Biological Effects of Antiprotons

Are Antiprotons a Candidate for Cancer Therapy?

Michael H. Holzscheiter

For the ACE Collaboration

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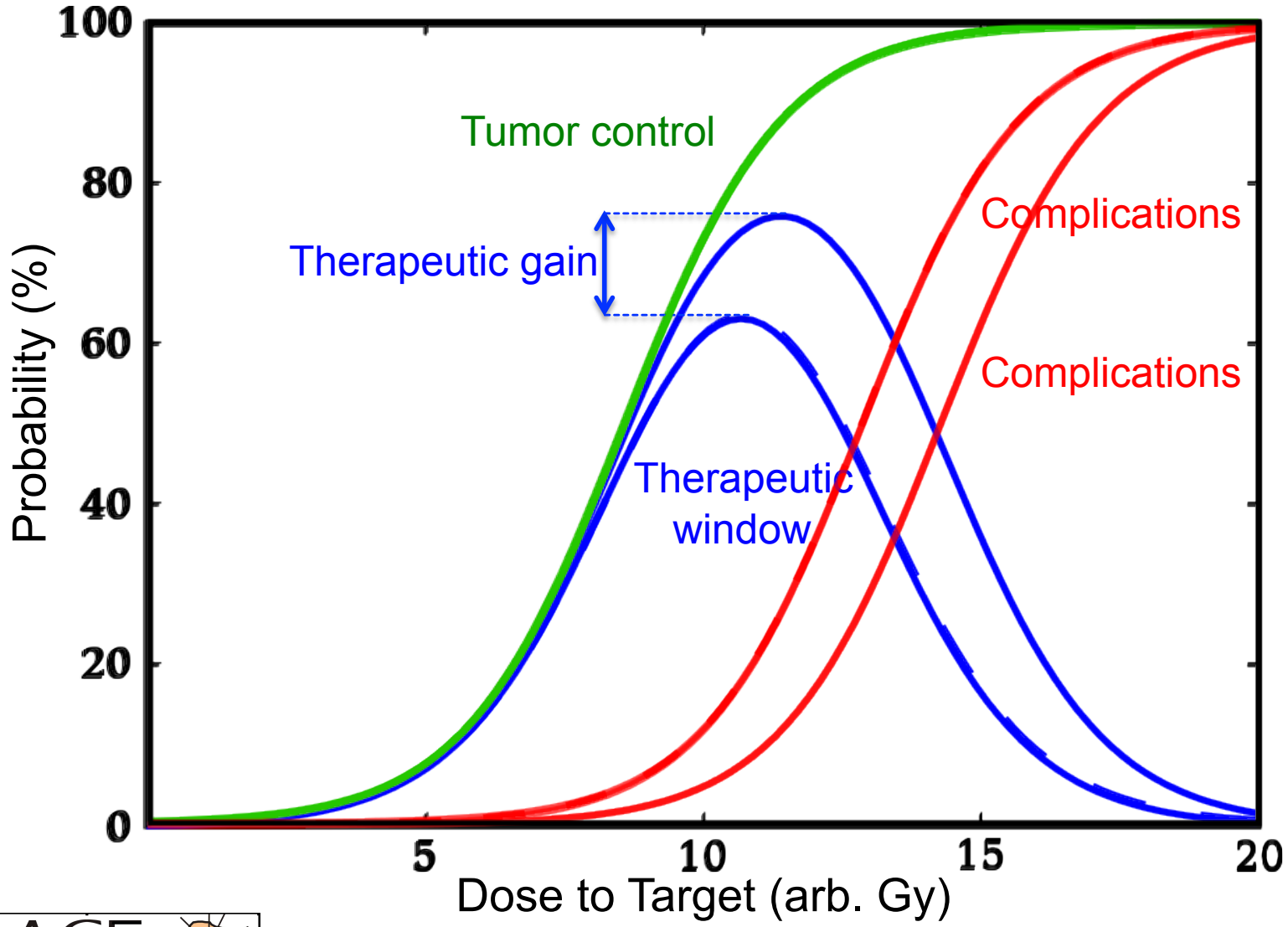
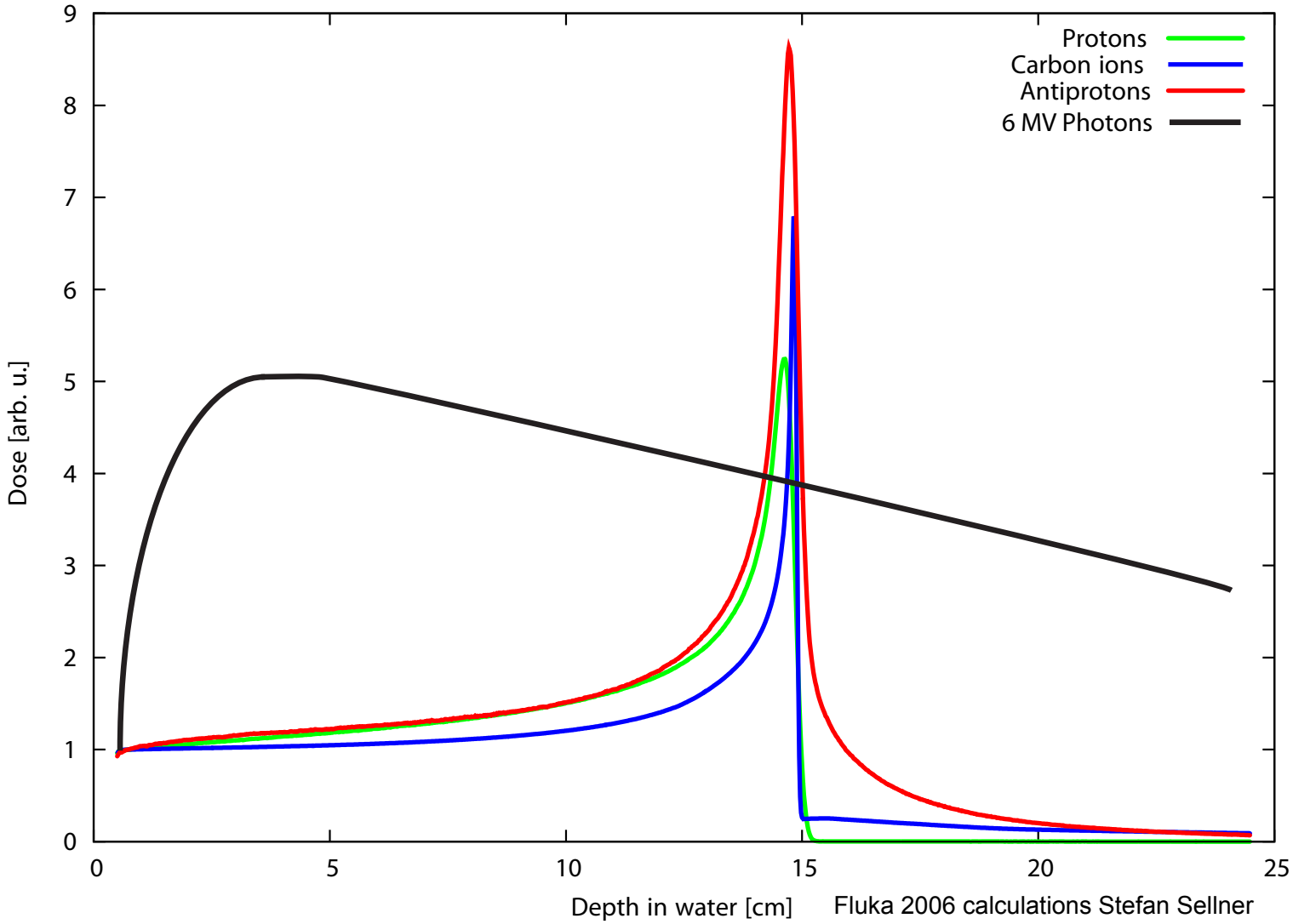
ACE

Rationale for Conformal Radiotherapy

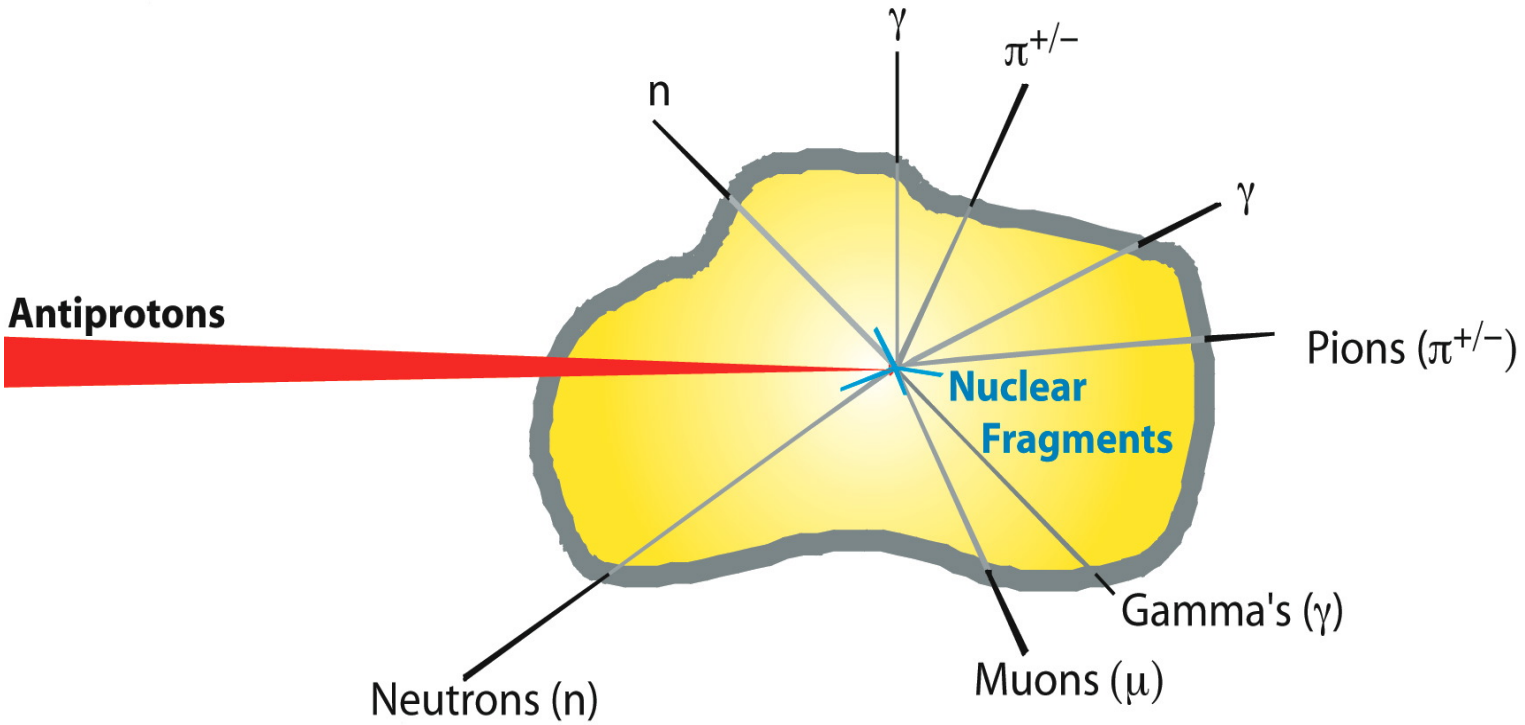
Dose and tumor control are limited due to organs at risk.



Physical Advantage of Antiprotons



Antiprotons?



The Good Fragments

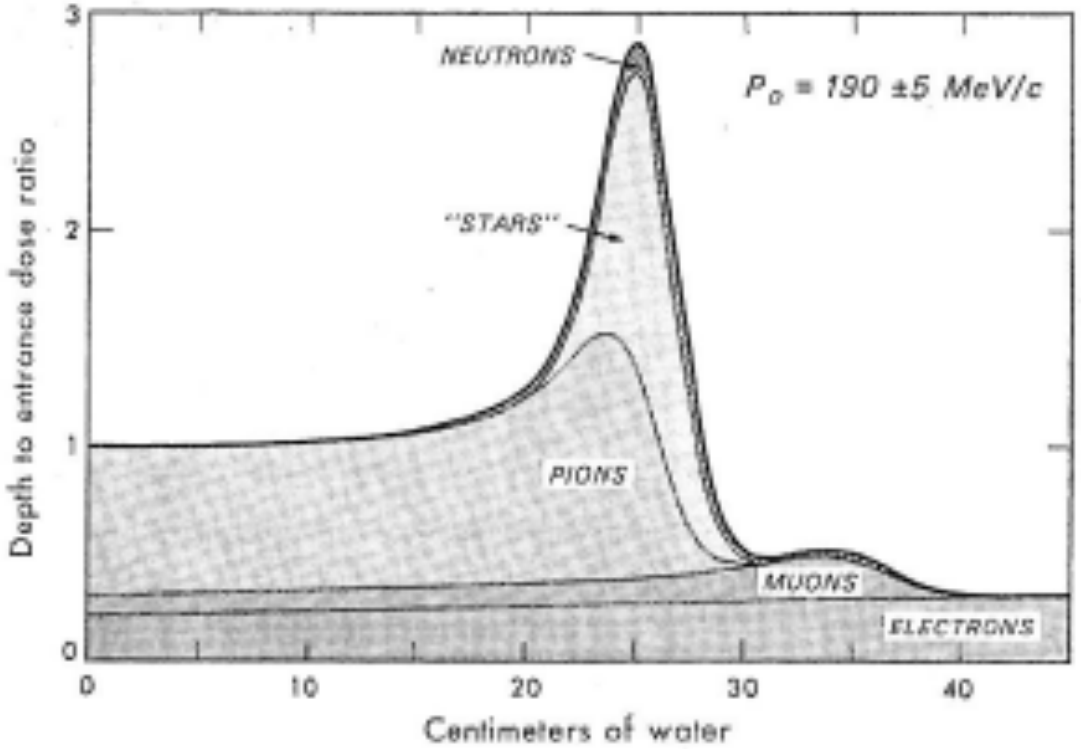
The (not so) Bad Pions

The (probably not really) Ugly Neutrons

Initial Proposal: L. Gray, T. Kalogeropoulos, Radiation Research 97 (1984) 246-252

Not exactly a new idea……..

Dose enhancement expected from pion annihilation (star formation) led to active research in several centers (PSI, Los Alamos, TRIUMF) and was used in clinical applications on more than 1000 patients ……..

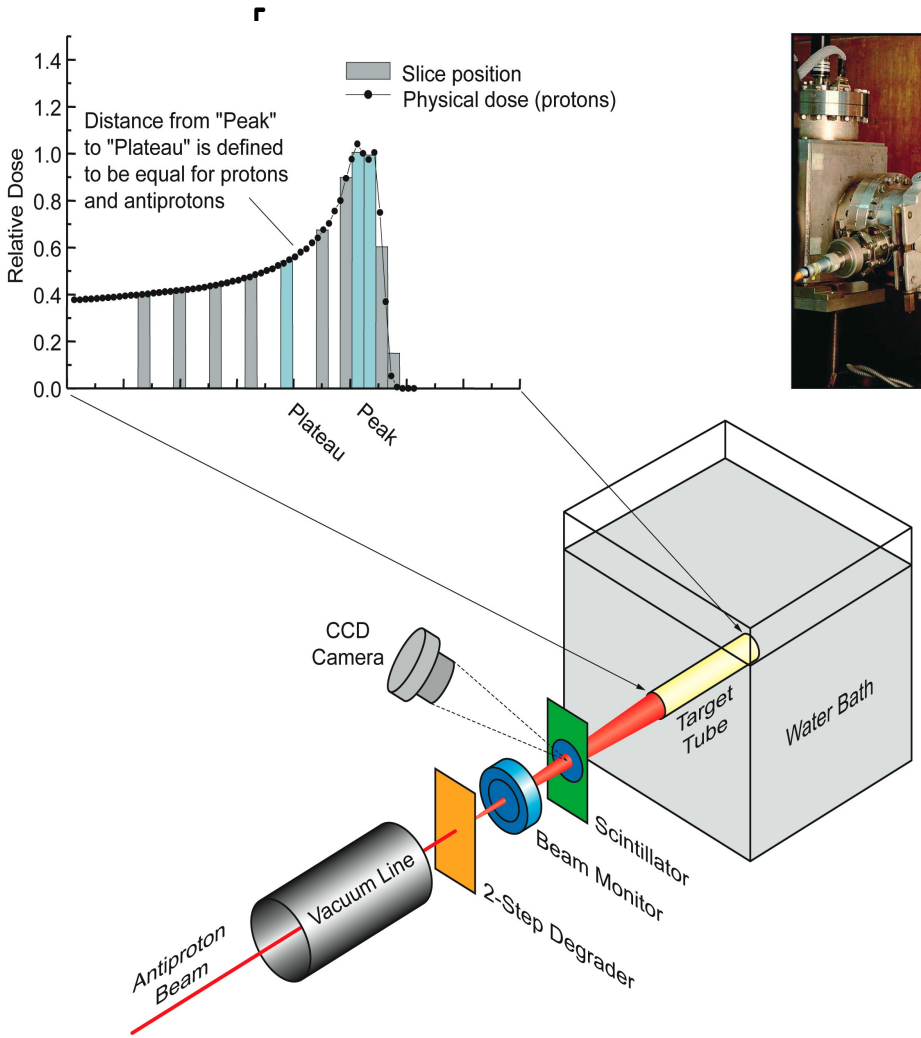


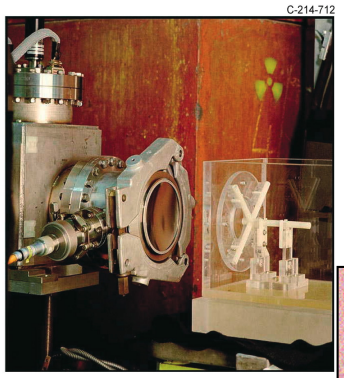
…despite poor dose confirmation to Bragg peak due to contaminations of beam from pion decay.

Antiprotons can do better!

Stanley B. Curtis and Mudundi R. Raju; Radiation Research 34, 239-255 (1968)

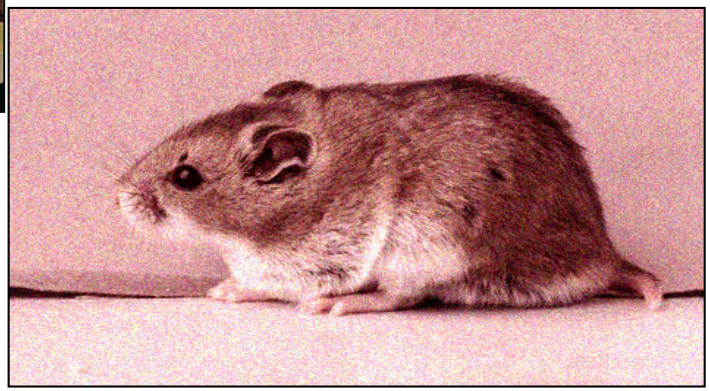
The AD-4 Experiment at CERN





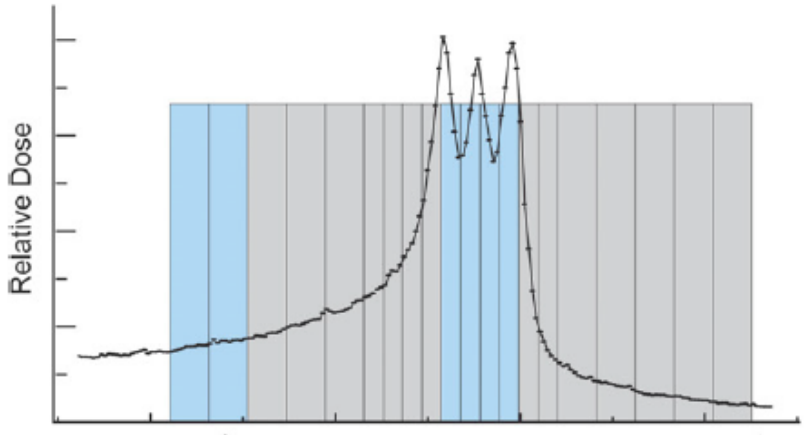
INGREDIENTS:

- **V-79 Chinese Hamster cells embedded in gelatin**
- **Antiproton beam from AD**



V79
Developed by Ford and Yerganian in 1958 from lung tissue of a young male Chinese Hamster (Cricetulus griseus)

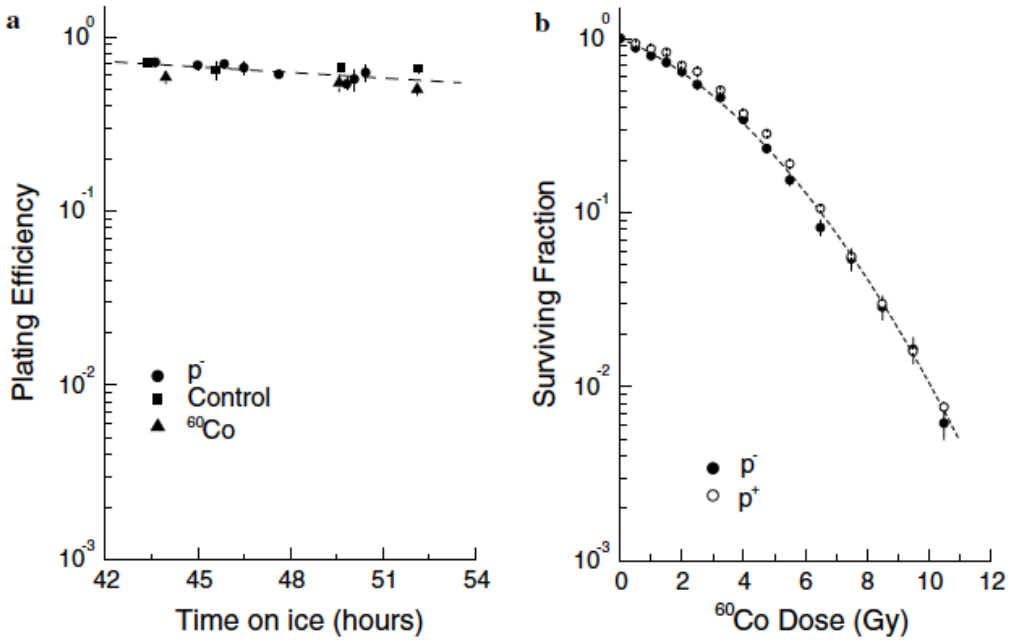
AD-4/ACE Phase I



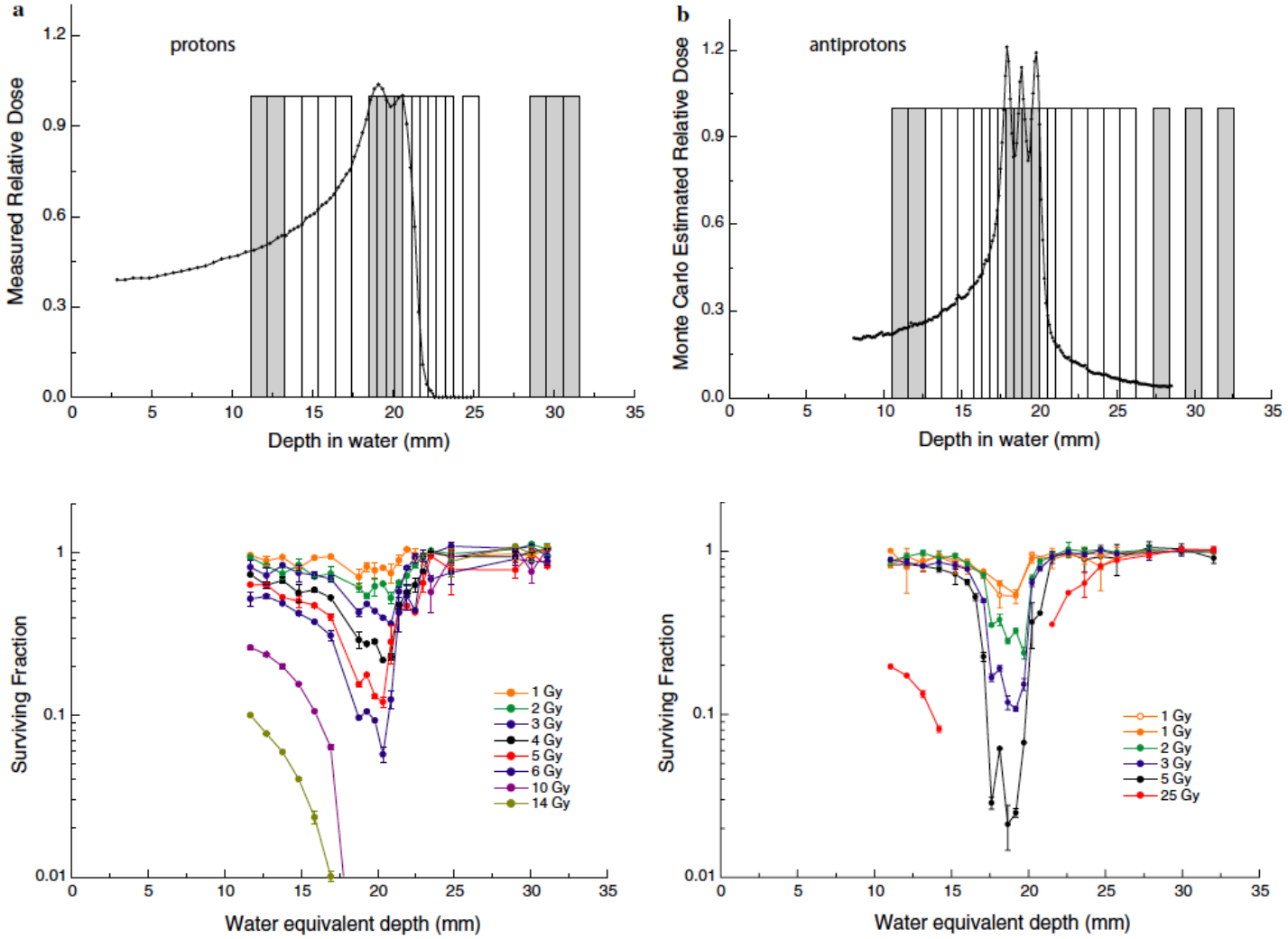
Antiprotons at **46.7 MeV** Energy
Penetration Depth in H_2O of **20 mm**
3 Thickness 2D Ridge Filter for “SOBP”

Plating Efficiency
> 60% for 50+ hours

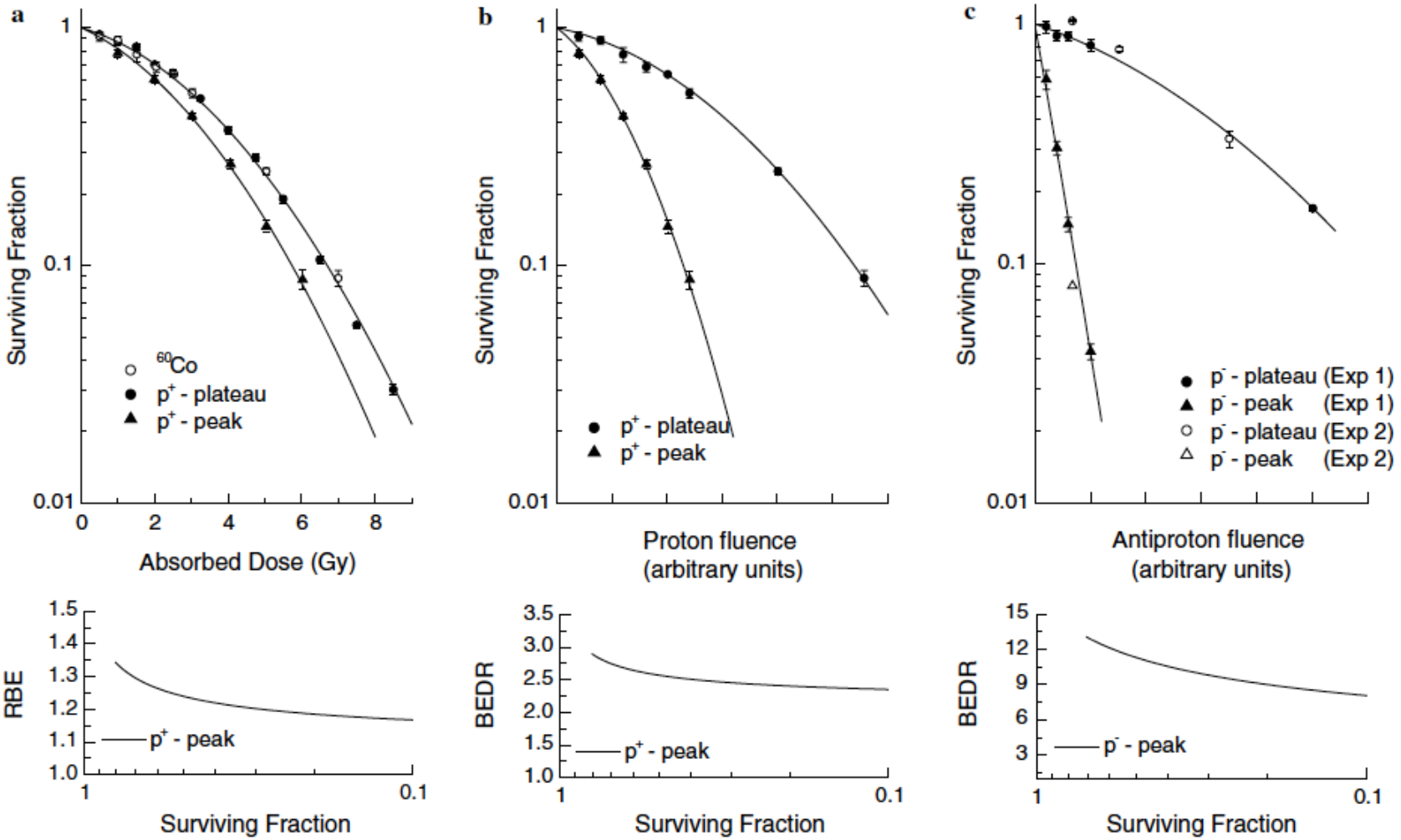
Reference Measurement with ^{60}Co for both proton and antiproton experiments at TRIUMF and CERN



AD-4/ACE Phase I Raw Data



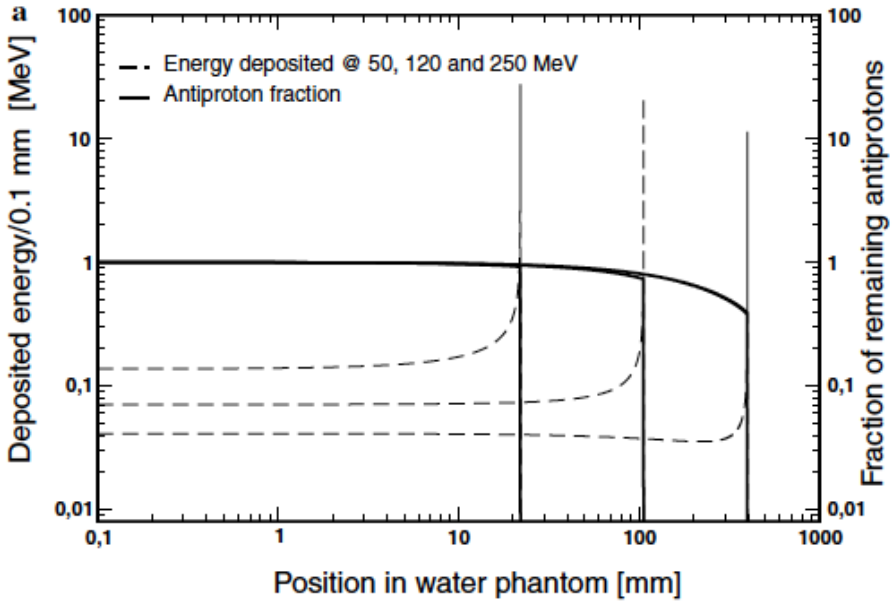
AD-4/ACE Phase I Results

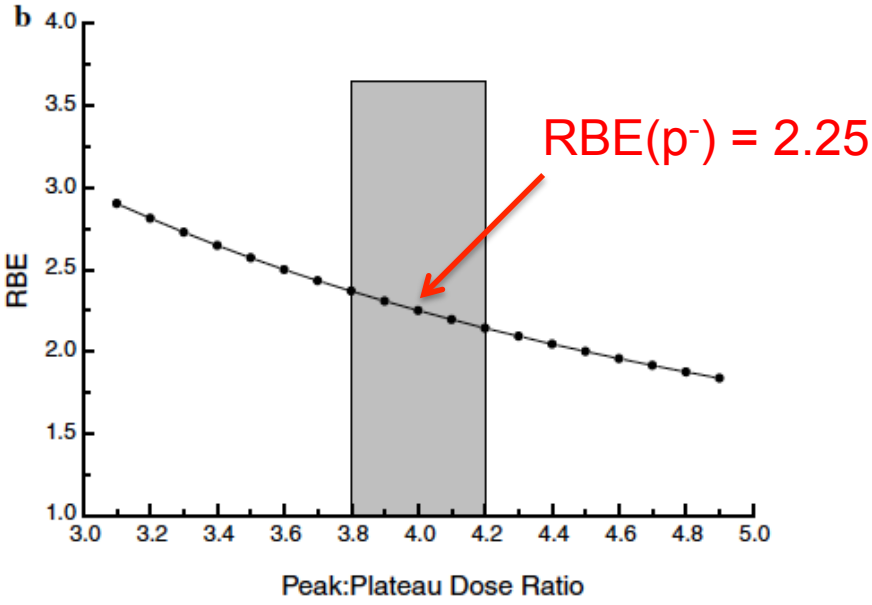


Antiproton RBE Estimate

$$\frac{BEDR(p^-)}{BEDR(p^+)} = \frac{F(p^-)}{F(p^+)} \cdot \frac{RBE(p^-)_{peak}/RBE(p^-)_{plateau}}{RBE(p^+)_{peak}/RBE(p^+)_{plateau}}.$$

$$RBE(p^-)_{peak} = \frac{BEDR(p^-)}{BEDR(p^+)} \cdot \frac{F(p^+)}{F(p^-)} \cdot \frac{RBE(p^-)_{plateau}}{RBE(p^+)_{plateau}} \cdot RBE(p^+)_{peak}.$$





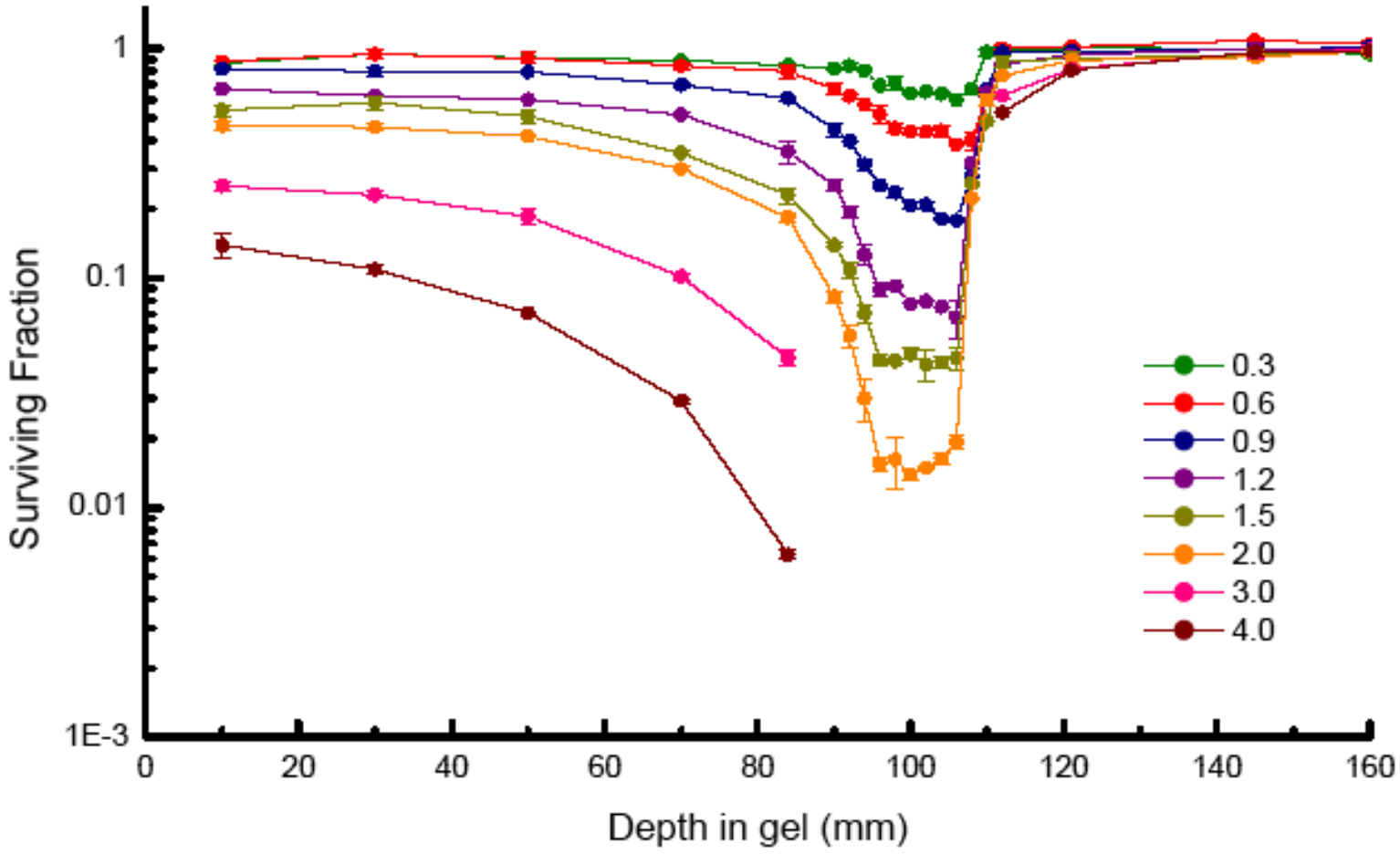
AD-4 ACE Phase II

Beam Energy increased to 126 MeV (502 MeV/c) allowing
…..clear Separation of Plateau Region and Bragg Peak
…..construction of a clinical relevant SOBP
(Spread Out Bragg Peak) of 12 mm depth

Increased Efforts in Beam Monitoring and Dosimetry
through Benchmarking Experiments with Ionization Chambers and extensive Alanine studies

- **Absolute Dose Estimation using FLUKA**
- **Determination of absolute RBE**

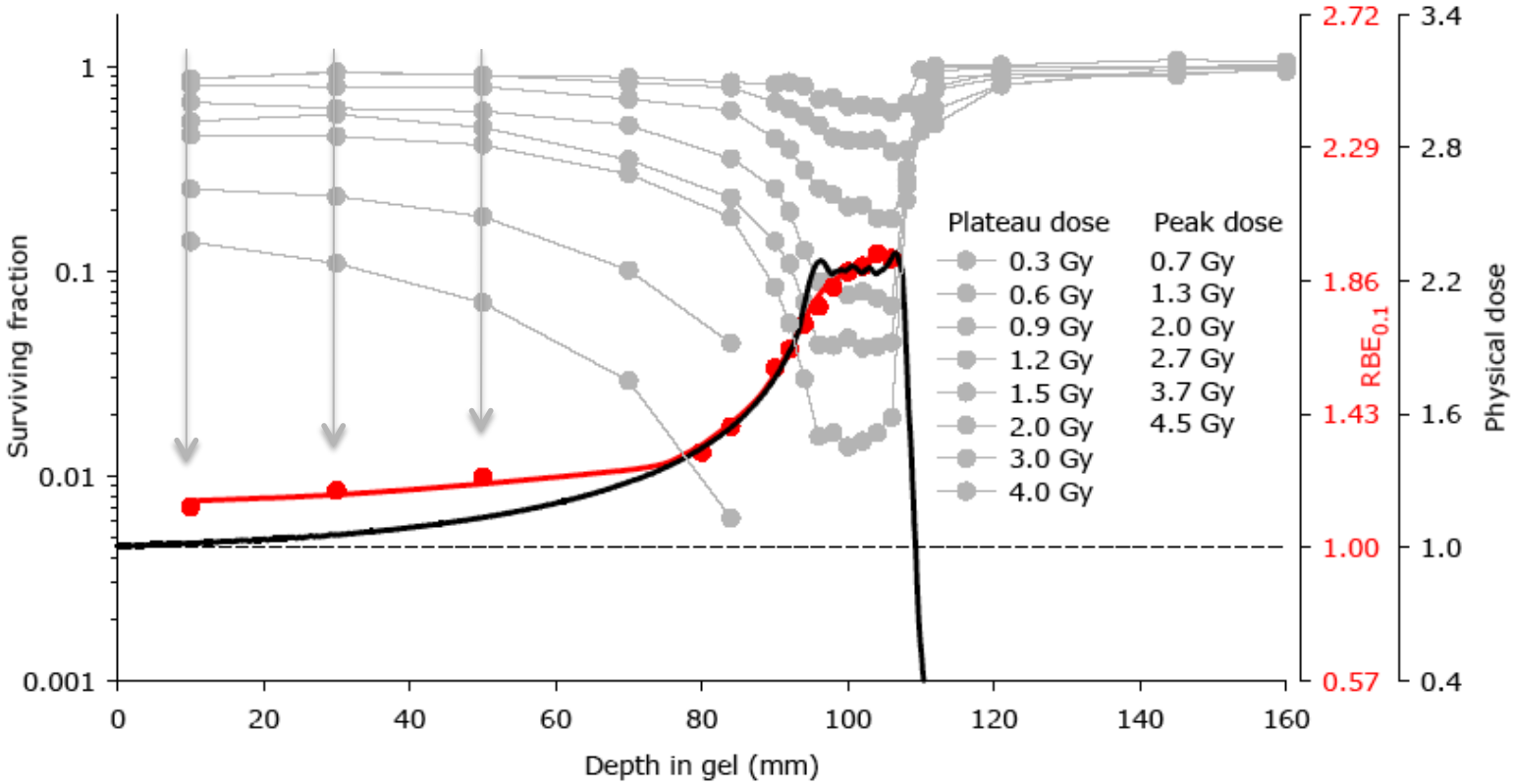
Carbon Ions – SOBP at GSI



note: clinical beams with precise dosimetry and fast dose delivery ……..

Energy to achieve same clinical relevant depth and form SOBP as at CERN….

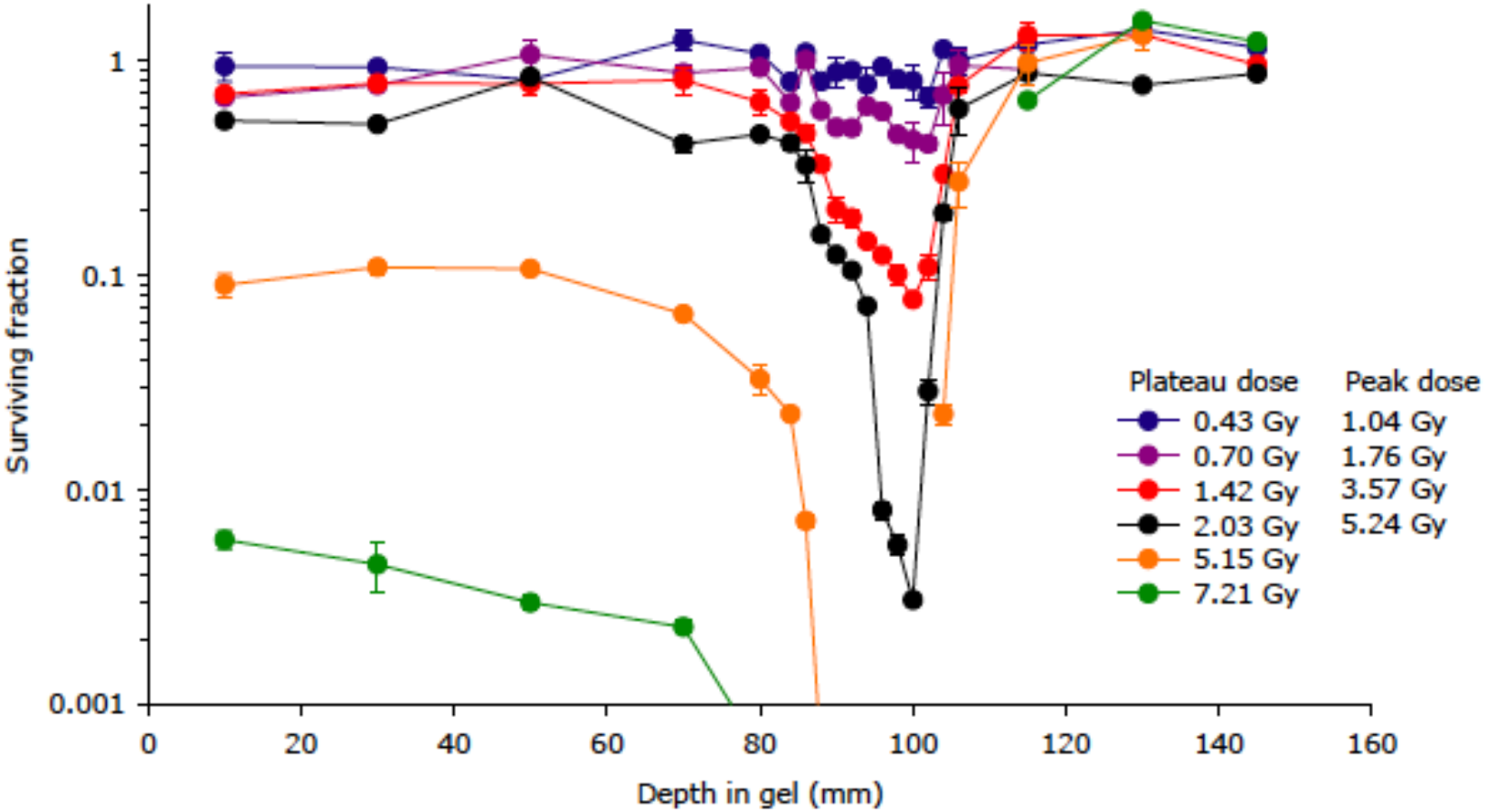
RBE for Carbon Ions



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

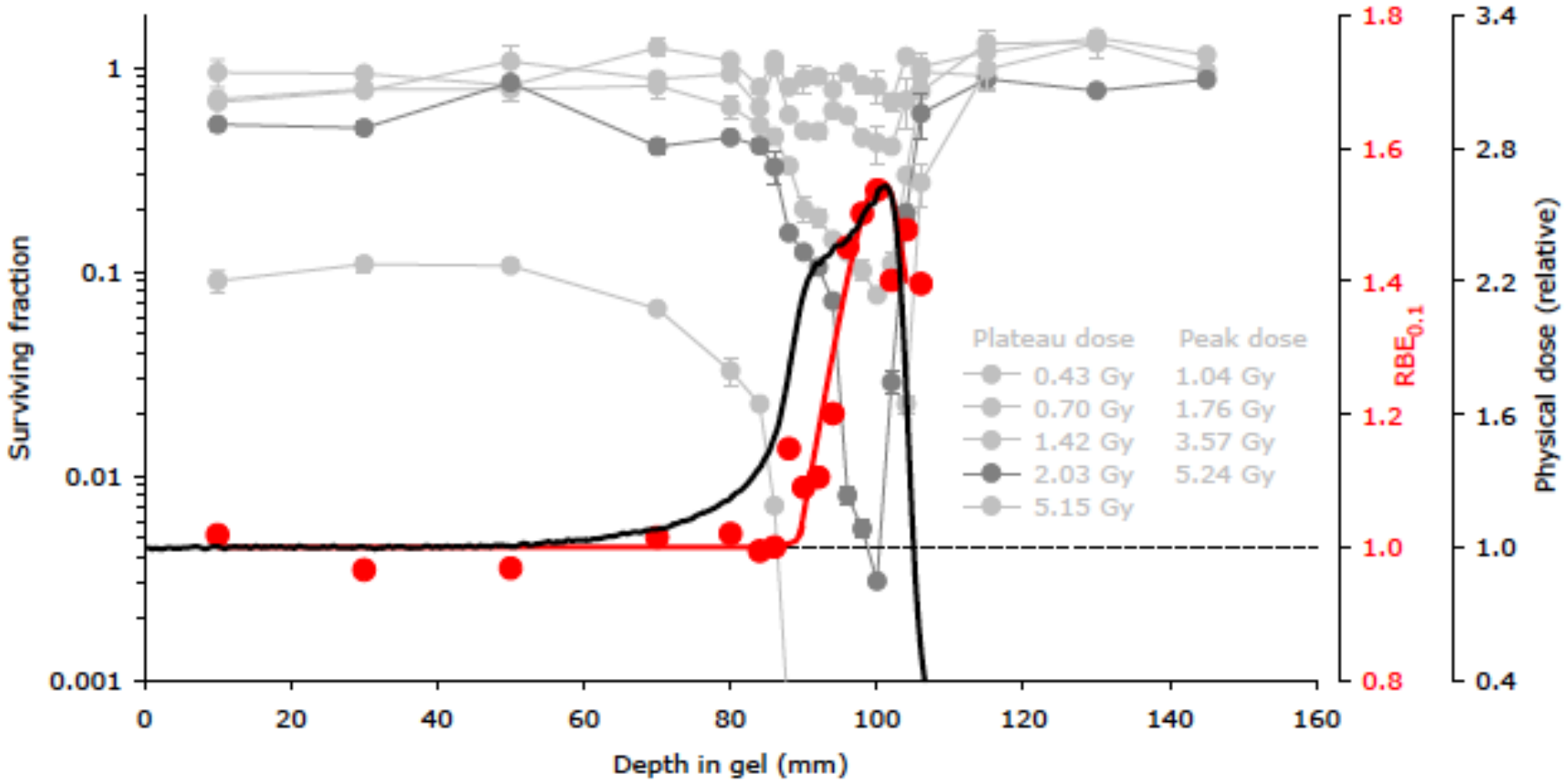
$RBE_{plateau} = 1.2$ $RBE_{peak} = 2.0$ $RBE_{distal} = 1.5$

CERN DATA 2007



Some remaining issues with SOBP build …… low statistics …..
…….uncertainties with dose calculations……

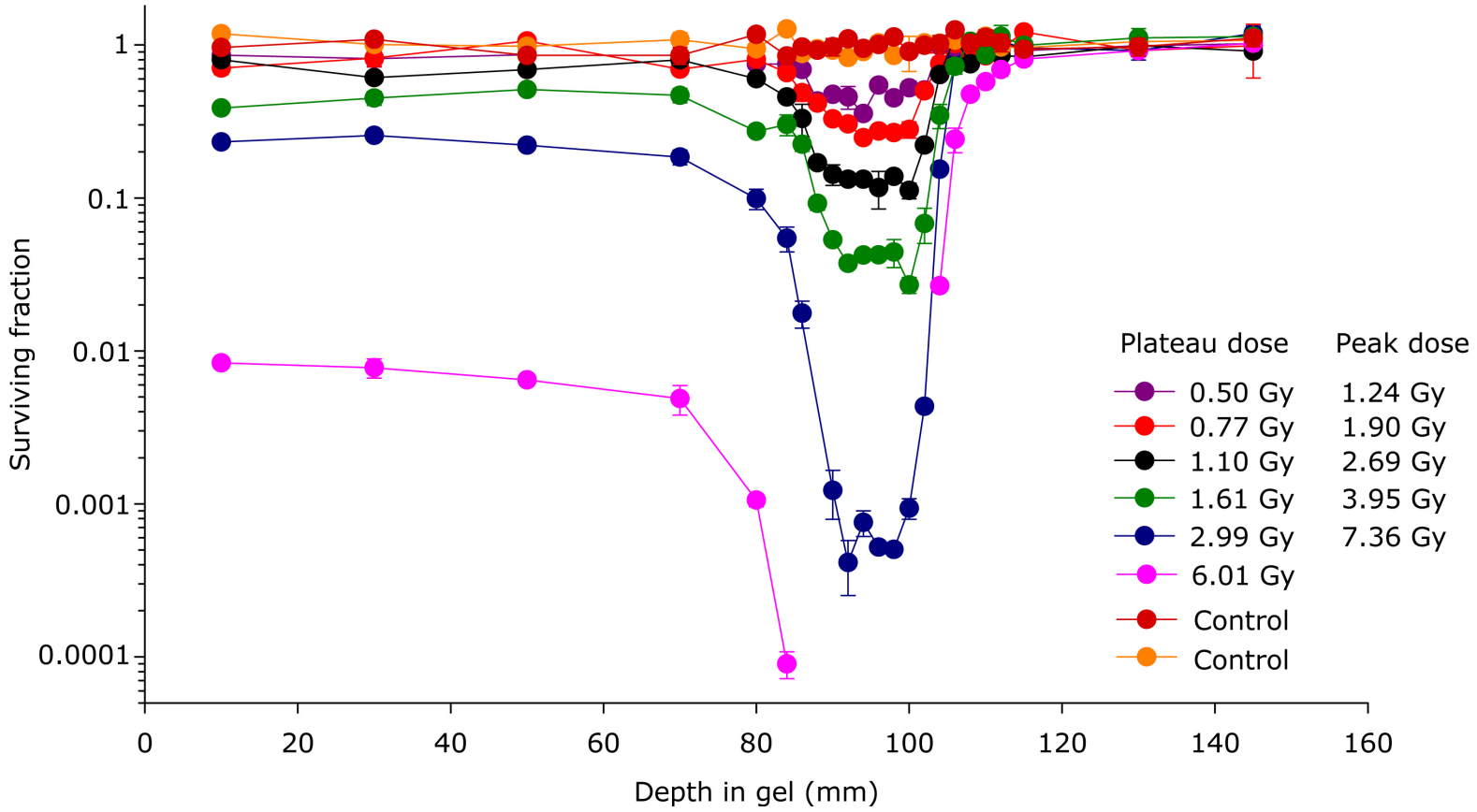
CERN DATA 2007 – RBE Analysis



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

$RBE_{plateau} = 1.0$ $RBE_{peak} = 1.57$

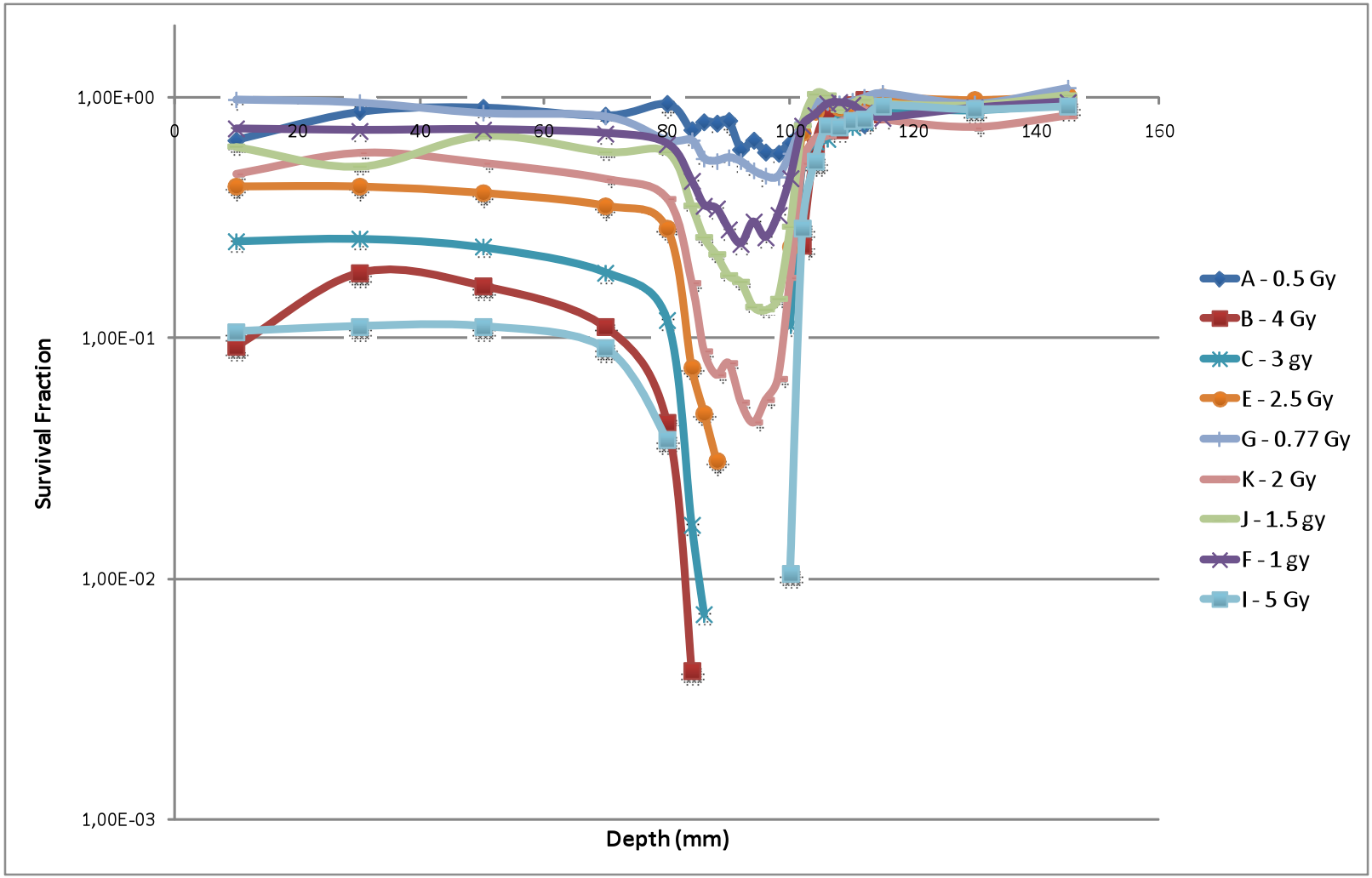
CERN DATA 2008



Dose planning for SOBP successful …….

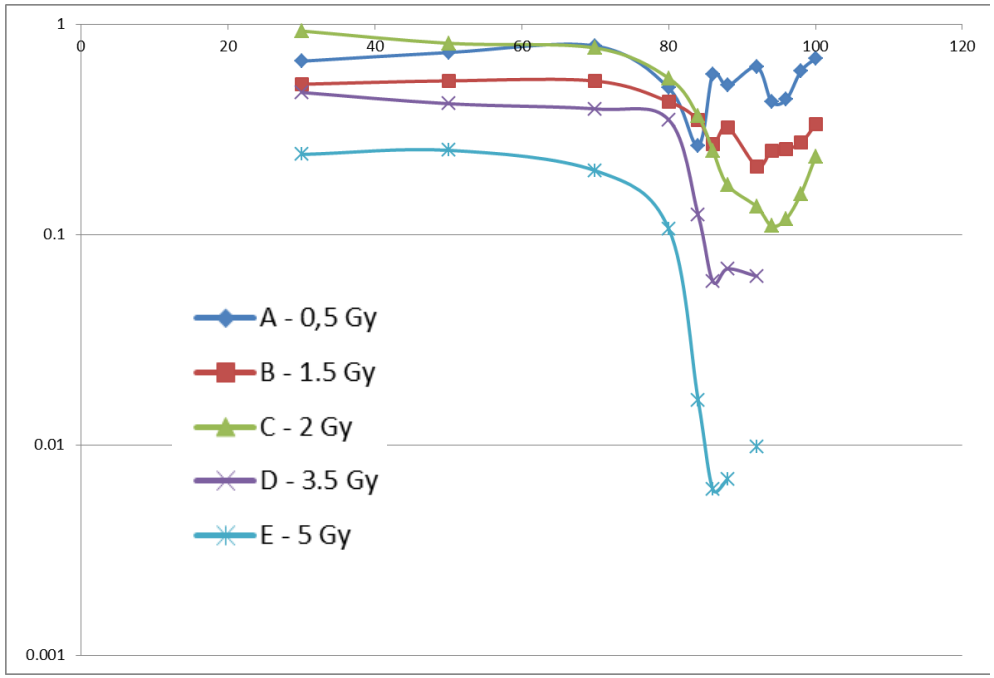
……..final doses need recalculations

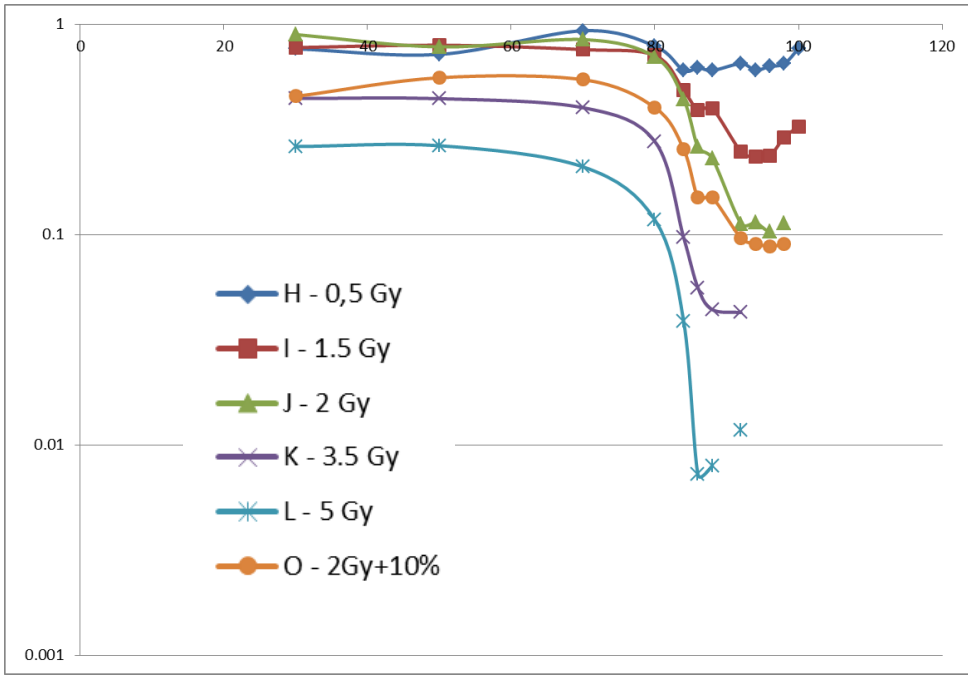
CERN DATA 2010



Complete data set ……

CERN DATA 2012

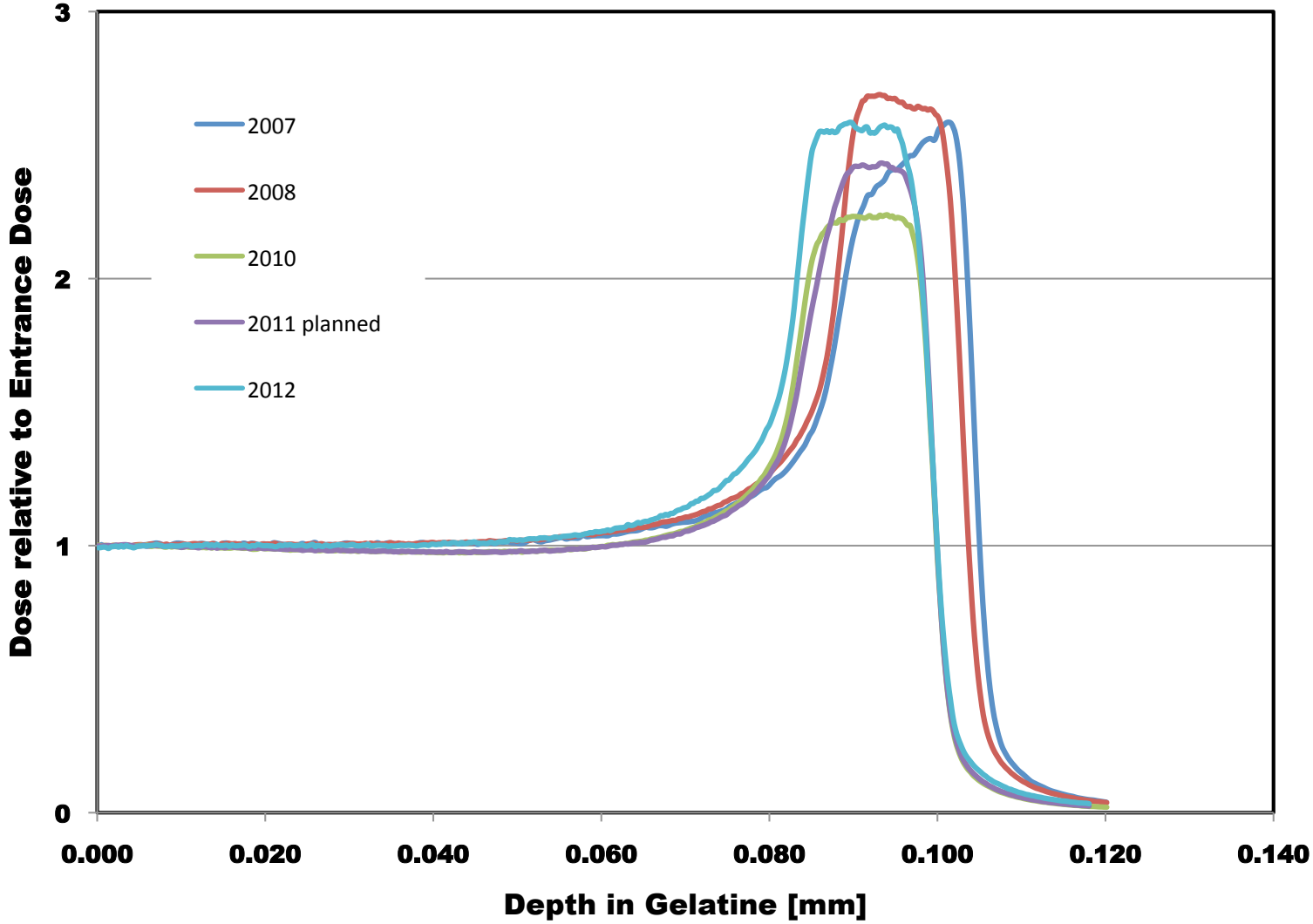




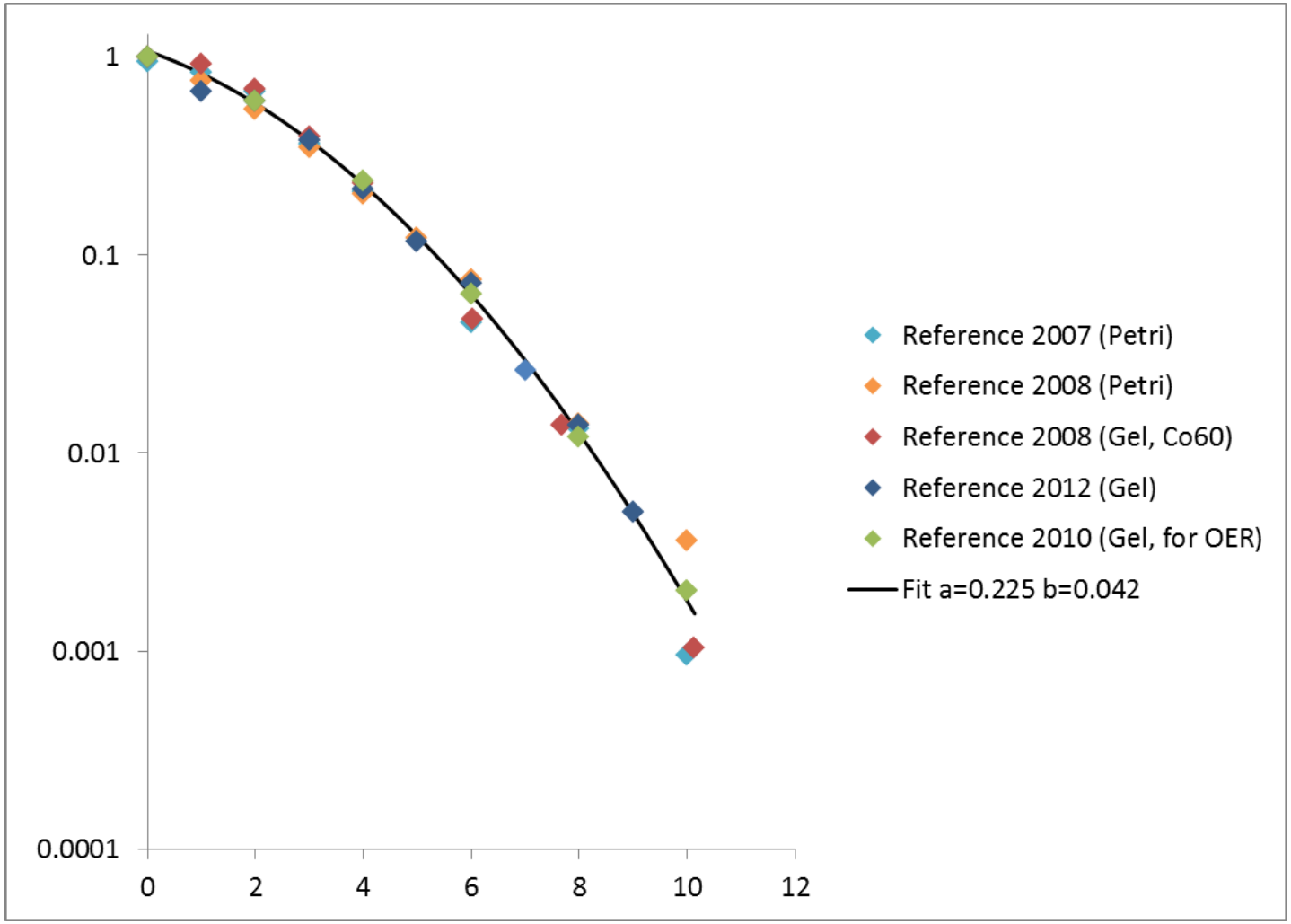
Two **independent experiments**

……under identical conditions!

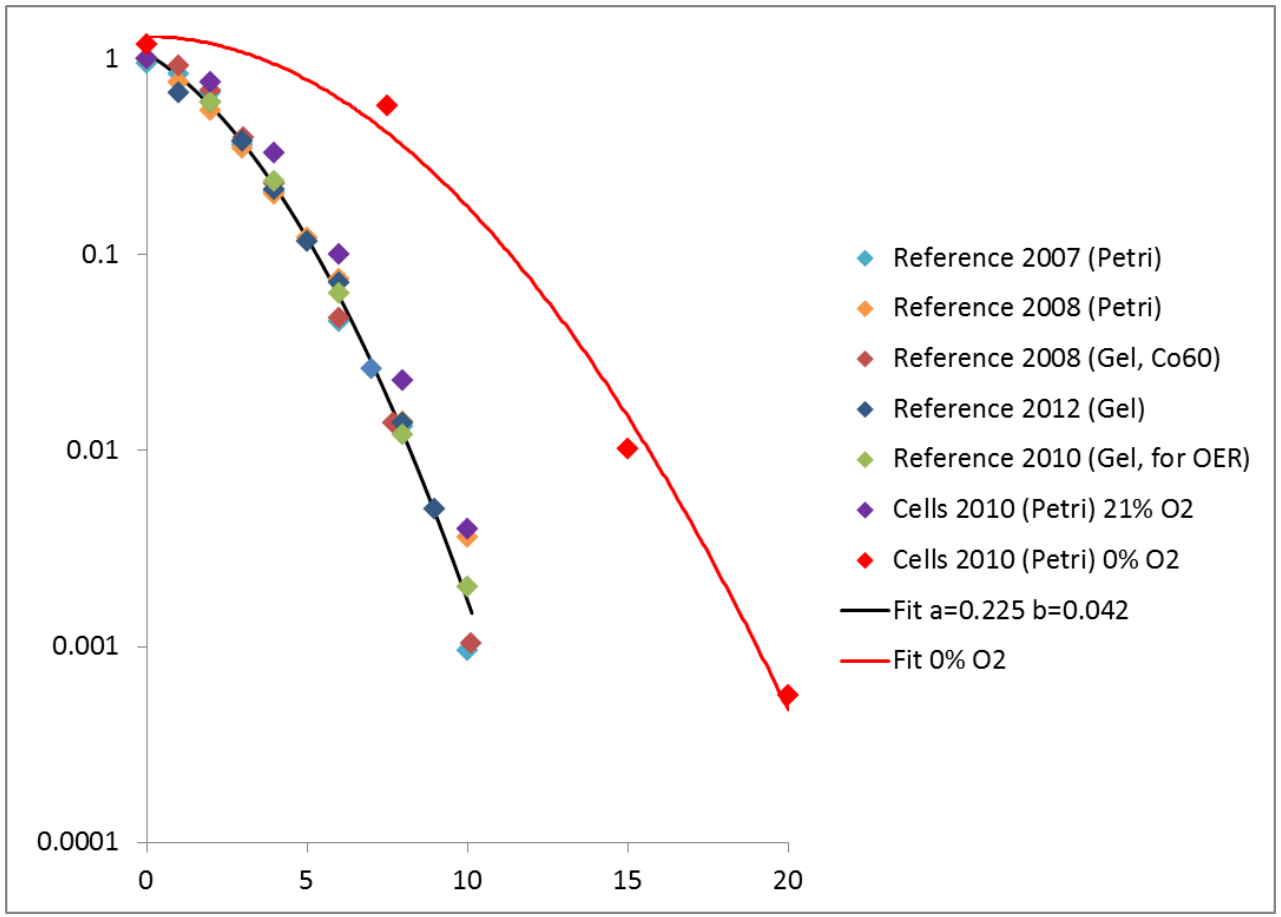
5 Years of Running –
5 Depth Dose Distributions



Biological Stability

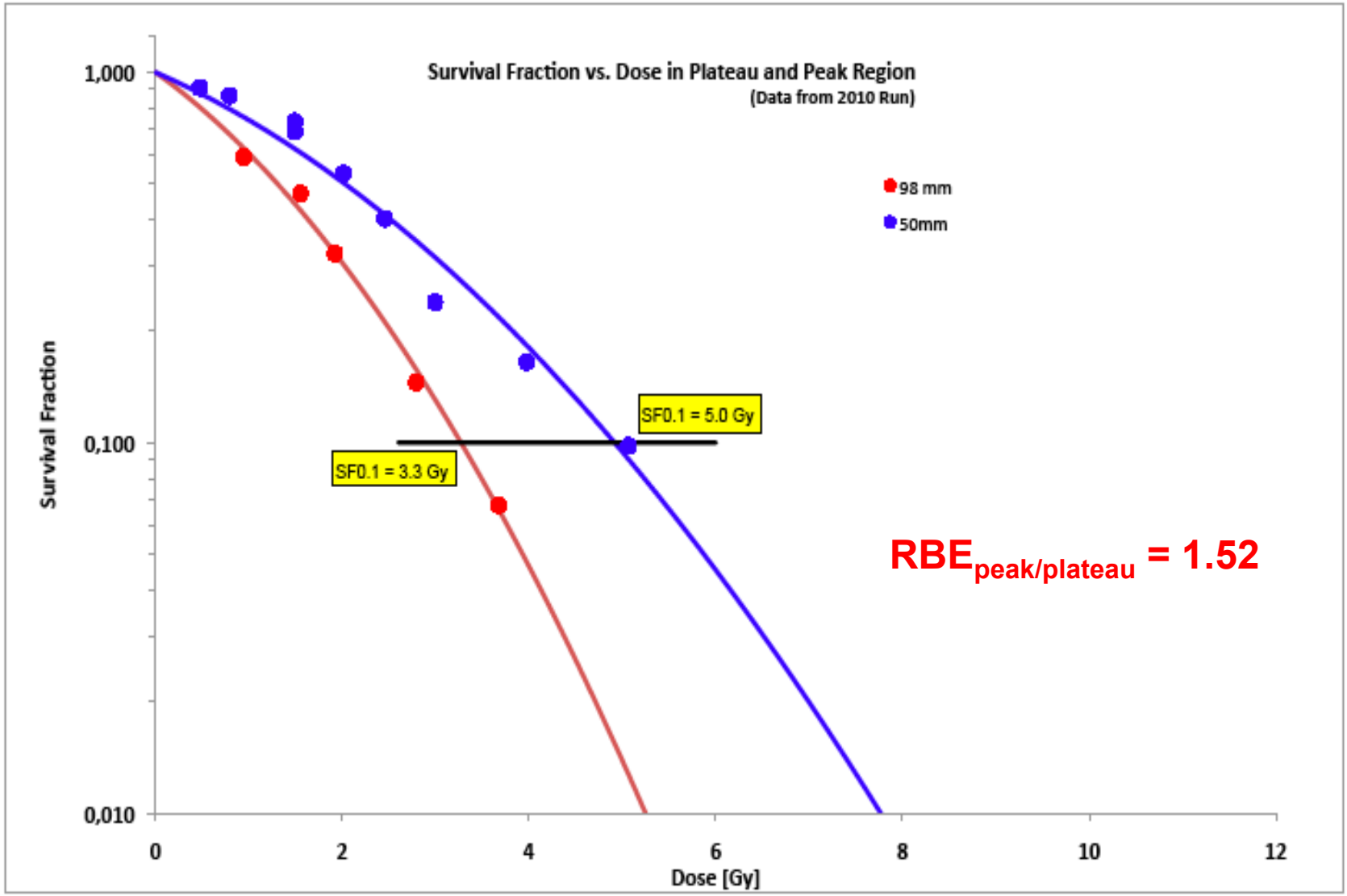


Cell Micro-Environment



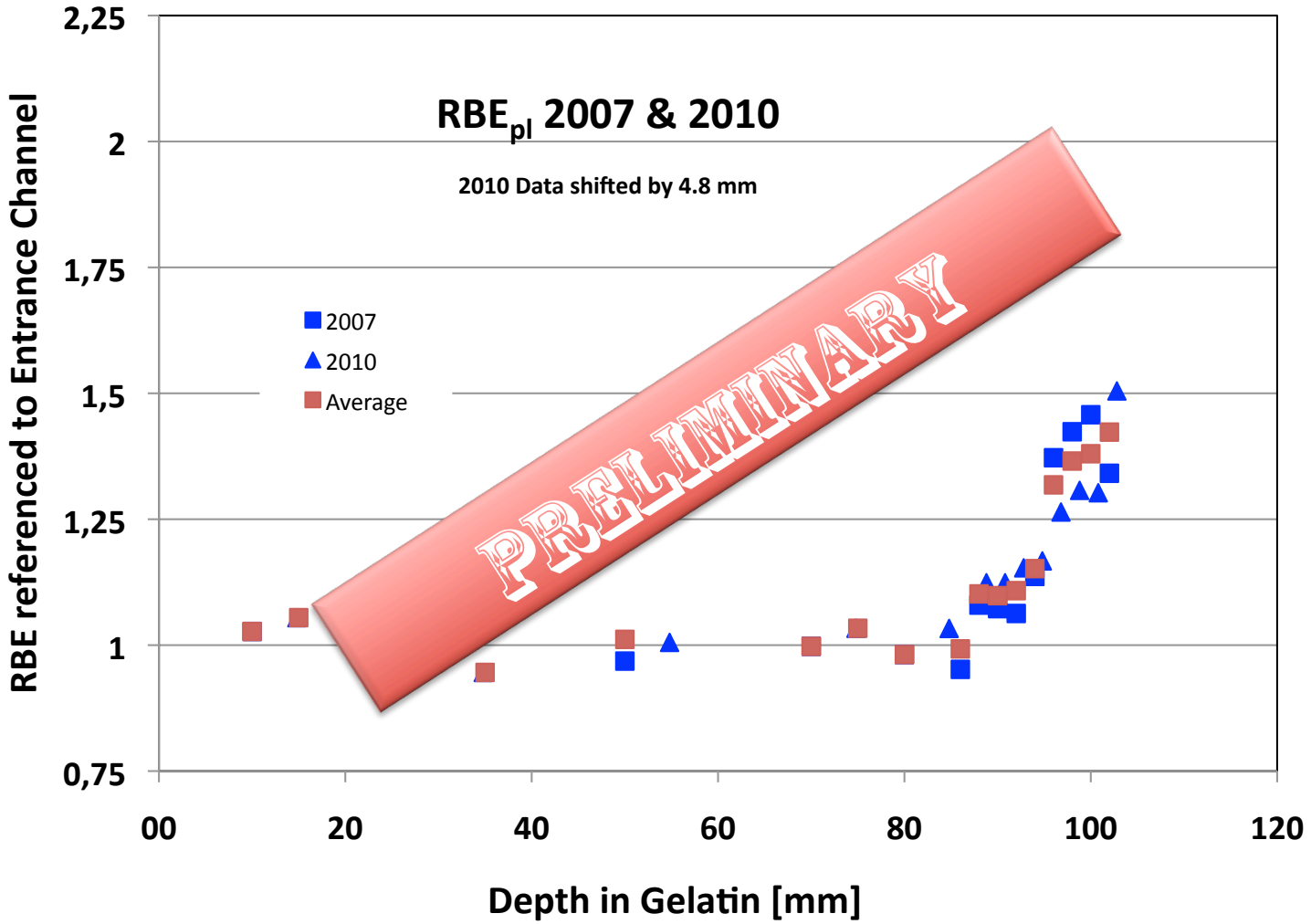
Cells are found to be fully oxygenated ✔

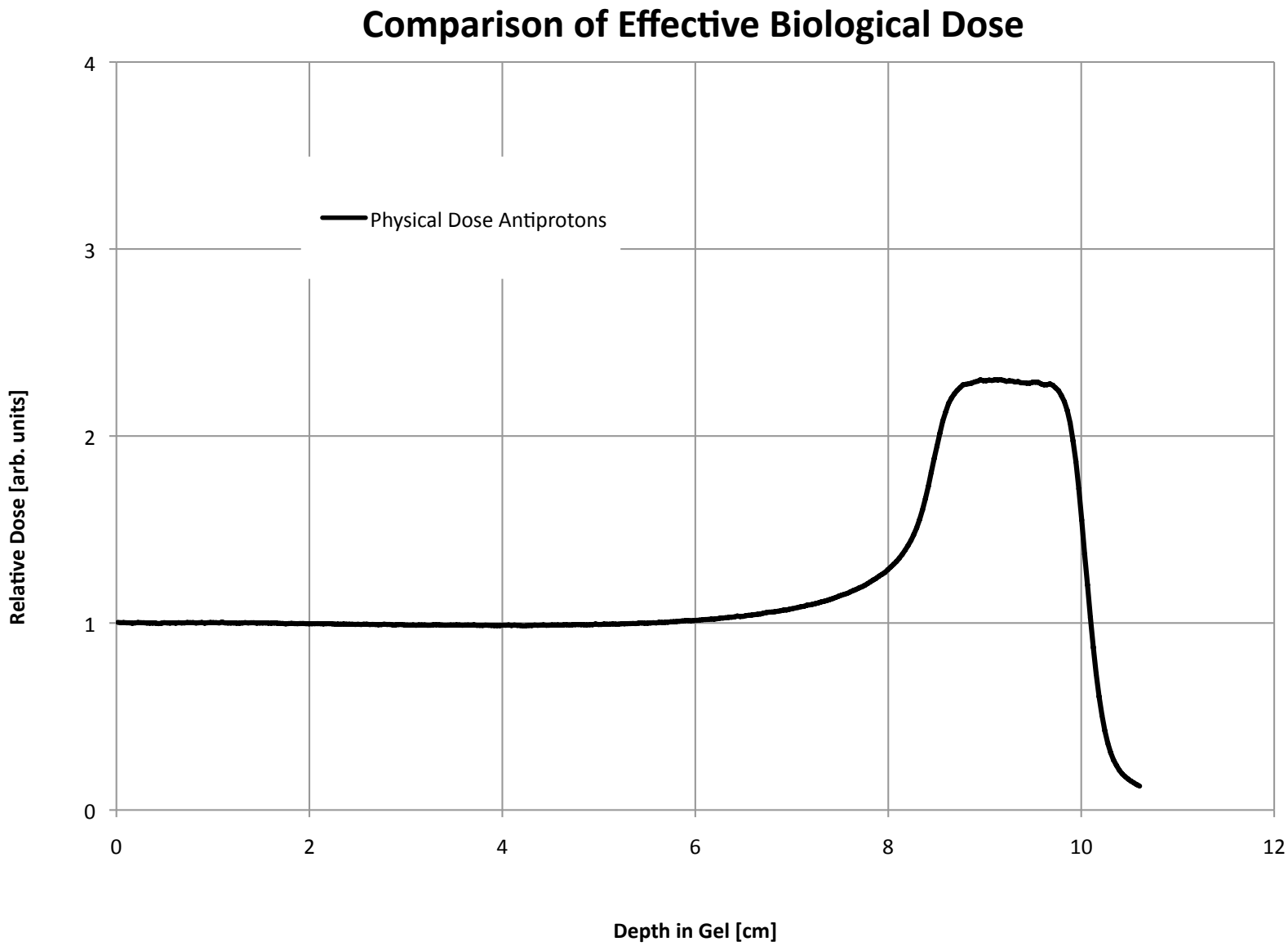
Cell Survival vs. Dose for 2010 Data

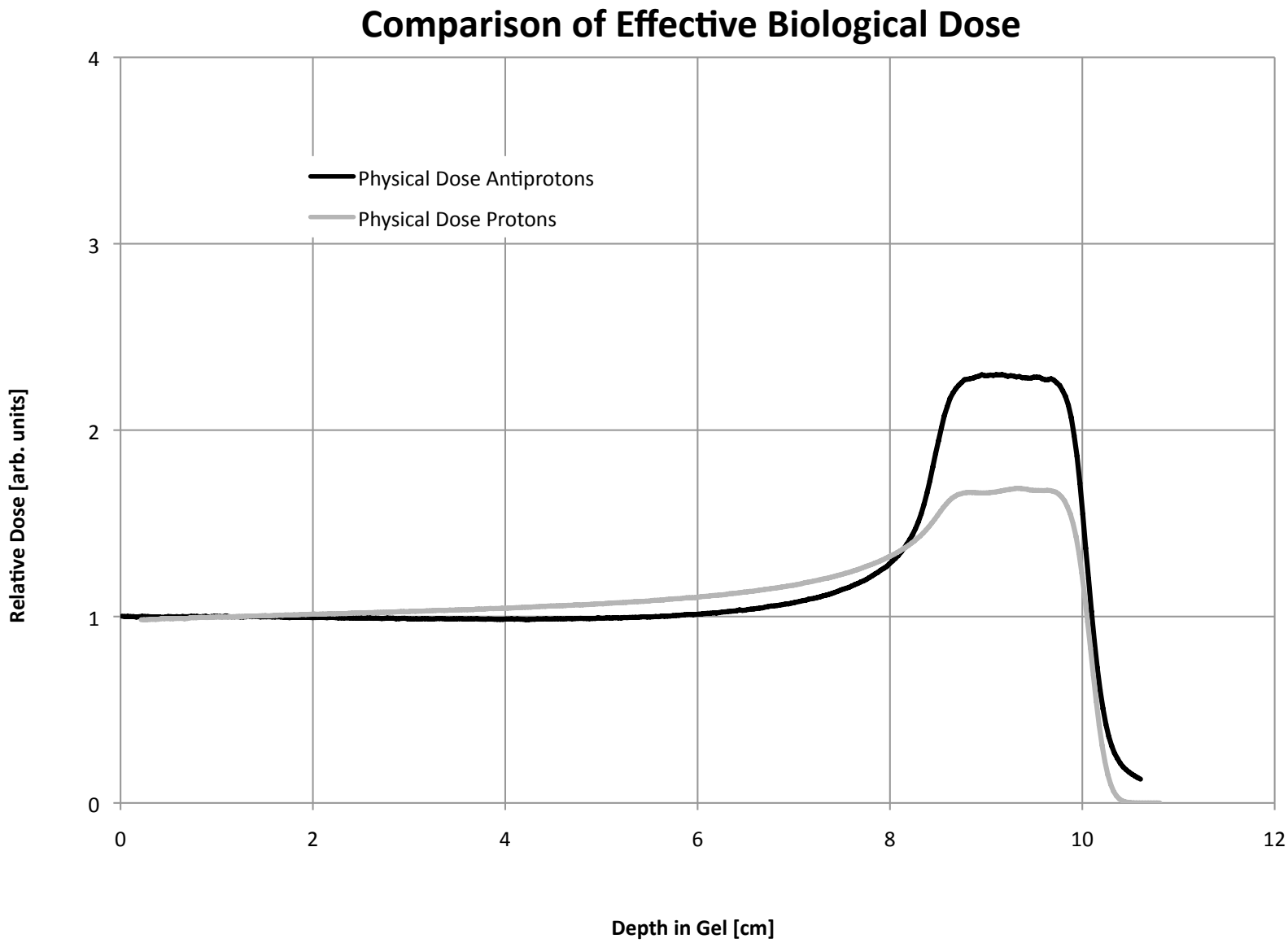


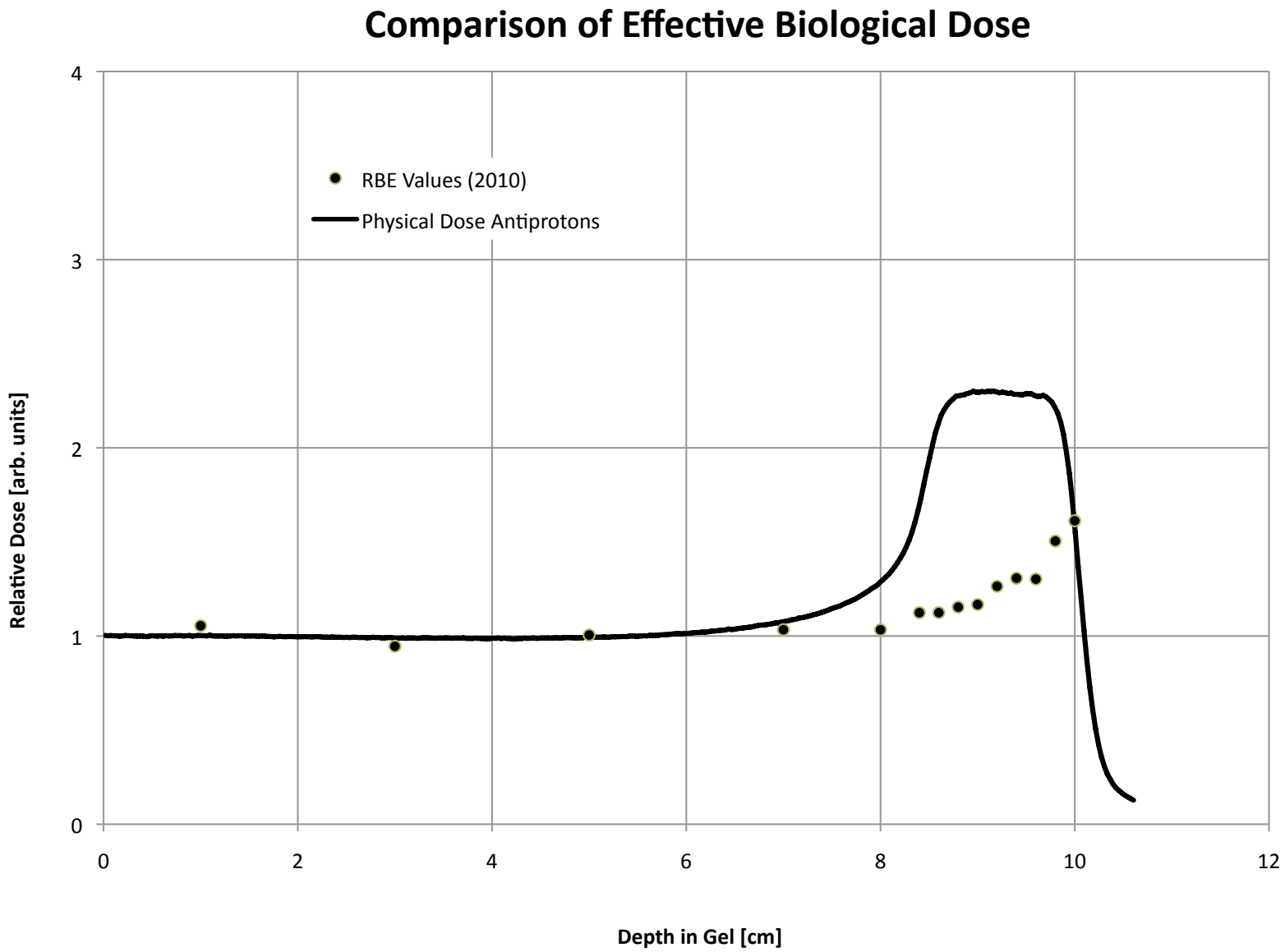
$RBE_{peak/plateau} = 1.52$

Combined $RBE_{plateau}$ for 2007 and 2010

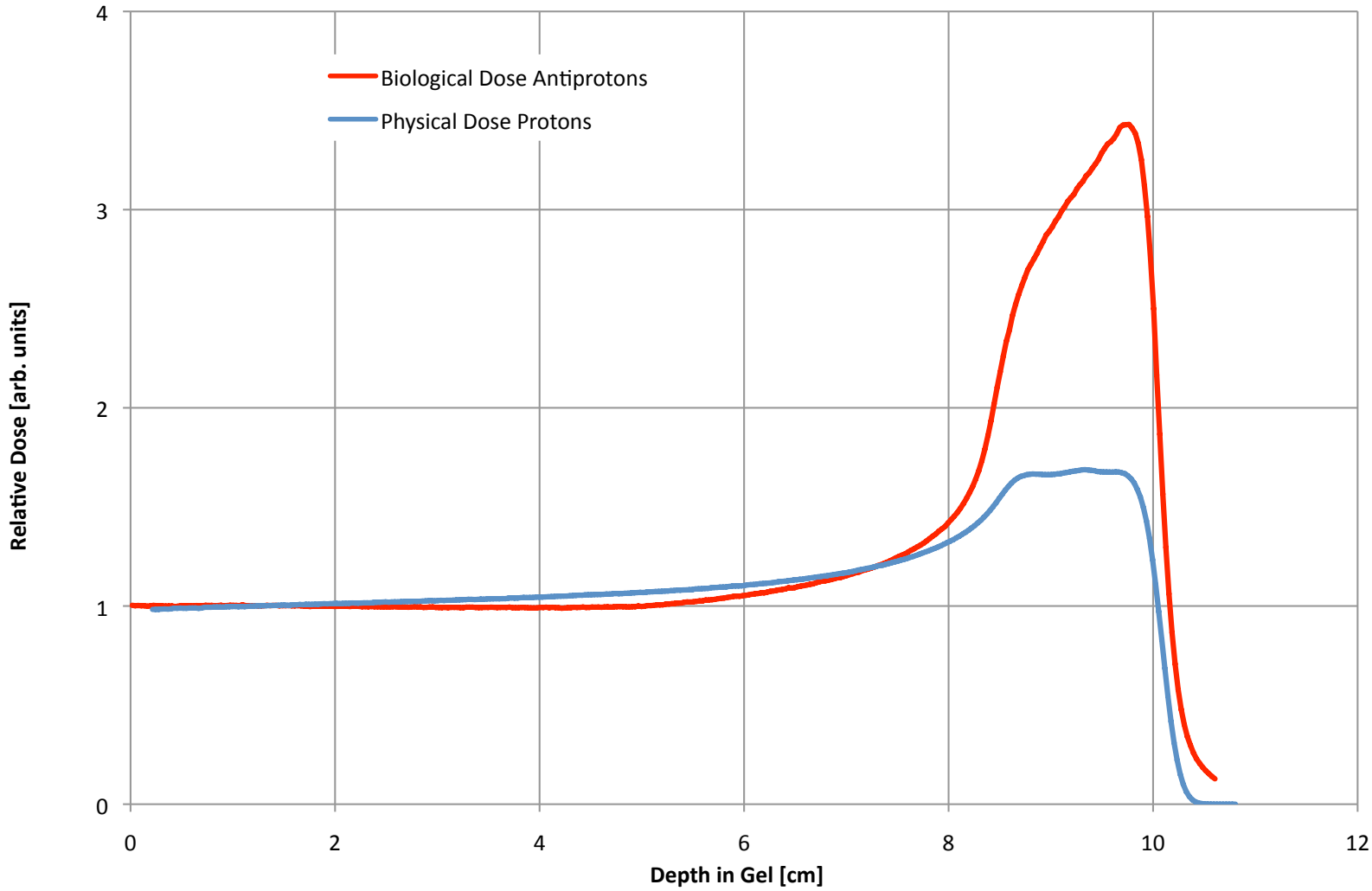



Comparison of Effective Biological Dose
Physical Dose Antiprotons
Relative Dose [arb. units]
0
1
2
3
4
0
2
4
6
8
10
12
Depth in Gel [cm]


Comparison of Effective Biological Dose
Physical Dose Antiprotons
Physical Dose Protons
Relative Dose [arb. units]
Depth in Gel [cm]
0
1
2
3
4
0
2
4
6
8
10
12


Comparison of Effective Biological Dose
RBE Values (2010)
Physical Dose Antiprotons
Relative Dose [arb. units]
Depth in Gel [cm]
0
1
2
3
4
0
2
4
6
8
10
12

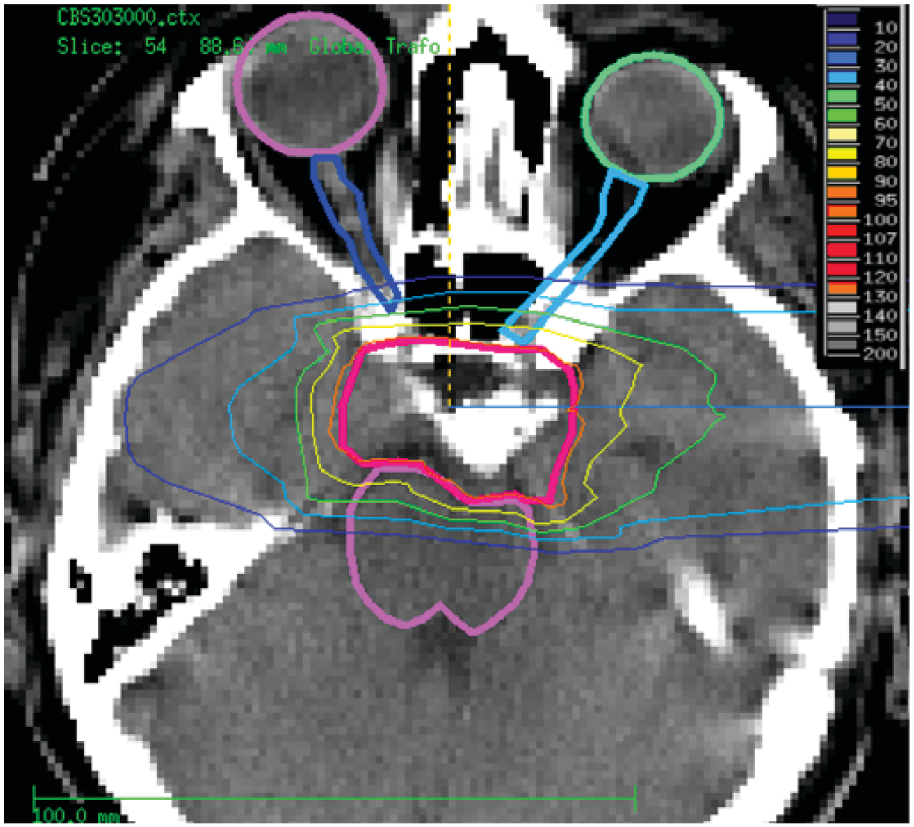
Comparison of Effective Biological Dose



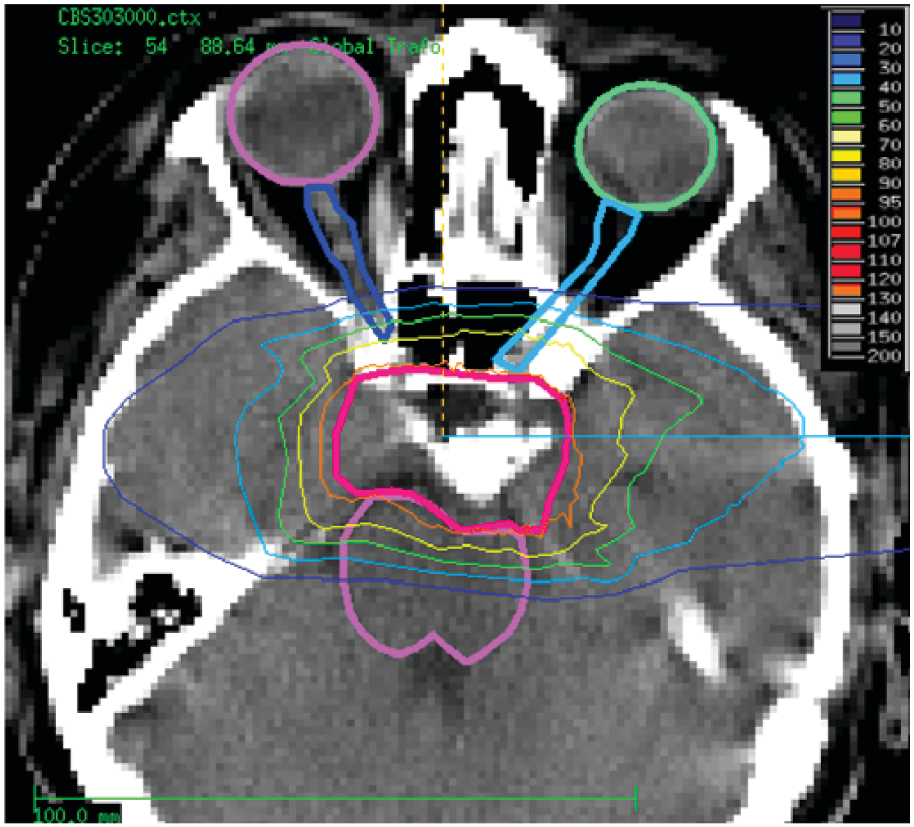
Remaining Work

- (re)do "forensic" dose calculations with latest (recommended) version of FLUKA (beta release)
- Combine data 2010 – 2012 and study inclusion of 2008 and 2009 data (changing set-up effects beam)
- Calculate RBE for antiprotons at every point along depth dose curve

Treatment Plan based on Physical Dose only.....



PROTONS



ANTIPROTONS

....shows reduction of normal tissue volume receiving low to medium dose

Antiproton annihilation causes spatially correlated DNA damage

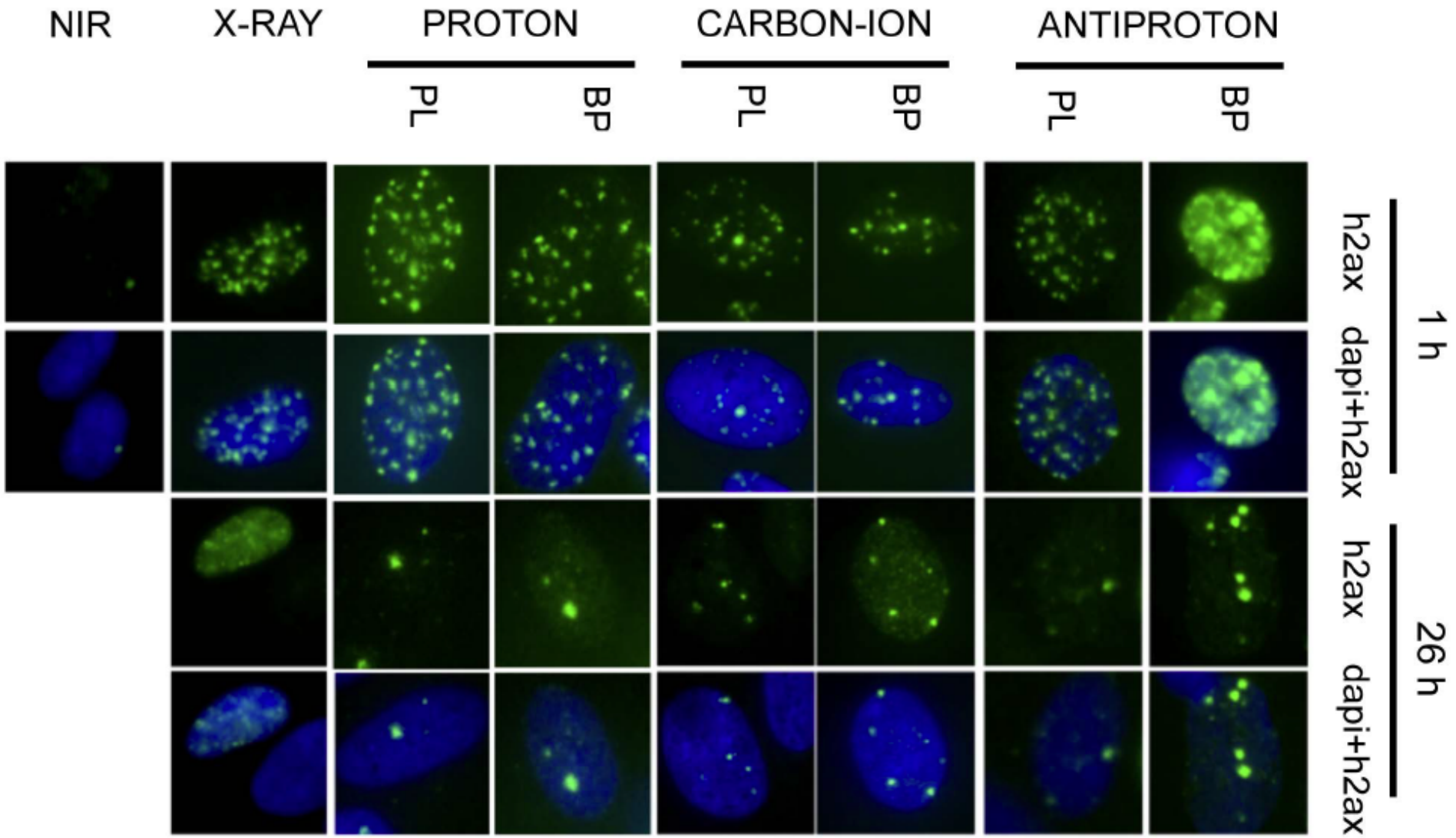


Figure 1 | Initial and residual γ-H2AX foci were observed in charged particle irradiated fibroblasts. (a) γ-H2AX foci (green) were imaged at 1 and 26 h after irradiation with antiprotons (top), carbon ions, protons or 225 kVp X-rays. (b) 'Cut-view' images taken from compiled Z-stack images through irradiated cells show stacks of foci along antiproton paths in SOBP irradiated cells that were fixed 1 h after irradiation. (c) Restoration deconvolution was applied to images of cell nuclei from antiproton-irradiated fibroblasts. Antiproton SOBP irradiated nuclei (top) contained large clustered foci that were smaller and less frequent in antiproton plateau irradiated fibroblasts (bottom).

SCIENTIFIC REPORTS

OPEN

Antiproton induced DNA damage: proton like in flight, carbon-ion like near rest

SUBJECT AREAS:
RADIOTHERAPY
CELL BIOLOGY
PHYSICS
DNA

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Biological validation of new radiotherapy modalities is essential to understand their therapeutic potential.

Thank You

CERN
the AD-Team
the AD-Users

And You for your attention