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Relative Biological Effectiveness and Peripheral Damage of Antiproton Annihilation

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Executive Summary

The use of ions to deliver radiation to a body for therapeutic purposes can be a significant improvement over the use of low linear energy transfer (LET) radiation because of the improved energy deposition profile and the enhanced biological effects of ions relative to photons. Proton therapy centers exist and are being used to treat patients. In addition, the initial use of heavy ions such as carbon is promising to the point that new treatment facilities are planned. Just as protons or heavy ions, antiprotons can also be used to deliver radiation to the body in a controlled way, however antiprotons will exhibit additional energy deposition due to the annihilation. The slowing down of antiprotons in matter is similar to that of protons except at the very end of range beyond the Bragg peak. Gray and Kalogeropoulos estimated the additional energy deposited by heavy fragments within a few millimeters of the annihilation vertex to be approximately 30 MeV (Gr84). Kalogeropoulos and Muratore also mentioned the advantage of using the fast pions leaving the body to image the annihilation (Ka89). The relative magnitude of the enhanced energy deposition was measured by Sullivan at LEAR in 1985 but not the biological effect (Su85). Our proposed experiment is the first to measure directly the biological effects of antiproton annihilation. The experiment can only be done at CERN at this time because only the AD has a monoenergetic beam of antiprotons able to deliver a biologically meaningful dose at an appropriate dose rate.

We propose to use a monochromatic beam of antiprotons at 300 MeV/c momentum extracted from the AD into the DEM line to irradiate biological cell samples. Preliminary study by the members of the AD operations team indicate that no significant modifications of the AD or the DEM beamline will be required. The physical footprint of the proposed experiment is approximately 2 m^2 and will fit in the space currently available at the end of the DEM beamline. It will not interfere in any way with the existing AD experiments. After characterizing the beam profile, cell samples will be exposed to various doses of antiprotons and their survival will be measured. For the purpose of cell preparation and biological analysis we plan to install a small biolab outside the AD accelerator hall in an existing container presently owned by the ATHENA collaboration. All expenses for any modifications or upgrades will be completely covered by the collaboration. We will make no

financial or manpower requests to CERN, except for the request to the AD operations team for beam extraction into the DEM line at 300 MeV/c.

The total number of full 8 hour shifts requested is nine. The proposed test beam experiment is designed to have minimal impact on the existing AD experiments and can make use of gaps in the usage of the AD caused by experimental downtime. Once these measurements are completed, there will be an evaluation phase and a presentation of the results. If these results promise significant enhancement over other methods, we will consider a follow up proposal..

I. Purpose

The purpose of the proposed experiment is to measure the biological effectiveness of the annihilation of stopped antiprotons relative to protons and to determine the peripheral damage profile associated with the possible therapeutic use of antiprotons for radiosurgery.

II. Background and Importance

The use of antiprotons for treatment of tumors was first proposed by Gray and Kalogeropoulos. (Ga84) in 1984. They observed that the added energy deposited by the nuclear fragments generated during the final annihilation could provide a significantly greater biological effect than protons or ions. All ions share the specific profile of increased energy deposition at the end of their range in materials, which has the potential to make them far superior to x-rays and photons for radiation therapies. The observation of Gray and Kalogeropoulos came at the time when quality beams of antiprotons were just emerging and they correctly predicted much future development in this area. A year later Sullivan performed an experiment measuring the actual energy deposition of antiprotons stopping in tissue-equivalent plastic and found an enhancement over protons of at least 20 MeV/antiproton (Su85). While this is small compared to the total annihilation energy of 2 GeV, for biological purposes this is very significant. Most of the energy of the annihilation is carried away by the charged pions or by the high-energy gamma's (resulting from immediate decay of the neutral pions) with minimal interactions with the surrounding tissue. The higher energy neutrons emitted in the annihilation process have intermediate ranges and result in a diffuse neutron radiation background centered on the tumor, but extending beyond it. Similarly, the higher energy protons and pions can produce some background radiation beyond the immediate region of annihilation. The main biological efficacy of antiprotons stems from the heavy recoils and fragments that result from a fraction of the many annihilation events where one of the pions may interact with a proton or neutron in the nucleus to cause nuclear excitation with subsequent break-up. These heavy fragments and recoils have a very short range and deposit all their energy in a localized region around the annihilation vertex. Kalogeropoulos also noted that the high energy pions can be used for 3-D imaging of the annihilation point, which is an important enhancement compared to both proton and heavy ion treatments.

No experimental measurement of the biological effect of antiprotons annihilating in human-like tissue exists, and it is this important quantity that is the focus of our proposed experiment. Using monochromatic antiprotons from the Antiproton Decelerator at CERN

(AD) we propose to directly measure the biological effect of antiprotons on living cells. These cells will be uniformly distributed in agarose, a biological culture medium, for their exposure to antiprotons. We will examine the survival of cells in response to different radiation doses generated by antiproton annihilations. This is the first measurement of this kind ever performed and will thus have an important impact on the field of particle beam-based cancer therapy. Even if the enhanced energy deposition is not as biologically significant as expected by many researchers in this field, the resulting measurement is very important and noteworthy. Twenty years after Kalogeropoulos introduced the idea of antiproton treatments as a future possibility, antiproton beams of the needed quality exist at the CERN AD that can enable us to evaluate this potentially powerful treatment methodology with high precision.

The response of biological systems to radiation is given in terms of dose, biological effect, and type of radiation. Dose (absorbed energy/mass) is measured in units of Gray where 1 Gy = 1 joule/kg in any material. The type of radiation and the energy are important because the same dose delivered by photons, electrons, protons, neutrons, alpha particles, carbon ions, etc. at different incident energies and dose rates can have significantly different biological effects. Comparisons between the biological effect of different types of radiation are usually expressed in terms of Relative Biological Effectiveness (RBE). RBE is the ratio of the dose of photon radiation to the dose of a reference radiation that produces the same biological effect. However, the RBE can also be measured for biological response in the Bragg peak region compared with that in the incident plateau region of an ion energy loss distribution. We propose to measure an RBE for antiprotons by comparing the biological effect of specific doses of antiprotons at a fixed energy relative to proton beams of similar energy and ^{60}Co beams. ^{60}Co has replaced 250 kVp (250 kV peak) x-rays as the reference radiation and has been used historically in biological characterization of this nature. **In this manner, the measurements of antiproton RBE will enable us to compare antiprotons to all the previous work that has been done in the field of charged particle delivery of radiation.**

Antiproton annihilation in biological material and the complexity of biological response does not lend itself to calculation from first principles. In fact, there is considerable misunderstanding of the source of the enhanced biological effects of annihilation. The majority of the annihilation products in the peak such as pions, gammas, or other low LET radiation contribute to a diffuse non-localized background dose to the whole body. From a potential therapeutic perspective the short-range, low energy recoils and fragments are the most significant because they deposit high LET radiation that is known to have enhanced biological effect. Comparing biological effectiveness of antiproton annihilation in the peak versus plateau regions of the stopping ionization distribution will give us some idea of the potential differentials in "biological" dose in the tumor and the normal tissues for an therapeutic beam of antiprotons. The peripheral biological damage associated with annihilation is a second measurement to be made in this experiment. The non-localized mixed radiation fields (neutrons, pions, muons, gammas) due to annihilation will also produce biological effects that must be measured as a function of distance from the point of annihilation. The measurement of the degree of therapeutic localization possible with

antiproton delivery and the relative biological effectiveness of ionizations in the peak versus those in the plateau will determine the potential efficacy of antiproton radiation therapy.

III. Scientific Approach

We propose to perform a test experiment using approximately 300 MeV/c (50 MeV) antiprotons from the AD extracted into a biological phantom situated in air at the end of the DEM beam line as shown in Figure 1. The choice of energy is motivated by the range and straggling of antiprotons at this energy. The phantom surrounding the actual biological sample is essentially a volume of tissue-equivalent material simulating the effect of backscattering and energy absorption in the body. The tube containing the cells will be designed to hold dispersions of living cells in agarose, a semi-solid biological culture medium that holds cells in a contained position within it. The quantitative cell survival studies involve counting the number of colonies that grow during an incubation period after irradiation, compared with controls receiving zero dose. A standard cell line of known radiation sensitivity will be exposed to varying doses of antiprotons. The beam pulses and the repetition rate of the AD can provide radiation dose rates in the cell-containing volume of interest of approximately 9 Gy/hr for a 1 cm^2 spot size. The total doses of biological interest are expected to be in the range of 0.1 - 10 Gy/hr, although lower doses may be sufficient in the peak if the RBE is high. The analysis of cell survival at serial 1 mm depths along the beam central-axis will enable us to determine the RBE as a function of depth along the path of antiprotons. The RBE will reflect the net effect of all different ionization species along the antiproton path and will be measured by comparing the survival of cells versus depth. The response relative to both protons and ^{60}Co will also be determined to standardize the biological effectiveness of antiprotons. The peripheral biological effects of the non-localized mixed radiation fields away from the point of annihilation will be measured in cell samples located at appropriate distances from the region of annihilation.

The test beam experiment will be designed to have minimal impact on the existing AD experiments. The required number of antiprotons for a complete set of biological samples can be delivered in nine shifts of AD operation including necessary beam characterization and physical dose measurements (See Table III & IV). The experiment to measure the relative biological effect of the annihilation of stopped antiprotons is highly interdisciplinary. The collaborators for this experiment cover the scientific disciplines needed. The collaborative relationship will include personnel from Pbar Medical, UCLA Medical School, the University of Aarhus, and CERN.

IV. Experimental Design

Even with the limited amount of beam time requested the proposed measurements will give crucial information about the potential of therapeutic tratments using antiprotons. Table I lists the experimental parameters relevant to the design of this test experiment.

Table I – Experimental Parameters

Typical linear cell dimension	10^{-3} cm
Cell number density (tumor)	10^{9} per cm^3
Tissue density	1 g/cm^3
Cell number density (suspension)	$7x10^{5}$ / cm^3
Culture medium (agarose)	1 g/cm^3
Range (300 MeV/c antiproton) in water	2.2 cm
Longitudinal straggling	1.5 mm
Antiproton source from AD	$2x10^{7}$/200 nsec pulse every 3 minutes
5 Gy dose	~10^{9} annihilations/gm

The usual method of measuring RBE involves comparing the dose of specific radiation to produce a given biological effect with the dose of ^{60}Co required to produce the same biological effect. The dose is delivered uniformly over relatively large volumes (several cubic centimeters). In the case of ^{60}Co, this is straightforward; but for the radiation produced by the annihilation of antiprotons, this is very difficult. The radiation from annihilation is mixed (pions, gammas, neutrons, fragments, recoils) and it is not easily possible to expose a several cubic centimeter volume to a uniform dose of "annihilation radiation." In the case of protons and antiprotons, the localized dose is dependent on depth as the particles slow down.

The sliced gel technique of Skarsgard will be adopted for these studies (Sk82, Sk98). In brief, cells will be suspended in solidified agarose growth medium within a tube. The tubes will be placed in a phantom, positioned collinear to the axis of the beam, and irradiated to a certain total dose with the antiproton beam. After the exposure is complete the gel will be extruded from the tube using a plunger connected to a delivery mechanism that advances the gel by 1 mm each time. The gel will be sliced every 1 mm using a taut wire, collected, and weighed to determine the amount of gel, and therefore the number of randomly distributed cells in each serial section. Each slice will be dissolved in warm medium and cells plated in Petri dishes at numbers likely to give 100 colonies per dish (which requires different starting cell densities in the medium). After incubation in a controlled environment for 8-10 days, the colonies that develop will be stained and counted. Only those colonies estimated as having more than 50 cells will be counted as having been derived from a single surviving cell (some small colonies represent cells that successfully negotiated a series of doublings before their reproductive death). Survival curves will be fitted using the usual non-linear curve fitting routines and effective equivalent RBE values will be calculated (Wo96) as a function of depth in the sample. The changes in the surviving fraction of cells with depth are due to the combined effects of the change in local dose (Bragg peak + fragments) and the RBE. Lateral uniformity of the beam will be determined at a few selected depths by also measuring cell survival versus radial position within selected slices. The same procedure will be followed for determining survival curves for proton irradiation. The ^{60}Co gamma

biological control reference irradiations are technically easier and will be performed using the same medium but standard in-vitro cell culture conditions.

V. Experimental Set-up

Figure 2 is a schematic diagram of the proposed test experiment at CERN. We request permission to use the DEM beam line at an extraction momentum of approximately 50 MeV (300 MeV/c). Because the experimental set-up will be in air, the beam will exit the AD vacuum system through a thin window. This window shall be optimized to minimize energy straggling and radial scattering and can be either a standard beryllium window from the CERN group or a specially fabricated window like the titanium window used at the entrance of the ATHENA experiment. This window will be designed and certified in close collaboration with the CERN AD staff. Monitoring of the beam intensity and profile will be accomplished using a parallel plate secondary emission chamber. These systems have been used in varying designs by several experiments at LEAR and the AD, including Crystal Barrel, PS200, TRAP, and ASACUSA. Due to the well-defined electric fields present in these designs, many of the non-linear features of wire chambers can be avoided. Linear response to the antiproton intensity has been obtained by both PS200 and ASACUSA over a range of antiproton intensities from 10^5 to 10^8 antiprotons/200 ns. The basic design consists of three thin foils, coated with electrically conducting surfaces, a common anode plane and two cathode planes. The cathode planes contain horizontal and vertical strips that allow a full measurement of the 2-D beam profile. We intend to use an ultra-high vacuum-compatible system designed and built by the ASACUSA collaboration (Ho99) that can be mounted internally to the DEM beam line vacuum at the very exit of this line. This monitor has a 99% transmission for the antiproton beam and adds only insignificantly to the energy and spatial straggling of the beam pulse. As a secondary beam monitoring system we plan to use scintillators coupled to hybrid photo diodes (HPD's) (Fu02) as in the ATHENA experiment. These detectors will surround the biological experiment set-up and monitor the high-energy pions and gammas resulting from antiproton annihilations in the set-up. The large dynamic range of these systems again assures a linear response to the intensity of the AD pulse delivered to the experiment. Both the secondary emission chamber and the HPD-scintillator combinations will be calibrated against an aluminum activation measurement as used by the ATHENA and ASACUSA collaborations and described in detail in reference (Fu00).

Biological response is a function of the absolute dose delivered. Thus the determination of absolute absorbed dose is one of the most important measurements required for this project. Additionally, absorbed dose to water (which closely resembles human tissue) is the quantity that is used to specify the amount of radiation to be used in clinical practice. Calorimetry is considered the gold standard for the determination of absolute dose, although impractical and difficult to perform with a high degree of precision in short beam time periods. Calorimetry is further hindered by the small field size of the antiproton beam available for this project. For practical reasons then, (calibrated) ionization chambers are most commonly used. For megavoltage electron and photon beams, the absolute dose in a medium, $D_{med}(z)$, is typically determined using a dosimetry protocol (AA83, IA87, IC84). These dosimetry protocols are based on the Spencer–Attix cavity theory (Sp55). Several

investigators have extended this formalism to proton beams (AA86, Me95, Va96a, Va96b, Vy91, Vy94). The extension to dosimetry of pion beams has also been described (Di76). However, two characteristics prevent successful implementation for antiproton dosimetry. First, the secondary radiation produced in an annihilation event is highly energetic and reasonably isotropic in nature. Therefore the requirement of charged particle equilibrium in the Spencer–Attix theory is violated. Second, the high instantaneous dose rate of CERN AD beam precludes the use of ionization chambers. Therefore, in lieu of a direct determination of absolute dose, we propose two alternate mechanisms. First, absolute dose can be calculated using Monte Carlo if an appropriate means of measuring integrated beam current is available. Second, we propose a systematic evaluation of beam characteristics using a variety of detectors with antiproton response correlated to appropriate reference beams including ^{60}Co and protons of a similar quality. With absolute dosimetry obtained for the reference beams, the antiproton response can be correlated with absolute dose and a meaningful determination of the RBE obtained.

Monte Carlo Overview

The number of antiprotons and the required beam time to deliver a prescribed dose is based upon calculations using the MCNPX Monte Carlo code. MCNPX is an extension of earlier MCNP codes with the addition of multiple particle transport and the incorporation of high-energy particle physics models to compute interaction probabilities where table-based data are not available. The code combines the traditional MCNP particles (neutrons, photons, and electrons) with the high-energy, multi-particle transport features of the LAHET(TM) code package. The INC model currently used in MCNPX for simulating antiproton annihilation is based upon the ISABEL (Ya79, Ya81) and VEGAS (Ch68) nuclear interaction codes including the emission of charged and neutral pions and kaons. The de-excitation of the residual nucleus after the initial annihilation reaction is modeled using a multistage, multi-step pre-equilibrium exciton model or MPM (Pr88) and includes the emission of protons, neutrons, deuterons, tritons, He3ions, and He4 ions. Upon reaching an equilibrium condition the Fermi-Breakup model (Br81) is applied to the residual nucleus and simulates the multi-fragmentation of light nuclei based upon two- or three-body breakup channels. Based upon an incident antiproton energy of approximately 50 MeV, pulse rate of $2x10^7$ antiprotons per 3 minute AD beam pulse, and a uniform 1x1 cm^2 spot size we estimate a dose rate of approximately 45 cGy per 3 minute AD beam pulse or 9 Gy per hour in the region of annihilation. The assumption of a uniform spot size represents a best-case scenario with respect to required beam time and lateral dose uniformity at the annihilation point. The MCNPX calculations will also be compared to Geant calculations and benchmarked against existing experimental data.

Measurement Overview

Characterization of relative dose requires a detector linearity of response within the assumed range of measurement conditions. In addition to response linearity of a detector used for relative measurement, appropriate sensitivity, energy independence, and spatial resolution are desired. We propose to investigate several detectors and methodologies for the

purpose of evaluating and verifying the depth-dose characteristics of an antiproton beam. These include the following: thermoluminescent dosimeter (TLD), film, and BANG gel dosimeters. The specific measurements, with a conservative estimate of required beam time, are shown in Table III.

TLD Measurements

Thermoluminescent dosimeters (TLD's) have been used extensively in pion dosimetry as described by Raju et al. and Dicello (Ra65, Di76). Thermoluminescent dosimetry relies on the "trap" phenomenon in which radiation energy is stored via impurities intentionally introduced into a crystalline material such as LiF. When heated, the stored energy is released in the form of visible light which is then collected via a photomultiplier tube. For these experiements we will employ TLD microcubes measuring 1 mm on a side. The microcubes are available in ^{6}LiF and ^{7}LiF compositions. Arrays of ^{6}LiF and ^{7}LiF TLD chips will be used to measure the radiation dose distributions in a phantom similar to that depicted in Figure 4. ^{6}LiF TLD will be employed as an indirect fast neutron dosimeter. ^{6}LiF and ^{7}LiF TLD's both respond to beta and gamma radiation. In addition, ^{6}LiF responds to slow neutrons (0.025 eV to 0.6 MeV) via the $^{6}Li(n,\alpha)^{3}H$ reaction, for which the cross section is 945 barns Two sets of measurements will be conducted in the phantom described in this proposal. The first set will be conducted with the use of ^{7}LiF, and the second set of measurements with ^{6}LiF. The ^{6}LiF TLD measures slow neutrons that are generated by higher energy neutrons incident on the phantom and which reflect back into the dosimeter. Such a dosimeter is referred to as an *albedo* dosimeter. The ^{7}LiF thermal neutron cross section for $^{7}Li(n,\alpha)^{8}Li$ is only 3.3 barns and practically measures the gamma dose while the ^{6}LiF gives the dose due to both gamma rays and neutrons. The difference in the readings will determine the neutron dose.

BANG Gel and Film Measurements

Three dimensional dose distributions resulting from photon beams have been successfully measured with the use of BANG (Bis Acrylamide Nitrogen Gel) gel (Lo99, Ma93, Ma96a, Ma96b, Ma97). BANG gels are muscle tissue equivalent in both elemental composition and density. These are aqueous gels infused with acrylic monomers that polymerize in proportion to radiation dose. During this process, sub-micron sized polymer particles are created, which are trapped in the gel. The dose distribution can be obtained by an MRI scan, using simple pulse sequences easily implemented on any MRI scanner. Photon equivalent dose distribution of an antiproton beam in BANG gel will be characterized by exposing a cylindrical flask of BANG gel to the AD antiproton beam. Similarly, photon equivalent dose distribution of antiproton beams may be measured using a film as a dosimeter, which is a standard method of obtaining two-dimensional dose distributions. Because the accuracy and precision of the film measurements are dependent on measurement conditions and processing, film dosimetry is not a reliable method of absolute measurements, but it is a valuable tool for relative measurements and beam alignment.

Bonner Sphere Measurements

To obtain some neutron spectral measurements on which to compare the Monte Carlo calculations to, we will use a series of Bonner spheres incorporating ^{7}LiF and ^{6}LiF thermoluminescent detectors and located at a fixed distance from the Bragg peak location in the other experimental phantoms (Sw98). This measurement will be concurrent with other experiments and thus will not require any additional beam time. The TLD readings will substitute for the traditional scintillation detector counts (LiI) and their response is dose rate independent. The difference in their readings will be assumed to be due to neutrons alone and this information fed into the unfolding code "Bunkie" to obtain the neutron spectral information (Jo87)

Cell Irradiation & Post-Analysis

The biological cell sample (cells suspended in solidified agarose growth medium placed inside a sterile, thin-film covered tube) will be located immediately adjacent to the final window of the beam line and aligned collinear to the antiproton beam. Except for the front surface of the sample, the sample will be completely surrounded by a phantom, a rectangular assembly of tissue-equivalent material approximately 30 x 30 x 30 cm^3. The purpose of this phantom is to simulate the human body surrounding a tumor and to mimic backscattering and energy absorption in a real treatment example. To allow access to the sample the phantom will be mounted on a rotatable base on top of a lifting platform allowing for x, y, and z adjustment of the sample with respect to the beam. The overall footprint of the experiment is approximately 2 m^2. After each irradiation with a specific dose the sample tube will be removed from the beam line and transferred to a biological analysis station. Here the gel will be extruded from the tube in 1 mm slices and analyzed. The sample analysis procedure is outlined in Figure 3. For the purpose of cell preparation and biological analysis we plan to install a small biolab outside the AD accelerator hall in an existing container presently owned by the ATHENA collaboration. The requirements for this laboratory are: electrical power (220 V/3000 Watt), temperature control to ± 3°C, laboratory workbench, local self-contained sterile hood for specimen preparation, incubator, CO_2 gas bottle, and optical microscope. Our collaboration will cover all expenses for possible upgrades of existing infrastructure to this container or, if necessary for technical reasons, to install a new, more suitable one at this or a similar location. This small biolab will present no health or safety concerns to CERN. It will be in total compliance with all environmental, health, and safety regulations. The timeline for the assembly and execution of the external biological test beam experiment is shown in Table II.

Table II - Proposed timeline for assembly and execution of the experiment. (Note: The work at CERN will utilize nine full AD shifts interspersed with time periods of off-line sample preparation and data analysis.)

Time Period		Work description	Location
2002	4th Quarter	Design and build sample holder and phantom Develop cell handling and analysis protocols Develop biological dosimetry for proton irradiations	UCLA/ Aarhus
2003	1st Quarter	Modify DEM beam line Correlate physical and biological dosimetry with protons Measure cell response to proton irradiation Certify biological protocols	CERN Aarhus/ UCLA/ Loma Linda
	2nd Quarter	Develop 300 MeV/c beam extraction Characterize extracted beam	CERN
	3rd and 4th Quarter	Expose living cell suspensions Incubate and determine biological response Measure peripheral damage profile Analyze data and summarize results	CERN UCLA

We estimate that the total number of shots of antiprotons required to successfully complete the test beam experiment during the year 2003 can be delivered in nine full shifts. Some of the measurements can be performed utilizing shorter time periods. The timing of the experiment is flexible in the sense that we can make use of any gaps developing in the AD schedule caused by downtime of one of the main experiments. The test beam experiment will essentially remain in a "standby mode" throughout the run cycle, able to employ antiprotons not used by the present AD experiments. We estimate that two shifts will be required to characterize the beam profile and calibrate the detectors for dosimetry. The number of antiprotons required to deliver a total localized dose of 9 Gy in the region of annihilation over a uniform area of 1x1 cm^2 is approximately $4x10^8$ (20 shots at $2x10^7$ antiprotons/shot). This is the single highest dose we anticipate needing. Beam uniformity requirements dictate that only the central portion of the Gaussian distribution be used (20 % variation corresponds to 20 % of the beam) for cell irradiations. This quality beam from the AD would require approximately 5 times more shots (5 hours) for the single highest dose. The three highest doses required for the cell irradiations in this test experiment can be delivered in less than 12 hours. The additional smaller doses can be delivered in less than 4 hours. One additional shift would be required for the peripheral damage measurements. The 10 times higher dose needed for peripheral damage would be able to use all the beam. Physical characterization of the beam will require two shifts. Therefore, the number of shifts to perform the test beam experiment is nine (2 for dose characterization, 6 for cell exposures,

and 1 for peripheral damage). The estimate for the total beam request is outlined in Table IV. The 20 % uniform beam requirement of $2x10^9$ is based on preliminary Monte Carlo simulations and references (Gr84) and (Su89).

Once these measurements are completed, there will be an evaluation phase and a presentation of the results. If these results promise significant enhancement over other methods of delivering localized radiation for therapeutic purposes, we will consider a follow up proposal.

Table III - Time estimates for physical beam characterization based on a conservative dose rate and anticipated detector response

Measurement	Dose Required	Time Required	Repetitions	Total Beam Time
Bang gel *(Co^{60} equivalent 3D information)*	5Gy	30 mins	1	30 mins
TLD (Li6) *(multiple 2D information, excludes n)*	3 to 4Gy	30 mins	2	1 hour
TLD (Li6) spread peak *(multiple 2D information, excludes n)*	3*(3 to 4Gy)	2 hours	2	4 hours
TLD (Li7) *(multiple 2D information, includes n)*	3 to 4Gy	30 mins	2	1 hour
TLD (Li7) spread peak *(multiple 2D information, includes n)*	3*(3 to 4Gy)	2 hours	2	4 hours
Bonner sphere *(neutron spectroscopy)*	~ 5 Gy	Concurrently	2	0 hours
Film *(Co60 equivalent depth dose curves)*	~ 1Gy	15 mins	2	30 mins
Film *(cross sectional profiles at 4 different depths)*	~1Gy	15 mins	2	30 mins
Film spread peak *(Co60 equivalent depth dose curves)*	<3*1Gy	30 mins	2	1 hour
Current Calibration		2 hour	1	2 hour
			Total	**14.5 hours**

Table IV - Estimated total beam time requirement.

Requirement	# of Antiprotons	Total # of beam pulses	Time (hr)	# of Shifts
Beam/Dose/Detector Characterization	-	-	16	2
9 Gy uniform localized dose	$2x10^9$	-	-	-
Additional uniform doses	$4x10^9$	-	-	-
One complete set of samples	$6x10^9$	300	16	2
Replicate exposures (x2)	$12x10^9$	600	32	4
Peripheral damage	$\sim 3x10^9$	~150	8	1
Total beam-time requirement			~72	9

References

(AA83) AAPM Task Group 21. ‘‘A protocol for the determination of absorbed dose from high-energy photon and electron beams,’’ Med. Phys. 10, 741–771 (1983).

(AA86) American Association of Physicists in Medicine (AAPM), ‘‘Protocol for heavy charged-particle therapy beam dosimetry,’’ American Association of Physicists in Medicine, AAPM Report No. 16 (American Institute of Physics, Woodbury, 1986).

(Ag02) N. Agazaryan, et. al., Meeting of the Particle Therapy Co-Operative Group **XXXVI**, Catania, Italy, May 29-31, 2002.

(Br81) D. J. Brenner, R. E. Prael, J. F. Dicello, and M. Zaider. “Improved calculations of energy deposition from fast neutrons”, Proceedings of the 4th Symposium on Neutron Dosimetry, EUR-7448, Munich-Neuherberg (1981).

(Ch68) K. Chen et al.Phys. Rev. 166, 949 (1968).

(Di76) Dicello, JF. Dosimetry of Pion Beams. In: Particle Radiation Therapy; Proceedings of an International Workshop. VP Smith Ed. Published by the American College of Radiology, Philadelphia, PA, 1976.

(Fu00) M. C. Fujiwara, Antiproton Intensity Measurement in ATHENA beam line at CERN AD, ATHENA Technical Report AT/00-01, Dec 2000.

(Fu02) M. C. Fujiwara and M. Marchesotti, NIM A 484 (2002) 162-173

(Gr84) L. Gray and T. E. Kalogeropoulos, Radiation Research **97**, 246-252, (1984)

(Ho99) M. Hori, Cascade of Metastable Antiprotonic Helium Atoms, Doctoral Thesis, Univ. of Tokyo, 1999.

(IA87) International Atomic Energy Agency (IAEA) ‘‘Absorbed dose determination in photon and electron beams: An international code of practice,’’ IAEA Technical Reports Series No. 277 (IAEA, Vienna, 1987).

(IC84) International Commission on Radiation Units and Measurements (ICRU), ‘‘Radiation dosimetry: Electron beams with energies between 1 and 50MeV,’’ ICRU Report 35, ICRU, Bethesda, MD, (1984).

(JO87) T.L. Johnson, Y. Lee, K.A. Lowery, S.G. Gorbies, Proceedings Theory and Practice in Radiation Protection and Dosimetry, American Nuclear Society 83-92, (1987).

(Ka89) T. E. Kalogeropoulos and R. Muratore, Nucl Inst. and Meth. in Phys. Res. **B40/41**, 1322-1325, (1989).

(Kl91) Kleck, JH. Applications of positron emission tissue activation products in high energy particle and photon radiotherapy, Doctoral dissertation of the University of California Los Angeles, 1991.

(Lo99) A. J. Lomax, T. Bortfeld, G. Goitein, J. Debus, C. Dykstra, P. Tercier, P. A. Coucke, R O. Mirimanoff, “A treatment planning inter-comparison of proton and intensity modulated photon radiotherapy,” Radiother. Oncol. **51,** 257-271 (1999).

(Ma93) Maryanski, MJ; Gore, JC; Kennan, RP; Schulz, RJ. "NMR relaxation enhancement in gels polymerized and cross-linked by ionizing radiation: a new approach to 3D dosimetry by MRI," Magnetic Resonance Imaging, Vol. 11, No. 2, 1993, pp. 253-258.

(Ma96a) Maryanski, MJ; Ibbott, GS; Eastman, P; Schulz, RJ; Gore, JC. "Radiation therapy dosimetry using magnetic resonance imaging of polymer gels," Medical Physics, Vol. 23, No. 5, 1996a, pp. 699-705.

(Ma96b) Maryanski, MJ; Zastavker, YZ; Gore, JC. "Radiation dose distributions in three dimensions from tomographic optical density scanning of polymer gels: II. Optical properties of the BANG polymer gel," Physics in Medicine and Biology, Vol. 41, No. 12, 1996b, pp. 2705-2717.

(Ma97) Maryanski, MJ; Audet, C; Gore, JC. "Effects of crosslinking and temperature on the dose response of a BANG polymer gel dosimeter," Physics in Medicine and Biology, Vol. 42, No. 2, 1997, pp. 303-311.

(Me95) Medin, J; Andreo, P; Grusell, E; Mattsson, O; Montelius, A; Roos, M.‘‘Ionization chamber dosimetry of proton beams using cylindrical and plane-parallel chambers. Nw versus Nk ion chamber calibrations,’’ Phys. Med. Biol. 40, 1161–1176 (1995).

(Pr88) R. E. Prael and M. Bozoian. “Adaptation of the multistage, pre-equilibrium model for the Monte Carlo method”, Los Alamos National Laboratory Report LA-UR-88-3238 (Sep 1998).

(Ra65) Raju, MR; Aceto, H; Richman, C. Pion studies with silicon detectors. Nucl. Inst. Meth. 37: 152-158, 1965.

(Sk82) L. D. Skarsgard, et. al., Int J Rad Biol. Phys. **8**(12), 2127-2132, (1982).

(Sk98) L. D. Skarsgard, Phys. Med. **14**, Supl. 1, 1-19, (1998).

(Su85) A. H. Sullivan, Phys. Med. Biol. **30**(12), 1297-1303, (1985).

(SW98) J. E. Sweezy, N.E. Hertel, K.G. Veinot, R.A. Karon, Radiation Protection Dosimetry **78**, 263-272, (1998).

(Va96a) Vatnitsky, SM; Siebers, J; Miller, DW. ‘‘kQ factors for ionization chamber dosimetry in clinical proton beams,’’ Med. Phys. 23, 25–31 (1996).

(Va96b) Vatnitsky SM, et al. ‘‘Proton dosimetry intercomparison,’’ Radiother. Oncol. 41, 169–177 (1996).

(Vy91) Vynckier, S; Bonnet, DE; Jones, DTL. ‘‘Code of practice for clinical proton dosimetry,’’ Radiother. Oncol. 20, 53–63 (1991).

(Vy94) Vynckier, S; Bonnet, DE; Jones, DTL. ‘‘Supplement to the code of practice for clinical proton dosimetry,’’ Radiother. Oncol. 32, 174–179 (1994).

(Wo96) B. G. Wouters, et. al., Rad. Res. **146**, 159-170, (1996).

(Ya79) Y. Yariv and Z. Fraenkel, “Intranuclear cascade calculation of high-energy heavy ion interactions”, Phys. Rev. C 20, 2227 (1979).

(Ya81) Y. Yariv and Z. Fraenkel, “Intranuclear cascade calculation of high-energy heavy ion collisions - Effect of interactions between cascade”, Phys. Rev. C 24, 488 (1981).

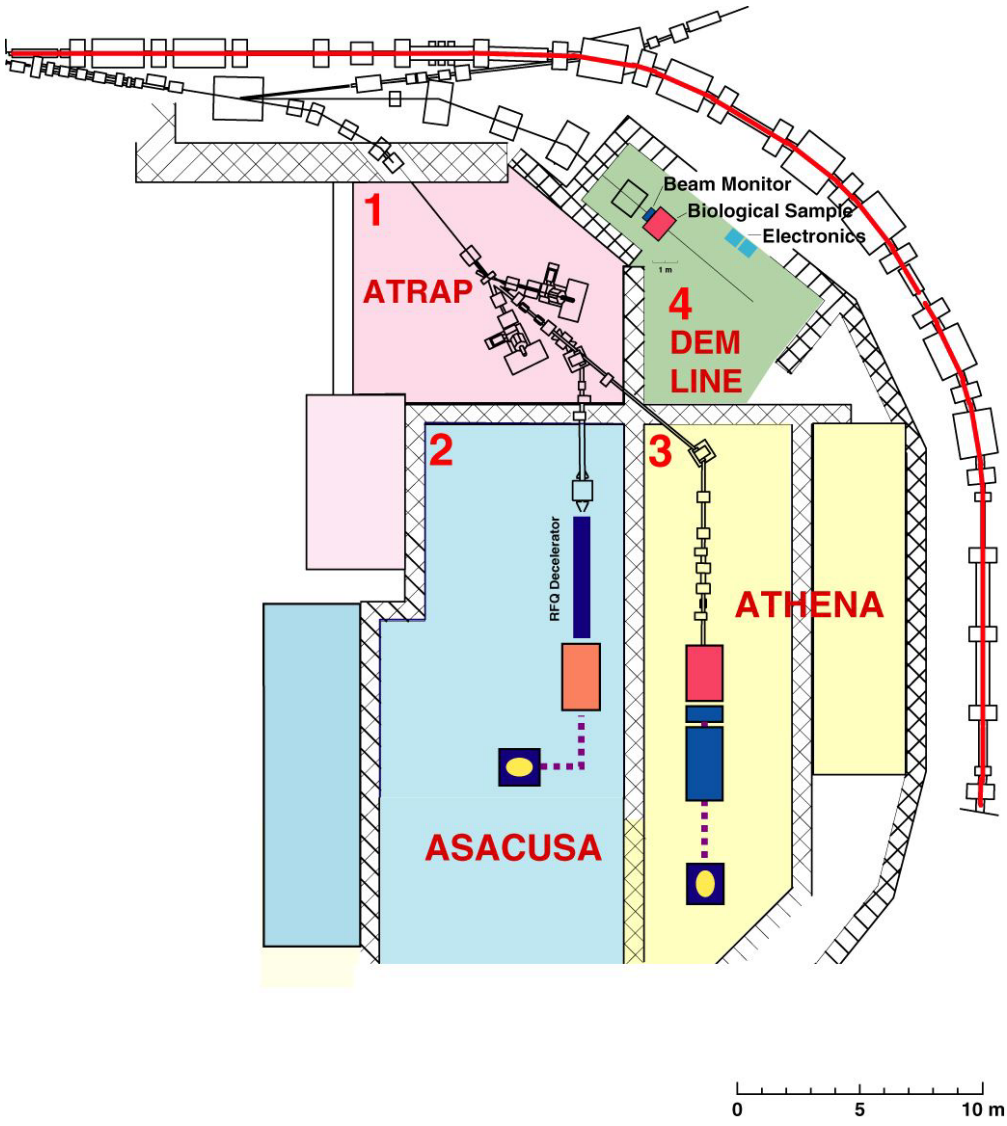

Figure 1 - Layout of the test experiment in the AD accelerator hall.

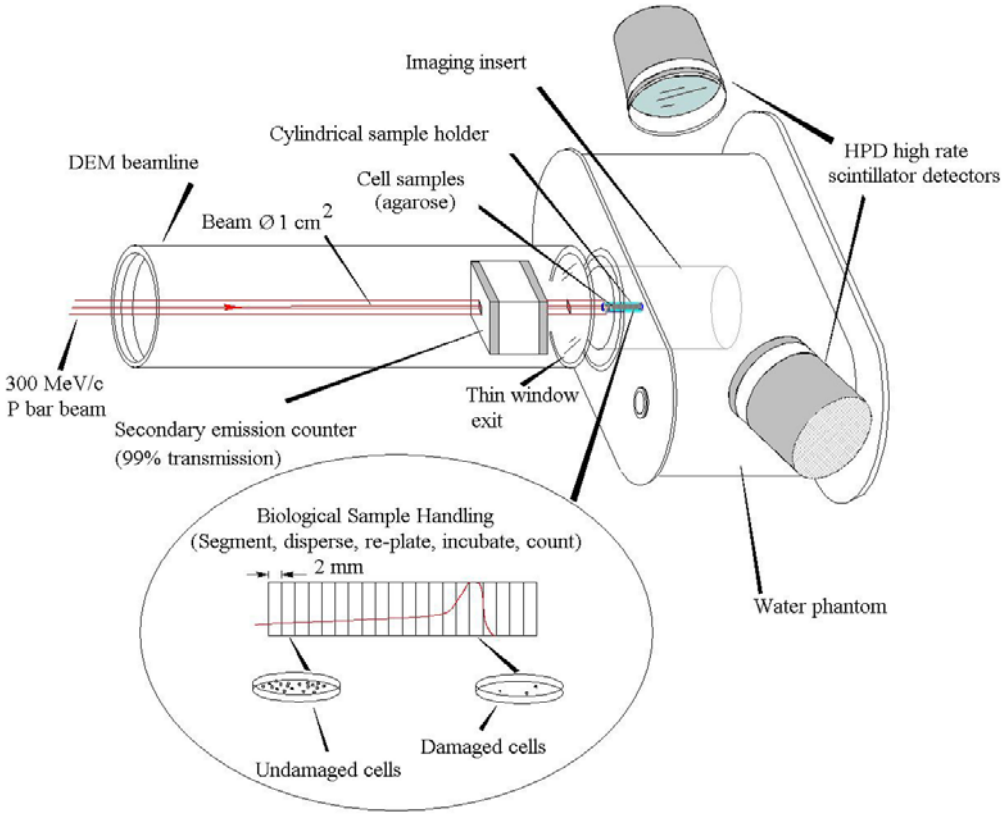

Figure 2 - Overview of the test bio-experiment. The HPD high rate scintillator detectors are not shown to scale.

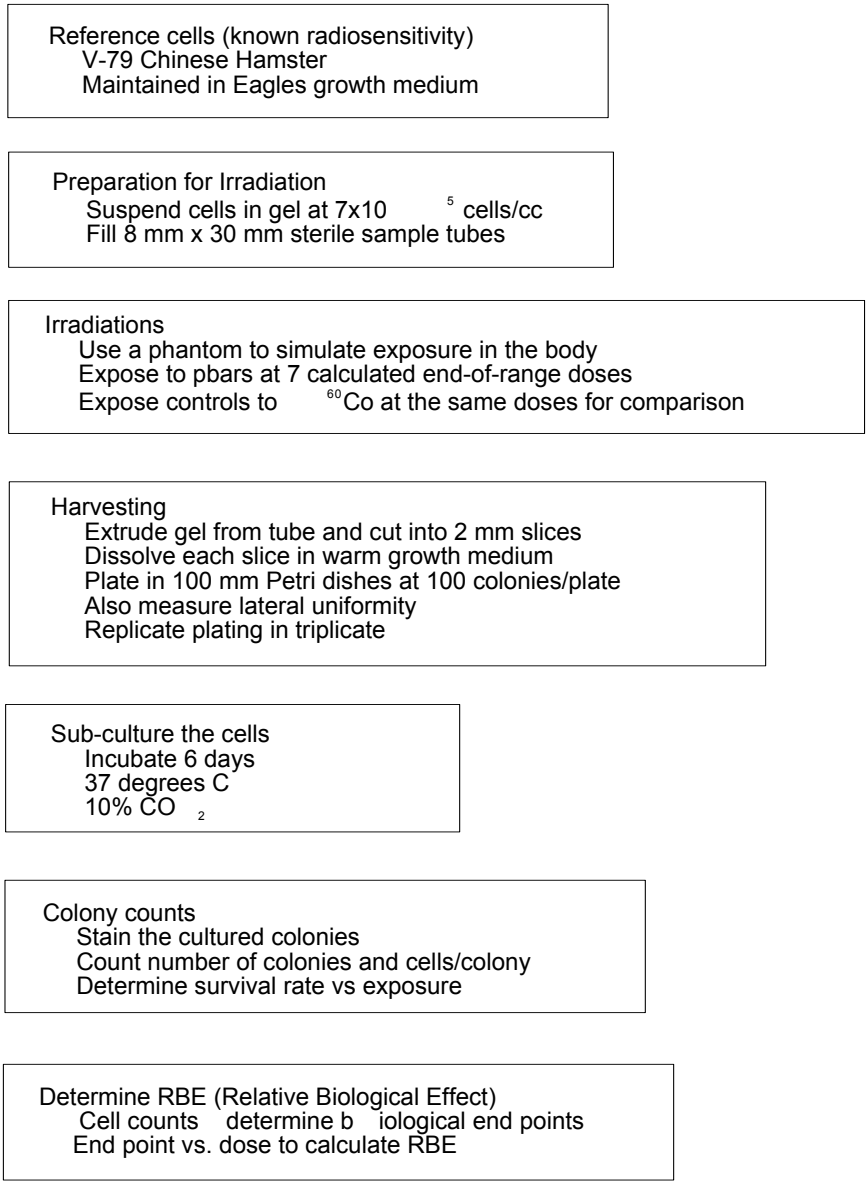

Figure 3 - Outline of the biological sample analysis protocol. The experiment will be performed In triplicate with all doses given within two 8 hour shifts. There will be a delay between exposures to allow for sample Incubation and analysis. Two additional 8 hour shifts will be required to determine the peripheral damage profile.

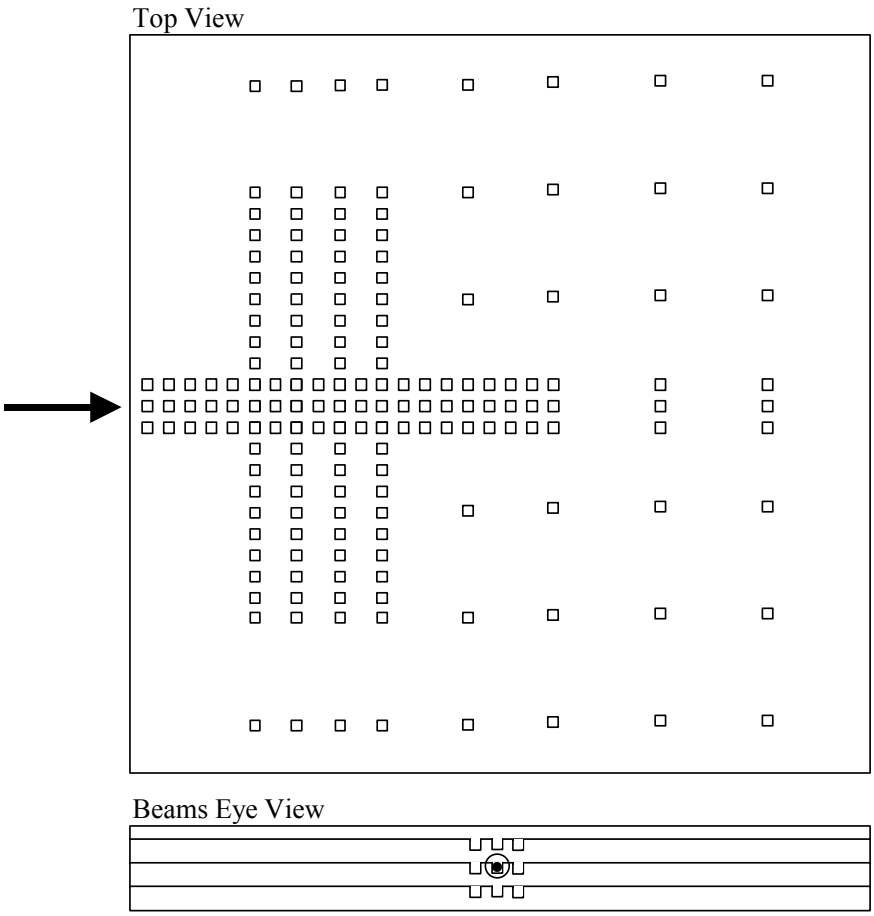

Figure 4 - Cross sectional diagram of the TLD array (top view) measuring 6x6 cm^2 in dimension, with positions of the 1 mm^3 microcubes indicated by squares. The assembly will be placed Into a larger phantom for full scatter. The beam direction is indicated the arrow at left. 2 dimensional arrays will stacked upon one another as shown in the beam's eye view (bottom).