Status Report on AD-4/ACE Antiproton Cell Experiment

The Biological Effectiveness of Antiproton Annihilation

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Background:

"highly concentrated energy transfer is a desirable and critical element to some applications such as, for example, the radiation treatment of small tumors in sensitive regions of the body ..."

L. Gray and T. E. Kalogeropoulos, Radiation Research **97**, (1984)

*"the ratio of the dose in the **antiproton** stopping peak to that in the plateau is "only" about twice that found for protons."*

A. H. Sullivan, Phys. Med. Biol. **30**, (1985)

Question:

Proton therapy exists world wide

heavy-ion therapy is very promising (GSI, HIMAC)

What do antiprotons have to offer?

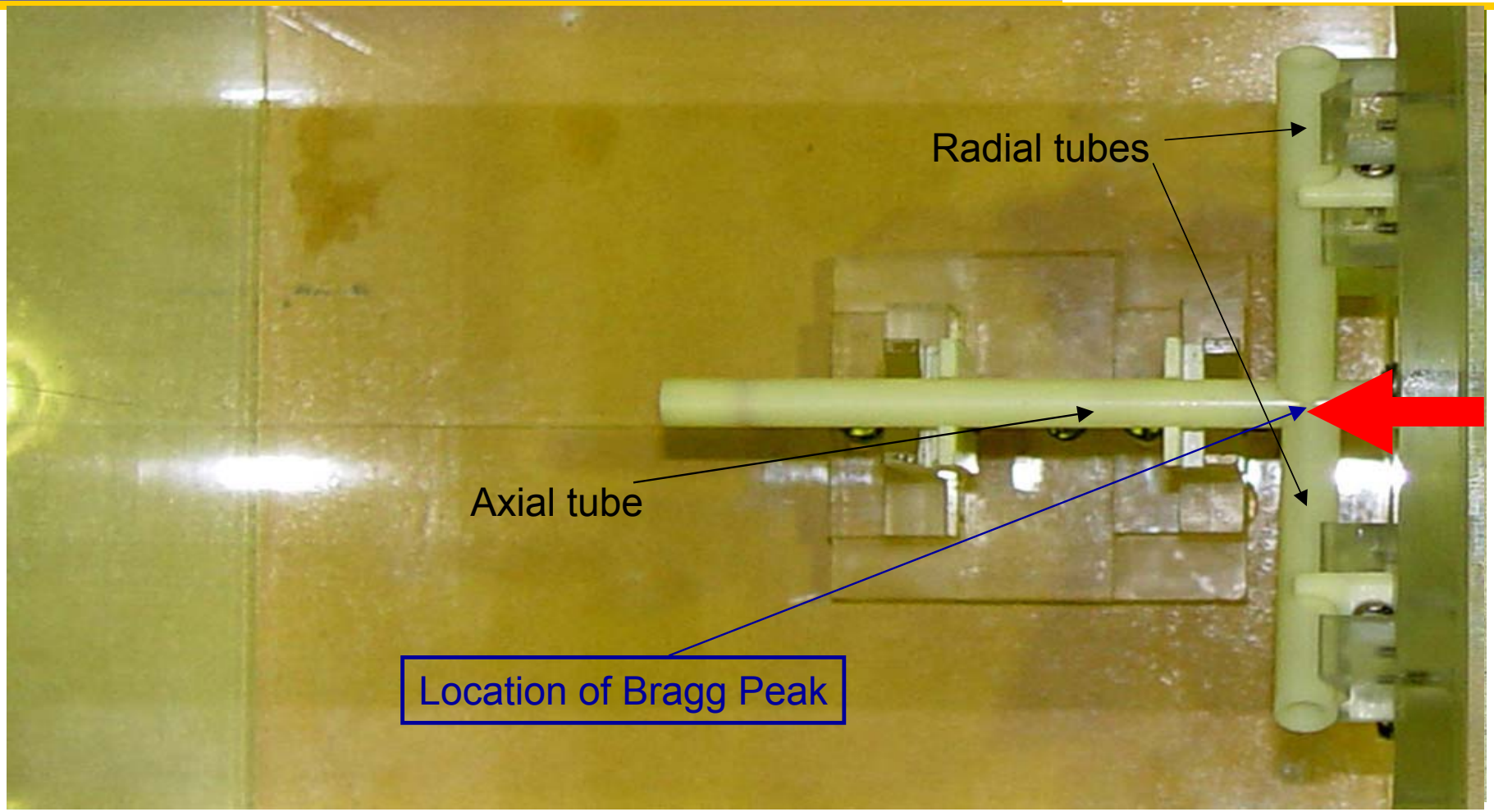
Antiproton Therapy is based on three claims which need proof:

- Antiprotons deliver a higher biological dose for an equal effect in the entrance channel than protons
- The damage outside the beam path due to long and medium range annihilation products is small and does not significantly effect treatment planning
- Antiprotons offer the possibility of real time imaging using high energy gammas and pions, even at low (pre-therapeutical) beam intensity

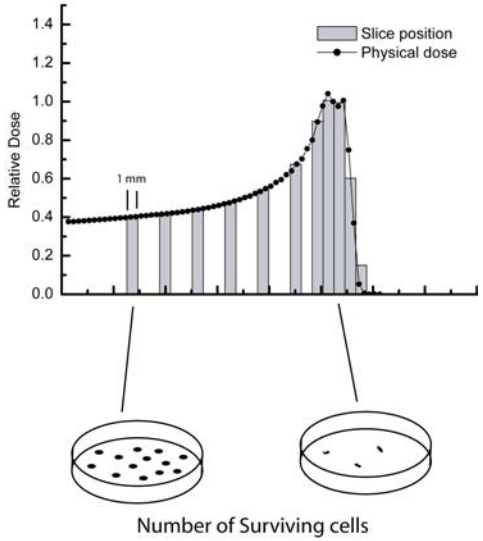
Results from the 2003 run period

- **We have measured cell survival in the peak and plateau regions of an antiproton beam stopped in a biological medium.**
- **The ratio of the doses which produce equivalent cell kill in the peak and the plateau region gives the Biological Effective Dose Ratio (BEDR). For this we only need to know the relative dose.**
- **We can compare these results to the same experiment using a proton beam of comparable energy.**

Cell Survival Measurements

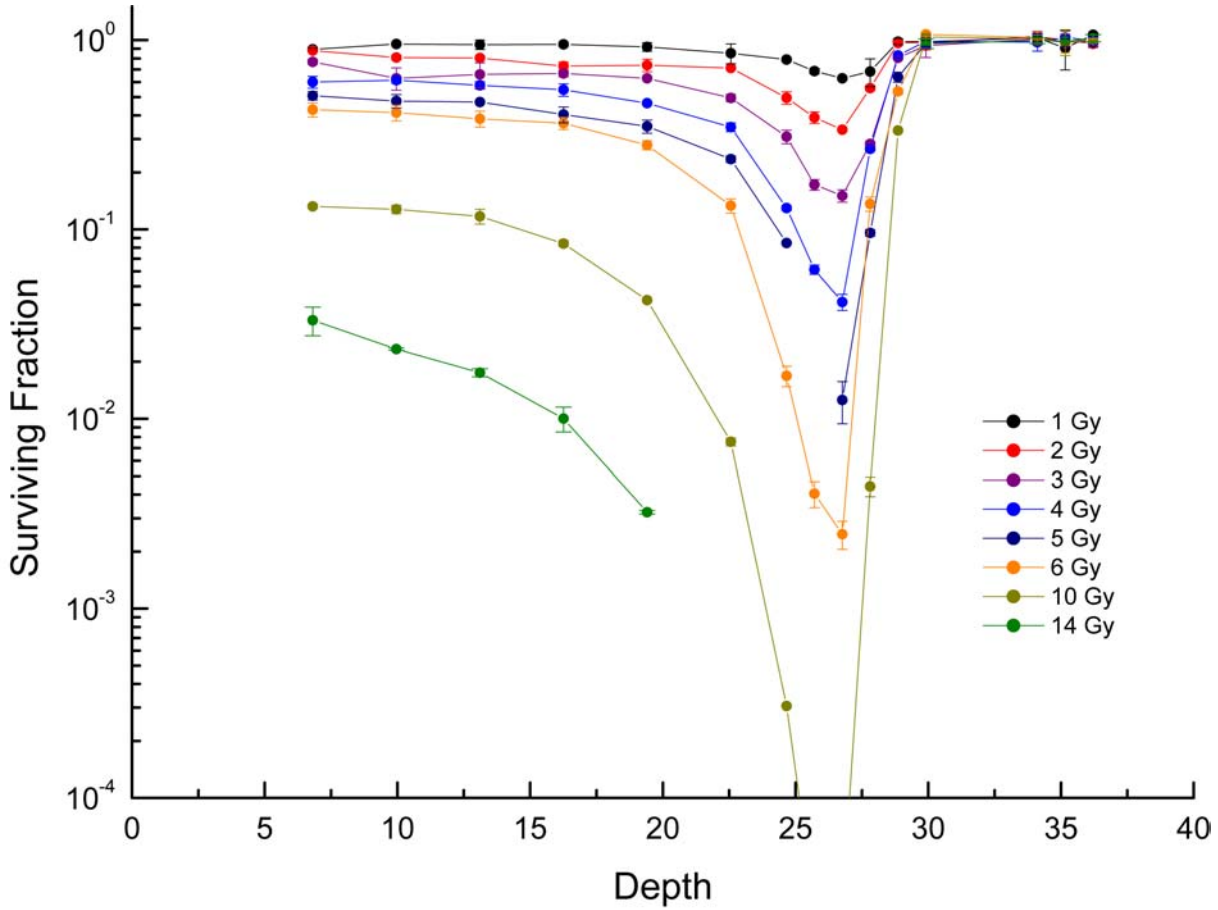


Biological Analysis Technique

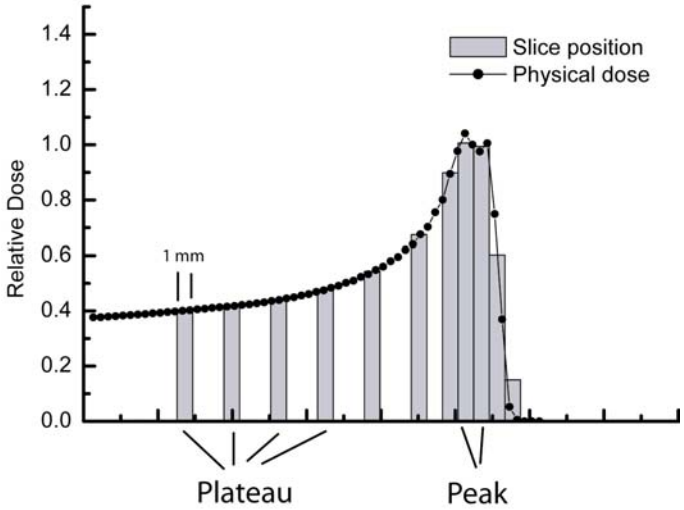


- Irradiate sample tube with living cells suspended in gel.
- Slice sample tube in ≤1 mm slices and determine survival fraction for each slice.

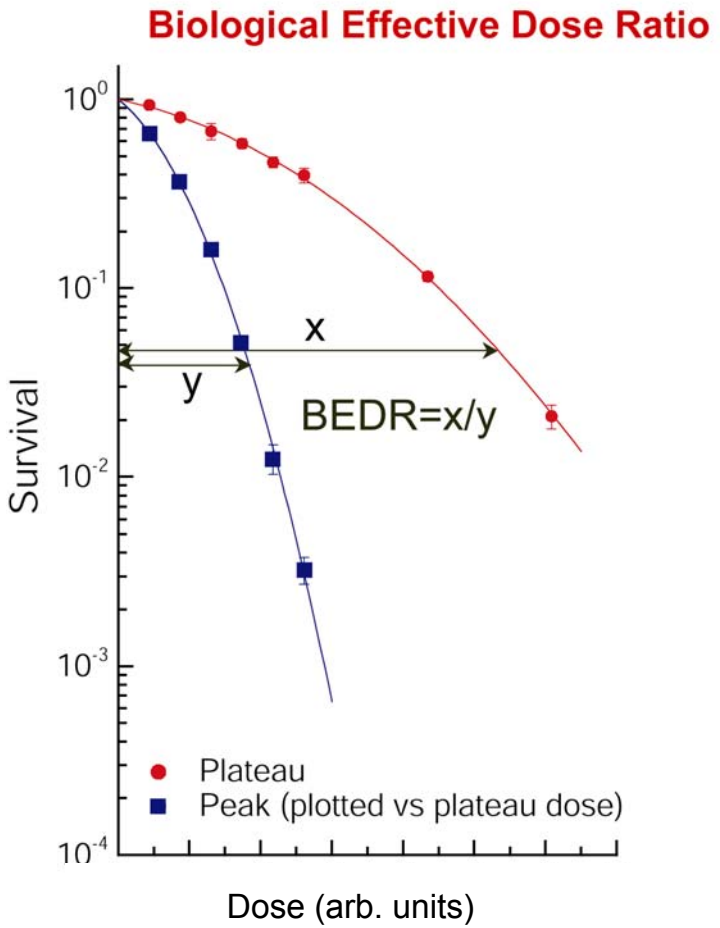
➢Repeat for varying (peak) doses.



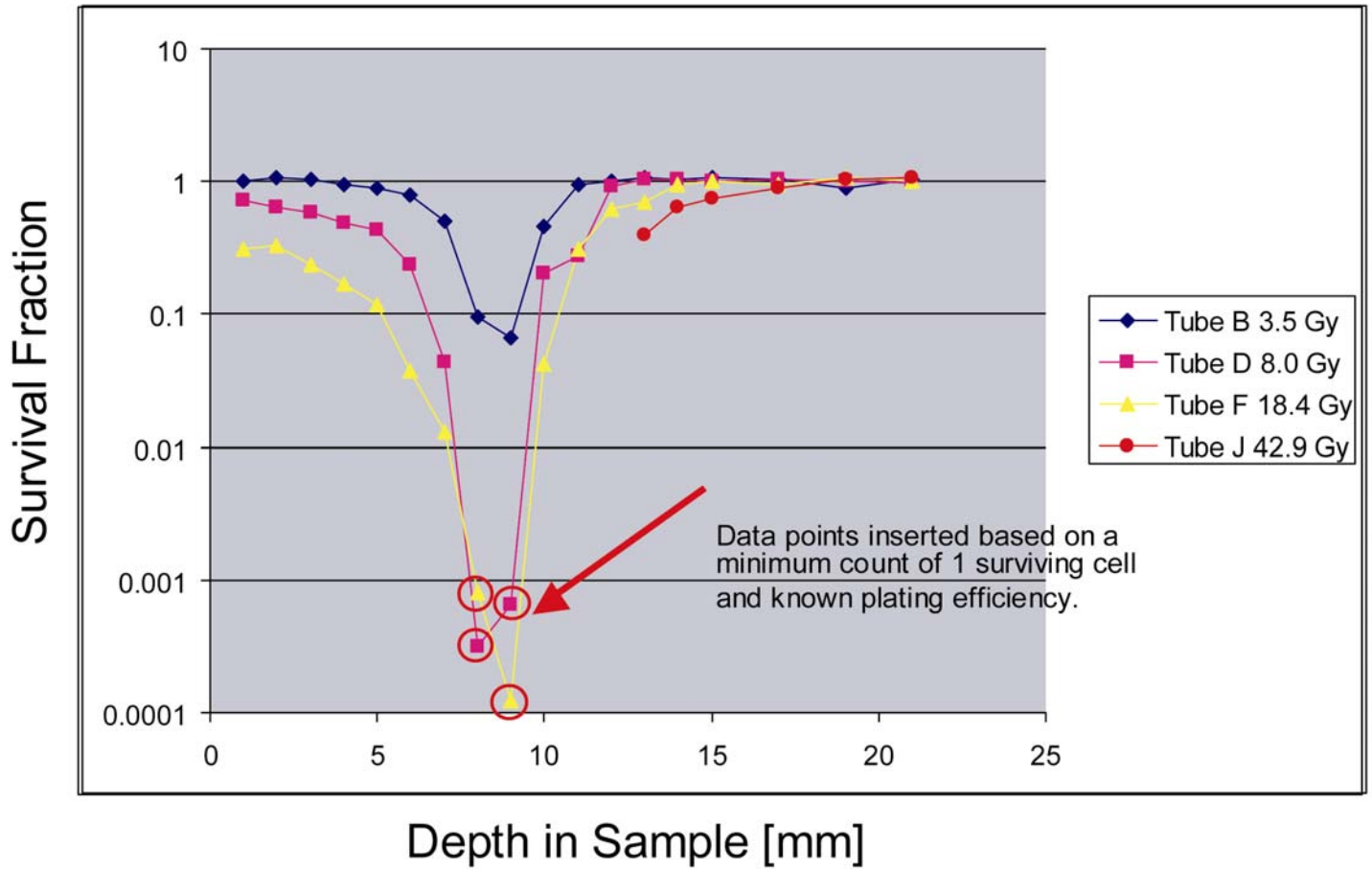
Biological Analysis Technique



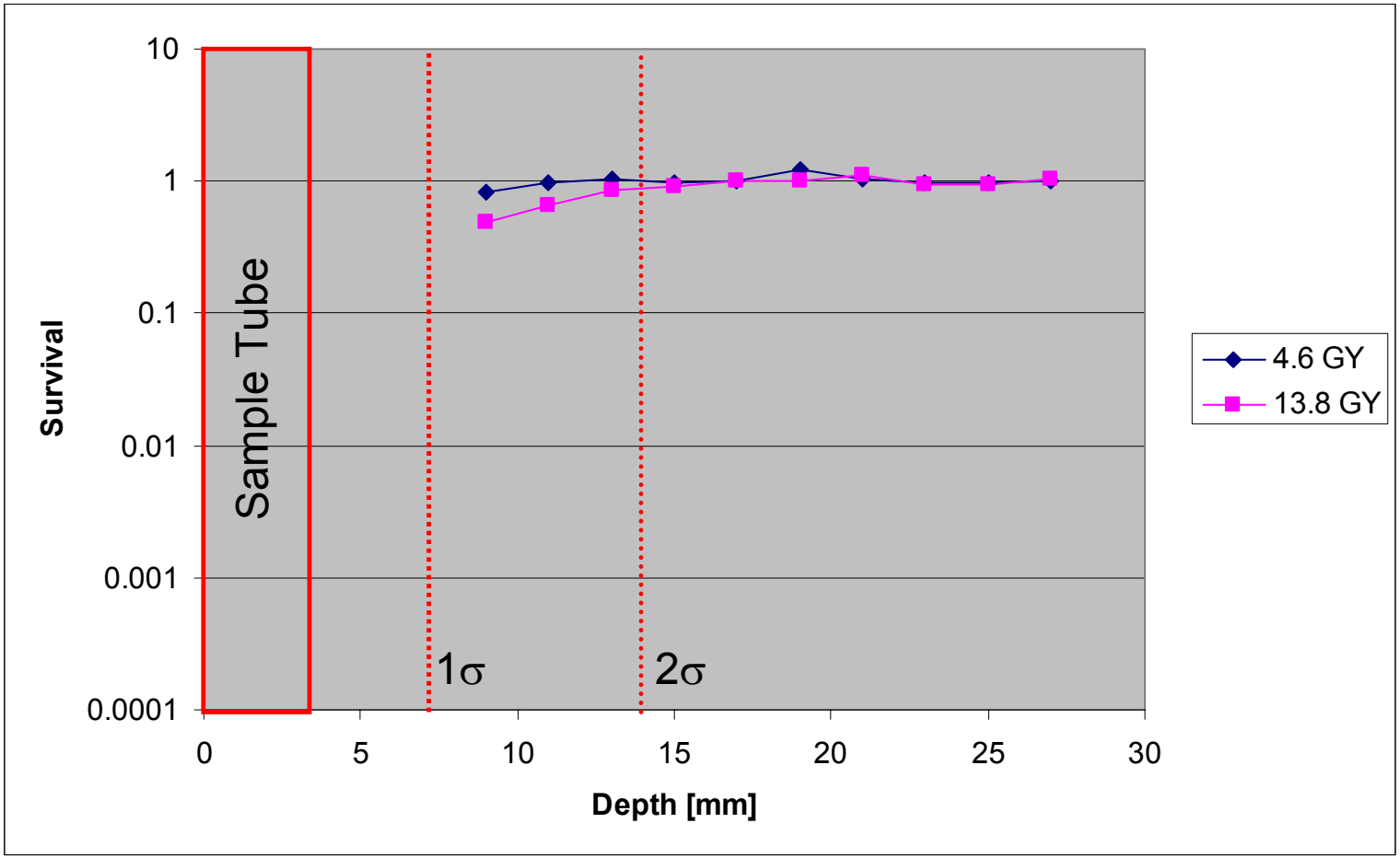
- Calculate "plateau" survival using slices 1 – 4.
- Determine "peak" survival from slice 8 and 9.
- ✓Plot "peak" and "plateau" survival vs. relative dose (Plateau dose, particle fluence, etc.) and extract the Biological Effective Dose Ratio (BEDR).

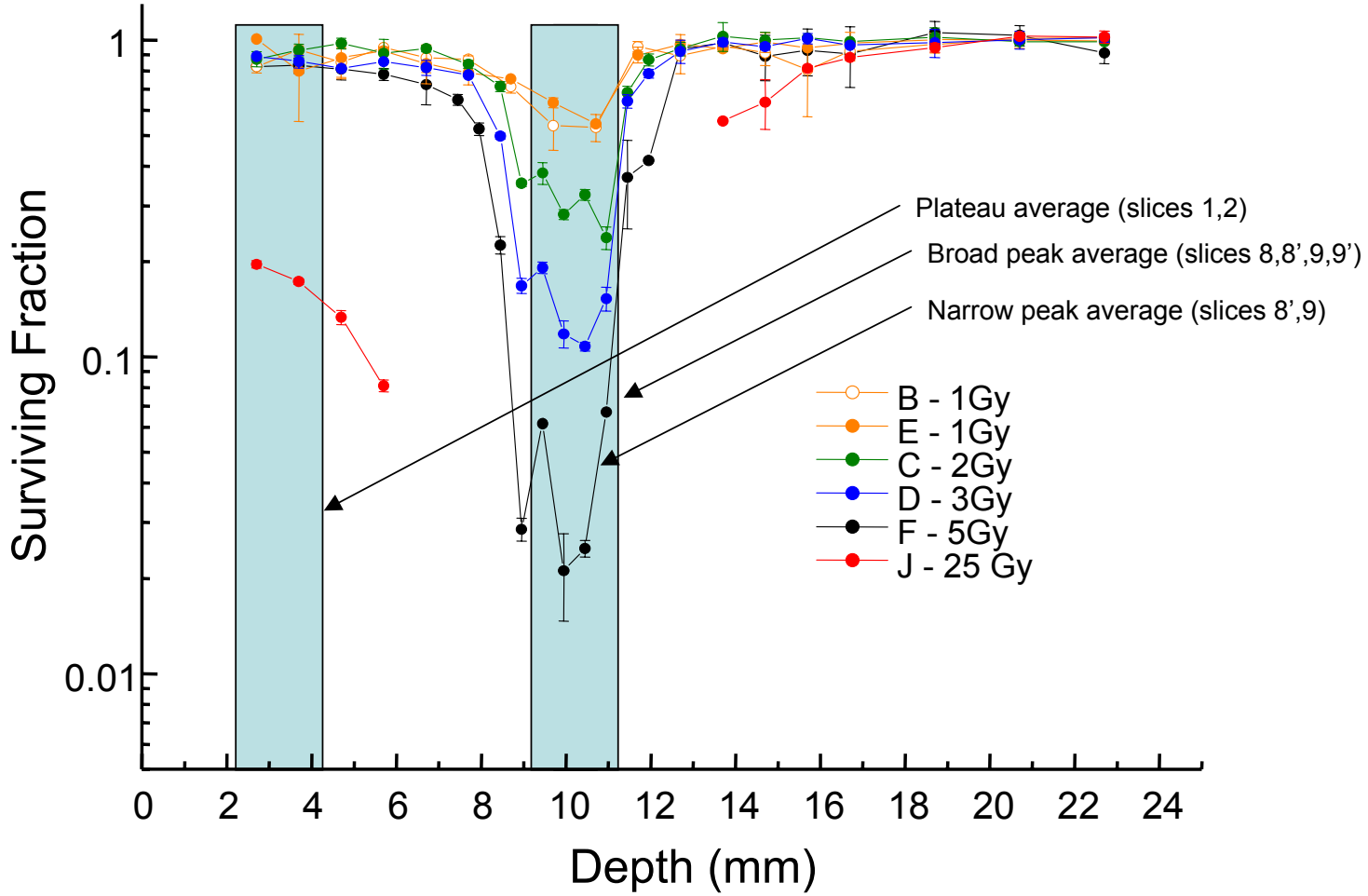


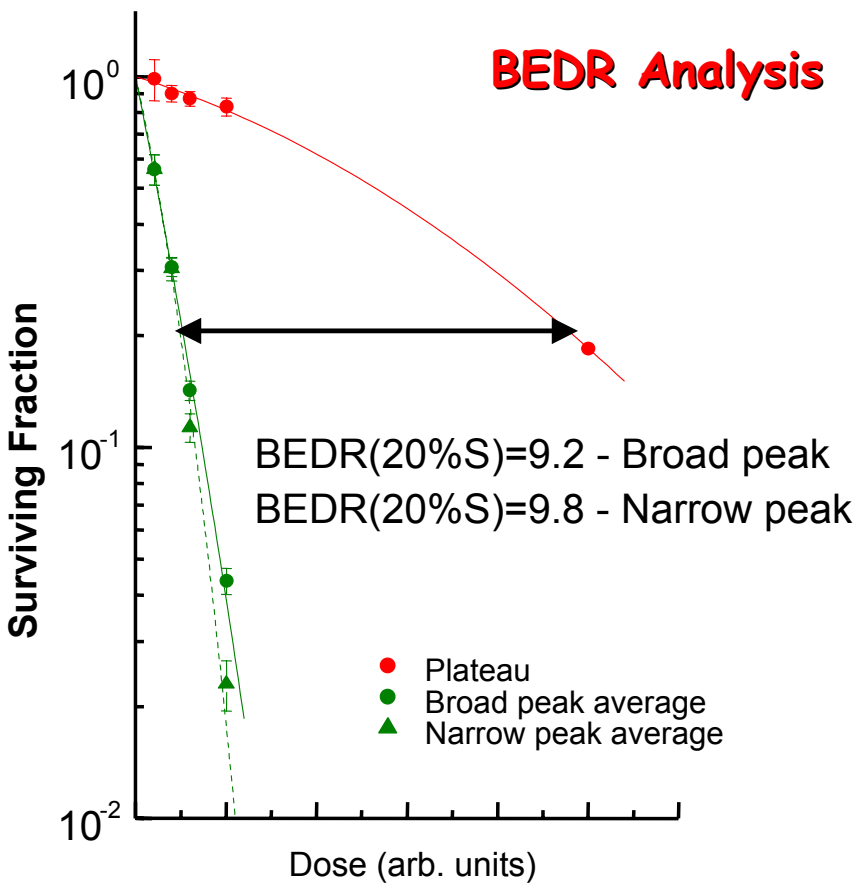
Cell Survival Measurements

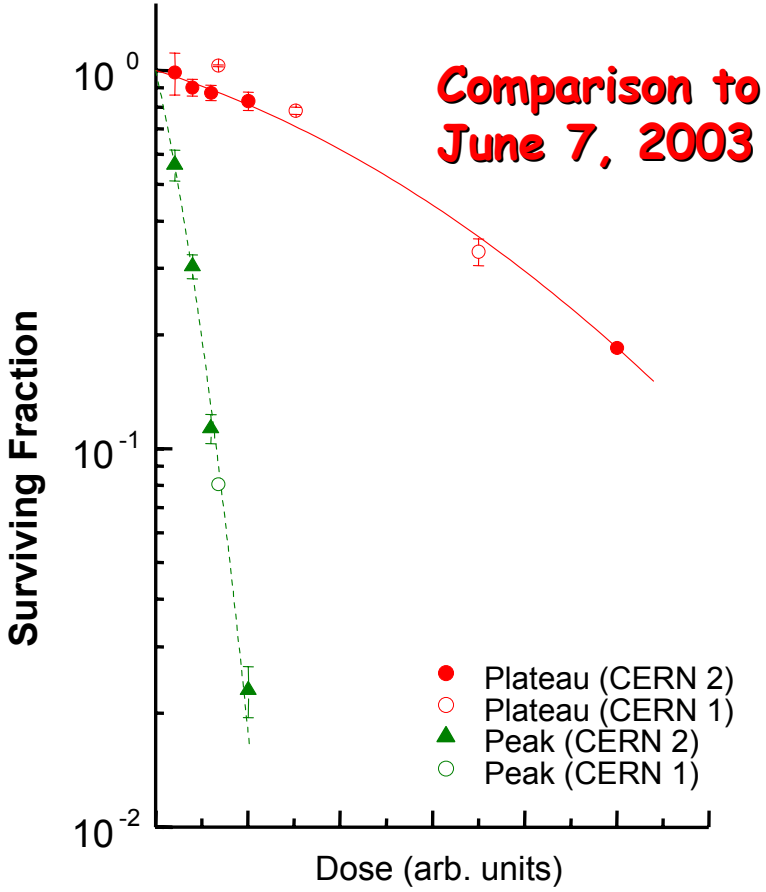


Peripheral Damage

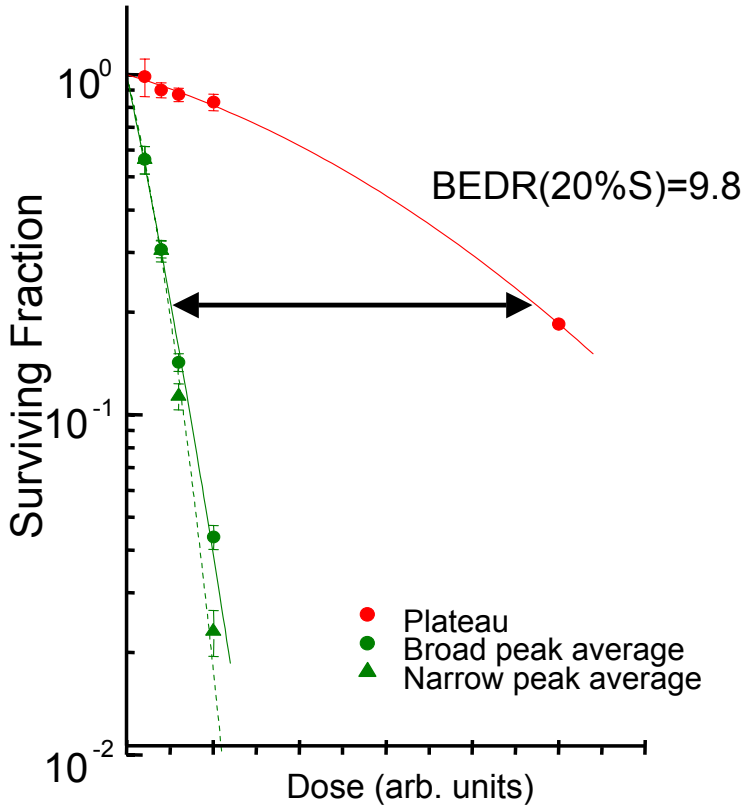



Surviving Fraction
1
0.1
0.01
0
2
4
6
8
10
12
14
16
18
20
22
24
Depth (mm)
Plateau average (slices 1,2)
Broad peak average (slices 8,8',9,9')
Narrow peak average (slices 8',9)
B - 1Gy
E - 1Gy
C - 2Gy
D - 3Gy
F - 5Gy
J - 25 Gy

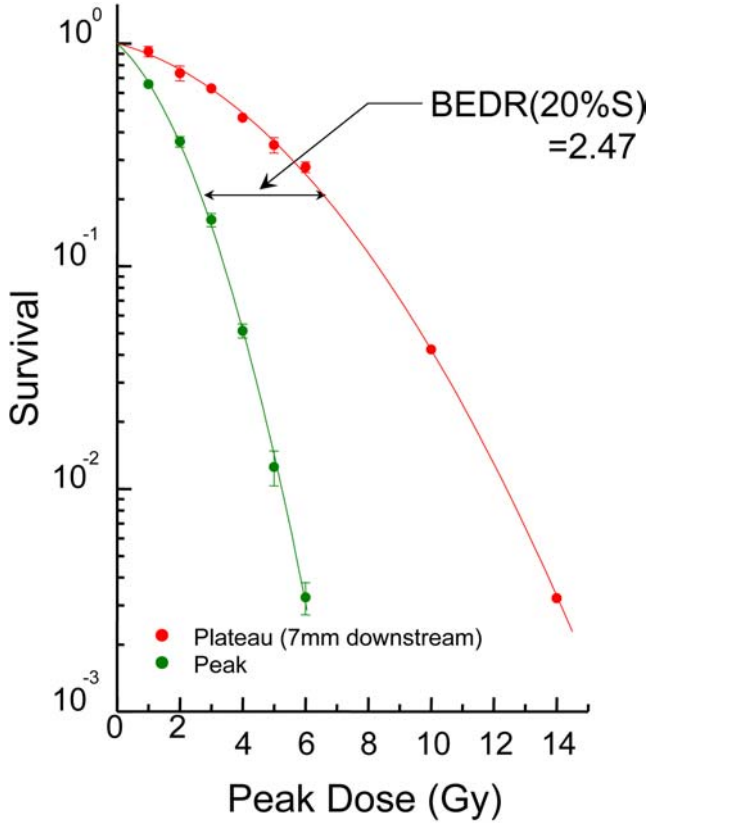

BEDR Analysis
Surviving Fraction
10^0
10^{-1}
10^{-2}
BEDR(20%S)=9.2 - Broad peak
BEDR(20%S)=9.8 - Narrow peak
Plateau
Broad peak average
Narrow peak average
Dose (arb. units)


Comparison to June 7, 2003
Surviving Fraction
10^0
10^{-1}
10^{-2}
Plateau (CERN 2)
Plateau (CERN 1)
Peak (CERN 2)
Peak (CERN 1)
Dose (arb. units)

CERN (50 MeV Antiprotons)



TRIUMF
(analyzed for 50 MeV Protons)



Summary at end of 2003

- The method works very well.
- We are able to measure the survival response of V79-WNRE cells in the plateau and peak regions of a SOBP antiproton peak.
- In the early test experiment we obtained good data at 3 different doses in the plateau, and one dose in the peak.
- In the second experiment we obtained complete survival curves for 5 different doses (in 6 measurements). The sensitivity in axial direction is high enough to detect the dose modulation due to the degrader used.

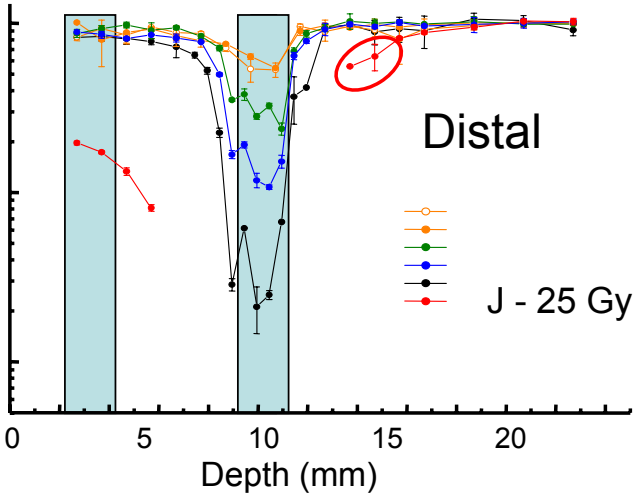
- An analysis of the data for the BEDR gives a result which is significantly higher than the value for protons (obtained at slightly higher energy and using a different degrader) .
- We observe only negligible cell kill outside of the beam in either the radial or axial (beyond the peak) position at even the highest dose.

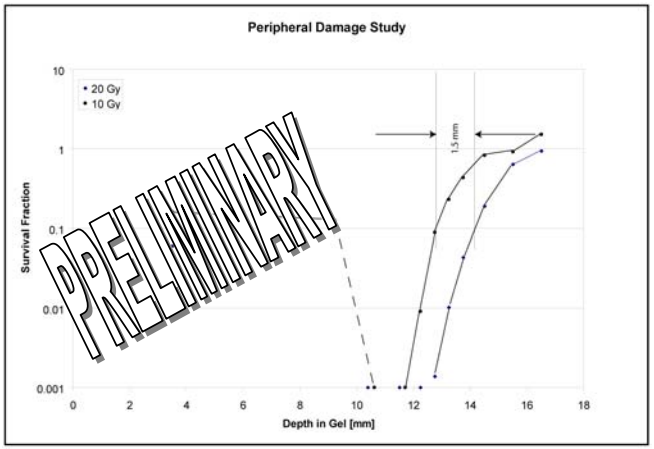
The BEDR enhancement has been proven to be significant.

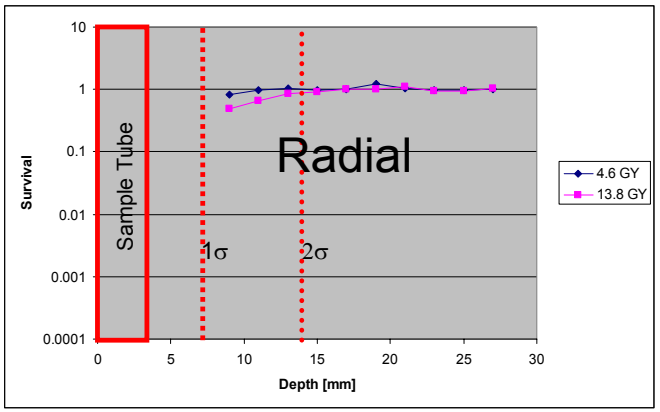
NEXT STEPS:

- **Detailed studies of the peripheral damage due to the medium and long range products from the antiproton annihilation.**
- **Increased efforts on dosimetry in the periphery to the beam**
- **Systematic studies to find faster (and more automated) methods to extract biological data.**
- **Preparatory studies towards real time imaging.**

Evidence of LOW peripheral damage





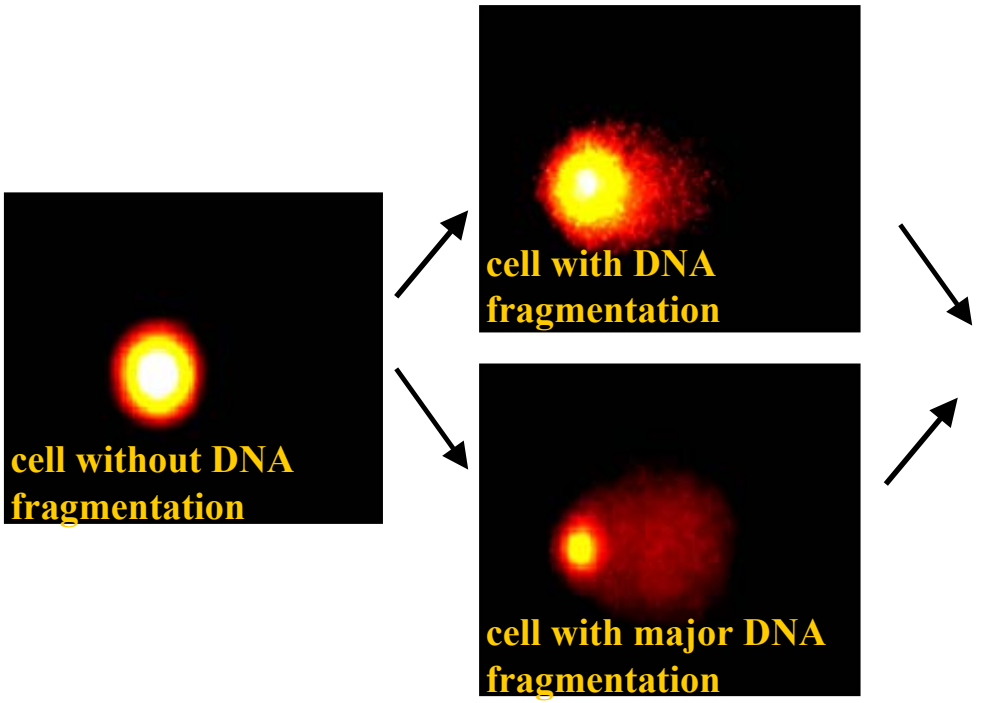


At the highest doses we can see a small effect outside the Bragg peak up to 1 – 2 mm distance

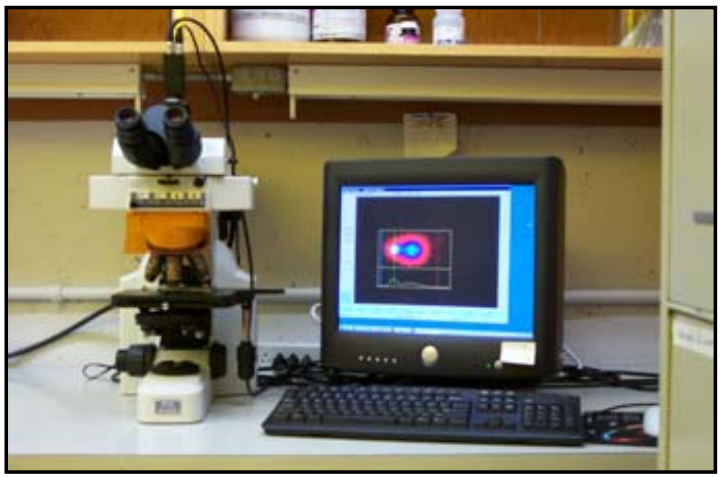
- Need more sensitive assay
- Clonogenic assay may not be best
- Can we detect DNA damage?

The COMET Assay

The comet assay is a gel electrophoresis method used to visualize and measure DNA strand breaks in individual cells using microscopy:



Automated Analysis on individual cells

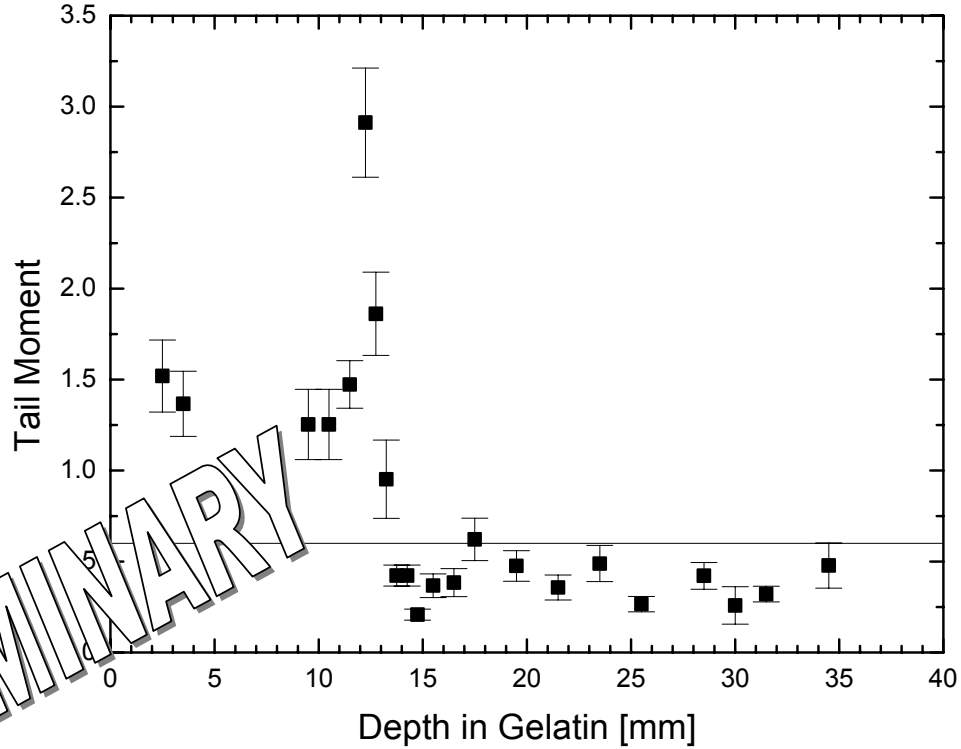


Statistical accuracy through analysis of > 100 cells per sample

The COMET Assay – Early Results

- Cell sample irradiated with 15 Gy
- Slices (0.5 mm and 1 mm) for
  - plateau
  - peak
  - peripheral (distal)
- COMET Assay performed by the Inst. for Occup. Medicine, Zagreb

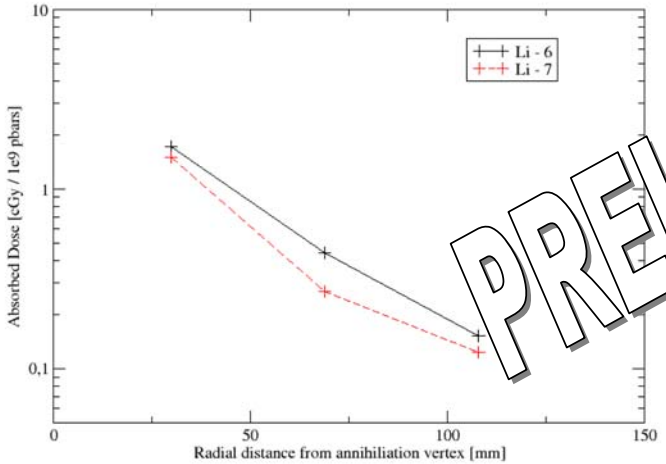
No detectable damage above control sample

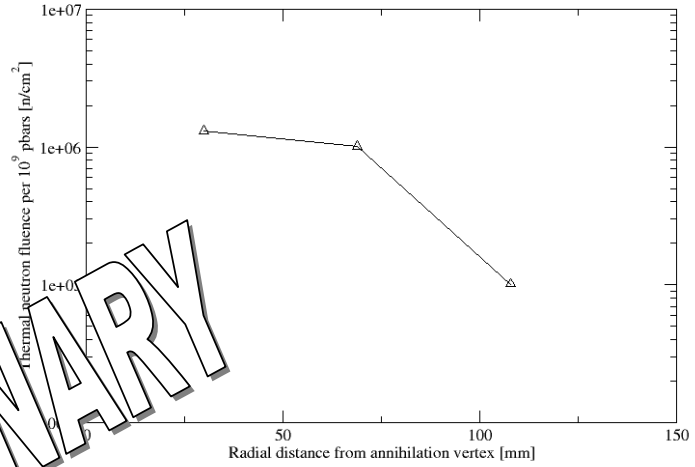


Peripheral Damage – Neutron Dosimetry

Placement of ^{6}Li and ^{7}Li TLD chips at 30 to 120 mm from annihilation volume

Total dose in Peak ~ 7 Gy
Dose seen at 20 mm < 2 cGy





PRELIMINARY

Additional dose in ^{6}Li from thermal neutrons only

Additional measurements to establish neutron spectrum started on 24. September

Future Directions

Finish Laying the Foundations (2004/2006)

- Finalize Clonogenic Assay Studies
- Intensify Peripheral Damage Studies
- First Demonstration of Real Time Imaging

Source of Pbars: AD (3 – 5 x 10^7/85 seconds, ΔT = 100 – 500 ns)

Comparison with protons and heavy ions (2005)

Moving Forward: R&D towards final certification (2006 +)

- Development of beam delivery and energy modulation
  ~ 1 mm focus, scanning possibility (Complete DEM line)
- Real time imaging of shaped target
  Implement semi-slow extraction (10^6 – 10^7/second)?
- Initial in vivo testing?
  4 x 10^8 pbars deliver 1 Gy to 1 cc tumor (10 shots or 15 minutes)
  (possibilities to increase intensity per shot?)

Future Directions

PBAR MEDICAL

Finish Laying the Foundations (2004/2006)

- Finalize Clonogenic Assay Studies
- Intensify Peripheral Damage Studies
- First Demonstration of Real Time Imaging

Source of Pbars: AD (3 – 5 x 10^7/85 seconds, ΔT = 100 – 500 ns)

Comparison with protons and heavy ions (2005)

AD can do this !

(some minor modifications would be desirable)

~ 1 mm focus, scanning possibility (Complete DFM line)

Experiments run on a biological clock

(analysis time between runs can be several weeks)

➔ Low demand on overall beam time (<10%)