Conclusions, Recommendations & Minutes of the Scientific Consultants Group Meeting

April 6-7, 1992
Arlington, Virginia

Approved: ________________
Robin D. Powell, M.D.
Chairman

Date: 5-14-92
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I: Other Malaria Vaccine Efforts—DoD
J: Other Malaria Vaccine Efforts—Industry
K: Other Malaria Vaccine Efforts—Non-U.S.
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M: A.I.D.'s Vector Biology Control Project
N: Procedures for the Protection of Human Subjects
O: PI/Industry Relationship
P: Ethical Standards for A.I.D. Program
Conclusions and Recommendations of the Meeting of the A.I.D. Malaria Vaccine Development Program Scientific Consultants Group April 7, 1992

The charge to the Scientific Consultants Group (SCG) was to provide advice on three specific issues, as well as in any other areas relating to the A.I.D. Malaria Vaccine Development Program (MVDP) direction and strategy deemed appropriate. The three specific requests were for the SCG's advice regarding:

1. future activities in the MVDP supported Papua New Guinea and Kenya field sites in the context of the just completed evaluations of both sites;

2. the MVDP 1992 funding plan, including several new awards to institutions that responded to the Requests for Applications (RFA) published in 1991; and:

3. the draft RFA's for publication in 1992 in the context of overall Program strategy, as presented by staff during the meeting.

The SCG's response is as follows:

1. Papua New Guinea (PNG) and Kenya Visits

1a. PNG: The SCG notes that significant progress has been made in achieving the goals stated in the original proposal. We are particularly encouraged by the development of the facilities, staffing, working relationships with the local populations, and apparent resolution of equipment procurement difficulties. The IMR should provide AID with full, clear, updated protocols. We recommend continued funding subject to submission of protocols and compliance with U.S. human subjects requirements.

1b. Kenya: The SCG appreciates the progress in some areas as noted in the evaluation team's report but is disappointed with overall progress relating to the original proposal. Noteworthy were the substantial departures from the original protocols and initial failure to take into account local conditions. The SCG urges pursuit of the important goals stated in the original proposal. We encourage A.I.D. to expand the potential for the Kenya activities to include the possibility for testing of malaria vaccine candidates as appropriate.

1c. The SCG concurs with the proposed "implementation letters" as discussed.
2. The SCG concurs with the 1992 A.I.D. MVDP funding plans and with current A.I.D. plans for new solicitations.

3. The SCG views as important the field activities and the continued encouragement and development of basic research-clinical research linkages.

4. The SCG concurs with the alternative methods to achieve goals of the vaccine production initiative as presented.

5. The A.I.D. MVDP program appears to have reasonable overall balance and direction.

6. The SCG is pleased by the multi-agency information presented at this meeting and the malaria vaccine research information coordination between those agencies. The SCG encourages further work to coordinate malaria vaccine research and development in the U.S. and internationally.
Minutes
Agency for International Development
Malaria Vaccine Development Program
Scientific Consulting Group Meeting
April 6 & 7, 1992, 9 - 5 pm
held at 1901 North Fort Meyer Drive, Suite 400
Arlington, VA 22209

Present:

Scientific Consultant Group (Advisory Committee Members)
Dr. Adetokunbo Lucas
Dr. Ian McGregor
Dr. Margaret Perkins
Dr. Robin Powell
Dr. Peter Reeve
Dr. Frederick Robins
Dr. Kenneth Stuart
Dr. William Weidanz

A.I.D. Employees
Dr. Ann Van Dusen, Director – Office of Health
Mr. Robert Wrin, Chief – Communicable Diseases Division
Dr. Kirk Miller, Project Officer – Malaria Vaccine Development Project
Dr. Dennis Carroll, Project Officer – Vector Biology & Control Project
Dr. Steve Landry, AAAS Fellow – Malaria Vaccine Development Project
Dr. Hiram Larue, Research Coordinator – Office of Strategic Planning

Invited Guests who Presented Statements
Dr. Dan Gordon - Walter Reed Army Institute of Research
Dr. Lee Hall – National Institute of Allergy & Infectious Diseases
Dr. David Kaslow – National Institute of Allergy & Infectious Diseases
Dr. Robert Lennox, Director – Vector Biology & Control Project
Dr. Andy Arata, Deputy Director – Vector Biology & Control Project

Other Attendees
Dr. Carter Diggs, Consultant - Atlantic Resources Corporation
Ms. Cathy Savino, Project Director – Atlantic Resources Corporation
Ms. Lolita Jackmon, Project Assistant – Atlantic Resources Corporation
Ms. Laura Hillier, Admin. Assistant – Atlantic Resources Corporation

Scientific Consultants Group Members not Present
Dr. Wenceslaus Kilama
Dr. Kamini Mendis
Dr. Harry Rozmirek
1.0 Welcome
Dr. Robin Powell opened the meeting and welcomed the Scientific Consultant Group (SCG) members. Dr. Ann Van Dusen, Director of the Office of Health, was introduced and brought an official welcome from A.I.D. Dr. Van Dusen noted the importance of the SCG and the high regard with which their recommendations were taken. Dr. Van Dusen also gave some background into A.I.D.'s work in the area of the Children's Vaccine Initiative (CVI), and suggested that the SCG evaluate the need for links between the CVI and the Malaria Vaccine Development Program (MVDP) and the CVI at a future meeting.

2.0 Adoption of the Agenda
The agenda was adopted. (see Appendix A)

3.0 SCG Minutes, Principle Investigators/SCG Meeting October 1991
It was moved, seconded and duly carried that the minutes from the October 7-9, 1991 meeting be adopted.

4.0 Review of the Role of the SCG
4.1 SCG Duties/Responsibilities (see Appendix B)
Robert Wrin, Chief of the Communicable Disease Division of the Office of Health, discussed the role of the SCG in terms of their scope of activities. He noted that the objective of the SCG was to provide broad scientific overview of malaria vaccine programs to the Assistant Administrator of A.I.D. and the advisory nature of their role.

4.2 SCG Operations/Meetings
4.3 Evaluation of the SCG
An open critique of the SCG was suggested as an appropriate agenda item for future meetings.

5.0 Outline of MVDP - Scope, Status & Strategy (see Appendix C)
Dr. Kirk Miller outlined the organizational framework of MVDP within A.I.D. He presented the project goal and discussed the three functional components of the portfolio.

An inquiry was made as to the status of the Institute of Medicine report recommendation regarding the constituting of an executive committee. No action to date has been reported on forming this committee. It was noted that the IOM recommendations were not just for oversight but also stressed coordination to avoid duplication of effort.

6.0 Kenya & PNG Field Proj.
Dr. Carter Digs led off with a slide show of the Papua New Guinea and Kenya evaluations. Drs. Reeve, Powell and McGregor gave their individual perspectives of the trip. Dr. Miller reported on the funding for each of these projects. The directives to be included in an implementation letter (see Appendix D) for each project was presented for discussion. The SCG members made specific wording recommendations for incorporation into the final letters. A major focus of the discussion was the need for protocols for each study and consultation with A.I.D. whenever deviations from protocols are contemplated. Comments were also made regarding the political sensitivity of A.I.D.'s bilateral agreement with Papua New Guinea.
Items 6.0 through 6.5 were addressed in closed session since they related to procurement activities.

6.0 Pending Program Actions
6.1 Update of Vaccine Production Initiative
   The background of the VPI was presented. A representative from NIH discussed the current status of the initiative from their perspective.
6.2 1992 Funding Plan
6.3 Planning Process for New solicitations
6.4 Review of 1992 RFAs
6.5 The MVDP Project Paper (see Appendix E)
   Bob Wrin presented general information about the Project Paper defining its purpose and content. The Malaria Vaccine Project Paper, which provides the framework under which the MVDP will operate, was currently being reviewed within A.I.D. and was to be available for distribution in the near future.

7.0 Review of Other Malaria Vaccine Development Efforts
7.1 NIH (extramural) (see Appendix F)
   Dr. Lee Hall presented information on the organizational structure of NIAID. He presented their funding portfolio and distributed a handout of research grants and career programs. In particular, he discussed the Parasite and Tropical Diseases Branch within the Division of Microbiology and Infectious Diseases.

7.2 NIH (intramural) (see Appendix G)
   Dr. David Kaslow presented a summary of NIH intramural placing it within the organizational structure of NIH. He went on to discuss their basic research and goals in vaccine development. In particular, he focused on the status of a transmission blocking vaccine within the Laboratory of Malaria Research.

7.3 WHO/TDR (see Appendix H)
   Dr. Peter Reeve talked about the World Health Organization’s TDR program. He discussed the activity within the Product Development Unit (PDU), the funding, and presented a strategic workplan used within the PDU. He announced an important upcoming meeting on vaccines to be attended by pharmaceutical representatives in The Gambia in October.

7.4 U.S. Department of Defense (see Appendix I)
   Dr. Dan Gordon of the Walter Reed Army Institute of Research presented information regarding their malaria vaccine program including the objectives of basic research, exploration and advanced development. Specifically, he discussed *P. falciparum* vaccine trials in humans from 1986-1995.

7.5 Pharmaceutical Industry (see Appendix J)
   Dr. Peter Reeve highlighted the companies currently involved in vaccine development. It was noted that interest in commercial development was lacking. Some ascribed this reluctance to the lack of a promising vaccine candidate. Others, however, thought that the pharmaceutical companies were focusing their interest towards a very small population within the market, specifically the developed world traveller.

7.6 Other/Miscellaneous (see Appendix K)
   Dr. Carter Diggs presented a brief synopsis of non-industrial malaria vaccine efforts being conducted outside the U.S.
8.0 Review of Other A.I.D. Malaria Control Activities
8.1 A.I.D. Malaria Control Efforts (see Appendix L)
Dr. Dennis Carroll presented overall trends in malaria mortality. He delineated A.I.D.'s approach to the prevention and treatment of malaria including pesticides and bednets.

8.2 Vector Biology & Control Project (see Appendix M)
Dr. Andy Arata of the VBC Project discussed the scope of their project highlighting their training program and interest in needs assessment, control, management and strategy.

9.0 Miscellaneous Program Items
9.1 Human Subjects Procedures (see Appendix N)
Dr. Steve Landry discussed new federal guidelines for the protection of Human Subjects and presented procedural steps that need to be followed.

9.2 PI/Industry relationship (see Appendix O)
Dr. Carter Diggs discussed the current status of A.I.D. regulations regarding patents. He noted the requirement for inclusion of a formula price clause in all cooperative agreements which protects A.I.D.'s interest in developing a vaccine.

9.3 Ethical Standards for A.I.D. Programs (see Appendix P)
Bob Wrin presented the A.I.D. Code of Ethics for Government Service pointing out its applicability to SCG members and contractors.

10.0 Miscellaneous Items for Discussion and Comment
10.1 Finalization of Report of October 1992 meeting (see item 3.0)
10.2 Indices/Markers/Milestones for Evaluation MVDP
This item was postponed until the next meeting
10.3 Appraisal of MVDP General Direction/Strategy
A general consensus was reached supporting the MVDP general direction and strategy
10.4 Appraisal of MVDP Portfolio Balance
A general consensus was reached supporting the MVDP portfolio balance
10.5 Special Needs, Recommendations
No topics were taken up in this category.
10.6 Planning for Fall '1992 PI/SCG Meeting
It was suggested that the Fall PI meeting was not a highly useful forum for the exchange of information. The opinion was expressed that PIs seemed protective of their research and mostly presented already published information and that little sense of mission was evident nor was it clear to the PIs what role the SCG members played.

One member inquired as to the need for a PI/SCG meeting at all. If a meeting is required, he called for a reorganization of that meeting so that it would be more productive. One member recommended a workshop format for the meeting be investigated. The October 1991 SCG suggestions merit consideration.

It was noted that time constraints are a consideration if the format is expanded. The last suggestion was to conduct a poll among PIs to get their opinion or to involve a small subgroup of PIs in planning the fall meeting.

11.0 Adjournment
Dr. Robin Powell adjourned the meeting at 5:00 pm.
1992

Spring Meeting

---AGENDA---
I. WELCOME & ANNOUNCEMENTS

Dr. Ann Van Dusen
Ms. Cathy Savino
Dr. Kirk Miller

II. REVIEW OF THE ROLE OF THE SCG:

Discussion
—SCG Duties/ Responsibilities
—SCG Operations/ Meetings
—Evaluation of the SCG

Mr. Robert Wrin
Dr. Robin Powell
& SCG Members

III. KENYA AND PNG FIELD PROJECTS:

Report on Comprehensive Evaluation

Discussion
Tentative Implementation Plans

Dr. Robin Powell
Dr. Peter Reeve
Sir Ian McGregor
SCG Members
Dr. Kirk Miller

IV. OUTLINE OF MVDP:

Scope, Status & Strategy

Dr. Kirk Miller
V. PENDING PROGRAM ACTIONS:

1. Update of Vaccine Production Initiative 
   Dr. Carter Diggs  
   Dr. Lee Hall

2. 1992 Funding Plan  
   Discussion  
   —Implications Beyond 1992  
   —Relationship to Other Agencies  
   Dr. Kirk Miller  
   SCG Members

3. Planning Process for New Solicitations  
   Dr. Kirk Miller

4. Review (Draft) 1992 RFAs  
   Dr. Carter Diggs  
   Dr. Steven Landry

5. The MVDP Project Paper  
   Mr. Robert Wrin
VI. Review of Other Malaria Vaccine Development Efforts:

- NIH (extramural)  
  Dr. Lee Hall
- NIH (intramural)  
  Dr. David Kaslow
- WHO/TDR  
  Dr. Peter Reeve
- U.S. Department of Defense  
  Dr. Dan Gordon
- Pharmaceutical Industry  
  Dr. Peter Reeve
- Other/Miscellaneous  
  Dr. Carter Diggs

VII. Review of Other A.I.D. Malaria Control Activities:

- A.I.D. Malaria Control Efforts  
  Dr. Dennis Carroll
- Vector Biology & Control Project  
  Dr. Andy Arata
VIII. MISCELLANEOUS PROGRAM ITEMS:

—Human Subjects Procedures  Dr. Stephen Landry
—PI/Industry Relationship  Dr. Carter Diggs
—Ethical Standards for A.I.D. Programs  Mr. Robert Wrin

IX. MISCELLANEOUS ITEMS FOR DISCUSSION & COMMENT  D. Robin Powell & SCG Members

—Finalization of Report of October 1991 Meeting
—Indices/ Markers/ Milestones for Evaluating MVDP
—Appraisal of MVDP General Direction/ Strategy
—Appraisal of MVDP Portfolio Balance
—Special Needs, Recommendations
—Planning for Fall '92 PI/SCG Meeting

X. ADJOURNMENT
<table>
<thead>
<tr>
<th>Scientific Consultants Group</th>
<th>Invited Guests</th>
<th>A.I.D. &amp; ARC</th>
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<tbody>
<tr>
<td>Dr. Wenceslaus Kilama</td>
<td>Dr. Dan Gordon&lt;br&gt;Walter Reed Army Institute of Research</td>
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<td>Dr. Andy Arata, Deputy Director&lt;br&gt;Vector Biology &amp; Control Project</td>
<td>Dr. Dennis Carroll, Project Officer&lt;br&gt;Vector Biology &amp; Control Project</td>
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<tr>
<td>Dr. Margaret Perkins</td>
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<td>Dr. Steve Landry, AAAS Fellow&lt;br&gt;Malaria Vaccine Development Project</td>
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<td>Dr. Robin Powell</td>
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<td>Dr. William Weidanz</td>
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* Denotes unable to attend this meeting.
★ Value of field activities.
★ 1992 Funding plan.
★ Plans for new solicitations.
★ Overall direction and strategy.
ROLE

of the

SCG
CHARTER
of the
Agency for International Development
Advisory Committee of the Malaria Vaccine Program
To provide *broad* senior scientific *overview* of Malaria Vaccine Programs
**DUTIES & SCOPE OF ACTIVITY**

- To ensure Malaria Vaccine *Program focus and coherence*, and to ensure the application of the *highest standards of technical and scientific excellence*.

- To assist in the development of *overall Program strategy* and in the monitoring of Program *goals*.

- To *provide strategic advice and guidance*, based upon periodic review of ongoing and proposed Program activities.

- To *help identify new opportunities* for lines of research as well as to identify appropriate additional institutions and scientists to participate in the Program.
The Advisory Committee of the Malaria Vaccine Program will provide advice to the Assistant Administrator for Research and Development of the Agency for International Development.
Agency Organization Chart: Operations

Operations

- Management Resources Coordination Staff
  - Research & Development
  - Food & Humanitarian Assistance (FVA/OFDA)
  - Private Enterprise
  - AFR
  - ASIA
  - EUR
  - LAC
  - NE

- Program & Research Staff Coordination
Project Goal
(circa 1989)

Develop vaccine(s) that will reduce malaria-associated mortality and morbidity in developing countries, especially in children.
Three functional components within the portfolio:

1. Discovery
2. Production
3. Evaluation
★ Support
Allocation of MVDP Funds 1992

- Discovery: 55%
- Production: 19%
- Support: 7%
- Evaluation: 19%
Discovery Component: Resource Allocation by Stage of Parasite

- Pre-erythrocytic: 52%
- Erythrocytic: 40%
- Sexual Stage: 8%
Discovery Component: Resource Allocation by Species of Parasite

- **P. vivax**: 10%
- **P. falciparum**: 90%
Discovery Component

Cooperative Agreements

- Limited to domestic, non-U.S. Government institutions;
- Proposals solicited annually by announcements in:
  - Science, Nature, Commerce & Business Daily,
  - Secondary excerpting process, and
  - Direct mailings to ASTM&I members.
- Results in a full and open competition;
- Review for responsiveness by MVDP; and
- Peer review for scientific merit by NIH.
Evaluation and Monitoring of Agreements

- Competitive Renewal — every 3 years
- Presentation at SCG Meeting — every year
- Progress Reports, Administrative — quarterly
- Progress Reports, Technical — 9, 18, 36 months
- Site Visits
Production Component

- Potential linchpin of program: linkage between discovery and evaluation;
- Adds clinical product development component; and
- Allows the development of orphan vaccines.
Evaluation Component

The MVDP currently maintains the capability to:

- Conduct monkey trials at CDC;
- Conduct Phase I and II trials in the United States;
- Repeat Phase I and II trials in endemic areas; and
- Conduct Phase III trials in endemic areas.
New Trends

- Increased collaboration with other U.S. Government Agencies (NIAID, WRAIR);

- Increased capability to expedite antigen evaluation to the point of clinical testing;

- Increased effort to communicate with program investigators; and

- Continued effort to focus the program.
Implementation Letter - Kenya

—Studies will be supported at current level until present agreement expires (April 1993).

—Major emphasis should be placed on defining clinical malaria and attempting to correlate development of immunological markers with clinical immunity; minimal emphasis shall be placed on other types of studies unless there is clearcut relationship to immunologic studies (i.e., bednet studies, anemia studies, and entomological studies).

—A protocol should be developed to make the best possible use of specimens collected during already completed cohort studies.

—All newly developed protocols shall be submitted to A.I.D. for internal review for program relatedness and external review for scientific merit. A format for protocols will be provided by A.I.D.

—Progress will again be evaluated prior to negotiation of a new Interagency Agreement with CDC for field studies in Kenya.
—Studies will be supported at negotiated level until present until expiration of extended agreement (September 1994).

—As soon as possible, detailed scientific protocols should be constructed and submitted to A.I.D. for all ongoing studies. These will be reviewed by an external panel for scientific merit. A format for protocols will be provided by A.I.D.

—If suitable protocols are developed and submitted demographic studies and epidemiologic surveillance should be continued as planned for the next 2 years; genetic studies underway should be completed; and entomologic studies should be continued until the end of this year. Immunologic studies should continue on an ongoing basis and should correlate specific immune responses with naturally acquired immunity to malaria.

—Similarly, in the future, detailed scientific protocols should be constructed and submitted to A.I.D. for all planned studies well in advance of contemplated start date.

—Progress will again be evaluated prior to negotiation of a new Project Grant Agreement in 1994.
The

Project

Paper
PROJECT PAPER

Purpose:

*Formalize Long-term Commitment*

- A.I.D.

(Executive Branch)

Congress

Usual Functions of Project Paper

Provides HQ commitment to field-mission's program

Process allows for consensus-building among various development specialities, as well as between A.I.D. and host country staff.

Content:

*Goal & Purpose of Project*

*Management Plan*

*Implementation*

*Evaluation*
Location of NIAID in the Department of Health and Human Services

September 1991
"... NIAID has maintained its strong commitment to basic research and to studies on other infectious and immunologic diseases within its mission by continuing to conduct and support work in the prevention and treatment of sexually transmitted diseases, asthma and allergies, and parasitic and fungal diseases; diagnostics for infectious diseases; evaluation of antiviral drugs; and transplantation immunology. NIAID also continues to provide support for research on international health issues and in tropical medicine."

- Anthony S. Fauci, M.D.
  Director, NIAID
  Profile, Fiscal Year 1991
NIAID and NIH Funding
By Budget Mechanism: FY 1991

NIAID
Total: $906,003,000

- Research Project Grants 61.6%
- Intramural Research 12.6%
- Other Research 1.6%
- Training 2.2%
- Research and Development Contracts 14.6%
- Research Management and Support 5.2%
- Centers 2.2%

NIH
Total: $7,825,011,000

- Research Project Grants 57.7%
- Intramural Research 11.8%
- Other Research 5.3%
- Training 3.9%
- Research and Development Contracts 7.6%
- Research Management and Support 4.7%
- Centers 9.0%

* Excludes funds for cancer control; construction; National Library of Medicine; Office of the Director, National Institutes of Health; and buildings and facilities.
Emerging and Re-Emerging Infectious Diseases
Pathogenesis
Molecular Biology and Genetics of Infectious Agents
Structural Biology and Drug Development
Vaccine Research and Development
Control of Infectious Diseases
DMID: SPECIFIC AREAS OF INTEREST - I

- Antimicrobial Drug Resistance
- Malaria and Other Tropical Diseases
- STD's/Women's Health
- Hepatitis, Cholera, and Other Enteric Diseases
- Pertussis, GBS and Other Respiratory Diseases
- Mycology
- Tuberculosis
**DMID: SUMMARY OF FY 1991 ACTIVITY**

<table>
<thead>
<tr>
<th>Grants</th>
<th># Mechanisms</th>
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<td>Research Projects</td>
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<td>Research Centers</td>
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<td>Career</td>
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<td>Other</td>
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<td>Training, Individual</td>
<td>67</td>
<td>1,828</td>
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<td>Training, Institute</td>
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<td>7,029</td>
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<td><strong>Contracts</strong></td>
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<tr>
<td>Contracts</td>
<td>56</td>
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<td><strong>Total</strong></td>
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DMID: A SUMMARY OF CLINICAL ACTIVITY

- 47 Active INDs
- 123 Clinical Trials
  - 11 Drugs
  - 54 Vaccines
- 26 Collaborating Companies
RESEARCH OBJECTIVES
Parasitology and Tropical Diseases Branch, DMID

Vaccine Development
♦ To characterize the role of the immune system in protection and disease
♦ To identify suitable candidate vaccine antigens
♦ To facilitate clinical testing of candidate vaccines

Diagnosis
♦ To develop rapid, sensitive, cost-effective diagnostic assays
♦ To facilitate application of these assays in endemic areas

Therapy
♦ To identify new therapeutic agents and targets
♦ To improve the efficacy of currently available therapy
♦ To facilitate clinical testing of promising agents

Vector Biology
♦ To develop methods to control vector populations and block pathogen transmission
Parasitology and Tropical Diseases Branch
DMID, NIAID

♦ Individual investigator-initiated research grants
   Approximately 300 grants in the areas of parasitology and vector biology

♦ Special Programs
   Tropical Disease Research Units - P01
   International Collaborations in Infectious Diseases Research - P01
   Tropical Medicine Research Centers - P50

♦ Contracts
   Supply of schistosome materials
   Supply of filarial materials
   Testing of candidate malaria vaccines in human volunteers (with USAID)
PTDB Funding: 1981 - 1991

(Million $)

Source: NIAID Award Books, 1981-1990
Distribution of funds in PTDB: 1990 (million $)

Malaria: 6
Schistosomiasis: 6.2
Protozoal Diseases: 5.7
Vector Biology: 6.6
Helminthic Diseases: 1.8
Filarial Diseases: 1.5
Trypanosomiasis: 9
Leishmaniasis: 6.6

Total $ grants: $43.5

Source: NIAID 1990 Awards Book
Malaria Research Development 1985-90
Sponsored Vaccine Related Work

Number of grants

Malaria Vaccine  Total Malaria


0  10  20  30  40  50
Malaria as % of grants funded

## Research Grants and Career Programs
### Animal Parasites & Parasitic Diseases

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Grant Number</th>
<th>Amount</th>
<th>Institution/Title</th>
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<tr>
<td>Ainsworth, Avery J</td>
<td>R15 AI 26264-01</td>
<td>0x</td>
<td>Mississippi State University&lt;br&gt;Potential use of anti-idiotypic antibodies as vaccines</td>
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<td>Aikawa, Masamichi</td>
<td>R22 AI 10645-19</td>
<td>114,296</td>
<td>Case Western Reserve University&lt;br&gt;Electron microscopy of Plasmodium host interactions</td>
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<td>Barnwell, John W</td>
<td>R22 AI 24710-04</td>
<td>137,827</td>
<td>New York University&lt;br&gt;Molecular analysis of Plasmodium vivax surface antigens</td>
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<td>Beier, John C</td>
<td>R22 AI 29000-01</td>
<td>190,143</td>
<td>Johns Hopkins University, Baltimore&lt;br&gt;Anopheles vector potential for malaria transmission</td>
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<td>Brey, Robert N, III</td>
<td>R01 AI 25232-03</td>
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<td>Praxis Biologics, Inc.&lt;br&gt;Oral malaria vaccine development in a P. berghei model</td>
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<td>Bzik, David J</td>
<td>R29 AI 26651-03</td>
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<td>Dartmouth College&lt;br&gt;Gene expression and regulation in P. falciparum</td>
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<td>Chang, Sandra P</td>
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<td>93,184</td>
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(*)=ACTIVE; NO FY 1990 FUNDS
### RESEARCH GRANTS AND CAREER PROGRAMS
#### ANIMAL PARASITES & PARASITIC DISEASES

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Total: 5,852,714

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### MOSQUITOES

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<td>Craig, George B, Jr</td>
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(*)=active, no FY 1990 funds  
(**)=reimbursable funds

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(M)=ACTIVE; NO FY 1990 FUNDS
NIAID INTRAMURAL PROGRAM
Laboratory of Malaria Research

TRANSMISSION BLOCKING VACCINE

BASIC RESEARCH
Molecular Vaccine Section
Kim Williamson
Pat Duffy
Michal Fried
Mohammed Shahabuddin
David Keister

VACCINE DEVELOPMENT

Yeast
Chiron Corporation
Ian Bathurst
Phil Barr

Vaccinia/Live virus vectors
LVD,NIAID
Stuart Isaaccs
Bernie Moss

US Army
Joel Dalrymple

Virogenetics
Enzo Paoletti

Bacterial/Mammalian
Smith, Kline, Beecham
Mitch Gross
NIAID INTRAMURAL PROGRAM
Laboratory of Malaria Research

Plasmodium vivax Duffy RECEPTOR
RED BLOOD CELL INVASION

BASIC RESEARCH
Cell Biology and Immunology Section
Chatan Chitinis
Diana Hudson
Louis H. Miller

VACCINE DEVELOPMENT
Yeast/Mammalian Cell
Chiron Corporation
Ian Bathurst
Phil Barr
NIAID INTRAMURAL PROGRAM
Laboratory of Malaria Research

*Plasmodium vivax* DUFFY RECEPTOR
RED BLOOD CELL INVASION

Immediate goals:

- Mammalian cell expression
- Immunogenicity
- Identify domains involved in erythrocyte binding
- Invasion blocking activity
- Polymorphism
NIAID INTRAMURAL PROGRAM
Laboratory of Malaria Research

- TRANSMISSION BLOCKING VACCINE

- *Plasmodium vivax* DUFFY RECEPTOR (RED BLOOD CELL INVASION)

- ASEXUAL VACCINE
Immediate Goals:

**Pfs230-** Complete cloning and DNA sequencing
- Bacterial/mammalian cell expression
- B and T cell epitope mapping

**Pfs40-** Yeast/mammalian cell expression
- Transmission blocking activity
- B and T cell epitope mapping

**Pfs28-** Clone and sequence gene
- Yeast/vaccinia/mammalian cell expression
- Transmission blocking activity
- P. vivax equivalent

**Pfs25-** Preclinical/Phase I human trials
- Aotus vociferans monkey trial
  - in vivo efficacy
  - boosting following natural infection
- P. vivax equivalent

**Chitinase-** Clone and sequence gene
- Recombinant expression
- Transmission blocking activity
STAC 1992
PDU Budget forecast

1992 to 1991

Malaria
- Artemesenin 800.0
- BC-7 350.0
- Pfs 25 600.0
- Drug assay 150.0

Schistosomiasis
- Multidisease 200.0

Leishmaniasis
- LAMBS 300.0
- DAT.VL 250.0

African Tryps.
- FILARIASIS

Filariasis
- UMF 078 350.0

Total allocated 3000.0
# Malaria vaccine development

**TDR PDU**

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<th>Activity</th>
<th>Status</th>
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<td>Pilot study CB-6</td>
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<td>Pilot study BC-7</td>
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<td>Phase III trial</td>
<td>Planned Fall 1992</td>
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<td>BC-7 &amp; artemether</td>
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<tr>
<td>Transmission blocking vaccine</td>
<td>Phase I &amp; II</td>
<td>Planned Fall 1992</td>
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<td>Pfs 25Kd</td>
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# Malaria Vaccine Development Efforts

**WHO**

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<th>Objectives</th>
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<td>WHO-CVI</td>
<td>Childrens vaccines</td>
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# Malaria vaccine development efforts
IMMAL Workplan, 1992-1993

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<th>Plans</th>
<th>Activities</th>
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<td>Vaccine development</td>
<td>Basic research</td>
<td>T&amp;B antigens</td>
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<td>T cell immunity</td>
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<td>Combat severe malaria</td>
<td>Understand pathology</td>
<td>Role of cytokines in vitro assays</td>
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<td>Diagnostics</td>
<td>Identify therapies</td>
<td>CM, man &amp; rodents</td>
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<td>Examine antigens</td>
<td>Role of cytokines</td>
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<td></td>
<td>antibodies</td>
<td>TNF antagonists</td>
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<td>Chemotherapy</td>
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**OBJECTIVES:**

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<th>To develop effective malaria vaccines</th>
<th>To understand and prevent the (immuno)pathology seen in severe malaria</th>
<th>To develop and evaluate new tools for diagnosis and monitoring of malaria and its transmission</th>
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**PLANS:**

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<tr>
<th>To promote research on the basic understanding of the mechanism(s) of protective immunity in malaria.</th>
<th>To investigate the pathogenic mechanisms involved in severe malaria.</th>
<th>To promote research on the detection of malaria parasites, antigens and antibodies in humans and relevant vectors (with FIELDMAL and CID/MAL).</th>
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**ACTIVITIES:**

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<th>Identification of relevant T and B cell antigens/epitopes for the pre-erythrocytic, asexual and sexual forms of malaria parasites.</th>
<th>Characterization of T cell immunity in immune individuals.</th>
<th>Analysis of immune responses to malaria in field studies of naturally-exposed populations, and impact of chemotherapy.</th>
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**PRIORITY:**

| A | A | B | C | B |

**DRAFT**
## COLLABORATING STEERING COMMITTEE

### MAJOR DIRECTIONS

#### 1. MALARIA

1.1 Develop novel treatments for severe and cerebral malaria

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<td>(b) Multicentre Phase III trials anti-tumour necrosis factor MAB B-C7</td>
<td>March 1992-March 1993</td>
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<td>- Clinical plans</td>
<td>June 1992</td>
<td>A</td>
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<tr>
<td>- Clinical studies</td>
<td>Oct. 1992/June 1993</td>
<td>A</td>
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<td>(c) Advise and assist with Centochor proposed trials</td>
<td>Ongoing 1992-1993</td>
<td>B</td>
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<tr>
<td>(d) Identify low molecular weight TNF antagonists</td>
<td>Ongoing</td>
<td>B</td>
</tr>
<tr>
<td>(e) Assist in French registration of artemether</td>
<td>Ongoing 1992-1993</td>
<td>A</td>
</tr>
<tr>
<td>- Complete regulatory dossier file for registration</td>
<td>December 1992</td>
<td>A</td>
</tr>
</tbody>
</table>

1.2 Development of malaria vaccines

<table>
<thead>
<tr>
<th>Specific Activities</th>
<th>Status</th>
<th>Priority</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Malaria transmission blocking vaccine Pfs 25:</td>
<td>Planned to begin:</td>
<td>A</td>
</tr>
<tr>
<td>- Complete preclinical development</td>
<td>March 1992</td>
<td>A</td>
</tr>
<tr>
<td>- File IND</td>
<td>March 1992</td>
<td>A</td>
</tr>
<tr>
<td>- Phase I trials Washington</td>
<td>April-June 1992</td>
<td>A</td>
</tr>
<tr>
<td>- Phase I(b) Kenya</td>
<td>June-Sept. 1992</td>
<td>A</td>
</tr>
<tr>
<td>- Phase II Kenya</td>
<td>September 1992</td>
<td>A</td>
</tr>
<tr>
<td>(b) Other vaccines:</td>
<td>December 1993</td>
<td>B</td>
</tr>
<tr>
<td>- Bring at least one blood stage antigen and one exoerythrocytic antigen to development</td>
<td>October 1993</td>
<td>B</td>
</tr>
<tr>
<td>- With IMMAL review vaccine clinical studies</td>
<td>April 1992</td>
<td>C</td>
</tr>
</tbody>
</table>

1.3 Malaria diagnostics

<table>
<thead>
<tr>
<th>Specific Activities</th>
<th>Status</th>
<th>Priority</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Test to determine drug levels in body fluids:</td>
<td>Trials planned to begin:</td>
<td>A</td>
</tr>
<tr>
<td>- Complete field testing of kit</td>
<td>December 1992</td>
<td>A</td>
</tr>
<tr>
<td>- Seek commercial manufacturer</td>
<td>December 1993</td>
<td>A</td>
</tr>
</tbody>
</table>
Malaria vaccine development
Pharmaceutical industry

<table>
<thead>
<tr>
<th>Company</th>
<th>Projects</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>SmithKline Beecham</td>
<td>Multiple sporozoite vaccines. RecDNA vaccines</td>
<td>Phase III studies improved responses;</td>
</tr>
<tr>
<td></td>
<td>E.coli/yeast expr.</td>
<td>efficacy critical to continuation;</td>
</tr>
<tr>
<td>Hoffmann-LaRoche</td>
<td>Sporozoite vaccine synthetic vaccine; rec DNA</td>
<td>Poor responses; Phase III</td>
</tr>
<tr>
<td></td>
<td>vaccines</td>
<td></td>
</tr>
<tr>
<td>HLR-Suramane</td>
<td>merozoite vaccines</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Behringwerke</td>
<td>Merozoite vaccines E.coli expression</td>
<td>Preclinical Primate protection</td>
</tr>
</tbody>
</table>
DOD Malaria Vaccine Program

WRAIR - Dept of Immunology
Dept of Bacterial Diseases
Dept of Bacterial Immunology

NMRI - Malaria Program

Special Foreign Activities

AFRIMS
USAMRU-K
NAMRU - Jakarta
DOD Malaria Vaccine Development Program

Basic Research → Exploratory Development → Advanced Development
Objectives

Basic Research

• Develop molecular/immunological basis for malaria vaccines
• Identify, clone, and sequence candidate parasite antigens
• Assess functional regions of target antigens
• Develop methods of measuring protective responses
• Characterize vaccine candidates using in vitro and in vivo models
Objectives

Exploratory Development

- Expression of recombinantly expressed malaria antigens
- Production of synthetic peptide malaria vaccines
- Establishment of fermentation and protein purification capabilities
- Development of live attenuated vaccines expressing malaria genes
- Development of novel antigen delivery and presentation systems
- Identification of cellular immune mechanisms involved in protection
Objectives

Advanced Development

- Formulation, preclinical studies, IND preparation
- Experimental vaccine studies in primate models
- Phase I studies for safety and immunogenicity in human volunteers
- Phase IIa studies for safety, immunogenicity & experimental challenge
- Phase IIb studies for safety, immunogenicity & natural challenge
- Serological and cellular immunology support for vaccine studies
DOD Malaria Vaccine Development Program

Basic Research → Exploratory Development → Advanced Development

Pre-erythrocytic
NMRI

ERYTHROCYTIC
Engineered attenuated live vectors
WRAIR

IND/Phase I/IIa
Phase I/IIb
SFA
P. falciparum malaria vaccine trials in humans

1986 87 88 89 90 91 92 93 94 95

- R32tet32
- R32NS1
- R32- Ps. Toxin A
- R16-HBsAg
- R32NS1 - DETOX®
- R32NS1 - Liposomes
- RTS,S
- RLF - Liposomes
- SPf66 - Alum
- Pfs25 - TBA
- NYVAC (heptavalent vaccinia)
- Salmonella
- Mycobacteria (BCG)
# Malaria vaccine development

## Pharmaceutical industry

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<td>Merozoite vaccines E.coli expression</td>
<td>Primate protection</td>
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</table>
NON—INDUSTRIAL EFFORTS OUTSIDE U.S.A.

United Kingdom

- London School—transmission blocking immunity (Targett).
- Imperial College, London—pre-erythrocytic immunity (Sinden).
- National Institute for Medical Research, Mill Hil—gp195 (Holder), immunol (Brown).
- Middlesex School of Medicine, London—nonspecific immunity (Playfair).
- University of Edinburg—parasite genetics (Walliker, Carter).
- Wellcome Malaria Research Unit, Kalifi, Kenya—clinical immunology (Marsh).
NON—INDUSTRIAL EFFORTS OUTSIDE U.S.A. (CONTINUED)

The Netherlands

- University of Nijmegen—transmission blocking immunity (Meuwissen).
- TNO—Chimpanzee model, liver stage antigens (Mons), Pf83 (Thomas).

France

- Institute Pasteur—blood stage, liver stage antigens (da Silva, Druile).
- Groupe Pitié-Salpêtrière, Paris—Immunology (Mazier).
NON—INDUSTRIAL EFFORTS OUTSIDE U.S.A. (CONTINUED)

Australia

- Walter & Eliza Hall Institute, Melbourne—blood stage antigens (Anders).
- Queensland Institute, Brisbane—bloodstage antigens, immunology (Saul, Good).
- Australian National University, Canberra—nonspecific immunity (Clark).

Sweden

- Stockholm University—RESA, immune mechanisms.

Canada

- Montreal General Hospital Research Institute—role of cytokines (Stevenson)
NON—INDUSTRIAL EFFORTS OUTSIDE U.S.A. (CONTINUED)

Sri Lanka

- University of Colombo—transmission blocking, nonspecific immunity (Mendis)

Colombia

- Universidad de Valle, Cal—nonhuman primate trials, clinical immunology (Herrera)

- Universidad Nacional de Colombia, Bogotá—experimental vaccines (Patarroyo)
MALARIA AND CHILD SURVIVAL - AFRICA

MALARIA INFECTED MOSQUITO

HUMAN MALARIA INFECTION

MALARIA DISEASE

AT RISK: 100 million children <5
20 million pregnancies

ACUTE
- FEVER: 350 million episodes/yr
- SEVERE DISEASE: 3.5 million episodes/yr

CHRONIC
- ANEMIA: 15 million children
- SEVERE ANEMIA: 1.5 million children

PERINATAL
- LOW BIRTHWEIGHT: 3 million newborns

CFR*: 15-20% 5-10% 12-15%
Deaths: 700,000 150,000 400,000
IMPACT OF CHLOROQUINE RESISTANCE
CASE FATALITY IN ZAMBIA: 1980-1986

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IMPACT OF CHLOROQUINE RESISTANCE
CASE FATALITY IN TOGO: 1984-1989

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Source: CCCD
Distribution of drug resistant P. falciparum foci to Mefloquine
IMPACT OF DEVELOPMENT MALARIA IN THE AMAZON REGION

NUMBER OF CASES (THOUSANDS)

GENERAL STRATEGY

- **PREVENTION** through the use of chemoprophylaxis and personal prevention devices

- **TREATMENT** by providing timely and effective diagnosis and care for malaria cases

- **CONTROL** through early detection or forecasting of epidemics and rapid application of control measures
TARGET STRENGTHENING INSTITUTIONAL CAPABILITIES
CAPABILITY TRANSFER

- SURVEILLANCE
- MANAGEMENT
- HEALTH EDUCATION
- OPERATIONS RESEARCH
- **SUPPORTS 5000 TROPICAL DISEASE RESEARCHERS WORLDWIDE**

- **STRENGTHENS THE CAPACITY OF LDCs IN RESEARCH AND DEVELOPMENT**

- **TRAINS PEOPLE IN LDCs IN DETECTECTING AND RESPONDING TO THEIR MAJOR HEALTH PROBLEMS**

- **SUPPORTS THE DEVELOPMENT OF NEW DRUGS, VACCINES, DIAGNOSTIC TESTS AND CONTROL METHODS**
CDC PASA

Objectives

- Technical Assistance to A.I.D. assisted tropical disease control programs

b. Collaboration with the VBC project on directions, strategies, and priorities over the life of the VBC project.

c. Co-ordination with A.I.D. and CDC activities as they relate to tropical diseases.

d. To provide on request Laboratory Analysis of insecticides and pharmaceuticals to ensure quality.
WHO/CTD GRANT

Objectives

- Technical Collaboration with national control programs
- Management Information Systems development
- Training of nationals
- Operations Research
- Environmental Management
CASSET OF MALARIA
WORLD WIDE DISTRIBUTION

ASIA/NEAR EAST
LATIN AMERICA
AFRICA

Source: WHO

CAUSES OF CHILDHOOD DEATHS
SUB SAHARAN AFRICA

Other 6%
Measles 7%
Diarrheal diseases 36%
Malaria 25%
Neonatal diseases 26%

Source: WHO
CAUSES OF CHILDHOOD DEATHS
WORLD WIDE

SOURCE: WHO & UNICEF ESTIMATES
VBC I Project - Disease Breakout

- Malaria (58.2%)
- Dengue (13.3%)
- Chagas (4.1%)
- Guinea Worm (3.1%)
- Japanese Encephalitis (2.0%)
- Onchocerciasis (3.1%)
- Schistosomiasis (4.1%)
- Global (12.2%)
Schistosomiasis (2.8%)
Arboviruses (17.6%)
Malaria (41.5%)
Onchocerciasis (8.1%)
Lymphatic Filariasis (1.3%)
Dracunculiasis (10.2%)
African Trypanosomiasis (0.5%)
Leishmaniasis (0.7%)
Chagas' Disease (10.0%)
Other (1.6%)
Non Disease (5.7%)
VECTOR BIOLOGY AND CONTROL PROJECT
Major Areas of Emphasis (1992 - )

- Understanding and exploiting environmental relationships
- Implementing Malaria Training Module
- Surveillance H/MIS and GIS
- Vector control
  - management/efficiency/cost
  - new control tools
  - integration
- Information dissemination
- Policy development
  - national planning
  - regional programs
  - economic analysis
Vector Biology and Control Project

MALARIA CONTROL TRAINING MODULE

Units within Module:

Unit 1. Planning, Organizing, Monitoring and Evaluating

Unit 2. Collection of Planning Data (Surveys)

Unit 3. Implementation of Curative Services

Unit 4. Implementation of Preventive Services

Unit 5. Collection/Analysis of Data for Monitoring/Evaluation

Unit 6. Simulation Unit

Unit 7. Training of Trainers
Cooperative Agreements

Clinical trials

CDC field studies in Kenya

Field studies in Papua New Guinea (PNG) conducted by the Institute of Medical Research (IMR)
FIELD STUDIES IN PNG

- Requested a Multiple Project Assurance from OPRR
- Dialogue continued (September 1991)
- Recommendations of evaluation team
NEW FEDERAL POLICY FOR PROTECTION

"Whenever the U.S. Agency for International Development or the Agency's awardees or contractors conduct or support research involving human subjects in foreign countries, the research must be carried out in compliance with the new Common Federal Rule — Protection of Human Subjects for Research Risks."

A.I.D. MVDIP PI/Industry Relationships

CURRENT STATUS

✓ US Government Policy/A.I.D. options regarding patents
  — PIs own patent rights on inventions;
  — Decision to submit patent applications (at own expense) rests with PI; and
  — A.I.D. can submit patent applications (at Government expense) if PI declines.

✓ MVDP posture towards PI/industry relationships
  — PIs expected to develop industrial collaboration to produce clinical grade vaccines;
  — PI or PI institution can use licensure to company as incentive;
  — A.I.D. requires “formula price” clause as part of collaborative agreement
    ▲ if industrial collaborator develops vaccine as part of collaboration
    ▲ if A.I.D. supports evaluation of vaccine developed independently by industry; and
  — A.I.D. has “march in rights.”
RECENT TRENDS

- A.I.D. moving to NIAID/DoD ad hoc collaboration model
  - Direct A.I.D. MVDP negotiations with industry;
  - May involve expediting PI/industry agreements; and
  - Clinical/field trial potential provides incentive.

- Coordination with industry essential for MVDP planning
  - To avoid parallel development of similar constructs (*viz.*, gp195 by CHIRON); and
  - To better define companies' agendas (*viz.*, Roche attitude towards MAPs).
(Excerpted from the Code of Ethics for Government Service)
Any Person in Government Service

Should -
Seek to find and employ more efficient and economical ways of getting tasks accomplished.
Make no promises of any kind binding upon the duties of office, since a Government employee has no private word which can be binding on public duty.
Engage in no business with the Government, either directly or indirectly, ... inconsistent with the conscientious performance of his public duties.
Never use any information coming to him confidentially in the performance of governmental duties as a means for making private profit.
Expose corruption wherever discovered.
Any Person in Government Service Should -

Never discriminate unfairly by the dispensing of special favors or privileges to anyone, whether for remuneration or not; and never accept, for himself or his family, favors or benefits under circumstances which might be construed by reasonable persons as influencing the performance of his governmental duties.