Radiobiological characterization of clinical proton and carbon-ion beams :

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Improvement of radiotherapy

■ Ballistic selectivity

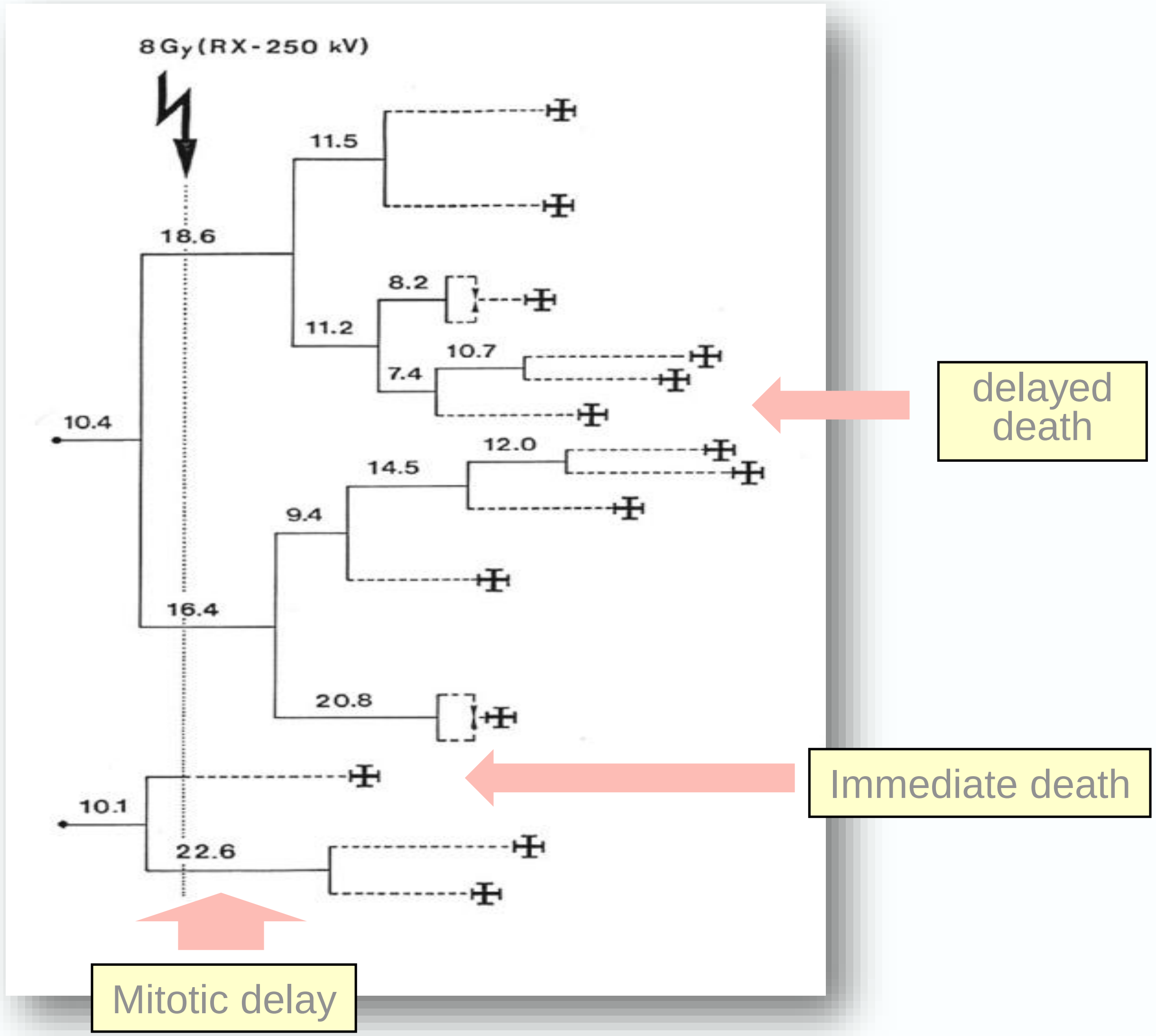
Increasing the dose to the tumo
while reducing the dose to th
surrounding normal tissues

■ Differential effect

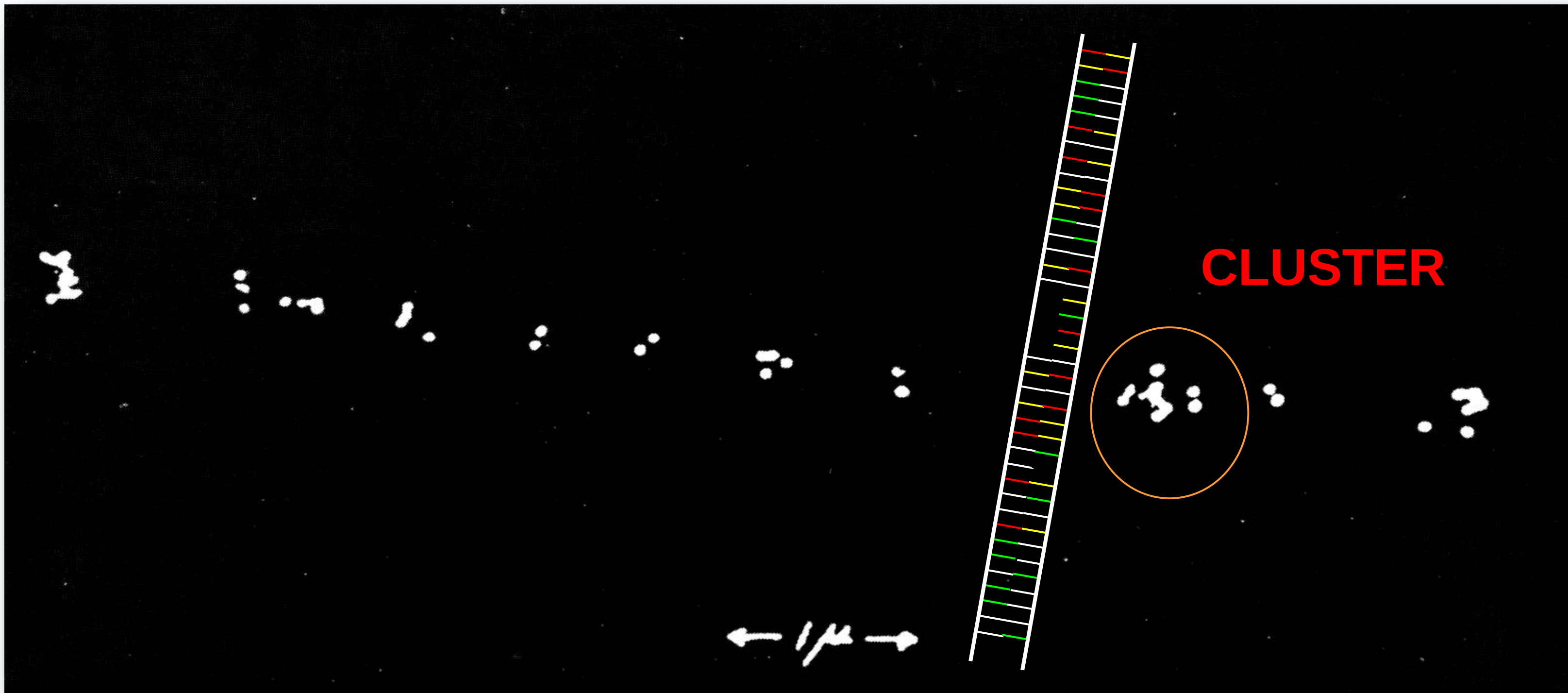
Compared to conventional radiation
the effect is relatively more marke
on the tumour than on the norm
tissues (RBE)

What is the biological effect of ionising radiation?

There are several arguments pointing at the DNA as the main target of ionising radiation

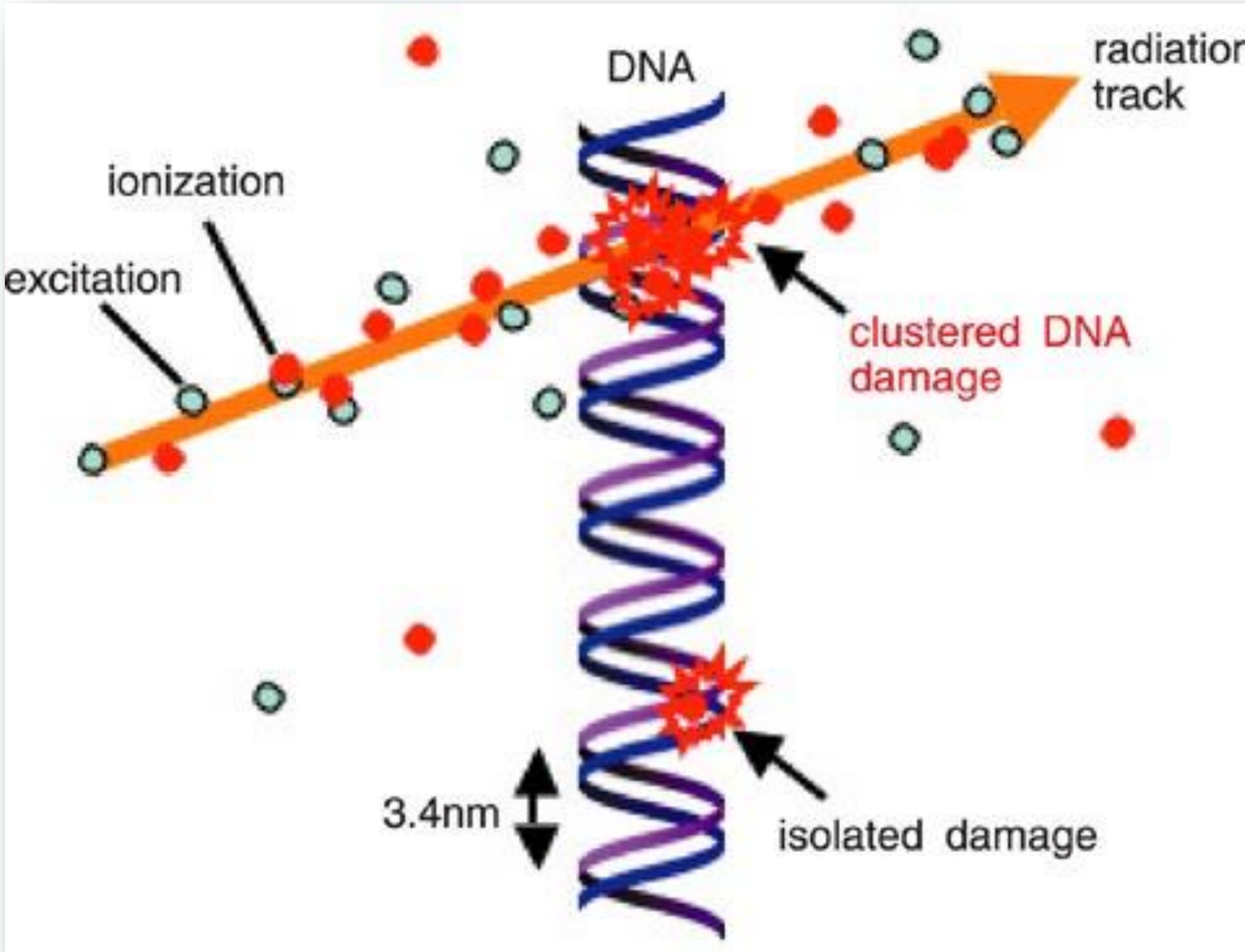


Ionisations along an electron track (secundary electron after low LET irradiation)

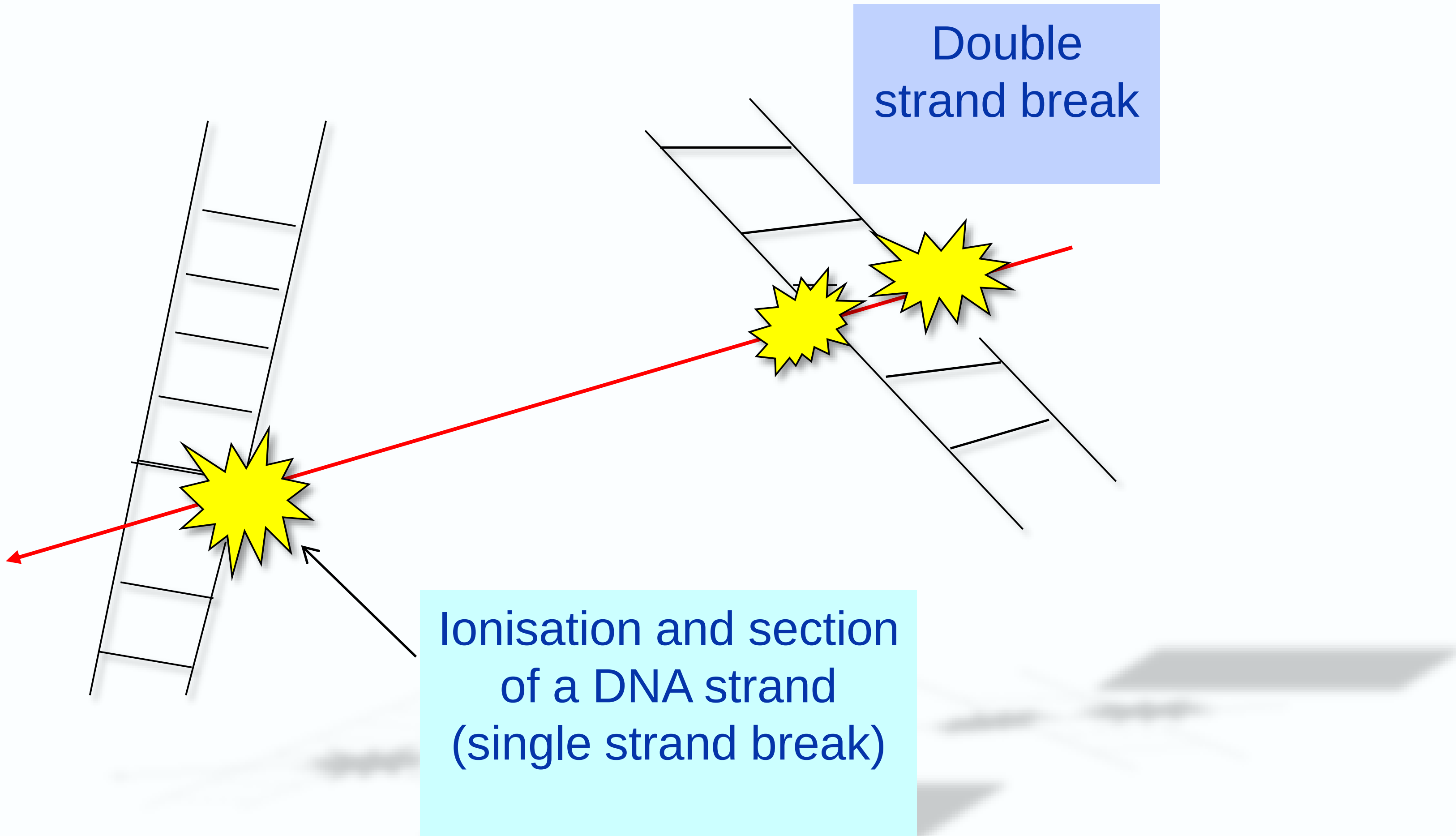


Sequence of events

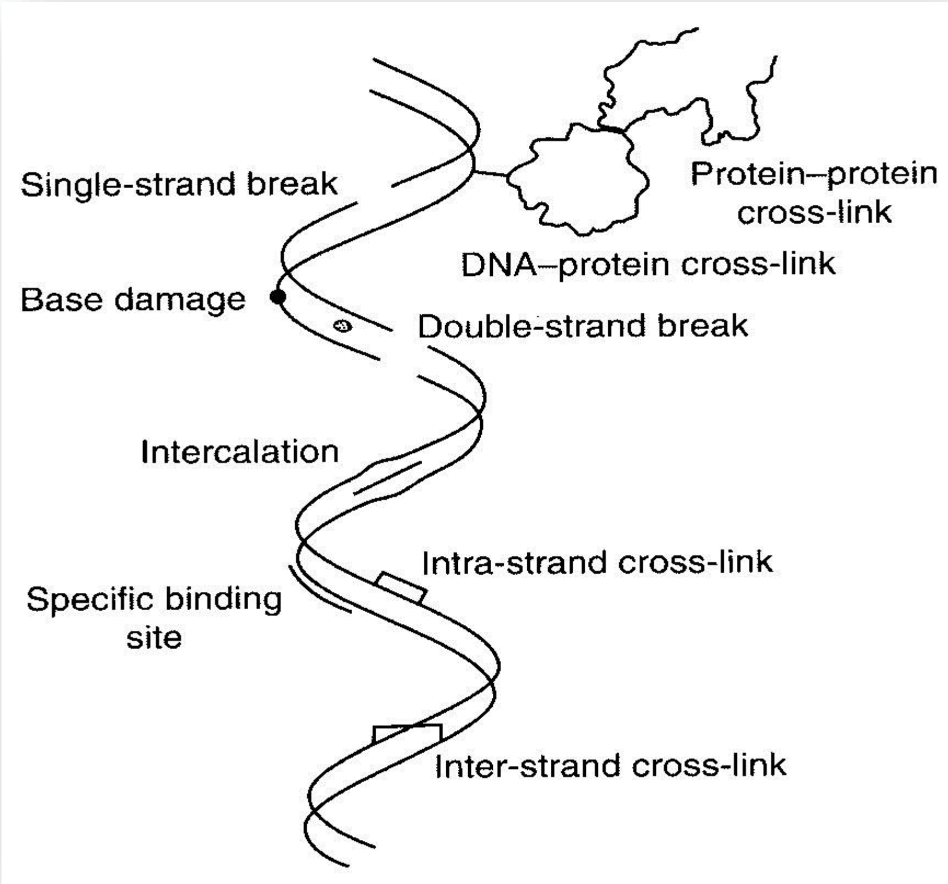
- Energy deposits (primary and secondary electrons)
- DNA damage.
- DNA re-arrangement.
- Repair induction (enzyme synthesis).
- Cell cycle arrest.
- Repair vs. apoptosis.
- Cell death
- Tissue failure


DNA
radiation track
ionization
excitation
clustered DNA damage
3.4nm
isolated damage

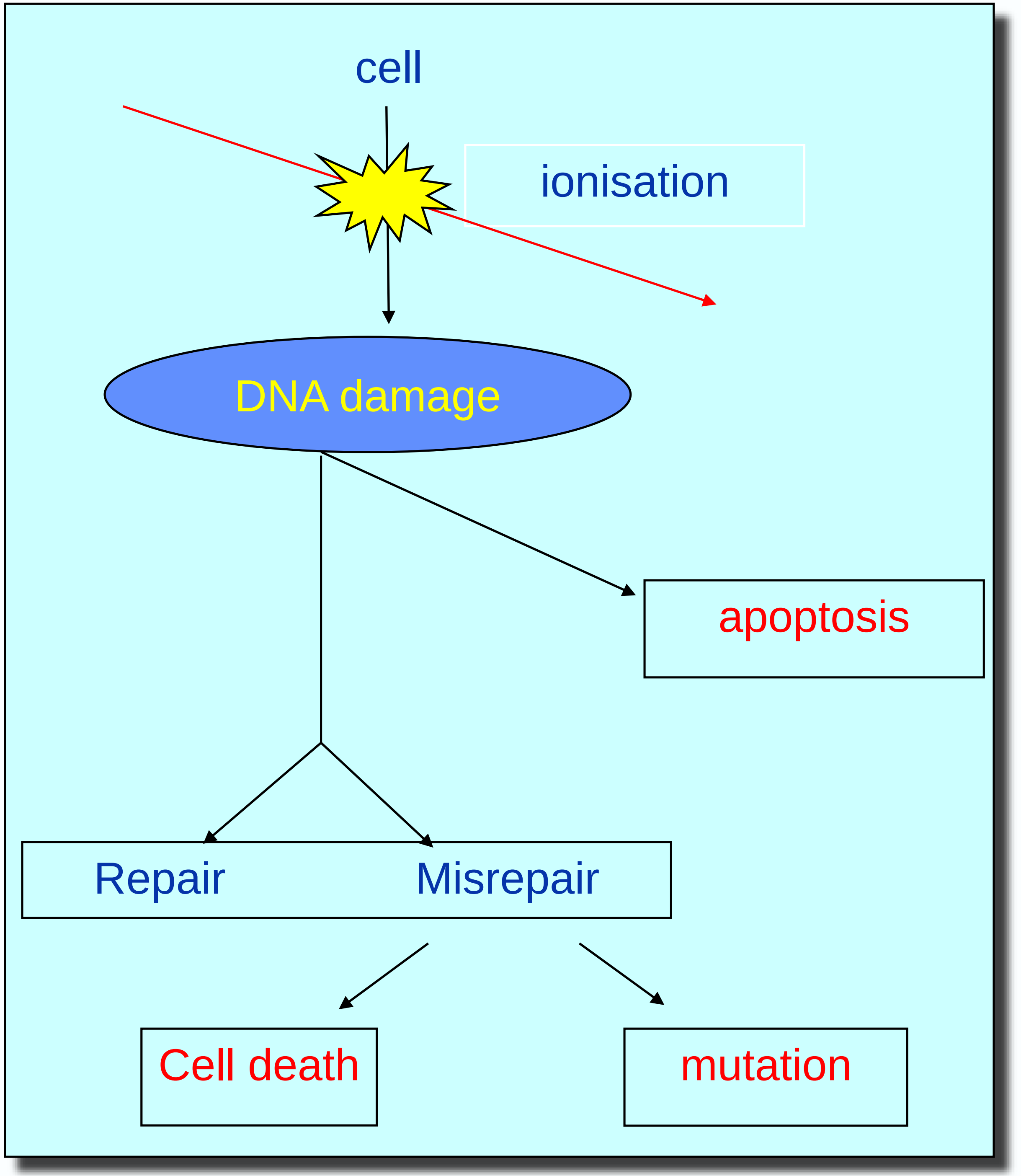
DNA is the primary target

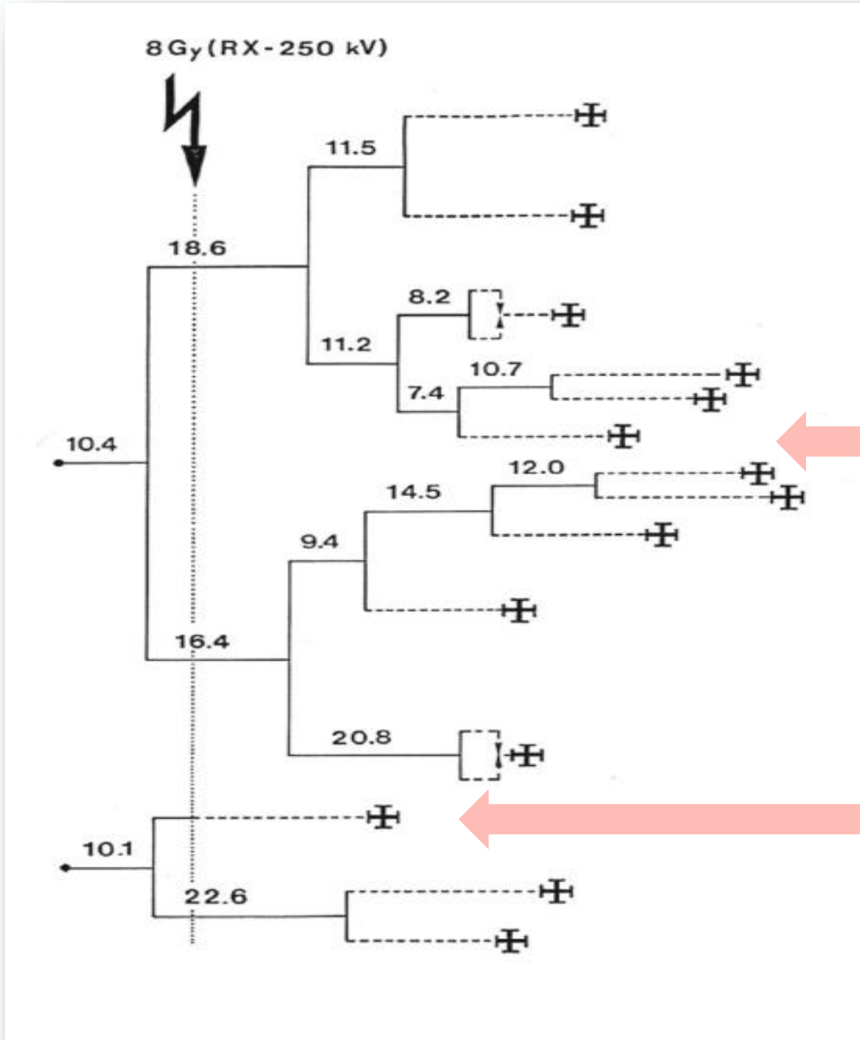


Various types of DNA damage



Possible consequence of DNA damage





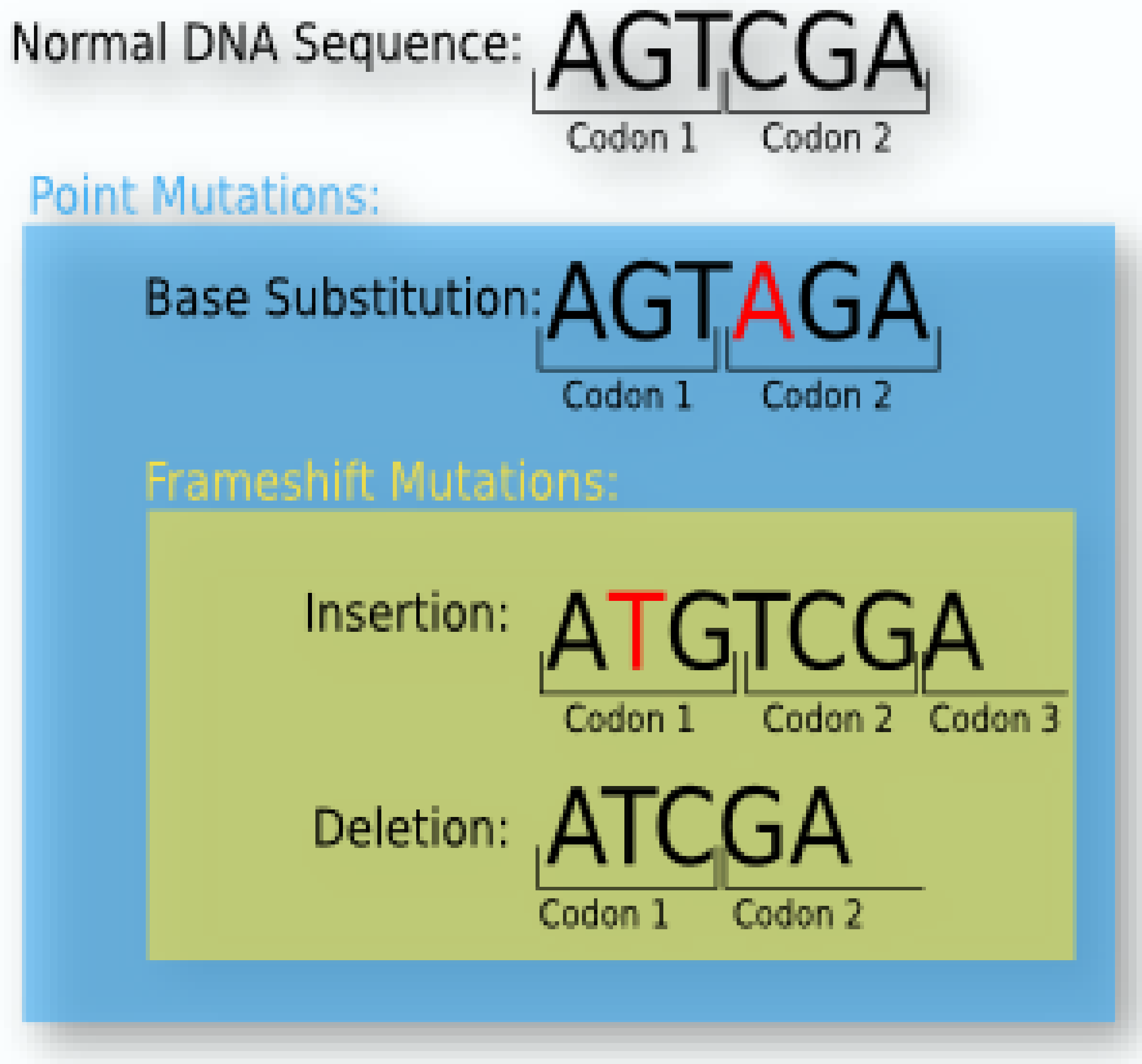
Cell death after misrepair (lethal mutation)

Apoptosis

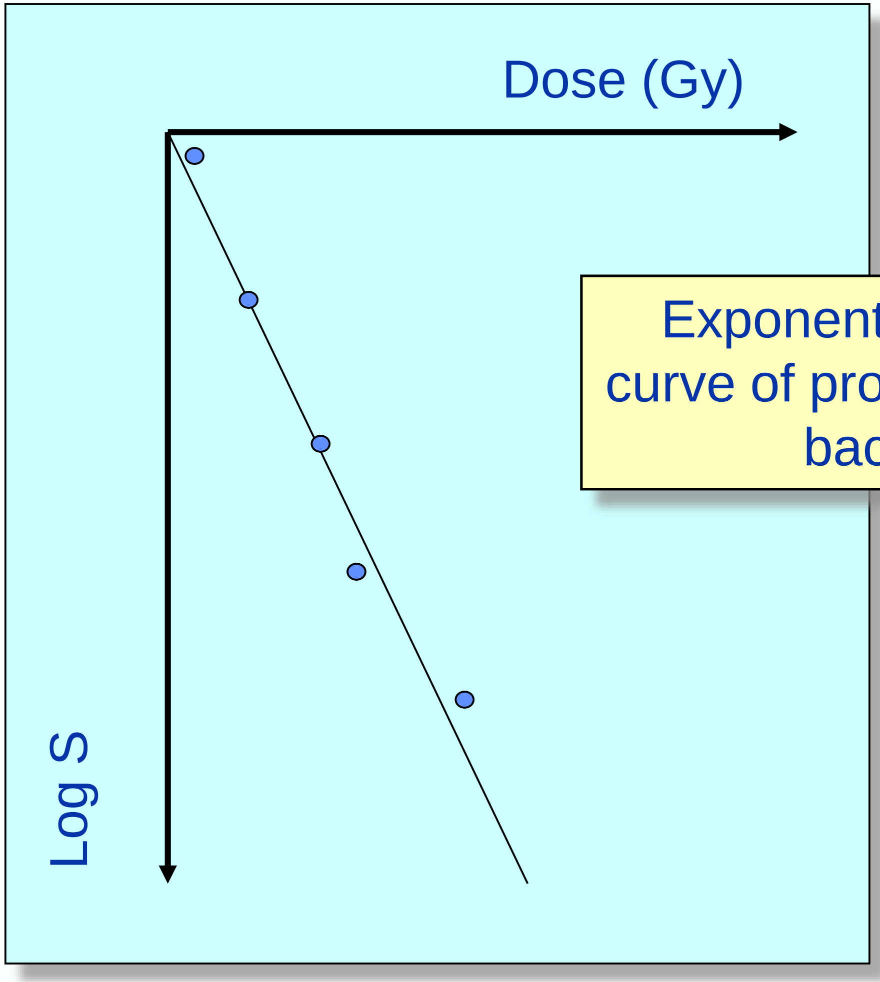
Base pairs can be substituted, or deleted, or added, all resulting in an alteration of information.

A gene can be inactivated or mutated.

A mutation can amplify or decrease the gene expression.



A dose increment kills a fixed proportion of cells

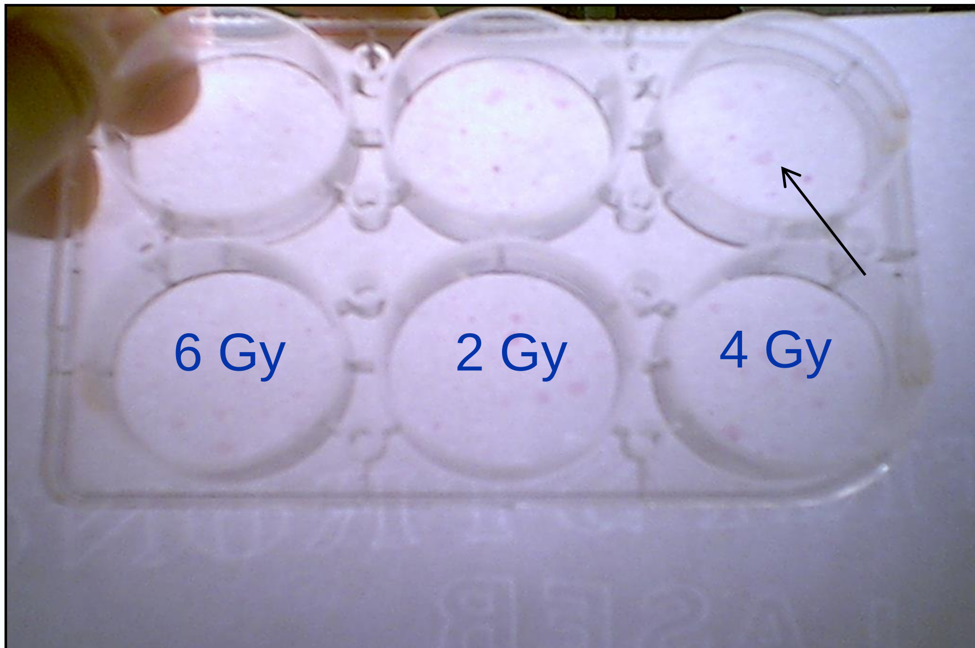


Exponential survival curve of prokaryotes and bacteria

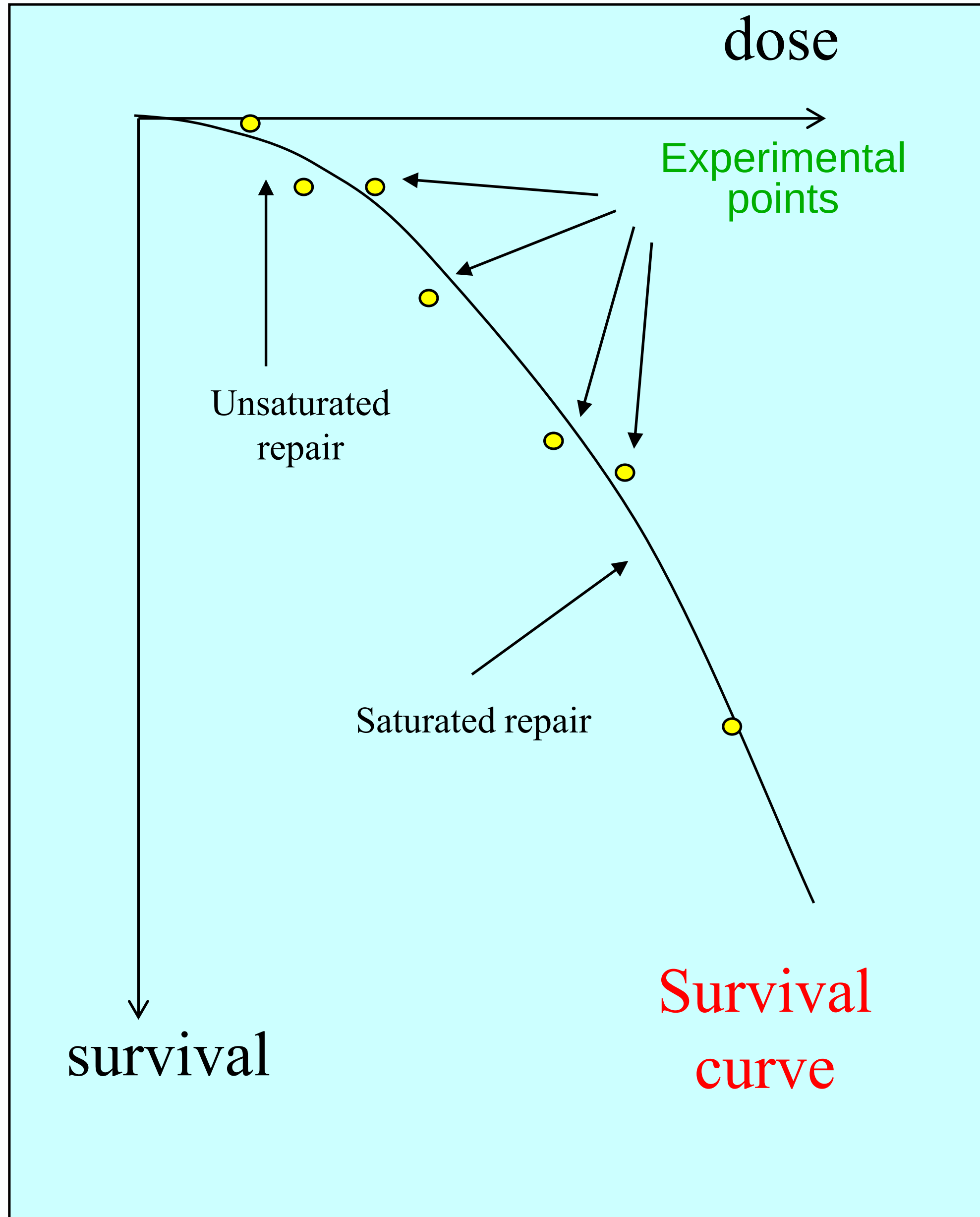
Poisson's law

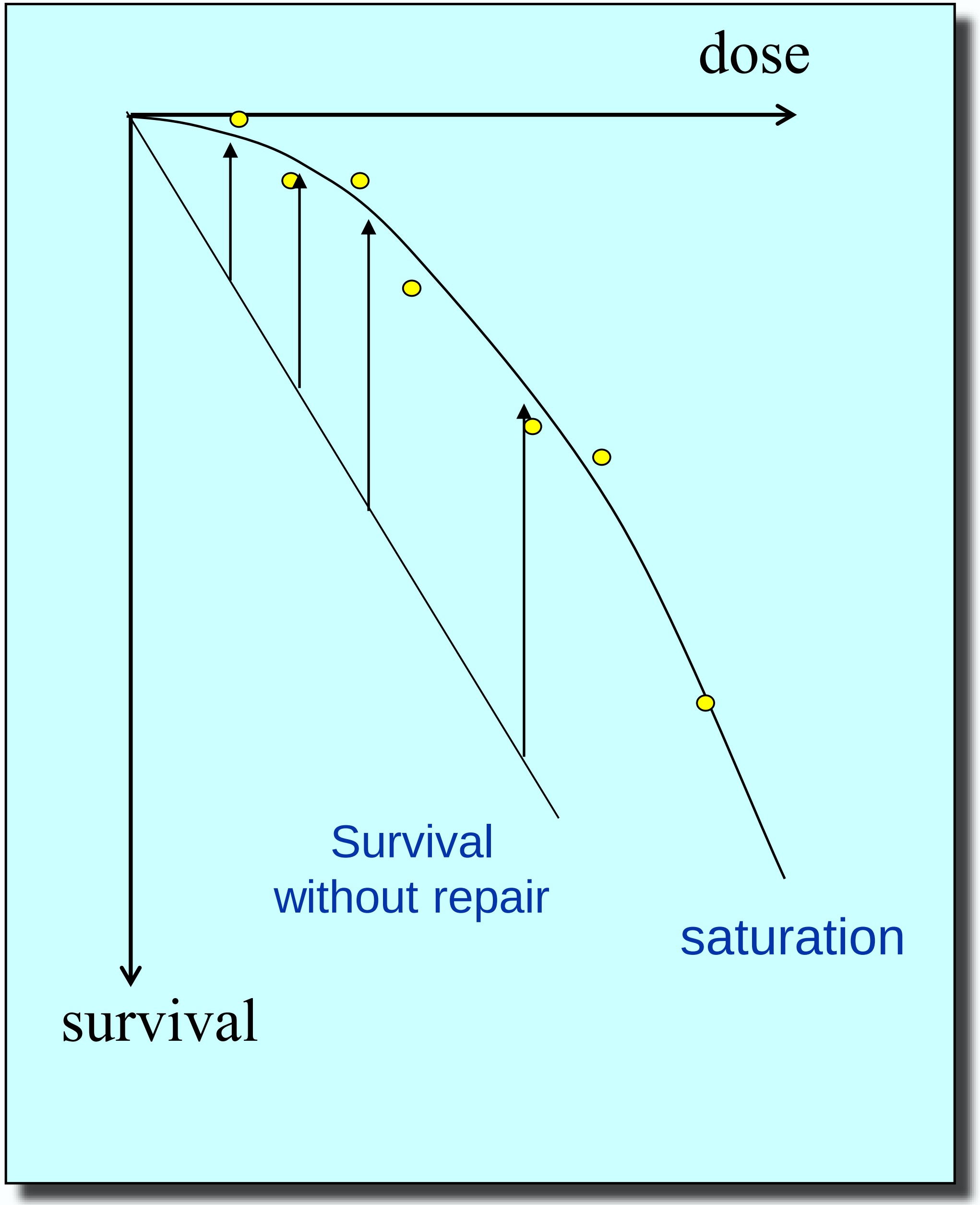
$S = e^{-\alpha D}$

Cell survival curve



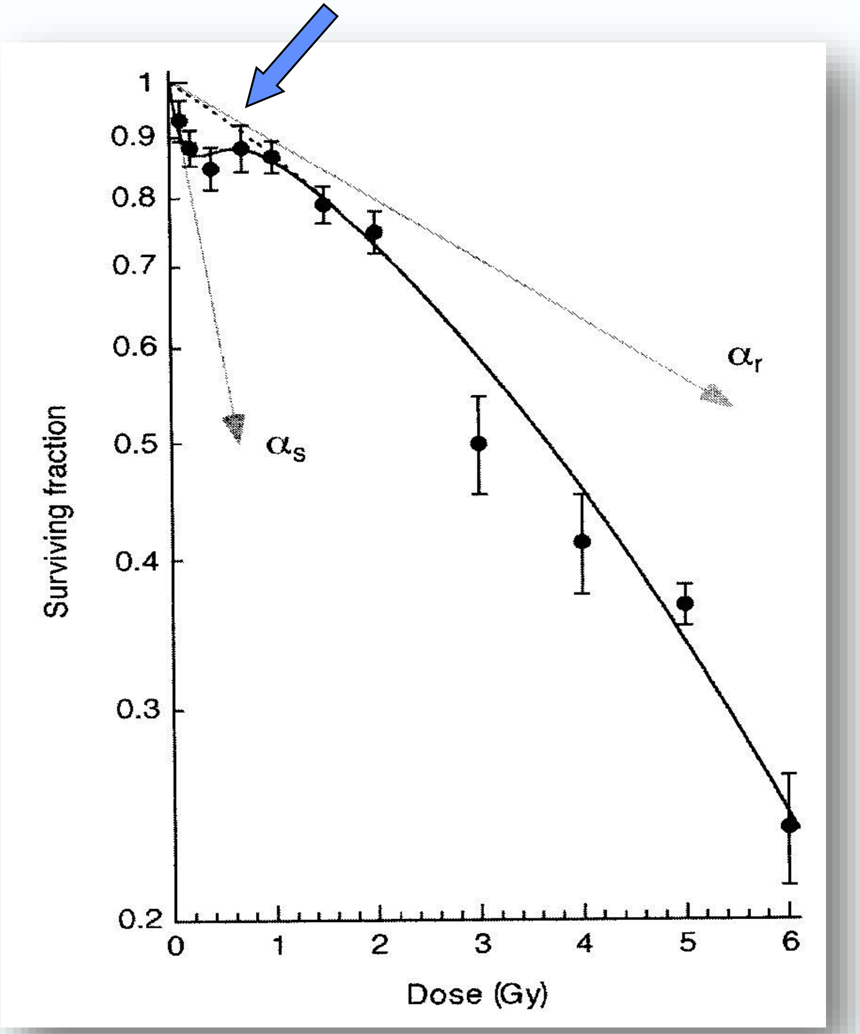
Clones can be seen



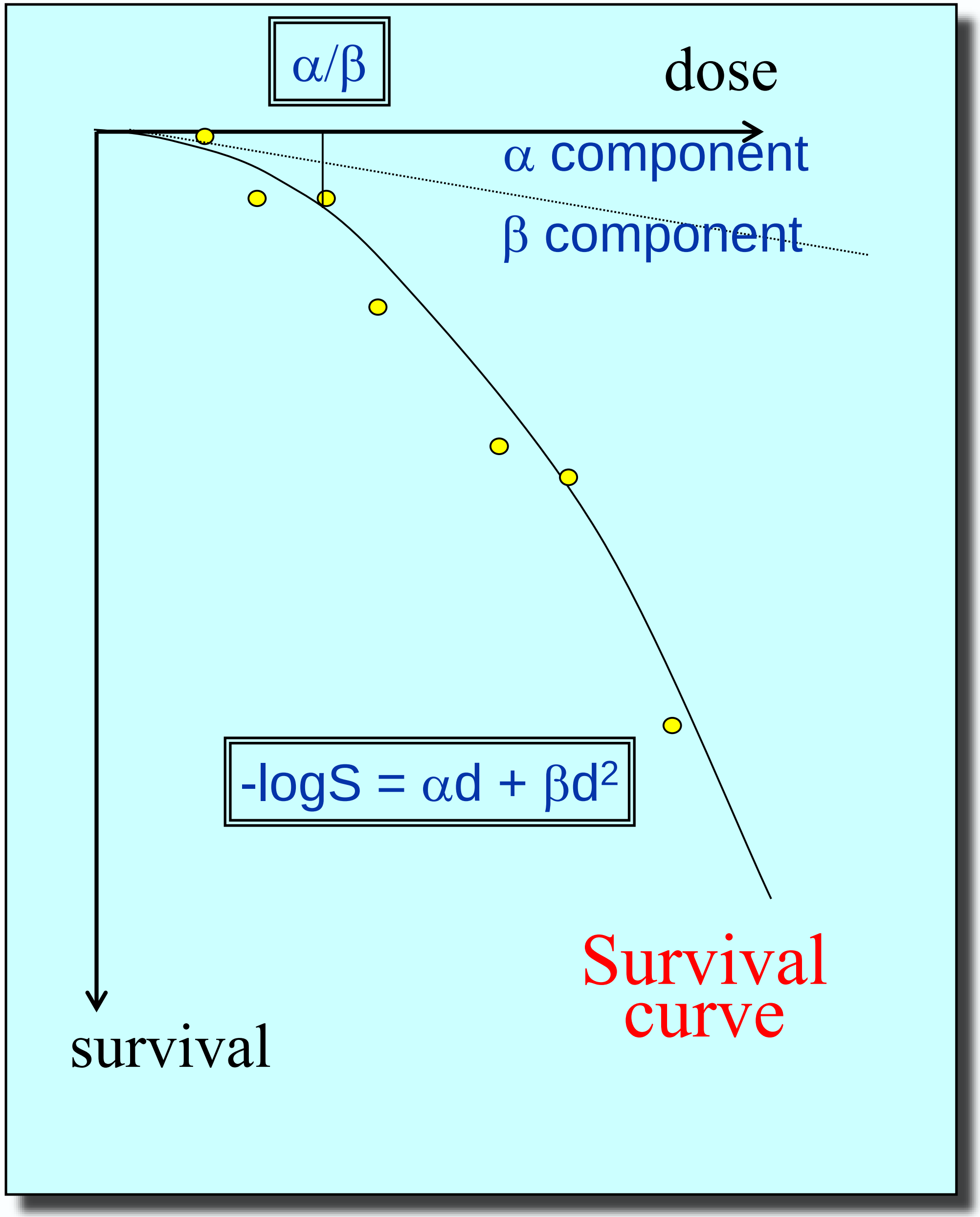

dose
Survival
without repair
saturation
survival

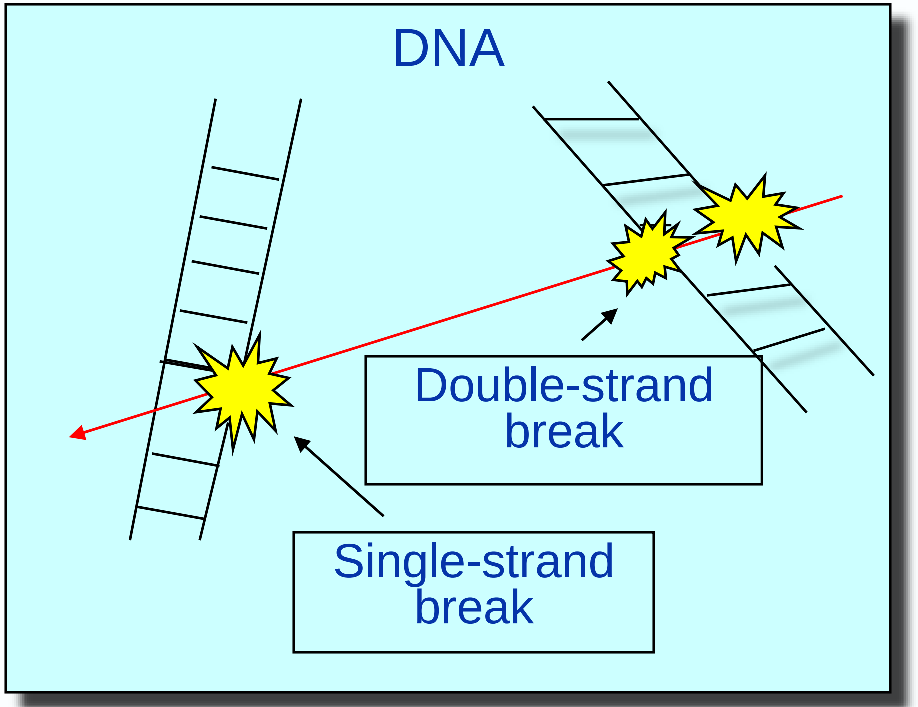
Initial part of the survival curve

A steep initial part exists on survival curves, particularely in resistant cells.
It is interpreted as a sign of repair induction when and if the damage concentration is sufficient to « trigger » repair enzyme synthesis.



The linear quadratic model



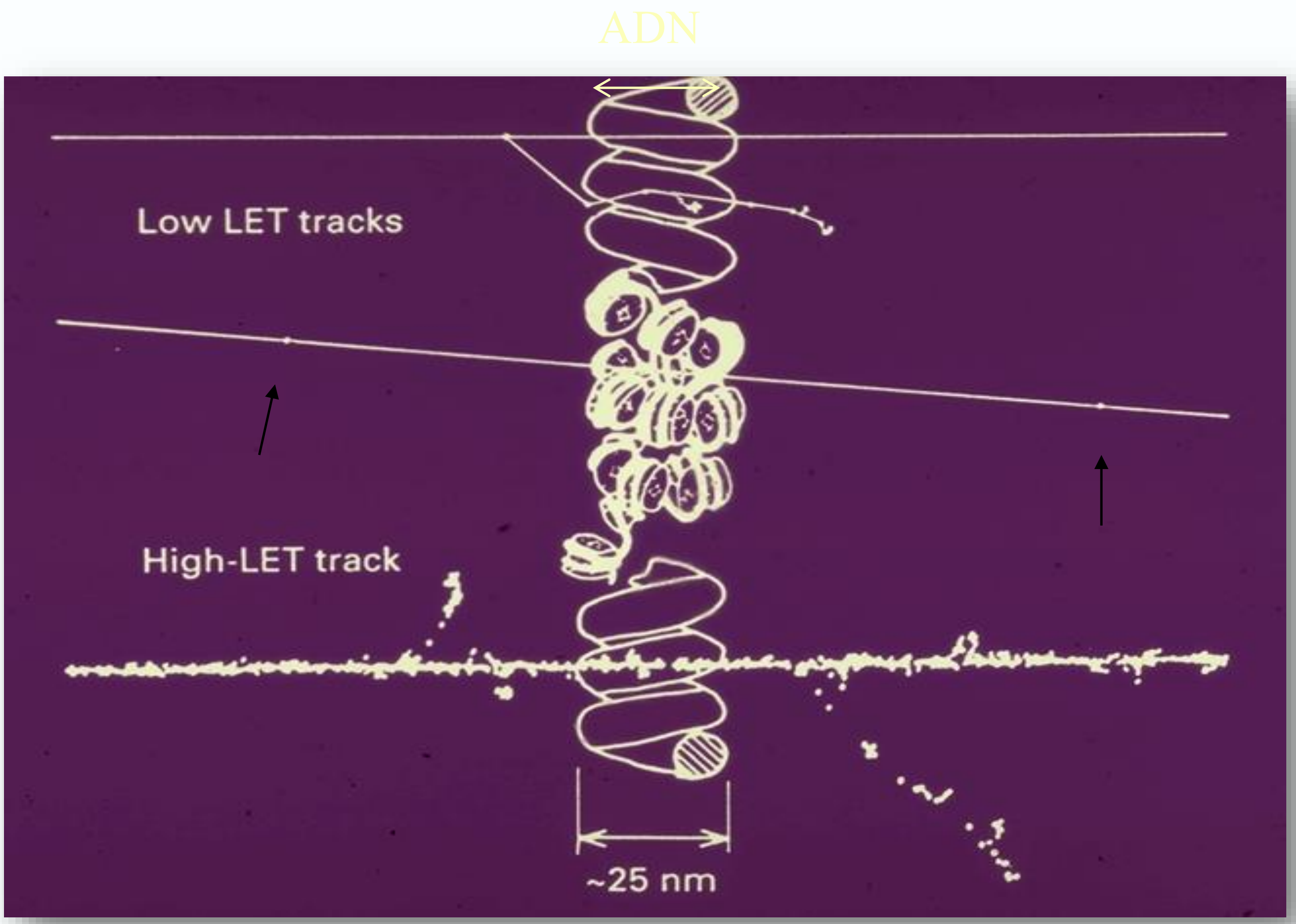


the model of radiation action

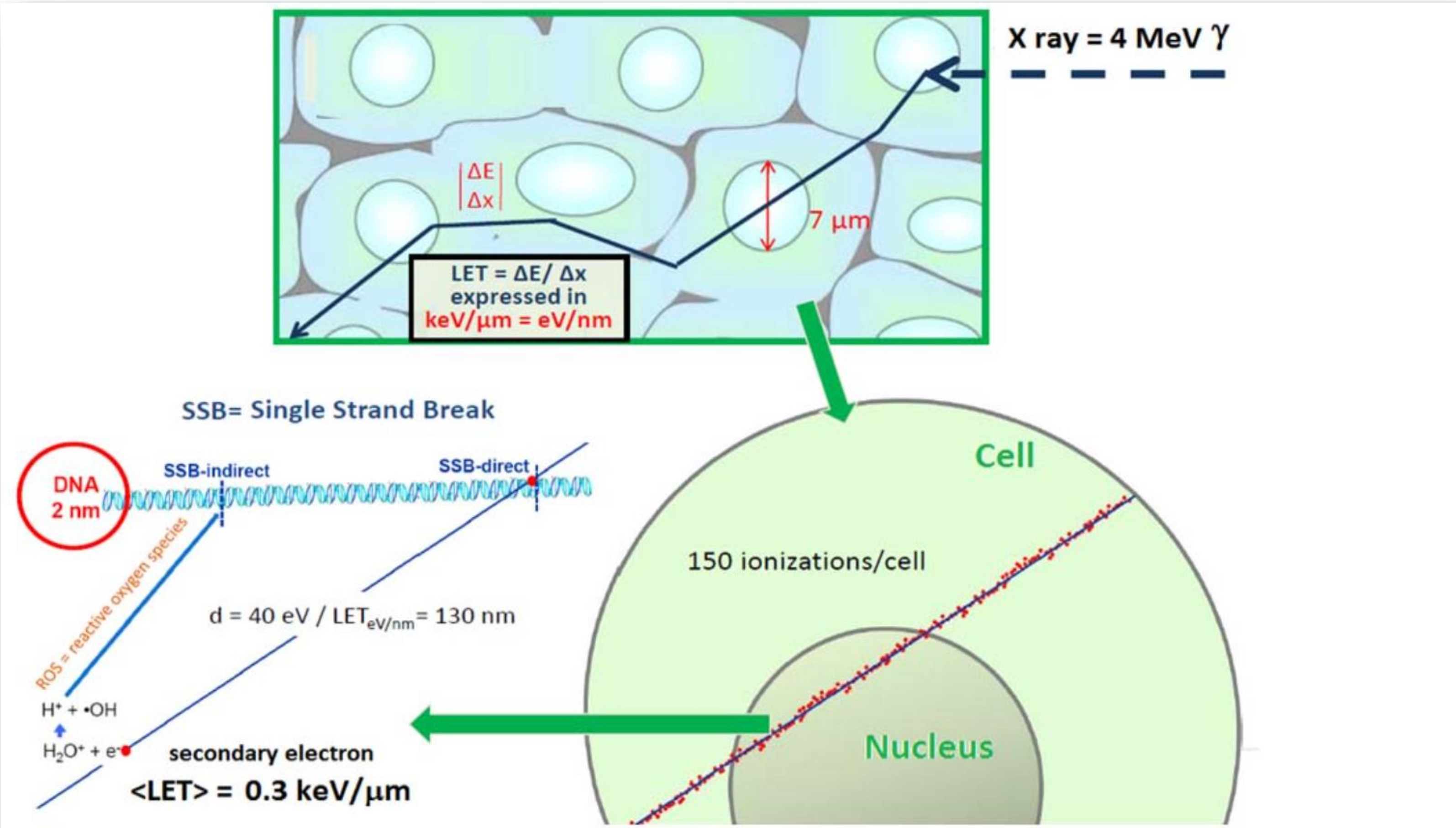
Ionisation along a particle track

Low density of ionisation

High density of ionisation

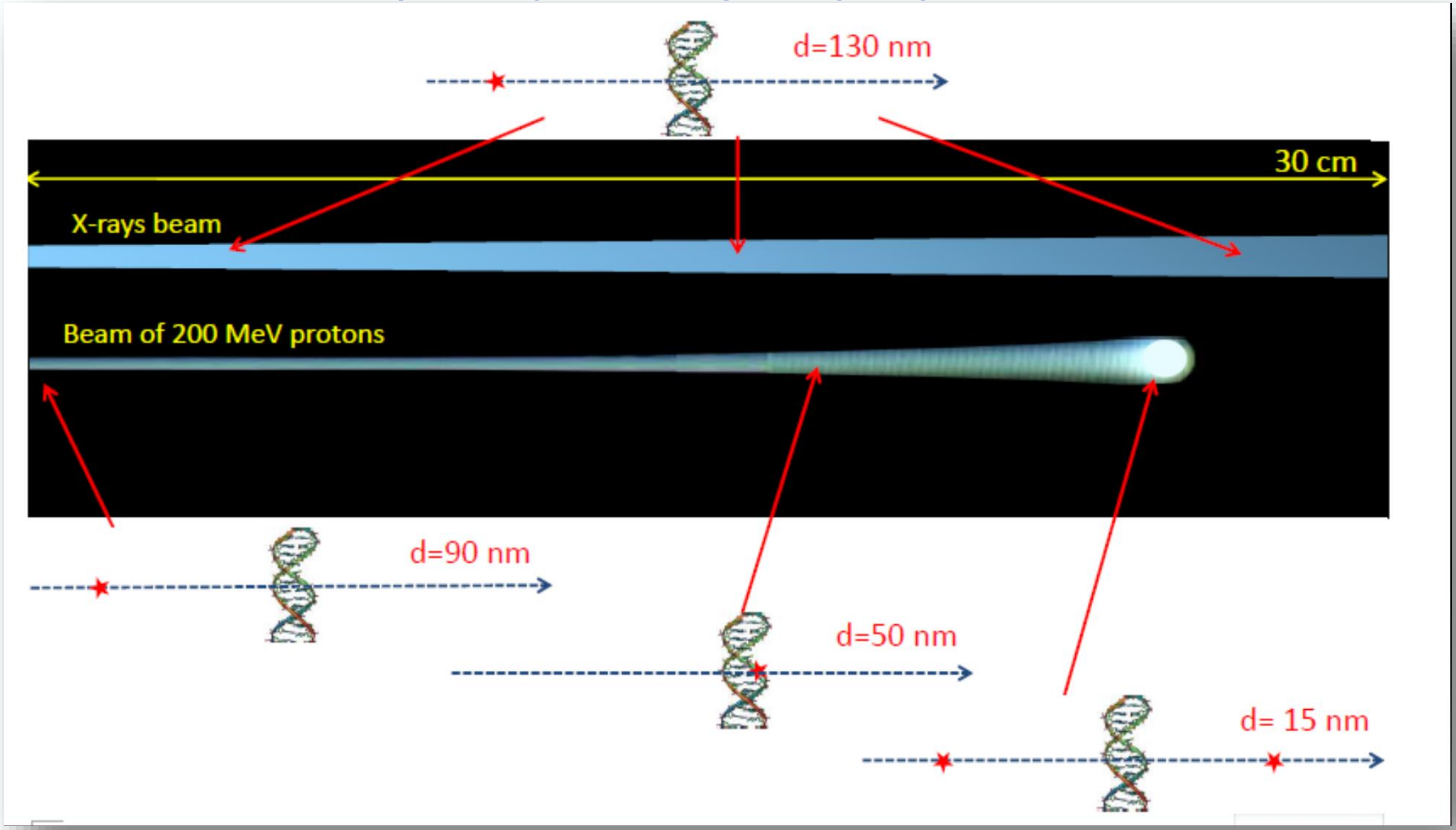


Direct and indirect effects



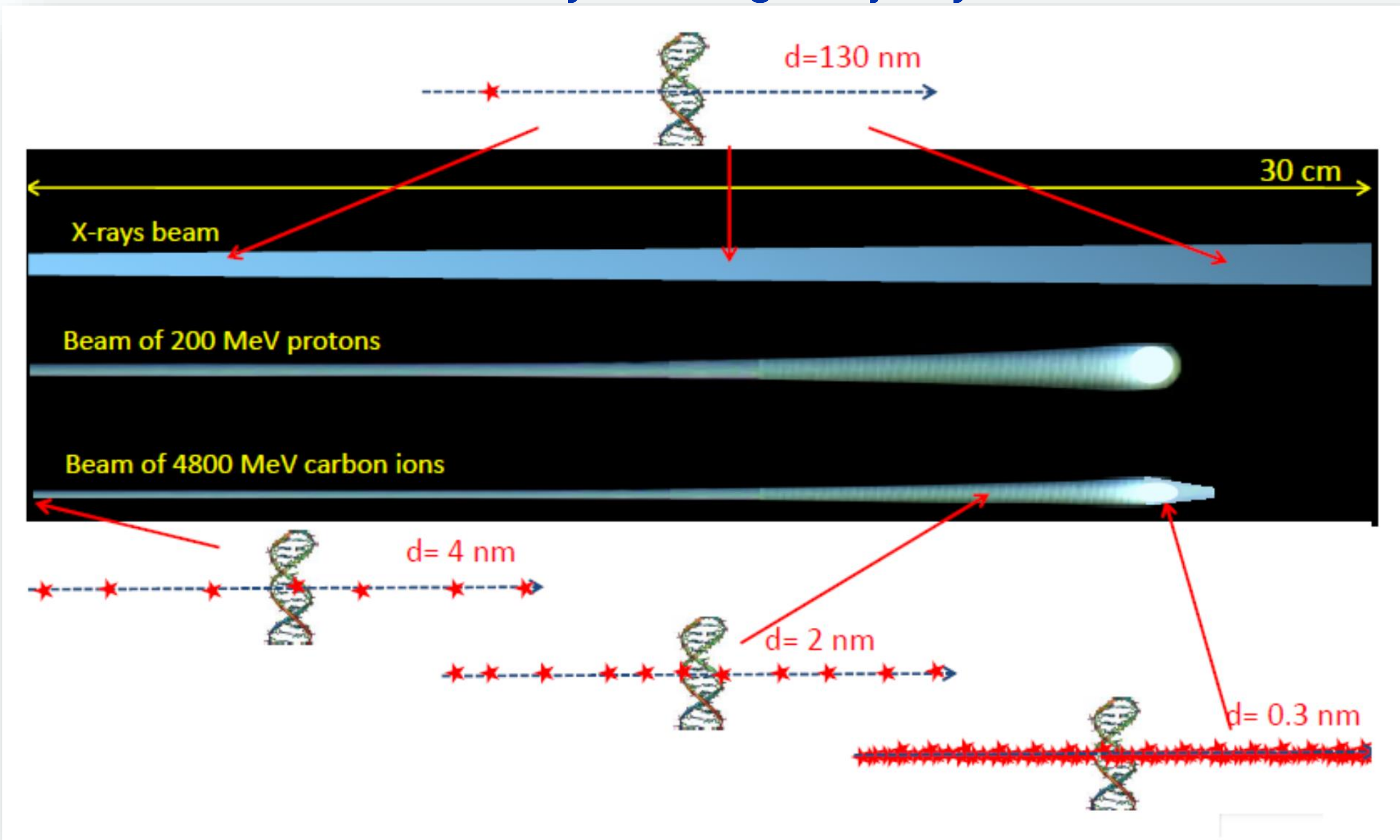
Protons

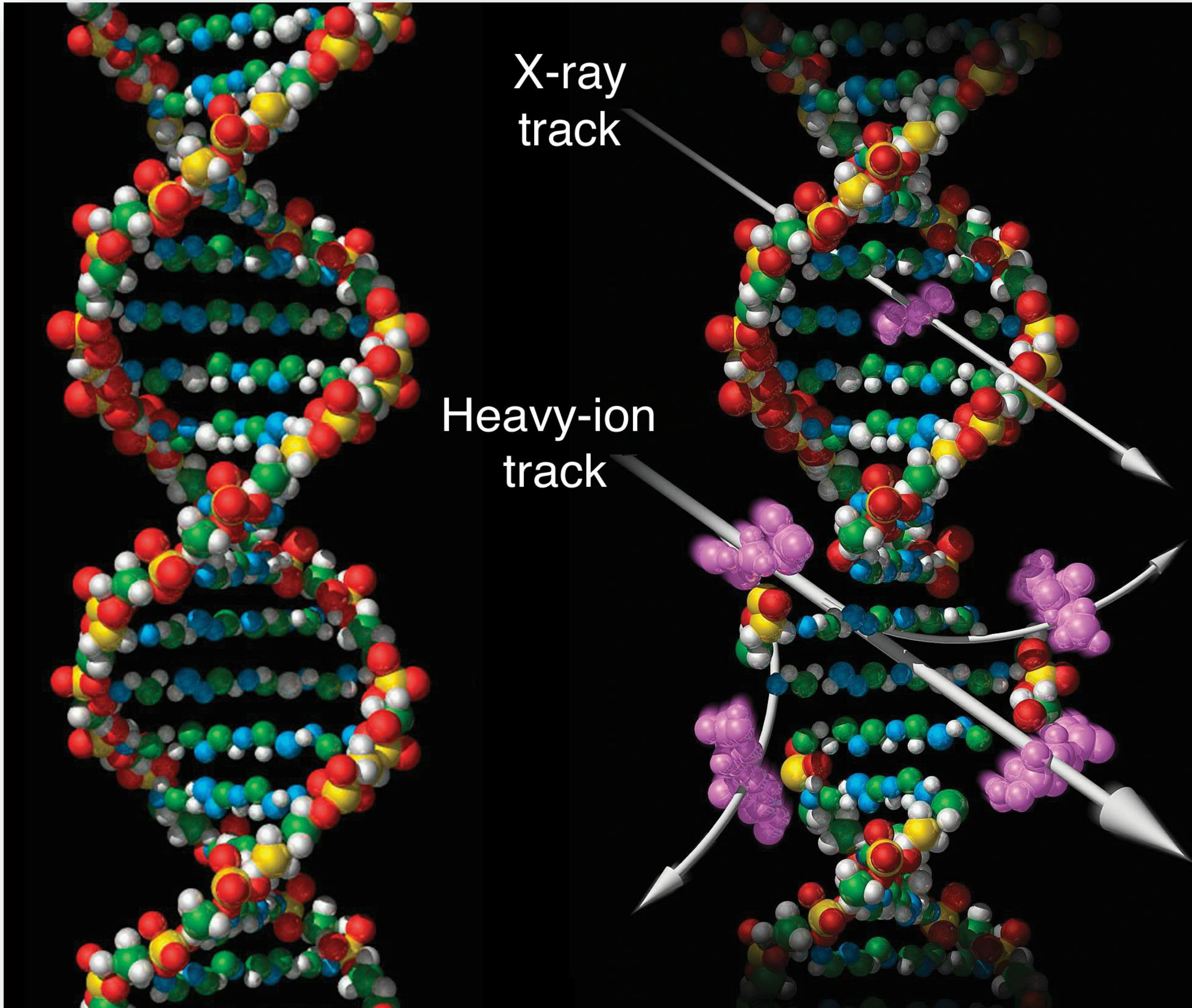
Protons are sparsely ionising, majority of indirect effects



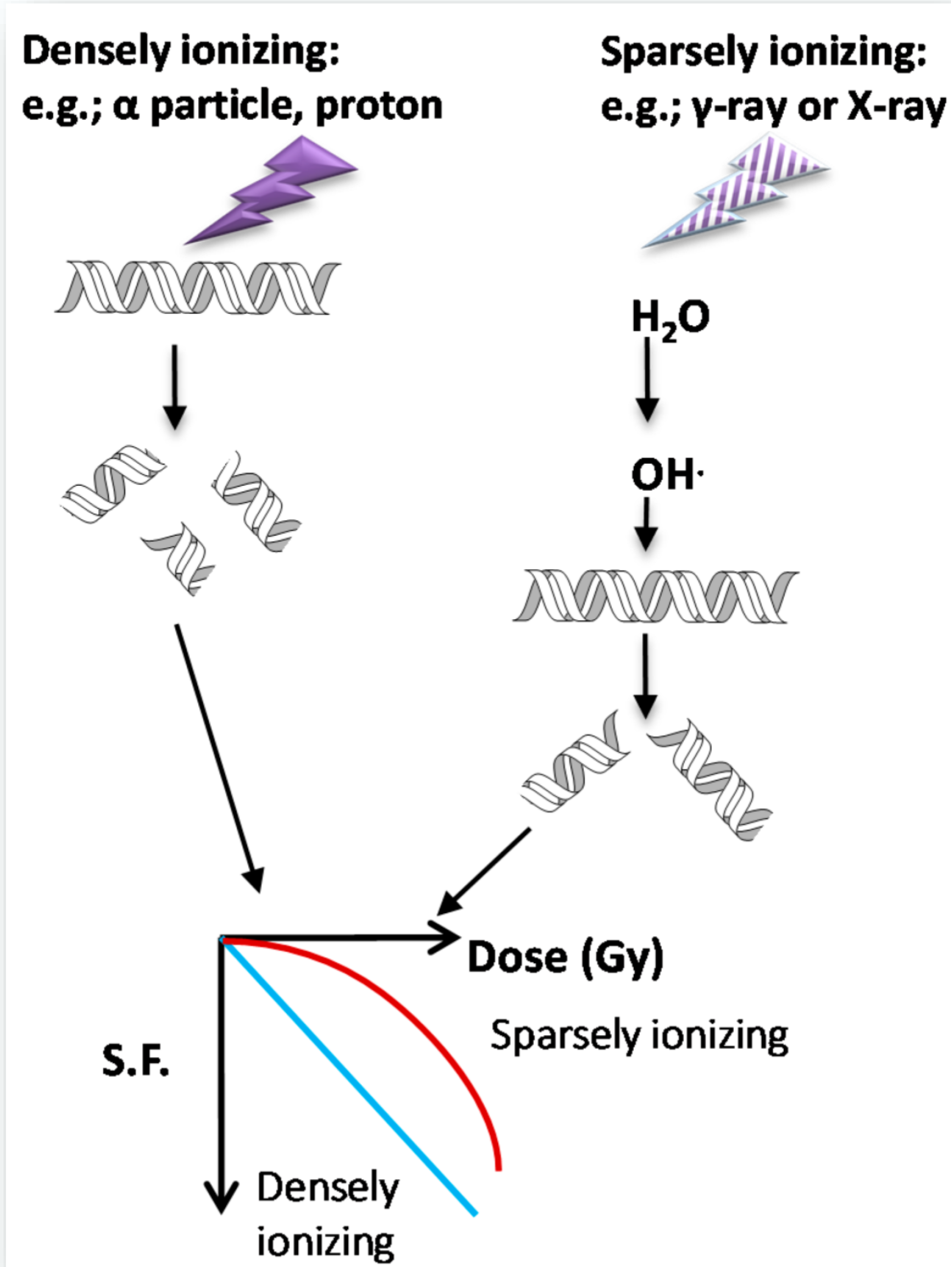
Carbon ions

Carbon ions are densely ionising, majority of direct effects



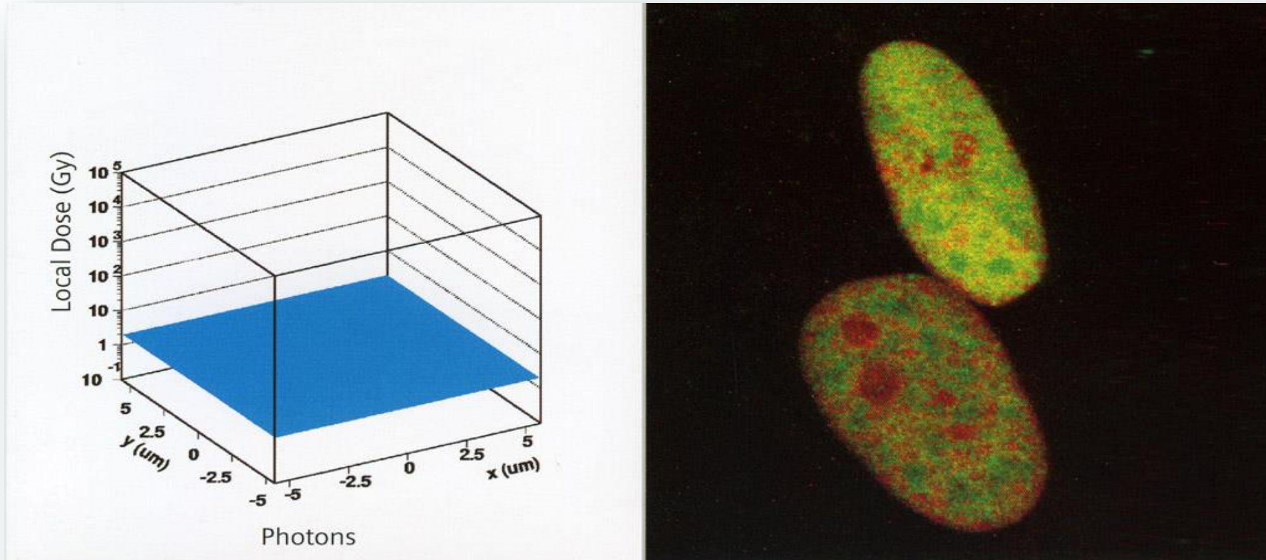

X-ray
track
Heavy-ion
track

Dense energy deposits, repair inefficient



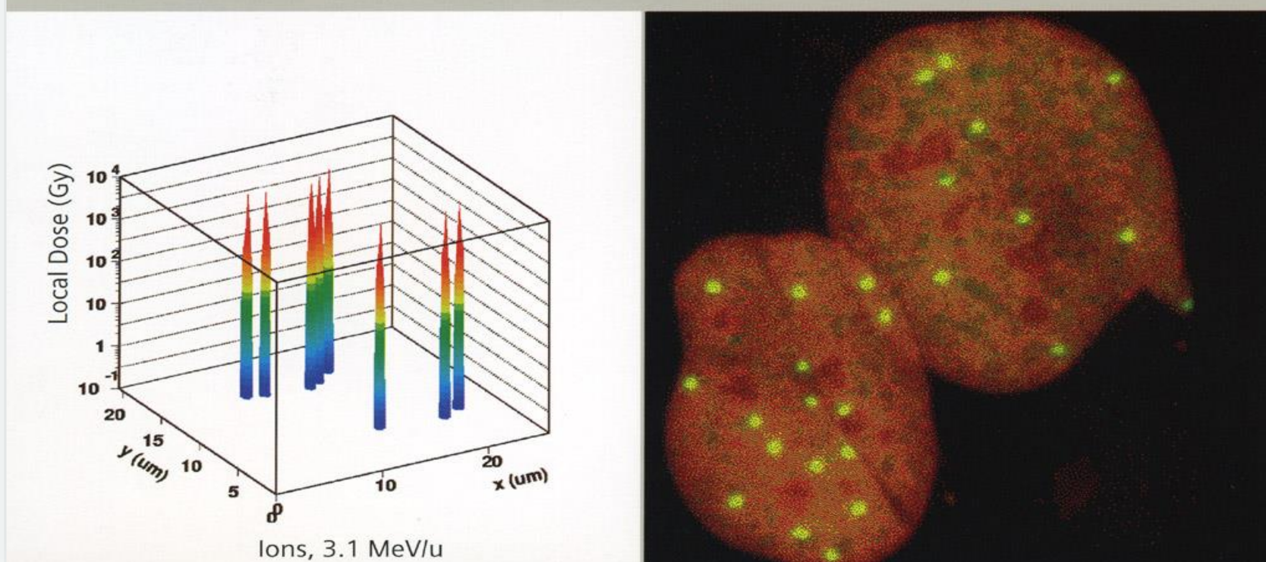
Scattered energy deposits, repair efficient

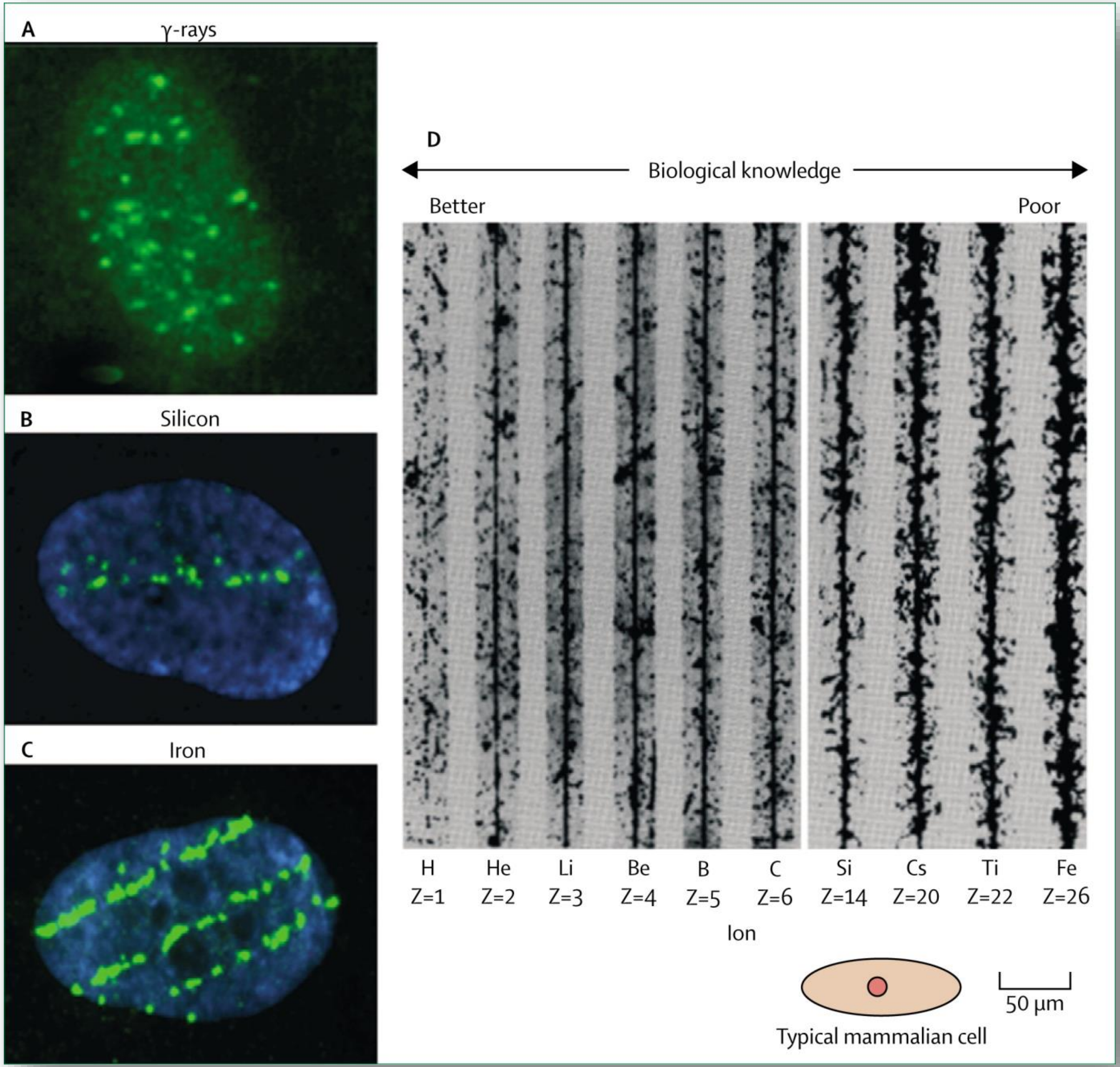
Induction of repair enzymes with X-rays and carbon ions, same absorbed dose



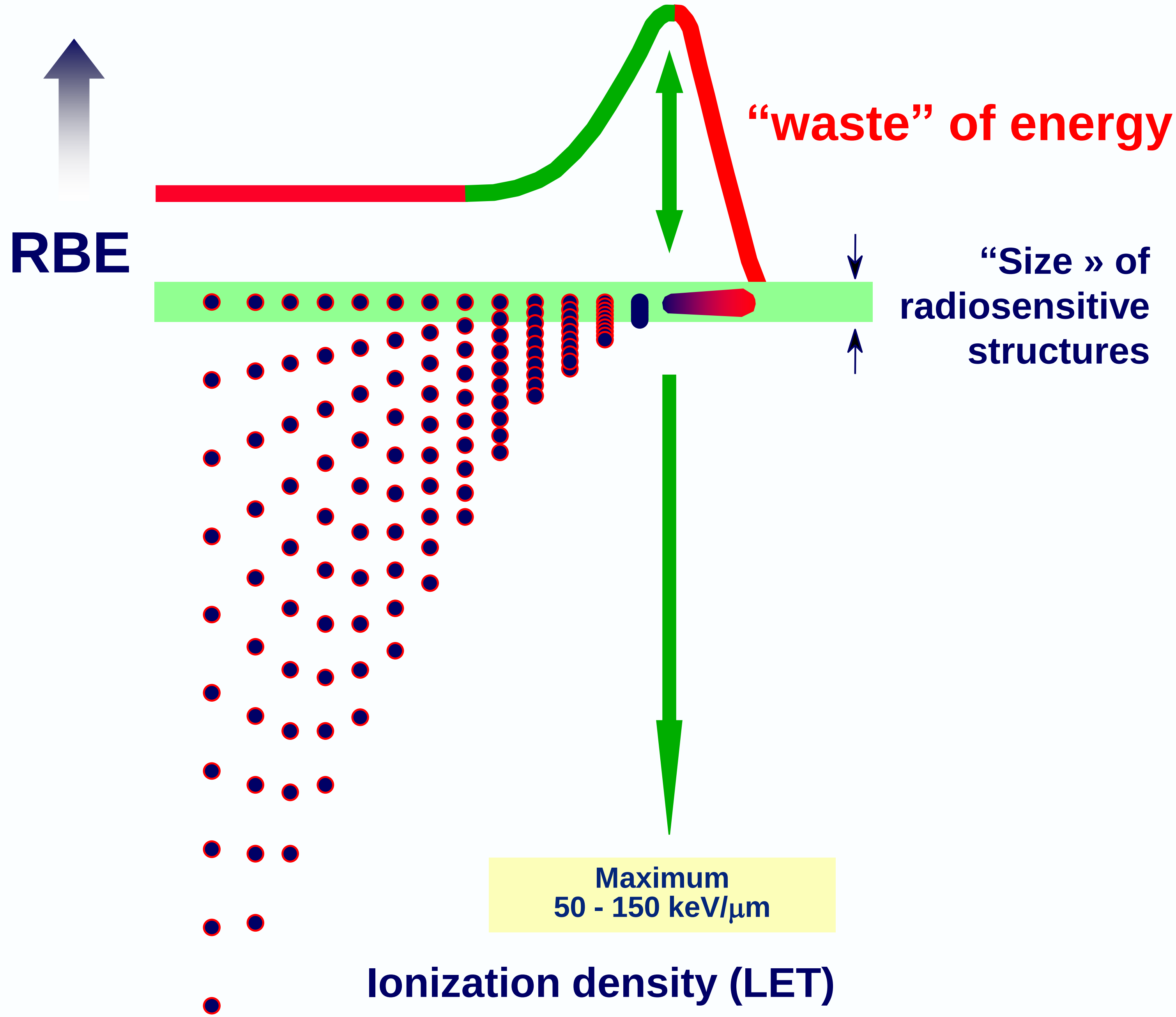
The microscopic dose is evenly distributed over the cell nuclei for photons.

The image shows cell nuclei after X-irradiation. Repair related proteins (yellow color) show up all over the cell nucleus in an immune fluorescent image. Cell repair is normally achieved after half an hour.





Track structure depends on energy and Z


“waste” of energy
RBE
“Size » of
radiosensitive
structures
Maximum
50 - 150 keV/µm
Ionization density (LET)

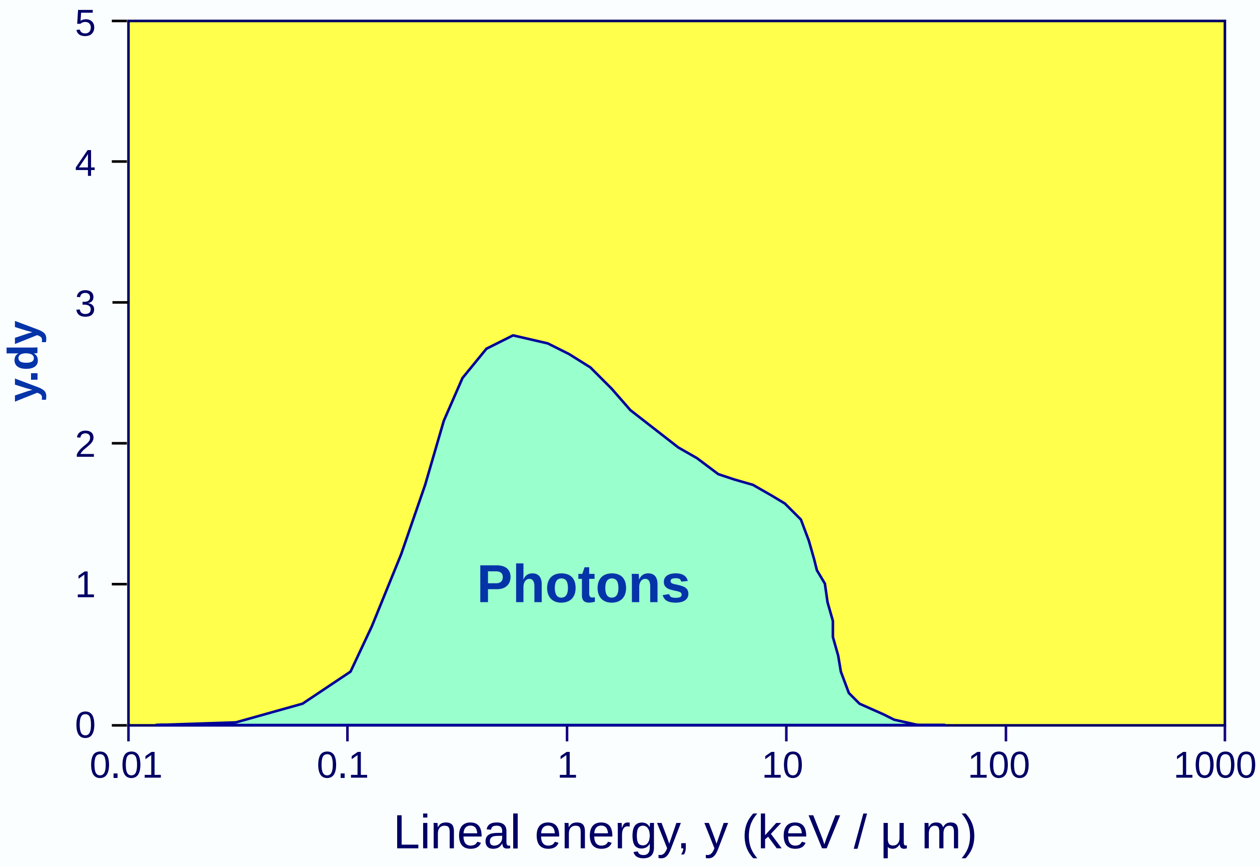
Microdosimetry

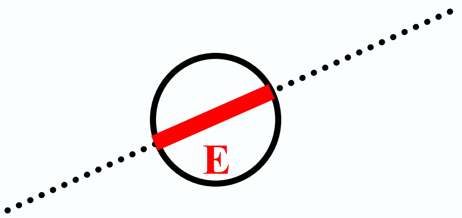
TEPC of Rossi, Columbia University

Tissue-equivalent proportional counter :

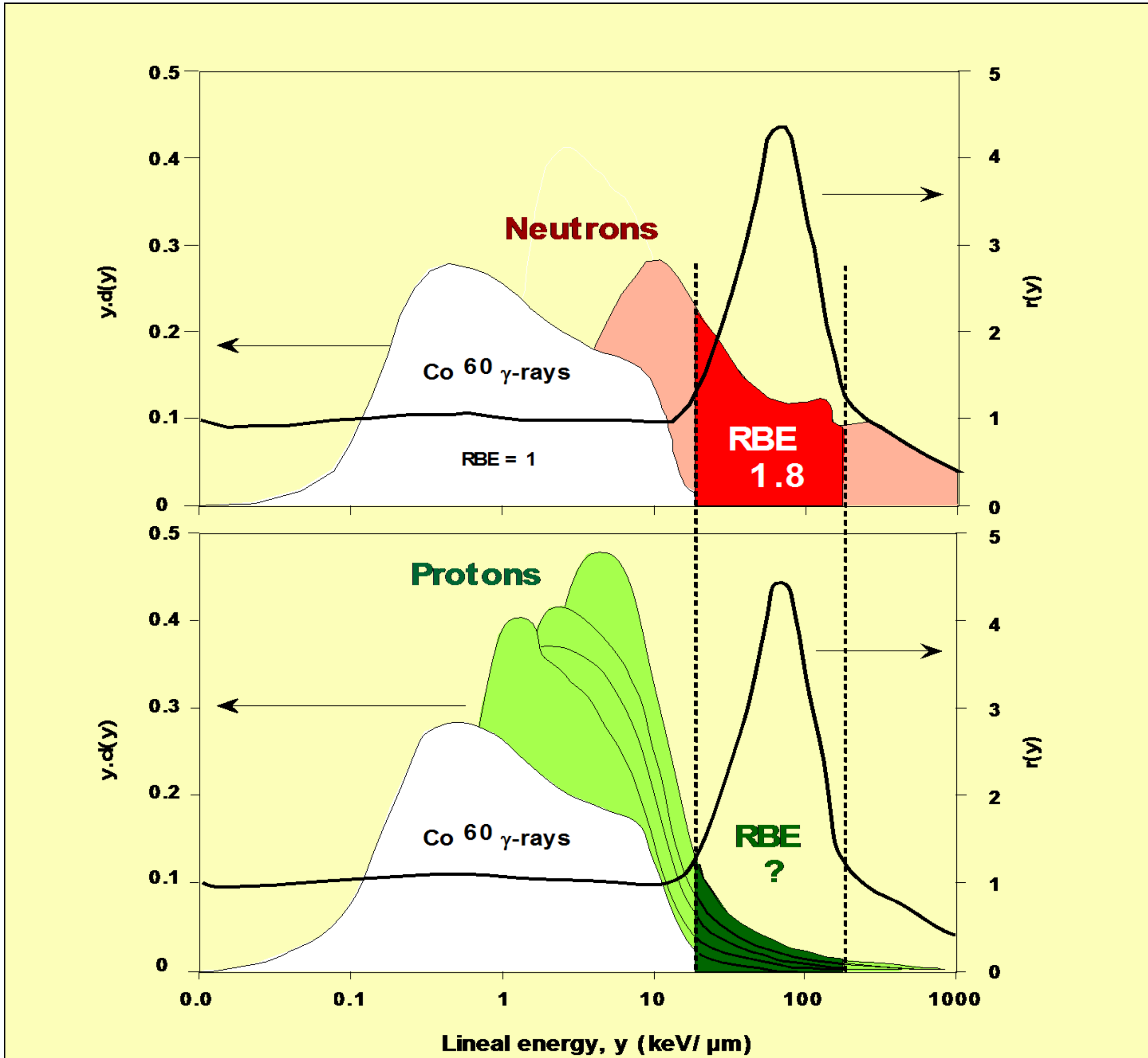
- The sphere is the cathode, in tissue equivalent material.
- The anode is central.
- The gas filling the sphere is tissue equivalent (C, N, O, H).
- Its pressure can be adjusted to simulate small volumes of tissue.
- Irradiation is delivered at extreme low dose rate.
- Electric charges are collected, proportional to the individual energy deposits.

Microdosimetric spectra : a tool for tracking the RBE variations



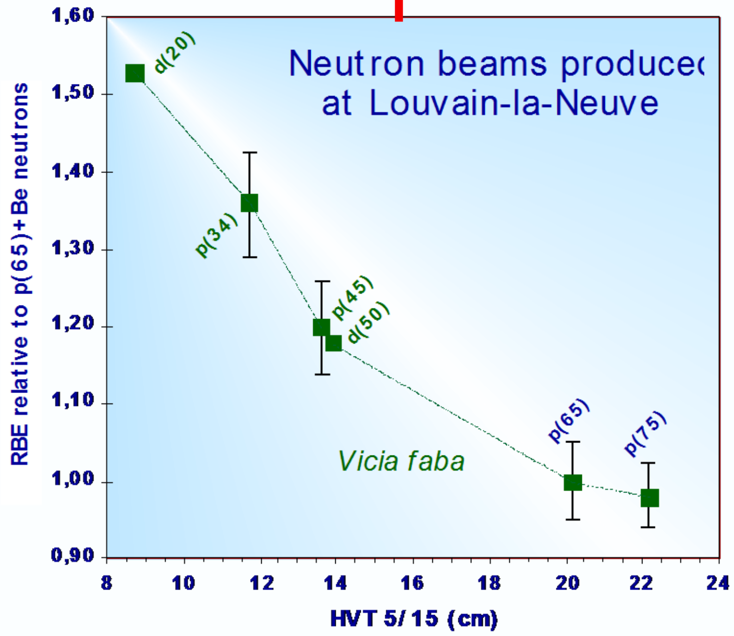


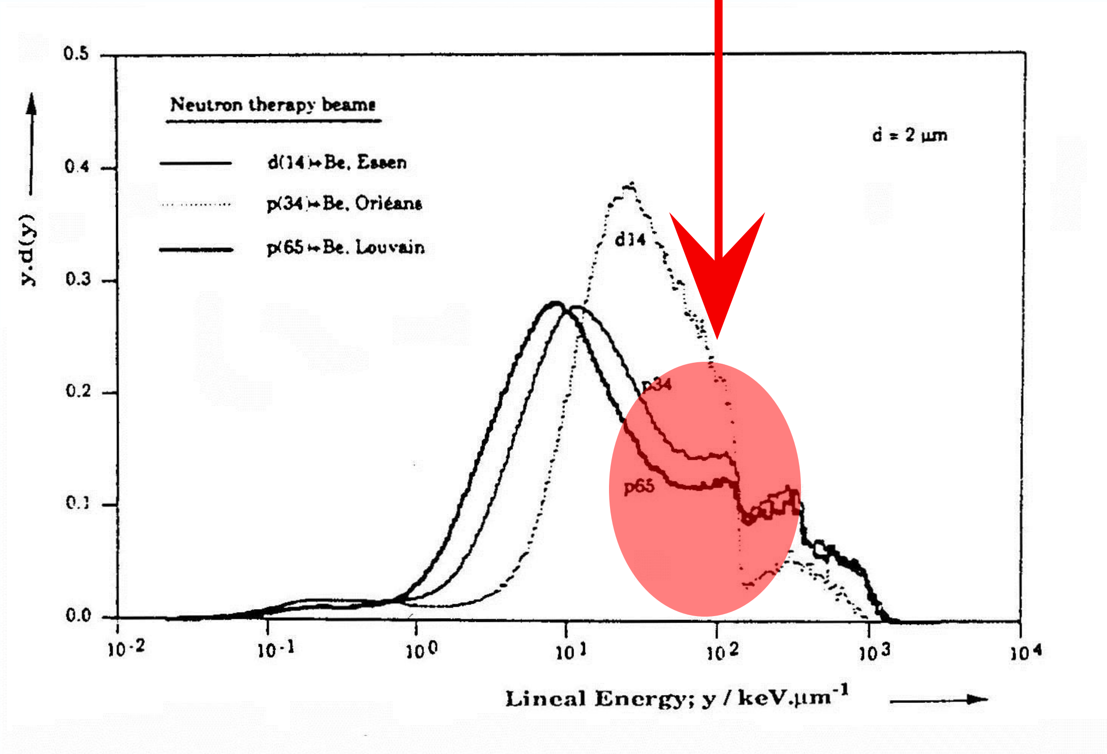
Energy deposition along the diameter of a sphere of the same size as the ***vital radiosensitive structures***



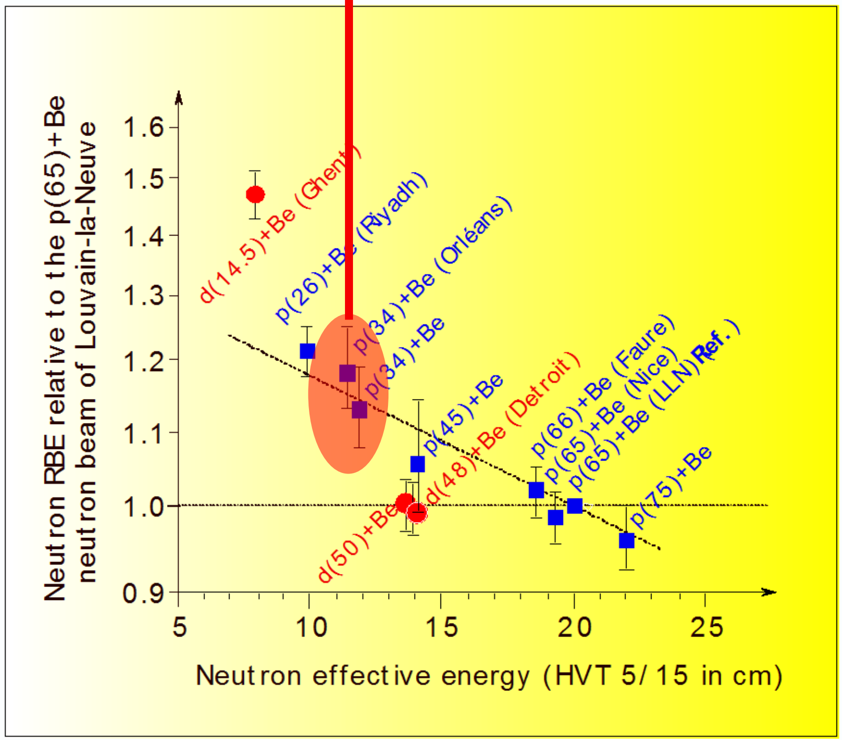
Neutrons
Co 60 γ-rays
RBE = 1
RBE 1.8
Protons
Co 60 γ-rays
RBE ?
y.d(y)
r(y)
0.5
0.4
0.3
0.2
0.1
0
5
4
3
2
1
0
0.0
0.1
1
10
100
1000
Lineal energy, y (keV/ μm)

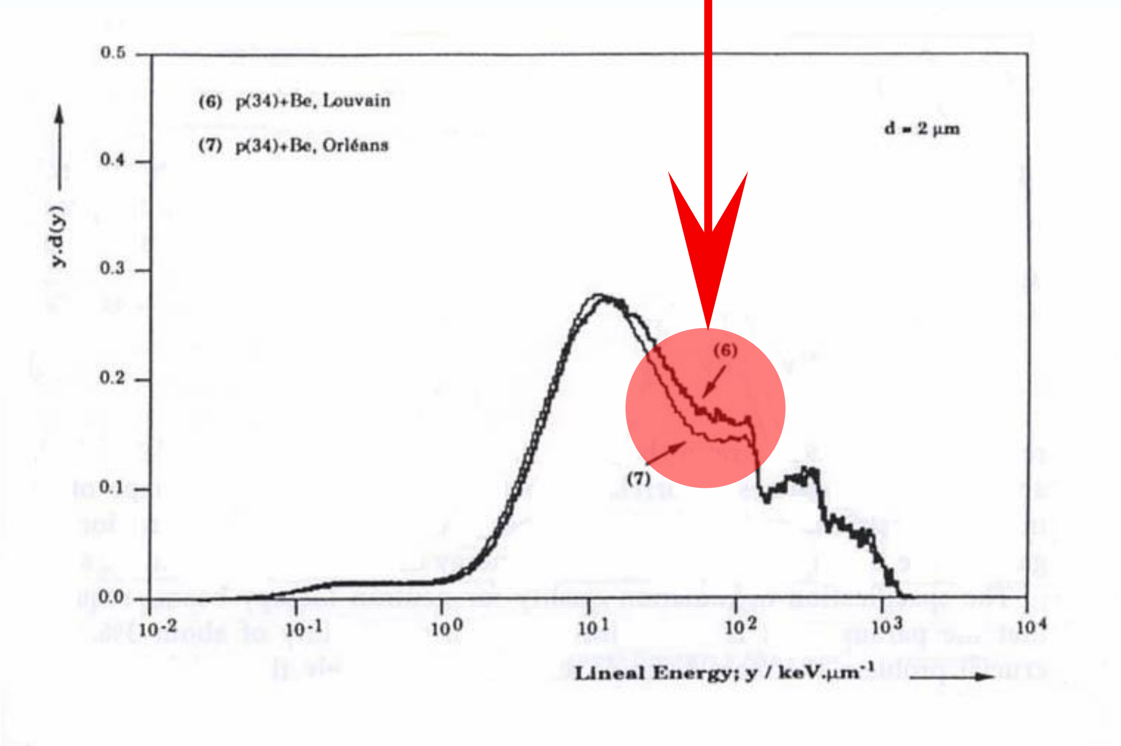
Energy of the incident particles...



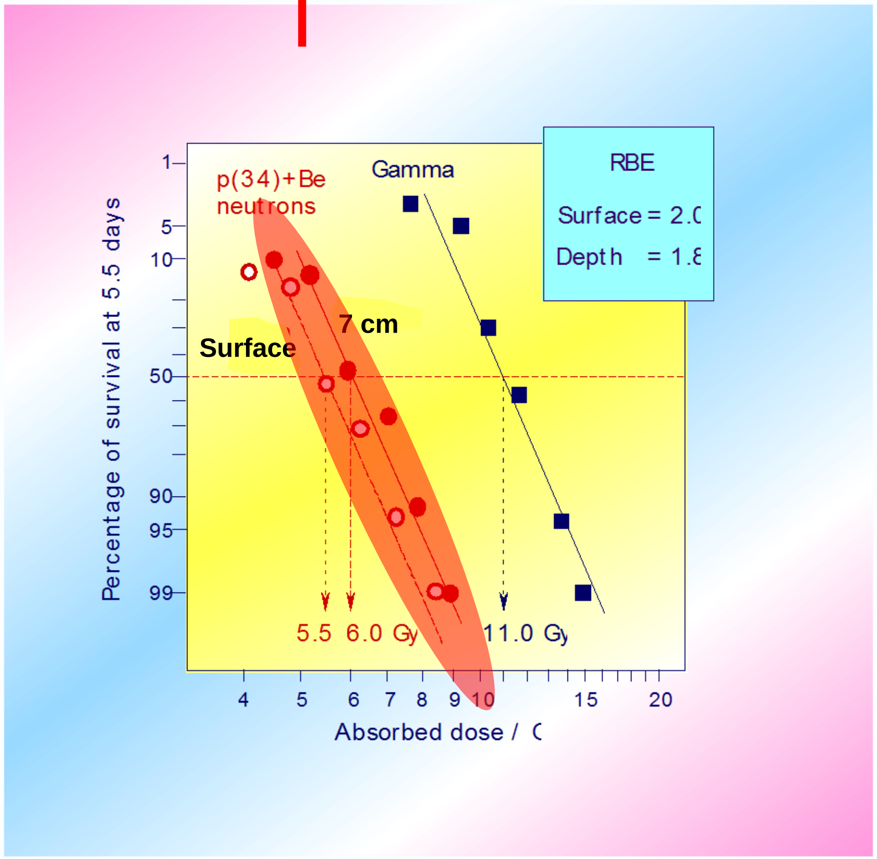


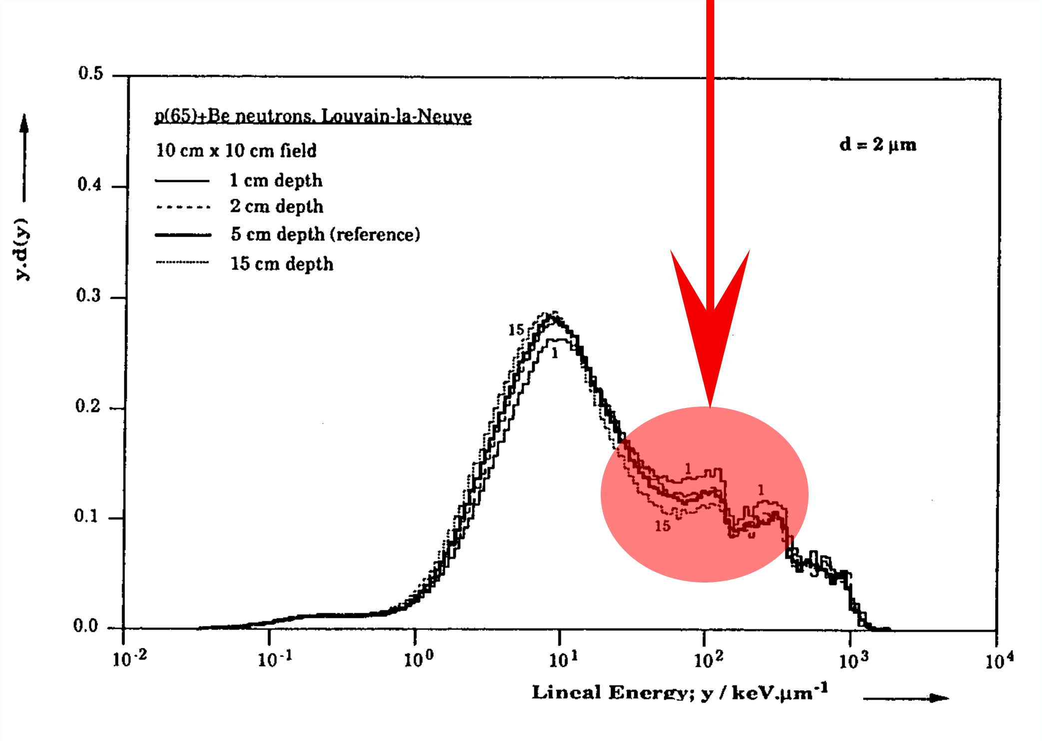
Indentical nominal energy and identical nuclear reaction ...





Depth ...


p(34)+Be neutrons
Gamma
RBE
Surface = 2.(
Depth = 1.8
7 cm
Surface
5.5 6.0 Gy
11.0 Gy
Percentage of survival at 5.5 days
Absorbed dose / (

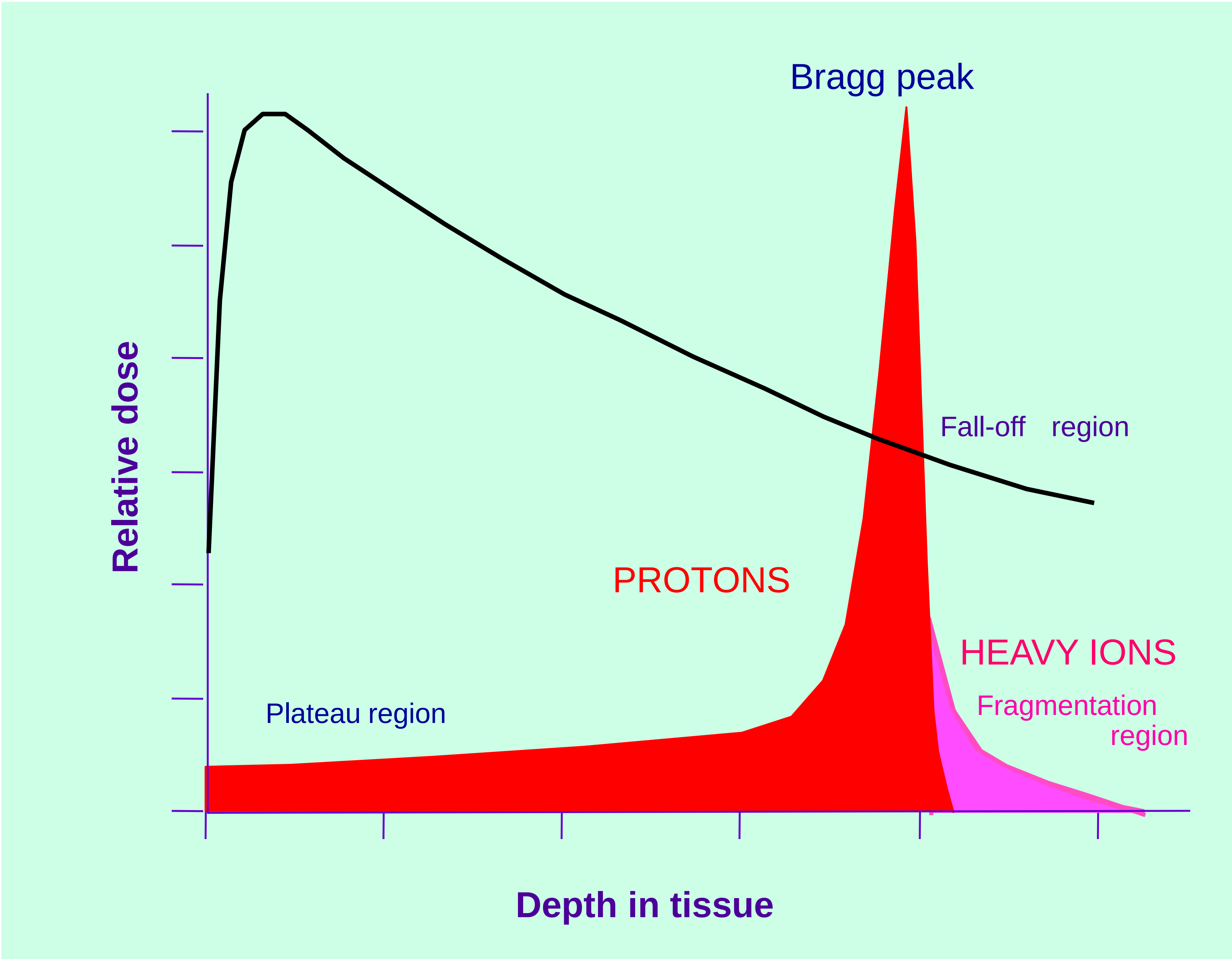

p(65)+Be neutrons, Louvain-la-Neuve
10 cm x 10 cm field
1 cm depth
2 cm depth
5 cm depth (reference)
15 cm depth
d = 2 μm
y.d(y)
Lineal Energy; y / keV.μm⁻¹

Summary of pertinent conclusions (1)

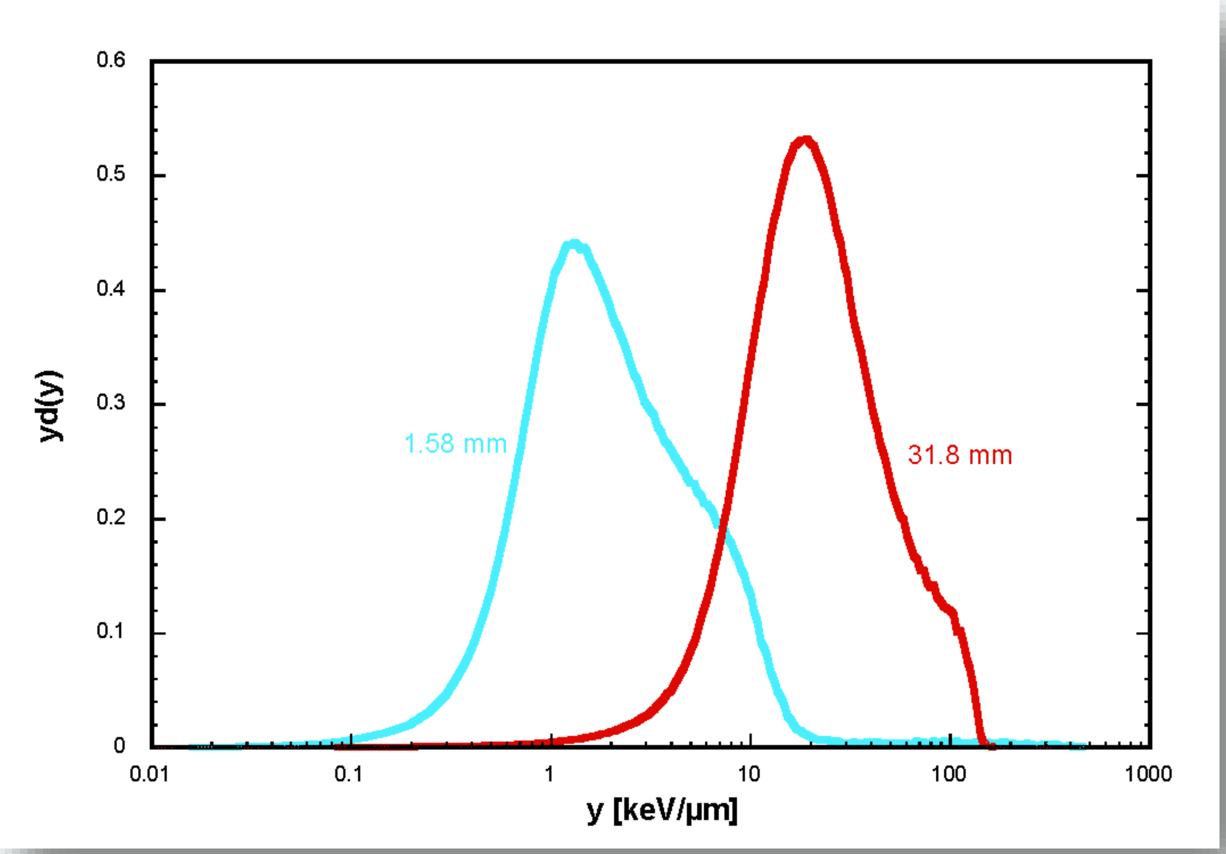
- Conceptually, RBE is a measure of the biological effectiveness differences related to *radiation quality* ***only***
- RBE is essentially variable and depends on numerous factors related 1) to biology or, 2) to the beam delivery technique
- **Biology** : the main sources of RBE variation are : • the biological system (tissue, endpoint, etc.) and • dose, dose rate and fractionation
- **Beam** : the main sources of RBE variation are : • Depth (for heavy ions), • filtration (for fast neutrons), • collimation, etc.
- RBE is correlated with ionization density. *Roughly speaking*, it increases with LET.

Summary of pertinent conclusions (2)

- When determining RBEs, all conditions - but the radiation quality - have to be the same for the intercompared beams
- Inherent performance of the beam generators as well as practical reasons (e.g, distance) prevent from adopting ideal experimental procedure
- Recourse to indirect method for RBE determination is often required (RBE ratios)
- Recourse to fractionated irradiations is most of the time required to determine RBEs for small doses
- Microdosimetry is a powerful tool for tracking the potential RBE variations


Bragg peak
Relative dose
Fall-off region
PROTONS
HEAVY IONS
Fragmentation region
Plateau region
Depth in tissue

Proton beam (Nice)



Plateau (entry beam)

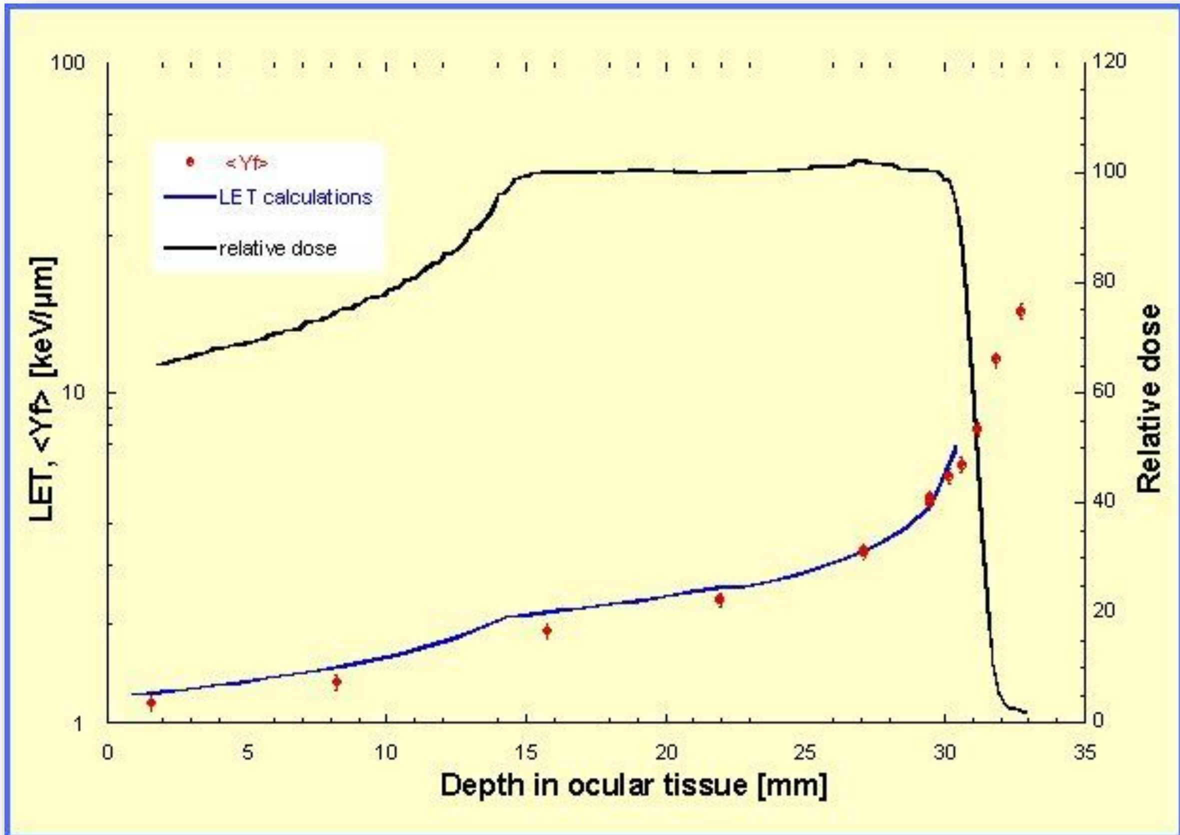
Most events are in the 1 keV/mm range, with a significant component around 10

End of Bragg peak

Most events are in the range 10-30 keV/mm range, with a significant component around 100.

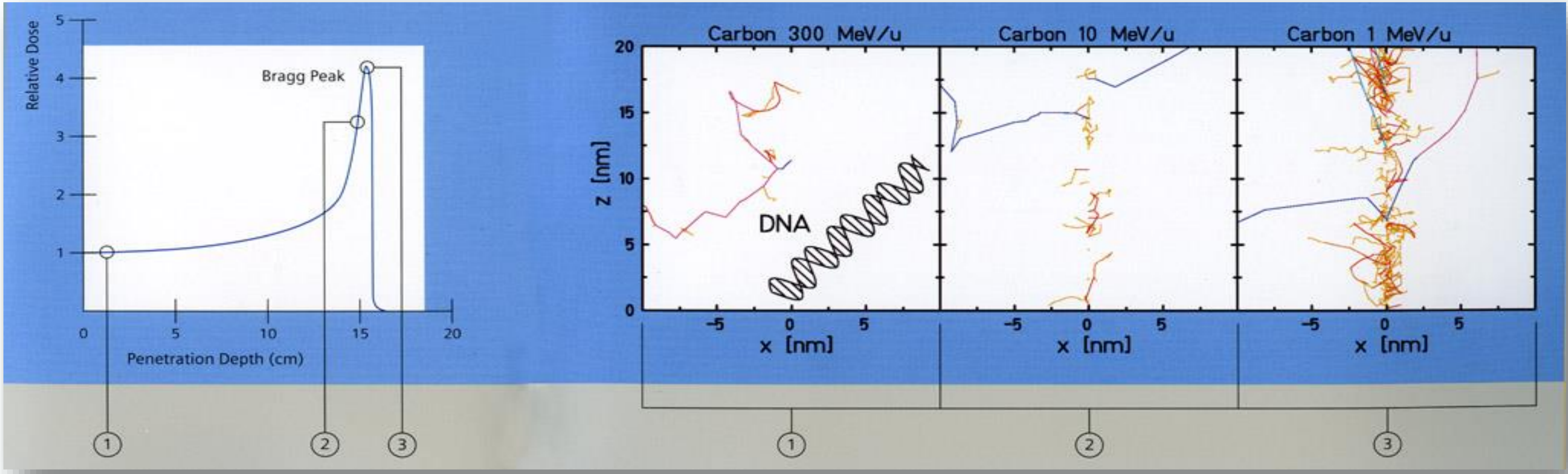
Spectrum : sum of individual energy deposits

Proton beam (Nice)



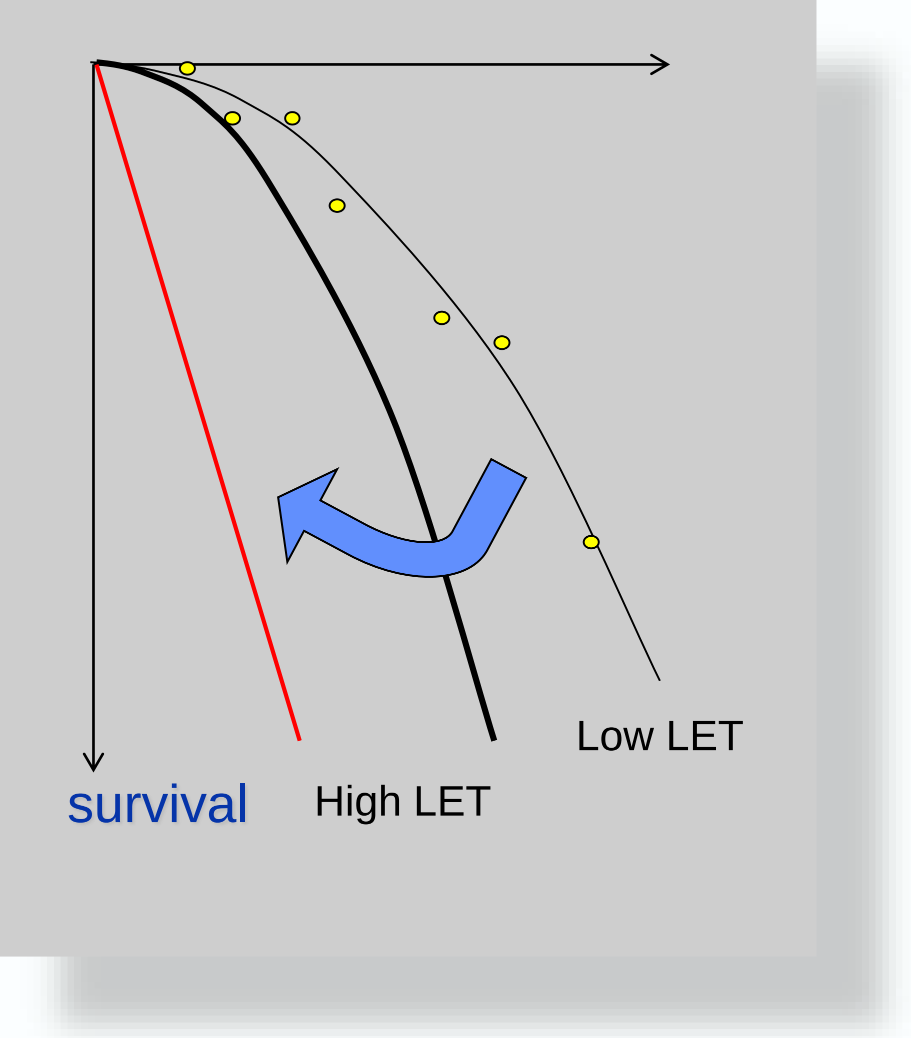
Let increases as the beam progresses in depth (SOBP)

Density of energy deposits in the Bragg peak of carbon ions



Linear energy transfer (LET)

- LET is the physical quantity of ionisation density; its unit is the keV/μm.
- The higher the LET, the broader the DNA damage and, hence, the larger the biological effect

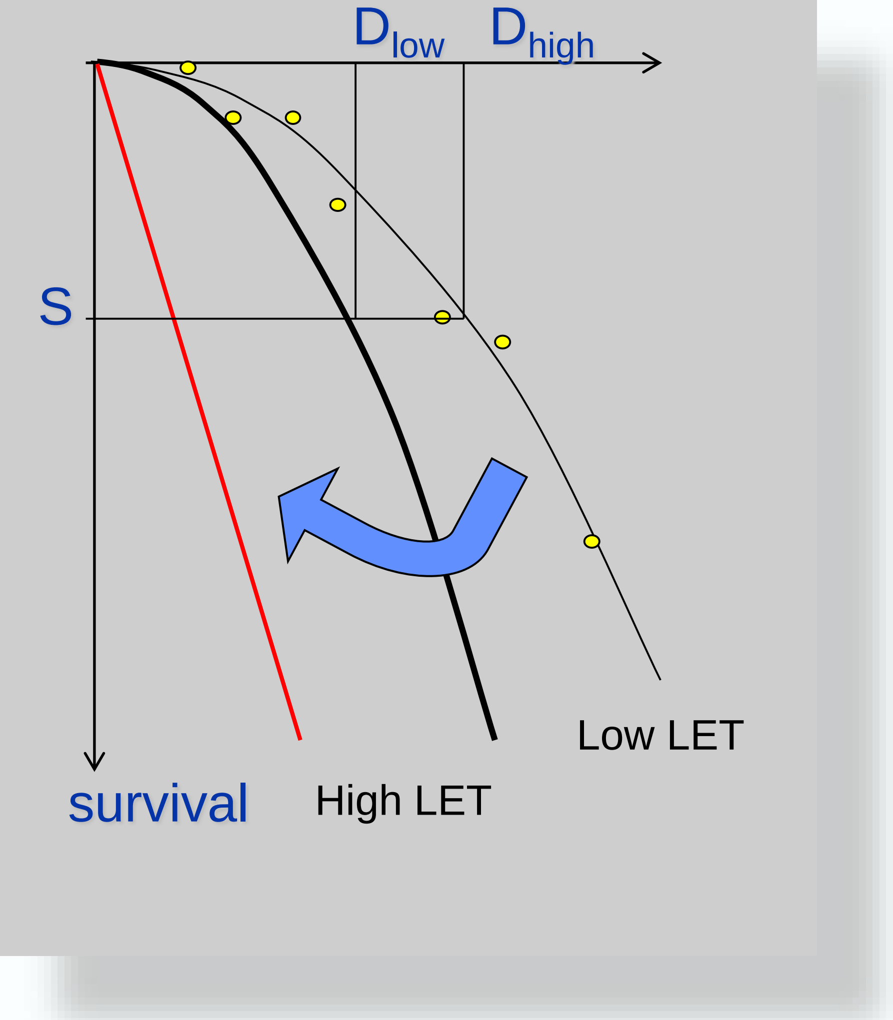


RBE ?

The relative biological effectiveness is a ratio of dose:

$D_{lowLET}/D_{highLET}$

for any given level of effect

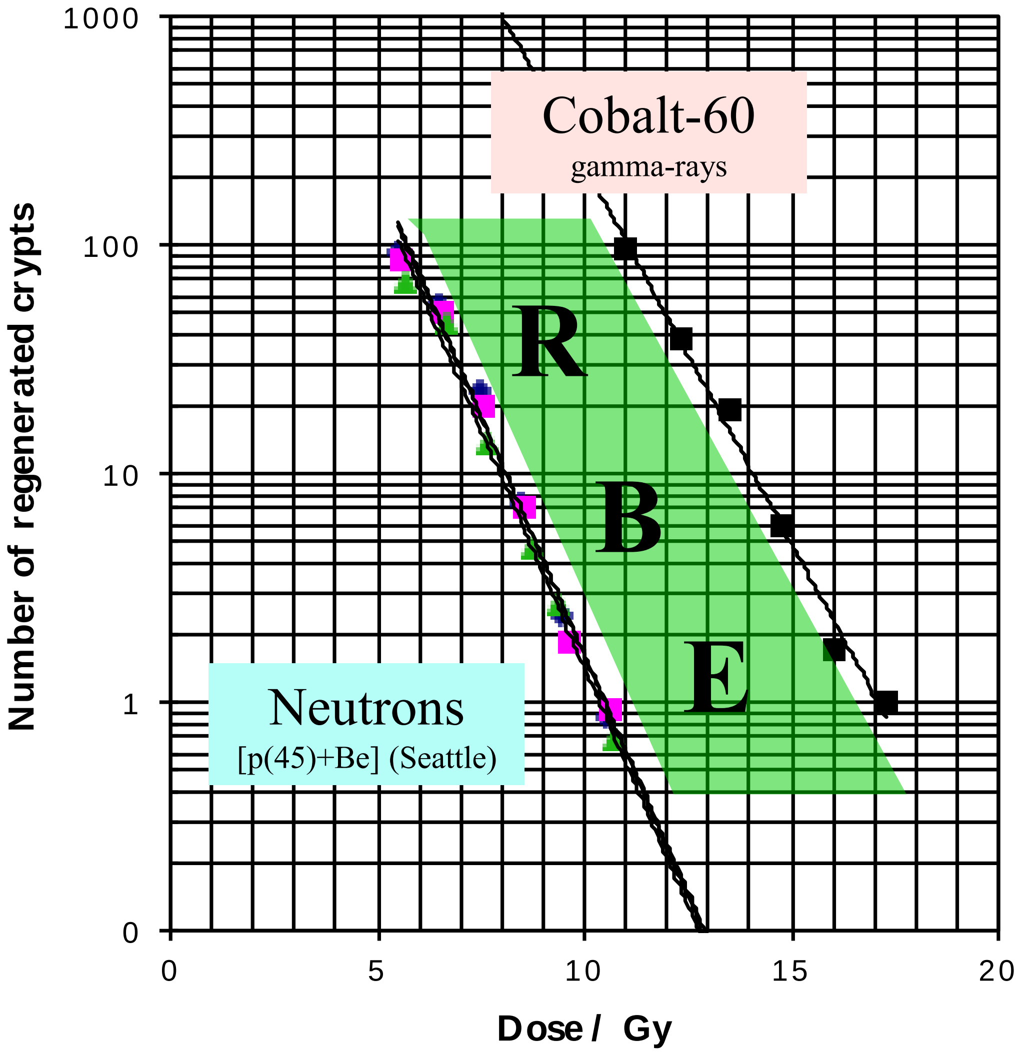


All the irradiations performed under the same conditions, e.g. :

- Irradiation in a single fraction
- Acute dose rate

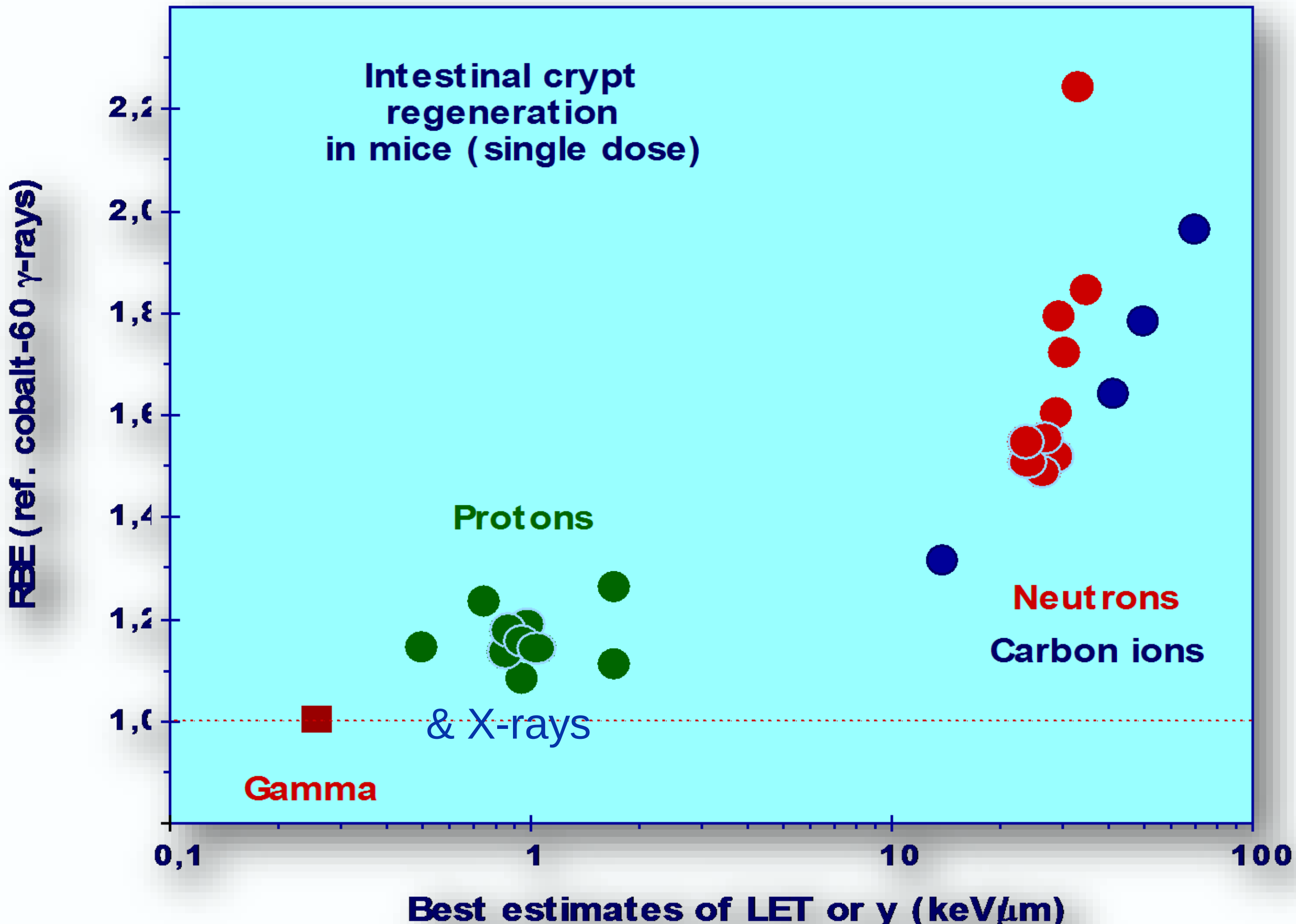
- Same day (and moment in the day)
- Animals from the same population
- Randomized (dose / radiation quality)

- Same experimenters
- Reliable dosimetry
- Etc.

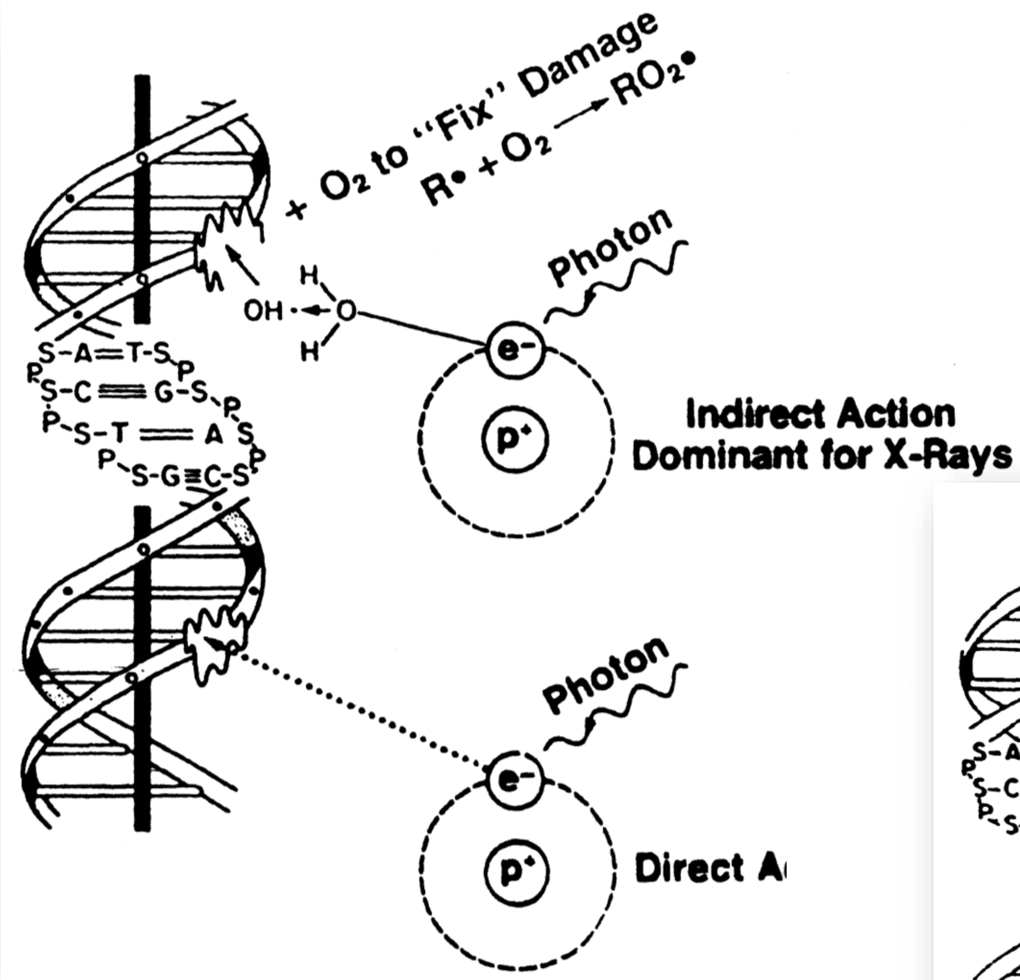


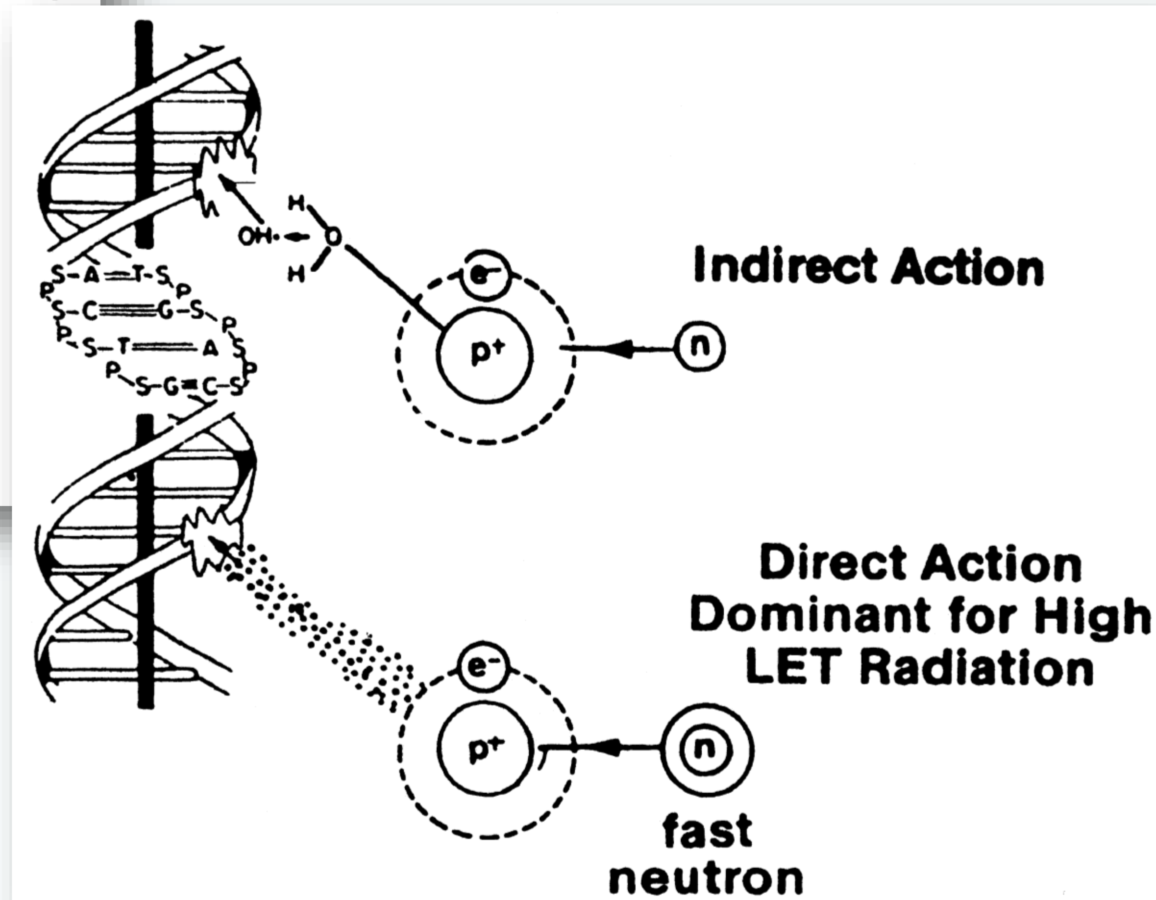
RBE accounts for the *biological effectiveness difference* related only to the *radiation quality difference*

Different radiation quality have different RBE's

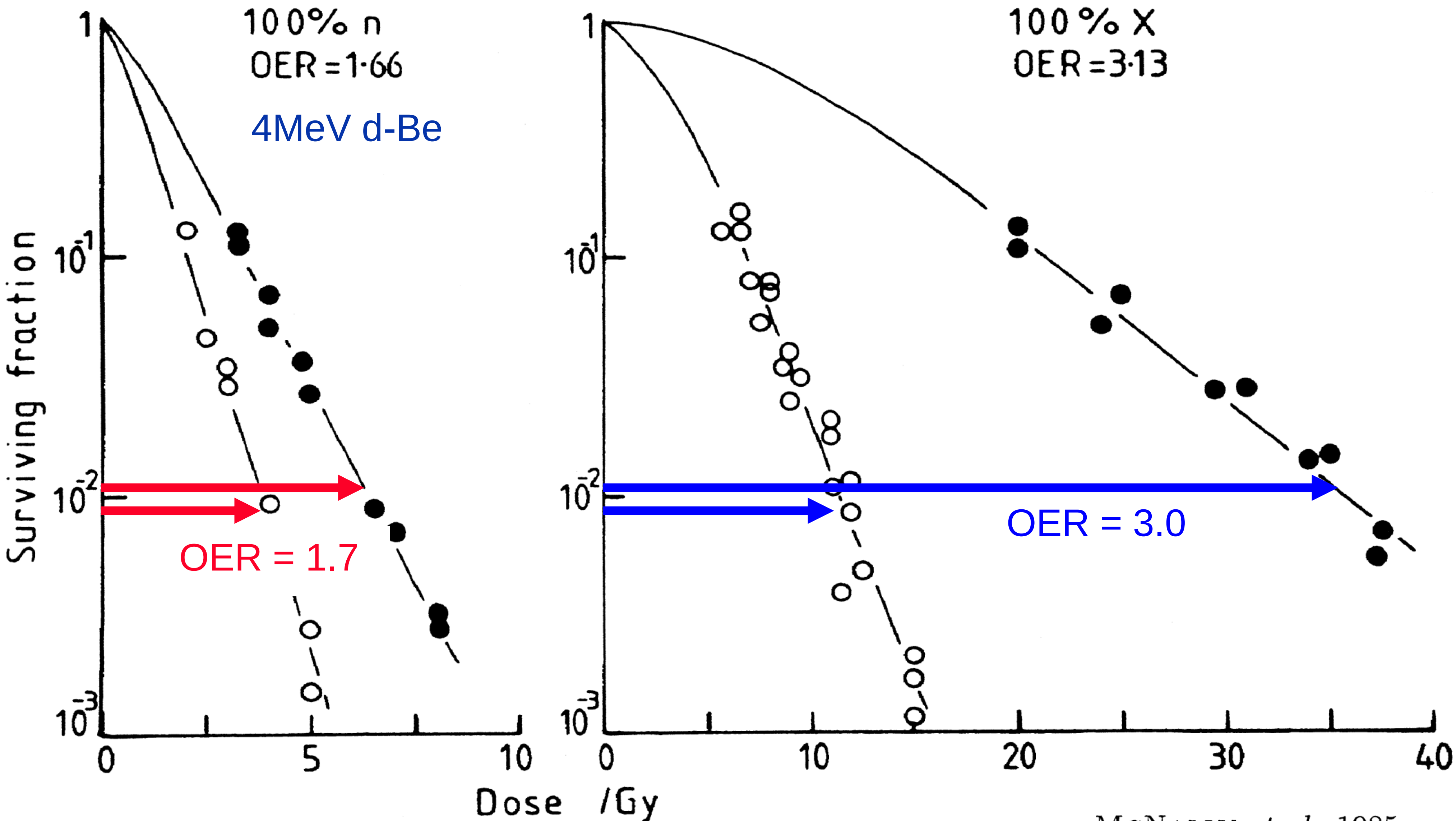


Oxygen effect



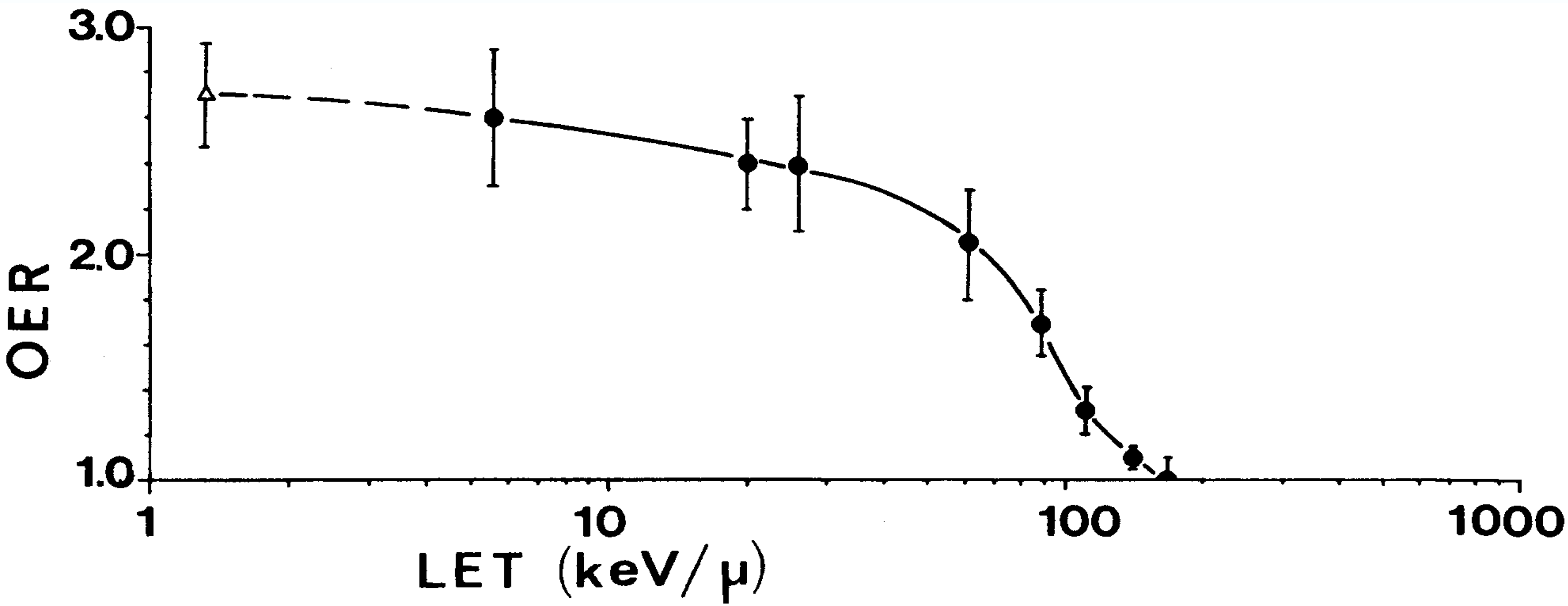


Reduced effect of oxygen



McNally *et al.*, 1985,
Int. J. Radiat. Biol., **48**, 847

As LET increases OER decreases



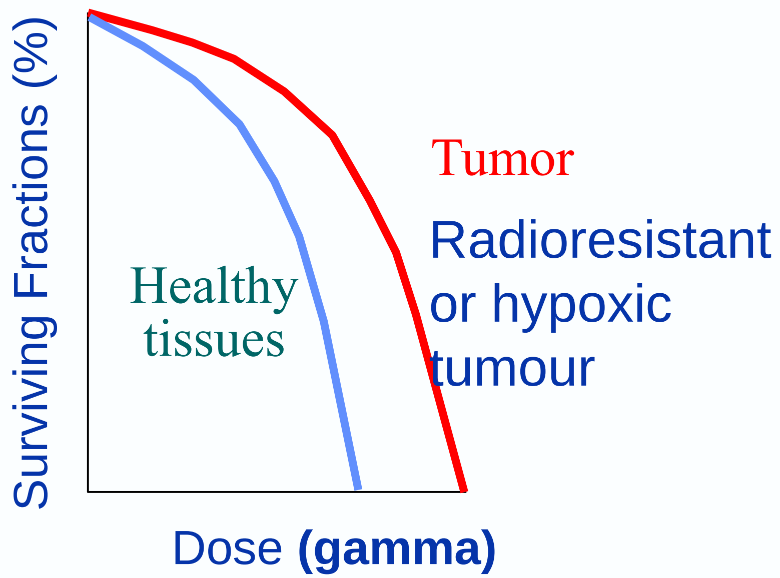
Reduction of radiosensitivity differences :

Potential therapeutic advantage

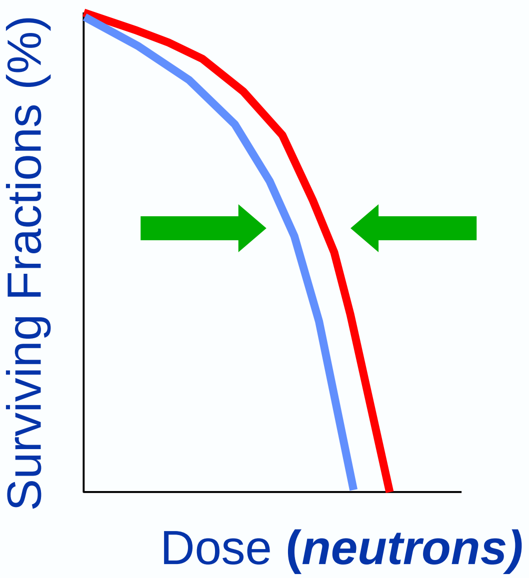
when the tumor is radioresistant

in comparison with healthy tissues

unfavourable !



less unfavourable !



Potential therapeutic benefit due to the ***reduction***

*of an **unfavourable** differential effect*

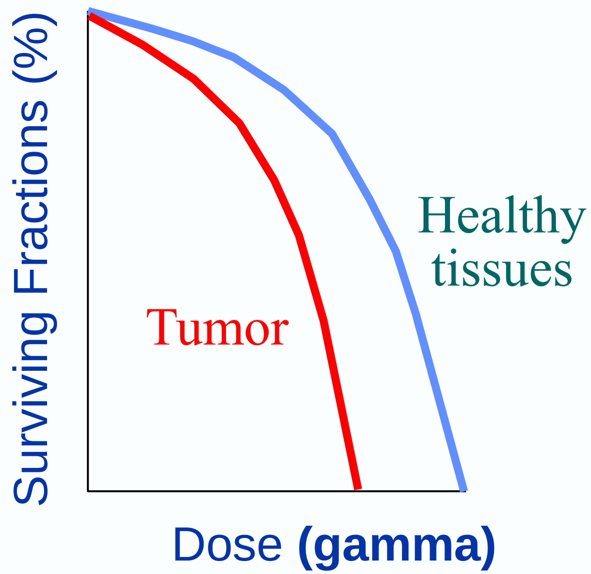
Reduction of radiosensitivity differences :

contra-indication

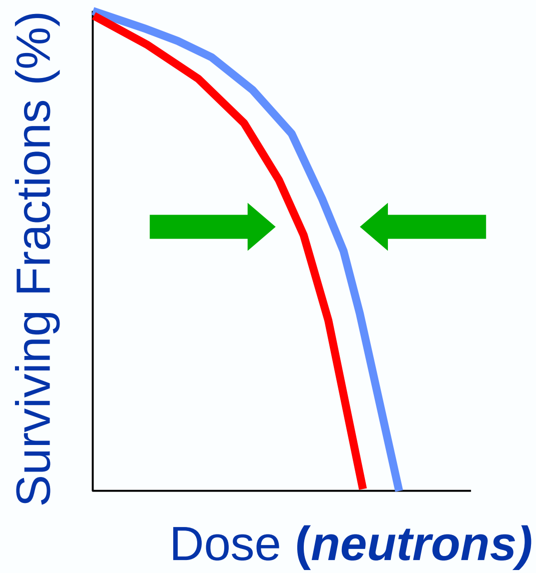
when the healthy tissues are radioresistant

In comparison with the tumor

favourable !



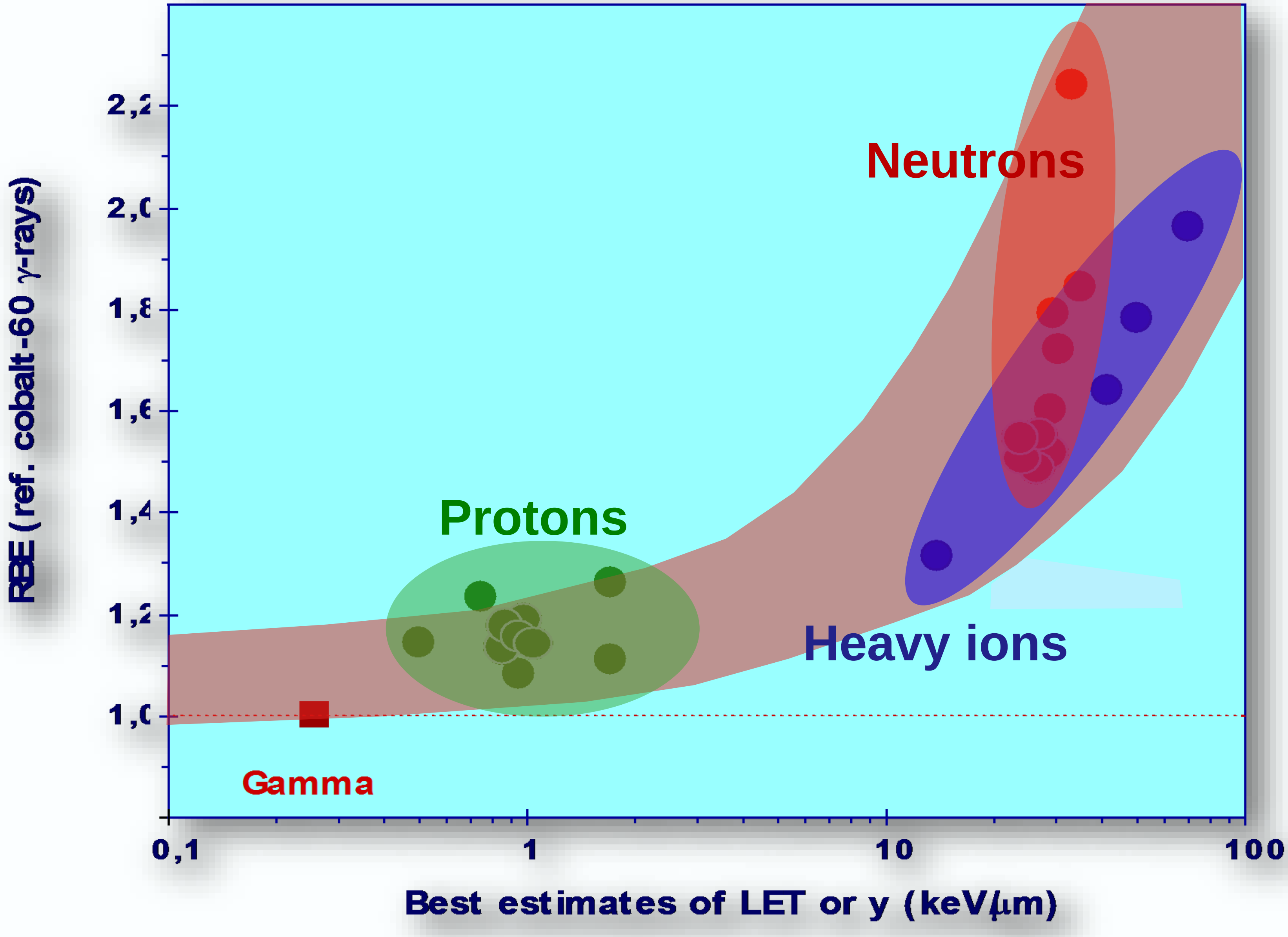
less favourable !



Contra-indication due to the ***reduction*** *of*

a ***favorable*** *differentiel effect*

Hadron RBE is different than that of photons	Buid-up of radiobiological experience and disclosure of potential benefits	**« Pretherapeutic »** experiments
RBE varies with « radiation quality »	**Safe and optimum clinical application**	**« Preclinical »** experiments
All the beams are different	Transfer of radiobiological / clinical information and coherency of treatments	**Radiobiological Calibration / Intercomparison**

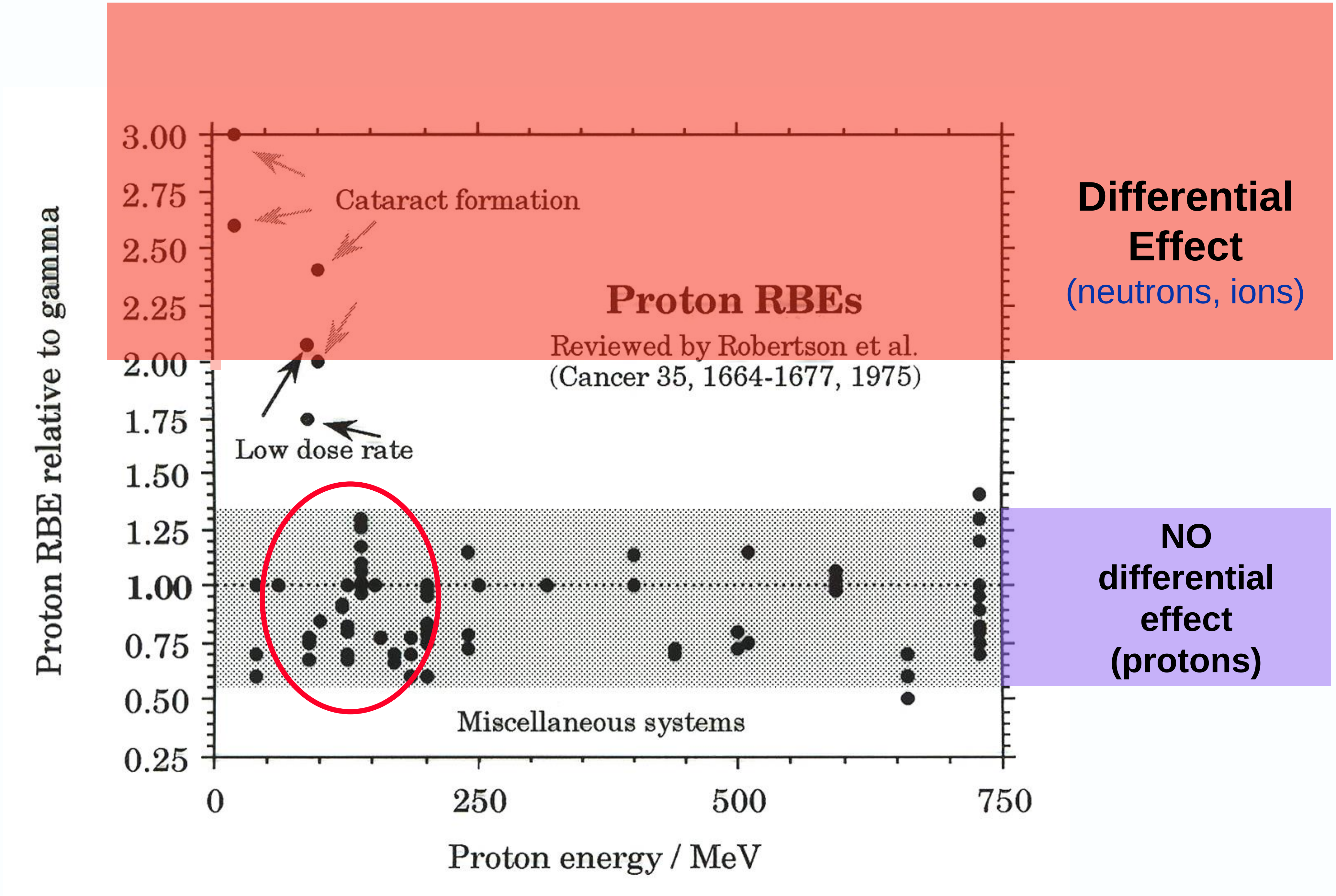


Summary of in vivo data on jejunal crypt cells

RBE variations related to biological system = **Rationale for clinical application of high-LET radiations**

RBE variation related to radiation quality (energy) = **Emergence of problems related to :**

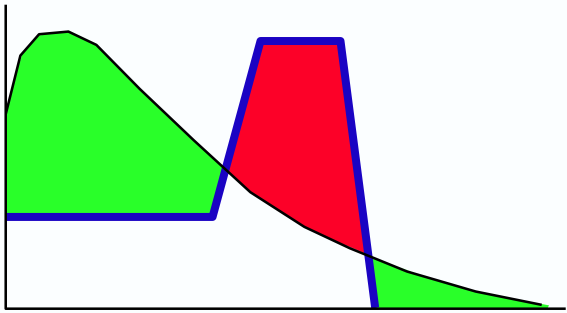
- **Transferring clinical and radiobiological information**
- **Pooling clinical data**
- **Optimizing clinical applications**
- **Comparing with conventional radiations**



Proton RBEs
Reviewed by Robertson et al.
(Cancer 35, 1664-1677, 1975)
Cataract formation
Low dose rate
Miscellaneous systems
Proton RBE relative to gamma
Proton energy / MeV
3.00
2.75
2.50
2.25
2.00
1.75
1.50
1.25
1.00
0.75
0.50
0.25
0
250
500
750
Differential Effect
(neutrons, ions)
NO differential effect
(protons)

Proton RBEs are **too small** to result in a ***workable*** **differential effect**

*Potential advantage of protons is essentially **ballistic***



Proton RBEs **are big** in comparison with **dose accuracy requirements ...**

and raise essentially
Bio-dosimetry questions

Gamma Equivalent Dose =
physical dose x **RBE**

Uncertainties in RBE values lead to **equal uncertainties** in the derived Gamma Equivalent Doses

The dose accuracy required in radiotherapy is 3.5 %

In vitro systems

(Proton RBE = 0.94 - 1.63)

Substantial spread between cell lines and conflicting conclusions about :

- RBE value in reference conditions (energy, depth)
- possible RBE increase with depth
- possible RBE increase with SF (or fractionation)

In vitro systems

(Proton RBE = 0.94 - 1.63)

Possible causes of the spread of the data :

- Dosimetry ?
- Underlying theory (model to fit the data)
- Randomization ?
- Platting efficiency ?

→ Uncertainties above 20 %

In vivo systems

Proton RBE 1.08 - 1.17

Limited amount of data. Present-day questions are :

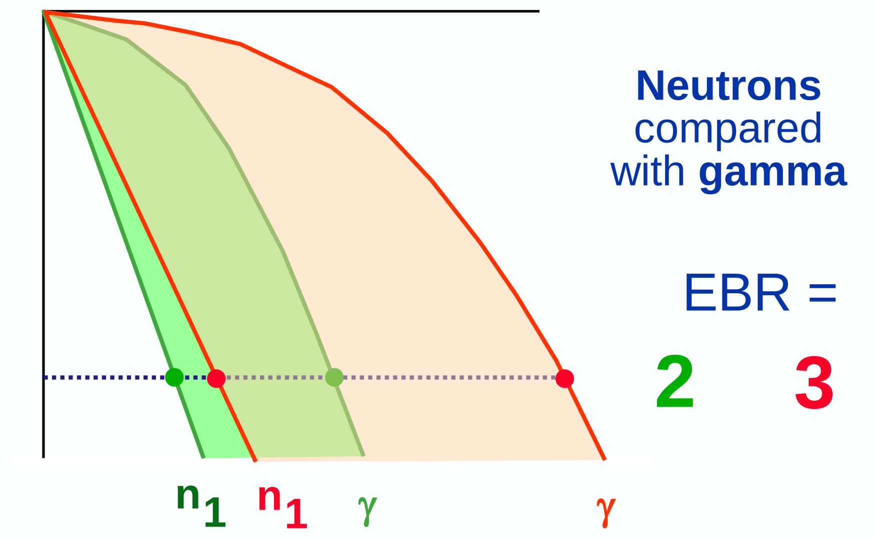
- RBE increase with fractionation ?
- RBE difference for early and late tissue tolerance ?
- RBE increase with depth ?

Which system to use for

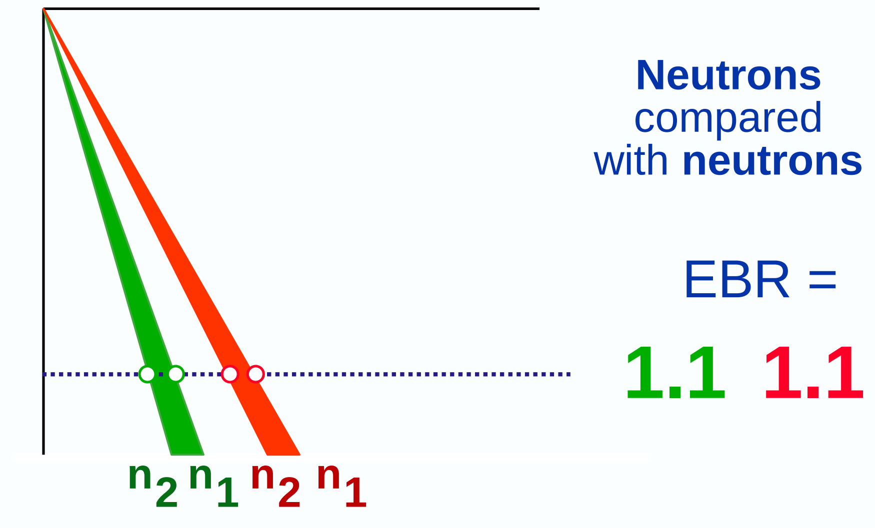
- calibrating
- intercomparing

clinical proton beams ?

Systems and endpoints which result in widely different values for the RBE of neutron relative to X-rays ...



... give similar values for the *RBE differences* between two closely related neutron energies



Consequently, the choice of a biological system for intercomparisons should be governed largely by its

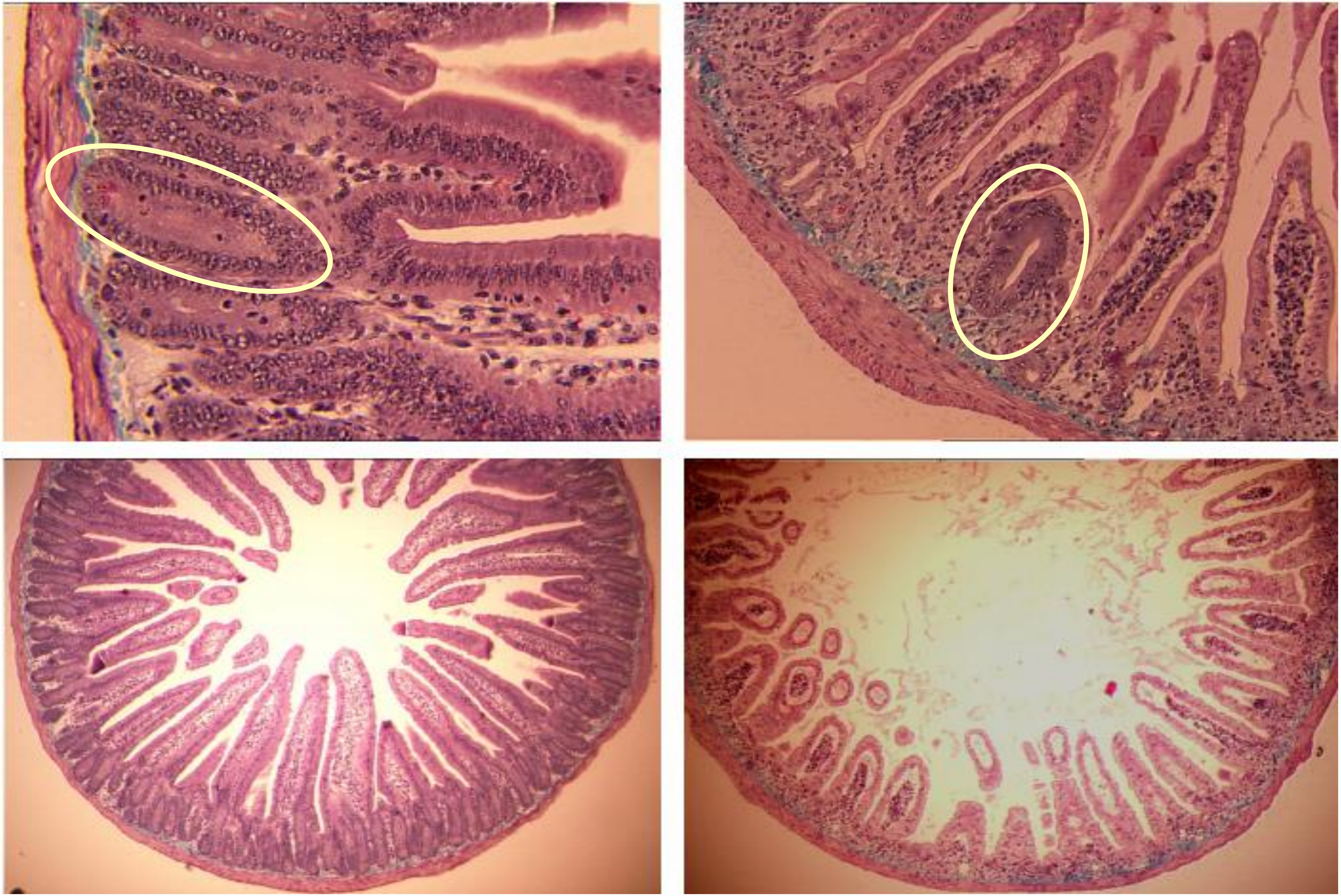
- ***portability,***
- ***repeatability***
- ***and convenience.***

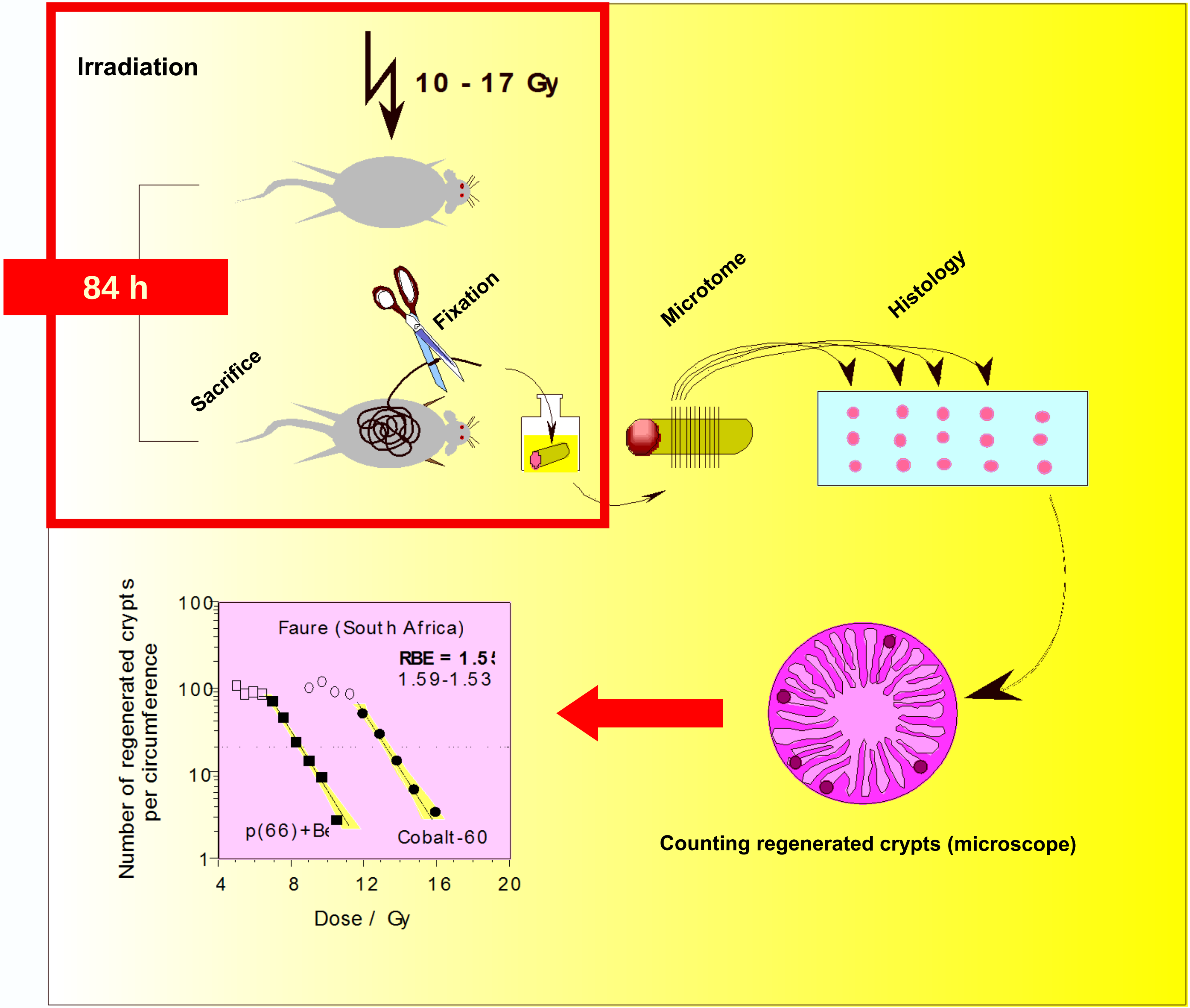
J. Hall, 1979

Intestinal crypts regeneration in mice

In - vivo system, based on

Cell lethality





- Single fraction
- Irradiation to the whole body

Tested beam

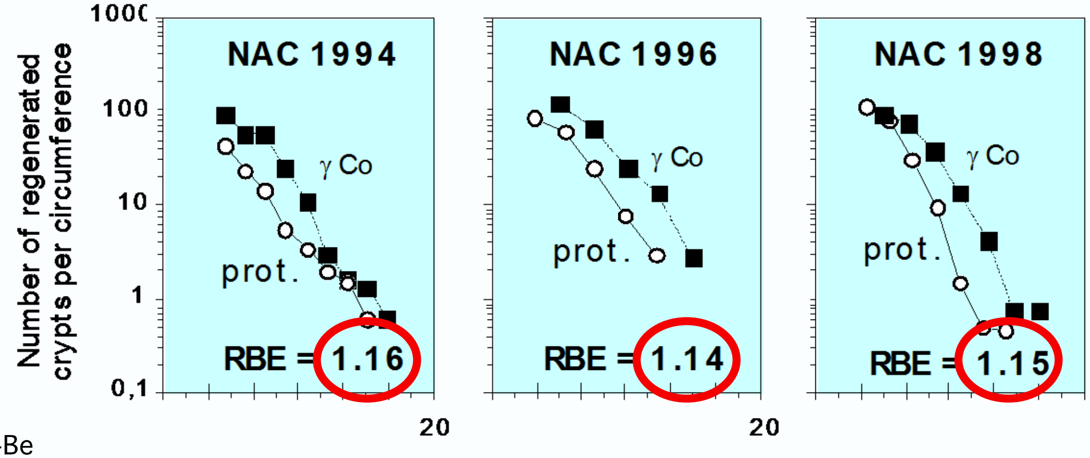
- Clinical dose rate
- Position depending on the type of beam

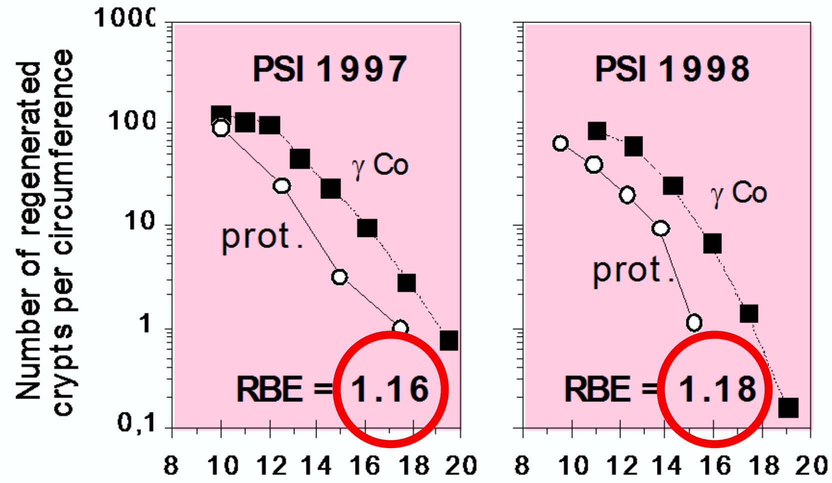
Reference beam

- Cobalt-60 or 7 MV
- 1 Gy / min
- Depth of the peak dose

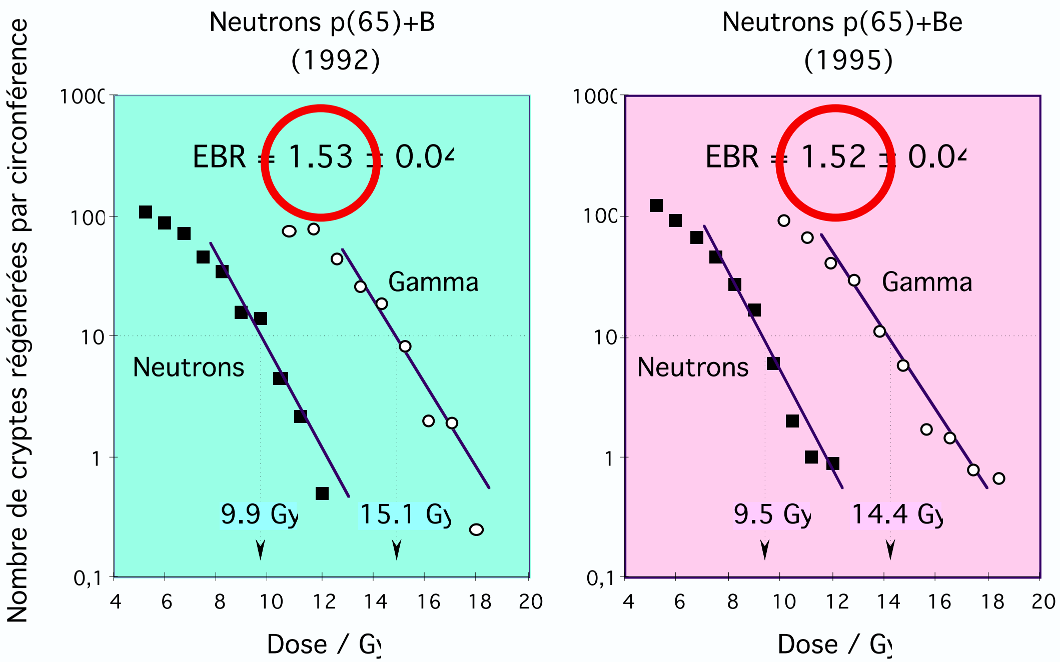
Reproducibility...

Protons





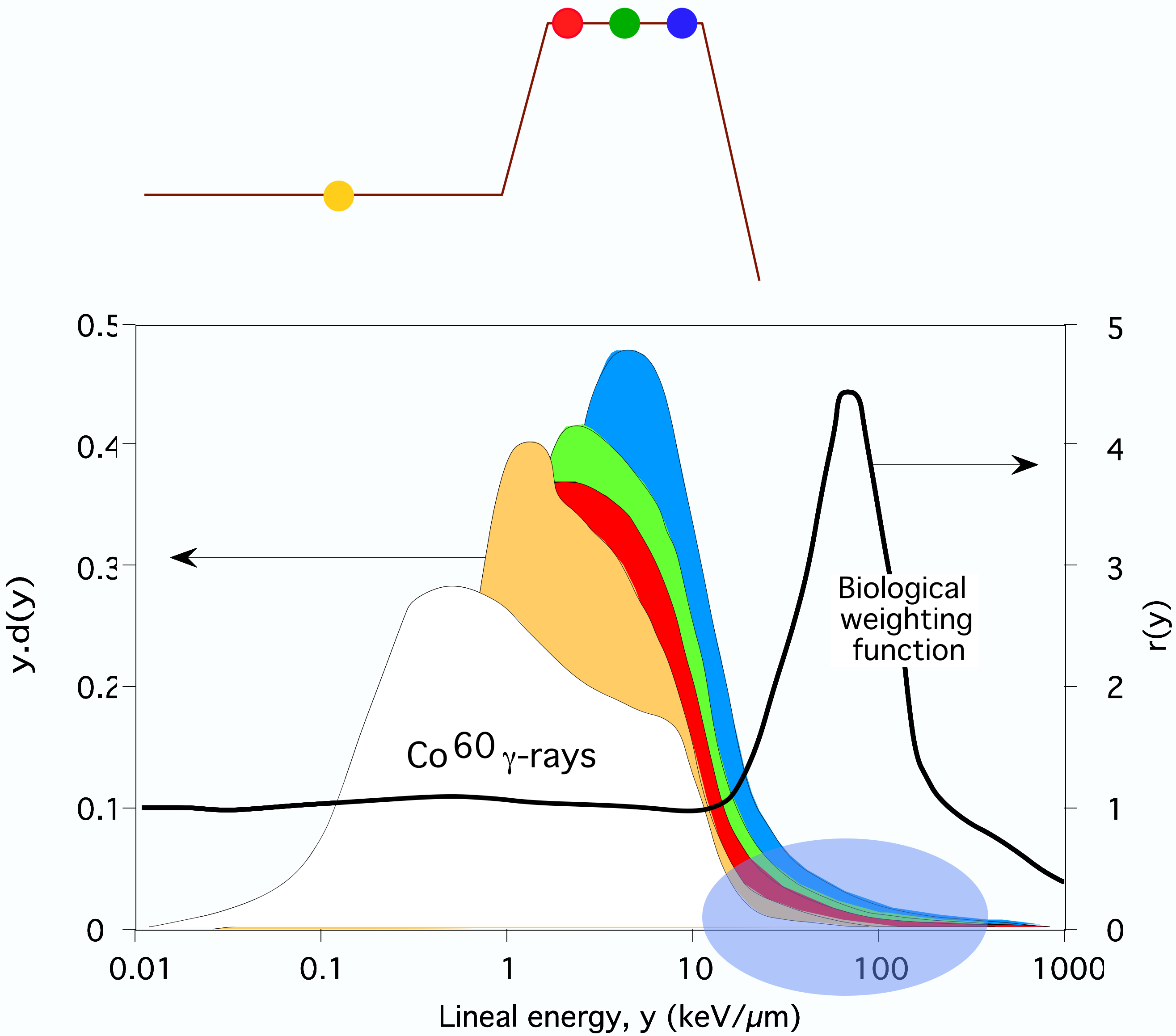
Neutrons



Radiobiological characterization

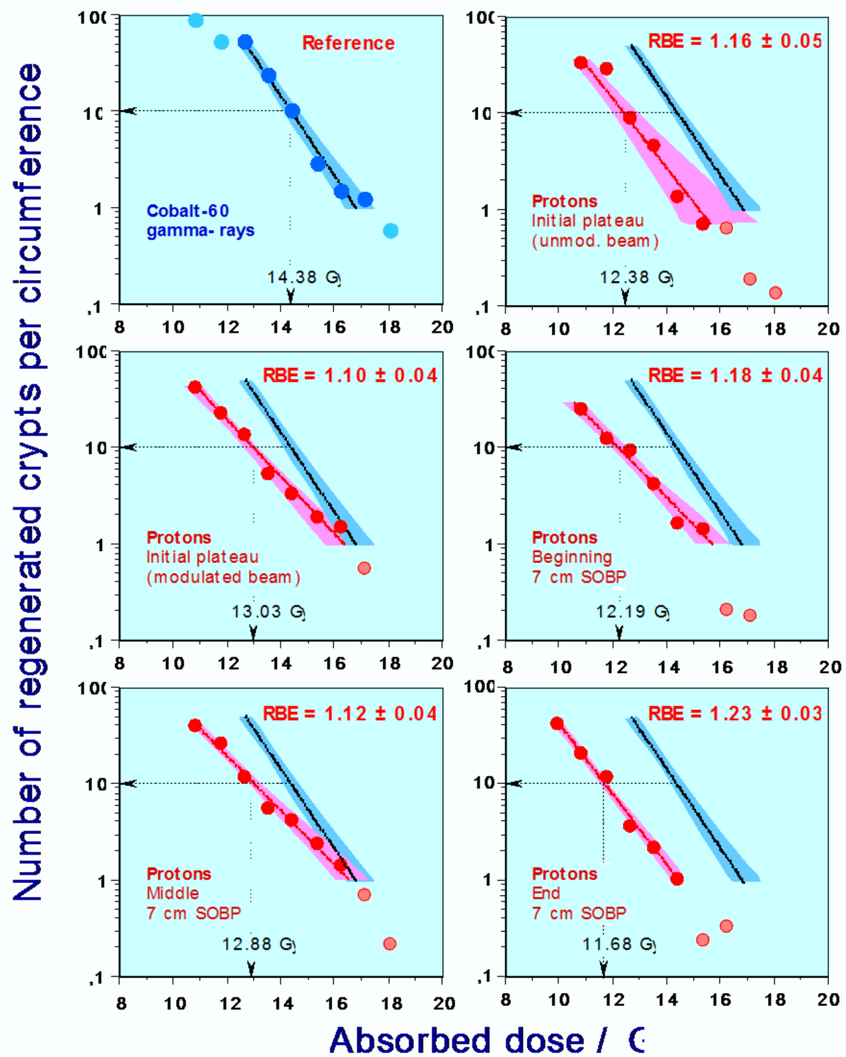
(protons)

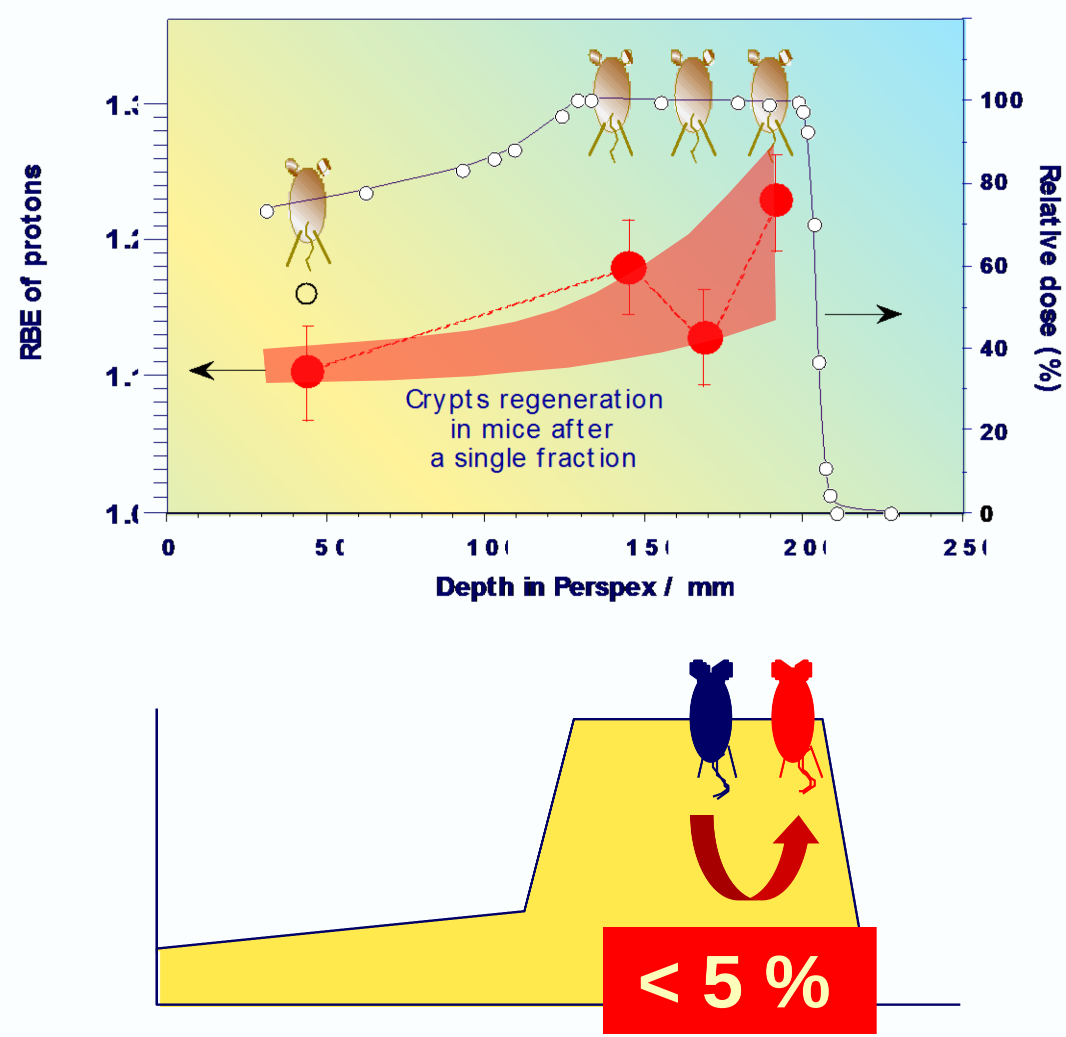
Influence of depth

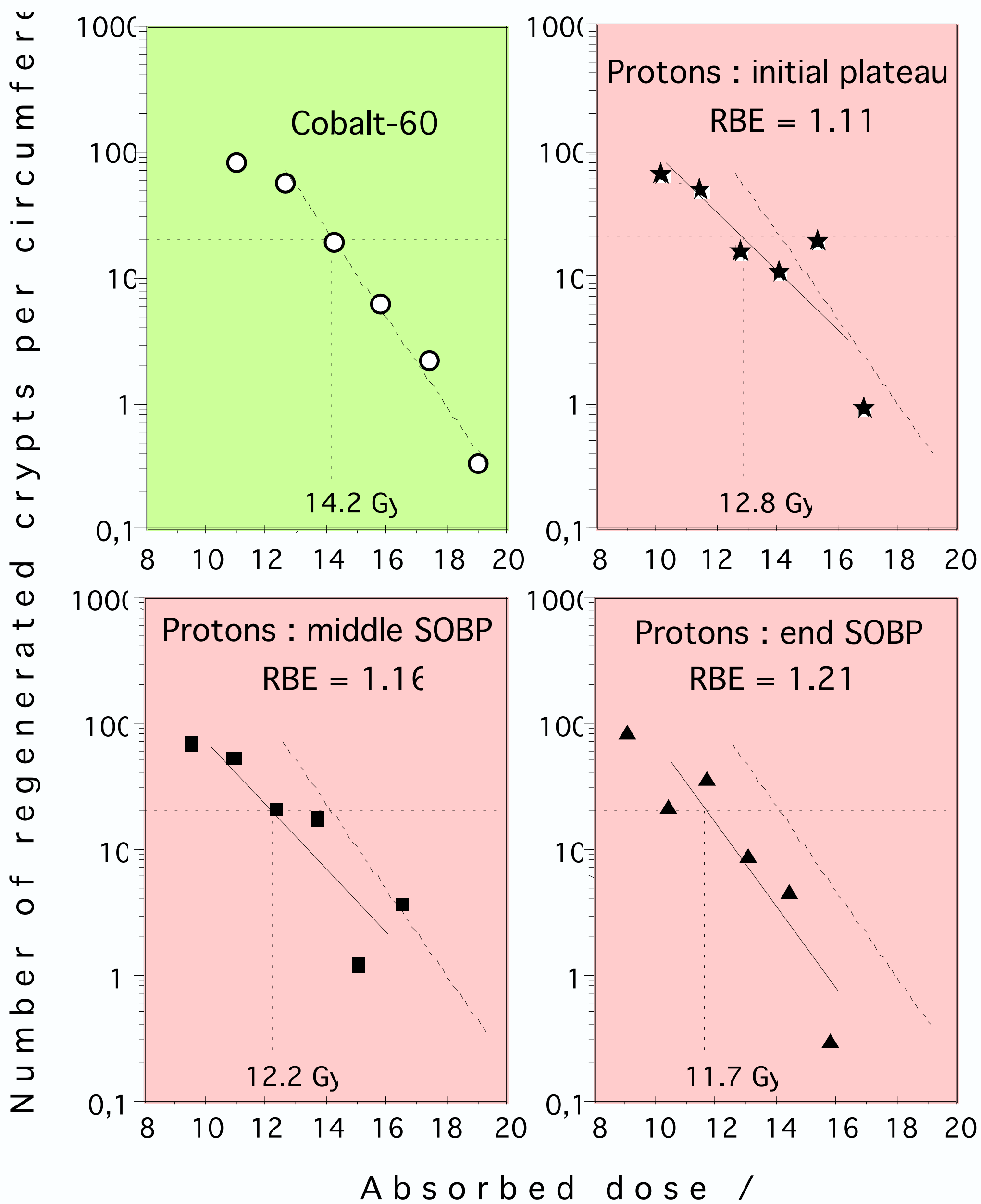


0.5
0.4
0.3
0.2
0.1
0
y.d(y)
5
4
3
2
1
0
r(y)
Co 60 γ-rays
Biological weighting function
0.01
0.1
1
10
100
1000
Lineal energy, y (keV/μm)

200 MeV protons
NAC (Faure, South Africa)



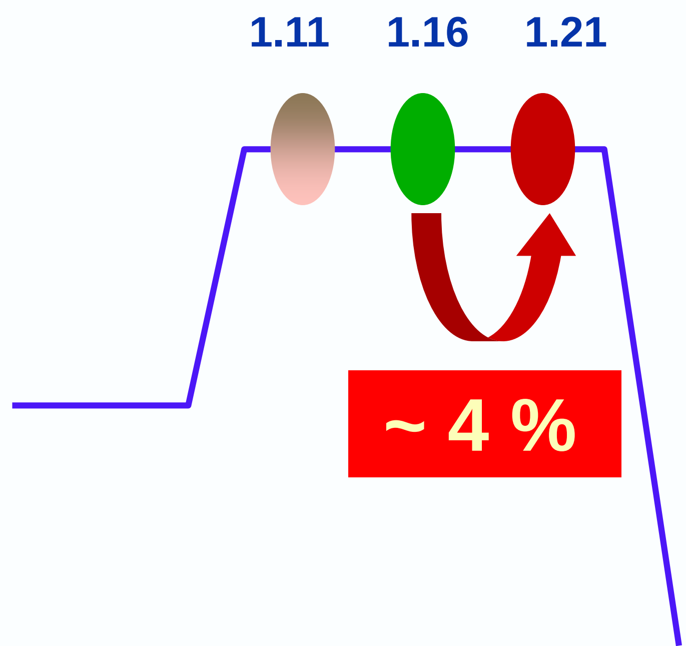


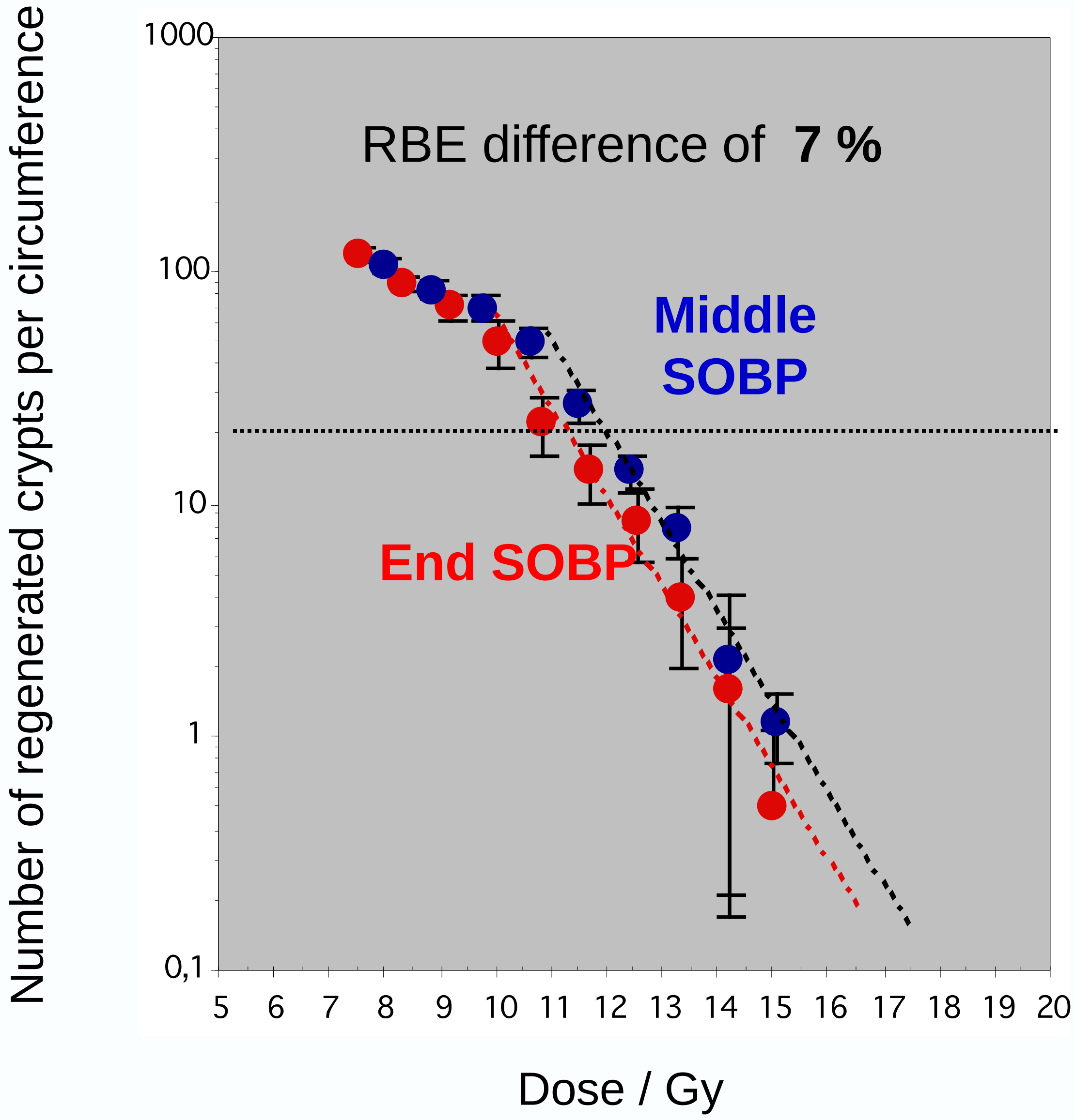


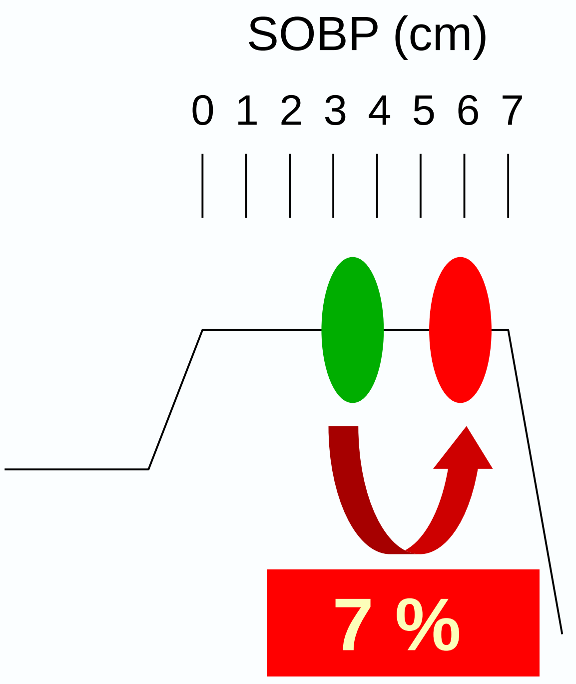
PSI

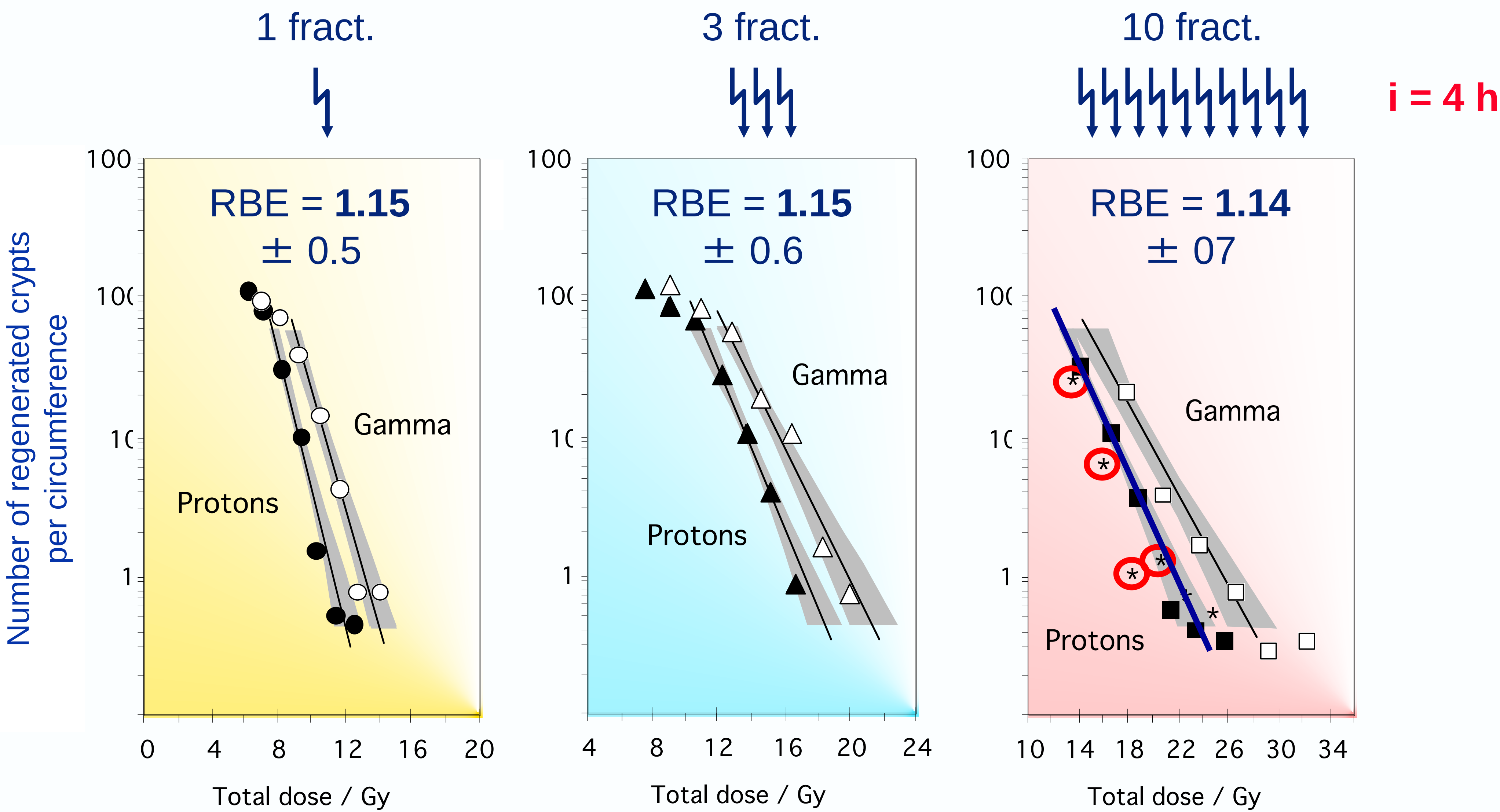
Spot scanning

RBE =




1000
100
10
1
0,1
5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
RBE difference of **7 %**
Middle
SOBP
End SOBP
Number of regenerated crypts per circumference
Dose / Gy


SOBP (cm)
0 1 2 3 4 5 6 7
7 %



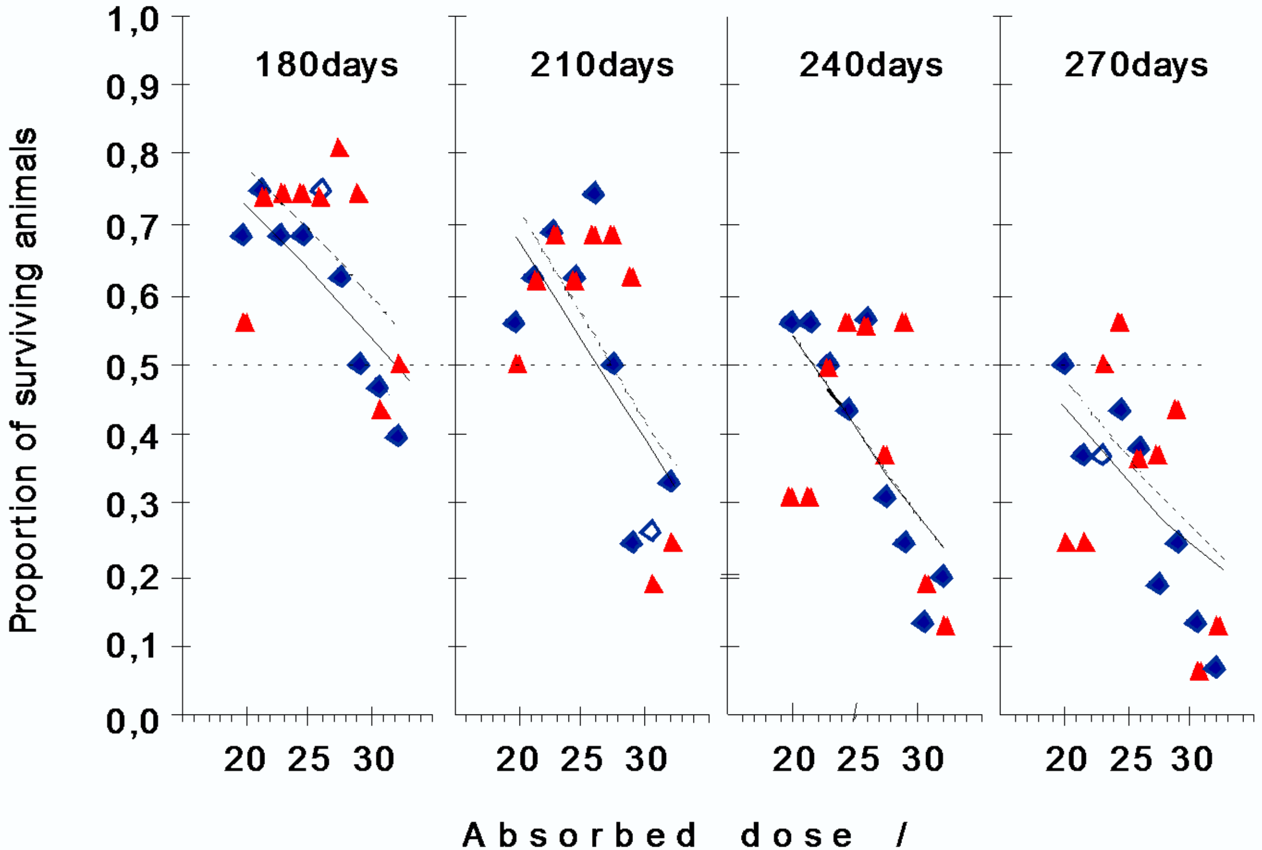
Intestine (10 fractions)

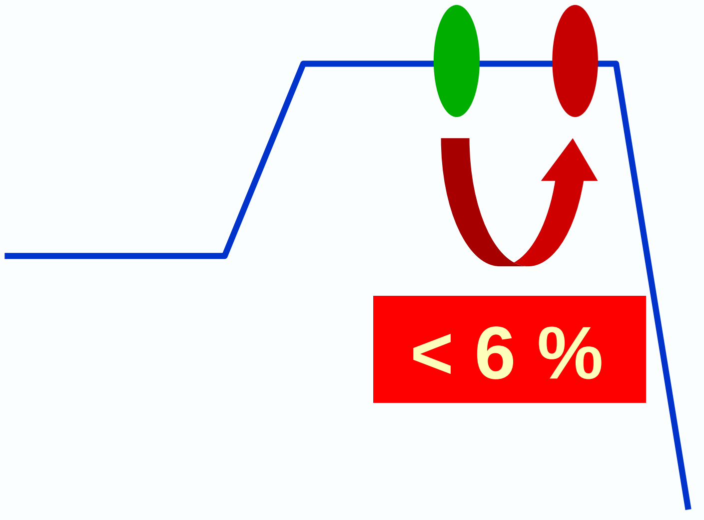
RBE (end) / RBE (middle) ~ 1.08

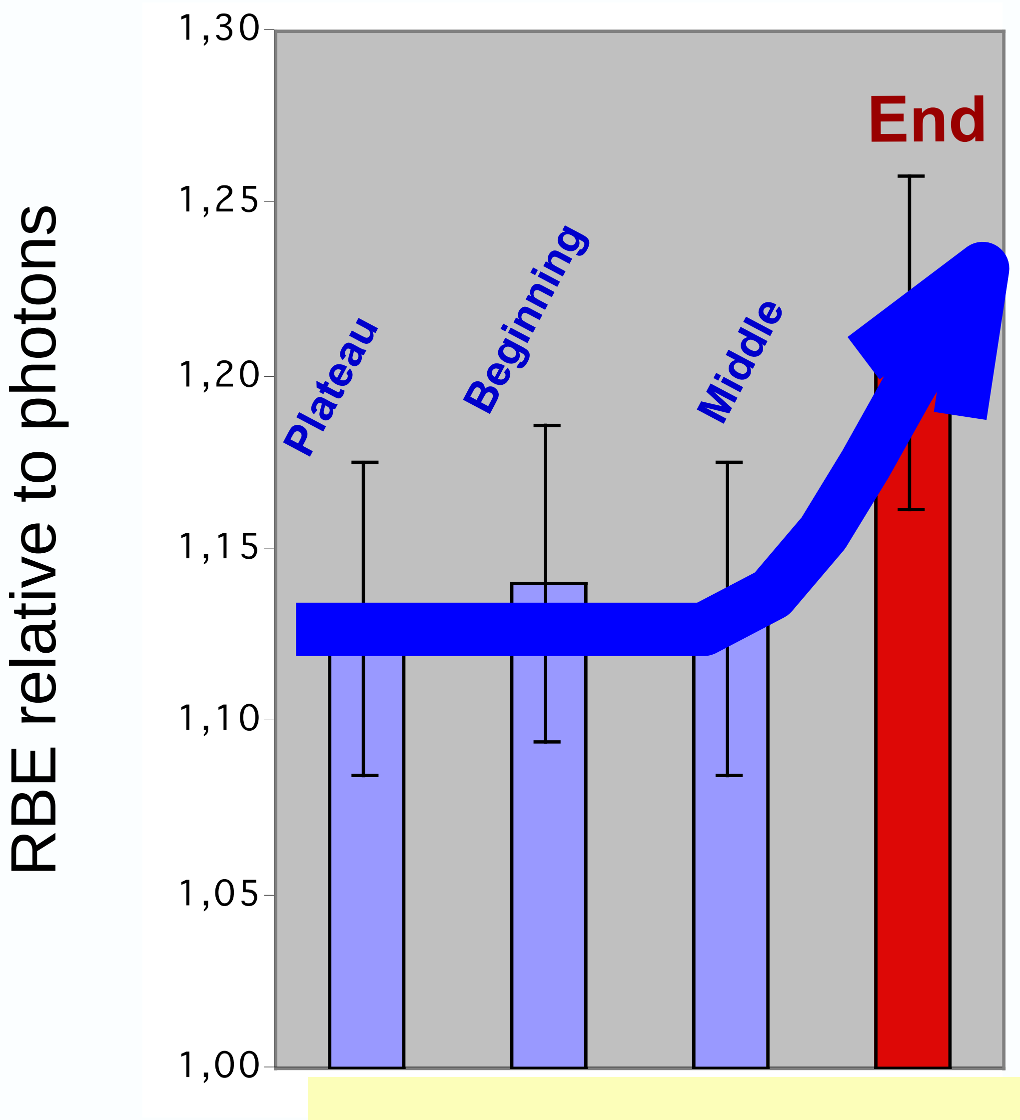
Selective thoracic irradiation *in mice*

Irradiation in 10 fractions (i = 12 h)

(middle *vs* **end** of the SOBP)

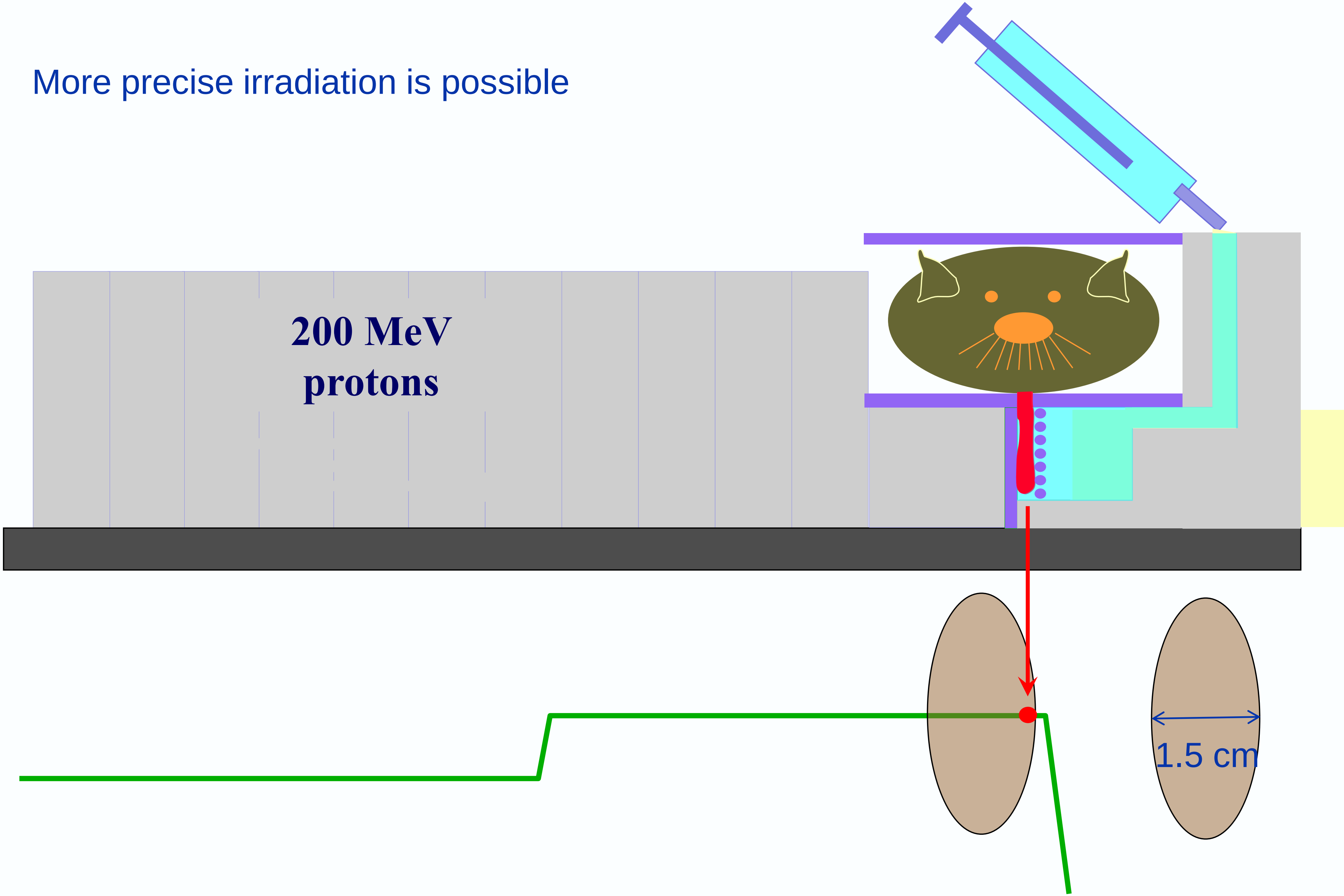


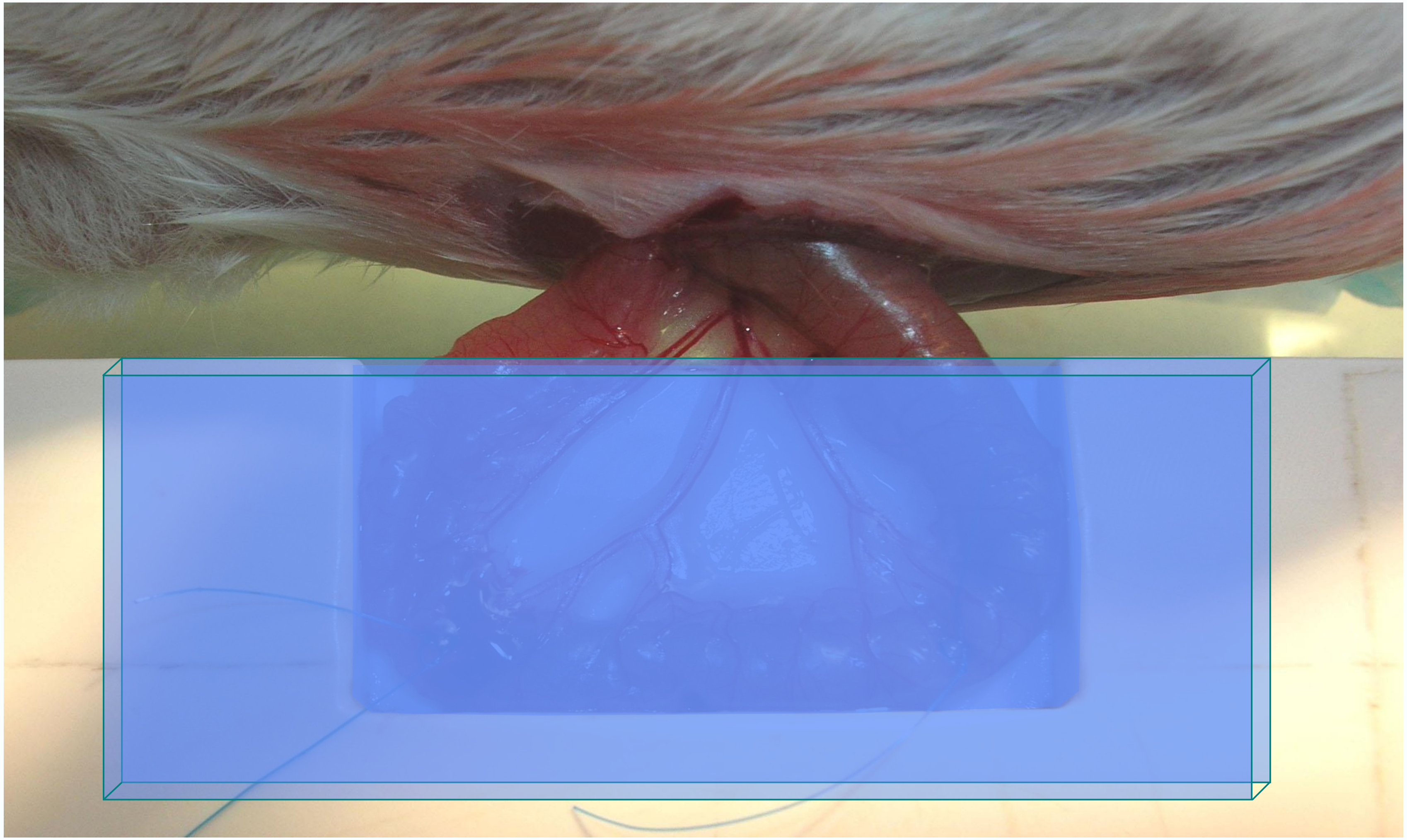




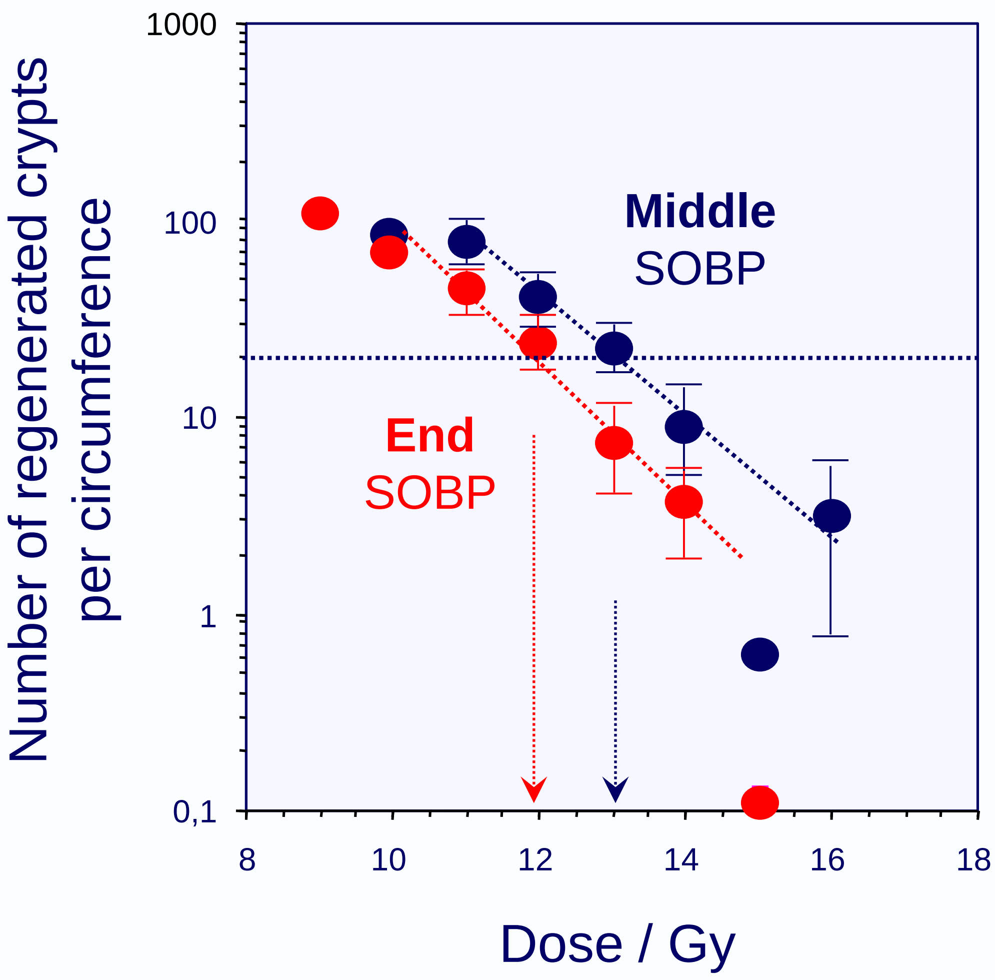
RBE increases suddenly by **6 - 10° %** from the **middle** to the **end** of the SOBP

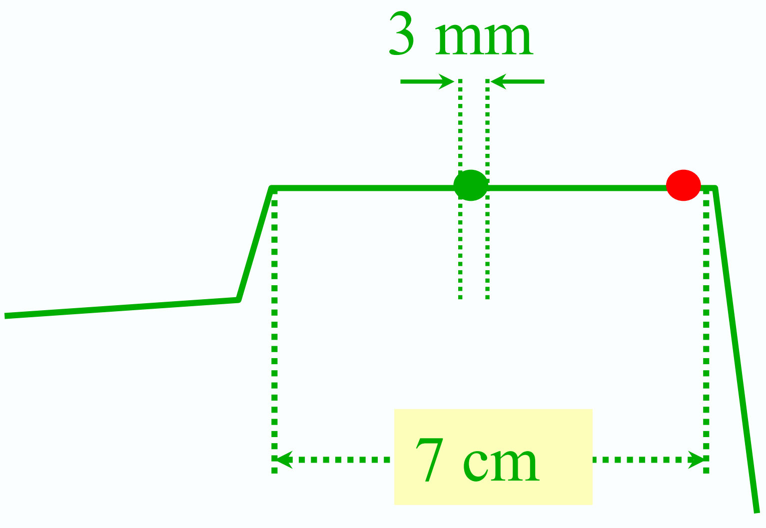
More precise irradiation is possible





iThemba LABS (2006)
200 MeV protons, 7-cm SOBP





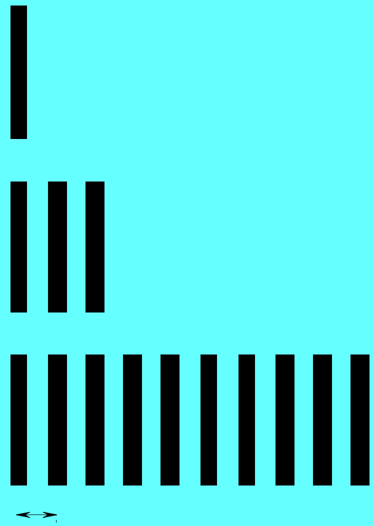
$$\frac{\text{RBE (end)}}{\text{RBE (middle)}} = \mathbf{1.10}$$

As an increase in RBE is observed at the end of the SOBP *in all biological systems*, **it is advisable to allow for it.**

TPS should include biological weighting functions

Influence of fractionation (or dose)

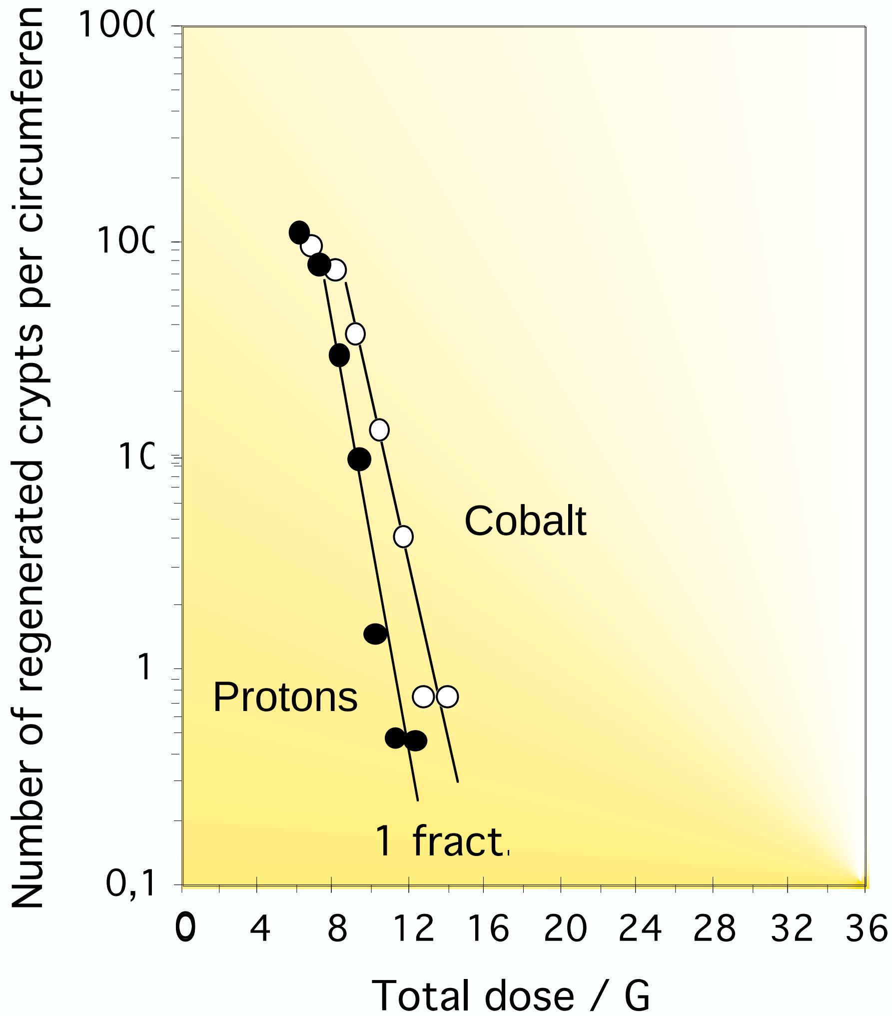
Crypt regeneration in mice



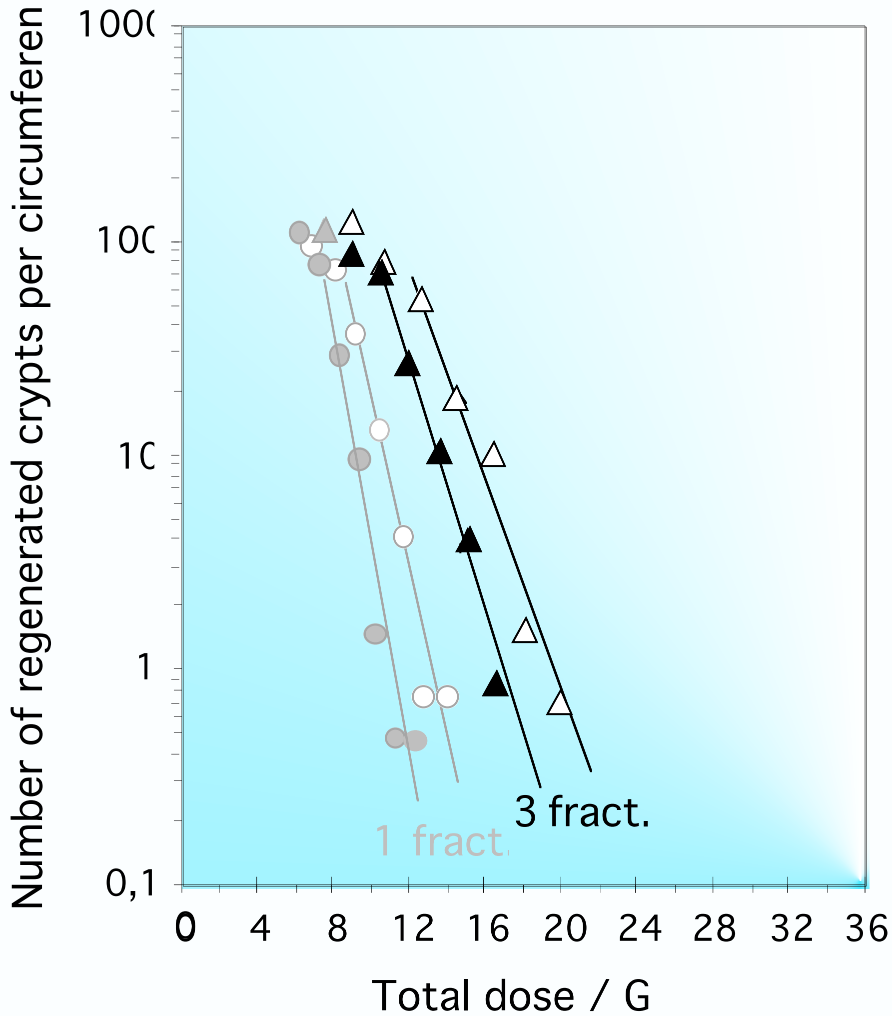
- 7 dose / effect relationshi
- 9 increasing doses
- 8 mice per poin

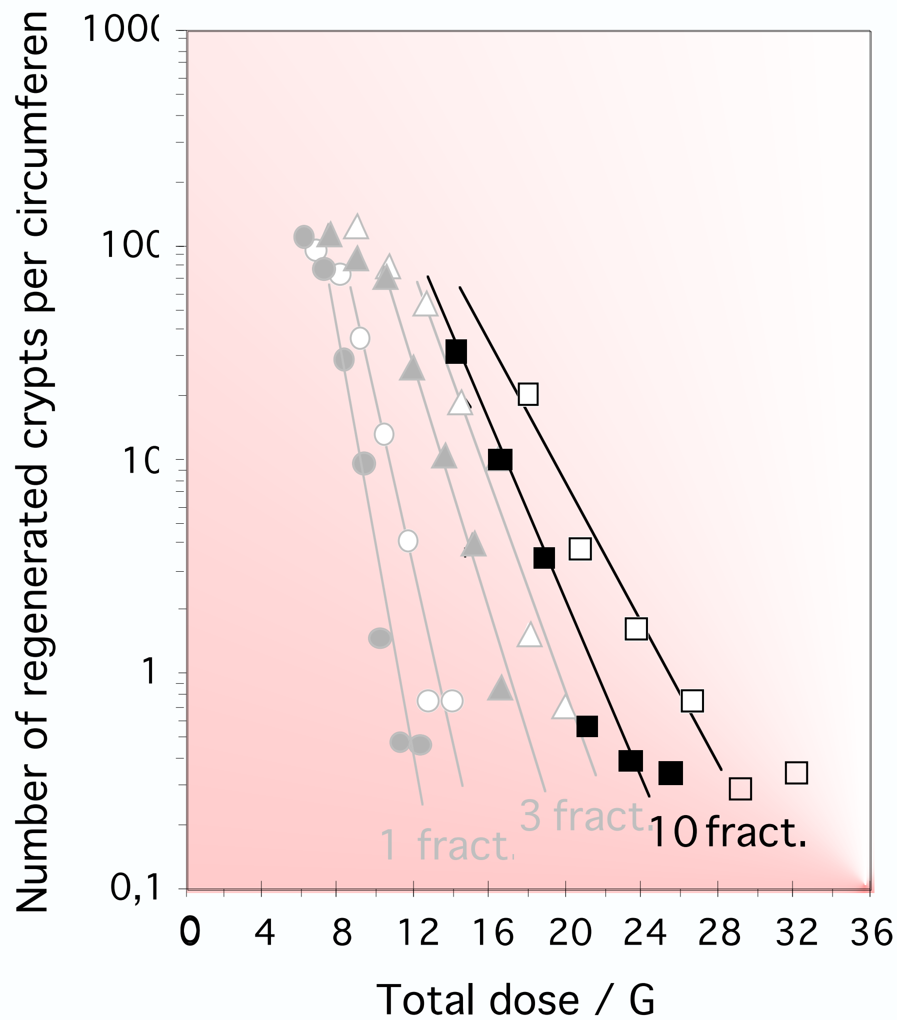
Cobalt-60 gamma-rays and 200 MeV protons

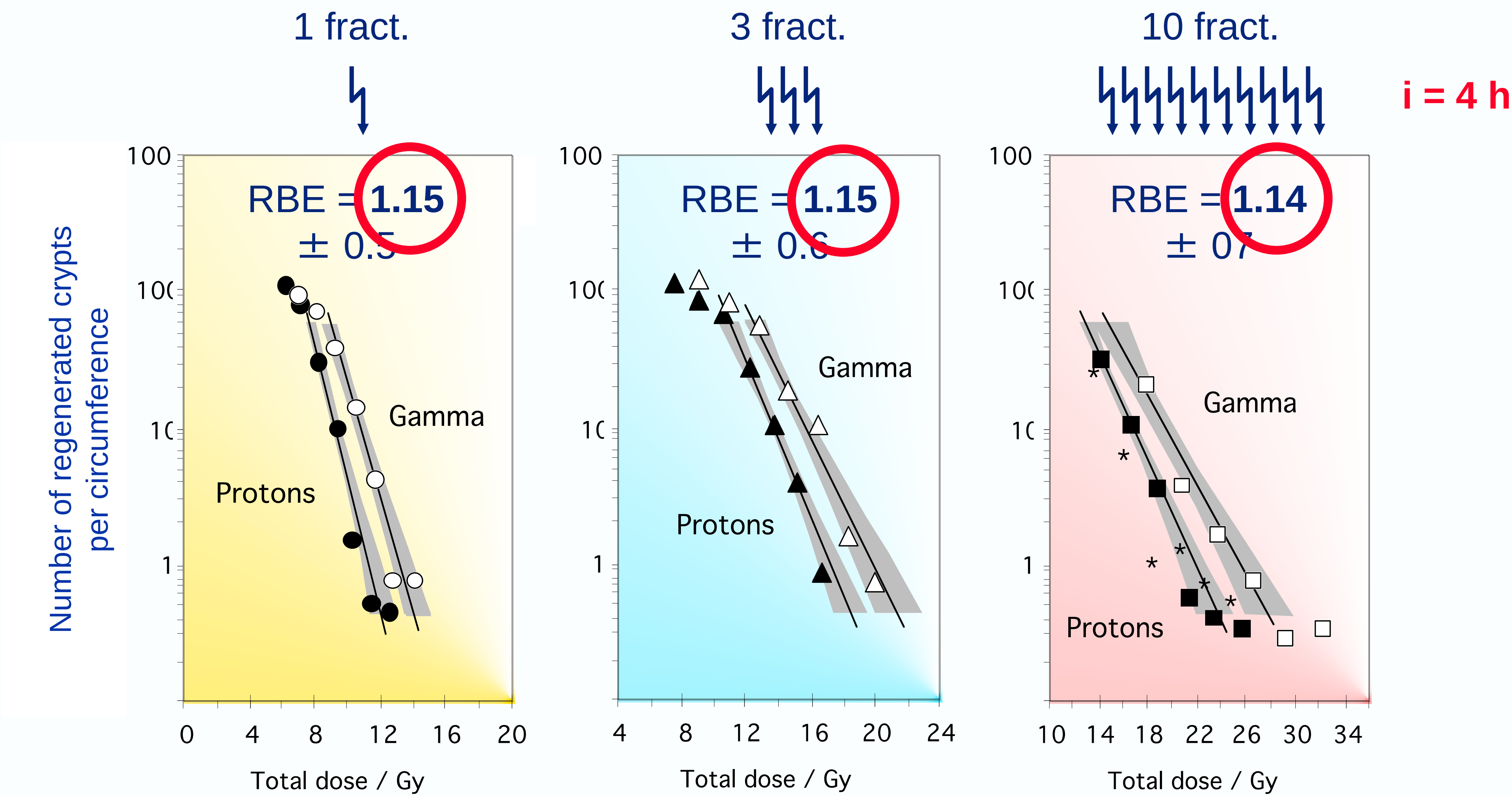
- Cobalt-60 irradiations at the depth of the peak dc
- Proton irradiations at the middle of a 7 cm SOBP (irradiation in 10 fractions were also performed at the end of the 7 cm SOBP)



Number of regenerated crypts per circumferen
1000
100
10
1
0,1
0
4
8
12
16
20
24
28
32
36
Total dose / G
Cobalt
Protons
1 fract.


Number of regenerated crypts per circumferen
1000
100
10
1
0,1
0
4
8
12
16
20
24
28
32
36
Total dose / G
1 fract.
3 fract.

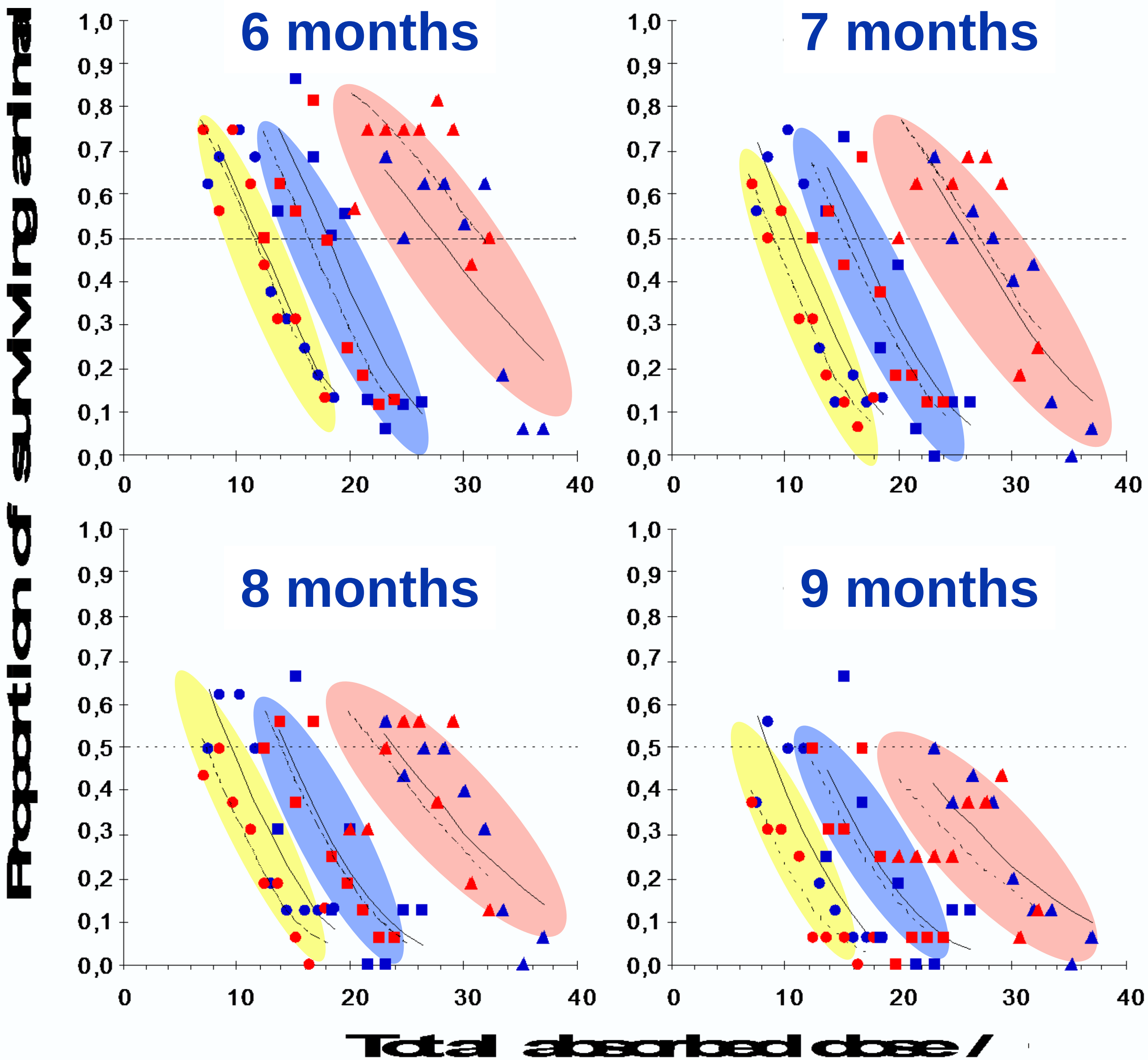

Number of regenerated crypts per circumferen
1000
100
10
1
0,1
0
4
8
12
16
20
24
28
32
36
Total dose / G
1 fract.
3 fract.
10 fract.



Irradiation at the middle of a 7 cm SOBP
in the 200-MeV proton beam produced at the
National Accelerator Centre (NAC) of Faure (South Africa).

Late tolerance

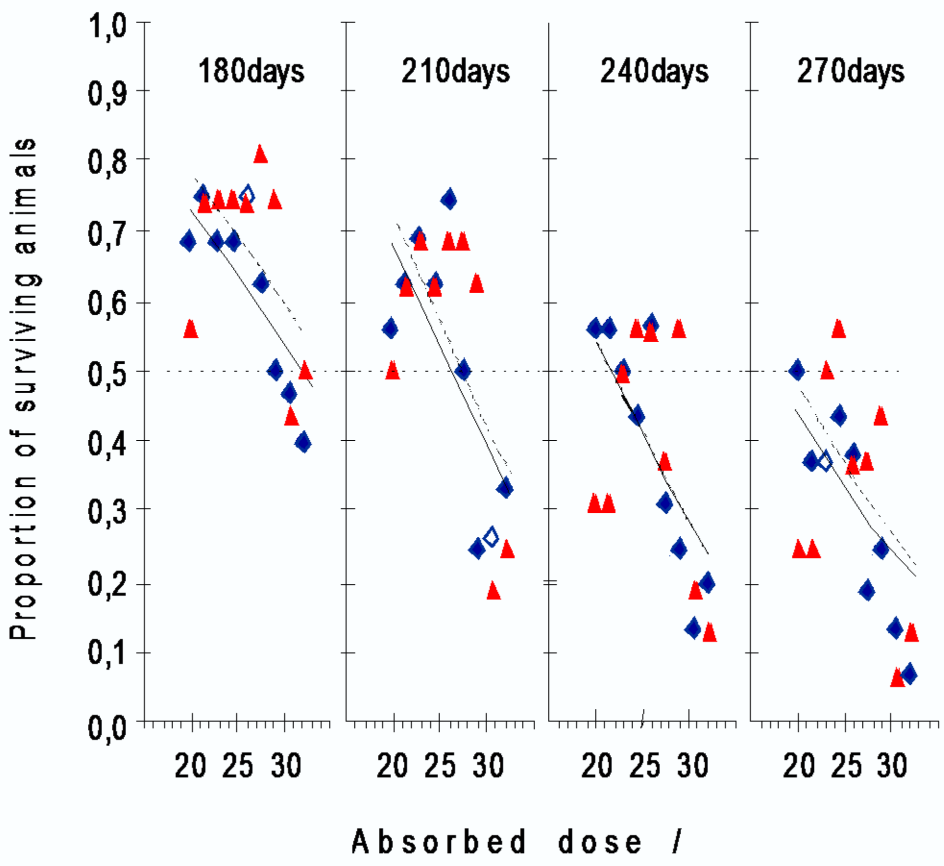
(Survival after selective irradiation
of the thorax in mice)



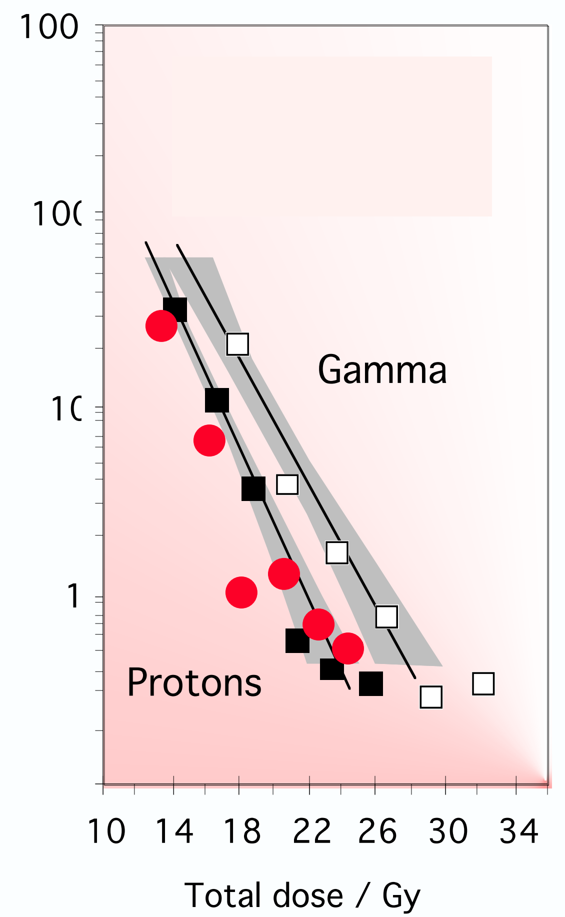
6 months
7 months
8 months
9 months
Proportion of surviving animal
Total absorbed dose /

For both systems (10 fraction irradiations)
RBE at the end of the SOBP **~ 6 % greater** that at the middle

Lung (10 fractions)



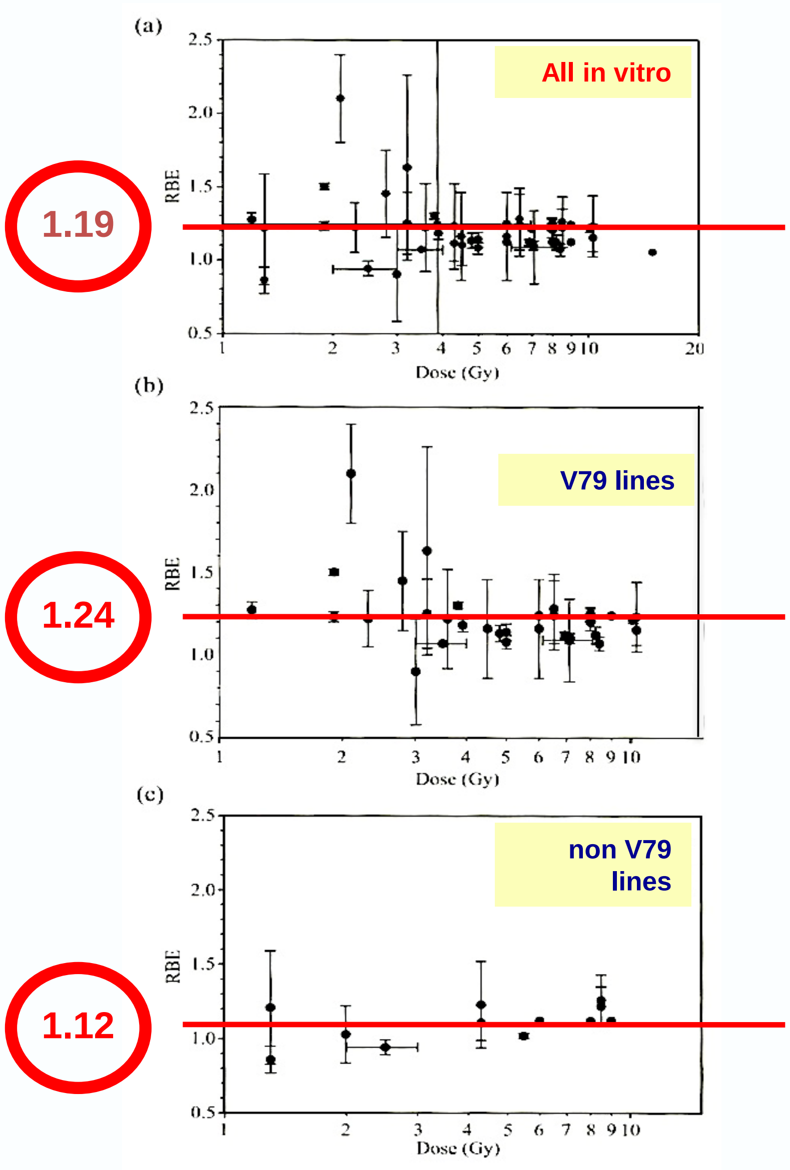
Intestine (10 fractions)



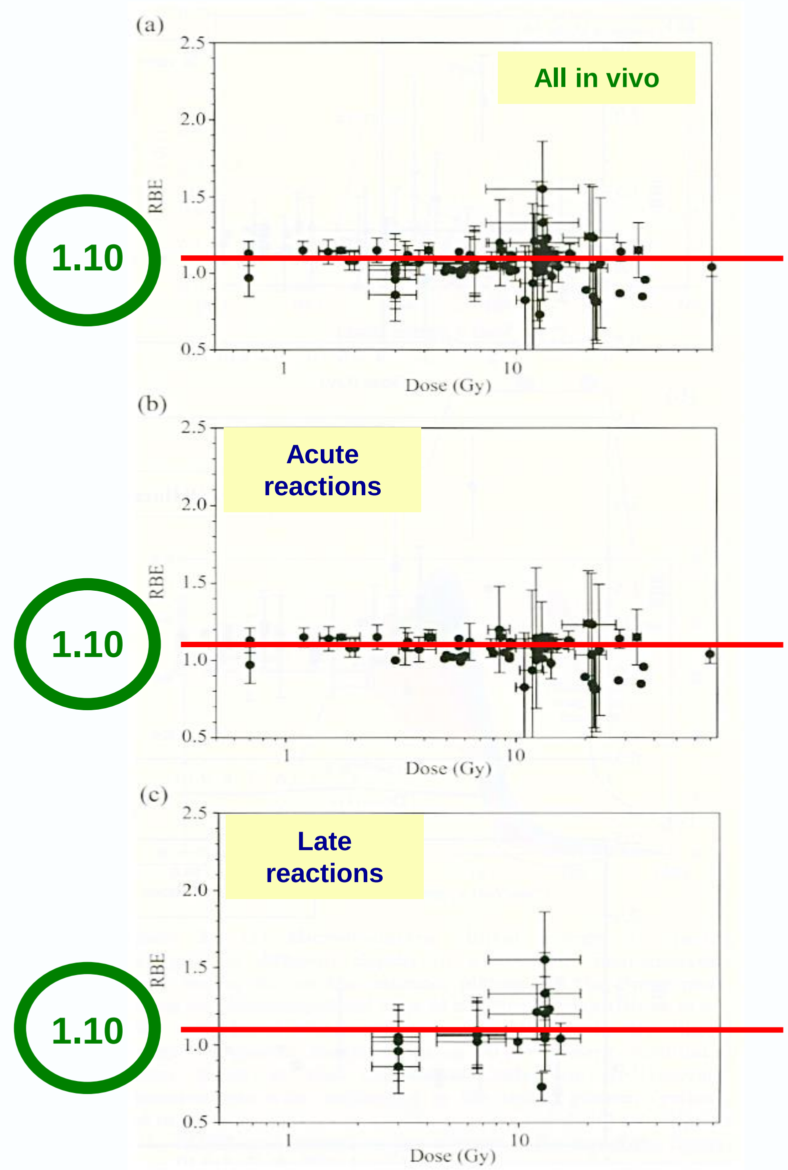
Proton RBE (at the middle of the SOBP) does not vary with dose (or fractionation) ***for in vivo systems***

A generic RBE value of **1.10** at the middle of the SOBP (i.e. point of dose specification) **seems to be appropriate**

Proton RBE In-vitro, as a function of dose, for all "**clinical**" energies

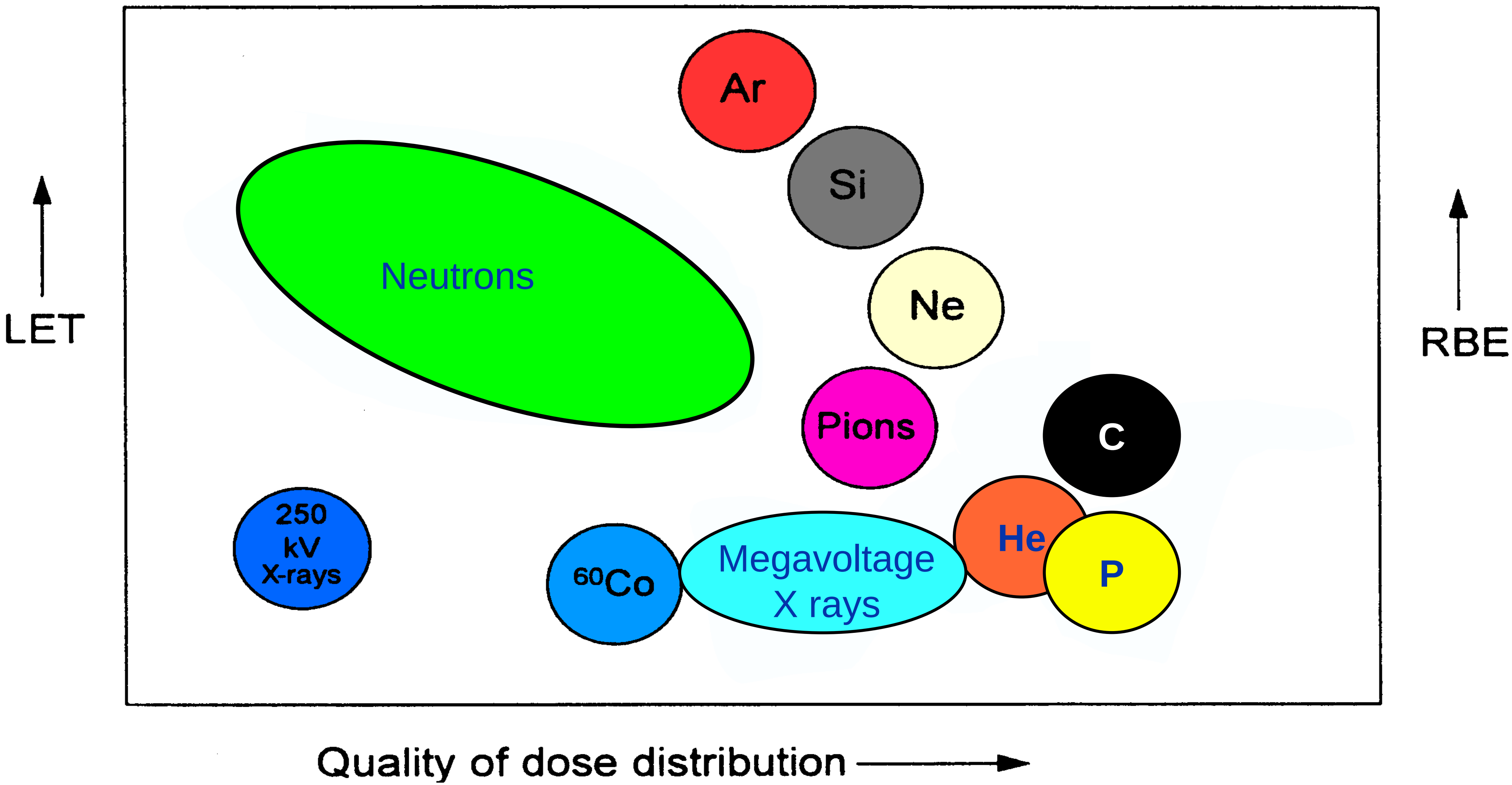


Proton RBE In-vivo, as a function of dose, for all "**clinical**" energies

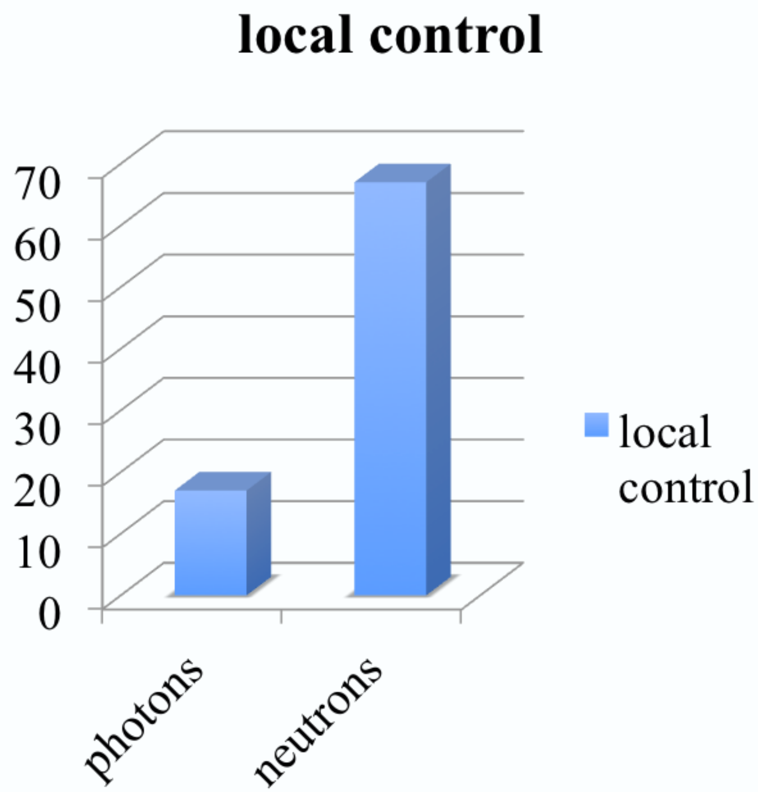


From Paganetti et al. (2002)

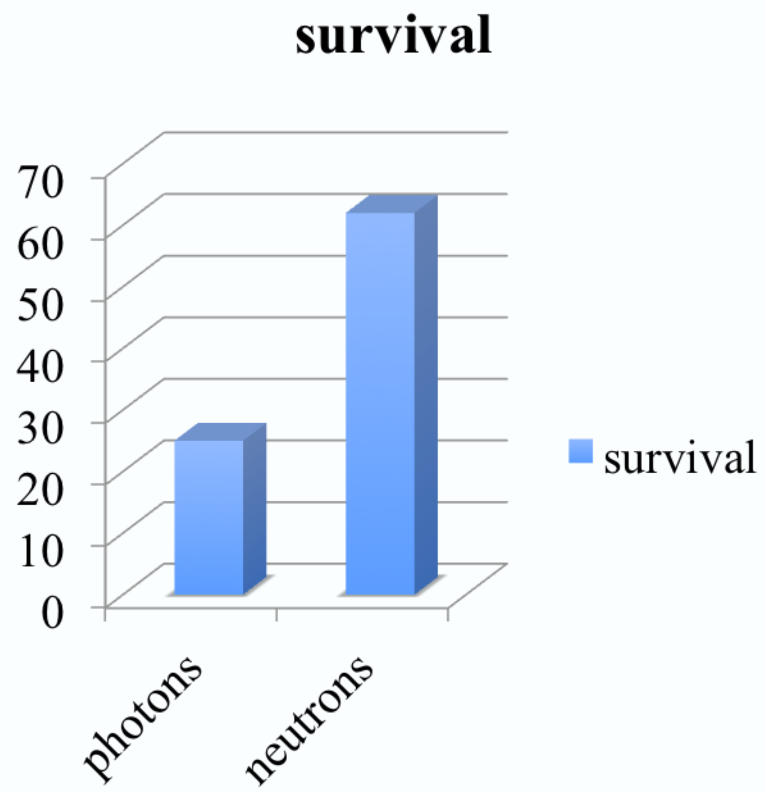
HEAVY IONS


LET
RBE
Ar
Si
Ne
Neutrons
Pions
C
250
kV
X-rays
60Co
Megavoltage
X rays
He
P
Quality of dose distribution

Salivary gland tumour treated with fast neutrons
Study results (± 1985)



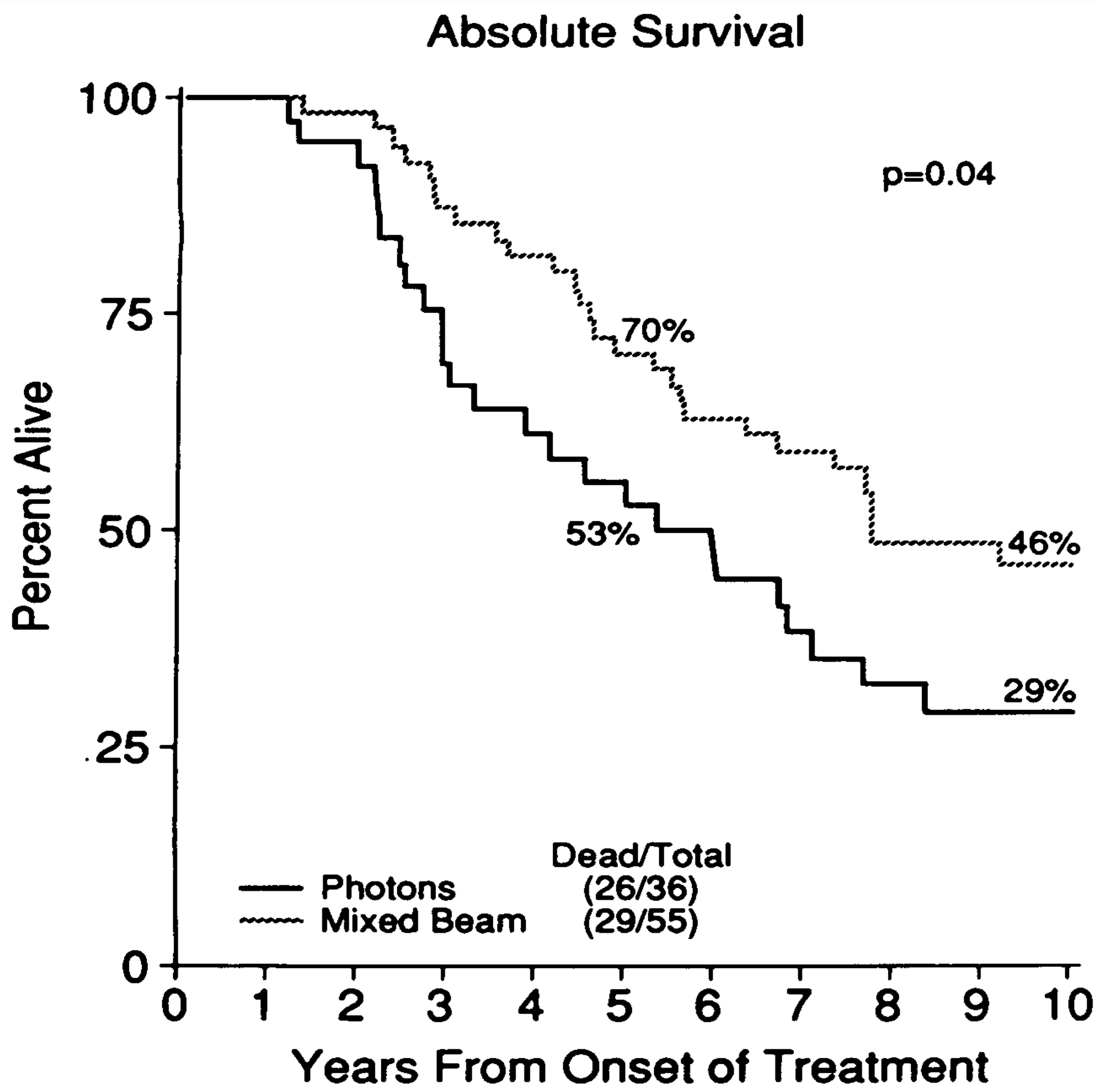
17% ± 11 vs. 67% ± 14



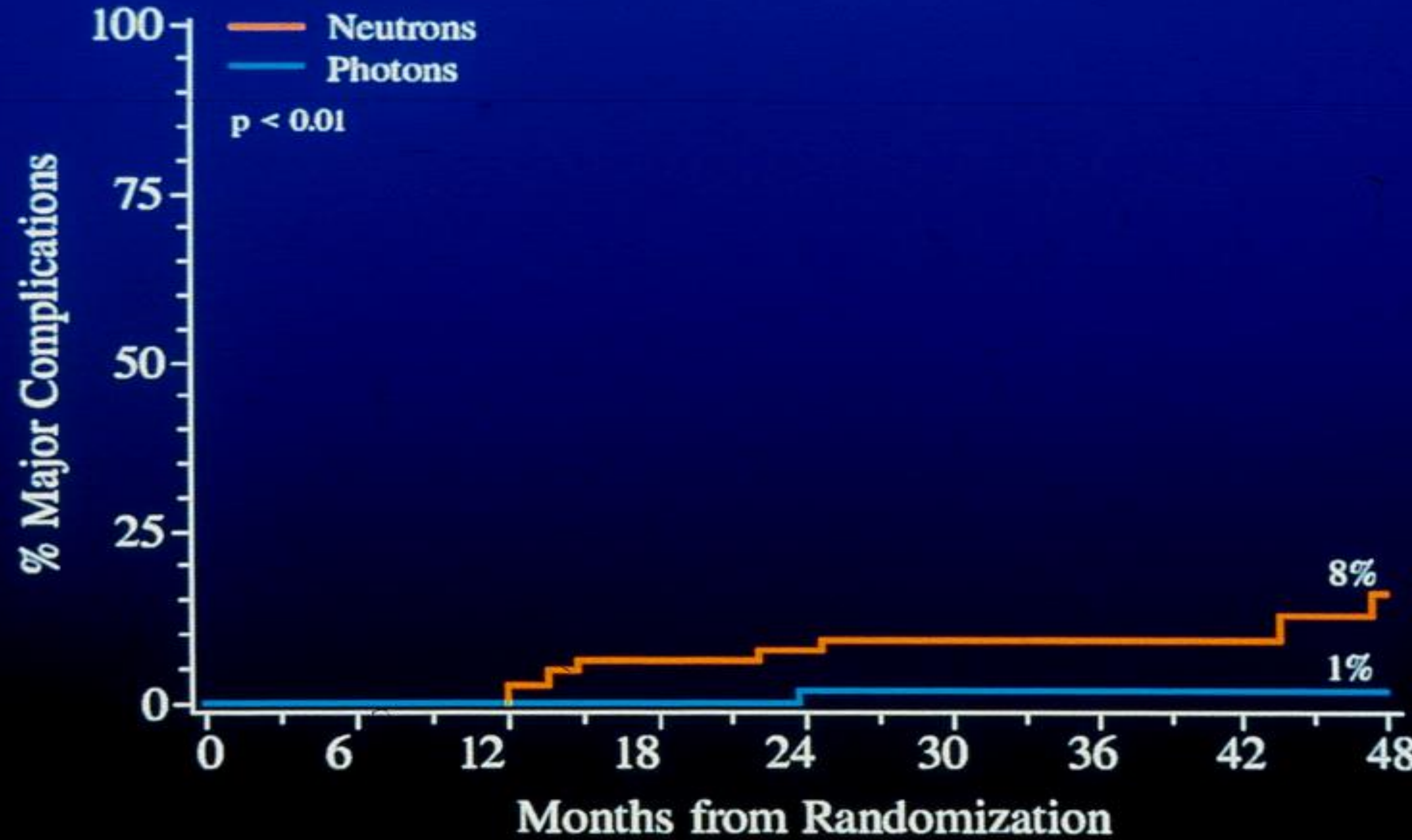
25% ± 14 vs. 62% ± 14

Randomized clinical trial of photons vs mixed beam neutrons plus photons for prostate Ca

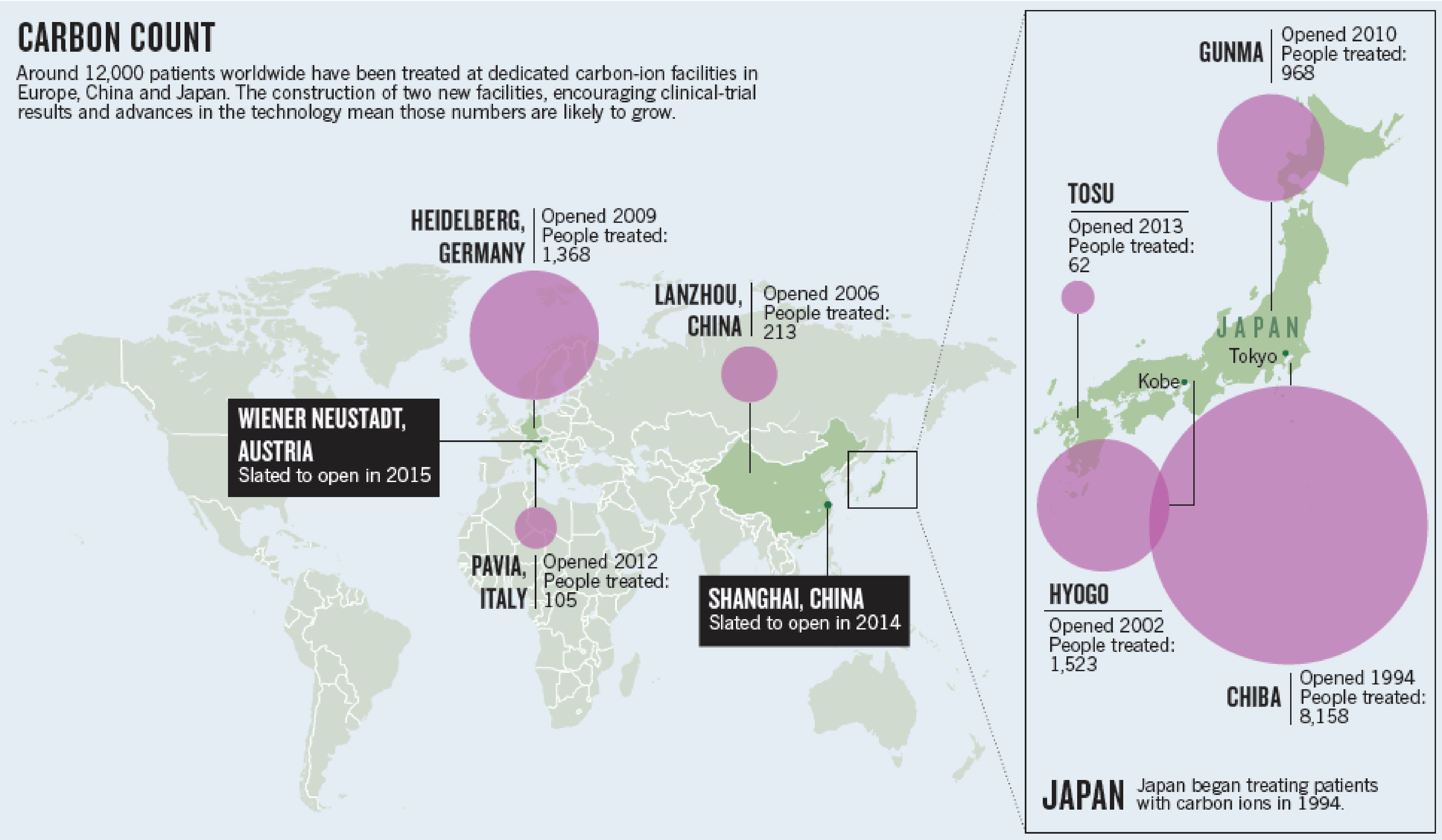
RTOG 77-04
Laramore *et al,* 1993.
Prostate carcinomas are slow growing and hence should be well suited for neutron therapy. The neutrons are usually used for the small “boost” volume in order to minimize late normal tissue damage.



Neutron Prostate Study
Major Complications



Laramore, 1993



Nature April, 2014

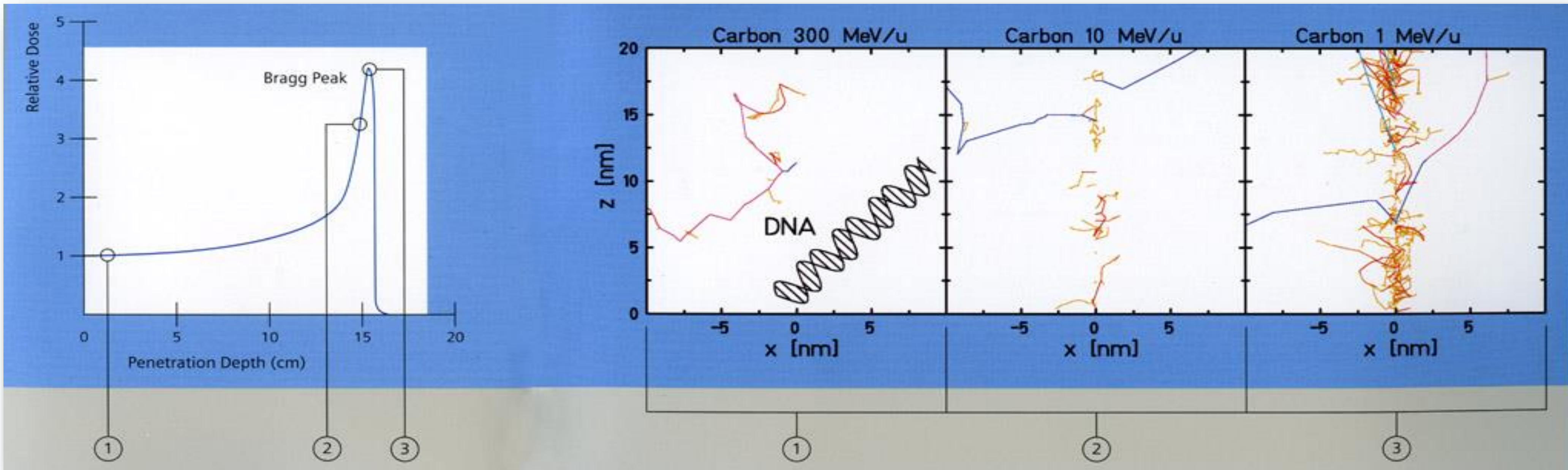
Which RBE to apply ?

- Late tolerance of healthy surrounding tissues
- Dose per fraction of 2 Gy photon equivalent

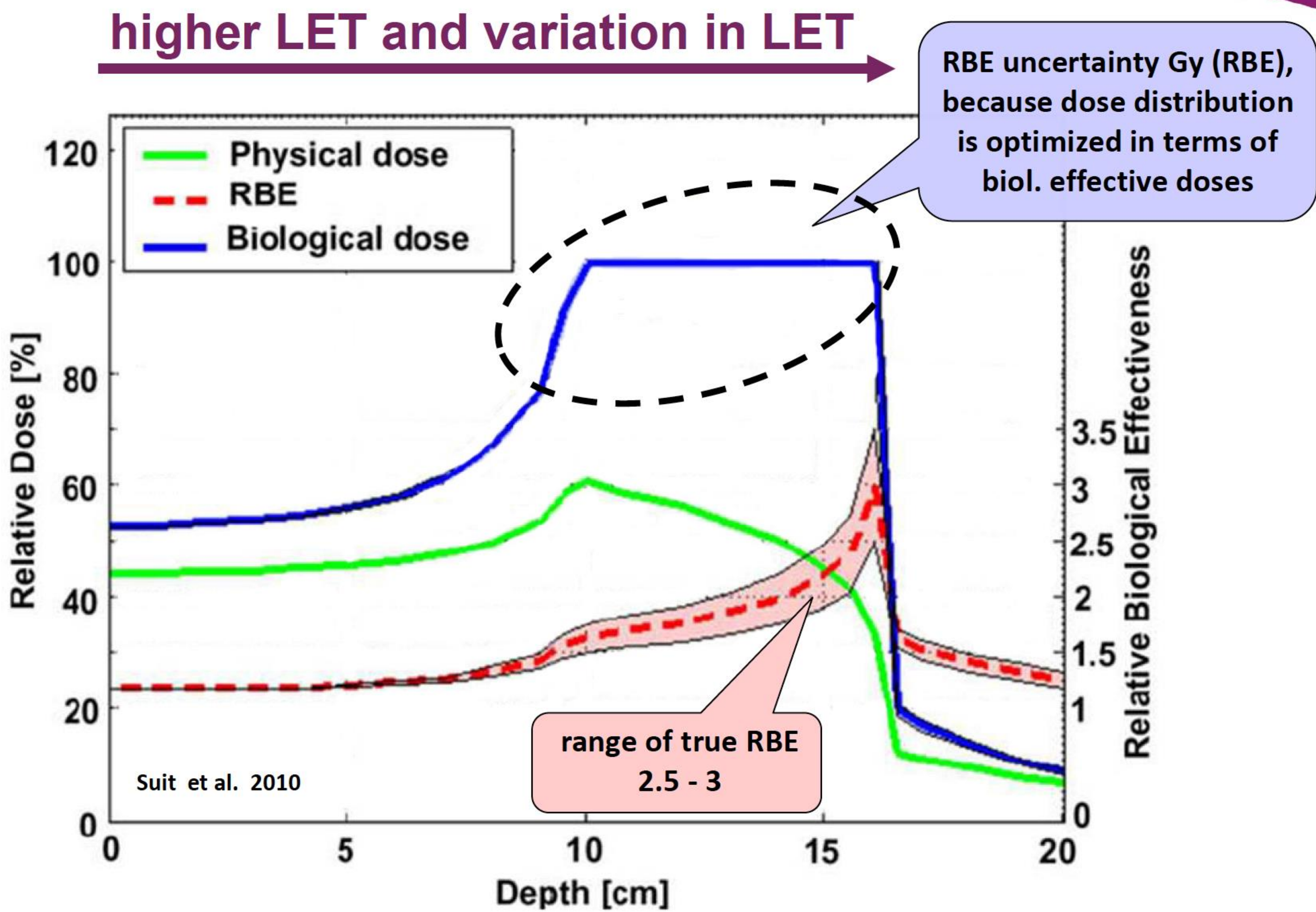
Not a single value

- due to the diversity of the clinical situations
- due to variation of RBE with depth/dose

Density of energy deposits in the Bragg peak of carbon ions

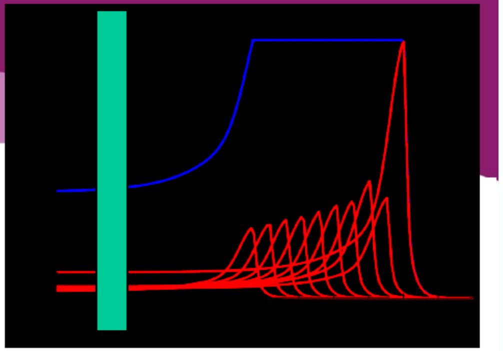


Carbon ions



From Peter Peschke, Heidelber

Results

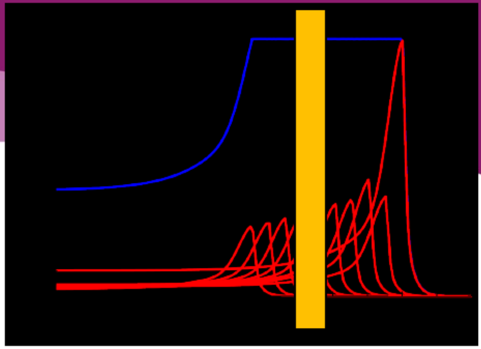


Set-up	Photons D_{50} [Gy]	Carbon Ions D_{50} [Gy]	Measured RBE
Plateau (13 keV/µm)			
1 Fx	24.5±0.8	17.1±0.8	1.43±0.08
2 Fx	34.2±0.7	24.9±0.7	1.37±0.05
6 Fx	57.0±4.0	42.8±1.5	1.33±0.10
18 Fx	88.6±2.0	62.2±3.5	1.42±0.09

Clear fractionation effect in the **plateau**, which allows sparing of normal tissues.

RBE constant, when number of fractions increase

Results

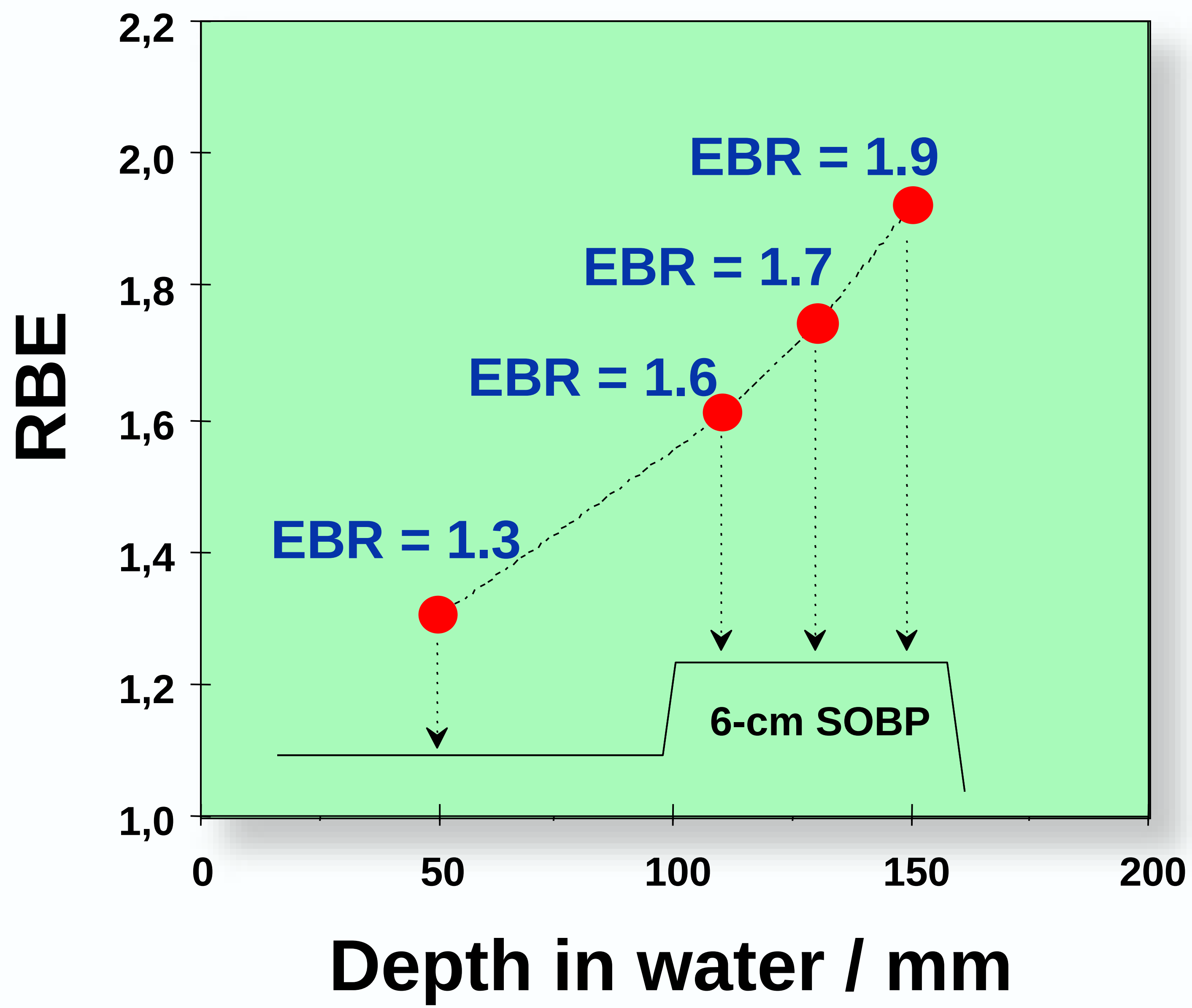


Set-up	Photons D_{50} [Gy]	Carbon Ions D_{50} [Gy]	Measured RBE
Plateau (13 keV/µm)			
1 Fx	24.5±0.8	17.1±0.8	1.43±0.08
2 Fx	34.2±0.7	24.9±0.7	1.37±0.05
6 Fx	57.0±4.0	42.8±1.5	1.33±0.10
18 Fx	88.6±2.0	62.2±3.5	1.42±0.09
Peak (91 keV/µm)			
1 Fx	24.5±0.8	13.9±0.8	1.76±0.12
2 Fx	34.2±0.7	15.8±0.7	2.16±0.11
6 Fx	57.0±4.0	19.2±0.2	2.97±0.21
18 Fx	88.6±2.0	17.7±1.3	5.01±0.37

Effective response in the **Bragg-Peak,** with little change in isoeffective total dose with fractionation

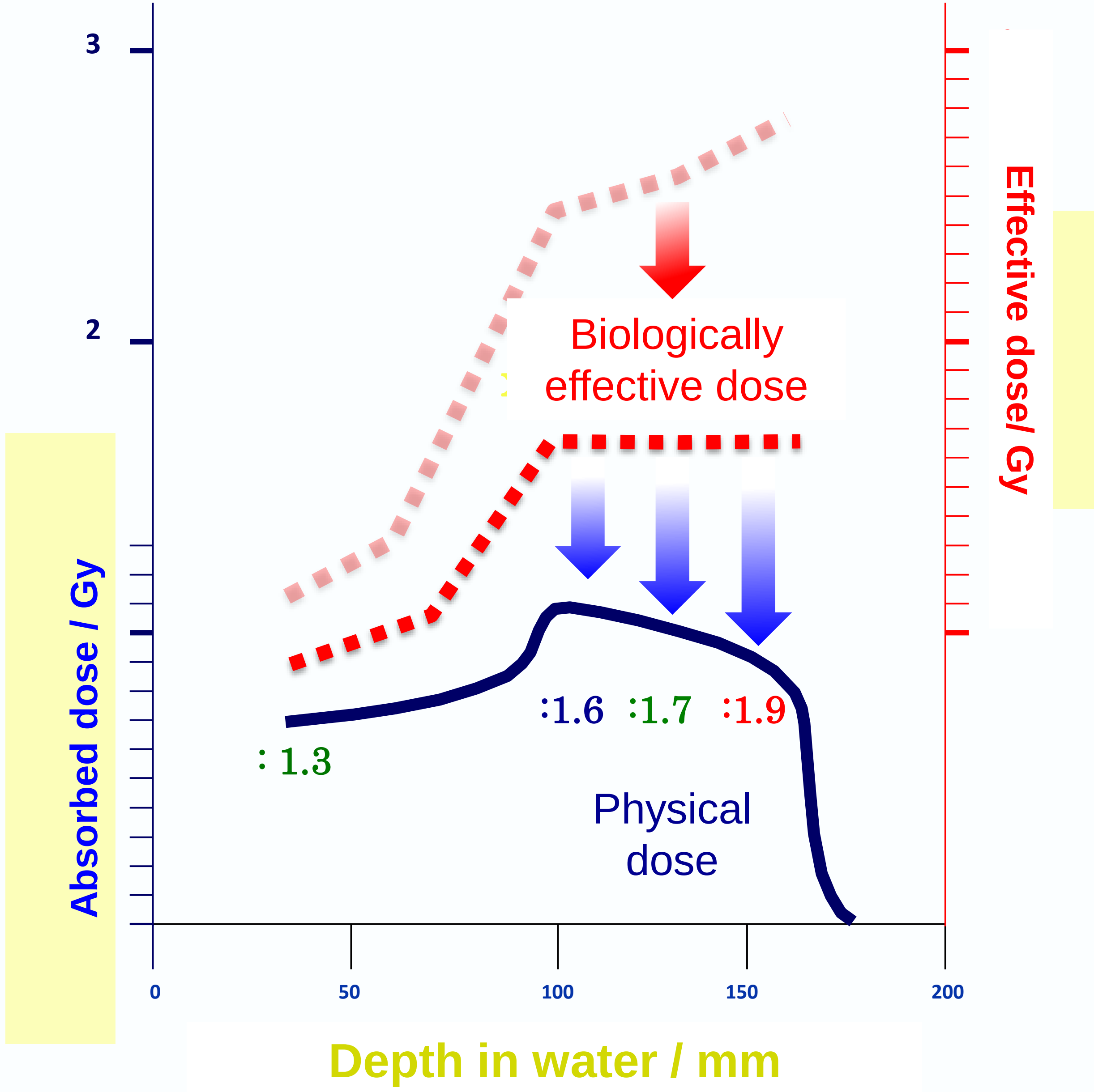
RBE raises rapidly with decreasing dose per fraction

HIMAC (Japan) : Carbon-12 (290 MeV/uma)



Compensate the RBE increase by **decreasing the physical dose** by factors corresponding to the (local) RBE

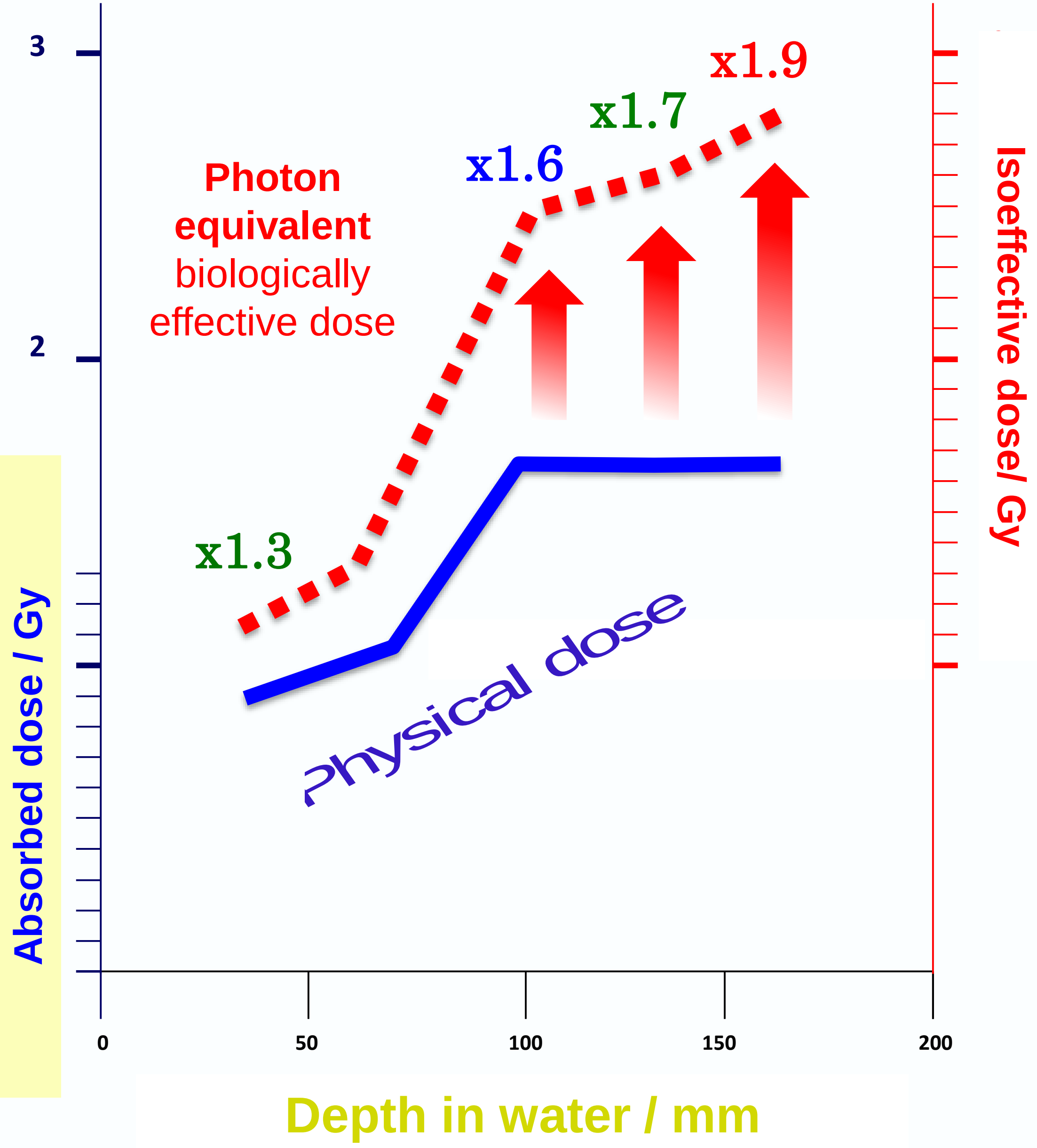
Method used in static beam delivery systems (Chiba, Japan)

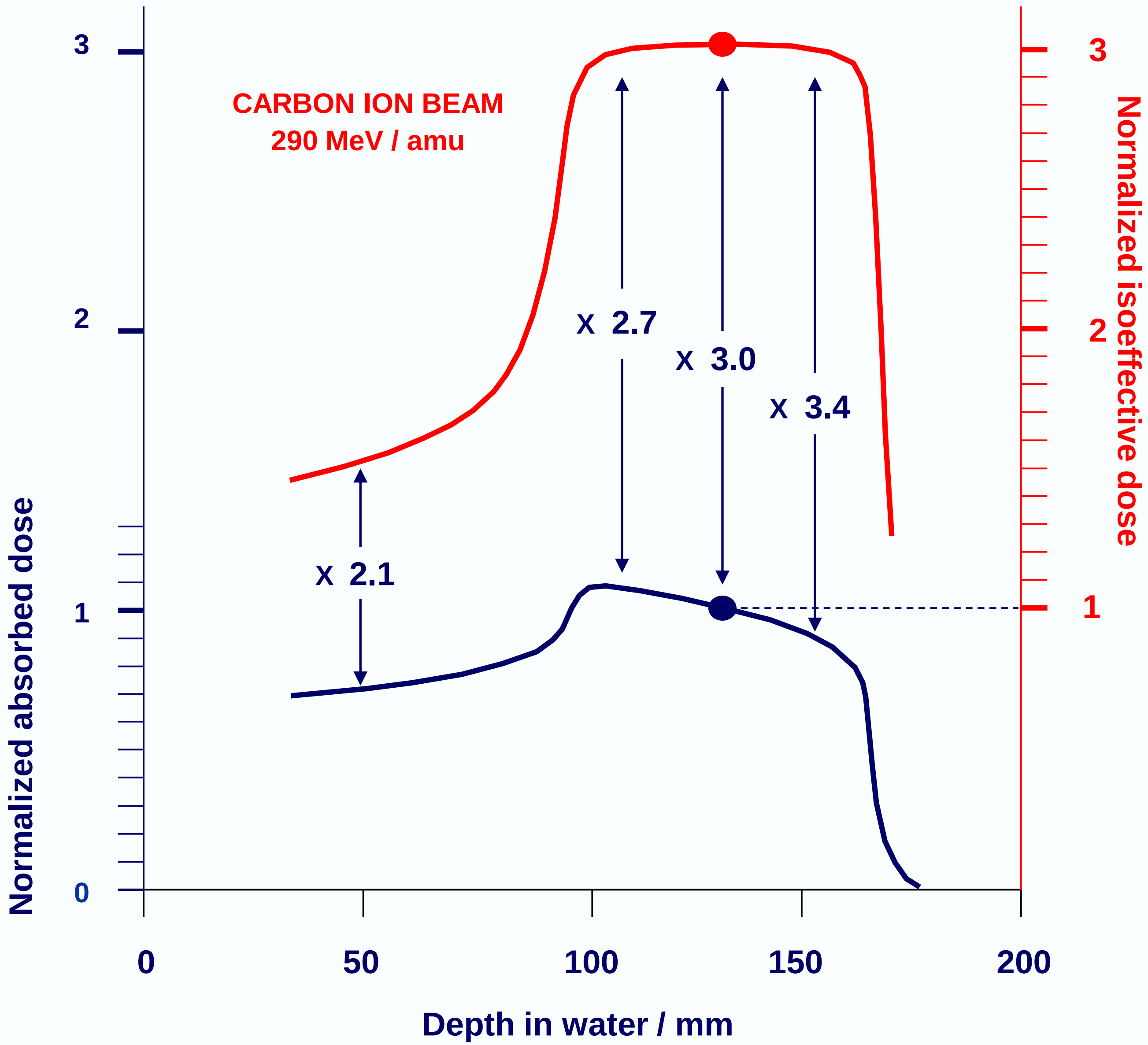


A given dose of carbon is biologically equivalent to the same dose of gamma multiplied by the carbon RBE

Carbon dose x **RBE**

Iso-doses (in Gy) *in a given tissue* **do no longer correspond to** iso-biologically effective doses !!!





CARBON ION BEAM
290 MeV / amu
x 2.1
x 2.7
x 3.0
x 3.4
Normalized absorbed dose
Normalized isoeffective dose
Depth in water / mm
0
1
2
3
50
100
150
200

LEM

"***Local effect Model***" (Scholz et Kraft, 1994)

Derivation of parametres determining the biological response to a Carbon ion exposure from the response parameters to a photon irradiation

Assumptions

- *The biological effect in a cell nucleus sub-volume is **exclusively** determined by the energy deposit in this sub-volume*
- *The biological effect is **independent** from the radiation quality of the beam*

Consequences

- A local dose deposit with Carbon ions produces the **same biological effect** than the same dose deposit with photons
- Therefore, the different biological effects of Carbon ion and photons result from **differences in spatial dose deposition**

Local Effect Model (LEM)

(Scholz and Kraft)

Parameters **exclusively** determined on the basis of :

- Dose-effect relationship **for photons** (low LET)

→ Probability of a letal event

- Physical data on **track structures**

→ Determination of local dose deposits

- **Experimental** measurement of cell nucleus size

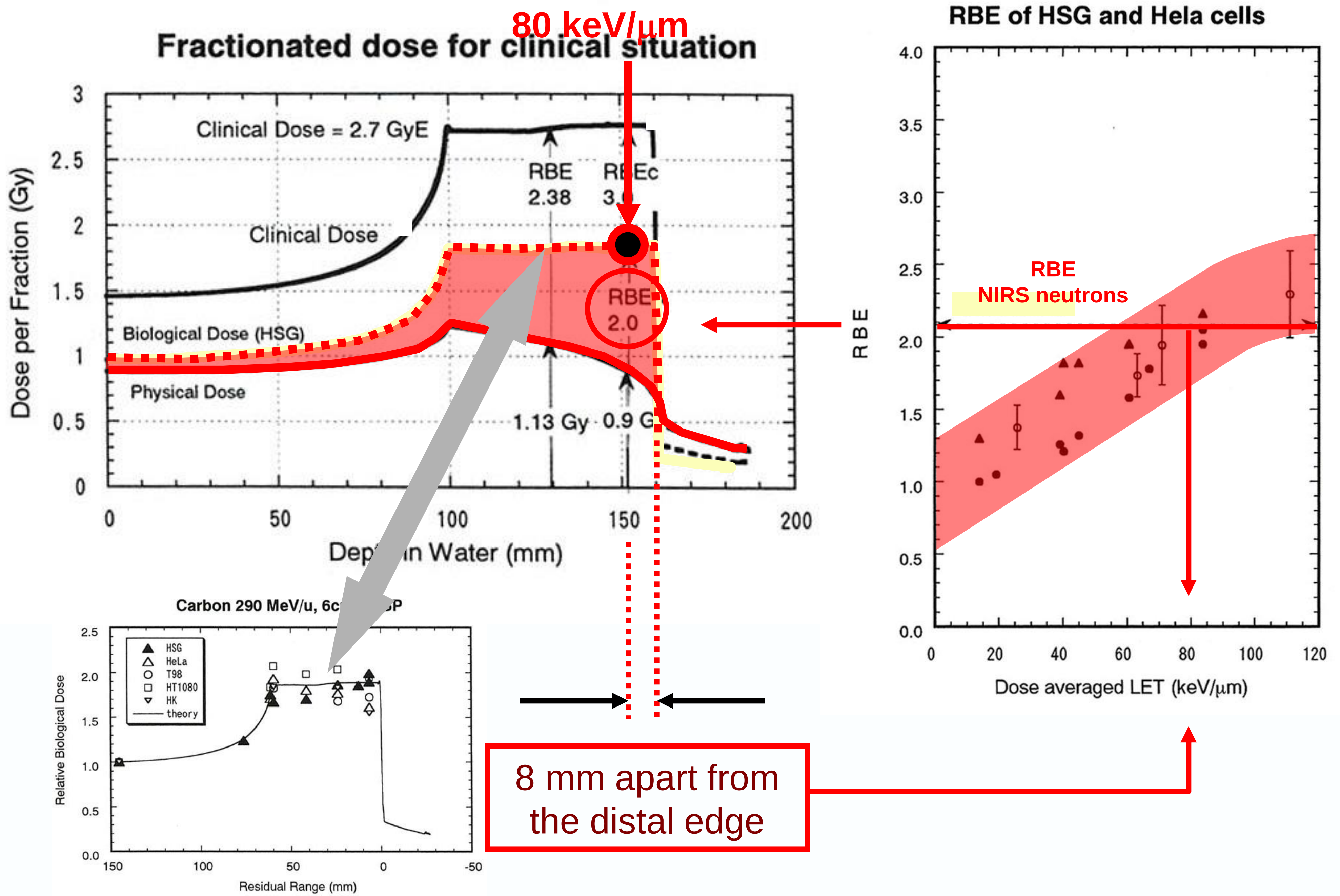
→ Determination of radiosensitive area size
(nucleus diameter)

Advantages :

- Conformational possibilities
- Possibility to treat sub-volumes
- Possibility of dose « modulation » within each volume of interest
- **all RBE variation taken into account**

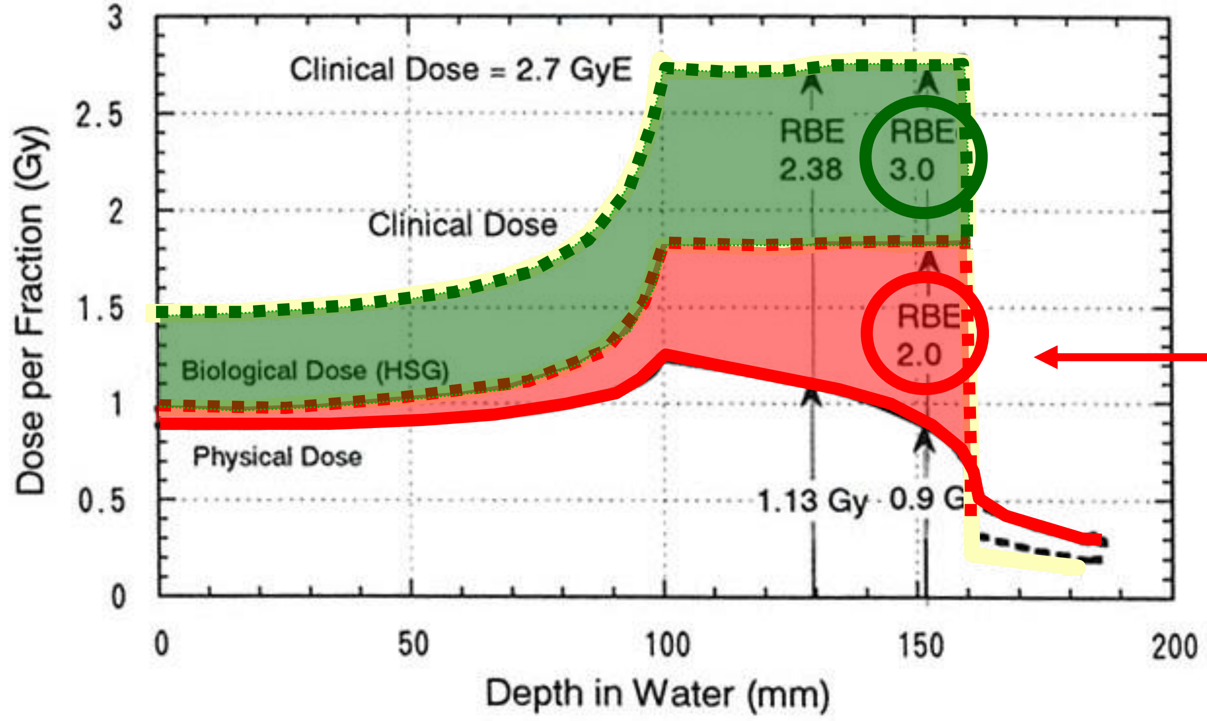
Inconvenients

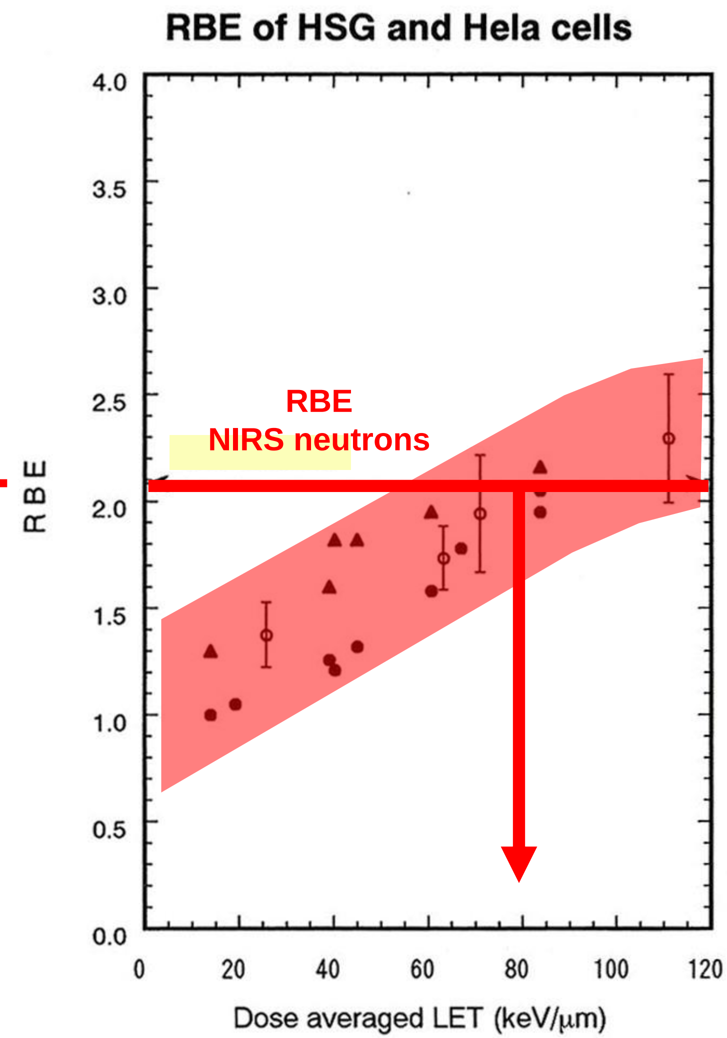
- Uncertainties on RBE calculation algorithm (LEM, other…)
- **Lack of transparency and total confidence in calculation model**
- Impossibility (*for the physician nor for the physicist*) to judge *directly* the appropriateness of treatments plans. Dose distributions have to be re-calculated with the model.



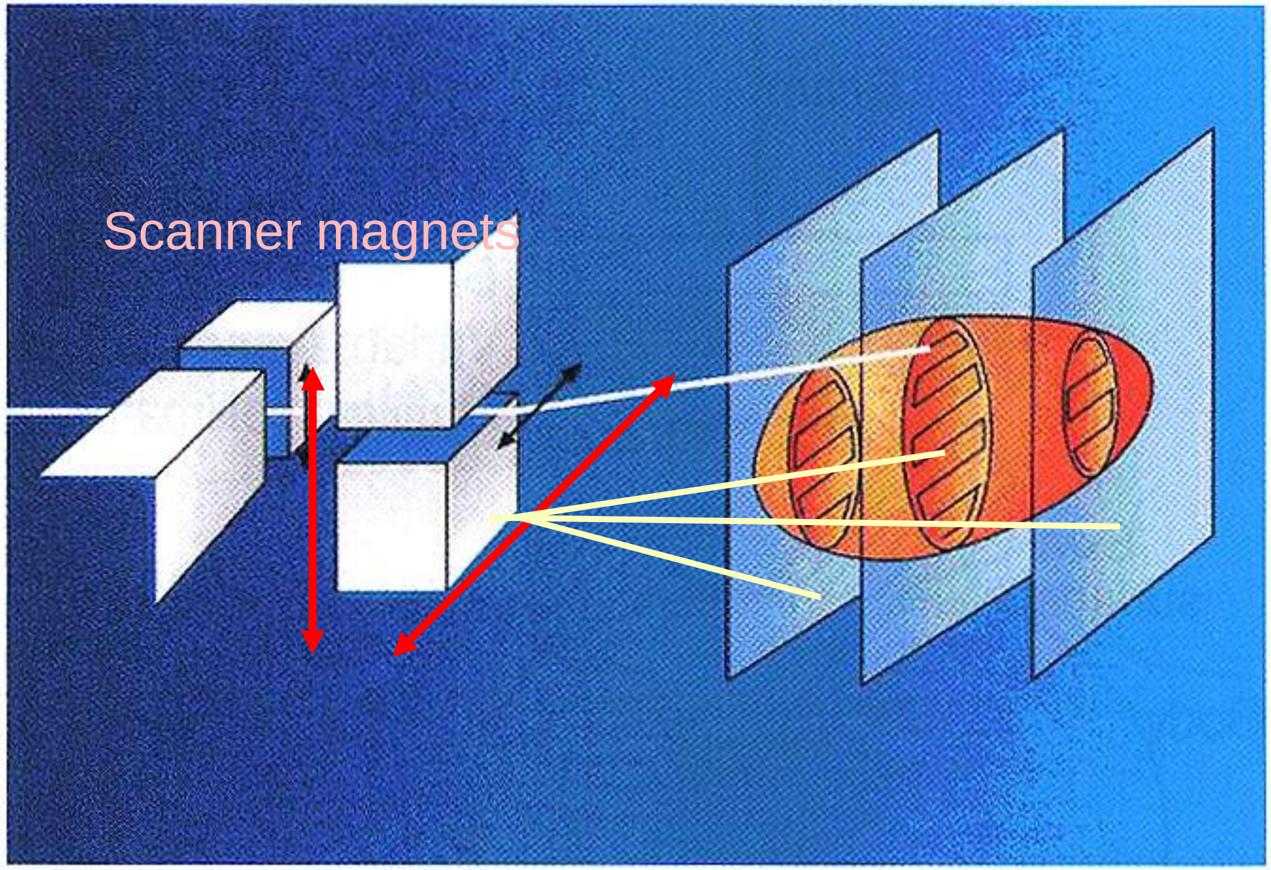
80 keV/μm
Fractionated dose for clinical situation
Clinical Dose = 2.7 GyE
RBE
2.38
RBEc
Clinical Dose
RBE
2.0
Biological Dose (HSG)
Physical Dose
1.13 Gy
Dose per Fraction (Gy)
Depth in Water (mm)
RBE of HSG and Hela cells
RBE
NIRS neutrons
Dose averaged LET (keV/μm)
Carbon 290 MeV/u, 6cm SOBP
HSG
HeLa
T98
HT1080
HK
theory
Relative Biological Dose
Residual Range (mm)
8 mm apart from the distal edge

Neutron clinical RBE = 3





Carbon clinical RBE at the center of the SOBP = 2.38



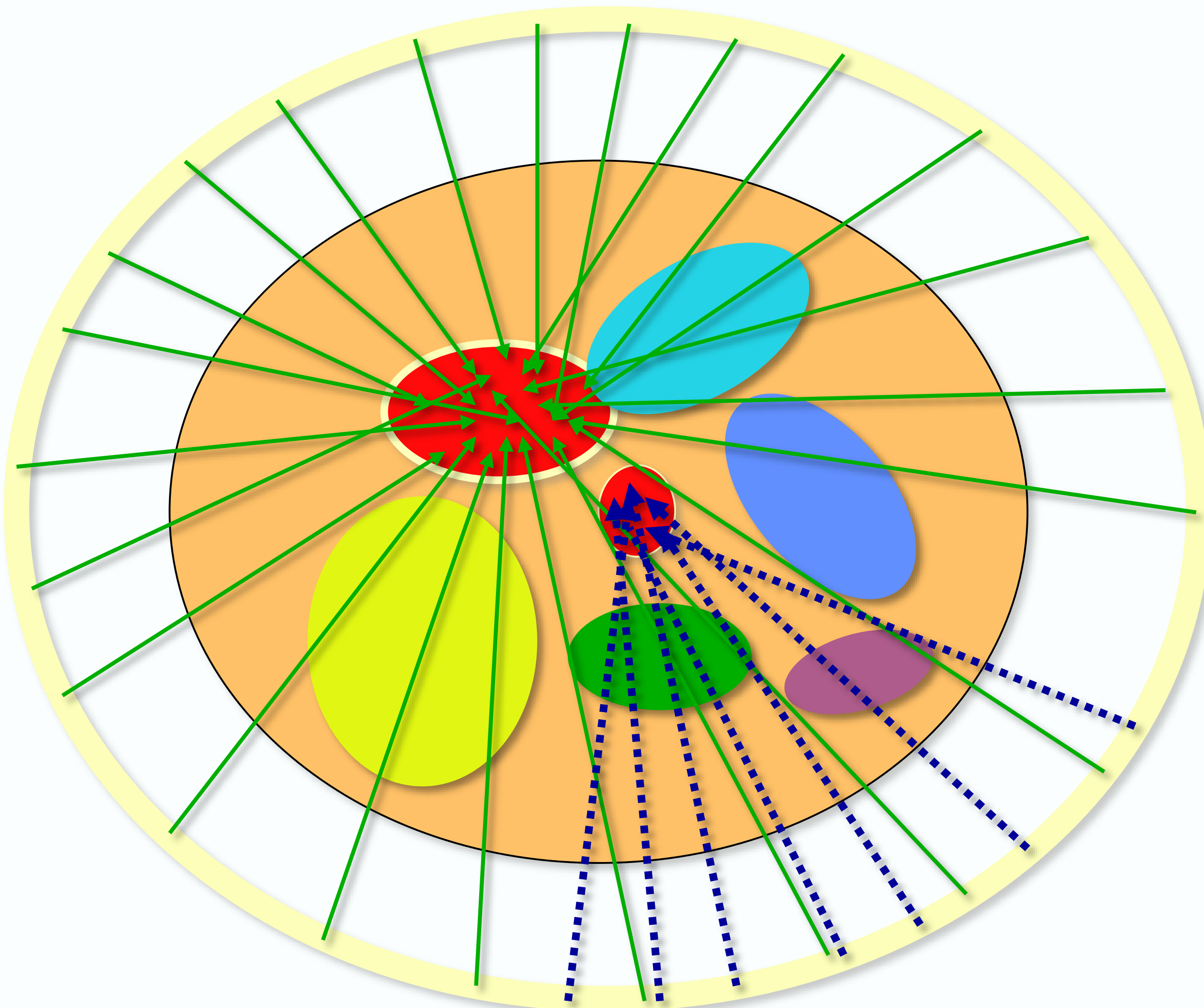
Raster scan system at GSI, Germany

from : D. Schulz-Ertner, O. Jäkel, W. Schlegel *i.e.* a system where :

“*several thousands of narrow ion pencil beams with individual lateral positions, ion energies and particle fluences are combined to form an intensity-modulated field of high granularity*”

(M. Krämer, 2001)

Consideration of RBE variations is only possible in an integrated calulation code allowing iterative interaction between both physical and biological input parameters

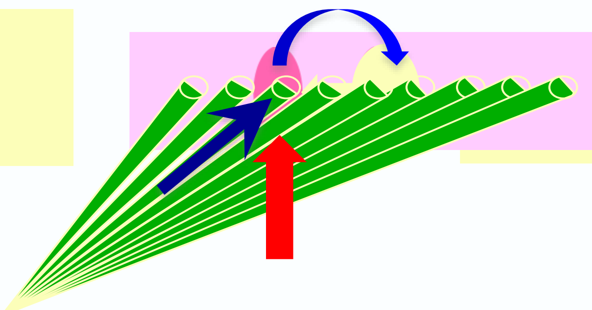


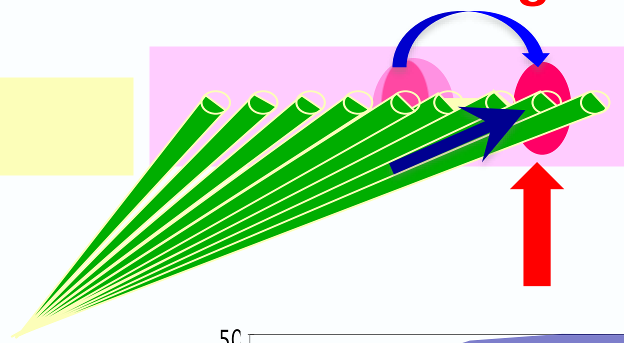
An **RBE weighting factor** should be applied at each point of the irradiated volume, taking RBE variation with **energy, dose, biological system**, etc, into account

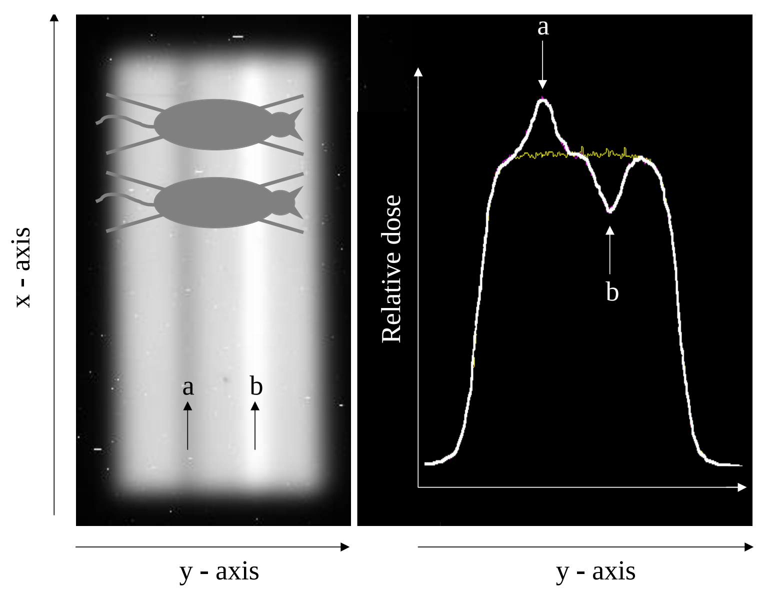
Particules of variable energy are also delivered at **variable dose rates** or in multi - *micro* fractions.

Integrated algorithm allowing for the **iterative interaction** between **physical** (*e.g. energy/LET*) and **biological parameters** (*e.g. intrinsic radiosensitivity, oxygenation, dose rates, micro-fractionation, etc.*

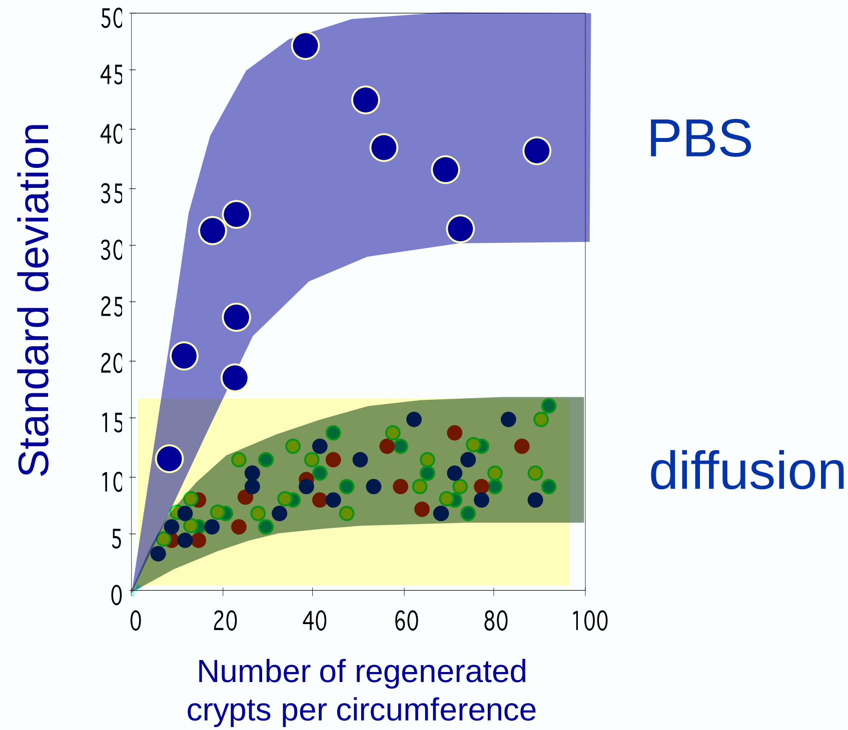
The "**Inter–play**" effect (Protons, PSI)



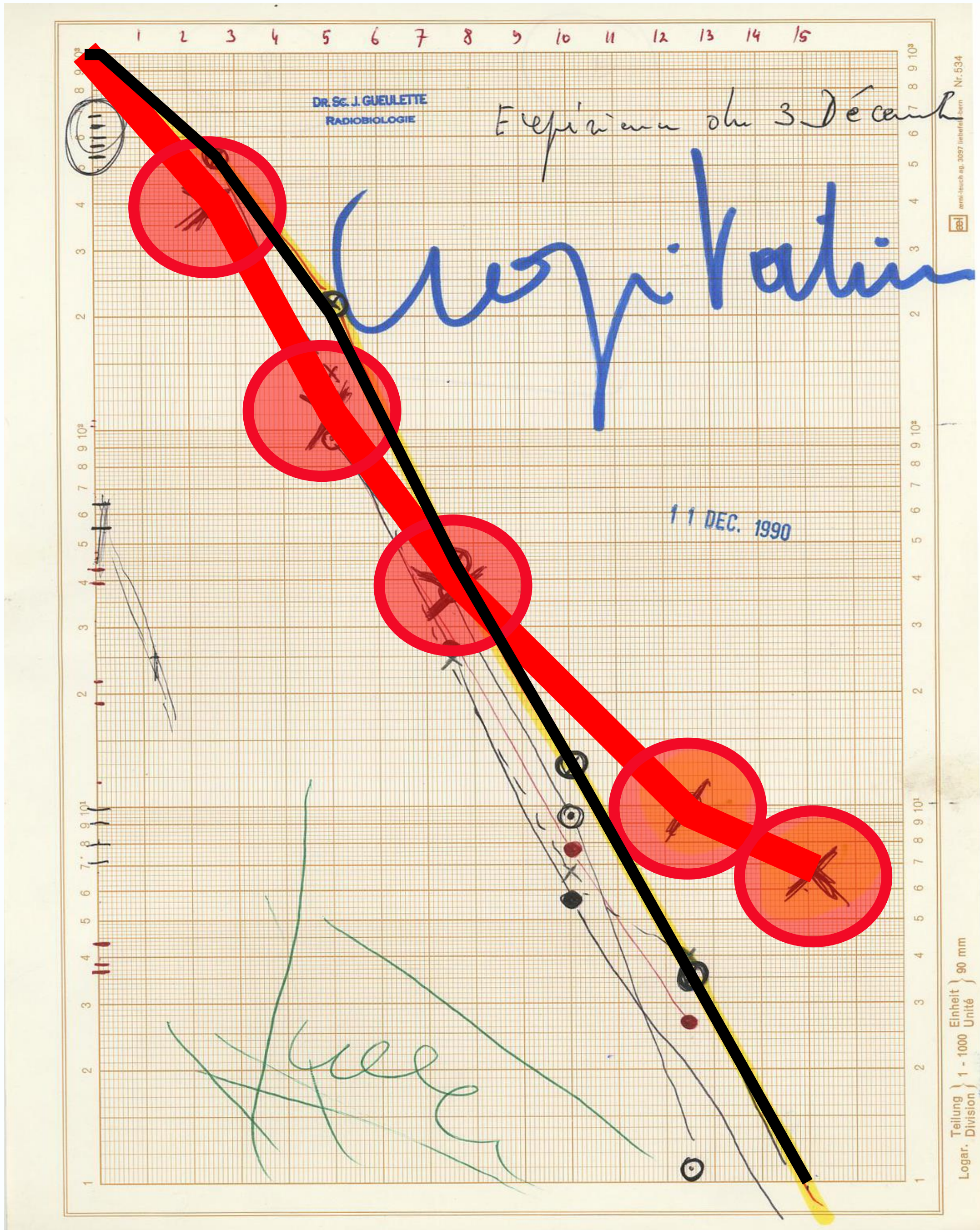


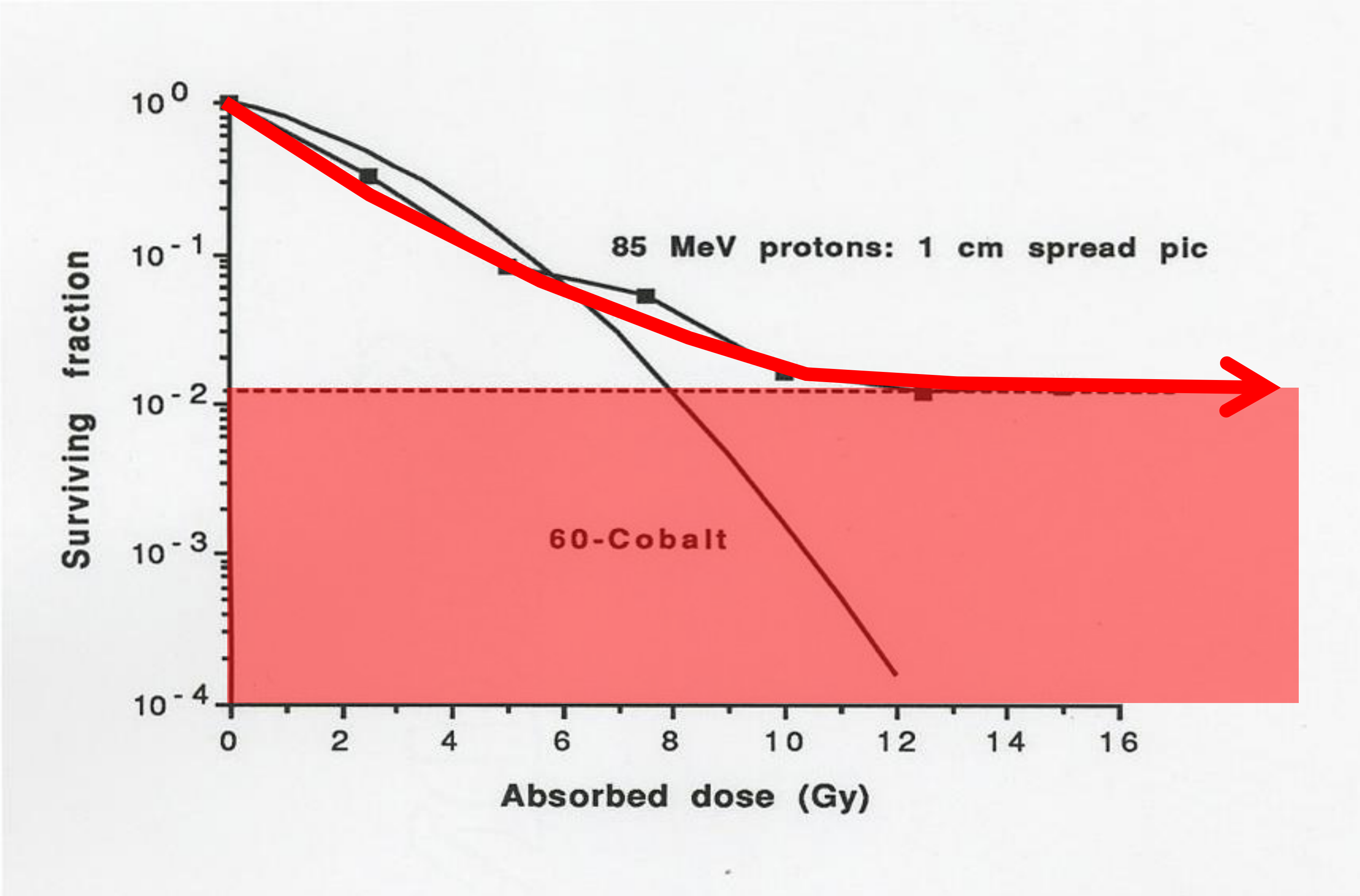


Dose heterogeneity
~ 15% / mm

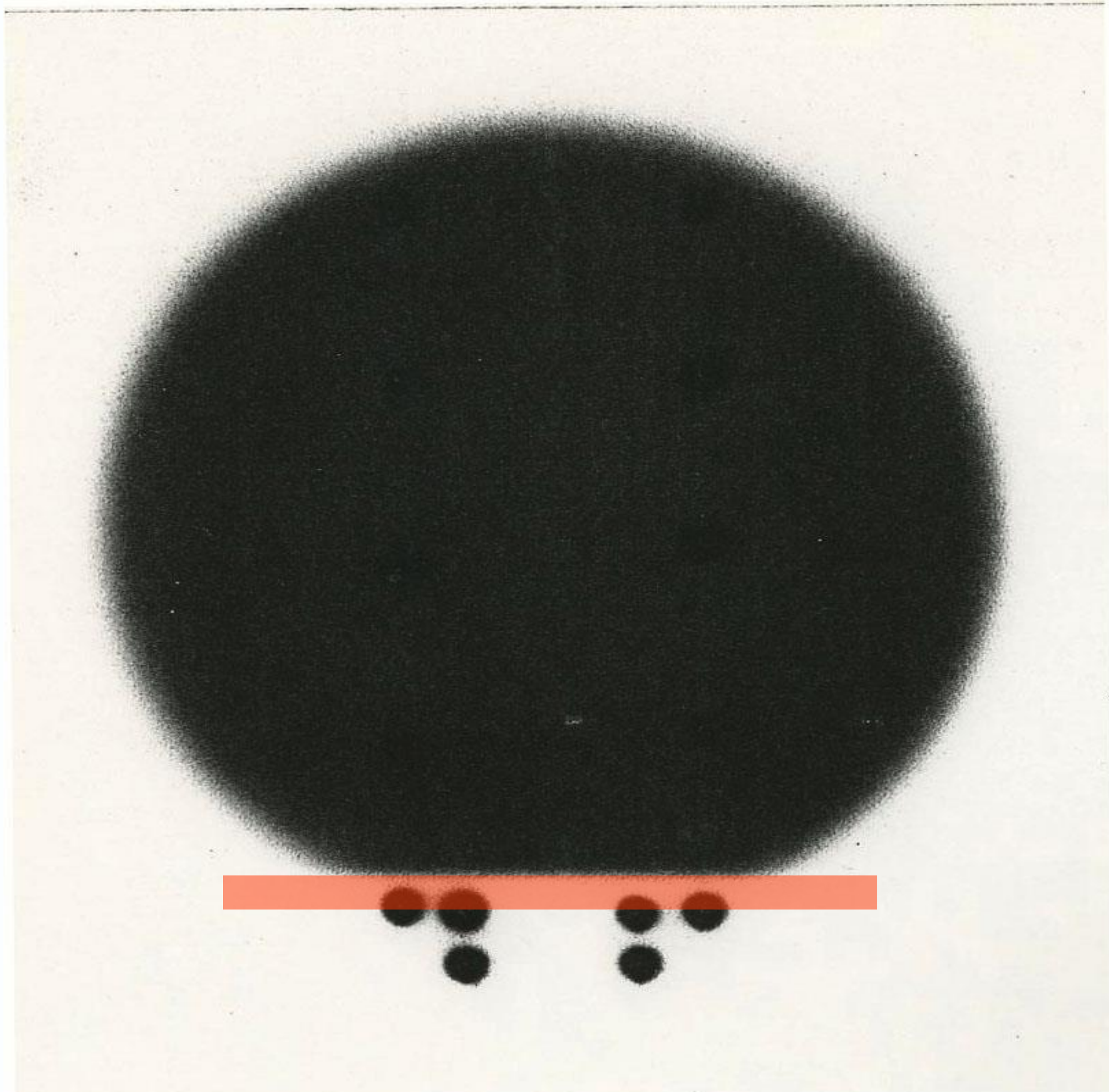


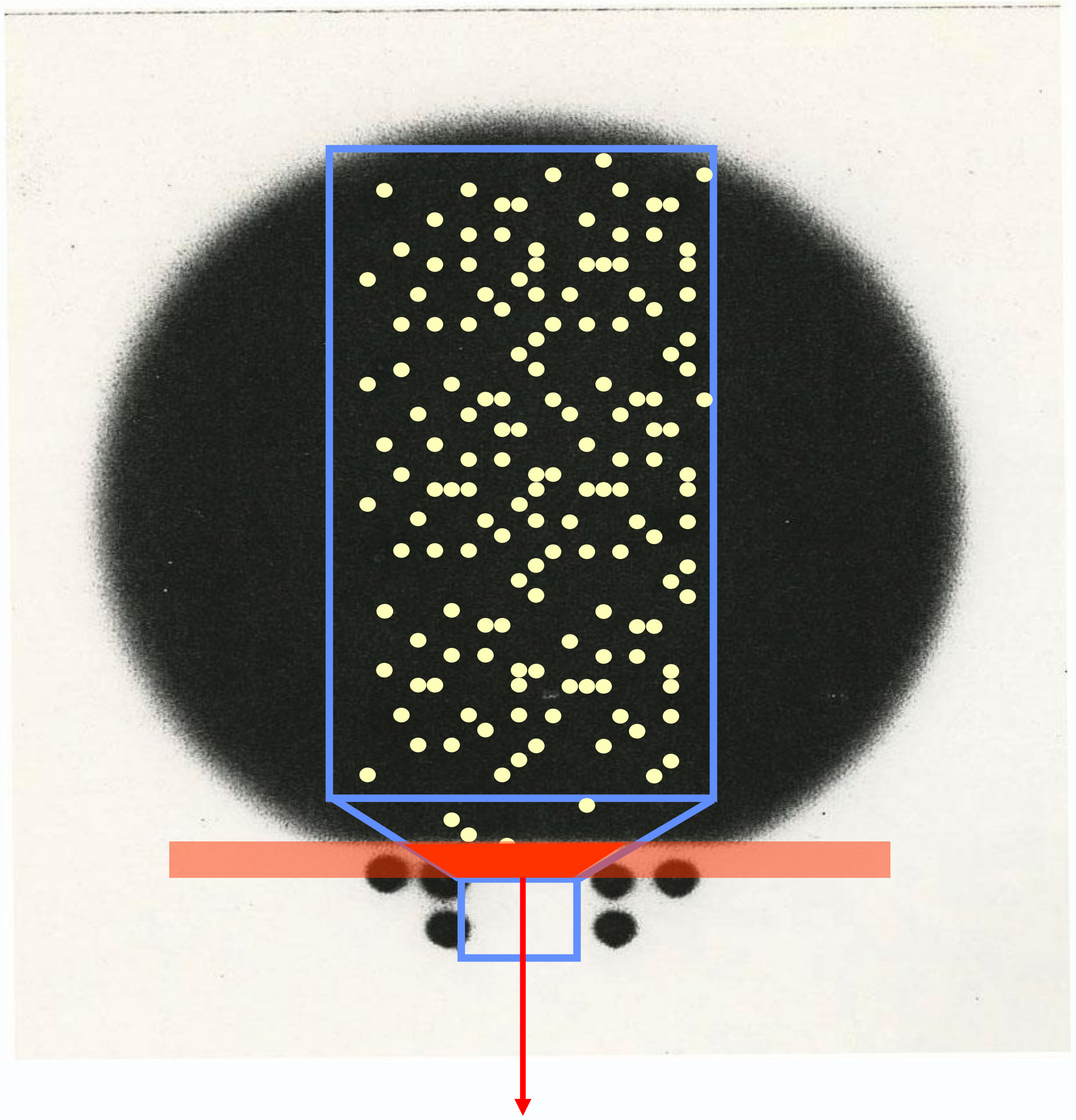
Pitfalls...


DR. SC. J. GUEULETTE
RADIOBIOLOGIE
11 DEC. 1990
Nr. 534

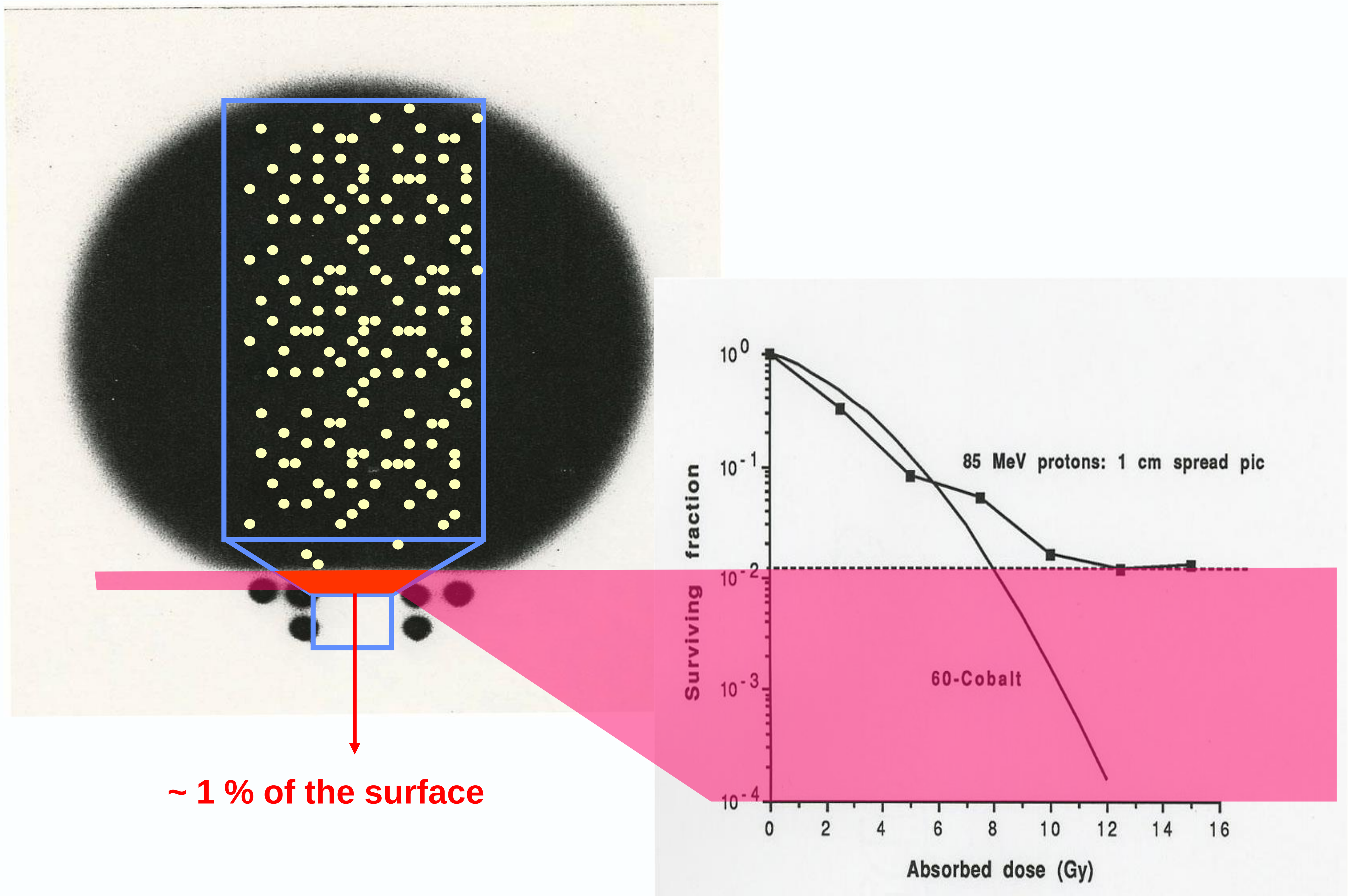


85 MeV protons: 1 cm spread pic
60-Cobalt
Surviving fraction
Absorbed dose (Gy)
10^0
10^{-1}
10^{-2}
10^{-3}
10^{-4}
0
2
4
6
8
10
12
14
16





~ 1 % of the surface



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6
8
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16

Finally, which recommendation for irradiation schedule?

Short hypofractionated schedules

- Less tumour repopulation.
- More damage to quiescent cells.
- More microvascular damage.
- Differential release of cytokines and special immunologic effects?
- Too much assumptions in radiobiological models??