710006

FIELD TASK PROPOSAL/AGREEMENT

1. WORK PACKAGE NUMBER	2. TASK NO.	3. REV. NO.	4. PROJECT NO.	5. DATE PREPARED	6. CONTRACTOR NUMBER
		0		04-01-84	4455-000332

7. TASK TITLE	8. WORK PACKAGE TITLE
Heavy Ion Radiosurgery	

BUDGET AND REPORTING CODE	10. TASK TERM Begin:	End:	11. CONTRACTOR NAME	12. CODE (see instructions)
HA-02-07-01-0	Continuing	Open	University of California Lawrence Berkeley Lab.	

13. CONTRACTOR TASK MANAGER (Name: Last, First, MI) (FTS No.)	14. PRINCIPAL INVESTIGATORS (Name: Last, First, MI)
Alden, Edward L. 451-5206 (FTS) (415) 486-5206	Fabrikant, Jacob I.

15. WORK LOCATION (See instructions): Name of facility, City, State, Zip Code	16. Is this task included in the Institutional Plan?	17. Does this task include any management services efforts?
Lawrence Berkeley Laboratory Berkeley, CAlifornia 94720	☒ YES ☐ NO	☐ YES ☒ NO

18. TASK DESCRIPTION (Approach, relation to work package, in 200 words or less)

OBJECTIVE: To establish stereotactic heavy-ion Bragg peak radiosurgery for brain disorders, including intracranial arteriovenous malformations (AVMs), as a nuclear medicine research method applied to the study of brain disease in man, to examine physical and biological properties of stereotactically-directed narrow heavy-ion beams in the CNS, for improving methods of dose-delivery and dose-distribution, and for establishing RBE/LET relationships for CNS tissue response. RATIONALE: Narrow beams of helium ions have superior biological and physical effects in brain over X- and γ-rays; heavy ions at the BEVALAC have advantages over helium ions and protons for CNS disorders in man, including less range straggling and multiple scattering for same residual range in tissues, improved dose-distribution in Bragg peak, and sharp lateral and distal borders, with greater sparing of critical adjacent CNS structures. EXPERIMENTAL APPROACH: Interactive charged-particle treatment planning and instrumentation/engineering design allow delivery of narrow heavy-ion beams to predetermined, 3-dimensional target volumes within brain or spinal cord; quantitative NMR and SPECT imaging at UCSF. PROGRESS: Clinical research program - over 55 radiosurgical brain patients with intracranial vascular disorders have been studied and treated with charged-particle beams. Research activities have expanded to applications of NMR and radionuclide SPECT imaging of CNS tissues treated with heavy ions. SIGNIFICANCE: On average, 500,000 people in the United States have life-threatening AVMs; the annual rate of rupture is 2-3%, the rate of rebleedin is 6% in the first year after hemorrhage and 2%/yr thereafter. About 10% die with first hemorrhage, 20% with each rebleeding. Stereotactic heavy-ion Bragg peak radiosurgery has the potential of conferring protection against rebleeding, in many cases leading to obliteration of the lesion with minimal morbidity and no mortality. FUTURE DIRECTIONS: Continued modifications and improvements of radiosurgical method to establish the long-term benefit of treatment of brain with stereotactically-directed narrow beams of accelerated charged particles; quantitation, using NMR and SPECT, of CNS tissue injury and repair and cerebral blood flow alterations following cerebral heavy-ion irradiation; development of the method of stereotactic heavy-ion Bragg peak cerebral irradiation (carbon and neon) at the BEVALAC.

19. CONTRACTOR TASK MANAGER

Edward L. Alden (Signature) (Date)

20. DETAIL ATTACHMENTS (See instructions)

☐ a. Facility requirements	☒ d. Background	☒ g. Future accomplishments	☐ j. Explanation of milestones
☒ b. Publications	☒ e. Approach	☒ h. Relationships to other projects	☐ k. ZBB Detail
Purpose	☒ f. Technical progress	☐ i. Environmental assesment	☒ l. Other (Specify):

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CONTRACTOR NAME

University of California, Lawrence Berkeley Laboratory

WORK PACKAGE NUMBER	TASK NO.	REV. NO.	DATE PREPARED	CONTRACTOR NUMBER
		0	04-01-84	4455-000332

21. STAFFING *(in staff years)*	PRIOR YEARS	BY-2	BY-1 PRESIDENT'S	BY-1 REVISED	AUTHORIZED	BY-FY 1986
a. SCIENTIFIC		2.8	2.5	2.5		2.5
b. OTHER DIRECT		.3	.3	.3		.3
c. TOTAL DIRECT		3.1	2.8	2.8		2.8
22. OBLIGATIONS AND COSTS *(in Thousands)*						
a. TOTAL OBLIGATIONS						
b. TOTAL COSTS		290	290	290		310
23. EQUIPMENT *(in Thousands)*						
a. EQUIPMENT OBLIGATIONS		0		100		100
b. EQUIPMENT COSTS						
24. OTHER COSTS *(specify)*						
a.						
b.						
c.						
d.						

25. OPTIONAL FIVE-YEAR PLAN *(in Thousands)* Constant BY dollars	BY+1	BY+2	BY+3	BY+4	TOTAL TO COMPLETE
a. TOTAL OPERATING OBLIGATIONS					
b. TOTAL OPERATING COSTS					
c. TOTAL EQUIPMENT OBLIGATIONS					
d. TOTAL EQUIPMENT COSTS					

26. MILESTONE SCHEDULE	PROPOSED SCHEDULE	AUTHORIZED SCHEDULE

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DETAIL ATTACHMENTS

1. WORK PACKAGE NUMBER	2. TASK NO.	3. REV. NO.	4. PROJECT NO.	5. DATE PREPARED	6. CONTRACTOR NUMBER
		0		04-01-84	4455-000332

7. TASK TITLE	8. WORK PACKAGE TITLE
Heavy Ion Radiosurgery	

20. DETAIL ATTACHMENTS:

Attachment a. Facility Requirements: N/A

Attachment b. Publications:

Publications Fiscal Year 1983

Fabrikant JI, Holley WR, McFarland EW, Tobias CA. Heavy-ion radiography and heavy-ion computed tomography. Lawrence Berkeley Laboratory Report LBL-14001 (1982).

Holley WR, Fabrikant JI, Tobias CA, Benton EV. The physics of heavy-ion radiography and heavy-ion computerized tomography. Lawrence Berkeley Laboratory Report LBL-14316 (1982).

Lyman JT. Computer modeling of heavy charged particle beams. (In) Pion and Heavy-ion Radiotherapy: Pre-clinical and Clinical Studies. Elsevier Biomedical. New York (Skarsgard LD, ed) pp 139-147 (1983).

Publications Fiscal Year 1984 - 1st Quarter

Fabrikant JI, Lyman JT, Hosobuchi Y. Stereotactic heavy-ion Bragg peak radiosurgery for intracranial vascular disorders: Method for treatment of deep arteriovenous malformations. Brit J Radiol (in press 1984).

Lyman JT. Heavy charged particle beam dosimetry. (In) Proceedings IAEA advisory group meeting on advances in dosimetry for fast neutrons and heavy charged particles for therapy applications (in press 1984).

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	2. TASK NO.	3. REV. NO.	4. PROJECT NO.	5. DATE PREPARED	6. CONTRACTOR NUMBER
		0		04-01-84	4455-000332

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20. DETAIL ATTACHMENTS:

Attachment c. Purpose:

NUCLEAR MEDICINE: STEREOTACTIC HEAVY-ION BRAGG PEAK RADIOSURGERY FOR INTRACRANIAL VASCULAR DISORDERS OF THE BRAIN

This nuclear medicine investigative program provides the radiosurgical research support for application of stereotactically-directed narrow heavy charged particle beams for the investigation and treatment of patients with intracranial vascular disorders, including deep arteriovenous malformations (AVMs) in the brain and spinal cord. Research is directed to:

(1) The investigation of the physical and biological properties of the helium-ion beam (184-inch Synchrocyclotron) and heavier (e.g., C, Ne) beams (BEVALAC) appropriate for producing narrow focal lesions in the central nervous system, including improved dose-distribution and dose-delivery within the brain and with rapid rate of energy loss without damage to adjacent critical CNS structures and neuroanatomical sites.

(2) To decrease or eliminate the threat of intracranial hemorrhage and progressive neurological deficit in persons with inoperable or inaccessible AVMs, using a safe, noninvasive heavy charged particle radiation procedure.

(3) To utilize current investigative nuclear medicine methods (including [illegible] and SPECT) to evaluate the CNS tissue response and altered cerebral blood flow dynamics in persons undergoing heavy charged particle stereotactic radiosurgery.

Attachment d. Background:

Intracranial arteriovenous malformations (AVMs) have been the object of investigation for over a century (Kunc, 1978; Nyström, 1978). However, deep intracranial arteriovenous malformations, including carotid artery-cavernous sinus fistulas (CCFs), have not been reported on or treated until the last two decades, primarily because of their variable symptoms, changeable pathoanatomical relationships, and inaccessibility to vascular brain surgery (Kunc, 1978). Recent advances in neurodiagnostic and microsurgical techniques have made direct neurosurgical treatment of some intracranial AVMs safer and more successful. Surgical treatment of AVMs involves total excision, where possible, or combined with ligation or intravascular occlusion of feeding arteries and shunting vessels (Kunc, 1978; Leksell, 1971). For deep-seated

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AVMs, including CCFs, surgical approaches are frequently too difficult and associated with significant risk of massive bleeding or severe neurological deficit, or failure of obliteration. Similar risks and complications are associated with electrothrombosis, cryocoagulation, balloon catheterization, and intravascular embolization with synthetic polymers (Kunc, 1978). Conventional radiotherapy as a method of induced thrombosis has been tried in the past (Johnson, 1975) but now has been generally abandoned as unsuccessful (Perret, 1975; Olivecrona and Ladenheim, J., 1957; Pool, 1962; French and Chou, 1969). Stereotactic charged-particle radiosurgery holds considerable promise for the treatment of deep-seated, large, or surgically inaccessible AVMs (Leksell, 1971; Kjellberg, 1977; Kjellberg et al., 1978; 1983; Kunc, 1978; Nyström, 1978; Backlund, 1978; Steiner et al., 1978; Fabrikant et al., 1980, 1983; Lawrence, 1983).

The incidence rate of known inoperable deep AVMs approaches one case per 100,000 annually for the whole population (Nyström, 1978). A fairly large number of deep AVMs escape diagnosis based on autopsy series; therefore the actual incidence rate might be twice as large. Inoperable deep AVMs comprise about 25% of all intracranial AVMs. In children, deep AVMs can comprise as much as 1% of neuropediatric hospital admissions. Deep AVMs appear most frequently in males; about 75% of patients with deep AVMs develop symptoms before 40 years of age. Mortality for all AVMs approaches 15%; it is much higher, perhaps approaching 25%, for deep AVMs owing to the more dangerous sites and the higher frequency of bleeding from some deep AVMs. Morbidity, including hemorrhage, neurologic disability, paresis, ataxia, brain stem dysfunction, coma and seizures, is often severe since deep AVMs are almost always located close to important brain structures. Hemorrhage occurs in up to 25% of patients; the incidence of severely neurologically disabled patients approaches 20%, although morbidity, as such, including severe intractable headaches, is very much higher (Kunc, 1978; Nyström, 1978).

A general concept in radiobiology is that blood vessels may be injured by ionizing radiation leading to thrombosis and hemostasis (Rubin and Casarett, 1968; Fabrikant, 1972). A mechanism is postulated involving three sequential factors: (1) vascular injury, (2) deviation of blood flow from the normal blood flow pattern, and (3) increased platelet activity, increased activation of coagulation, decreased fibrinolytic activity, leading to thrombosis and hemostasis. It appears that the small abnormal feeding or shunting vessels of an AVM possess hemodynamic flow conditions that differ from flow in normal vessels. These small shunting vessels are irradiated with the intent initiate thrombosis and hemostasis in the AVM with eventual complete obliteration.

Attachment e. Approach:

Charged-Particle Beams. A stereotactic radiosurgery beamline for the 230-MeV/u helium ion beam at the 184-inch Synchrocyclotron has been developed (Lyman et al., in press). This modified beam has a 14.7 cm range in water to the Bragg peak, with sharply delimited lateral and distal borders. The practical limits on beam diameter range from 0.6 cm to 4.0 cm. The unmodulated Bragg peak maximum dose is greater than 3 times the entrance dose and the width of the peak at 80% of the maximum is 0.7 cm. The range of the helium-ion beam can be modulated by a rotating acrylic variable thickness absorber to increase the width of the high dose region for this application to as much as 4.0 cm. The physical properties of this beam are similar to those of the proton beams

that have been available for stereotactic radiosurgery at the Harvard Cyclotron Laboratory (Koehler et al., 1974; Kjellberg, 1977; Kjellberg et al., 1978, 1983) and at the Gustaf Werner Institute at the University of Uppsala (Larsson, 1980, Larsson and Sarby, 1974). The maximum range of the 230-MeV/u helium-ion beam is greater than that of these proton beams; therefore, more energy degradation is necessary to obtain the same residual range. Since the nuclear charge and mass of helium is larger than the proton, the multiple scattering and the range straggling can be less for the same residual range in tissues.

This helium-ion beam has proven suitable for neuroscience research to induce focal lesions in the central nervous system (Fabrikant et al., 1980). It provides good dose-localization and dose-distribution for stereotactic helium-ion radiosurgery in all patients with AVMs, including CCFs, thus far treated. Studies are in progress to develop beam characteristics of heavier ions, such as carbon ions with small uniform transverse profile and modified Bragg peak for improved dose-distribution at the BEVALAC. These heavier-ion beams have physical characteristics with unique advantageas for application to stereotactic Bragg peak radiosurgery of the central nervous system (Budinger et al., 1977, Fabrikant et al., 1980).

Heavy Charged Particle Treatment Planning. Considerable study has gone into the development of a stereotactic system for delivery of heavy charged-particle beams to intracranial AVMs (Lyman, 1983; Lyman and Chong, 1974; Lyman and Howard, 1977; Lyman et al., 1971, 1973, 1979, 1980, in press; Tobias et al., 1952; Chen et al., 1979; Budinger et al., 1977; Fabrikant et al., 1980, 1983, in press). The present procedure begins with the fabrication of a vacuum-formed polystyrene head-holder for immobilization of the patient. A stereotactic frame (Leksell, 1971; Lyman et al., in preparation) is attached to the head-immobilization mask, and adapted to cerebral angiographic and X-ray CT equipment and to the patient-positioner at the 184-inch Synchrocyclotron. Stereotactic cerebral angiography and CT brain scans are performed. The data are transferred to a VAX 11/780 computer system in our laboratory for interactive charged-particle treatment planning and provide the basis for treatment planning (Lyman et al., in preparation). Entry angles and beam ports are chosen to confine the high-dose Bragg peak region to the defined target volume while carefully protecting adjacent normal brain structures. Treatment planning programs use the CT data on a pixel-by-pixel basis to (a) design and/or select a collimator for each entry portal, (b) select the appropriate spread Bragg peak for helium-ion radiation, (c) select the appropriate residual range for each beam entry, (d) design appropriate compensators to contour the stopping region of the helium-ion beams, and (e) generate isoeffect and physical dose-distributions overlayed on the CT image (Lyman et al., in preparation).

Patient Treatment. Treatment with helium-ion beams is based on the individual computerized dose-distributions calculated from CT scans and cerebral angiograms (Lyman et al., in press; Fabrikant et al., 1983; in press). The patient's head is secured to the ISAH system (Irradiation Stereotactic Apparatus for Humans) at the 184-inch Synchrocyclotron by the polystyrene head-immobilizer (Lyman et al., in press; Lyman and Chong, 1974; Tobias 1980; Lawrence, 1983; in press). Necessary minor corrections of the X, Y and Z coordinates are made during a final alignment period prior to therapy. Presently, total doses of 45 Gy equivalent (GyE) are delivered to treatment volumes of up to 25 cm^3; the smallest volumes treated with the unmodified Bragg

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peak are about 0.12 cm^3, and the average volumes treated for most patients are in the range of 1.5 cm^3 to 5 cm^3. Treatment occurs through 1 to 6 entry portals, delivered daily for 1 to 3 days, depending on the treatment volume, and the volume of normal brain tissue traversed by the beam. Irradiation times per portal range from 1 to 4 minutes (Lyman et al., in press). The dose to the critical normal brain structures immediately surrounding the AVM is considerably less than 45 GyE. For a single beam; fall-off to 10% of the maximum central dose occurs within 4-6 mm and is much sharper (within 2-3 mm) along the lateral margins of the helium-ion beam (Lyman et al., in press). The central AVM dose, the aperture size, the number of ports, the beam direction, and the spread Bragg peak all determine the isodose contours.

Attachment f. Technical Progress:

In late 1980, our first patient with an inoperable deep intracranial AVM was treated with stereotactic heavy charged-particle radiosurgery using 230-MeV/u helium ions at the 184-inch Synchrocyclotron at Lawrence Berkeley Laboratory (Fabrikant et al., 1980). Since then, 55 patients with deep intracranial vascular disorders have been treated, and additional patients are presently planned.

Cerebral angiography and CT brain scanning are carried out prior to stereotactic radiosurgery and at selected intervals following radiosurgery. Extended follow-up to 36 months is done on a regular basis, and 48 to 60 months is planned for each patient as necessary.

Clinical objectives are to achieve changes in the intracerebral hemodynamic condition resulting in a decrease in (1) frequency of hemorrhages, (2) in neurological deficiencies, (3) subjective complaints including headaches, or (4) in frequency of seizures. Initial observations in all 55 patients thus far treated indicate that these objectives are being achieved. There have been no neurologic complications of radiation damage to the normal brain tissue; thus far, no evidence of brain injury or progressive or fixed neurological deficiencies have occurred as a result of the stereotactic radiosurgical procedure.

Radiation treatment objectives are to achieve hemodynamic changes, e.g., decrease in blood flow through the AVM with decrease in the size of the AVM until total disappearance. It has been observed both by the Karolinska group (Backlund, 1980; Steiner, personal communication) and the Harvard group (Kjellberg, personal communication) that hemodynamic changes occur progressively and are usually present before morphological vascular alterations. Since it may require up to 12 to 18 months before initial changes are observed and may not be completed in some instances before 24 months, and since most patients in our clinical research study have been treated within the past 18 months, it is not possible to provide observations on long-term follow-up at this time. However, in 7 patients, significant decrease in size of and the rate of blood flow through the treated AVM has already occurred. In one patient with a CCF, the fistula was completely obliterated at 3 months, and her pulsating exophthalmos, headache, and visual disturbances are completely relieved.

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Attachment g. Future Accomplishments:

Patient Evaluation and Follow-up. During the next four years, studies of treated AVM brain patients will emphasize the results of stereotactic heavy charged-particle radiosurgery with time.

(1) Neurological condition. Patients most frequently present with one or more of the following clinical features: hemorrhage, seizure, headache, neurological deficits, and mental deficits. The extent to which the changes in the hemodynamic condition following treatment of the AVM may result in decrease of neurological deficiencies, subjective complaints, frequency of seizures, etc., will be evaluated.

(2) Radiological studies. Cerebral angiography, X-ray CT scanning and certain special investigative studies (e.g., positron emission tomography (PET) and/or single photon emission computed tomography (SPECT) scanning and nuclear magnetic resonance (NMR) scanning) are being carried out or planned for all patients prior to stereotactic radiosurgery, and at intervals following treatment. The following changes, if present, will be quantified. (a) Hemodynamic changes, e.g., decrease in blood volume and flow through the AVM with decrease in size of the feeder arteries and shunting vesseTs and draining veins. These changes may be best quantified with PET and/or NMR scans, or digital radiography which may measure blood flow changes more accurately. (b) Anatomical changes, e.g. progressive decrease in the size of the AVM until total disappearance, potential transient or permanent distrubances in myelination processes, leading to demyelination, and early and late delayed radiation-induced injury in the brain (Sheline et al., 1980). As yet, no disturbances of myelination processes have been observed in any of our patients thus far treated with stereotactically-directed helium-ion beams.

Program Goals. Research in stereotactic heavy charged-particle radiosurgery for intracranial deep-seated neurovascular disorders in brain patients is designed:

(1) To introduce technical modifications and improvements of the radiosurgical technique---including stereotactic neuroradiological studies for quantitating radiation changes in the brain, computer-based interactive treatment planning, and beam delivery --- to achieve a safe and reliable therapeutic procedure;

(2) To evaluate the long-term results in patients treated with helium ions for AVMs of the brain and spinal cord;

(3) To develop the method using heavier ions (carbon or neon ions) at the BEVALAC for improved biological and physical effects. The advantages of heavier ions, over helium ions and protons, include narrow beams with less range straggling and less multiple scattering for the same residual range in tissues, and improved dose-distribution in the Bragg peak, with very sharp lateral and distal borders, and with greater sparing of critical structures in adjacent CNS tissues in the brain and spinal cord. The carbon-ion beam also provides potential for using a carbon-11 ion radioactive beam which is presently being investigated for achieving precise localization of the stopping points of the beam inside the brain (Tobias, 1983; in press; Tobias et al., 1971; Chatterjee et al., 1981; Fabrikant et al., 1980; Lawrence, 1983; in press). And (4) to

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perfect the methods for stereotactic radiosurgery at the BEVALAC for application at the clinical level at future medical accelerators (Alpen, 1983).

Physics.

Dosimetry of heavy charged-particles

Our present work utilizes the helium ion beam which is available from the 184-inch LBL synchrocyclotron. In the near future the AVM radiosurgery project will be moving to the BEVALAC. The heavier beams available at the BEVALAC should have improved dose localization and distribution. We will investigate the relative biological effectiveness of helium, carbon, neon, and silicon ion beams for radiosurgery. By employing various ions, dose, and fractionation schemes we hope to find optimal conditions for charged particle irradiation of AVMs while protecting critical brain tissues. We plan to study tissue response using techniques such as NMR and SPECT.

Treatment planning

We will be developing three-dimensional treatment planning in order to better confine the radiation solely to the volume being treated: We plan to incorporate NMR imaging of AVM patients into our treatment planning method. The new methods developed will be compared to our present techniques. We hope to use NMR imaging to measure blood flow into AVMs. If these new methods utilizing NMR imaging are succesful, we will then have a safe, noninvasive technique for diagnosis, treatment planning, and follow-up.

SPECT. SPECT has been applied to physiological measurements of local cerebral glucose utilization, local cerebral blood volume, local cerebral blood flow and to demonstrate cerebral infarcts. Because of the desirable biological and chemical behavior of selected positron-emitting isotopes, there is emphasis now on positron-emission computed tomography in brain research. Winchell et al. (1980) proposed that the initial distribution of IMP [N-Isopropyl-p-[^{123}I]Iodoamphetamine might be useful for imaging relative regional brain perfusion in humans because first-pass extraction efficiency in rat brain was high, washout was slow, brain-blood ratios were high and the physical properties of I-123 ($T_{1/2}$ = 13 hr, 159-keV photon) were favorable for scanning. Localization in the brain was considered to be primarily in high-capacity, relatively nonspecific, binding sites for amines. Kuhl et al. (1982) demonstrated local cerebral blood flow mapping in humans by SPECT of IMP. They demonstrated the validation of a method for quantitative mapping of local cerebral blood flow in human brain by SPECT, using intravenously injected IMP combined with a modification of arterial input sampling. These results suggest that SPECT with IMP, or with other similar compounds such as HIPDM (N,N,N'-trimethyl-N'-[2-hydroxy-3-methyl-5-[^{123}I]iodobenzyl]-1,3-propanediamine has promise for diagnostic study of cerebrovascular disorders. We plan to assess the feasibility of evaluating regional cerebral perfusion in patients using SPECT and I-123 HIPDM (Kung et al., 1983) to detect acute or chronic blood perfusion changes in brain tissues. The patients examined will be those treated with stereotactic heavy charged-particle radiosurgery in this clinical research program. Accordingly, our program, in collaboration with Professor Robert Hattner, Division of Nuclear Medicine (Department of Radiology), University of California School of Medicine, San Francisco, will be using the new SPECT system at the Medical School in all our patients undergoing

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stereotactic heavy-ion Bragg peak radiosurge
disorders.

Attachment h. Relationship to other Projects:

The fundamental research program in physi
clinical program is (1) DOE Contractor Number 4
Central Nervous System -- Heavy-ion Medical Res
Principal Investigator. The clinical and lal
collaborative effort with the Department of Ne
Hosobuchi), the Department of Radiology (Profe
Newton, Professor Robert Hattner). Additional
(1) Cardiovascular Flow and Metabolism, NIH/HL
Principal Investigator, (2) Heavy-ion Radiobio
15184, Professor C.A. Tobias, Principal Investi
with Heavy Charged Particles, NIH/NCI/CA 1913
Professor C.A. Tobias, Principal Co-Investiga
Research, Heavy-Ion Medical Accelerator, NIH/C
Principal Investigator, (5) Additional collabor
include BEVALAC Beam Time and Operations, 4405,
Treatment Planning for Particle Beam Radiothera
J.T. Lyman, Principal Investigator.

Attachment i. Environmental Assessment: N/A

Attachment j. Explanation of Milestones: N/A

Attachment k. LBB Detail: N/A

Attachment l. Equipment List and Justification:

FY85: The Biology and Medicine Division has a V
Computer for use in three programs; cost i
allocated equally. For this project compu
is used for advanced image reconstruction
for stereotactic localization and treatmen
of AVM lesions for charged-particle radios
brain. Total: $300,000; allocated to this
project:

FY86: VAX 11-780 Computer use allocated to this
(cf FY85)

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20. DETAIL ATTACHMENTS:
REFERENCES

Alpen EL. The heavy ion medical accelerator. Preliminary design summary. Lawrence Berkeley Laboratory Report LBL-14316 (1983).

Backlund EO. Stereotactic radiosurgery in intracranial tumors and vascular malformations. Advances and technical standards in neurosurgery. (Krayenbuhl H, ed) 6: 3-37 Springer-Verlag, Vienna (1982).

Backlund EO, Ardt J, Dahlen TG, Leksell L,Steiner L. Radiosurgery in intracranial arteriovenous malformations. I.Technique. (In) Neurological Surgery with Emphasis on Non-invasive Methods of Diagnosis and Treatment. (Carrea R, LeVay D, eds) Excerpta Medica, Amsterdam (1978).

Barcia-Saloria JL, Hernandez G, Brosta J, Ballester B, Masbout G. Radiosurgical treatment of a carotid-cavernous fistula. (In) Stereotaxic Cerebral Irradiation (Szikla G, ed) pp. 162-167,INSERM, Amsterdam (1977).

Benton EV, Henke RP, Tobias CA, Holley WR, Fabrikant JI, Henshaw DL. Charged particle radiography and computed tomography. (In) Solid State Nuclear Track Detectors, (Fowler PH, Clapham VM, eds) pp. 661-666, Pergamon Press, Oxford (1982).

Bergstrom M, Greitz T, Steiner L. An approach to stereotaxic radiography. Acta Neurochir 54:157-165 (1980).

Budinger TF, Linfoot JA, Moyer BR, Lyman JT, Pelletier TL. Brain research with heavy-ion beams. (In) Biological and Medical Researchwith Accelerated Heavy Ions at the Bevalac 1974-1977. Lawrence Berkeley Laboratory Report LBL-5610 (University of California, Berkeley) pp. 187-197 (1977).

Chatterjee A, Alpen EL, Tobias CA, Llacer J, Alonzo J. High energy beams of radioactive nuclei and their biomedical applications. Inter J Rad Onc Bio Phys, 7:503-507 (1981).

Chen GTY, Singh RP, Castro JR, Lyman JT, Quivey JM. Treatment planning for heavy ion radiotherapy. Inter J Rad Onc Bio Phys, 5:1809-1819 (1979).

Fabrikant JI. Radiobiology. Year Book Medical, Chicago (1972).

Fabrikant JI. The effects of irradiation on the kinetics of proliferation in cell renewal systems. (In) CRC Critical Reviews in Radiological Sciences (Want C, ed), 2:525-576, CRC Press, Cleveland (1971).

Fabrikant JI. The effects of continuous irradiation. (In) Pathology of Irradiation. (Berdjis CC, ed), pp. 50-85, Williams and Wilkins, Baltimore (1971).

Fabrikant JI. Radiation carcinogenesis in man: Influence of dose-response models and risk projection models in the estimation of risk coefficients following exposure to low-level radiation. Lawrence Berkeley Laboratory Report LBL-14016 (University of California, Berkeley) (1982).

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20. DETAIL ATTACHMENTS:

Fabrikant JI. Estimation of risk of cancer induction in populations exposed low-level radiation. Invest. Radiol 17:342-349 (1982).

Fabrikant JI. Risk estimation and decision-making: The health effects on populations of exposure to low levels of ionizing radiation. Ped Dent 3:400-413 (1982).

Fabrikant JI. Decision-making and radiological protection at Three Mile Island: Response of the Dept. of Health, Education and Welfare. (In) Radiological Protection--Advances in Theory & Practice, Scotland II:756-763 (1982).

Fabrikant JI. The health effects in women exposed to low levels of ionizing radiation. Lawrence Berkeley Laboratory Report LBL-14198 (University of California) (1982).

Fabrikant JI. The BEIR III Report and its implications for radiation protectio and public health policy. (In) Radiation Protection, A Systematic Approach to Safety. 1:1213-1232, Pergamon Press, Oxford (1981).

Fabrikant JI. Carcinogenesis and low-level ionizing radiation with special reference to lung cancer and exposure to radon daughters. Lawrence Berkeley Laboratory Report LBL-14772 (University of California, Berkeley) (1982).

Fabrikant JI. Is nuclear energy an unacceptable hazard to health? Health Phys. 45:575-578 (1983).

Fabrikant JI. Radiation and health. West J Med 138:387-390 (1983).

Fabrikant JI. Nuclear energy, public health and public policy. Health Phys (in press 1984).

Fabrikant JI, Budinger TF, Tobias CA, Born JL. Focal lesions in the central nervous system. (In) Biological and Medical Research with Accelerated Heavy Ions at the Bevalac 1977-1980. (Tobias CA, Pirruccello MC eds) Lawrence Berkeley Laboratory Report LBL-11220 (University of California, Berkeley) pp. 399-405 (1980).

Fabrikant JI, Hilberg AW. Cost-benefit analysis in decision-making for diagnostic radiology. Lawrence Berkeley Laboratory Report LBL-14000 (University of California, Berkeley) (1982).

Fabrikant JI, Holley WR, McFarland EW, Tobias CA. Heavy-ion radiography and heavy-ion computed tomography. (In) Radiological Protection--Advances in Theory & Practice, Scotland 1:175-180 (1982).

Fabrikant JI, Lyman JT. Estimates of radiation doses in tissues and organs and risk of excess cancer in the single-course radiotherapy patients treated for andkylosing spondylitis in England and Wales. Lawrence Berkeley Laboratory Report LBL-13999 (University of California, Berkeley) (1982).

Fabrikant JI, Lyman JT, Hosobuchi Y. Stereotactic heavy-ion Bragg peak radiosurgery for intracranial vascular disorders. (In) Heavy Particle

1066956

20. DETAIL ATTACHMENTS:

Irradiation of Intracranial Lesions. (Lawrence JH, ed) Lawrence Berkeley Laboratory Report No. LBL-16011 (University of California, Berkeley) pp. 35-42 (1983).

Fabrikant JI, Lyman JT, Hosobuchi Y. Stereotactic heavy-ion Bragg peak radiosurgery for intracranial vascular disorders. (In) Neurosurgery (Wilkins RH, ed) (in press 1984).

Fabrikant JI, Lyman JT,Hosobuchi Y. Stereotactic heavy-ion Bragg peak radiosurgery: Method for treatment of deep arteriovenous malformations. Br J Rad (in press 1984).

Fabrikant JI, Lyman JT, Hosobuchi Y. Stereotactic heavy-ion Bragg peak radiosurgery for intracranial vascular disorders. (In) Heavy Particle Irradiation of Intracranial Lesions. (Lawrence JH, ed). To be published in Neurosurgery (Wilkins RH, Rengcharry SS, eds) McGraw-Hill, New York (in press).

Fabrikant JI, Lyman JT, Hosobuchi Y. Stereotactic heavy-ion Bragg peak radiosurgery for intracranial vascular disorders: Method for treatment of deep arteriovenous malformations Br J Radiol (in press 1984).

French LA, Chou SN. Conventional methods for treating intracranial arteriovenous malformations. Progress in Neurological Surgery 3:274-391 (1969).

Greitz T, Bergstrom M, Boethius J, Kingsley D, Ribbe T. Head fixation system for integration of radiodiagnostic and therapeutic procedures. Neuroradiol 19: 1-6 (1980).

Holley WR, Fabrikant JI, Tobias CA, Benton EV. The physics of heavy-ion radiography and heavy-ion computed tomography. (In) International Workshop on Physics and Engineering in Medical Imaging, IEEE, Computer Society Press, Los Angeles (1982).

Holman BL, Hill TC, Magistretti PL. Brain imaging with emission computed tomography and radiolabeled amines. Invest Radiol 17:206-215 (1982).

Hosobuchi Y, Fabrikant JI, Lyman JT. Stereotactic radiosurgery for intracranial vascular disorders. (ab) Western Neurosurgical Society, San Francisco, p. 1 (1982).

Johnson RT. Radiotherapy of cerebral angiomas. With a note on some problems on diagnosis. (In) Cerebral Angiomas. Advances in Diagnosis and Therapy. (Pia HW, Gleave JRW, Grote E, Zierski, eds) pp. 256-267, Springer-Verlag, NY (1975).

Kjellberg RN. Stereotactic Bragg peak proton radiosurgery results. (In) Stereotaxic Cerebral Irradiation. (Szikla G, ed) INSERM, Amsterdam, pp. 233-240 (1977).

Kjellberg RN, Poletti, CE, Roberson GH, Adams RD. Bragg peak proton beam treatment of arteriovenous malformations of the brain. (In) Neurological

Surgery with Emphasis on Non-invasive Methods of Diagnosis and Treatment. (Carrea R, LeVay D; eds) Excerpta Medica, Amsterdam, pp. 184-187 (1978).

Kjellberg RN, Hanamura T, Davis KR, Lyons SL, Adams RD. Bragg-peak proton-beam therapy for arteriovenous malformations of the brain. New Eng J Med 309:269-274 (1983).

Koehler AM, Schneider RJ, Sisterson JM. Range modulators for protons and heavy ions. Nuclear Instruments and Methods 131: 437-440 (1975).

Kuhl DE, Barrio JR, Huang SC, Selin C, Ackermann RF, Lear JL, Wu JL, Lin TH, Phelps ME. Quantifying local caerebral blood flow by N-isopropyl-p[^{123}I]iodoamphetamine (IMP) tomography. J Nucl Med 23: 196-203 (1982).

Kung HF, Tramposch KM, Blau M. A new brain perfusion imaging agent: [I-123]HIPDM:N,N,N′-trimethyl-N′[2-hydroxy-3-methyl-5-iodobenzyl]-1,3-propanediamine. J Nucl Med 24: 66-72 (1983).

Lawrence JH. Heavy particle irradiation of intracranial lesions. Lawrence Berkeley Laboratory Report LBL-16011 (University of California, Berkeley). (In) Neurosurgery. (Wilkins RH, Rengcharry SS, eds) McGraw-Hill, Philadelphia (in press).

Leksell L. Stereotaxis and Radiosurgery--An Operative System. Charles C. Thomas, Springfield (1971).

Linfoot JA, Lawrence JH, Tobias CA, Fabrikant JI. The treatment of pituitary tumors with high energy helium ions. J Endocrinol (in press, 1983).

Lyman JT. Computer modeling of heavy charged particle beams. (In) Pion and Heavy-Ion Radiotherapy. Pre-clinical and Clinical Studies. (Skarsgard LD, ed) Elsevier Biomedical, New York, pp. 139-147 (1983).

Lyman JT, Chen GTY, Kanstein L, Howard J. Heavy particle facilities at the Lawrence Berkeley Laboratory. (In) Proceedings of the First International Seminar on the Uses of Proton Beams in Radiation Therapy, Atomistadt, Moscow, 1: 122-134 (1979).

Lyman JT, Chong CY. ISAH: A versatile treatment positioner for external radiation therapy. Cancer 34: 12-16 (1974).

Lyman JT, Howard J. Dosimetry and instrumentation for helium and heavy ions. Inter J Rad Onc, Biol and Phys 3: 81-85 (1977).

Lyman JT, Howard J, Kanstein L, Alonzo JR. Radiological physics of heavy charged particle beams used for therapy. (In) Biological and Medical Research with Accelerated Heavy Ions at the Bevalac 1977-1980. (Tobias CA, Pirruccello MC, eds) Lawrence Berkeley Laboratory Report LBL-11220 (University of California, Berkeley) pp. 319-324 (1980).

Lyman JT, Howard J, Maccabee HD, Raje MR, Sperinde J, Walton R, Welch CP, Tobias CA. Experimental set-up and physical measurements of a heavy-ion beam for initial biological irradiation at the Bevatron. (In) Initial Radiobiological Experiements with Accelerated Nitrogen Ions at the

1. WORK PACKAGE NUMBER	2. TASK NO.	3. REV. NO.	4. PROJECT NO.	5. DATE PREPARED	6. CONTRACTOR NUMBER
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Heavy Ion Radiosurgery	

20. DETAIL ATTACHMENTS:

Bevatron. Lawrence Berkeley Laboratory Report LBL-529 (University of California, Berkeley) pp. 1-19 (1971).

Lyman JT, Howard J, Welch GP, Schimmerling W, Tobias CA. Experimental set-up and physical measurements of the heavy-ion beams used for biological irradiations. (In) Radiobiological Experiments Using Accelerated Heavy Ions at the Bevatron. Lawrence Berkeley Laboratory Report LBL-2016 (University of California, Berkeley) pp. 100-111 (1973).

Lyman JT, Kanstein L, Yeater F, Fabrikant JI, Hosobuchi Y. A helium ion beam for stereotactic radiosurgery. Med Phys (in press 1984).

Norén G. Stereotactic Radiosurgery in Acoustic Neuromas. A New Therapeutic Approach. Karolinska Sjukhuset, Stockholm (1982).

Nyström SHM. Epidemiology and clinical diagnosis of deep intracranial arteriovenous malformations including carotid-cavernous fistulas. (In) Neurological Surgery with Emphasis on Non-Invasive Methods of Diagnosis and Treatment. (Carrea R, LeVay D eds) Excerpta Medica, Amsterdam, pp. 188-193 (1978).

Olivecrona H, Ladenheim J. Arteriovenous Malformations of the Carotid and Vertebral Artery Systems. Springer-Verlag, Berlin (1957).

Parkinson D, Bachers G. Arteriovenous malformations. Summary of 100 consecutive supratentorial cases. J Neurosurg 53: 285-299 (1980).

Perret GE. Conservative management of inoperable arteriovenous malformations. (In) Cerebral Angiomas. Advances in Diagnosis and Therapy. (Pia HW, Gleave JRW, Grote E, Zierski J eds) Springer-Verlag, NY, pp. 268-270 (1975).

Pool JT. Treatment of arteriovenous malformations of the cerebral hemispheres J Neurosurg 19: 136-141 (1962).

Rubin P, Casarett GW. Clinical Radiation Pathology. Saunders, Philadelphia (1968).

Sheline GE, Wara WM, Smith V. Therapeutic irradiation and brain injury. Inter J Rad Onc Biol Phys 6:1215-1228 (1980).

Steiner L, Backlund EO, Greitz T, Leksell L, Noren G, Rahn T. Radiosurgery and intracranial arteriovenous malformations. Neurological Surgery with Emphasis on Non-Invasive Methods of Diagnosis and Treatment. (Carrea R, LeVay D eds) Excerpta Medica, Amsterdam (1978).

Steiner L, Greitz T, Backlund EO, Leksell L, Noren G, Rahn T. Radiosurgery in arteriovenous malformations of the brain. Undue effects. (In) Stereotactic Cerebral Irradiation (Szikla G, ed) pp. 257-269. Elsevier/North Holland Biomedical Press, Amsterdam (1979).

Steiner L. Radiosurgery in arteriovenous malformations of the brain. (In) Textbook of Cerebro-Vascular Surgery. (Flamm E, Fein J, eds) Springer-Verlag, New York (in press 1983).

Steiner L. The Treatment of Arteriovenous Malformations by Radiosurgery (in press 1984).

Steiner L, Berggren BH, Bergstrom M, Blomgran H, Greitz T, Lax I, Ribbe T. Stereotactic radiotherapy in intracranial arteriovenous malformations - methodological aspects (in press 1984).

Szikla G, (ed), Stereotactic Cerebral Irradiation. Elsevier/North Holland Biomedical Press, Oxford (1979).

Tobias CA. Pretherapeutic investigations with accelerated heavy ions. Radiology 108: 145-158 (1973).

Tobias CA. Pituitary irradiation: Radiation physics and biology. (In) Recent Advances in the Diagnosis and Treatment of Pituitary Tumors. (Linfoot JA, ed) Raven Press, New York, pp. 221-253 (1980).

Tobias CA, Anger HO, Lawrence JH. Radiologic use of high energy deuterons and alpha particles. Amer J Roentg Rad Ther Nucl Med 67:1-27 (1952).

Tobias CA, Chatterjee A, Smith AR. Radioactive fragmentation of N^{7+} ion beams observed in a beryllium target. Phys Letters, A, 37:119-120 (1971).

Tobias CA, Chu W, Chatterjee A, Benton EV, Fabrikant JI, Holley WR, Schmidt J, Blakely E, Hayes TL. Special topics in heavy-ion research. (In) Pion and Heavy-ion Radiotherapy: Pre-clinical and Clinical Studies. (Skarsgaard L, ed) Elsevier, New York (in press 1983).

Tobias CA, Van Dyke DC, Simpson ME, Anger HO, Hugg RL, Knoeff AA. Irradiation of the pituitary of the rat with high-energy deuterons. Am J Roentg Rad Ther Nucl Med 72: 1-21 (1959).

Winchell HS, Baldwin RM, Lin TH. Development of I-123-labeled amines for brain studies: localization of I-123 iodophenylaklyl amines in rat brain. J Nucl Med 21: 940-946 (1980).