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# Relative Biological Effectiveness and Peripheral Damage of Antiproton Annihilation

Carl Maggiore[1], Nzhde Agazaryan[2], John DeMarco[2], Michael Doser[4], Tony Giorgio[1], Cai Grau[5], Charles Gruhn[1], Michael Holzscheiter[1], Toshiyasu Ichioka[3], Helge Knudsen[3], Rolf Landua[4], Bill McBride[2], Søren Pape Møller[3], Jorgen Petersen[5], Jim Smathers[2], Tim Solberg[2], Ulrik Uggerhøj[3], Rod Withers[2]

[1] PBar Medical, Inc., [2] UCLA Medical School, [3] University of Aarhus, [4] CERN, [5] Aarhus University Hospital

## Executive Summary

The use of ions to deliver radiation to a body for therapeutic purposes has the potential to 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 with protons or heavy ions, antiprotons can be used to deliver radiation to the body in a controlled way; however antiprotons will exhibit additional energy deposition due to annihilation of the antiprotons within the body. The slowing down of antiprotons in matter is similar to that of protons except at the very end of the range beyond the Bragg peak. Gray and Kalogeropoulos estimated the additional energy deposited by heavy nuclear 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 event (Ka89). In 1985, Sullivan measured the relative magnitude of this enhanced energy deposition at the Low Energy Antiproton Ring (LEAR) at CERN, but he did not measure 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 Antiproton Decelerator (AD) at CERN 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 discussions with 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. 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 the measurements described in this document 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**

Gray and Kalogeropoulos (Gr84) first proposed using antiprotons for treating tumors 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 heavy 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 observations of Gray and Kalogeropoulos came at a 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 high-energy gammas (resulting from the immediate decay of 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 the targeted region. 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 measure directly 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 Gray and 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.

The response of biological systems to radiation is given in terms of dose, type of radiation, and biological effect. Dose (absorbed energy/mass) is measured in units of Gray (Gy) where 1 Gy = 1 joule/kg in any material. The energy and type of radiation 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 effects 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 radiation. $^{60}$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 do not lend themselves to calculations 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 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 surrounding normal tissues for a 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 biological test beam 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 beamline as shown in Figure 1. The choice of momentum is motivated by the range and straggling of antiprotons at this momentum. The phantom surrounds a biological sample of live cells and is essentially a volume of tissue-equivalent material that simulates the effect of backscattering and energy absorption in a human body. The biological sample is contained within a tube, which is designed to hold dispersions of the live cells in agarose, a semi-solid biological culture medium.. The quantitative cell survival studies involve counting the number of colonies that grow during an incubation period after irradiation, compared with controls receiving zero doses. A standard cell line of known radiation sensitivity will be exposed to varying doses of antiprotons. The beam pulses and 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, although lower doses may be sufficient 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.

This biological test beam experiment is 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 includes personnel from PBar Medical, Inc., UCLA Medical School, 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 treatments using antiprotons. Table I lists the experimental parameters relevant to the design of this biological test beam 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 density (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 2 minutes |
| 5 Gy dose | ~$10^{9}$ annihilations/g |

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 strongly dependent on depth as the particles slow down and has a steep maximum at the end of the range.

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 for 8-10 days in a controlled environment, the colonies that develop will be stained and counted. Only those colonies having more than 50 cells will be counted as having been derived from a single surviving cell (smaller 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.). Initial discussions with members of the AD operations team indicate that extraction at this energy is feasible with existing instrumentation of the AD ring with a few modifications and upgrades as indicated below. The beam line is fully operational and has been used for tests at 100 MeV/c. To increase the momentum to 300 MeV/c may require an upgrade of some of the power supplies, and all costs related to this upgrade will be covered by our collaboration. The extraction will be performed on the standard 300 MeV/c plateau after the normal electron cooling of the beam. It has been indicated to us that the capture on h=1 instead of the normal h=3 harmonic can be accomplished with the existing low-level hardware, allowing some time for recabling, set-up and testing. Some changes to the software program and a possible change of the power supply for the extraction septum should allow the switching between 300 MeV/c and 100 MeV/c extractions to be as simple and fast as the present switching between the three main experiments.

The preferred beam profile for our experiment is one that is constant in spot size over the length of the active experiment of 10 cm and has intensity variations of less than 20% over the central 1 cm diameter. For a Gaussian profile this requires a FWHM of the beam of 3 cm. The DEM beam line with a schematic layout of the experiment is shown in figure 3. With the 5 quadrupoles indicated in this drawing we expect to have enough control over the beam to achieve this requirement. While this is contingent on the results of further and more detailed calculations, we would like to point out that we can also accommodate different beam profiles by altering the experimental procedure followed. For example, a smaller beam diameter can be accommodated through lateral scanning of the beam across the target. 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, due to the insignificant amount of material it presents to the beam, has only minimal impact on the energy and spatial straggling of the beam pulse. Therefore, this detector can remain in the beam during the entire experiment. In addition, the AD team has informed us that a silicon strip detector was installed last year at the focal point of the DEM line. This detector can be left in place and used as a secondary detector to establish beam profile, direction, and emittance. As a secondary beam monitoring system, we plan to use scintillators coupled to hybrid photo diodes (HPD's) (Fu02) as in the ATHENA experiment. Alternatively, we may also explore using fine mesh Cherenkov detectors, which have been shown to be less prone to saturation effects. These detectors will surround the biological experimental 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 it is 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, $D_{\mathrm{med}}(z)$, 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 the CERN AD beam precludes the use of ionization chambers. Therefore, in lieu of a direct determination of absolute dose, we propose two alternate methods. First, absolute dose can be calculated using Monte Carlo codes 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 an extension of the general-purpose Monte Carlo N-Particle (MCNP) code, MCNPX, the Monte Carlo N-Particle Transport Code System for Multiparticle and High Energy Applications. 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 Los Alamos High Energy Transport (LAHET™) code system (LCS™). The Intra-Nuclear Cascade (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, $^{3}$He ions, and $^{4}$He 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 200 nsec AD beam pulse every two minutes, and a uniform 1 cm x 1 cm spot size we estimate a dose rate of approximately 45 cGy per AD beam pulse or 13.5 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 Geant4 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 dosimeter. The specific measurements, with a conservative estimate of required beam time, are shown in Table III.

**TLD Measurements**

Both Raju et al. (Ra65) and Dicello (Di76) described using thermoluminescent dosimeters (TLDs) extensively in pion dosimetry. 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

experiments we will employ TLD microcubes measuring 1 mm on each 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 TLDs 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 and Film Measurements**

Three dimensional dose distributions resulting from photon beams have been successfully measured with the use of Bis Acrylamide Nitrogen Gel (BANG) (Lo99, Ma93, Ma96a, Ma96b, Ma97). BANGs 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 will be characterized by exposing a cylindrical flask of BANG 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 for comparison with Monte Carlo calculations, we will use a series of Bonner spheres incorporating $^{7}$LiF and $^{6}$LiF thermoluminescent dosimeters 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 and 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 beamline 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 cm x 30 cm x 30 cm. The purpose of this phantom is to simulate the human body surrounding a tumor and to mimic backscattering and energy absorption as they would occur in an actual treatment. 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 beamline and transferred to a biological analysis station. There the gel will be extruded from the tube in 1 mm slices and analyzed. The sample analysis protocol for this step is outlined in Figure 5. 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 as follows: electrical power (220 V/3000 Watt); temperature control to ± 3°C; laboratory workbenches; a local self-contained sterile hood for specimen preparation; an incubator; a $CO_2$ gas bottle; and an optical microscope. Our collaboration will cover all expenses for possible upgrades of existing infrastructure to this container or, if necessary for technical reasons, installation of a new, more suitable container 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 external biological test beam 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<br>Develop cell handling and analysis protocols<br>Develop biological dosimetry for proton irradiations<br>Develop external 50 MeV proton beam at Aarhus | UCLA<br>Aarhus |
| 2003 | 1st Quarter | Modify DEM beamline<br>Correlate physical and biological dosimetry with protons<br>Measure cell response to proton irradiation<br>Certify biological protocols | CERN<br>Aarhus<br>UCLA<br>Loma Linda |
| | 2nd Quarter | Develop 300 MeV/c beam extraction<br>Characterize extracted beam | CERN |
| | 3rd and 4th Quarter | Expose living cell suspensions<br>Incubate and determine biological response<br>Measure peripheral damage profile<br>Analyze data and summarize results | CERN<br>UCLA |

We estimate that the total number of shots of antiprotons required to complete the test beam experiment successfully during the year 2003 can be delivered in nine full shifts, although some of the measurements can be performed utilizing shorter time periods. The timing of the experiment is flexible in that we can make use of gaps in the AD schedule caused by downtime 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 current 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 1 cm x 1 cm is approximately $4x10^8$, or 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 (15 % variation corresponds to 15 % of the beam) be used for cell irradiations. This quality beam from the AD would require approximately 7 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 will 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 9 (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 $2x10^9$ antiprotons is based on preliminary Monte Carlo simulations and references (Gr84) and (Su85).

Once these measurements are completed, there will be an evaluation phase and a presentation of the results. If the 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** *($^{60}$Co equivalent 3D information)* | 5 Gy | 0.5 hour | 1 | 0.5 hour |
| **TLD ($^{6}$Li)** *(multiple 2D information, excludes n)* | 3 to 4 Gy | 0.5 hour | 2 | 1 hour |
| **TLD ($^{6}$Li) spread peak** *(multiple 2D information, excludes n)* | 3x(3 to 4 Gy) | 2 hours | 2 | 4 hours |
| **TLD ($^{7}$Li)** *(multiple 2D information, includes n)* | 3 to 4 Gy | 0.5 hour | 2 | 1 hour |
| **TLD ($^{7}$Li) spread peak** *(multiple 2D information, includes n)* | 3 x (3 to 4 Gy) | 2 hours | 2 | 4 hours |
| **Bonner sphere** *(neutron spectroscopy)* | ~ 5 Gy | Concurrently | 2 | 0 hours |
| **Film** *($^{60}$Co equivalent depth dose curves)* | ~ 1 Gy | 0.25 hour | 2 | 0.5 hour |
| **Film** *(cross sectional profiles at 4 different depths)* | ~1 Gy | 0.25 hour | 2 | 0.5 hour |
| **Film spread peak** *($^{60}$Co equivalent depth dose curves)* | <3x1 Gy | 0.5 hour | 2 | 1 hour |
| **Current Calibration** | | 2 hour | 1 | 2 hour |
| | | | **Total** | **14.5 hours** |

**Table IV - Estimated total beam time requirement**

| Requirement | Number of Antiprotons | Total Number of Beam Pulses | Time (hours) | Number 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** | | | ~72 | 9 |

**References**


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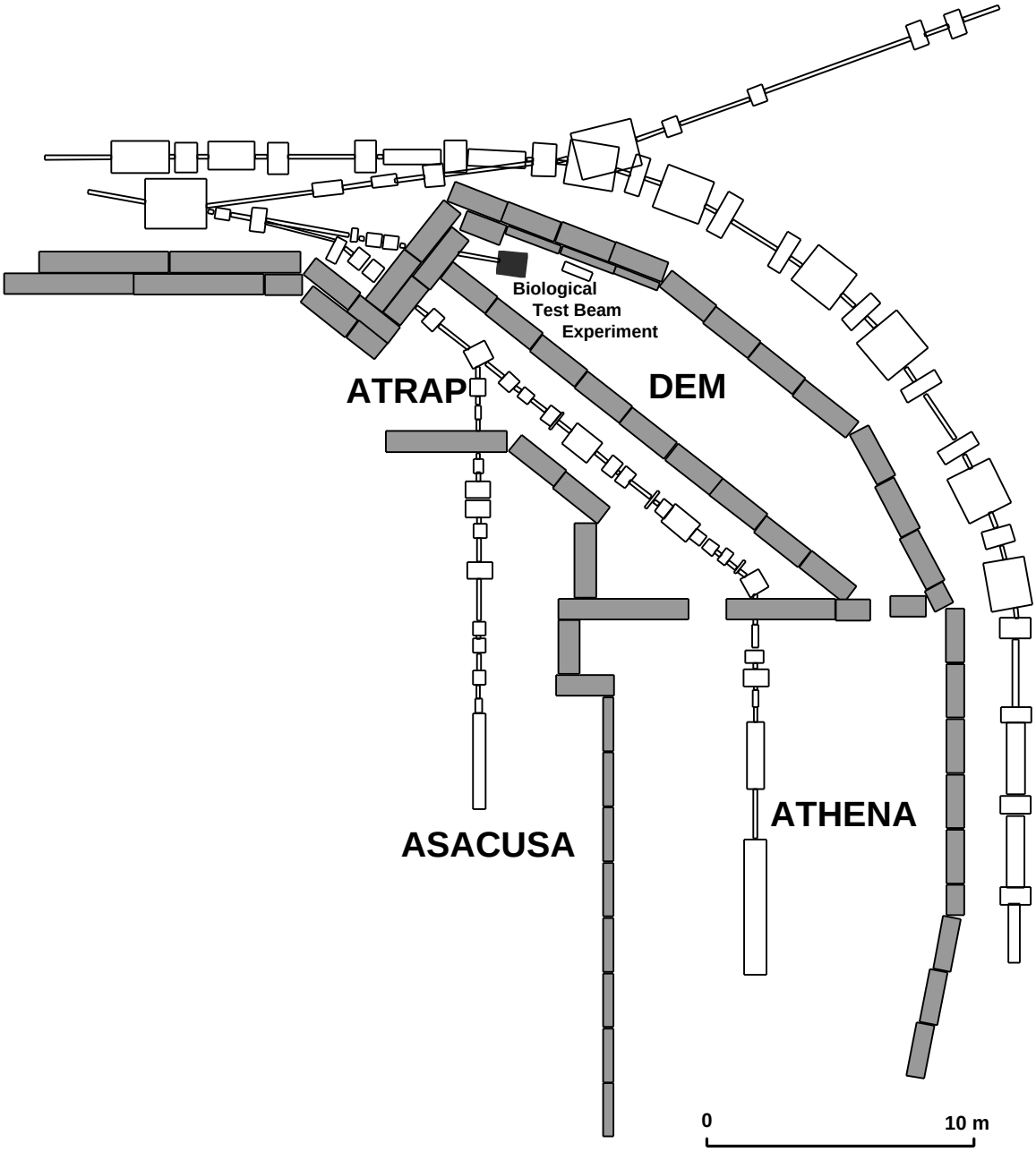


**Figure 1 - Layout of the biological test beam experiment in the AD accelerator hall.**

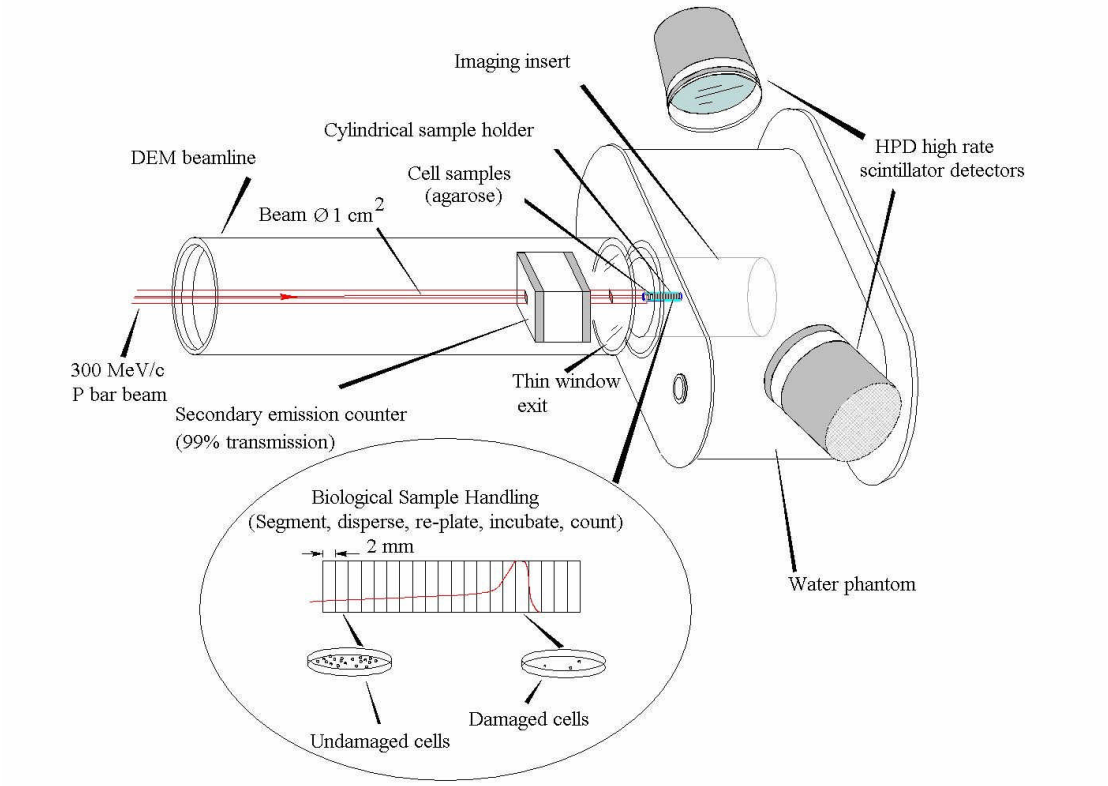


**Figure 2 - Overview of the biological test beam experiment. The HPD high-rate scintillator detectors are not shown to scale.**

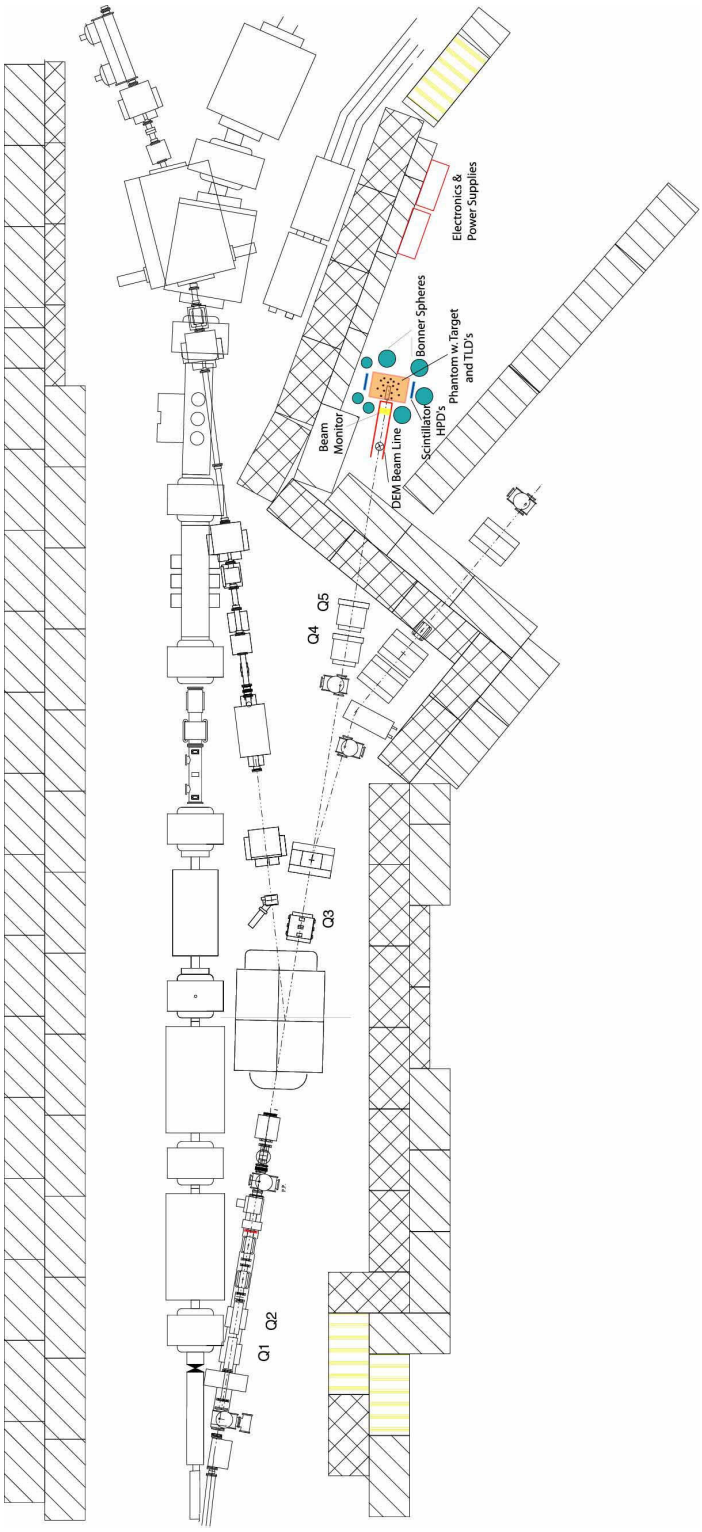


**Figure 3 – Layout of the DEM beamline. Each "Q" on the beamline indicates one of the five quadrupoles.**

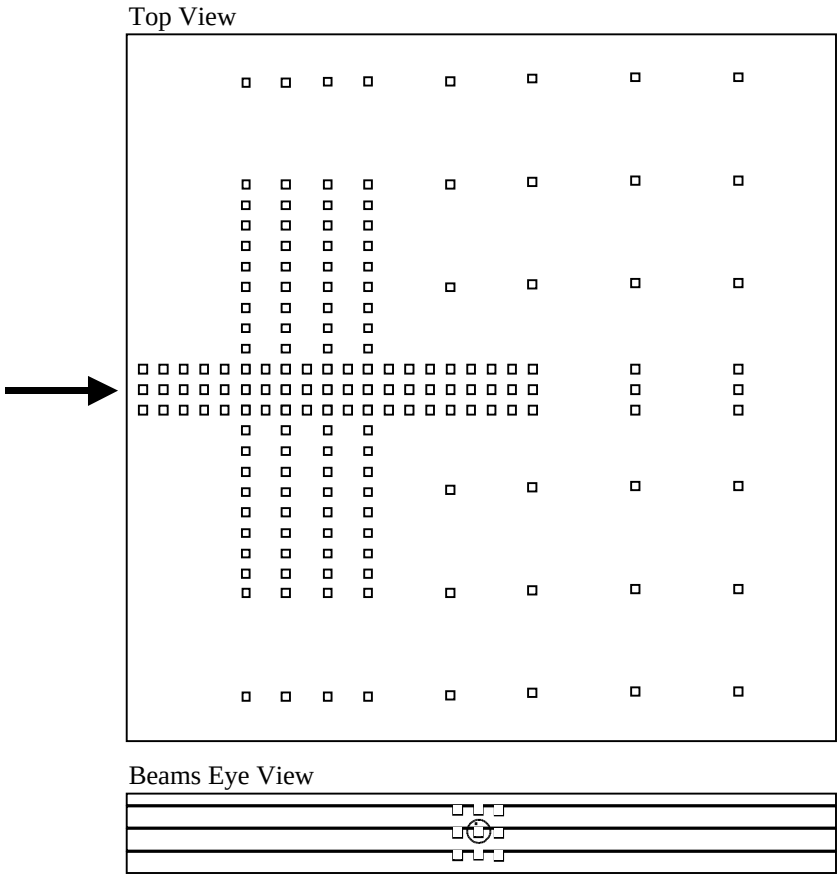


**Figure 4 - Cross sectional diagram of the TLD array (top view) measuring 6 cm x 6 cm, with positions of the 1 mm$^3$ microcubes indicated by squares. The assembly will be placed into a larger phantom for full scatter. The arrow drawn at left indicates the beam direction. Two-dimensional arrays will stack upon one another as shown from the beam's-eye-view at the bottom of the figure.**

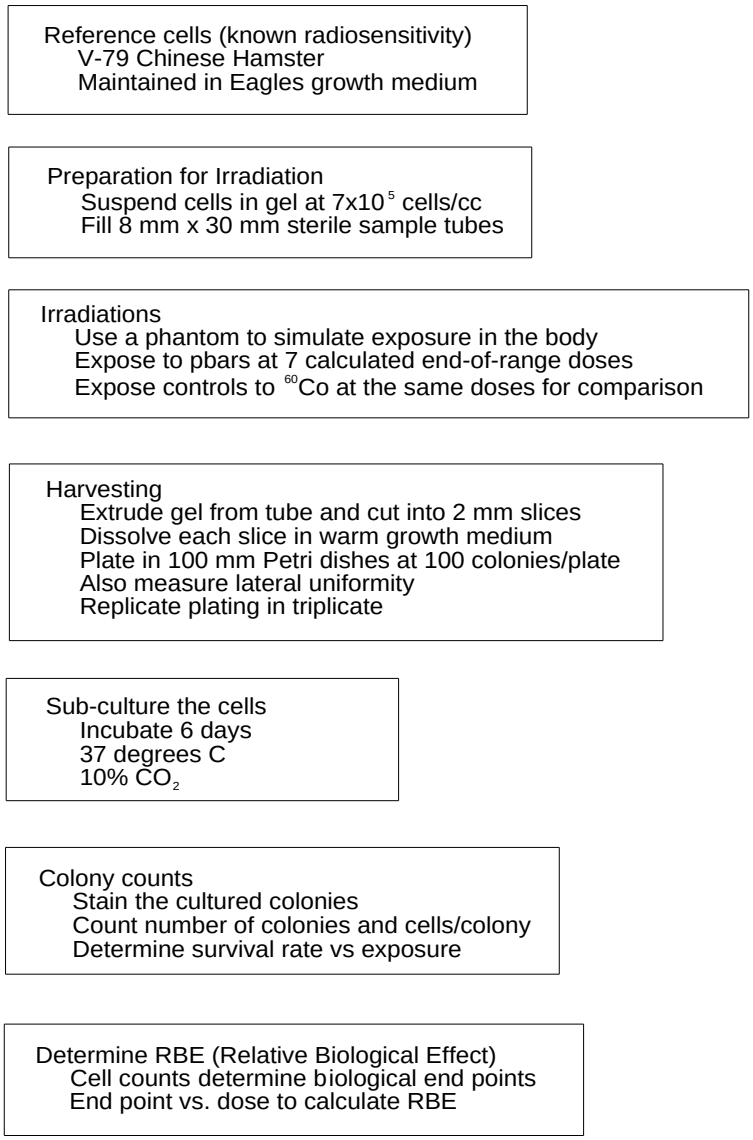


**Figure 5 - Outline of the biological sample analysis protocol. The experiment will be performed in triplicate with all doses given within two 8-hour shifts. There will be a delay between exposures to allow for sample incubation and analysis. Two additional 8-hour shifts will be required to determine the peripheral damage profile.**

## Appendix A

### Biographical Sketches of the Members of the Collaboration

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**Nzhde Agazaryan, Ph.D.**
**UCLA Medical School**
**Los Angeles, CA, USA**

**Education:**

- Ph.D. Biomedical Physics, 2001, UCLA Medical School
- M.S. Biomedical Physics, 2001, UCLA Medical School
- B.S. Physics, 1997, University of California, Los Angeles

**Appointments:**

- 2002 – present, Assistant Clinical Professor, Department of Radiation Oncology, and Assistant Professor, Interdepartmental Graduate Program in Biomedical Physics, David Geffen School of Medicine at UCLA
- 2002 – present, Director, Hands-on Course in Intensity Modulated Radiation Therapy, UCLA Medical Physics Division, Department of Radiation Oncology, University of California, Los Angeles
- 2000 – present, Adjunct Assistant Professor, Department of Health Sciences, California State University, Northridge
- 2000 – present, Collaborator in Intensity Modulated Radiotherapy, BrainLAB AG, ammerthalstrasse 8, 85551 Heimstetten, Germany
- 2000 – present, Chairperson, Electronic Media Committee, American Association of Physicists in Medicine, Southern California Chapter

**Awards/Honors:** Young Investigator Finalist, American Association of Physicists in Medicine (AAPM), Annual Meeting, 2002, and recipient of the Norman Baily Award, American Association of Physicists in Medicine, Southern California Chapter, 2001.

**Publications:** Over 17 peer-reviewed publications and professional presentations.

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**John J. DeMarco, Ph.D.**
**UCLA Medical School**
**Los Angeles, CA, USA**

**Education:**

- Ph.D. BioMedical Physics, 1997, University of California, Los Angeles
- M.S. BioMedical Physics, 1995, University of California, Los Angeles
- B.S. Nuclear Engineering, 1991, The Pennsylvania State University, University Park, Pennsylvania, USA

**Appointments:**

- 1999 – present, Assistant Professor (In-residence), Department of Radiation Oncology, University of California, Los Angeles
- 1998 – 1999, Assistant Clinical Professor, Department of Radiation Oncology, University of California, Los Angeles

**Publications:** 26 peer-reviewed publications.

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**Michael Doser, Ph.D.**
**CERN**
**Geneva, Switzerland**

**Education:**
- Ph.D. Physics, 1988, University of Zurich, Switzerland
- Diploma, Physics, 1983, ETH Zurich, Switzerland

**Appointments:**
- 2001 – present, Group Leader, EP-Antiproton experiments, CERN
- 1998, Sabbatical, Stanford University, USA
- 1994 – present, Research Physicist, CERN
- 1993 – 1996, PS/LEAR Coordinator, CERN
- 1991 – 1993, Research Fellowship, CERN
- 1988 – 1991, Research Fellowship, KEK, Japan
- 1988 – present, Group Leader, Meson Spectroscopy, Particle Data Group

**Research Interests:** Antihydrogen production and spectroscopy, meson spectroscopy.

**Publications:** More than 100 peer-reviewed publications.

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**Anthony Joseph Giorgio, M.D.**
**PBar Medical, Inc.**
**Newport Beach, CA, USA**

**Education:**
- M.D. Medicine, 1957, Boston University
- M.S. Public Health, 1953, Columbia University
- A.B. Biology, 1952, Boston University

**Appointments:**
- 2001 – present, Medical Director, PBar Medical, Inc.
- 1988 – 2001, Chairman Oncology Division Department Medicine San Pedro Peninsula Hospital
- 1996 – 1998, Chairman Department Medicine San Pedro Peninsula Hospital
- 1978 – 2001, Member, Cancer Care Association fulltime hematology/oncology practice
- 1976 – 1978, Professor of Medicine, C.R. Drew School of Medicine
- 1973 – 1978, Associate Professor of Medicine, University of Southern California and C.R. Drew School of Medicine
- 1973 – 1978, Chief, Hematology/Oncology Division Martin Luther King Hospital, Los Angeles County/University of Southern California
- 1970-1973, Assistant Professor of Medicine, University of Pittsburgh Hematology/Oncology Divisions
- 1966 – 1970, Assistant Professor of Pediatrics, New York Medical College

**Certifications:**
- Certified by the American Board of International Medicine, 1974
- Certified by the American Board of Hematology, 1974

**Awards/Honors:** Fellow of the American College of Physicians.

**Publications:** 50 publications including abstracts, short communications, book chapters, and 25 peer-reviewed publications.

**Charles R. Gruhn, Ph.D.**
**PBar Medical, Inc.**
**Geneva, Switzerland**

**Education:**

- Ph.D. Physics and Mathematics (Nuclear Physics), 1961, University of Washington
- B.A. Physics and Mathematics, 1956, University of Montana

**Appointments:**

- 1992 – 2002, Medical Retirement with low profile contacts with the ATLAS experiment at CERN
- 1982 – 1992, Collaborator on various experiments at CERN
- 1978 – 1992, Senior Scientist, Detector Instrumentation and Physics, Lawrence Berkeley National Laboratory
- 1975 – 1978, E10 Group Leader, Los Alamos National Laboratory
- 1970 – 1975, CERN/Max Planck Institut fur Physik und Astrophysik Geneva, Switzerland and Munchen, Germany, Sabbatical Michigan State University, and Humboldt Stiftung Sonder Program award
- 1964 – 1974, Professor, Michigan State University (Full Professor, 1968)

**Honors/Awards:** Humboldt Stiftung Sonder program, given to selected American full professors of exceptional talent to work in Europe by the German government.

**Publications:** One patent, U.S. Patent 4,243,888, Jan. 6, 1981, Laser Beam Alignment Apparatus and Method, and numerous publications concerned with detector and detector physics in high-energy and nuclear physics.

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**Michael H. Holzscheiter, Ph.D.**
**PBar Medical, Inc.**
**Los Alamos, NM, USA**

**Education:**

- Ph.D. Physics, 1978, University of Mainz, Germany
- M.S. Physics, 1972, University of Mainz, Germany

**Appointments:**

- 1986 – present, Staff Member, Los Alamos National Laboratory
- 1998, CERN fellowship
- 1996 – 1999, Spokesperson for CERN experiment AD-1/ATHENA
- 1992 – 1995, Visiting Professor, Pennsylvania State University
- 1990 – 1995, Spokesperson for CERN experiment PS200
- 1983 – 1986, Visiting Assistant Professor, Texas A&M University
- 1981 – 1983, Research Assistant, University of Mainz, Germany
- 1978 – 1981, Postdoctoral Fellow, Texas A&M University

**Research Interests:** Experimental physics of trapped ions and electrons, quantum computing with trapped ions, and low-energy antiproton physics.

**Publications:** More than 60 peer-reviewed publications.

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**Toshiyasu Ichioka, Ph.D.**

**University of Aarhus**
**Aarhus, Denmark**

**Education:**

- Ph.D. Multi-Disciplinary Sciences, 2001, Institute of Physics, Graduate School of Arts and Sciences, University of Tokyo
- M.S. Multi-Disciplinary Sciences, 1996, Institute of Physics, Graduate School of Arts and Sciences, University of Tokyo
- B.S. Faculty of Science, 1994, Kyoto University

**Appointments:**

- 2001 – present, Assistant Research Professor, University of Aarhus
- 1998 – 1999, Junior Research Associate (JRA) at RIKEN
- 1995 – 1998, Teaching Assistant

**Research Interests:** Low-energy collisions of antimatter with matter, especially ionization/excitation by antiprotons and initial formation processes of antiprotonic atoms and/or molecules.

**Publications:** 6 publications including conference proceedings.

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**Helge V. Knudsen, Ph.D.**
**University of Aarhus**
**Aarhus, Denmark**

**Education:**

- Ph.D. Experimental Atomic Collision Physics, 1977, University of Aarhus
- M.S. Experimental Atomic Collision Physics, 1973, University of Aarhus

**Appointments:**

- 1999 – present, Chairman of IFA's PR committee
- 1998 – present, Member of the Board of the ASACUSA Collaboration at CERN
- 1997 – present, Member of the AD Users Committee (ADUC) at CERN
- 1997 – 2001, Member of the EUROTRAP TMR EEC network
- 1997 – 2001, Member of CRY RING Program Advisory Committee (CPAC) at Stockholm University
- 1996 – 1999, Member of the ATHENA Collaboration at CERN
- 1995 – 1997, Spokesman for PS194 Collaboration at CERN
- 1990 – 1996, Member of the Board of IFA
- 1987 – 1988, Scientific Consultant, Los Alamos National Laboratory
- 1978 – present, Professor (lector), University of Aarhus

**Research Interests:** Experimental investigations of charge-changing atomic collisions, with special emphasis on the behaviour of few electron systems; multiple electron processes and electron correlation in dynamic systems; impact of particles and their antiparticles on atoms and molecules; positron physics; production of antihydrogen; photoionization of ions; ultrarelativistic atomic collisions.

**Publications/Conferences:**

- Over 200 scientific articles published, the majority of which are published in peer-reviewed journals
- Organizer of two international workshops and one international conference

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**Rolf Landua, Ph.D.**
**CERN**
**Geneva, Switzerland**

**Education:**
- Ph.D. Physics, 1980, University of Mainz, Germany
- Diploma, Physics, 1978, University of Mainz, Germany

**Appointments:**
- 2002, Member of Program Advisory Committee, TSL Uppsala, Sweden
- 1999 – present, Spokesperson for CERN experiment AD-1/ATHENA
- 1999 – present, Chairman, CERN Courier Advisory Board
- 1999 – present, Member of Program Advisory Committee, COSY Julich, Germany
- 1997 – 2001, Group leader, EP-Antiproton experiments, CERN
- 1996 – present, AD Physics Coordinator, CERN
- 1995 – 1999, Member of SPSLC Committee at CERN
- 1992 – 1997, Group leader, CERN EP-Crystal Barrel experiment
- 1990 – 1991, PS/LEAR Coordinator, CERN
- 1987 – present, Research Physicist, CERN
- 1985 – 1986, Research Associate, University of Mainz, Germany
- 1983 – 1984, Research Fellowship, CERN

**Research Interests:** Antihydrogen production and spectroscopy.

**Publications/Conferences:**
- More than 100 peer-reviewed publications
- More than 40 Invited Talks and Colloquia at Conferences and Universities
- Organizer and Director of 6 international workshops and schools
- Member of 6 International Advisory Committees

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**Carl J. Maggiore, Ph.D**.
**PBar Medical, Inc.**
**Los Alamos, NM, USA**

**Education:**
- Ph.D. Nuclear Physics, 1972, Michigan State University
- B.S. Physics, 1965, Creighton University

**Appointments:**
- 2000 – present, Chief Scientist, PBar Medical, Inc.
- 1987 – 2000, Head of Ion Beam Materials Lab, Los Alamos National Laboratory
- 1976 – 2000, Staff Member, Center for Materials Science, Los Alamos National Laboratory
- 1974 – 1976, Head of X-Ray Spectrometer Division, Princeton Gamma Tech, Inc.
- 1970 – 1974, Research Associate, Mount Sinai Medical School

**Research Interests:** Ion-solid interactions, radiation damage, characterization, analysis, and modification of materials using ion beam methods, channeling of ions in solids, surface damage in materials.

**Honors/Awards:** Recipient of a Distinguished Performance Award, Los Alamos National Laboratory, 1992, and Member of the New York Academy of Sciences and the Bohmische Physical Society.

**Publications:** More than 100 peer-reviewed publications in the fields of nuclear physics, health, radiation damage, ion beam analysis, and materials science.

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**William H. McBride, D.Sc.**
**UCLA Medical School**
**Los Angeles, CA, USA**

**Education:**

- FRC Path, Pathology, 1990, Royal College of Pathologists, England
- D.Sc. Medical Sciences, 1987, University of Edinburgh, Scotland
- Ph.D. Medical Sciences, 1971, University of Edinburgh, Scotland
- B.Sc. Honors, Zoology, 1966, University of Edinburgh, Scotland

**Appointments:**

- 1995 – present, Vice-Chair (Research), Department of Radiation Oncology, University of California, Los Angeles
- 1994 – present, Director, Division of Experimental Radiation Oncology, Department of Radiation Oncology, University of California, Los Angeles
- 1984 – present, Professor, Department of Radiation Oncology, University of California, Los Angeles
- 1982 – 1984, Sr. Lecturer, Department of Bacteriology, University of Edinburgh Medical School
- 1972 – 1982, Lecturer, Department of Bacteriology, University of Edinburgh Medical School, Edinburgh, Scotland

**Research Interests:** Radiobiology; involvement of growth factors and signal transduction pathways in the radiation response of normal tissues and tumors.

**Publications:** Over 220 peer-reviewed publications.

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**Søren Pape Møller, D.Sc.**
**University of Aarhus**
**Aarhus, Denmark**

**Education:**

- D.Sc. Physics, 1998, University of Aarhus
- Ph.D. Physics, 1986, University of Aarhus
- M.S. Physics and Mathematics, 1981, University of Aarhus

**Appointments:**

- 1999 – present, Director of ISA
- 1997 – present, Consultant for DANFYSIK A/S in accelerator physics
- 1996 – 1999, Technical Director of ISA, Institute for Storage Ring Facilities
- 1988 – 1996, Head of Laboratory at the ASTRID storage ring
- 1983 – 1988, Research Associate in CERN physics at Institute of Physics, University of Aarhus
- 1981 – 1983, Fellow at CERN

**Honors/Awards:** Recipient of the European Particle Accelerator Prize, European Physical Society, 1998.

**Research Interests:** Interaction of high-energy particles with matter (channeling, gamma-radiation,

etc.), antiproton interactions with matter (LEAR, AD), and accelerator physics, related to ion-accelerators and storage rings, and electron storage rings for synchrotron radiation production.

**Publications:** Author/co-author on over 80 international publications in scientific journals and proceedings.

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**James B. Smathers, Ph.D.**
**UCLA Medical School**
**Los Angeles, CA, USA**

**Education:**

- Ph.D. Nuclear Engineering, 1967, University of Maryland
- M.S. Nuclear Engineering, 1959, North Carolina State College
- B.N.E. Nuclear Engineering, 1957, North Carolina State College

**Appointments:**

- 2001 – present, Professor Emeritus, Department of Radiation Oncology, University of California, Los Angeles
- 1980 – 2001, Professor and Director of Medical Physics, Department of Radiation Oncology, University of California, Los Angeles
- 1976 – 1980, Professor and Head of Bioengineering, Texas A&M University
- 1973 – 1980, Professor of Nuclear Engineering, Texas A&M University
- 1971 – 1973, Associate Professor, Nuclear Engineering, Texas A&M University
- 1967 – 1971, Assistant Professor, Nuclear Engineering, Texas A&M University
- 1961 – 1967, Section Chief, Walter Reed Army Institute of Research

**Honor/Awards:** Principal U.S. Representative, I.A.E.A Advisory Group on Advances in Dosimetry for Fast Neutrons and Heavy Charged Particles, 1982.

**Publications:** Over 100 peer-reviewed publications.

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**Timothy D. Solberg, Ph.D.**
**UCLA Medical School**
**Los Angeles, CA, USA**

**Education:**

- Ph.D. Medical Physics, 1996, University of California, Los Angeles
- M.S. Physics, 1988, University of California, Davis
- B.S. Physics, Mathematics, 1985, Augsburg College

**Appointments:**

- 2001 – present, Director of Medical Physics, Department of Radiation Oncology, University of California, Los Angeles
- 2000 – present, Associate Professor, Department of Radiation Oncology, University of California, Los Angeles
- 1996 – 2000, Assistant Professor, Department of Radiation Oncology, University of California, Los Angeles
- 1996 – present, Associate Professor, Biomedical Physics Graduate Program, University of California, Los Angeles
- 1996 – present, Co-Director, Radiosurgery Program, Department of Radiation Oncology and Division of Neurosurgery, University of California, Los Angeles

**Honors/Awards:** Recipient of a Research Scholar Grant, American Cancer Society, 2002, and The Whitaker Foundation Research Award, 1999.

**Publications:** 87 peer-reviewed publications.

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**Ulrik I. Uggerhøj, Ph.D.**
**University of Aarhus**
**Aarhus, Denmark**

**Education:**

- Ph.D. High-Energy Physics, 1997, University of Aarhus/CERN
- M.Sc. Atomic Physics, 1994, University of Aarhus

**Appointments:**

- 2000 – present, closely involved in various test beam experiments at the CERN Super Proton Synchrotron (SPS)
- 1999 – present, Associate Professor, Department of Physics and Astronomy, University of Aarhus
- 1997 – 1999, Postdoc, worked on the construction of the CERN Antiproton Decelerator (AD), designed the optics for the AD beam lines and extraction from the AD in collaboration with Massimo Giovanozzi and Pavel Belochitski
- 1992 – present, Researcher, CERN, various experiments starting with antiprotons at the Low Energy Antiproton Ring (LEAR)
- 1992 – present, member of several collaborations including PS194, NA43, P305, NA59, ATHENA, ASACUSA and LPM

**Publications:** 63 publications in peer-reviewed journals.

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**H. Rodney Withers, M.D., Ph.D., D.Sc.**
**UCLA Medical School**
**Los Angeles, CA, USA**

**Appointments:**

- Professor and Chair, Department of Radiation Oncology, UCLA Medical School
- Clinical Research Professor of the American Cancer Society

**Honors/Awards:** Recipient of the Henry S. Kaplan Distinguished Scientist Award from the International Association for Radiation Research, the Gold Medal from the American Society for Therapeutic Radiology and Oncology, the Polish Academy of Science Medicine Prize, and the Gray Medal (1995).

**Research Interests:** Post radiation repair and the effects of ionizing radiation on normal tissues.

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