ENLIGHT, PAVIA, September 2012

A Biomedical facility at CERN - why do we need this?

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Strengths and weaknesses ....

Homer told us about the bravest - Achilles, fatally struck by the arrow of Paris

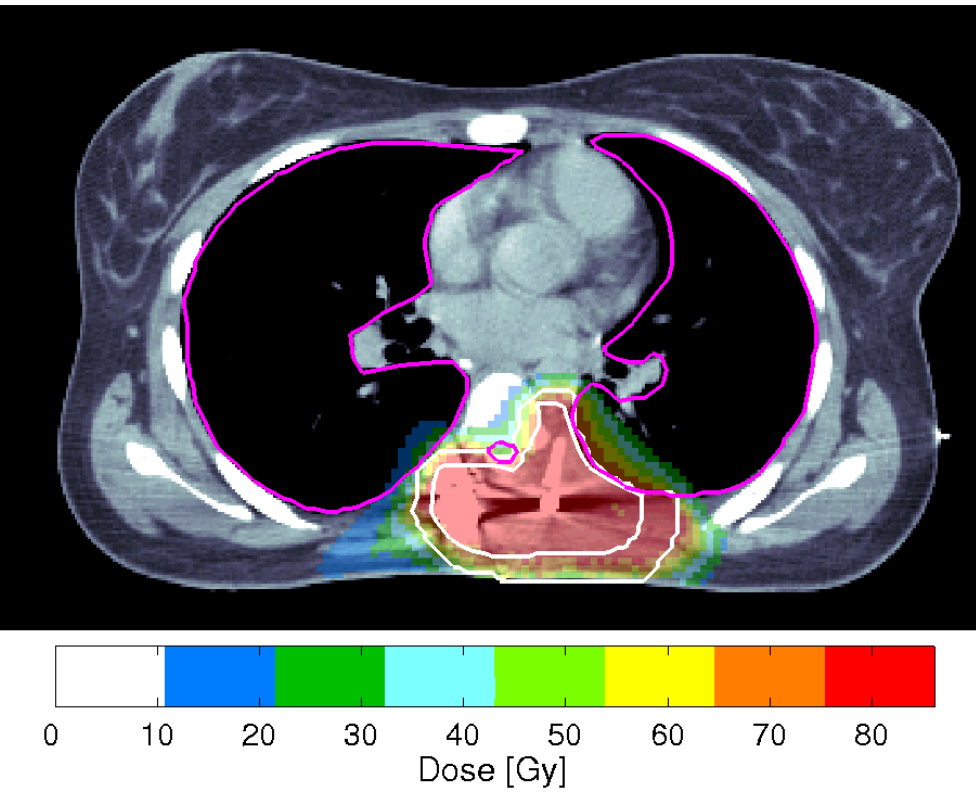
Particle therapy has intrinsic uncertainties or weaknesses: Two Achilles heels

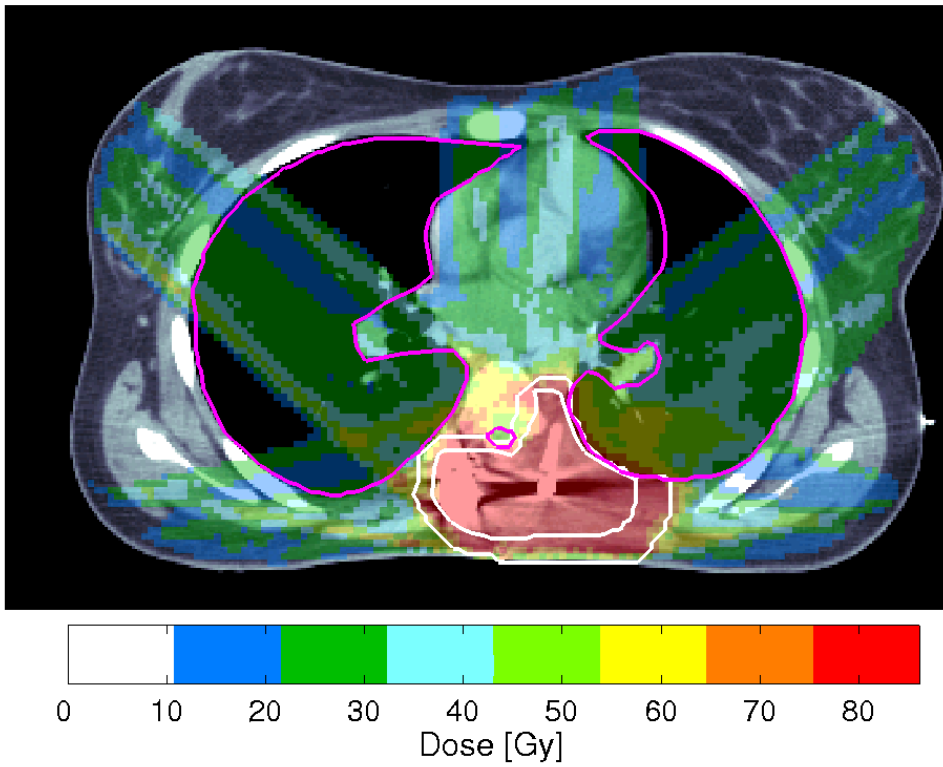
- **Physics** : dose, the correct position of Bragg peaks in the body
- **Biology** – how do different tissues & tumours respond to changes in dose **and** ionisation density (greater complexity of DNA damage) with Particles compared with megavoltage photons/x-rays?

Paravertebral Epithelioid Sarcoma Intensity Modulated Protons (IMPT) vs. Intensity Modulated X-ray (IMXRT) 7 (field)

IMProtonT

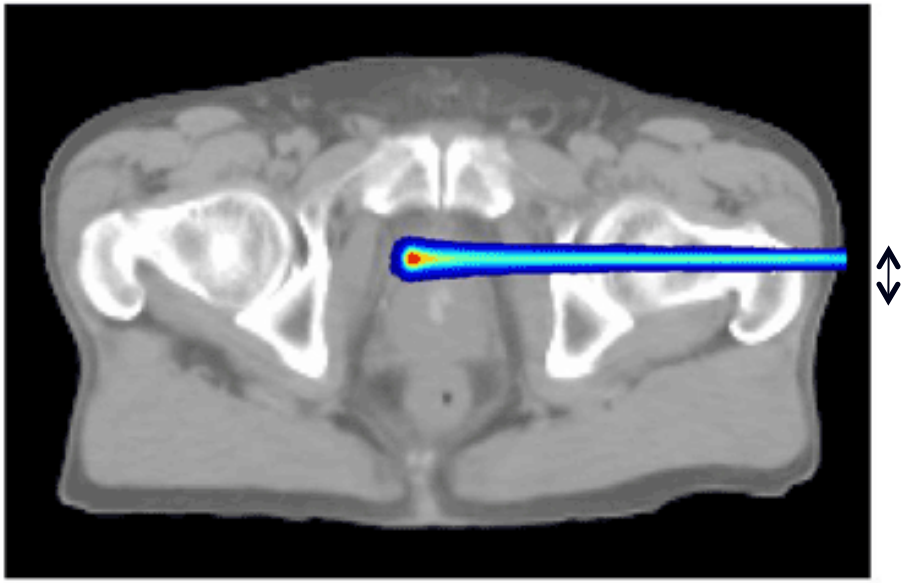
IMXRT





Minor changes in patient position or shape can change the range of a particle

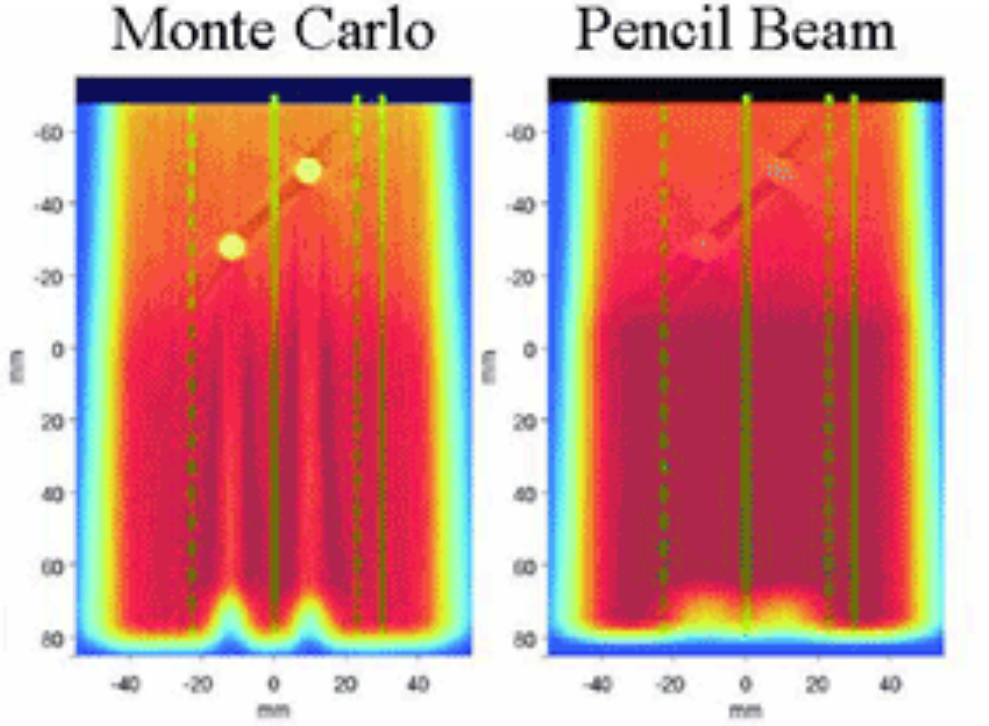
Issues 1: Range uncertainties due to setup



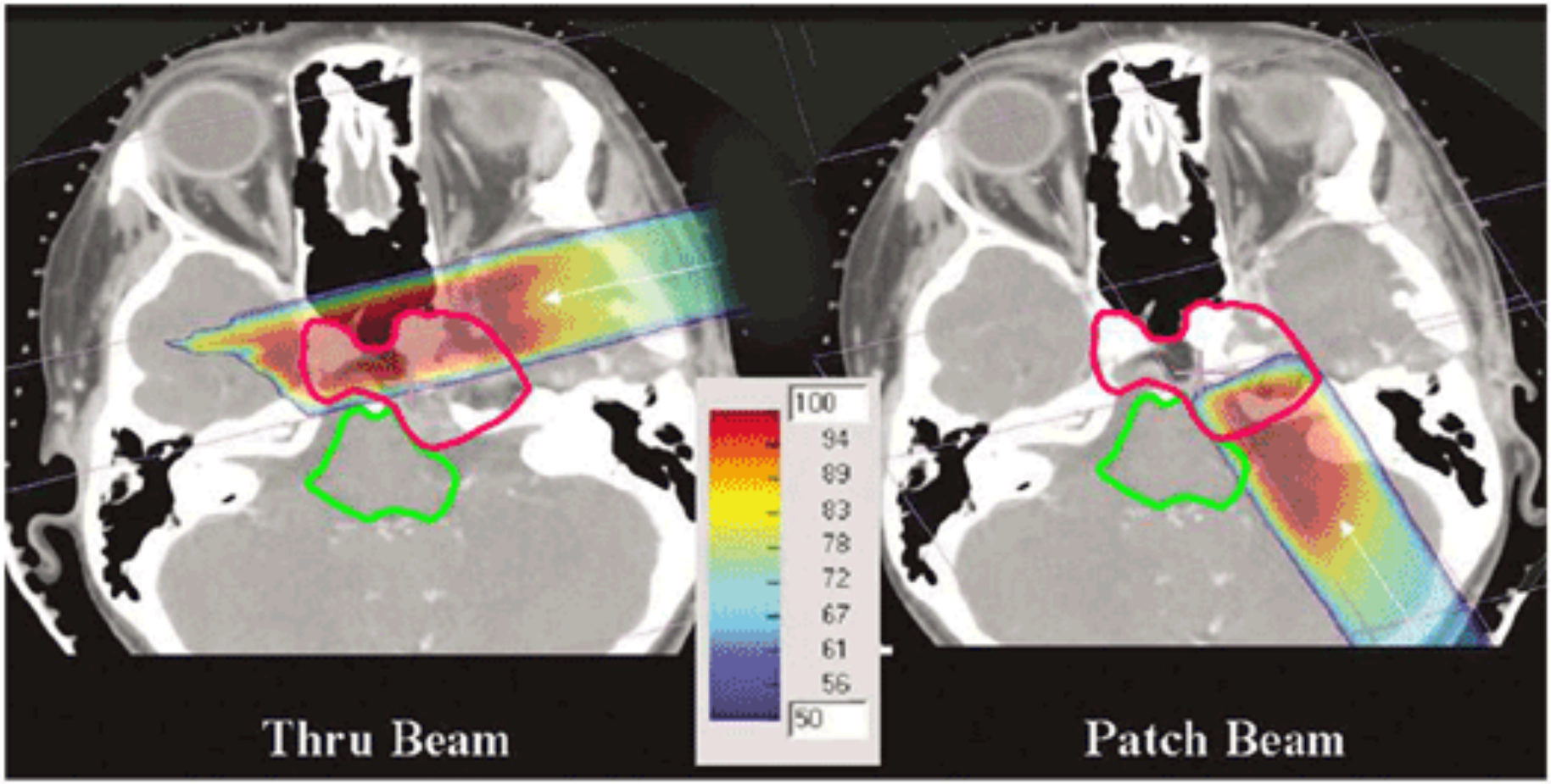
Jan 11

Chen, Rosenthal, et al., IJROBP 48(3):339, 2000

Issues 4: Range uncertainties due to metallic implants and CT artifacts



Accounting for range uncertainties by "field patching"



J. Adams and M. Bussiere

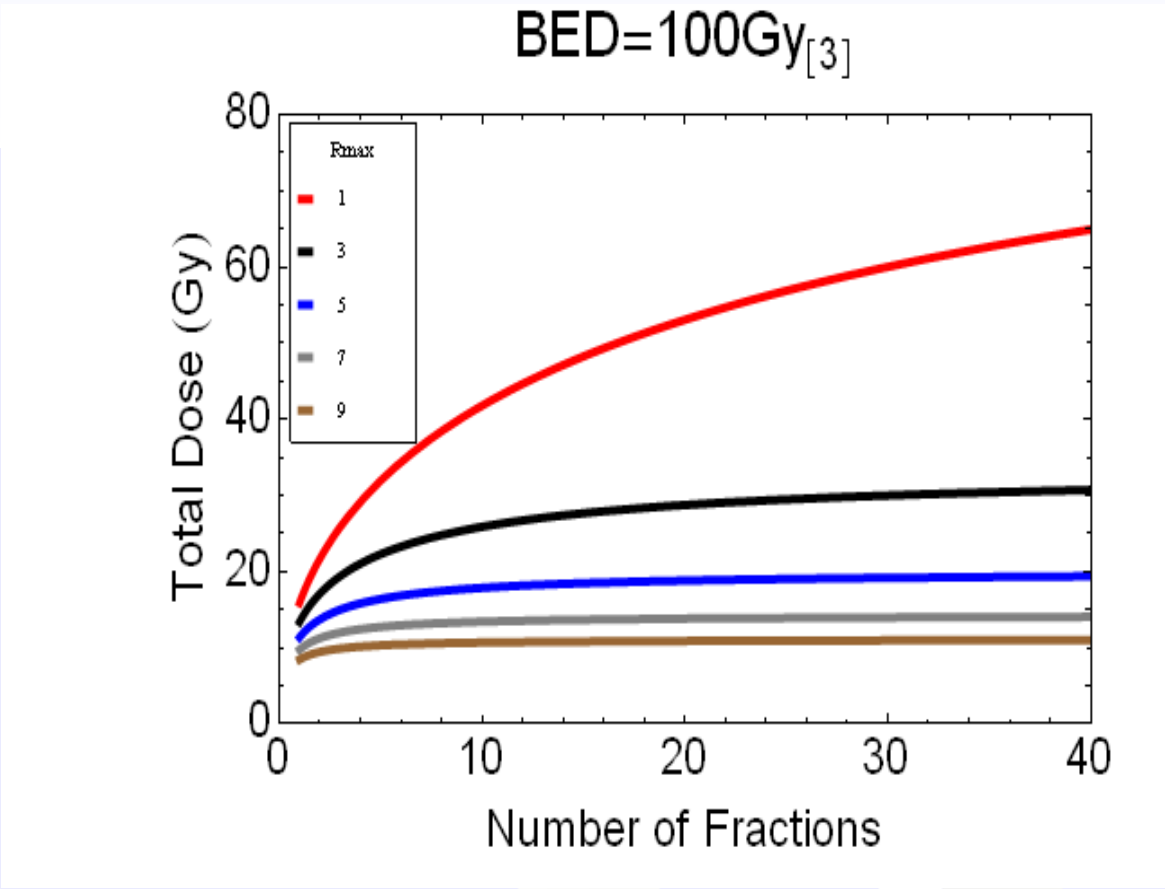
Relative Biological Effect –a simple ratio?

Changes with dose per fraction and cell cycling in repair proficient cells

$$RBE = \frac{Dose_{[LowLET]}}{Dose_{[HighLET]}}$$

Little or no changes in required dose with dose per fraction and cell cycling

Relationship between total dose and number of fractions for the *same bio-effect* for different RBE 'qualities' of radiation: *non-linearity!*



RBE converts x-ray dose to particle dose

- Relative Biological Effect is used to divide the 'equivalent' x-ray dose to provide dose given to patient.
- Uncertainties in physical dose compounded with RBE uncertainty can lead to significant patient effects: combined error can be 5-50%++.
- Dose –Effect relationship is non-linear

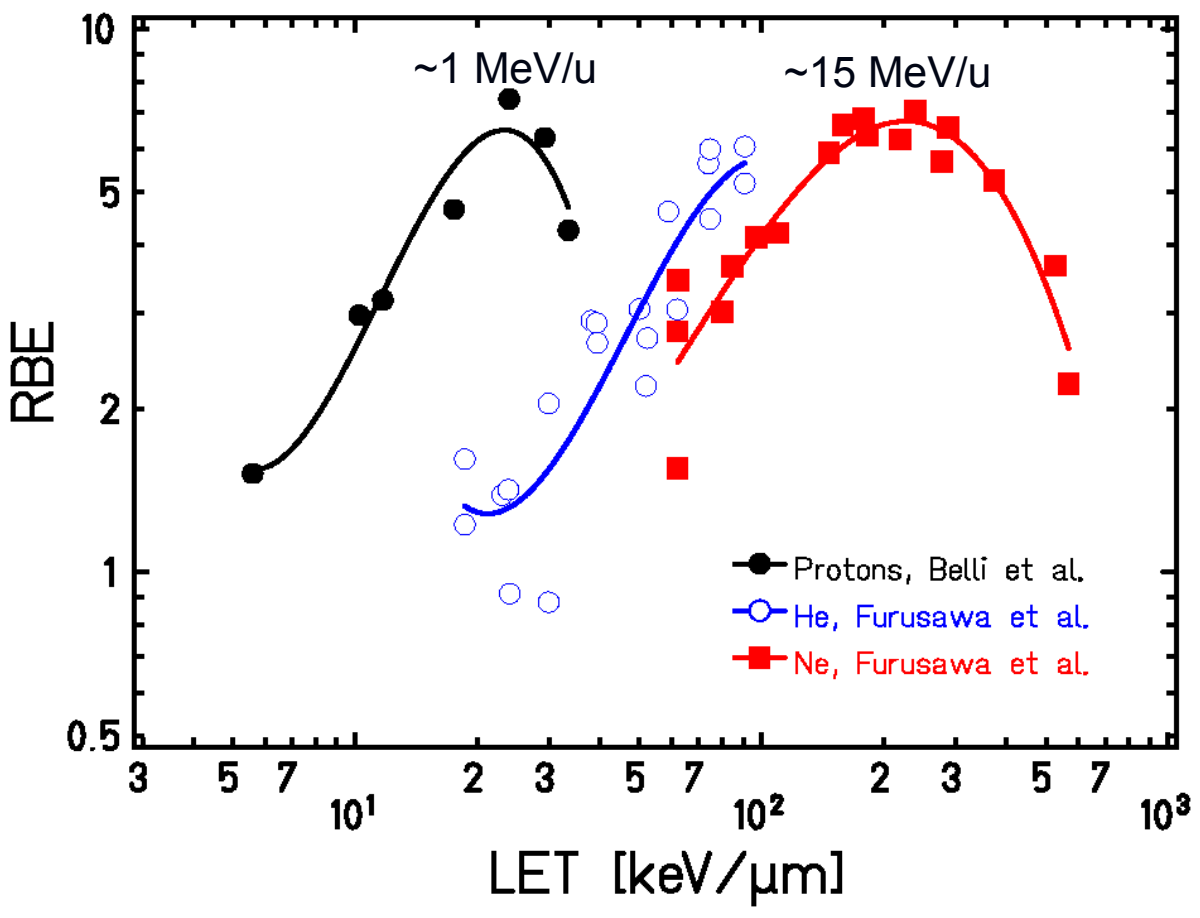
RBE depends on ……..

- **Particle [Z], Energy & Depth**
- Target **Volume** [mix of high LET Bragg peaks + low LET entry beams]
- **Dose** per treatment ..RBE varies inversely with dose. A treatment plan contains many dose levels.
- **Facility: neutron & γ-ray contamination**
- **Cell & Tissue type : slow growing cells have highest RBEs.**

The problems: past research

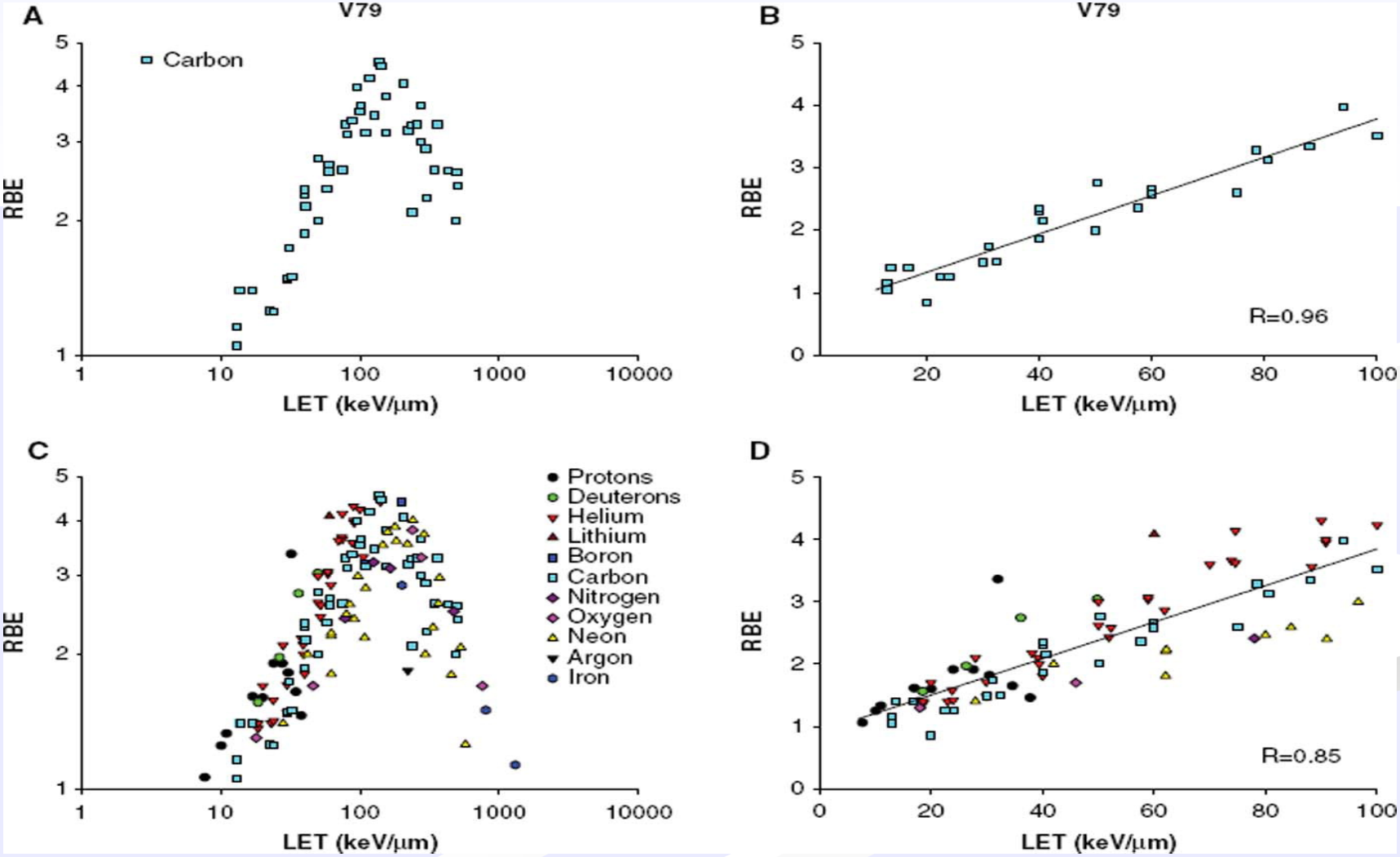
- Variation in physical beam parameters, dose , LET
- Limited beam availability
- Cells…..variable, often rapidly growing, some not even human derived.
- Few 3-D studies, limited computing power
- Few tumour-bearing animal model expts.
- Very limited normal tissue expts. on relevant 'late' end points, such a spinal/brain/kidney /gut etc.
- Clinical facilities also have limited beam time

RBE depends on Atomic number [Z] and Neutron number [N]

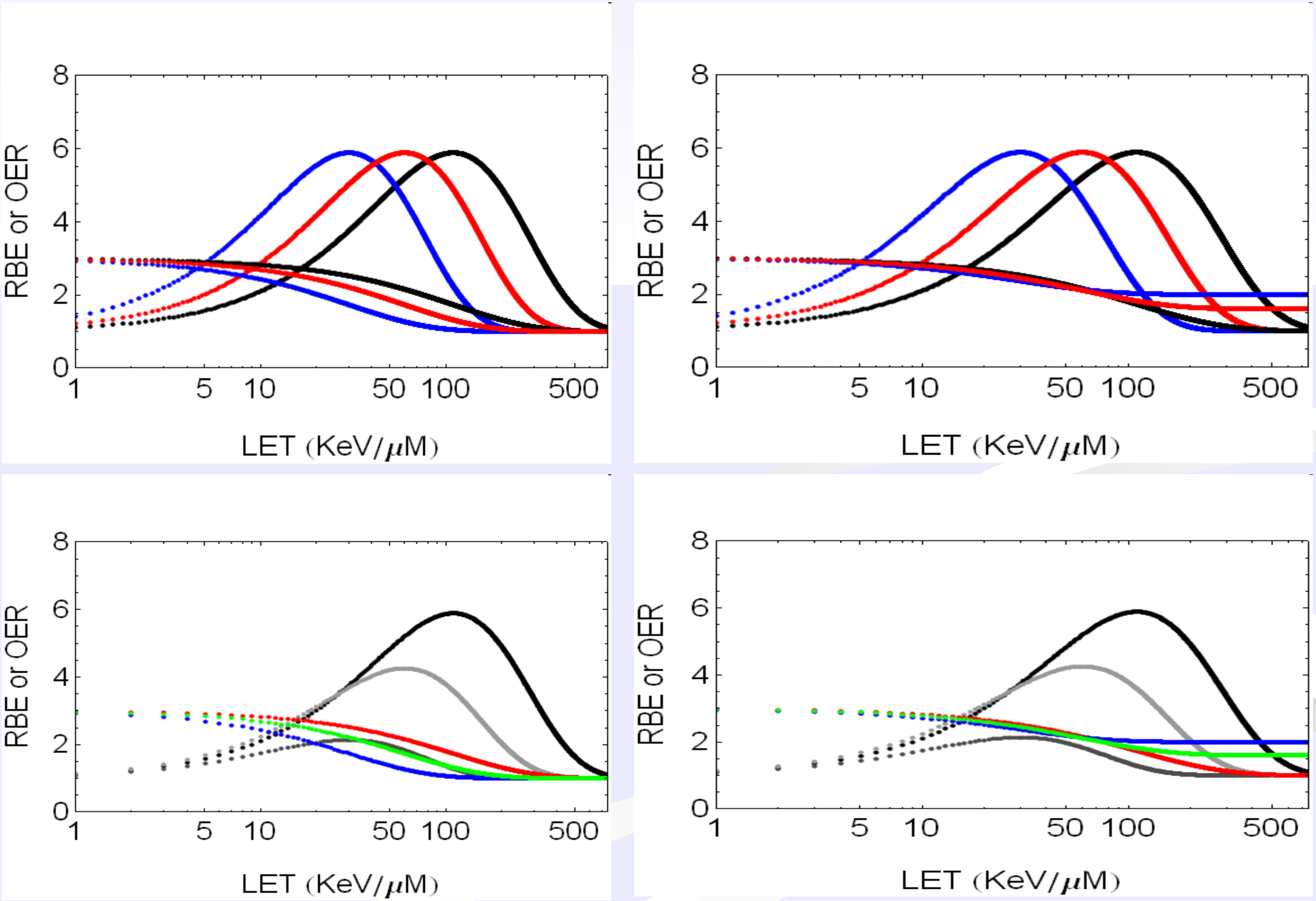


- RBE maximum is shifted to higher LET for heavier particles
- The shift corresponds to a shift to higher energies

Heterogenous Data Mining: Acta Oncol 2011, Sorensen, Overgaard and Bassler….V79 cells



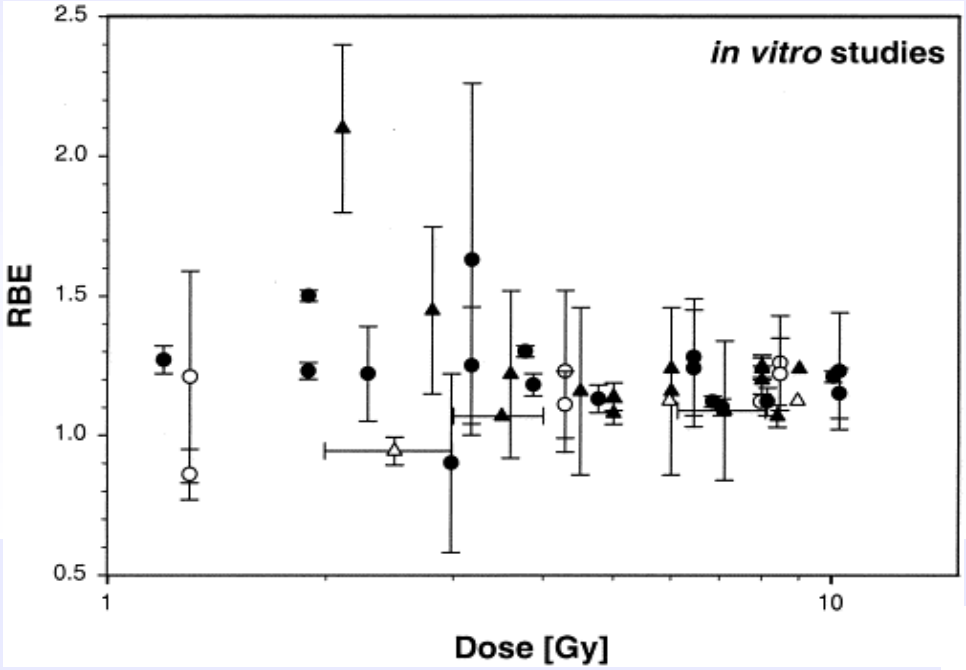
LET, RBE and OER……some hypotheses



Solution:

Build International Facility at CERN

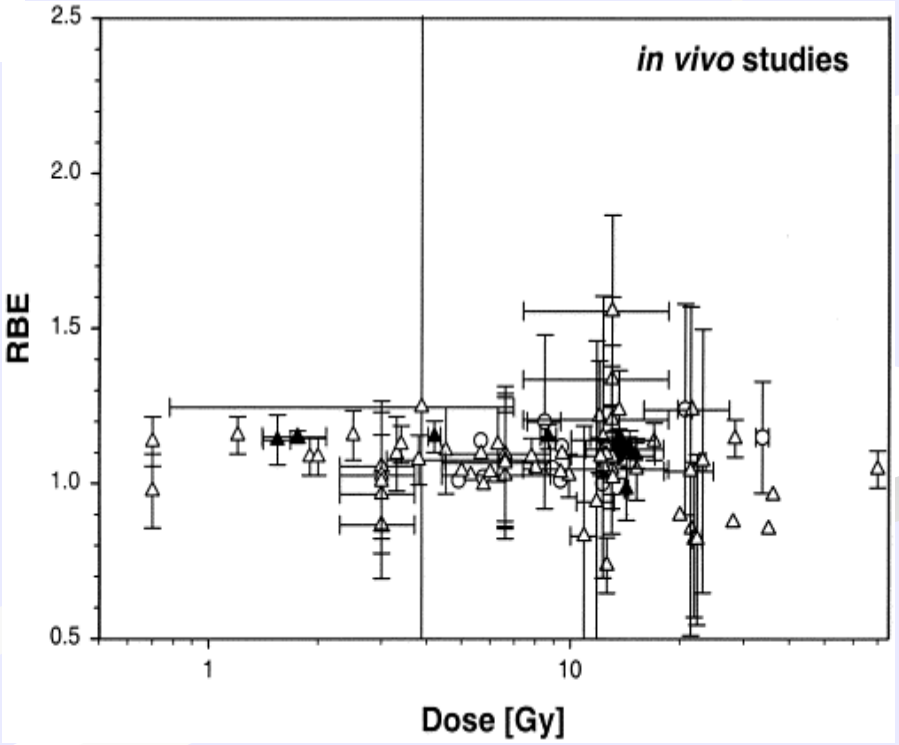
- Cost sharing between governments & other sources.
- Standardisation of experimental conditions
- Aim for <2% tolerance for Dose and RBE !!!
- Check ICRU system in 3-D (-5%+7%) in PTV
- **Physical** (z, mass, energy, fragmentation products, high & low LET fields, ballistics & dose distributions in humanoid phantoms) → **biomedical experiments**
- Proof of principle expts. in panel of human cell lines +drug modifiers etc.



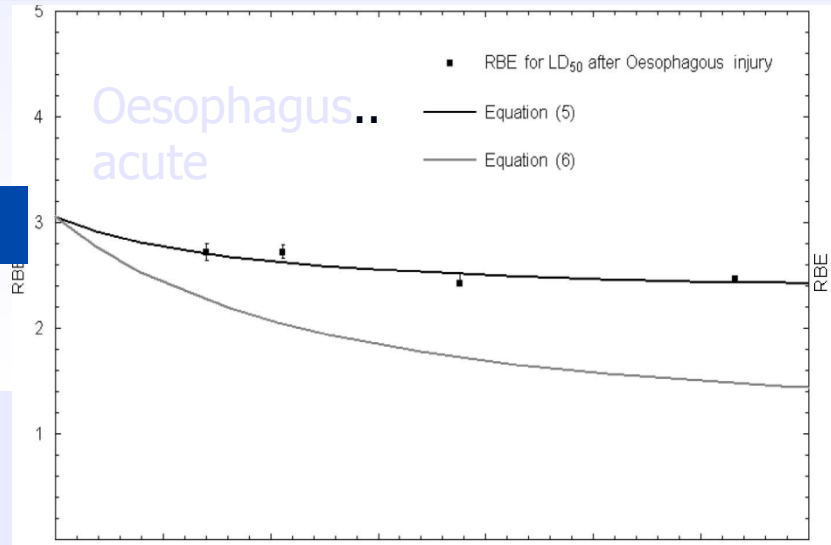
Boston review of proton RBE studies: Paganetti et al IJROBP 2002

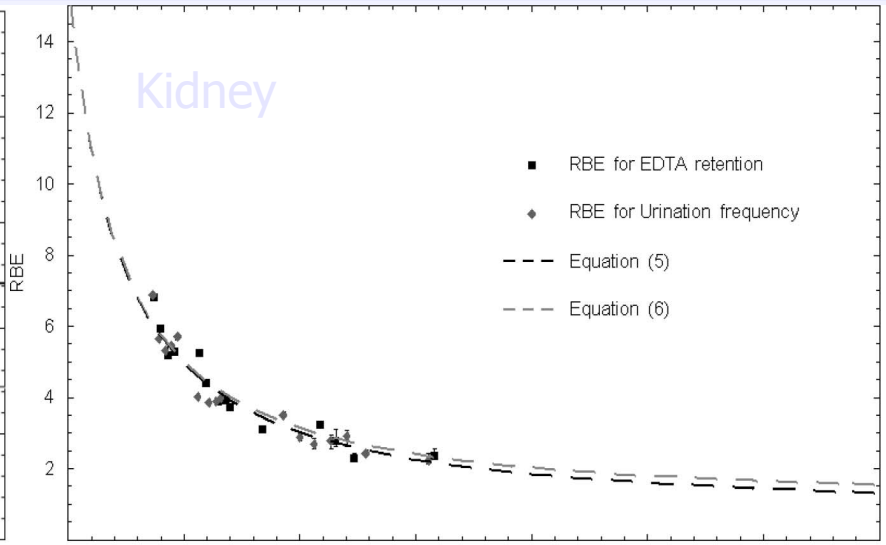
In vitro ? shows trend to higher RBE at low dose

In vivo and *in vitro* results are consistent with ***high α/β ratio endpoints***, as expected from rapidly growing CHO-V79 cells and acute small intestine crypt assay

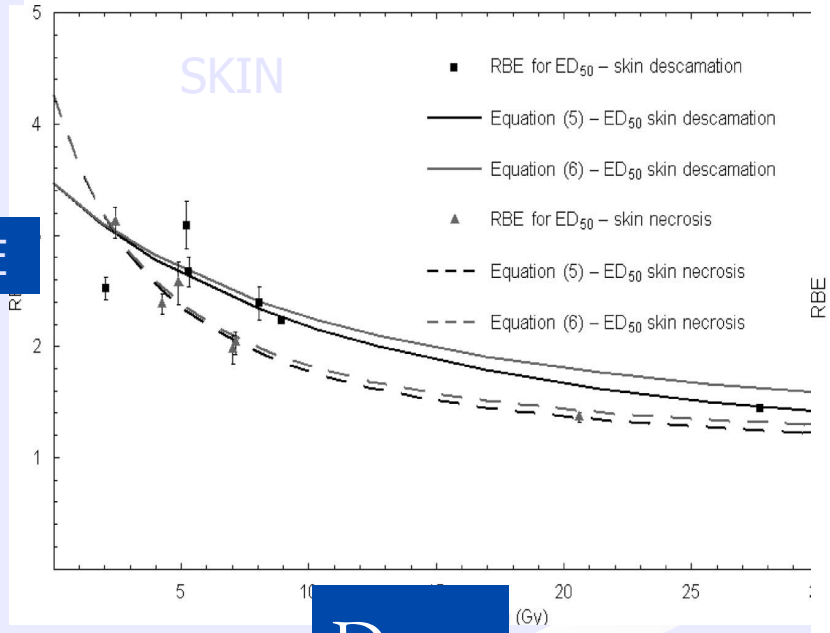


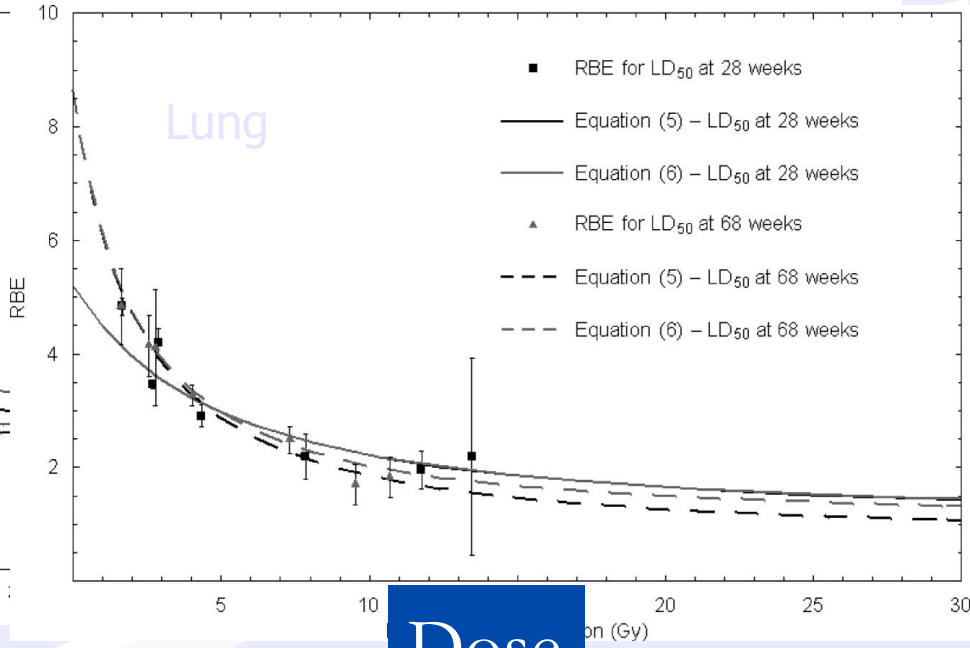
Examples of Hammersmith animal neutron experiments – Carabe-Fernandez et al IJRB 2007





RBE



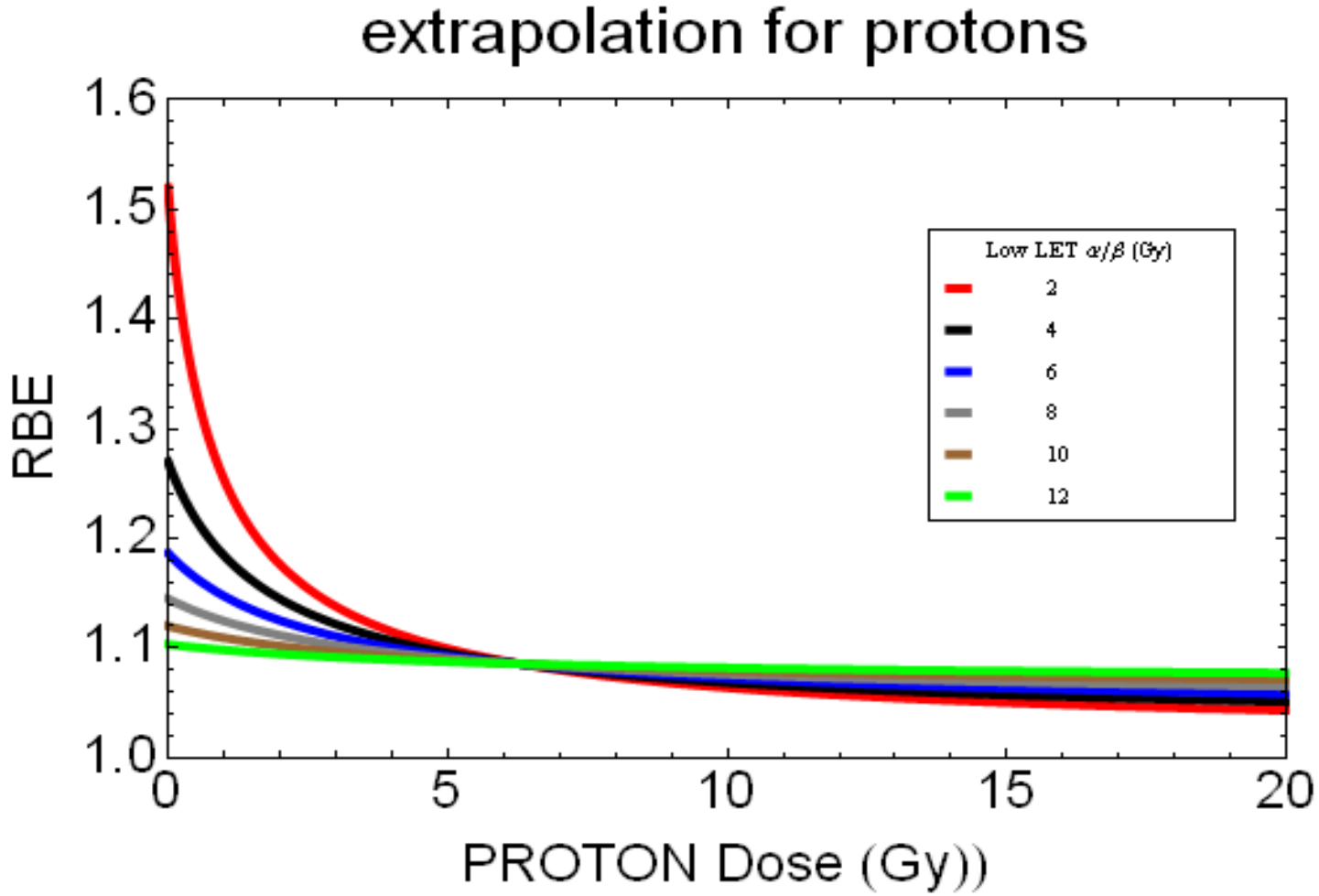


RBE

Dose

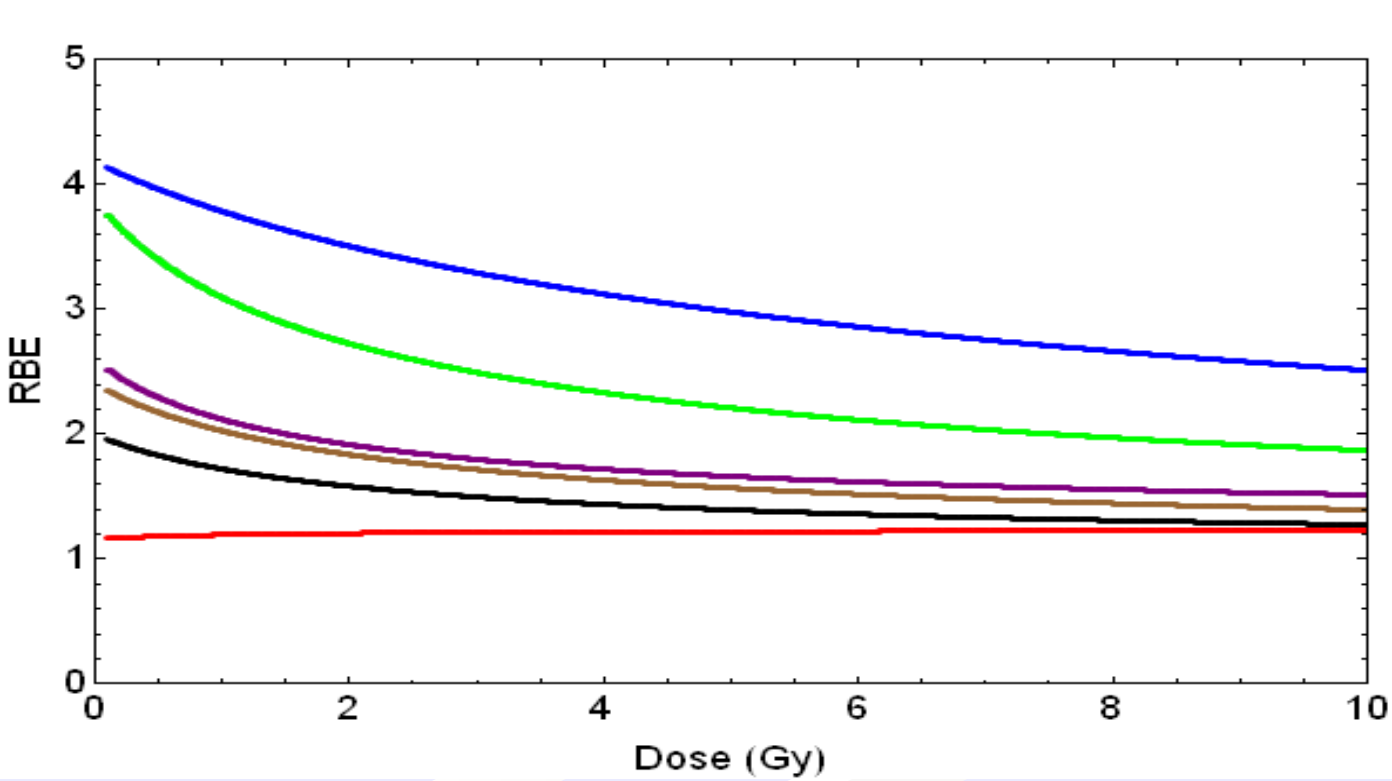
Dose

UK fast neutron data sets scaled down for average SOBP proton RBE



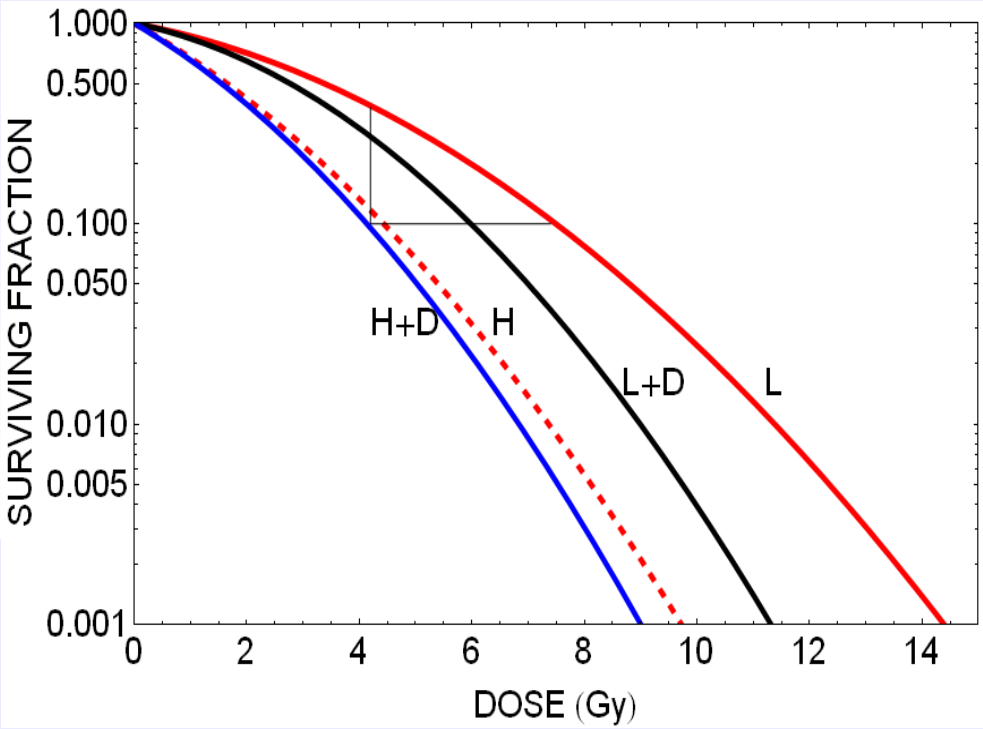
Jones, Underwood ,Timlin and Dale (Brit J Radiol –2011)

Proton RBEs modelled in UK from cell survival expts (Human hep2 cells) done by Richard Britten et al East Virginia Univeristy, Norfolk, USA) in SOBP in Bloomington (Indiana) beam at increasing depth

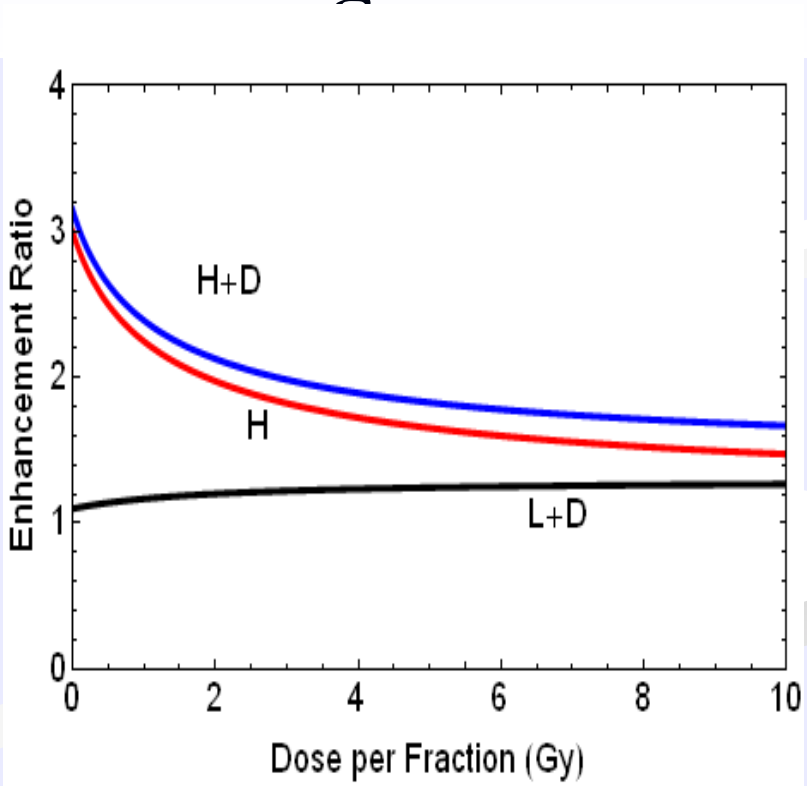


Particle - Drug Interactions

L=low LET
H=High LET
D=Drug



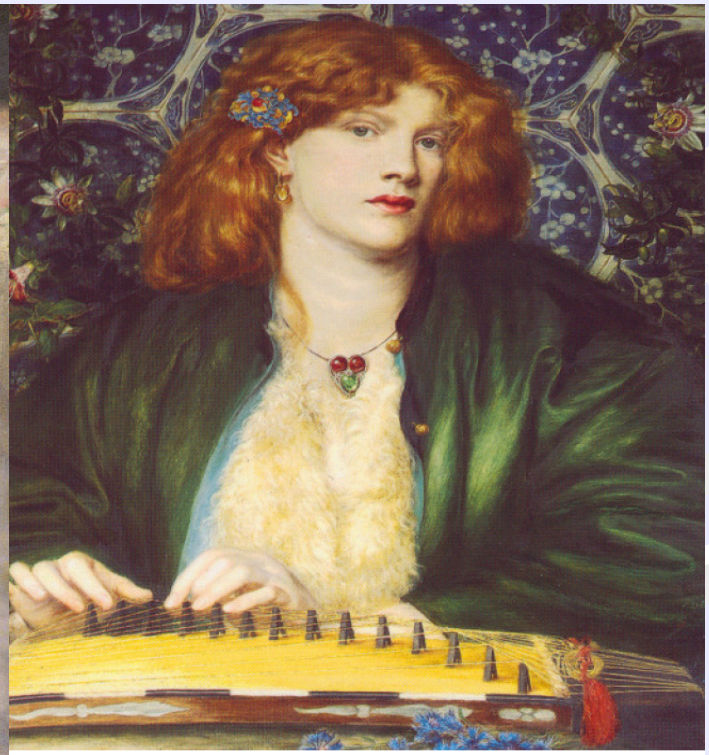
BED Ratios for:	*d=2 Gy*	*d=4 Gy*	*d=6Gy*
High LET/ Low LET	**2.54**	**2.29**	**2.13**
Low LET +SD / Low LET alone	**1.27**	**1.37**	**1.43**
High LET+ SD/High LET alone	**1.12**	**1.16**	**1.20**
Combined High LET + Drug Sensitised/Low LET alone	**2.83**	**2.66**	**2.55**



Mathematical modelling

- Scaling of cellular micro-dosimetry predictions to complex tissues
- Unification of present dose-time-fractionation models for megavoltage photons[x-rays] with high LET particles
- Sensitivity to dose per fraction for each tissue
- Influence of biological modifiers/drugs
- Low dose threshold effects previously thought to be stochastic [carcinogenesis, circulatory disorders]

CERN is ideal place for definitive & comprehensive 3-D dosimetry in humanoid phantoms along with biomedical experiments, and their analysis, to improve particle therapy



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