Carbon Ion Radiobiology:
Tissue experiments

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Ultimate Goal of Radiation Therapy

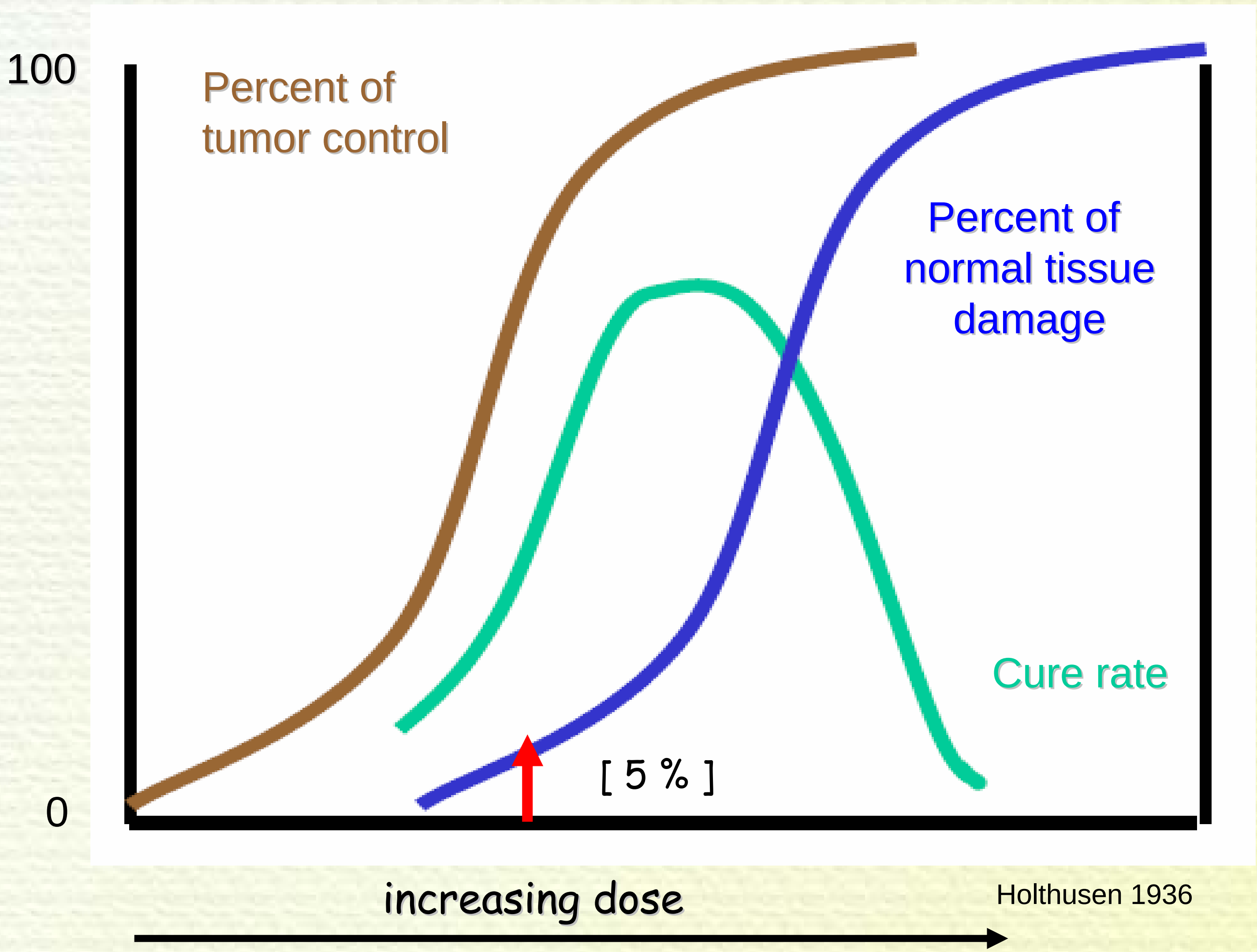
….. **to achieve complication free tumor control**

Effective erradication of all tumor cells

Janus, roman god

Avoiding injury to the normal tissues

Dose-Response Relation for Tissue/Tumor Damage

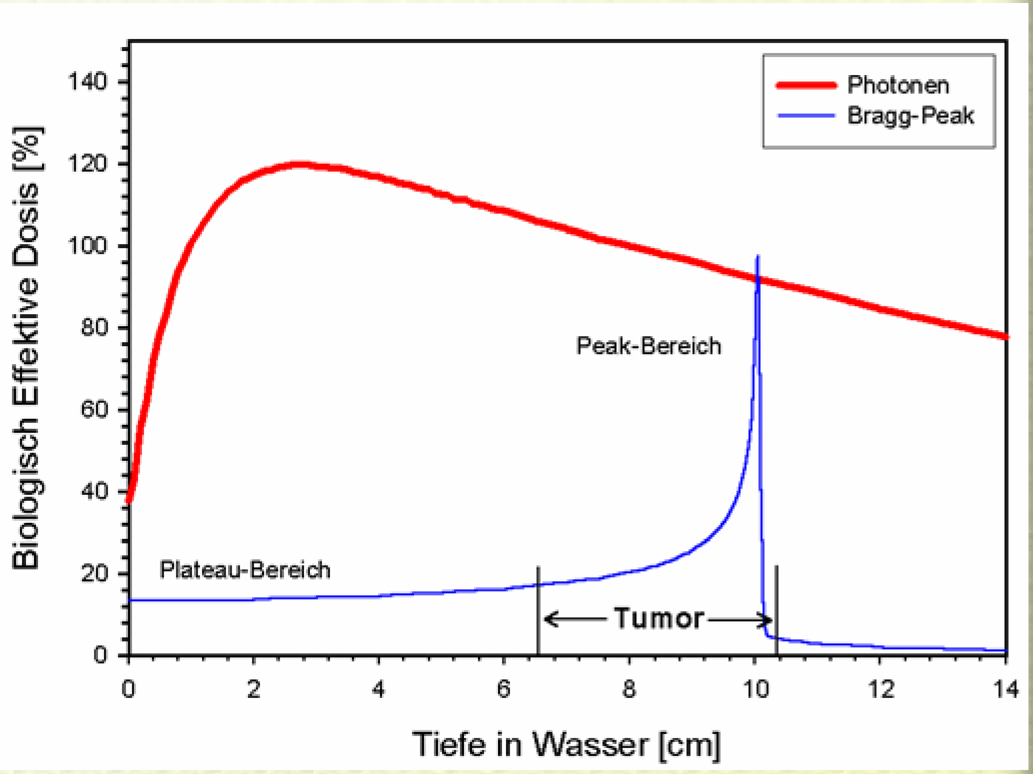


Holthusen 1936

Advantages of Carbon Ions

Physical selectivity

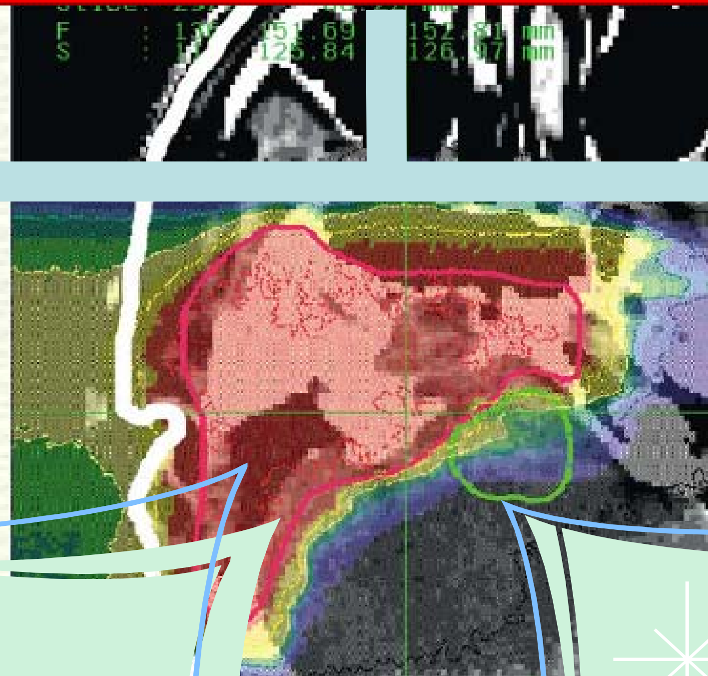
Depth dose curve (Bragg-peak)
Active field shaping (scanning)
Reduction of integral dose
Less lateral scatterung
In vivo Monitoring by PET



Biological efficiency

High local efficiency (high-LET)
Increased RBE in the Bragg-peak

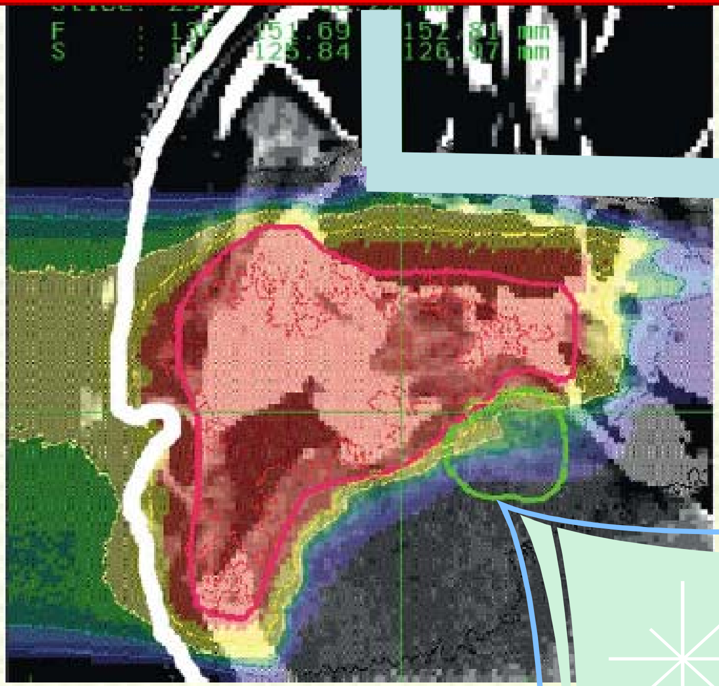
How can in vivo experiments help to improve Carbon Ion Radiotherapy ?



Response of tumor tissue

Response of dose limiting normal tissues

Carbon Ion Radiotherapy



Response of dose limiting normal tissues

Radiation response of normal tissues is determined on large part by the structural organization of the tissue

!

Normal Tissue Response to Radiation

Tolerance depends not only on the intrinisic radiosensitivity of the target cell

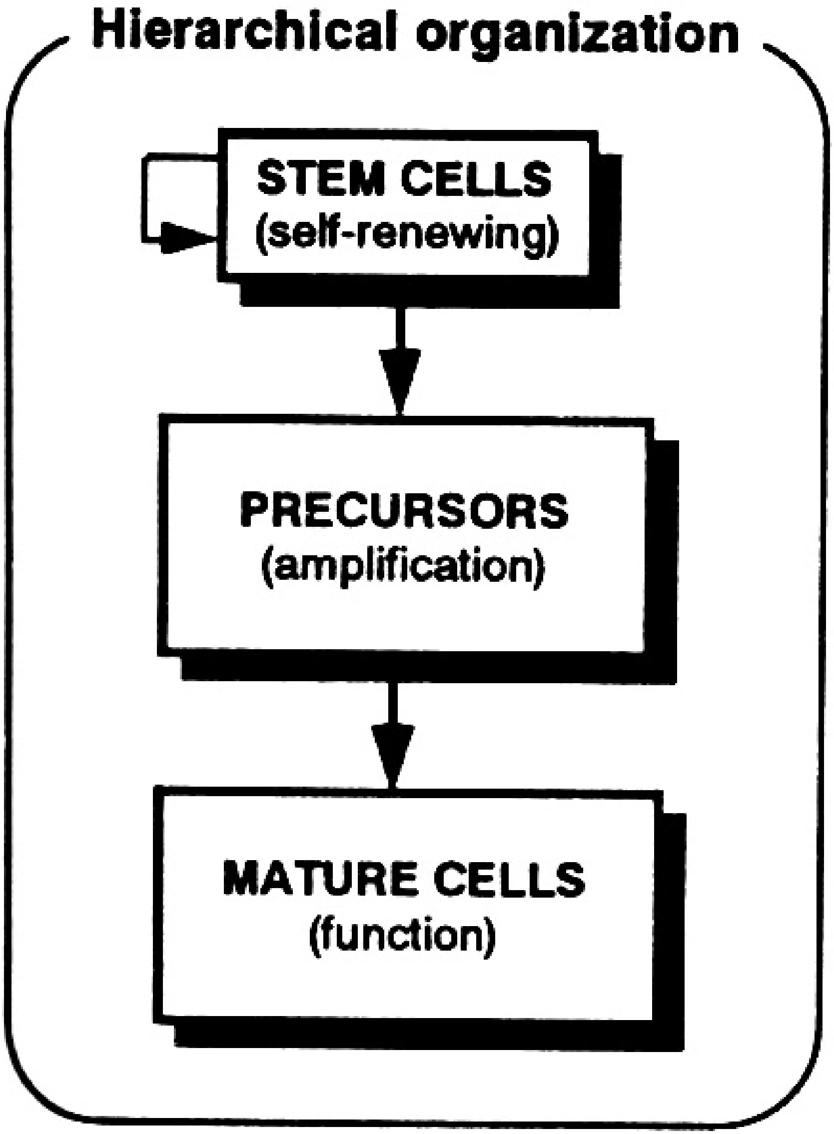
...... but also on the number of clonogens (stem cells) required to make a

Functional Subunit [FSU]

Survival of a FSU requires survival of at least

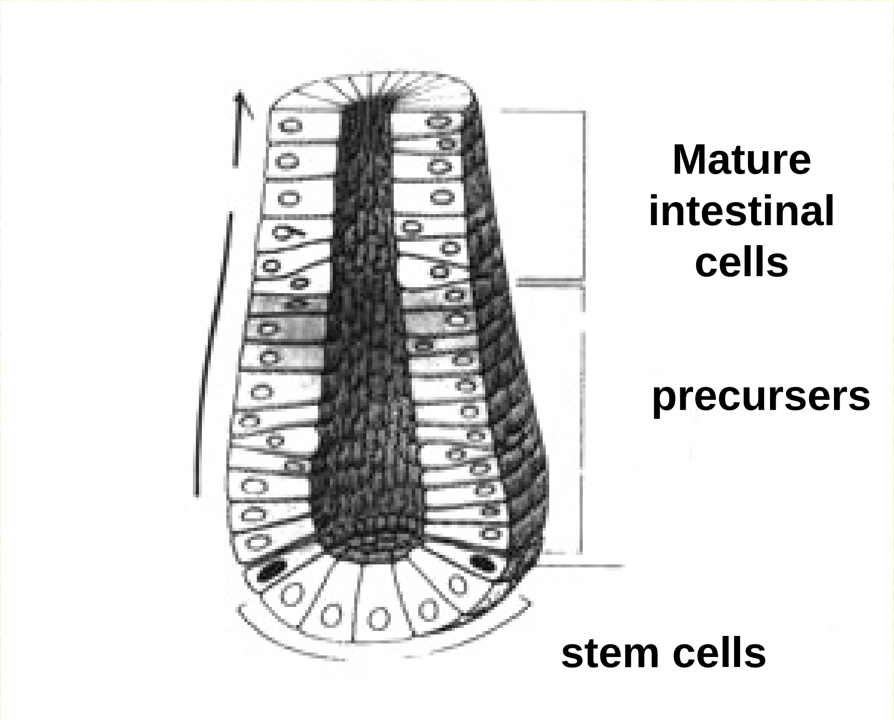
One Colonogen

Normal Tissue Organization



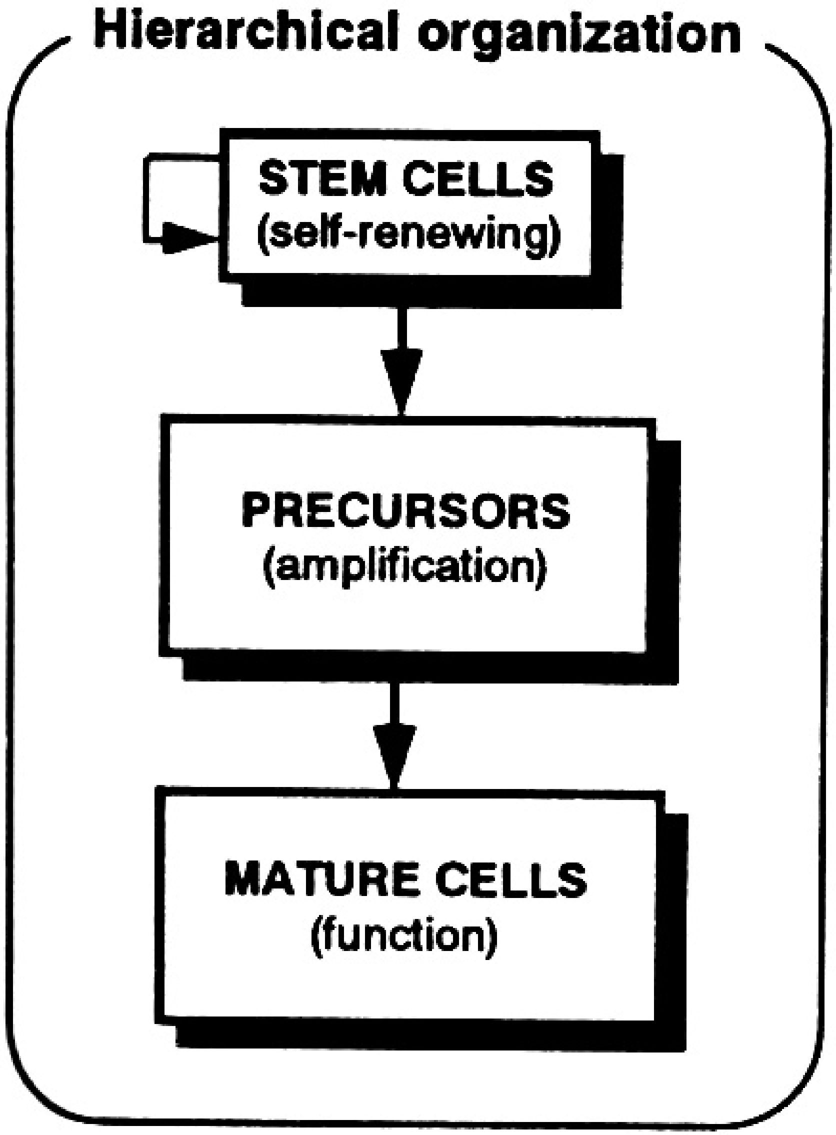
van der Kogel 1993

Clearly recognizable seperation between **stem cell** compartment and **differentiated cells**



Intestinal crypt

Normal Tissue Organization



van der Kogel 1993

Clearly recognizable seperation between stem cell compartment and differentiated cells

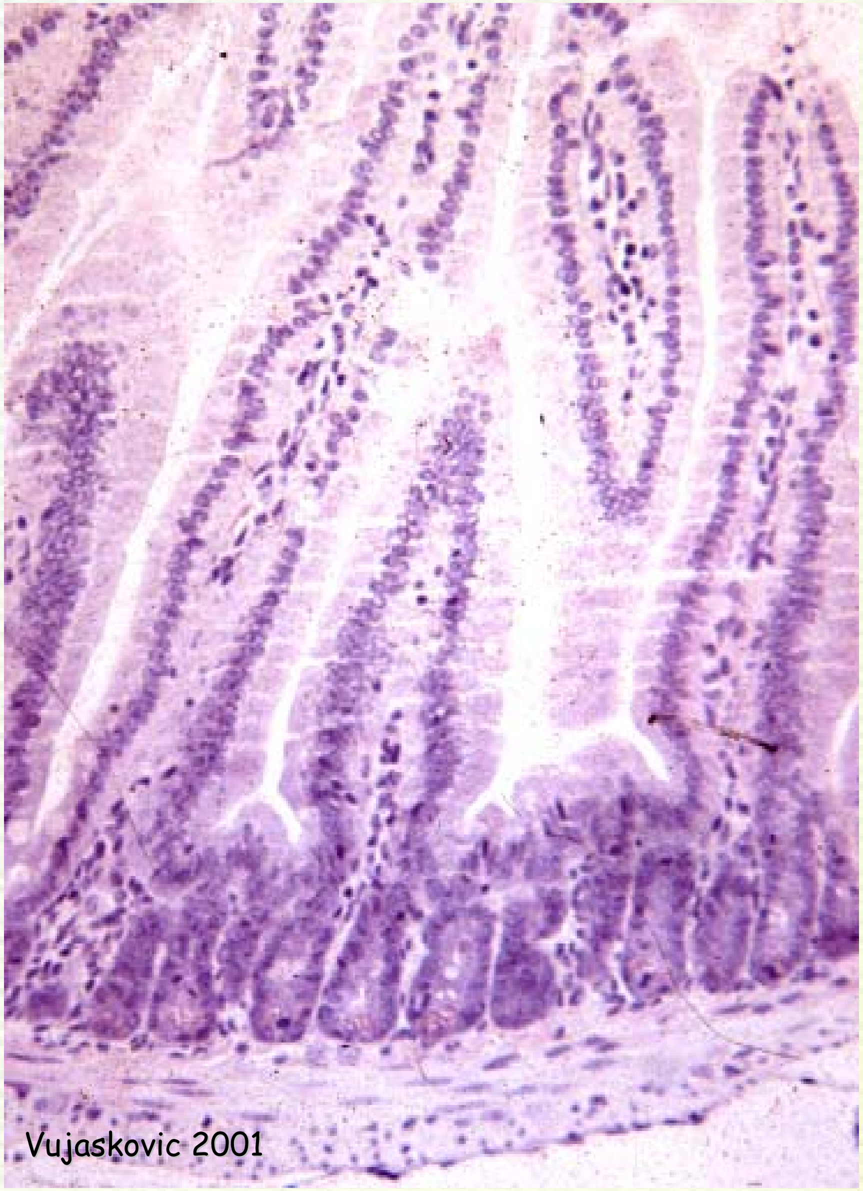
Mostly rapidly renewing cell systems:

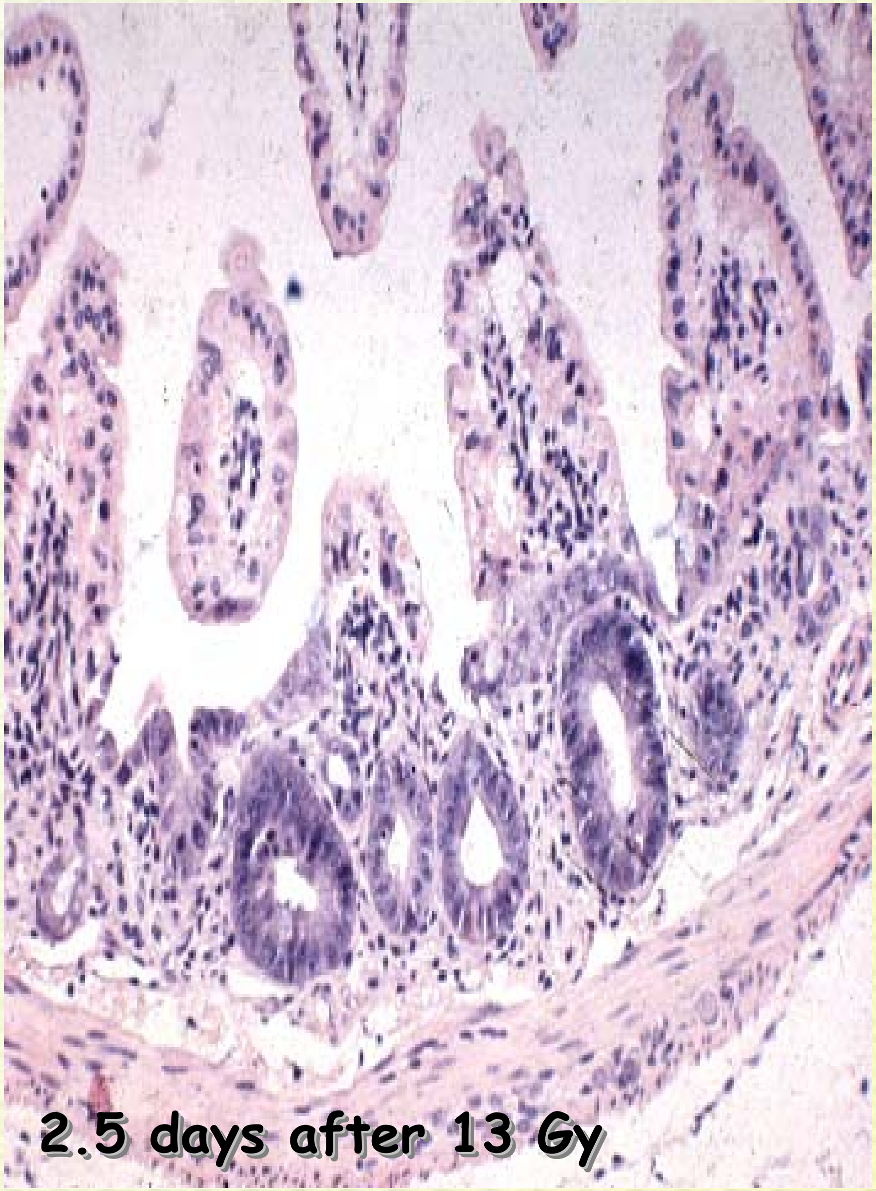
- Skin
- Mucosae
- Haematopoetic systems
- Intestinal epithelia

Acute responding tissues

(in humans 2-3 weeks after radiotherapy)

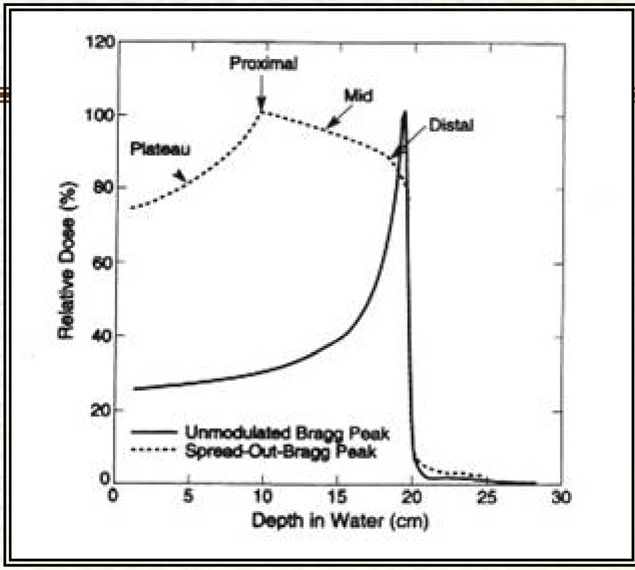
Normal Tissue Response to Radiation





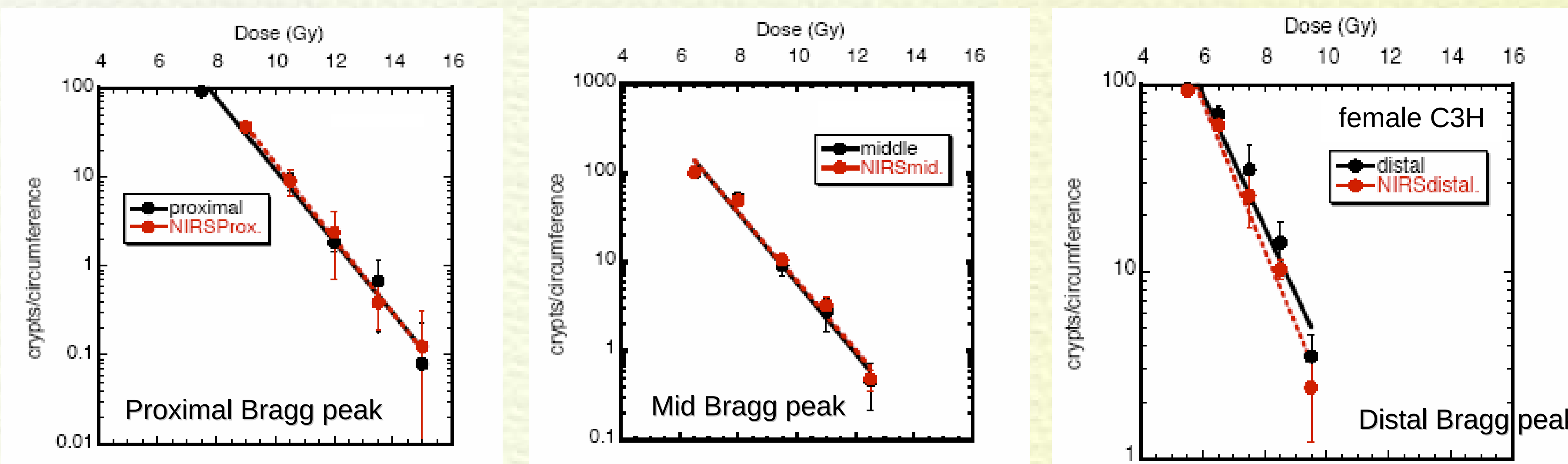
The intestinal crypt assay:

A biological dosimeter !!!



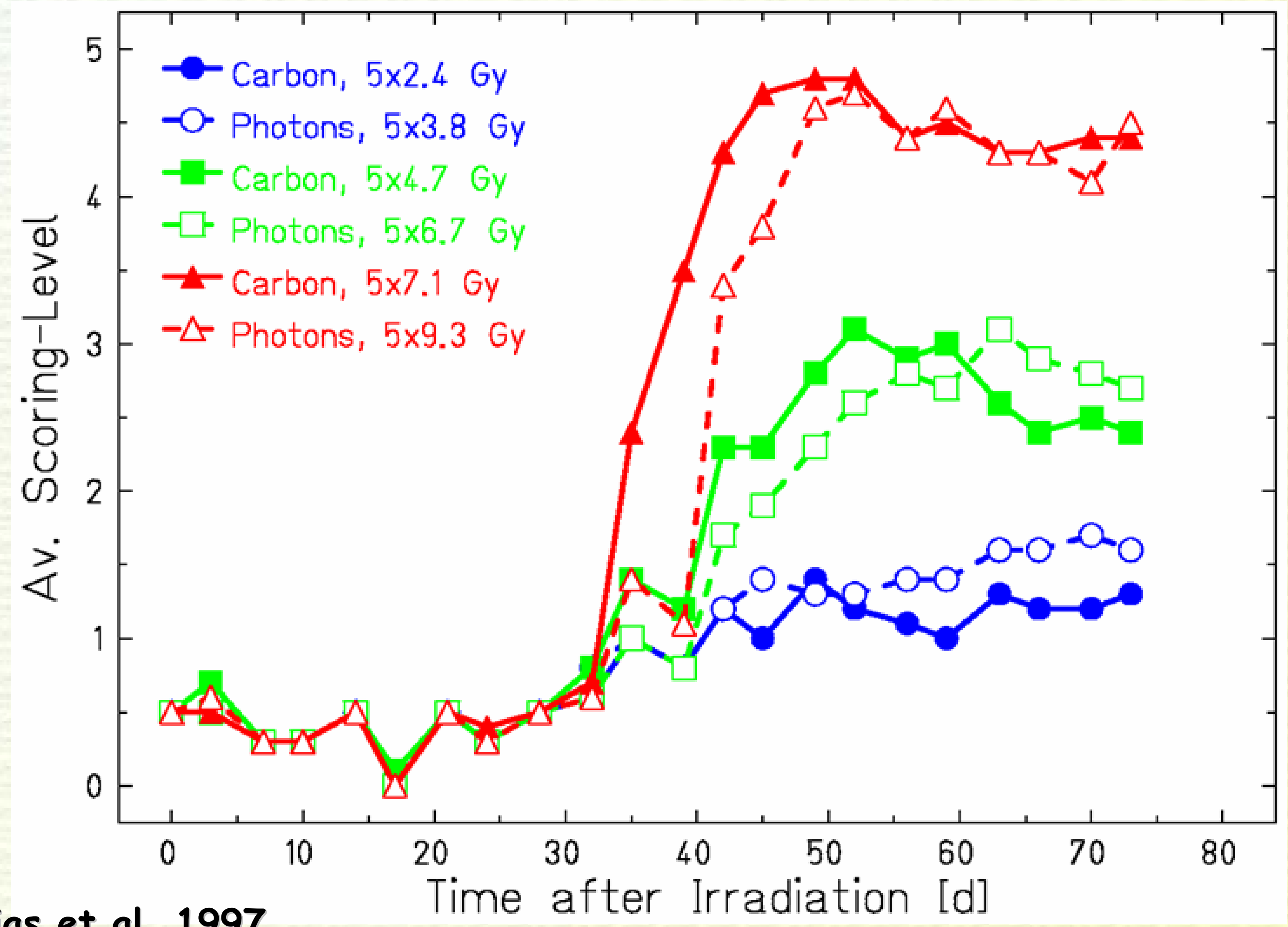
Purpose:

to compare the different NIRS and GSI different beam delivery systems with respect to its biological effectiveness.



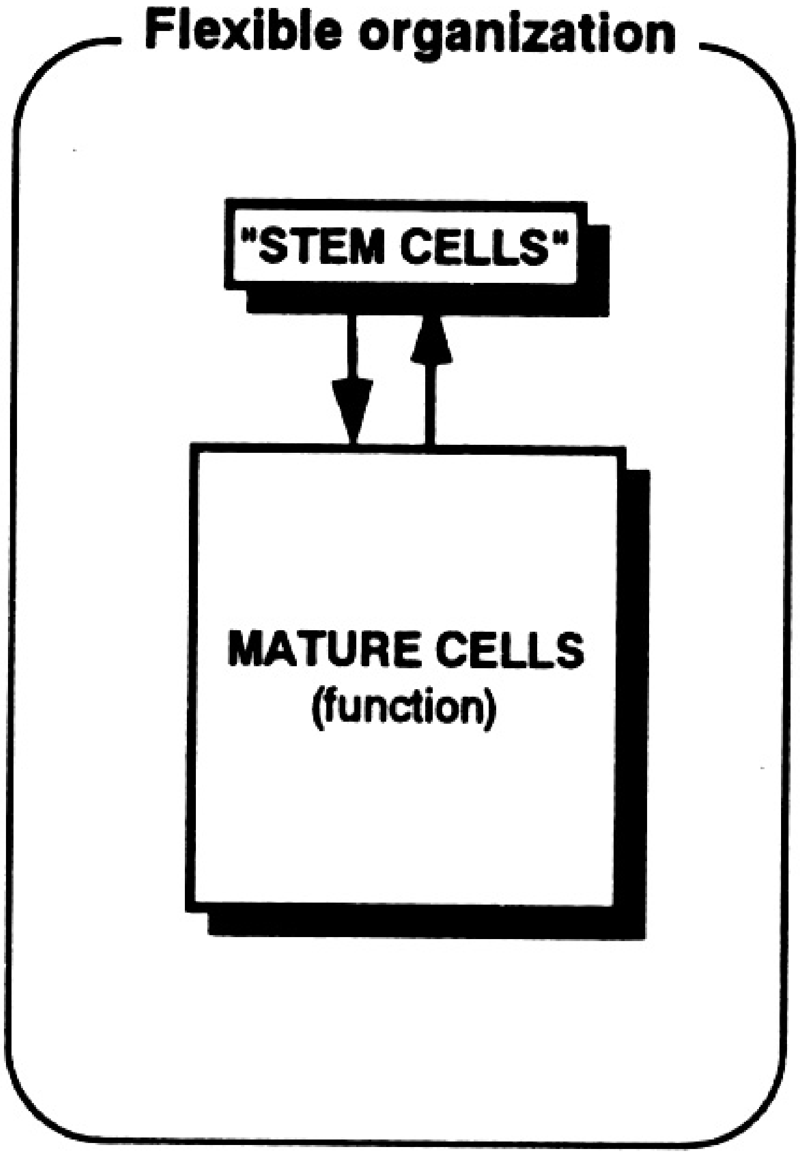
Ando et al. unpublished data

Early response of pig skin to irradiation with ^{12}Carbon Ions or 200 kV X-rays.



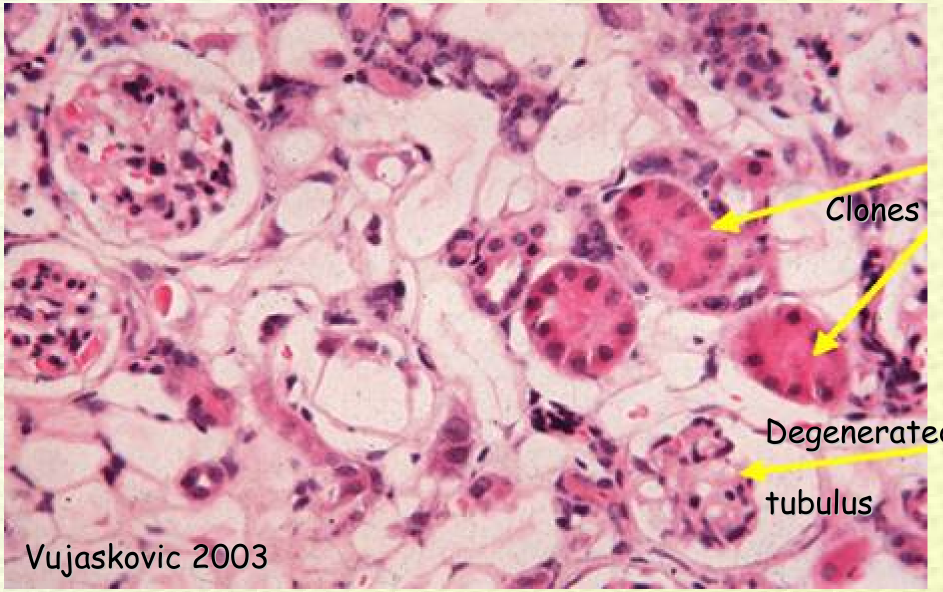
Zacharias et al. 1997

Normal Tissue Organization

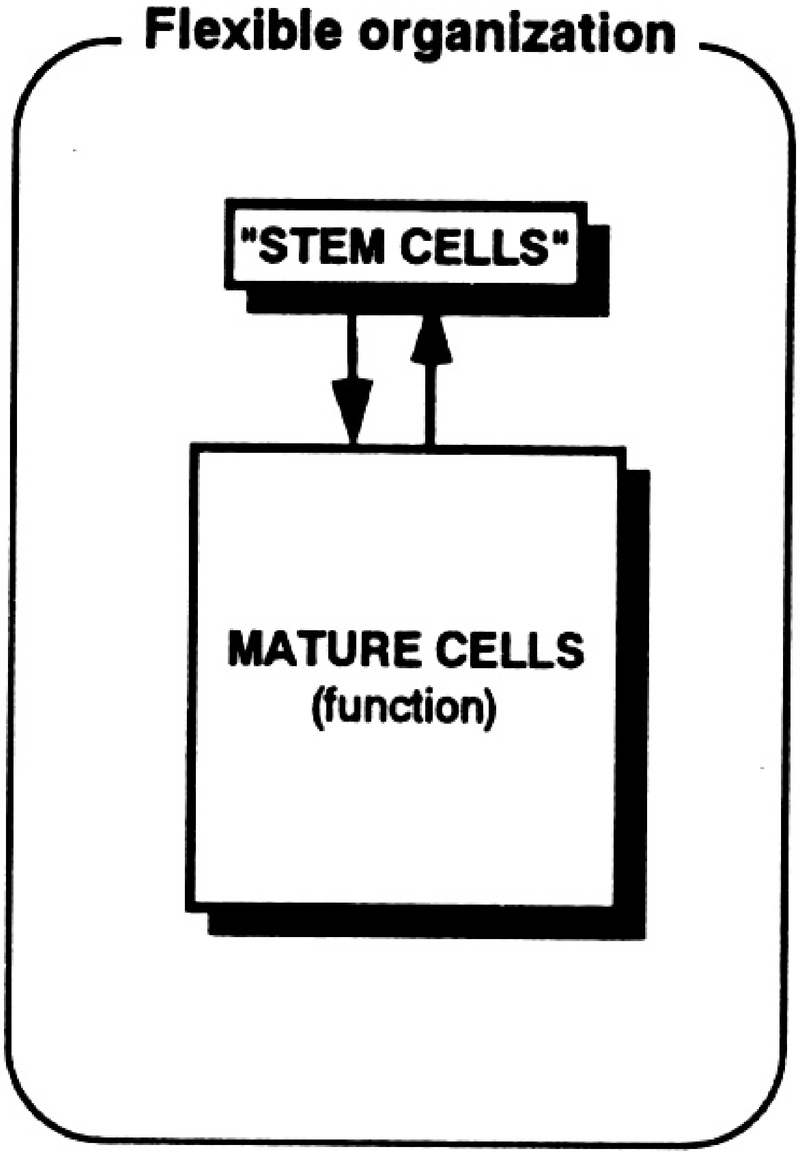


van der Kogel 1993

No clearly recognizable seperation between stem cell compartment and differentiated cells



Normal Tissue Organization



van der Kogel 1993

No clearly recognizable seperation between stem cell compartment and differentiated cells

Mostly slowly renewing cell systems:

Liver

Kidney

Lung

Central Nervous System

Late responding tissues

(in humans years after radiotherapy)

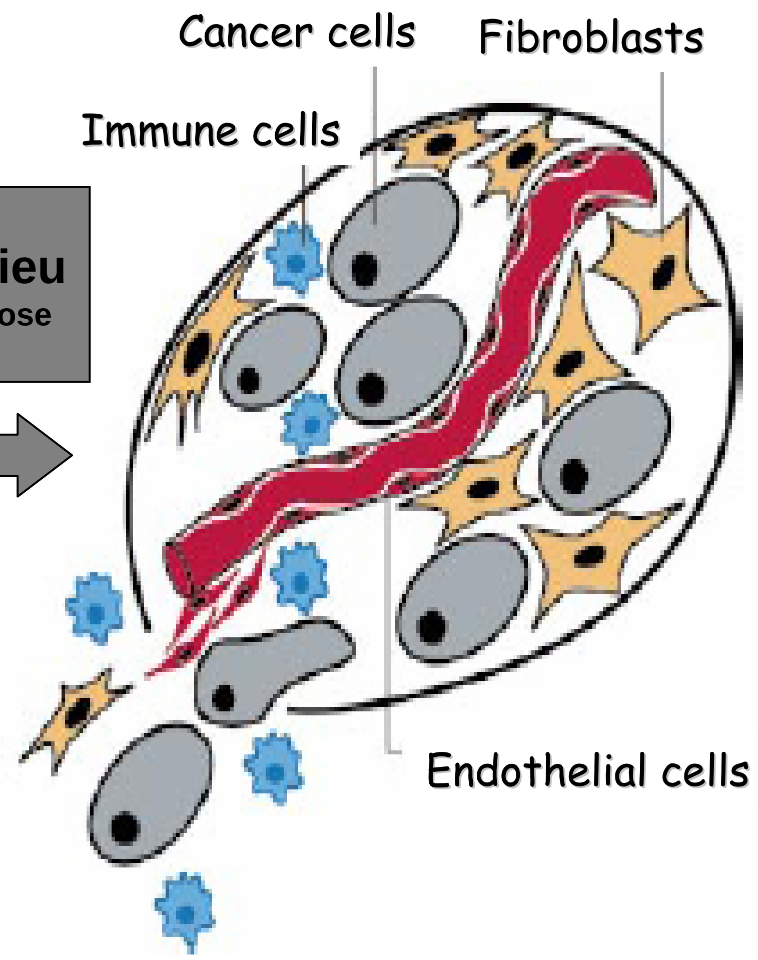
Tolerance doses and RBEs for rat spinal cord in the literature

Setup	Carbon ions D_{50} [Gy]	RBE	Study
Plateau region of a 4 cm SOBP (400 MeV/u, 10 keV/μm)			
1 Fx	17.9±1.8	1.45±0.17	Leith et al. 1982
4 Fx	37.6±9.0	1.31±0.32	
Midpeak region of a 4 cm SOBP (400 MeV/u, 80 keV/μm)			
1 Fx	17.5±0.7	1.48±0.12	Leith et al. 1982
4 Fx	25.1±1.2	1.95±0.12	
Midpeak region of a 6 cm SOBP (290 MeV/u, 70 keV/μm)			
1 Fx	18.5	1.38	Okada et al. 1998

Carbon Ion Radiotherapy

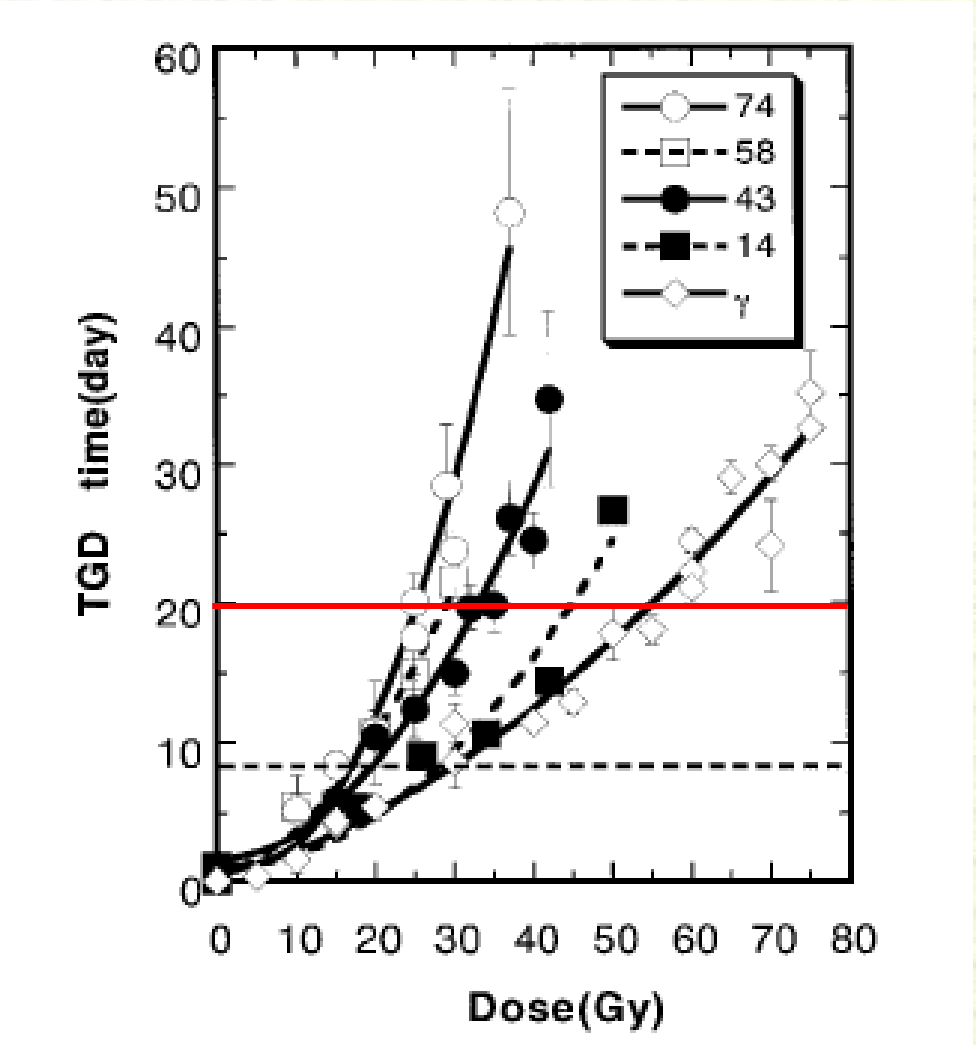
Response of tumor tissue

Micromilieu
O_2, pH, glucose



Complex summary of opposing signals !

Growth response of a murine fibrosarcoma after treatment with ^{12}Carbon Ions



Ando et al. 1999/2002

The isoeffect doses to produce a TGD of 20 days were

55, 45, 33, 29 and 25 Gy

for photon and carbon ions with

14, 43, 58 and 74 keV/μ, respectively.

RBE rise from

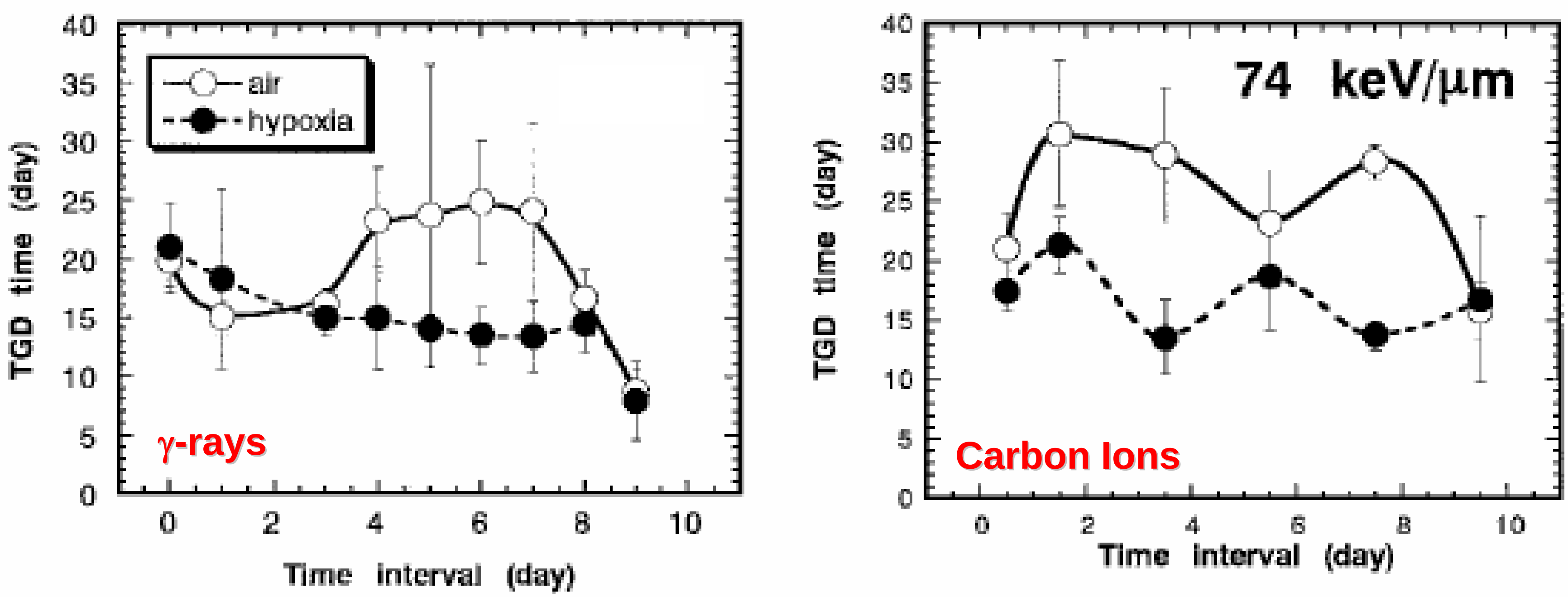
1.8 to 2.3 (43 keV/μ)

2.4 to 3.0 (74 keV/μ)

when the number of fractions increased from 1 to 4.

Accelerated reoxygenation of a murine fibrosarcoma after Carbon Ion radiation

Conditioning irradiation with either carbon ions or γ-rays was followed by test irradiation after the interval indicated on the horizontal scale. Tumor regrowth was measured after irradiation and the difference in the tumour regrowth between the clamped and non-clamped tumors was used to assess reoxygenation.



Mean and SD calculated from five mice/point.

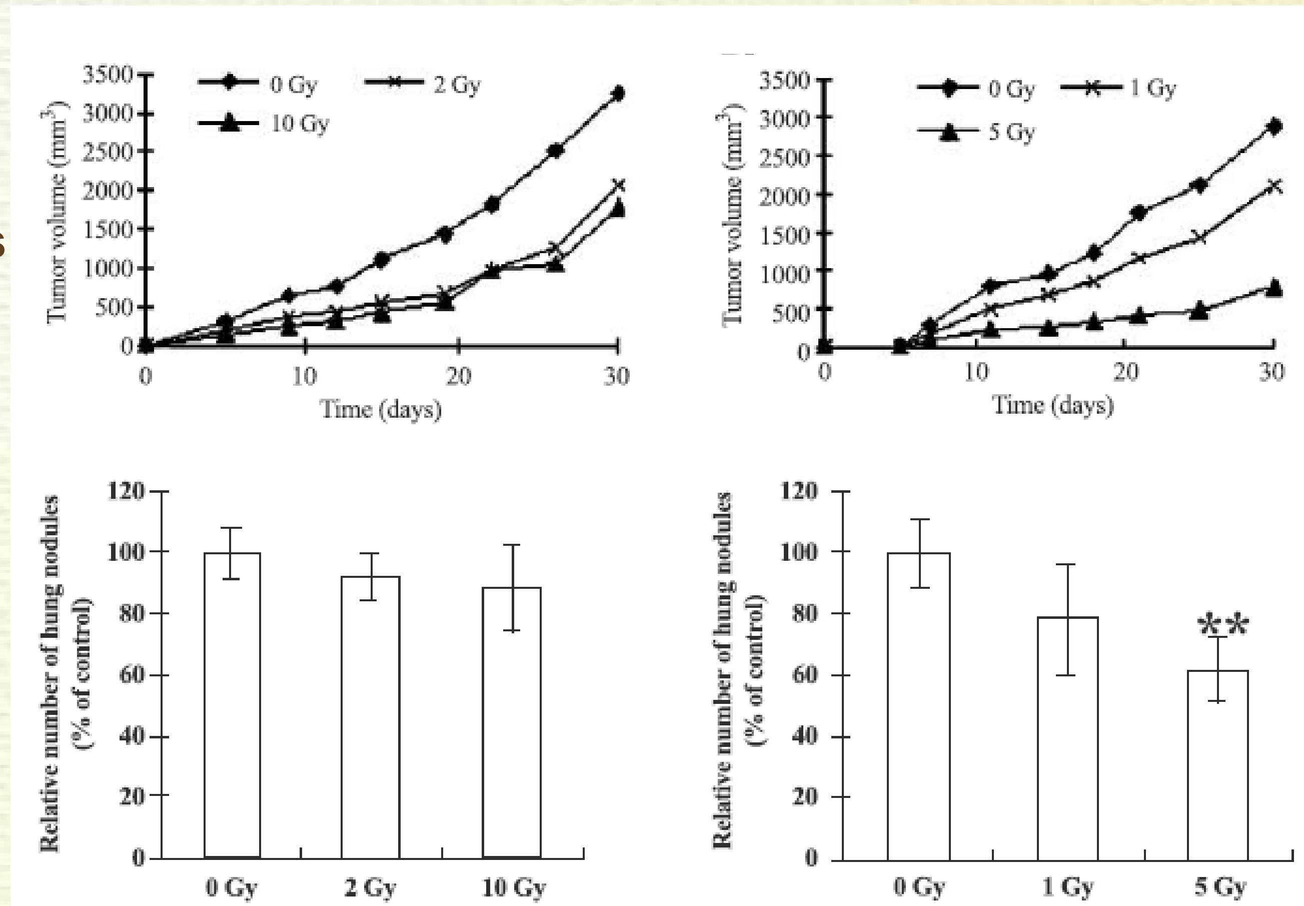
Ando et al. 1999

Particle Irradiation Suppresses Metastatic Potential of Cancer Cells

Photons | **Carbon Ions**

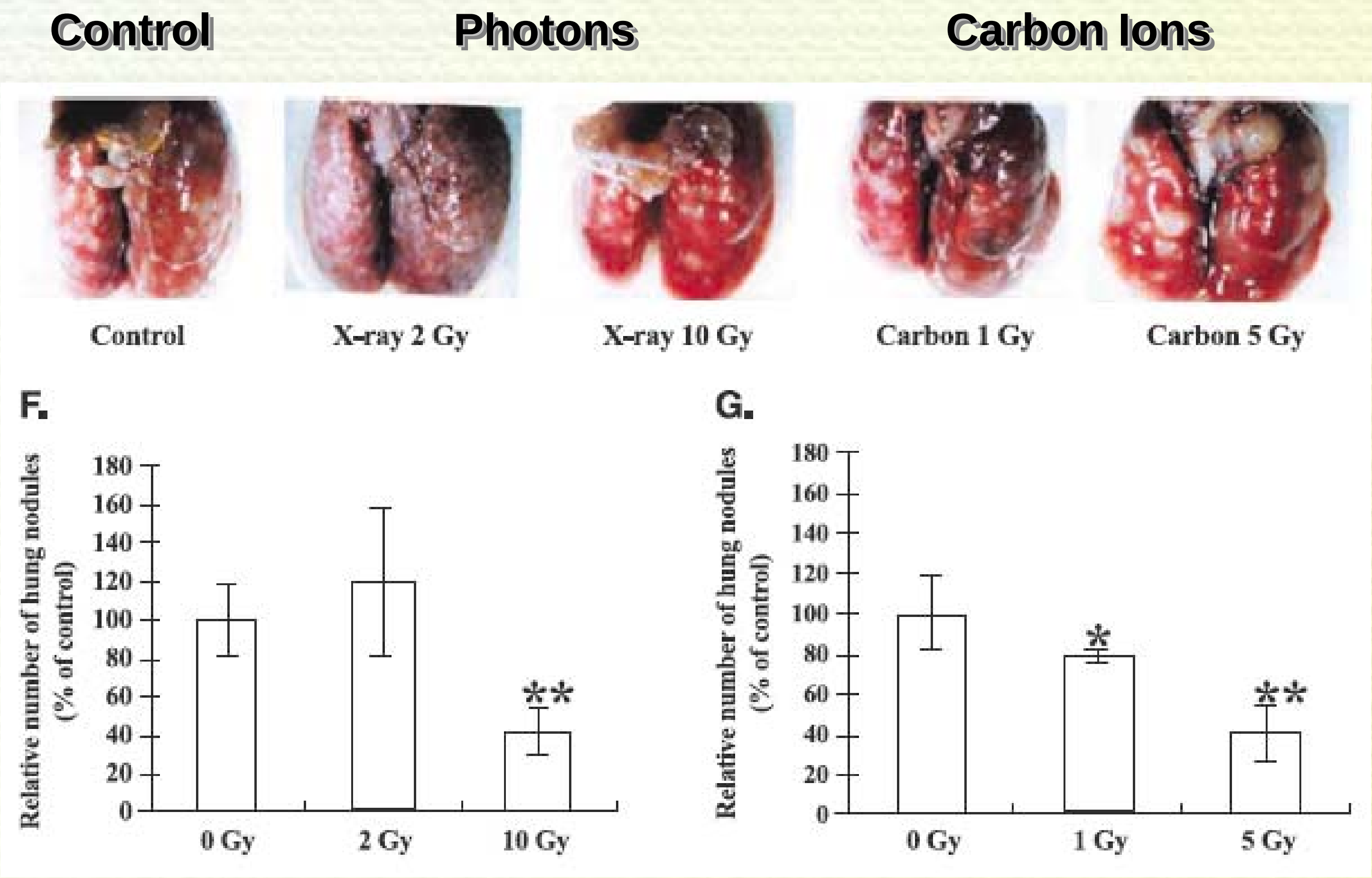
Growth curves of s.c. osteosarcomas
[mouse LM8]

Number of lung metastases post radiatio



Ogata et al. 2005

Particle Irradiation Suppresses Metastatic Potential of Cancer Cells



Number of lung nodules following i.v. injection of tumor cells, irradiated with photons or carbon ions

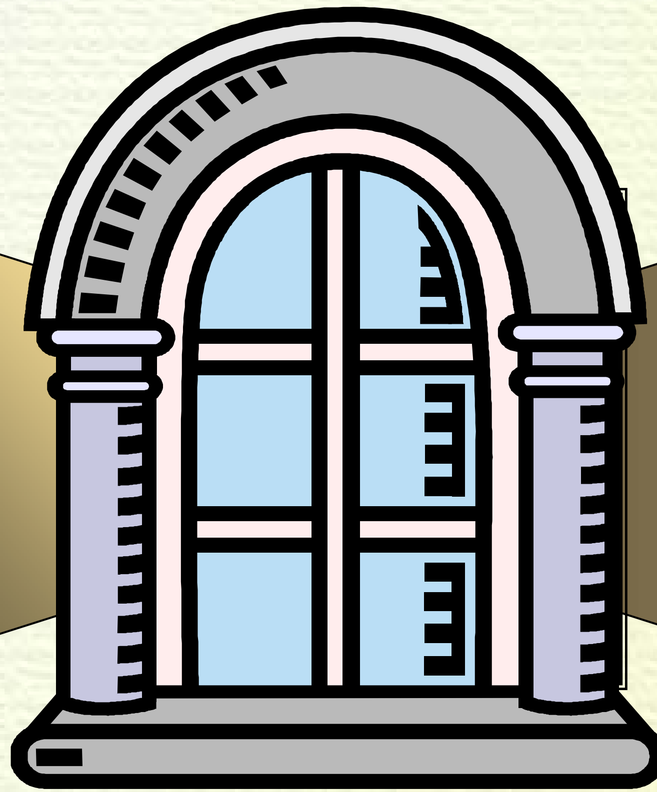
Ogata et al. 2005

Suggested underlying biological mechanisms in tumors undergoing fractionated radiotherapy

4 R's

Photons	^{12}Carbon Ions
Recovery	Repair of DNA damage reduced Benefit: Radioresistant tumors
Repopulation	Indications: Alterations of the ECM, Endothelial cell response, Inactivation of the survival response network ?
Redistribution	Less dependent on cell cycle effects Benefit: Slow growing tumors
Reoxygenation	Less dependent on oxygen Benefit: Tumors with hypoxic fractions

How can in vivo experiments help to improve Carbon Ion Radiotherapy ?



Tumors

- RBEs
- Fractionation effects
- Factors influencing high-LET response
- Combined treatment modalities

NormalTissues

- RBEs
- Fractionation effects
- Volume effects
- Molecular mechanisms of high-LET damage