

PROPOSAL FOR

Pre-Clinical Trials of Pion Radiotherapy (Fiscal Year 1975 Continuation)

To be performed by

The Los Alamos Scientific Laboratory (LASL) under AEC Contract  
(W-7405-ENG-36)

for the

University of New Mexico

Supported by the National Cancer Institute and under a Contract

between the University of California and the University of New Mexico

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## I) General

The Los Alamos Scientific Laboratory (LASL) of the University of California is presently carrying out a project entitled "Pre-Clinical Trials of Pion Radiotherapy." The project is a joint effort of the University of New Mexico (UNM) Medical School and the LASL funded via a grant from the National Cancer Institute to the UNM (Grant No. CA-14052-01). The portion of the work being conducted at LASL is authorized by a contract between the UNM and the University of California, entered into effective 30 June 1973, and covering the period 30 June 1973 through 31 May 1974.

In response to proposals submitted to the National Cancer Institute (NCI) by the UNM, the NCI has awarded Grant No. CA-14052-02 to the UNM which provides in part for a Continuation of the Pre-Clinical Trials project for a one-year period, and has also awarded Grant No. 1-P01-CA 16127-01 to the UNM which provides in part for other activities at LASL in support of the project. Grant CA-14052-02 covers a term beginning June 1, 1974 and ending May 31, 1975. Grant 1-P01-CA 16127-01 covers a term beginning May 1, 1974 and ending April 30, 1975. The work which the LASL proposes to perform under sponsorship of the referenced grants is described below in sufficient detail to permit a determination by the AEC that the proposed use of its facilities is appropriate, and to provide work statements for consideration by representatives of The Regents of the University of California. We believe the work statements below are consistent with the proposals submitted by the UNM to the NCI as a basis for award of the cited grants. If the work statements are acceptable to the University of California, we recommend that they be incorporated into an extension of the referenced contract for the effective period 1 May 1974 through May 31, 1975.

## II) Work Statement

Task I) (Grant CA-14052-02)

A) Medium Energy Physics (MP) Division Effort

A-1) Pi-Meson Beam Development

The biomedical channel and the biomedical facility comprise one of the capabilities of the Clinton P. Anderson Meson Physics Facility which was constructed by the AEC Division of Physical Research and is now operated as a National Facility. The capability of the biomedical channel, originally funded by NCI, to provide beams of Pi Mesons suitable for both biomedical experimentation and patient therapy will be further developed. The development will consist of making minor modifications to the apparatus which produces, focuses, and guides the beam into the biomedical experimentation area of the Clinton P. Anderson Meson Physics Facility, of perfecting the control mechanisms, computer codes etc., which control the beam, by tuning of the magnetic guide fields, and developing experience and skill in operation of the apparatus and control systems. The emphasis

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will be upon achieving a reliable procedure for delivery of a Pi-Meson beam of the characteristics and intensity required for experiments and for patient therapy, and developing the beam channel into a reliable instrument for routine use.

#### A-2) Pi-Meson Beam Characterization

The instrumentation required to measure the properties and character of the Pi-Meson beam present in the experimental area will be further developed, and required measurements of the characteristics of the beam will be made. The characteristics of interest include beam total intensity beam intensity as a function of position with respect to a control beam axis, energy distribution of the particles in the beam, dose vs. depth-of-penetration of the beam into representative materials.

#### A-3) Operation of the Biomedical Channel

During FY 75 the channel will be operated approximately 50% of the time for pre-clinical trials and experiments related thereto.

#### B) Health (H) Division Effort

Experiments will be conducted using biological materials, organisms, and animals to acquire and provide - at the earliest possible date - certain information prerequisite to the initiation of a clinical trial evaluation of the effectiveness of negative Pi Mesons for treatment of human neoplasms. In Vitro cell systems will be irradiated and measurements made of relative biological effectiveness (RBE) and Oxygen Enhancement Ratio (OER) of Pi Mesons both in the region where the mesons stop in the sample, and in adjacent regions. The dose vs. depth-of-penetration in the cell systems will be determined. The repair capability of the cells, the variation of cell sensitivity to radiation during the life cycle of the cell, and variations in RBE due to a variety of fractionation regimes will be studied.

Tissues of intact animals will be irradiated with Pi Mesons, and both prompt and delayed effects on the tissues will be observed. Both acute and fractionated irradiations will be made. Tumors in animals, both spontaneous and transplanted, will be irradiated and the effects observed.

In all experiments, comparison data will be acquired for both the peak and plateau region of the Pi Meson beam to materials irradiated with equivalent doses of ortho-voltage x-rays.

We anticipate that significant progress in characterization of the beam will be accomplished by the fall of 1974. Initial RBE measurements currently in progress employ cultured human kidney cells, Chinese hamster cells and mouse cells. The dose/depth profile of the beam as evidenced by cell survival rates will be observed in these samples for comparison with instrumental measurements of dose vs. depth in phantoms. With the

anticipated increase in available beam intensity in the latter part of the grant year, initial studies of late effects on animal tissue will begin. Mice, rats, rabbits and pigs will be used with emphasis on brain, spinal cord, heart, lung, gut, and kidney. We will attempt to initiate experimental series of adequate size and diversity during the current grant year that when long-term, late effects are observed in the future, the need to repeat some irradiations will be minimized. (Observations are expected to continue into the 3rd grant year.) Two in Vivo clonogenic systems in mice, i.e., spleen colony formation by bone-marrow stem cells and regeneration of intestinal crypt cells, will be employed, contingent upon availability of adequate beam intensity, to make RBE measurements for comparison with results obtained in vitro.

As much of the work as possible will be initiated during the current accelerator operations cycle (ending Nov. 1974). No priority is being given to dosimetry and RBE measurements.

Task II) (Grant CA-16127-01)

The Medium Energy (MP) Division of the Los Alamos Scientific Laboratory will provide, on a best effort basis, and as a service to the University of New Mexico, the irradiation of human patients in the Biomedical Research Area of the Clinton P. Anderson Meson Physics Facility. The radiation therapy program of the biomedical channel is under the supervision of Dr. Morton M. Kligerman, Assistant Director for Radiation Therapy. Patients to be irradiated will be selected by and will be under the care and supervision of the University of New Mexico. The MP Division will maintain and operate the biomedical beam channel, including all apparatus, equipment, and controls required to produce a Pi Meson beam. The beam will be directed so as to irradiate the patients in accord with instructions and protocols to be provided to the MP Division by agreed-upon representatives of the UNM. It is understood that authorized representatives of the UNM will have primary responsibility for all human irradiations, be present in the Biomedical Research Area at all times when patients are also present, will assume responsibility for the care and general well-being of the patients, and will specify and direct the irradiation of the patients. It is understood that the UNM will provide all information and assistance as necessary to assure a complete understanding on the part of MP-Division personnel of the character of the irradiations requested, e.g., as to beam intensity, beam intensity distribution, time duration of irradiation, dose to be delivered, desired location and distribution of delivered dose within the patient, rate of delivery of dose, permissible deviations from the desired beam and irradiation characteristics, and any other information as may be requested by MP-Division personnel. All such instructions and information is to be provided in writing and become part of the patient treatment history.

The following description of the human-subject irradiations placed during the grant period has been provided by the UNM.

## Human Radiobiology

It is expected that sufficient biology will have been completed by August 1974 to permit refinement of the estimated RBE of 2.2 for the biomedical beam. This will permit the start of human radiobiology studies while laboratory work continues. Patients with multiple metastatic skin nodules, multiple metastatic cervical lymphnodes and multiple metastatic pulmonary nodules will be used to determine the response of human tumors and normal tissues to the pion beam especially in the peak stopping region. Dose levels will be kept low at the start to ensure against untoward responses.

A two hundred-fifty kilovolt x-ray generator will be used as reference irradiation for superficial nodules. Supervoltage irradiation will be used as reference for the pulmonary nodules. After suitable experience a dose response curve will be developed for 15 fractions in 19 days, so that a three-fourths curative dose of peak pions can be determined. The treatment time will then be increased to four, five and seven weeks - using five fractions a week - at the approximate three-fourths curative dose. Then the dose at seven weeks will be carefully raised to obtain the curative dose. The importance of this human biology experiment is that experience in the responses and reactions will make possible the cautious beginning of human trials of pion radiotherapy.

## Human Trials of Pion Radiotherapy

Fourteen protocols have been established for several anatomic sites. These were developed by a committee chaired by M. M. Kligerman, and were the principal basis of Grant Application CA-16127-01. The sites and stages chosen are diseases not well managed by any cancer therapy method today. Even though tolerances, acute and semi-longer term, of human tissues will be established by the human radiobiology mentioned above, each new site will start with an estimated 50% curative dose and this gradually increased, to minimize the possibility of damage to normal tissues. The pion therapy committee decided, and this has been accepted by the North American Particle Irradiation Committee, that specific anatomic site lesions will not be randomized to conventional irradiation if current 5 year survival rates are less than 10%. Table I lists the sites and stages of the approved protocols for Human Trials of Pion Radiotherapy, and indicates whether these will be randomized against supervoltage irradiation or not. These protocols and their corresponding consent forms have been approved by the Human Research Committee at the University of New Mexico. They have been offered to the corresponding committee at LASL. Human trials will not begin unless the LASL committee is satisfied.

*type*  
*who is on this & who selected*  
*the committee*

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III) Cost Estimates

TASK I

(Grant No. CA-14052-02)

|                |                   |
|----------------|-------------------|
| Personnel      | \$ 318,160        |
| Travel         | \$ 8,800          |
| Equipment      | \$ 75,200         |
| Supplies       | \$ 53,300         |
| Other Expenses | \$ 22,000         |
| Indirect Costs | <u>\$ 162,580</u> |
| Total          | \$ 640,040        |

TASK II

(Grant No. 1-P01-CA 16127-01)

|                |                  |
|----------------|------------------|
| Personnel      | \$ 48,000        |
| Supplies       | \$ 10,000        |
| Other Expenses | \$ 65,000        |
| Indirect Costs | <u>\$ 24,528</u> |
| Total          | \$ 147,528       |

TABLE I

SITE/STAGE FOR PION CLINICAL TRIALS

|                           | <u>Nonrandom</u>                     | <u>Random</u>                     |
|---------------------------|--------------------------------------|-----------------------------------|
| <b>Glioma, Brain</b>      | X                                    |                                   |
| <b>Oral Cavity</b>        | T3, N3, MO                           | T3, NO-1-2, MO                    |
| <b>Oropharynx</b>         |                                      | T3, NO-1-2, MO                    |
| <b>Hypopharynx</b>        |                                      | T3, NO-1, MO or<br>T1-2-3, N2, MO |
| <b>Thoracic Esophagus</b> | X                                    |                                   |
| <b>Larynx</b>             | T1-2-3-4, N3, MO                     | T3-4, NO-1-2, MO                  |
| <b>Superior Sulcus</b>    |                                      | X                                 |
| <b>Stomach</b>            | T4, NO-1, MO, or<br>T1-2-3-4, N2, MO |                                   |
| <b>Pancreas</b>           | X                                    |                                   |
| <b>Cervix</b>             | T3-4; PN, positive                   | T3-4; PN, negative                |
| <b>Prostate</b>           | T3-4; PN, positive                   | T3-4; PN, negative                |
| <b>Bladder</b>            | T4, PN, positive                     | T4, PN, negative                  |
| <b>Rectum</b>             | Inoperable/non-<br>resectable        |                                   |
| <b>Osteogenic Sarcoma</b> | X                                    |                                   |