

PD = AAJ-428

ISN = 929

931-0453.2

July 29, 1980

49

PD-AAJ-428

ISN 929

ISN 671

**ACTION MEMORANDUM FOR THE DEPUTY ASSISTANT ADMINISTRATOR
FOR HUMAN RESOURCES DEVELOPMENT**

FROM: DS/HEA, John Aiden

Problem: Approval of a PAF amendment to a contract with the New York University under project number 931-0453.02, Malaria Immunity and Vaccination Research.

Discussion: The subject amendment to this activity was reviewed and approved at the October 29-30, 1979 meeting of the Research Advisory Committee. The RAC recommended modifications and reduction in the proposed budget have been considered and included in the present proposal. Authority for funding above the amount shown in the current budget is requested because we anticipate an increase in University overhead rates sometime in the near future. (FY 80 funding authorization of \$26,000 rather than the \$23,000 shown in the budget and FY 81 approval for \$130,000 rather than the \$108,000 shown in the budget.) The initial PIO/T will be submitted for the amount shown in the budget but the need for additional funding may emerge during the contract negotiation. Copies of the RAC recommendation and the Action Memorandum for the Administrator are attached.

Funds for the activity are included in the FY 1980 Congressional Presentation and the FY 1980 OYB for the Office of Health. The proposed project modification and expansion has been reviewed and approved by the following:

Office of Health (DS/HEA)
Program Office (DS/PO)
DSB Project Review Committee
Research Advisory Committee (RAC)

The proposal has been found to be technically sound and to meet all the requirements of an unsolicited proposal contained under AID PR 78.4.

Recommendation: That you sign the attached PAF amendment.

Attachments:

PAF, with attachments

Clearance:

DS/PO, B. Chapnick *Allen* Date 8/1/80
h

AGENCY FOR INTERNATIONAL DEVELOPMENT

PROJECT DATA SHEET

1. TRANSACTION CODE

A = Add
 C = Change
 D = Delete

Amendment Number

1

DOCUMENT CODE

3

2. COUNTRY/ENTITY

Interregional

3. PROJECT NUMBER

931-0453.02

4. BUREAU/OFFICE

DS/HEA

10

5. PROJECT TITLE (maximum 40 characters)

Malaria Imnty & Vacntn Rsrch7 (NYU)

6. PROJECT ASSISTANCE COMPLETION DATE (FACD)

MM DD YY
 10 3 1 83

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

A. Initial FY 79 B. Quarter 4 C. Final FY 81

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

A. FUNDING SOURCE	FIRST FY 79			LIFE OF PROJECT		
	B. FX	C. L/C	D. Total	E. FX	F. L/C	G. Total
AID Appropriated Total	299		299	1105		1105
(Grant)	(299)	()	(299)	(1105)	()	(1105)
(Loan)	()	()	()	()	()	()
Other U.S. 1.						
Other U.S. 2.						
Host Country						
Other Donor(s)						
TOTALS	299		299	1105		1105

9. SCHEDULE OF AID FUNDING (\$000)

A. APPRO- PRIATION	B. PRIMARY PURPOSE CODE	C. PRIMARY TECH. CODE		D. OBLIGATIONS TO DATE		E. AMOUNT APPROVED THE ACTION		F. LIFE OF PROJECT	
		1. Grant	2. Loan	1. Grant	2. Loan	1. Grant	2. Loan	1. Grant	2. Loan
(1)	540	542				155		1105	
(2)									
(3)									
(4)									
TOTALS						150		1105	

10. SECONDARY TECHNICAL CODES (maximum 8 codes of 3 positions each)

11. SECONDARY PURPOSE CODES

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

A. Code

B. Amount

13. PROJECT PURPOSE (maximum 400 characters)

Research on Sporozite-Induced Immunity in Simian Malaria-
 use of hybridoma for the characterization of protective sporo-
 zoite antigens.

14. SCHEDULED EVALUATIONS

15. SOURCE/ORIGIN OF GOODS AND SERVICES

MM YY MM YY MM YY
 0 6 8 1 0 6 8 2 005 041 Local Other (Specify)

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

This amendment supplements the current project to allow for an expansion of the scope of work to include the use of hybridoma technology for the characterization of protective sporozoite antigens. The total supplemental amount for the grant \$156,000 over a period of approximately 17 months.

This funding supplement was reviewed and approved by the Research Advisor Committee (RAC) at its October 29-30, 1979 meeting. RAC requested modification in budget have been incorporated into this funding request.

17. DATE DOCUMENT RECEIVED

July 29, 1980

PROJECT AUTHORIZATION AND REQUEST FOR ALLOTMENT OF FUNDS

PART II

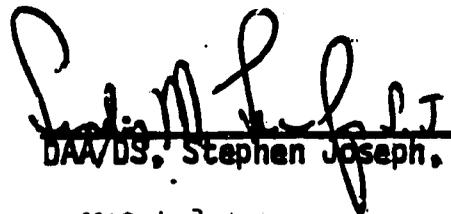
Entity: DS/HEA/M

Project: Malaria Immunity and Vaccination, Sub-project with New York University

Project Number: 931-0453.02

I hereby authorize an additional \$26,000 of FY 1980 funds to supplement the current contract with New York University to conduct research on the use of hybridoma technology for the characterization of the protective antigens of the sporozoite stage of malaria parasites. The \$26,000, when added to the \$315,000 of FY 80 funds and \$299,000 of FY 79 funds previously authorized will fund the project through 1980.

I approve an increase of one hundred fifty-six thousand dollars (\$156,000) to a new total of not to exceed one million one hundred and five thousand dollars (\$1,105,000), including the previous funding, during the period FY 1979 through FY 1981. I approve further increments during the period of the contract up to four hundred sixty-five thousand dollars (\$465,000), subject to the availability of funds in accordance with A.I.D. allotment procedures.


DAA/DS, Stephen Joseph, M.D.

AUG 1 3 1980

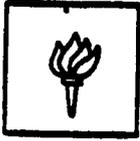
Date

Attachments:

- A. Supplemental Request
- B. IEE
- C. RAC Recommendation
- D. Action Memorandum

Clearances:

DS/HEA, J. Alden my date 7/29/80
DS/PO, B. Chapnick my date 8/1/80
DS/PO, M. Rechcigl draft date 8/1/80



NEW YORK UNIVERSITY MEDICAL CENTER

School of Medicine

350 FIRST AVENUE, NEW YORK, N.Y. 10016

AREA 212 679-3200

CABLE ADDRESS: NYUMEDIC

Division of Parasitology
Department of Microbiology

October 2, 1979

Dr. James Erickson
Agency for International Development
(DF-HEA), Room 5000
Office of Health
Washington, D.C. 20523

Dear Dr. Erickson:

Enclosed please find the request for support of the hybridoma work, and the corresponding budget.

I hope this format meets with your approval. If this information is not sufficient, I would modify it accordingly.

I will call you on Friday, October 5th to discuss this further.

Sincerely,

R.S. Nussenrweig, M.D., Ph.D.
Professor and Head
Division of Parasitology

RSN:shp
Encl.



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Division of Parasitology
Department of Microbiology

October 2, 1979

Dr. James Erickson
Agency for International Development
Office of Health
(DF-HEA), RPE
Washington, D.C. 20523

Dear Dr. Erickson:

I would like to state my position regarding the overall funding of the presently proposed hybridoma work as applied to the characterization of the protective sporozoite antigen(s). It is devastating to be suspected of requesting duplicate funding even though there is no basis for such an accusation.

I have decided against applying for funds from any other sources for this hybridoma methodology before a decision has been reached by A.I.D. later this month. Consequently, I have missed both the current N.I.H. and W.H.O. grant application deadlines. I have taken this decision because I am most hopeful that no further applications will be necessary, and that the A.I.D. will approve this amendment to my contract.

On Dr. Edgar Smith's advice, and through Dr. Richard Beaudoin, I did apply to the U.S. Navy at the end of July of this year, when it became apparent that I was running a deficit, and that the A.I.D. supplemental funding request would not be forthcoming in July or August. At that time, Dr. Beaudoin felt that a decision from the Navy would be a matter of only a few weeks, and that funding could be initiated early this Fall and that it could only be approved for one year. As far as I was concerned it was a stop-gap measure only. In the meantime I have not heard from the Navy. I would now only accept the Navy award—should it be approved—if there were further delays in funding from the A.I.D.

I am conveying this information to you so that there is no further misunderstanding as to the status of my funding.

Thank you for all your kind consideration.

Sincerely,


Ruth S. Nussenzweig, M.D., Ph.D.
Professor and Head

Proposed Amendment to

Agency for International Development, Washington D.C.

Title: Sporozoite-Induced Immunity in Simian Malaria -
Use of Hybridoma for the Characterization of
Protective Sporozoite Antigen(s)

Desired Starting Date: October 1, 1979

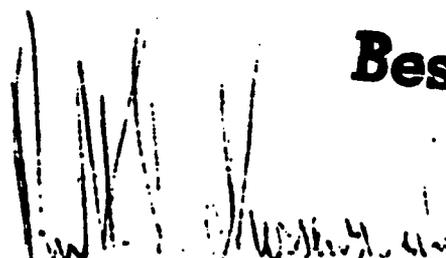
Duration of Support: 27 months

Principal Investigator: Ruth S. Nussenzweig, M.D., Ph.D.
Professor
Head
Division of Parasitology
Department of Microbiology
New York University Medical Center
550 First Avenue
New York, New York 10016

Social Security No.: 128-40-5431

Telephone No.: (212) 679-3200,
Ext. 2973, 2970

Best Available Document


Ruth S. Nussenzweig, M.D., Ph.D.
Professor and Head
Division of Parasitology

Thomas A. Fitzgerald, Director
Office of Grants Administration
and Institutional Studies

Best Available Document

Research Outline

We have recently obtained a series of important new findings, which have permitted us to obtain unlimited amounts of protective monospecific antisporozoite antibodies directed against a defined sporozoite surface antigen.

These findings were obtained by using a new, powerful immunological approach, i.e. the hybridoma technique, which we had not foreseen using when we applied for our ongoing A.I.D. contract last year. This technology, however, has turned out to enormously advance one of the research objectives of our current contract, namely, 'the characterization of the surface antigen(s) of sporozoites' as stated in Item 3, page 5, of our approved research proposal.

These recent findings were reported in full detail to two A.I.D. site visiting teams (August 17, and September 19-20, 1979), and are the subject of a publication entitled, "Hybridoma produces protective antibodies directed against the sporozoite stage of malaria parasites" written by N. Yoshida, R.S. Nussenzweig, M. Aikawa, P. Potocnjak and V. Nussenzweig (Science, in press).

The results of this approach can be summarized as follows:

Hybrid cells secreting antibodies against sporozoites of P. berghei were obtained by fusion of plasmacytoma cells with immune murine spleen cells. The monoclonal antibodies bound to a protein with an apparent molecular weight of 44,000 (Pb44), which envelops the surface membrane of sporozoites. In vitro incubation of sporozoites with antibodies to Pb44 abolished their infectivity.

Furthermore, we have found that (a) 3D11 tumour-bearing mice are protected against sporozoite challenge; (b) passive transfer of either the serum of these animals, or purified monoclonal antibodies protects recipients against sporozoite challenge and (c) these antibodies are of the γ_1 class of immunoglobulin.

We are therefore presently purifying relatively large amounts of this mono-specific antibody from the ascitic fluid of 3B11 inoculated mice - antibody which will be used to isolate the protective antigen present in sporozoite extracts. This should permit the further immunochemical characterization of the protective sporozoite antigen(s) and to verify if, and under what conditions, the isolated antigen(s) is able to induce protection.

Exploratory work on the hybridoma in the P. berghei-rodent system, should facilitate the hybridoma approach for the investigation of surface antigen(s) of simian and human malaria sporozoites. We plan in fact to attempt to obtain monoclonal antibodies against sporozoites of P. knowlesi and P. falciparum in the near future.

In order to permit us to continue the hybridoma work, and to fully explore the enormous potential of this approach for the development of a sporozoite vaccine, we request an amendment to our ongoing A.I.D. contract.

Justification of the budget request

The needs for the hybridoma work are the same for the entire contract period, i.e., two years, and three months covered by this request. It is a very laborious approach which demands research and technical personnel for the tissue culture work, assaying of supernatants, cloning and in vivo maintenance of the hybridoma. It also involves considerable additional work in obtaining large numbers of purified sporozoites for labeling, purification of antigen, etc.

At present, the two researchers most involved (100% of their time in this project) are being paid from international sources. Dr. N. Yoshida has a Brazilian

Research Council Post-Doctoral Fellowship, and Dr. Pedro Potocnjak has a World Health Organization Training Fellowship which terminates October, 1980. Therefore, as of November, 1980, and during the entire following year, Dr. Potocnjak's salary will have to be covered from these research funds.

An additional, rather large expenditure for the year 1981, essentially unrelated to hybridoma, derives from the fact that Dr. Robert Gwadz (N.I.H.) will have to change the framework of his collaboration with us on the P. knowlesi immunization work. The Malaria Division (N.I.H.) foresees considerable limitation of their capacity to provide us with A. balabacensis mosquitoes. This is due to the projected move of the Malaria Division of the Laboratory of Parasitic Diseases in 1981, and the consequent restriction of their insectary facilities. These A. balabacensis mosquitoes - which have to be force-mixed - will, therefore, be bred and infected in our insectaries. This demands considerable additional technical help, budgeted for 1981.

In order to avoid considerable disruption of our research, I would be very grateful for a prompt decision on this request, and if favorable, for its activation at the earliest possible date.

Estimated Budget -- Supplemental Request

AID/DSPE-c-0031

	<u>8/15/80- 12/31/80</u>	<u>01/01/81- 12/31/81</u>
Personnel	6376	43000
Fringe--18%	1148	7783
Overhead--52% STW	3912	26661
Animal & Insectary Ccsts	4300	10000
Maintenance of Insectary	3200	10000
Maintenance of Animal Facility	1115	3500
Supplies	1972	6000
Publications	<u>600</u>	<u>600</u>
	22623	107544

Grand total \$130,167.

Attachment #13
to F.A.F.

ENVIRONMENTAL THRESHOLD DETERMINATION

TO: AA/DS, Mr. Sander Levin
THRU: OS/PPU, Mr. John Gunning
FROM: OS/H, Lee Howard, M.D.
SUBJECT: Environmental Threshold Determination

Project Title: Malaria Immunity & Vaccination
Project #: 931-0453
Specific Activity (if applicable)
REFERENCE: Initial Environmental/Examination (IEE) contained in Smith to Howard memo dated January 24, 1978

On the basis of the Initial Environmental/Examination (IEE) referenced above and attached to this memorandum I recommend that you make the following determination:

- X 1. The proposed agency action is not a major Federal action which will have a significant effect on the human environment.
- 2. The proposed agency action is a major Federal action which will have a significant effect on the human environment, and:
 - a. An Environmental Assessment is required; or
 - b. An Environmental Impact Statement is required.

The cost of and schedule for this requirement is fully described in the referenced document.

 3. Our environmental examination is not complete. We will submit the analysis no later than _____ with our recommendation for an environmental threshold decision.

Approved: _____
Sander M. Levin
Disapproved: _____

Health and Population

Sporozoite-Induced Immunity in Simian Malaria - Use of Hybridoma for the Characterization of Protective Sporozoite Antigen(s) (Project Augmentation) - New York University. Duration of expansion, 27 months; estimated additional cost, \$203,318.

Project Summary and Background: This proposal is to amend an ongoing project in the network of projects for the development of an anti-malaria vaccine. Additional funds are required to take advantage of new discoveries made possible by a powerful new immunological technique. The technique is based on the observation that mice which have been inoculated with a tumor causing substance have been found to be protected from the sporozoite stage of the malaria parasite. Large amounts of the antibody containing the protective antigen can now be produced from inoculated mice. This will permit the researcher to carry out the further immunochemical characterization of the antigen and to verify if, and under what conditions, the antigen is able to induce protection.

The RAC strongly supported the proposed amendment to the project. The principal investigator was described as one of the most productive scientists in the anti-malaria vaccine network and is the head of the only group working on this particular approach to malaria immunity. The amendment to the project was found to be fully justified by the new developments. The proposed additional work, if successful, should have high utility throughout the network of institutions involved in the development of the anti-malarial vaccine.

RAC Recommendation: That the request for supplementation of current support for sporozoite vaccine research be approved to permit exploitation of new discoveries stemming from application of the hybridoma technique. Specifically, it is recommended that the additional funding at an annual level of \$83,945 plus overhead be provided. This deletes the \$15,000 requested for replacement of NIH insectary services - a contingency that may not materialize.

Related Research Projects Funded by AID: This project is one of two in the network focusing on a mosquito stage (sporozoite) vaccine and is currently the only project utilizing the hybridoma technology to isolate and produce sporozoite antigenic material. Each of the remaining projects in the network deals with a separate aspect of the blood stage (merozoite) of the malarial parasite. Research on both stages is essential to the development of a polyvalent vaccine for use by humans in endemic malarious areas. Related research projects are listed below:

In Vitro Production Methods of Human Malaria Parasites (New York University)
This project focuses on the Sporozoite stage of malaria.

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Evaluation of Blood Stage Antigens (University of New Mexico)

Cultivation of Human Malaria Parasites (Rockefeller University)

In Vitro Cultivation of Malaria Parasites (University of Hawaii)

Merozoite Antigen Vaccine Research and Development (Parke-Davis Co.)

In Vitro Cultivation of Malaria Parasites in Cell Culture (Parke-Davis Co.)

In Vitro Cultivation of Malaria Parasites (Gorgas Memorial Institute)

Primate Studies in Central and South America Contributing to Development of a Malaria Vaccine (Instituto Nacional de Salud - Bogota, Colombia)

DB Notes

January 10, 1980

~~RESPECTIVE SECRETARIES~~
ACTION MEMORANDUM FOR THE ADMINISTRATOR

COB8 also approved
Mar. 7, 80
DB

THRU: ES *Randy*
FROM: AA/DS, Sander Levin

Problem: Your approval is requested for the implementation of three research projects along the lines of recommendations of the AID Research Advisory Committee (RAC).

Discussion: We are submitting for your approval three research projects following the recommendations of the RAC which reviewed the project proposals at its meeting on October 29-30. One proposal is for a new project and two proposals are for the extension of ongoing activities. All of these projects are included within the program activities described in the FY 80 Congressional Program Presentation. All three research projects have been approved by the regional bureaus. A list of the projects and funds proposed for their implementation is attached (TAB A).

Appended at TAB B are for each project: a summary of the project with a brief statement on the substance of RAC discussion, the RAC recommendation. As per your request of August 17, information on related research is provided for each project.

In brief, the RAC endorsed one project as proposed, recommended approval of two projects subject to specified modifications and conditions, and recommended rejection of a fourth project. The RAC also recommended support for a newly proposed project from Michigan State University on the isolation and purification of malaria antigens which has not been budgeted for this year funding. We basically agree with the RAC recommendations regarding the first three projects and shall incorporate them into the Project Authorizations (PAFs) to be approved by the sponsoring bureaus. Regarding the fourth project, DSB is reviewing the record and will recommend a course of action shortly.

The initial environmental examinations (IEEs) for the three recommended projects have been completed and threshold determinations have been made by the respective Bureaus that none of these projects will have a significant effect on human environment.

This report is for fund review & authorization - King

In addition to reviewing specific project proposals, RAC was also requested to review the DHEW proposed regulations relating to Protection of Human Research Subjects. The Committee's comments and recommendations regarding this point are provided in TAB C. DSB, PPC and GC will be reviewing the RAC recommendations on this subject and will advise you of the results of that review.

Your approval of the three projects listed at TAB A constitutes the authorization to initiate negotiation of contracts pursuant to the RAC recommendations in accordance with applicable provisions of AID Procurement Regulations and Procedures and as required by PI-47 (Supp. A ZB1, September 1972).

Recommendation: That you approve the implementation of three RAC endorsed projects listed at TAB A.

APPROVED: _____
DISAPPROVED: _____
DATE: Feb 14

Attachments:

- TAB A - List of Projects and Funds Proposed for Implementation
- TAB B - Project Summaries with RAC Recommendations
- TAB C - RAC statement on the proposed DHEW Regulations Relating to Protection of Human Research Subjects

Clearances:

GC: NHolmes *WHA* Date *12/20/79*
 GC/TFEA: ARichstein *ARC* Date *12/17*
 AA/PPC: AShakov *AS* Date *12/17*
 DS/DAA/FR: EBabb *EB* Date *12/6*
 DS/DAA/FRD: SJoseph *SJ* Date *12/5*
 DS/PO: BChapnick *BC* Date *1/5*

UP
DS/PO/RES: Rrechigl:cev:11/14/79

*Approved 0633 and
 filed on DSB +
 [unclear]
 [unclear]
 [unclear]
 [unclear]
 14*

Project	Funding Proposed for Authorization	Period Proposed for Authorization
<u>A. Endorsed as Proposed</u>		
0633 Fortification of Sugar with Iron: Field Study Prior to Implementation at a National Level - Pan American Health Organization	\$ 310,000	1 year
<u>B. Endorsed with Modifications or Conditions</u>		
0453 Sporozoite-Induced Immunity in Simian Malaria - New York University	\$ 202,318 ^{1/}	27 months
0068 The Family in Economic Development; Promoting Growth through People - The Rand Corporation	\$1,814,879 ^{1/}	3 years
<u>C. Not Endorsed</u>		
0625 Effects of Protein-Calorie Interventions on Human Growth, Mortality and Morbidity - Pan American Health Organization	\$1,500,000 ^{2/}	2 years

In view of the RAC recommendations, the budget may be reduced.

RAC estimated the limit cost of \$306,000 for a 6-month phase-out.

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