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DEPARTMENT OF STATE
AGENCY FOR INTERNATIONAL DEVELOPMENT
WASHINGTON, D.C. 20523

CERTIFIED A TRUE COPY THIS

17th DAY OF February
BY Suzanne Stevens

Dr. H. Mahler, Director-General
World Health Organization
1211 Geneva 27
Switzerland

9310001

Subject: Grant No. AID/ta-G-1402
PIO/T 931-0001-73-3177704

Dear Dr. Mahler:

Pursuant to the Foreign Assistance Act of 1961, as amended, the Agency for International Development (hereinafter referred to as "A.I.D."), hereby grants to the World Health Organization (hereinafter referred to as "WHO"), the sum of Twenty Five Thousand Dollars (\$25,000) to provide support to WHO for organizing and conducting workshops on malaria immunity research.

This Grant is effective as of the date of this letter and the amount of funds stated herein is obligated as of that date. Such funds shall apply, for a period of four months subsequent to the effective date of this Grant, to costs incurred in convening malaria research workshops to be held at The Rockefeller University, New York, New York, from March 7-12, 1977, as set forth in the WHO proposal attached to your letter dated November 1, 1976 (Attachment No. 1 hereto).

This Grant is made by A.I.D. to WHO with the following understandings:

1. The funds being contributed under this Grant, as set forth in the illustrative Budget (Attachment No. 1), shall be used in support of two Workshops. A general description of the subjects to be addressed at these Workshops is as follows:

a - The Biology of the Malaria Parasite, i.e. biochemistry, metabolic pathways, anabolism and growth, penetration into host cells, host/parasite membranes, material and energy transfer, etc.

b - The In-vitro Cultivation of the Malaria Parasite. Determine the metabolic needs and growth determining parameters leading to mass production of the various stages of the malaria parasites. This parasite production is a prerequisite to immunologic studies and will lead to a greater understanding of the requirements for the production of an effective malaria vaccine.

2. These funds are granted as set forth in the exchange of correspondence between the Director-General, WHO, dated November 1, 1976, and the Assistant Secretary for Health, Department of Health, Education and Welfare, dated January 19, 1977.

3. The funds contributed by A.I.D. will be used to support the travel and expenses of U.S. and Developing Country participants and for local workshop administrative costs.

The funds provided hereunder shall be administered by WHO in accordance with the terms and conditions provided herein. Upon depletion of Grant funds or expiration of this Grant, whichever occurs first, WHO shall execute the Grant Fiscal Report (Attachment No. 2), and forward it to A.I.D. Any funds disbursed to but not expended by WHO at the time of expiration of this Grant shall be refunded to A.I.D. Any interest on A.I.D.-granted funds shall accrue to and be paid to A.I.D.

4. Upon receipt of acknowledgement of this Grant, the funds provided by this Grant shall be deposited to WHO Account No. 015-002527, Chemical Bank, United Nations Office, New York, New York.

Sincerely yours,



Michael Snyder
Grant Officer
Central Operations Division
Office of Contract Management

WORLD HEALTH
ORGANIZATION



ORGANISATION MONDIALE
DE LA SANTE

1211 GENEVA 27 - SWITZERLAND
Télex: UNISANTE-Geneva

1211 GENÈVE 27 - SUISSE
Télex: UNISANTE-Geneve

Tél. 34 60 67 - Télé. 27821

1 Nov 1976

In reply please refer to TDR/M2/133/1
Pour le rappeler la référence:

Sir,

I have the honour to refer to the WHO/UNDP Special Programme for Research and Training in Tropical Diseases. The WHO Special Programme has two Scientific Working Groups in the field of malaria, one on the Chemotherapy of Malaria and the other on the Immunology of Malaria. ...
Summaries of the reports of the first meetings are attached. These groups met in November 1975 and July 1976 respectively. Both have established research programmes as well as Steering Committees which are to be instrumental in implementation and execution of the programmes. Both Scientific Working Groups have, in the context of their chemotherapeutic and immunological research, indicated the priority for establishing the in vitro cultivation of malaria parasites both as a means of producing parasite material and for the development of in vitro screening models. Basic information on the biology of the malaria parasite, i.e., biochemistry, metabolic pathways, antigenic components, anabolism and growth, penetration into host cells, host/parasite membranes, material and energy transfer that subsequently could be derived, may be indispensable to progress in these research programmes.

Recently considerable advances have been made by Dr W. Trager and by others in the in vitro cultivation of Plasmodium falciparum blood forms. While it is now possible to grow the parasite on a very modest scale,

The Assistant Secretary for Health
Department of Health, Education, and Welfare
Washington, D.C. 20201
U.S.A.

cc: The Secretary of State, Attention: IC-HDC, Department of State,
Washington

The Director, Office of International Health, Department of Health,
Education, and Welfare, Washington

United States Mission to the United Nations Office and other
International Organizations at Geneva, Attention: International
Health Attaché, Geneva

... ENCLS. (2)

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further efforts are required to develop these methods, especially with regard to the mass production of parasite material -- these are unlikely to succeed unless optimum growth and harvest conditions can be established. The latter again may depend on advances in our knowledge of the parasite's biology.

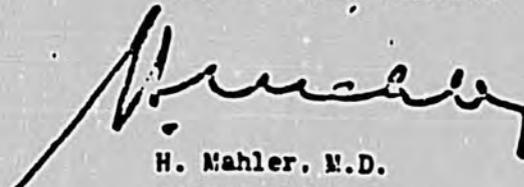
In this connection, it is proposed to hold two Workshops' on the Biology of the Malaria Parasite and on the in vitro Cultivation of Malaria Parasites. The Workshops would be held from 7-9 and 10-12 March 1977 respectively at the Rockefeller University, New York. It is understood that the United States Agency for International Development is interested in these particular Workshops and would be willing to consider financial assistance towards them. The expected allocation of the World Health Organization for this purpose is \$25,000. The funds are to be taken from extra-budgetary funds available to the Special Programme for Research and Training in Tropical Diseases. It is anticipated that the total cost of the two Workshops will amount to approximately US \$50,000 (see attached costing). Due to the already heavy demands on our budget, the Organization would find it difficult to obtain the total amount from our own resources. We are writing to enquire, therefore, if it would be possible for the USAID to make a one-time grant of US \$25,000 for this purpose.

The Government of the United States of America has, on many occasions in the past, contributed with special allocations towards projects of world-wide interest undertaken by the World Health Organization and I would like to take this opportunity to offer my thanks and appreciation for this assistance. I hope that your Government will give favourable consideration to our request for assistance.

I have the honour to be,

Sir,

Your obedient Servant,


H. Mahler, M.D.
Director-General

SUMMARY OF DISCUSSIONS

The Scientific Working Group set as its first objective a decision as to whether an intensive programme on antimalarial chemotherapy is or is not required. Considering the essential role that chemotherapy plays in both individual and community control of malaria, the evidence presented demonstrated that there was a real and urgent need for further research into malaria chemotherapy and its associated problems.

This Group started from a position of strength unlike research on chemotherapy of some other parasitic diseases, as a number of institutions and research groups, i.e. in universities and industry, have made considerable efforts towards improving the chemotherapy of malaria. In particular, the antimalarial drug development programme of the Walter Reed Army Institute of Research (WRAIR) is developing several new antimalarial drugs effective against multiple drug-resistant malarias. However, it was also recognized that this programme was not designed to produce agents suitable for use in a Mass Drug Administration (MDA) campaign.

The Group devoted attention to the identification of major gaps in our knowledge relative to malaria chemotherapy; it soon became evident that the state of ignorance on such fundamental matters as the mode of action on malaria parasite and host cell, and even the basic pharmacokinetics, of commonly used well-established antimalarial drugs such as chloroquine, pyrimethamine and primaquine is profound. A considerable amount of basic research directed to the development of new antimalarials is still needed in these areas, both in relation to currently used compounds and to newer drugs being prepared for or already in clinical trial. It was agreed that advances in technology in the broader biomedical field should now permit us to consider seriously both the improvement of existing compounds and the rational development of new ones. Despite the reluctance, that existed hitherto, to the use of drug mixtures in malaria, an advantage in the development of potentiating combinations is their value in minimizing the risk of the development of further drug resistant parasites.

Implicit in this approach to the development of new chemotherapeutic agents is the realization that scientists from the developing world should be involved to the greatest extent possible in all stages of the programme. At the same time, it is recognized that many research centres, for example in tropical Africa, require strengthening in skilled manpower, materials and resources. It is essential to integrate a major training element into the plan of operations wherever this is seen to be applicable, so that as far as possible the very people who at present carry the burden of parasitic diseases can make a greater contribution to the solution of their own problems. The Group recognized that involvement in malaria chemotherapy programmes would also be an excellent way of training young people of all nationalities for research in a wider area of biomedical research.

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OBJECTIVES

The objectives of the Group therefore become:

- (a) to develop new and improved chemotherapeutic agents to prevent and treat malaria; and
- (b) to strengthen research in the countries affected, by training of scientists and technicians in the relevant disciplines.

Basic approaches for developing chemotherapeutic agents require a good knowledge of the parasites and the mode of action of drugs or drug mixtures. It is recognized that the development and production of new chemotherapeutic agents will require time, and, as an interim measure, research aimed at a better understanding of existing antimalarials could lead to improvements in their activity.

Present basic research efforts are to be expanded beyond the restricted levels now possible, thereby bringing the disciplines of molecular biology and biochemistry to bear fruitfully on the field and to attract basic researchers who would not otherwise be involved. This will further understanding of fundamental malarial biology, of the mode of action of existing and future antimalarials, and the development of new therapeutic strategies.

SPECIFIC PROJECTS

Projects for early implementation were identified as follows.

Improvement of existing drugs already in clinical use to the following characteristics:

- causal prophylactic and tissue schizontocide
- blood schizontocide
- gametocyte sterilizing agent
- long-acting (longer than three months)
- safe and cheap

(For areas outside Africa, the drug or drug mixtures should also be active against drug-resistant P. falciparum and P. vivax.)

1. Programmed-release forms of existing drugs: (a) primaquine; (b) chloroquine.
 2. Development of long-acting drugs (more than three months residual action) (i.e. polymer incorporation, salts, chemical modifications): e.g. (a) pyrimethamine; (b) sulfa + sulphones; (c) primaquine; (d) 4-aminoquinolines; (e) quinazolines.
 3. Mouse efficacy test of 1/2.
 4. Simian test
 5. Synthesis of radio-labelled compounds.
 6. To investigate the nature of parasite-drug interactions an erythrocyte and hepatocyte culture method is needed.
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7. To investigate modes of action and drug resistance mechanisms of existing drugs in culture systems of in vitro erythrocytic stages and in vitro erythrocytic stages.

8. Preparation and isolation techniques in parasite biochemistry for coenzyme biosynthesis and phospholipid metabolism.

II Development of new drugs.

1. Further evaluation of: (a) mefloquine; (b) quinazoline and mixtures; (c) other compounds.

2. Develop long-acting form of most promising compounds.

3. Explore mixtures of new compounds: (a) potentiation; (b) prevention of resistance development.

4. Aotus screen for resistant P. falciparum. Test system development for gametocytocidal/sporontocidal screens.

5. Cercopithecidae screen for P. cynomolgi (Vivax type malaria), e.g. rhesus or veret

6. Design of receptor blocking agents.

7. Design of lysosomotropic drugs.

8. Lead-directed synthesis.

9. Computer aided structure activity analysis.

III Clinical studies

Phase I and II testing, and sporontocidal trials: can be conducted in Africa for drug-sensitive P. falciparum and for monitoring development of drug resistance; and in Asia, Americas for drug-resistant P. falciparum and for P. vivax.

Scientific Working Group on the Immunology of Malaria
Geneva, 8-14 July 1976

SUMMARY OF DISCUSSIONS

Malaria is recognized as a disease of major public health importance. The Group considered how knowledge of the immunology of malaria could be developed to obtain improved measures for control in populations of tropical countries. The most promising developments appear to be in the field of vaccines and diagnostic tests. Immunopathological consequences of malaria are known to be important, but further studies are required before practical measures for their prevention and treatment can be evolved.

Vaccines

There has been a marked change of view over recent years concerning the possibilities of developing vaccines against malaria. Former pessimism concerning such vaccines was based on the view that since natural infections did not induce complete immunity, vaccination was unlikely to succeed. Recent advances in knowledge of the immune response and, in particular, the demonstration of immunization of man and of various animal models against malaria have caused this view to be revised. The Group believes that vaccination against malaria is feasible and that the time is now appropriate for a major international collaborative effort to be made to develop and test such vaccines. This activity has the highest priority.

The Group examined recent evidence for different aspects of immunity to malaria, including immunity against merozoites, sporozoites and other stages, and evidence of non-specific immunity. They also noted recent successes in continuous in vitro cultivation of human malaria parasites which open up entirely new horizons for antigen production and research on vaccines. On the basis of present knowledge, they considered it unwise to assume that any one type of vaccine would necessarily be successful, so that research on all potential approaches should be undertaken in the following order of priorities:

1. The development of vaccines based on blood stage antigens - The effectiveness of such a vaccine has been demonstrated in a primate model. In vitro cultivation now opens the way to obtain sufficient material to prepare a vaccine. The major obstacle is the development of a suitable adjuvant for use in man; once this has been achieved and all necessary investigations have been undertaken on safety and efficacy, including studies in the most suitable primate models, such a vaccine would be available for clinical trial in man. This stage may well be achieved within the next five years.
2. The development of vaccines based on sporozoite antigens - In some respects, research on a sporozoite vaccine is more advanced since mosquito

inoculation of irradiated sporozoites has been shown to induce protection in man; adjuvants were not required in these experiments. The obstacle to sporozoite vaccination of large populations appears to lie in the development of in vitro culture techniques to produce sporozoites in adequate numbers. It will be necessary to evaluate the effectiveness of immunization of this type in affected populations.

Diagnostic Tests

Effective control measures for malaria require tests for recent infection, the status of immunity to infection, and transmission. There is now a reasonable prospect that such tests can be developed by selection of appropriate antigens and antibodies and the use of new serological techniques which are simple to perform. New tests should become available for field study within the next three years.

The Need for Broadly-Based Research

The Group recognized that there are many important gaps in knowledge of immunity to malaria, and considered that it would be wise to continue to develop research on immunity to malaria on a broad basis, including studies of the clinical immunology of the disease. The priorities proposed here reflect work required to achieve defined specific goals for the WHO programme. The pursuit of these goals should not adversely affect research on other aspects of the immunology of malaria.

SYMPOSIUM WORKSHOPS ON THE BIOLOGY OF MALARIA PARASITE AND ON THE
IN VITRO CULTIVATION OF MALARIA PARASITES, NEW YORK, 7-9 AND 10-12
MARCH 1977

Provisional Cost Estimate - Tourist Class Air Travel

11 participants from the U.K.	\$15,325
30 participants from the U.S.	12,095
2 participants from FRG	3,060
1 participant from Kenya	2,980
1 participant from Hungary	1,760
1 participant from India	3,270
1 participant from Panama	790
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47 participants	38,280
WHO Secretariat	3,978
Insurance	235
Refreshments for approximately 30 people for first meeting and 50 for second meeting	235
Rental of meeting rooms	2,090
Incidentals including projectionist and other special services	1,000
Documents	1,000
Contingencies	<u>2,182</u>
	<u>\$50,148</u>

**UNITED STATES OF AMERICA
AGENCY FOR INTERNATIONAL DEVELOPMENT**

GRANT FISCAL REPORT (Interim) (Final)

Grantee

Address

Grantor

Date

Address

Grant Number

Reporting Period

From (Day, Month, Year)

To (Day, Month, Year)

Item	Amount of Expenditures
1. Salaries and wages	\$
2. Equipment (major items) (list vessels in separate)	
3. Supplies, materials, and expendable equipment (itemize below)	
4. Travel	
5. Publication costs (Total-page costs, reprints, direct labor, etc.)	
(a) Page costs only, if available	\$
(b) Reprints, direct labor, and all other	
publication costs	
6. Other (specify)	
7. Total direct costs - Add lines 1 through 6	
8. Indirect costs	
9. Total expenditures -- Add lines 7 and 8	
10. Unexpended balance	

COMMENTS: (Continue on reverse side if necessary)

This fiscal report is correct and the expenditures included herein are deemed properly chargeable to the grant.

Typed Name and Title:

Signature:

Best Available Document