CCRCB
Centre for
Cancer Research
& Cell Biology

Queen's University
Belfast

Investigating the impact of a variable RBE on proton dose fractionation across an actively scanned spread-out Bragg peak

Kevin M. Prise
Centre for Cancer Research & Cell Biology, Queen's University Belfast, UK



Outline of presentation

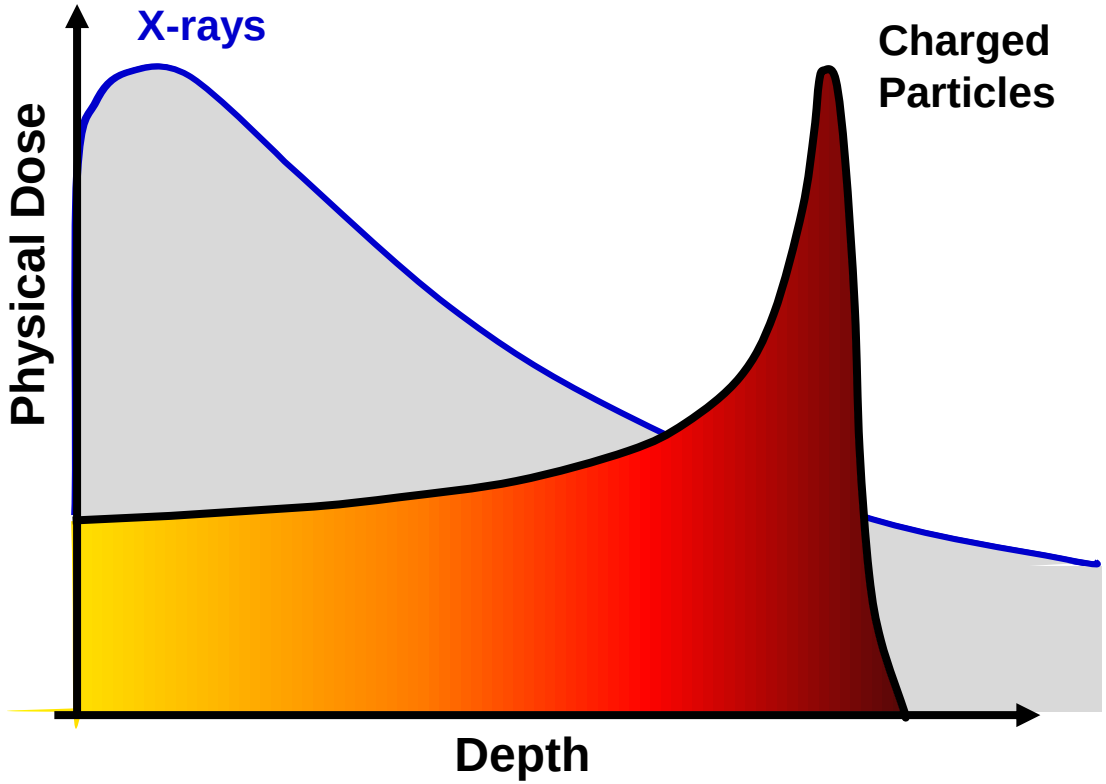
- Introduction to radiation quality, dose and RBE for charged particles
- Studies comparing pristine and SOBP proton beams to set the baseline
- Understanding clinically relevant treatment protocols at the cellular level - fractionation

Background

Charged particles are being increasingly used in cancer treatment

- Inverse energy deposition
- Elevated RBE for cell killing

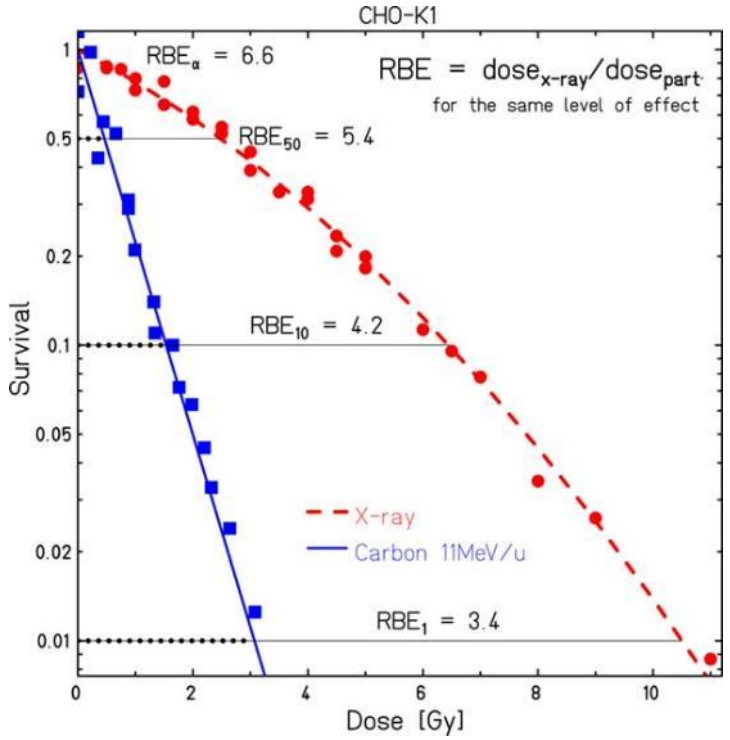
→ Selective dose localization
Improved tumour control



- The Bragg curve represents only the physical dose
  - Primary and secondary particles effects
  - Biological effects

CCRCB

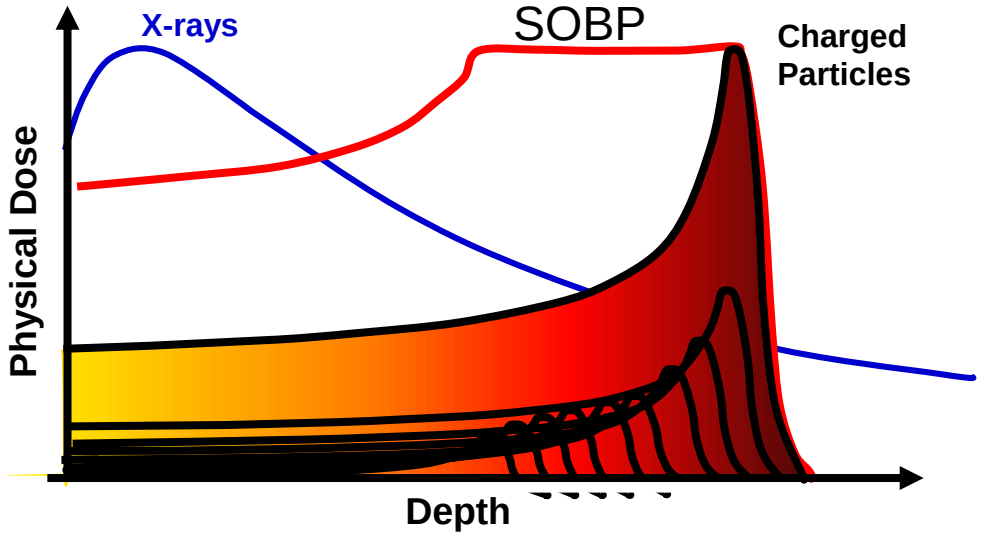
RBE: Relative Biological Effectiveness



RBE critically depends on both physical and biological parameters:

- **Dose & Dose Rate**
- **Cell line radiosensitivity**
- **Ion mass**
- **Ion energy**
- **SOBP shape/size**

.....



Currently fixed RBE values are used clinically and disregard any physical and biological dependency potentially limiting particle therapy effectiveness.

- Dose accuracy required in radiation therapy = 3.5 %
- Any uncertainty on the RBE will translate in the same uncertainty for biological effective dose

CCRCB

Proton RBEs

- A **range of RBE values** *in vitro* and *in vivo* have been reported
- Average value at mid-SOBP over all dose levels of 1.2, **ranging from 0.9 to 2.1.**
- Studies using **human cells** show significantly **lower RBE** values compared with other cells owing to higher α/β ratios.
- The average RBE value at mid-SOBP **in vivo** is 1.1, ranging from **0.7 to 1.6**.
- The majority of RBE experiments have used ***in vitro* systems and V79 cells with a low α/β ratio**, whereas most of the ***in vivo*** studies were performed in **early-reacting tissues with a high α/β** ratio.
- A value of **1.1 is used clinically**

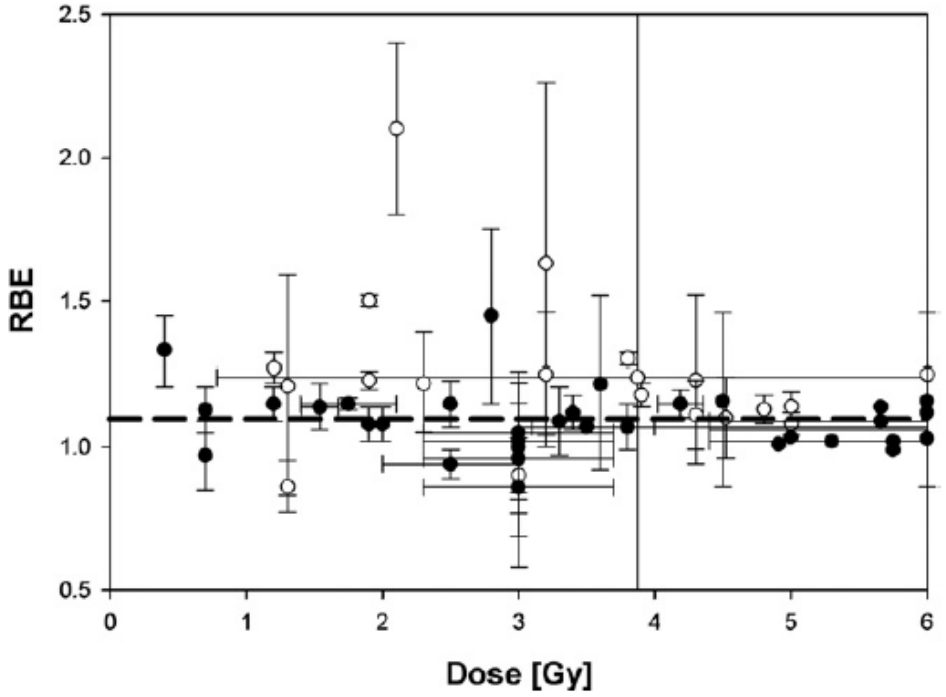


Figure 1 Experimental proton relative biological effectiveness (RBE) values (relative to ^{60}Co) as a function of dose/fraction for cell inactivation measured in vitro (open circles) and in vivo (closed circles). The thick dashed line illustrates an RBE of 1.1. Data taken from Paganetti et al.[15]

Paganetti and van Luijk, 2013, Sem Rad Oncol 23, 77-87

See also Friedrich *et al.*, 2013, *J Rad Res*, **54,** 494

CCRCB

Proton RBEs

- Paganetti, H., 2014, *Phys Med Biol* **59,** R419-R452
- 367 datapoints from 100 publications
- Considerable uncertainty but increasing RBE with LET

Table 1. Average RBE values based on the data shown in figure 8 considering all $(\alpha/\beta)_x$. LET_d values are given relative to the reference photon radiation. Uncertainties are based on 95% confidence intervals.

	Average RBE (2 Gy)	Average RBE (2 Gy); weights=1	Average RBE (6 Gy)	Average RBE (6 Gy); weights=1
LET_d = photon LET_d (from linear fit with $LET_d \leq 15\,keV\,\mu m^{-1}$)	1.02 (0.98, 1.06)	1.08 (1.02, 1.14)	0.99 (0.97, 1.02)	1.08 (1.03, 1.13)
$2 < LET_d < 3\,keV\,\mu m^{-1}$	1.12 (1.07, 1.16)	1.18 (1.13, 1.24)	1.09 (1.07, 1.12)	1.15 (1.11, 1.19)
$LET_d < 3\,keV\,\mu m^{-1}$	1.10 (1.07, 1.13)	1.15 (1.11, 1.19)	1.06 (1.04, 1.08)	1.13 (1.10, 1.15)
$3 \leq LET_d < 6\,keV\,\mu m^{-1}$	1.21 (1.16, 1.26)	1.38 (1.28, 1.49)	1.14 (1.11, 1.18)	1.33 (1.24, 1.41)
$6 \leq LET_d < 9\,keV\,\mu m^{-1}$	1.35 (1.25, 1.44)	1.38 (1.21, 1.55)	1.27 (1.19, 1.35)	1.36 (1.18, 1.54)
$9 \leq LET_d \leq 15\,keV\,\mu m^{-1}$	1.72 (1.54, 1.89)	1.74 (1.53, 1.95)	1.60 (1.36, 1.84)	1.53 (1.34, 1.72)

CCRCB

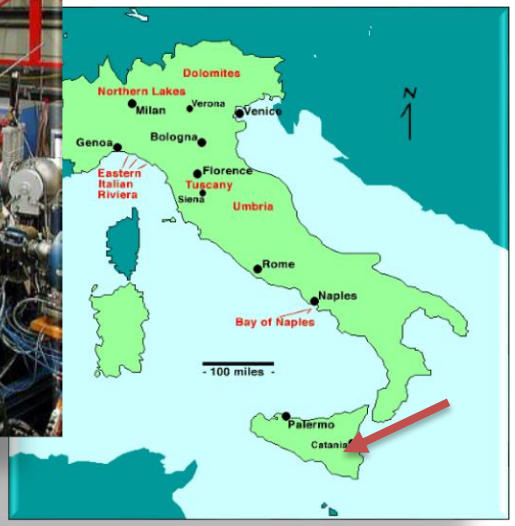
Overall aim

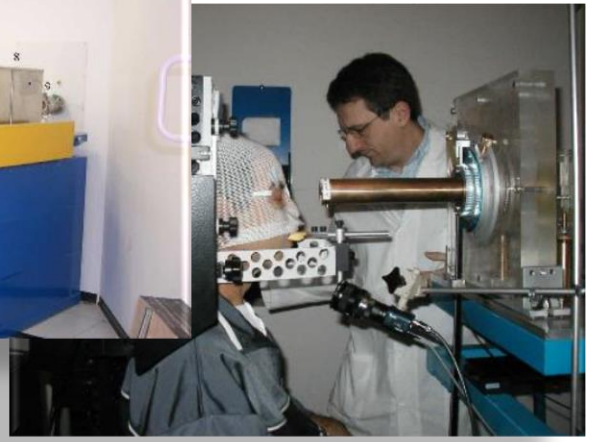
Combined assessment of early and late cellular response including DNA damage in a range of relevant cell lines to provide systematic high resolution information to develop a rigorous theory of ion radiation action at the cellular and molecular level.

- **How does cell response vary across a pristine Bragg curve?**
- **How biological effectives of a pristine curve relates to a Spread Out Bragg Curve?**
- **What impact does fractionation have on SOBP effectiveness?**
- **What other biological parameters play a role?**

CCRCB

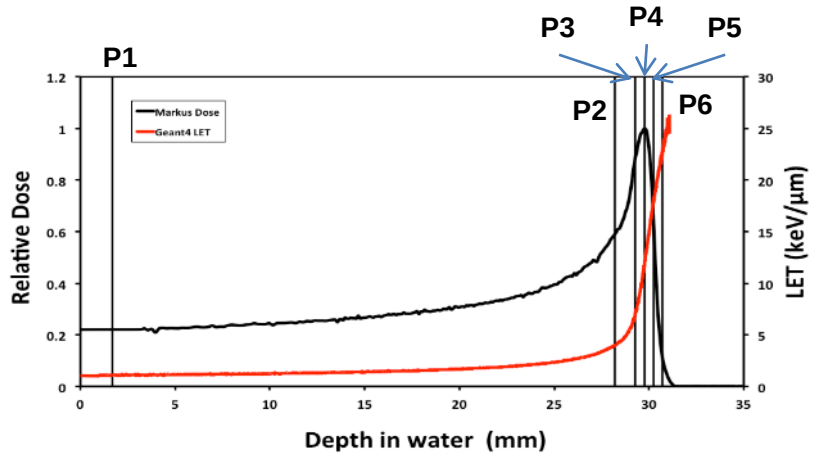
INFN Catania



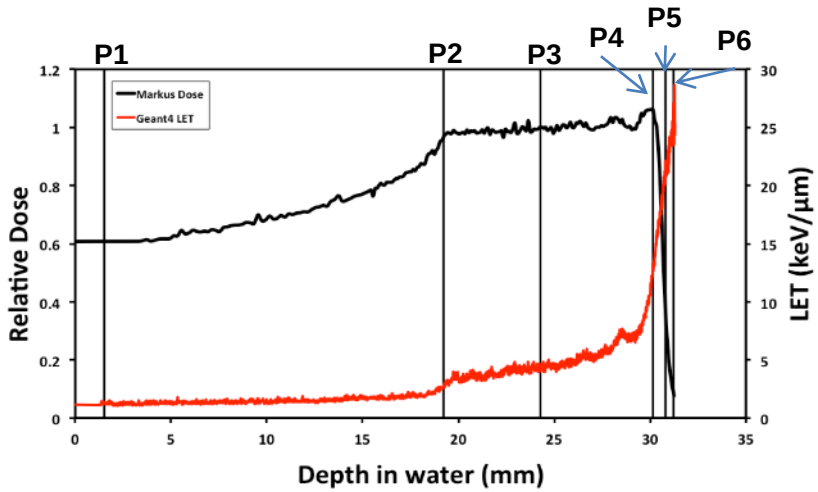


Catana Proton Therapy Facility

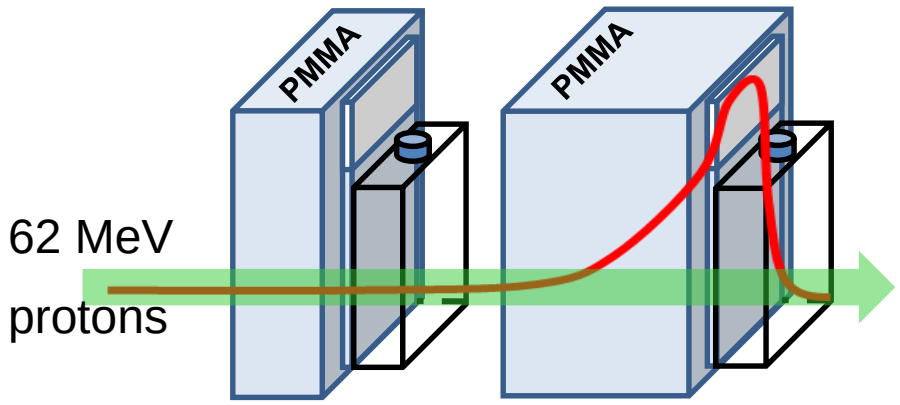
Irradiation Setup – INFN Catania

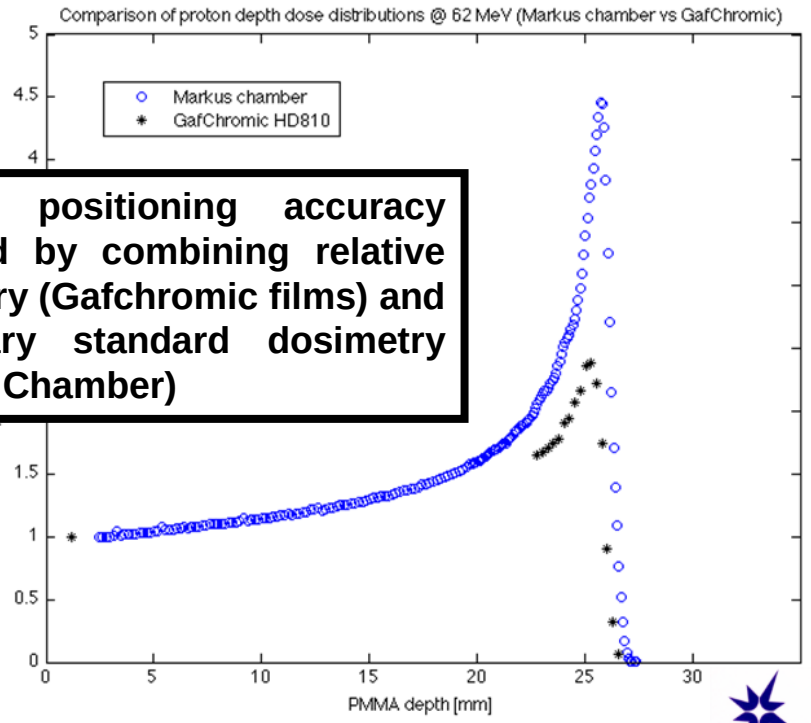


	P1	P2	P3	P4	P5	P6
Depth water [mm]	1.38	20.23	24.59	27.69	29.48	30.08
LET [keV/µm]	1.2	2.6	4.5	13.4	21.7	25.9



	P1	P2	P3	P4	P5	P6
Depth water [mm]	1.38	27.42	29.21	29.8	30.7	31.29
LET [keV/µm]	1.11	4.0	7.0	11.9	18.0	22.6





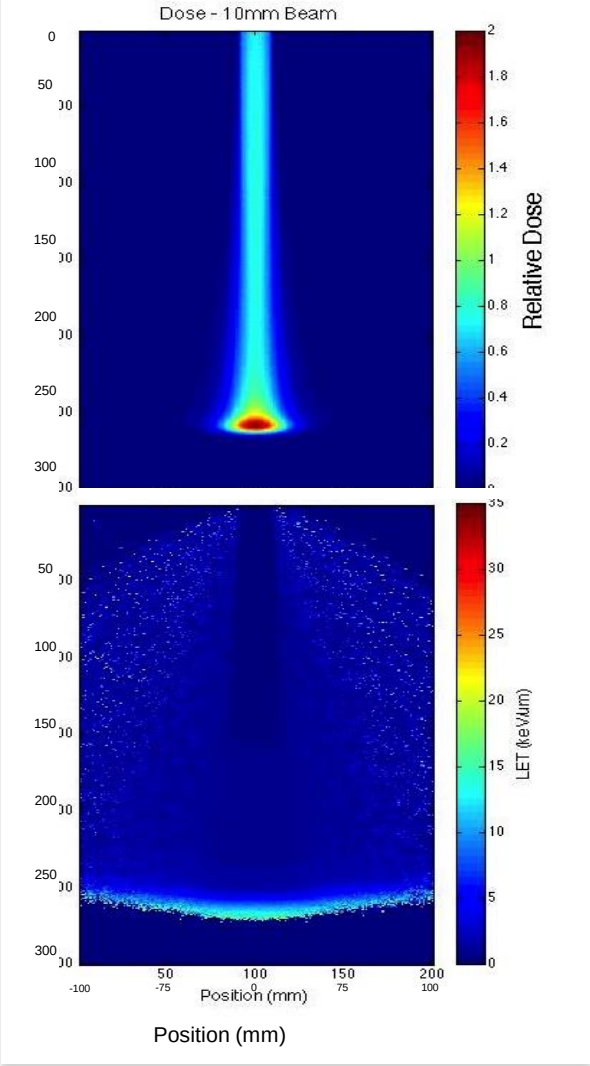
50 µm positioning accuracy achieved by combining relative dosimetry (Gafchromic films) and secondary standard dosimetry (Markus Chamber)

CCRCB

Geant4 Simulation

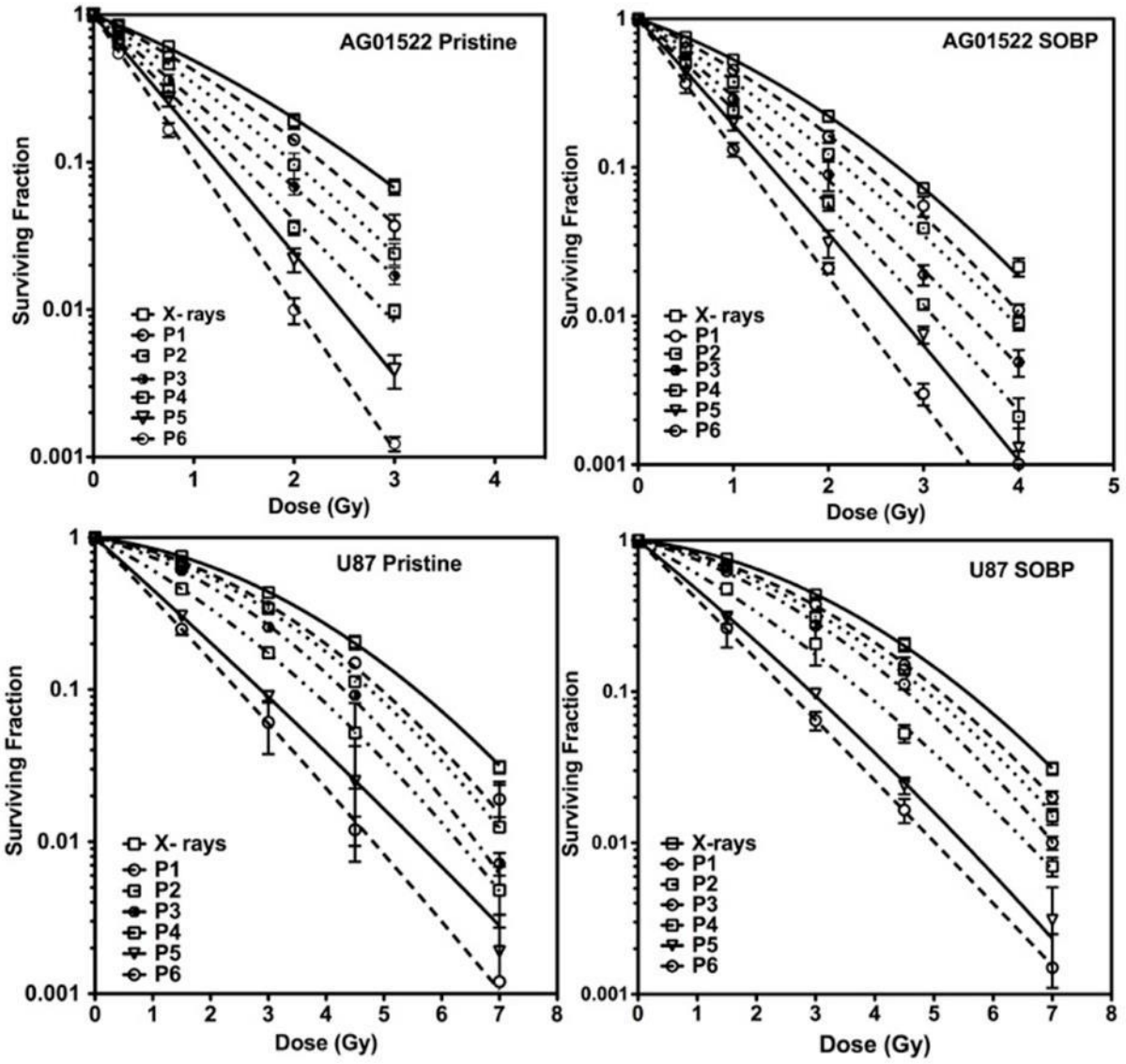
CATANA Beamline – INFN, Catania

- Not all quantities measurable experimentally ***e.g. LET***.
- The *Geant4* simulation toolkit allows us to model the experimental beam line to predict particle behaviour using the probability sampling *Monte Carlo* method.



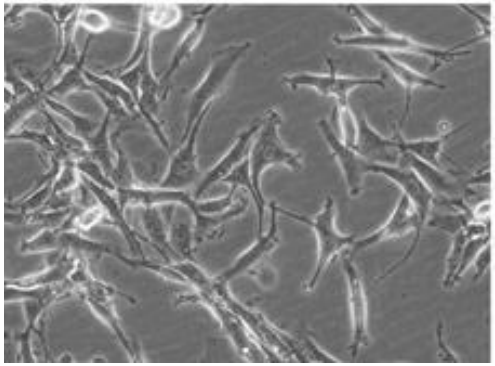
Top: Geant4 Depth - Dose distribution.
Bottom: Geant4 Depth - LET distribution.

Survival data



AG01522 normal human fibroblast cell line

U87- human primary glioblastoma cell line with epithelial morphology, obtained from a stage four cancer patient



Chaudhary *et al.*,(2014) *Int J. Radiation Oncol Biol Phys*, **90**:27-35

CCRCB

Curve fitting and RBE Calculations

Linear quadratic equation

$$SF = e^{-\left(aD+bD^2\right)}$$

$$RBE = D_{X\text{-}ray} / D_{Proton} \text{ @ } isoeffect$$

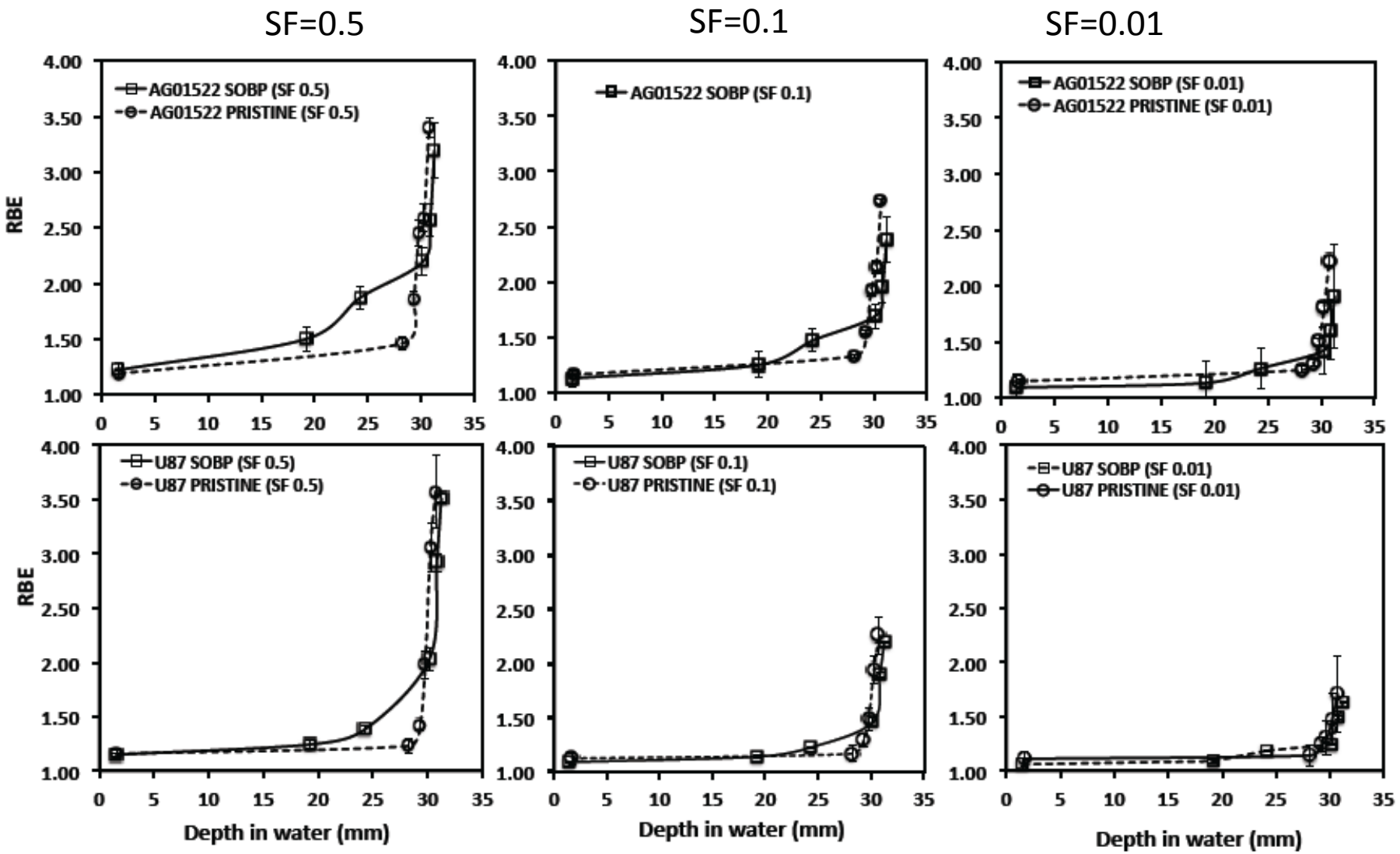
$$RBE = \left(\left(\alpha_{x^2} + 4\beta_x D_p \left(\alpha_p + \beta_p D_p\right)\right)\text{^}(1/2) - \alpha_x \right) \Big/ \left(2\beta_x D_p\right)$$

Where α_x, β_x, α_p and β_p are the α and β parameter from the X-ray and proton exposure and D_p is the proton dose delivered

X-rays	α / Gy^{-1}	β / Gy^{-2}	α/β
AGO1522B	0.54 ± 0.06	0.062 ± 0.02	8.71
U87	0.11 ± 0.03	0.060 ± 0.01	1.83

CCRCB

RBE versus Depth

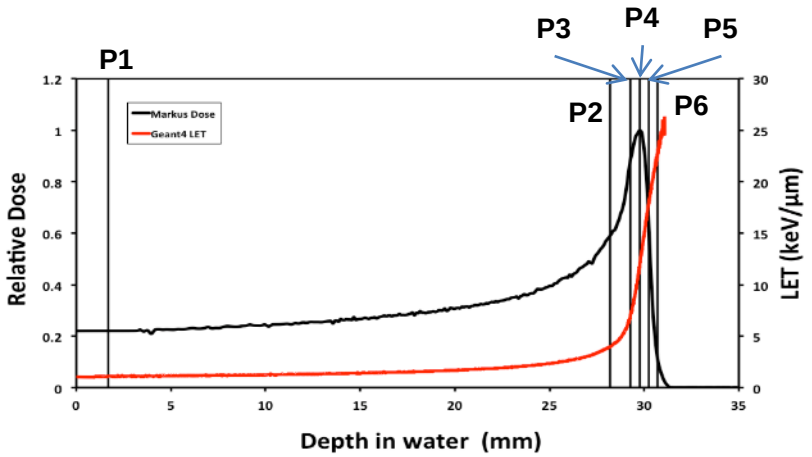


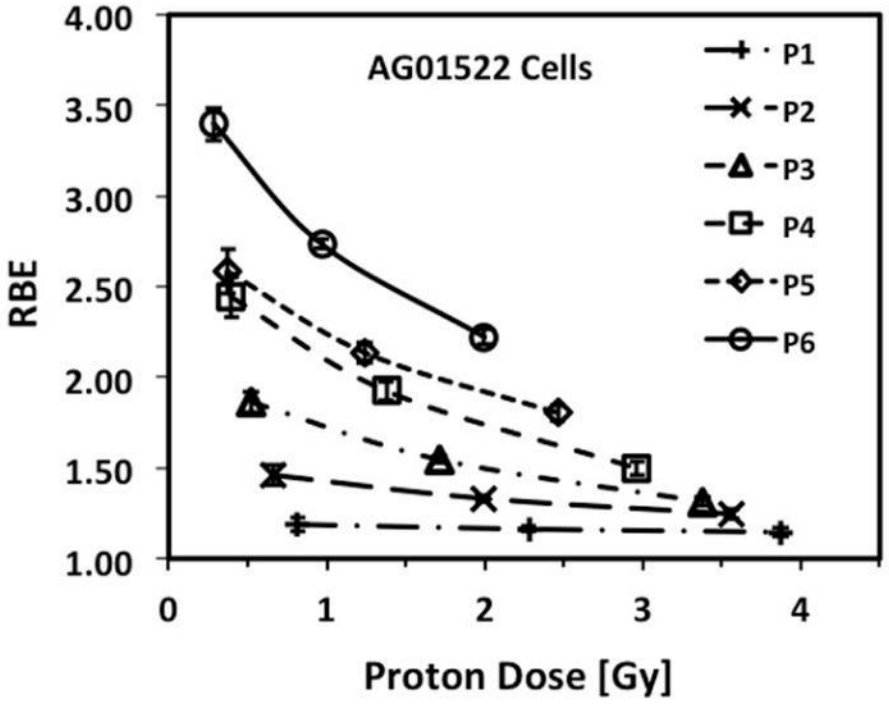
Chaudhary *et al.*,(2014) *Int J. Radiation Oncol Biol Phys*, **90**:27-35

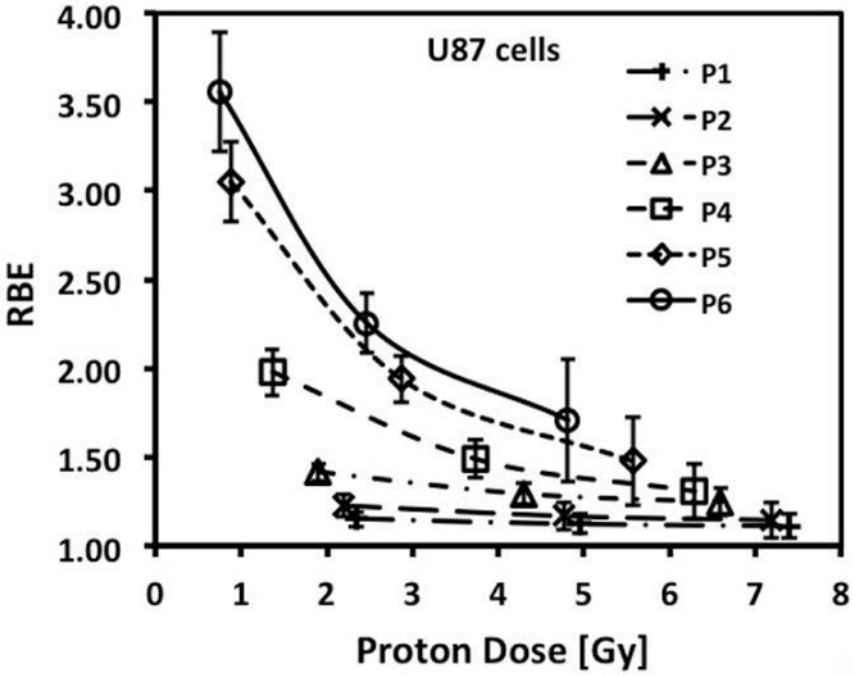
CCRCB

RBE versus Dose

Monoenergetic beam

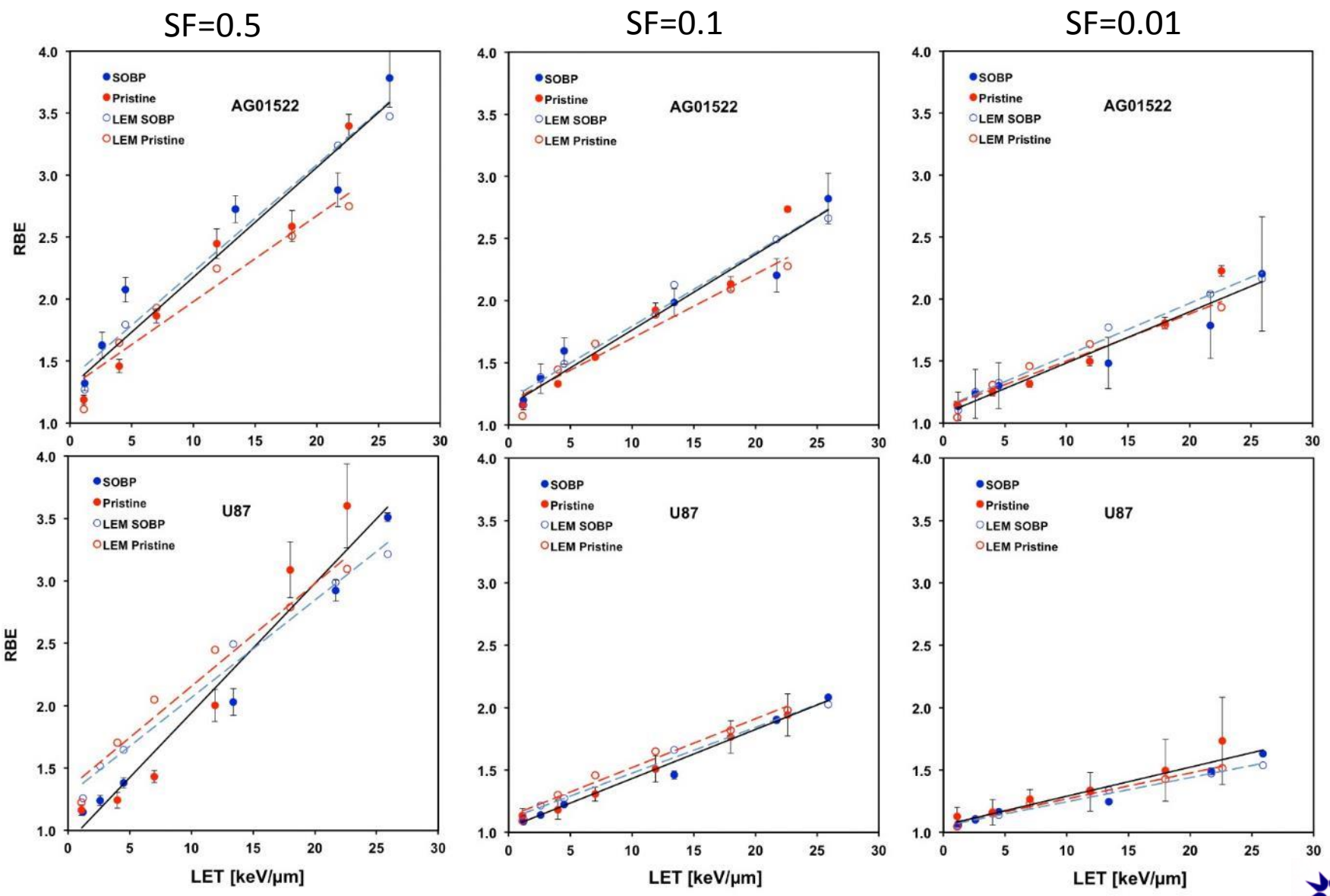






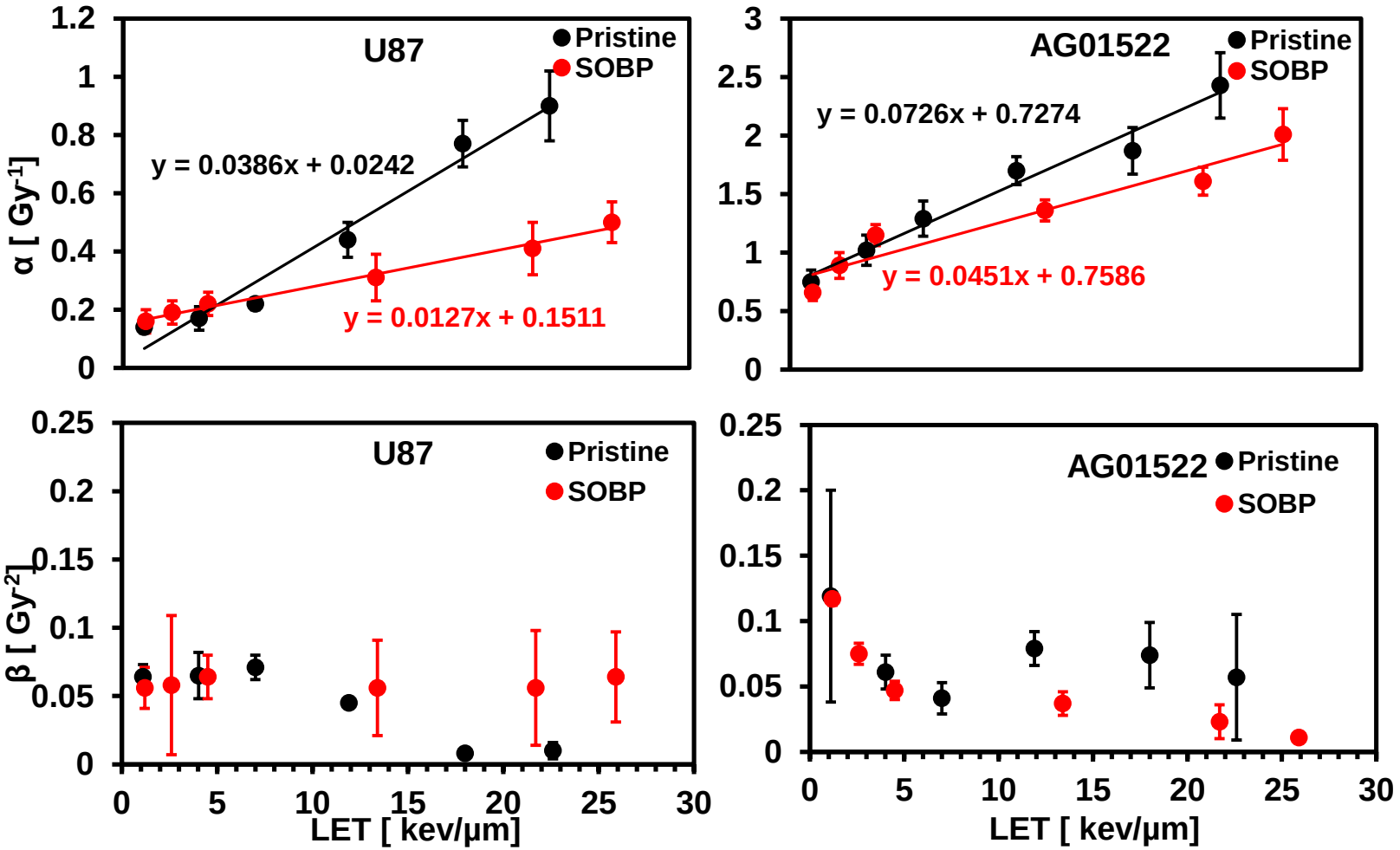
Chaudhary *et al.*,(2014) *Int J. Radiation Oncol Biol Phys*, **90**:27-35

RBE versus LET



Chaudhary *et al.*,(2014) *Int J. Radiation Oncol Biol Phys*, **90**:27-35

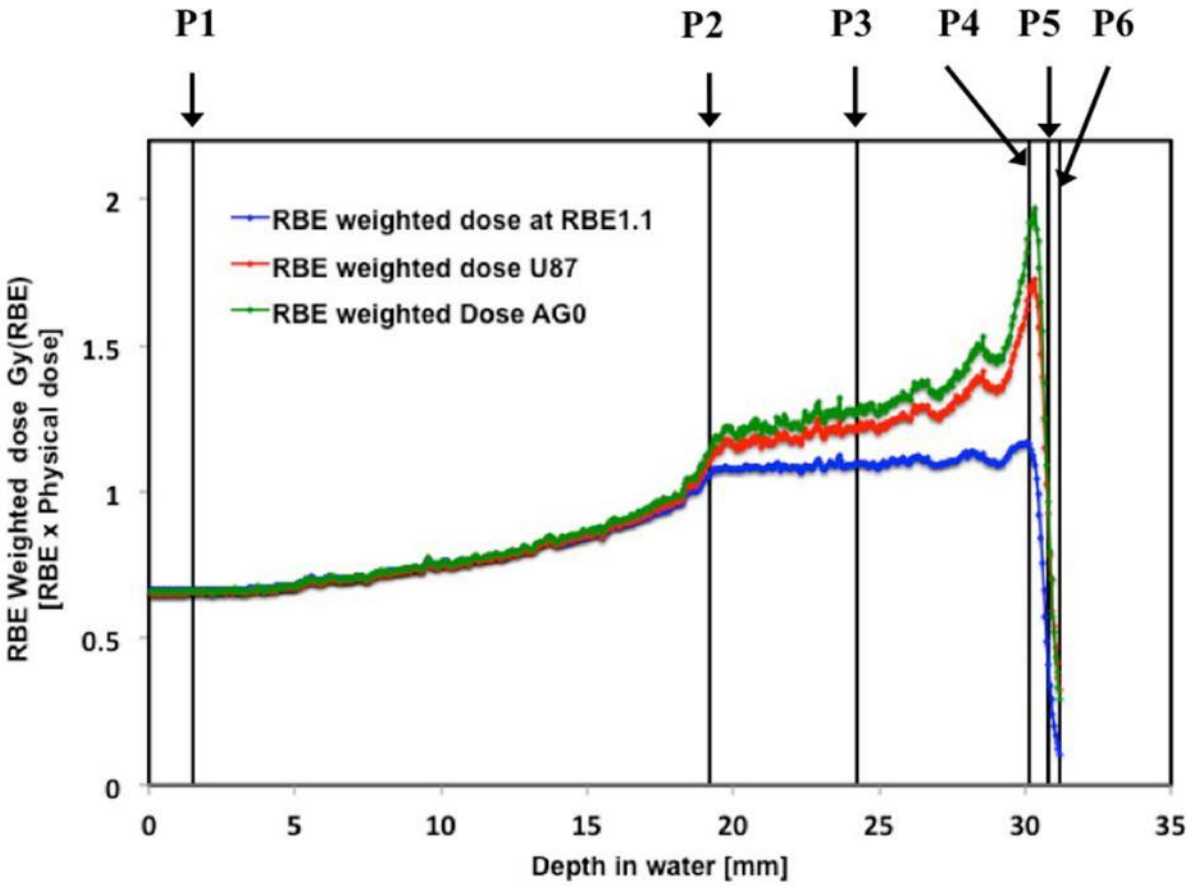
α and β versus LET



$$\alpha_p = \alpha_x + \lambda \, LET$$

Chaudhary *et al.*,(2014) *Int J. Radiation Oncol Biol Phys*, **90**:27-35

Biological Effective Dose Profile

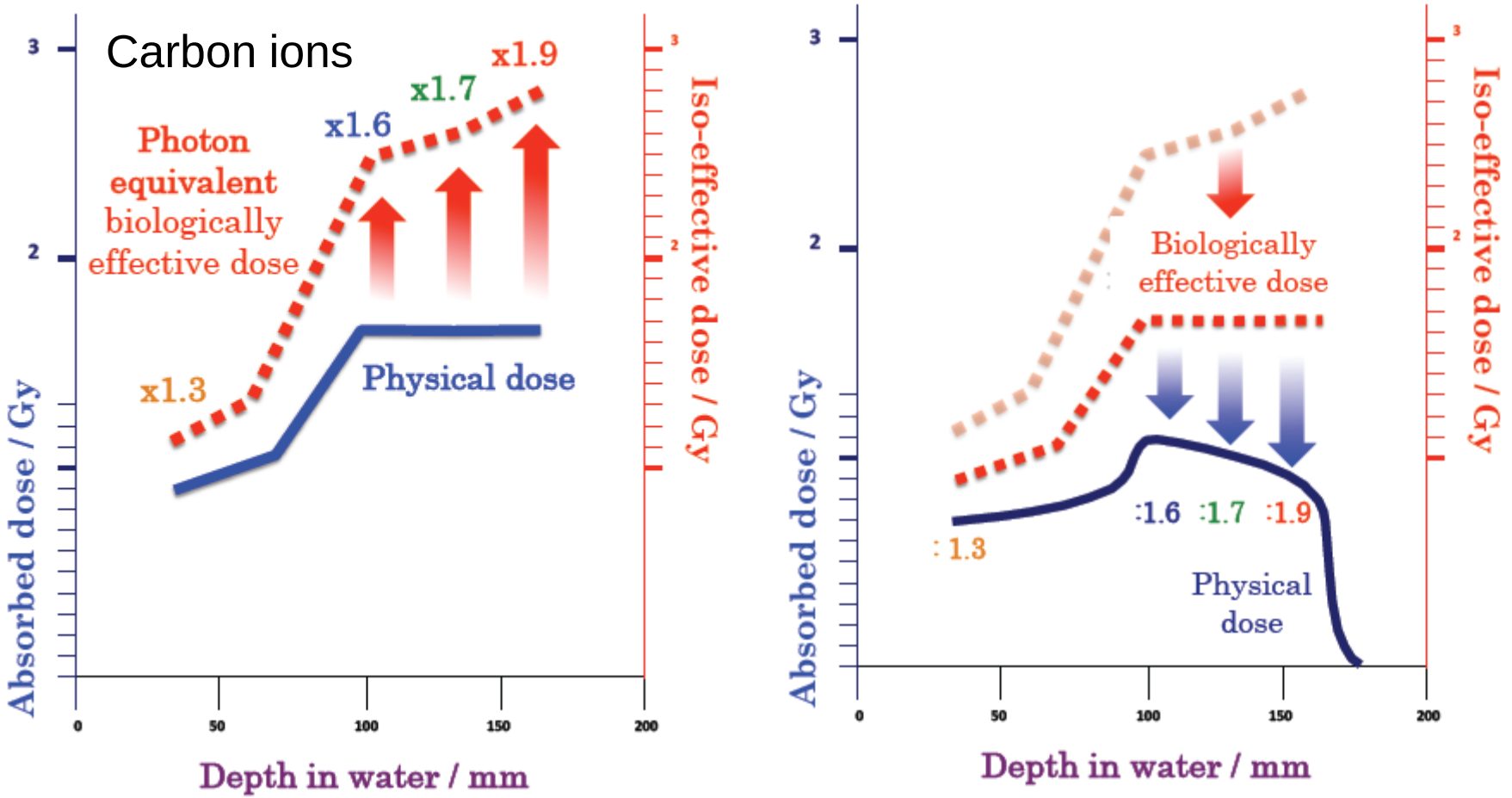


- A parameterised RBE model has been used
- In tumour region (SOBP) 17% and 18% increase in biological dose for AGO and U87 cells
- Extension of distal region by 130 and 150 µm respectively

Chaudhary *et al.*,(2014) *Int J. Radiation Oncol Biol Phys*, **90**:27-35

CCRCB

RBE - painting



Gueulette *et al* 2010

- **A homogeneous biologically effective dose requires an inhomogeneous physical dose distribution – even for protons**

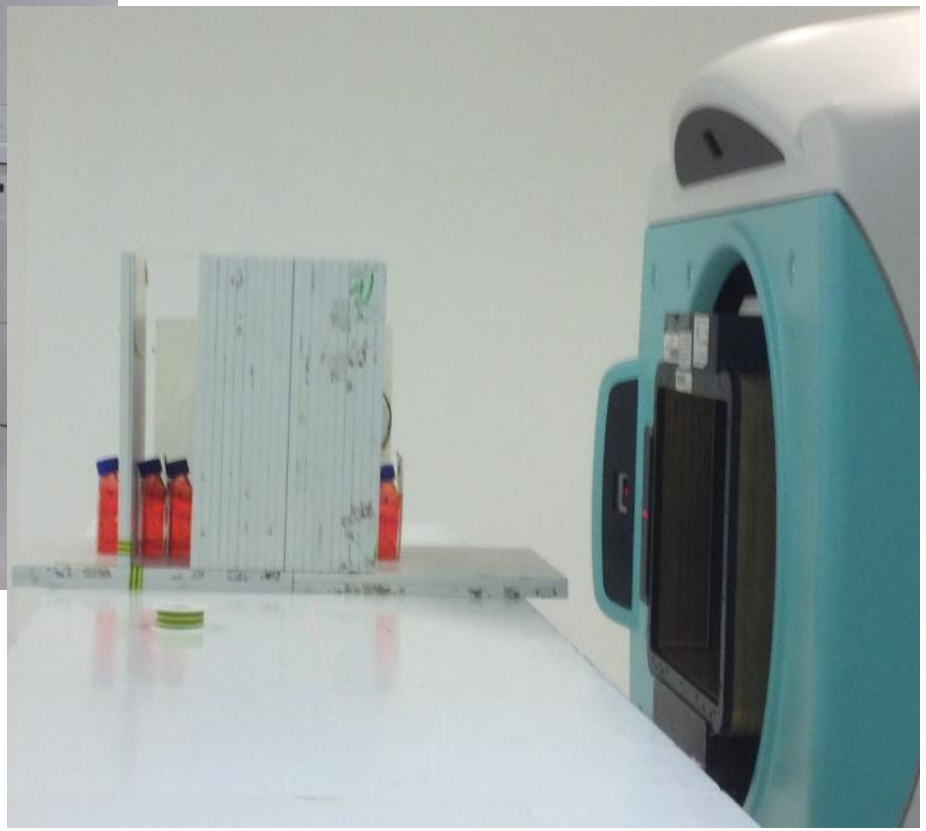
Proton Therapy Center, Prague

PROTON THERAPY CENTER

Marie Davidkova, Anna Michaelidesova, Vladimir Vondráček

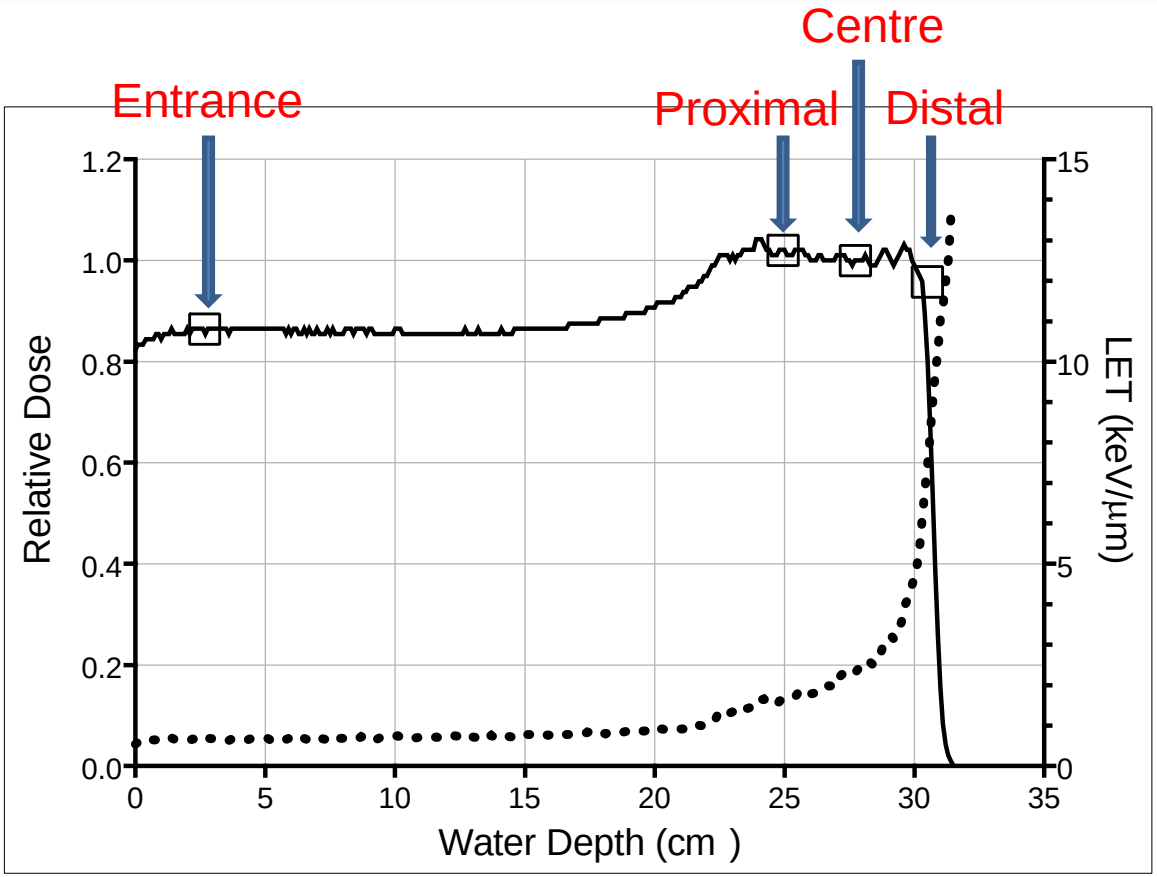
CCRCB

Treatment room



CCRCB

Prague Proton - uniform exposures



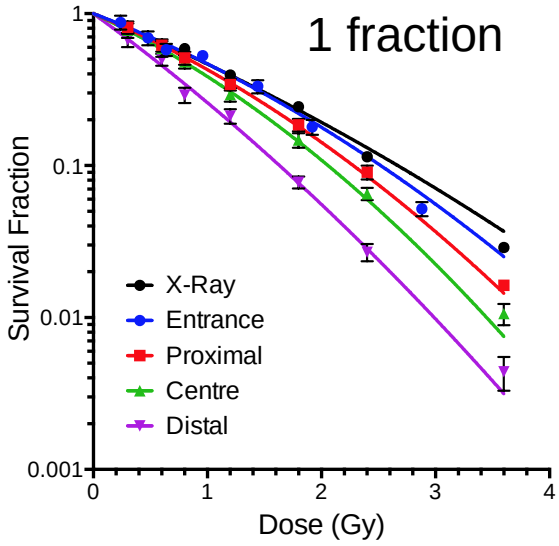
Dose and dose averaged LET profiles for actively scanned modulated proton beam with maximum energy 219.65 MeV. Vertical lines mark the four cell irradiation positions at the Entrance, Proximal, Centre and Distal positions. Relative dose and GEANT4 derived dose averaged LET values are indicated in dashed and solid black lines respectively.

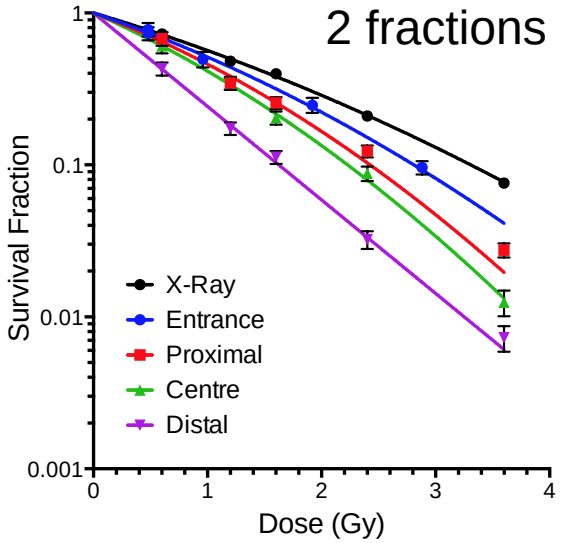
Marshall *et al., Int J. Radiat Oncol Biol Phys* **in press**

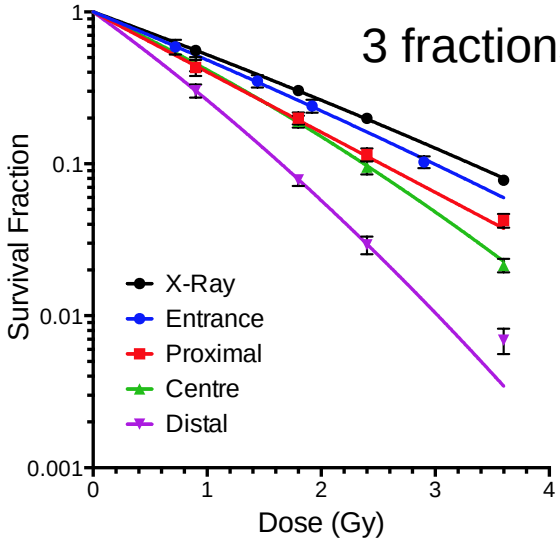
CCRCB

Fractionated protons exposures – total dose

- AGO1522 fibroblasts irradiated with X-rays or protons at entrance, proximal, centre or distal positions with either 1, 2 or 3 fractions, 24 hours apart



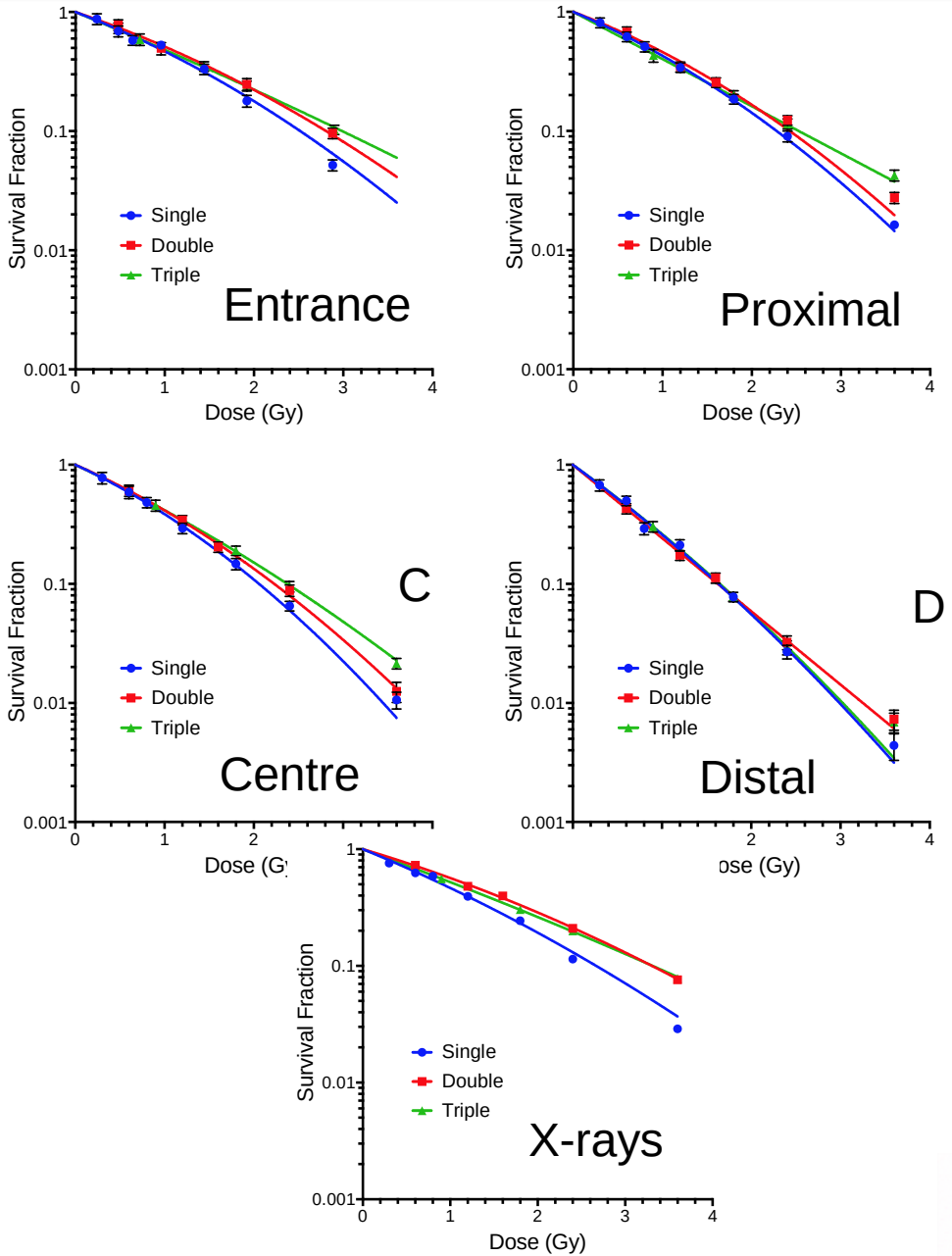




Marshall *et al., Int J. Radiat Oncol Biol Phys* **in press**

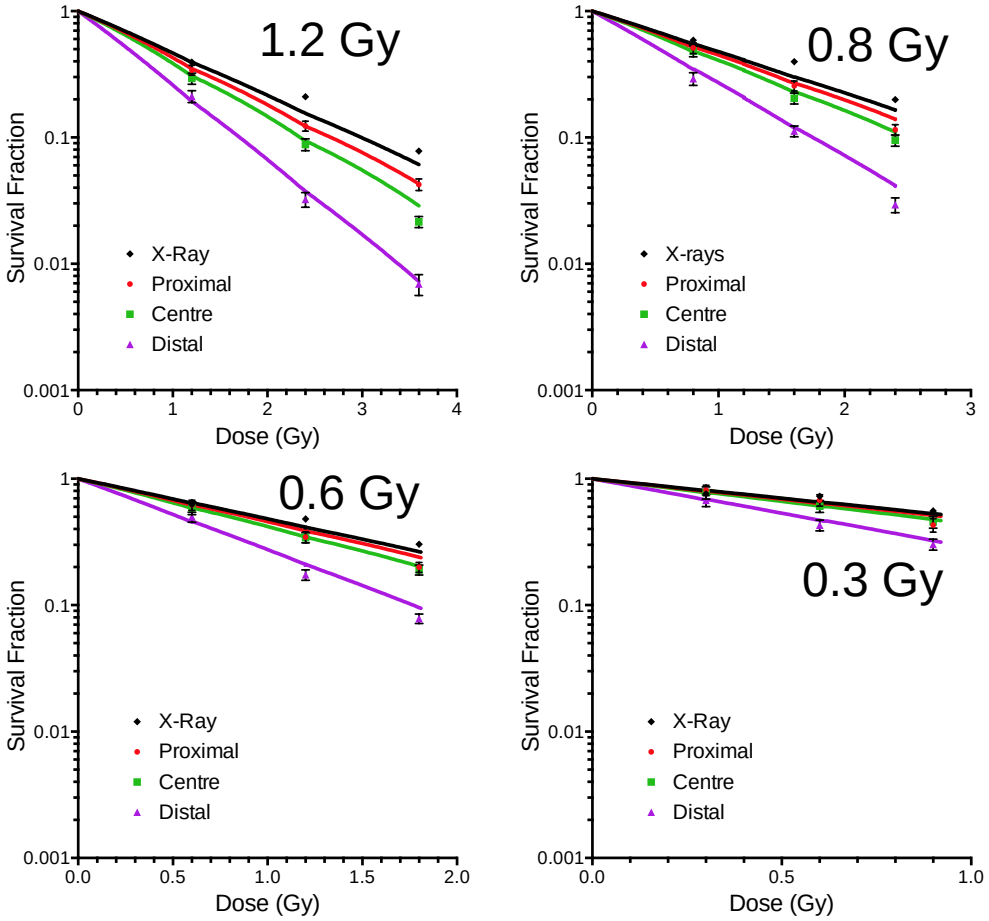
Fractionated protons exposures – position

- AGO1522 fibroblasts irradiated with X-rays or protons at entrance, proximal, centre or distal positions with either 1, 2 or 3 fractions, 24 hours apart



Marshall *et al.*, *Int J. Radiat Oncol Biol Phys* **in press**

Fractionated exposures – dose per fraction



Fits obtained using the Linear Quadratic Model to estimate survival based on repeated acute response.

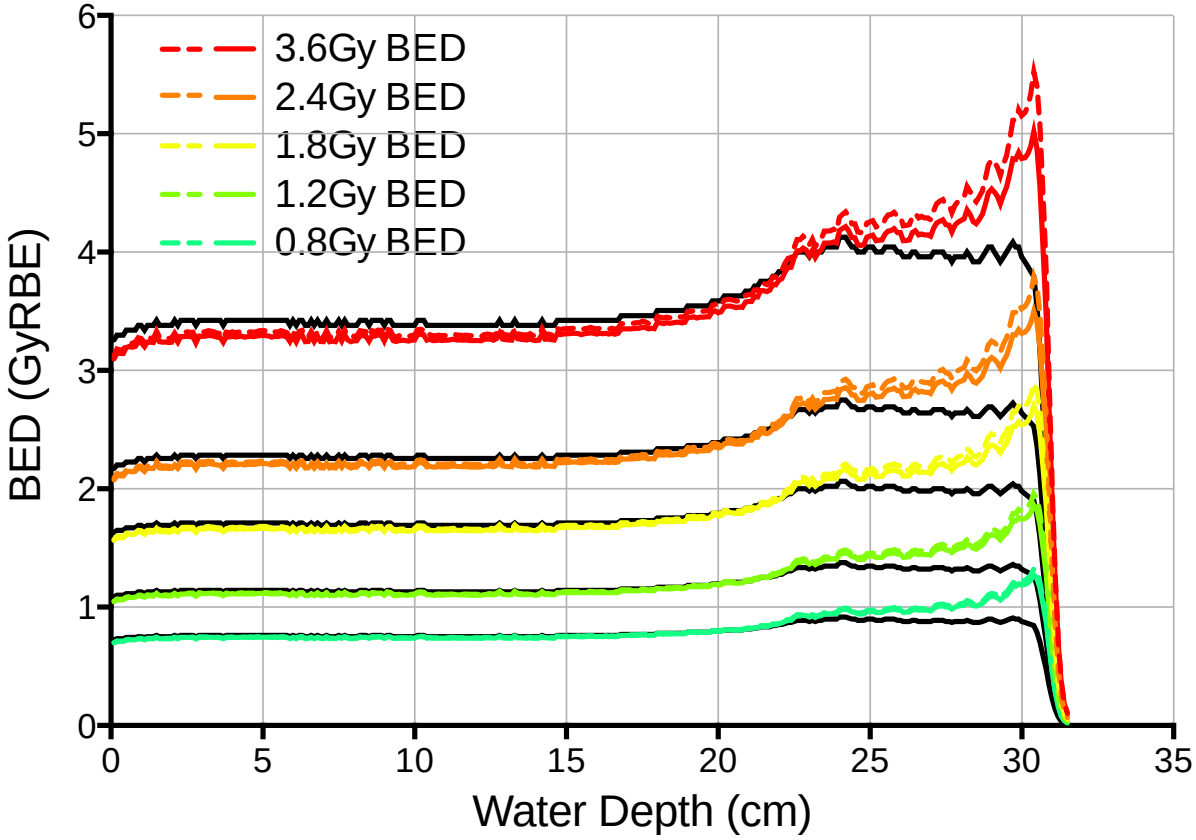
$$SF = \exp(-\alpha nD - \beta nD^2)$$

Marshall *et al., Int J. Radiat Oncol Biol Phys* **in press**

CCRCB

SOBP – Biologically effective dose

- SOBP Biologically Effective Dose (BED) profile comparing analytically obtained BED values (RBE x Physical Dose (Gy)) when delivering a plateau dose of 3.6, 2.4, 1.8 and 0.8 Gy in both acute (solid colour) and fractionated (dashed colour) regimes.
- Fractionation can be seen to further increase this effect in the plateau region, seeing increases of 8.3 – 12.1 % in integral BED over the clinical case in comparison to 4.6 – 10.6 % for the acute delivery of the same doses.



Marshall *et al., Int J. Radiat Oncol Biol Phys* **in press**

Conclusions

RBE varies significantly across the Bragg curve with strong dependency on LET, Dose, and Radiosensitivity

- Differences between the response to pristine and SOBP indicate that **LET** alone **might not be the best parameter** for RBE predictions

- RBE variation for 60MeV proton beams **does not significantly extend the range** of the SOBP (compared to fixed RBE = 1.1)

- Fixed RBE of 1.1 for protons **underestimates the dose delivered to the tumour volume**

- **Biophysical models** need to be optimised for advanced radiotherapies to include clinically relevant exposure scenarios **including fractionation**

- Future treatment planning systems will input **biological parameters** to personalise the delivery of radiotherapy

Acknowledgements

CCRCB

- **Pankaj Chaudhary**
- **Thomas Marshall**
- Stephen McMahon
- Karl Butterworth

QUB Physics

- Marco Borghesi
- Fred Currell
- Fiona Hanton

National Physical Laboratory (NPL)

- **Giuseppe Schettino**

INFN Catania

- Pablo Cirrone
- Francesco Romano

University of Naples

- Lorenzo Manti
- Francesca Perozziello

Clatterbridge Cancer Centre

- Andrzej Kacperek

Prague Proton Therapy Centre

- Marie Davídková
- Anna Michaelidesová
- Vladimir Vondráček
- Jana Vachelová

MGH Boston

- Kathryn Held
- Harald Paganetti

SECOND ANNOUNCEMENT

14th INTERNATIONAL WORKSHOP ON RADIATION DAMAGE TO DNA

MELBOURNE | AUSTRALIA

March 20-24th, 2016

LOCAL ORGANIZING COMMITTEE

Roger Martin | Olga Martin | Pavel Lobachevsky
Martin Lavin | Michael Fenech | Eva Bezak | Robert Anderson
Tony Hooker

INTERNATIONAL SCIENTIFIC COMMITTEE

Marie Davidkova (Czech Republic) | Peter Dedon (USA)
Miral Dizdaroglu (USA) | Paul Doetsch (USA)
Alexandros Georgakilas (Greece) | Kathryn Held (USA)
Hiroshi Ide (Japan) | Olga Kovalchuk (Canada)
Hooshang Nikjoo (Sweden) | Kevin Prise (UK) | Jean-Luc Ravant (France)
Masatoshi Ukai (Japan) | Akinari Yokoya (Japan)
Keiji Suzuki (Japan)

VISIT US AT
www.14thIWRDD.com