AD-4/ACE

Biological Effects of Antiprotons

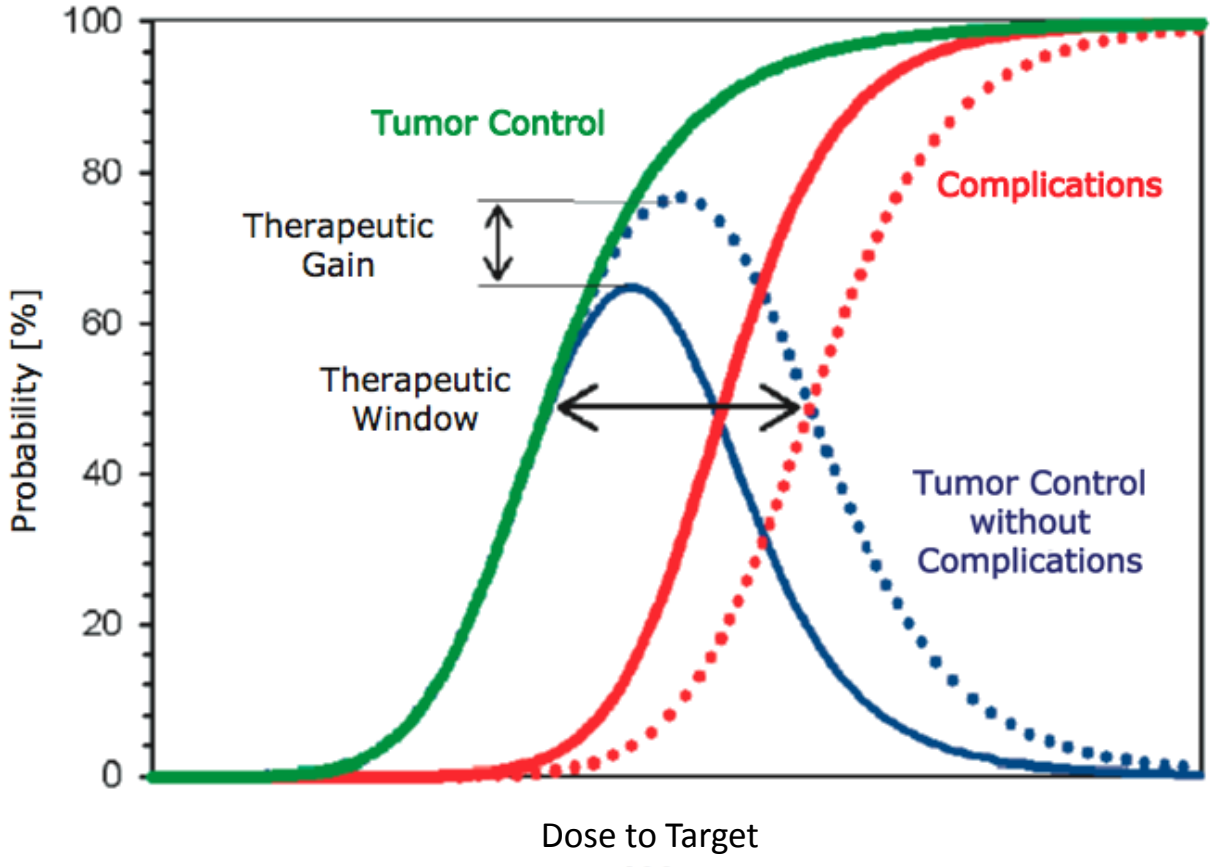
Are Antiprotons a Candidate for Cancer Therapy?

32 Scientists from 10 Institutions

University of Aarhus
University Hospital of Aarhus
University of New Mexico, Albuquerque
University of Athens
University of Umeå
Queen's University Belfast
CERN, Geneva
Hôpital Universitaire de Geneve
German Cancer Research Center, Heidelberg
Max Planck Institute for Nuclear Physics, Heidelberg

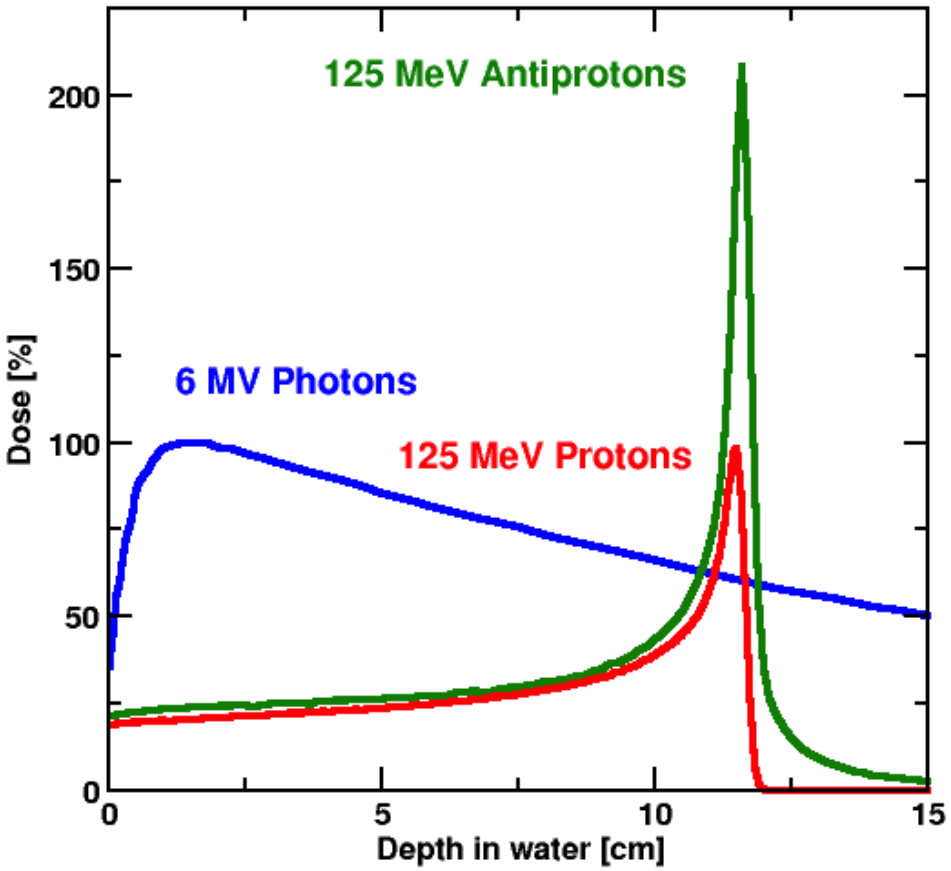
Rationale for Conformal Radiotherapy

Dose (and tumor control) are limited due to tolerance of organs at risk

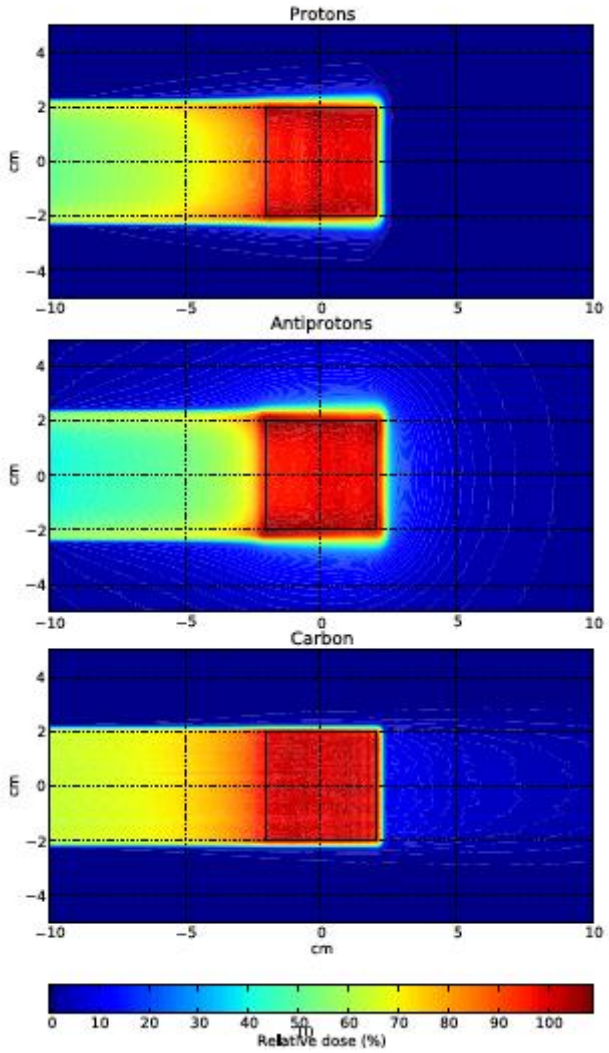


Better conformity of dose to target enables application of higher doses & higher tumor control without increasing normal tissue complication rate

Physical Advantage of Antiprotons



Potential Clinical Advantages?

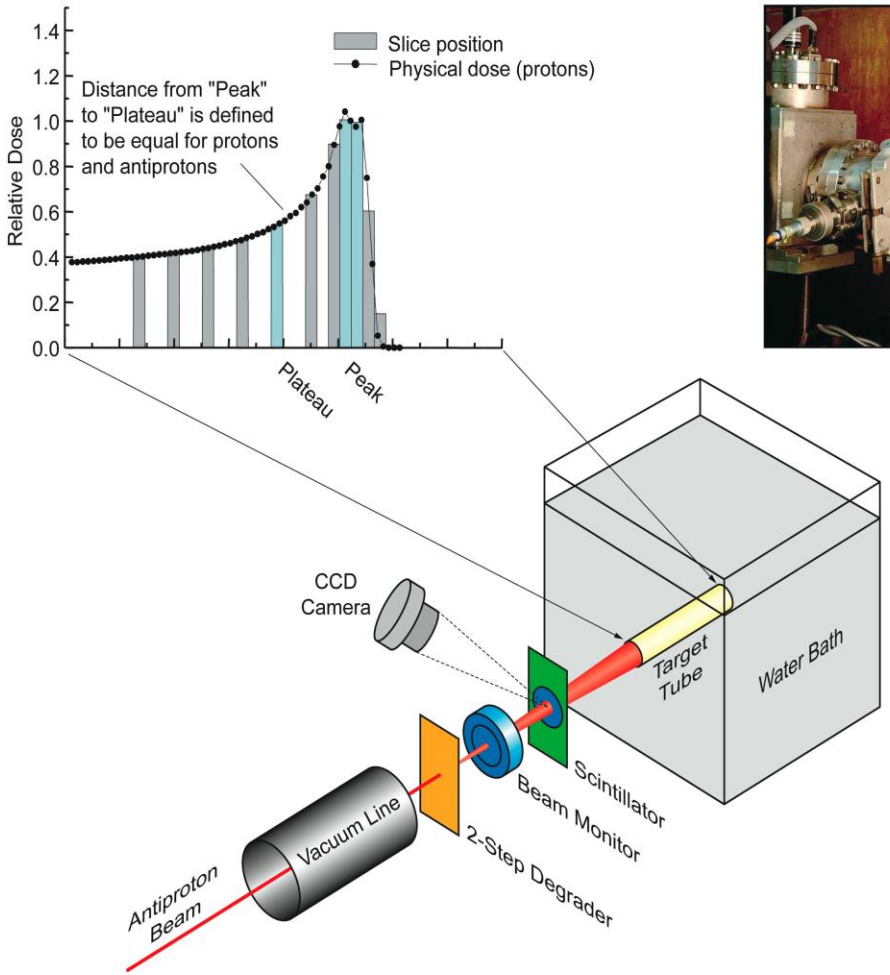


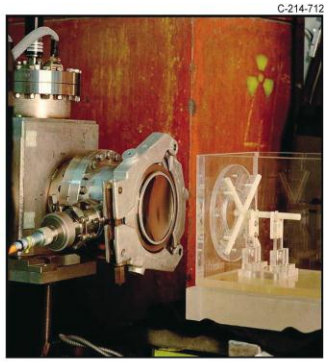
Each Particle Type shows distinct features

- Protons are well known and easy to plan (RBE = 1) which is the reason they are most widely adopted.
- Antiprotons have lowest entrance dose for the price of an extended isotropic low dose halo.
- Carbon ions have sharpest lateral penumbra but comparatively higher entrance dose than even protons (no RBE included here), but show forward directed tail due to in beam fragmentation.

Detailed dose plans (including RBE) will need to be developed to assess applicability of particle types for different tumor types and locations!

The AD-4 Experiment at CERN





INGREDIENTS:

- **V-79 Chinese Hamster cells embedded in gelatin**
- **Antiproton beam from AD (126 MeV)**

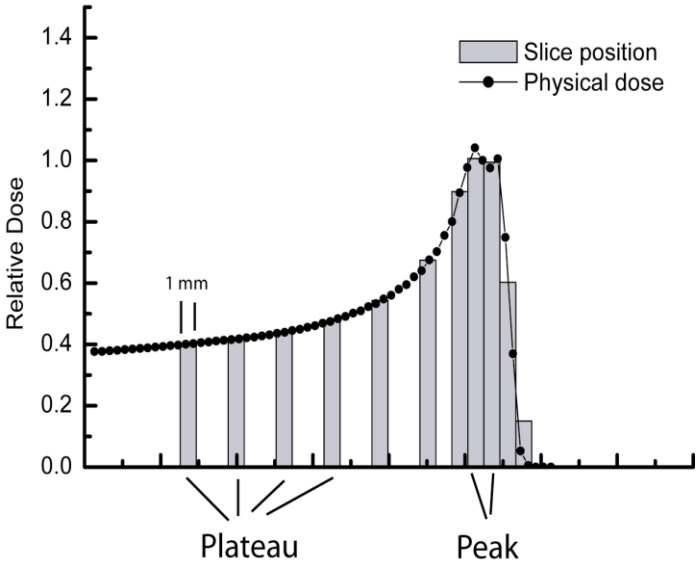
METHOD:

- **Irradiate cells with dose levels to give survival in the peak is between 0 and 90 %**
- **Slice samples, dissolve gel, incubate cells, and look for number of colonies**

ANALYSIS:

- **Study cell survival in peak (tumor) and plateau (skin) and compare the results to protons (and carbon ions)**

Biological Analysis Method

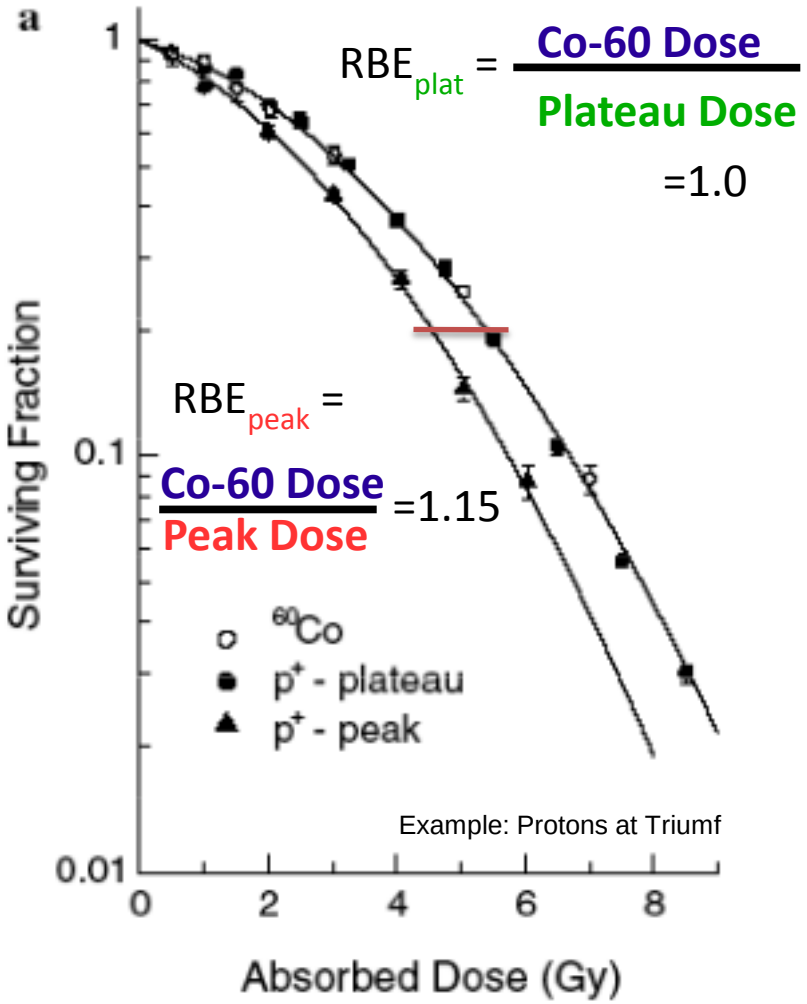


Plot "peak" or "plateau" survival vs. absolute dose and compare to ^{60}Co irradiation comparing dose values needed for

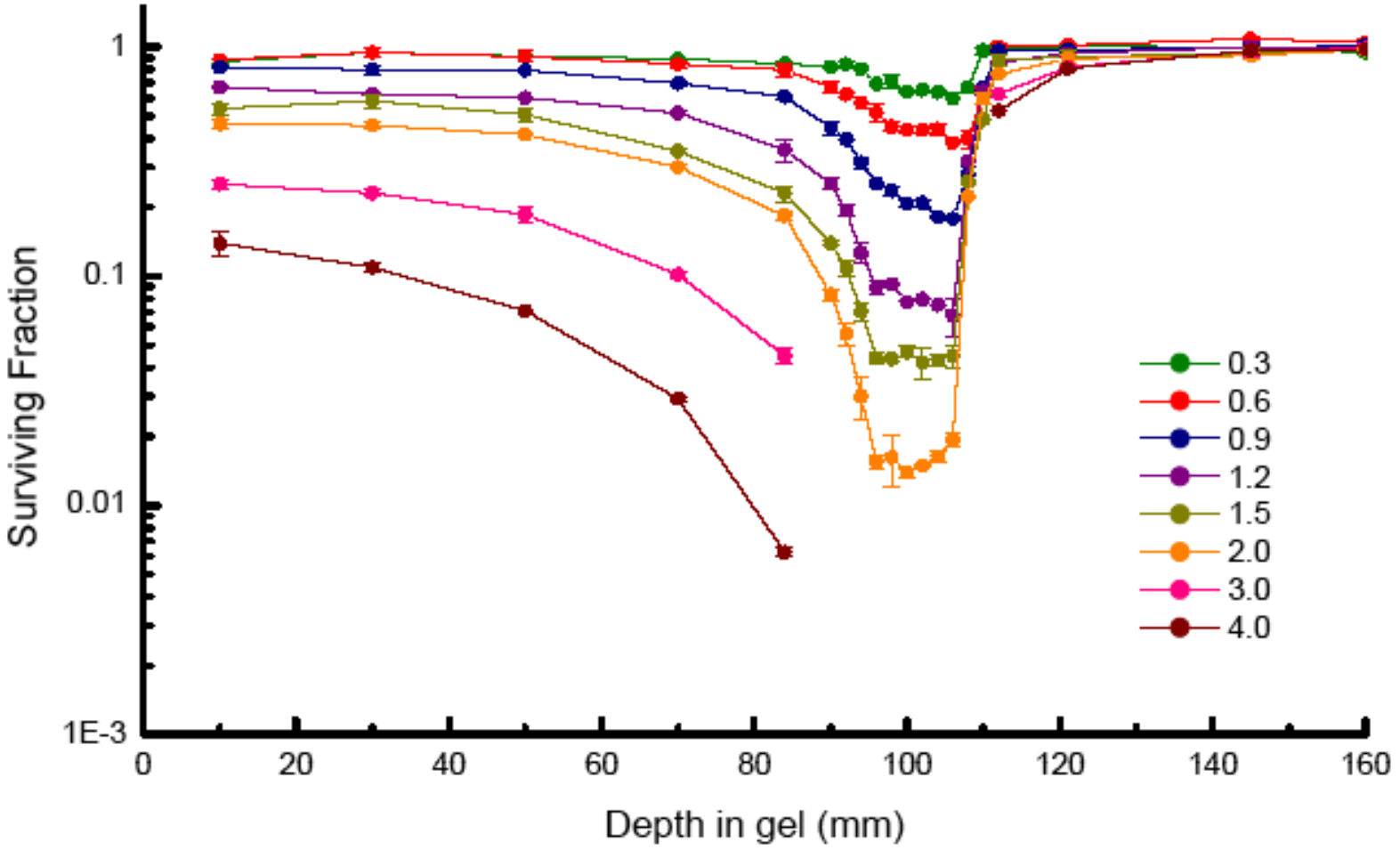
Iso-Effect

for peak, plateau, and ^{60}Co irradiation:

Relative Biological effectiveness RBE

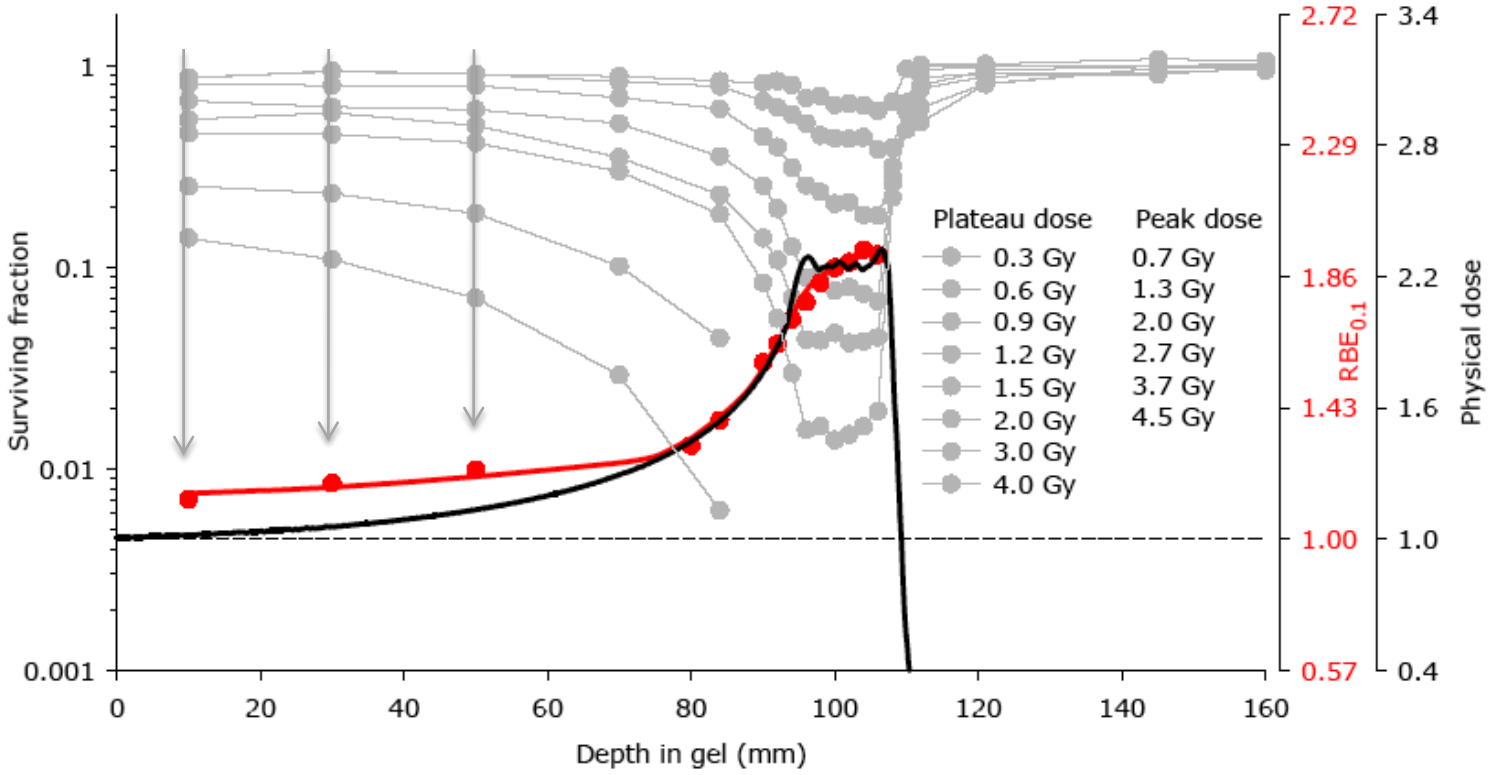


Carbon Ions – SOBP at GSI



note: clinical beams with precise dosimetry and fast dose delivery ……..
Energy to achieve same clinical relevant depth and form SOBP as at CERN….

RBE for Carbon Ions

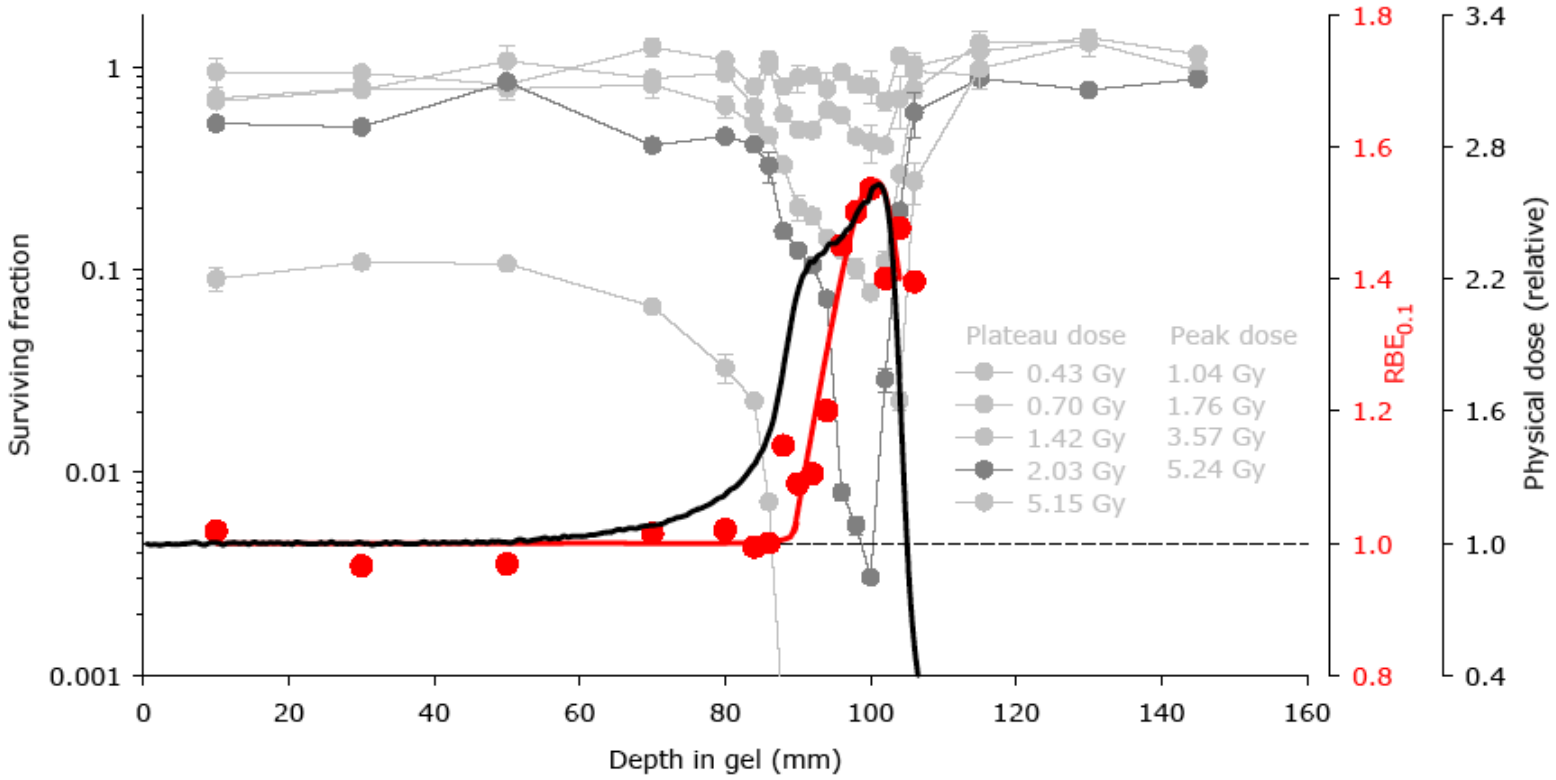


Extract survival vs. dose plot for each depth slice and calculate $RBE_{SF=10\%}$

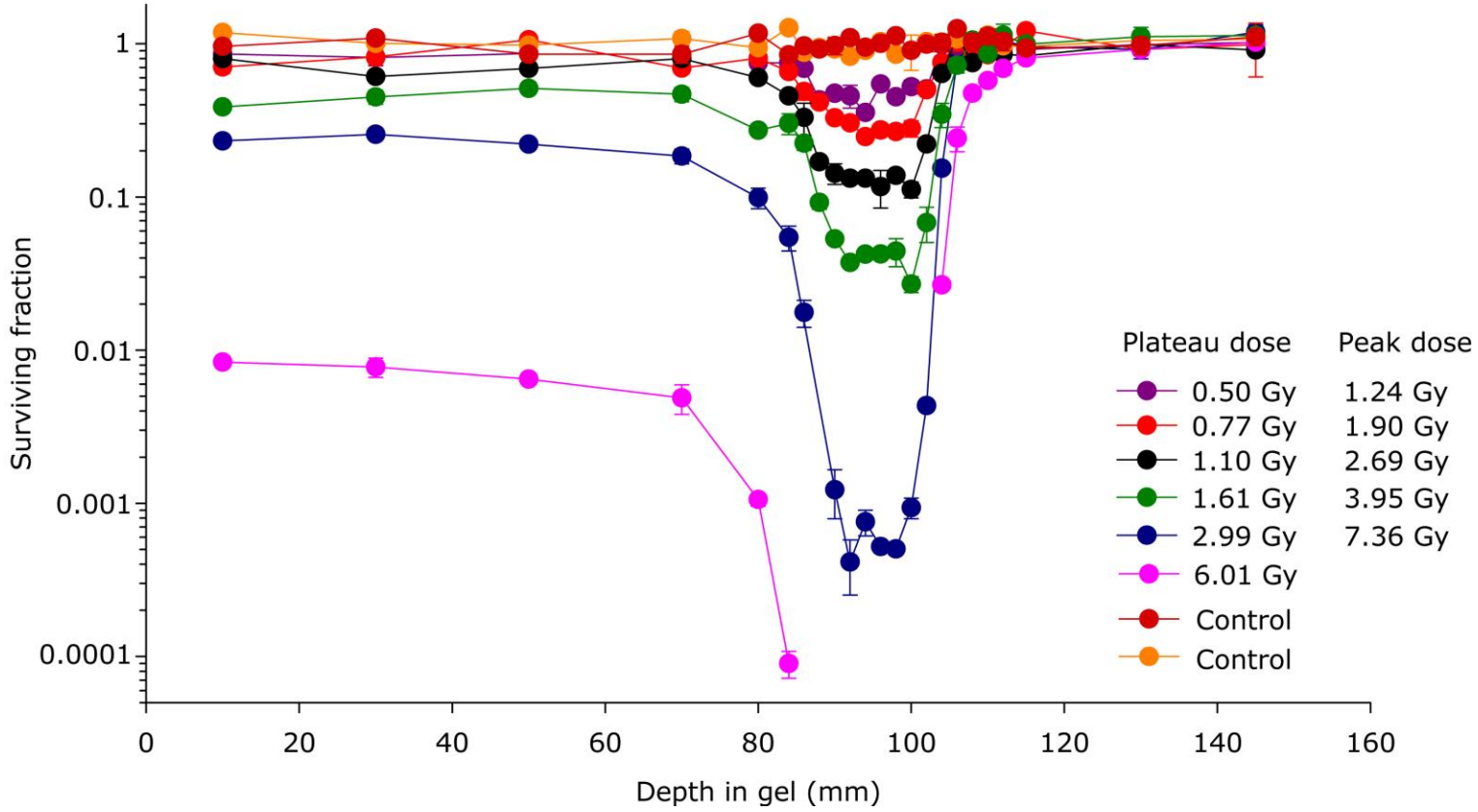
$RBE_{plateau} = 1.2$ $RBE_{peak} = 2.0$ $RBE_{distal} = 1.5$

RBE of Antiprotons

Antiprotons 2007



CERN DATA 2008



note: good control over dose planning for SOBP……..

$RBE_{plateau}$ = 1.2 RBE_{peak} = 1.73 – 2.2

Current Status of Analysis

- Data sets from 2006, 2007, 2008, and 2010 are being combined for statistical relevance (2011 data may suffer from infection of cell samples).
- Normalization issues concerning reference irradiations are being resolved.
- Error propagation due to different beam conditions and therefore different RBE mix of beams need to be addressed.
- With addition of 2012 data we hope to be able to show final result and apply to dose planning studies.

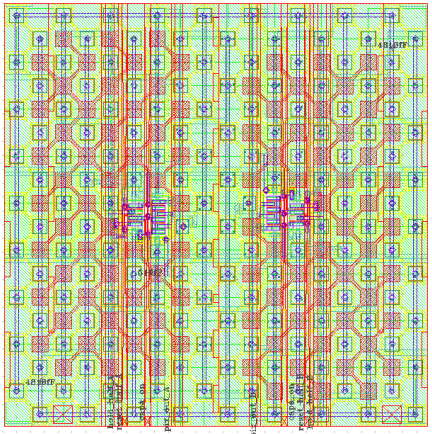
Summary and Outlook

- Extended data set on Biological Effect of Antiprotons for preliminary dose planning studies
- Confinement of RBE Enhancement to Bragg peak has been confirmed (preliminary analysis)
- DNA damage assays for studies of late effects achieved higher resolution
- Fast Beam Monitoring implemented
- Real Time Imaging of Stopping Distribution
  – Proof of principle experiment performed
- Try to finish this phase of AD-4 in 2012

New Beam Monitor

- Purpose: Shot-to-shot monitoring of beam spot
  shape, size, and position for precise dose calculations
- to replace Gafchromic film, facilitate alignment, and have instant feed back on beam changes
- Solution: Solid state pixel detector (**Monolithic Active Pixel Sensor**)

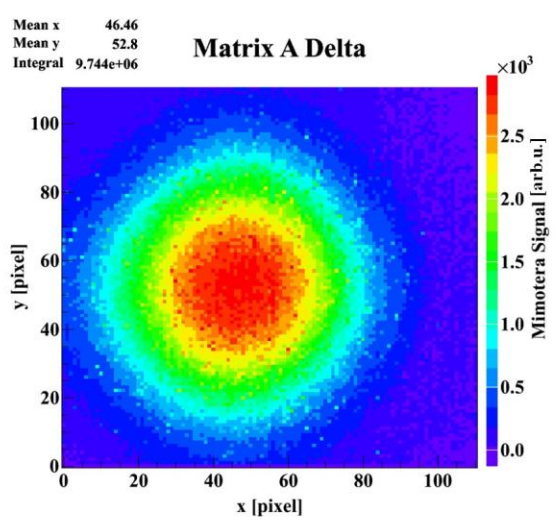
  - **Dedicated MAPS design to beam monitoring**
  - **pixel 153×153 μm² squares**
  - **two 9×9 interdigited arrays of n-well/p-epi diodes + two independent read-out circuits – avoiding dead time**
  - **In-pixel storage capacitors – choice ~0.5 pF or ~5 pF to cope with signal range**

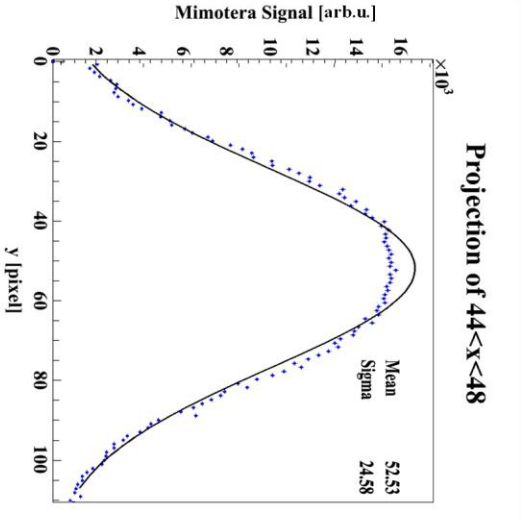


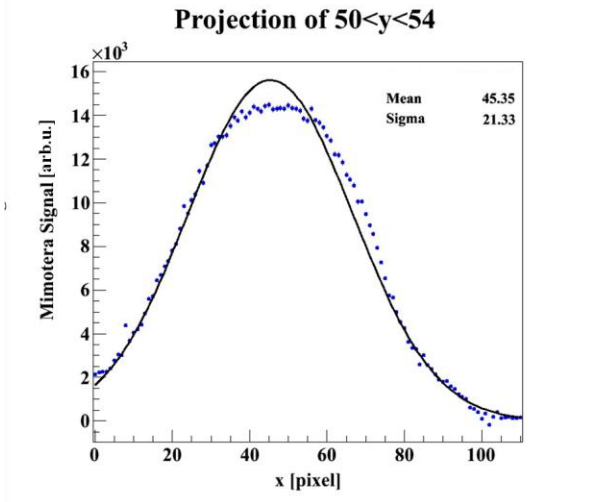
Mimotera, Massimo Caccia
(Universita' dell'Insumbria Como, Italy)

Long term goal: Measure LET distributions in 2D/3D

Complete Info on Beam Shot

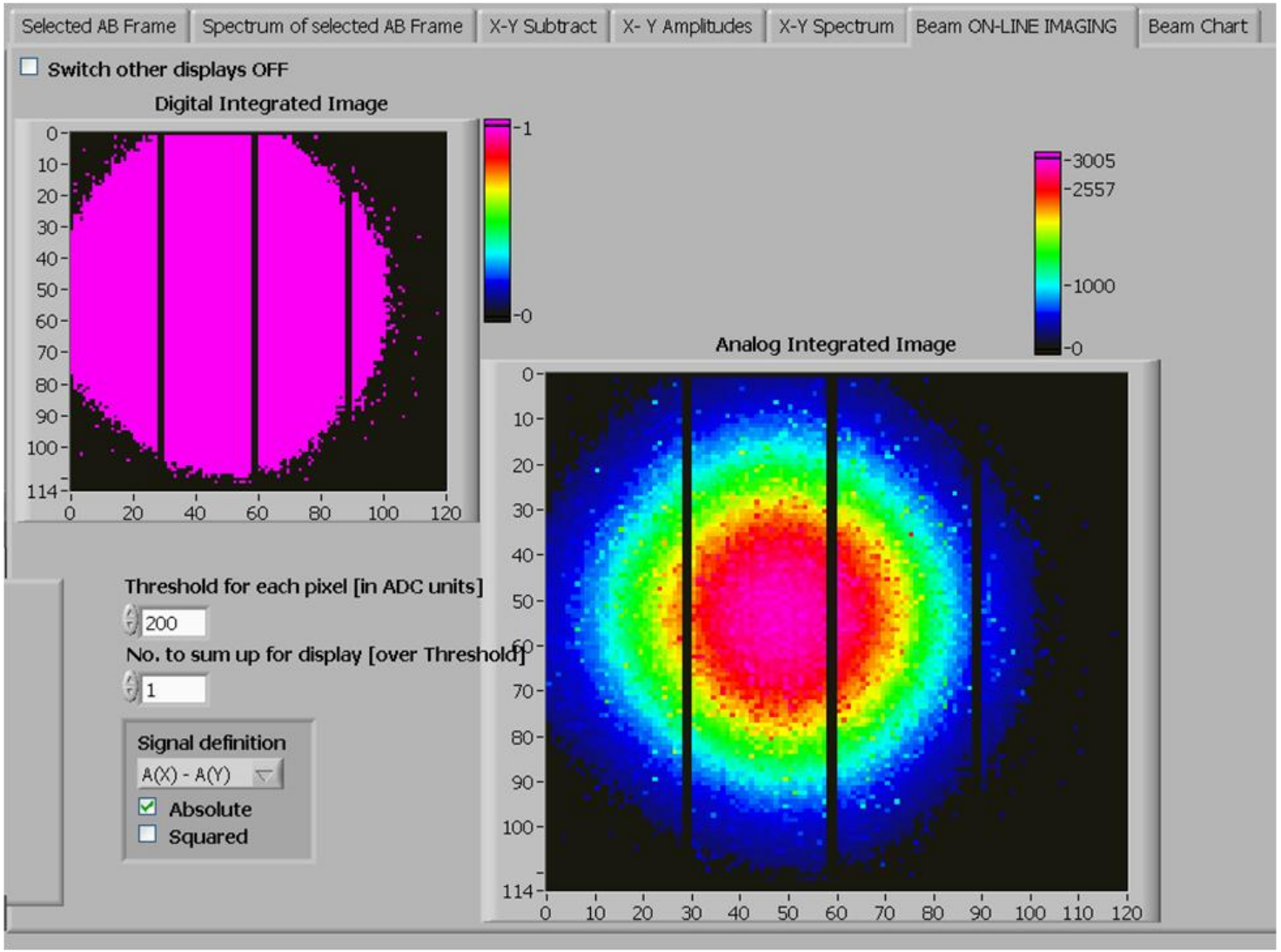






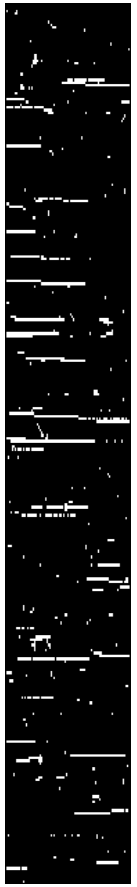
Integral, Width in X and Y for each shot at a glance

Online Display of Beam



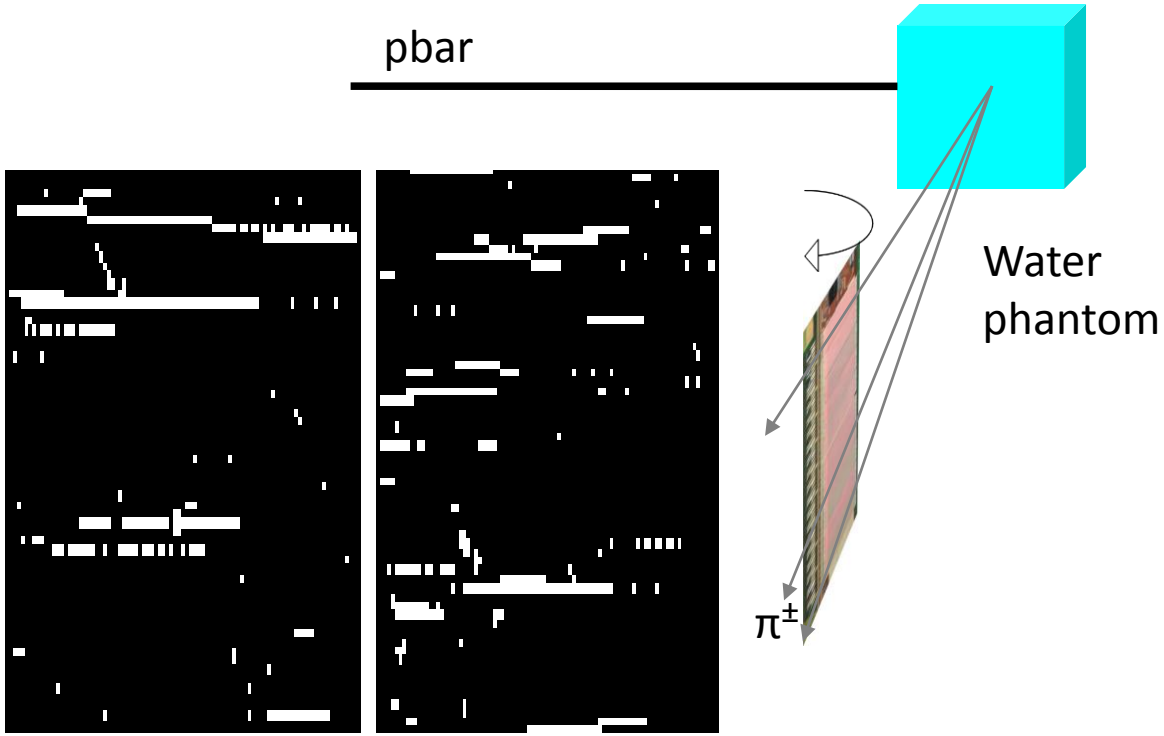
Real Time Imaging
Proof of Principle Experiment

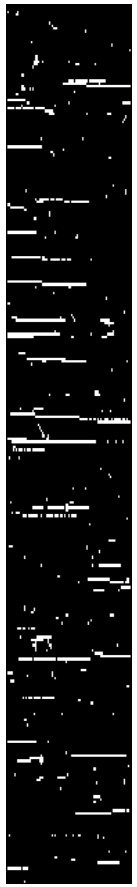
- Q: How to minimize material and cost
- A: Instead of 3 layers use one layer and look at grazing incidence.



- Q: What detector to use for first test?
  A: Turn to our friends in ALICE and use one (spare) module of the Alice Silicon Pixel Detector (SPD)

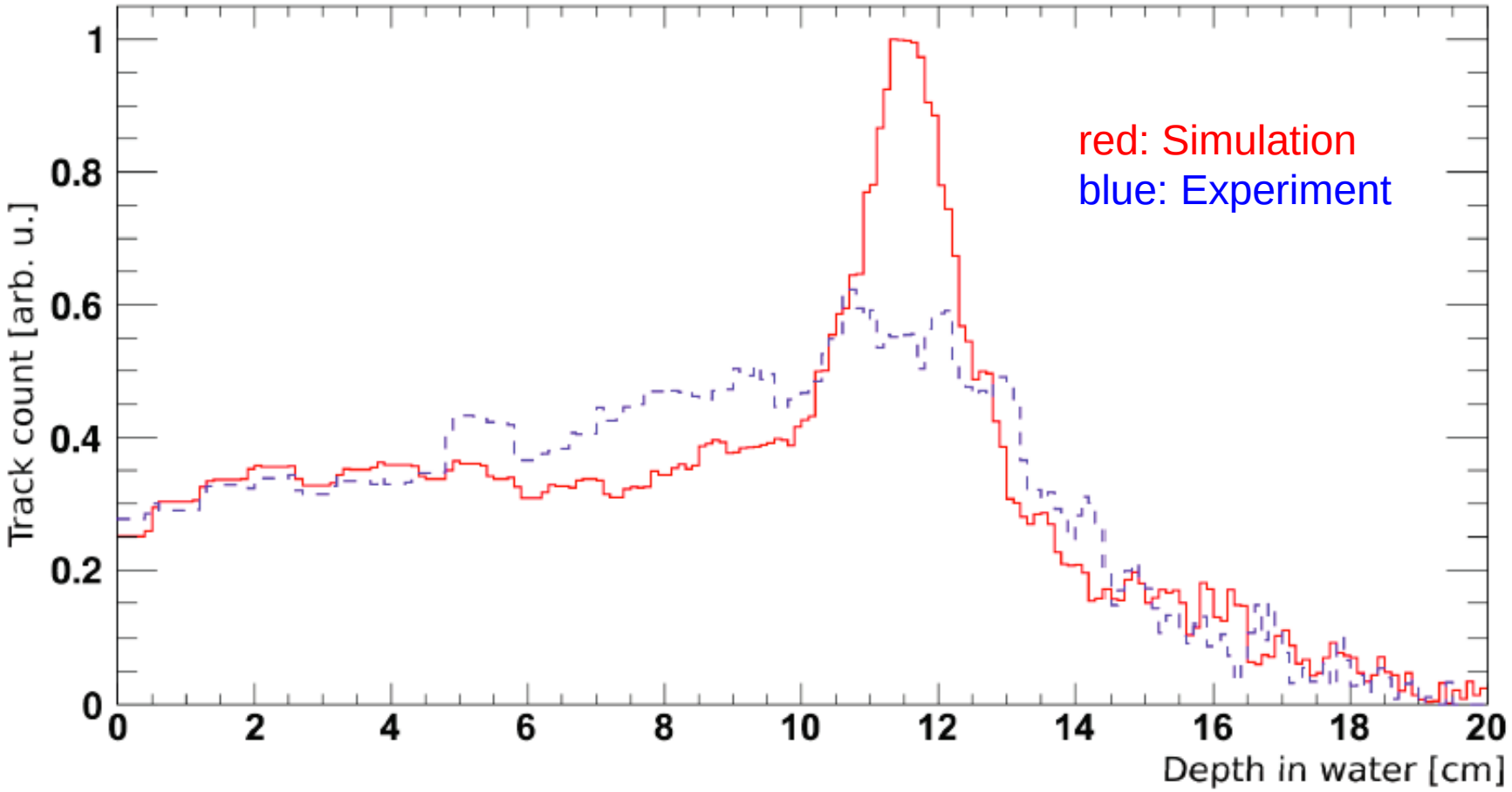
First Experimental Realization





- grazing incidence of pions produce long tracks
- length distribution changes with angle
- stopping distribution along z-axis can be inferred
- Future work: Expansion to 3 - D

First Results



Distal Edge of Depth Dose Profile is detected
Resolution is limited due to distance from target and pion scattering

DNA Damage and Repair

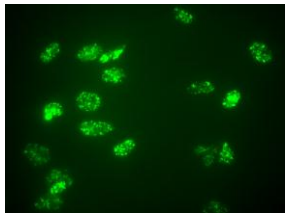
- **Quantify DNA damage in human cells along and around a 126 MeV antiproton beam at CERN.**
- **Investigate immediate and longer term DNA damage.**
- **Investigate non-targeted effects outside the beam path due to secondary particles or bystander signaling.**

DNA Damage and Repair Assays

There is more to biology than just clonogenics – especially outside the targeted area:

- Immediately after attack on DNA proteins are recruited to the site
- This event signals cell cycle arrest to allow repair
- If damage is too extensive to repair programmed cell death (apoptosis) is induced
- Cells also deficient of cell cycle check point proteins may enter mitosis (cancer cells are often deficient in repair proteins and continue dividing)

γ-H2AX: Phosphorylation of H2AX in the presence of Double Strand Breaks

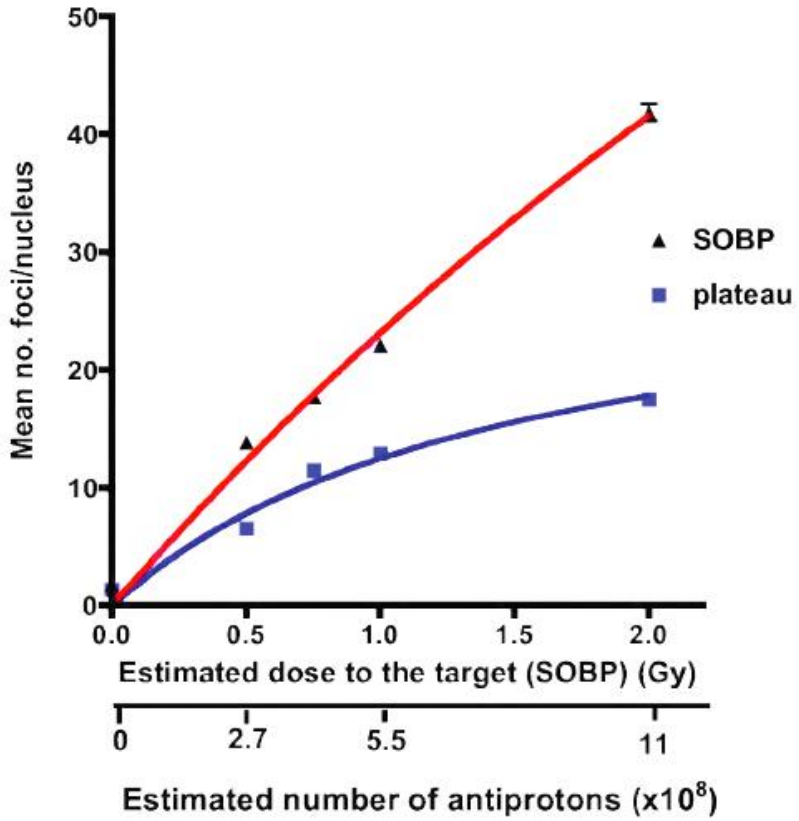


Micronuclei: Fluorescent detection of micronuclei (parts of whole chromosomes) formed due to DNA damage, which are indicating potential of tumorigenesis

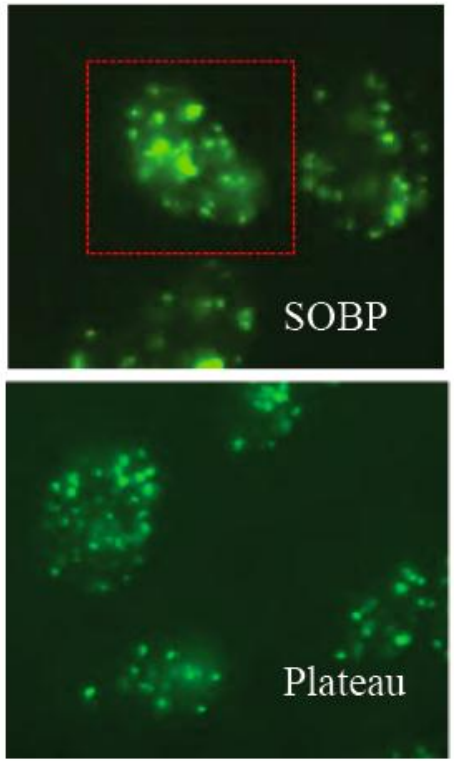
γ-H2AX and Micronucleus assays are typically used to study immediate and long term DNA damage respectively

Results γ-H2AX Assay

a)



b)



γ-H2AX foci in cells irradiated with up 1.1×10^9 antiprotons in the plateau (blue) or SOBP (red).