(C O P Y)

UNIVERSITY OF CINCINNATI
COLLEGE OF MEDICINE

Mailing address:
Radioisotope Laboratory
K-4 General Hospital
Cincinnati 29, Ohio

November 24, 1950

Dr. Donald E. Scantlebury
Executive Secretary
Physiology Study Section
National Institutes of Health
Bethesda 14, Maryland

Reference: Your H-925

Dear Dr. Scantlebury:

The following information is submitted to cover the 3 points raised in your letter of November 15th, in regard to my application H-925.

"1. A letter from the Atomic Energy Commission that permission will be granted to use the isotopes requested (iodine-131) for the purpose indicated:"

1. In our original permit from the Atomic Energy Commission for the use of radioactive iodine-131, we are permitted to use iodine-131 for tracer studies in infants and children, giving one microcurie per kilogram of body weight. Our application and permit did not define whether such a dose would be given orally or intravenously, and no limitation was made by the Atomic Energy Commission as to the route of administration. At least 95% of this dose is absorbed into the blood. In developing this project further it now appears desirable to give the iodine-131 as radioactive di-iodofluorescein or as radioactive iodinated human serum albumin, since there will be a smaller uptake by the thyroid which will be chemically blocked before making the test. Applications for such studies are now pending with the Atomic Energy Commission. I will notify you as to the outcome as soon as possible.

In human adults approximately 35-50 microcuries of radioactive iodinated human serum albumin are used. Since radioactive di-iodofluorescein has a biological half life of 2 - 3 days as compared to a biological half life of 6.5 for radioactive sodium iodide, safe ranges for infants and children can be approached easily.

"2. Have any studies been carried out on your animals, i.e. puppies, to get a preliminary indication of the dosage required for adequate detection with your equipment:"

2. No studies as yet have been carried out on animals. One of the chief purposes in requesting this grant is to develop detecting devices which are more directional and more sensitive than the currently

available Geiger tubes. These tubes at present have large windows and if of the "needle" type are rather insensitive with high background counting rates. Geiger tubes in general have sensitivities for gamma radiation of 0.1 to 0.3% of all gamma photons, whereas scintillation counters have 30 - 40 times this sensitivity. It is planned to develop small phosphors of 3 - 6 mm. in diameter which will be quite long in relation to their diameters, so that a highly directional probing counter will be obtained. Such detecting devices should permit the use of tracer doses of about 10% the present doses which are based in part on detection by Geiger counters.

Preliminary studies of the method on puppies and dogs, approximating human infant size, will be done.

"3. A question that arose, was, in what way will the proposed method be better than existing methods of measuring circulation time in children. A statement from you on this point should be helpful:"

3. The measurement of circulation times in children by present methods is adequate only if the child is well able to cooperate and is not crying or struggling. Such methods as decholin, cyanide and ether times depend largely on subjective cooperation and hence are valueless in infants and children under the age of three years. The fluorescein method does not have a sharp end point, and also the end point is subjective to the observer and may vary with individual observers. It is our desire to develop a method of measuring circulation times which is completely objective. Also by using several detectors, several end points can be recorded simultaneously. In addition the blood volume can be determined.

The problem of accurate diagnosis of congenital heart disease in infants and children under the age of three is especially difficult, and this study will help to improve our diagnoses. We have available many patients with abnormal hearts at the Children's Hospital and our circulation time studies will be correlated with the findings of angiocardiography, cardiac catheterization, surgery and autopsy.

Respectfully submitted,

/s/ Eugene L. Saenger

Eugene L. Saenger, M.D., Director
Radioisotope Laboratory
Asst. Professor of Radiology

ELS:L

FEDERAL SECURITY AGENCY
PUBLIC HEALTH SERVICE

APPLICATION FOR GRANT-IN-AID
Rec. 6/2/50

NUMBER: C 396(C3)

No S.S.

Date May 1, 1950

(Extension Application for Grant C-396(C2))

Application is hereby made for a grant-in-aid in the amount of $ 117,207.43 (Rq) for the period from January 1 1951 to December 31 1951, inclusive,

TITLE OF PROJECT

Physiology of patients with cancer and experimental therapy of cancer

TITLE OF PRINCIPAL INVESTIGATOR	NAME OF PRINCIPAL INVESTIGATOR
Dean of the Medical School and Professor of Pediatrics	Dr. Francis Scott Smyth

ADDRESS OF PRINCIPAL INVESTIGATOR
University of California School of Medicine
Medical Center, San Francisco 22, California

TITLE OF FINANCIAL OFFICER TO WHOM CHECK SHOULD BE MAILED	NAME OF FINANCIAL OFFICER
Vice-President - Business Affairs	Mr. James H. Corley

ADDRESS OF FINANCIAL OFFICER
250 Administration Building, University of California,
Berkeley 4, California

Name of institution University of California School of Medicine

(Name and title of official authorized to sign for institution) Robert G. Sproul
President of the University

Form No. 68 - 12/49

PAGE 1

COPIED: 4/19/94
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NUMBER (Do not write in this space) G 396(C3) Ho S.S.

(a) Budget proposed for the year 1/1/52 through 12/31/52 (This date to be the same as those given on page 1)

ITEM	FUNDS REQUESTED FROM THE PUBLIC HEALTH SERVICE	FUNDS FROM OTHER SOURCES
PERSONNEL (Itemize all positions; give names of professional personnel, if available)		
See attached breakdown	$ 68,223.90	$ 8,940.00
PERMANENT EQUIPMENT NEEDED (Itemize)		
None	—	—
CONSUMABLE SUPPLIES NEEDED (Itemize)		
See attached breakdown	17,554.00	7,060.00
TRAVEL		
None	—	—
OTHER EXPENSE (Itemize)		
Contractual, for bed space: Reimburse Laguna Honda Home 15 patients @ $4.10 per day, 365 days	22,347.50	—
SUBTOTAL	108,525.40	(RA) x x x x x x x x
OVERHEAD (Not to exceed 5% of subtotal)	5,662.03	(RA) x x x x x x x
TOTAL FOR THE YEAR	$ 117,207.43	(RA) $ 16,000.00

(b) Estimate of future requirements:

First additional year $ 115,000.00 Third additional year $ 120,000.00

Second additional year $ 120,000.00 Fourth additional year $ 120,000.00

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APPLICATION FOR GRANT-IN-AID C-396(02)

NUMBER: (Do not write in this space) C 396(C3)

No S.S.

Budget proposed for the year 1/1/51 through 12/31/51

PERSONNEL (1(a) cont.)

		Per Mo.	Per Annum	Total
Ward Nurses:				
Day Duty	(4)	220.00	2,640.00	10,560.00
Night Duty	(4)	230.00	2,760.00	11,040.00
Dietitian	(1)	260.00	3,120.00	3,120.00
Ward Helpers	(3)	175.00	2,100.00	6,300.00
Orderlies	(4)	190.00	2,280.00	9,120.00
Kitchen Helpers	(3)	173.50	2,082.00	6,246.00
Secretary	(1)	200.00	2,400.00	2,400.00
Janitor	(1)	185.00	2,220.00	2,220.00
The above represents the actual number of people on our personnel rolls. The per annum figure represents the entrance salary for a beginning employee. No professional (M.D. or Ph.D.) personnel are employed on these funds.				(51,006.00)

Allowance for yearly honor merit increase for personnel:

Nurses	1,800.00
Dietitian	120.00
Ward Helpers	720.00
Orderlies	840.00
Kitchen Helpers	720.00
Secretary	360.00
Janitor	240.00
This figure represents increases already in effect and for increases anticipated for the period of this budget.	(4,800.00)

General Assistance:

Relief Dietitian (1)	(yearly basis) @ $1,269 hr.	960.00
Dietitian, relief	(1 mo. period) @ $1,269 hr.	220.00
Kitchen Helper, relief	(3 mo. period) @ $1.001 hr.	520.50
Ward Helper, relief	(3 mo. period) @ $1.010 hr.	525.00
Orderly, relief	(3 mo. period) @ $1.096 hr.	570.00

Allowance for accumulated vacation leave for personnel on permanent status (based on 1 month period):

Nurses	(8)	1,800.00
Dietitian	(1)	270.00
Ward Helpers	(3)	585.00
Orderlies	(4)	820.00
Kitchen Helpers	(3)	581.00
Secretary	(1)	230.00
Janitor	(1)	205.00
		(7,286.50)

Matching contributions to the State Employees Retirement System at 8% of total gross non-academic salaries, plus a $4.00 service charge for each participant.	5,047.40 84.00 (5,131.40)

TOTAL..... $68,223.90

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APPLICATION FOR GRANT-IN-AID

0-396(02)

0-396(03)

No S.S.

Budget proposed for the year 1/1/51 through 12/31/51

CONSUMABLE SUPPLIES NEEDED (1(a) cont.)

	Total
Supplemental food for diets:	
15 patients @ $0.65 per day, 365 days	3,559.00
Drugs, including fluids, antibiotics, heparin	8,219.00
Surgical Dressings	1,278.00
Kitchen Equipment, expendable	230.00
Glassware, syringes, surgical supplies, catheters	1,526.00
Surgical Instruments, enamelware, replacement items for permanent equipment on hand	841.00
X-ray film, photographic supplies	552.00
Linen replacements	774.00
Household supplies (soap, paper towels, lysol, etc.)	627.00
Minor repairs and maintenance of equipment	248.00
Total.....	$17,854.00

These items are based on actual expenses incurred during past full year of operation. No additional permanent equipment is requested. Many items not covered by this request for the operation of the research ward are to be covered by the anticipated grant from the University of California of $16,000.

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APPLICATION FOR GRANT-IN-AID

C-396(02)

C 396(03)

No S.S.

BUDGET SUMMARY COMPARISON SINCE ESTABLISHMENT OF RESEARCH WARD

	C-396(01) 1948 1/	C-396(03) 1949	C-396(02) 1950	C-396(03) 1951
Personnel.....	35,150.56	54,111.00	60,732.00	68,223.30
Permanent Equipment.....	14,196.00	2,877.50	—	—
Consumable Supplies.....	5,500.00	14,495.00	12,743.00	17,854.00
Contractural-Bed space..	18,246.50	18,450.65	20,422.00	22,447.50
Other Expenses.....	400.00	—	—	—
Overhead.....	5,879.44	7,194.73	7,511.76	8,682.03
Total.....	$79,372.50	$97,128.88	$101,408.76	$117,207.43 2/

1/ The research ward was actually opened on July 6, 1948.

2/ As seen from the budget, the increase of $15,798.67 is due to three major factors: (a) merit and other increases in salaries, as authorized by the University, plus the State Employment Retirement System contributions, as agreed by the United States Public Health Service and the Secretary of the Regents of the University of California, (b) increased cost of reimbursement for beds to Laguna Honda Home from $3.72 to $4.10 per day per bed, and, (c) an additional $5,000.00 is requested for drugs such as antibiotics, fluids, etc., which were underestimated last year.

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C 396(03) No S.S.

all support, including that from own institution, on this or related research projects from sources other than Public Health Service

TITLE OF PROJECT	SOURCE	AMOUNT	YEARS OF SUPPORT (From ___ to ___)
VIOUS			
Laboratory	Univ. of California School of Medicine	$ 3,000.00	1/47 - 6/30/47
Research Ward	Univ. of California State Funds	28,000.00	11/47 - 6/30/48
Laboratory	Univ. of California School of Medicine	3,000.00	7/1/47 - 6/30/48
Research Ward - Isotope Unit	Univ. of California State Funds	7,000.00	11/47 - 6/30/48
Research Ward - Pathology Unit	Univ. of California State Funds	10,000.00	11/47 - 6/30/48
Research Ward	Univ. of California State Funds	12,500.00	7/1/48 - 6/30/49
Laboratory	Ditto	4,500.00	7/1/48 - 6/30/49
Research Ward - Isotope Unit	Ditto	9,500.00	7/1/48 - 6/30/49
Research Ward - Pathology Unit	Ditto	7,000.00	7/1/48 - 6/30/49
CURRENT			
Research Ward and Laboratory	Univ of California State Funds	15,000.00	7/1/49 - 6/30/50
Research Ward - Isotope Unit	Ditto	7,400.00	7/1/49 - 6/30/50
Research Ward - Pathology Unit	Ditto	11,000.00	7/1/49 - 6/30/50
arch Ward	Damon Runyon Fellowship	500.00	7/1/49 - 6/30/50
NDING			
Research Ward and Laboratory	Univ. of California State Funds	16,000.00	7/1/50 - 6/30/51
Research Ward - Isotope Unit	Ditto	5,000.00	7/1/50 - 6/30/51
Research Ward - Pathology Unit	Ditto	11,000.00	7/1/50 - 6/30/51

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0-396(03) No 3.3.

previous and current Public Health Service grants in support of this project

GRANT NUMBER	TITLE OF PROJECT	AMOUNT	YEARS OF SUPPORT From To
ous			
l.Cancer Inst.	Direct Allocation - Laboratory	51,500.00	1/1/47 - 6/30/47
l.Cancer Inst.	Direct Allocation - Laboratory	94,594.58	7/1/47 - 6/30/48
396(2)	Research Ward	78,372.50	3/1/48 - 12/31/48
l.Cancer Inst.	Direct Allocation - Laboratory	117,525.00	7/1/48 - 6/30/49
396(3)	Research Ward	83,064.20	1/1/49 - 12/31/49
396(03)	Research Ward	12,064.66	1/1/49 - 12/31/49
ent			
l.Cancer Inst.	Direct Allocation - Laboratory	113,000.00	7/1/49 - 6/30/50
396(02)	Research Ward	101,408.76	1/1/50 - 12/31/50
ount shown includes 8% overhead			

OPOSED PLAN

Specific aims of project.
Method of procedure.
Relationship of anticipated results to general problems in field.
Facilities available including list of major items of permanent equipment.

Previous work done on this or closely related projects by the investigator(s).
Most important publications of investigator(s) pertaining to this problem.

Results bearing on this project obtained by other investigators.
Publications of other investigators related to this proposed project.

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APPLICATION FOR GRANT-IN-AID

4. PROPOSED PLAN (Continuation Sheet)

NUMBER: (Do not write in this space)
C 396(C3)
No S.S.

4(a). Specific Aims of Project. The specific aim of the project is clinical research in cancer. With the cancer patient as the focal point of the investigations, the work is oriented along four broad approaches: (1) Experimental therapy, providing clinical material for other studies as well as permitting evaluation of such procedures on neoplastic diseases; (2) Physiology, particularly cardiovascular and respiratory physiology of patients with neoplastic diseases; (3) Biochemistry, including metabolic studies on cancer patients, and investigations of specific biochemical reactions; and, (4) The study of protein fractions of cancer and normal tissues of human and animal origins, utilizing physicochemical and immunochemical techniques.

4(b). Method of Procedure. Patients for investigation are selected through the Consultative Tumor Board of the University of California School of Medicine, by referral of physicians of the Bay Area. Such patients as are not applicable for curative therapy by surgery or irradiation are evaluated for their applicability to experimental procedures. For admission to the research ward, each patient signs a release which indicates that the patient understands that he will be used for experimental work, and that he agrees to this and to a necropsy (See attached Release Form). Each patient receives a full clinical and pathology work-up, an observation period, and is then applied toward one or another of the investigations underway at the Laboratory (see Progress Report). Each investigative program on patients is reviewed by the Cancer Board of the University of California School of Medicine for its clinical safety.

4(c). Relationship of Anticipated Results to General Problems in the Field. The results of the investigations, since they are of work being done on patients, is directly applicable to the clinical management of patients with cancer. The chief interests of the Laboratory, however, are the study of the biology, physiology and biochemistry of human cancer, with particular emphasis on how the presence of various neoplastic diseases affects the human host.

4(d). Facilities Available. The Laboratory and its research ward occupy two floors of a wing of the Laguna Honda Hospital. This space was made available by arrangement between the University of California and the San Francisco Department of Public Health; the Laboratory will move to its new quarters at the Medical Center toward the end of 1952. Two-thirds of the area is occupied by laboratories, including 2 clinical biochemical laboratories, 1 hematology laboratory, 1 protein chemistry and immunochemistry laboratory, 1 clinical isotope laboratory, 1 biochemical isotope laboratory, 1 physiology laboratory and an animal room. The pathology laboratory (supported by University of California funds) is in another area. All these laboratories and the research ward are fully equipped for their designated work. Special equipment includes: electrophoresis (Aminco), preparatory ultracentrifuge (Spinco), microchemical assembly (Kirk), and a full clinical physiology complement of strain-gage indicators, recording oximeters, oscillographs, electroencephalographs, etc.

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APPLICATION FOR GRANT-IN-AID
PROPOSED PLAN (Continuation Sheet)

NUMBER: (Do not write in this space)
C 396(C3)

No S.S.

5(a). Previous Work Done on This (or closely related) Project. The Laboratory of Experimental Oncology was initiated in January 1947 and the research ward, which is supported by Grant C-396, was opened on July 6, 1948. The attached project report indicates the lines of investigation being undertaken and the publications indicate the segments of work which have been pursued to the point of publication.

5(b). Personal Publications Pertaining to this Problem. The list of 19 publications which have appeared or have been submitted during the past year are given in the progress report. Five additional papers are in the process of preparation. At least 40 copies of reprints of all publications have been submitted to the National Cancer Institute and the National Institutes of Health and additional reprint copies are not being submitted with this application at this time.

6(a). Results Bearing on This Project Obtained by Others. The wide program being undertaken at the Laboratory of Experimental Oncology would refer to such an extensive review of previous literature in cancer research that it is considered inappropriate to include this here. The paper entitled, "Experimental chemotherapy in neoplastic diseases" by Shimkin and Bierman (Radiology, 53:518-529, October, 1949), for example, lists 64 references on this segment of the program alone.

It is believed that some specific investigations were first initiated at this Laboratory. These include: (1) the effects of virus infections on clinical cancer, which is now also being studied at the Memorial Hospital in New York, (2) intra-arterial catheterization including the use of chemotherapeutic agents by this route which is now also being explored at Georgetown University at Washington, D.C., and, (3) concentration upon the exploration of cardiovascular effects of cancer.

6(b). Publications by Others on Related Work. Refer to 6(a). The listing of references from the literature for this wide program would be too extensive to justify inclusion here. References to publications by others on similar or related work are, of course, always included in the publications.

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