MALARIA

Malaria, a serious disease caused by parasites of the genus *Plasmodium* and transmitted by mosquitoes, continues to pose a tremendous public health burden for people living in the tropics, particularly in Africa. Globally, malaria causes more than 1 million deaths each year and continues to be the most important tropical parasitic disease in terms of annual mortality. Approximately 60 percent of malaria deaths occur in the poorest 20 percent of the total global population, with the majority of deaths occurring in children aged 5 years and younger in sub-Saharan Africa.[41] Unfortunately, malaria parasites have developed a variety of mechanisms to evade host immune responses, thus making the development of a successful vaccine very challenging.

Malaria research at the NIH dates back to the 1930s, when malaria was still a major public health problem in the United States. NIAID is currently one of the world's leading supporters of malaria research. NIAID maintains a broad malaria research portfolio that includes parasite biology, pathogenesis, drug development, vaccine development, epidemiology, and vector control. NIAID-funded malaria research is conducted by scientists at institutions throughout the United States, including NIAID's own intramural laboratories, and overseas.

NIAID's intramural malaria vaccine research program is centered in the Malaria Vaccine Development Branch (MVDB). The MVDB collaborates with a number of investigators within the United States and throughout the world, as well as with the extramural NIH malaria program and a variety of funding organizations such as the U.S. Agency for International Development and the Malaria Vaccine Initiative supported by the Program for Appropriate Technology in Health (PATH). The MVDB has produced multiple vaccine components using the quality control practices required for manufacturing clinical materials. Two of these have been combined into a vaccine called AMA1-C1, which was well tolerated in a phase I trial in U.S. adults and further tested in a phase I study in adults in Mali, marking the first time that MVDB products have been tested in a malaria endemic area. MVDB researchers are working to improve the immunogenicity of this formulation, in collaboration with Coley Pharmaceutical Group, Inc., and to broaden the reactivity of anti-AMA1 antibody response. In addition, they have completed the preclinical studies for two other vaccine candidates and have initiated a phase I clinical trial in U.S. adults as a prelude to anticipated future studies in an endemic area in Africa. Thus, the past year has seen a significant expansion of phase I clinical trials for multiple malaria vaccine candidates. The lack of significant adverse reactions to these vaccine formulations provides the basis for moving to additional studies in malaria-endemic areas in order to answer critical questions about the safety and efficacy of these vaccines in African children.

Intramural investigators also are conducting basic studies aimed at providing fundamental biological information for the development of diagnostics, therapeutics, and other control measures against the disease. For example, Division of Intramural Research scientists are using the malaria parasite genome databases and microarray analysis to identify genes that may be involved in drug resistance and parasite sexual development. Identifying these genes is an important step in developing measures to interrupt parasite transmission and will provide critical information for drug and vaccine development. In addition, to understand the factors that determine the severity of malaria, NIAID investigators are studying how hemoglobin C and hemoglobin S (sickle-cell hemoglobin) protect children from severe and fatal complications of malaria caused by *Plasmodium falciparum*.

Through its extramural malaria research program, NIAID also supports extensive research on malaria vaccines conducted by researchers from academia and industry. The Institute currently

funds multiple studies aimed at developing vaccines against different stages of the malaria parasite and has conducted clinical trials in the U.S. and abroad of the most promising candidates. These research efforts represent a critical component of NIAID's Research Plan for Malaria Vaccine Development, which is designed to accelerate research leading to the development of malaria vaccines. Under a contract with Science Applications International Corporation, NIAID established a capability to undertake targeted research essential to translating basic research concepts into prototype vaccine products for clinical evaluation. Recent activities included process development for production of novel candidate vaccines, production and qualification of critical reagents for quality control of new candidate vaccines, and preclinical safety evaluation of promising candidate vaccines prior to entry into clinical trials. Reagents were also provided to the Malaria Research and Reference Reagent Resource, which will make them available to the international malaria research community.

NIAID has undertaken a phase I trial of a novel candidate malaria vaccine at the University of Maryland Center for Vaccine Development. This vaccine was developed with grant support from the Small Business Innovation Research Program administered at NIAID, and with additional support and collaboration from the Malaria Vaccine Initiative at PATH. Results of this trial are expected to be available for analysis in mid-2005. Additional clinical trials of promising vaccine candidates are planned through the Vaccine and Treatment Evaluation Units.

A key component of the NIAID Research Plan to Accelerate Malaria Vaccine Development has been the establishment of research centers in malaria-endemic areas that can support epidemiological and clinical research relevant to malaria, as well as conduct clinical trials. In June 2003, in collaboration with the Walter Reed Army Institute of Research, the University of Maryland Center for Vaccine Development, and the University of Bamako (in Mali), NIAID launched its first trial of a novel candidate malaria vaccine in Mali. A full analysis of this phase I trial will be completed in 2004. A second clinical trial with a different candidate vaccine was begun in Mali in late 2004.

Identification, validation, and evaluation of new antimalarial therapies remain NIAID priority activities. In 2004, NIAID issued a renewal of the Tropical Diseases Research Units (TDRU) program. The objective of the TDRU program is to support translational research leading to the discovery and preclinical development of new drugs or vector control methods to reduce or eliminate morbidity and mortality resulting from parasitic infection. One of the three new awards made under this program will focus on development of novel antimalarials. Requests for applications for collaborations with private companies for the development of new compounds and strategies for malaria treatment and mosquito control have been funded by the Challenge Grants and Partnerships program. These initiatives are currently supporting studies aimed at the clinical development of two new antimalarial compounds in collaboration with large pharmaceutical companies, screening and candidate validation of novel classes of compounds, exploring the use of larval control strategies for certain areas of malaria transmission in Africa, mitigating insecticide resistance, and developing new environmentally safe insecticides targeting mosquito activities. NIAID also supported a phase I clinical trial of a chloroquine-analog effective against chloroquine-resistant *P. falciparum,* as well as investigator-initiated research on preclinical development and evaluation of novel compounds. The Institute is also supporting preclinical and clinical studies of combination therapies for malaria, especially those including artesunate.

Clinical research capacity continues to be strengthened in overseas sites in Ghana and Mali in West Africa with support by contracts under the "Malaria: Clinical Research and Trial

Preparation Sites in Endemic Areas" initiative. Research staff members have and continue to participate in training in epidemiology, bioethics, good clinical practice, good laboratory practice, and financial management. Clinical facilities, research and clinical safety laboratories, and satellite Internet connectivity have been established or expanded.

NIAID also continues to participate in the Federal Malaria Vaccine Coordinating Committee, and provides support to the Multilateral Initiative on Malaria and the World Health Organization (WHO) Special Programme for Research and Training in Tropical Diseases Task Force to advance malaria research and research capacity strengthening activities at African institutions. NIAID also participates in the Malaria Vaccine Advisory Committee established at the WHO Initiative for Vaccine Research, and in the External Scientific Advisory Committee of the Medicines for Malaria Venture, a public-private partnership that fosters the accelerated development of new antimalarial compounds. NIAID has also worked with the European Commission and the European-Developing Countries Clinical Trial Partnership to coordinate product development and clinical trial activities in vaccines and drugs.

In addition to the targeted activities listed above, malaria-related research and training activities are supported under a number of other programs, such as the TRDUs, International Centers for Tropical Diseases Research Network, U.S.–Japan Cooperative Medical Science Program, Indo–U.S. Vaccine Action Program, and Clinical Research and Training Opportunities. Additional information is available at the following Web site: *http://www.niaid.nih.gov/ictdr/tdru.htm*.