

WEW/md/37845

6 MAR 1970

MKDDH-RNO

ARM2.941121.014A

John P. Colmore, M.D.
Professor of Medicine & Pharmacology
University of Oklahoma Medical Center
800 N.E. Thirteenth Street
Oklahoma City, Oklahoma 73104

Dear Doctor Colmore:

Your proposal, entitled "Toxicity and Tolerance Studies of Anti-Radiation Compounds in Healthy Male Volunteers," has been reviewed. I regret that we will be unable to provide funding support for renewal of this project at this time.

At the present time, the development and testing of antiradiation compounds is such that there are no compounds available for testing in your facility. It is hoped that during the next few months one or two compounds will be available in supplies necessary to proceed with the Phase I studies. My staff maintains an interest in your proposal and the facilities you have to offer and with your permission we will retain a copy of your proposal in our files in the event compounds do become available.

We appreciate your interest in the US Army Medical Research and Development Command program and the opportunity we have had in working with you on this project. We look forward to the possibility of renewing this cooperative effort at some later time.

Sincerely,

Signed
I. C. P.

IRVIN C. FLOUGH
Colonel, MC
Commanding

MFR: (See attached sheet).

RETURN TO NBC SCIENCES DIVISION

6 MAR 1970

MFR:

Due to the overrun of research on antimalarial funds, there are insufficient funds available to extend this contract for an additional period without additional funds. Budget restrictions have precluded adding funds to this contract at this time. Dr. Colmore and Dr. Desper have been notified by MAJ Woodward that the contract would not be renewed, but that it was quite possible that a new contract might be awarded during FY 71 if funds are then available. It is of importance to have Phase I studies on compounds 2529, 2721 and 2823, but sufficient quantities are not now available. It is estimated that about \$60,000 will be needed for these studies.

COORDINATION: None required.

ACTION OFFICER: ^{WEM} William E. Woodward, MAJ, MSC, X-37845. ^{Rix}

CO/SATSG
Dep Cdr <i>[Signature]</i>
XO <i>[Signature]</i>
ADJ <i>[Signature]</i>
SCM
JA
MUST
AIDRB
Dir, Medical <i>[Signature]</i>
Dir, Surgical
Dir, PP&B
Ch, STINFO
Ch, P&C
Ch, Admin

DO NOT WRITE IN THIS SPACE

NEW RENEWAL

CONTRACT OR GRANT NUMBER

APPLICATION FOR RESEARCH CONTRACT GRANT - PART I

1. TITLE OF PROJECT
 Toxicity and Tolerance Studies of Anti-Radiation
 Compounds in Healthy Male Volunteers

2. DATE RESEARCH PROJECT TO BEGIN
 1 January, 1970

3. RESPONSIBLE INVESTIGATOR (Name and official position)
 John P. Colmore, M.D., Director, Experimental Therapeutics Unit
 Professor of Medicine and Pharmacol., Univ. Okla. School of Medicine

4. DATE OF APPLICATION
 11 November, 1969

5. PRINCIPAL PROFESSIONAL ASSISTANT (S) (Last name-first name-middle initial)

Desper, Paul C., M.D.
 Evenson, Kenneth L., M.D.
 Vloedman, Derk A., Jr., M.D.

6. OTHER PROJECTS IN WHICH YOU ARE PARTICIPATING AND SOURCE OF SUPPORT (Other government contracts or funds from civilian foundations, etc.) (Applicable to items 3 and 5 above)

Research projects funded by various civilian corporations and independent research projects funded by various civilian foundations and sources in support of clinical pharmacology

Acknowledged by *J. G.*
 Admin. Services Branch
 Log Number 511-69
 Date: 17 Nov 69

7. NAME AND LOCATION OF INSTITUTION WHERE WORK WILL BE PERFORMED

Oklahoma State Penitentiary
 McAlester, Oklahoma

8. RESPONSIBLE INVESTIGATOR (Signature)

APPLICATION APPROVALS

9. APPROVAL BY HEAD OF DEPARTMENT WHERE WORK IS TO BE DONE

APPROVED (Signature)

10. APPROVAL BY OFFICIAL AUTHORIZED TO SIGN FOR INSTITUTION

APPROVED (Signature)

NAME (Printed or typed)

John P. Colmore, M.D.

NAME (Printed or typed)

Arnold E. Pontesso

OFFICIAL TITLE

Director of Medical Research
 Oklahoma State Penitentiary
 McAlester, Oklahoma

OFFICIAL TITLE

Director

INSTITUTION

Department of Corrections

APPLICATION FOR RESEARCH CONTRACT GRANT - PART II

TITLE OF PROJECT **Toxicity and Tolerance Studies of Anti-Radiation Compounds in Healthy Male Volunteers**

FUNDS REQUESTED (One year only)

REQUIREMENTS	BUDGET	
	REQUESTED FROM USA MEDICAL R & D COMMAND	OTHER SOURCES ¹ (Code whether Actual (A) or Requested (R))
1. PERSONNEL (List positions, percent of time each will devote to the research; annual rate of pay; total amount to be paid annually from this budget to each)	\$ None	\$ None
2. ON-CAMPUS CONSULTANT FEES (Itemize and justify)	\$ None	\$ None
3. EQUIPMENT (Itemize)	\$ None	\$ None
4. CONSUMABLE SUPPLIES (Itemize)	\$ None	\$ None
5. TRAVEL (State purpose)	\$ None	\$ None
6. PUBLICATION COSTS (Types)	\$ None	\$ None
7. OTHER DIRECT COSTS	\$	\$
Cost Reimbursement (See Part III, paragraph 6) PER SUBJECT	2,243.00	
8. SUBTOTAL - DIRECT COSTS (Item 1 through item 7)	\$ 2,243.00	
9. OVERHEAD (Established by official auditors with concurrence of institution or research agency and contracting office, and may be based upon percentage of total salaries and wages, or percentage of total cost of project. Indicate in item a or b below, and complete items c and d.)	\$	
a. PERCENT OF SALARIES	None %	c. FISCAL YEAR BEGINS ?
b. PERCENT TOTAL COST	None %	1 July, 1970
d. COGNIZANT GOVERNMENT AUDITOR (Name and address if known)		
10. TOTAL BUDGET (Item 8 plus item 9) PER SUBJECT	\$ 2,243.00	

ESTIMATE OF FUTURE REQUIREMENTS (Complete only if type of project indicates that it will continue for more than a year)

	ADD'L YEARS	PERSONNEL	ON-CAMPUS CONSULTANT FEES	EQUIPMENT	CONSUMABLE SUPPLIES	TRAVEL	PUBLICATION COSTS	SUBTOTAL (Direct costs)	INDIRECT COSTS	TOTAL
11	1 ST	\$	\$	\$	\$	\$	\$	\$	\$	\$
12	2 ND									
13	3 RD									
14	4 TH									

¹ OTHER SOURCES - from the school, other contracts or grants, other government agencies, foundations, etc.

² This denotes the accounting year of the activity, organization or institution.

X

Toxicity and Tolerance Studies of Anti-Radiation Compounds in Healthy Male Volunteers

1. Type of Proposed Plan: Definitive Study

2. Specific Aims:

- 2.1 Objectives: The purpose of these studies will be to investigate the toxicity of tolerance to and acceptability of various anti-radiation agents developed by the U.S. Army's division of Medicinal Chemistry in male volunteers.
- 2.2 Hypothesis: It is anticipated that healthy male volunteers would be able to tolerate these compounds, at least as well as individuals exposed to radiation and it is therefore suggested that the data so derived would be applicable to persons exposed to radiation.

3. Background:

- 3.1 Basis: This is similar to the statements made in paragraph 2.2 above.
- 3.2 Previous Work: The Medical Research Unit of the Oklahoma State Penitentiary which is under the supervision and control of the Director of the University of Oklahoma's Experimental Therapeutics Unit has, for the past 6 years, been involved in Phase I testing of a variety of investigational new drugs under contract with many pharmaceutical firms as well as conducting clinical and pharmacologic investigations of assorted compounds. To cite this work would be to cite I.N.D. and N.D.A. applications in the files of the F.D.A. This Unit has completed and reported to the Department of the Army a study of an antiradiation compound, WR-633.
- 3.3 Work by Others: Not applicable.

4. Methods:

For each study up to 4 studies per year, 24 healthy male volunteers who are inmates of the Oklahoma State Penitentiary and between the ages of 21 through 55, inclusive, will be selected for study. Prior to admission to the study, voluntary informed consent will be obtained from each subject. Subjects will be selected on the basis of normal physical findings and normal laboratory determinations, which would consist of serum sodium, potassium chloride, bicarbonate, fasting blood glucose, total proteins, albumin, calcium, phosphorus, cholesterol, BUN, uric acid, creatinine, total bilirubin, SGOT, SGPT, alkaline phosphatase, hemoglobin, hematocrit, white blood count and differential, platelet count, reticulocyte count, prothrombin time, partial thromboplastin time, urinalysis and stool examination for occult blood.

X

Toxicity and Tolerance Studies of Anti-Radiation Compounds in Healthy Male Volunteers

4. Methods (Continued)

- < The total duration of each study would be 17 weeks. Six subjects will be started in the study each week for 4 consecutive weeks and each group of 6 will continue actively in the study for a total of 13 weeks. Within each group of 6, 3 subjects will receive active pharmacologic agent and 3 subjects will receive its matching placebo. Each group will receive 91 consecutive days of medication and the dosage schedule is listed on the accompanying sheet. Thus, subjects in Group 1 will receive the maximum daily dose from the 6th week through the 13th week, inclusive.

Group 2 will receive the maximum dosage from the 5th week through the 13th week; Group 3 from the 4th through the 13th week and Group 4 from the 3rd through the 13th week. The starting dose for each group will differ and will be predicated on the experience of the preceding group. The entire laboratory screen outlined above will be carried out on each subject on the 1st, 8th, 15th, 22nd, 29th, 36th, 43rd, 50th, 57th, 64th, 71st, 78th and 85th days of drug administration, as well as on the morning after the last medication day.

In addition to the above, a CBC and urinalysis will be carried out on Days 4, 11, 18, 25, 32, 39, 46, 53, 60, 67, 74, 81 and 88 of drug administration. An electrocardiogram will be carried out prior to beginning drug administration and on the morning after the last medication day. Body weight and blood pressure (seated) will be recorded on each subject once weekly. Each subject will be interviewed daily for possible side effects. Repeat physical examinations will be carried out on any subject when symptomatology dictates a need and will be carried out on each subject on the last day of drug administration. (See attached flow sheet of the schedule of drug administration).

A completed report will be submitted within one month of the completion date of the study.

5. Military Significance:

The direct military significance of this study would be to establish the safety in man of anti-radiation compounds which could then be further evaluated in humans exposed to radiation of various sorts. The need to be able to protect military personnel against the hazards of radiation are obvious.

6. Budget:

The cost per subject for completing the study is outlined. It is appropriate to point out that all volunteers are paid for each day they participate in the study. This has been a long-established practice in this prison population and in view of the nature of the captive population, it is considered ethical and commensurate with voluntary participation.

Tolerance and Toxicity Studies of Anti-Radiation Compounds in Healthy Male Volunteers

6. Budget (Continued)

92 Man Days @ \$3	\$ 276.00	2 ECGs @ \$15	\$ 30.00
27 venipunctures	81.00	1 repeat physical exam- ination @ \$10	<u>10.00</u>
14 laboratory screens @ \$118	1,652.00		
14 laboratory screens @ \$9	117.00		
14 blood pressure & weight determinations @ \$5.50	77.00	<u>Per Subject Total</u>	<u>\$2,243.00</u>
		<u>24 Subject Total</u>	<u>\$53,832.00</u>

X

DOSAGE SCHEDULE:

Total daily dose (mgms)	100	200	400	600	800	1000	1200	1400	1600	1800	2000	2000	2000
Q.I.D. dose (mgms)	25	50	100	150	200	250	300	350	400	450	500	500	500
Week of medication for Group 1 (6 men*)	1 x x		2 x x		3 x x		4 x x		5 x x		6 thru 13 x x x		
Week of medication for Group 2 (6 men*)	o o		1 x x		2 x x		3 x x		4 x x		5 thru 13 x x x		
Week of medication for Group 3 (6 men*)	o o		o o		1 x x		2 x x		3 x x		4 thru 13 x x x		
Week of medication for Group 4 (6 men*)	o o		o o		o o		1 x x		2 x x		3 thru 13 x x x		

* Note: Half of the subjects will receive active drug and half will receive its matching placebo.

HEADQUARTERS
U. S. ARMY MEDICAL RESEARCH
AND DEVELOPMENT COMMAND
WASHINGTON 25, D. C.

Form Approved
Budget Bureau No. 49-R3441

APPLICATION FOR RESEARCH CONTRACT - PART IV

BIOGRAPHY

(Biographical sketches required on responsible investigator and principal professional assistants only. If this is a request for renewal utilizing essentially the same personnel as previously, biographical sketches will not be necessary.)

1. NAME	2. ADDRESS	3. AGE
John P. Colmore, M.D. Prof. Medicine & Pharmacology	University of Oklahoma Medical Center 800 N. E. 13th Street, Oklahoma City, Okla.	48
4. EDUCATIONAL BACKGROUND (College and/or University)		73104

See Original Contract application.

5. RESEARCH TRAINING (List of institutions, research director, subject and dates)

6. OTHER INFORMATION BEARING ON QUALIFICATIONS (Hospital appointments, professional societies, specialty board, etc.)

7. BIBLIOGRAPHY (Do not list more than ten publications)

3 March 1970

~~CPT. KERNEN~~ *[Handwritten mark]*

DIRECTOR OF MEDICAL RESEARCH *[Handwritten signature]*

IN TURN

Captain Kernen

Correction has been made.

Signature block should read "Commanding" not "Commander."

K. HIGHFILL

[Handwritten signature]

W. V. DAVIS
Colonel, MSC
Executive Officer