

NIAID Malaria Working Group

NIAID Research Agenda for Malaria

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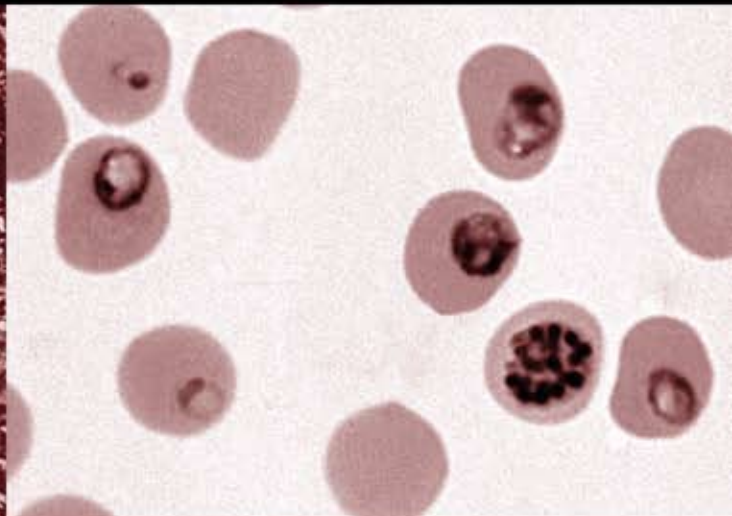


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NIAID Research Agenda for Malaria

Introduction

The National Institute of Allergy and Infectious Diseases (NIAID), a component of the National Institutes of Health (NIH), is firmly committed to enhancing its malaria research portfolio while maintaining an emphasis on basic research: the foundation of any robust and comprehensive malaria research enterprise. While recent progress in malaria research has been encouraging, NIAID recognizes that many unanswered scientific questions and under-studied areas of malaria research must be addressed in order to advance our understanding of this disease and develop next-generation tools to: 1) initially, support global efforts to control malaria; 2) then, eliminate the disease at the local and regional levels; and 3) finally, eradicate malaria worldwide. In this effort, NIAID is fully committed to increasing collaboration with the many governments and non-governmental organizations, including private industry, nonprofit organizations, and public-private partnerships that recently have made malaria research a priority. Such an approach will help ensure that promising scientific discoveries are translated rapidly into effective and accessible malaria prevention and control measures.

The NIAID Malaria Research Agenda provides guidance on promising opportunities and needs in malaria research and lays out a comprehensive set of high priority research activities that will need to be addressed in a timely manner to provide the tools required for the control—and ultimately, eradication—of malaria. It is intended to highlight the critical importance of research partnerships and the need for enhancement of essential and under-supported international malaria research capacity. Malaria research cannot be effectively pursued without robust support from and cooperation among malaria investigators and research organizations around the world. Through this support and cooperation, researchers working with malaria-affected communities are poised to make unprecedented scientific progress, which will save or improve the lives of millions. A separate *NIAID Strategic Plan for Malaria Research and Development: Efforts to Accelerate Control and Eradication of Malaria Through Biomedical Research* lays out the vision that guides the Institute in developing the tools and strategy needed for the control, elimination, and ultimately the global eradication of malaria.

The NIAID Malaria Research Agenda addresses four major goals identified in the *NIAID Strategic Plan for Malaria Research and Development*:

1. Increase fundamental understanding of the complex interactions among malaria parasites, the mosquito vectors responsible for their transmission, and the human host.
2. Strengthen the ability to identify, develop, validate, and evaluate new tools and strategies for treatment, prevention, and control of malaria.
3. Enhance both national and international research and research training infrastructure to meet malaria research needs, particularly for community-based and -supported clinical trials in malaria-endemic countries.
4. Advance research to develop tools to support and sustain global efforts to control, eliminate, and eventually eradicate malaria.

The Challenge

Malaria is an urgent threat to global health. Malaria-related death rates have doubled over the last thirty years and nearly 1.3 million people—mostly children under the age of five—die from malaria every year [1-5]. Over forty percent of the world's population is at risk of becoming infected and in many of the poorest tropical and subtropical regions of Africa, Asia, the Middle East, and Central and South America, malaria causes more than 500 million cases of clinical disease annually [3]. In societies with a high prevalence of malaria, health systems are overburdened and economic growth and social development are severely reduced [6, 7].

Although malaria currently is not endemic in most temperate countries, there are significant concerns that it may resurge as drug-resistant parasite strains and pesticide-resistant mosquitoes emerge and spread. In this regard, climate change could have a powerful effect on the distribution of malaria-transmitting mosquitoes [8]. Ten to thirty thousand cases of malaria are diagnosed throughout the world each year among travelers from non-endemic countries to endemic countries, resulting in small outbreaks, including some deaths, and the risk of establishing malaria in new areas [9]. In 2005, the U.S. Centers for Disease Control and Prevention (CDC) reported 1,528 cases of imported malaria, including seven fatalities, in the United States [10].

Malaria is a biologically complex disease, caused by a protozoan parasite that carries out its life cycle in two distinct hosts—the human and the *Anopheles* mosquito—and involves complicated interactions among these three organisms (Figure 1). The parasite evades and disables the human immune system, making it difficult for the immune system to fight the disease. In addition, there are four human malarias that are each caused by a different species of malaria parasite, and it is possible to be infected by more than one species at any given time. Clinical manifestations of malaria vary according to many factors, not all of which are well-delineated, including the species and variants of the parasites, host immune response, the rate of transmission by mosquitoes, and co-infection with other pathogens such as HIV. Unlike other infectious agents for which effective vaccines and drugs have been developed, malaria parasites have a large genome that adapts quickly in response to selection pressures. Effectively addressing malaria, both in terms of research and interventions, also is made more complex because the parasite and its impact on populations and age groups vary greatly from region to region.

Over the last century, valiant efforts were made to control, eliminate, and eradicate malaria using tools such as antimalarial drugs and insecticides. However, these efforts met with failure as the maintenance of control programs waned, as logistical and behavioral factors limited the effective use of interventions, and as the parasites and mosquitoes rapidly developed resistance to common drugs and insecticides. In the last few decades, however, some new tools have been developed that have the potential to contribute to significant progress towards malaria control. The global community has called for new efforts to use these tools effectively and to develop new ones to try to manage malaria worldwide, with the ultimate goal of elimination, and possibly eradication, of the disease. If we are to make a commitment to revitalize malaria control, elimination, and eradication efforts, a continuous flow of new tools, including vaccines, improved diagnostics, and new drugs and vector management approaches, is critically needed. The pace of malaria research also needs to accelerate to support the timely development of those tools and to generate a broad knowledge base that will assure their eventual use is effective, reliable, and sufficiently widespread to achieve elimination and eradication.

Malaria primarily affects impoverished areas of the world where product sales are unlikely to be profitable. Basic research on malaria has been slow to generate new product concepts due to insufficient funding and the complexity of the disease. Because of these factors, private sector engagement in the development of new therapeutics, diagnostics, and vaccines for malaria has

been limited. Within the last decade, public-private partnerships, such as the Malaria Vaccine Initiative (MVI) and the Medicines for Malaria Venture (MMV), have been established to begin to fill some of the gaps in the malaria product development pipeline. In addition, the devastating impact of malaria has captured the attention of many governmental and nongovernmental organizations. The U.S. President's Malaria Initiative, the Roll Back Malaria Partnership, the World Bank Global Strategy and Booster Program, the World Health Organization (WHO) Global Malaria Program, the Global Fund to Fight AIDS, Tuberculosis and Malaria, the Bill & Melinda Gates Foundation, and the Wellcome Trust, among others, have made public commitments to revitalize and support malaria research and control. In October 2007, at its Malaria Forum held in Seattle, WA, the Bill & Melinda Gates Foundation reaffirmed its commitment to confront malaria and challenged the world to strive towards the ambitious goal of eradicating malaria worldwide.

As efforts accelerate to strengthen malaria control, the challenge for organizations committed to fighting the disease will be to interact effectively with individuals and populations most affected by malaria so that available interventions are rapidly assimilated and effectively used in a variety of settings. Sustaining any progress made over a long period of time will also be a continuing challenge. Therefore, the efforts of all organizations and governments striving for these goals must be well-coordinated. As malaria control efforts become more successful in reducing the burden of disease, research will play a critical role in evaluating the success of interventions, and establishing and maintaining effective disease surveillance. This research will provide critical information needed to determine the best course of action in moving toward the goal of malaria eradication.

To make and sustain progress toward the ambitious goals of worldwide malaria control, elimination, and eradication, the global community must coordinate and collaborate in unprecedented ways, with each stakeholder contributing critical human capital and resources. NIAID is prepared to continue its support for the basic and translational research that is essential to understand better the biological underpinnings of malaria and to accelerate development of new and improved antimalarial tools. Effective partnerships between NIAID, other governmental and non-governmental organizations, and private industry must play a crucial role in building a solid product development pipeline to translate key basic science discoveries into needed, field-relevant tools. With commitment from the global community, a set of tools that is already achieving some success, and the promise of a future with a full pipeline of new antimalarial tools, public health agencies and organizations have an unprecedented opportunity to work together to end malaria. NIAID will do its part to support global efforts toward this ambitious goal.

Status of the NIAID Malaria Research Program

NIAID is the leading U.S. government agency that supports basic, translational, and clinical research and research training in malaria. NIAID-supported malaria research is undertaken in four large intramural laboratories and through grants, cooperative agreements, and contracts awarded by its extramural program to scientists in the United States and in over 20 other countries^{*}, including many malaria-endemic countries [11].

In fiscal year 2007 (FY07), NIAID spent \$88.9 M on malaria research including 175 projects in the following categories:

- 98 projects in basic biology and pathogenesis: \$36.2 million (including 27 projects in vector biology: \$ 10.7 million)
- 36 projects in drug discovery and development: \$16.3 million
- 38 projects in vaccine discovery and development: \$35.3 million
- 3 projects in diagnostics: \$1.2 million

In addition to individual research awards, NIAID extramural divisions support several special programs that focus on globally important infectious diseases including malaria. These include the U.S.-based Tropical Disease Research Units (TDRU), as well as programs designed to enhance international research capacity, such as the International Collaboration in Infectious Disease Research (ICIDR), the Tropical Medicine Research Centers (TMRC), and the International Research in Infectious Diseases (IRID) programs. To encourage malaria research worldwide, NIAID also provides an array of freely available research resources, reagents, and training opportunities through programs such as the Malaria Research and Reference Reagent Resource Center (MR4) program and the NIH Tetramer Facility (Table 1).

NIAID intramural laboratories conduct a wide variety of research on basic malaria biology, including pathogenesis, vector biology, parasite drug resistance, and immunology, as well as drug and vaccine development. A unique component of the NIAID intramural program is the Malaria Research and Training Center (MRTC), which the Institute has established with the University of Bamako in Bamako, Mali. The MRTC, one of only three NIAID International Centers for Excellence in Research (ICER), fosters collaborative research that involves Malian scientists working with NIAID-supported intramural and extramural investigators. Research at the MRTC includes malaria vaccine clinical trials and studies of genetic resistance to malaria infection, as well as other topics.

In the past decade, public-private partnerships have emerged as major drivers in the development of interventions against diseases for which market factors do not stimulate sufficient private sector investment. NIAID launched a new program in 2007, the "NIAID Partnerships with Public-Private Partnerships" to stimulate the development of new drugs, vaccines, and diagnostics for malaria and other high-priority, neglected infectious tropical diseases [12]. Two new awards on malaria drug discovery and development have been made under this initiative.

As scientific collaboration and the efficient use of scarce resources become ever more essential to research progress, NIAID strives to coordinate its activities with other key supporters of malaria research including the Bill & Melinda Gates Foundation, the Commission of the European Community, the Multilateral Initiative on Malaria, the Centers for Disease Control and Prevention (CDC), the Department of Defense (DoD), and the U. S. Agency for International Development (USAID). Much remains to be done to fully engage private sector resources and innovation in the

* These include: Brazil, Burkina Faso, Cambodia, Cameroon, China, Colombia, Gabon, the Gambia, Ghana, India, Indonesia, Kenya, Laos, Madagascar, Malawi, Mali, Mozambique, Panama, Papua New Guinea, Peru, Tanzania, Thailand, and Uganda.

struggle to better understand and confront malaria. Additional resources are an important stimulus in a field that often has lacked such resources.

Given the magnitude of malaria as a global health problem, the urgent need for additional scientific progress and effective interventions is compelling. At the same time, scientific advances in areas such as malaria genomics and proteomics have created promising new research opportunities that are ready for investigation. NIAID is well positioned to accelerate the pace of malaria research if additional collaborative opportunities and financial resources become available. NIAID is also well prepared to help guide the global malaria research enterprise by providing expert advice, collaboration, and coordinated research support.

Basic Biology of Malaria

Malaria is transmitted from one individual to another through the bites of female *Anopheles* mosquitoes. Malaria-infected mosquitoes transmit *Plasmodium* parasites through the skin, where they enter the bloodstream, travel to the liver and multiply, and then re-enter the bloodstream where they invade and destroy red blood cells and cause disease. Most malaria parasites persist in the human bloodstream as regularly multiplying (asexual) forms, but some undergo fundamental transitions to female and male (sexual) forms that circulate in the blood and can be ingested by a mosquito when it is feeding. In the mosquito, these sexual forms of the parasite mate and reproduce, and are available for transmission into a human to begin the cycle again (Figure 1).

Parasite Biology

Our understanding of the biology of *Plasmodium* parasites provides a vital framework for laboratory and field studies of malaria including deeper investigations in such sub-specialty areas as immunology, pharmacology, biochemistry, genetics, molecular and cellular biology, physiology, pathology, and systems biology. At least four malaria parasite species (*Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, and *Plasmodium malariae*) infect humans. In addition, some human infections are known to be caused by at least one species that naturally infects monkeys (*Plasmodium knowlesi*). Among the *Plasmodium* species, *P. falciparum* and *P. vivax* cause the greatest morbidity and *P. falciparum* causes the greatest mortality, mostly among young children in Africa. These parasites each have their own unique life cycle features and are transmitted in various malaria-endemic environments by specific subsets of *Anopheles* mosquito species.

Research in recent decades has shed light on many aspects of *Plasmodium* biology, broadening understanding of how parasites interact with the human immune system, invade liver and red blood cells, cause human disease, and are transmitted by mosquitoes. Still, in these fundamental areas and others, important questions remain unanswered and new questions have arisen. For example, more research is needed to better understand disease transmission processes, tissue invasion pathways, parasite immune evasion mechanisms, emerging drug resistance, and the transitions the parasites undergo when they invade insect tissues and human liver and blood cells during their life cycle. Additional fundamental information is also needed on parasite epidemiology and population biology to support efforts to control and eliminate malaria.

Vector Biology

Diversity among the mosquito vectors that harbor and transmit malaria to humans contributes significantly to the complexity of disease control. The *Anopheles* genus encompasses approximately 400 species distributed across all continents except Antarctica; 30-50 of those species have been identified as vectors of the *Plasmodium* parasite species that cause human

malarial disease [13]. Several physiological, behavioral, and ecological characteristics determine the effectiveness of various *Anopheles* species as malaria vectors including: susceptibility to *Plasmodium* parasite infection, geographic distribution, preference for feeding on humans versus animals, tendency to enter houses, tendency to feed or rest indoors versus outdoors, ability of populations to rebound following dry seasons, longevity of individual mosquitoes, and susceptibility to control measures such as insecticides. Understanding the characteristics of various malaria vector species has important practical implications for selecting and designing effective strategies for mosquito management. For example, indoor insecticide spraying efforts may be expected to yield better results when used against species that have a tendency to rest indoors and are not resistant to that particular insecticide. Similarly, bed nets are more likely to be effective against mosquitoes that primarily feed on humans during the night, rather than at dusk.

Many current malaria intervention strategies are based on what we know about the African species *Anopheles gambiae*, the most commonly studied mosquito vector; however, many other *Anopheles* species that are major and minor malaria vectors in other regions of the world remain understudied. In some parts of the world, it has not even been determined which species are the main vectors responsible for transmitting malaria to local human populations. Fundamental research is needed to identify vector species, characterize vector behavior and ecology, and predict risk and disease transmission.

Mosquito-parasite interactions and mosquito immunology are also areas of significant research interest. Molecular interactions between the vector and parasite influence the ability of *Plasmodium* to infect mosquito tissues in order to complete stages of their development. For example, malaria parasites must recognize and invade the midgut and eventually the salivary glands in order to be successfully transmitted. Mosquito vectors mount innate immune responses against malaria parasites, consisting of humoral and cellular defense mechanisms. A better understanding of the molecular and immunological interactions that allow mosquitoes to either support parasite development or fight off *Plasmodium* infections may reveal potential targets for transmission-blocking vaccine strategies or for novel interventions to reduce malaria transmission.

Increasing knowledge about the basic biology of malaria vectors will serve as both the basis for the development of new interventions to disrupt the transmission cycle of malaria and as a guide for development of malaria prevention strategies and policies. Disruption of transmission, which will require a detailed understanding of the interactions between parasite, vector, and human host, as well as knowledge of vector ecology and behavior, will play a crucial role in any efforts to move beyond local and regional elimination of disease toward global eradication.

Malaria Pathogenesis

Malaria pathogenesis is the process by which malaria parasites cause illness, abnormal function, or damage in their human hosts. Malaria transmission begins with the inoculation of *Plasmodium* parasites into a human. As noted in the Figure 1, parasites initially travel through the bloodstream to the liver, where they differentiate and replicate prior to re-entering the bloodstream in a form that is capable of infecting red blood cells. Some relapsing forms of malaria are caused by parasites that establish dormant liver stages that emerge from the liver as blood-stage parasites long after the initial infection. The subsequent cyclical infection of human red blood cells causes symptomatic malarial illness, which manifests as recurring episodes of chills, fever, and sweating. Other symptoms such as headache, malaise, fatigue, and body aches can last for weeks. In some cases of *P. falciparum* infection, “uncomplicated malaria” can progress to “severe malaria,” which manifests as coma and seizures (cerebral malaria), severe anemia, respiratory distress, kidney and liver failure, and cardiovascular collapse. Children, travelers to endemic areas, and populations that live in areas of low malaria transmission are at highest risk of severe disease because they have lower exposure to malaria and therefore less opportunity to build immunity. Severe malaria also can occur in cases in which infection is untreated or caused by drug-resistant parasites. Pregnant women are particularly susceptible to placental infection by *P. falciparum*, which can result in severe forms of malaria that contribute to premature delivery and low-birth-

weight infants. Overall, hospitalized children and adults with severe forms of malaria have a 20 percent chance of dying, and many others experience varying levels of short- and long-term physical and cognitive/behavioral disabilities, creating significant socioeconomic burdens on families and societies [14].

Malarial disease manifestations such as coma, kidney failure, and severe anemia may each have different underlying processes. Parasite-host interactions are believed to play a common and particularly important role in malaria pathogenesis. For example, the binding of *P. falciparum*-infected red blood cells to the inner surfaces of blood vessels initiates complex inflammatory processes that cause fever and other symptoms of malaria. If left untreated, malaria caused by *P. falciparum* may have a fatality rate that is relatively high in individuals without genetic or immune protection from the disease (for example, American travelers to malaria endemic areas). In contrast, nearly all African children in endemic areas repeatedly experience malaria episodes, but only some of them develop severe, life-threatening forms of the disease. To reduce the morbidity and mortality of malaria, a better understanding of the biological processes underlying the progression of infection to disease is urgently needed.

Appropriate animal models can provide a useful tool to study malarial disease processes and to develop new drugs and vaccines. While several models are currently available for parasite biology, all have limitations. Although some non-human primates such as *Aotus* or rhesus monkeys can be infected by species of human *Plasmodium* parasites, the observed pathogenesis does not often replicate what occurs in humans. Moreover, the supply of these primate species is often quite limited. Models of *Plasmodium* infection exist for laboratory rodents but the parasite species are not those that infect humans. In addition, these models do not represent a natural host-parasite system since they were adapted for laboratory rodents from parasites infecting African thicket rats. However, a severe combined immunodeficient (SCID) mouse model containing *P. falciparum*-infected human red cells has been useful for tests of drug candidates against *P. falciparum* *in vivo*.

Genomics

Genomic studies are critical for a rational approach to vaccine and drug discovery, especially because the parasite has a worldwide distribution and an extreme level of genetic diversity. Genomics are also important for understanding the genetic diversity of vector species and parasite-vector interactions. Within the last five years, the genomes of the human host, the mosquito *Anopheles gambiae* (the major malaria vector), and the parasite *Plasmodium falciparum* (the deadliest malaria parasite) have been sequenced [15]. The genome sequence of *Plasmodium knowlesi*, a strain that primarily infects primates, has recently been made available [16]. Sequencing of the *Plasmodium vivax* parasite and four strains of human *P. falciparum* from the Indian subcontinent and one strain of chimpanzee parasite, *Plasmodium reichenowi*, is underway. Additional species of *Anopheles* vectors are also being considered for sequencing. The next challenge for scientists will be mining and interpreting available genomic data. Although new tools are available to interpret large genome datasets, gaps remain in translating genomic- and proteomic-based knowledge into specific hypothesis-driven research questions. Creative funding mechanisms may be needed to support studies of malaria-related parasite and vector genomes and proteomes to identify innovative concepts and questions for future research.

Immunology

Despite considerable effort, many aspects of malaria immunology remain unclear. Due to the complex nature of both the malaria parasite and the human immune system, interactions between the parasite and the host during infection result in a tenuous balance between eliciting protective immunity and triggering harmful immune responses. During its life cycle, each developmental stage of *Plasmodium* is characterized by the expression of a distinct set of antigens that elicit different types of immune responses from the host. The parasite also has developed a number of

mechanisms to evade and disable the host immune response. Moreover, we do not know which mechanisms are most important in leading either to protection or to pathology in humans. Scientists are just beginning to understand the contributions of innate immunity to early defenses, as well as its role in the regulation of antibody and cell-mediated responses, critical components of long-term protection.

Unlike the response to many other infections, immunity to malaria following natural exposure is acquired only slowly and after repeated infections. This naturally acquired immunity provides some protection against parasites and severe clinical disease, but it does not produce the “sterilizing immunity” that results from completely clearing the body of parasites and it appears to be short-lived in the absence of ongoing exposure to malaria parasites. The presence of malaria through much of human history has actually driven the evolution of human genetic polymorphisms that confer resistance to the disease, as evidenced through genetic studies of human populations. The fact that a large number of these polymorphisms lie in genes affecting immune responses supports the view that immune responses are important determinants of the outcome of infection.

As the interface between the malaria parasite and the immune system seems to lie at the threshold of disease versus protection, an improved understanding of the immunology of malaria is likely to provide key insights into ways to enhance human immunity to the disease while reducing pathogenesis. These insights will be critical for the development of an antimalarial vaccine and will have a variety of other applications toward improved therapeutic and preventive strategies to reduce the burden of disease.

Epidemiology

A solid base of epidemiological data is critical both for developing and evaluating new vaccines, drugs, and other interventions and for the successful implementation of malaria research, surveillance, and control programs. Understanding malaria on a population level, and understanding the biological, behavioral, and environmental factors that influence malaria epidemiology and transmission are especially important as the global community strengthens antimalaria efforts and begins working toward elimination of malaria from populations and geographic areas. While malaria epidemiology is an area led by other U.S. government agencies and international organizations such as CDC and WHO, NIAID would like to strengthen partnerships with those groups to enable further progress and, where applicable, foster more collaboration between epidemiologists and other malaria researchers.

Malaria epidemiology research faces many challenges. The epidemiology of malaria itself is changing in the areas surrounding well-established field stations and research sites along the east and west coasts of Africa, where much of the epidemiological data guiding current activities were originally gathered. The successful implementation of research studies and of programs to strengthen healthcare infrastructure and deliver interventions to those who need them has resulted in reduced transmission and burden of disease in those areas, as well as a change in the clinical patterns of disease. It is now thought that the areas of highest malaria transmission in Africa are in the central region, where epidemiology research has been extremely scarce due to lack of basic roads, communication systems, health/research infrastructure, research resources including personnel, and political stability. It is essential to identify and monitor changes in malaria epidemiology brought about by factors such as successful and failed disease interventions, drug and insecticide resistance, different species/strains of parasites and vectors, as well as less understood factors such as human behavior and cultural practices, environmental modification, and climate change.

Malaria Prevention and Control Strategies

Historically, products such as antimalarial drugs, chemical and environmental vector control measures, and conventional and insecticide-treated mosquito nets helped eliminate malaria from North America and most of Europe and have greatly reduced the burden of malaria in other parts of the world. The effectiveness of these elimination programs waned as malaria parasites and mosquito vectors became resistant to commonly used drugs and insecticides, as individual and public use of these interventions decreased, and as public commitment to vector and parasite control programs diminished or suffered from resource constraints. Without new malaria treatment and control products being developed quickly enough to replace failing ones, and without addressing critical issues affecting malaria control program implementation, malaria has resurged worldwide. To reverse the trend toward rising malaria prevalence and its return to countries where it had been eliminated, new drugs, diagnostics, and vector management tools, as well as effective vaccines, are urgently needed. There also is an acute need to understand the factors that favor the effective use of new interventions and of prevention and control interventions already available. To develop both new products and a more complete understanding of factors that assure their effective introduction and use, public-private partnerships are essential. The engagement of regulatory organizations and product distribution networks are also needed to assure rapid and wide public access and rational and consistent use, especially in malaria-endemic regions (Figure 2).

Malaria Prevention and Treatment in Pediatric Populations

Malaria mostly affects infants, young children, and pregnant women—population groups that present special challenges for researchers [2, 5]. More than 800,000 African children under the age of five die of malaria each year [2]. Malaria also contributes to malnutrition in children, which indirectly causes the death of half of all children under the age of five throughout the world [2, 5]. Fifty million pregnant women throughout the world are exposed to malaria each year; in malaria-endemic regions, one-fourth of all cases of severe maternal anemia and 20 percent of all low-birthweight babies are linked to malaria [5]. Research in these groups presents several challenges. For example, on a technical level, many of the experimental assays used in basic malaria research require more blood than reasonably can be obtained from a child, especially if that child is anemic. In addition, findings from studies conducted in standard adult populations may not apply to children and pregnant women due to differences in the physiology, immunological status, course and severity of disease, and drug metabolism. While much remains to be done, scientists are working to better understand how malaria uniquely affects children and pregnant women and to develop new research tools, methods, and products appropriate for these populations, such as microassays that require smaller volumes of blood.

Additional challenges arise in interventional and vaccine studies in which trials must first be carried out in healthy adults and older children before they can be conducted in younger children, the primary target population. This age de-escalation approach, while critical to assess safety, requires substantial time and resources to obtain even initial evidence of likely effectiveness in the pediatric target population. Similarly, for drug licensure, additional studies may be required to optimize dosing for pediatric populations. This need for specialized studies and the challenges of research in children can diminish private sector enthusiasm for the development of new and even urgently needed pediatric drugs and vaccines. Additional complications arise during late-stage clinical trials, which must be carried out in pediatric and pregnant female populations in regions where malaria is endemic. These populations occur where limited resources and infrastructure may compromise the ability to obtain robust data in a timely manner or where substantial investment is required to adequately reduce research-related risks. Finally, interventions targeted to pregnant women often are perceived as carrying increased risk because of potential harm to the fetus as well as the mother. As a result, risk-averse research-funding organizations and product development companies have been reluctant to undertake studies of critical importance

to the population groups most affected by malaria. Consequently, the public sector will continue to play a crucial role in facilitating clinical trials in these populations.

Once new interventions targeting the special needs of children and pregnant women do become available, it will be important to understand the community factors that will facilitate their introduction and use in the target populations. As a result, studies addressing these issues will be needed as effective interventions approach licensure or registration. After efficacy has been demonstrated, post-licensure studies to improve effectiveness will also be warranted and could contribute significantly to reducing the burden of malaria in children and women worldwide.

Vaccine Development

A safe and effective malaria vaccine, when developed, will be essential for the long-term control of malaria globally, and will play an important role in elimination and eradication efforts. At present, there is no such vaccine currently licensed for malaria (or any other parasitic disease that afflicts humans). Understanding the natural immune mechanisms that confer protection against the parasite and using this fundamental knowledge to inform the process of vaccine development is essential. The complexity of the malaria parasite life cycle, in which each developmental stage is immunologically distinct and multiple mechanisms are involved in generating protective immunity against the parasite, has hampered the efforts of scientists to develop promising vaccine candidates. These technical challenges, combined with the perception that a malaria vaccine will have only limited market potential, have resulted in the absence of substantial private sector interest in developing malaria vaccine candidates.

Recent scientific progress may help foster private sector interest because several technical issues have been resolved and recently a recombinant protein-based vaccine was found to confer partial protection against malaria in clinical trials. Several other candidate vaccines that target various life cycle stages of the malaria parasite are also in development (Tables 2 and 3). Because of the complexity of the parasite, compared to viruses and bacteria for which we have vaccines, there is also renewed interest in developing a whole parasite vaccine. As large scale implementation of basic malaria control measures begins to have an impact and the vision for malaria eradication builds momentum, the malaria vaccine strategies will continue to evolve, requiring the engagement of additional partners.

Drug Discovery and Development

Antimalarial drugs, in combination with mosquito control programs, have historically played a key role in controlling malaria in endemic areas and reducing the geographic range of malarial disease. In recent decades, however, the emergence of drug-resistant parasites has contributed to the spread of malaria in areas and populations where malaria had previously been controlled. Because this emerging drug resistance is making a once-curable disease unresponsive to available therapies, a continuous pipeline of new and effective antimalarial drugs to achieve and sustain progress in disease control is essential.

To address this urgent need, NIAID has long supported basic research studies of *Plasmodium* to identify key developmental, signaling, biosynthetic, and genetic pathways that may provide targets for rational drug design. To better understand and confront drug resistance, NIAID-supported investigators seek to: elucidate mechanisms of drug resistance; identify drug combinations that may be safe and effective while limiting drug resistance; and develop ways to restore efficacy of drugs in known classes of antimalarials.

The antimalarial drug development pipeline includes many promising candidates at various stages in the discovery, development, and clinical evaluation process (Table 4). As the malaria parasite increasingly becomes resistant to available drugs, it is critical to ensure that new, effective drugs emerge from the development pipeline (Figure 2) with regularity. It is also

important to develop new classes of antimalarial drugs that are safe and effective in infants, children, and pregnant women. All drug interventions must be affordable for those who need them most if the spread of malaria is to be contained. Public-private partnerships are critically important at all stages of drug discovery and development, and these partnerships are essential to bring promising products to licensure and into the market. There also is a need to understand better the behavioral aspects of how antimalarial drugs are used both therapeutically and prophylactically in order to assure optimal use of current and future drug interventions.

Diagnostics

New and improved diagnostics are essential to increase the accuracy of clinical diagnosis, to provide more appropriate and effective treatment, to facilitate clinical trials, to conduct international surveillance more accurately, to understand the dynamics of malaria transmission, and to monitor the emergence of drug-resistant parasites and insecticide-resistant mosquitoes. The most reliable technique for diagnosing malaria is, as it was throughout the last century, labor-intensive, relying on highly trained technicians using microscopes to analyze blood smears. Such microscopic analysis is time-consuming, variable in quality, difficult to use in resource-poor field settings, and cannot detect drug resistance. Given the current state of malaria in the world, the need for more accurate, rapid, economical, and comprehensive diagnostic tools is acute.

To help develop modern diagnostics, NIAID has supported the discovery of parasite proteins that can be detected by sensitive, inexpensive, and field-deployable, rapid diagnostic tests. Such tests already can distinguish some malaria species and, as their accuracy improves, such tests will become increasingly important in resource-limited settings. The ultimate goal is to develop easy-to-use tests that diagnose the malaria parasite causing an infection and identify its drug resistance profile.

Vector Management Approaches

The interruption of parasite transmission (from humans to mosquitoes and from mosquitoes to humans) and the reduction of mosquito populations are both critically important for controlling malaria and for efforts to eliminate and eventually eradicate the disease. Vector management tools such as insecticides, environmental modification, and bed nets contributed greatly to successful malaria control efforts in the past. In recent years, with the emergence of insecticide-resistant mosquitoes, insecticide-dependent interventions have diminished in effectiveness. Concerns about the environmental impact of some vector control methods, limited financial resources, unreliable individual and community use of vector control interventions, and waning political will also have restricted effective vector control programs. Partially as a result of all these factors, malaria has resurged and this has underscored the critical need for safe, effective, and sustainable vector management tools as key elements of overall strategies to control malaria in endemic areas.

Vector biology research is an essential component of effective vector management approaches. NIAID supports the discovery of key concepts that may be important for the development of vector management strategies through research on the basic biology of mosquito development, mosquito immunology, metabolic pathways that are susceptible to interventions, and host-seeking and feeding behaviors that can be interrupted to prevent transmission. In addition, NIAID supports studies to identify mosquito genes that could lead to the generation of transgenic mosquito strains that interfere with parasite development or transmission. NIAID also supports a small number of translational research projects on vector management strategies. Ultimately, discoveries emerging from NIAID's basic vector biology research program and concepts refined through translational projects will support the private sector's efforts to develop new and improved vector management tools. In order to support the long-term vector management goals of the malaria research community, NIAID will need to identify partners in non-profit and private sector

organizations to contribute to the development of promising strategies for malaria vector management.

Strategic Partnerships and Research Capacity

To accelerate malaria research, collaboration involving scientists from diverse disciplines is necessary. Over the next several years, creating global opportunities for basic scientists, epidemiologists, vector biologists, clinicians, and product development experts to interact and coordinate research efforts will be critical to advancing an interdisciplinary approach to malaria research. Recent scientific progress has led to promising research opportunities that can only be explored with commitment, focus, and adequate research capacity and support. Well-integrated public-private efforts will play a crucial role in meeting the urgent need for new prevention, diagnosis, treatment, and vector-control products. In addition, global research partnerships that engage local communities, institutions, and individual investigators must be fostered in malaria-endemic countries to undertake essential clinical research that demonstrates the effectiveness of new antimalaria interventions.

NIAID will continue to partner with organizations such as USAID, WHO, the Commission of the European Community, the European-Developing Countries Clinical Trials Partnership, the European Malaria Vaccine Initiative, the Wellcome Trust, the Bill & Melinda Gates Foundation, the Malaria Vaccine Initiative, and the Medicines for Malaria Venture. With so many organizations engaged in efforts to enhance malaria research, improved coordination and leadership become critically important.

In 1997, NIAID joined with the NIH Fogarty International Center and the National Library of Medicine, the Special Programme for Research and Training in Tropical Diseases at WHO, and other institutions to form the Multilateral Initiative on Malaria (MIM), the mission of which is to increase and enhance research on malaria by facilitating multinational research cooperation and by supporting the career development and research efforts of African scientists working in malaria-endemic areas. In 2007, NIAID established a new initiative, the “NIAID Partnerships with Public-Private Partnerships,” to develop new drugs, vaccines, and diagnostics for malaria and other neglected tropical diseases [12]. NIAID takes an active approach in addressing global health concerns, including malaria, by supporting research that provides the evidence needed to inform effective prevention and intervention strategies and policies that meet the needs of disease-affected communities.

NIAID also invests heavily in developing and strengthening sustainable local research capacity in disease-endemic countries. To assist capacity strengthening, NIAID provides scientists working in the U.S. and in malaria-endemic countries with access to critical malaria research resources (Table 1) and, working with the Fogarty International Center, it helps train and educate new investigators in the field. While NIAID will continue to support robust intramural and extramural research programs to address global malaria research needs, a growing malaria research effort will require an expanded capacity to undertake translational and clinical research in disease-endemic areas. As additional drugs, vaccines, and vector management strategies require clinical and field testing, this need is likely to grow and, as control programs succeed in reducing the incidence of disease, trial sites may need to expand their geographic boundaries to ensure they recruit adequate numbers of study participants. Furthermore, as patterns of malaria infection and distribution change, research opportunities and limitations in some populations also will be altered. Therefore, it will be important to enhance the flexibility of global malaria research infrastructure to respond to changing research needs and locality-related factors.

Future Directions: Enhancing Malaria Research to Support Sustainable Solutions

Despite recent scientific progress, malaria continues to be among the most daunting global public health challenges faced by humankind. The impact of the disease on women and children and its limitation of economic productivity in poor countries, as well as the resurgence of malaria worldwide, fueled by growing drug and insecticide resistance, have led to unprecedented interest in and support for additional research and international malaria control efforts. An essential aspect of this growing attention will be the need to ensure long-term investment over the time required to achieve research and product development objectives and to establish sustainable international research capacity—both human and institutional.

A major challenge for the immediate future of malaria research will be to accelerate the pace of malaria basic research that will yield novel biomarkers, and drug, vaccine, and vector control targets. An equally critical challenge will be to form and sustain the public-private partnerships required to translate fundamental discoveries into accessible, field-appropriate diagnosis, treatment, and vector management products, as well as vaccines for the appropriate target populations, especially infants, children, and women of child-bearing age. Another important challenge will be to understand the complex context in which malaria interventions are being implemented and to design tools that can contribute to sustainable malaria control and elimination programs that are tailored to the specific needs of different areas of the world.

Given the high rate of attrition of candidates in the vaccine and pharmaceutical product development pipeline, expanded support is urgently needed to ensure that early pipeline activities (discovery, target validation, exploitation of genomic and proteomic data, etc.) are robust enough to provide a sufficient “flow” of promising leads for preclinical and clinical development. To date, primarily because of limited resources, too many vaccine and drug development activities have focused on a small universe of targets. The challenge for NIAID and other organizations leading and funding malaria research will be to catalyze innovative ideas and new approaches that will revitalize the global malaria research enterprise. To achieve this, NIAID and other malaria research funding organizations must reinforce their commitment to international collaboration and the enhancement of research capacity in malaria-endemic countries to facilitate the translation of basic science into field-relevant, sustainable interventions. In this effort, important responsibilities also need to be undertaken by local governments and academic institutions, because ultimately they will be responsible for sustained and high quality research efforts and for the movement of new antimalarial products into local clinical and public health practice. Local capacity will be essential in the ongoing effort to reverse the spread and impact of malaria on a global basis.

While most malaria research has appropriately focused on Africa, which is currently the most severely affected region of the world, malaria is also a significant health burden elsewhere, including parts of Latin America, Asia, and Oceania. Furthermore, the presence of the malaria parasite and its mosquito vectors in other parts of the world, combined with globalization of travel, climate change, and the remarkable adaptability of both parasite and vector, make further resurgence of malaria a possibility, particularly in countries and regions where malaria’s devastating impact, experienced only a few generations ago, has been nearly forgotten. In light of these realities, the call for a revitalized effort toward malaria control, elimination, and eradication becomes even more timely and urgent. Through additional research, evidence-based interventions, and disease control activities, humankind has the ability to eliminate malaria as a major threat to human health. NIAID is prepared to do its part to make this dream a reality.

Current Research and Resource Gaps

The NIAID Malaria Working Group recognizes that in order to achieve the long-term goals of malaria elimination and eradication, it will be essential to pursue aggressively our current portfolio of research activities in the basic sciences and in support of the continued development of malaria prevention and control strategies. However, several research and resource gaps have been identified that need to be enhanced or expanded to meet our stated goals (page 1 and below). These priority gaps include:

Goal 1: Increase fundamental understanding of the complex interactions among malaria parasites, the mosquito vectors responsible for their transmission, and the human host.

Research and resource gaps:

- Understanding the natural mechanisms of protection against malaria
- Expanding studies of *Plasmodium vivax* and other parasite species
- Understanding malaria pathogenesis in special populations
- Understanding mechanisms of drug and insecticide resistance
- Developing animal models of malaria pathogenesis

Goal 2: Strengthen the ability to identify, develop, validate, and evaluate new tools and strategies, for treatment, prevention, and control of malaria.

Research and resource gaps:

- Understanding the “field reality,” or conditions in the field
- Developing field-ready diagnostics

Goal 3: Enhance both national and international research and research training infrastructure to meet malaria research needs, particularly for community-based and -supported clinical trials in malaria-endemic countries.

Research and resource gaps:

- Expanding clinical research capacity and strengthening strategic partnerships

Goal 4: Advance research to develop tools to support and sustain global efforts to control, eliminate, and eventually eradicate malaria.

Research and resource gap:

- Continuing efforts to populate the pipeline with research interventions including drugs, diagnostics, vaccines, and vector management tools

NIAID Malaria Research Priority Objectives and Activities

Based on the challenges, needs, goals, and current research and resource gaps described in the previous sections, the NIAID Malaria Working Group has identified the following specific, priority objectives, related research activities, and expected outcomes for the NIAID Malaria Research Program. Each objective directly corresponds to a specific research and resource gap identified in the previous section. The research activities to achieve each priority objective are listed by scientific category, providing a sense of the scope and complexity required to meet each objective. The broad range of research disciplines underscores the need for a multidisciplinary, integrated approach to addressing each gap and objective identified in this Malaria Research Agenda. There may be some overlap among these activities and expected outcomes, since some activities may help address more than one objective and contribute to more than one anticipated outcome.

These research activities also have been designated as short term, medium term, or long term. The short-term activities relate to efforts that should be initiated now to address urgent priorities. The medium-term activities will require a longer lead time or will build on results from short-term activities. The long-term activities, building on short-term and medium-term activities, will be undertaken as the Institute's Malaria Research Program moves from control toward elimination and eradication. Some of these objectives and related activities may be continued throughout the full period of malaria control, elimination, and eradication efforts. Many of these activities will need to be addressed by NIAID in collaboration with other agencies and organizations.

Objective 1: Understand the natural mechanisms of protection against malaria and integrate research on basic immunology and genetics with vaccine development efforts

Research Activities

Short term:

Parasite biology

- Understand mechanisms leading to antigenic switching and immune evasion by the parasite
- Understand the interplay between the parasite and human immune responses in the development of severe complications of malaria
- Identify biomarkers of therapeutic response
- Delineate the interactions between drugs and the immune system that result in clearance of infection

Malaria Pathogenesis

- Identify the mechanisms by which human factors, including hemoglobin mutations and red blood cell polymorphisms, mediate protection against malaria
- Characterize the relationship of parasite-host interactions to molecular, immunologic, and physiologic changes, as well as clinical manifestations, in patients with malaria

Genomics

- Identify novel human genes and genotypes related to protection
- Correlate genomic, functional genomic, and proteomic data with clinical phenotypes and outcomes

Immunology

- Identify the mechanisms by which immunity to malaria is induced, maintained, and regulated after parasite infection or vaccination, including improving the understanding of why naturally acquired immunity to malaria takes so long to develop and why natural immunity is not sustained over the long term
- Determine the nature and specificity of the host responses that lead to pathology or protection during malaria infection, including the roles of innate and acquired immune responses to different stages of the parasite life cycle
- Identify correlates of immune protection that can be applied to vaccine design and testing
- Determine immune mechanisms contributing to severe disease manifestations such as cerebral malaria or anemia
- Elucidate the mechanisms by which the malarial parasite evades and disables the host immune response
- Identify and characterize immune epitopes from parasites species and strains
- Discover novel adjuvants that improve the generation of protective immunity to malarial antigens

Medium term:

Immunology

- Develop *in vitro* immunologic assays that correlate with protection *in vivo*
- Develop adjuvants that enhance protection against all stages of malaria infection

Vaccine Development

- Identify new target parasite antigens from *P. falciparum* and *P. vivax* as vaccine candidates

Long term:

Vaccine Development

- Develop a safe, effective vaccine to prevent infection, especially in pregnant women, infants, children, and immune-compromised populations

Expected Outcomes:

- Maintenance of robust pipeline for clinical evaluation of vaccine candidates
- More tractable model systems for investigations of disease processes caused by *P. falciparum* and other human malaria parasites
- Development of novel interventions based on mechanisms of innate and adaptive immune responses in human hosts
- New strategies to prevent severe manifestations of disease, including complications of co-infections, cerebral malaria, and malaria-induced anemia
- Pipeline of new adjuvants for vaccine design and development
- Increased understanding of the molecular and biological processes by which female mosquitoes are able to identify a human host for feeding
- Improved knowledge of the genetic differences between vectors that are competent to host/transmit malaria parasites and those that are not
- Improved understanding of factors affecting infectivity, virulence, pathogenesis, and transmission

Objective 2: Expand studies of Plasmodium vivax and other human parasite species

Research Activities

Short term:

Parasite Biology

- Understand the mechanism by which the dormant forms of *P. vivax* and *P. ovale* are formed and activated
- Develop and characterize an *in vitro* culture system for *P. vivax*
- Determine the ecology and behavior of parasite species involved in malaria transmission, and their relationship to malaria transmission cycles
- Understand how parasites survive and develop in the mosquito

Malaria Pathogenesis

- Determine mechanisms involved in the pathogenesis of *P. vivax* malaria

Genomics

- Support functional comparison of other human malarial parasites such as *P. vivax*, and define genetic determinants of relapsing malaria

Epidemiology

- Identify mosquito vectors for *P. vivax* and interventions/tools needed to be most effective

Expected Outcomes:

- Matching of new drug and vaccine candidates to appropriate parasite and patient populations for clinical evaluation
- Improvement of malaria diagnostics based on identification of parasite antigens
- New drugs specifically targeting *P. vivax*, the most common cause of clinical attacks of malaria outside of sub-Saharan Africa
- Well-tolerated drugs that are amenable to Mass Drug Administration campaigns that will target *P. vivax* and facilitate disease elimination efforts
- Understanding the ecology and epidemiology of *P. vivax* transmission cycles
- Understanding *P. vivax*-vector interactions

Objective 3: Understand malaria pathogenesis for special populations, such as pregnant women, infants, children, and those with co-infections, such as HIV

Research Activities

Short term:

Immunology

- Identify and characterize differences in immune responses, including differential recognition of malaria antigens among infants, children, and adults
- Understand the immunological bases for the increased susceptibility of pregnant women to malaria

Medium term:

Malaria Pathogenesis

- Characterize pathogenesis associated with malaria co-infections, particularly with HIV/AIDS, tuberculosis, and helminth infections
- Characterize pathogenesis associated with severe complications of malaria
- Identify biomarkers of disease progression
- Identify biomarkers predicting severe disease
- Determine the consequences of co-infections with multiple parasite species/strains on generation and maintenance of protective immunity

Immunology

- Understand immune response of various populations to vaccines and develop *in vitro* correlates of immune protection
- Develop techniques that can be used to measure cellular and humoral immune responses in infants and children using small amounts of sera and peripheral blood cells

Malaria Prevention and Control in Special Populations

- Conduct pharmacodynamics, pharmacokinetic and comparative immunogenicity and efficacy studies to optimize drug and vaccine doses for use in infants, children, and pregnant women
- Develop diagnostic tests appropriate for children and infants

Long term:

Immunology

- Develop adjuvants that can be used in immune compromised individuals, pregnant women, infants, and children
- Develop mechanisms for safely testing new interventions in pediatric populations and in pregnant women

Vaccine Development

- Accelerate development and evaluation of promising vaccine candidates to address the needs of these special populations

Expected Outcomes:

- Discovery of biomarkers of severe disease that could potentially be used for development of diagnostic tools to identify patients at high risk of developing severe complications, thus enabling earlier intervention
- New therapies and preventive approaches targeted toward infants, children, pregnant women, and adults, tailored to reflect differences in their immune responses
- New strategies to prevent severe manifestations of disease, including complications of co-infections, cerebral malaria, and malaria-induced anemia
- Availability of diagnostics, drugs, and vaccines for use in infants, children and pregnant women, the populations most affected by malaria
- Development of immunotherapeutics that could prevent progression to severe forms of malaria
- In young children, priming of protective immune responses that could then be boosted throughout childhood by natural parasite infection

Objective 4: Elucidate mechanisms of drug and insecticide resistance

Research Activities

Short term:

Parasite Biology

- Understand mechanisms by which certain parasite strains/isolates acquire higher propensities to develop drug resistance

Vector Biology

- Investigate genetic, biochemical, and behavioral mechanisms of insecticide resistance

Drug Discovery and Development

- Elucidate the mechanisms of action of artemisinins and possible mechanisms of drug resistance so that strategies can be developed to prolong the therapeutic life of this class of drugs

Expected Outcomes:

- New parasite-specific, unique drug targets that will ensure that drug development remains a step ahead of the parasite's ability to develop resistance
- Resistance reversal agents to prolong the effective life of the artemisinin class of antimalarials
- Improved understanding of the mechanisms of insecticide resistance that will lead to strategies to avoid or minimize its effects
- Effective monitoring of mosquito populations for development of insecticide resistance that can inform control strategies

Objective 5: Develop animal models to understand malaria pathogenesis and to evaluate drug and vaccine candidates

Research Activities

Short term:

Malaria Pathogenesis

- Improve animal models of malaria that are practical, affordable, and appropriately reflect mechanisms of malaria pathogenesis and immunity in humans

Medium term:

Vaccine Development

- Develop reliable predictive animal models for preclinical vaccine evaluation

Drug Discovery and Development

- Develop *in vitro* assays and animal models that can accurately predict drug combinations that will maximize safety and efficacy while minimizing development of resistance

Expected Outcomes:

- Improved systems for screening drugs and vaccines against parasites under conditions that occur *in vivo*
- Rationally devised antimalarial fixed-dose combination drugs

Objective 6: Better understand “field reality” (conditions in the field), including parasite, vector, behavioral, social, environmental, and other factors that contribute to changing malaria epidemiology and the use and effectiveness of interventions in the field

Research Activities

Short term:

Parasite Biology

- Improve understanding of *Plasmodium* species diversity, and the interplay of diversity and host factors in malaria transmission and pathogenesis

Vector Biology

- Understand which *Anopheles* species are the main vectors of malaria to humans
- Understand the ecology, genetics, population biology, and behavior of *Anopheles* mosquitoes in malaria-endemic areas
- Understand how mosquitoes identify human hosts
- Determine the genomic sequences and support comparative genomic studies of *Anopheles* species, including those of importance in Africa, Latin America, and Asia
- Develop reliable mathematical models that can inform rational approaches for effective vector management

Genomics

- Expand genome sequencing activities to ensure that geographic and species variation in the parasite and vector populations is appropriately represented

Immunology

- Determine consequences of co-infections with multiple parasite strains/species on the generation and maintenance of protective immunity

Epidemiology

- Support molecular epidemiologic investigations to understand prevalence and incidence of variation in vaccine targets, drug targets, and drug resistance markers in naturally occurring parasite populations
- Understand the population structure of parasites circulating in communities
- Understand the immunoepidemiology of malaria
- Track the epidemiologic evolution of parasites and vectors and its effect on transmission cycles
- Support studies of behavioral, cultural, and environmental factors that contribute to malaria epidemiology in different settings
- Support studies of social and behavioral factors that influence the use and effectiveness of interventions

- Support epidemiologic studies to establish reference standards and normal ranges of biological parameters in endemic settings in order to inform intervention studies

Malaria Prevention and Control in Special Populations

- Support behavioral research to identify key factors that determine individual and community acceptance and reliable use of malaria prevention and control strategies with special focus on use of effective drugs and vaccines
- Expand host immunogenetics research in different geographic areas, in susceptible populations (such as infants, young children, and pregnant women), and in individuals with different clinical manifestations

Vaccine Development

- Strengthen global research on parasite strain diversity, polymorphisms of malaria antigens, and immunoepidemiology studies to facilitate rational vaccine design and field evaluation

Expected Outcomes:

- Increased ability to match and tailor vector management strategies to specific *Anopheles* species in specific geographic regions in order to limit or eliminate *Plasmodium* transmission
- Improved understanding of the vector species involved in malaria transmission, their ecology and behavior, and their relationship to malaria transmission cycles
- Foundation for evaluating and monitoring novel strategies to control vector populations
- Establishment of normal range of biological, safety and baseline immunogenicity parameters to be used as standards for clinical trials
- Improved understanding, at the human population level, of factors predisposing to susceptibility and resistance to malaria and intervention effectiveness
- New or enhanced capacity for interventions and product evaluation in areas where burden of disease may be higher and where the pattern of disease is changing
- Development of strategies that encourage rapid and reliable adoption and use of effective interventions by malaria-affected populations

Objective 7: Develop field-ready diagnostics that identify parasite and vector species and detect drug and insecticide sensitivity in parasites and mosquitoes

Research Activities

Short term:

Genomics

- Develop a molecular “tool-box” for the parasite, including tools for conducting rapid genome-wide surveys and tools for analysis of parasite genotypes in the field
- Develop tools for accurate field identification of vector species, detection of insecticide resistance, and improved understanding of vector genetic diversity
- Identify biomarkers predicting severe disease

Diagnostics

- Identify genetic markers for rapid tests of drug resistance that can replace more labor-intensive, culture-based methods

Medium term:**Diagnostics**

- Facilitate research on new tools to conduct drug susceptibility assays
- Develop PCR-based and immunodiagnostic tools to characterize antigens
- Foster new and improved rapid diagnostic techniques and technologies for the rapid detection of malaria infection by the four common species of *Plasmodium* infecting humans
- Support research on new tools for strain typing and parasite sample collection
- Support development of rapid field assays for rapid detection of drug resistance
- Use data gathered about changing malaria epidemiology to inform diagnostics development efforts
- Identify biomarkers of disease progression
- Identify biomarkers of severe disease
- Identify biomarkers of therapeutic response

Long term:**Diagnostics**

- Continue to develop sensitive, accurate, field-ready diagnostics that can be used in a variety of settings to detect changes in parasite and vector populations
- Develop new serological and biological techniques to detect low levels of infection for use in the post-malaria control era

Expected Outcomes:

- Advances in diagnostics for the rapid detection and characterization of malaria infections (including parasite antigen profiles of patterns of drug resistance against first-line malaria drugs) and predictors of disease outcomes
- Improved evaluation of efficacy of malaria drugs and therapeutics in clinical and field trials
- Better quantitative and qualitative information on *Plasmodium* infections that will promote advances in patient care and epidemiological understanding of the global malaria burden
- Diagnostic tools that predict severe disease and can be used to monitor disease progression and therapeutic responses
- Improved ability to identify vector species in the field, assess rates of parasite infection and transmission, detect and identify malaria parasites in mosquito specimens, and monitor insecticide resistance

Objective 8: Expanding clinical research capacity and strengthening strategic partnerships

Research Activities

Short term:

Vaccine Development

- Strengthen the capacity of existing field sites and establish new sites for advanced clinical development, including clinical laboratories to carry out research and clinical assays and analysis for vaccine trials

Building Strategic Partnerships and Research Capacity

- Strengthen the capacity of field sites to carry out research and clinical trials on vaccines, drugs, and diagnostics
- Cultivate long-term relationships with overseas scientists, volunteer, and support personnel
- Maintain and enhance research infrastructure including international laboratories and clinical research sites to ensure that sustainable capability is available where needed to support the science
- Support networks of interactive monitoring in endemic areas and promote use of standardized protocols and databases at these sites to assess drug responses and treatment failures
- Through resources such as the Malaria Research and Reference Reagent Resource Center (MR4), provide training, validated malaria blood smear microscope slides, and access to molecular markers and rapid diagnostic tests
- Use knowledge gained about the changing epidemiology of malaria to guide appropriate expansion of clinical trial sites
- Partner with industry and others to move existing drug, vaccine, and diagnostic candidates forward

Medium term:

Building Strategic Partnerships and Research Capacity

- Engage industry and other partners to translate promising scientific discoveries into marketable, field-ready products

Long term:

Epidemiology

- Support activities that build epidemiologic and surveillance capacity in areas where transmission is being rapidly reduced in order to develop models of detection and response that can be implemented in areas focusing on elimination

Building Strategic Partnerships and Research Capacity

- Establish facilities to monitor emergence of drug resistance in both *P.falciparum* and *P.vivax* across all endemic countries

Expected Outcomes:

- Improved understanding, at the population level, of factors predisposing to susceptibility and resistance to malaria and intervention effectiveness
- Engagement of industrial and clinical partners in efficient collaboration for development and testing of malaria vaccine candidates

- Networks of reference centers that can track patterns of emerging resistance and help target appropriate interventions to patients
- Improved evaluation of the geographic breadth of the potential use of new vaccines, drugs, and diagnostics
- Robust, continuous development and deployment of effective intervention tools in affected areas
- Accelerated and sustainable capability to evaluate novel interventions in affected populations
- Ability to respond to changing patterns of disease throughout the world
- Development of improved insecticides and repellents that will be mosquito-specific and effective at low doses/volumes

Objective 9: Continue to populate the pipeline with research interventions, including drugs, diagnostics, vaccines, and vector management targets and devices

Research Activities

Short term:

Parasite Biology

- Improve *in vitro* culture techniques for all stages of the parasite, including the sporozoite and liver stages
- Characterize pathways of liver and red blood cell invasion by malaria parasites and vulnerability of blood and liver stage parasites to drug intervention
- Characterize the pathways by which parasites infect mosquitoes and develop into sporozoites in the insect salivary glands
- Understand the process by which the parasite develops inside the mosquito host

Vector Biology

- Understand mosquito immunity and related vector-parasite interactions that determine parasite survival in the mosquito host
- Expand the number of molecular tools available to facilitate genetic manipulation of malaria vectors
- Identify essential molecules in pathways associated with parasite transmission
- Identify molecules associated with essential mosquito biological functions, both in the larval and adult stages

Genomics

- Define the “infectome” for malaria: genes and gene products in the human, vector, and parasite that contribute to infection and disease
- Identify genetic biomarkers of severe and fatal disease
- Maintain and curate up-to-date genomic sequences and provide bioinformatics resources to the research community

Malaria Pathogenesis

- Identify the processes by which *Plasmodium* parasites infect and persist in red blood cells and tissues such as the liver and placenta
- Increase understanding of the biology of dormant stages

- Determine the mechanisms by which *P. falciparum* interacts with the inner surfaces of blood vessels to cause inflammation and impair circulation

Vector Management

- Identify new targets for the development of novel vector management strategies, including effective and environmentally acceptable insecticides/larvicides and repellents with minimal or no unintended toxicity and long-lasting effects
- Continue research toward the development of transgenic mosquito strains that are unable to be infected by or transmit malaria parasites to humans, or that are unable to reproduce

Vaccine Development

- Develop better methods to select high priority antigens for inclusion in a vaccine
- Systematically assess the hurdles to cost-effective mass production of novel vaccine candidates, including multicomponent vaccines and attenuated whole parasites, and identify means to address them
- Expand research on structural vaccinology of malaria antigens
- Identify potent adjuvants/immunostimulators, explore their immunologic properties, and better understand their mechanism(s) of action and methods of optimal formulation
- Develop well-characterized challenge strains of *Plasmodium* that reflect geographic variation of the parasite to facilitate the development of vaccines
- Develop and refine delivery systems that will allow optimal administration of vaccines, including multicomponent and whole parasite vaccines
- Improve understanding of biomarker profiles of infection and disease, and explore strategies and new technologies to better define vaccine efficacy and end points for clinical trials
- Identify appropriate external partners to further develop existing vaccine candidates

Drug Development

- Mine the genomes of *P. falciparum* and *P. vivax* to identify possible targets for rational drug design

Medium term:

Parasite/Vector Biology

- Develop mathematical models of transmission that incorporate environmental variables that can help predict outcomes under different management strategies
- Develop mathematical models that assess response to and predict future success or failure of intervention strategies in specific locations and environments

Vaccine Development

- Explore strategies to improve immunogenicity, including alternate formulations, delivery systems and immunization regimens, and to optimize combinations of antigens in vaccines
- Develop vaccines that prevent transmission
- Use data gathered about changing malaria epidemiology to inform vaccine development efforts

- Initiate clinical trials of vaccine candidates that match the locally prevalent species of malaria parasite

Drug Development

- Support identification of new and improved drug candidates through a variety of means, including combinatorial chemistry and identification of natural products with anti-parasitic activity
- Develop a new class of antimalarial drug that has a better safety and pharmacodynamic profile while retaining anti-hypnozoite and anti-gametocyte activity against *P. vivax*
- Identify drug approaches that may be safe, efficacious, and practical for specific target populations, such as pregnant women, infants, and children
- Support Phase I and II clinical trials of candidate malaria therapeutics
- Evaluate potential interactions of new and existing antimalarial drugs with other drugs, such as antiretrovirals

Epidemiology

- Use data gathered about changing malaria epidemiology to inform drug development efforts
- Support development of tools for field identification of vector species
- Support development of tools to detect the species of malaria parasites in mosquitoes collected in the field and to assess the rate of transmission of parasites by vector species
- Develop field-based technologies for rapid and accurate monitoring of insecticide resistance in field populations of mosquitoes

Vector Management

- Support development of long lasting insecticide-impregnated nets (LLINs) that use non-pyrethroid insecticides
- Develop approaches such as transmission-blocking vaccines and chemical entities that can block parasite development within the vector, preventing the spread of malaria
- Use data gathered through surveillance that reflects the changing epidemiology of malaria to inform efforts to implement adequate vector management strategies

Long term:

Drug Development

- Develop evidence-based strategies to introduce and maintain effective malaria treatment and control strategies on a long-term basis and evaluate these strategies in populations with resurgent malaria linked to prior poor compliance

Diagnostics

- Continue to develop sensitive, accurate, field-ready diagnostics that can be used in a variety of settings to detect changes in parasite and vector populations
- Develop new serological and biological techniques to detect low levels of infection for use in the post-malaria control era

Vector Management

- Partner with agencies and organizations to support development of new insecticides that are safer and more environmentally-friendly or that have other desirable characteristics

- Support studies exploring the relationships between mosquito behavior, physiology, and ecology, and the potential effectiveness of various vector management strategies such as bed nets, in and outside of Africa
- Assess the effectiveness of integrated multi-pronged approaches to the management of vector populations

Vaccine Development

- Develop a safe, effective vaccine to prevent infection, especially in pregnant women, infants, children, and immune-compromised populations

Expected Outcomes:

- Identification of novel targets and pathways for rational design of novel therapeutics, vaccines, and vector management strategies
- Development of models that can inform effective integrated approaches to vector management and interruption of malaria transmission
- Development of interventions for relapsing malaria
- Development of drugs that block parasite invasion of host tissues or enable parasite-infected red blood cells to activate inflammatory processes in blood vessels
- Improved systems for the screening of drugs and vaccines against these parasites under conditions that occur *in vivo*
- Significant expansion of the pipeline of promising malaria vaccine candidates, targeting all phases of the malaria parasite life cycle

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Cover photos of African children and mosquito: courtesy of the Centers for Disease Control and Prevention (CDC) image base; all other photos and graphics produced by NIAID.

Table 1. NIAID Malaria Resources for Researchers

(As of April 2008. See also <http://www3.niaid.nih.gov/topics/Malaria/research/resources.html>)

| Activity/Area | Resource/URL | NIAID Contact |
|--|--|---|
| Cross-cutting Parasite Biology Vector Biology | <p>Malaria Research and Reference Reagent Resource Center (MR4) Materials available to qualified, registered users include parasites, mosquito vectors, antibodies, antigens, gene libraries, molecular probes, and constructs. Special projects:</p> <ul style="list-style-type: none"> • Validated microscope slides • Specialized reagents • Microarrays <p>http://www.malaria.mr4.org/</p> | <p>Dr. John Rogers</p> <p>E-mail: jrogers@niaid.nih.gov</p> |
| Genomics | <p>NIAID Microbial Sequencing Centers Rapid and cost-efficient resources for production of high-quality, microbial genome and invertebrate vector genome sequences. http://www3.niaid.nih.gov/research/resources/mscs</p> <p>Pathogen Functional Genomics Resource Center (PRGRC) Centralized facility providing the research community with resources necessary to conduct functional genomics research on human pathogens and invertebrate vectors of infectious diseases. http://www.niaid.nih.gov/dmid/genomes/pfgrc/default.htm</p> <p>Bioinformatics Resource Center (BRC) Relational databases containing a variety of data types, such as genome sequencing, comparative genomics, genome polymorphisms, gene expression, proteomics, host/pathogen interactions and pathways. http://www3.niaid.nih.gov/research/resources/brc</p> <ul style="list-style-type: none"> • PlasmoDB (<i>Plasmodium</i> Genome Resource) http://www.plasmodb.org/plasmo/home.jsp • VectorBase http://www.vectorbase.org/index.php <p>Proteomics Research Centers NIAID supports seven Proteomic Research Centers (PRCs) that utilize a variety of technologies to analyze proteins and provide the scientific community with newly discovered proteomic information about NIAID's Category A, B, and C Priority Pathogens. This program includes an Administrative Resource that maintains a publicly accessible web site containing data and technology protocols generated by each PRC, as well as a catalog that lists reagents and products developed by the sites and available for public distribution. The web site for the Administrative Resource Center is www.proteomicsresource.org.</p> | <p>Dr. Maria Giovanni</p> <p>E-mail: mgiovanni@niaid.nih.gov</p> |

| Activity/Area | Resource/URL | NIAID Contact |
|----------------------------|--|--|
| Immunology | <p>NIH Tetramer Facility MHC class I, class II and non-classical MHC tetramers for analysis of T cell responses. MHC alleles are available for human, non-human primates, and mice. Tetramer production costs are covered by the Tetramer Facility. http://www.niaid.nih.gov/reposit/tetramer/index.html</p> <p>Immune Epitope Database and Analysis Resource Comprehensive database of antibody and T cell epitope information curated from the literature. Analysis resource includes a suite of epitope data analysis and visualization tools. http://www.immuneepitope.org/home.do</p> <p>Taconic Emerging Mouse Models Program Immunologically-related, gene-targeted mouse strains (in partnership with Taconic Farms, Inc.). The costs of this Program are partially underwritten by NIAID funds to provide ready access to emerging mouse models. http://www.taconic.com/wmspage.cfm?parm1=1437</p> | <p>Dr. Alison Deckhut Augustine</p> <p>E-mail: augustine@niaid.nih.gov</p> |
| | <p>NIH Nonhuman Primate Reagent Resource Sponsored by NIAID and NCRR to facilitate access to existing and new immunological and other reagents used in nonhuman primate models. Information also is available on commercial antibody reactivity and other reagents with different primate species and documented SOPs for working with reagents and for selected nonhuman-primate-specific assays and techniques. http://nhpreagents.bidmc.harvard.edu/NHP/default.aspx</p> | <p>Dr. Kristy Kraemer</p> <p>E-mail: kkraemer@niaid.nih.gov</p> |
| | <p>NIH AIDS Research and Reference Reagent Program https://www.aidsreagent.org Access to thousands of high quality reagents, such as monoclonal antibodies, peptides, and cell lines, for HIV research. Many of the reagents may also be used in the study of the human immune response to malaria.</p> | <p>Dr. Opendra Sharma</p> <p>E-mail: osharma@niaid.nih.gov</p> <p>And Dr. Diana Finzi</p> <p>E-mail: dfinzi@niaid.nih.gov</p> |
| Vaccine Development | <p>Malaria Vaccine Production and Support Services Contract NIAID-supported contract for preclinical and non-clinical services to support and accelerate development of promising malaria vaccine candidates</p> | <p>Dr. Annie X. Mo</p> <p>E-mail: moa@niaid.nih.gov</p> |
| | <p>Clinical Research and Clinical Trials NIAID-supported contracts and subcontracts for Phase I and II clinical trials of promising investigational malaria vaccine candidates both in the United States and in malaria-endemic sites in Africa http://www.niaid.nih.gov/factsheets/vteu.htm</p> | <p>Dr. Lee Hall</p> <p>E-mail: lhall@niaid.nih.gov</p> |

| Activity/Area | Resource/URL | NIAID Contact |
|------------------|---|---|
| Drug Development | <p>Services for Pre-clinical Development of Therapeutics Agents – Supports and accelerates development of therapeutic agents by providing preclinical drug development resources to the scientific community and industry partners</p> | <p>Ms. Beth Spinelli</p> <p>E-mail: spinellib@niaid.nih.gov</p> |
| | <p>Clinical Research and Clinical Trials NIAID-supported HIV/AIDS clinical trials networks conduct therapeutic studies involving HIV-infected patients enrolled in malaria-endemic sites around the world</p> <p>http://www3.niaid.nih.gov/about/organization/daids/Networks/daidsnetworks.htm http://www3.niaid.nih.gov/about/organization/daids/Networks/daidsnetworkunits.htm</p> | <p>Dr. Jeffrey Nadler</p> <p>Email: nadlerj@niaid.nih.gov</p> |

Table 2. Current Portfolio of NIAID Candidate Malaria Vaccine R&D Activities

| Pathogen | Target Identification & Validation | Proof of Concept | Preclinical Development | Currently in Clinical Trials |
|-------------------------------------|---|---|--|---|
| <i>Plasmodium falciparum</i> | Epitope Mapping <ul style="list-style-type: none"> • CS • LSA-1 • AMA-1 • MSP-2 Antigen Screening (Partial or Entire Genomic Approach) | Pre-erythrocytic: <ul style="list-style-type: none"> • Recombinant protein: PfCS • Viral-like Particle(VLP): HBcAg/CS • Attenuated Sporozoite <ul style="list-style-type: none"> • Radiation-attenuated • Genetically-attenuated Asexual Blood Stage: <ul style="list-style-type: none"> • Recombinant protein • Transgenic goat MSP-1 42kD Sexual Stage/TBV: <ul style="list-style-type: none"> • Recombinant protein: <ul style="list-style-type: none"> • Pfs 230 • Pfs 48/45 • Pfs 28 • DNA • Pfs230, • Pfs48/45 • Pfs28 | Pre-Erythrocytic: <ul style="list-style-type: none"> • Radiation Atten. Sporozoite <ul style="list-style-type: none"> • (Single or Multiple strains) • Polyepitope DNA vaccine • CS Protein Asexual Blood Stage: <ul style="list-style-type: none"> • AMA-1 conjugate vaccine • AMA-1/MSP-1 combination Sexual Stage/TBV: <ul style="list-style-type: none"> • Pfs conjugate vaccines Multistage/Multiantigen Cross-reacting Determinant (CRD): <ul style="list-style-type: none"> • GPI Anchor-conjugate vaccine | Pre-erythrocytic*: <ul style="list-style-type: none"> • Adenovirus 35-Vectored CS Asexual Blood Stage: <ul style="list-style-type: none"> • Recombinant protein <ul style="list-style-type: none"> • AMA-1C1 in various formulations • MSP-1C1 in various formulations • EBA175 RII NG/AdjuPhos |
| <i>Plasmodium vivax</i> | Epitope Mapping <ul style="list-style-type: none"> • DBP Pre-erythrocytic Antigen Screening (Genomic Approach) | Pre-erythrocytic: <ul style="list-style-type: none"> • Recombinant CS protein Asexual Blood Stage: <ul style="list-style-type: none"> • Recombinant protein <ul style="list-style-type: none"> • MSP-3, MSP-9 Multi-stage: <ul style="list-style-type: none"> • Polyepitope fusion protein | | |
| Other <i>Plasmodium</i> spp. | Basic Vaccinology Studies | | | |

*Pre-erythrocytic stages include both sporozoites and liver-stage parasites.

Abbreviations: CS: circumsporozoite protein; LSA: liver stage antigen; AMA: apical merozoite antigen; DBP: Duffy blood group Binding Protein; MSP: merozoite surface protein; EBA: erythrocyte binding antigen; Pfs: Plasmodium falciparum sexual stage antigen; HBc: recombinant hepatitis B core antigen; TBV: transmission blocking vaccine

Table 3. Summary of NIAID-Supported Candidate Malaria Vaccine Clinical Trials

| | Phase 1a | Phase 1b | Phase 2a (Experimental Challenge Study in nonendemic area) | Phase 2b |
|----------------|--|---|--|---|
| Current | <ul style="list-style-type: none"> Ad35.CS01 AMA-1C1 (various formulations) AMA-1C1/ISA 720 MSP-1 42C1 (Alhydrogel + CpG 7909) EBA 175 RII NG/AdjuPhos® | <ul style="list-style-type: none"> FMP-2.1/ASO2A (AMA-1) AMA-1C1/Alhydrogel + CpG 7909 | | <ul style="list-style-type: none"> FMP 2.1/ASO2A (AMA-1) AMA-1C1/Alhydrogel |
| Planned | <ul style="list-style-type: none"> AMA-1C2 (Alhydrogel + CpG 7909) BSAM-1 (AMA-1C1+MSP-1 42C1)/Alhydrogel +CpG 7909 Pre-erythrocytic stage polyepitope DNA vaccine | <ul style="list-style-type: none"> Ad35.CS01 AMA-1C1/Alhydrogel +CpG 7909 AMA-1C2 (Alhydrogel +CpG 7909) BSAM-1 (AMA-1C1+MSP-1 42C1)/Alhydrogel +CpG 7909 EBA 175 RII NG/AdjuPhos® | <ul style="list-style-type: none"> Ad35.CS01 AMA-1C1/Alhydrogel + CpG 7909 | <ul style="list-style-type: none"> AMA-1C1/Alhydrogel + CpG 7909 |

Abbreviations: Please see table 2 for antigen abbreviations. Additional abbreviations included here are: FMP: falciparum malaria protein; BSAM: blood-stage antigen mixture; CpG 7909: a proprietary nucleic acid-based adjuvant

NB: Phase 1 refers to studies carried out in a small number of humans to provide an initial assessment of safety, tolerability, and immunogenicity of the candidate vaccine. Phase 2 refers to subsequent studies also carried out in humans which are designed to provide additional information on immunogenicity and often a preliminary assessment of efficacy; these additional data allow for optimization of dosing and immunization regimens, and for definition of appropriate endpoints for later clinical trials in the desired target population(s) which are intended

to provide statistically robust evidence of efficacy necessary for licensure by appropriate regulatory authorities. The designation a or b following Phase 1 or 2 refers to whether the trial is carried out in malaria-naïve individuals in non-endemic areas (a) or in potentially malaria-experienced individuals residing in malaria-endemic areas (b).

Table 4. Summary of NIAID-Supported Candidate Malaria Drug R&D Projects and Clinical Trials

| Early Discovery & Evaluation | Preclinical Development | Compounds in Clinical Development | Efficacy Trials |
|--|---|---|---|
| <ul style="list-style-type: none"> • Protein farnesyl transferase inhibitors • Cation channel and kinase inhibitors • Supercritical carbon dioxide extraction of <i>Artemisia annua</i> leaves • Endoperoxides and trioxanes | <p><u>MMV Discovery Portfolio:</u></p> <ul style="list-style-type: none"> • <i>P. falciparum</i> enoyl-ACP reductase inhibitor • Falcipain inhibitors • DHFR inhibitors • 4(1H)-pyridone compounds • PSAC antagonists • DHODH antagonists | <ul style="list-style-type: none"> • AQ-13 (completed Phase 1; sponsorship now pending) • DB 289 (being developed by Immtech) • Tafenoquine (being developed by MMV) | <ul style="list-style-type: none"> • Comparison of safety and efficacy of chloroquine combination therapy for malaria (Malawi) • Comparison and safety of antimalarial combination therapy (Uganda) |

Abbreviations: ACP: acyl carrier protein; DHFR: dihydrofolate reductase; PSAC: Plasmodium surface anion channel; DHODH: dihydroorotate dehydrogenase.

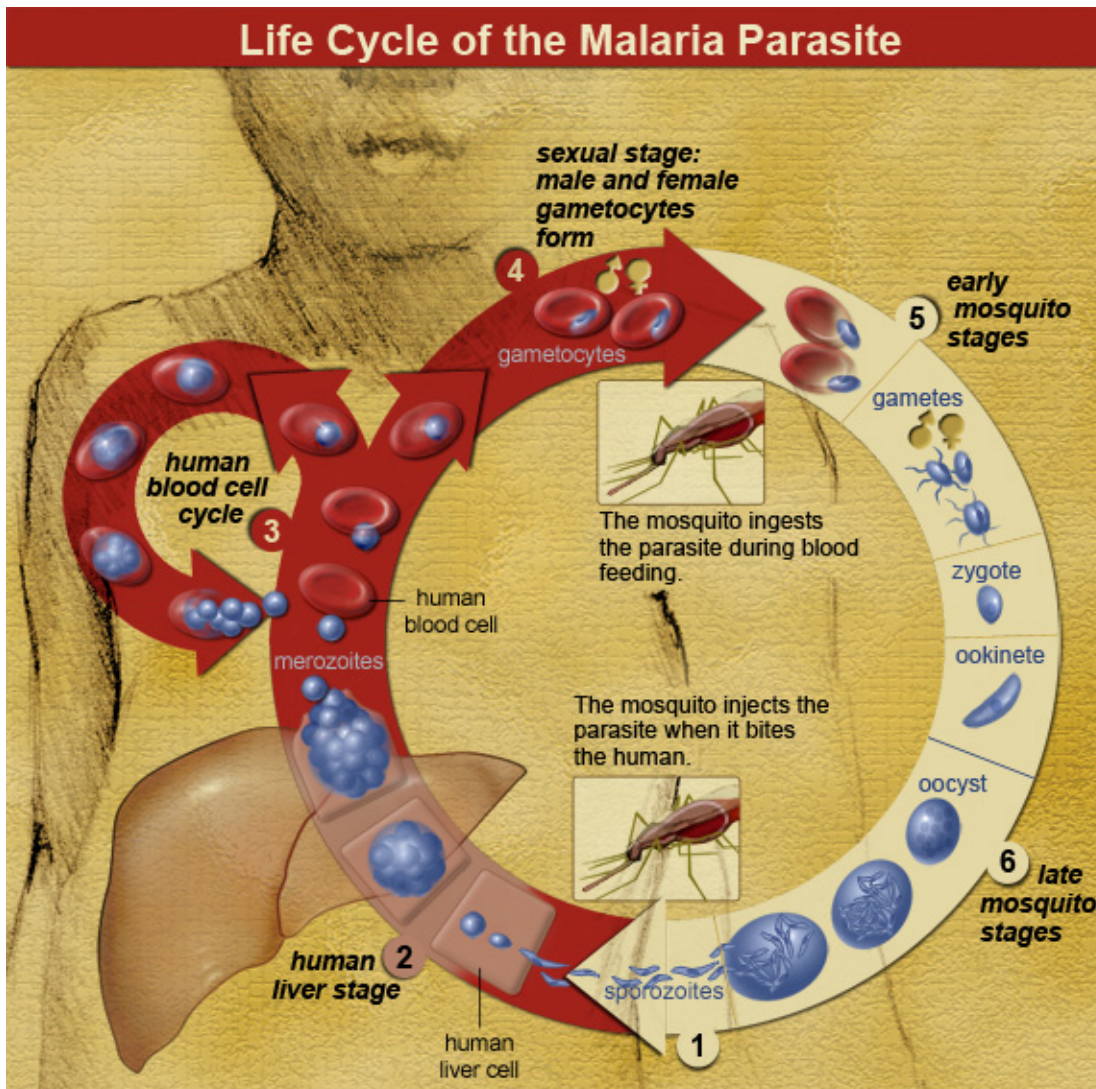


Figure 1. Life Cycle of the Malaria Parasite

- (1) A female Anopheles mosquito carrying malaria-causing parasites feeds on a human and injects the parasites in the form of sporozoites into the bloodstream. The sporozoites travel to the liver and invade liver cells.
- (2) Over 5-16 days*, the sporozoites grow, divide, and produce tens of thousands of haploid** forms, called merozoites, per liver cell. Some malaria parasite species remain dormant for extended periods in the liver, causing relapses weeks or months later.
- (3) The merozoites exit the liver cells and re-enter the bloodstream, beginning a cycle of invasion of red blood cells, asexual replication, and release of newly formed merozoites from the red blood cells repeatedly over 1-3 days*. This multiplication can result in thousands of parasite-infected cells in the host bloodstream, leading to illness and complications of malaria that can last for months if not treated.
- (4) Some of the merozoite-infected blood cells leave the cycle of asexual multiplication. Instead of replicating, the merozoites in these cells develop into sexual forms of the parasite, called male and female gametocytes, which circulate in the bloodstream.
- (5) When a mosquito bites an infected human, it ingests the gametocytes. In the mosquito gut, the infected human blood cells burst, releasing the gametocytes, which develop further into mature sex cells called gametes. Male and female gametes fuse to form diploid*** zygotes, which develop into actively moving ookinetes that burrow into the mosquito midgut wall and form oocysts.
- (6) Growth and division of each oocyst produces thousands of active haploid forms called sporozoites. After 8-15 days*, the oocyst bursts, releasing sporozoites into the body cavity of the mosquito, from which they travel to and invade the mosquito salivary glands. The cycle of human infection re-starts when the mosquito takes a blood meal, injecting the sporozoites from its salivary glands into the human bloodstream.

* Time-frame depends on the malaria parasite species.

** Haploid: Cells containing a half set of chromosomes.

***Diploid: Cells containing a full set of chromosomes.

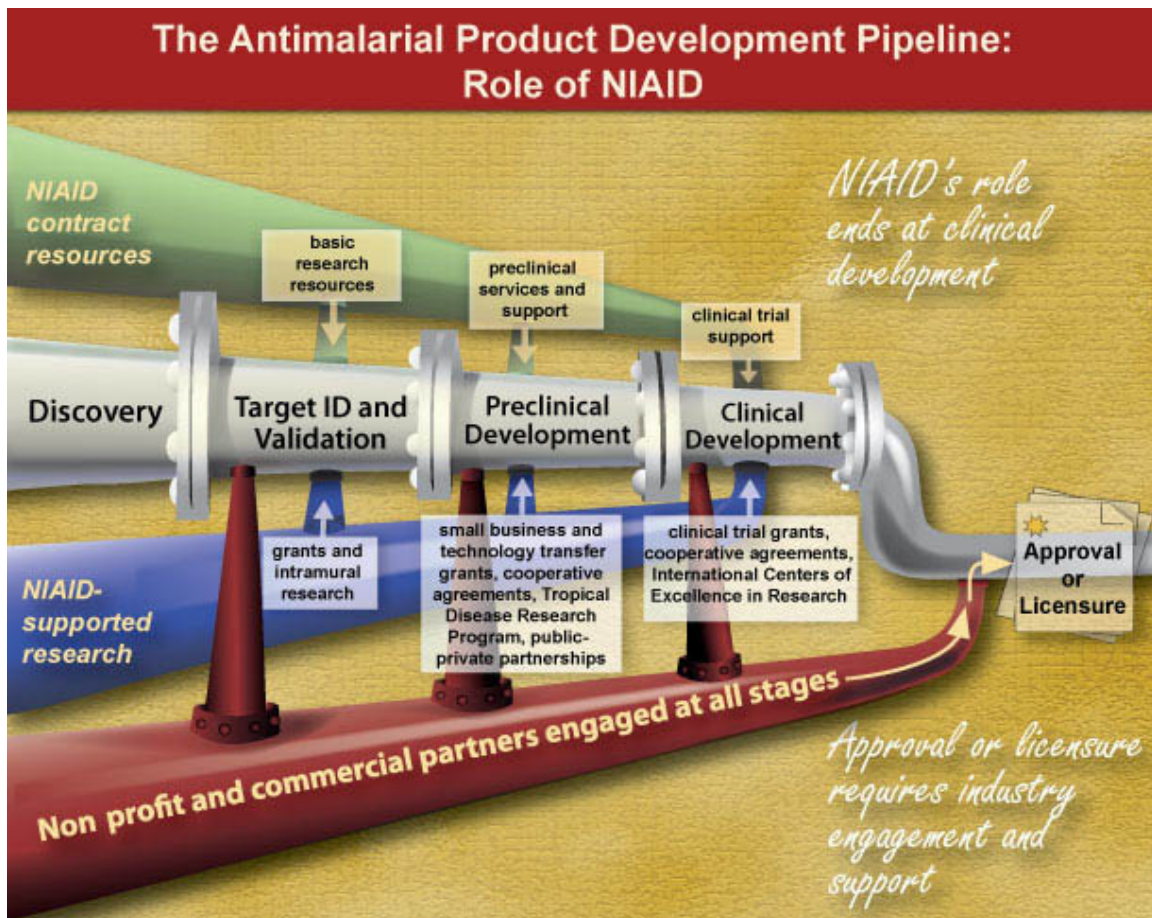


Figure 2: The Antimalarial Product Development Pipeline

describes the role of NIAID in the development and clinical testing of candidate antimalarial drugs or vaccines. The central silver pipeline illustrates how promising malaria vaccine or drug candidates move through successive stages of product development, including discovery (basic science), target identification and validation, preclinical development (*in vitro* and animal studies), clinical (human) testing, and finally toward Food and Drug Administration (FDA) approval or licensure as a new drug or vaccine. Many promising candidates are considered at the earliest discovery or basic science stage, so the pipeline is broadest at this end. The pipeline gradually narrows as some candidates are eliminated and efforts focus on the few candidates that continue to perform well in testing. Only the most promising candidates proceed through all the stages of development. Successful candidates will emerge from the development pipeline for approval or licensure as new drugs or vaccines.

Three other parallel pipelines connect with and support the central product development pipeline at its various stages. The green pipeline represents how NIAID contract resources support the product development process at various stages. NIAID basic research resources contracts provide tools and services to aid the discovery and target identification and validation stages; preclinical services and support contracts provide tools and services to facilitate preclinical product development research; and clinical trial support contracts provide tools and services to support clinical development and evaluation of candidate products. The blue pipeline shows how NIAID intramural and extramural research support various stages of antimalarial product development. NIAID extramural grants and intramural research support and conduct basic discovery as well as target identification and validation studies. NIAID-funded small business and technology transfer grants, cooperative agreements, the Tropical Disease Research program, and public-private partnerships generate and refine candidate products that feed into preclinical studies. Mechanisms and programs such as NIAID clinical trial grants, cooperative agreements, and the International Centers for Excellence in Research support the clinical development and evaluation of malaria drugs and vaccines. The red pipeline represents the important role that NIAID's partnerships with non-profit and commercial partners play in all stages of the antimalarial product development. Because NIAID's role in the process ends at clinical development, commercial and non-profit partners play a critical role in facilitating the movement of candidate products through the advanced stages of product development and on to FDA approval or licensure.