CERN-SPSC-2004-031
SPSC-M-725
October 24, 2004

Status Report on AD-4
Biological Effectiveness of Antiprotons

Michael H. Holzscheiter
for the AD-4 Collaboration

Nzhde Agazaryan[1], Niels Bassler[2], Gerd Beyer[3], John J. DeMarco[1], Michael Doser[4], Dragan Hajdukovic[5], Michael H. Holzscheiter[6*], Toshiyasu Ichioka[2], Keisuke S. Iwamoto[1], Sandra Kovacevic[5], Helge V. Knudsen[2], Rolf Landua[4], Carl Maggiore[6], William H. McBride[1], Søren Pape Møller[2], Jorgen Petersen[7], Vesna Popovic[5], James B. Smathers[1], Lloyd D. Skarsgard[8], Timothy D. Solberg[1], Ulrik I. Uggerhøj[2], Sanja Vranjes[9], H. Rodney Withers[1], Michelle Wong[8], Bradly G. Wouters[10]

[1] David Geffen School of Medicine at UCLA, UCLA Medical Plaza, Los Angeles, CA 90095
[2] University of Aarhus, Dept.of. Phys. & Astronomy, DK 8000 Aarhus C, Denmark
[3] Centre Medicale Universitaire, 1 rue Michel Servet, 1211 Geneve 4, Switzerland
[4] CERN, Division EP, 1211 Geneva, Switzerland
[5]University of Montenegro, Podgorica, Serbia & Montenegro
[6] PBar Labs, 410 Old Santa Fe Trail, Santa Fe, NM 8750, USA
[7] Aarhus Kommunehospital, Bygning 5, Norrebrogade 44, DK-8000 Aarhus
[8] British Columbia Cancer Res. Centre, 601 West 10th Avenue, Vancouver, BC, V5Z 4E6 Canada
[9]Vinca Institute, Belgrade, Serbia & Montenegro
[10] Res. Inst. Growth and Development, University of Maastricht, The Netherlands

Summary

Our experimental proposal to study the biological effect of antiprotons was approved by the SPSC in January of 2003 for beam time in the run cycle of 2003.

After successful running in 2003 the preliminary results indicated a significant enhancement in the biological effectiveness of antiprotons compared to protons delivered under similar conditions to a biological target. Based on these results we requested additional beam time for 2004 to continue the biological measurements and develop enhanced dosimetry capabilities which would allow us a more direct comparison of antiprotons to other hadrons used in radiotherapy.

This document describes these experiments and highlights the problems, challenges, and achievements of our collaboration during the summer of 2004. We also comment on the upcoming final two runs for this year and present an outlook for the future, detailing a program for the continuation in 2006 and beyond.

*) Michael H. Holzscheiter
Pbar Labs, LLC
410 Old Santa Fe Trail
Santa Fe, NM 87501

Tel: +41 22 767 8374;
Fax: +41 22 767 8955;
E-mail: mholzscheiter@pbarmedical.com

Introduction

The use of ions to deliver radiation to a body for therapeutic purposes is advantageous because the profile of deposited energy peaks at the end of range of the charged particle rather than near the surface as is the case with photon based therapy. This is particularly important for deep-seated tumors or tumors located near radiation sensitive regions that must be spared. Furthermore, the biological effectiveness of charged particle radiation varies widely with the density of ionization or LET (linear energy transfer) of the particle as it moves through the body. LET depends strongly on the charge, mass , and the velocity of the ion. These facts have supported the development of proton and heavy ion therapy centers. Alternatively, antiprotons can also be used to deliver radiation to the body in a controlled way and may have additional advantages over other types of radiation currently used in radiation therapy. The slowing down of antiprotons is similar to that of protons except at the very end of range beyond the Bragg peak. When the antiprotons stop they annihilate producing a variety of low and high-energy particles. The relatively low energy particles deposit biologically effective high LET radiation in the immediate vicinity of the annihilation point. The high-energy pions, muons, and gammas leave the body and have the potential to be used for imaging.

Gray and Kalogeropoulos [1] estimated the additional energy deposited by heavy nuclear fragments within a few millimeters of the annihilation vertex to be approximately 30 MeV. While this is small compared to the total annihilation energy of 1.88 GeV, for biological purposes it can be very significant, especially considering that the energy is delivered in the form of high LET radiation resulting from heavy fragments and recoils depositing all their energy in a localized region around the annihilation vertex.

In 1985, Sullivan [2] measured the relative magnitude of the enhanced energy deposition at the Low Energy Antiproton Ring (LEAR) at CERN, but did not measure the biological effect. Our experiment AD-4/ACE [3,4] is the first to aim at a direct measurement of the biological effects of antiproton annihilation. At this time the experiment can only be done at CERN where the AD (Antiproton Decelerator) has a low energy, mono-energetic beam of antiprotons able to deliver a biologically meaningful dose at an appropriate dose rate.

Experimental Procedure

The main challenge in the design of this experiment is obtaining the maximum of biological information with the limited number of antiprotons available. The experimental design aims to capture enough data for an initial evaluation of the potential for radiotherapy using antiprotons. It is clearly not all that is needed for a definitive assessment of possible therapeutic applications of antiprotons, but it will determine if further studies are warranted.

The experiment uses a beam of 300 MeV/c (46.8 MeV) antiprotons from the AD extracted into a biological sample of live cells. The biological sample is contained within a tube that is designed to hold dispersions of the live cells in a semi-solid biological culture medium. This tube is placed within a phantom situated in air at the end of the DEM beam line. The phantom consists of a refrigerated glycerin and water solution of the same density as the gelatin and sample tubes containing the cells and is used to maintain the cells at 2 degrees C. This ensures that at any given depth, the stopping power is independent of lateral position and thus avoids any artifacts that could result from scattering of antiprotons annihilation products from points outside

the gel.

The quantitative cell survival studies involve counting the number of colonies that grow during an incubation period after irradiation. The analysis method is described in detail in reference 5. The analysis of cell survival at serial 1 mm (0.5 mm) depths along the beam central axis enables us to determine the lethality of antiprotons as a function of depth along the path of antiprotons. The detailed analysis method is described in the previous reports to the SPSC [3,4].

Comparing biological effectiveness of antiproton annihilation in the peak versus plateau regions of the stopping ionization distribution will give us a measurement of potential differentials in "biological" dose in the tumor and surrounding normal tissues for a therapeutic beam of antiprotons. In other words, the questions we are addressing with our experiment are the following: *"If we compare two particle beams, i.e. protons and antiprotons, having the same physical characteristics (energy, momentum distribution, beam geometry) and delivering identical dose to the entrance channel, by how much will the biological effectiveness of the antiproton stopping peak be enhanced by the densely ionizing annihilation products? Will this enhancement be significant enough to make antiproton beams potentially useful for tumor treatment?"*

Cell survival is a direct measurement of the net effect of all the different ionization species along the antiproton path. The response relative to both protons and ^{60}Co gamma radiation is used to standardize the biological effectiveness of antiprotons. The possible peripheral biological effects of the non-localized mixed radiation fields away from the point of annihilation can be measured in cell samples located at appropriate distances from the region of annihilation, either radial or distal (beyond the Bragg Peak).

BEDR Measurements

Antiproton measurements at CERN

In 2003 two independent experiments were performed measuring the cell survival vs. depth for a variety of antiproton flux delivered to the target tubes. The beam in both cases was set up with a diameter sufficiently larger than the sample tube to limit the variation of beam intensity across the diameter of the sample tube to about 5%. In the first run, described in last years report [5], two independent problems in beam monitoring produced a compound effect and let to a misjudgment of dose by nearly a factor of 4. Therefore only three data points in the plateau region and one data point in the Bragg peak were obtained. Completing the missing data points based on a known detection efficiency for a single surviving cell in the sample allowed us to obtain initial survival vs. dose curves for peak and plateau and a preliminary value for the BEDR of antiprotons.

In the subsequent irradiation experiment in September of 2003 we had improved our beam monitoring capabilities and could perform 6 irradiations at 5 different doses. (Fig. 1). Extracted survival values for peak and plateau are plotted in figure 2 together with the data obtained in the earlier run. As can be seen, the two data sets agree very well, indicating the stability of the biological analysis method. The ratio of dose necessary to produce 20% cell survival in the plateau and the peak region ($BEDR_{20\%}$) extracted from these data is between 9.2 and 9.8, depending on the exact definition for the peak region used. (Two different definitions were used to

study the effect of the axial dose variation caused by the static degrader used in the experiment.)

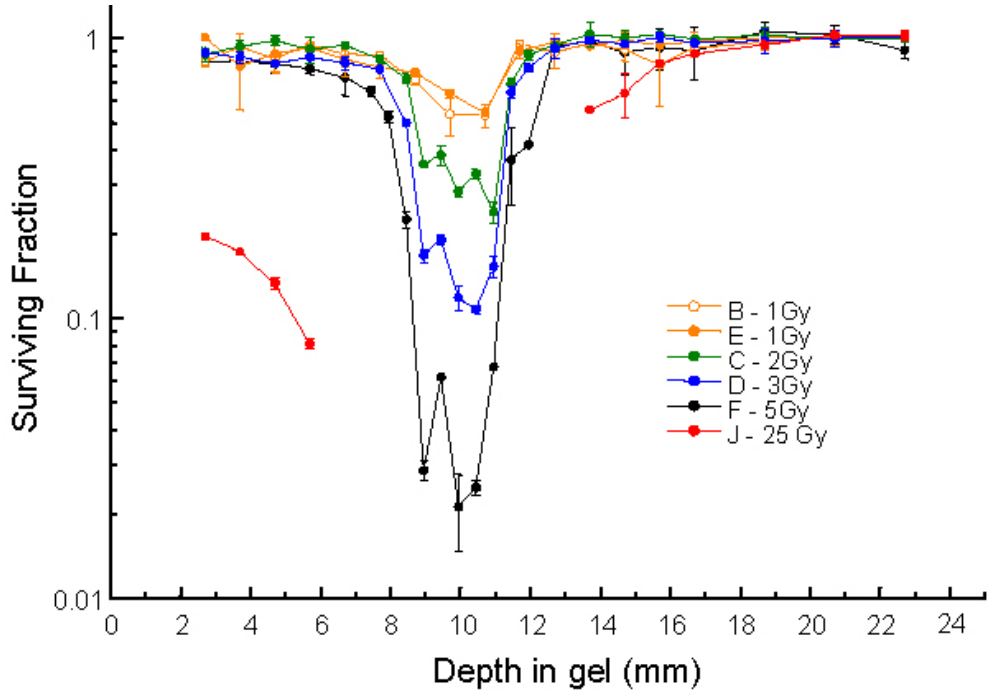


Figure 1: Survival of V79 Chinese Hamster cells vs. depth in gelatin irradiated with an antiproton beam of 300 MeV/c momentum. A static degrader was used to introduce an energy spread to the monochromatic beam in order to increase the width of the Bragg peak to about 2 mm. The variation of survival fraction in the peak is an artifact of the structure of this degrader.

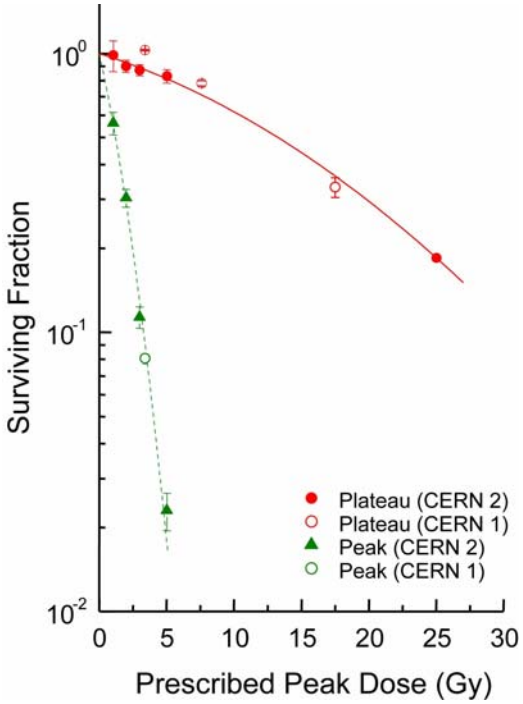


Figure 2: Survival vs. relative dose for the peak and plateau regions in an antiproton beam stopped in the biological target. Open symbols are for the run in June 2003, closed symbols are data obtained at the end of the 2003 run period.

Proton Measurements at TRIUMF and AARHUS

In order to understand the significance of the results obtained with antiprotons a comparison to a beam of protons with as close as possible the same beam conditions is necessary. Two options for this are available to our collaboration, a clinical beam at the British Columbia Cancer Agency in Vancouver, Canada, and a neutral hydrogen beam extracted from the ASTRID storage ring in Aarhus Denmark. The TRIUMF beam operates at a lowest energy of 70 MeV, higher than the energy obtainable at CERN, but has a high intensity, allowing a large number of irradiations to be performed in a short time window. This facility has been used for many years by our collaborators L. Skarsgard and B. Wouters, and the system is well understood. At Aarhus the beam intensity is much lower, allowing fewer samples to be irradiated within a reasonable time window (cells, once prepared for irradiation, can at the most kept in these conditions for about 72 hours. On the other hand the beam energy and the beam profile can be adjusted to be exactly the same as at CERN. Therefore the first choice was to use the ASTRID facility. An experiment was mounted for the first week in January of 2004 and several sample tubes were irradiated at a multitude of different dose values. After irradiation the cells were transported to Vancouver for the clonogenic analysis. This process requires several weeks before the data are available for analysis, and only at that time was it found that somewhere in the process between cell preparation and final cell analysis a change in condition happened and led to an apparent change of dose in the middle of the experiment. This could have been a change in beam profile, beam steering, or beam intensity which possibly went unnoticed, but it could also have its cause in the biologicy. At the time it was discovered it was no longer possible to trace the cause of the shift nor to correct for it, and the data set had to be abandoned.

With the run schedule for both the AD and the ASTRID facility being fixed for the year already, the only alternative was to return to the TRIUMF data we had taken on request from the SPSC in early 2003. These experiments had yielded a large set of data with high precision, but they were performed in a 70 MeV beam using a different degrader than used at CERN. The overall width of the spread-out Bragg Peak (SOBP) obtained at TRIUMF using a rotating two step degrader was very similar to the one obtained with the three step static degrader used at CERN. Therefore the data could be re-interpreted as follows:

The 70 MeV beam enters the phantom material and starts to lose energy by collisions with the material. After 18 mm of travel the average energy of the beam will be 50 MeV. The only difference from the CERN beam at this time (aside from the temporal structure) is the energy spread of the beam which is about 500 KeV here, compared to 10 keV at the AD. It is actually this difference in energy spread which allowed the use of a two step degrader at TRIUMF and which caused the three peak structure obtained in the dose profile at the Bragg peak at CERN, reflecting the three step degrader at CERN.

In order to compare the CERN and TRIUMF data we define the initial portion of the phantom material as a degrader to reduce the energy from 70 to 50 MeV and then redefine the position of the “plateau” as that slice which has the same distance from the Bragg peak as was used for the analysis of the CERN experiments. Figure 3a shows this definition and in figure 3b we give the results obtained from this analysis. The BEDR for 50 MeV protons, for the specific choice of cell line,

biological end-point (20% survival), width of the spread-out Bragg peak, etc. obtained is 2.47. This is about a factor of 4 below the value obtained for antiprotons at CERN.

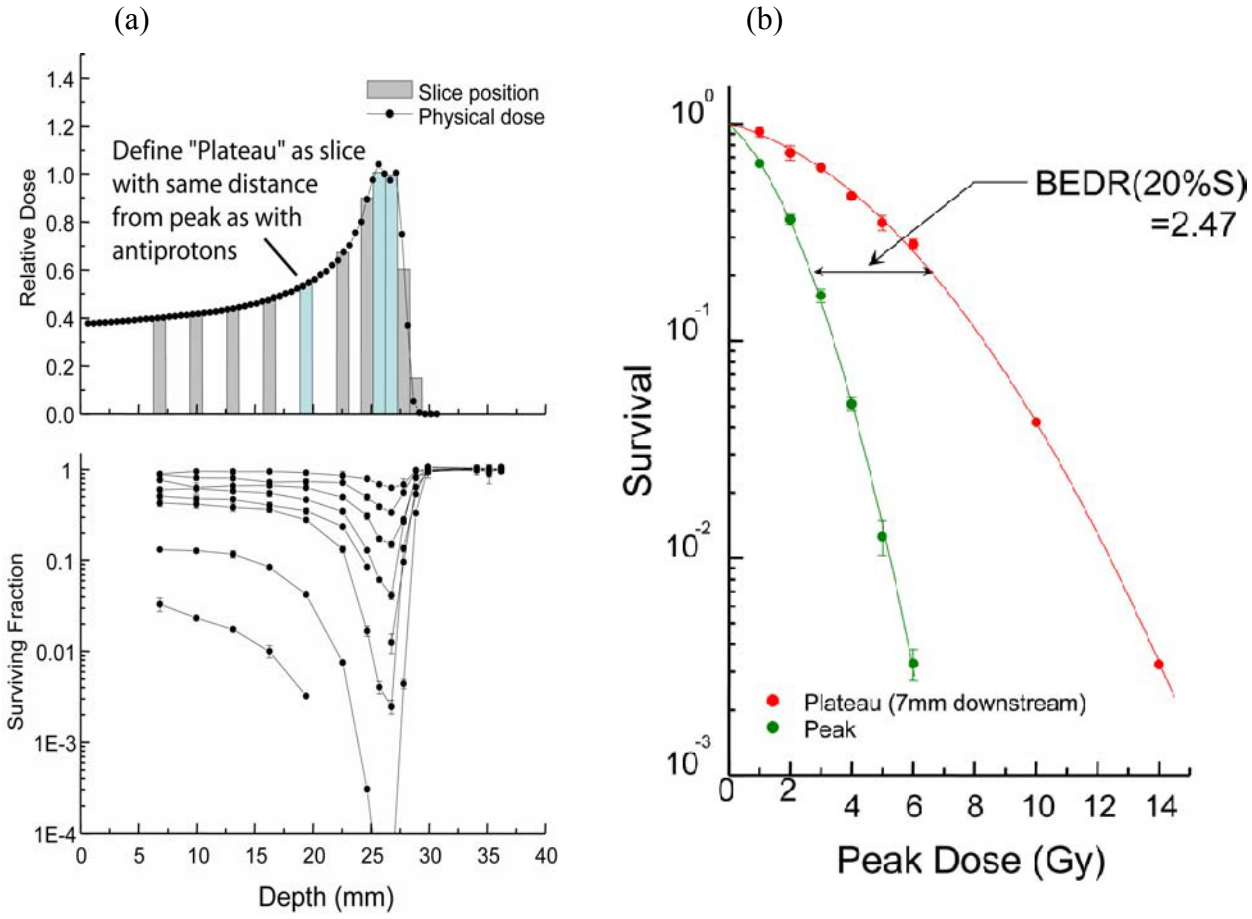


Figure 3: (a) Dose profile at the TRIUMF facility showing the slice locations used for the original demonstration experiment. The blue bars indicate the location for the plateau and peak for the current analysis. The material left of the "plateau" (slice at 20 mm) is simply a degrader used to reduce the energy of the beam to 50 MeV. The width of the Bragg peak (measured at 80% of the total dose) is the same as was obtained at the CERN experiment. (b) Survival vs. Dose for BEDR analysis (compare to figure 2)

We are currently planning an experiment at TRIUMF for late November to duplicate the original measurements. This will allow us to fine tune the position of the slices and the degrader design to obtain an exact match of the beam profile. We do not expect that this will produce changes in the analysis described here of more than 10%.

With the initial results for the enhancement of the BEDR for antiprotons compared to protons the collaboration decided to concentrate on two other important issues: damage to cells outside the direct beam (peripheral damage) which could possibly be caused by medium and long range annihilation products and initial tests and demonstrations for the real-time imaging capability offered by antiprotons.

Peripheral Damage Studies

During the clonogenic measurements in 2003 we obtained first indications that the damage to cells outside the direct beam was minimal. These indications came from the observation that the survival of cells beyond the Bragg peak (distal) rapidly returned to 100%, even for the highest dose values. In a sense, here the accidentally overdosing in the first experiment produced valuable data. At the highest dose (more than 40 Gy) which produced total cell kill in the plateau and the peak slices, survival recovered to 50% 3 mm past the Bragg peak and within the uncertainty of the analysis returned to 100% at 5 mm distance. (see figure 4).

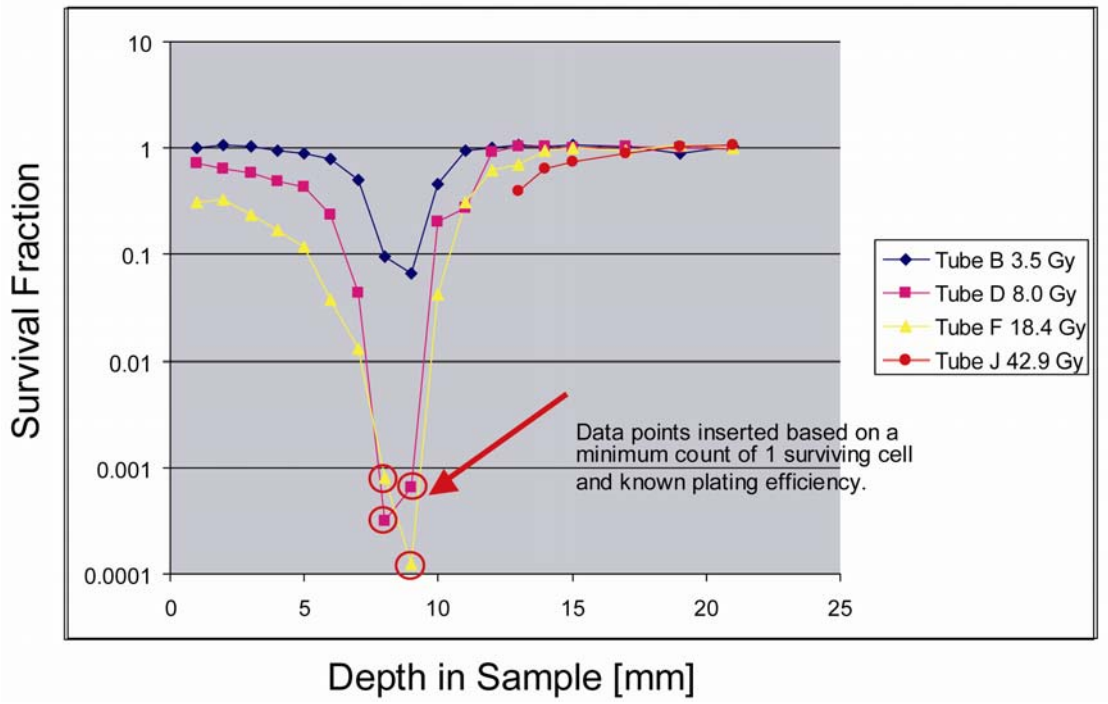


Figure 4: Survival curves vs. depth for antiprotons entering a biological target. At the dose of 42.9 Gy no surviving cell was observed in the plateau nor the peak region. The survival recovered to about 50% about 2 mm distal to the Bragg peak position and returned to 100% at around 5 mm distance beyond the Bragg peak.

Similarily, samples placed in radial direction away from the Bragg peak showed only a minimal effect. Even this small effect can not be interpreted as peripheral damage as the wide beam chosen for these measurements, and the fact that no beam collimation was used, allowed a portion of the direct beam to interact with the cell samples.

To address the problem of peripheral damage in more detail we proposed to use several different approaches.

(a) Using a specialized phantom we placed ^{7}Li and ^{6}Li thermo-luminescence detectors (TLD) at distances of several centimeters away from the annihilation point. To shield these detectors from any direct irradiation and to increase the maximum dose we could reach in a given time we used the tightest focus the AD could offer in the DEM line at 300 MeV/c (σ = 7 mm) and a collimator,

restricting the beam diameter to 10 mm. These TLD's were read out at the University Hospital in Aarhus generating complete glow curves (intensity vs. temperature), because additional information on high LET radiation can be obtained using specific sections of the glow curve spectrum. The observed signal vs. distance obtained for the ^{7}Li TLD's is shown in figure 5. As these dosimeters are not sensitive to low energy neutrons the observed $1/r^2$ dependence observed agrees well with the expectations.

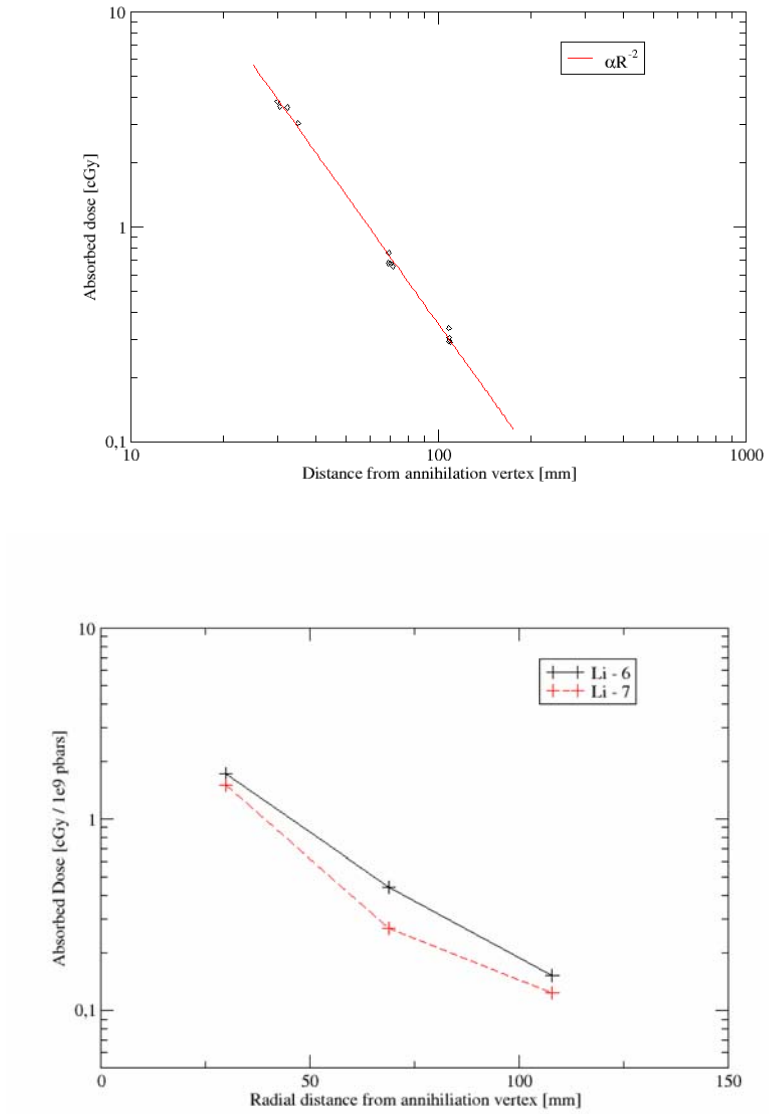


Figure 5: Upper frame: Absorbed dose measured vs. the distance from the center of the annihilation volume. At each radial distance several ^{7}Li TLD's were placed at an axial distance of a few millimeters from each other, producing the 4 data points shown for each block of data. The overall 1/r2 dependence reflects the fact that ^{7}Li chips are not sensitive to low energy neutrons. Lower frame: ^{6}Li dose compared to ^{7}Li dose vs. distance from annihilation point.

The signal observed with the ^{6}Li TLD's shows a clear excess of dose. Since ^{7}Li is not sensitive to thermal neutrons, the observed excess of signal in the ^{6}Li chips

can be interpreted as the intensity of thermal neutrons due to moderation of fast neutrons in the phantom material. Taking the difference between the two data sets yields the spectrum shown in Figure 6.

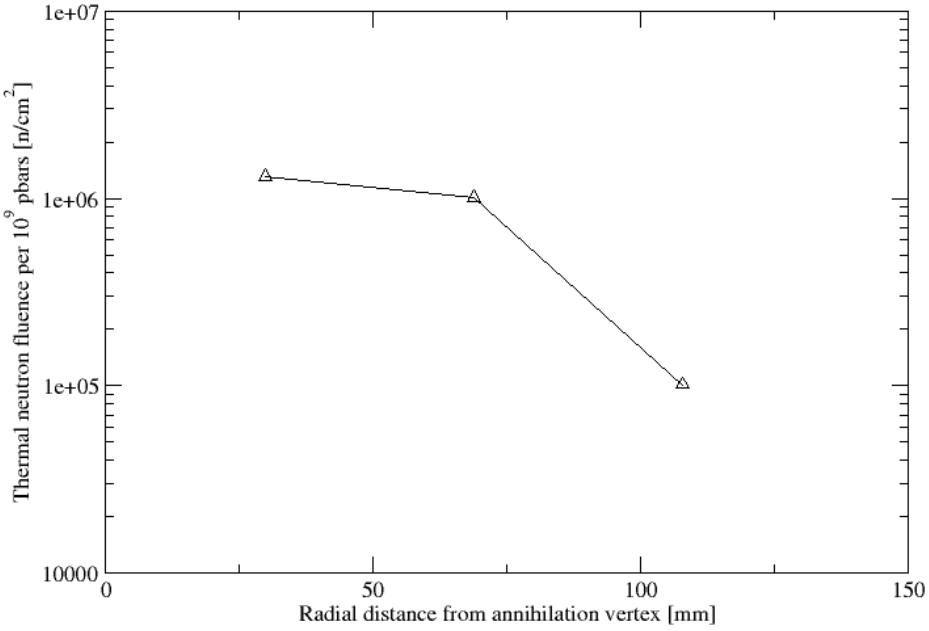


Figure 6: Fluence of thermal neutrons vs. distance from the annihilation point obtained as excess of dose measurements between ^{6}Li and ^{7}Li TLD's.

To obtain more information on the neutron background we performed a measurement using a neutron dosimeter from BTI – Buble Technology Industries [6] suggested to us by Marco Silari from CERN. Superheated Freon bubblets are embedded in a polymer gelatin under high pressure. When a neutron strikes one of these bubblets it undergoes a phase transition and the bubble size increases from nearly invisible to 1 – 2 mm in diameter. The detectors have been calibrated so that the number of bubbles which have formed can be related to a specific dose-equivalent. The sensitivity of these detectors is very high (typically a few bubbles per mrem). Two type of detectors were procured for our experiment, a dosimeter wich is sensitive to a wide spectrum of fast neutrons, and a neutron spectrometer, consisting of several detectors with different threshold values. Using a complete set of these detectors with varying thresholds one can deconvolve the results to extract information on the energy spectrum of the fast neutrons in 6 bins ranging from 10 keV to 20 MeV. A first set of irradiations was performed on September 30 and analysis of the data is in progress. The figure below shows the response of the bubble detectors at different dose rates, the overall set-up in the beam, and the energy dependent threshold for different detector types.

Initial analysis showed that the fast neutron field is isotropic and falls off as $1/r^2$. By eliminating the central core of the target, allowing the beam to pass through

the set-up unimpeded, no signal above background is observed. This shows that there is no significant contamination in the beam from upstream events.

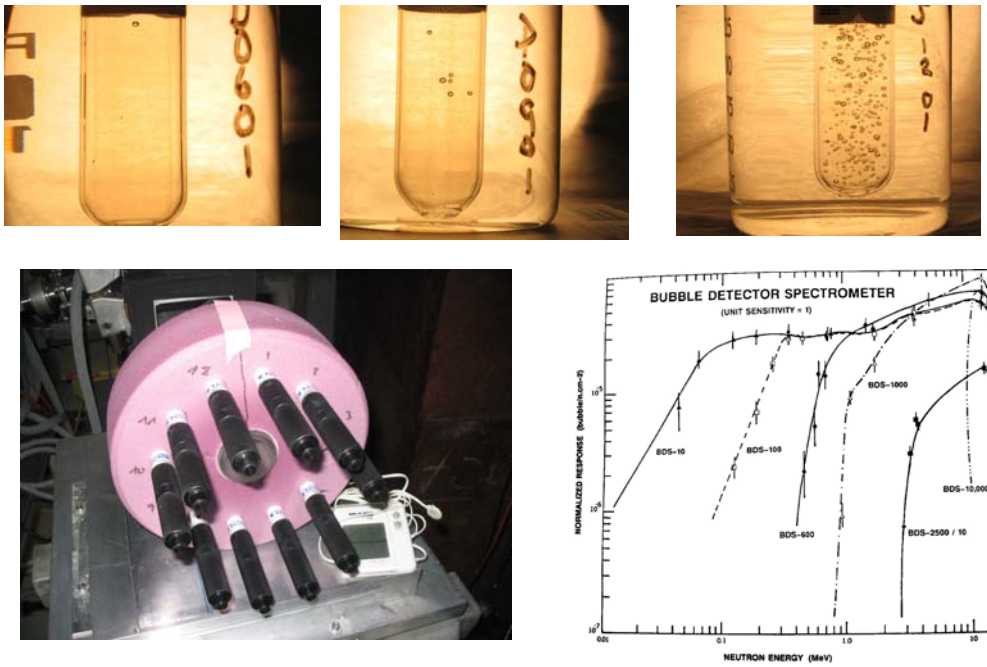


Figure 7: Bubble detectors for neutron flux measurements. Top row from left to right: no, low, and medium dose-rate irradiations. Bottom left: experimental set-up used at AD-4. Bottom right: spectral response for different types of spectrometers.

(b) From the biological point of view studies on peripheral damage are normally conducted using the standard clonogenic assay, preferably in a clinical beam with a large spread-out Bragg peak. In order to discern a biological effect at a distance from the annihilation point or outside the beam in the entrance channel a high irradiation dose is needed. This would be difficult to achieve with a large SOBP as the dose rate obtainable from the AD is small. Therefore we initiated in addition to the dosimetry studies described above a search for alternatives to the clonogenic assay which would offer a higher sensitivity in detecting biological effects. This would allow us to obtain information on peripheral biological damage to cells using smaller allocations of beam time. One possible candidate identified is the COMET assay [7], used routinely for more than 15 years to study effects of low level exposure of radiation and by hazardous environmental agents of industrial workers. The comet assay is a gel electrophoresis method that is used to visualize and measure DNA strand breaks in individual cells using microscopy. The COMET assay is a method to qualitatively and quantitatively detect genetic damage, specifically DNA strand breaks at the cellular level.

Cells taken from irradiated samples are embedded in a thin agarose gel on a microscope slide. The cells are lysed to remove all cellular proteins and lipids and subsequently the DNA is allowed to unwind under alkaline or neutral conditions. During electrophoresis broken DNA fragments (damaged DNA) migrate away from the nucleus and can be visualized using a fluorescent dye. The images obtained look like a ″comet″ with a distinct head, comprised of intact DNA and a tail, consisting of damaged or broken pieces of DNA (figure 8).

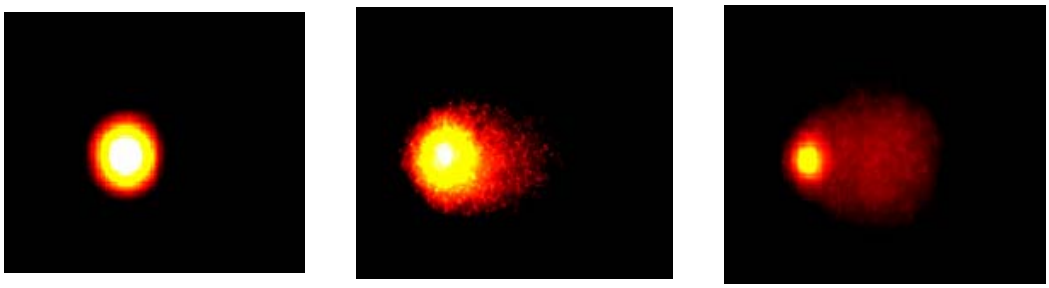


Figure 8: COMET assay images of cells with no, minor, and major DNA damage (left to right).

Through the use of CCD and computer technology, the cells are imaged and stored electronically for analysis. The standard way to analyze COMET data is to compute characterizing geometric properties of the comet, e.g. the tail moment or the comet moment. The level of DNA damage is determined largely by the length of the comet tail or by the tail moment (the length of the comet tail multiplied by the intensity of fluorescence in the tail).

We took a total of 35 samples in the plateau, the peak, and the distal region of a tube irradiated with approximately 15 Gy of antiproton dose in the Bragg peak. These samples were prepared and studied using the COMET assay protocol at the Institute for Medical Research and Occupational Health in Zagreb, Croatia and the average tail moments were calculated for each sample using 100 cells per sample for the statistical analysis. The results are shown in figure 9:

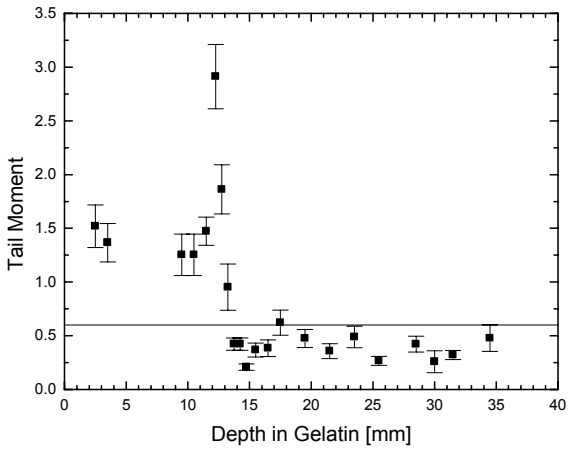


Figure 9: Tail moments obtained using the COMET assay for samples taken from different depths into the gelatin. The damage detected distal to the Bragg peak is within the error bars compatible with the damage seen in the un-irradiated control sample (horizontal line).

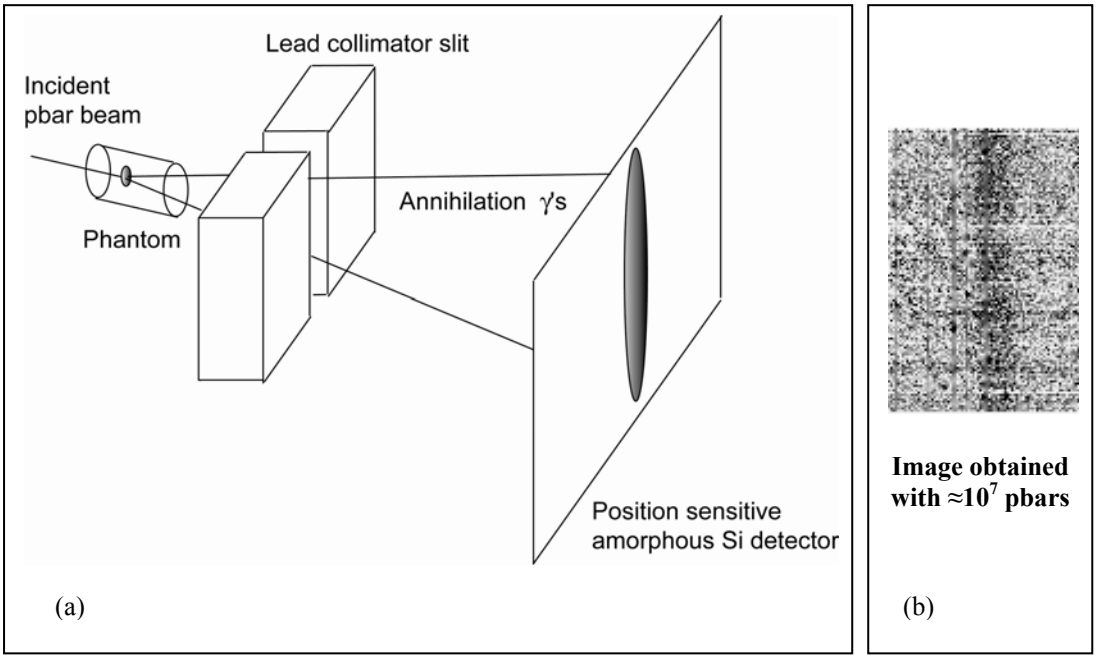
While the effect of the irradiation is clearly visible in the peak and plateau regions, we cannot detect any damage above background in the distal region at this dose. Further studies are currently being performed, using a higher peak dose to obtain a non-zero reading in the distal region close to the Bragg peak to quantify the level of effect seen. This measurement can then be correlated with clonogenic studies in the same region.

Real Time Imaging

The annihilation of antiprotons also produces high energy particles which can escape the target region without depositing significant energy. Two types of particles are most interesting to us: the charged pions (typically 3 per annihilation) and the neutral pions which convert instantaneously into high energy gammas. If these particles can be detected outside the target in a way that their path can be traced backwards to the annihilation point, a 3-dimensional image of the annihilation volume can be obtained. Due to the high sensitivity of modern particle detectors the intensity needed for the reconstruction of a high resolution image is small and initial low intensity beams could be used to obtain a perfect match between the desired target and the actual annihilation volume. Then, after establishing conformality, the beam intensity can be increased to therapeutic level. This could be a great advantage especially in the case of small, well defined tumors close to sensitive areas in the body, and where the exact density of the overlying material cannot be established with 100% accuracy.

As an initial step towards this goal we have identified two existing detectors and tested their applicability to our problem. For the charged pions a standard multi-plane silicon pixel detector can be used. A prototype of the ALICE chip, developed at CERN, was provided together with the necessary read-out electronics by Georgio Stefanini and Petra Riedler from the AIT group. In the initial runs we were unable to establish proper trigger conditions but have decided to continue tests of this system in the next run.

For the gamma (neutral pion) detection a position sensitive amorphous silicon detector was provided to us by BIOSCAN, S.A. [8]. Here the initial question was to see if the efficiency of the detector, routinely used for high precision medical imaging using 10 – 20 MeV gamma's, would have sufficient detection efficiency for the 100+ MeV gamma's from neutral pion conversion. As these detectors cannot be set up in multiple layers like the ALICE silicon pixel detector, the idea is to use a shadow mask between the source and the detector, which allows the detection of gamma's only if they travel co-axial to a fine channel in a shield between the annihilation point and the position sensitive detector. Only those channels which point directly at a point in the annihilation volume will be able to transmit gamma's to the detector and a two-dimensional shadow is generated. To test this method we needed to establish that the generation of secondary showers in the material used for the shadow mask would not lead to an unacceptable background level. First tests of this system using a simple slit collimator (figure 10) were successful and we will continue developing this technology in future experiments. The slit width imaged with the detector correlates well with the 1 cm slit used.



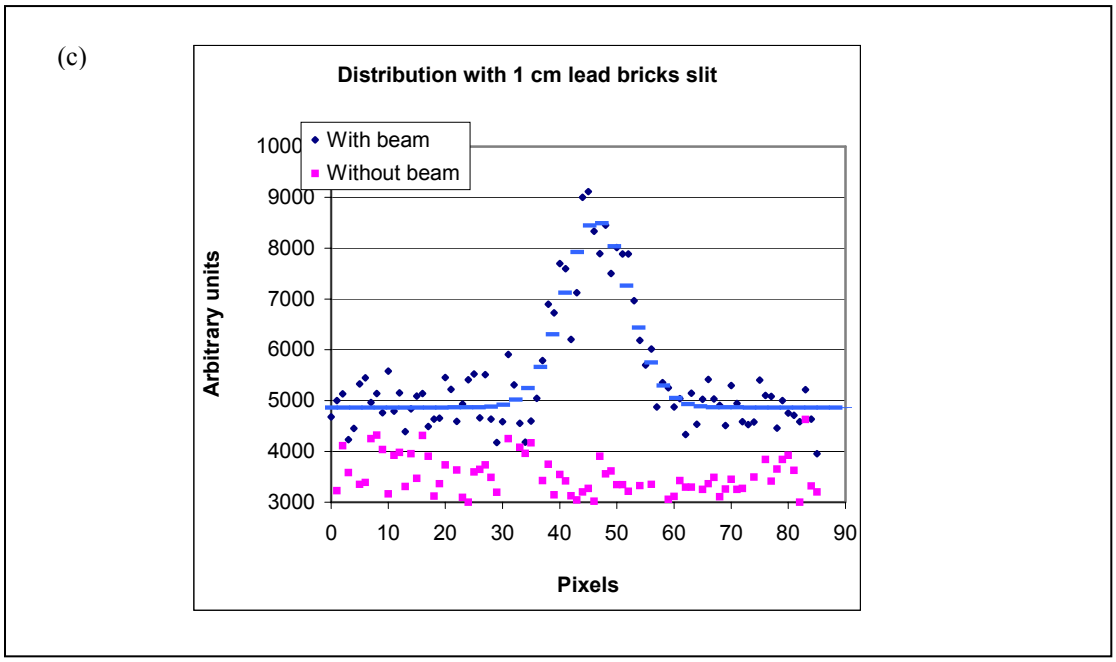


Figure 10: (a) Schematic set-up for testing the use of high energy gammas for real time imaging. (b) single shot image obtained using the position sensitive amorphous silicon detector from BioScan, S.A. with a 1 cm slit between source and detector (c) Counts/pixel for an integration time of 200 ms showing the level of electronic noise and the signal-to-noise ratio obtained with 1 x 10^7 antiprotons in a single shot of 300 ns duration.

Monte Carlo Simulations

Having only limited access to antiproton beams it is extremely important to understand the details of the annihilation event on a microscopic level. This knowledge could then be used as data entry into biological models. Such an approach has been used successfully in the development of heavy ion therapy. Not many experimental data exist on the physics of the annihilation event and we have to resort to Monte Carlo calculations, which then must be benchmarked against existing experimental data.

For the initial experiments at the AD in 2003 we had developed a calculation model based on the MCNPX code [9]. This gave us a way of predicting dose delivered at various depth in the target for a specific antiproton flux and target materials. One benchmark comparison was performed against a measurement by Agnew et al. [10] for 220 MeV antiprotons stopped in a propane bubble chamber. While the overall dose calculations seemed reasonably reliable, it was not apparent from these comparisons how accurately the details of the reactions in terms of secondary ion production were predicted. This is especially important for the biological effect modeling as it is these fragments and recoils which have the highest LET.

We therefore initiated a program to modify the GEANT4 code to include fragmentation and ion recoil as well as full energy deposition of these products in the target – all effects which are not included in the standard GEANT4 package.

As an example, figure 11 shows the details for the energy deposition of antiprotons annihilating in the target for protons, deuterons, tritons, alpha particles, ^{3}He, and other (heavier) secondaries.

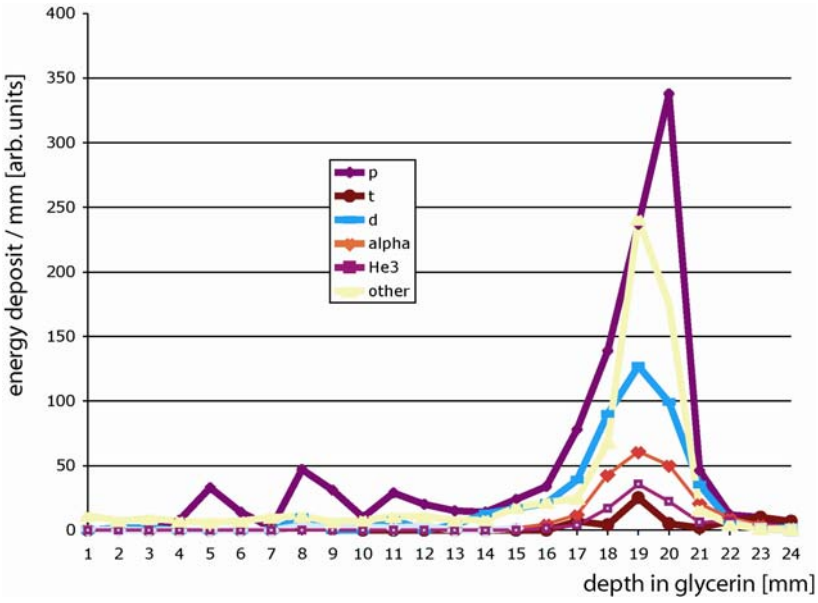


Figure 11: Contribution to the energy deposition of an antiproton stopping in a biological medium from protons, deuterons, tritons, α's, ^{3}He, and heavier fragments.

There are still many open questions to be solved before this code can be used for detailed predictions and the collaboration is actively pursuing this line of work.

Future Plans

Having shown a significant enhancement in the therapeutic ratio (peak-to-plateau ratio of damage to cells) possibly achievable with antiprotons we plan to move forward with more detailed studies.

These will include:

- Completion of the BEDR measurements, adding also a direct comparison to heavy ions to the data set.

- Establishing reliable dosimetry for the mixed antiproton annihilation radiation to extract RBE values from the survival curves

- Performing measurements using a pristine peak, thereby avoiding any artifacts from the degrader systems. This will allow us a more direct comparison to data available in the literature.

- Developing real-time imaging systems.

- Possible first in-vivo testing.

These experiments can be performed at the AD facility under current conditions but would benefit from some upgrades and enhancements of the AD performance. Specifically, a better control over the beam optics at the end of the DEM line, extraction of antiprotons at slightly higher energies (ranging from 70 – 150 MeV kinetic energy), semi-slow extraction, and last-but-not-least an increase in the intensity available for individual experiments, would greatly benefit this program.

Specific Requests to the SPSC and Research Board

- We propose to complete the DEM line according to the original design study for this beam line. Most necessary components (quadrupole magnets, dipole magnet, etc.) are available at CERN. Additional instrumentation as well as the necessary man-power to install the components in the zone would be provided by our collaboration.

- We have had preliminary discussions concerning semi-slow extraction with the AD operations team and it appears that by adding a new septum and rearranging some diagnostics pick-ups in the ring, a system for slow extraction could be prepared without impacting the operation of the AD. We would like to ask the committee to encourage the AD team to study this option in more detail. We would provide all necessary support for the studies and for the fabrication and installation of the components.

- We also discussed different options for stacking into the AD ring at 3.6 GeV/c before deceleration and cooling. This would require asking for a modified

super cycle in the PS for the specific shifts in question. Additionally, issues concerning radiation protection could be a limiting factor in this scenario. We again would like to encourage these studies and would be interested in collaborating in this development.

Moving forward in 2006 we would like to return to the current mode of operations of 4 individual 24 hour shifts per run period for major biological studies with an additional number of 8 hour shifts for R&D, dosimetry, detector development, etc. interspersed throughout the year. A specific beam time request will be submitted closer to the actual date of AD restart, when a full plan for the next run cycle is available.

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Appendix 1: Run Statistics for 2004

After the success in 2003 based on 80 hours beam time we had requested a similar arrangement of 4 x 24 hour shifts with an additional 10 x 8 hour shifts for development of dosimetry and imaging techniques. Due to the initial delay in start-up and the septum failure in the PS much of the time in the initial runs was lost to technical problems. This caused a compression of work in the second half of the year which could not be supported by the biological analysis techniques. Therefore, out of the requested 160 hours only 112 hours of beam time were used in 2004.

Date	Time Scheduled	Topics	Comments
May 21	*8 hours*	*Beam Development*	*Cancelled due to PS delay*
June 11	*8 hours*	*Focussing tests/Dosimetry*	*Cancelled due to AD/PS Problems*
June 28	**16 hours**	**Dosimetry using TLD's**	**Significant time lost to AD problem**
July 2	**8 hours**	**Alanin tests**	**Misalignment of beam line**
July 19	*24 hours*	*Peripheral damage studies*	*Cancelled to PS problem (septum)*
August 6	**8 hours**	**^{6}Li, ^{7}Li dosimetry**	**First smooth run of the year**
August 23	**24 hours**	**Alternative assay studies**	**Initial studies of COMET**
August 27	**8 hours**	**Dosimetry**	**Peripheral neutron dose**
September 10	**8 hours**	**Dosimetry**	
September 20	*24 hours*	*Biological studies*	*Cancelled due to collaboration timing*
September 24	**8 hours**	**Neutron Bubble Spectrometer**	
October 15	**8 hours**	**Imaging tests**	**First high energy gamma detection**
October 25	**24 hours**	**Peripheral damage studies**	**COMET and clonogenic assays**