U.S. DEPARTMENT OF ENERGY

UNIVERSITY RESEARCH INSTRUMENTATION PROGRAM

9102-154

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COVER PAGE

(THIS PAGE MUST BE THE FIRST PAGE OF THE APPLICATION)

709236

1. Name of Institution: Washington University (Michael J. Welch, Ph.D)
2. Department: Radiology, Division of Radiation Sciences
3. Street: 510 South Kingshighway 4. City: St. Louis
5. County: - 6. State: MO 7. ZIP: 63110 8. Congressional District: 1
9. Telephone: Area Code 314 Office: 362-8435 Home: [redacted]
10. Title of Application: A Tandem Cascade Accelerator for Radioisotope Production
11. Area of Proposed Research (Select ONE) A *

A. Biomedical/Environmental	C. Geosciences	E. Plant Science/Microbiology
B. Chemical/Coal Science	D. Materials Research	F. Other

12. Research Subcategory (See Section II of DOE/URI FY 91 Announcement) 1
13. Total DOE Funding for Research in Selected Area (During the last two fiscal years): $ 615,055
14. Estimated Purchase Price of Equipment: $ 260,015 15. Amount requested from DOE: $ 260,015

List all Federal agencies which are currently considering proposals from the institution involving the same or similar equipment.

16. Agency: none Agency Proposal Number: _____
17. Agency: _____ Agency Proposal Number: _____

NOTE: The institution is responsible for immediately informing the URI program manager in writing if a proposal involving similar or related equipment is submitted to a federal agency prior to the announcement of DOE's URI awards.

18. List and federal agency which has provided funds to the institution during the past two years for the same or similar equipment.

Agency: none Amount of Funds: _____

19. Please check one of the following:
- ☒ I authorize outside peer review of this proposal.
- ☐ I do not authorize peer review of this proposal.**

Signature of Principal Investigator: [signature] Date: 12/4/90

Name and Title of Institutional Official (President or Designee)

Susan E. Cullen, Ph.D. Signature: Susan E. Cullen

Director, Spon. Project Services Date: 12-7-90

Area Code/Telephone: (314) 362-5866

20. Is Applicant Delinquent on any Federal Debt? ☐ Yes (If, "Yes," attach an explanation) ☒ No

* Note – The application will be evaluated by reviewers in this field.

** Note – May prevent full consideration of this application.

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BOX No. H-182-17 Bldg. 2714-H
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REPOSITORY Oak Ridge Operations
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SUMMARY

This equipment request is to obtain funds to allow the Division of Radiation Sciences, Department of Radiology, to obtain a Tandem Cascade Accelerator (TCA) for production of radiopharmaceuticals for positron emission tomography. The TCA is a new accelerator designed by Science Research Lab of Sommerville, MA which produces beams of protons and deuterons with energies of 3.7 MeV and of beam currents up to 1 Milliamp. This type of accelerator can produce positron-emitting radiopharmaceuticals in yields comparable to those produced with cyclotrons, however, the accelerator has lower cost, is much lighter, uses considerably much less power than the cyclotrons, and is simpler to operate. The TCA will be utilized in the funded DOE projects "Labeling of Receptor Ligands and Other Compounds with Halogen Radionuclides" (DE-FG02-84ER60218, PI: M.J. Welch) and "Preparation of Radiopharmaceuticals Labeled with Metal Radionuclides (DE-FG02-87ER60512, PI: M.J. Welch). These projects have the express goals of developing techniques that will simplify the production of positron-emitting radiopharmaceuticals. The use of a TCA in the funded projects will allow us to compare production of radiopharmaceuticals utilizing the TCA with a conventional cyclotron and to evaluate the production of simple oxygen-15 radiopharmaceuticals using the TCA as a "radiopharmaceutical generator." In the funded proposal "Preparation of Radiopharmaceuticals Labeled with Metal Radionuclides" we are investigating par-ent/daughter generator systems which will simplify radiopharmaceutical production for PET. There is a possibility that the application of the TCA will, in fact, negate the need for parent/daughter generators. It is essential that we evaluate these two approaches as

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rapidly as possible. The only way to do this is to install a TCA at Washington University. In the second proposal "Labeling of Receptor Ligands and Other Compounds with Halogen Radionuclides," we are developing and evaluating new radiopharmaceuticals to image tumor receptors. This work is limited by the availability of short-lived radionuclides, particularly fluorine-18. The availability of fluorine-18 at any time will greatly enhance our ability to accomplish the goals of this project.

If the TCA proves to be a reliable means of producing oxygen-15, carbon-11, nitrogen-13, and fluorine-18, and is able to deliver these radionuclides to a PET center, this will have a major impact upon positron emission tomography. It will simplify the types of accelerators and allow the many advances made in this area under DOE support to be more readily available to the U.S. population.

Over the last four years, four graduate students have received their Ph.D.'s in the DOE funded areas of research from Washington University. There are currently three graduate students enrolled whose research will benefit from the acquisition of this equipment. The impact upon graduate training is, however, greater than this as the principal investigator on this proposal has a long term collaboration with another DOE contractor, Dr. John A. Katzenellenbogen of the Department of Chemistry at the University of Illinois. Over the same time period, an equivalent number of graduate students who have obtained their Ph.D. degrees from the University of Illinois have carried out the radiochemistry/radiopharmaceutical component at Washington University. The obtaining of the accelerator will have a major impact upon Dr. Katzenellenbogen's program (see letter of collaboration).

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UNIVERSITY RESEARCH INSTRUMENTATION PROGRAM

BUDGET PAGE

ESTIMATED COSTS

Instrumentation	Requested of DOE	Institution's Cost Sharing	Other Federal Funds	TOTAL
A. Purchase Price	$260,015	NA	NA	$260,015
Maintenance	NA	XXXX	XXXX	NA
Subtotal:	$260,015	NA	NA	$260,015
B. Other Allowable Costs				
1. Shipping/Handling	XXXX	NA	NA	NA
2. Building/Laboratory	XXXX	NA	NA	NA
Subtotal:		NA	NA	NA
C. TOTAL	$260,015	NA	NA	$260,015

A. Purchase Price

Description/Vendor	Quantity	Total Estimated Unit Price	Requested of DOE	Institution's Cost Sharing	TOTAL
Accelerator Applications Inc. 218 Beethoven Avenue Newton, MA 02168					
Tandem Cascade Accelerator (see quote)	1	$260,015	$260,015	NA	$260,015

DEPARTMENT OF ENERGY
UNIVERSITY RESEARCH INSTRUMENTATION PROGRAM
GRANT AND CONTRACT SUMMARY FORM

Institution Name: Washington University

Current Grant No.	Principal Investigator	Title	From MO	From YR	To MO	To YR	Total Award Value	$AMT Awarded for FY Period 1988 to 1990	DOE Technical Monitor/Location
DE-FG02-84 ER60218	Welch, M.J.	Labeling of receptor ligands with halogen radionuclides	4	84	3	93	$843,981	$308,981	Donald W. Cole, Jr. Human Health & Assessments Division Office of Health & Environmental Research Office of Energy Research Department of Energy Washington, D.C. 20545
DE-FG02-87 ER60512	Welch, M.J.	Preparation of radiopharmaceuticals labeled with metal radionuclides	1	87	12	92	$491,074	$306,074	see above

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NARRATIVE

The institution has two research programs in the applicable energy area. These two are "Labeling of Receptor Ligands and Other Compounds with Halogen Radionuclides" (DE-FG02-84ER60218, PI: M.J. Welch) and "Preparation of Radiopharmaceuticals Labeled with Metal Radionuclides (DE-FG02-87ER60512, PI: M.J. Welch). Major accomplishments have been made in both of these areas. Listed below are short reports pointing out these important advances made in the two funded areas as well as publications over the last four years.

Besides the two supported Department of Energy grants, the institution has strong NIH funded research programs in the area of positron emission tomography. Of particular note are the three program project grants (HL13851 Cyclotron Produced Isotopes in Biology and Medicine; NS06833 Brain and Its Vasculature; and HL17646 IHD SCOR) which have a total annual direct costs of $3,530,135. The major areas of research in grants (NS06833 and HL13851) are involved in positron emission tomography and at least 35% of HL17646 is involved in this area. It is due to the demand on the current accelerators that the requested accelerator will be advantageous for the DOE projects.

PREPARATION OF RADIOPHARMACEUTICALS LABELED WITH METAL RADIONUCLIDES

The goals of this project are:

1. To carry out routine production of Ga-68 labeled radiopharmaceuticals for use, particularly in pulmonary studies;

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2. To continue work on the development of Ga-68 labeled radiopharmaceuticals that could be used with positron emission tomography;

3. To evaluate indium-111 and possibly gallium-68 labeled antibodies in animal models;

4. To continue development of new chelates and bifunctional chelates for use as radiopharmaceuticals labeled with indium, gallium, and copper;

5. New approaches to the delivery of radiopharmaceuticals to the brain.

We have made major advances in all of these areas. In area 1, we have shown that gallium-68 radiopharmaceuticals can be produced routinely under robotic control for patient studies. This has resulted in several publications by us and by our collaborators in the Pulmonary Division at Washington University.

In area 2, we have continued to study gallium-68 labeled radiopharmaceuticals and have carried out the work to allow gallium-68 labeled macroaggregated albumin to be administered to patients. This was necessary due to the fact that our previous gallium-68 particulate tracer, gallium-68 labeled microspheres could not be prepared due to the fact that the microsphere kit from 3M was removed from the market. In the area of labeled antibodies, we have studied indium-111 labeled antibodies in two animal models and compared gallium-68 labeled antibodies with indium and iodine antibodies in one of these models. It appears that gallium-68 or fluorine-18 labeled antibody fragments may have promise as radiopharmaceuticals.

In the area of the preparation of new blood flow tracers, we have investigated not only gallium compounds but copper-62 compounds. A new copper-62 labeled radiophar-

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maceutical appears to have great potential for the use as a blood flow agent in the brain, heart, and kidney. The agent has a higher extraction in the brain than any other metal complex studied and quantitative images provide values of blood flow in good agreement with those obtained with O-15-labeled water by a well validated technique. The comparison of O-15 labeled flow tracers with copper-62 flow tracers will be one of the major users of the requested equipment.

Publications resulting from this project include:

Otsuka, F.L., Fleishman, J.B., Welch, M.J.: Comparative studies using ^{125}I-and ^{111}In-labeled monoclonal antibodies. Nucl Med Biol 13:325-334, 1986.

Cance, W.G., Wells, Jr., S.A., Dilley, W.G., Welch, M.J., Otsuka, F.L., and Davie, J.M.: Human parathyroid antigen: Characterization and localization with monoclonal antibodies. Proceedings of the National Academy of Sciences 83:6112, 1986.

Mintun, M.A., Dennis, D.R., Welch, M.J., Mathias, C.J., Schuster, D.P.: Measurements of pulmonary vascular permeability with positron emission tomography and Ga-68 transferrin. J Nucl Med 28:1704, 1987.

Otsuka, F.L., Welch, M.J.: Methods to label monoclonal antibodies for use in tumor imaging. Nucl Med Biol 14:243-249, 1987.

Welch, M.J., Kilbourn, M.R.: Potential labeling of monoclonal antibodies with positron emitters. In Radiolabeled Monoclonal Antibodies for Imaging and Therapy, S.C. Srivastava (ed), Plenum Press, 1988, pp 261-267.

Otsuka, F.L., Welch, M.J.: Use of an animal model system for evaluating labeled monoclonal antibodies. In Radiolabeled Monoclonal Antibodies for Imaging and

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Therapy, S.C. Srivastava (ed), Plenum Publishing Corp, New York, 1988, pp 343-361.

Cance, W.G., Otsuka, F.L., Dilley, W.G., Scott, R.W., Davie, J.M., Welch, M.J., Wells, Jr., S.A..: A potential new radiopharmaceutical for parathyroid imaging: radio-labeled parathyroid-specific monoclonal antibody - I. Evaluation of ^{125}I-labeled antibody in a nude mouse model system. Nucl Med Biol 15:299-303, 1988 (Int J Radiat Appl Instrum Part B).

Otsuka, F.L., Cance, W.G., Dilley, W.G., Scott, R.W., Davie, J.M., Wells, Jr., S.A., Welch, M.J.: A potential new radiopharmaceutical for parathyroid imaging: radiolabeled parathyroid-specific monoclonal antibody - II. Comparison of ^{125}I- and ^{111}In-labeled antibodies. Nucl Med Biol 15:305-311, 1988 (Int J Radiat Appl Instrum Part B).

Mathias, C.J., Sun, Y., Welch, M.J., Green, M.A., Thomas, J.A., Wade, K.R., Martell, A.E.: Targeting radiopharmaceuticals: Comparative biodistribution studies of gallium and indium complexes of multidentate ligands. Nucl Med Biol 15:69-81, 1988 (Int J Radiat Appl Instrum Part B).

Mathias, C.J., Welch, M.J., Schwartz, D.B., Spaethe, S.M., Needleman, P.: Differentiation in vivo of the sequential blood cell invasion following ureter obstruction of the rabbit kidney. Nucl Med Biol 16:25-32, 1989 (Int J Radiat Appl Instrum, Part B).

Moore, D.A., Fanwick, P.E., Welch, M.J.: Synthesis, characterization, and solid-state structure of a new hexachelating ligand and its complex with gallium(III). Inorg Chem 28:1504-1506, 1989.

Shelton, M.E., Green, M.A., Mathias, C.J., Welch, M.J., Bergmann, S.R.: Kinetics of copper-PTSM in isolated hearts: A novel tracer for measuring blood flow with

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positron emission tomography. J Nucl Med 30:1843-1847, 1989.

Moore, D.A., Fanwick, P.E., Welch, M.J.: A novel hexachelating amino-thiol ligand and its complex with gallium(III). Inorg Chem 29:672-676, 1990.

Mathias, C.J., Welch, M.J., Raichle, M.E., Mintun, M.A., Lich, L.L., McGuire, A.H., Zinn, K.R., John, E.K., Green, M.A.: Evaluation of a potential generator-produced PET tracer for cerebral perfusion imaging: Single-pass cerebral extraction measurements and imaging with radiolabeled Cu-PTSM. J Nucl Med 31:351-359, 1990.

Brodack, J.W., Kaiser, S.L., Welch, M.J.: Laboratory robotics for the remote synthesis of generator-based positron-emitting radiopharmaceuticals. LRA 1:285-294, 1989.

Mathias, C.J., Sun, Y., Connett, J.M., Philpott, G.W., Welch, M.J., Martell, A.E.: A new bifunctional chelate, $BrMe_2HBED$: An effective conjugate for radiometals and antibodies. Inorganic Chem 29:1475-1480, 1990.

Shelton, M.E., Green, M.A., Mathias, C.J., Welch, M.J., Bergmann, S.R.: Assessment of regional myocardial and renal blood flow with copper-PTSM and positron emission tomography. Circulation 82:990-997, 1990.

Madsen, S.L., Bannochie, C.J., Martell, A.E., Mathias, C.J., Welch, M.J.: Investigation of physicochemical and in-vivo behavior of diastereomeric iron-59, gallium-68, and indium-111-EHPG trivalent metal complexes. J Nucl Med 31:1662-1668, 1990.

Mathias, C.J., Margenau, W.H., Brodack, J.W., Welch, M.J., Green, M.A.: A remote system for the synthesis of copper-62 labeled Cu(PTSM). Int J Appl Isotopes Part A (in press).

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Green, M.A., Mathias, C.J., Welch, M.J., McGuire, A.H., Perry, D., Fernandaz-Rubio, F., Perlmutter, J.S., Raichle, M.E., Bergmann, S.R.: [^{62}Cu]-labeled pyruvaldehyde bis(N^4-methylthiosemicarbazonato)copper(II): synthesis and evaluation as a positron emission tomography tracer for cerebral and myocardial perfusion. J Nucl Med (in press).

Sun, Y., Mathias, C.J., Welch, M.J., Madsen, S.L., Martell, A.E.: Targeting radiopharmaceuticals II: evaluation of new trivalent metal complexes with different overall charges. Int J Appl Radiat Biol Part II (in press).

Moerlein, S.M., Daugherty, A., Sobel, B.E., Welch, M.J.: Metabolism imaging with gallium-68 and indium-111-labeled low-density lipoprotein. J Nucl Med (in press).

Schuster, D.P., Haller, J.: A quantitative correlation of extravascular lung water accumulation with vascular permeability and hydrostatic pressure measurements: a positron emission tomography study. J of Critical Care (in press).

Kaplan, J.D., Calandrino, F.S., Schuster, D.P.: A positron emission tomographic comparison of pulmonary vascular permeability during the adult respiratory distress syndrome and pneumonia. Am Rev of Resp Dis (in press).

LABELING OF RECEPTOR LIGANDS AND OTHER COMPOUNDS WITH HALOGEN RADIONUCLIDES

Major research accomplishments of this grant are:

1. To continue our studies on the usefulness of fluorine-18 labeled 16α-fluoroestradiol-17β (^{18}FES) for detecting estrogen receptor containing tumors and metastases and to attempt to correlate the uptake of the radiolabeled estrogen with the receptor levels.

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2. To attempt to develop new labeling techniques for synthesizing halogen labeled radiopharmaceuticals in high yield. Of particular importance is the synthesis of fluorine-18 labeled estrogens designed for reduced or directed metabolism.

3. To test the new fluorine-18 labeled estrogens using an in vivo rat model.

4. To attempt to label estrogens with iodine-123 for single photon studies.

5. To investigate the synthesis and biologically evaluation of fluorine-18 labeled ligands for the androgen and progesterone receptors.

6. To apply robotics for synthesizing potentially useful compounds.

Major advances have been made in all the above areas. Specifically in area 1, patient studies have been carried out. This work has shown that the uptake of fluorine-18 labeled 16α-fluoroestradiol-17β correlates well with receptor levels measured in vivo and also that the uptake of the tracer is blocked in humans by the administration of the antiestrogen tamoxifen. An image from this work was designated "Image of the Year" by Dr. Wagner, Jr. following his summary of the 1987 Society of Nuclear Medicine Meeting. We have also evaluated the brain uptake of both estrogen and progesterone and this work was awarded the Berson-Yalow Award from the Society of Nuclear Medicine in 1988. This publication represents a new application of radiolabeled sex hormones. Hines and coworkers (M Hines, Psycol Bull 92:56, 1982) have suggested that hormone levels in the brain are important for sexual differentiation of human behavior. We have shown that both 16α-[F-18]-fluoroestradiol-17β and 21-[F-18]-fluoro-16α-ethyl-19-norprogesterone (FENP) accumulate in the hypothalamus and pituitary tissues of primates and humans; and, in primates, this uptake can be blocked by administration of

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nonradioactive competing ligands. This presents an opportunity for studying sex hormone receptors in mammalian brain.

In research area 2, we have developed new labeling techniques, both for fluorination and for radiolabeling with other halogens. The labeled estrogens have been evaluated in an in vivo model to compare their possible clinical potential with the 16α-[F-18]-fluoroestradiol-17β.

In area 5, we have investigated new ligands for the progesterone, androgen, and glucocorticoid receptor systems.

We have continued our work in the application of robotics to radiopharmaceutical production. A laboratory robot now prepares four cyclotron produced radiopharmaceuticals and is involved in the preparation of the majority of fluorine-18 labeled radiopharmaceuticals prepared at Washington University.

Recent publications resulting from this project include:

Chi, D.Y., Kilbourn, M.R., Katzenellenbogen, J.A., Welch, M.J.: A rapid and efficient method for the fluoroalkylation of amines and amides. Development of a method suitable for incorporation of the short-lived positron-emitting radionuclide F-18. J Org Chem 52:658-664, 1987.

Mathias, C.J., Welch, M.J., Katzenellenbogen, J.A., Brodack, J.W., Kilbourn, M.R., Carlson, K.E., Kieswetter, D.O.: Characterization of the uptake of 16α-([^{18}F]fluoro)-17β-estradiol in DMBA-induced mammary tumors. Nucl Med Biol 14:15-25, 1987.

Moerlein, S.M., Hwang, D-R., Welch, M.J.: No-carrier-added radiobromination via cuprous chloride-assisted nucleophilic aromatic bromodeiodination. Appl Radiat Isot

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39:369-372, 1988.

Welch, M.J., Kilbourn, M.R.: Potential labeling of monoclonal antibodies with positron emitters. In Radiolabeled Monoclonal Antibodies for Imaging and Therapy, S.C. Srivastava (ed), Plenum Press, 1988, pp 261-267.

Welch, M.J., Katzenellenbogen, J.A., Mathias, C.J., Brodack, J.W., Carlson, K.E., Chi, D.Y., Dence, C.S., Kilbourn, M.R., Perlmutter, J.S., Raichle, M.E., Ter-Pogossian, M.M.: N-(3-[F-18]Fluoropropyl)-spiperone: The preferred F-18 labeled spiperone analog for positron emission tomographic studies of the dopamine receptor. Int J Nuc Med Biol 15:83-97, 1988.

Brodack, J.W., Dence, C.S., Kilbourn, M.R., Welch, M.J.: Robotic production of 2-deoxy-2-[^{18}F]fluoro-D-glucose: A routine method of synthesis using tetrabutylammonium [^{18}F]fluoride. Int J Appl Radiat Isotop 39:699-703, 1988.

Brodack, J.W., Kilbourn, M.R., Welch, M.J.: Automated production of several positron-emitting radiopharmaceuticals using a single laboratory robot. Appl Radiat Isot 39:689-698, 1988 (Int J Radiat Appl Instrum, Part A).

Pomper, M.G., Katzenellenbogen, J.A., Welch, M.J., Brodack, J.W., Mathias, C.J.: 21-[^{18}F]Fluoro-16α-ethyl-19-norprogesterone: Synthesis and target tissue selective uptake of a progestin receptor based radiotracer for positron emission tomography. J Medicinal Chem 31:1360, 1988.

Mintun, M.A., Welch, M.J., Siegel, B.A., Mathias, C.J., Brodack, J.W., McGuire, A.H., Katzenellenbogen, J.A.: Breast cancer: PET imaging of estrogen receptors. Radiology 169:45-48, 1988.

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Chesis, P.L., Griffeth, L.K., Mathias, C.J., Welch, M.J.: Sex-dependent differences in N-(3-[^{18}F]fluoropropyl)-N-nordiprenorphine biodistribution and metabolism. J Nucl Med 31:192-201, 1990.

Moerlein, S.M., Lannoye, G.S., Welch, M.J.: No-carrier-added radiosynthesis of [^{123}I]HIPDM: N,N,N'-trimethyl-N'-(2-hydroxy-3-methyl-5-[^{123}I]iodobenzyl)-1,3-pr opanediamine. Appl Radiat Isot 41:253-257, 1990 (Int J Radiat Appl Instrum Part A).

Moerlein, S.M., Parkinson, D., Welch, M.J.: Radiosynthesis of high effective specific-activity [^{123}I]SCH 23982 for dopamine D-1 receptor-based SPECT imaging. Appl Radiat Isot 41:381-385, 1990 (Int J Radiat Appl Instrum Part A).

Pomper, M.G., Pinney, K.G., Carlson, K.E., Van Brocklin, H., Mathias, C.J., Welch, M.J., Katzenellenbogen, J.A.: Target tissue uptake selectivity of three fluorine--substituted progestins: Potential imaging agents for receptor-positive breast tumors. Nucl Med Biol 17:309-319, 1990 (Int J Radiat Appl Instrum Part B).

Pochapsky, S.S., VanBrocklin, H.F., Welch, M.J., Katzenellenbogen, J.A.: Synthesis and tissue distribution of fluorine-18 labeled triflkuorohexadecanoic acids. Considerations in the development of metabolicaly blocked myocardial imaging agents. Bioconjugate Chem 2:231-244, 1990.

VanBrocklin, H.F., Brodack, J.W., Mathias, C.J., Welch, M.J., Katzenellenbogen, J.A., Keenan, J.F., Mizejewski, G.J.: Binding of 16α-[^{18}F]fluro-17β-estradiol to alphafetoprotein in sprague-dawley female rats affects blood levels. Nucl Med Biol (in press).

Pomper M.G., VanBrocklin, H., Thieme, A.M., Thomas, R.D., Kiesewetter, D.O., Carlson, K.E., Mathias, C.J., Welch, M.J., Katzenellenbogen, J.A.: 11β-methoxy-, 11β-

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ethyl, and 17α-ethynyl-substituted 16α-fluoroestradiols: receptor-based imaging agents with enhanced uptake efficiency and selectivity. J Med Chem (in press).

Liu, A., Katzenellenbogen, J.A., VanBrocklin, H.F., Mathias, C.J., Welch, M.J.: 20-[^{18}F]fluoromibolerone, a positron-emitting radiotracer for androgen receptors: synthesis and tissue distribution studies. J Nucl Med (in press).

Otsuka, F.L., Welch, M.J., Kilbourn, M.R., Dence, C.S., Dilley, W.G., Wells, S.A.: Antibody fragments labeled with fluorine-18 and gallium-68: in vivo comparison with indium-111 and iodine-125 labeled fragments. Nucl Med Biol (in press).

Impact of the equipment on the two funded projects:

With the widespread use of sophisticated positron imaging devices, there is an increase in demand for positron-emitting radiopharmaceuticals. The two funded projects are aimed at improving the supply of such radiopharmaceuticals. The goal of Project DE-FG02-87ER60512 is to provide positron-emitting radiopharmaceuticals at a lower cost than these available with a cyclotron. The ability to compare the production of new radiopharmaceutical utilizing a generator with those available from the tandem cascade accelerator radiopharmaceutical delivery system would allow us to evaluate which approach is most likely to succeed. The comparison of flow tracers such as copper-PTSM developed under this proposal with O-15-labeled water or O-15-butanol produced with the tandem cascade accelerator would allow us to decide which approach would most beneficial for the widespread application of PET. We would be able to evaluate whether a simple accelerator could produce the total variety of PET radiopharmaceuticals or be utilized in conjunction with regional distribution centers to produce only

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oxygen-15. Our comparison of oxygen-15-labeled radiopharmaceuticals produced with the tandem cascade accelerator with radiopharmaceuticals produced by generators would be an important comparison.

The second proposal, "Labeling of Receptor Ligands and Other Compounds with Halogen Radionuclides," is aimed at producing fluorine-18 labeled radiopharmaceuticals. These radiopharmaceuticals are aimed at the estrogen, progestin, androgen, and glucocorticoid corticoid receptor. The accelerator would be important in two areas. It would allow a continuous access to fluorine-18 in order to evaluate the new synthetic routes prepared as well as the evaluation and comparison of these compounds. A second important area would be in the evaluation of fluorine-18 produced from this low energy accelerator in the production of complex receptor based radiopharmaceuticals. This would allow a greater number of students to be involved in this project. It is interesting to note that a recent report published by the National Academy of Sciences (Training Requirements for Chemists in Nuclear Medicine, Nuclear Industry, and Related Areas, Report of a Workshop, National Academy Press, 1988) points out a real need for individuals whose primary specialization may be in organic synthesis, analytical chemistry, or biochemistry, but who have a sound background in radiochemical techniques and instrumentation. The availability of this small accelerator would allow the training of a greater number of people. This training would be both from individuals at Washington University but also graduate students from our long term collaborator, John A. Katzenellenbogen, Professor of Chemistry at the University of Illinois (see appended letter). The types of experiments that would be carried out would be those to show the

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feasibility of developing O-15 and fluorine-18 radiopharmaceuticals using the tandem cascade accelerator and then the experiments outlined in our proposal "Labeling of Receptor Ligands and Other Compounds with Metal Radionuclides." Initially we would evaluate new target approaches and then utilize the targets to synthesize ligands for the progestin, androgen, glucocorticoid receptor systems.

Impact on Other Programs

As previously discussed, this accelerator will have a major impact on other federal supported proposals at Washington University. Also, the application of an inexpensive accelerator will impact upon DOE's programs in nuclear medicine. A significant portion of the funded DOE nuclear medicine program is in positron emission tomography and the TCA will allow the transfer of this technology to a much greater section of the population as PET will become affordable and isotope production simpler. As discussed above, graduate students who have been involved in the DOE supported projects over the last many years and the accelerator will increase this involvement. Examples of representative experiments follow:

Experiments to Evaluate Targetry with the TCA

The group at Sciences Research Laboratory has shown that conduction cooled foils with a high aspect ratio geometry can be utilized at the high beam currents of the TCA. Conventional gas targets will be utilized to produced oxygen-15 which will be converted into oxygen-15-labeled oxygen, carbon monoxide water, and butanol using conventional techniques.[1-3] We are currently under other support producing a system that can consecutively produce 8 batches of O-15-butanol. This device will be utilized

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with the TCA.

We will investigate the production of fluorine-18 using several approaches. One of these approaches will be to irridate O-18-oxygen gas and remove the fluoride with various scavengers. We have experience with this in the past utilizing cyclotron targets. Nitricoxide has been utilized to trap fluorine NOF.[4] A heated ingaseous $H_2{}^{18}O$ target will also be investigated seeing if the radioactivity can be removed from the target. The final approach will be the study of various types of solid target to produce fluorine-18. We have experience in solid targets[5] and have begun to utilize O-18 enriched barium carbonate on our current cyclotrons to allow the production of high yields of F-18. With these approaches we are confident that high yields of F-18 can be produced with TCA.

Synthesis of Ligands for the Progestin, Androgen, and Glucocorticoid Receptor Systems

Fluorine-18-labeled 21-fluoro-16α-ethyl-19-norprogesterone (FENP) is currently being evaluated in humans.[6] We have investigated in animal models analogs of R5020 and find that these agents defluoronate in vivo. A novel synthetic retroprogestin DU41165 (Scheme 1), which has high in vitro binding affinity has been evaluated in its tritiated form and shows uterus to nontarget ratios of up to 71, 4 hours after administration. This compound does contain a fluorine atom but we do have available the chlorinated analog as a precursor. We will initially attempt to prepare the compound by fluorine for chlorine exchange. If this does not result in high yield, analogs will be prepared where the acetate group is substituted with other esters such as the fluoropropionate group.

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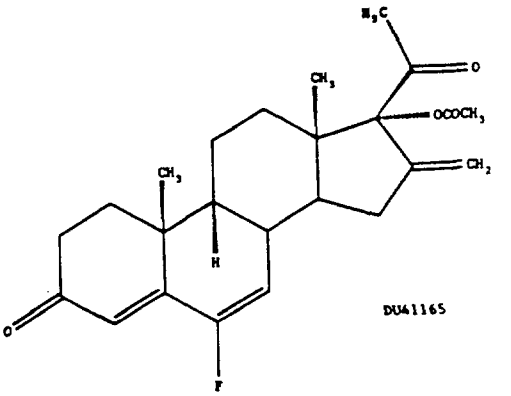
Scheme 1



Androgen receptors are present in high concentrations in the prostate and are also found in prostate tumors. Androgen receptor concentration is useful in predicting the clinical response to endocrine therapy.[7] Although the majority of prostatic androgen receptors are usually fully occupied by the normal levels of endogenous androgens, prostatic cancer patients on hormonal therapy (which consists of estrogen administration to suppress androgen biosynthesis) the androgen receptors are largely unoccupied. This, an androgen receptor ligand with suitable binding properties may be useful as an in vivo imaging agent. Brades and Katzenellenbogen[8] have analyzed the effect of known structural changes in the testosterone, 19-nortestosterone, and 5α-dihydroxy-testosterone systems on the binding affinity for the androgen receptor. Brandes and Katzenellenbogen have reported the androgen receptor binding affinity of a number of fluorine substituted androgens. If is apparent from their work that compounds with affinities higher than that of testosterone will be required for successful in vivo imaging of androgen target tissues.

Carlson and Katzenellenbogen (unpublished data) have measured the tissue distribution of 5 tritium-labeled androgens; this work will be the basis for the develop-

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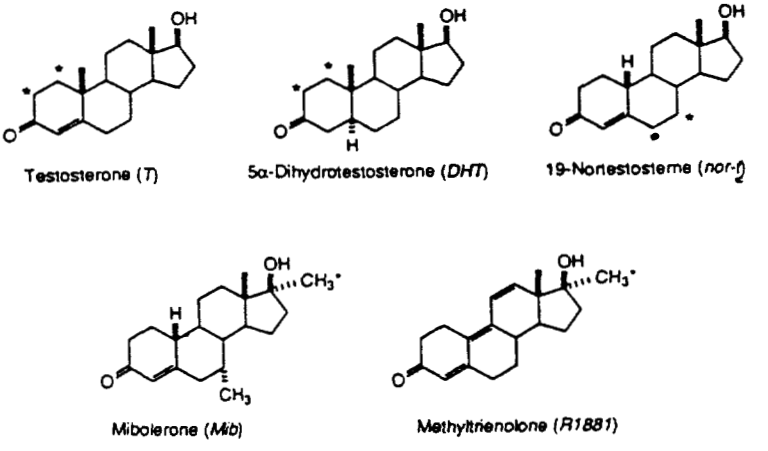
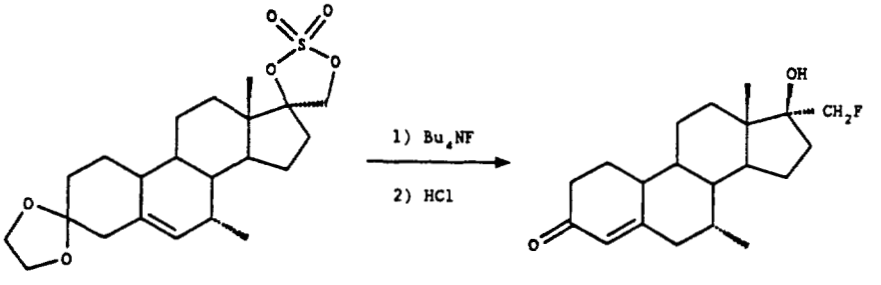
ment of a fluorine-18-labeled androgen. The structures of the compounds investigated by Carlson and Katzenellenbogen are given in Scheme 2 high binding affinities have been measured for several analogs.

Scheme 2



The work of Carlson and Katzenellenbogen showed the highest prostate uptake and higher prostate/muscle ratio for tritiated-mibolerone and tritiated-methyl trienolone with target to nontarget ratios approaching 20 at 1h after administration (Table 1). We have recently prepared a fluorine-18 derivative of mibolerone utilizing a cyclic sulphate intermediate (Scheme 3).



Scheme 3

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This was studied in rats that were pretreated with diethylstilbestrol (DES) to suppress androgen biosynthesis thereby increasing the concentration of unoccupied androgen receptors. This preliminary data is presented in Table 3 and shows that reasonable target to nontarget ratios are obtained with this compound. We will continue to evaluate this compound and study its metabolism. We will also prepare similar analogs of methyltrienolone (R1881) and compare the uptake of this compound with the analog of mibolerone. Metabolism and biodistribution studies will be carried out on promising agents.

TABLE 1

UPTAKE OF TRITIUM-LABELED ANDROGENS

Compound	RBA	% ID/g Prostate (Prostate/Muscle) 1 h	4 h
Testosterone	6	0.44 (4.5)	0.26 (3.9)
19-Nortestosterone	31	0.38 (3.0)	0.15 (2.9)
5α-Dihydrotestosterone	61	0.39 (2.8)	0.27 (3.8)
R1881	100	1.50 (4.6)	1.16 (13)
Mibolerone	115	0.65 (3.7)	0.50 (6.2)

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TABLE 2

Biodistribution of ^{18}F-Mibolerone in Adult Male S.D. Rats
Pretreated with 1mg DES (3 & 24h, s.q.)
% ID/g (n = 4; $\bar{x}$ ± s.d.)

	30 min	1 hour	2 hour	2 hour (no DES tx)	2 hour▽ Blocked*	4 hour▽
blood	.23 ± .01	.16 ± .03	.09 ± .01	.06 ± .01	.08 ± .02	.05 ± .002
lung	.47 ± .02	.30 ± .02	.17 ± .02	.11 ± .01	.08 ± .03	.08 ± .01
liver	2.36 ± .15	1.84 ± .19	.80 ± .07	.51 ± .07	.67 ± .01	.42 ± .05
spleen	.24 ± .02	.17 ± .03	.09 ± .01	.06 ± .00	.07 ± .02	.05 ± .002
kidney	.88 ± .08	.75 ± .07	.42 ± .04	.27 ± .02	.29 ± .09	.17 ± .02
muscle	.23 ± .01	.18 ± .02	.09 ± .01	.07 ± .01	.06 ± .02	.06 ± .02
fat	.57 ± .09	.26 ± .02	.13 ± .04	.11 ± .03	.13 ± .04	.07 ± .008
bone	.19 ± .02	.20 ± .02	.25 ± .03	.24 ± .11	.27 ± .02	.23 ± .01
v.prostate	.89 ± .07	.97 ± .28	.60 ± .11	.38 ± .15	.16 ± .02	.61 ± .08
d.prostate	.92 ± .06	1.19 ± .61	.77 ± .27	.39 ± .14	.11 ± .02	.54 ± .14
v.prostate/ blood	3.78 ± .21	6.38 ± 2.60	6.71 ± 1.34	6.13 ± 2.78	2.05 ± .93	12.30 ± 2.25
v.prostate/ muscle	3.83 ± .38	5.58 ± 1.89	6.51 ± 1.09	5.62 ± 2.23	2.64 ± 1.19	11.35 ± 2.83
d.prostate/ blood	3.95 ± .21	8.17 ± 4.82	8.82 ± 3.91	6.20 ± 2.41	1.42 ± .80	10.95 ± 2.53
d.prostate/	3.98 ± .28	6.91 ± 3.85	8.56 ± 3.55	5.68 ± 1.95	1.82 ± 1.02	10.82 ± 5.44

▽ n=3
* Blocked = 36µg testosterone coinjected

Glucocorticoid Receptors

Corticoid steroid hyposecretion has been demonstrated in patients with Alzheimer's disease.[9] This is presumably due to an absence of certain corticoid receptors containing hippocampal neurons which mediate feed-back inhibition of adrenal corticoid steroid production. We have, therefore, been interested in synthesizing ligands for the glucocorticoid receptors. In the brain at least three high affinity glucocorticoid binding proteins have been identified. These are designated Type 1 (mineralocorticoid or corticosterone preferring, CR). Type 2 (glucocorticoid or dexamethozone preferring, GR), and Type 3 (corticoid steroid binding globulin, CBG) receptors.[10,11]

In vivo autoradiography and cytosol binding assays have localized CR almost

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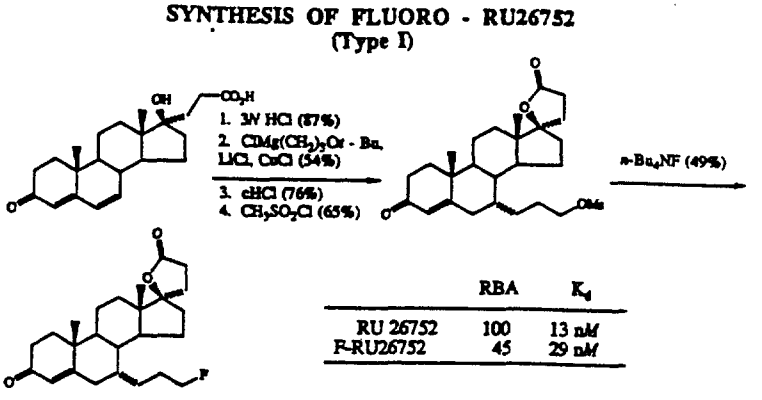
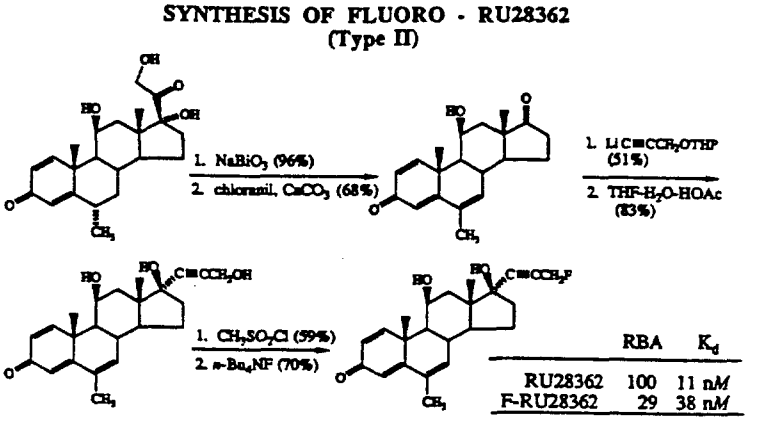
entirely in the septal hippocampal region of the brain complex while the GR are present throughout the brain.[12] A fair degree of heterologous binding by natural corticoid steroids is known to occur. Ligands have recently been synthesized that should be capable of differentiating between CR and GR in vivo (based on their in vitro affinities).[13]

We have synthesized Type 1 and Type 2, glucocorticoid receptor ligands as shown in Scheme 4 and 5.

Scheme 4



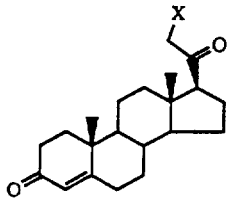
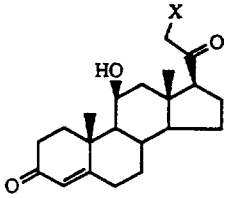
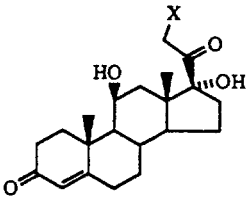
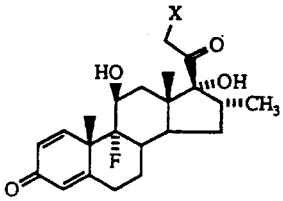


Scheme 5

Preliminary biological distributions of these compounds have been carried out and although the Type I ligand accumulated in the hippocampus, blocking with cold ligands was not observed. The binding affinity of other corticoid steroids are shown in Table 4. As seen in Table 4, the derivatives do exist which have significantly higher binding affinities for the corticoid Type 1 and Type 2 receptor systems than those studied to date. We will attempt to synthesize these compounds utilizing the triflate or mesylate used to prepare other analogs of receptor ligands.

Table 3

OTHER FLUORO - CORTICOSTEROIDS

	X	RBA I (RU26752 = 100)	RBA II (RU28362 = 100)
	OH	234	---
	F	204	0.35
	OH	141	7.9
	F	36	2.1
	OH	138	4.5
	F	19	7.9
	OH	10	52
	F	3.4	71

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10. Emadian SM, Kuttge WG, Densmore CLJ: Steroid Biochem 24:953, 1986.

11. DeKloet ER, Reul JHHM, DeRonde FSW, et al: Steroid Biochem 25:723, 1986.

12. Reul JMHM, DeKloet ER: Steroid Biochem 24:269, 1986.

13. Coirini H, Magarinos AM, DeNicola AF, et al: Brain Res 361:212, 1985.

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Science Research Laboratory, Inc.

15 WARD STREET
SOMERVILLE, MA 02143
TELEX 322584
(617) 547-1122

November 28, 1990

Dr. Michael Welch
Mallinkrodt Institute of Radiology
4939 Audubon St.
Rm 4468
St. Louis, MO. 63110

Dear Mike:

With regard to your grant application to the DOE University Research Instrumentation Program, Science Research Laboratory, Inc. (SRL) agrees to transfer to Washington University a Tandem Cascade Accelerator (TCA) constructed under a research program funded by the National Cancer Institute. In conjuction with this transfer, Accelerator Applications Inc. (AAI) is submitting a quotation for all auxilary equipment required to render this acclerator fully operational for the production of PET radioisotopes. AAI is a manufacturing company founded by the principals of SRL to commercialize the TCA and other related accelerator technologies. The TCA will be delivered to Washington University concurrently with the equipment manufactued by AAI.

With best regards,

Jonah Jacob
President

1063040

AAI

218 Beethoven Ave.
Newton, MA. 02168
Telephone:617-965-7975
November 28, 1990
Quotation No. Q190

Prof. Michael Welch
Mallinckrodt Institute of Radiology
4939 Audubon St.
Rm 4468
St. Louis, MO. 63110

QUOTATION

ITEM	DESCRIPTION	QUANTITY	PRICE
1	H^-/D^- TCA ion injector, 1mA, 30keV including all ion source and lens power supplies. Provided with one 240 l/sec turbomolecular pump and one 8 in dia. cryopump and compressor.	1	$128,419.
2	TCA automated touch panel control system	1	$17,180.
3	TCA gas target system, with vacuum interlock and 8 in. dia. cryopump and compressor	1	$29,020
4	TCA pressure vessel, ASME code certified	1	$44,100.
5	TCA stripping foil carousel	1	$12,276.
6	Upgrade and test TCA high voltage power supply and driver, 1.85 MV, 2.5 mA.	1	$29,020.

DELIVERY: 12 months A.R.O.
TERMS: 50% on placement of order
25% on delivery of parts and materials to AAI
10% on shipment to Washington University
15% on acceptance by Washington University
F.O.B. Destination
This quotation is valid until December 31, 1991

Sincerely,

Robert E. Klinkowstein

1063041

ACCELERATOR APPLICATIONS, INC. NEWTON

ATTACHMENT 1

Faculty Resumes:

Michael J. Welch, Ph.D.

Stephen Moerlein, Ph.D.

Marcus E. Raichle, M.D.

Steven R. Bergmann, M.D., Ph.D.

1063042

WELCH, Michael J. Professor of Radiation Chemistry; Birthdate: [redacted]

EDUCATION:

[redacted]

EXPERIENCE:

1962 - 1965	Queen Mary College, Department of Chemistry, University of London, London, England
1965 - 1967	Research Associate, Brookhaven National Laboratory, Upton, NY
1967 - 1970	Assistant Professor, Chemistry, Washington University, St. Louis, MO
1970 - 1974	Associate Professor of Radiation Chemistry in Radiology, Mallinckrodt Institute of Radiology, Washington University
1970 - 1976	Associate Professor, Chemistry, Washington University, St. Louis, MO
1976 - 1978	Adjunct Professor, Chemistry, Washington University, St. Louis, Mo.
1978 - present	Professor, Chemistry, Washington University, St.Louis, MO.
1974 - present	Professor of Radiation Chemistry in Radiology, Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, MO

HONORS: Open Scholarship to St. Catharines College, Cambridge University, 1958 -1961; Paul C. Aebersold Award for Outstanding Achievement in Basic Science Applied to Nuclear Medicine, 1980; Berson-Yalow Award (Society of Nuclear Medicine), 1988, 1990; American Chemical Society St. Louis Award, 1988; American Chemical Society Nuclear Award, 1990

SOCIETIES: American Chemical Society; The Chemical Society (London); The Radiation Research Society; Sigma Xi; The Society of Nuclear Medicine: President Elect 1983 - 1984, President 1984 - 1985; Member, Board of Trustees, 1980 - 1983; General Program Chairman, 1988 - present; President, Radiopharmaceutical Science Council, 1980 - 1981; President, Missouri Valley Chapter, 1977 - 1979. National Academy of Sciences: Member, Subcommittee on Nuclear and Radiochemistry: 1980 - 1982. Member, Committee on Nuclear and Radiochemistry: 1983-1986. Diagnostic Radiology Study Section, NIH: Member, 1986-1989; Chairman, 1989-

PUBLICATIONS:

Chesis, P.L., Hwang, D-R., Welch, M.J.: N-(3-[^{18}F]Fluropropyl)-N-nordiprenorphine: Synthesis and characterization of a new agent for imaging opioid receptors with positron emission tomography. J Med Chem 33:1482-1490, 1990.

Shelton, M.E., Dence, C.S., Hwang, D-R., Herrero, P., Welch, M.J., Bergmann, S.R.: In vivo delineation of myocardial hypoxia during coronary occlusion using fluorine-18 fluoromisonidazole and positron emission tomography: A potential approach for identification of jeopardized myocardium. J Am Coll Cardiol 16:477-485, 1990.

Pochapsky, S.S., VanBrocklin, H.F., Welch, M.J., Katzenellenbogen, J.A.: Synthesis and tissue distribution of fluorine-18 labeled triflkuorohexadecanoic acids. Considerations in the development of metabolicaly blocked myocardial imaging agents. Bioconjugate Chem 2:231-244, 1990.

Mathias, C.J., Welch, M.J., Raichle, M.E., Mintun, M.A., Lich, L.L., McGuire, A.H., Zinn, K.R., John, E.K., Green, M.A.: Evaluation of a potential generator-produced PET tracer for cerebral perfusion imaging: Single-pass cerebral extraction measurements and imaging with radiolabeled Cu-PTSM. J Nucl Med 31:351-359, 1990.

Pomper, M.G., Pinney, K.G., Carlson, K.E., Van Brocklin, H., Mathias, C.J., Welch, M.J., Katzenellenbogen, J.A.: Target tissue uptake selectivity of three fluorine-substituted progestins: Potential imaging agents for receptor-positive breast tumors. Nucl Med Biol 17:309-319, 1990 (Int J Radiat Appl Instrum Part B).

MOERLEIN, Stephen Michael, Associate Professor Birthdate: [redacted]

EDUCATION: [redacted]

EXPERIENCE:

1978 - 1981	Director of Radiopharmacy, Division of Nuclear Medicine, Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, MO
1982 - 1985	Staff Scientist (Radiopharmaceutical Chemistry), Institut fuer Chemie 1: Nuklearchemie der Kernforschungsanlage Juelich, Fed. Rep. Germany
1985 - 1986	Staff Scientist II, Donner Laboratory, Biology and Medicine Division, Lawrence Berkeley Laboratory, University of California, Berkeley, CA
1986 - 1989	Assistant Professor, Department of Radiology, Washington University School of Medicine, St. Louis, MO
1989-present	Associate Professor, Department of Radiology, Washington University School of Medicine, St. Louis, MO
1989-present	Associate Professor, Department of Biochemistry and Molecular Biophysics, Washington University School of Medicine, St. Louis, MO

AWARDS & SOCIETIES

American Association for the Advancement of Science; American Chemical Society; American Pharmaceutical Society; Royal Society of Chemistry; Society of Nuclear Medicine; Society for Neuroscience;

Research Fellowships: Department of Chemistry, Washington University, 1978-1981; Teaching Fellowships: Department of Chemistry, Washington University, 1976-1978; Sigma Xi, 1976; Women's Auxiliary to the Univ. of Illinois College of Pharmacy Scholarship, 1975; Michael Reese Medical Research Fellowships, 1974, 1975; Illinois State Scholarships 1972-1974; NIH/PHS National Research Service Awards 1982-1984; NIH FIRST Award 1988-present

PUBLICATIONS: (Chosen from 47 manuscripts)

Coenen HH, Moerlein SM: Regiospecific aromatic fluorodemetallation of group Ivb metalloarenes using elemental fluorine or acetyl hypofluorite. J Fluorine Chem 36:63-75, 1987.

Hwang D-R, Moerlein SM, Lang L, Welch MJ: Application of microwave technology to the synthesis of short-lived radiopharmaceuticals. J Chem Soc, Chem Commun 1799-1801, 1987.

Moerlein SM, Daugherty A, Welch MJ: Ga-68 DTPA-VLDL: A potential radiopharmaceutical for PET quantitation of tissue low-density lipoprotein receptor activity. J Nucl Med 30:763, 1989.

Moerlein SM, Brodack JW, Welch MJ, Siegel BA: Elimination of contaminant Kryptofix 2.2.2 in the routine production of 2-[^{18}F]fluoro-2-deoxy-D-glucose. Appl Radiat Isot, Int J Radiat Appl Instrum Part A 40:741-743, 1989.

Lannoye GS, Moerlein SM, Parkinson D, Welch MJ: N-Fluoroalkylated and N-alkylated analogues of the dopamine D-2 receptor antagonist raclopride. J Med Chem 33:2430-2437, 1990.

RAICHLE, MARCUS E. Professor of Neurology Birthdate: [redacted]

EDUCATION:

[redacted]

CURRENT POSITIONS:

1975 - present	Consulting Neurologist, St. Louis Children's Hospital St. Louis, MO
1978 - present	Professor of Neurology, Washington University School of Medicine St. Louis, MO
1978 - present	Neurologist, Barnes Hospital, St. Louis, MO
1979 - present	Professor of Radiology and of Biomedical Engineering, Washington University School of Medicine, St. Louis, MO
1982 - present	Senior McDonnell Fellow, McDonnell Center for Studies of Higher Brain Function, Washington University, St. Louis, MO

HONORS AND PROFESSIONAL ACTIVITIES:

E.O. Jones Scholarship Prize, University of Washington Medical School, 1964
American Neurological Association, 1975
NINDS Teacher-Investigator Special Traineeship Award, 1972 - 1977
Stroke Council, American Heart Association, 1974 - present
Neurology Study Section A, National Institutes of Health, 1975 - 1979
Cardiovascular D Research Study Committee, American Heart Association, 1975 - 1978
Committee on Cerebrovascular Diseases, NINCDS Long Range Planning Effort, 1978
Basic Science Task Force, NINCDS, 1978
American Academy of Neurology; American Association for Advancement of Science; American Medical Association; American Physiological Society; Society for Neuroscience
Editorial Boards: BRAIN 1985 - present; BRAIN RESEARCH 1985 - present; ANNALS OF NEUROLOGY 1979 - 1986; NEUROLOGY 1976 - 1982; JCBF&M 1981 - 1986; SYNAPSE 1987 - present; STROKE 1974 - 1980

PUBLICATIONS (most recent papers from 113 published in refereed journals)

Early, T.S., Posner, M.I., Reiman, E.M., and Raichle, M.E.: Left striato-pallidal hyperactivity in schizophrenia. Part II: Phenomenology and thought disorder. Psychiatric Developments 2:109-121, 1989.

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Pardo, J.V., Pardo, P.J., Janer, K.W., and Raichle, M.E.: The anterior cingulate cortex mediates processing selection in the Stroop attentional conflict paradigm. P.N.A.S. (USA) 87:256-259, 1990.

Mathias, C.J., Welch, M.J., Raichle, M.E., Mintun, M.A., Lich, L.L., McGuire, A.H., Zinn, K.R., John, E.K., and Green, M.A.: Evaluation of a potential generator-produced PET tracer for cerebral perfusion imaging: single-pass cerebral extraction measurements and imaging with radiolabeled Cu-PTSM. J. Nucl. Med. 31:351-359, 1990.

Petersen, S.E., Fox, P.T., Snyder, A.Z., and Raichle, M.E.: Specific extrastriate and frontal cortical areas are activated by visual words and word-like stimuli. Science 249:1041-1044, 1990.

Steven R. Bergmann, M.D., Ph.D. Associate Professor of Medicine [redacted]

[redacted]

1977 - 1980	NIH Postdoctoral Fellow, Cardiovascular Division, Washington University, St. Louis, Missouri
1979 - 1980	Research Instructor in Medicine, Cardiovascular Division, Washington University, St. Louis, Missouri
1980 - 1989 (part-time 1982-1985)	Assistant Professor of Medical Physiology in Medicine, Cardiovascular Division, Washington University, St. Louis, Missouri
1989 - present	Associate Professor of Medicine, Cardiovascular Division, Washington University, St. Louis, Missouri

Honors and Societies:
John R. Smith Memorial Fund Prize for Meritorious Work in Cardiovascular Disease; American Association for the Advancement of Science; American Heart Association, Basic Science and Radiology Councils; American Physiological Society; American Society of Clinical Investigation; Society of Nuclear Medicine; Fellow, American College of Cardiology.

Other Professional Activities:
Editorial Board - Coronary Artery Disease; Editorial Reviewer - American Journal of Physiology, Circulation, Circulation Research, Journal of Nuclear Medicine; Member - American Heart Association, Missouri Affiliate, Research Committee.

Bibliography: (Selected from 97 published manuscripts)

1. Bergmann, S.R., Herrero, P., Markham, J., Weinheimer, C.J., and Walsh, M.N.: Noninvasive quantitation of myocardial blood flow in human subjects with oxygen-15 labeled water and positron emission tomography. J. Am. Coll. Cardiol. 14:639-652, 1989.
2. Gropler, R. J., Siegel, B. A., Lee, K. J., Moerlein, S. M., Perry, D. J., Bergmann, S. R., and Geltman, E. M.: Nonuniformity in myocardial accumulation of fluorine-18-fluorodeoxyglucose in normal fasted humans. J. Nucl. Med. 31:1749-1756, 1990.
3. Shelton, M. E., Dence, C. S., Hwang, D.-R., Herrero, P., Welch, M. J., and Bergmann, S. R.: In vivo delineation of myocardial hypoxia during coronary occlusion using fluorine-18 fluoromisonidazole and positron emission tomography: a potential approach for identification of jeopardized myocardium. J. Am. Coll. Cardiol. 16:477-485, 1990.
4. Shelton, M. E., Green, M. A., Mathias, C. J., Welch, M. J., and Bergmann S. R.: Assessment of regional myocardial and renal blood flow with copper-PTSM and positron emission tomography. Circulation 82:990-997, 1990.
5. Herrero, P., Markham, J, Shelton, M.E., Weinheimer, C.J., and Bergmann, S.R.: Noninvasive quantitation of regional myocardial blood flow with rubidium-82 and positron emission tomography: exploration of a mathematical model. Circulation 82:1377-1386, 1990.

1063046

ATTACHMENT 2

Assurances of Compliance

1063047

DOE F 1600.5
(10-86)

OMB Contol N
1910-0400

U.S. Department of Energy

Assurance of Compliance

Nondiscrimination in Federally Assisted Programs

Washington University (Hereinafter called the "Applicant") HEREBY AGREES to comply with Title VI of the Civil Rights Act of 1964 (Pub. L. 88-352), Section 16 of the Federal Energy Administration Act of 1974 (Pub. L. 93-275), Section 401 of the Energy Reorganization Act of 1974 (Pub. L. 93-438), Title IX of the Education Amendments of 1972, as amended, (Pub. L. 92-318, Pub. L. 93-568, and Pub. L. 94-482), Section 504 of the Rehabilitation Act of 1973 (Pub. L. 93-112), the Age Discrimination Act of 1975 (Pub. L. 94-135), Title VIII of the Civil Rights Act of 1968 (Pub. L. 90-284), the Department of Energy Organization Act of 1977 (Pub. L. 95-91), and the Energy Conservation and Production Act of 1976, as amended, (Pub. L. 94-385). In accordance with the above laws and regulations issued pursuant thereto, the Applicant agrees to assure that no person in the United States shall, on the ground of race, color, national origin, sex, age, or handicap, be excluded from participation in, be denied the benefits of, or be otherwise subjected to discrimination under any program or activity in which the Applicant receives Federal assistance from the Department of Energy.

Applicability and Period of Obligation

In the case of any service, financial aid, covered employment, equipment, property, or structure provided, leased, or improved with Federal assistance extended to the Applicant by the Department of Energy, this assurance obligates the Applicant for the period during which Federal assistance is extended. In the case of any transfer of such service, financial aid, equipment, property, or structure, this assurance obligates the transferee for the period during which Federal assistance is extended. If any personal property is so provided, this assurance obligates the Applicant for the period during which it retains ownership or possession of the property. In all other cases, this assurance obligates the Applicant for the period during which the Federal assistance is extended to the Applicant by the Department of Energy.

Employment Practices

Where a primary objective of the Federal assistance is to provide employment or where the Applicant's employment practices affect the delivery of services in programs or activities resulting from Federal assistance extended by the Department, the Applicant agrees not to discriminate on the ground of race, color, national origin, sex, age, or handicap, in its employment practices. Such employment practices may include, but are not limited to, recruitment, recruitment advertising, hiring, layoff or termination, promotion, demotion, transfer, rates of pay, training and participation in upward mobility programs; or other forms of compensation and use of facilities.

Subrecipient Assurance

The Applicant shall require any individual, organization, or other entity with whom it subcontracts, subgrants, or subleases for the purpose of providing any service, financial aid, equipment, property, or structure to comply with laws cited above. To this end, the subrecipient shall be required to sign a written assurance form, however, the obligation of both recipient and subrecipient to ensure compliance is not relieved by the collection or submission of written assurance forms.

10630 48

Data Collection and Access to Records

The Applicant agrees to compile and maintain information pertaining to programs or activities developed as a result of the Applicant's receipt of Federal assistance from the Department of Energy. Such information shall include, but is not limited to,the following: (1) the manner in which services are or will be provided and related data necessary for determining whether

CERTIFICATION REGARDING DRUG-FREE WORKPLACE REQUIREMENTS

This certification is required by the Drug-Free Workplace Act of 1988 (Pub. L. 100-690, Title V, Subtitle D) and is implemented through additions to the Debarment and Suspension regulations, published in the Federal Register on January 31, 1989.

An organizational applicant certifies that it will provide a drug-free workplace by:

(a) Publishing a statement notifying employees that the unlawful manufacture, distribution, dispensing, possession, or use of a controlled substance is prohibited in the grantee's workplace and specifying the actions that will be taken against employees for violation of such prohibition;

(b) Establishing a drug-free awareness program to inform employees about–

(1) the dangers of drug abuse in the workplace;
(2) the grantee's policy of maintaining a drug-free workplace;
(3) any available drug counseling, rehabilitation, and employee assistance programs; and
(4) the penalties that may be imposed upon employees for drug abuse violations occurring in the workplace;

(c) Making it a requirement that each employee to be engaged in the performance of the grant be given a copy of the statement required by paragraph (a);

(d) Notifying the employee in the statement required by paragraph (a) that, as a condition of employment under the grant, the employee will–

(1) abide by the terms of the statement; and
(2) notify the employer of any criminal drug statute conviction for a violation occurring in the workplace not later than five days after such conviction;

(e) Notifying the agency within ten days after receiving notice under subparagraph (d)(2) from an employee or otherwise receiving actual notice of such conviction;

(f) Taking one of the following actions, within 30 days of receiving notice under subparagraph (d)(2), with respect to any employee who is so convicted–

(1) taking appropriate personnel action against such an employee, up to and including termination; or
(2) requiring such employee to participate satisfactorily in a drug abuse assistance or rehabilitation program approved for such purposes by a Federal, State, or local health, law enforcement, or other appropriate agency;

(g) Making a good faith effort to continue to maintain a drug-free workplace through implementation of paragraphs (a), (b), (c), (d), (e), and (f).

1063049

CERTIFICATION REGARDING LOBBYING

This certification is required by Section 319 of Public Law 101-121 and the OMB Governmentwide Guidance for New Restrictions on Lobbying; Interim Final Guidance, as published in the *Federal Register* on December 20, 1989.

NOTE: Based on OMB guidance dated March 23, 1990, and Civilian Agency Council Letter No. 90-04 dated April 4, 1990, this certification applies only to the instant transaction and not to all transactions.

Certification for Contracts, Grants, Loans, and Cooperative Agreements

The undersigned certifies, to the best of his or her knowledge and belief, that:

a. No Federal appropriated funds have been paid or will be paid, by or on behalf of the undersigned, to any person for influencing or attempting to influence an officer or employee of any agency, a Member of Congress, an officer or employee of Congress, or an employee of a Member of Congress in connection with the awarding of any Federal contract, the making of any Federal grant, the making of any Federal loan, the entering into of any cooperative agreement, and the extension, continuation, renewal, amendment, or modification of any Federal contract, grant, loan, or cooperative agreement.

b. If any funds other than Federal appropriated funds have been paid or will be paid to any person for influencing or attempting to influence an officer or employee of any agency, a Member of Congress, an officer or employee of Congress, or an employee of a Member of Congress in connection with this Federal contract, grant, loan, or cooperative agreement, the undersigned shall complete and submit Standard Form-LLL, "Disclosure Form to Report Lobbying," in accordance with its instructions.

c. The undersigned shall require that the language of this certification be included in the award documents for all subawards at all tiers (including subcontracts, subgrants, and contracts under grants, loans, and cooperative agreements) and that all subrecipients shall certify and disclose accordingly.

This certification is a material representation of fact upon which reliance was placed when this transaction was made or entered into. Submission of this certification is a prerequisite for making or entering into this transaction imposed by section 1352, title 31, U.S. Code. Any person who fails to file the required certification shall be subject to a civil penalty of not less than $10,000 and not more than $100,000 for each such failure.

Washington University
Organization Name

Award Number

Susan E. Cullen, Ph.D., Director
Name and Title of Authorized Representative

Susan E. Cullen
Signature

12-7-90
Date

1063050

CERTIFICATION REGARDING DEBARMENT, SUSPENSION, AND OTHER RESPONSIBILITY MATTERS - PRIMARY COVERED TRANSACTIONS

1. The prospective primary participant certifies to the best of its knowledge and belief, that it and its principals:

a. Are not presently debarred, suspended, proposed for debarment, declared ineligible, or voluntarily excluded from covered transactions by any Federal department or agency;

b. Have not within a three-year period preceding this proposal been convicted of or had a civil judgment rendered against them for commission of fraud or a criminal offense in connection with obtaining, attempting to obtain, or performing a public (Federal, State or local) transaction or contract under a public transaction; violation of Federal or State anti-trust statutes or commission of embezzlement, theft, forgery, bribery, falsification or destruction of records, making false statements, or receiving stolen property;

c. Are not presently indicted for or otherwise criminally or civilly charged by a governmental entity (Federal, State or local) with commission of any of the offenses enumerated in paragraph 1.b. of this certification; and

d. Have not within a three-year period preceding this application/proposal had one or more public transactions (Federal, State or local) terminated for cause or default.

2. Where the prospective primary participant is unable to certify to any of the statements in this certification, such prospective participant shall attach an explanation to this proposal.

Washington University
Organization Name

Award Number

Susan E. Cullen, Ph.D., Director
Name and Title of Authorized Representative

Susan E. Cullen

12-7-90
Signature

Date

(See Reverse)

USDOE-ORO (7/90)

PCDFA-083

1063051

ATTACHMENT 3

Letters of Collaboration

Steven R. Bergmann, M.D., Ph.D.

Ronald G. Evens, M.D.

John A. Katzenellenbogen, Ph.D.

Marcus E. Raichle, M.D.

1063052

WASHINGTON UNIVERSITY SCHOOL OF MEDICINE
AT WASHINGTON UNIVERSITY MEDICAL CENTER

DEPARTMENT OF INTERNAL MEDICINE

Cardiovascular Division

December 3, 1990

Michael J. Welch, Ph.D.
Director, Division of Radiation Sciences
Professor of Radiation Chemistry and Radiology
Washington University School of Medicine
Box 8053
St. Louis, MO 63110

Dear Michael,

This letter will simply serve to inform you that I am enthusiastic about the possibility of using a tandem cascade accelerator for production of PET radioisotopes. As you know, our research in the field of myocardial perfusion and metabolism is quite dependent on the availability of positron-emitting radionuclides, and the availability of a TCA would be a great boon to our work. As always, our laboratory will be happy to work with you in the evaluation of radiopharmaceuticals that are produced from the TCA.

Best wishes.

Sincerely,

Steve

Steven R. Bergmann, M.D., Ph.D.
Associate Professor of Medicine

SRB/brl

1063053

Box 8086
660 South Euclid Avenue
St. Louis, Missouri 63110
(314) 362-5000 (Barnes Hospital)

MALLINCKRODT
INSTITUTE OF
RADIOLOGY
AT WASHINGTON UNIVERSITY MEDICAL CENTER

RONALD G. EVENS, M.D.

Elizabeth Mallinckrodt Professor
Head, Department of Radiology
School of Medicine

Director of the Institute

December 3, 1990

Dr. Michael J. Welch
Director of Radiation Sciences
Department of Radiology

Dear Mike:

I am very excited about the possibility of us obtaining a tandem cascade accelerator from Science Research Lab. It shows high promise of being an important answer in the development of clinical PET by providing isotopes at a reasonable cost. The department of radiology will certainly provide the appropriate space for installing and evaluating the accelerator. Let me know if I can provide further information.

Best regards.

Sincerely,

Ronald G. Evens, M.D.
Professor and Head

RGE:kl

1063054

510 South Kingshighway Boulevard
St. Louis, Missouri 63110
(314) 362-7100 FAX: (314) 362-7182

University of Illinois
at Urbana-Champaign

School of Chemical Sciences
1209 West California Street
Urbana, IL 61801

November 26, 1990

Michael J. Welch, Ph.D.
Division of Radiation Sciences
Mallinckrodt Institute
Washington University Medical School
510 S. Kingshighway
St. Louis, MO 63110

Dear Mike:

I was very excited to hear that you are hoping to set up a tandem cascade accelerator that would enable the production of fluorine-18 on a dedicated basis. An accelerator dedicated to the production of fluorine-18 would be of great help to us in evaluating fluorine-18 labeled steroids for in vivo imaging. As you know, under support of my DOE grant DE FG02 86ER 60401 (Fluorine-18 Labeled Androgens and Progestins for Imaging Prostate and Breast Tumors), we are preparing at least 16 fluorine-substituted androgens and progestins as potential in vivo diagnostic agents for prostate and breast cancer. In addition, under our support from the NIH (PHS 5R01 CA 25836 - Rational Design of Breast Tumor Imaging Agents), we have prepared about 24 fluorine-substituted estrogens for breast tumor imaging. Your Department of Energy support is geared to the development of methods for labeling these compounds with fluorine-18 and their evaluation in experimental animals and eventually human patients.

There is no doubt that in the past the availability of fluorine-18 has proved to be a major obstacle in evaluating these compounds in a timely fashion. When my students make working visits to your lab, they find themselves in severe competition for cyclotron time for fluorine-18 production. Thus, if a dedicated accelerator for fluorine-18 production were available, it would enable us to do much more in the evaluation and development of these compounds and would provide a major increase in effectiveness of our research efforts on these grants.

I look forward to hearing more about the prospects of your acquisition of the accelerator.

Sincerely yours,

John A. Katzenellenbogen
Professor of Chemistry

JAK:cjc

1063055

MALLINCKRODT INSTITUTE OF RADIOLOGY
AT WASHINGTON UNIVERSITY MEDICAL CENTER

DIVISION OF
RADIATION SCIENCES

December 4, 1990

Michael J. Welch, Ph.D.
Director
Division of Radiation Sciences
Washington University School of Medicine
510 S. Kingshighway
St. Louis, MO 63110

Dear Mike:

This letter is to indicate my enthusiasm and support of your application to the Department of Energy for the acquisition of a Tandem Cascade Accelerator from Science Research Laboratory.

I look forward to future collaborations with your laboratory and to using radiopharmaceuticals produced by this accelerator.

Sincerely yours,

Marcus E. Raichle, M.D.
Professor of Neurology and Radiology

1063056

510 South Kingshighway Boulevard
St. Louis, Missouri 63110
(314) 362-7116

ATTACHMENT 4

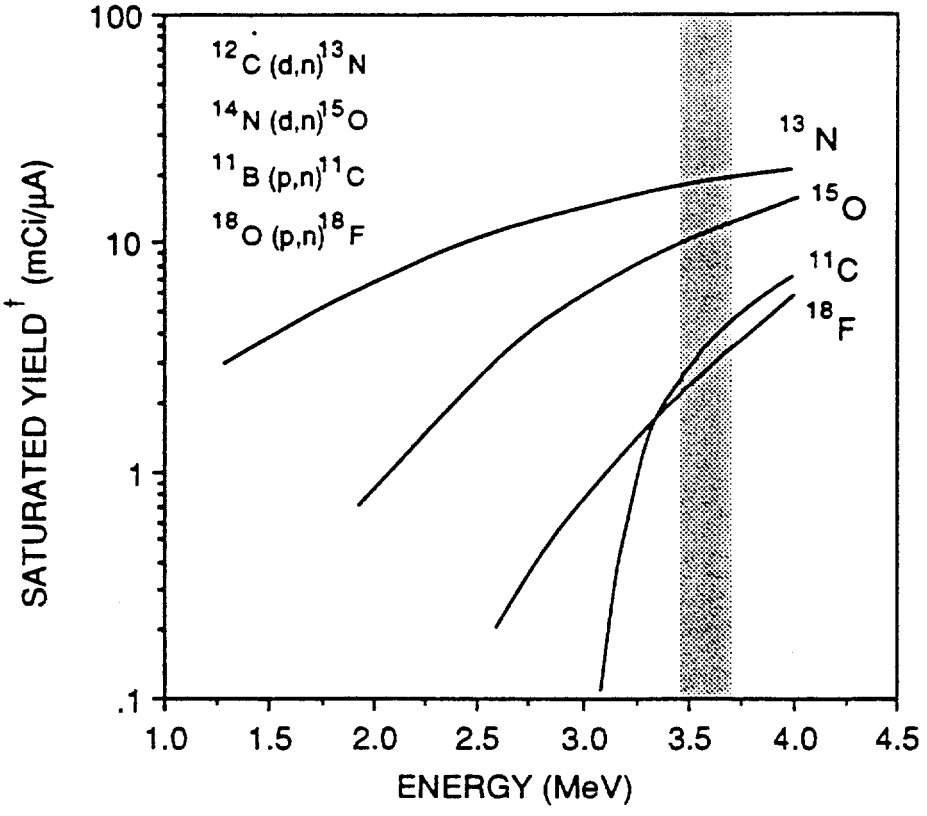
Information on the Tandem Cascade Accelerator

1063057

THE TANDEM CASCADE ACCELERATOR CAN PRODUCE THE FULL COMPLEMENT OF SHORT-LIVED PET RADIOISOTOPES

- Two particle operation with 3.7 MeV protons and deuterons at currents of 0.1 - 1 mA can provide 1 - 2 Curie batches of ^{15}O, ^{11}C, ^{13}N and ^{18}F.

- Cost and size of accelerator are minimized by choosing lowest possible beam energy compatible with PET isotope production.



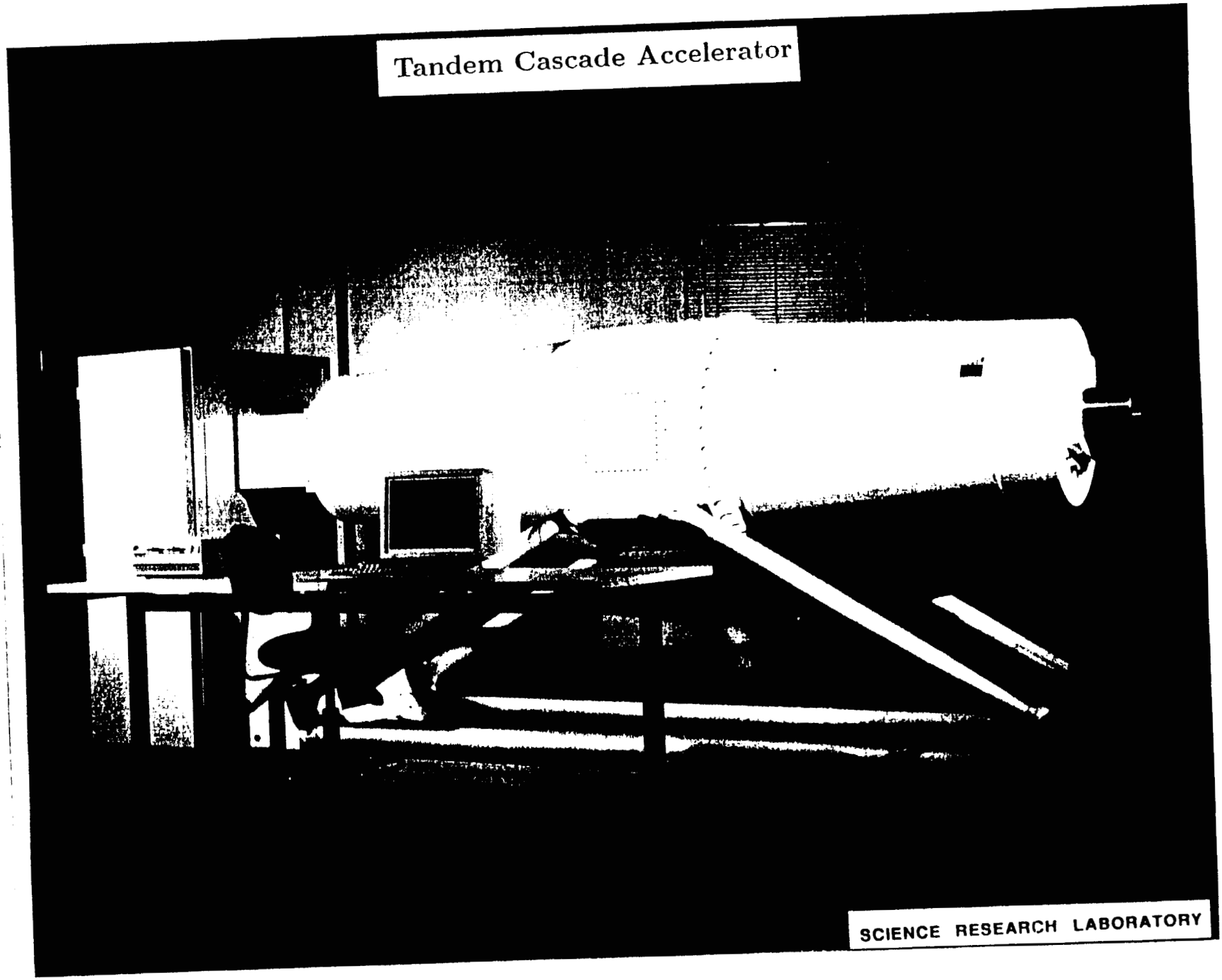
83m790

† ^{13}N: R. J. Jaszczak, R. L. Macklin, J. H. Gibbons, Phys. Rev. 181 (1969) 1428.
^{15}O: M. Sajjad, R. M. Lambrecht and A. P. Wolf, Radiochimica Acta 38 (1985) 57.
^{11}C: G. J. F. Legge and I. F. Bubb, Nucl. Phys. 26 (1961) 616.
^{18}F: T. J. Ruth and A. P. Wolf, Radiochimica Acta 26 (1979) 21.

SCIENCE RESEARCH LABORATORY

10b3058

10630591



ADVANTAGES OF PET ISOTOPE PRODUCTION WITH A HIGH CURRENT ELECTROSTATIC ACCELERATOR

- REDUCED CAPITAL COST

  Projected capital cost of TCA system is approximately one-third that of commercially available small cyclotrons with comparable performance.

- REDUCED FACILITY REQUIREMENTS

  Accelerator (unshielded) weighs less than 1 ton.

  Low final beam energy and high extraction efficiency (>90%) result in reduced accelerator shielding requirements.

  Power consumption is approximately one-tenth that of cyclotrons with comparable performance. Accelerator "plugs in" to a conventional 220 V circuit.

- SIMPLIFIED SYSTEM CONTROLS

  Two particle operation requires no retuning.

  Fully automated control system can be operated by a non-specialist.

1063060

MAJOR TECHNICAL CHALLENGE: DEVELOPMENT OF RELIABLE TARGETS FOR HIGH CURRENT BOMBARDMENT

OBJECTIVES:

1) Develop target window and chamber designs for high current, low energy bombardment of gaseous and liquid target materials.

2) Develop chemical synthetic techniques for solid target materials.

ISSUES:

- Foil window lifetime.
- Uniformity of irradiation of gases and liquids.
- Rapid dissolution or decomposition of solid targets.

APPROACHES:

- High aspect ratio, conduction cooled windows.
- Rotating foil windows.
- Composite foil materials.
- Slack-mounting of foils.
- Closed-cycle vortex flow of target gas.
- Target dissolution in acid or base, or combustion in reactive gas.

1063061

UNIQUE TARGETRY ASPECTS OF TCA PET SYSTEM

Lower beam energy than cyclotron systems.

- Shorter range of bombarding ions in target material.
  - Gas target can operate at lower pressure (2 atm versus > 10 atm).
  - Stress on foil window is greatly reduced.

- Higher current required for clinically significant yields changes thermal considerations for target chamber design.
  - Conduction cooled foil design has advantages over standard convection cooled foil designs
    - Less complex.
    - Eliminates loss of beam power in second foil and cooling gas.
  - However, standard convection cooling is a good back-up possibility.

1063062

GAS TARGET DESIGN FEATURES

- Large area, high aspect ratio rectangular foil has good thermal conductance to cooled support structure.
  - Large area decreases areal cooling requirements.
  - High aspect ratio shortens thermal path to cooled support.
  - Ion beam matched to foil geometry with two small permanent magnet quadrupoles.
- Slack-mounting of foil reduces peak stress and increases foil lifetime.
  - Targets can operate at lower pressure because of lower beam energy.
- Closed cycle vortex flow results in uniform irradiation of target gas.
- Another possibility for reducing areal cooling requirements is the use of a rapidly rotating target assembly.

1063063