

# Brainstorming discussion for a possible biomedical facility at CERN – June 25, 2012

## Problems and Solutions

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**MRC**

Medical  
Research  
Council

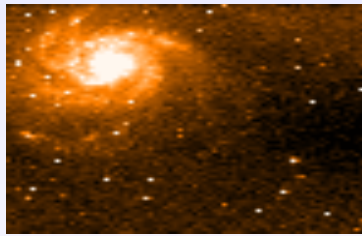
**CANCER RESEARCH UK**



# **Particle therapy has intrinsic uncertainties**

**They include:**

- Physics (dose and its correct position in the body)**
- Biology – how do different cells/ tissues & tumours respond to these treatments compared with photons/ x-rays?**



# **Prolonged Air and Space travel also has uncertainties**

Solar flares, Cosmic rays, high energy  $\gamma$ , protons & heavier ions, all pose health threats from acute and late [cancer, circulatory/organ failure] tissue effects.

Journey to Mars could be a  
'one way ticket'.



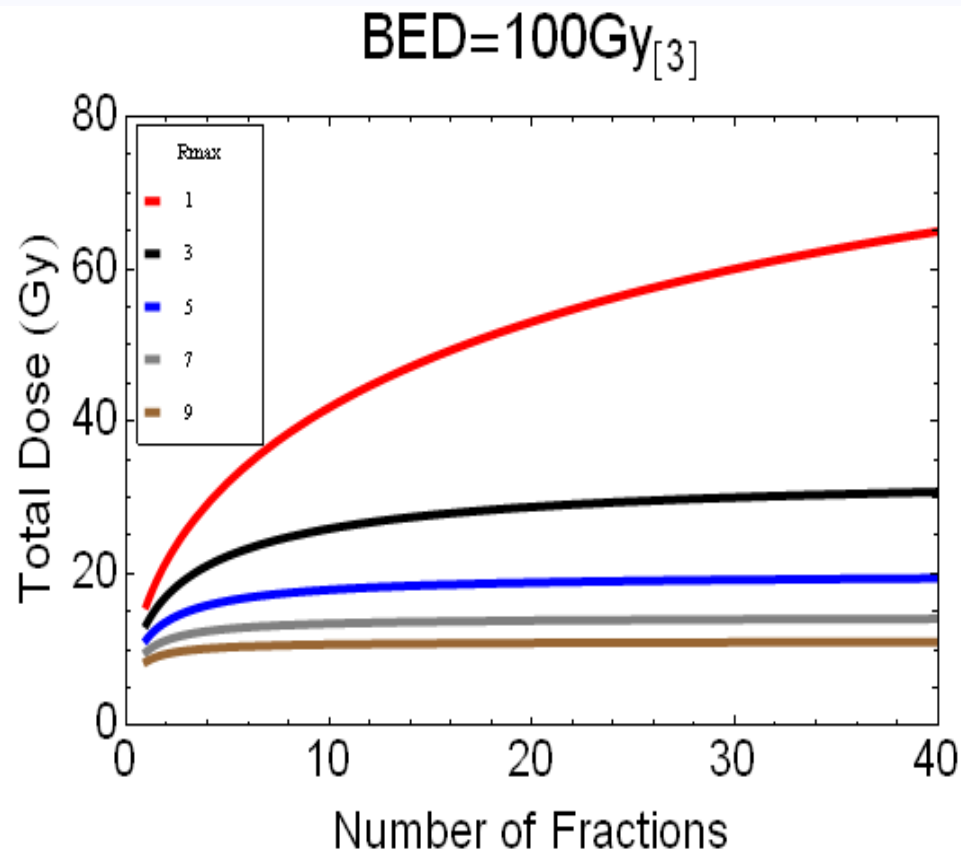
# Relative Biological Effect –a simple ratio?

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 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 &  $\gamma$ -ray contamination
- **Cell & Tissue** type : slow growing cells have highest RBEs.

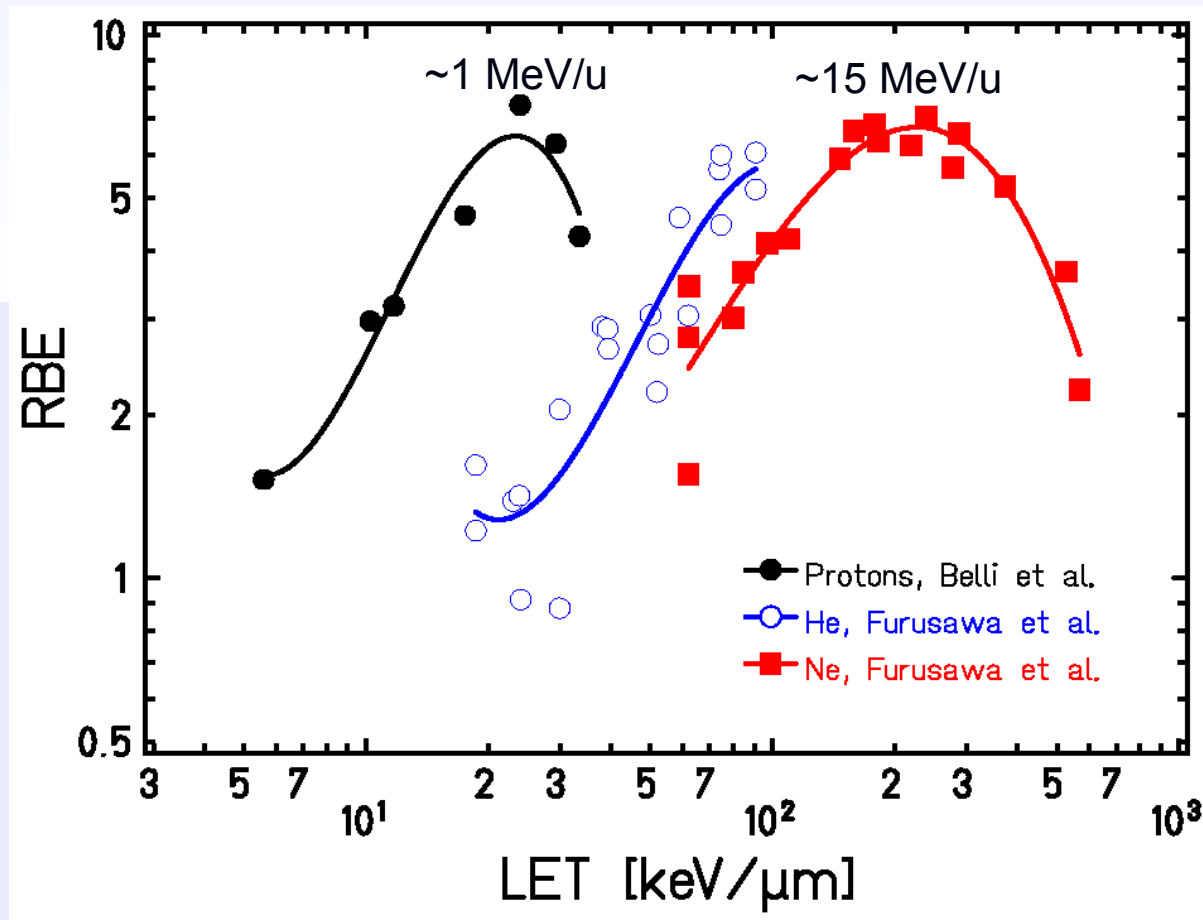


# The problems: past research

- Various physics labs: USA, Holland, UK, Germany, France, Belgium, Japan etc.
- Variation in physical beam parameters, dose , LET
- Limited beam availability
- Cells.....variable, often rapidly growing
- 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

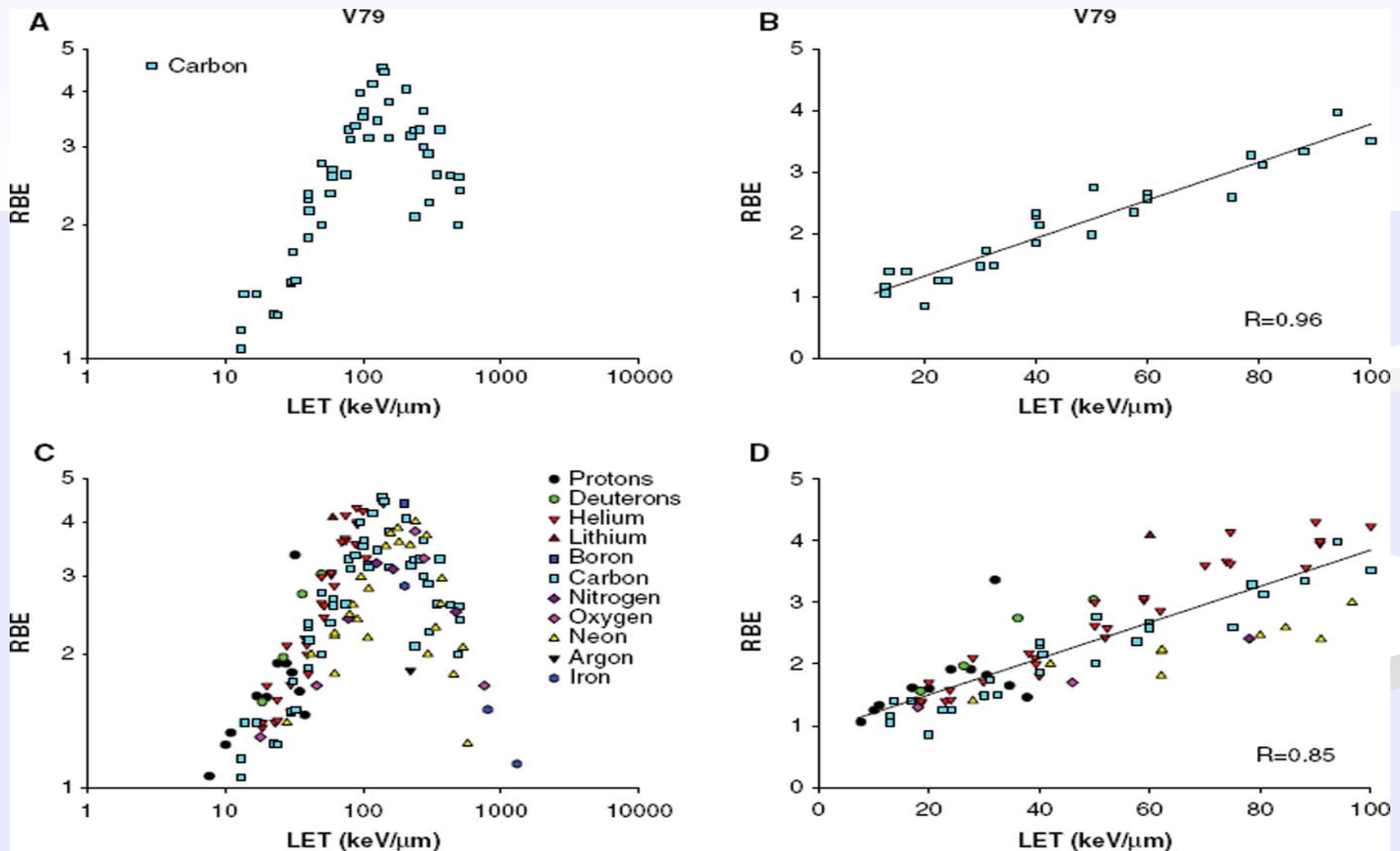


# RBE depends on Atomic number [Z] and Neutron number [N]

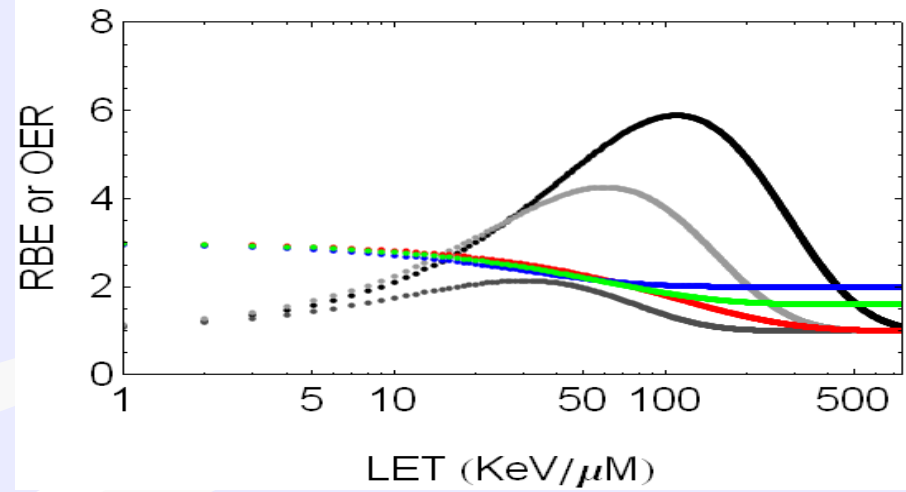
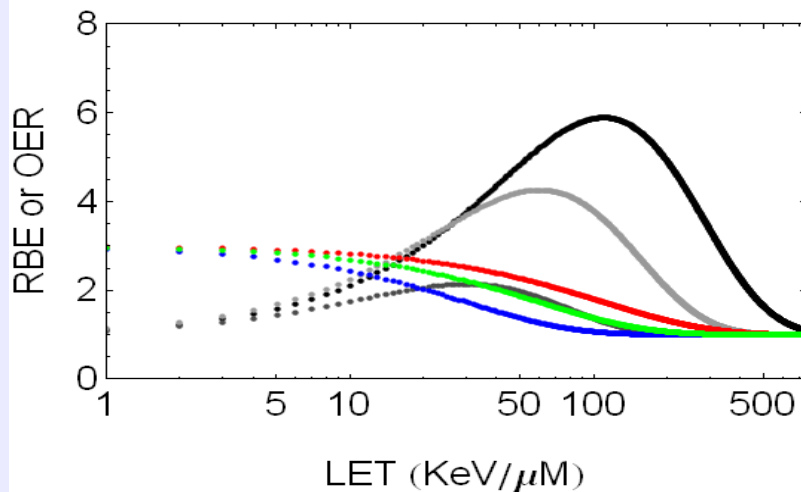
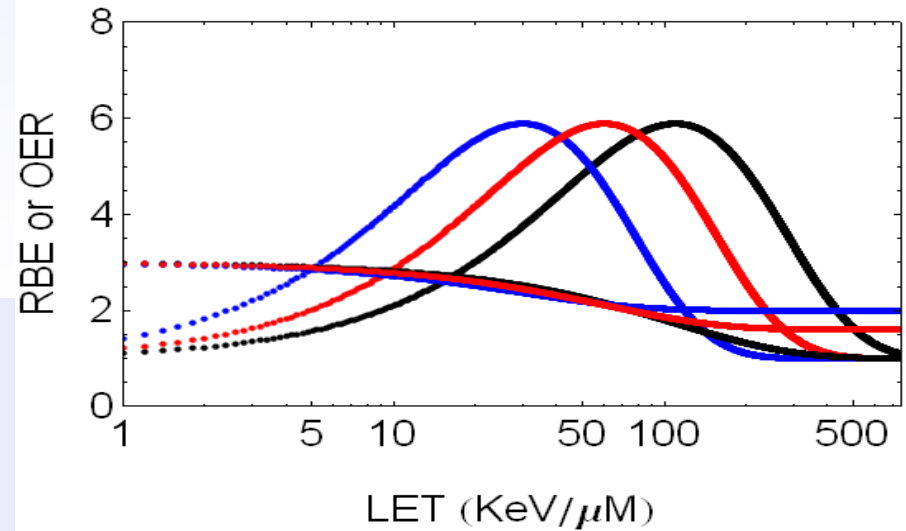
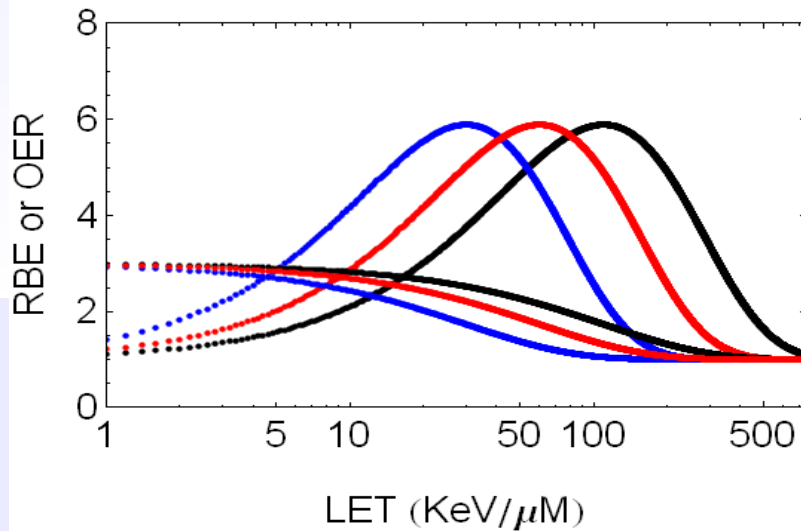


- RBE maximum is shifted to higher LET for heavier particles
- The shift corresponds to a shift to higher energies

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



# LET, RBE and OER.....some hypotheses

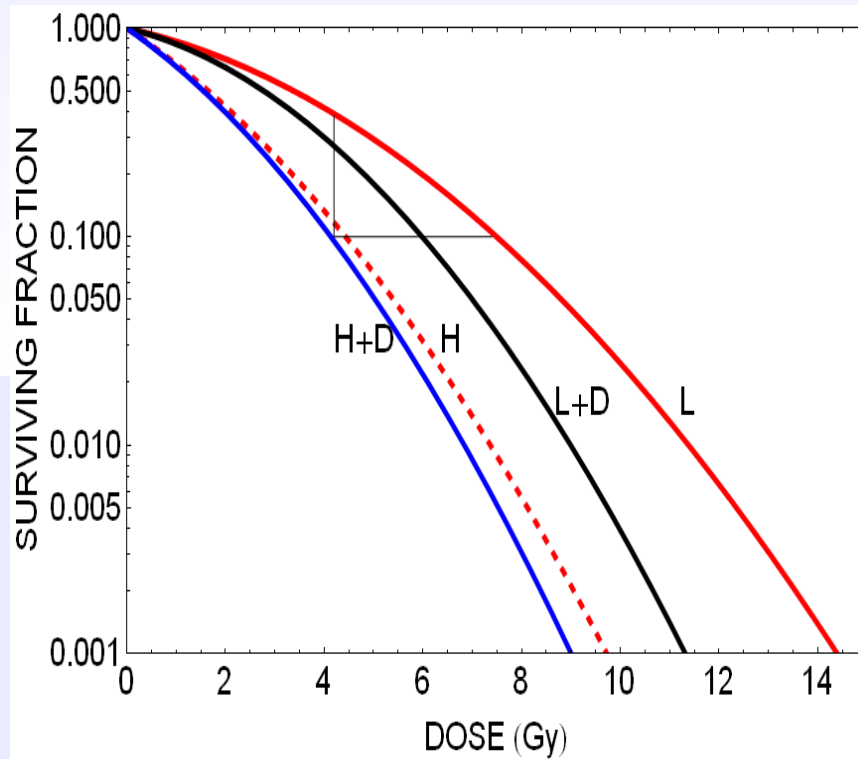


# **Solution:**

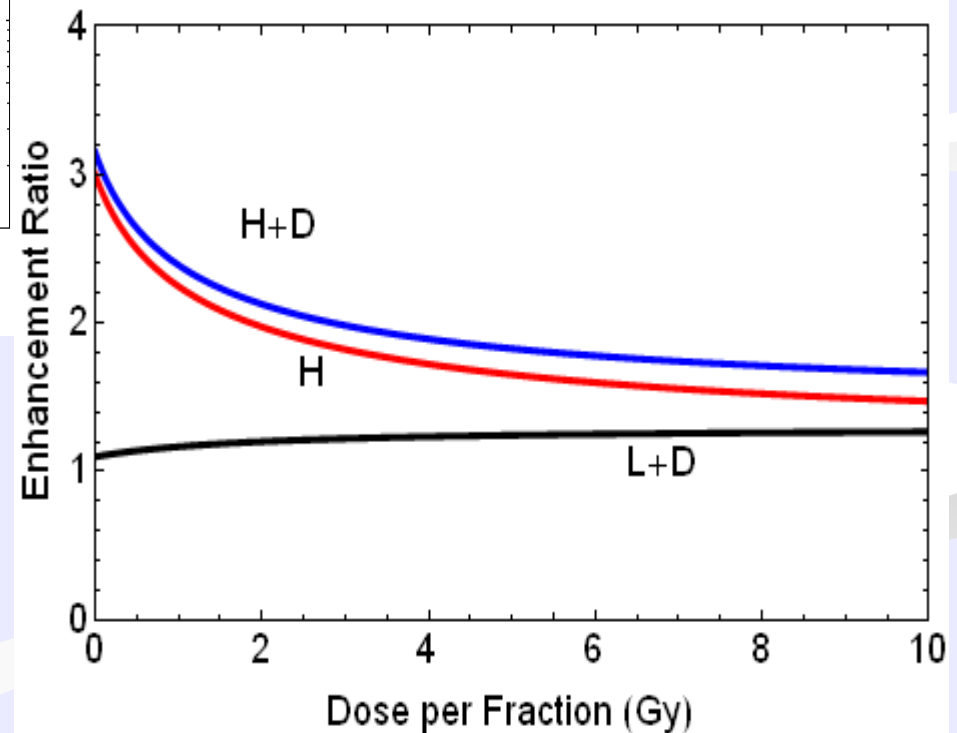
## **Build International Facility at CERN**

- Cost sharing between governments & other sources.
- Standardisation of experimental conditions
- Aim for <2% tolerance for Dose and RBE !!!
- **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
- Then tissue expts.+drug modifiers etc. → clinical aps.

# Particle - Drug Interactions



L=low LET  
H=High LET  
D=Drug



# Why normal tissue?

- Just as particle physics experiments on isolated atoms/subatomic particles will not predict aggregate behaviour, e.g. superconductivity etc.

So, need vascularity and complete tissue architecture to assess bio-effects as a function of time.

- Pre or Post exposure Drug modification (sensitisation and protection) of tissue radiation effects inc. carcinogenesis, vascular
- At CERN/or with other facilities?

**Obtaining RBE at any dose per fraction, use:**

$$BED = D_L \left( 1 + \frac{d_L}{\left(\frac{\alpha}{\beta}\right)_L} \right) = D_H \left( RBE_{max} + \frac{RBE_{min}^2 d_H}{\left(\frac{\alpha}{\beta}\right)_L} \right)$$

**Replace RBE<sub>max</sub> & RBE<sub>min</sub> by functions of  $\alpha/\beta$  ,  
then solve as:**

$$RBE = \frac{0.5}{d_H} \left( -\left(\frac{\alpha}{\beta}\right)_L + \sqrt{\left(\frac{\alpha}{\beta}\right)_L^2 + 4d_H \left(\frac{\alpha}{\beta}\right)_L \left( C + \frac{A}{\left(\frac{\alpha}{\beta}\right)_L} \right) + 4d_H^2 \left( K + B \sqrt{\left(\frac{\alpha}{\beta}\right)_L} \right)} \right)$$

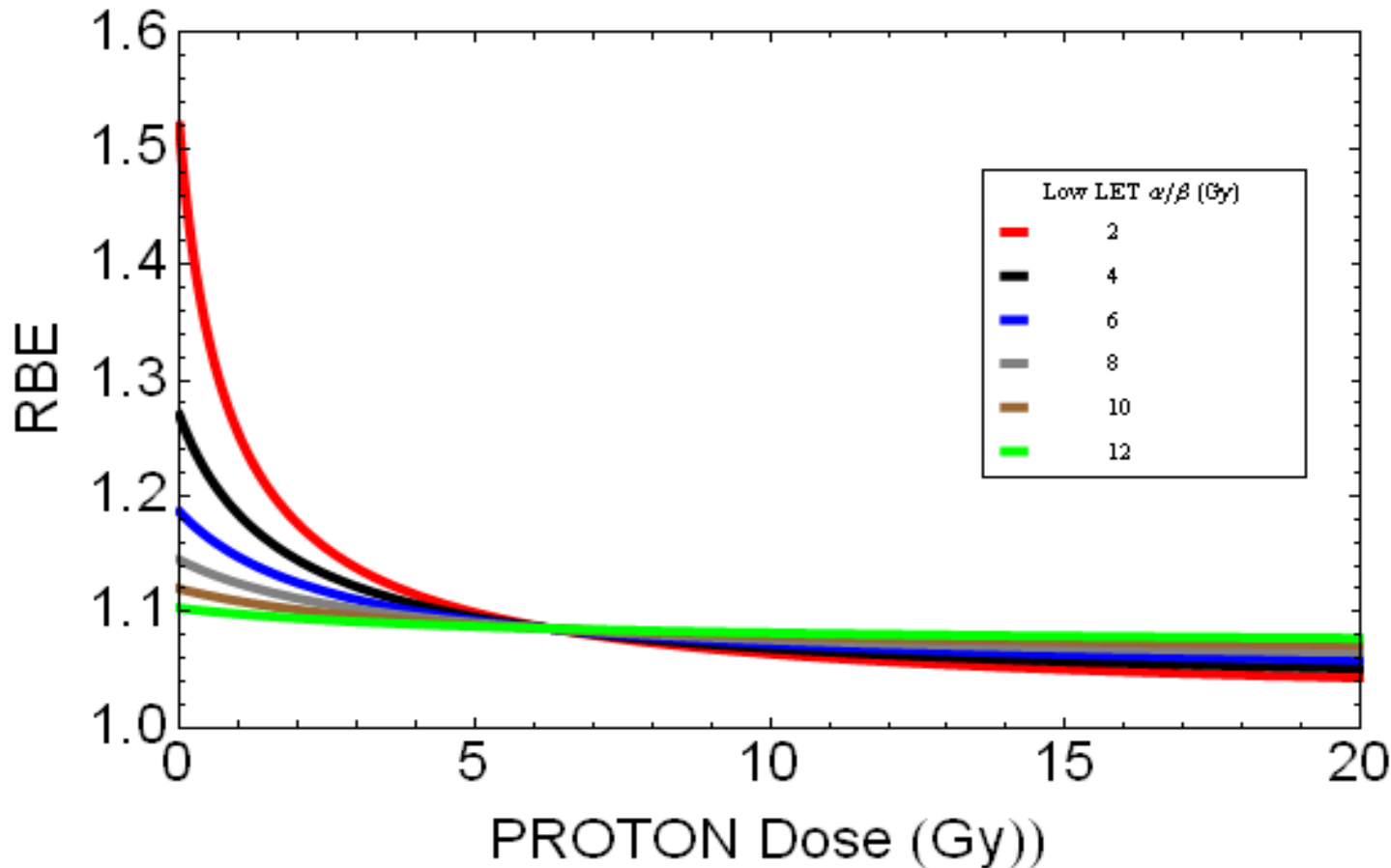


If relationship scaled down for protons as:

$$\text{RBE}_{\text{max}} = 1.0 + 1.2 / (\alpha / \beta)_L$$

$$\text{RBE}_{\text{min}} = 1.0 + \text{Sqrt}[0.0005 \cdot (\alpha / \beta)_L]$$

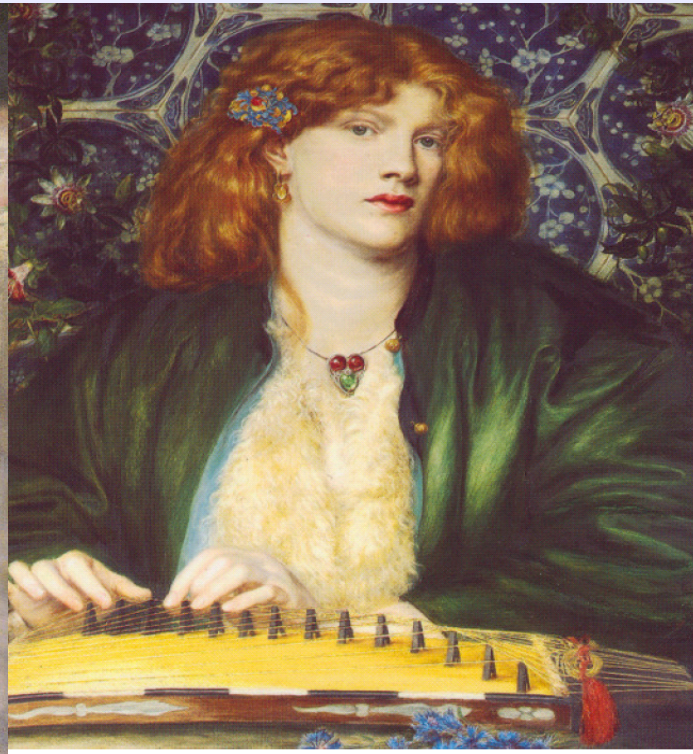
extrapolation for protons



# 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 biomedical experiments,  
and their analysis, to better inform  
Clinical Oncology & Radioprotection**



**Barber Institute of  
Art**

**University of  
Birmingham UK**