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RESEARCH PROPOSAL

LOS ALAMOS MESON PHYSICS FACILITY

BIOLOGICAL EFFECTS OF NEGATIVE PIONS

M. R. RAJU, SPOKESMAN

M. R. Raju, J. H. Jett, T. T. Trujillo, E. Bain, and J. Frank (LASL Group H-10)

L. L. Deaven, R. A. Walters, and R. A. Tobey (LASL Group H-9)

L. M. Holland, D.V.M. (LASL Group H-4)

H. Amols and J. Dicello (LASL Group MP-3)

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BIOLOGICAL EFFECTS OF NEGATIVE PIONS

SUMMARY OF EXPERIMENT

The biological effects of negative pions at the plateau and at the peak for at least two different widths (4 cm, 8 cm) will be measured using (1) cells in culture (T_1, V79); (2) early and late effects on mouse foot; (3) tumor regression of KHT sarcoma; and (4) tumor cell survival (exposure in vivo and assay in vitro). A limited number of fractionation experiments will also be carried out. In addition, stage sensitivity variations as a function of cell cycle will be studied using CHO cells at the plateau and peak for the nearly monoenergetic negative pion beam.

A proposal was submitted to the National Cancer Institute on "The Pretherapeutic Potential of Heavy Charged Particles," and it was recommended for funding. Some of these proposed studies at LAMPF comprise part of the experiments proposed to the NCI. Most of the proposed experiments in this proposal to LAMPF are complementary to the ongoing pretherapeutic radiobiology program at LAMPF.

PROPOSAL INFORMATION

Beam Area: A East

Secondary Channel: Biomedical channel

Primary Beam Requirements: $\geq$ 50 uA

Running Time Required: This approximate time estimate was a result of consultation with Group MP-3 members

Installation Time Required (no beam): 30 hr total

Tune-up Time: 50 hr total

Data Runs: 200 hr

Scheduling: These experiments will be performed over a one-year period

September 1975 to September 1976

Major LAMPF Apparatus Required: Standard equipment in the biomedical area

Special Requirements: None

Space Required: Cell-culture laboratory and animal radiobiology laboratory in the biomedical area

DETAILED STATEMENT OF THE EXPERIMENT

Heavy charged particles (π^-, protons, helium ions, and heavy ions) have potential applications in radiotherapy of cancer. The biological effects such as RBE and OER of these particles vary with the width of the Bragg peak. The complementary nature of these particles can be assessed by measuring biological effects of these particles using relatively simple biological systems under similar physical conditions such as the width of the peak. There is currently widespread interest in the use of these particles in radiation therapy but there is relatively much less data for comparing the therapeutic potential of these particles. A proposal entitled "The Therapeutic Potential of Heavy Charged Particles" was submitted to the National Cancer Institute nearly a year ago, and it was recommended for funding. Some of the proposed experiments in this proposal to LAMP are part of the NCI proposal.

The RBE of π^- mesons decreases with increasing width of the Bragg peak. Hence, unlike other radiations used in radiotherapy, different correction factors for RBE have to be applied when tumors of different sizes are treated with π^- mesons. At least two peak widths (~4 cm, ~8 cm) will be used in this investigations. Typical doses that are used are in the range of 100-5000 rads. Each experiment will be performed at least twice. These studies are complementary to the ongoing radiotherapy program at LAMPF.

1. Cell Survival as a Function of Depth (T_1, V79):

The radiation quality of π^- mesons changes as pions traverse matter and hence cell survival measurements as a function of depth of penetration of π^- mesons are necessary in addition to dose measurements. Preliminary measurements were already made at LAMPF for nearly monoenergetic π^- mesons (Raju et al., 1974a; Todd et al., 1974).

Cell survival measurements as a function of depth will be measured for different beams and doses. These will be measured using gelatin techniques as described by Raju et al., 1974a.

2. Aerobic and Hypoxic Cell Survival Curves at the Plateau and Peak.

Cells at a concentration of 3×10^4/ml remain oxygenated, whereas cells at a concentration of 3×10^6/ml become hypoxic after about 4 hr of storage. This method is described by Hall et al., 1974. Preliminary measurements were already made at LAMPF using this technique and the results were reported (Raju et al., 1974a). Cell survival measurements under oxygenated and hypoxic conditions will be made at the plateau and at the peak positions for different peak widths.

3. Stage Sensitivity

Variation of radiosensitivity as a function of the cell cycle is one of the important phenomena in radiobiology relevant to radiotherapy. It is known that with increasing LET, the variation in radiation sensitivity in different stages becomes reduced. It is important to know the alteration in radiosensitive variations during the cell cycle for π^- mesons compared to X rays.

We have conducted an extensive study of variations of radiosensitivity as a function of the cell cycle for X rays and alpha particles from plutonium using CHO cells synchronized by mitotic selection alone and also by mitotic selection and hydroxyurea (Raju et al., 1974b). We propose to use the same techniques to study stage sensitivity variations at the plateau and peak position for π^- mesons that are nearly monoenergetic. If significant variations are found, then the experiment will be repeated for broad peaks.

4. Early and Late Effects (Mouse Foot)

The skin of one of the hind feet of a mouse is commonly used to study the radiation response while the other foot serves as a control. The early reactions of the skin and the late reactions of the foot (deformity) are visually observed

using an arbitrary scale (Fowler, 1963; Field et al., 1967). The skin reactions using a mouse foot as a model gave the same RBE for neutrons as human skin (Field and Hornsey, 1971). Hence, the mouse foot system is very practical for studying the biological effectiveness of π^- mesons.

We have already performed a series of extensive experiments with X rays for different fractionation schedules (Raju et al., 1972, 1975). We propose to measure RBE at the plateau and peak for two different widths.

5. Tumor Growth Measurements (KHT Sarcoma in Mice)

The growth of tumors is delayed with increasing doses of radiation. Thomlinson and Craddock (1967) suggested that amount of time tumors take to grow to a fixed size after radiation treatment is a criterian of the effectiveness of treatment. This endpoint manifests chiefly the cellular response of tumor cells. However, the gross response of a tumor is a compound effect of tumor cell killing and damage to the vascular stroma. Hence, Thomlinson and Craddock cautioned against deducing the effects of radiation in cell killing from the gross response of tumors. However, tumor regression measurements are useful to measure the biological effectiveness of π^- mesons. We have data for this system for single and fractionated doses of X rays (Raju et al., 1972, 1974c). We propose to measure the biological effectiveness of π^- at the plateau and peak for two widths. This tumor system is chosen for two reasons: (1) it is a rapidly proliferating tumor with relatively few non-cycling cells, and (2) this system is being planned to be used also at Stanford and hence it makes it easier to compare the data.

6. EMT6 Mouse Tumor Cell Survival

There are very few tumor systems that are adopted to grow both in vivo as well as in vitro. EMT6 tumor systems in mice is one of the methods developed at Stanford (Rockwell et al., 1972). This tumor system permits advantages of in vivo and in vitro assays. The tumor can be exposed in vivo. We have already done

experiments with X rays using this system (Raju et al., 1974c). We propose to measure tumor cell survival for π^- mesons at the plateau and peak for two different widths.

This tumor system is relatively a slow growing with relatively large proportions of non-cycling cells. This system is also being planned to be used at Stanford.

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Munundi R. Raju
Health Research Laboratory
Los Alamos Scientific Laboratory
P. O. Box 1663
Los Alamos, NM 87544
Tel: 505-667-4231

Date of Birth: [redacted]

Research Interests: Dosimetry and Radiobiology of π^- Mesons and other High LET Particles towards their Application in Radiotherapy.

Member: Sigma Xi
Radiation Research Society
American Association of Physics in Medicine

1971 – Staff Member, H-10 Group, Los Alamos Scientific Laboratory.

1968 - 1971 Associate Professor, [redacted] and guest scientist at [redacted]

July-Dec. 1967 Visiting Scientist, [redacted] supported by the U. S. Atomic Energy Commission and the Medical Research Council of England.

1966 - 1968 Assistant Professor, [redacted] and guest scientist at [redacted]

1964 - 1966 Biophysicist, [redacted]

[redacted] Post Doctoral Research Fellow in Biophysics, [redacted]

[redacted] Post Doctoral Research Fellow in Biophysics, [redacted]

[redacted] D.Sc. Nuclear Physics
Lecturer, Nuclear Instruments.

[redacted] M.Sc. Physics.

[redacted] B.Sc. and M.A. Physics.

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