



Oak Ridge  
Associated  
Universities

January 14, 1980

Mr. Kenneth M. Haythorn, Director  
Energy Programs and Support Division  
Department of Energy  
Oak Ridge, Tennessee 37830

Subject: DRAFT APPLICATION FOR A GRANT ENTITLED "BRAIN TUMOR IMAGING  
USING POSITRON EMISSION TOMOGRAPHY"

Dear Mr. Haythorn:

Enclosed are four copies of a draft grant application entitled "Brain Tumor Imaging Using Positron Emission Tomography" which is to be submitted by Dr. Leon Partain of Vanderbilt University to NIH. Dr. Partain has included ORAU as a sub-contractor on this grant. The ORAU effort will be led by Dr. Karl Hübner of the Medical and Health Sciences Division.

The research outline in the proposal involves the use of positron emission tomography for the purpose of brain tumor imaging. This effort relates directly to work already being accomplished within the M&HSD and we consider it a normal extension of our programmatic effort. This project, if approved, would be carried out under a purchase order issued by Vanderbilt University to ORAU for the amount of \$59,300 (see page 3A for budget outline.) Should any questions arise during your review please do not hesitate to call Dr. Hübner at extension 6-3098.

Formal copies of this application should be forwarded to NIH no later than February 25.

Sincerely,



Philip L. Johnson  
Executive Director

CROCKETT:br

Enclosures

1079467

20-7-1980  
2 321

DEPARTMENT OF  
HEALTH, EDUCATION, AND WELFARE  
PUBLIC HEALTH SERVICE

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TYPE PROGRAM NUMBER

REVIEW GROUP FORMERLY

COUNCIL Month, Year DATE RECEIVED

GRANT APPLICATION

Brain Tumor -- 12-28-77  
Tumor - 12-14-79

TO BE COMPLETED BY PRINCIPAL INVESTIGATOR (Items 1 through 7 and 15A)

1. TITLE OF PROPOSAL (Do not exceed 53 typewriter spaces)

BRAIN TUMOR IMAGING USING POSITRON EMISSION TOMOGRAPHY

2. PRINCIPAL INVESTIGATOR

2A. NAME (Last, First, Initial)  
PARTAIN, C. LEON

3. DATES OF ENTIRE PROPOSED PROJECT PERIOD (This application)

FROM 12-1-80  
July 1, 1980 THROUGH 11-30-82  
June 30, 19822B. TITLE OF POSITION Associate Professor of  
Radiology and Biomedical Engineering, and  
Director, Radiological Sciences Division4. TOTAL DIRECT COSTS RE-  
QUESTED FOR PERIOD IN  
ITEM 3

\$217,678

5. DIRECT COSTS REQUESTED  
FOR FIRST 12-MONTH PERIOD

\$103,718

2C. MAILING ADDRESS (Street, City, State, Zip Code)

Radiological Sciences Division  
Department of Radiology  
Vanderbilt University  
Nashville, Tennessee 37232

6. PERFORMANCE SITE(S) (See Instructions)

Department of Radiology  
Vanderbilt University School of Medicine  
Nashville, TN 37232  
5th Congressional District

2D. DEGREE Ph.D. (Nucl. Engr.) and M.D.

2E. SOCIAL SECURITY NO.

Medical and Health Sciences Division  
Oak Ridge Associated Universities  
Oak Ridge, TN 37830  
3rd Congressional District2F. TELEPHONE NUMBER AND EXTENSION  
Area Code 615 TELEPHONE NUMBER AND EXTENSION  
322-2501 322-2942G. DEPARTMENT, SERVICE, LABORATORY OR EQUIVALENT  
(See Instructions)

Department of Radiology

2H. MAJOR SUBDIVISION (See Instructions)

School of Medicine

7. Research Involving Human Subjects (See Instructions)

A.  NO B.  YES Approved: Pending  
C.  YES - Pending Review Date

8. Inventions (Renewal Applicants Only - See Instructions)

A.  NO B.  YES - Not previously reported  
C.  YES - Previously reported

TO BE COMPLETED BY RESPONSIBLE ADMINISTRATIVE AUTHORITY (Items 8 through 13 and 15B)

9. APPLICANT ORGANIZATION(S) (See Instructions)

Vanderbilt University  
Nashville, TN 37232

IRS # 16-204-7682

5th Congressional District

11. TYPE OF ORGANIZATION (Check applicable item)

 FEDERAL  STATE  LOCAL  OTHER (Specify)

Private, Non-Profit

12. NAME, TITLE, ADDRESS, AND TELEPHONE NUMBER OF  
OFFICIAL IN BUSINESS OFFICE WHO SHOULD ALSO BE  
NOTIFIED IF AN AWARD IS MADEJames S. Kramer  
Asst. Vice-Res. for Health Affairs  
Vanderbilt University School of Medicine  
21st and Garland Avenues  
Nashville, TN 37232  
Telephone Number (615) 322-215110. NAME, TITLE, AND TELEPHONE NUMBER OF OFFICIAL(S)  
SIGNING FOR APPLICANT ORGANIZATION(S)John H. Hash, Ph.D., Associate Dean  
Biomedical Sciences

Telephone Number (s) (615) 322-2281

13. IDENTIFY ORGANIZATIONAL COMPONENT TO RECEIVE CREDIT  
FOR INSTITUTIONAL GRANT PURPOSES (See Instructions)

O1 School of Medicine

14. ENTITY NUMBER (Formerly PHS Account Number)

1620476822 A1

15. 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)

A. SIGNATURE OF PERSON NAMED IN ITEM 2A

DATE

B. SIGNATURE(S) OF PERSON(S) NAMED IN ITEM 10

DATE

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE  
PUBLIC HEALTH SERVICE

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PROJECT NUMBER

## RESEARCH OBJECTIVES

## NAME AND ADDRESS OF APPLICANT ORGANIZATION

Department of Radiology, School of Medicine  
Vanderbilt University, Nashville, TN 37232

## NAME, SOCIAL SECURITY NUMBER, OFFICIAL TITLE, AND DEPARTMENT OF ALL PROFESSIONAL PERSONNEL ENGAGED ON PROJECT, BEGINNING WITH PRINCIPAL INVESTIGATOR

C. Leon Partain, Ph.D., M.D., Associate Professor of Radiology and Biomedical Engineering  
and Director, Radiological Sciences DivisionOther personnel listed on Pages 2-a and 2-b.

## TITLE OF PROJECT

BRAIN TUMOR IMAGING USING POSITRON EMISSION TOMOGRAPHY

USE THIS SPACE TO ABSTRACT YOUR PROPOSED RESEARCH. OUTLINE OBJECTIVES AND METHODS. UNDERSCORE THE KEY WORDS (NOT TO EXCEED 10) IN YOUR ABSTRACT.

The purpose of this study is to quantitatively determine the in-vivo localization and kinetics of amino-acids in brain tumors using serial transverse images from positron emission computed tomography. Patients will be studied before surgical intervention, 10-14 days post-operatively, and every 6-8 weeks following the institution of adjunctive anti-tumor therapy (i.e. radiotherapy, chemotherapy, immunotherapy, and/or diet therapy). The radiopharmaceutical delivery system and positron emission CT scanner at Oak Ridge Associated Universities, Oak Ridge, Tennessee, will be utilized in this study. Patients who participate in this study will be under the care of neurosurgeons at Vanderbilt University Hospital, Nashville, TN; North Carolina Memorial Hospital, Chapel Hill, NC; University of Tennessee Medical Center, Memphis, TN; and The Knoxville Neurological Clinics, Knoxville, TN.

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PRIVILEGED COMMUNICATION

Co-Investigators

SS No.

R. Edward Coleman, M.D.

Professor, Radiology  
Director, Nuclear Medicine  
Duke University

Burton P. Drayer, M.D.

Associate Professor  
Radiology  
Duke University

Gary W. Duncan, M.D.

Associate Professor  
Neurology  
Vanderbilt University

Raymond L. Hayes, Ph.D.

Chief Radiochemist  
Oak Ridge Associated  
Universities

F. Ralph Heinz, M.D.

Professor, Radiology  
Duke University

Karl F. Hubner, M.D.

*Director, Department Nuclear Medicine*  
~~Senior Research Clinician~~  
Oak Ridge Associated  
Universities

A. Everette James, Jr. M.S., J.D., M.D.

Professor & Chairman  
Radiology Department  
Vanderbilt University

M. Stephen Mahaley, M.D., Ph.D.

Professor & Chairman  
Neurosurgery Department  
Univ. of N. C.

John D. Mann, M.D.

Assistant Professor  
Neurology  
Univ. of N. C.

William F. Meacham, M.D.

Professor and Chairman  
Neurosurgery Department  
Vanderbilt University

James A. Patton, Ph.D.

Associate Professor  
Radiology  
Vanderbilt University

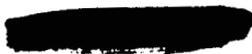
Stephen M. Pizer, Ph.D.

Associate Professor  
Computer Science  
University of N.C.

Ronald R. Price, Ph.D.

Associate Professor  
Radiology, Medical Physics  
Vanderbilt University

PRIVILEGED COMMUNICATION

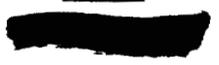


Co-Investigators (cont'd.)

SS No.

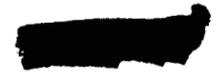
John T. Purvis, M.D.

Neurosurgeon, Knoxville  
Neurosurgical Clinic P.C.



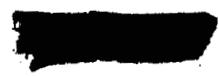
James T. Robertson, M.D.

Professor and Chairman  
Neurosurgery  
Univ. of Tennessee



E. Stanfield Rogers, M.D.

Neurosurgery  
Univ. of Tennessee



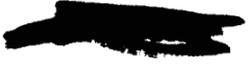
F. David Rollo, M.D., Ph.D.

Associate Professor &  
Director, Nuclear Medicine  
Vanderbilt University



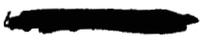
James H. Scatliff, M.D.

Professor and Chairman  
Radiology Department  
Univ. of N. C.



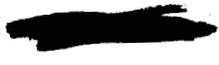
Edward V. Staab, M.D.

Professor and Acting  
Chairman, Radiology  
Univ. of N. C.



Lee C. Washburn, Ph.D.

Radiochemist  
Oak Ridge Associated  
Universities





THE UNIVERSITY OF NORTH CAROLINA  
AT  
CHAPEL HILL

The School of Medicine  
Department of Radiology

December 20, 1979

Division of Imaging  
Second Floor  
The North Carolina Memorial Hospital  
Chapel Hill, North Carolina 27514

TO: PROJECT INVESTIGATORS

TO: R. Edward Coleman, M.D., Radiology Dept., Duke University  
 Burton P. Drayer, M.D., Radiology Department, Duke University  
 Gary W. Duncan, M.D., Neurology Department, Vanderbilt University  
 x Raymond L. Hayes, Ph.D., Health Sciences Division, Oak Ridge Assoc. Univ.  
 F. Ralph Heinz, M.D., Radiology Department, Duke University  
 x Karl F. Hubner, M.D., Health Sciences Division, Oak Ridge Assoc. Univ.  
 A. Everette James, M.D., Radiology Department, Vanderbilt University  
 M. Stephen Mahaley, M.D., Ph.D., Neurosurgery Department, UNC.  
 John D. Mann, M.D., Neurology Department, UNC  
 William F. Meacham, M.D., Neurosurgery Department, Vanderbilt  
 James A. Patton, Ph.D., Radiology Department, Vanderbilt University  
 Stephen M. Pizer, Ph.D., Computer Science, UNC  
 Ronald R. Price, Ph.D., Radiology Department, Vanderbilt University  
 John T. Purvis, M.D., Neurosurgeon, Ft. Sanders Presbyterian Hosp., Knoxville  
 James T. Robertson, M.D., Neurosurgery Department, Univ. of Tennessee  
 E. Stanfield Rogers, M.D., Neurosurgery Department, Univ. of Tennessee  
 F. David Rollo, M.D., Ph.D., Radiology Department, Vanderbilt University  
 James H. Scatliff, M.D., Radiology Department, UNC  
 Edward V. Staab, M.D., Radiology Department, UNC  
 Lee C. Washburn, Ph.D., Health Sciences Division, Oak Ridge Assoc. Univ.

FROM: C. Leon Partain, Ph.D., M.D., Principal Investigator  
 Radiology, Vanderbilt University Tel: (615) 322-2394 after 1/1/80.

RE: "Brain Tumor Imaging Using Positron Emission Tomography" NIH Grant  
 Application, First Draft.

\* \* \* \* \*

Attached please find the first draft of the subject NIH proposal. Please review and give me your comments and suggestions for modification at your earliest convenience.

The first deadline for this proposal is the Department of Energy deadline at Oak Ridge on January 15. The next deadline at NIH is March 1, 1980.

The earlier review of this project is part of a large multi-institutional positron emission tomography grant from Duke/UNC, and received favorable reviews. However, reviewers' comments indicated the need for improvement in the following areas:

1. The purpose for this investigation needs to be more clearly described.
2. The data analysis procedure should be described in detail.

TO: Project Investigators

-2-

December 20, 1979

Please promptly transmit any changes in budget or research protocol which you care to suggest. Also, please promptly submit your CV if not already a part of the proposal.

Thank you very much for your cooperation in this project. I look forward to our further interaction.

\* \* \* \* \*

1079473

SECTION II - PRIVILEGED COMMUNICATION

DETAILED BUDGET FOR FIRST 12-MONTH PERIOD

FROM

July 1, 1980

THROUGH

June 30, 1981

DESCRIPTION (Itemize)		TIME OR EFFORT (HRS)	AMOUNT REQUESTED (Dollars)		
PERSONNEL	SALARY		FRINGE BENEFITS	TOTAL	
NAME	TITLE OF POSITION				
C. Leon Partain, Ph.D., M.D.	PRINCIPAL INVESTIGATOR	25			
William F. Meacham, M.D.	Neurosurgeon	5			
A. Everette James, Jr., M.D.	Radiologist	5			
Gary W. Duncan, M.D.	Neurologist	5			
F. David Rollo, M.D., Ph.D.	Nuclear Medicine	5			
James A. Patton, Ph.D.	Radiation Physics	5			
Ronald R. Price, Ph.D.	Radiation Physics	5			
(to be named)	Secretary	25			
(to be named)	Biomed. Engr. Grad. Asst	*			
(to be named)	Rad. Sci. Grad. Res. Asst.	*			
*50% Academic year, 100% Summer					
TOTALS			31,000	3,743	
				34,743	
CONSULTANT COSTS	Round trip travel expenses for three consultants per year to Oak Ridge, Tennessee			1,000	
EQUIPMENT (See ORAU budget for cyclotron and scanner time)					
SUPPLIES	Computer time			1,000	
TRAVEL	DOMESTIC 12 trips, Nashville to Oak Ridge; round trip one national meeting			600	
	FOREIGN			500	
PATIENT COSTS (See instructions)					
(See ORAU budget)				0	
ALTERATIONS AND RENOVATIONS					
OTHER EXPENSES (Itemize) Publication costs				200	
Subcontracts: 1. Oak Ridge Associated Universities, Oak Ridge, TN 37830				58,535.59, 30	
2. Univ. of North Carolina, Chapel Hill, N.C. 27514				6,390	
3. Univ. of Tennessee, Memphis, TN				250	
4. Duke University, Durham, N.C. 27710				500	
TOTAL DIRECT COST (Enter on Page 1, Item 5)				103,718	

INDIRECT COST (See Instructions)

65

% S&W & SF

% TDC\*

DATE OF DHEW AGREEMENT:

WAIVED Indirect 22,583

UNDER NEGOTIATION WITH:

Total D&S\* \$126,301

\*IF THIS IS A SPECIAL RATE (e.g. off-site), SO INDICATE.





BRAIN TUMOR IMAGING USING POSITRON EMISSION TOMOGRAPHY

- RESEARCH PLAN -

1.0. Introduction .....

    1.1. Objectives .....

    1.2. Background .....

    1.3. Rationale .....

2.0. Specific Aims .....

3.0. Methods of Procedure .....

4.0. Significance .....

5.0. Facilities Available .....

    5.1. Vanderbilt University .....

    5.2. Oak Ridge Associated Universities .....

    5.3. University of North Carolina .....

6.0. Collaborative Arrangements .....

7.0. Principal Investigator Assurance .....

8.0. References .....

9.0. Appendices .....

    9.1. Appendix A: Scientific Basis for Investigation: Relative Specificity of Utilization of Certain Amino Acids by Malignant Gliomas.....

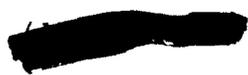
    9.2. Appendix B: Amino Acid Uptake in Brain Tumors Collaborative Agreement. ....

    9.3. Appendix C: <sup>11</sup>C-DL-Valine, IND 12,459 .....

    9.4. Appendix D: <sup>11</sup>C-DL-Tryptophan, IND 12,967 .....

    9.5. Appendix E: Amendment for <sup>11</sup>C-DL-Valine, IND 12,459 for Brain Tumor Imaging .....

    9.6. Appendix F: Amendment for <sup>11</sup>C-DL-Tryptophan, IND 12,967 for Brain Tumor Imaging .....



BRAIN TUMOR IMAGING USING POSITRON EMISSION TOMOGRAPHY

- RESEARCH PLAN -

1.0. INTRODUCTION

This project was one of seven subprojects included in the Duke University proposal, "Neurological Investigation Using PET," #1P01 NS 15653-01, E. Ralph Heinz, M.D., Principal Investigator, which was submitted in response to the 1979 NINC DS RFP for positron emission tomography projects. The overall project was not funded. In response to the reviewers' comments, the current project has been modified in the following way:

1. Further development of goals and objectives.
2. Addition of data analysis procedures.
3. Modification to provide an interdisciplinary team of radiologists, neurosurgeons, neurologists, radiochemists, physicists, and a computer scientist from several institutions; including, Vanderbilt University, University of North Carolina, University of Tennessee, Duke University, Knoxville Neurological Clinics, and Oak Ridge Associated Universities (ORAU).
4. Utilization of the radiopharmaceutical delivery system (including the 86 inch cyclotron at Oak Ridge National Laboratory) and positron emission tomography scanner at Oak Ridge Associated Universities.
5. Inclusion of preliminary pilot images from patients with known gliomas; image with C-11 valine.

1.1 Objectives

The purpose of this study is to determine quantitatively the in vivo localization of amino acids in brain tumor and surrounding brain tissues in patients before surgical intervention, 10-14 days postoperatively and every 6-8 weeks following the institution of adjunctive anti-tumor therapy (i.e. radiotherapy, chemotherapy, immunotherapy, and/or diet therapy). Substances to be studied initially would include C-11 methionine, DL-valine, isoleucine, and DL-phenylalanine.

Specific objectives include:

1. Demonstrate feasibility of brain tumor imaging in patients with known gliomas using carbon-11 labeled amino acids. Initially, <sup>11</sup>C-DL-valine and <sup>11</sup>C-DL-tryptophan will be used since IND's are already available for this study.
2. Determine the optimal carbon-11 labeled amino acid for glioma imaging; in addition to valine, likely candidates include methionine and isoleucine.
3. Determine sensitivity, specificity, and accuracy, of each carbon-11 amino acid evaluated, in glioma imaging.

4. Plan more extensive evaluation of this imaging modality for a future study of a large number of brain tumor patients from Vanderbilt University, University of North Carolina, University of Tennessee, Duke University, and Knoxville Neurological Clinics.
5. Develop protocols for future studies of brain tumor metabolism and physiology using positron-labeled glucose, immunoglobulins, and other neurological substrates and transmitters. X

## 1.2 Background

Malignant gliomas account for 23% of all human brain tumors (8) and 55% of primary intracranial gliomas (6,7). These tumors are invariably fatal with a median survival time after surgery of approximately 23 weeks if otherwise untreated (11). The treatment that has proved to be most effective up to the present time is a combination of surgical resection, whole brain radiotherapy, and systemic chemotherapy with BCNU (1,3 bis-chloroethyl-1-nitrosourea), but the median survival with this treatment protocol is only 51 weeks from time of surgery (11). Therefore, investigations of other agents and combinations of therapies are being carried out (i.e., immunostimulation, use of radiosensitizers, diet therapy).

Insofar as metabolism of gliomas is concerned, it has been determined in vivo that these tumors utilize glucose at a relatively slow rate and that anaerobic metabolism is important (3). Advances in tumor biochemistry have now made it possible to identify the single most preferred essential amino acid in vitro (5,6). Using radioiodine labeled heterologous anti-glioma globulins, it has previously been shown that there is a preferential localization of immunoglobulin within human glioma tissue (1-3). The more recent demonstration of glioma surface specific antigens has been accomplished by the purification of a vastly more specific anti-glioma antibody (10,13). X

The scientific basis for this investigation is presented in detail in Appendix A.

## 1.3 Rationale

The availability of positron emission tomography (PET) of radiolabeled substances that should localize in or be utilized by human brain tumors should permit in vivo analysis of the quantitative uptake of these substances within glioma and adjacent brain tissues. Such localization could be quantitated prior to surgical intervention, following surgical resection and histological diagnosis, and during the course of subsequent adjunctive therapy. Such data should aid in the characterization of human gliomas with reference to certain aspects of amino acid metabolism and may prove to be a useful means of serially evaluating the results of therapy, used in conjunction with serial neurological examinations and conventional computed tomography.

## 2.0 SPECIFIC AIMS

The goals of this project are:

1. To quantitate the in vivo localization of amino acids, relevant to tumor growth and the host's response to neoplasia, at the time of first diagnosis and to follow these pharmacokinetic parameters during subsequent treatments and evaluations of patients with malignant gliomas.



2. To determine alterations in glioma metabolism that may occur during the course of the disease and to relate any such alterations to:
  - a. Therapeutic interventions (i.e., radiotherapy, chemotherapy, immunotherapy, diet therapy);
  - b. Tumor regrowth (as compared with other indices of recurrence such as changes in the neurological exam and/or conventional computed tomogram).
3. To compare these in vivo data with previous as well as concurrent determinations in vitro or glioma activity.

### 3.0. METHODS OF PROCEDURE

Patients who will be studied in this project will be selected from those with anaplastic gliomas who are followed in the brain tumor therapy program of the Divisions of Neurosurgery at Vanderbilt University, The University of North Carolina, and Knoxville Neurological Clinic. A certain number of these patients will be seen in the clinic of their respective institutions prior to surgery, and during the course of their workup, a set of positron emission tomograms (PET) can be obtained, using isotopically-labeled amino acids. Post-operatively, all patients will be re-evaluated with a battery of PETs as a baseline set of studies prior to adjunctive therapy; this battery will be repeated when each patient is re-admitted for re-treatment every 8 weeks.

The battery of PETs will consist of a selected number of essential amino acids (methionine, phenylalanine, tyrosine, and/or histidine). Dosimetry calculations indicate that the whole body absorbed dose from IV carbon-11 glucose is 10 mrad/mCi (see Ref. 9). Dosimetry data are provided in Appendices C and D.

Selected patients will be transported to Oak Ridge Associated Universities, Oak Ridge, Tennessee.

Therapy protocols currently consist of:

1. Whole head radiotherapy plus BCNU chemotherapy intravenously, or,
2. Whole head radiotherapy, chemotherapy, and lavamisola immunostimulation.

2.  
question

Therapy protocols that will be instituted in the next year will likely include:

1. Whole head radiotherapy, BCNU chemotherapy, and diet therapy. Diet therapy will be designed to include a restriction of essential amino acid(s) proven by in vitro or in vivo study to be metabolized by an individual patient glioma. In vitro evaluations will be carried out in the laboratory of Drs. Rogers and Robertson in Memphis on tissue forwarded from us to them.
2. Whole head radiotherapy, BCNU chemotherapy, and immunotherapy. Immunotherapy will consist of active inoculation of glioma patients with tissue from glioma cell lines or with heterologous anti-glioma antibody.
3. Whole head radiotherapy, misonidazole radiation, potentiation, and BCNU chemotherapy.

x

?

Kinetics data will be interpreted in light of compartmental mathematical models (4).

Data analysis procedures will include:

1. Decision theory calculations will be performed, including:

- a. True positive fraction
- b. False positive fraction
- c. True negative fraction
- d. False negative fraction

for each radiopharmaceutical.

2. In addition:

- a. Sensitivity,
- b. Specificity, and
- c. Accuracy

will be calculated from the data in 1. above, using standard definition.

3. Conclusions <sup>agent giving the</sup> as to the most sensitivity, specific<sup>ity</sup>, and accurate image<sup>agent</sup> can then be drawn. X

4. Perception and recognition tests, using receiver-operator-characteristic (ROC) curves will be planned for further studies ( ). X

#### 4.0 SIGNIFICANCE

These studies should permit in vivo characterization of certain important factors relevant to glioma growth within the patient host:

- 1. Amino acid metabolism.
- 2. Future application to brain tumor metabolism studies; including, glucose metabolism.
- 3. Future application to immunoglobulin localization since glioma surface specific antigens have recently been demonstrated.

The knowledge of such data should serve:

- 1. To relate subsequent alterations in those parameters to active adjunctive therapy protocols postoperative.
- 2. To compare in vivo data derived from this study to in vitro observations of glucose metabolism from the past and in vitro observations that will be made concurrently regarding amino acid uptake.
- 3. To correlate changes in such PET observations with the other more conventional standards for detecting glioma recurrence: neurological deterioration and CT brain scanning.
- 4. To gain more insight into the potential of antibody localization in glioma tissues, as compared with adjacent brain, which in turn may serve as an index of the practicality of immunotherapy effectiveness in this disease.

PRIVILEGED COMMUNICAT

5. To determine the consistency of uptake by glioma tissues of certain essential amino acids and whether this quantitative pattern is influenced by attempts at diet therapy for this disease.
6. To follow the effects of radiotherapy and chemotherapy upon the glucose and amino acid metabolism in glioma tissues.

5.0 FACILITIES AVAILABLE

5.1 Vanderbilt University

Vanderbilt University Hospital is a 500 bed teaching hospital of Vanderbilt University School of Medicine. The 500 bed Veterans Administration Hospital is adjacent to the Medical School. The Medical School Library has 75,000 volumes and 1200 periodicals and participates in regional and national cooperative library arrangements.

Laboratory Space:

1. Approximately 100,000 radiographic examinations per year; includes diagnostic radiology, ultrasound, computed tomography, nuclear medicine, radiological sciences, radiopharmacy, radiation therapy, and radiobiology clinical and research laboratories.
2. 7,000 square feet devoted to Radiological Research under the direction of Dr. C. Leon Partain. This area includes a dedicated animal research imaging laboratory.

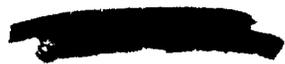
Equipment includes:

1. Interactive digital image processing system (PDP-11/55, PDP-11/05, 2 PDP-9's and a PDP-LSI/11, video display, graphic output, tape, disk, and video digitizer).
2. Central computing facilities (hardware connections with PDP-11/55 and PDP-9's) Dec-1099 and Xerox Sigma-7.
3. Searle Pho-TRAX-4000 whole-body CT scanner (interdata 8-32 processor, mag tape and floppy disk).
4. EMI MARK II head CT scanner (Data General Eclipse-magtape and floppy disk).
5. Searle Digi Sonic digital ultrasonic scanner (LSI-11 with parallel line interface).
6. Nicolet digital averager/transient recorder (RS-232 communications link, Department of Physics).
7. Colorado Video Corporation CVI-270 video compressor (interfaced to PDP-11/55 and PDP-9).
8. X-Ray Fluorescence Analyzer (SiLi detector-16Ci Am-241) (RS-232 coupling to PDP-9 computer).

Other:

1. Animal storage and surgery laboratory.

1079481



- 2. Medical, Chemistry, Biology, engineering, physics, and Joint University Libraries.
- 3. Medical Illustration Department
- 4. Vanderbilt University Medical and Graduate School (access to formal courses in statistics, signal processing and physiology).

5.2 Oak Ridge Associated Universities

not ORAU's!

The radiopharmaceutical delivery system, including 86 inch cyclotron, hot cells with remote control capability, chemical processing laboratory, radiopharmaceutical laboratory, and positron emission tomography-scanner (ECAT) are available in support of this project.

This research grant application includes a segment of activity which would be performed in facilities of the U. S. Department of Energy and governed by an existing contract between Oak Ridge Associated Universities (ORAU) and the DOE. The DOE has reviewed this proposal and has concurred in ORAU conducting the described work in the DOE facilities made available for biomedical research, subject to payment to the DOE by ORAU from NIH funds of the applicable direct and indirect cost of the work (not including any charge for the use of DOE facilities) as determined by the provisions of the DOE's contract with ORAU. It is believed that in large measure the requirements of the DOE contract parallel conditions which NIH ordinarily applies to its grants. In the event of differences between NIH grant terms and the DOE contract terms, ORAU is agreeable to meeting both to the extent that they are not in conflict, and to applying those most favorable to the United States Government where this is involved. If NIH is aware of problems which such an approach would produce or suggest, ORAU upon receipt of such advice would refer the matter to the DOE for direct resolution with NIH.

By way of general information, ORAU's contract with the DOE is a cost-type contract financed under a Government-fund account. The specific contract work is formulated in cooperation with the DOE and authorized within general guidelines in the contract. Contract terms include DOE responsibility for Government ownership and control of inventions, data, and other research products. Ownership of all equipment and facilities acquired by ORAU with DOE funds is vested in the U. S. Government at the time of acquisition. The contract also contains all the terms generally common to Government contracts of the type under which ORAU conducts research operations in Government-owned facilities.

5.3 University of North Carolina

North Carolina Memorial Hospital is a 750 bed teaching hospital of the University of North Carolina School of Medicine. The Nuclear Medicine Division at UNC presently occupies 600 square feet of space. This space includes clinical imaging areas, radiopharmacy, radioassay laboratory, counting laboratory and offices. An additional research laboratory is expected to be available within a year.

The Van der Graff radiopharmaceutical delivery system and positron emission CT scanner planned by Duke University will be used in this study.

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The major imaging systems include a Searle Gamma Camera HP, a Picker 4/15, A searle LFOV camera, and an Ohio Nuclear Dual Probe Scanner. All of these instruments are coupled to a PDP-11 Computer Gamma II data acquisition system. The PDP-11 has 28 K core, foreground/background operating system, disc and magnetic tape for data storage, and CRT display. A computed tomography total body system (Delta 2010 scanner, including a PDP-11 Computer System) was installed in the Department of Radiology in March 1978 (2 seconds per slice).

Other counting systems available include: 4 scintillation well-counters, 2 radioisotope dose calibrators, a multi-channel analyzer and 2 automatic sample changing scintillation well-counters.

The University Computation Center is equipped with IBM 360/70 and 370/55 computers and provides software support as needed. The University Computer System is coupled to the Triangle University Computer Center (TUCC) IBM 370/165 computer. In addition, we have access to an IBM 1130 terminal located in the hospital (Biomedical Computation Center) which is on line to the TUCC computer.

Nuclear Medicine also has a radiopharmacy quality control laboratory. These facilities include automatic thin layer radiochromatic analysis systems, storage and preparation areas for radiolabeling, assay and calibration of radiopharmaceuticals.

Other facilities include: A well-equipped electronics shop in Nuclear Medicine, a machine shop in Radiology, a Nuclear Medicine and Radiology Library of 825 volume, a Medical School Library with 130,200 volumes a Physics and Mathematical Sciences Library with 50,000 volumes and Medline computer based literature search facility.

#### 6.0 COLLABORATIVE ARRANGEMENTS

Vanderbilt University, Nashville, Tennessee will provide administrative, scientific and clinical direction of this project in cooperation with the University of North Carolina, University of Tennessee, Duke University, and Oak Ridge Associated Universities (see Appendix B).

Oak Ridge Associated Universities will provide scientific support in radiopharmaceutical synthesis and positron emission tomography.

Technical assistance in amino acid uptake assays from malignant gliomas will be provided by Drs. James T. Robertson and Stan Rogers, University of Tennessee, Memphis.

#### 7.0. PRINCIPAL INVESTIGATOR ASSURANCE

The undersigned agrees to accept responsibility for the scientific and technical conduct of the research project and for provision of required progress reports if a grant is awarded as the result of this application.

Date

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C. Leon Partain, Ph.D., M.D.  
Principal Investigator