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712368

**OR** Oak Ridge  
**AW** Associated Post Office Box 117  
Universities Oak Ridge, Tennessee 37831-0117

July 26, 1984

Dr. William R. Bibb, Director  
Energy Programs and Support Division  
Department of Energy  
Oak Ridge, TN 37830

SUBJECT: TERMINAL PROGRESS REPORT TO NCI FOR GRANT ENTITLED "CARBON-11  
AMINO ACIDS/POSITRON ECT FOR PANCREATIC STUDIES", NIH 5-R01-  
CA29490-03, DOE # 20-81-80.

Dear Dr. Bibb:

Enclosed are three copies of the terminal report to National Cancer  
Institute on the subject grant. This project was under the direction of  
Dr. Karl Hubner. The termination date was June 30, 1984.

Sincerely yours,

*W. E. Felling*  
William E. Felling  
Executive Director

RYAN:sm

Enclosure

REPOSITORY Oak Ridge Operations  
COLLECTION Records Holding Area  
Documents 1944-94  
BOX No. B-87-9 Bldg. 2714-H  
FOLDER 20-81-80 NIH 1983

107944b

20-81-80  
1-152

Copy sent to DNMS/24



Oak Ridge  
Associated Post Office Box 117  
Universities Oak Ridge, Tennessee 37831-0117

Executive  
Office

July 26, 1984

Dr. Floyd Frazier  
National Cancer Institute  
5333 Westbard Avenue, Room 849  
Bethesda, MD 20205

Dear Dr. Frazier:

We are enclosing three copies of the terminal report on Grant Number CA-29490-03 entitled "C-11 Amino Acids/Positron ECT for Pancreatic Studies". This grant was under the direction of Dr. Karl Hubner. If there are any questions during the review of this report, please do not hesitate to phone Dr. Hubner at 615/576-3098.

Sincerely yours,

Original signed by  
WILLIAM F. COUNTISS

William E. Felling  
Executive Director

RYAN:sm

Enclosure

cc: Leo F. Buscher, Jr.  
Grants Management Officer, NCI

bcc: ✓ William R. Bibb, DOE (3)  
Executive Office w/o attachments  
W. F. Countiss  
C. C. Lushbaugh  
K. F. Hubner  
B. P. Ryan

1079447

TERMINAL PROGRESS REPORT

CARBON-11 AMINO ACIDS/POSITRON ECT FOR PANCREATIC STUDIES

July 18, 1984

NCI GRANT NO. CA-29490

PRINCIPAL INVESTIGATOR - KARL F. HUBNER, M.D.

1079448

## PROGRESS AND RESULTS

The goal of this research project was to test various carbon-11 labeled amino acids for their potential use in the differential diagnosis of pancreatic disease and metabolic studies in pancreatic cancer. In order to reach this goal several technical objectives had to be met: (1) the development of methods for resolution of  $^{11}\text{C}$ -labeled amino acid racemates; (2) improvements in computer-assisted quantitative image analysis, and (3) clinical application of PET (Positron Emission Tomography) imaging methods. The project was carried out over a 3-year period and specific endpoints were expected for each year.

Accomplishments in the area of radiopharmaceutical development for this project were (1) developing HPLC methods for resolution of  $^{11}\text{C}$ -DL-valine and  $^{11}\text{C}$ -DL-tryptophan; (2) improving reliability of technique and production yields for  $^{11}\text{C}$ -L-valine and  $^{11}\text{C}$ -L-tryptophan through the study of critical variables of the HPLC technique such as the presence of metal ions, pH of the reaction mixture, flow rate of the eluent, and concentration of ethanol in the eluent; (3) demonstrating that the HPLC columns used for resolving  $^{11}\text{C}$ -DL-valine and  $^{11}\text{C}$ -DL-tryptophan can be regenerated by washing the columns with methanol and then with water; and (2) preparing the IND's for clinical studies of  $^{11}\text{C}$ -L-valine and  $^{11}\text{C}$ -L-tryptophan.

Several goals have been accomplished in the area of computer application and software development for PET imaging. ECAT-I programs and software were rewritten and adapted to make them compatible with the ECAT-II system. These programs are body subline calculation, a noise removal program, expansion of rectilinear scans, and listing of sort files. Also a program was developed

to transfer patient data acquired on the original ECAT scanner. Special purpose computer programs were developed such as programs to remove scatter from sort files of emission or transmission data, and a region of interest analysis routinely needed for determining the activity distribution and concentration of carbon-11 in vivo.

Clinical applications of PET imaging using  $^{11}\text{C}$ -labeled amino acids in patients with pancreatic diseases resulted in several important findings.

1. In comparative studies using  $^{11}\text{C}$ -L-valine and  $^{11}\text{C}$ -DL-valine, the L- versus DL-valine concentration ratio in the head of the normal pancreas was found to be 2.6. This finding correlates with L versus DL differences in pancreas uptake of amino acids in mice and indicates that for physiologic imaging of the pancreas, especially for measuring the utilization of amino acids for protein and enzyme syntheses, the natural L-form of amino acids is necessary because the presence of  $^{11}\text{C}$ -D-valine is likely to interfere with an accurate assessment of regional amino acid utilization.

2. In 22 patients with proven cancer of the pancreas examined with either  $^{11}\text{C}$ -DL-valine or  $^{11}\text{C}$ -DL-tryptophan, PET scan findings were abnormal 16 times (76% true positives). The true positive rate was improved (87.5%) when using  $^{11}\text{C}$ -L-valine or  $^{11}\text{C}$ -L-tryptophan.

3. A comparison of L- versus DL-tryptophan in humans revealed a pancreas-to-liver concentration ratio of 3:1 for the L-form and approximately 2:1 for the DL-form of tryptophan, indicating that L-tryptophan is probably the best scanning agent for the human pancreas. For valine, however, the pancreas to liver ratio was found to be 1.5:1 for both forms. For future studies designed to make a direct comparison between L-tryptophan and D-tryptophan

and L-valine versus D-valine, IND's have been prepared for the D-enantiomers of these amino acids. Approval for clinical investigation has been obtained from the FDA.

4. Even though the number of cases studied under this grant is limited, analyses of PET images of pancreatic cancer and normal pancreatic tissue indicate that the DL-form of amino acids have a higher affinity to cancers than the natural L-forms by a factor of 1.5 to 2.5. This finding warrants consideration of the use of the pure D-enantiomers in future studies.

5. Progress has been made in applying the unnatural alicyclic amino acid [ $^{11}\text{C}$ ]1-aminocyclobutanecarboxylic acid ([ $^{11}\text{C}$ ]ACBC), and PET imaging to study tumor growth as it may be reflected by amino acid uptake. [ $^{11}\text{C}$ ]ACBC and its cyclopentane analog ([ $^{11}\text{C}$ ]ACPC) are excellent tumor-localizing agents that appear to be less dependent on tumor type than the universally used tumor-scanning agent  $^{67}\text{Ga}$ -citrate. In reviewing our cases that have been studied using [ $^{11}\text{C}$ ]ACBC or [ $^{11}\text{C}$ ]ACPC, we have concluded however that positron tomography, because of its limited spatial resolution, at least with the ECAT-II<sup>TM</sup> scanner used in this project, cannot play a significant role in the early detection of neoplasms. PET imaging, however, permits in vivo quantitation of the biodistribution of positron-emitting radiopharmaceuticals, and one should be able to determine the metabolic state of large tumors by measuring amino acid transport. The question is whether it is possible to measure the rate of protein synthesis in tumors analogous to determining the same parameter for the brain.

A mathematical model for quantifying the metabolic rate of L-leucine in the human brain has been developed and normal values have been established for various regions of the brain which under normal conditions function as a physiologically and chemically well controlled organ. In contrast, in

malignant tumors regulation of metabolic processes is less controlled and even tumors of the same histologic type do not necessarily have the same growth rate. It also would not be practical to try to establish metabolic models for all the different types of cancer and different amino acids. In view of these considerations it seems most reasonable to measure the metabolic state of tumors by looking at relative tumor activity with the pre-treatment value being 100%, using the patient as his/her own control in subsequent PET studies. With limited cyclotron time and irregular scheduling, this approach could only be tested in a small number of patients. Also, pancreatic cancer (with sometimes early deterioration or even death of the patient) does not seem to be the most practical model for longitudinal interventional studies. Nevertheless, with more refinement of quantitation this technique may eventually be useful for determining more precisely the pharmacologic and cytotoxic effect of drugs and radiation on tumors, and could provide important information with regard to therapeutic and prognostic needs of cancer patients in general.

Personnel Changes Effected by Grant

Karl F. Hubner continues some of the work related to this grant with DOE support. Likewise, Lee C. Washburn's salary is covered by DOE. William D. Gibbs' position was terminated through attrition. Tan Tan Sun, research associate to Dr. Washburn, is also supported by DOE and continues to do basic research in amino acid radiosynthesis.

1079452

Publications

Hubner, K.F., Washburn, L.C., and Hayes, R.L.

The potential of positron emission tomography (PET) in the diagnosis of pancreatic disease.

In: Proceedings, American Pancreatic Association, Inc., and National Pancreatic Cancer Project Joint Meeting, Chicago, Illinois, 1982, p. 25.

Washburn, L.C., Sun, T.T., Byrd, B.L., and Callahan, A.P.

C-11-L-Tryptophan, a potential diagnostic agent for pancreatic disease.

In: Proceedings, American Pancreatic Association, Inc., and National Pancreatic Cancer Project Joint Meeting, Chicago, Illinois, 1982, p. 55.

Hubner, K.F. and Buonocore, E.

Alimentary tract radiology positron emission tomography (P.E.T.).

In: Alimentary Tract Radiology, 3rd Edition, S. E. Harshberger, Editor, The C.V. Mosby Co., St. Louis, Missouri, 1982, pp. 2486-2494.

Hubner, K.F., Washburn, L.C., and Hayes, R.L.

The potential of carbon-11-labeled amino acids for the diagnosis and study of tumors by positron emission tomography.

In: Abstracts, Third International Symposium on Radiopharmacology, Freiburg, West Germany, 1983, p. 34.

Washburn, L.C., Hubner, K.F., Sun, T.T., Byrd, B.L., Coffey, J.L., and Callahan, A.P.

C-11-L-Tryptophan, a potential agent for diagnosis of pancreatic disease using PET.

J. Nucl. Med., 24:P121, 1983.

Washburn, L.C., Sun, T.T., Byrd, B.L., and Callahan, A.P.

Resolution of [<sup>11</sup>C]DL-leucine and [<sup>11</sup>C]DL-tryptophan by high-performance liquid chromatography.

J. Labelled Compd. Radiopharm. (In press).





Oak Ridge  
 Associated Universities  
 Post Office Box 117  
 Oak Ridge, Tennessee 37830

August 23, 1983

Dr. William R. Bibb, Director  
 Energy Programs and Support Division  
 U. S. Department of Energy  
 Oak Ridge, Tennessee 37830

Subject: RECEIPT OF NIH GRANT 5 R01 CA 29490-03

Dear Dr. Bibb:

ORAU has received the subject renewal grant in the amount of \$33,997 from the National Cancer Institute for continuation of work related to C-11 Amino Acids/Positron ECT for Pancreatic Studies. The total amount of funds available for the period July 1, 1983 through June 30, 1984 is \$80,734 (\$46,737 balance from prior budget periods plus \$33,997).

This project will be conducted by the Medical and Health Sciences Division as work under DOE Contract DE-AC05-76OR00033. The following personnel will be assigned to this activity:

<u>Name</u>	<u>Percent of Time</u>
Karl F. Hubner	20%
Jack L. Coffey	20%
Lee C. Washburn	10%
Anita Forester	20%

After the close of each monthly accounting period, ORAU will reimburse the DOE account for all direct and indirect costs applicable to this project.

Sincerely yours,

*William E. Felling*  
 William E. Felling  
 Executive Director

COUNTISS:dh

20-81-80  
 ORAU  
 5-3000

1079455

5 R01 CA29490-03

TERMS OF AWARD

This award reflects the budget and the budget period negotiated between representatives of the National Cancer Institute and Mr. William Countiess on June 7, 1983.

This award has been reduced by 4% in accordance with the National Cancer Institute funding plan of November 1982.

The activity code for this grant has changed from R26 to R01.

1079456

**NOTICE OF GRANT AWARD**

DATE ISSUED: JUN 20 1983  
 GRANT NUMBER: 5 R01 CA29490-03 SRC  
 TOTAL PROJECT PERIOD: From 07/01/81 Through 06/30/84

TYPE OF AWARD: RESEARCH  
 AUTHORIZED BY: 42 USC 241 42 CFR 52  
 AWARDED BY:

NATIONAL CANCER INSTITUTE

Title of Project or Area of Training

C-11-AMINO ACIDS/POSITRON ECT FOR PANCREATIC STUDIES

Grantee Institution OAK RIDGE ASSOCIATED UNIVERSITIES P O BOX 117 OAK RIDGE, TENN 37830	Principal Investigator/Program Director/Awardee HUBNER, KARL F MD OAK RIDGE ASSOCIATED UNIV P O BOX 117 OAK RIDGE, TENN 37830
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APPROVED BUDGET	AWARD COMPUTATION
FOR BUDGET PERIOD 07/01/83 Through 06/30/84	1. DIRECT COSTS ..... \$ 80,734
Salaries and Wages ..... \$ 35,759	2. INDIRECT COSTS ..... \$ 0
Fringe Benefits ..... 6,720	(Calculated at _____ rate)
Total Personnel Costs ..... \$ 42,479	3. TOTAL ..... \$ 80,734
Consultant Costs ..... 4,000	4. Less Unobligated Balance From
Equipment ..... 4,650	Prior Budget Period(s) . . . 01A1 ROE ..... \$ 46,737
Supplies ..... 1,700	
Travel - Domestic ..... 1,700	
- Foreign ..... 0	
Patient Care - Inpatient ..... 0	5. AMOUNT OF THIS AWARD → \$ 33,997
- Outpatient ..... 0	
Alterations and Renovations ..... 0	COST SHARING (1) Per Instl. agreement dated 01/01/73
Contractual or Third Party Costs ..... 0	CONTRIBUTION (2) Per Indiv. agreement, minimum
Other ..... 27,905	SUPPORT RECOMMENDED FOR REMAINDER OF PROJECT PERIOD*
Trainee Stipends ..... 0	Budget Total Direct Costs Stipends
Trainee Tuition and Fees ..... 0	Period (Includes Stipends)
Trainee Travel ..... 0	04 NONE
TOTAL DIRECT COSTS → \$ 80,734	

When PHS Prior Approval is required for rebudgeting, submit request to Grants Management Official below. #SEE REMARKS \*Subject to availability of funds and satisfactory progress.

REMARKS:  
 APPLICABLE INDIRECT COSTS WILL BE PROVIDED ON A SUMMARY NOTICE.

REFER TO ADDITIONAL TERMS AND CONDITIONS OF AWARD.  
 #GRANTS MANAGEMENT CONTACT: MS. ROSLYN BACON RB PHONE: 301 496-7800

TERMS OF ACCEPTANCE: By acceptance of funds awarded under this grant, the grantee acknowledges that it will comply with terms and conditions in the following: (1) Legislation cited above; (2) Regulations cited above; (3) Provisions on or attached to this award notice and signed by the official(s) named below; (4) PHS Grants Administration Manual Chapters in effect on the beginning date of the grant Budget Period; (5) PHS Grants Policy Statement in effect on the beginning date of the grant Budget Period; (6) 45 CFR Part 74. The above order of precedence shall prevail.

FY-Common Accounting Number 3-8422641	CRS/Entity Identification No. 1620476816A1	PHS List No./Object Class Code /41.4E	Document Number (08)R6CA29490A
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PROGRAM OFFICIAL FOR THIS GRANT  WILLIAM E. STRAILE, PH.D. DIVISION OF RESOURCES, CENTERS & COMMUNITY ACTIVITIES, NCI 301 427-8818	PHS Grants Management Official <i>Leo F. Buscher, Jr</i> LEO F. BUSCHER, JR. GRANTS MANAGEMENT OFFICER NATIONAL CANCER INSTITUTE
---	--



Oak Ridge  
Associated Universities Post Office Box 117  
Oak Ridge, Tennessee 37830

615/576-3000  
January 27, 1983

Dr. William R. Bibb, Director  
Energy Programs and Support Division  
Department of Energy  
Oak Ridge, TN 37830

Subject: APPLICATION TO NCI FOR CONTINUATION SUPPORT OF A GRANT ENTITLED  
"C-11-AMINO ACIDS/POSITRON ECT FOR PANCREATIC STUDIES"

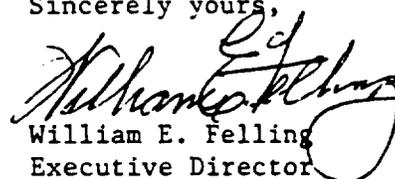
Dear Dr. Bibb:

Enclosed are three copies of an application to NIH for continuation of the subject grant. NCI has requested receipt of this grant by February 1. In order to meet this accelerated deadline we are transmitting final copies to NCI simultaneously with this submission for DOE review. This action was discussed with Dr. Richard Benson of your office and his approval obtained. Should changes be necessary, an amendment can be made any time prior to the meeting of the Review Group in June.

This project is under the direction of Dr. Karl HUBNER and was most recently approved in your letter of July 26, 1982.

We will keep you advised of NIH action on this proposal.

Sincerely yours,

  
William E. Felling  
Executive Director

RYAN:sm

Enclosure

20-81-80

1079458

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SECTION I

DEPARTMENT OF  
HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE

REVENUE GROUP	5	PROGRAM	B26	GRANT NUMBER INSERT	CA29590-03
TOTAL PROJECT PERIOD					
FROM		07/01/81	THROUGH		06/30/84
REQUESTED BUDGET PERIOD					
FROM		07/01/83	THROUGH		06/30/84

APPLICATION  
FOR CONTINUATION GRANT

TO BE VERIFIED BY APPLICANT. CHECK INFORMATION IN ITEMS 1 THROUGH 6 IF INCORRECT. FURNISH CORRECT INFORMATION IN ITEM 13

1. TITLE <b>C-11-AMINO ACIDS/POSITRON ECT FOR PANCREATIC STUDIES</b>	
2A. PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR (Name and Address, Street, City, State, Zip Code) <b>HUBNER, KARL F OAK RIDGE ASSOCIATED UNIV P O BOX 117 OAK RIDGE, TENN 37830</b>	4. APPLICANT ORGANIZATION (Name and Address, Street, City, State, Zip Code) <b>OAK RIDGE ASSOCIATED UNIVERSITIES P O BOX 117 OAK RIDGE, TENN 37830</b>
2B. DEGREE <b>M.D.</b>	2C. SOCIAL SECURITY NO. <b>[REDACTED]</b>
2D. DEPARTMENT, SERVICE, LABORATORY OR EQUIVALENT <b>NUCLEAR MEDICINE</b>	5. PHS ACCOUNT NUMBER <b>1620476816A1</b>
2E. MAJOR SUBDIVISION <b>Medical and Health Sciences</b>	6. TITLE AND ADDRESS OF OFFICIAL IN BUSINESS OFFICE OF APPLICANT ORGANIZATION <b>HEAD, OFFICE OF FISCAL SERVICES OAK RIDGE ASSOCIATED UNIVERSITIES P O BOX 117 OAK RIDGE, TENN 37830</b>
3. ORGANIZATIONAL COMPONENT TO RECEIVE CREDIT FOR INSTITUTIONAL GRANT PURPOSES <b>60 OTHER RESEARCH ORGANIZATION</b>	

COMPLETE THE FOLLOWING (See Instructions)

7. RESEARCH INVOLVING HUMAN SUBJECTS (See Instructions) <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES APPROVED: <u>10/01/82</u> DATE	8. INVENTION CERTIFICATION (See Instructions) <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES - NOT PREVIOUSLY REPORTED <input type="checkbox"/> YES - PREVIOUSLY REPORTED
9. PERFORMANCE SITE(S) <b>Medical and Health Sciences Division Oak Ridge Associated Universities P.O. Box 117 Oak Ridge, TN 37830</b>	TELEPHONE INFORMATION
10. DIRECT COSTS REQUESTED FOR BUDGET PERIOD <b>\$84,098.</b>	11A. PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR (ITEM 2A) <b>William F. Countiss</b> AREA CODE: <b>615</b> TELE. NO. & EXT.: <b>576-3098</b>
12A. CONGRESSIONAL DISTRICT OF APPLICANT ORGANIZATION SHOWN IN ITEM 4 <b>Third</b>	11B. NAME OF BUSINESS OFFICIAL (ITEM 6) <b>William F. Countiss</b> AREA CODE: <b>615</b> TELE. NO. & EXT.: <b>576-3056</b>
	11C. NAME AND TITLE OF ADMINISTRATIVE OFFICIAL (ITEM 15B) <b>William E. Felling Executive Director</b> AREA CODE: <b>615</b> TELE. NO. & EXT.: <b>576-3300</b>
	12B. COUNTY OF APPLICANT ORGANIZATION SHOWN IN ITEM 4 <b>Anderson</b>

13. USE THIS SPACE FOR CORRECTIONS TO ITEMS 1 THROUGH 6. INDICATE THE NUMBER(S) WHERE ANSWER(S) APPLY

Please note the following change for Item 6:

HEAD, OFFICE OF FISCAL SERVICES should be changed to: MANAGER OF FINANCE

14. CERTIFICATION AND ACCEPTANCE. WE, THE UNDERSIGNED, CERTIFY THAT THE STATEMENTS HEREIN ARE TRUE AND COMPLETE TO THE BEST OF OUR KNOWLEDGE AND ACCEPT, AS TO ANY GRANT AWARDED, THE OBLIGATION TO COMPLY WITH PUBLIC HEALTH SERVICE TERMS AND CONDITIONS IN EFFECT AT THE TIME OF THE AWARD.

SIGNATURES (Signatures required on original copy only. Use ink. "Per" signatures not acceptable.)	15A. PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR <b>Karl F. Hubner</b>	DATE <b>1/27/83</b>
	15B. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION	DATE

**SECTION II—BUDGET** (USUALLY 12 MONTHS)

SECTION II

FROM 07/01/83

THROUGH 06/30/84

GRANT NUMBER CA 29490-03

A ITEMIZE DIRECT COSTS REQUESTED FOR NEXT BUDGET PERIOD

DOLLAR AMOUNT REQUESTED (omit cents)

PERSONNEL (Applicant organization only) (See instructions)

TIME EFFORT

NAME	TITLE OF POSITION	TIME EFFORT		SALARY	FRINGE BENEFITS	TOTALS
		•	Hours per Week			
Hübner, Karl F.	Principal Investigator	20	8	\$ 11,731	\$ 1,983	
Washburn, Lee C.	Scientist	10	4	4,056	734	
Haves, Raymond L.	Chief Scientist	5	2	No charge		
Coffey, Jack L.	Scientist	20	8	7,213	1,356	
Forester, Anita	Research Associate	100	40	15,544	3,226	
SUBTOTALS				\$ 38,544	\$ 7,299	

(Indicate cost of each item listed below)

TOTAL \$45,843

CONSULTANT COSTS (See instructions) Paul King, Ph.D., Associate Professor, Bioengineering, Vanderbilt University; George Avant, M.D., Chief, Div. of Gastroenterology, Vanderbilt; R.J. Collmann, M.D., Gastroenterology, University of Tennessee;

4,000

EQUIPMENT (Itemize) A.P. Callahan, Oak Ridge National Laboratory.

SUPPLIES (Itemize by category)

Computer discs \$1,950  
 Photographic and patient supplies 1,200  
 Chemicals and chromatography supplies 1,000  
 Glassware 500

4,650

TRAVEL

DOMESTIC Consultant travel: Four trips to Oak Ridge (P.King)

1,700

FOREIGN

PATIENT CARE COSTS

INPATIENT

OUTPATIENT Patient transportation and lodging (30 trips).

1,500

ALTERATIONS AND RENOVATIONS (Itemize by category)

CONTRACTUAL OR THIRD PARTY COSTS (See instructions)

OTHER EXPENSES (Itemize by category)

Cyclotron time - 12 runs @ approx. est. 1,775: \$21,305  
 ECAT maintenance and repair - \$4,500  
 Publication costs 600

26,405

TOTAL DIRECT COST (Enter on Page 1, Item 10)

84,098

INDIRECT COST

(See instructions)

54.7 % S&W\*  
 % TDC\*

\*If this is a special rate (e.g. off-site), explain.

Date of DHHS Agreement

11/17/82 (Provisional)

Not Requested

Under negotiation with:

**SECTION II—BUDGET (Continued)**

CA 29490-03

B Supplemental information regarding ITEMS in the proposed budget for the next period which require explanation or justification (See instructions)

Consultant Costs

As during the past and current budget periods, we anticipate that Dr. Paul King will continue to serve as a consultant to this project for a total of 20 days at \$150.00 fee per day (\$3,000.00). Dr. King's input into this project during the third year is required primarily in the area of quantitative image interpretation and the development of an amino acid utilization model for pancreatic cancer. Other consultants will be available on an as needed basis.

Travel

Travel expenses for Dr. Paul King's consultant services (four times 5 days during the year) will add up to approximately a total of \$425.00 per trip:

\$ 75.00	Transportation
200.00	Hotel
<u>150.00</u>	Per diem
\$425.00	Total

1079461

## SECTION III

SECTION III—DATA FOR  
CURRENT BUDGET PERIOD  
(USUALLY 12 MONTHS)

FROM

07/01/82

THROUGH

06/30/83

GRANT NUMBER

CA 29490-02

The following pertains to your CURRENT PHS budget. Do not include cost sharing funds. This information in conjunction with that provided on Page 2 will be used in determining the amount of support for the NEXT budget period.

A. BUDGET	CURRENT BUDGET (As approved by awarding unit) (1)	ACTUAL EXPENDITURES THRU 12/31/82	ESTIMATED ADDITIONAL EXPENDITURES AND OBLIGATIONS FOR REMAINDER OF CURRENT BUDGET PERIOD (3)	TOTAL ESTIMATED EXPENDITURES AND OBLIGATIONS (Col. 2 plus Col. 3) (4)	ESTIMATED UNOBLIGATED BALANCE (Subtract Col. 4 from Col. 1) (5)
		(Insert Date) (2)			
TOTAL DIRECT COSTS	76,376	28,313	48,063	76,376	0
INDIRECT COSTS (As Provided) **	41,778	15,454	26,324	41,778	0
TOTALS	\$118,154	\$43,767	\$74,387	\$118,154	\$ 0

## B. THROUGH F.

See instructions and provide the information required in items B. through F. Use this page and continuation pages as necessary.

B. Professional Personnel

Name	Title	Category	Less than 25%	26-50%	51-75%	More than 75%
Karl Hübner	Chief Clinician	2	*			
Lee Washburn	Scientist	2	*			
Raymond Hayes	Chief Scientist	2	X			
Jack Coffey	Scientist	2	*			
Anita Forester,	Research Assoc.	2				*

C. Equipment NoneD. Travel

Two trips by Dr. Paul King, consultant, to Oak Ridge for five days each.

Two additional trips are planned during remainder of budget year.

## E. None

F. Other Support

Karl Hübner, M.D., Lee Washburn, Ph.D., and Raymond Hayes, Ph.D., and Jack Coffey are supported in part under Department of Energy Contract DE-AC05-76OR00033, "Preclinical Development of Radiopharmaceuticals", \$439,000; "Clinical Development of Radiopharmaceuticals", \$230,000; "Radiation Emergency Assistance Center/Training Site (REAC/TS)", \$1,011,500.

\*\*As provided through the NIH Indirect Cost Management System.

APPLICANT REPORT GRANT NUMBER SHOWN ON PAGE 1		GRANT NUMBER	
<b>SECTION IV—SUMMARY PROGRESS REPORT</b>		CA 29490	
PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR (Last First Initial)		PERIOD COVERED BY THIS REPORT	
Hübner, Karl F.		FROM	THROUGH
NAME OF ORGANIZATION		07/01/82	06/30/83
Oak Ridge Associated Universities			
TITLE (Repeat title shown in Item 1 on first page)			
C-11-AMINO ACIDS/POSITRON ECT FOR PANCREATIC STUDIES			

- 1 List all publications not previously reported, resulting from work supported by this grant (author(s), title, page numbers, year, journal or book). List manuscripts separately as submitted for publication or accepted for publication.  
 2 Provide two reprints of publications not previously submitted to the awarding unit.  
 3 Progress Report. (See instructions)

1. In preparation for publication, a paper and a poster session presentation have been given at the American Pancreatic Association, Inc., and National Pancreatic Cancer Project Joint Meeting on November 4-5, 1982:
  - 1.1 The Potential of Positron Emission Tomography (PET) in the Diagnosis of Pancreatic Disease.  
K. F. Hübner, L. C. Washburn, and R. L. Hayes, November 4, 1982 (Abstract).
  - 1.2 C-11-L-Tryptophan. A Potential Diagnostic Agent for Pancreatic Disease.  
C. L. Washburn, T. T. Sun, B. L. Byrd, and A. D. Callahan. November 4, 1982.

A short book chapter is now in press, but reprints have not been received as yet.

  - 1.3 Positron Emission Tomography (PET).  
K. F. Hübner and E. Buonocore  
In: Alimentary Tract Radiology, pp. 2486-2494, 3rd Edition, The C. V. Mosby Co., St. Louis, MO, December 1982.
  - 1.4 Advantages and Disadvantages of Three Different Ring Source Designs for Use in Positron Tomography.  
J. L. Coffey, E. C. Holloway, and K. F. Hübner.  
To be presented at the 30th Annual Meeting of the Society of Nuclear Medicine in St. Louis, MO, June 7-10, 1983.
  - 1.5 Recent Progress in X-ray Stereoscopes.  
Z. Fen, P. Xiaodong, and P. King.  
Submitted to Medical Physics.
2. No reprints are available at the time of submission of this application.
3. Progress has been made in the three areas of the project as listed in the 07/01/81 - 06/30/82 summary progress report.
  - 3.1 Work on resolving  $^{11}\text{C}$ -DL-tryptophan by high-performance liquid chromatography (HPLC) for the production of  $^{11}\text{C}$ -L-tryptophan has continued. Although the procedure is not completely reliable as yet, generally useful amounts of  $^{11}\text{C}$ -L-tryptophan can be produced for clinical investigative studies which have begun during this reporting period. An amendment of IND's 12,967 and 12,459 ( $^{11}\text{C}$ -DL-tryptophan and  $^{11}\text{C}$ -DL-valine) has been prepared, approved by the IRB and submitted to FDA for permission to use the D-form of these amino acids for clinical studies. Using the D-enantiomers rather than the racemic mixtures would allow for an easier and certainly more meaningful comparison to the natural L-forms of these amino acids. Since the D-form of the amino acid comes off the HPLC column first, we should have no difficulties in getting sufficient amounts for clinical studies.

- 3.2 The difficulties in getting enough cyclotron time as explained in the previous progress report continued more or less through August 23, 1982. Since then we have had ten cyclotron runs funded by this grant. Four patients with cancer of the pancreas and four patients with pancreatitis were studied.  $^{11}\text{C}$ -DL-tryptophan was used nine times,  $^{11}\text{C}$ -L-tryptophan five times,  $^{11}\text{C}$ -DL-valine twice, and  $^{11}\text{C}$ -L-valine twice. Measurements of pancreas and liver concentrations confirmed the previously reported difference between L- versus DL-valine uptake (ratio 2.6) and L- versus DL-tryptophan uptake found to be 5:1.

The PET scan findings were abnormal in all of the four patients with pancreatic cancer and abnormal in three out of four patients who had pancreatitis (not in an acute phase at the time of the study).

The most encouraging result of this study so far has been the observation in one patient who has pancreatic cancer and demonstrated uptake of DL-tryptophan in the region of the tumor and no uptake of L-tryptophan. In another case, a similar distribution difference could be seen with DL-valine and L-valine. These preliminary findings tend to support the hypothesis made in the original proposal, - namely that the natural L-form of essential amino acids is expected to concentrate primarily in normal pancreatic tissue whereas the D-forms would have a higher affinity to neoplastic pancreatic tissue, and the DL-mixture would localize in both.

- 3.3 Progress has been made in various areas of software development and computer applications. All useful software programs have been converted to the new ECAT-II system. Most of the old pancreas data files have been transferred to the new system. Additional special purpose computer programs developed during this reporting period include region of interest analysis and summing up scan data from different planes for single image display. A comparison of Dr. King's noise removal programs with the online noise removal capability of the ECAT-II scanner/computer has shown that the program formerly developed for ECAT-I does not further improve or correct ECAT-II image data. Consequently, this portion of Dr. King's work on the project was dropped.



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Executive  
Office 615/576-3300  
January 27, 1983

Division of Research Grants  
National Institutes of Health  
5333 Westbard Avenue  
Bethesda, Maryland 20205

Gentlemen:

We are submitting for your consideration seven copies of a grant application for continuation support of Grant No. CA 29490-03 entitled "C-11-Amino Acids/Positron ECT for Pancreatic Studies" under the direction of Dr. Karl Hübner. This is a NPACP grant and should be considered under the Organ Systems Program.

This project will continue to be carried out in facilities operated by Oak Ridge Associated Universities under policies and procedures previously established between ORAU and the Department of Energy.

We would appreciate your favorable consideration of this proposal and will be pleased to supply additional information if requested.

Sincerely yours,

DA.  
~~William E. Felling~~

William E. Felling  
Executive Director

RYAN:sm

Enclosure

bcc: Jon Lee Poche', Assistant Project Director, NPACP  
✓ William R. Bibb, DOE (3)  
Executive Office, w/o attachments  
W. F. Countiss  
Karl F. Hübner  
B. P. Ryan

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