

PROJECT DATA SHEET

1. TRANSACTION OF

- A = Add
- C = Change
- D = Delete

PD-AM-924
Amendment Number

DOCUMENT CODE

3

2. COUNTRY/ENTITY

S&T Interregional

3. PROJECT NUMBER

931-0453, 34

42

SN 30066

4. BUREAU/OFFICE

S&T/H

10

5. PROJECT TITLE (maximum 60 characters)

Malaria Immunology - Univ. of Illinois

6. PROJECT ASSISTANCE COMPLETION DATE (PACD)

MM DD YY
06 01 86

7. ESTIMATED DATE OF OBLIGATION
(Under "B." below, enter 1, 2, 3, or 4)

A. Initial FY 83

B. Quarter 3

C. Final FY 85

8. COSTS (\$000 OR EQUIVALENT \$1 =)

| A. FUNDING SOURCE | FIRST FY | | | LIFE OF PROJECT | | |
|------------------------|----------|--------|----------|-----------------|--------|-----------|
| | B. FX | C. L/C | D. Total | E. FX | F. L/C | G. Total |
| AID Appropriated Total | | | | | | |
| (Grant) | (710) | () | (710) | (2,500) | () | (2,500) |
| (Loan) | () | () | () | (2,500) | () | (2,500) |
| Other U.S. | | | | | | |
| 1. | | | | | | |
| 2. | | | | | | |
| Host Country | | | | | | |
| Other Donor(s) | | | | | | |
| TOTALS | 710 | | 710 | 2,500 | | 2,500 |

9. SCHEDULE OF AID FUNDING (\$000)

| A. APPROPRIATION | B. PRIMARY PURPOSE CODE | C. PRIMARY TECH. CODE | | D. OBLIGATIONS TO DATE | | E. AMOUNT APPROVED THIS ACTION | | F. LIFE OF PROJECT | |
|------------------|-------------------------|-----------------------|---------|------------------------|---------|--------------------------------|---------|--------------------|---------|
| | | 1. Grant | 2. Loan | 1. Grant | 2. Loan | 1. Grant | 2. Loan | 1. Grant | 2. Loan |
| (1) ST/H | 540 | 542 | | | | 2,500 | | 2,500 | |
| (2) | | | | | | | | | |
| (3) | | | | | | | | | |
| (4) | | | | | | | | | |
| TOTALS | | | | | | 2,500 | | 2,500 | |

10. SECONDARY TECHNICAL CODES (maximum 5 codes of 3 positions each)

11. SECONDARY PURPOSE CODE

12. SPECIAL CONCERNS CODES (maximum 7 codes of 4 positions each)

A. Code

B. Amount

13. PROJECT PURPOSE (maximum 680 characters)

The purpose of this project is to conduct research on the exo-antigens freely released by malaria parasites in in-vitro culture as a potential malaria vaccine.

14. SCHEDULED EVALUATIONS

Interim MM YY MM YY Final MM YY
06 84 05 85 06 86

15. SOURCE/ORIGIN OF GOODS AND SERVICES

000 941 Local Other (Specify)

16. AMENDMENTS/NATURE OF CHANGE PROPOSED (This is page 1 of a _____ page PP Amendment)

17. APPROVED BY

Signature

George Curlin, M.D.
Director
Office of Health

George Curlin for

Date Signed

MM DD YY
05 09 83

18. DATE DOCUMENT RECEIVED IN AID/W, OR FOR AID/W DOCUMENTS, DATE OF DISTRIBUTION

MM DD YY

18 MAY 1983

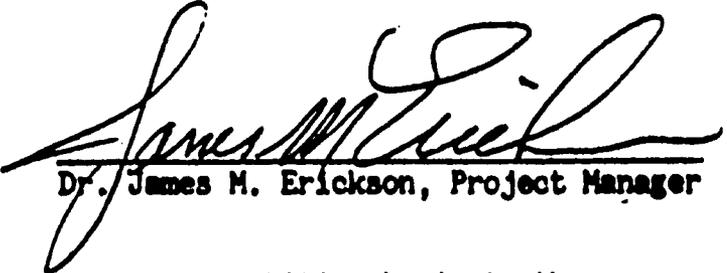
MEMORANDUM

TO : CM/COD/PE, Ms. Johni Pittenger
FROM : S&T/HP, Francis R. Herder
SUBJECT: Justification for non-competitive procurement of unsolicited proposal from the University of Illinois entitled "Malaria Vaccine Development"

The subject research proposal is an unsolicited proposal. The substance of the proposal is not available to the Government without restriction from another source, nor does it resemble any pending competitive solicitation. The substance is sufficiently unique to justify acceptance as an unsolicited proposal.

The project officer certification with reference to A.I.D. PR Notice 78-4 follows:

I certify that neither I nor, to the best of my knowledge and belief, any other A.I.D. employee solicited the proposal or had any prior contact with the proposing institution, other than to convey interest in the field of malaria immunity and vaccination relative to the efforts described in the unsolicited proposal.


Dr. James M. Erickson, Project Manager

I request that you award this contract on a non-competitive basis to the University of Illinois without consideration of other sources.

Clearances: 
S&T/PO, G. Eaton Date 5/10/83
ST/HEA, G. Curlin Date 5/9/83

May 9, 1983

**ACTION MEMORANDUM FOR THE ACTING AGENCY DIRECTOR
FOR HEALTH AND POPULATION**

FROM: S&T/HP, George Curlin, M.D. 

Action: Your approval is requested for a grant of \$2,500,000 from Section 104 of the Foreign Assistance Act of 1961 as amended for project 931-0453.34, Malaria Immunity and Vaccination Research, University of Illinois.

Discussion: The project is designed to follow-up successful research conducted at the University of Illinois to develop a vaccine against Babesia bovis, a disease agent of domestic animals very closely related to malaria. Naturally released antigens will be utilized to immunize monkeys to establish protection. Serum from protected monkeys will then be used to isolate the protective molecules from the exhausted P. falciparum cultures.

This research project was reviewed by the Agency's external review panel on February 4, 1983 and unanimously approved for funding. According to FPR 1-4.909, the proposed contractor is unique, being the only research group working on the soluble antigens released by the malaria parasites; the scientists involved have substantial experience and over five publications on the subject in the past five years. The use of naturally released exo-antigens is unique among the various projects worldwide working on a malaria vaccine against human malaria. Previous success with the development of a vaccine against Babesia bovis gives these investigators an advantage for this scope of work over other laboratories working on malaria. The equipment and facilities are outstanding, and the intellectual atmosphere is absolutely the highest.

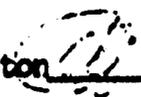
Justification to the Congress: Project Funding is included in the FY 1983 Congressional Presentation, Annex V, Centrally Funded Programs, page 57.

Clearances Obtained: This project was approved by the AID external Expert panel at the February 4, 1983 meeting.

- Recommendations:**
1. That you sign the attached authorization.
 2. That you sign the attached justification for non-competitive procurement.

Attachments:

1. Project Authorization
2. Project Paper

Clearance:
S&T/PO, G. Eaton  Date 5-16-83

PROJECT AUTHORIZATION

Name of Entity: Interregional

Project Title: Malaria Vaccine
Development

Project No.: 931-0453.34

Grantee: University of
Illinois

1. Pursuant to Section 104 of the Foreign Assistance Act of 1961, as amended, I hereby authorize the research project entitled "Malaria Vaccine Development" involving not to exceed \$2,500,000 of S&T Bureau grant funds over a three year period from the date of authorization subject to the availability of funds in accordance with the A.I.D. OYB/Allotment process to help in financing the costs of the project.

2. The project will conduct research on the intraerythrocytic protozoan agent, Plasmodium falciparum, to develop a vaccine based upon soluble antigens released by the parasite during infection.

Clearances:

- A. ST/H: G. Curlin ^{4/16} Date 5/9/83
- B. ST/PO: G. Eaton ^{5/11} Date 5-11-83



S&T/HP, F. Harder
Acting Agency Director
for Health and Population

5-16-83

.(Date)

DESCRIPTIVE PROJECT TITLE: Malaria Vaccine Development: An Integrated Transatlantic Research Effort of the Universities and the Industry

SPECIFIC PROJECT TITLE: Development of Malaria Vaccine Using Soluble Plasmodium falciparum Antigens

PARTICIPATING INSTITUTIONS: College of Veterinary Medicine
University of Illinois
Urbana, IL 61801 USA

School of Medicine
University of Grenoble
Grenoble, France

Institute Merieux
Lyon, France

RESPONSIBLE INVESTIGATORS: Professor Miodrag Ristic
Department of Pathobiology
College of Veterinary Medicine
University of Illinois
Urbana, IL 61801

Professor Pierre Ambroise-Thomas, Head
Department of Parasitology and
Tropical Medicine
School of Medicine
University of Grenoble
Grenoble, France

Dr. Vre Y. Moreau, Head
Department of Parasitology
Institute Merieux
Lyon, France

PROJECT COORDINATOR: Dr. Micha Roumiantzeff
Institute Merieux
Lyon, France

SPONSORS: Malaria Program
United States Agency for International
Development
Washington, D.C.

Marcel Merieux Foundation
Lyon, France

I. THE PURPOSE OF THE PROPOSAL:

The concept of the vaccine using an organism-free soluble antigen system was originally developed by long term studies of infections caused by another intraerythrocytic protozoan agent, Babesia bovis. A great portion of these studies, including those conducted abroad (Mexico), was sponsored by the Rockefeller Foundation and the American Industry. It is this successful effort and the biologic similarity between B. bovis and Plasmodium falciparum that has instigated an interest of the Institute Merieux to support an investigation in order to ascertain whether the protective system of bovine babesiosis may be applicable to human malaria. Using a primate model for human malaria, an intensive evaluation of all pertinent parameters of the vaccine, described in the proposal submitted to the USAID in February 1983, suggests that the system is functional as a means of protection against the disease caused by P. falciparum, the most virulent strain of human malaria. This evidence and prior careful consideration of other research approaches for malaria vaccine development by the Merieux scientists prompted the leadership of this institution to a commitment toward a joint pursuance of malaria vaccine development. To this goal, the Institute Merieux has made a considerable research investment in its own plant, and provided collaborative research funds in support of a similar investigation at the School of Medicine at Grenoble, France, and at the University of Illinois.

The task of a full exploration of the protective system and its implementation toward vaccine development for the most important infectious disease of man requires multi-disciplinary efforts. Consequently, the funds obtained from a single source may not be sufficient for an expeditious and early solution to the problem. More important, the funds from the USAID would serve to strengthen and augment research efforts and assure participation in the program of scientists of the highest caliber. Furthermore, an integration of this research into the family of network programs sponsored by the USAID would provide an opportunity for direct sharing of data with various prominent and experienced malariologists which in turn will be mutually advantageous to all participating parties. Finally, by virtue of its world-wide prestigious role, the malaria program of the USAID may assist the proposed research effort by providing opportunities for an independent laboratory and field evaluation of the vaccine in regions less accessible to the investigators. For example, in Colombia, South America, the agency maintains a well established and successful cooperative malaria program with the Ministry of Health of that country. In this sequence, some of the Aotus monkeys available to the agency in Colombia may be utilized for test and challenge experiments of the vaccine under development. Finally, human malaria is indigenous to certain regions of Colombia, thus cooperative arrangements may be possible for a field evaluation of the vaccine in that country.

II. PROGRAM RESOURCES AND ITS COORDINATION:

A. Resources

Each of the three participating institutions possess well established material resources and scientific and technical manpower essential for successful development of the vaccine. Scientifically, the assets of the three groups are harmoniously complementary and logically sequenced for bringing the vaccine from its laboratory conceptual phase through all developmental aspects and into the human test trials. The following are estimated current resources available at each station:

1. University of Illinois (UI): Over the years, the University of Illinois administration has considered the programs in hemotropic diseases of man and animals as a highly prestigious segment of its overall research potential and, accordingly, has provided continuous support with all available resources. In addition, this hemotropic disease program has received continuous support through funds awarded by various agencies represented by the U.S. and foreign governments and philanthropic and commercial organizations. Academic accomplishments of the program are reflected by a volume of scientific literature consisting of more than 250 pieces over the last 15 years while practical accomplishments resulted in development of vaccines and serodiagnostic procedures for various leukocytic and erythrocytic agents.

The hemotropic disease research unit is housed in its own building at the southern outskirts of the campus. The building possesses modern laboratory facilities and equipment and is staffed with young and competent researchers ranging from professors to post doctoral associates, graduate students and technical staff. Adjacent to the building are animal holding units which house primates, food producing and laboratory experimental animals. In addition to these facilities, the Hemotropic Disease Program occupies four laboratories and three offices in the new Veterinary Basic Science Building on the campus of the University of Illinois. All these facilities are provided with modern laboratories, equipment and scientific and clerical staff. The leader of the current malaria program is Mary Lynn Chilbert, PhD. She and her staff conduct the research in malaria under the direction of the overall director of the Hemotropic Disease Programs, Miodrag Ristic, DVM, PhD. Cooperating with the programs are several well recognized immunologists, biochemists and pathologists on the faculty at the University of Illinois.

Aside from its domestic activity, the Hemotropic Disease Program has a contractual arrangement with the Veterinary Institute of the Government of Venezuela in Maracay, Venezuela, where field testing of the newly developed bovine babesiosis vaccine is currently underway. Representing the University of Illinois in this program in Maracay, Venezuela, are two assistant professors

of the College of Veterinary Medicine, Dr. Mark James and Dr. Sonia Montenegro-James. Similar arrangements for the study of the malaria vaccine is in progress with the Institute Merieux of Lyon, France. This arrangement provides for a constant flow and exchange of scientists between the two institutions.

2. Institute Merieux (IM): Institute Merieux is a uniquely qualified worldwide human and veterinary biologic house with a foremost reputation for its professional excellence. The tradition of this organization dates back to the era of Louis Pasteur and his assistant, Dr. Marcel Merieux, the original founder of the present Institute Merieux. At the home-base in Lyon, France, and in many of its subsidiaries throughout the world, the Institute Merieux produces and distributes products useful for the prevention and diagnosis of nearly every single infectious disease of man and animals. One of many unique features of the biopharmaceutical industry of Merieux is its capability for rapid deployment of technical and material resources to distant and frequently remote regions of the world where such may be urgently needed. It is through this mechanism that Merieux was successful in a rapid identification of the strain responsible for the meningococcal epidemic in Brasil and promptly developed and produced an autologous vaccine which, according to the government of Brasil, has prevented further outbreaks of the disease and saved thousands of

lives. There are other similar examples of the mobile scientific ability of the Institute Merieux in both the human and veterinary field.

The current leadership of Merieux feels that the research area most neglected lies within protozoan diseases of man and animals. It is for this reason that the research department in parasitology has recently been reorganized and provided with additional scientific manpower and research space. Currently there are a half-dozen research programs underway in that department covering the most important infectious protozoan diseases. Foremost among these are canine babesiosis and human malaria. The development of a babesiosis vaccine using the soluble antigen approach is in its final field testing phase. Malaria research has been greatly accelerated by the addition of capable staff and collaborative scientific arrangements. Research programs in parasitology are under the direction of Dr. Vre Moreau.

Due to difficulties with the currently available live Polio vaccine, several years ago the Institute Merieux initiated a study in collaboration with Dr. Johathon Salk of the U.S.A. toward the development of a high potency killed Polio vaccine. This vaccine is currently under field study in various parts of the world. Engaged in this study on behalf of Merieux are public health experts, epidemiologists and physicans. This program is scheduled to terminate during the next 1 to 2 years. At this

time, Merieux plans to transfer this trained staff toward a malaria vaccine evaluation program.

A right hand of the Institute Merieux is the non-profit Merieux Foundation, which is involved in sponsorship of research, holding scientific symposia and promoting publication of literature relevant to human and animal health. It is this foundation that is contributing to the organization of the forthcoming Second International Conference on Malaria and Babesiosis in Annecy, France.

3. Department of Tropical Medicine at the University of Grenoble (UG): The Department of Tropical Medicine at the University of Grenoble is under the direction of the Professor Pierre Ambroise-Thomas, M.D. Professor Ambroise-Thomas is eminently qualified and experienced in basic and practical aspects of malaria and other protozoan infectious diseases of man and animals. The department, with a substantial professional staff of medical doctors and medical scientists at the PhD level, constitute a multi-disciplinary team actively engaged in research, diagnostic service and hospital care. The research on malaria at this department is sponsored in part by the Institute Merieux. Currently, major biochemical and immunochemical efforts are underway in this laboratory toward isolation of protective fractions from the soluble crude P. falciparum antigens. In addition, Professor Ambroise-Thomas and the Institute Merieux have jointly

developed a highly specialized group of immunologists solely devoted to Hybridoma technology. It is this group of scientists that has developed monoclonal antibodies for B. canis and more recently, the first such antibody to soluble fraction "E" of P. falciparum.

B. Coordination*

1. General Principle: Specific responsibilities are being assigned to individual participating parties on the basis of availability of particular research skills at that station. However, depending upon the magnitude of the problem, and a need for a rapid procurement of data, certain subjects may be jointly tackled by two or all three stations. An example to this effect would be the isolation and characterization of protective antigens and development of monoclonal antibodies for these antigens. In this manner, and by comparative examination of individual antigen-antibody systems, the identification and procurement of protective antigens suitable for human inoculations should be accomplished more rapidly.

2. Time Table: The first segment of this study covering a 3-year period anticipates the development of a protective vaccinal model. This model will be thoroughly investigated in

*The objective of this second document is to chronologically relate responsibility of each station and describe their research interactions. A detailed description of materials and methods that will be used in this study has been given in the first document, pages 36-64.

primates and then subjected for preliminary tests in human beings. The vaccine used during this period will be that derived from the currently available in vitro culture system. At the termination of this 3-year period, and depending upon preliminary tests in humans, the second segment of the vaccine study will be initiated. The major aspect of this second segment will focus on the human host, although supporting laboratory data will be used as correlates of immune responses in man. The first segment of the study will be divided into 3 phases of one year each.

a. Phase 1: Intensive evaluation of protective effects induced in monkeys by crude and purified antigens will be a dominant feature of this first phase of study. For safety reasons, and as required for subsequent human studies, the antigens will be treated with inactivating (sterilizing) reagents i.e., formalin, and also fortified with adjuvants applicable for human inoculations. Development of methods for in vitro quantitation of antigens and more exact formulation of a vaccinal dose will be an important research obligation of this first study phase. Finally, initial steps toward production of monoclonal antibodies to selected antigens will be undertaken during this period.

Specific research activities and interactions: The University of Illinois will continue to produce crude soluble antigens using primarily P. falciparum strains known to be pathogenic for squirrel and Aotus monkeys. Individual production lots will be

divided into three portions and made available to each station for isolation, purification and characterization of individual fractions. Physicochemical properties of each fraction will be determined and their abilities to induce antibody formation evaluated. Protective abilities of these antibodies will first be tested by means of an in vitro growth inhibition system. Selected antigen fractions will then be subjected to actual immunization studies in primates at the UI. In this sequence, the Institute Merieux will be conducting in vitro studies on the selection and formulation of appropriate adjuvants and antigen/sterilization systems. These findings will be promptly transferred to the UI for animal inoculation studies. IM and the UG will focus on the development of in vitro methods for quantitation of antigens. For this purpose, Radioimmunoassay (RIA) and Enzyme-linked Immunosorbent (ELISA) tests should be particularly useful.

Once protective abilities of certain fractions have been documented following immunization and challenge of primates, these fractions will be promptly selected for monoclonal antibody production using Hybridoma technology. The latter work will be done at UI and by a joint IM-UG Hybridoma team. The latter team has a great deal of practical experience, as over the years it has produced monoclonal antibodies against various viral proteins and, more recently, selected soluble antigens of Babesia bovis.

b. Phase II: The thrust of this second phase of study will be an augmented effort on monoclonal antibody production which was initiated in phase one. Such antibodies will be used for identification and isolation of protective antigens. The latter antigens, in combination with selected adjuvants, will then be used as immunogens for a very critical evaluation in primates. Quantitation and/or dosing of such antigens will be done by means of one of the in vitro systems developed during the previous year of support. Protective effects of monospecific antibodies to these antigens will also be examined by biologic tests such as growth inhibition and blocking antibody tests. The latter test is designed to demonstrate, by in vitro endothelial cell cultures, that the serum of immunized monkeys blocks the attachment of infected erythrocytes to these cells. Once the optimal protective system using purified antigens has been selected, it will be used to immunize monkeys which will then be challenged by exposure to infected mosquitoes.

Specific research activities and interactions: Initiation for the production of monoclonal antibodies will be made by the Hybridoma team now jointly operated between IM and UG. Although this team is already in operation and has considerable experience in the art, additional technical assistance is needed. Similar studies, although maybe at a slower pace, will be underway at the UI. At both locations, UI and IM-UG, monoclonal antibodies will

be used for further purification of antigens by means of immuno-adsorbent column chromatography. Quantitations and dosing of these antigens, by adsorbant affinity chromatography, will be done at IM. The latter station will also be engaged in the formulation of antigen-adjuvant systems. Immunization studies with these vaccine preparations will be done at the UI. For correlation with in vivo protection, the sera of immunized monkeys will be tested at the UI for their protective effects by means of in vitro growth inhibition and blocking antibody tests. In one of the more advanced immunization experiments, experimental animals will be challenged by the use of infected mosquitoes. An independent and confirmatory vaccination and challenge experiment will be conducted in collaboration with the USAID malaria program in Bogota, Colombia, South America.

c. Phase III: The final vaccine product which, based upon the results of the immunization studies in monkeys, meets essential safety and protection criteria, will be used as a model for production of a vaccine lot intended for human studies. Such a vaccine will then be subjected for preliminary evaluation in selected groups of human subjects. These initial human trials are planned to be executed in continental Europe and Northwest Africa.

Specific research activities and interactions: The vaccine lots to be used for human inoculation will be produced by the

Certified Department for Human Biologics at the IM. At this station, these vaccine lots will be subjected to all established safety test procedures as prescribed for human biologics. Particular attention will be made with reference to potential immunopathologic and toxic effects of the product. While the product is intended for human studies in Europe and Africa, a duplicate sample will be tested by vaccination and challenge of primates at UI. By joint initiative of UG and IM, various human trials will be planned. These trials include: 1) susceptible, Plasmodium-free French volunteers, 2) French and/or European malaria-susceptible subjects, who, following vaccination, will be entering malaria endemic regions of North Africa, 3) field tests in the regions of low, medium and heavy incidence of malaria.

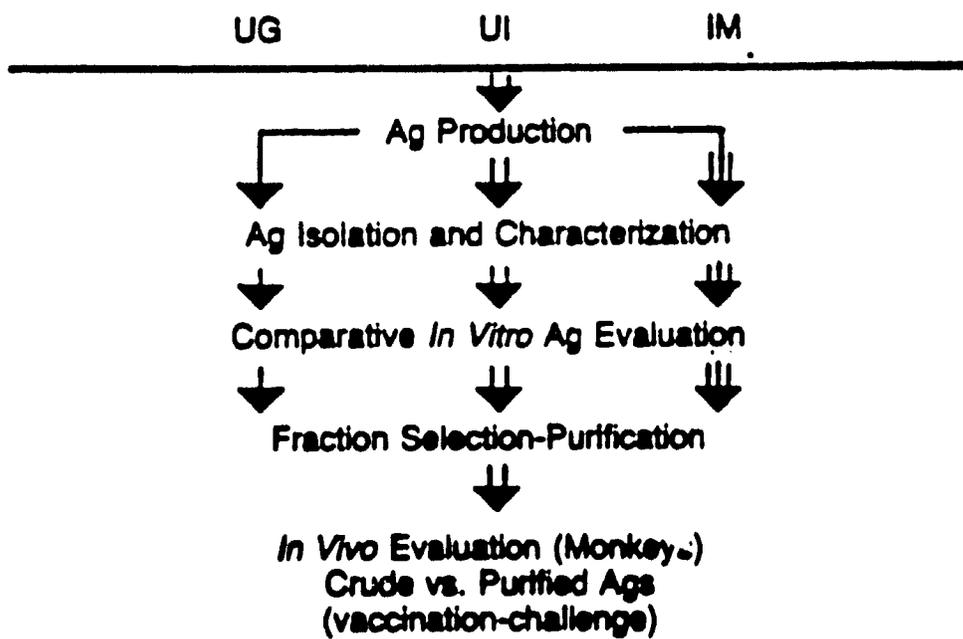
Teams of medical specialists organized by UG and IM will be responsible for examination of the clinical and epidemiologic parameters of this study. Supporting work, consisting of careful examination of sera of immunized patients, will be done at all three stations. At the UI for example, serologic activity of the sera will be examined by the IFA test while functional (protective) properties of these sera will be examined by growth inhibition and blocking antibody tests. All other research in support of the field evaluation may be done at any of the three stations depending on the skills available at each place.

III. DIAGRAMATIC PRESENTATION OF RESEARCH INTERACTIONS

An abbreviated version of research interactions among the three participating institutions is presented by way of diagrams on the following three pages.

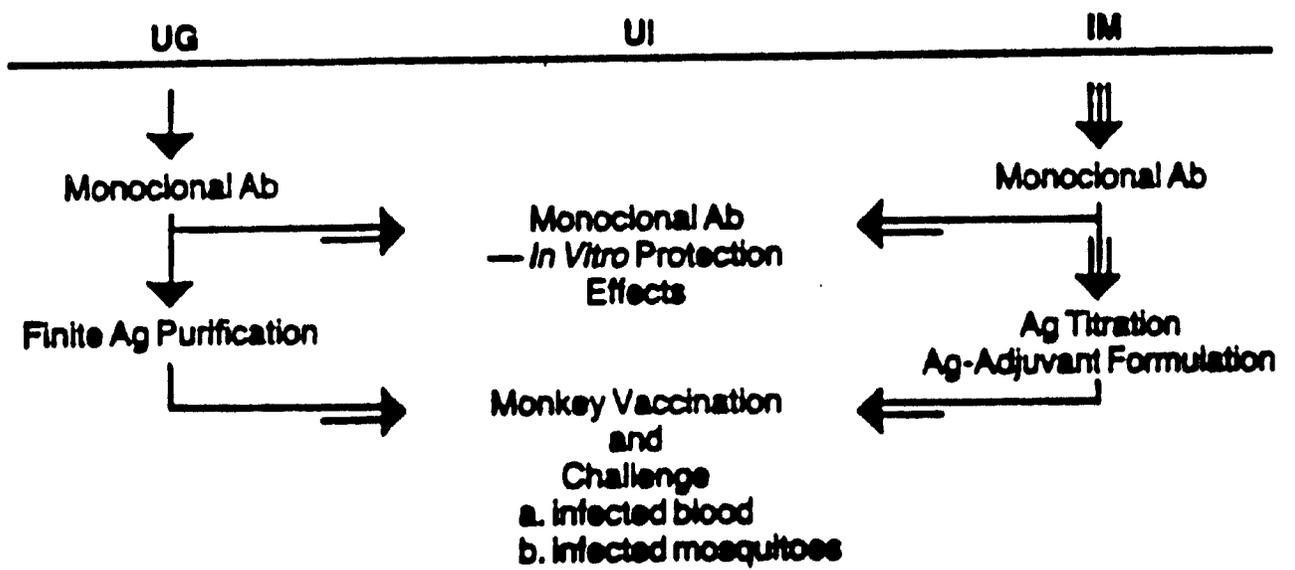
Research Interactions Among Participating Institutions

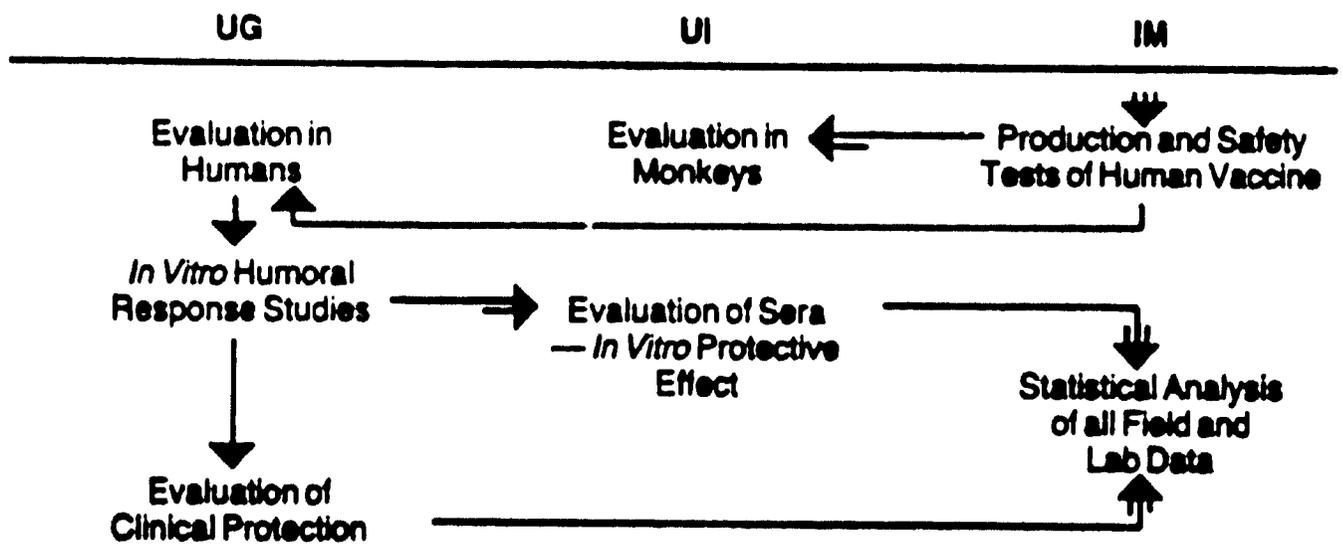
Phase I: Protection with Crude and Partially Purified Antigens



UG (↓) — University of Grenoble
 UI (↓↓) — University of Illinois
 IM (↓↓↓) — Institute Merieux

Phase II: Protection with Fully Purified Antigens



Phase III: Human Vaccination Studies

IV. INVENTION STATEMENT

An application for a patent right for the use of soluble malaria antigens as immunogens in the formulation of a vaccine against this disease is being processed by the University of Illinois.

The general concept presented in this application has been introduced in the study which led to the development of a vaccine against B. bovis. The actual protection data using squirrel monkeys and Plasmodium falciparum has been generated at the University of Illinois during September 1981 and May 1982. The funds used for the procurement of these data have been those of the University of Illinois and research grant allocations from the Institute Merieux of Lyon, France.

V. BUDGET

The first line of support for this project will come from the established available resources of the three participating institutions. Most of these resources are represented by available laboratory and animal facilities, laboratory equipment, and scientific, technical and supporting manpower as described under II-A of this proposal. Merieux Foundation is expected to continue with its annual research support at the level of \$100,000 to the University of Illinois for research on malaria vaccine development. Since September of 1981 the foundation has made research grant allocations to the University of Illinois totaling

\$245,000. Funds requested from the USAID are necessary for the strengthening of our cadre with the engagement of additional highly specialized scientists and laboratory technicians, purchase and maintenance of experimental animals, acquisition of special pieces of equipment, laboratory supplies, publication costs, scientific travel and communication. The USAID funds will be assigned to the University of Illinois, which in turn will arrange for a subcontract with the collaborating institution(s). The funds of the Institute Merieux will be assigned by direct allocation to each participating institution.

A three-year budget requested from USAID, to be allocated to the University of Illinois on an annual basis, is presented on the following pages.