical efficacy testing of atovaquone was conducted at the WRAIR and subsequent dose ranging was conducted in clinical trials at the AFRIMS, Bangkok, Thailand. In the treatment of acute uncomplicated *falciparum* malaria, it proved to be consistently effective in clearing the initial parasitaemia. However, unacceptable rates of recrudescence precluded its further development as monotherapy. Concurrent administration with proguanil, selected for its synergistic activity, solidified its role as antimalarial drug in studies when evaluated at the WRAIR laboratory in Thailand, the AFRIMS. Subsequent studies were conducted world-wide including WRAIR labs in Brazil and in Kenya which demonstrated 99 % efficacy for treatment of uncomplicated multidrug resistant malaria and 98 % efficacy for prophylaxis in placebo controlled trials. Additional prophylaxis studies have been completed by the NAMRU-2 in Jakarta, Indonesia. Prophylactic regimens will be one tablet daily (with prophylaxis starting 1-2 days prior to exposure) and continued seven days after leaving the endemic area.

Clinical trials in Kenya demonstrated that the erythromycin analog, azithromycin, was effective in semi-immunes for preventing *falciparum* malaria in an area of intense malaria transmission. It was hoped that azithromycin might serve as an alternative daily drug for doxycycline which can not be used in pregnant women and children and exhibits phototoxicity. Subsequent trials in non-immune volunteers were completed in Indochina and Indonesia demonstrating marginal protective efficacy. A remaining hope for azithromycin prophylaxis is in combination with other drugs since recent *in vitro* studies suggest synergy between azithromycin and other antimalarial drugs such as primaquine analogs or chloroquine.

A multidisciplinary working group from Army and Navy has reviewed existing data on primaquine and formal discussions have been held with the FDA regarding primaquine prophylaxis in short term deployments. There are sufficient data available to justify submitting a supplement to the NDA which would add the indication of causal prophylaxis

to the current indication of primaquine as a radical curative agent to the product label. This collaborative effort between two branches of the DOD should make this niche prophylactic drug available to the military without a costly development effort. The Navy laboratory in Jakarta has completed a pivotal phase III study.

Concerns over resistance and severe allergic reactions curtailed the use of Fansidar® (pyrimethamine plus the long acting sulfonamide, sulfadoxine) for prophylaxis. Combinations of other antifolate combinations (paludrine or lapudrine plus dapsone) have been evaluated with some success in African as Fansidar® replacements. Parasites resistant to pyrimethamine and cycloguanil have been found to be markedly susceptible to certain biguanides and triazines. The enhanced activity and synergy with PABA antagonists and lack of cross resistance to other antifolate antimalarials provides valuable insight for selecting structural analogs and to begin lead directed synthesis of a second generation of Fansidar-like drugs for prophylaxis. Other drug candidates in various stages of pre-clinical development for prophylaxis at the WRAIR include analogs of floxacrine (WR243251) and a guanylhydrazone (WR182393), the only non 8-aminoquinoline drug observed to exhibit radical curative properties against *vivax* like relapsing malaria in *in vitro* and simian models.

Our drug development mission is to stay one step ahead, to learn more about our common malaria parasite enemy and then develop the means to combat it. Our experience with previous deployments such as Somalia has also taught us that post-deployment compliance with the prescribed drug regimens can be a chronic problem and the documentation of antimalarial drug resistance requires rigorous parasitologic and therapeutic criteria. As a result there are also which support an intensified surveillance program. With a surveillance network in place, researchers will better be able to understand the clinical relevance of antimalarial drug resistance. These surveillance data will also allow primary health care providers to more effectively manage patients and medical planners can effectively select the best possible drug regimens for different geographic areas. Critical to patient management and triage, is prompt and accurate diagnosis. A technology similar in concept to other home test kits has been identified and DOD is currently developing a «malaria test strip» that will be able to diagnose malaria from a drop of blood. The ability to rapidly diagnose malaria in far-forward military health care echelons will help healthcare professionals treat malaria patients sooner and avoid unnecessary evacuation.

The emergence of multidrug-resistant malaria will continue to confound our drug development process and we must have a better understanding of the mechanisms of drug resistance. With the formation of the Multilateral Initiative for Malaria (MIM), new global strategies are evolving for integrated approaches for studying drug resistance. Both the French and US Armies are playing pivotal roles to elucidate the clinical relevance of drug resistance and examine the potential for spread of resistance in the field. Currently, an improved version of the pLDH micro-test developed at the Pasteur Institute is being validated for predictive value of *in vitro* parasite resistance. There is mutual agreement that the critical methodology and approach needed to describe antimalarial drug resistance required a well-documented clinical studies with adequate follow-up, confirmation that adequate drug levels were reached at the target (pharmacokinetics), and demonstration of antiparasitic drug resistance *in vitro* and by using molecular markers (if available). Results of these studies have facilitated documentation of clinically relevant resistance to mefloquine, halofantrine, chloroquine, proguanil plus dapsone, and atovaquone. These and other data will help guide the drug discovery process for the next generation of candidate prophylactic drugs through a systematic examination of the molecular and cellular basis of drug resistance.

Our future scientific directions must focus on basic and applied research for a better understanding of the modes of action and mechanisms of resistance to standard and developmental drugs. Using structure based drug discovery, molecular modeling and lead directed synthesis, the design and synthesis of new drugs would hopefully result in the development of safe and effective drugs that circumvent the malaria parasites elusive mechanisms of drug resistance. Multiple drug resistance in *falciparum* malaria will continue to pose special problems for targeting the blood stages of malaria. There must also be increased emphasis toward developing drugs with true causal prophylactic or radical curative properties before blood stages emerge and cause clinical disease. The solution for the current malaria problem is to rebuild a necessary critical mass of investigators, collaborators and clinical centers that are focused and committed to discovering and developing new drugs. Proposed collaborations between the US and French Armies for clinical trials and drug resistance surveillance are pivotal to this process. No other private or government agency will adopt this as their mission. If we are not successful in this endeavor, we can not expect to protect deployed soldiers who will be scattered on missions in diverse geographic locations responding to the whims of a new world order.