

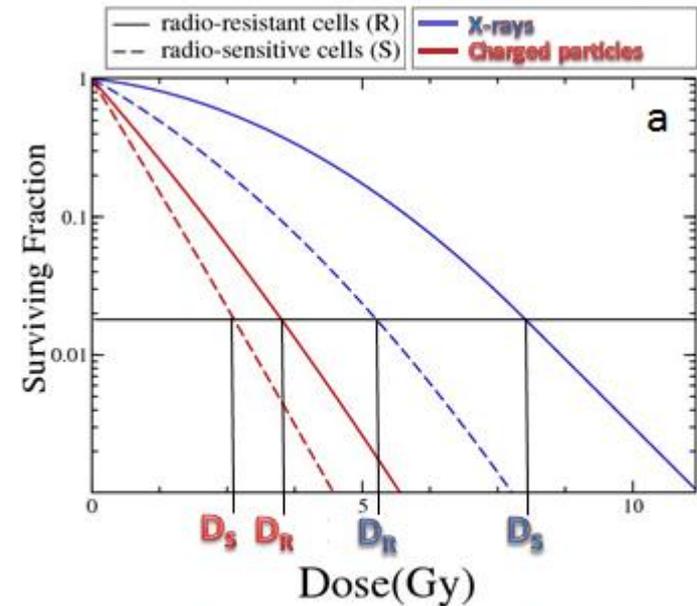
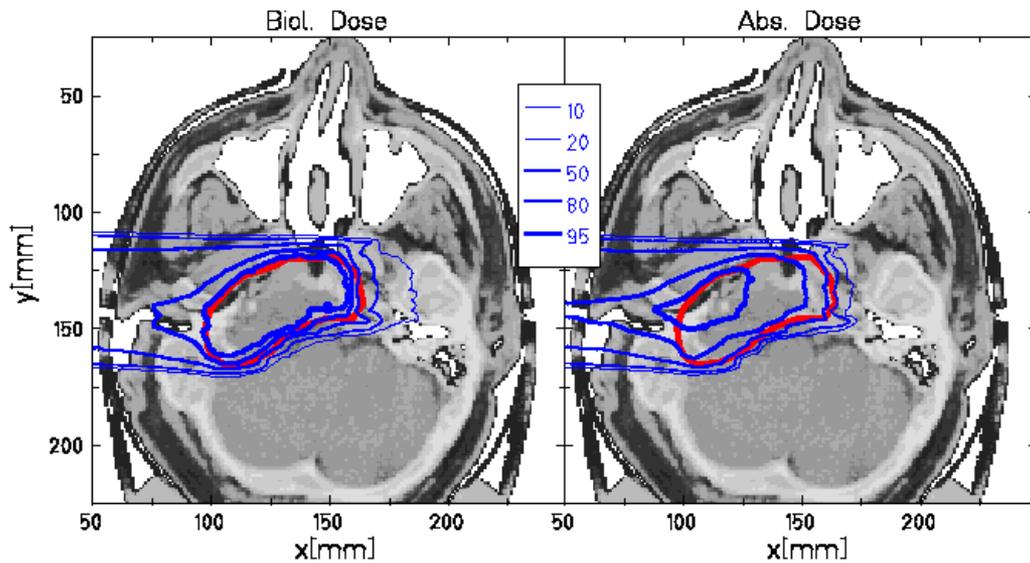
In vitro RBE

Marco Durante



ICTR-PHE meeting, Geneva, 18.2.2016

RBE: a power for particle therapy, and a source of uncertainty

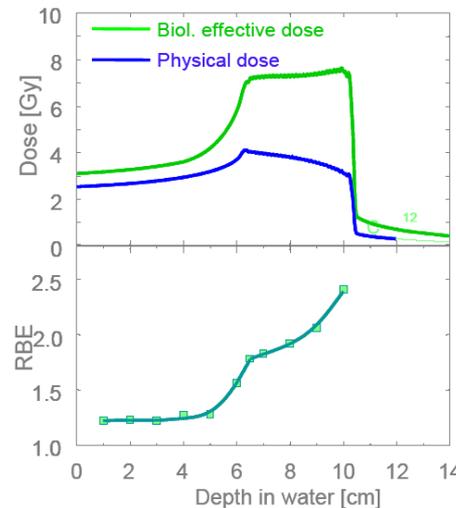


$$RBE_R = \frac{D_R(\text{photons})}{D_R(\text{ions})} > RBE_S = \frac{D_S(\text{photons})}{D_S(\text{ions})}$$

Overcoming resistance of cancer stem cells

www.thelancet.com/oncology Vol 13 May 2012

TRiP98,
courtesy of M.
Krämer



Many experiments over 50 years

Data collection of cell survival experiments with ion beams

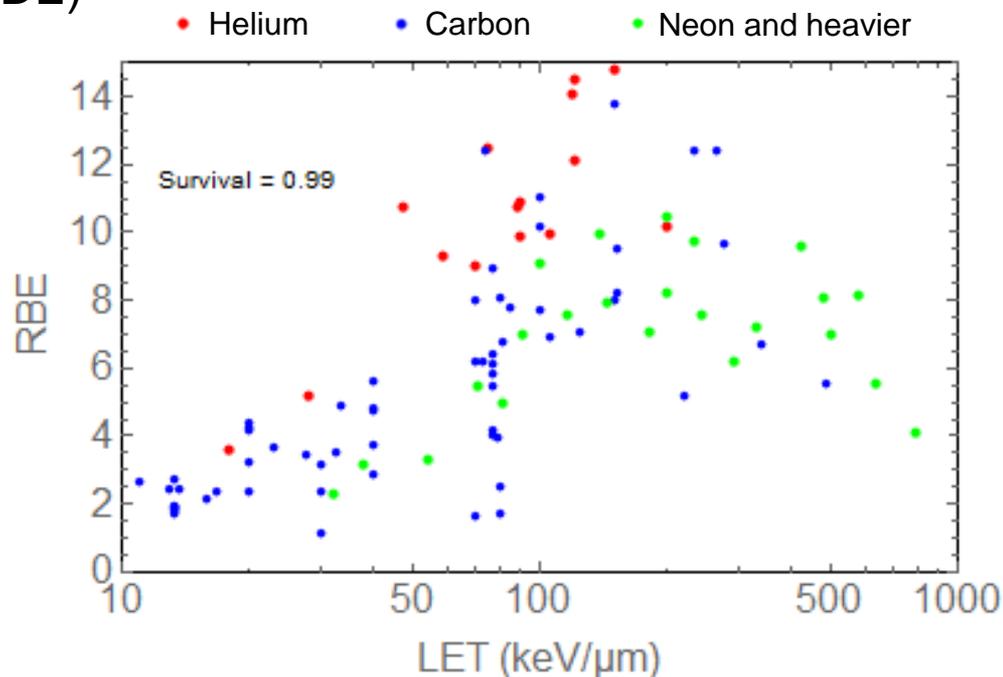
Particle Irradiation Data Ensemble (PIDE)

Collection:

- 845 pairs of cell survival curves (photons and ions)
- from 74 publications
- enhancement on the way including raw data

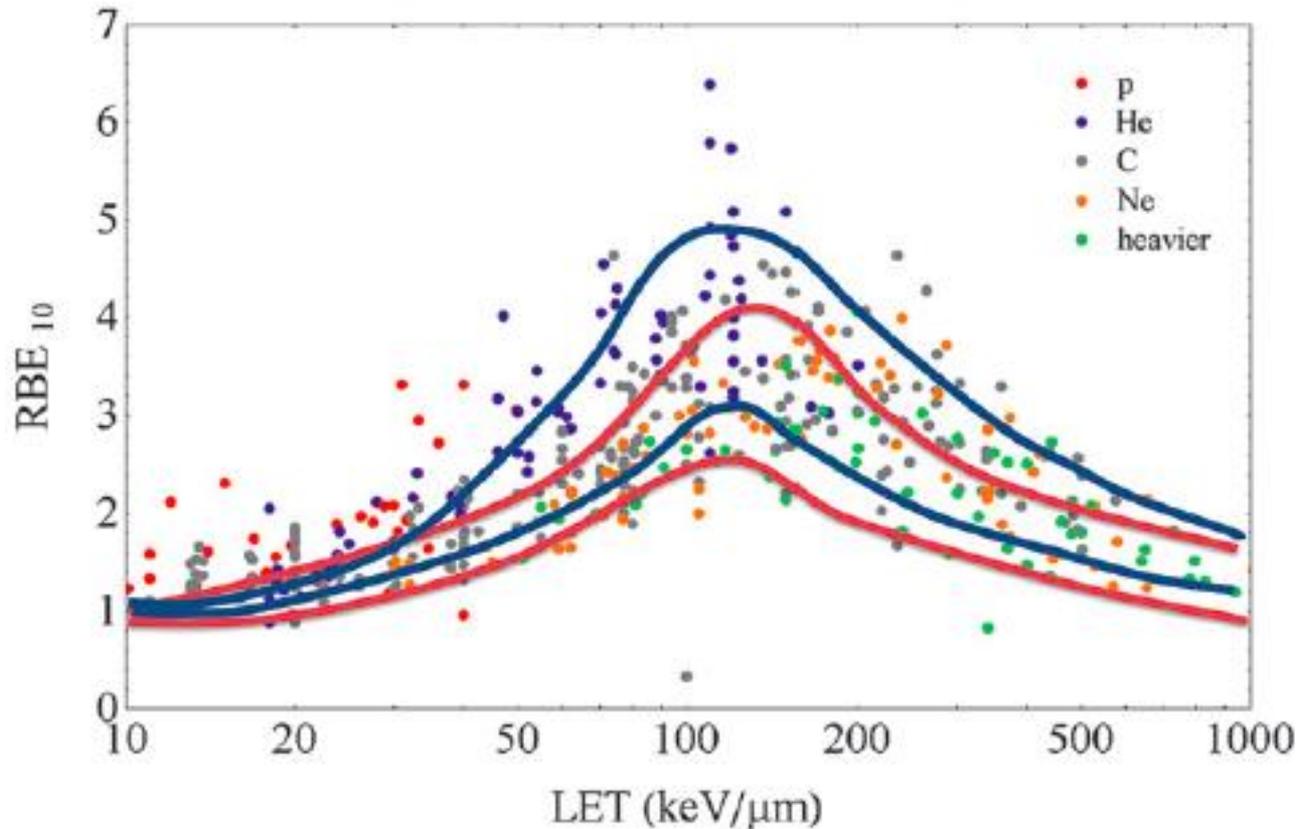
PIDE features experiments with:

- sensitive / resistant cells
- different ions, LETs, energies
- normal / tumor cells



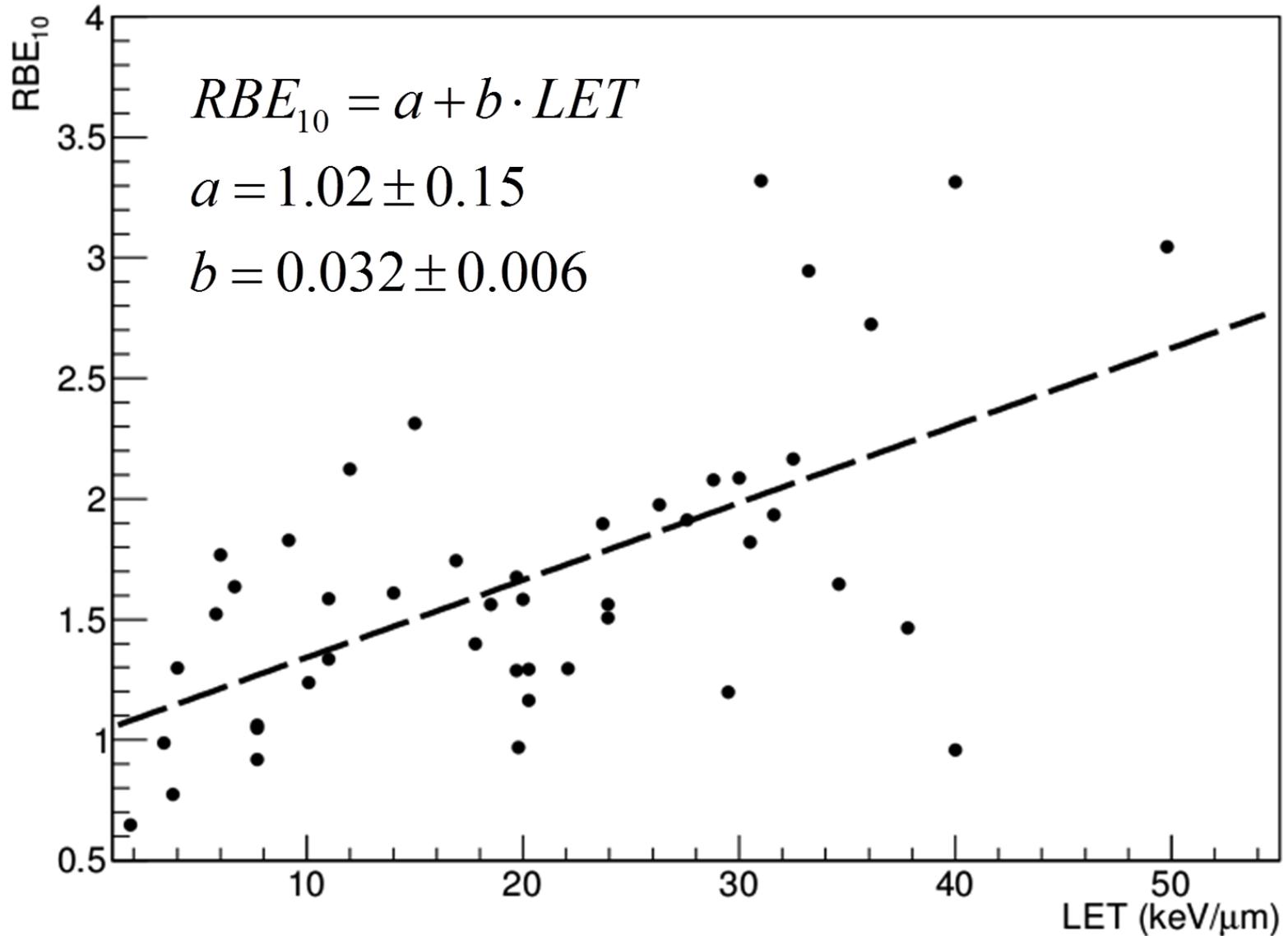
T. Friedrich, U. Scholz, T. Elsässer, M. Durante, M. Scholz: *Systematic analysis of RBE and related quantities using a database of cell survival experiments with ion beam irradiation*, J. Radiat. Res. **54**, 494 (2013).

RBE uncertainty is a variance



- Datapoints: PIDE database, www.gsi.de/bio-pide
- Red curves: T1 human cells, LBNL, Blakely et al. 1984
- Blu curves: V79 hamster cells, Sørensen et al. 2011

Proton RBE



Why are there so many measurements of in vitro RBE for tumor cell killing?

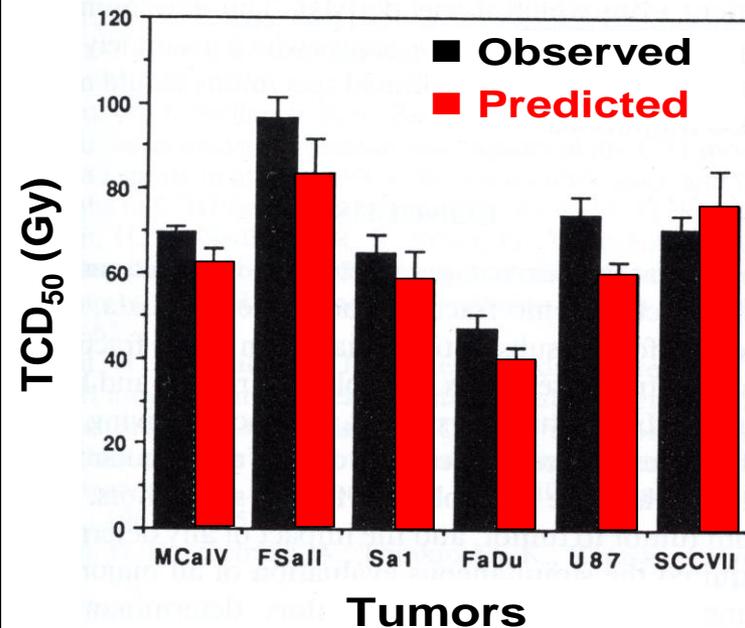
Slide from David Brenner's presentation, this meeting, Monday 15.2

1. Measure radiation-induced tumor cell killing *in vitro*
2. Use the results to predict tumor control probability *in vivo*

Similar studies...

- ✓ Reinhold & De Bree 1968
- ✓ Barendsen & Broerse 1969
- ✓ Rofstad 1989

Predicted TCD_{50} based on in-vitro cell survival, vs. observed TCD_{50}



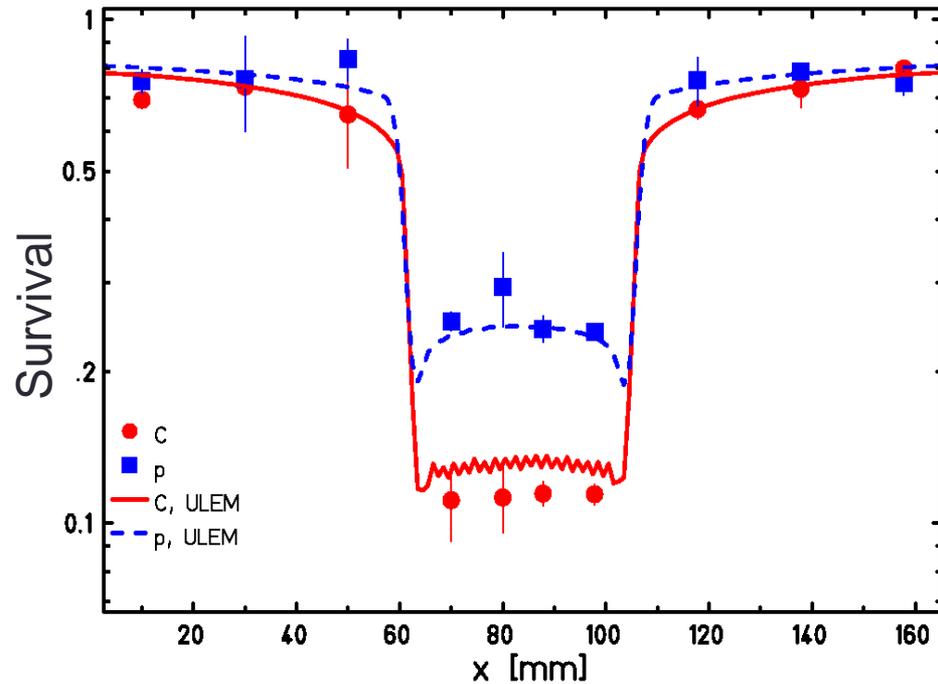
Gerweck, Zaidi & Zietman, 1994

There have been many laboratory studies to test the standard model, that tumor control is related primarily to direct radiation killing of tumor clonogens

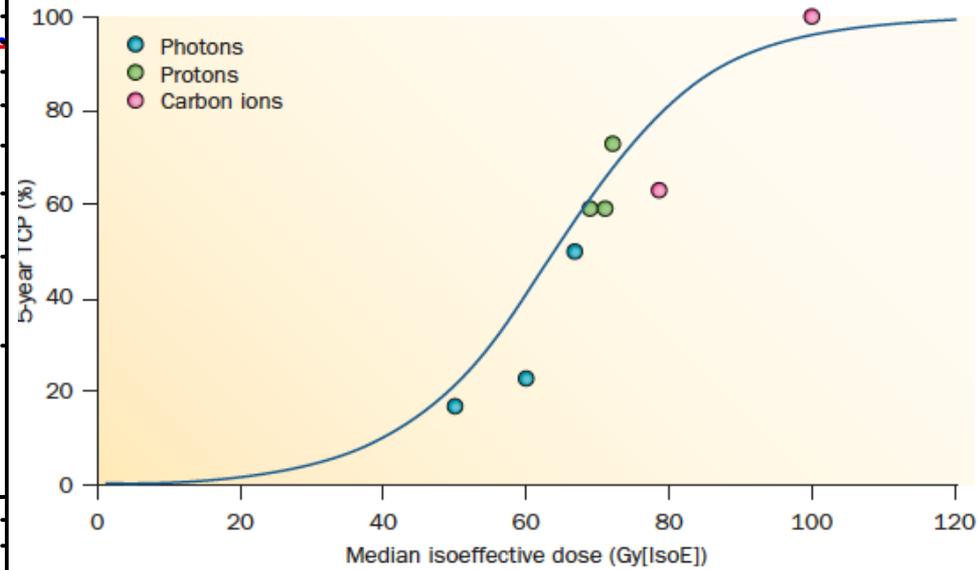
Biophysical models in clinics (if used...) are all based on in vitro RBE for cell killing

Center	Model
All protontherapy centers	RBE=const.=1.1
Europe (HIT, CNAO, MedAustron)	LEM
NIRS (scanning)	MKM
Japan (NIRS/HIBMC/GHMC/SAGA-HIMAT) passive modulation	Kanai model
SPHIC	LEM
Lanzhou	RBE=const.=1
LBNL (all ions)	LQ model

...and models work....



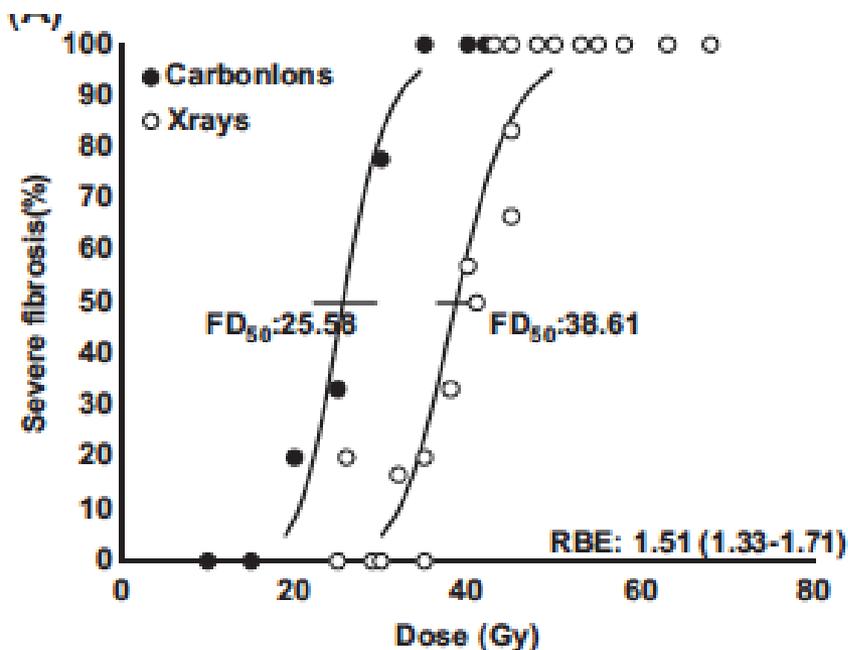
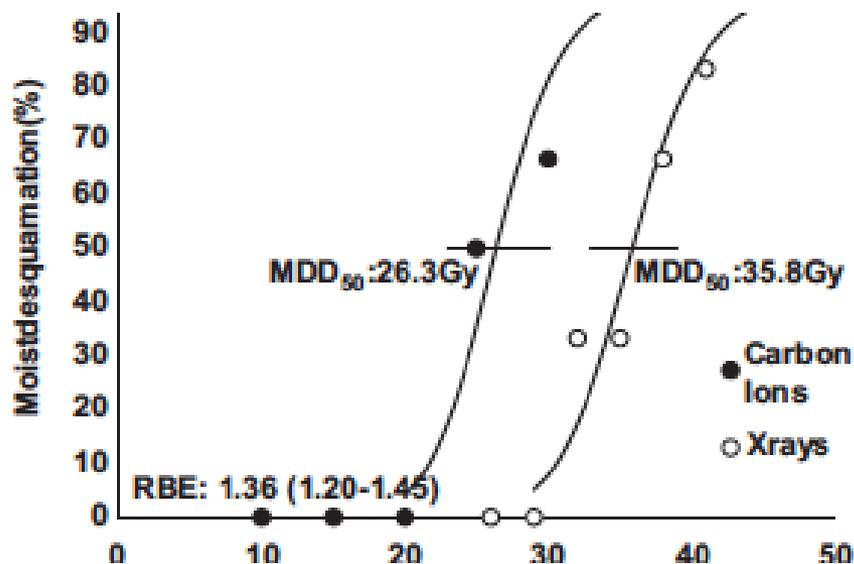
Experimental data: CHO cells
LEM IV: Elsässer et al, IJROBP 2010



Dose escalation for skull-base chordoma, Gruen et al., Phys. Med. Biol. 2012

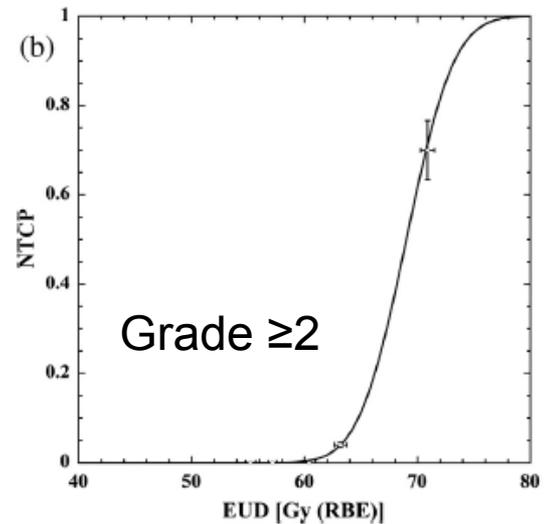
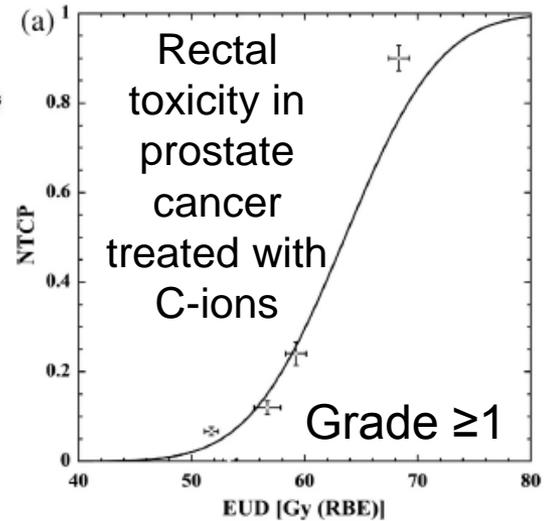
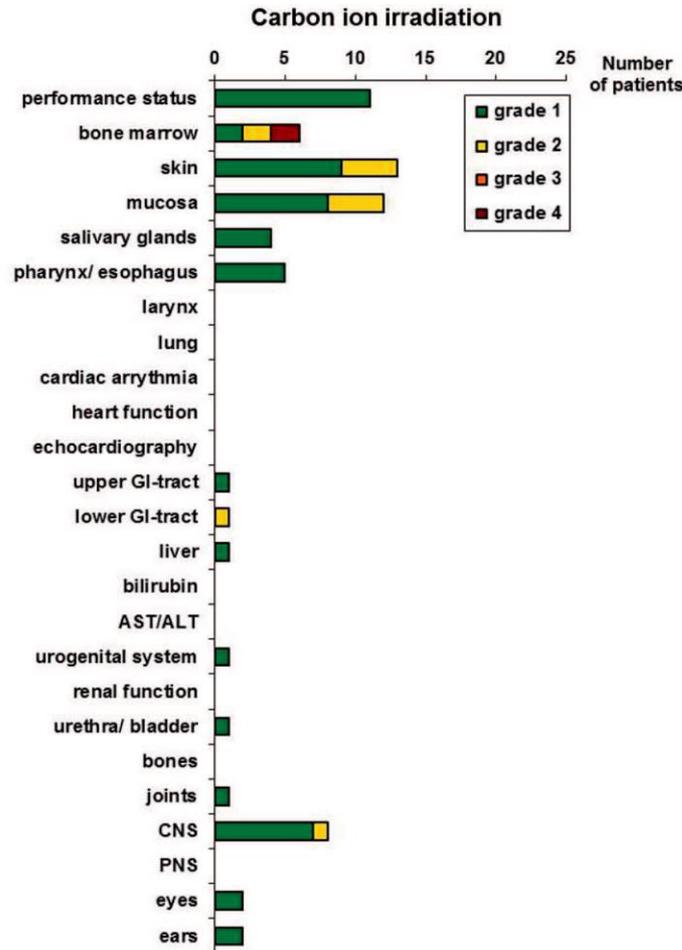
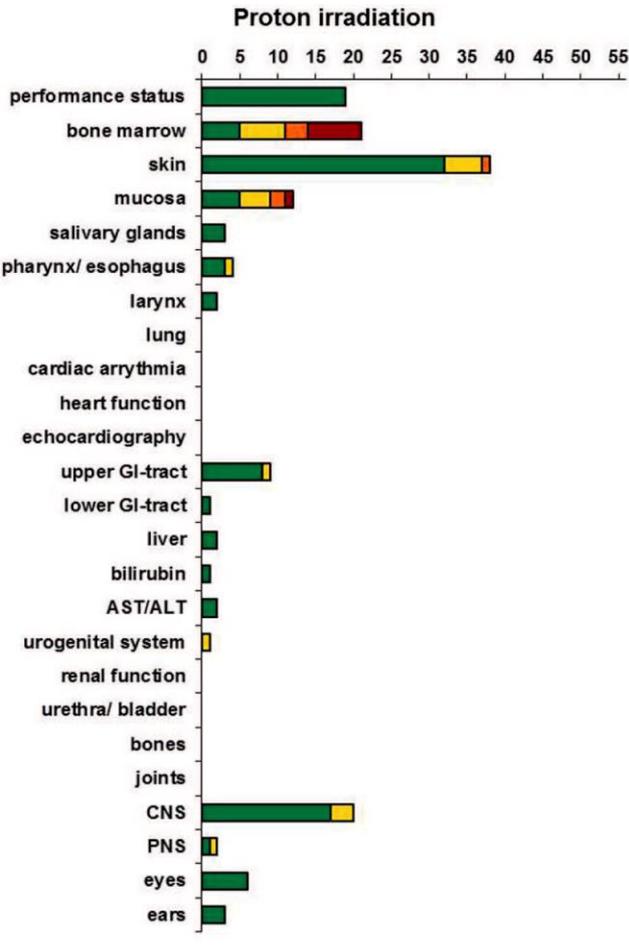
Normal tissue RBE – animal models

Measuring RBE for **normal tissue** is essential for tolerance dose – more important than tumor RBE for truly optimizing ion therapy



Acute skin reaction and late fibrosis in CDF1 mouse foot exposed to X-rays or 3 cm SOBP C-ions (Sørensen *et al.*, *Acta Oncol.* 2015) – model by LEM

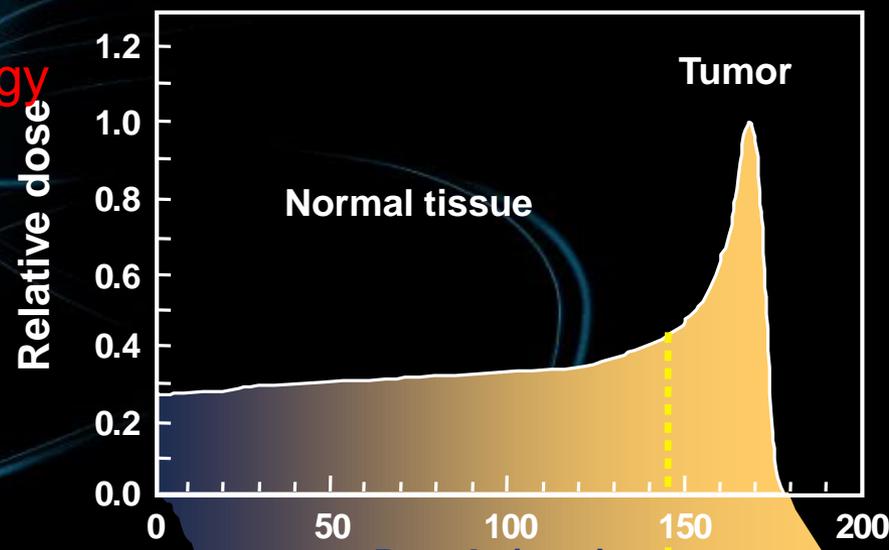
Normal tissue RBE – clinical studies



Acute toxicity in 83 pediatric patients treated at HIT with H- or C-ions (Rieber *et al.*, *Acta Oncol.* 2015)

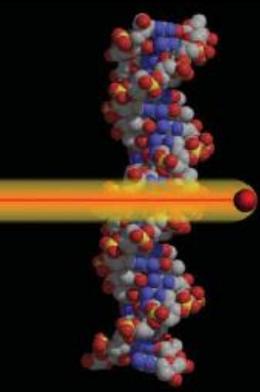
Fukahori *et al.*, *Radiother. Oncol.* 2015

New radiobiology



**Durante & Loeffler,
Nat. Rev. Clin. Oncol 2010**

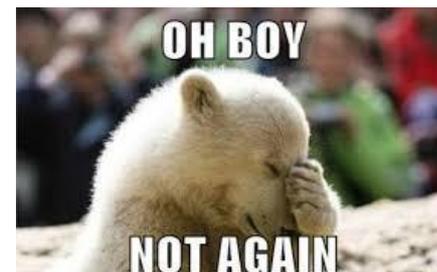
Potential advantages



	Normal tissue	Tumor
Energy	high	low
LET	low	high
Dose	low	high
RBE	≈ 1	> 1
OER	≈ 3	< 3
Cell-cycle dependence	high	low
Fractionation dependence	high	low
Angiogenesis	Increased	Decreased
Cell migration	Increased	Decreased

- High tumor dose, normal tissue sparing
- Effective for radioresistant tumors
- Effective against hypoxic tumor cells
- Increased lethality in the target because cells in radioresistant (S) phase are sensitized
- Fractionation spares normal tissue more than tumor
- Reduced angiogenesis and metastatization

In vitro RBEagain?



Yet in vitro RBE experiments remain essential to elucidate the mechanisms and plan targeted particle-specific therapies

Why are heavy ions so effective in cell killing?

A dose of 1 Gy in the cell nucleus corresponds to ~ 1000 tracks of γ -rays and to < 10 tracks of α -particles

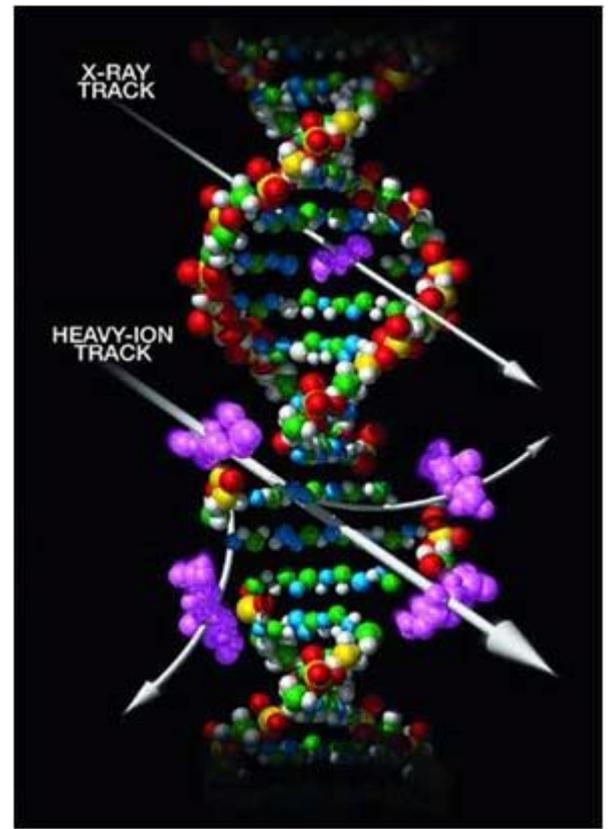
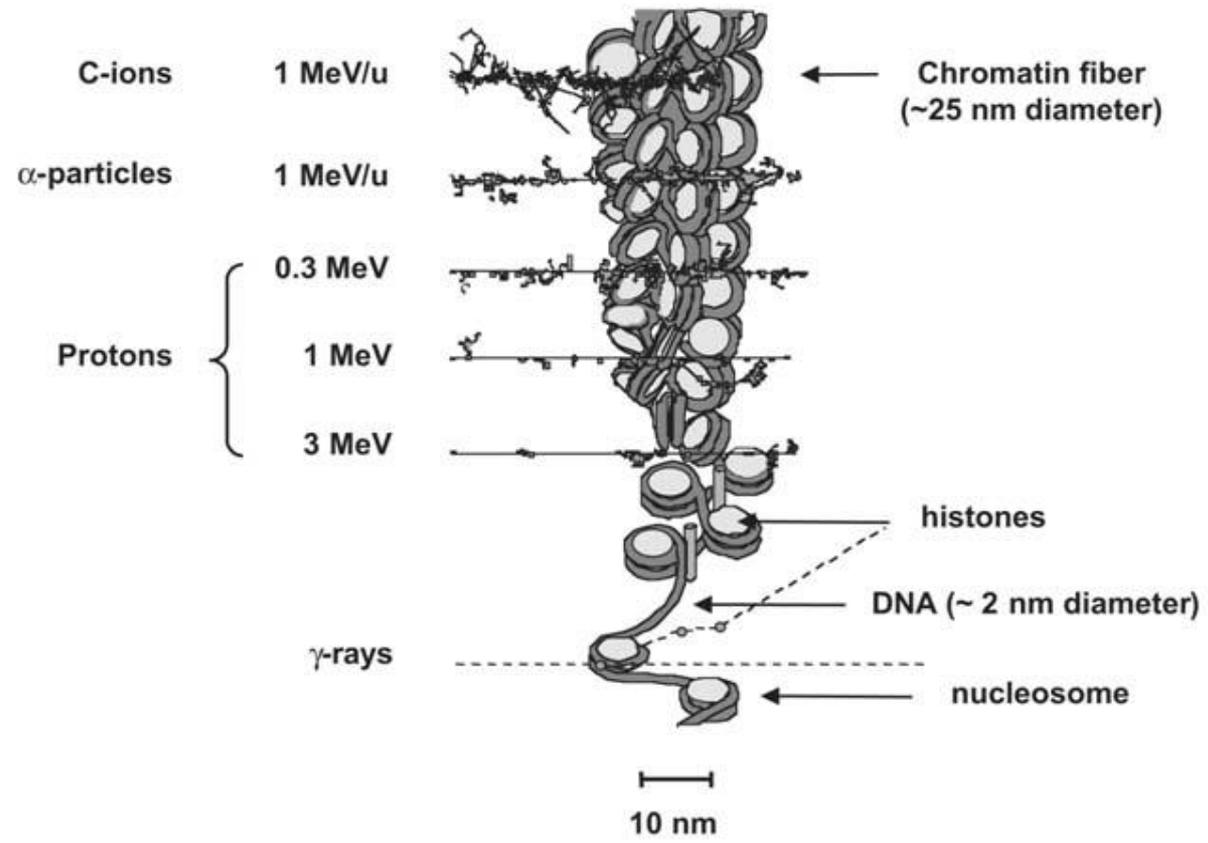
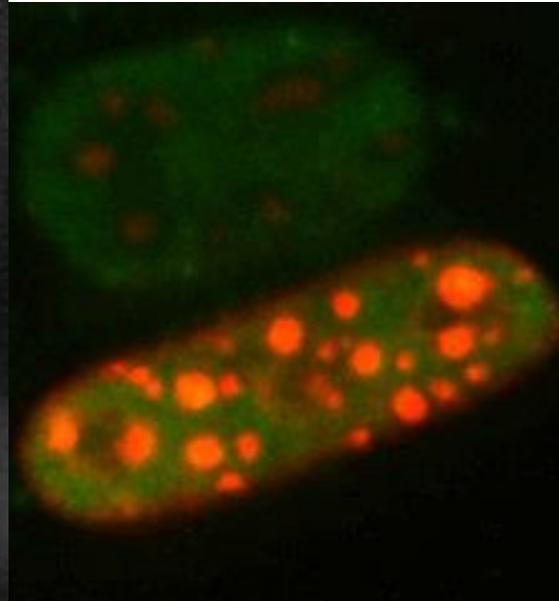
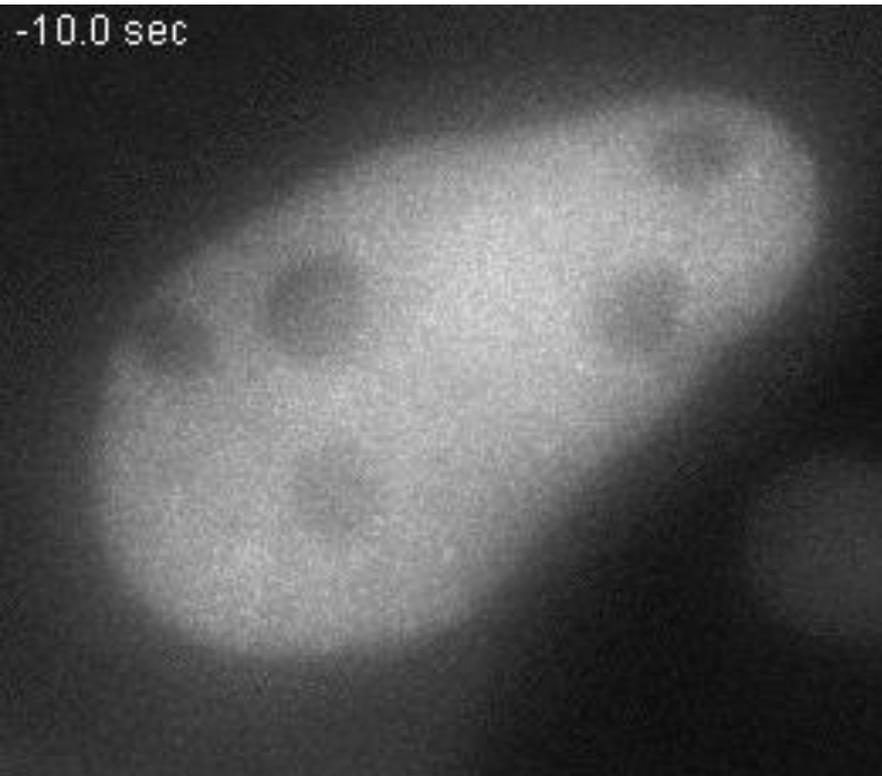


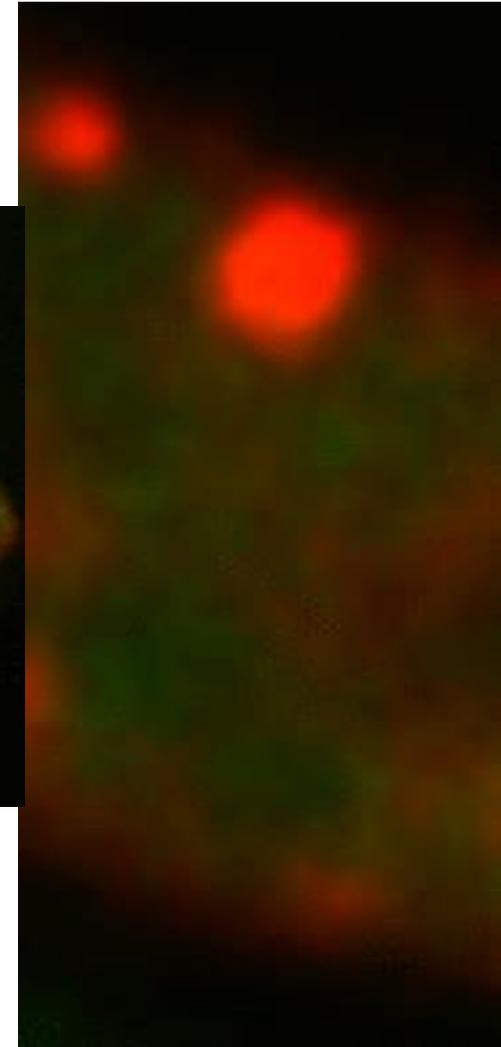
Image courtesy NASA

Live cell imaging of heavy ion traversals in euchromatin and heterochromatin

GFP-NSBS1



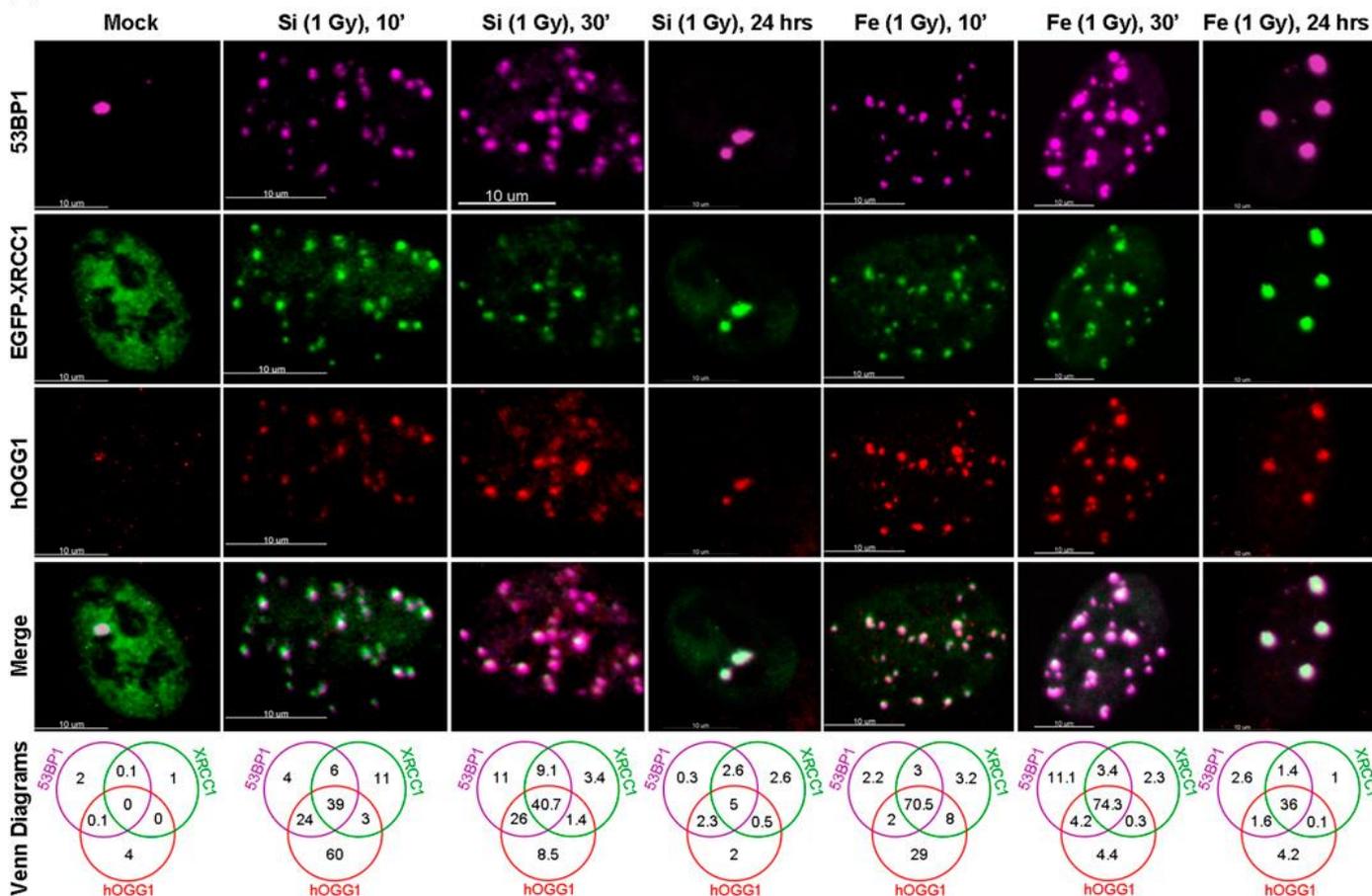
GFP-XRCC1



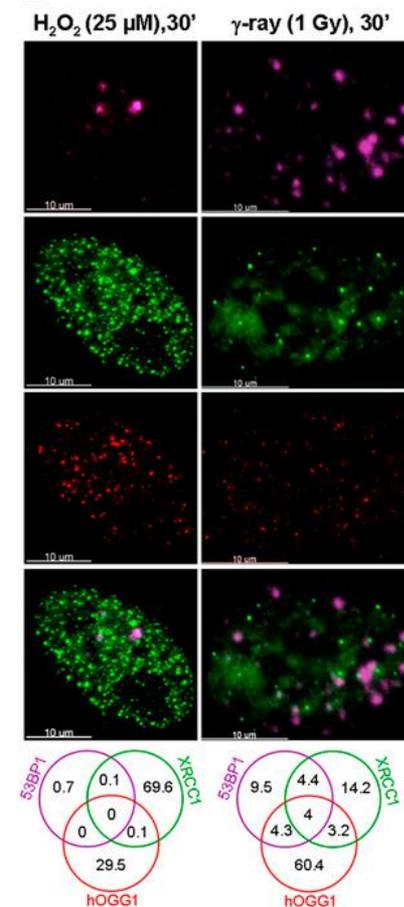
Clustered lesion induction and repair

UT Southwestern
Medical Center

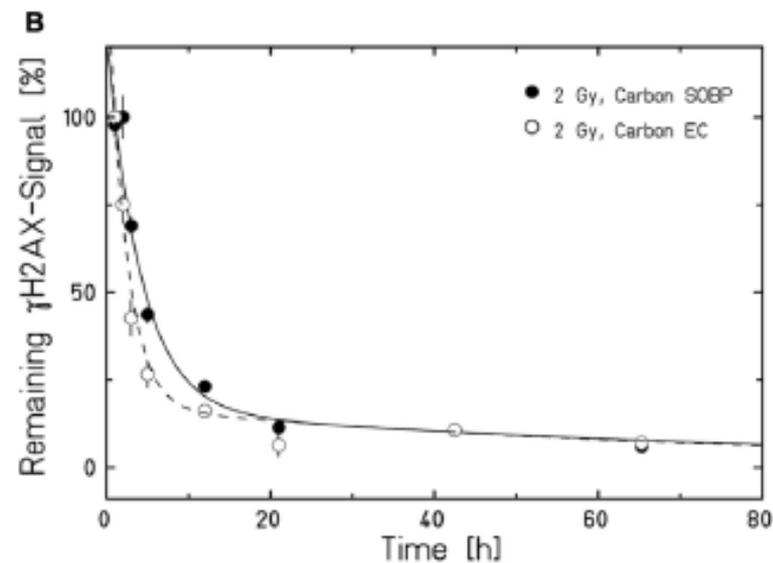
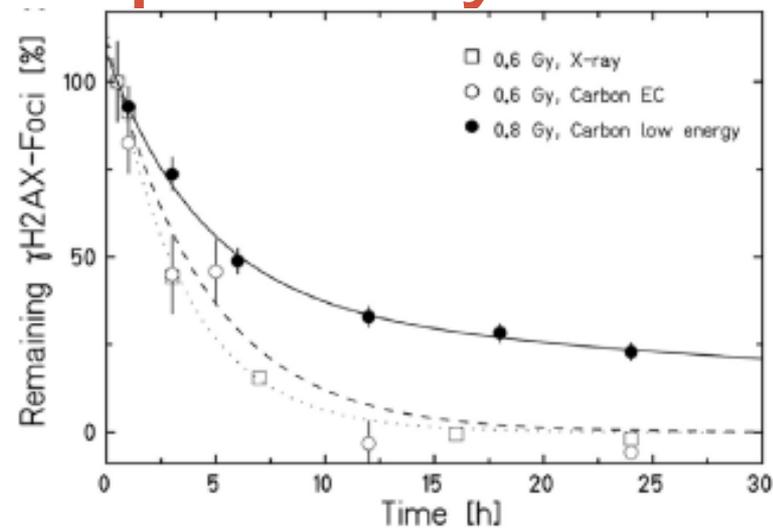
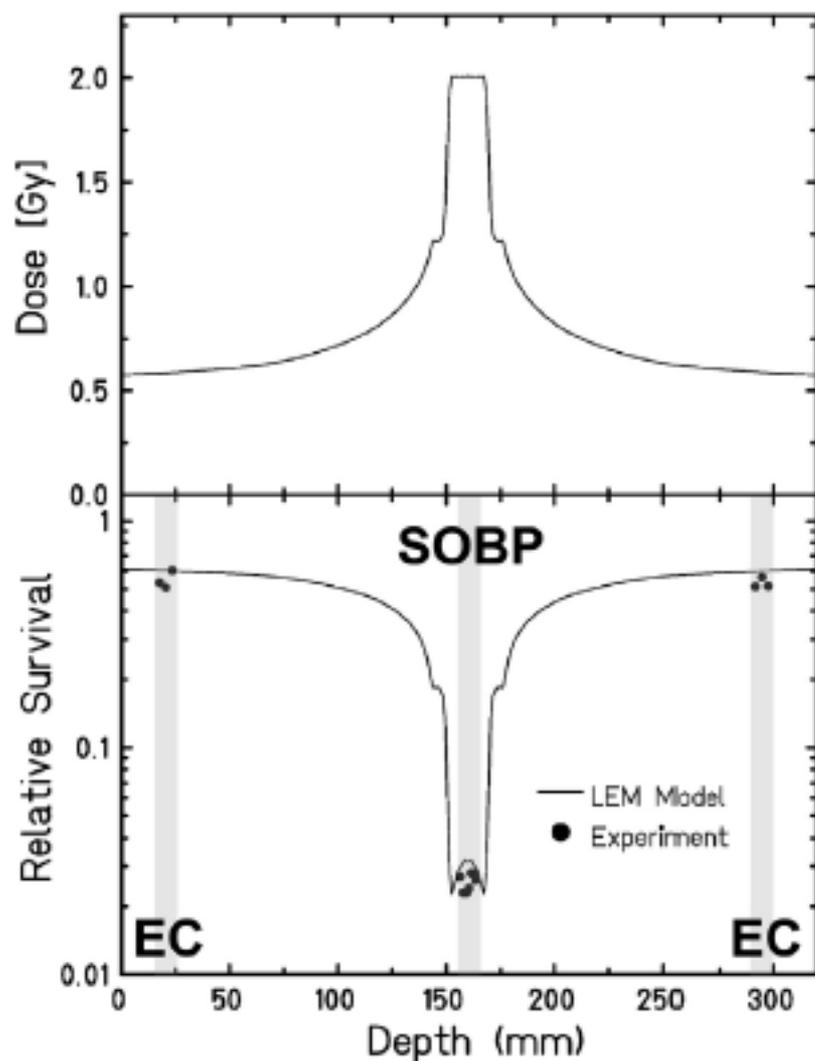
A



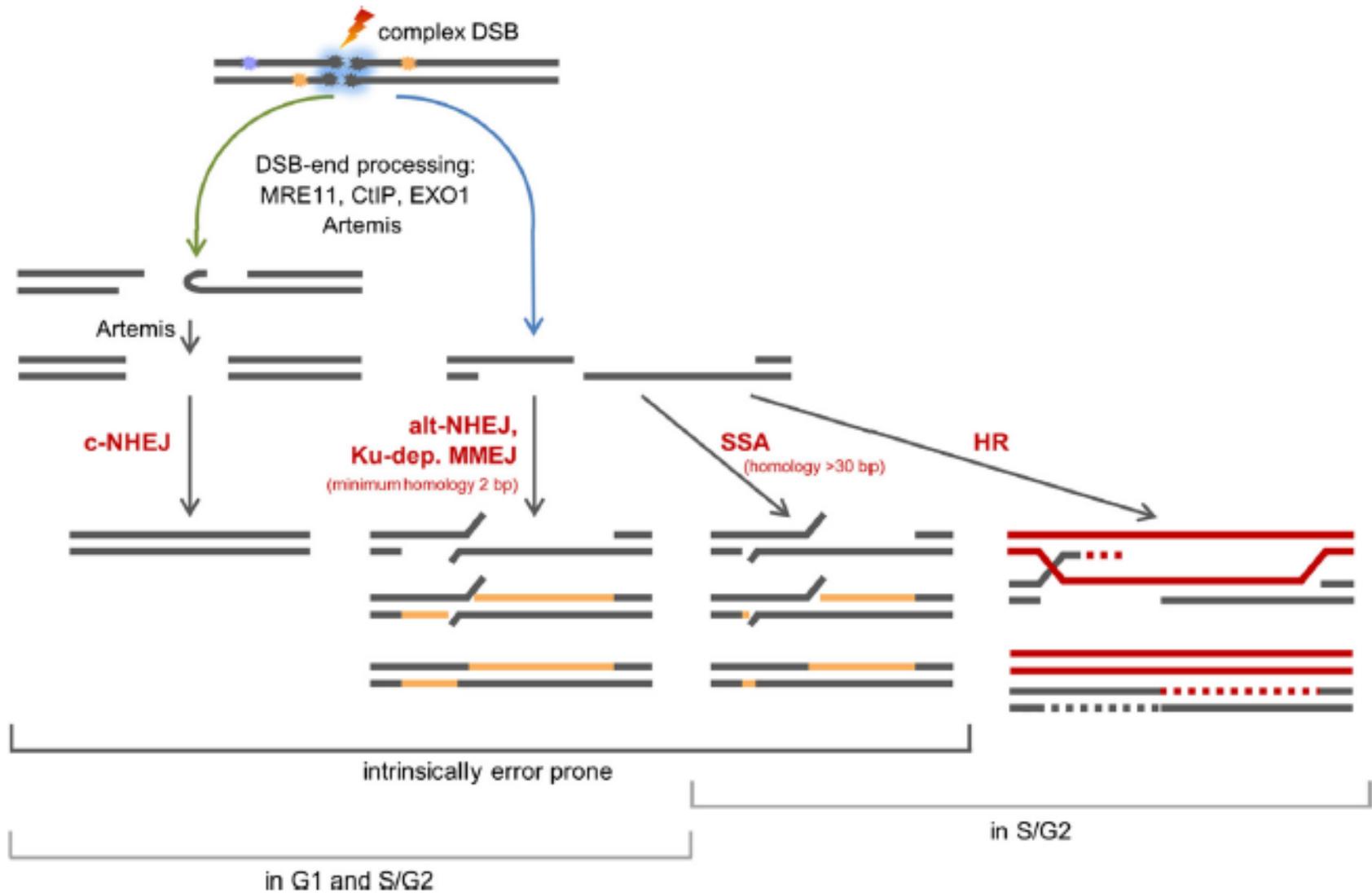
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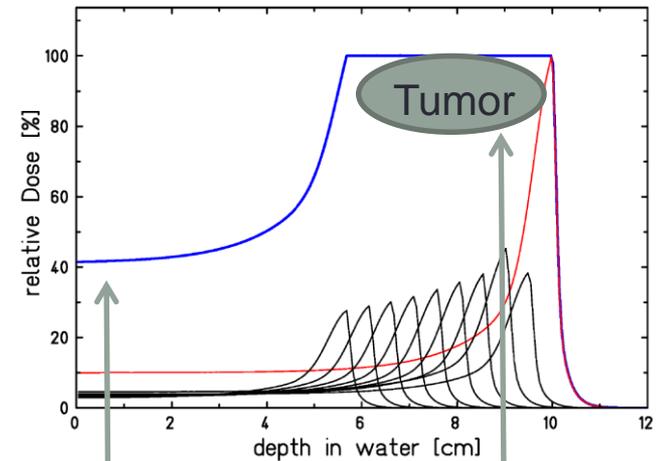
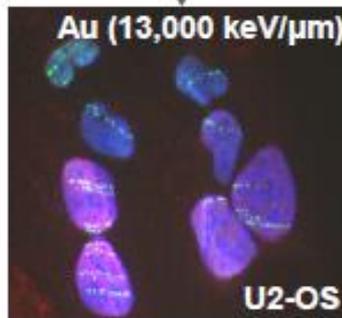
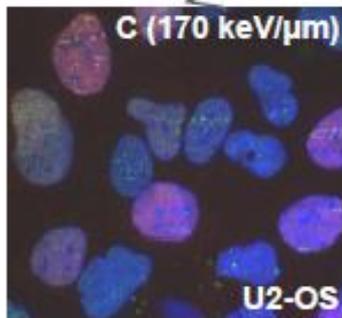
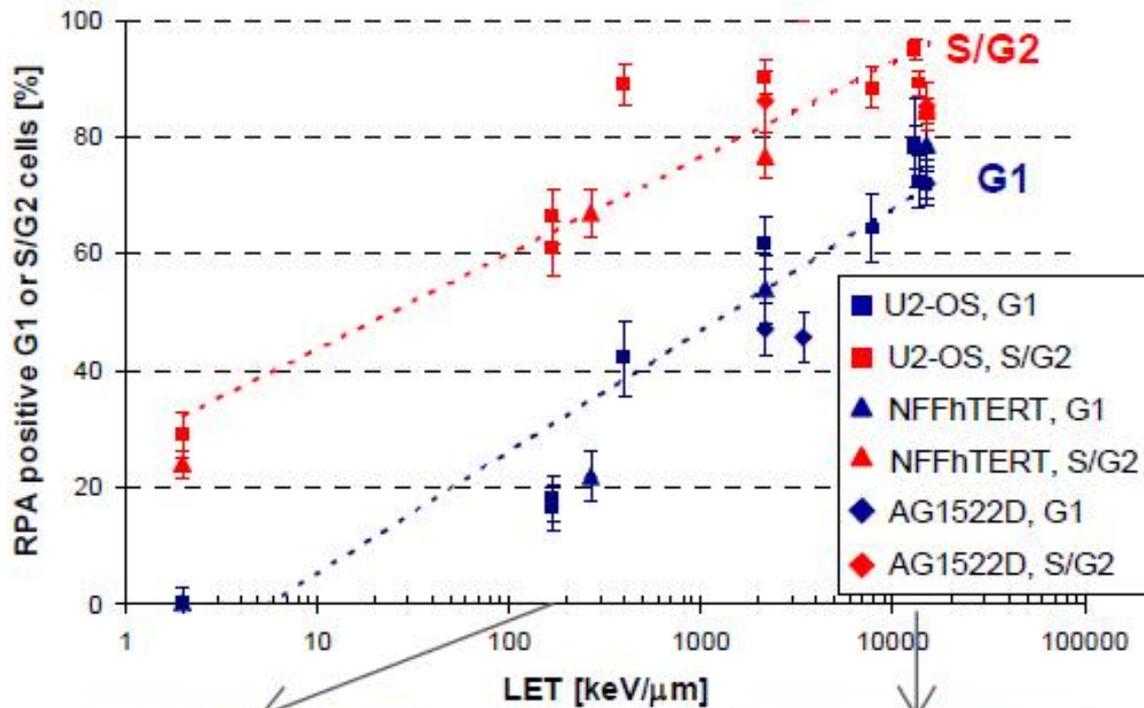
RBE and DNA repair pathway



Processing clustered DSBs



Targeting resection pathway to selective sensitization of the tumor



c-NHEJ (low-LET, G0-cells)

resection (high-LET, cycling cells)

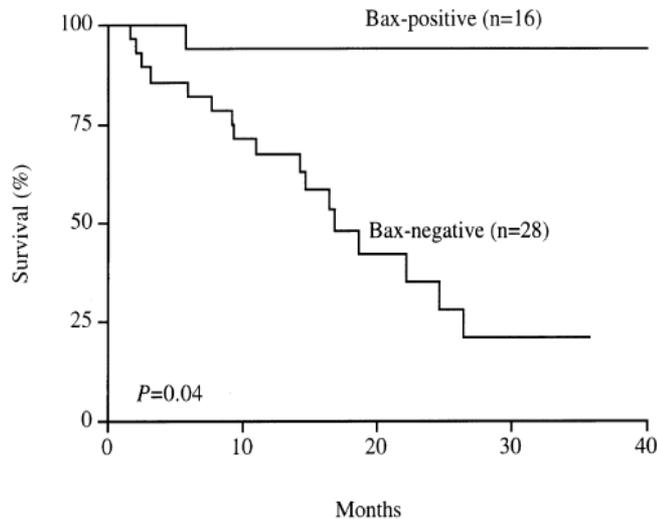


Fig. 2 Survival of patients with respect to Bax expression after 10.8 Gy radiation, plotted using the Kaplan-Meier method and analyzed by the Breslow-Gehan-Wilcoxon test

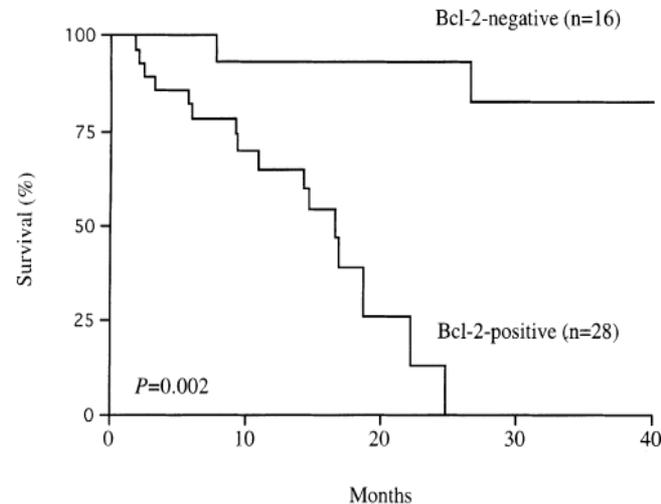
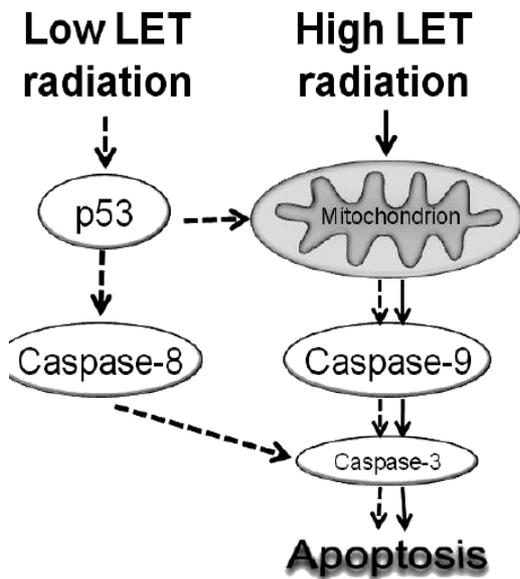


Fig. 3 Survival of patients with respect to Bcl-2 expression after 10.8 Gy radiation, plotted using the Kaplan-Meier method and analyzed by the Breslow-Gehan-Wilcoxon test

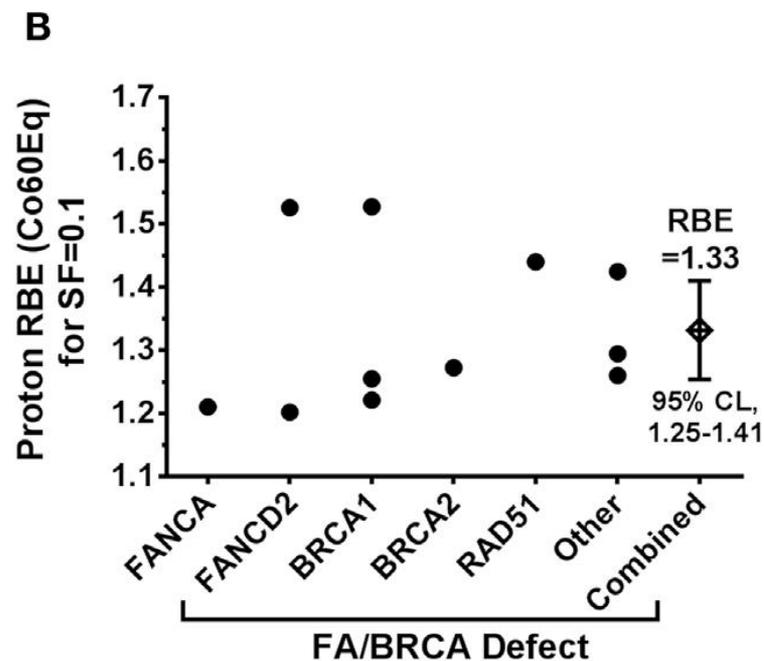
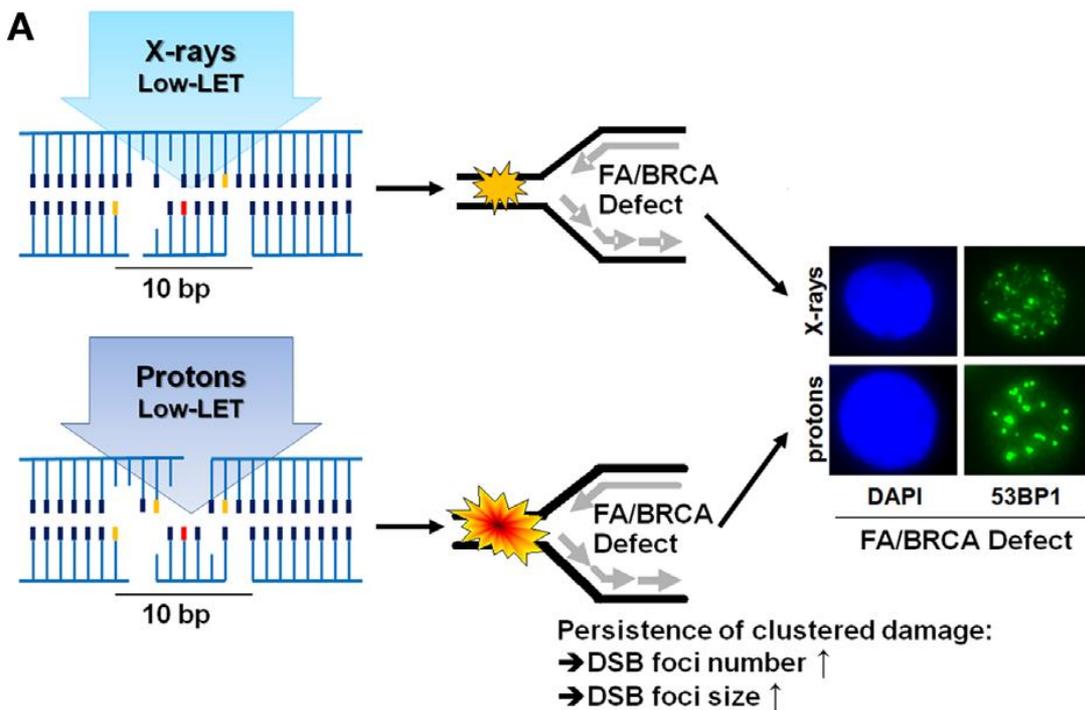


Yoko Harima · Keizo Harima · Nobuaki Shikata
Atsutoshi Oka · Takeo Ohnishi · Yoshimasa Tanaka

Bax and Bcl-2 expressions predict response to radiotherapy in human cervical cancer

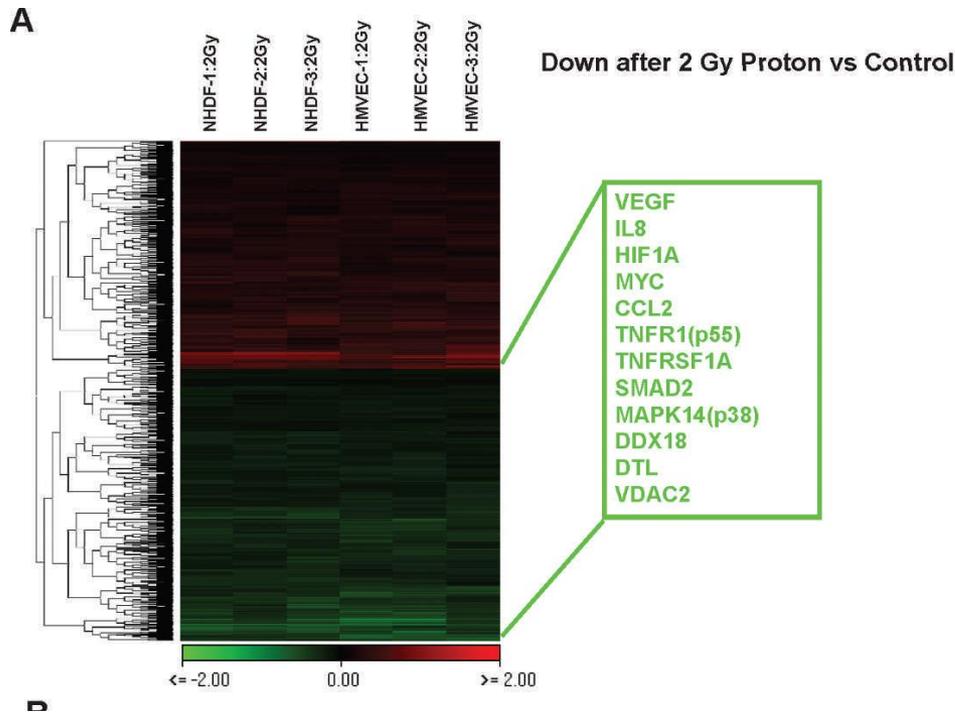
Hamada *et al.*, *J. Radiat. Res.* 2010

RBE and genetic defects

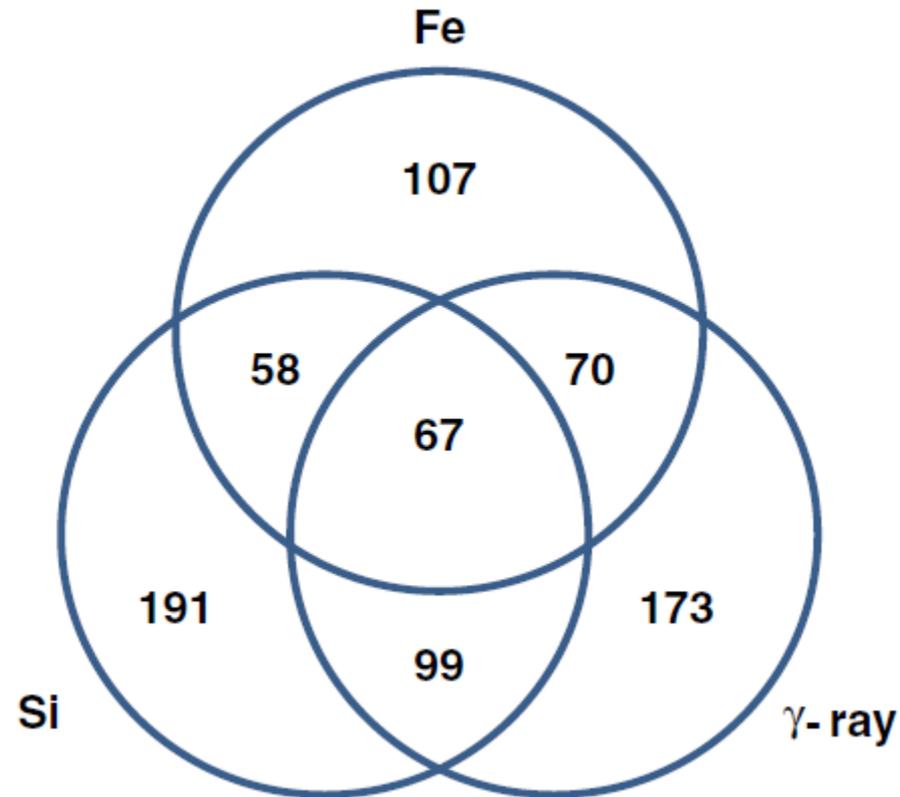


Held *et al.*, *Front. Oncol.*, 2016

Radiogenomics and RBE



Suppression of pro-angiogenic gene expression in human cells after exposure to protons but not to X-rays (Girdhani *et al.*, *Radiat. Res.* 2012)



Differentially expressed genes in human bronchial epithelial cells exposed to γ -rays or heavy ions (Ding *et al.*, *BMC Genomics* 2013)

Conclusions

- In vitro RBE has been measured in the past 50 years in different centers and we have accumulated an enormous amount of data
- With the new trend toward hypofractionation and non-uniform target coverage, more emphasis should go to normal tissue RBE, which should be measured in animal models or clinical studies
- However, in vitro studies remain very useful for studying the RBE molecular mechanisms
- Combination with targeted therapies (exploiting DNA repair pathways) and dependence on genetic background are promising fields