OncoRay – National Center for
Radiation Research in Oncology, Dresden

Particle effects: biological basis and models

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PTCOG, Essen 2013

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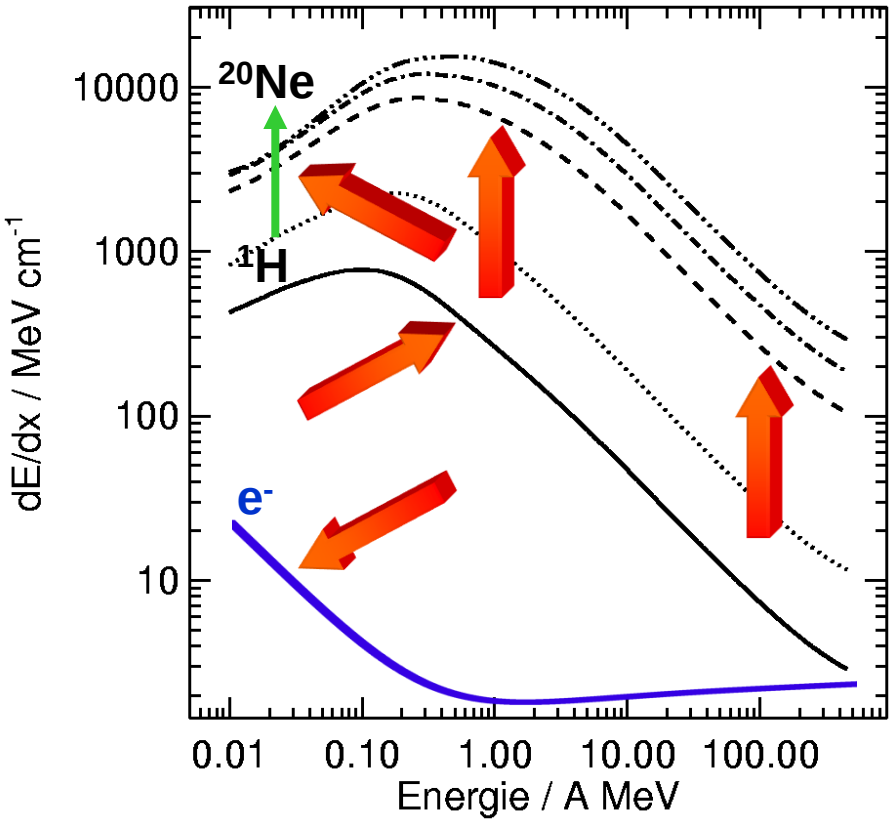
Biological basis of particle radiotherapy

- Biological efficacy increases with number of ionisations per distance
  ⇨ linear energy transfer (LET)

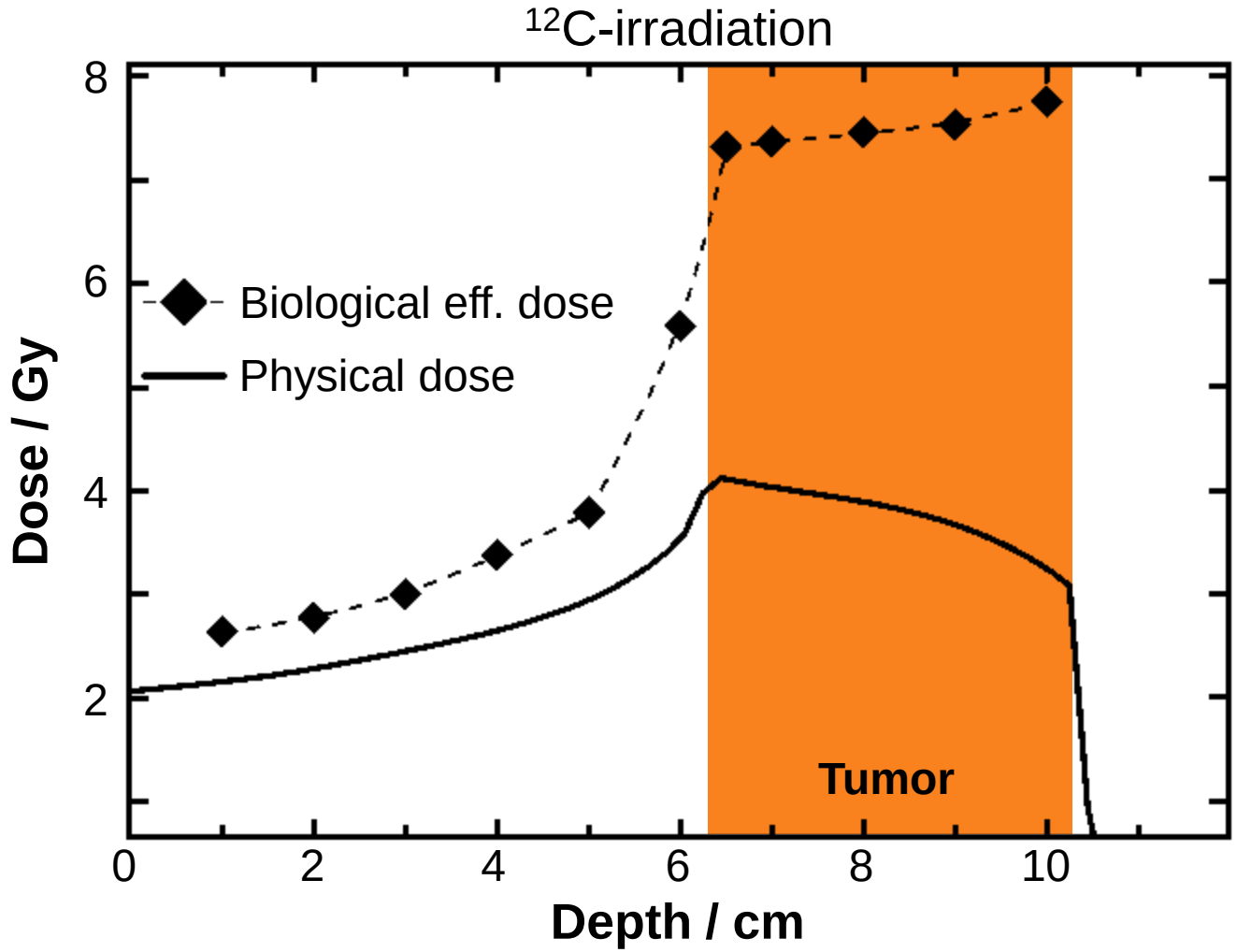
- Higher ionisation density for ions as for electrons/ photons
  ⇨ higher relative biological efficiency (RBE)

- Ionisation density increases with atomic number
  ⇨ higher RBE for heavy ions compared to protons

- Ionisation density increases with decreasing energy
  ⇨ higher RBE around the Bragg-peaks compared to the entrance channel



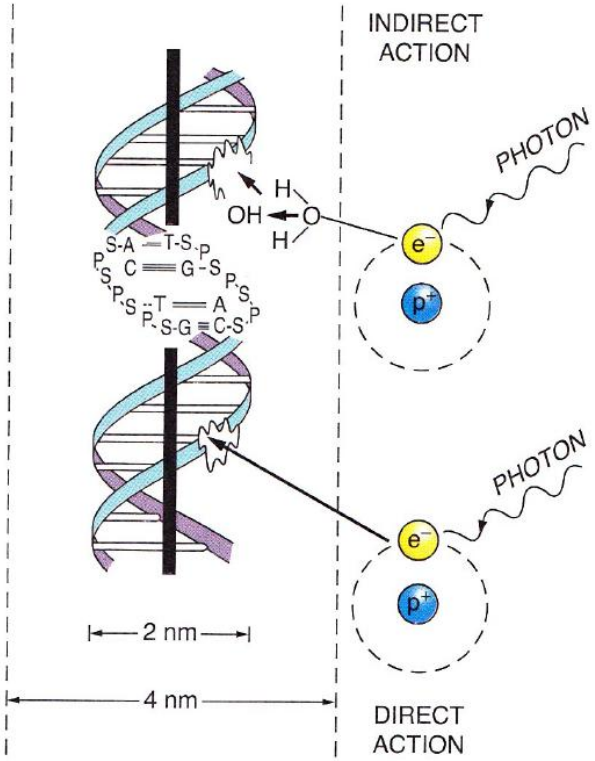
Biological basis of particle radiotherapy



Weyrather et al., J: Clin. Oncol. 15 (2003) S23

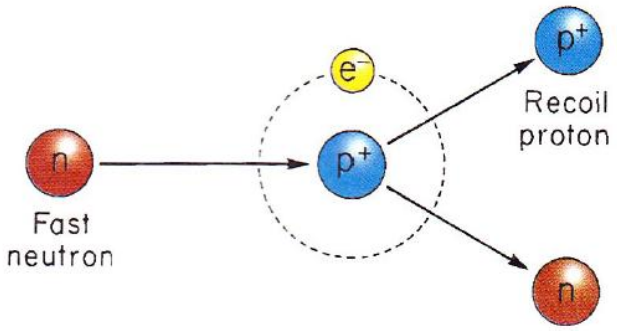
Direct and indirect action of radiation

depends on linear energy transfer (LET)

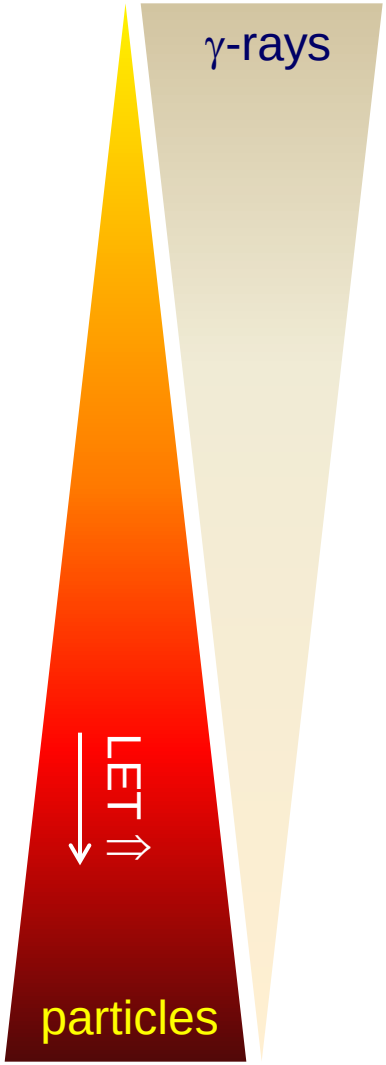


Indirect ionisation (mainly photons): Compton effect, radiolysis of water

Direct ionisation (mainly particles- e^-, H^+, C): atoms of the target are ionized or excited and lead to biological damage

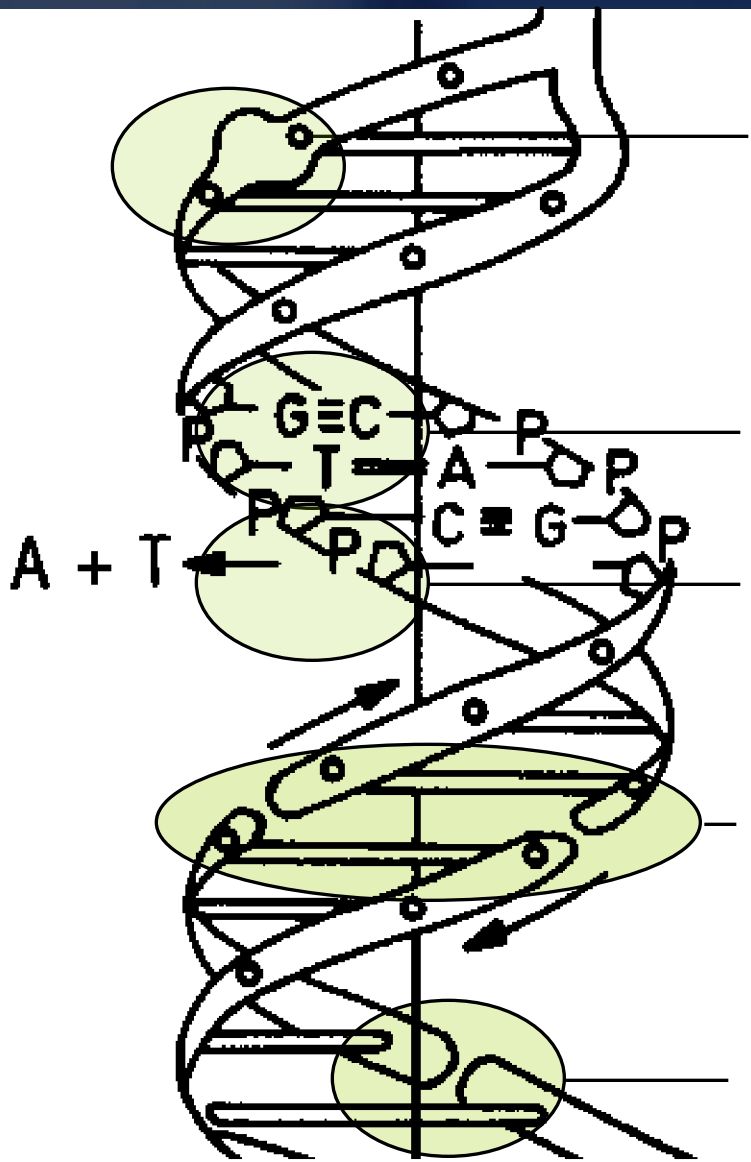


Direct interaction with the nucleus (neutrons, protons, heavy ions)



Hall/ Giaccia, In: „Radiobiology for the Radiologist“

DNA damage after irradiation



- cross-linking

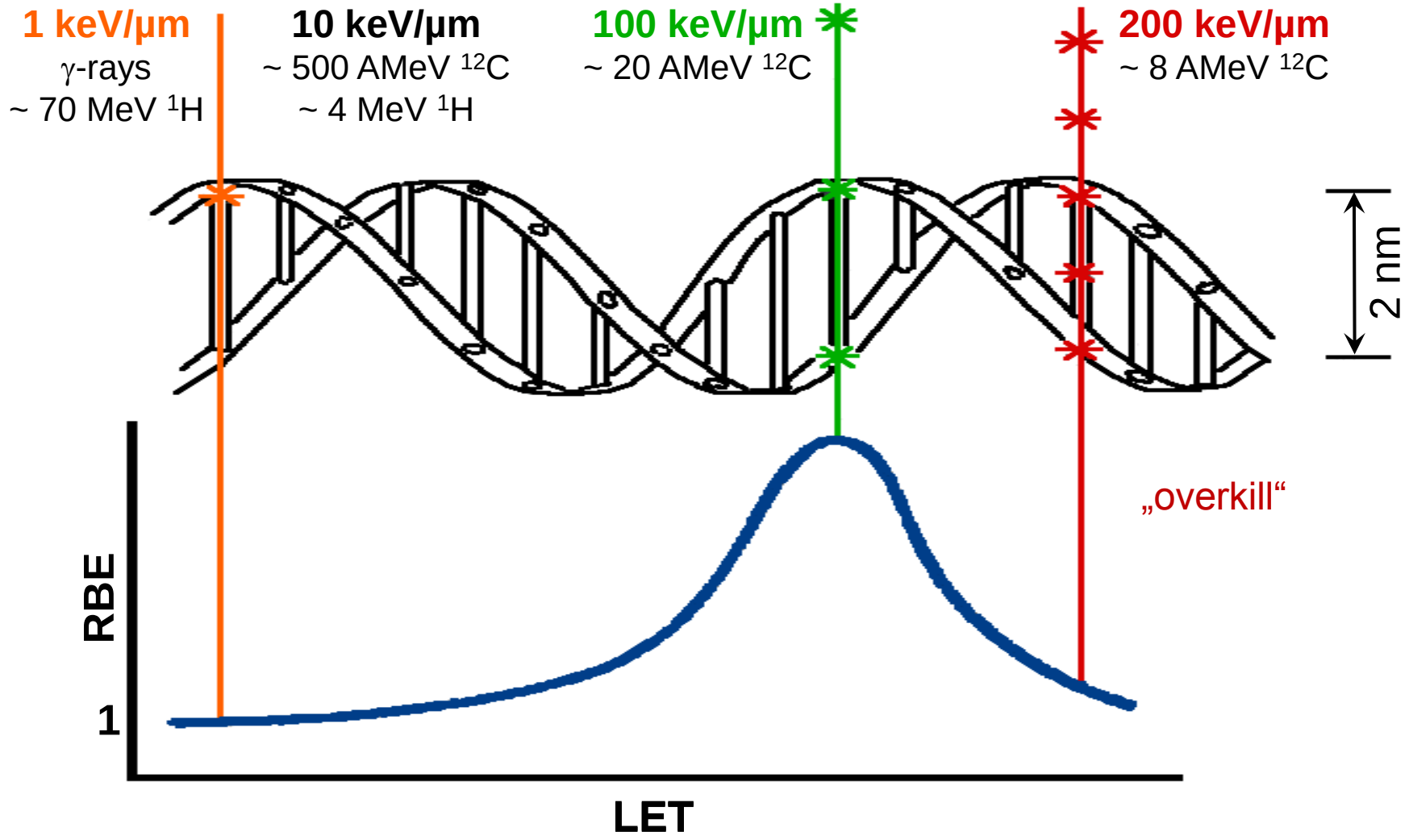
- hydrogen bond damage

- base damage (3000/Gy photons)

- double strand break (40/Gy photons)

- single strand break (1000/Gy photons)

Linear energy transfer (LET) and radiobiological effectiveness (RBE)

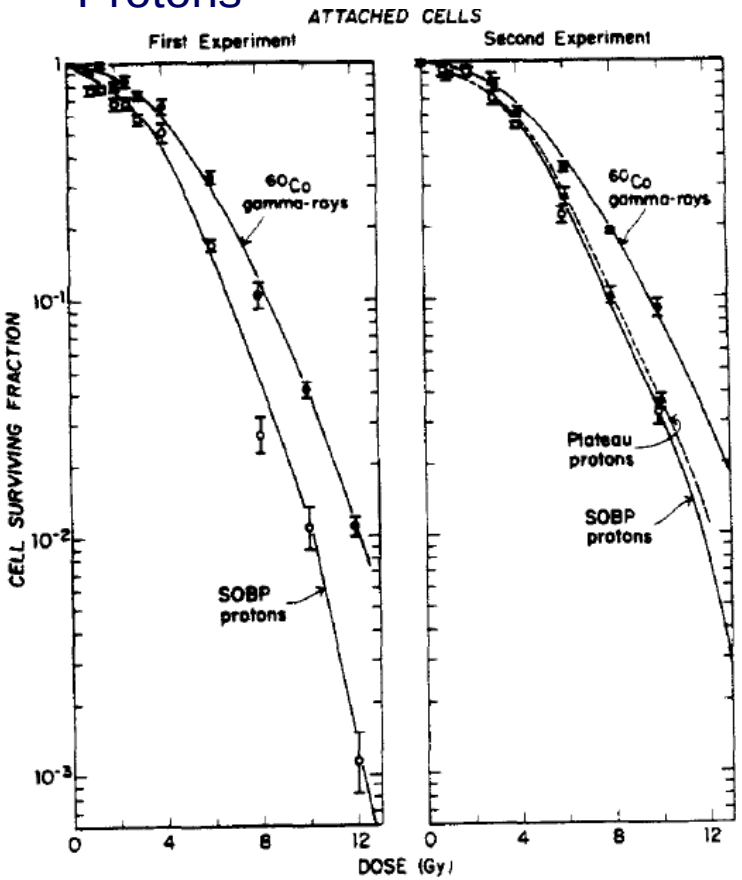


Hall/ Giaccia, In: „Radiobiology for the Radiologist“

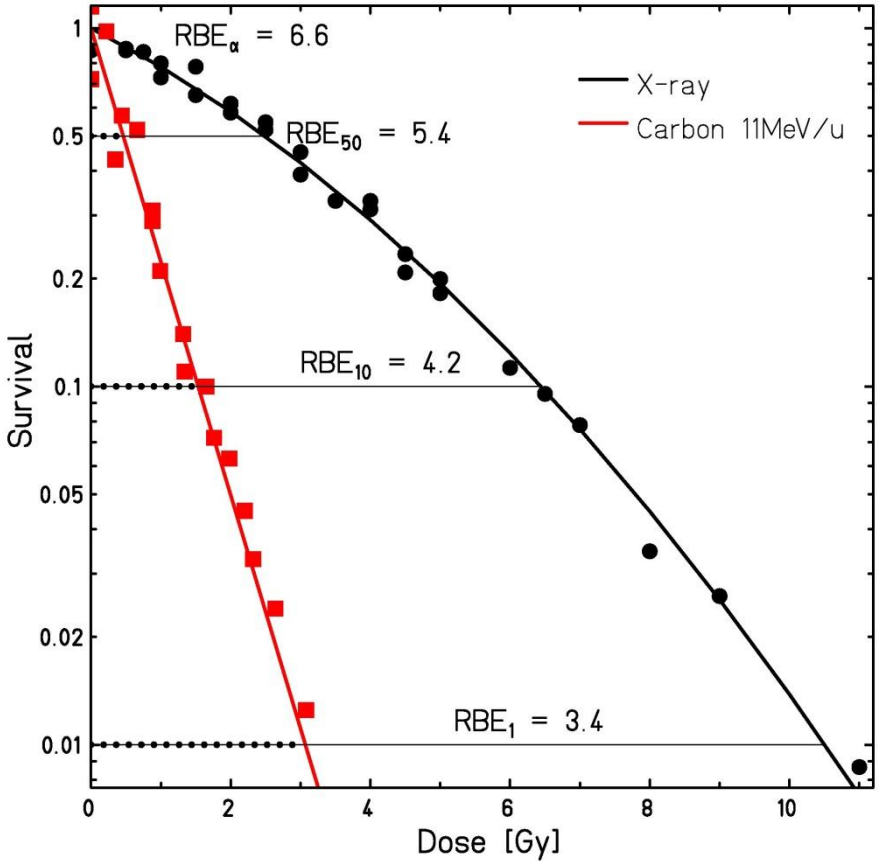
Relative biological efficacy in vitro (LQ model)

$$RBE = \left. \frac{D_{\mathrm{x-ray}}}{D_{\mathrm{ion}}} \right|_{\mathrm{isoeffect}}$$

Protons



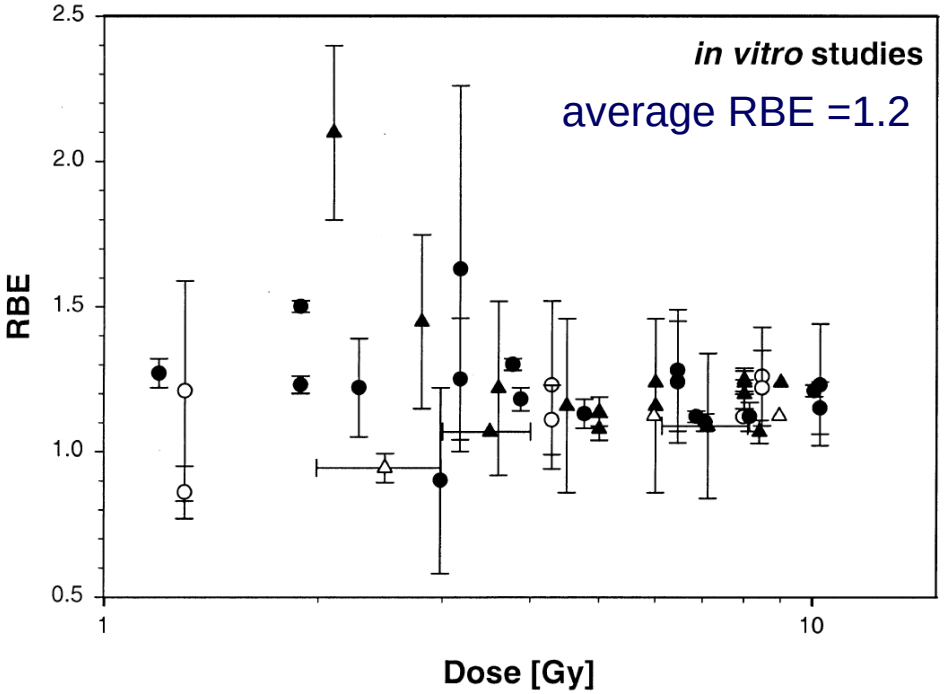
Carbon

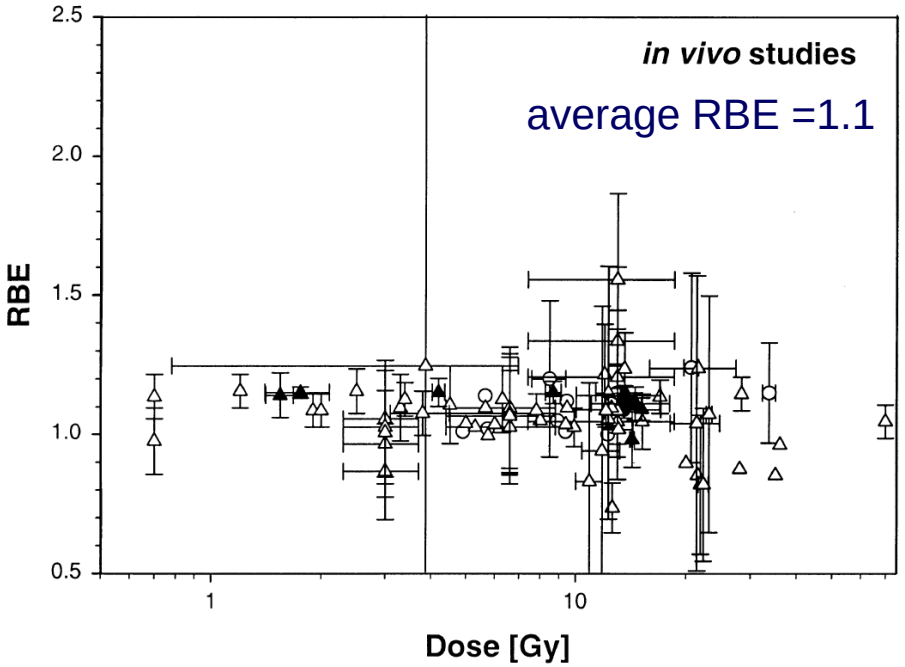


Hall et al., IJROBP 4, 1009-13, 1978

Weyrather/ Scholz

Relative biological effectiveness (protons)



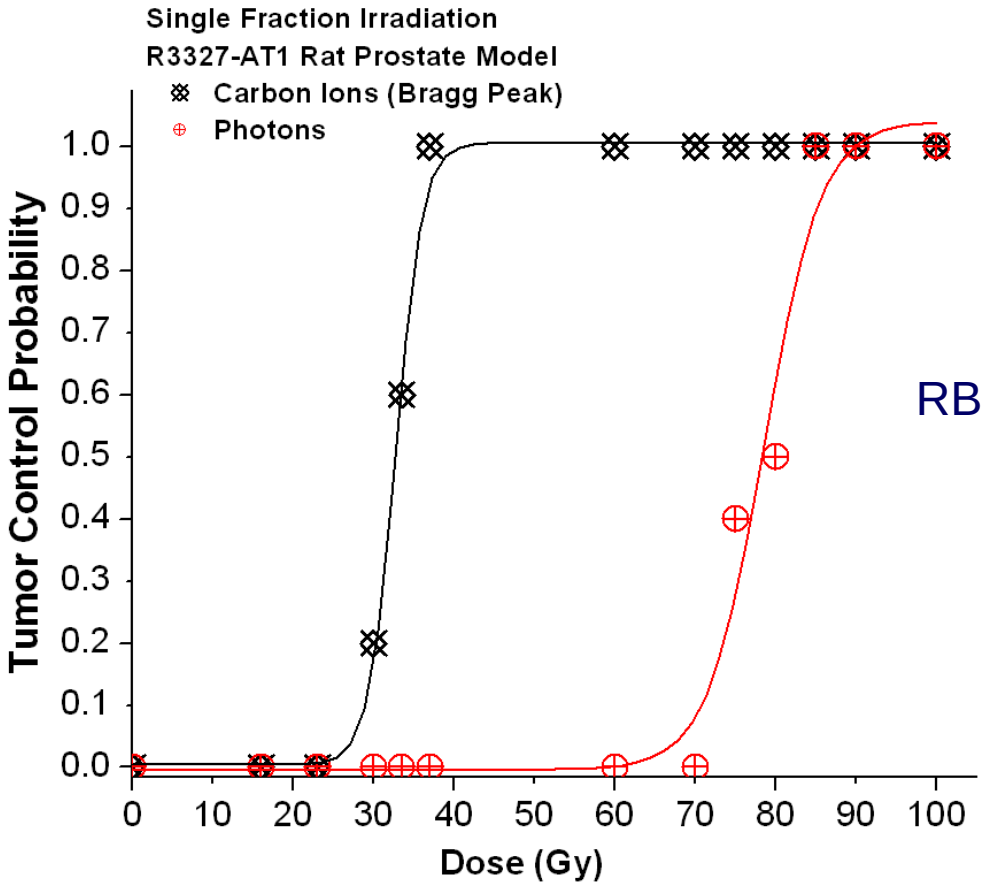


Data content:

- In vitro: most data on chinese hamster cells
- In vivo: most data on normal tissues, tumour data on mouse fibrosarcoma and mouse mammary carcinoma (mostly growth delay)

Paganetti et al., IJROBP 53, 407-21, 2002

Relative biological efficacy (C12) in vivo



RBE = TCD_{50} (photons)/ TCD_{50} (carbon)

Study	$D_{50} \pm SE$ (90% CL) (Gy) Photons	Carbon ions	RBE ± SE (90% CL)
1 fraction	75.7 ± 1.6 (69.9–78.6)	32.9 ± 0.9 (30.8–34.9)	2.30 ± 0.08 (2.17–2.44)
2 fractions	90.6 ± 2.3 (85.6–95.4)	38.0 ± 2.3 (33.7–42.6)	2.38 ± 0.16 (2.15–2.67)

Karger et al., IJROBP 79, 239-46, 2011

Relative biological effectiveness (RBE)

- No linear correlation of RBE and LET
- RBE depends on:
  - Kind of ion
  - Ion energy
  - Ion dose
  - Kind of tissue
  - Biological endpoint

⇨ RBE different for each position in the irradiation field

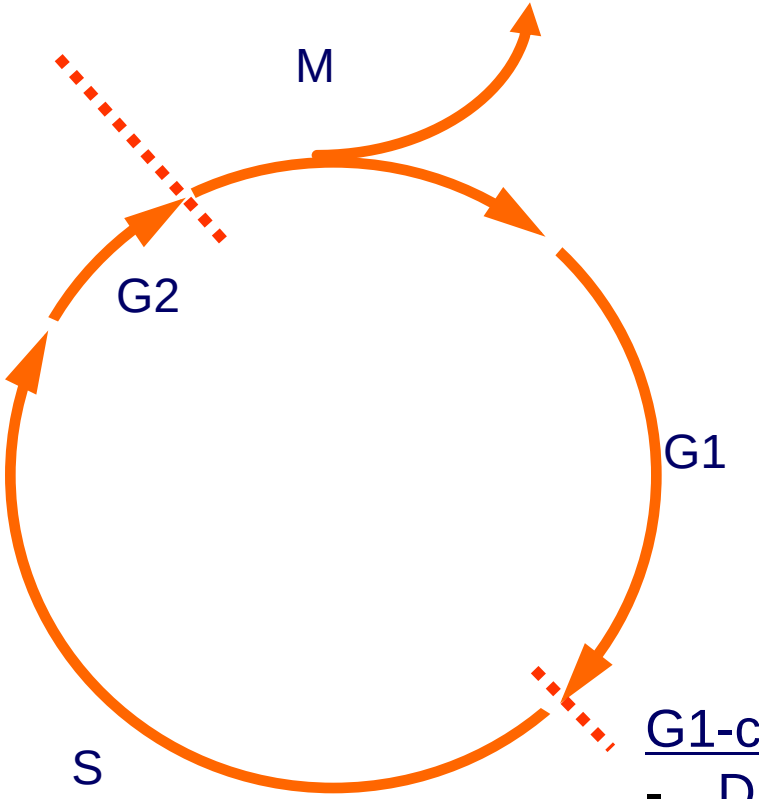
- Biological dose = physical dose * RBE

Cell cycle effects after irradiation

differenciation

G2-checkpoint

- DNA damage
- Cell volume
- surroundings

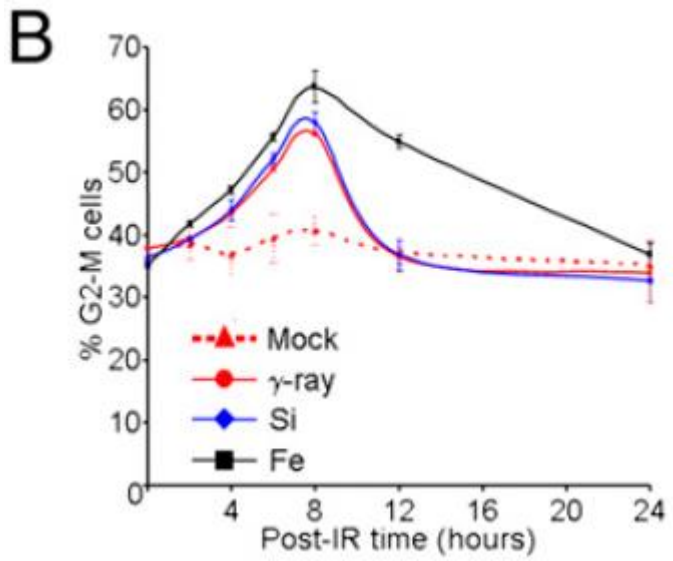


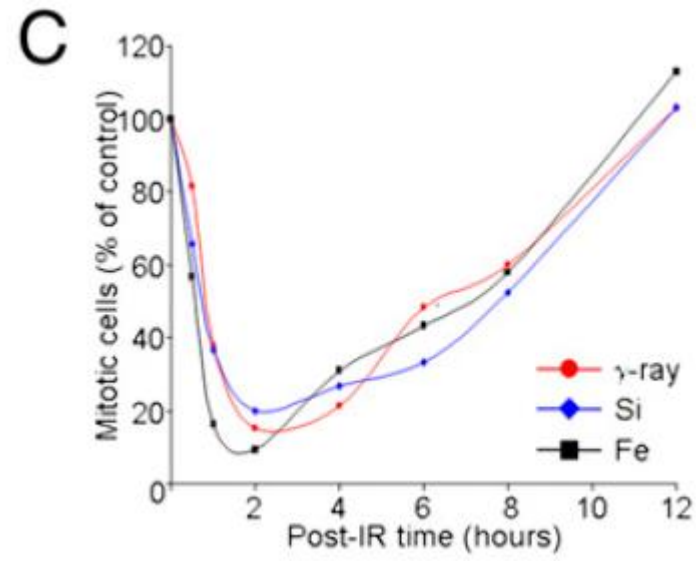
G1-checkpoint

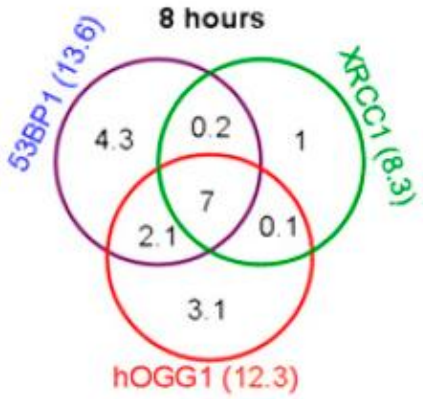
- DNA damage
- Cell volume
- surroundings

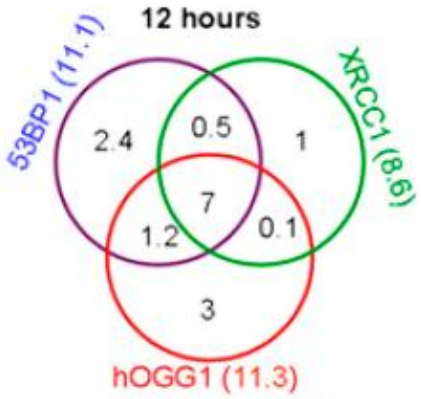
G2 checkpoint
Is activated after irradiation
leads to delay of ~10% of the cell cycle time (~2h/Gy)

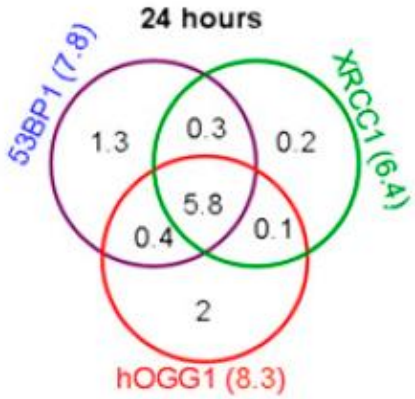
Unrepaired clustered DNA lesions lead to chromosomal damage (increase with high LET)

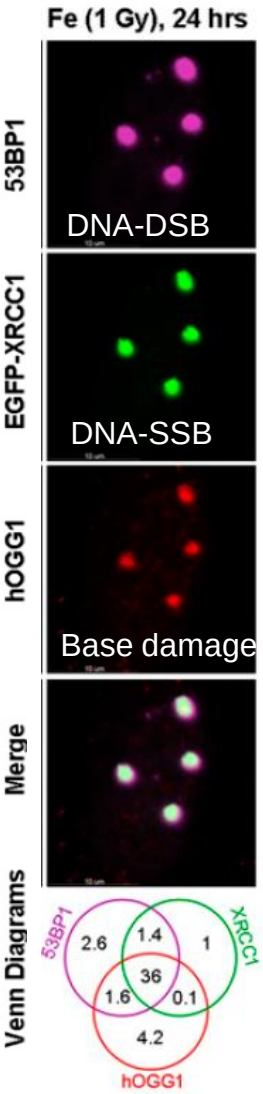










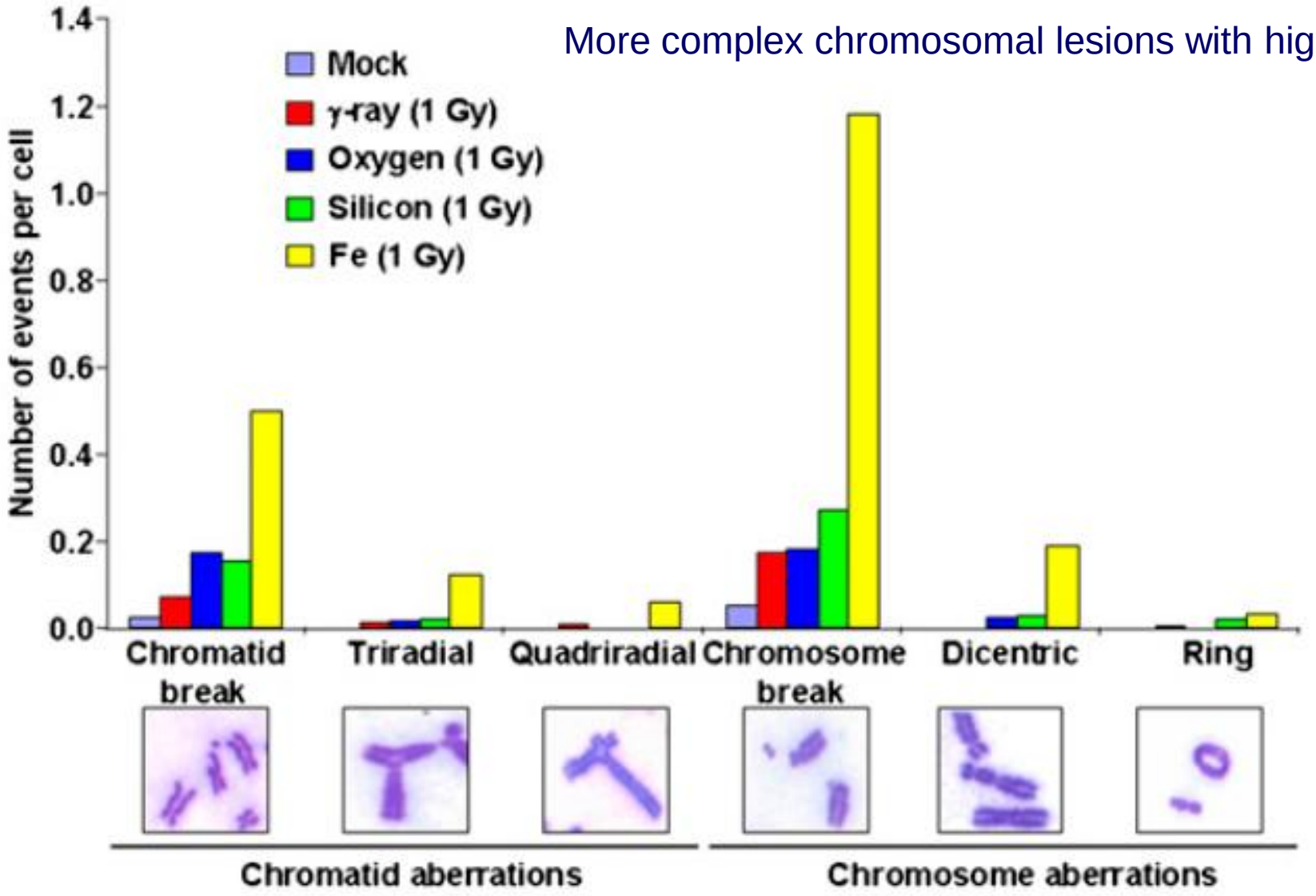


G2 arrest occurs, most cells with unrepairable complex lesions die, but some are relaesed to M-phase → chromosomal breaks

Asaithamby et al., PNAS 108, 8293-98, 2011

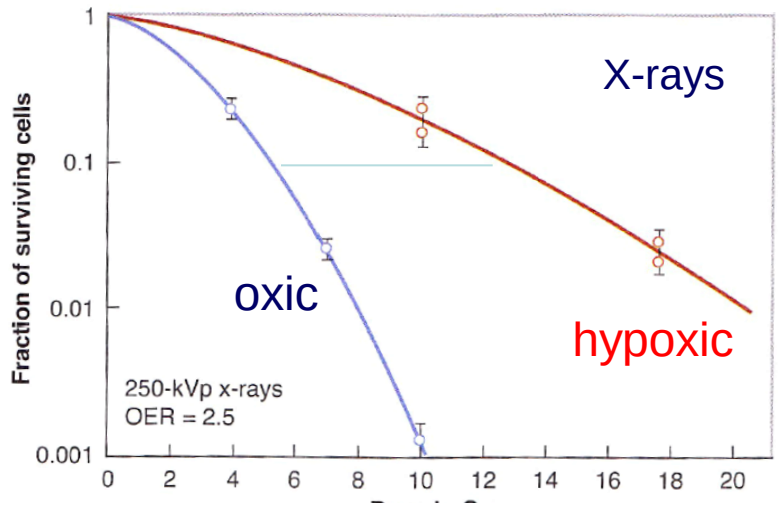
number of chromosome aberrations is higher after exposure to radiosensitizers or high-LET irradiation

More complex chromosomal lesions with higher LET



Asaithamby et al., PNAS 108, 8293-98, 2011

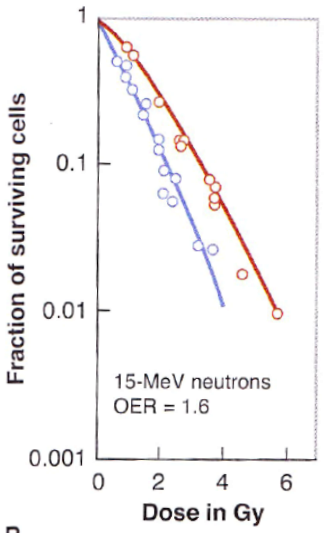
Hypoxia: Oxygen enhancement ratio (OER)



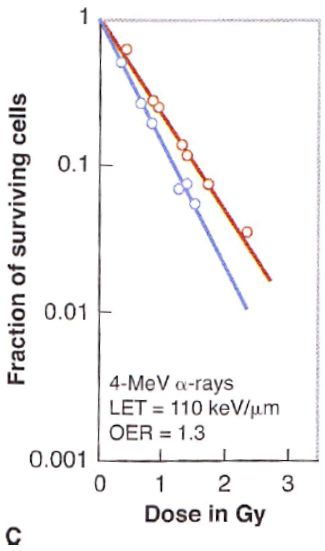
$$OER = \left. \frac{D_{\text{hypoxic}}}{D_{\text{oxic}}} \right|_{\text{isoeffect}}$$

- OER 2-3 for photons
- Less for higher LET particles
- Reason: OER is caused by the effect of radicals (i.e. higher for indirect ionizing irradiation)

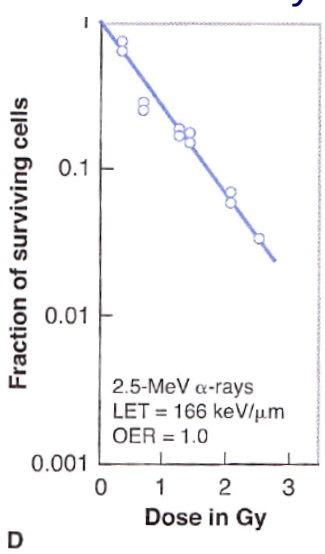
15 MeV neutrons



4 MeV α-rays

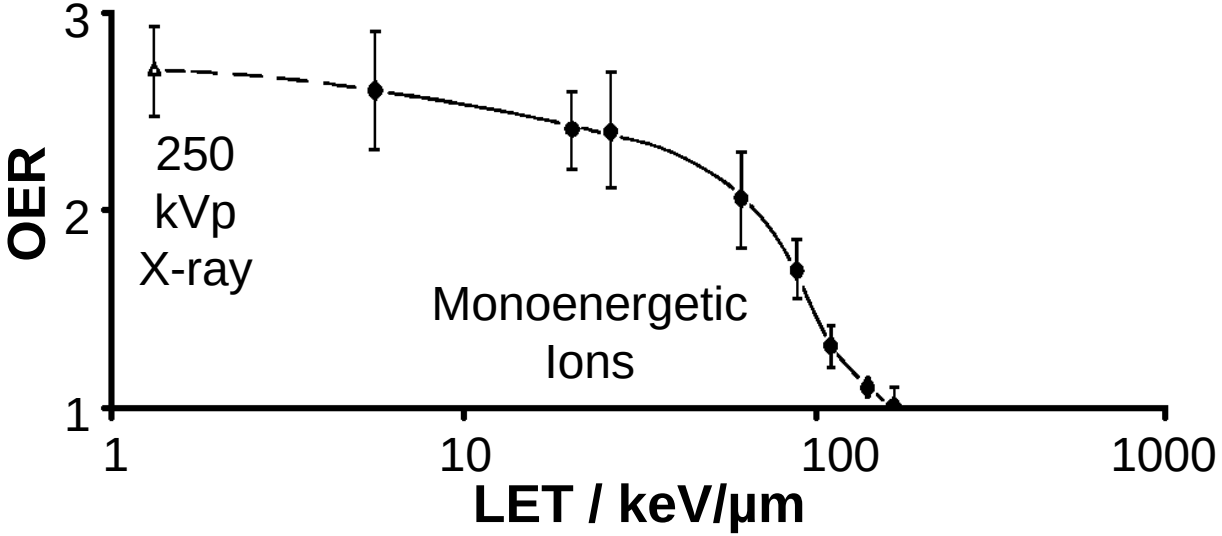


2.5 MeV α-rays

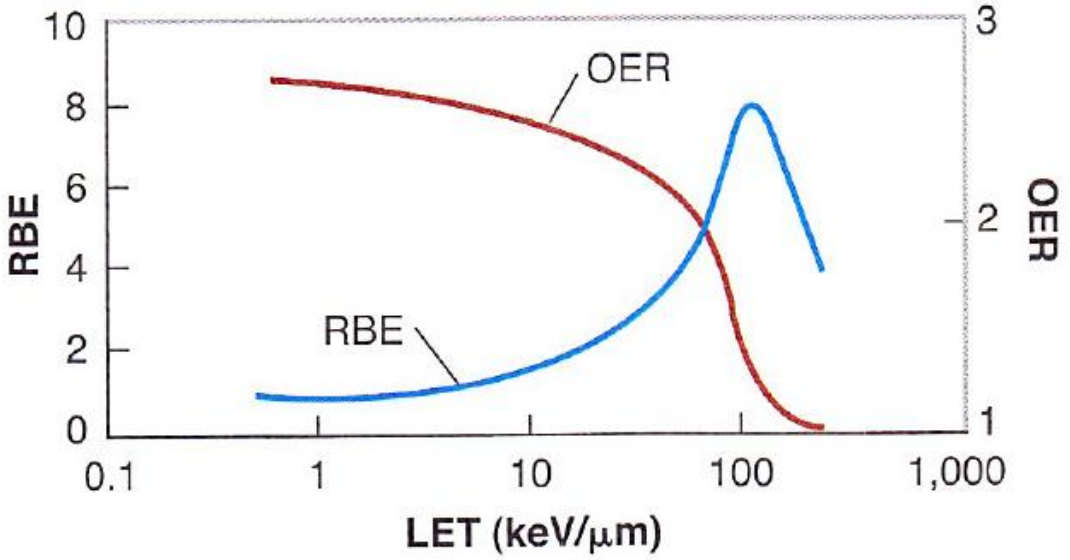


Hall & Giaccia „Radiobiology for the Radiologist“

Hypoxia: Oxygen enhancement ratio (OER)



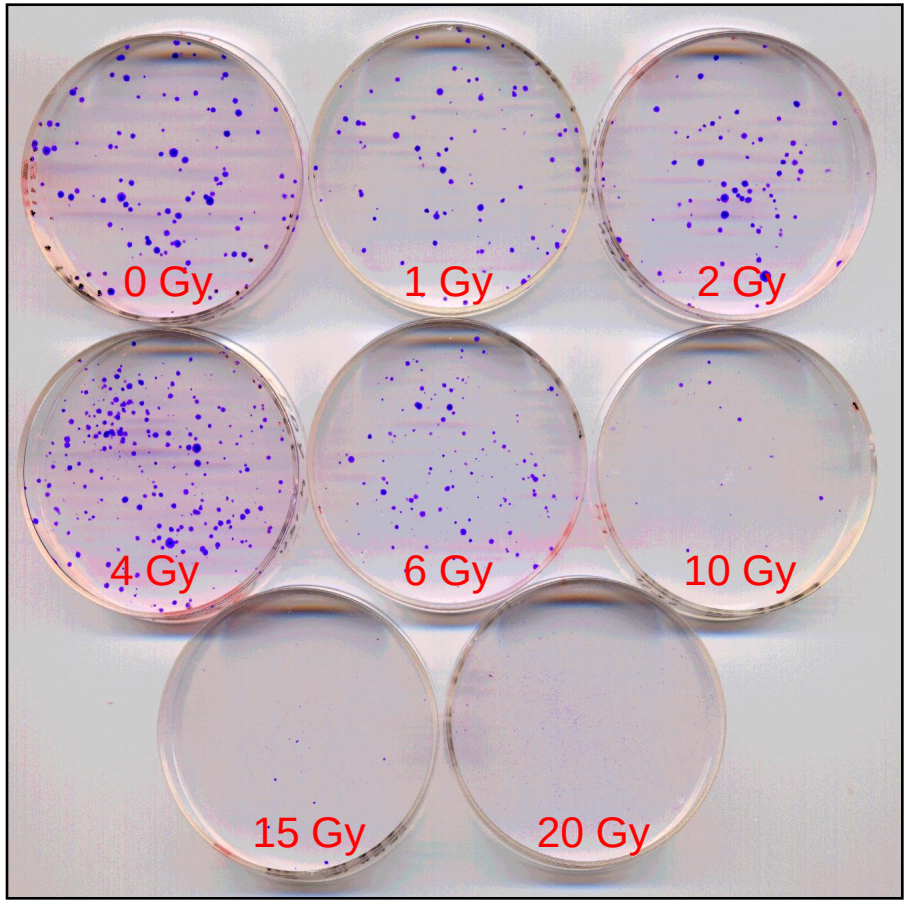
⇨ OER within the Bragg peak lower as in the entrance channel

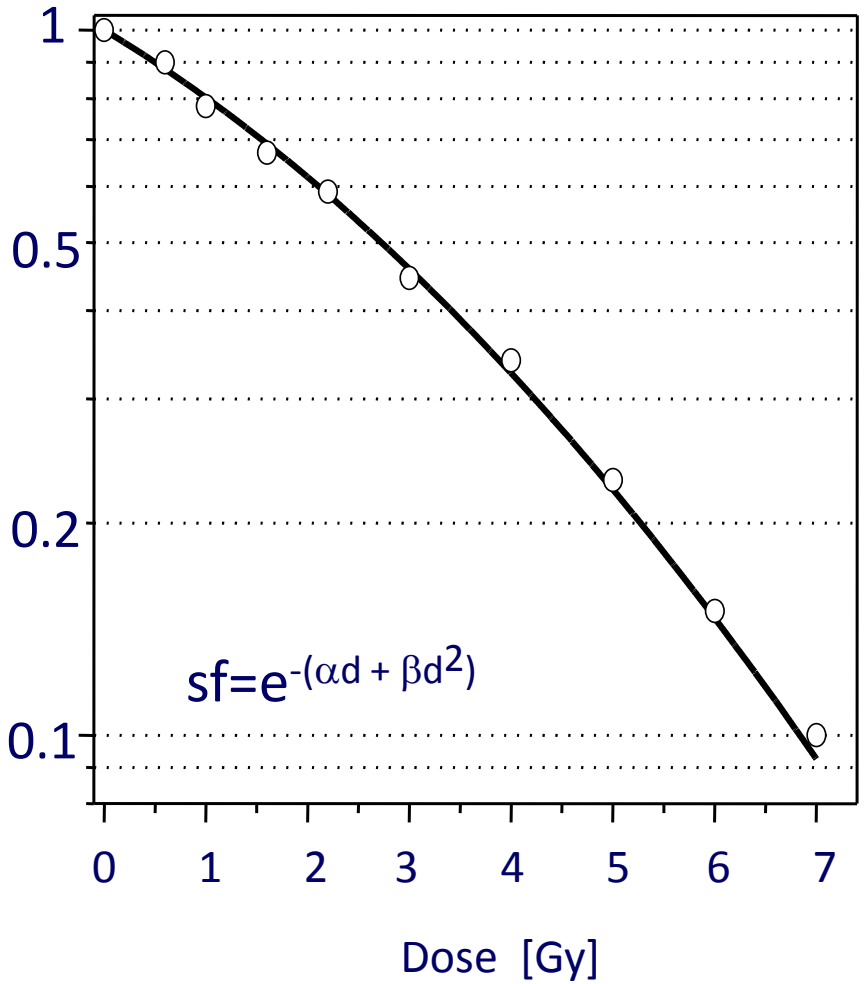


Barendsen (1968, 1972); Hall & Giaccia „Radiology for the Radiologist“

Relative biological effectiveness (protons): Preclinical models

Clonogenic cell survival in vitro





L.A. Kunz-Schughart

Linear-quadratic model

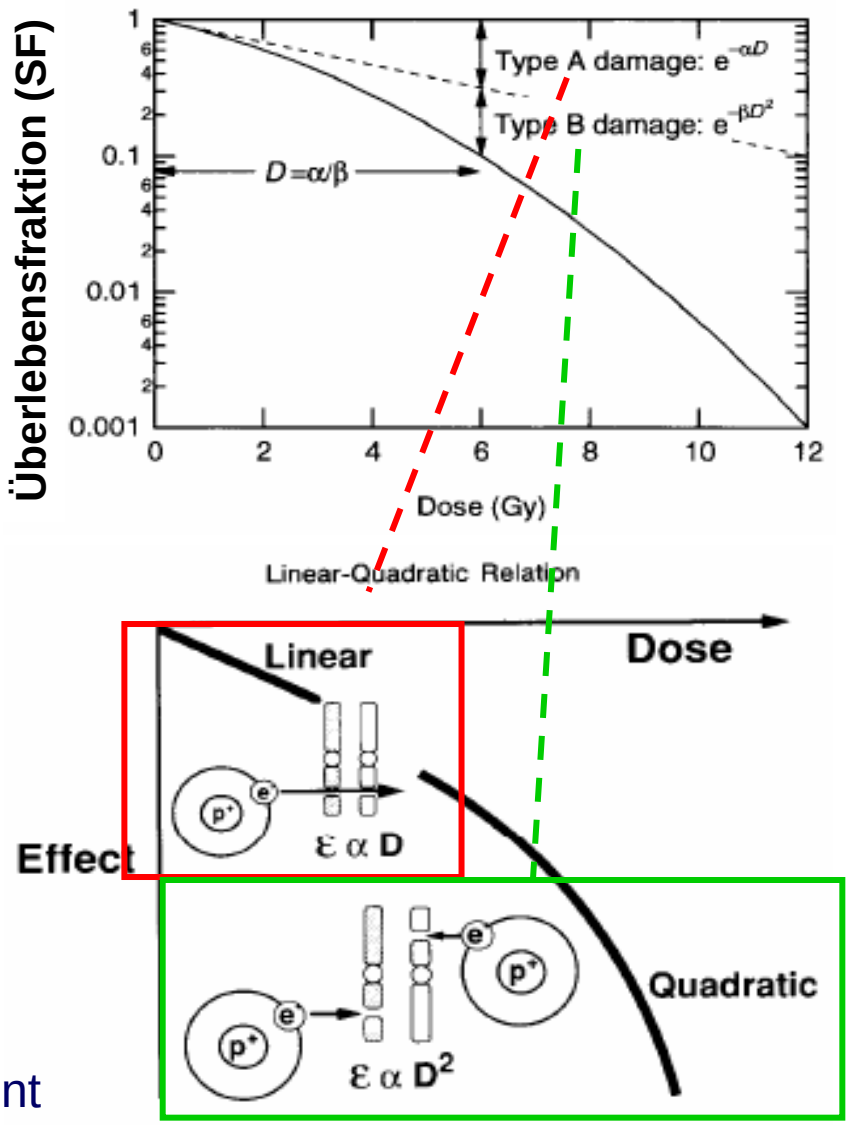
- Model assumes different DNA damages

αD:
- linear component
- 2 DSB, closed together, caused by one e-
- one-track event

→ Dicentric chromosom - LETHAL

βD^2:
- Quadratic component
- 2 DSB, closed together, caused by 2 e-
- Two-tracks-event

→ Subletalhal damage (NOT LETHAL)



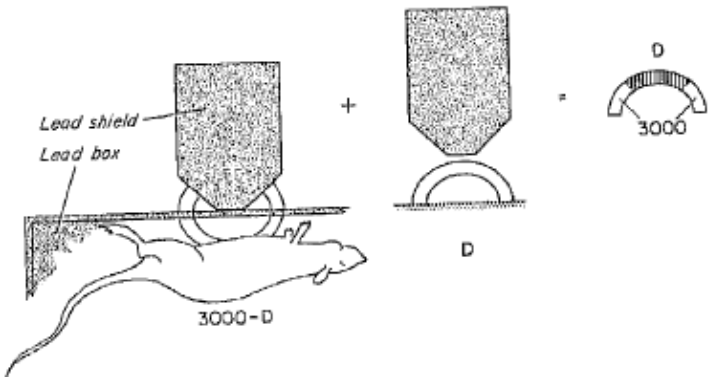
Cell survival curves steeper with higher LET
i.e. higher α/β due to higher α/ lower β component
i.e. more lethal lesions/ lower likelihood of correct repair

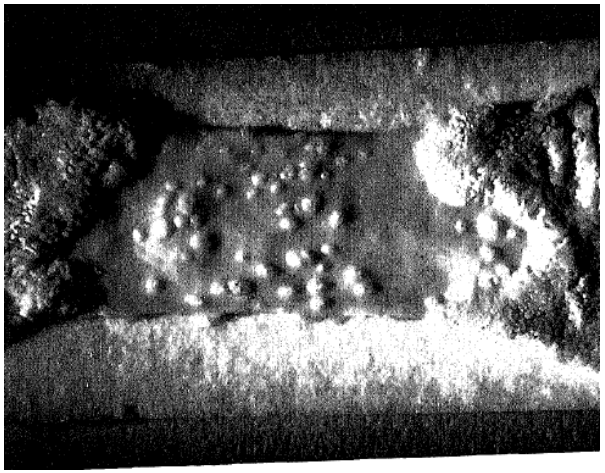
Kellerer & Rossi, 1973; Hall, 2000

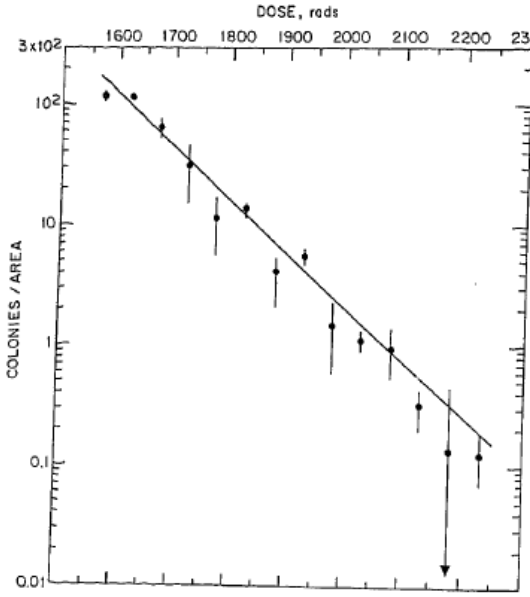
Relative biological effectiveness (protons): Preclinical models
Jejunal crypt assay

RBE = isoeffective ^{60}Co dose/ particle dose

Original:







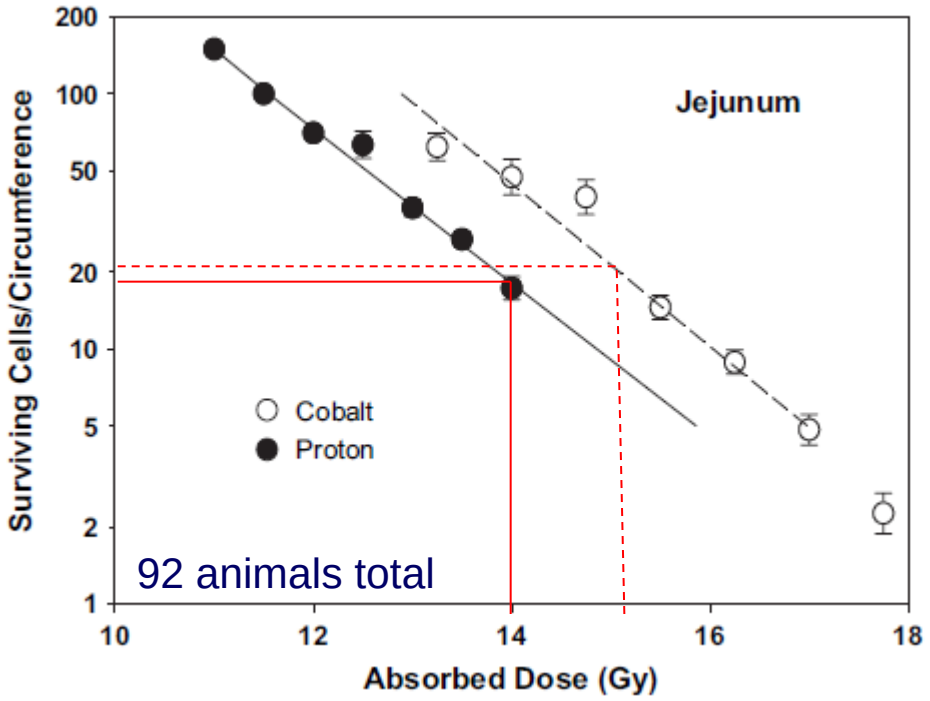
- Intestinal or whole body irradiation, graded doses
- count of surviving colonies in crypts
- estimation of e.g. D_0 (dose to reduce survival to e^{-1} =37%
- (time point for evaluation can differ with kind of treatment, i.e. speed of recovery)

Withers & Elkind, Rad Res 38, 598-613, 1969

Relative biological effectiveness (protons): Preclinical models

Jejunal crypt assay

Jejunal crypt assay, protons vs ^{60}Co



	Absorbed dose (Gy)		
Surviving cells (*n*)	Cobalt	Proton	RBE*
100	12.89	11.55	1.12
50	13.84	12.54	1.10
20	15.09	13.86	1.09
10	16.03	14.86	1.08
5	16.98	15.86	1.07

RBE = isoeffective ^{60}Co dose/ particle dose

Mason et al., IJROBP 68, 968-70, 2007

Relative biological effectiveness (protons): Preclinical models
Alternative normal tissue assays

RBE = isoeffective ^{60}Co dose/ particle dose

- Acute mucositis after tongue irradiation (mice): evaluation of ulceration
- Acute cystitis after pelvic irradiation (mice): evaluation of bladder capacity
- Late fibrosis after leg irradiation: leg contraction assay (mice or rats)
- Lung fibrosis after hemi-thoracal irradiation (rats or pigs) – imaging/ staining and breathing frequency
- Late myelitis after irradiation of a defined part of the spine

…

Important for all:

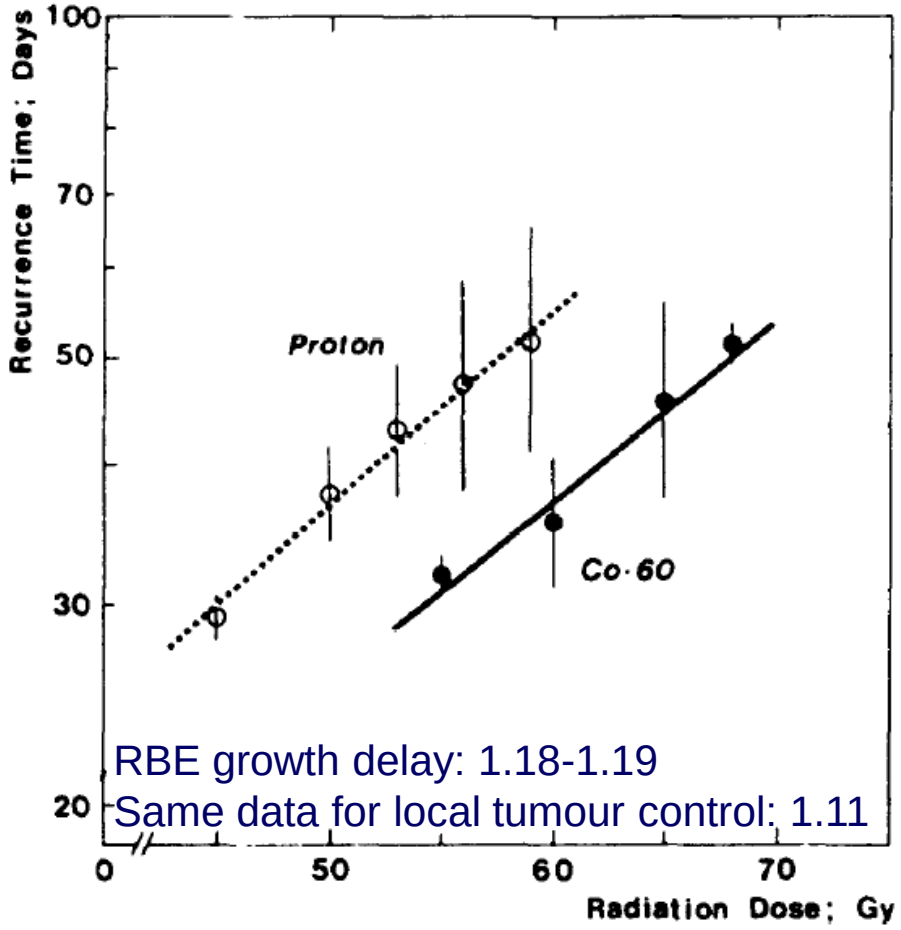
- Graded irradiation doses
- For fractionated irradiation: top-up assays (as RBE may change with dose per fraction)
- Endpoint: ED_{50} (dose that leads to a defined effect, e.g. ulceration, in 50% of the animals)

Withers & Elkind, Rad Res 38, 598-613, 1969

Relative biological effectiveness (protons): Preclinical models

In vivo tumour assays

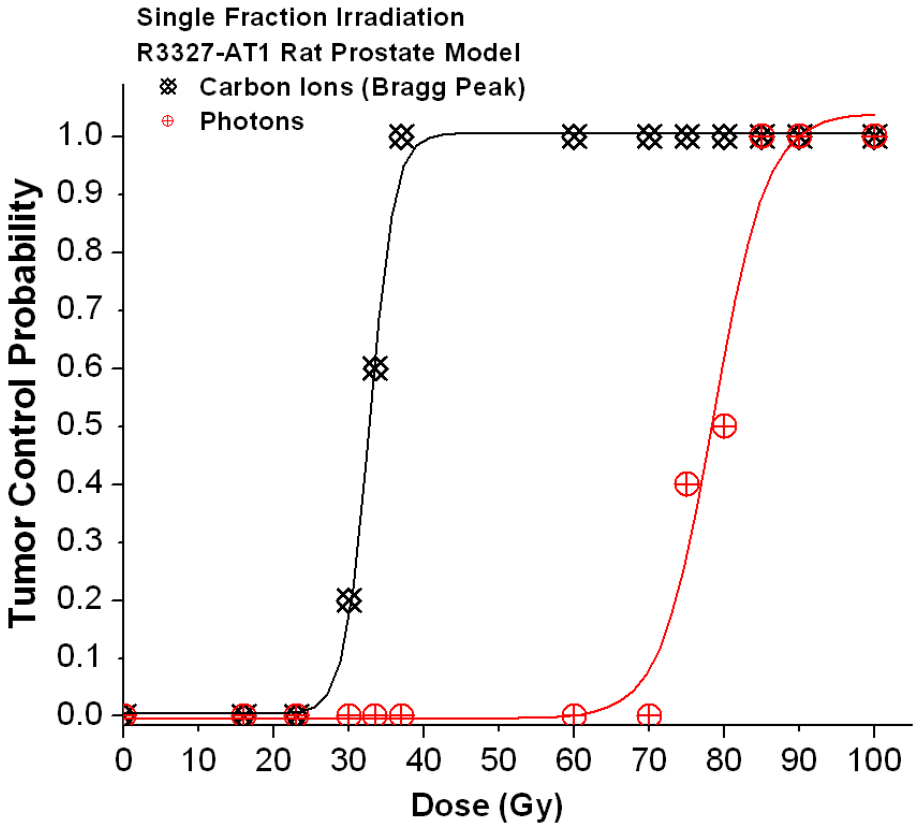
Tumour growth delay, graded doses



RBE growth delay: 1.18-1.19

Same data for local tumour control: 1.11

Local tumour control

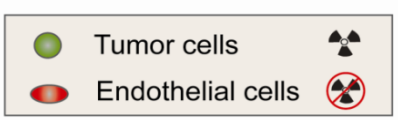


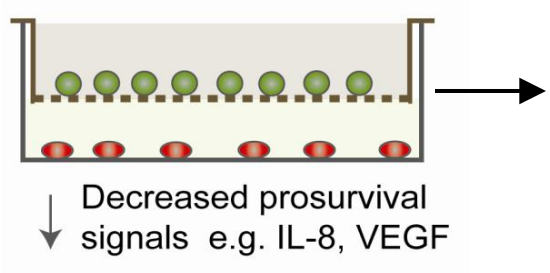
Always use different radiation doses to test the dose effect (also when growth delay is evaluated)

 Urano et al., IJROBP 10, 09-14, 1984 Karger et al., IJROBP 79, 239-46, 2011

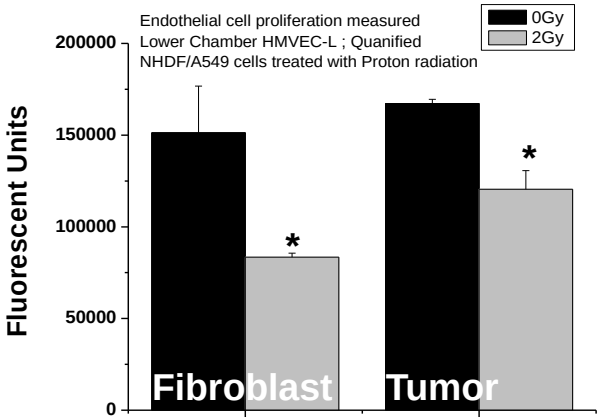
Beyond biological basis: molecular effects (examples)

Paracrine Effects on Endothelial Cell Proliferation after Proton vs. Photon in co-culture assay



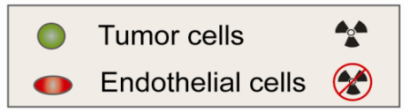


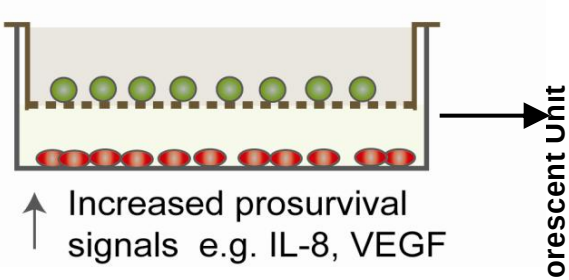
Endothelial cell proliferation

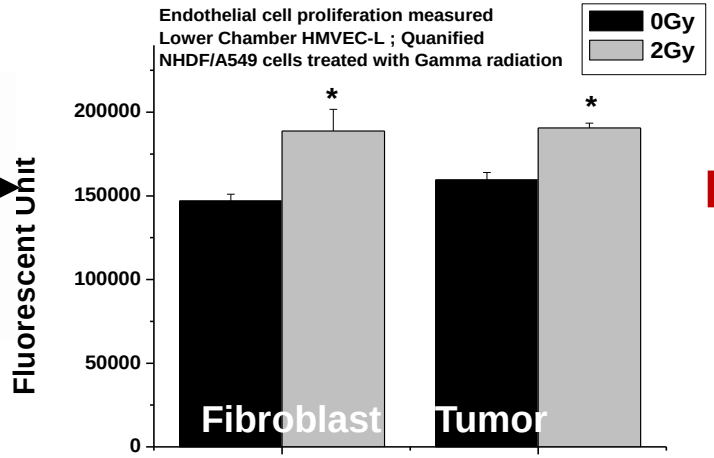


Proton

Photon



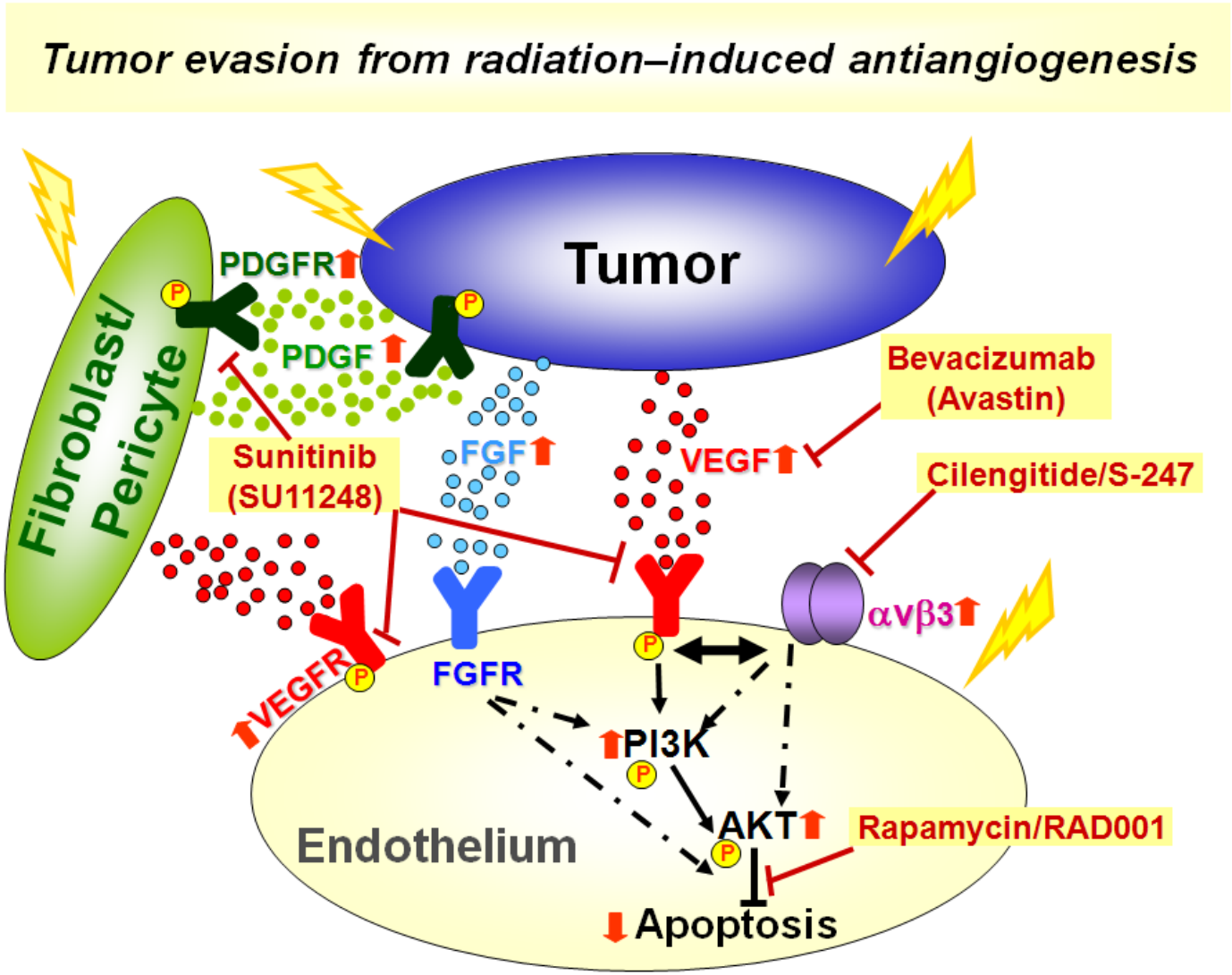




Photon

Girdhani et al. Rad Res. 2012

Different molecular effects may cause differential responses to combination approaches



Adapted from Abdollahi & Folkman DRU 2010

Further research fields/ open questions

- Dependence of RBE on tissue, dose per fraction, particle type, proton/ particle energy – still very heterogeneic data
- Differences in molecular/ genetic responses
- Differences in response to combined treatment regimens
- Different response of CSC/ non-CSC or migration
- …

Table 1 | Radiobiological advantages of heavy ion therapy

Effects	Bragg curve region		
	Plateau	Peak	Potential advantages
Irradiated tissue	Normal tissue	Tumor	NA
Energy	High	Low	NA
Linear energy transfer	Low	High	NA
Dose	Low	High	Highly conformal therapy
Relative biological effectiveness	~1	>1	Effective for radiotherapy-resistant tumors
Oxygen enhancement ratio	~3	<3	Effective against hypoxic tumor cells
Cell-cycle dependence	High	Low	Increased lethality in the target volume because cells in radiotherapy-resistant (S) phase are sensitized
Fractionation dependence	High	Low	Fractionation spares normal tissue more than the tumor
Effects on cell migration	Increased	Decreased	Potential reduction of tumor metastatic potential
Angiogenesis	Increased	Decreased	Potential reduction of angiogenesis in the tumor

Abbreviation: NA, not applicable.

Durante & Loeffler, Nat Rev Clin Oncol 7, 37-43, 2010