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PROPOSAL FOR

PION BEAM CHARACTERISTICS AND TREATMENT PLANNING

TO BE PERFORMED BY:

Los Alamos Scientific Laboratory

University of California

Los Alamos, New Mexico

Under AEC Contract (W-7405-ENG-36)

for the

American Cancer Society

Prepared by: Chaim Richman

Chaim Richman, Ph.D., LASL
Group H-9

Approved by: George L. Foelz, M.D.

George L. Foelz, M.D., LASL
Health Division Leader

A D McGuire

Austin D. McGuire, Ph.D., LASL
Special Project Office

LASL #P-115

March 1972

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SI-SIE-70A; REV. 6-64

NOTICE OF RESEARCH PROJECT
SCIENCE INFORMATION EXCHANGE
SMITHSONIAN INSTITUTION

SIE NO.

AGENCY NO.

SUPPORTING AGENCY: AMERICAN CANCER SOCIETY

TITLE OF PROJECT:

PION BEAM CHARACTERISTICS AND TREATMENT PLANNING

Give names, departments, and official titles of PRINCIPAL INVESTIGATORS and ALL OTHER PROFESSIONAL PERSONNEL engaged on the project.

Chaim Richman, Group Leader, Pion Radiobiology Group, H-9

Mudundi R. Raju, Staff Scientist, H-9

NAME AND ADDRESS OF INSTITUTION: Los Alamos Scientific Laboratory
P. O. Box 1663, Los Alamos, New Mexico 87544

SUMMARY OF PROPOSED WORK – (200 words or less.) – In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research, and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

A beam of π^--mesons is being designed for radiotherapy at the Los Alamos Meson Physics Facility. When this beam goes into operation measurements will be made of the electron and muon contaminations and the spatial distribution of the pions.

These measurements together with Monte-Carlo calculations will be used to do treatment planning for various lesions. The use of bolus, wedges and collimators will also be studied for the best treatment plans.

SIGNATURE OF PRINCIPAL INVESTIGATOR Chaim Richman

PROFESSIONAL SCHOOL (medical, graduate, etc.) Los Alamos Scientific Lab

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COST ESTIMATE

Project Term - Begin - January 1, 1973

Project Term - End - December 31, 1974

Termination Date of Funding -

	FY 73	FY 74	FY 75
Manyears			
A Scientific	0.5	1.0	0.5
B Other	0.0	0.0	0.0
Costs ($1,000)			
A. Direct Salaries	12.14	25.96	13.90
B. Materials & Services	4.16	8.65	4.50
C. Other Direct Charges			
1. Consultants	3.75	7.50	3.75
2.			
3.			
4.			
Total Direct Costs	20.05	42.11	22.15
D. Indirect Costs	6.06	12.98	6.93
Total Costs	26.11	55.09	29.08
Equipment Costs ($1,000)			
A. Obligation	7.50	12.50	7.50
B. Cost	7.50	12.50	7.50

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APPLICATION R A RESEARCH OR CLINICAL INVI IGATION GRANT

BIOGRAPHICAL INFORMATION

(Give the following information for all professional personnel listed on page 2, beginning with the Principal Investigator. Use continuation pages and follow the same general format for each person.)

NAME	TITLE	BIRTHDATE (Mo., Day, Yr.)
Chaim Richman	Group Leader, H-9	[redacted]
PLACE OF BIRTH (City, State, Country)	**PRESENT NATIONALITY** (If non-U.S. citizen, indicate kind of visa and expiration date)	**SEX**
[redacted]	U.S.A.	☒ Male ☐ Female

EDUCATION *(Begin with baccalaureate training and include postdoctoral)*

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	SCIENTIFIC FIELD
[redacted]	B.A. M.A. Ph.D.	[redacted]	Physics Physics Physics

HONORS [redacted] Sigma Xi; American Physical Society, Fellow
Ethel M. Rubelson Lecturer, Department of Radiology,
University of Minnesota Medical School

MAJOR RESEARCH INTEREST	ROLE IN PROPOSED PROJECT
Pion Physics and Treatment Planning	Principal Investigator

RESEARCH SUPPORT *(See instructions)*

$100,000, A.E.C.,for Group H-9, Chaim Richman, Group Leader, Pion Radiobiology Group

RESEARCH AND/OR PROFESSIONAL EXPERIENCE *(Starting with present position, list training and experience relevant to area of project, including teaching and clinical responsibilities. List all or most representative publications.*

Staff research scientist, Los Alamos Scientific Laboratory
Lecturer, Assistant Professor & Associate Professor, [redacted]
Staff member, [redacted]
Director of Research, [redacted]
Professor of Physics, [redacted]
Professor of Physics, [redacted]

Dr. Richman started work on pions at the [redacted] synchrocyclotron in 1949. Since 196[redacted] he has worked and directed a [redacted] radiotherapy with pions at [redacted] from the [redacted] This program involved various experiments on the dosimetry and radiobiology of negative pions.

Please see attached list of publications -

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PUBLICATIONS

Deuteron Disintegration by Electrons, with B. Peters, Physical Review, 59, 804 (1941)

Angular Distribution in Deuteron Disintegration by Electrons, (A), Physical Review, 61, 203 (1942)

The Production of Slow Neutrons in a Carbon Block, with T. Snyder and R. W. Williams, U.S. Atomic Energy Commission Report MDDC-302, Sept. (1946)

Drift Tubes for Linear Proton Accelerator, (A), with F. Oppenheimer and L. H. Johnston, Physical Review, 70, 447 (1946)

Initial Performance of a 32 MeV Proton Linear Accelerator, (A), with L. V. Alvarez, H. Bradner, H. Gordon, L. C. Marshall, F. Oppenheimer, W. K. H. Panofsky, R. Serber, C. Turner, and J. R. Woodyard, Science, 106, 506 (1947)

On the Neutron-Proton Scattering Cross Section, with D. Bohm, Physical Review, 71, 567 (1947)

Resonant Cavities, Electronic Lecture Series, BP-94, September 17 (1947)

Control of the Field Distribution in the Linear Accelerator Cavity, with W. K. H. Panofsky, Physical Review, 73. 535 (1948)

Apparatus for Measuring Proton-Proton Scattering at 32 MeV Using Proportional Counters, (A), with B. Cork and L. Johnston, Bulletin of the American Physical Society, 24. 214 (1949)

Berkeley Proton Linear Accelerator, with L. Alvarez and others, UCRL-236 (1949)

An Experiment for Measuring Heavy Meson Production by High Energy Particles, (A), with H. Wilcox, presented at the December 29-30, 1949 meeting of the American Physical Society at Stanford University, Physical Review, 78, 85 (1950)

Measurement of the Production of Positive and Negative Mesons by 345 MeV Protons on Carbon, (A), with H. A. Wilcox, presented at the December 20-30, 1949 meeting of the American Physical Society at Stanford University, Physical Review, 78, 85 (1950), also Classified Document #LA-38, Lawrence Radiation Laboratory

Production Cross-Sections for π^+ and π^- Mesons by 345 MeV Protons on Carbon at 90° to the Beam, (L), with H. A. Wilcox, Physical Review, 78, 496 (1950)

The Production of π^+ Mesons by Protons on Protons in the Direction of the Beam, (L), with F. Cartwright, M. Whitehead, and H. A. Wilcox, Physical Review, 78, 823 (1950)

Proton-Proton Scattering at 31.8 MeV Proportional Counter Methods, with B. Cork and L. Johnston, Physical Review, 79, 71 (1950)

Production of a π^+Meson Beam Using the Deflected Proton Beam of the 184-inch Synchrocyclotron, (L), with M. Skinner, J. Merritt, and B. Youtz, Physical Review, 80, 900 (1950)

Scattering of π^+ Mesons on Carbon, (A), with M. Skinner, Physical Review, 83, 217 (1951)

On the Angular Distribution of the π^+ Mesons from 341 MeV Protons on Protons, (L), with M. Whitehead, Physical Review, 83, 855 (1951)

On the Angular Distribution and the Polarization of the Deuteron in the Reaction $p + p \rightarrow d + \pi^+$, with K. M. Watson, Physical Review, 83, 1256 (1951)

The Production of π^+ and π^- Mesons by 340 MeV Protons at 90° to the Beam from Carbon and Lead, with M. Weissbluth and H. A. Wilcox, Physical Review, 85, 161 (1952)

The Production of Positive Pions by 341 MeV Protons on Protons, with W. F. Cartwright, M. N. Whitehead, and H. A. Wilcox, Physical Review, 91, 677 (1953)

The Berkeley Proton Linear Accelerator, with L. W. Alvarez, H. Bradner, J. F. Finch, H. Gordon, J. Gow, L. C. Marshall, F. Oppenheimer, W. K. H. Panofsky, and J. R. Woodyard, Rev. Sci. Insti., 26, 2, 111 (1955)

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PUBLICATIONS (Cont'd)

On the Dosimetry of Negative Pions with a View Toward Their Use in Cancer Therapy, with H. Aceto, M. R. Raju, B. Schwartz, and M. Weissbluth, Spring 1964, Semiannual Report Biology and Medicine, 114, Donner Lab, University of California, Berkeley, California

The Therapeutic Possibilities of Negative Pions, Preliminary Physical Experiments, with H. Aceto, M. R. Raju, and B. Schwartz, American Journal of Roentgenology

Pion Studies with Silicon Detectors, with M. R. Raju and H. Aceto, Nuclear Instruments and Methods, 37, 152-158 (1965)

Lithium-Drifted Silicon Detector Used as a Pulse Dosimeter, with M. R. Raju, E. J. Lampo, S. B. Curtis, and J. M. Sperinde, UCRL-16924 (delivered at the 13th Nuclear Science Symposium on Instrumentation in Space and Laboratory, Boston, Massachusetts) (1966)

π^- Mesons, Radiobiology, and Cancer Therapy, C. Richman, Proceedings of the First International Symposium on the Biological Interpretation of Dose from Accelerator-Produced Radiation, 346-348 (1967)

A Review of the Physical Characteristics of Pion Beams*, with M. R. Raju and S. B. Curtis, Proceedings of the First International Symposium on the Biological Interpretation of Dose from Accelerator-Produced Radiation, 349-367 (1967)

Studies of Vicia Root Meristems Irradiated with π^- Beam, with S. P. Richman, M. R. Raju, and B. Schwartz, Radiation Research, 7, 182-189 (1967)

Effect of Negative Pions on the Proliferative Capacity of Ascites Tumor Cells (lymphoma) in Vivo, with J. M. Feola, M. R. Raju, S. B. Curtis, and J. H. Lawrence, Radiation Research, 34, 70-78 (1968)

Physical and Radiobiological Aspects of Negative Pions with Reference to Radiotherapy, with M. R. Raju. Presented at the XII International Congress of Radiology, October 6-11, Tokyo, Japan. GANN Monograph on Radiology of Cancer, No. 9, 105 (1970

The RBE of Negative Pions in 2-day-old Ascites Tumors, with J. M. Feola, M. R. Raju, and J. H. Lawrence, Radiation Research, 44, 637 (1970

The Oxygen Effect of π^- Mesons in Vicia faba, with M. R. Raju, N. Amer, and M. Gnanapurani, UCRL-18644, Radiation Research, 41, 135-144 (1970)

Negative π Meson Therapy: Physical and Biological Considerations, with M. R. Raju, Chapter in Current Topics in Radiation Research, edited by M. Ebert and A. Howard, to be published by North-Holland Publishing Company, Amsterdam (1970

Recommendations for Implementing Radiotherapy with Negative Pions at LAMPF, LAMPF Biomedical Steering Committee, Chaim Richman, Los Alamos, LA Report 1972 (in preparation)

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1. AIM and METHOD of STUDY

There is now being constructed at our Laboratory at Los Alamos an accelerator (LAMPF) which will give a current of one milliampere of 800 MeV protons. One of the main purposes of this accelerator is to produce intense beams of negatively charged pions, and one of these beams is designed to be used for pretherapeutic radiobiology and then radiotherapy. In connection with this beam a facility is now on the drawing boards for this work. A photograph of the machine and drawings of all of the facilities being built and planned can be found in the set of recommendations prepared by the LAMPF Users Biomedical Steering Committee attached to this proposal.

When 800 MeV protons impinge on a target, negative pions are produced in all directions. To collect and focus the pions properly a series of magnets, both focusing and bending magnets, is used to bring the pions to the biological test object or the patient. This beam has now gone thru a number of designs, and it is expected that it will be ready early in 1973.

The aim of this work is -

1) To measure and study the origin of any electron and muon backgrounds in the beam.

2) To study and obtain the beam distributions produced by different settings of the target and the magnets.

3) To obtain beam configurations using bolus, wedges, and phantoms which are appropriate for the irradiation of different tumors guided by our experience with supervoltage therapy and especially electron beam therapy.

The technique that will be used in this work will be the semiconductor position sensitive detector which is a very versatile and linear detector. Its range of response is well known to be from minimum ionizing particles to heavy charged particles so that it can detect electrons, muons, and pions and with a proper converter even neutrons.

At a recent meeting of our dosimetry advisory subcommittee, there was a strong expression of the fact that on several occasions when new machines were brought into therapeutic use the work was rushed and the machines were used in therapy before sufficient experience and knowledge was obtained. We want to avoid this in every way at LAMPF. A basic need, both for radiobiology and of course for therapy, is the full and detailed knowledge of the beam.

With a new radiation like pions this knowledge is especially important: Pions are lightly ionizing particles which can be well-directed

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but stop at a finite range, whereupon the pions cause the break-up of nuclei with the emission of short range alpha particles and protons. The stopping region should be the treatment volume. Therefore the energies of the pions have to be chosen properly for each tumor and for each patient by means of the magnet settings and the slit openings. All the parameters have to be checked experimentally.

The break-up of the nucleus results in radiation being produced of a character entirely different from the pion. Up to now the pion in traversing the healthy tissue has been a lightly ionizing radiation (for much of its path it is at minimum ionization); thus the healthy tissue in front of the tumor experiences low dosage. The release of the short range nuclear fragments, especially the alpha particles, gives a much higher dose in the tumor region. From the radiobiological standpoint, a profound change has taken place. From a radiation with an RBE of about 1.0 like Co-60 or electrons, in the healthy tissue, a dose is now given to the tumor region with an RBE about 2.0 to 5.0. This greatly enhances the tumor to healthy tissue effects. Another effect is that from a radiation with an oxygen enhancement ratio (OER) of 3 in the healthy tissue, the radiation now has an OER of 1.5 to 2, and this means that much of the protection that anoxic cells have had with low LET radiations will be removed and the chances of these cells regrowing the tumor will be greatly lessened.

Several different approaches have been described for studying the beam characteristics. One approach is to use a time-of-flight method to separate the pions and the background particles. This is a good method but it requires very fast timing (nanosecond electronics) to accomplish and is not so suitable for distribution of particles. Measurements of total dose are essential but do not identify the backgrounds. The lithium drifted silicon detector can give dose distributions while at the same time identifying the particle by means of pulse height or if necessary in combination with energy loss in a small detector telescope. In addition, from a practical point of view, this employs conventional slow timing and standard pulse amplifiers. This method in combination with absolute dose measurements will go a long way in giving us a picture of the kinds of beams that we have.

Before therapy can begin, the data that will be obtained in the radiobiological experiments on the RBE for different tissues will have to be folded into the dose measurements. The data with silicon detectors also give a measure of the LET distributions for various beams; consequently the RBE measurements will then be correlated to the LET information and a sensible picture will be obtained of how the RBE varies with different momentum spreads of the beam.

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Treatment Considerations and Treatment Planning

At this time, the therapeutic beam is being designed, and it is clear that the beams will be essentially parallel, which is good. With Co-60 machines, the beams come from a point source so one gets high dose overlaps in using adjacent fields and cold spots near the surface. With pions, there should be no adjacency problems, and the uniformity over the field will be measured.

Of course there is lacking sufficient practical experience of the behaviour of this radiation in bone and in fat and its scattering in inhomogeneities. As part of this program calculations will be made to supplement the measurements of these practical and important properties: R. G. Alsmiller and T. W. Armstrong at Oak Ridge have a Monte-Carlo code which they have used successfully for calculating pion doses in water for a therapeutic beam. With such a code inhomogeneities are easy to follow since in the Monte-Carlo method each pion is followed separately and the statistics are accumulated by the computer.

The fact that there is very little exit dose beyond a range that is chosen makes pions similar but even better than electron beam therapy, and we can be guided by the experience and problems that have taken place in this field: It has been found that lung inhomogeneities may result in complications from overdosage or recurrences from underdosage. Chest radiographs have shown radiation pneumonitis and pulmonary fibrosis in electron beam therapy of the chest wall. A careful study will be made using the Monte-Carlo method; and subsequently, phantom measurements will be made of the behaviour of pions around inhomogeneities.

In treating with electron beams behind bone, there is some evidence that the dose is significantly decreased. This comes about because the scattering in calcium is much higher than in surrounding tissue and it therefore depletes the beam. Workers at M. D. Anderson Hospital and Tumor Institute have observed several recurrences of oral cavity and oropharingeal lesions located immediately behind the mandible. It is well known that electrons, because they're so light, undergo much more scattering than protons or mesons; nevertheless, the effect of bone with this new beam will be calculated by the Monte-Carlo method and will be measured when the beam becomes available.

It is expected that the pion beam can be shaped to almost any desired region of tissue wherein a high dose or a "boost" dose is required. If such shaping is indeed possible, pions may be expected to replace interstitial insertion of radioactive sources (as for floor of mouth and tongue lesions). This could be used then to treat the floor of the mouth with good control of the total volume brought to a high dose. Such a technique would lead to a greater dose homogeneity than is achievable with interstitial sources and should produce better results. This shaping will be studied

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in a phantom to see how far this could be accomplished by control of the magnets, especially so since special controls for this shaping will be included in the machine now.

The clinical use of pions brings with it some other basic issues that will be worked out - a) How is the dose distribution altered by angulating the field? b) What is the effect of a wedge on the field? c) How can two wedges be used to get special distributions of dose? d) How should bolus be used? And of what material?

As an example of the examination of lesions where pions might be useful let us take tumors of the nasopharynx: It is customary in treating tumors arising in this region to use a high dose volume extending from one side of the patient's head to the other and often, through the use of anterior angulated fields, to have the high dose zone extend forward to the skin surface of the cheek and posteriorly even into the brain stem. The incidence of complications in successful treatment of nasopharynx cancers has been rather high. These complications include central nervous system damage, difficulties in motion of the jaw due to high dose irradiation of the tempero-mandibular joints, hearing loss due to high dose irradiation of the auditory mechanism, loss of taste and dry mouth, and many others.

With pions, we will start with a high dose zone more generous than the size of the nasopharynx itself, but not so generous as the high dose zone in conventional treatment. This could be carried to doses approximately 75% of the final tumor dose, and at this time the fields in the phantom will be tailored more closely to the nasopharynx. The entire neck should be irradiated bilaterally; this will be done with the phantom with sparing of the spinal cord.

Treatment planning with pions will be developed and it promises to be simpler in nature than planning with X-rays because in general fewer fields are necessary to achieve a good distribution.

First, good isodose distributions will be generated theoretically and will be measured experimentally when the beam becomes available. Then the superposition of two fields can be done even without computers to study good treatment plans. At the present time most electron beam treatment planning is done by hand for the same reason.

There is available at this time, a compilation of preferred treatment plans for many types of lesions. The work will begin here with seeing what pions can accomplish in the way of improving these dose distributions. In this way a good feeling will be attained about what pions can do for different lesions.

Electron beams are now used primarily for head and neck lesions and breast cancer; the reason for this is that the cut-off for electrons is a sharp one only for the lower energy electrons and therefore for limited

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penetration. For energies of something like 30 MeV electrons, depth doses begin to look like X-ray distributions. With pions this isn't true: The range cut-off remains intact even for high energies. Consequently a new range of treatment plans can now be considered, that is a sharp cut-off radiation for deep-seated tumors. Here we will arrive at new possibilities of irradiation of different lesions and with greater comfort for the patient and with far fewer undesirable sequelea than with present modalities.

2. Work Accomplished

For the past year and a half, committees have been set up to study the various problems connected with therapy with patients. Of particular importance have been the requirements on the beam line: The parameters of the beam line determine the type and location of the different magnets and the very large amount of shielding necessary to protect the patient and the workers from the ambient neutrons at the machine. These decisions involve great expenditures of funds and once they are made, fix the therapeutic constraints.

Furthermore, in the studies of the groups, we have arrived at a much clearer picture of the various tissues that should be investigated. Particular importance was placed on skin, cartilage, spinal cord and heart and preliminary preparations are being made for these radiobiological studies. The dosimetry and the problems of treatment planning have also been set forth with great clarity and with very good advice. The entire set of deliberations and recommendations are given in the document enclosed with this proposal.

Our previous studies with the π^--beam at the Berkeley 184" synchrocyclotron have been written down and are contained in the reprints attached to this proposal. The data show that silicon detectors work well with pions and the beams can be characterized with these detectors. They also give depth dose distributions and isodose distributions.

We have also studied in a preliminary way some radiobiological effects of π^--mesons. This was done with a weak beam ($\sim$ 50 rads/hr) and are not applicable for therapy. They will simply serve to guide the future radiobiology of the intense beams at LAMPF. Preprints are included in this work.

3. Facilities Available

The LAMPF machine is now in construction in our laboratory and it has reached an energy of 211 MeV protons. It is expected that 800 MeV will be attained this summer sometime. The biomedical channel is now in the final design stages and the magnets will be ordered very soon; the channel will be ready early next year.

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A radiobiology and treatment facility is now on the drawing board and construction is expected to begin this summer, however work on the beam can begin early next year by using trailers to house the equipment and the people.

The electronics equipment for the silicon detectors is being assembled and tested and already approximately $30,000 has gone into this area of instrumentation. We have the support of the Electronics Division which is now designing the scanner for moving the detectors in the beam by remote control.

The beam channel and the console for controlling the beam is being built by members of the MP Division at Los Alamos.

4. Time to Accomplish the Work

The length of time estimated to complete this research is three year.

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UNIVERSITY OF CALIFORNIA
LOS ALAMOS SCIENTIFIC LABORATORY
(CONTRACT W-7405-ENG-36)
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IN REPLY REFER TO: SPO

March 23, 1972

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Dr. John Totter, Director
Division of Biology & Medicine
U. S. Atomic Energy Commission
Washington, D. C. 20545

Dear John:

Attached is a proposal (LASL #P-115) requesting continued financial support from the American Cancer Society for the work of Dr. Chaim Richman at Los Alamos in Pion Treatment Development and Planning. As you may recall, we have just been advised that the ACS has provided funds to support about one year of Dr. Richman's work. The attached proposes that the financial support be extended over an additional two year period. The first year of work is described in proposal #LASL-P-93.

The Los Alamos Scientific Laboratory would be very pleased to undertake the work described under ACS sponsorship, and can do so without interference with AEC commitments if funding of $138,000 is provided for the two-year period indicated. (Calendar 1973 and 1974). We would appreciate your review of our proposal, and hope for your endorsement of it to the ACS.

As you may recall, the Albuquerque Operations Office has been very helpful to us in negotiating the transfer of funds from the ACS to the AEC for use at LASL. We assume that, pending AEC endorsement, ALOO might assist us again by transmitting the proposal to the ACS and arranging for transfer to LASL of any funding which might be provided. Accordingly, we have provided copies to ALOO for their review and consideration.

Further correspondence regarding the proposal should be addressed to A. D. McGuire of the LASL Special Projects Office.

Sincerely,

W. M. Agnew
Director

Attach: LASL #P-115 (3 copies)

cc: A. D. McGuire, SPO, wo/attach.
ISD-5, wo/attach.

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