ENLIGHT, UTRECHT 2016

BIO-LEIR – what are the necessary experiments?

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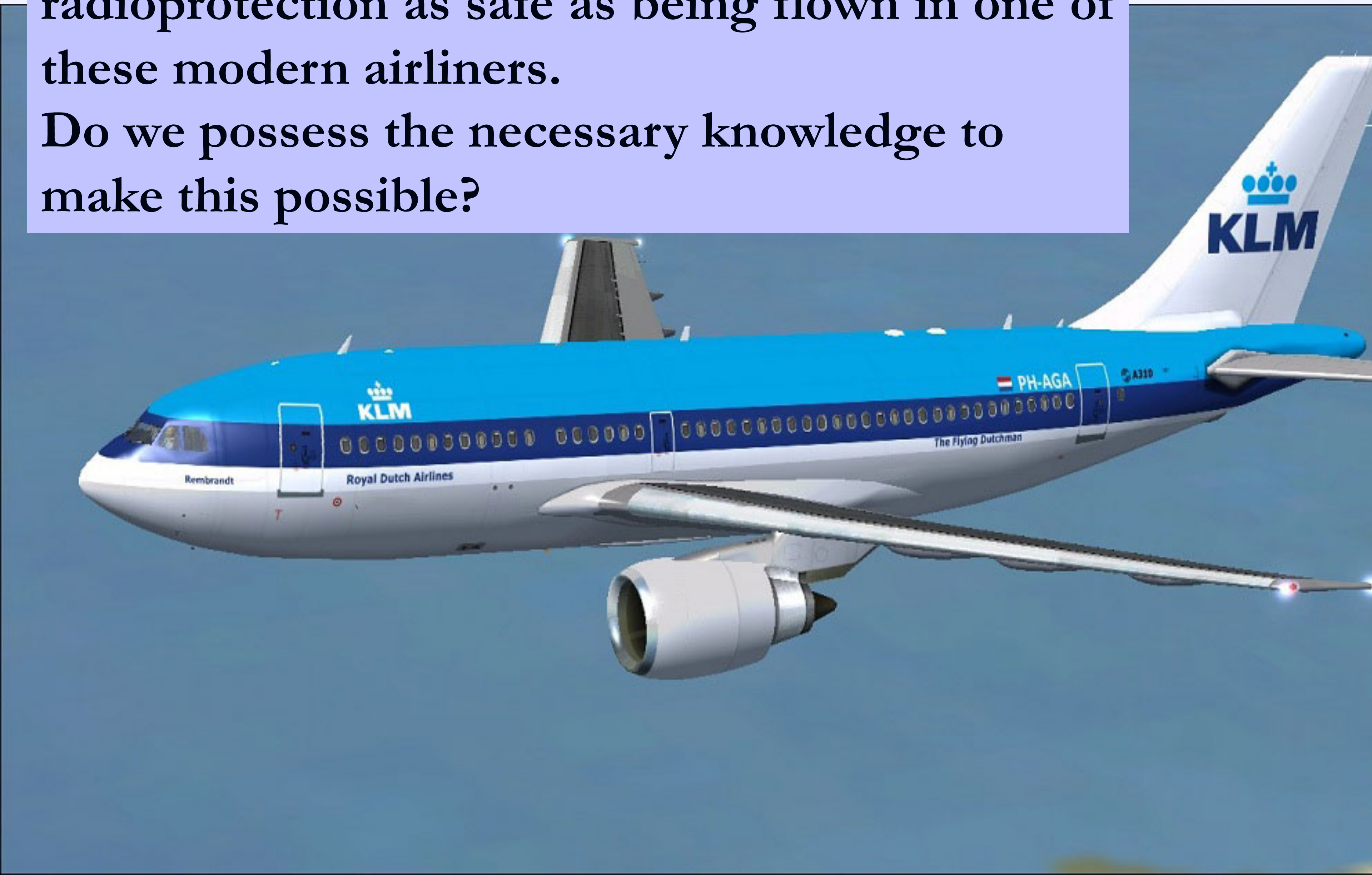
Can we make radiotherapy/nuclear medicine/ radioprotection as safe as being flown in one of these modern airliners.

Do we possess the necessary knowledge to make this possible?



Relative Biological Effect – ratio of doses for ISOEFFECT

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

The conventional radiation

The particle radiation

$$\text{Particle Dose to Patient} = \frac{Dose_{[Low\ LET]}}{RBE}$$

Implications of an incorrect RBE

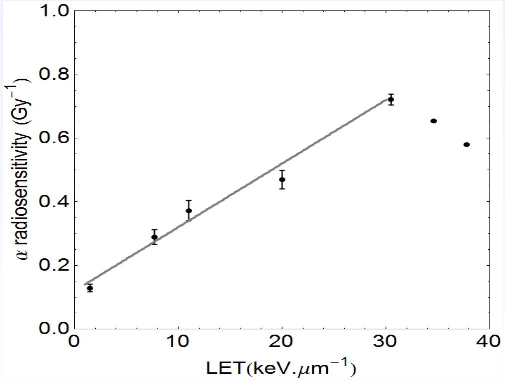
- Legal dose requirements are ± 2% from accelerator
- Recommended ICRU dose variation across a PTV target is -5 to 7%.
- IF: RBE is incorrect by say 10, 30, 50% in some instances, then the above recommendations can be breached, and possibly seriously.
- Applies to radiotherapy, nuclear medicine, radioprotection

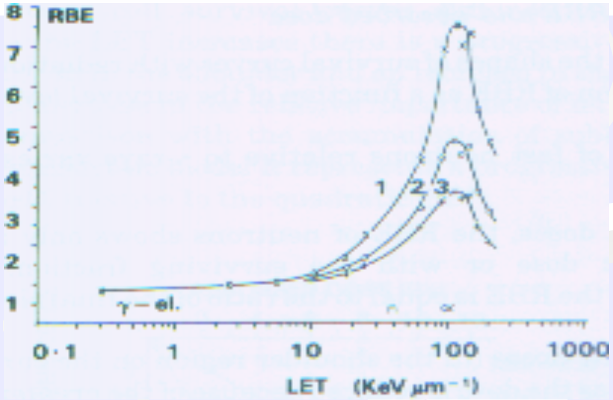
RBE depends on ……..

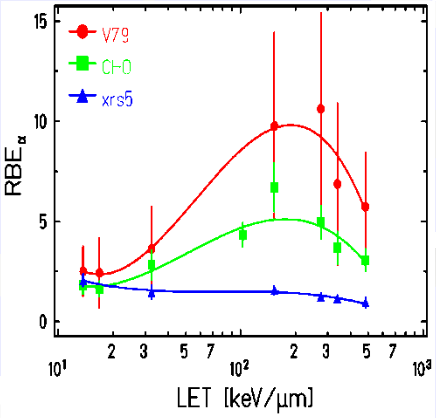
- **Particle Nuclear Charge [Z], Energy & Depth**
- Target **Volume** [mix of high LET Bragg peaks + low LET entry beams]
- **Dose** per treatment ...RBE varies inversely with dose.
- **Facility: neutron & γ-ray contamination**
- **Cell & Tissue type : slow growing and radiation repair proficient cells have highest RBEs, as in Normal Tissues.**

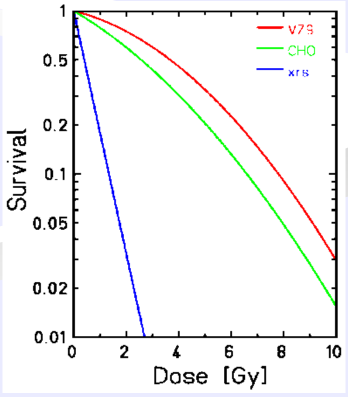
Any model of RBE must respect these six facts/phenomena

- RBE increases (LINEARLY) with LET until a maximum value LET_U is reached, followed by decreasing values.
- Increasing the radiation dose produces a **symmetrical** reduction in the LET-RBE relationship. The LET_U for each does not change with dose.
- It follows that RBE is inversely related to dose, but RBE magnitude depends upon the cell or tissue type.
- Systems with high radiosensitivity to the control radiation have a substantially lower RBE than cells which are more radioresistant to the control radiation.









Facts/phenomena II

- At any particular LET value on the overall LET-RBE plot, the relationship between RBE and dose varies between a maximum RBE (RBEmax) at near zero dose to a minimum value (RBEmin) at high dose.
- The magnitude of the RBE ceiling for each cell type is possibly independent of the ion species in some data sets, but again this needs to be determined by well-designed experiments using different ion beams.

260 The Radiobiology of Human Cancer Radiotherapy

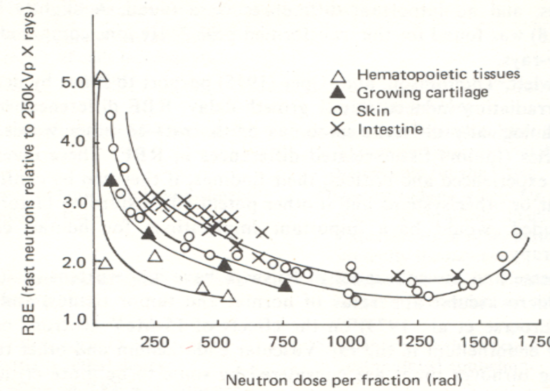
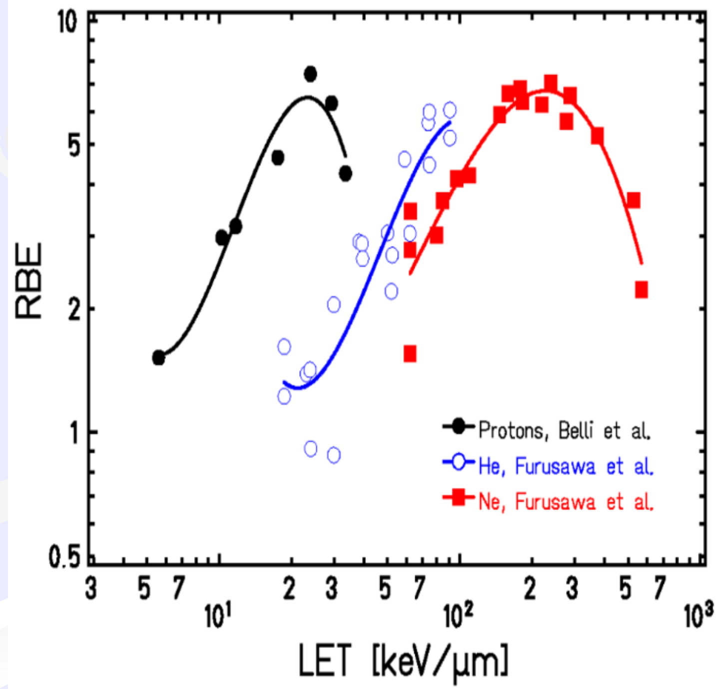


Figure 15.22. RBE for fast neutrons relative to 250-kV X-rays as a function of neutron dose for certain normal mammalian tissues, as indicated. Hornsey, 1970.

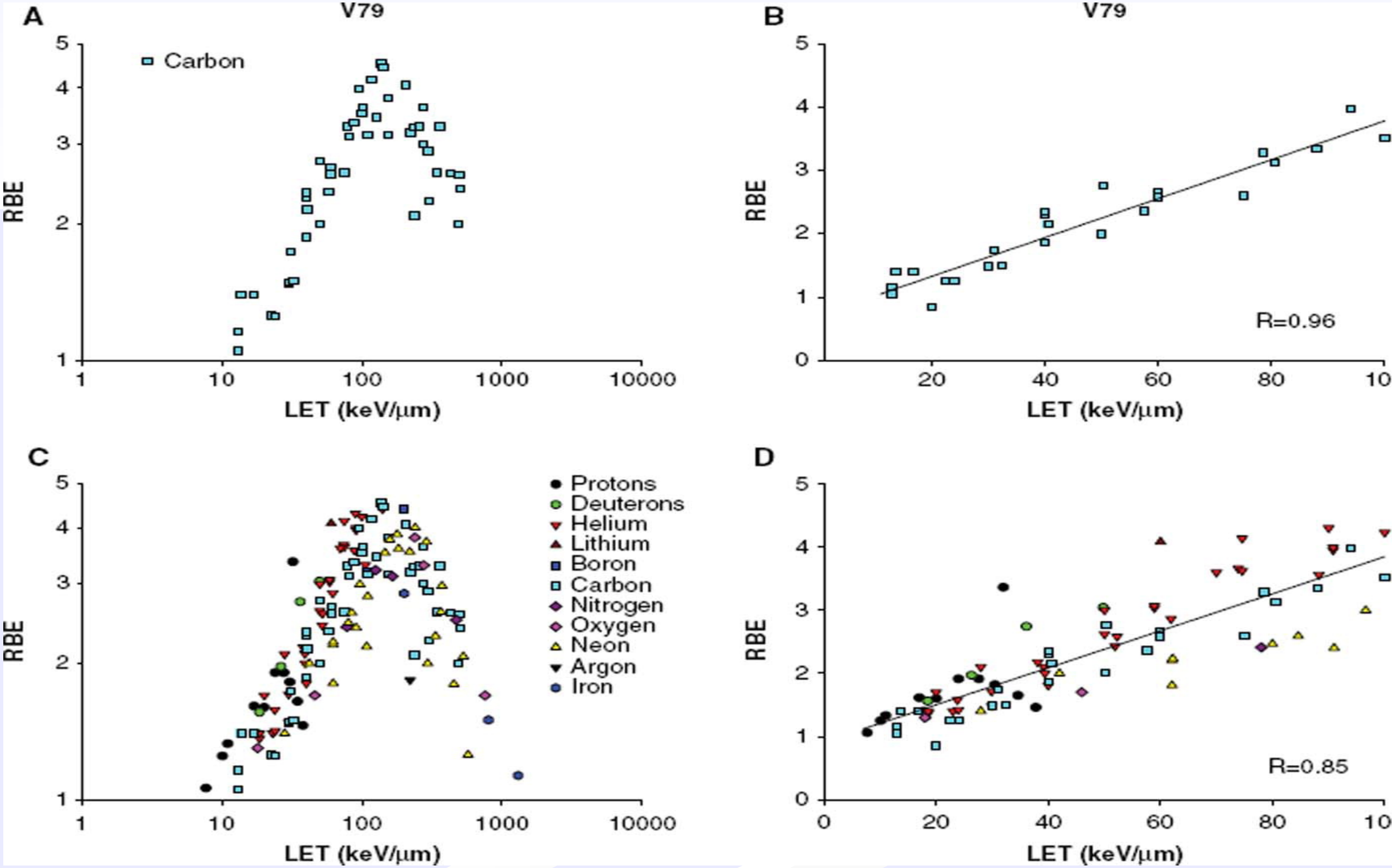


Textbook statements

- Leading textbooks such as Hall and Gaccia, maintain that all ions have max efficiency around 100-120 keV.μm^{-1}, and claim this is relevant to DNA dimensions.

This claim ignores the important radial distribution of δ-rays around a particle track, which will be unique for each ion and proportional to Z, the atomic charge.

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



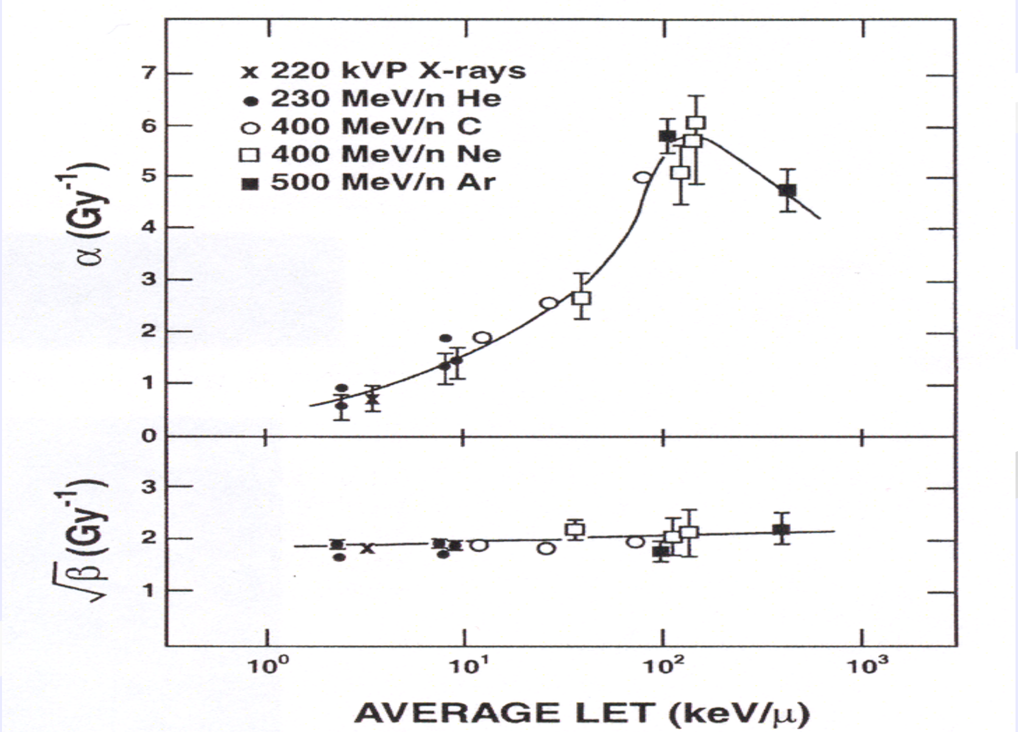
Does β parameter change with increasing LET ?

Since ratio $\sqrt{\beta_H}:\sqrt{\beta_L}$ is the RBE_{MIN} - at very high dose – then this ratio needs to be known if >1

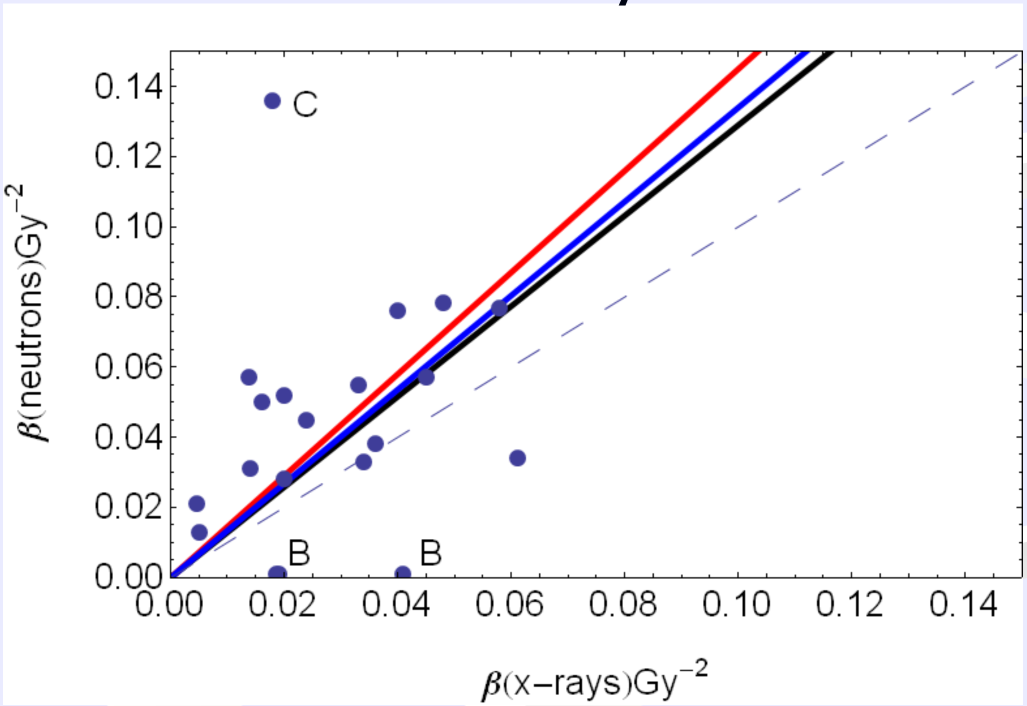
More research necessary to confirm if RBE_{MIN}>1 at range of high LET beam energies.

For each beam, each cell/tissue type would need to have this ratio estimated.

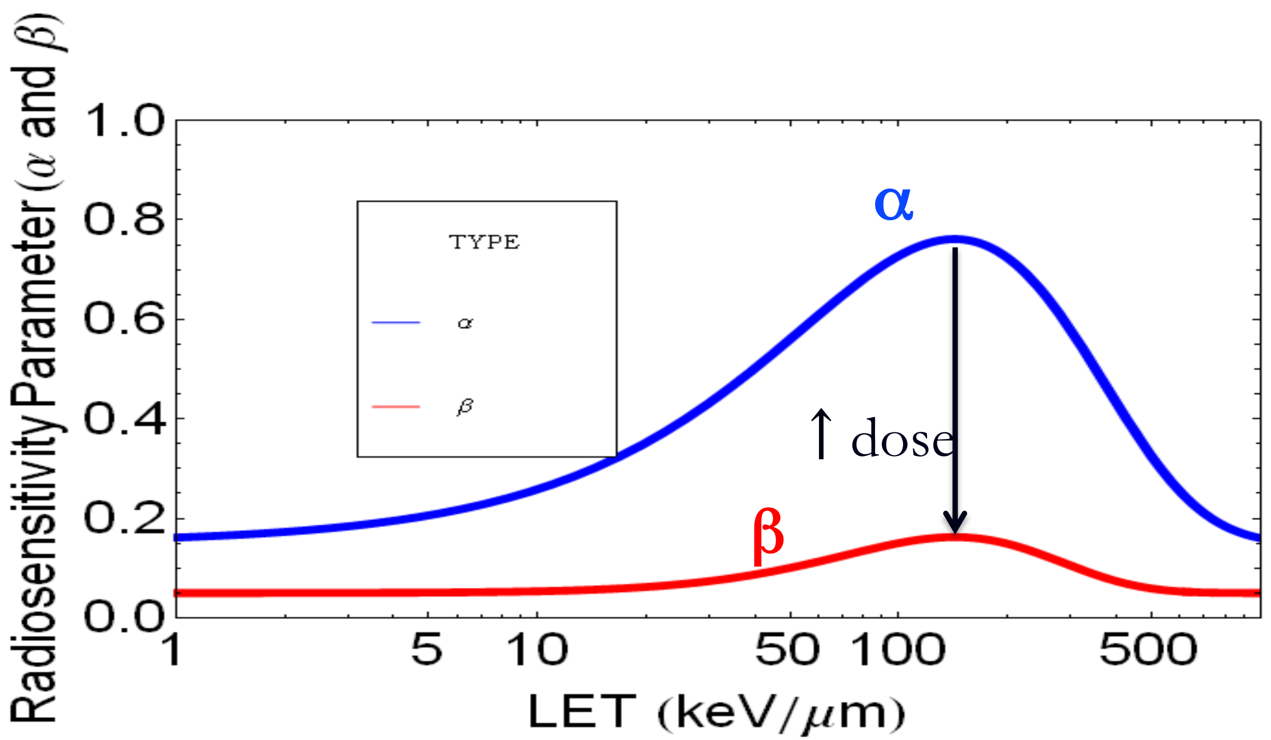
Chapman (IJRB 2003) measured √ β, a larger number than β, and found no significant difference with increasing LET in CH V-79 in plateau phase.



β increases with LET [in the case of fast neutrons] in 23 human tumour cell lines. BUT the increase is small compared to α.
(Jones B. Brit J Radiology, 2009) using data of Britten and Warenius et al, Clatterbridge UK, show that α increases by 3.17 , √β increases by 1.59 for 60 MeV Neutrons compared with 4 MeV x-rays.



To build a model that includes above phenomena, assume the same turnover point for increment in α and β with LET, unique for each ionic Z number, in order to preserve symmetry of relationship when dose changes.



Increasing dose gives greater proportion of β-mediated damage (linked to dose^2)

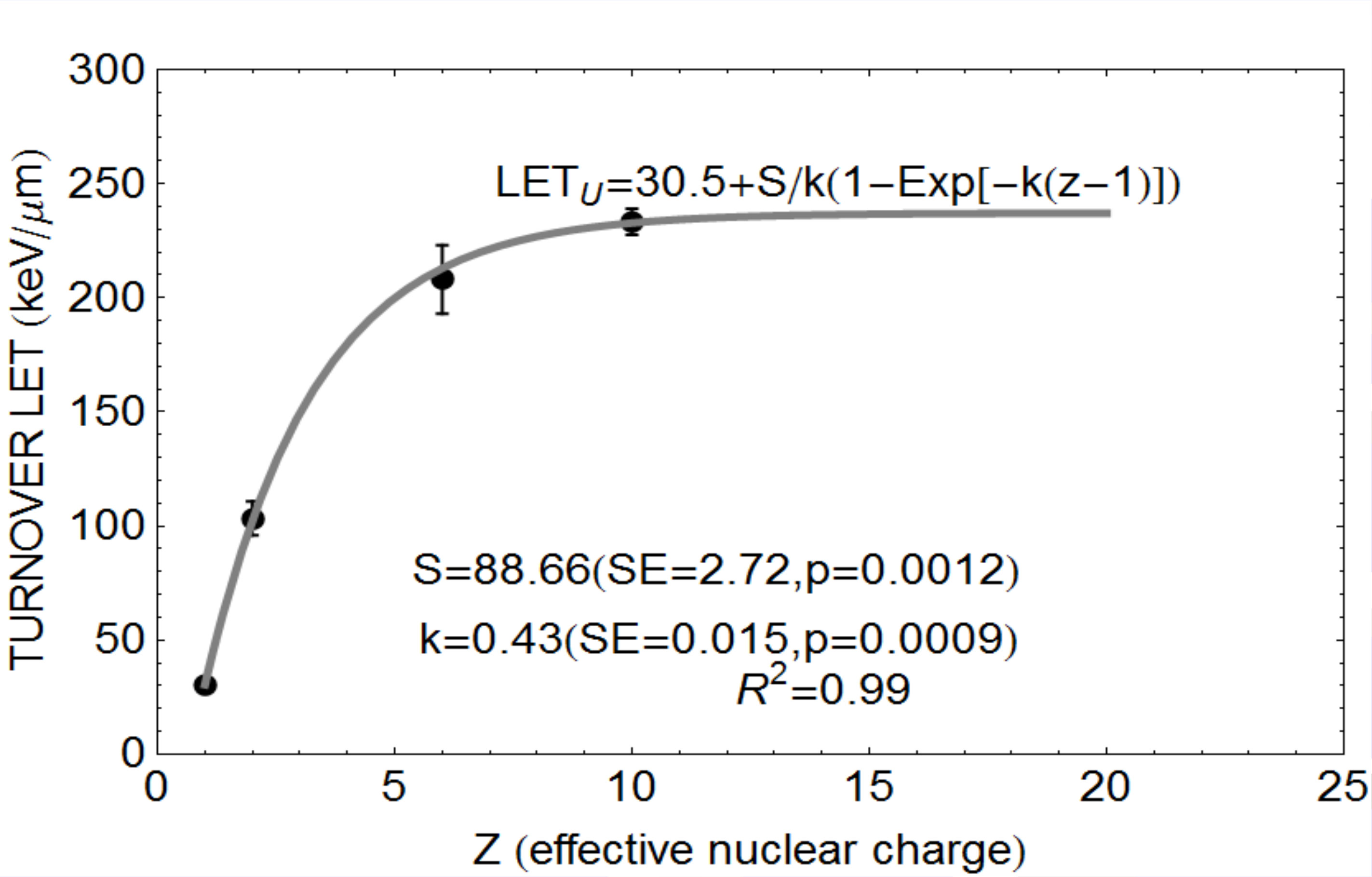
Important IF`s for charged hadrons when compared with megavoltage photons

IF: $RBE_{NT}>RBE_{Rx}$ in the normal tissue included to full dose (CTV+PTV), worse side effects could occur if these tissues are clinically important

IF: $RBE_{NT}>RBE_{Rx}$ outside the PTV, then the degree of tissue dose sparing achieved must exceed this difference, depending on the true tolerance level of the tissue of concern.

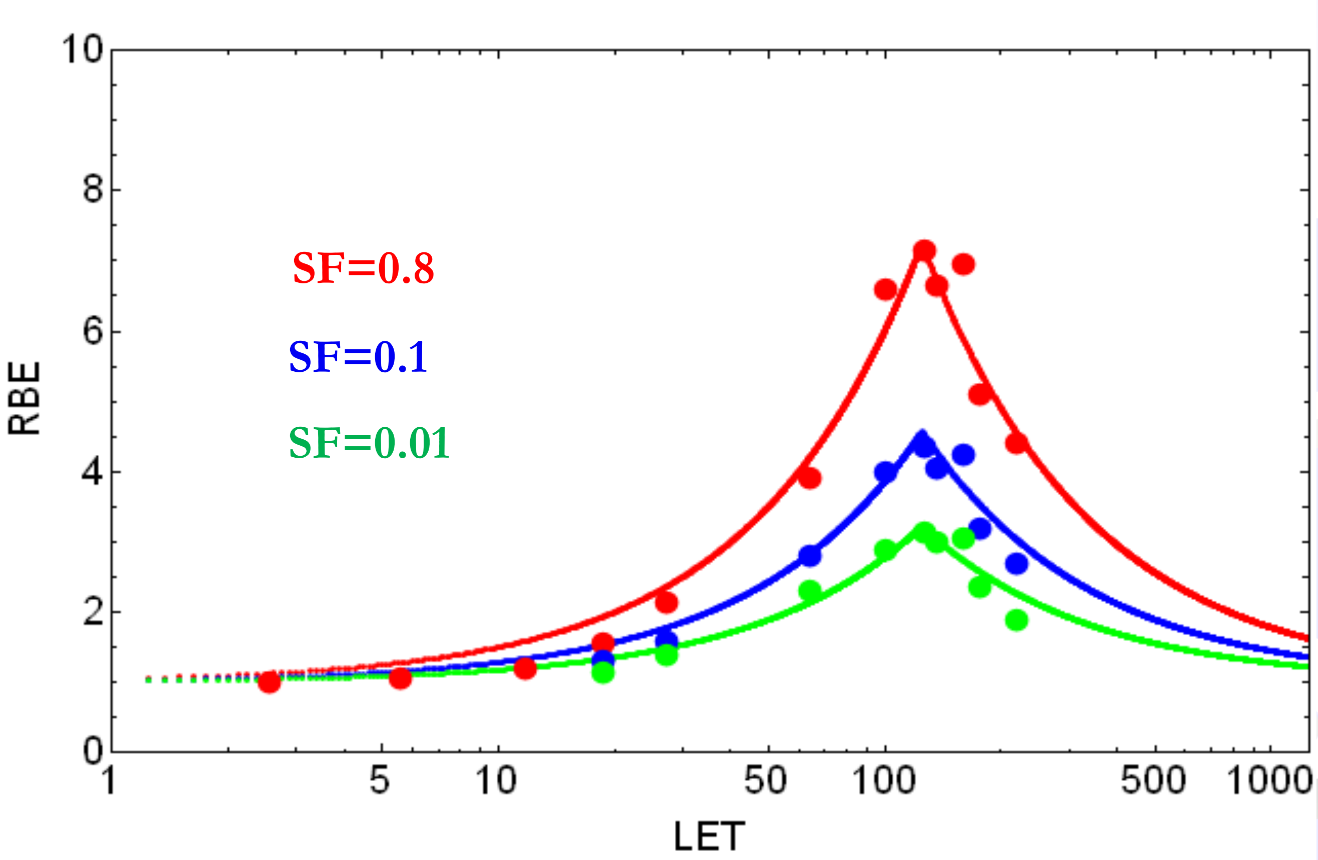
IF: $RBE_{CA}<RBE_{Rx}$, then cancer could be underdosed (applies mainly to tumours with high sensitivity to megavoltage x-rays).

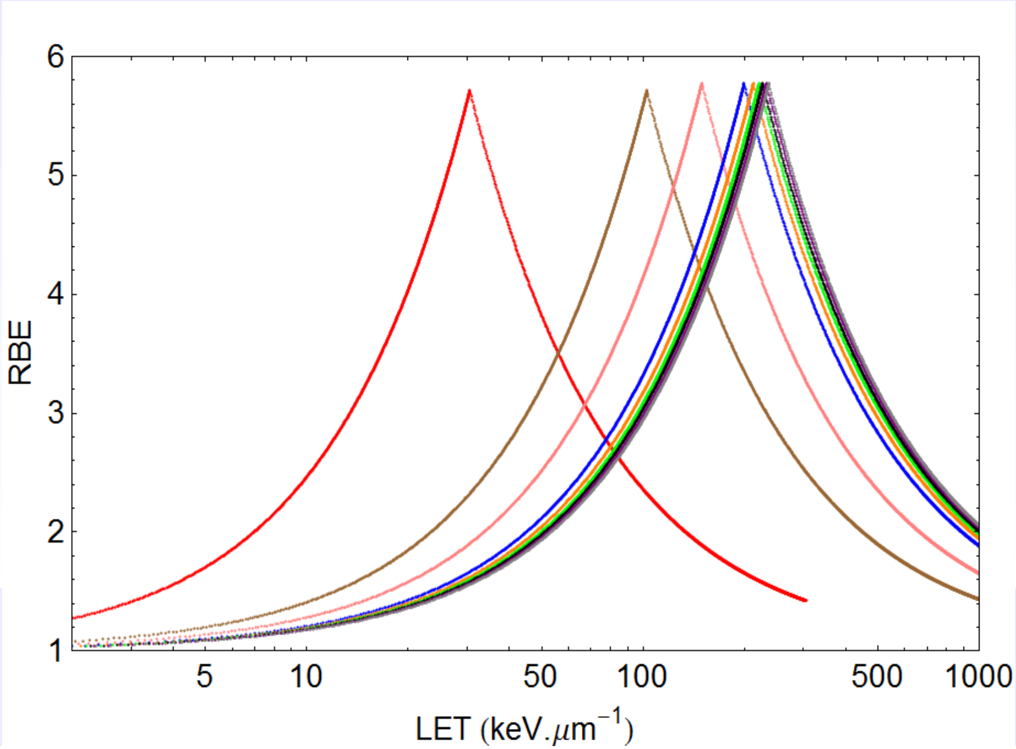
Estimating position of LET-RBE turnover point.

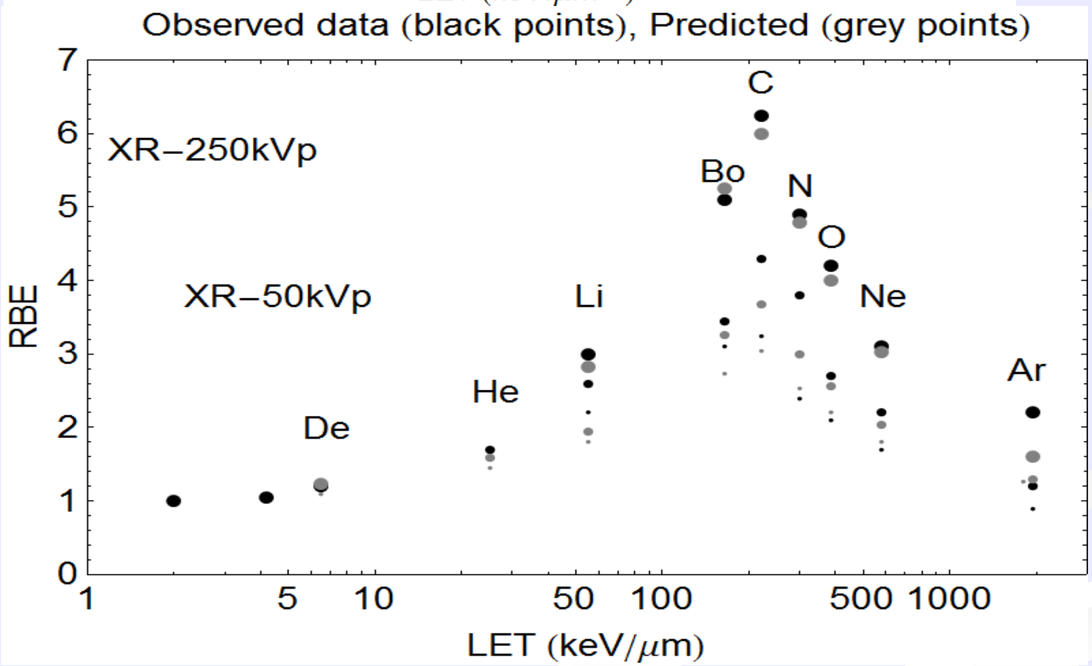


Data of Barendsen (1968), monoenergetic alpha particles and deuterons only for three levels of dose [cell surviving fraction]

Oxford Model





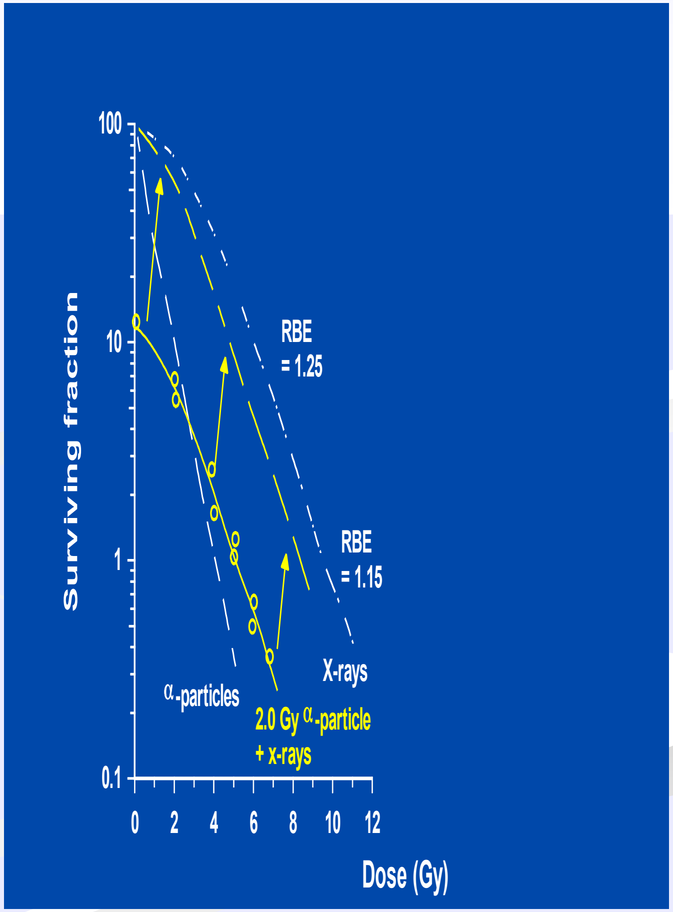


Data of Todd(1967). fitted using unique turnover LET_U for each ion species,

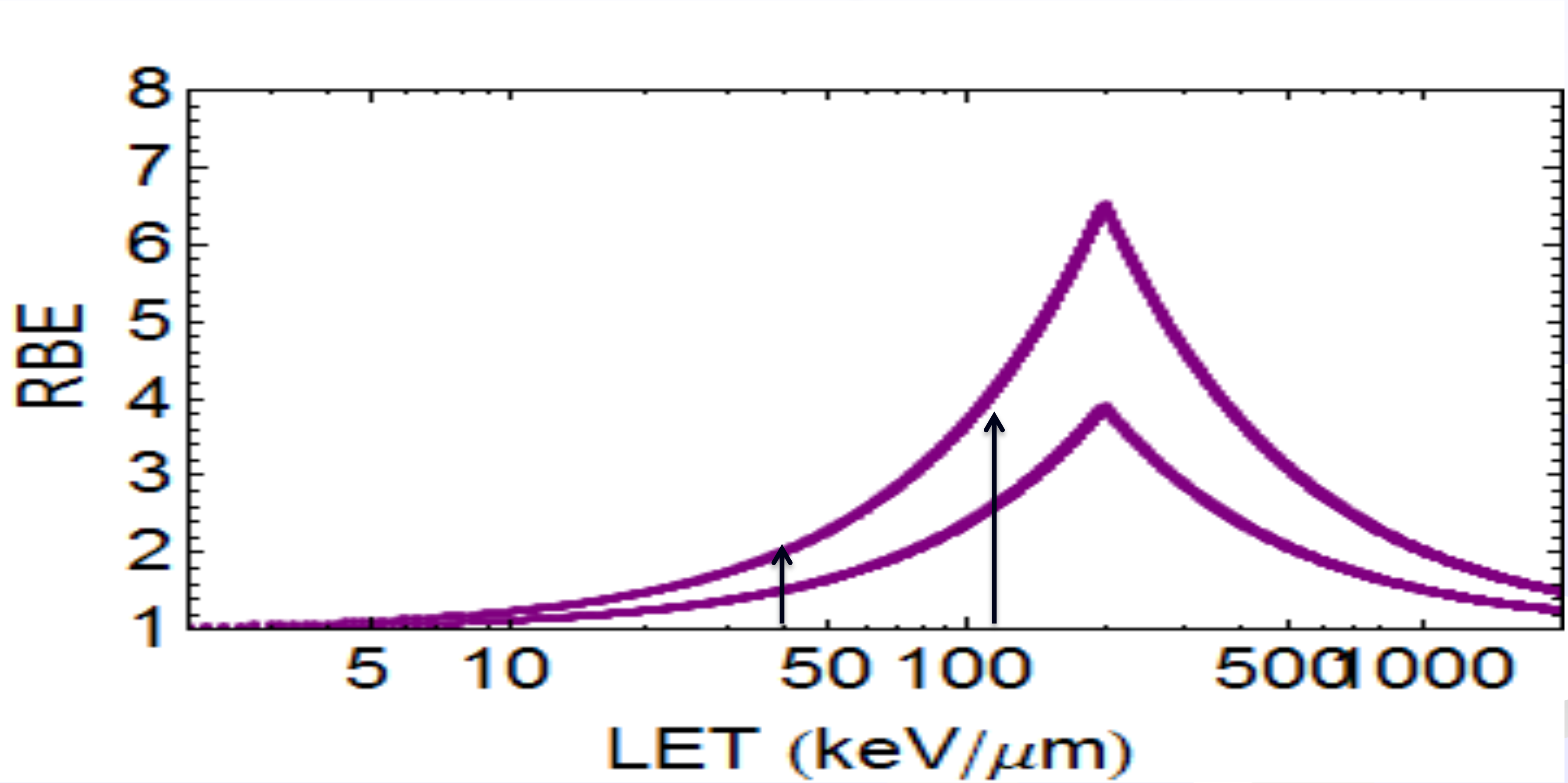
Jones B (2015, Frontiers of Radiation Oncology)

data sets on mixed fields

- Cells exposed to X-rays then given a series of neutron or Alpha particle doses regard the X-ray dose as equivalent to the higher LET radiation giving the same surviving fraction.
- If the cells exposed to neutrons or Alpha particles followed by X-rays the resulting survival is higher than would be obtained if first dose had been an iso-effective X-ray dose. It is lower than what would be expected if the two radiations acted independently.
- Results imply an interaction between low and high LET mixed radiation. McNally et al.



It may involve further processes, integrating neutron spectrum on this type of plot; with dose related changes in the plot



Are there significant differences in LET_U positions for different ionic Z numbers?

Ion and data source	Cell type	Estimated LET_U (keV. μ m^{-1}) (mean, standard error)
C ions, (Weyrather et al, GSI, Darmstadt, Germany)	CHO	145.81±9.88
	V-79	159.05±3.95
	Combined CHO +V-79 data	152.43±4.29
Helium, (Barendsen, Netherlands)	Human T cells	124.24±0.56

The locations of the combined C ion and Helium data are significantly different ((Mann-Whitney $p=0.028$, t-test $p<0.0001$).

Furusawa et al data (Japan). Estimated turnover point (LET_U) positions

	V-79 cells	HSG cells	T cells
carbon ions	151.6 (n=24)	108.8 (n=21)	No LET_U
neon ions	177.59 (n=18)	127.92 (n=21)	119.24 (n=9)

Problem areas: beam ‘quality’ parameters

- LET: energy lost per unti length of medium by a charged particle. (as e.g. 1 keV.μm^{-1}, or 1.602 J/m)
- Variants of LET: L_Δ, where Δ refers to max limit of energy (e.g. L_{100} would consider only energies below 100 keV.μm^{-1}).
- LET as total energy loss (L_∞). This reflects ‘stopping power’ in the medium, and so includes its density, so with units expressed as MeV.$cm^2.g^{-1}$, or J m^2 kg^{-1}.

Problem areas: beam 'quality' parameters

- When there are different energies in a beam, a LET spectrum can be used, calculated as either 'track average' or as 'absorbed dose average' (or energy average) LET.
- **Lineal Energy (*y*)** takes account of stochastic energy deposition (LET does not); $y=\varepsilon/d_{av}$, where ε is energy imparted in a volume with d_{av} being the mean chord length in the volume.

Problem areas: beam 'quality' parameters

- To account for δ-rays ejected from tracks, which are radially distributed and responsible for most bio-effects and ionisations collected by detectors, Katz(1970) proposed use of:

  $Z^{*2}.\beta^{-2}$,

[Z*= effective nuclear charge of atomic nucleus of atomic charge Z]

[β is the relativistic velocity (v/c)]

As fully stripped ions slow down they pick up electrons so Z* becomes less than Z.

Comparison of two 'quality' and two RBE parameters, alpha (Todd), alpha and deuterons (Barendsen)

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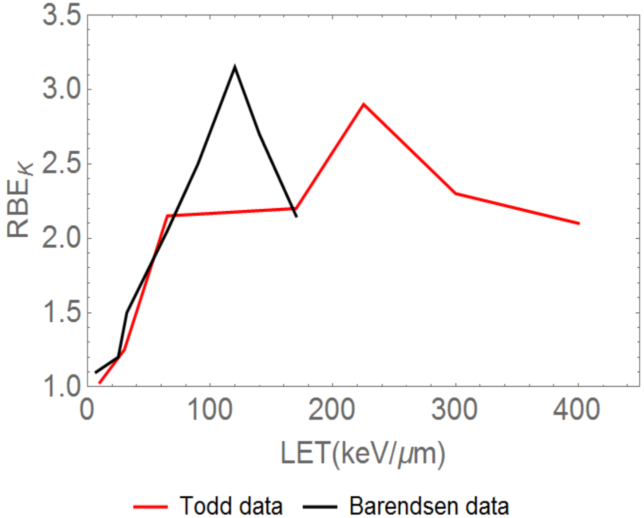

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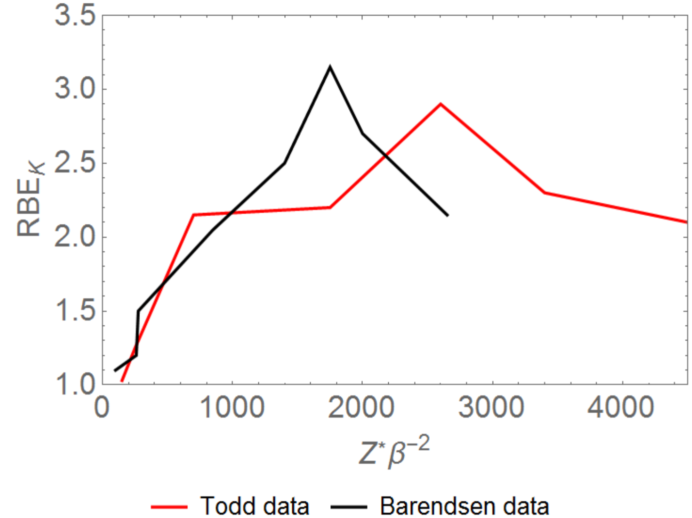

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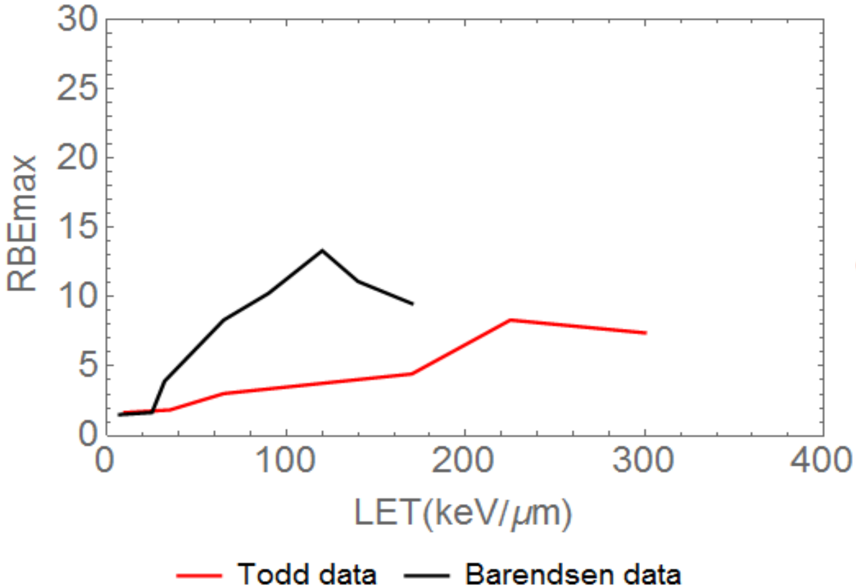

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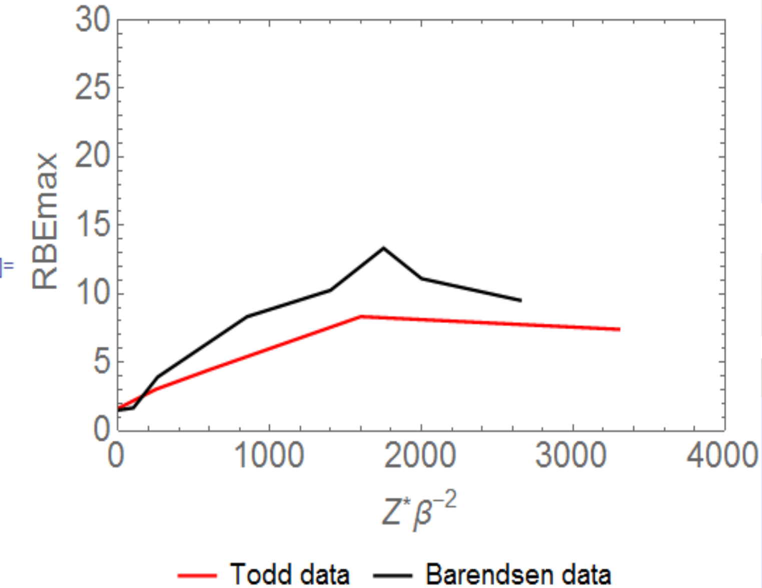
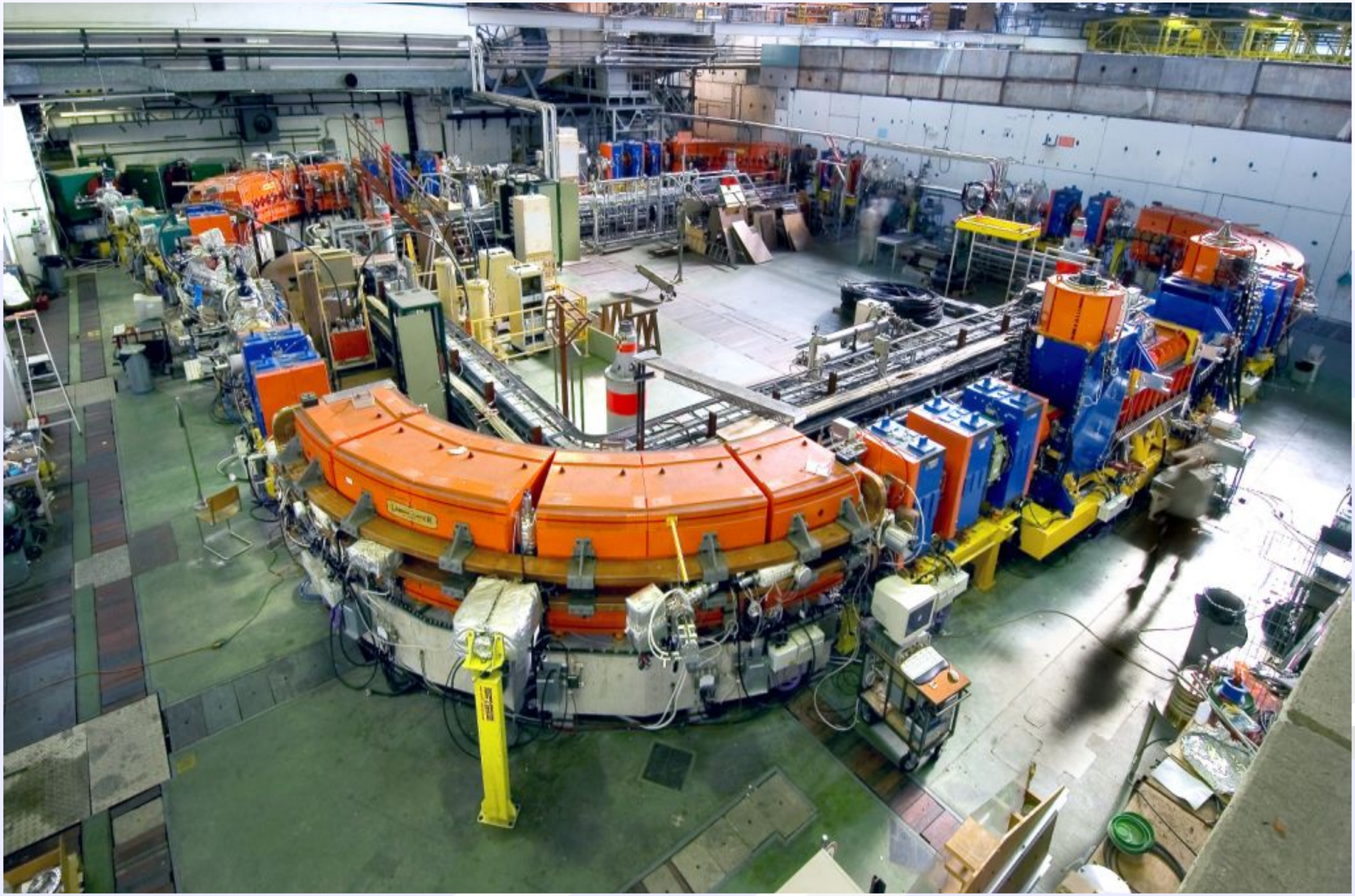


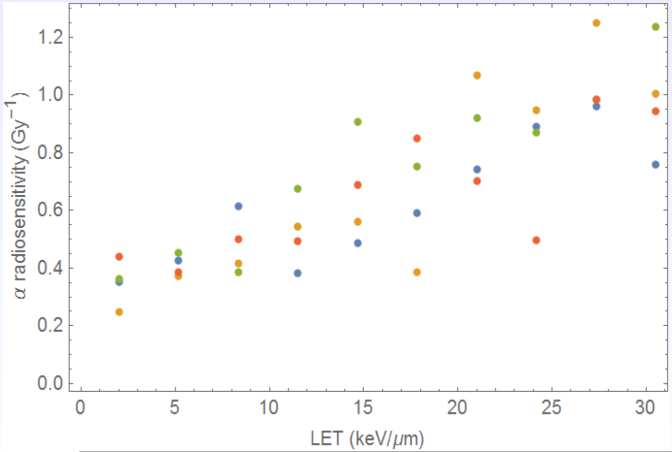
Proposed Biomedical Research Facility using existing LEIR Synchroton

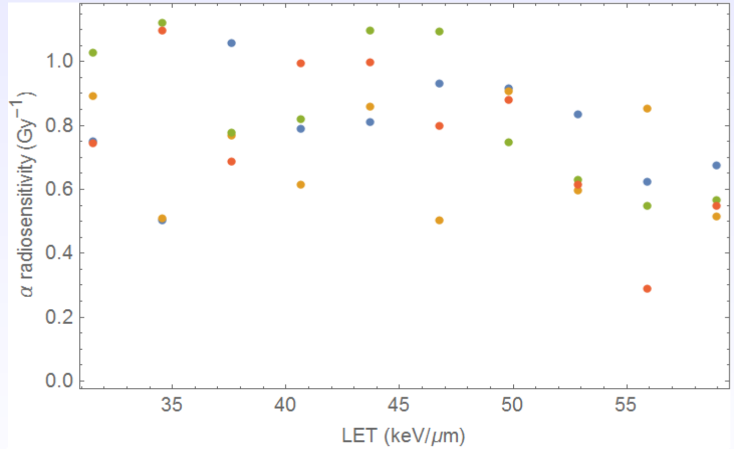


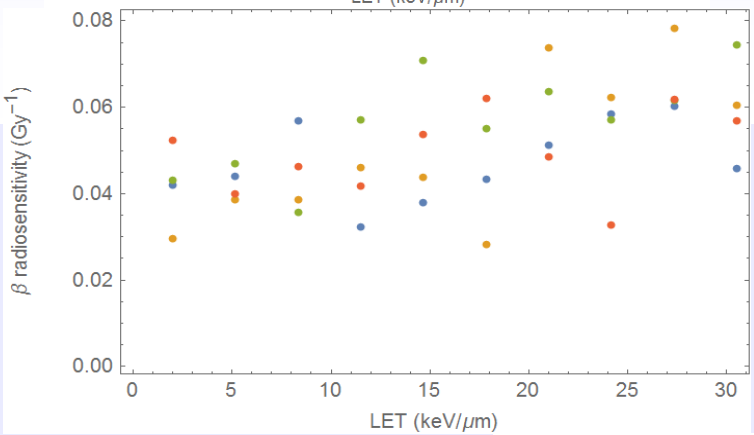
Example of a single *Mathematica* (Wolfram, USA) simulation of experiments to determine LET_U for protons, using variations in cellular radiosensitivities in cell survival assays.

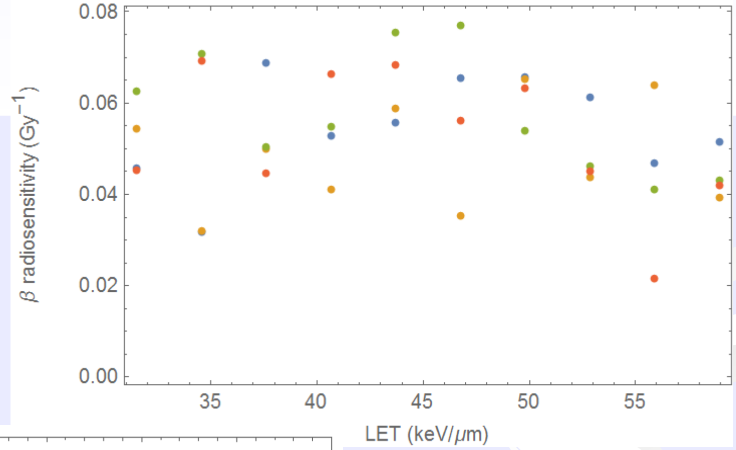
Here 20 RBE data points are used. The expected LET_U is assumed to be 30.5 keV. μm^{-1}.

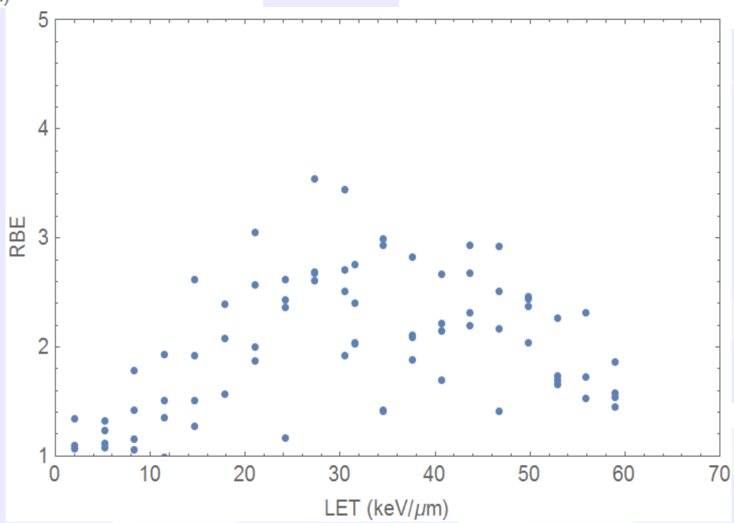
The LET_U value is obtained by obtaining the intersection point of the two upward and downward data linear regression fits.

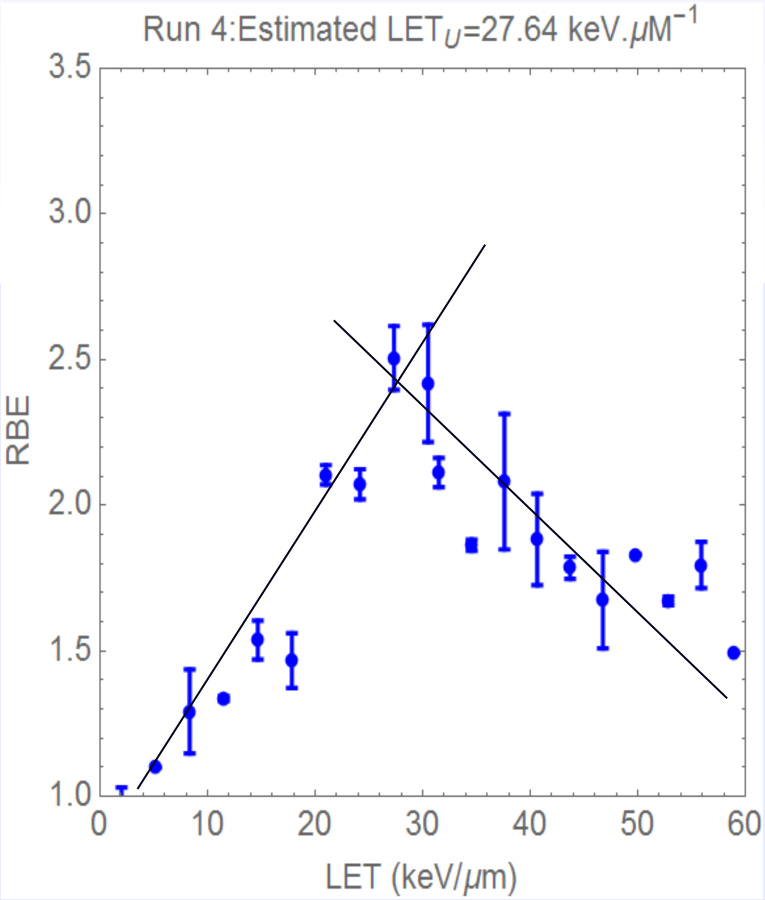

α radiosensitivity (Gy⁻¹)
LET (keV/μm)


α radiosensitivity (Gy⁻¹)
LET (keV/μm)


β radiosensitivity (Gy⁻¹)
LET (keV/μm)


β radiosensitivity (Gy⁻¹)
LET (keV/μm)


RBE
LET (keV/μm)



Four repeated simulations, using seeded random sampling, provides LET_U values of 29.6; 32.06; 33.73 and 27.64, [Mean =30.75±1.34 (SEM)] when there are 20 LET-RBE data points (N=20). This is a good result for medical purposes, but if N=16 the estimate falls to 29.96±1.24, and if N=12 the estimate is 31.5±1.92.

From geometrical considerations, an experimental LET_U result of 28.8 or 31.8 $keV.\mu m^{-1}$ instead of the assumed correct 30.5 would lead to a 5% error in RBE estimation. Then, using the BED equation

$$BED = nd_H\left(RBE_{max} + \frac{RBE_{min}.d_H}{\left(\alpha/\beta\right)_L}\right)$$

If LET_U=25 (BED error is 6.16%) and 26 (BED error=4.79%) for a neurological effect. [Generally severe late complications rise by 1-2% per unit BED].

Also, compared with standard use of RBE=1.1, then if LET ~ 9 $keV.\mu m^{-1}$, the calculated and normally given dose (normalised to 100%) are: 80.21% for use of the correct LET_U, and 76.92% for an incorrect LET_U of 27 $keV.\mu m^{-1}$.

Conclusion

There is ample scope for a world class centre that can improve:

- our fundamental particle physics knowledge for applications of RBE in Medicine.
- Resolution of diagnostic techniques for Medicine by an order of magnitude and with compact equipment
- Simulation of all forms of radiation therapies
- Data collection for advanced analysis