Perspectives in particle radiobiology

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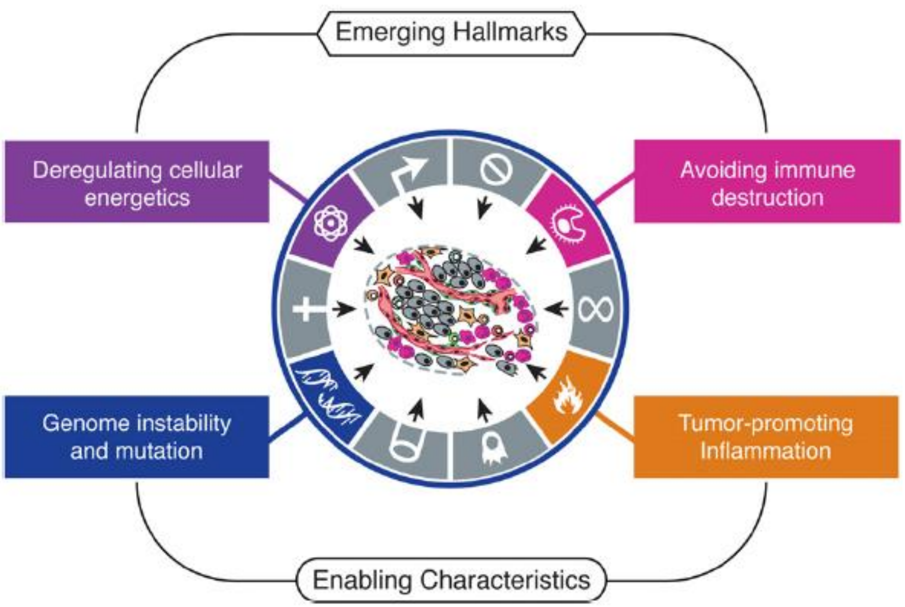
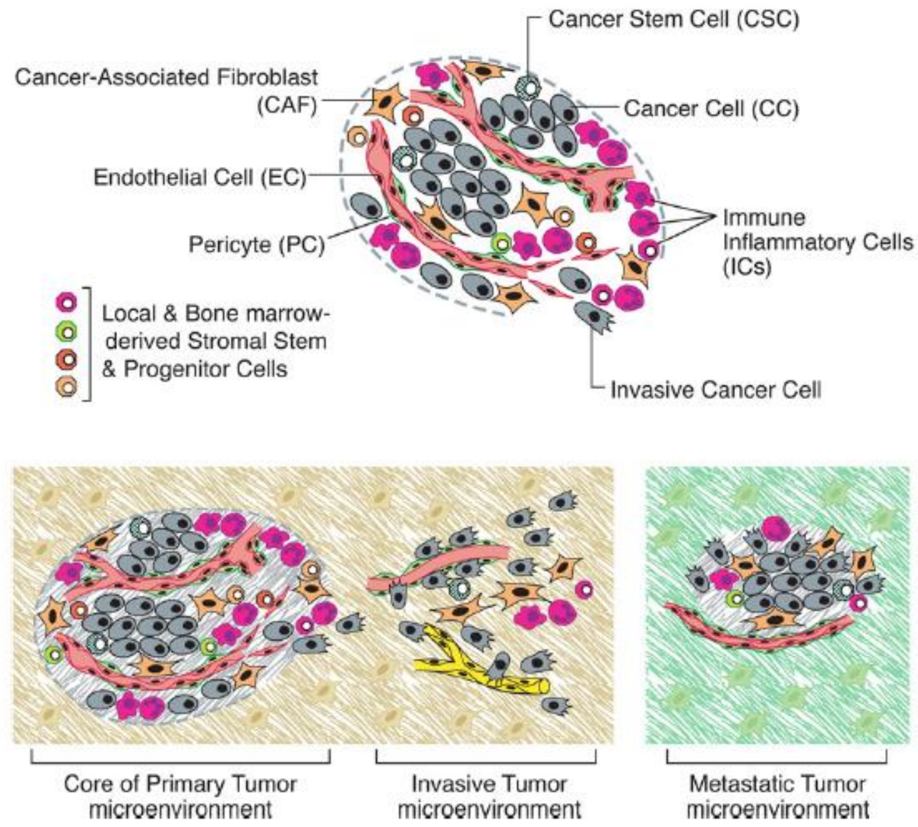
CNAO, Pavia, 17.12.2013

Future research trends in particle radiobiology

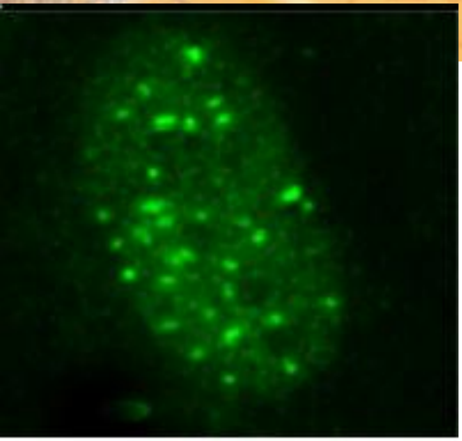
must be based on the **new** tumor biology



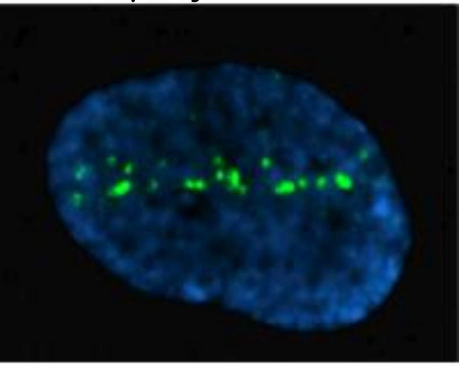


Hanahan & Weinberg, *Cell* 2012

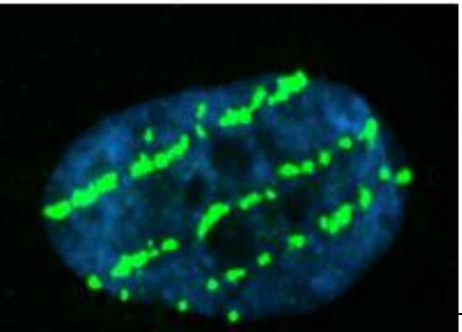
The role of *systems biology* in particle therapy



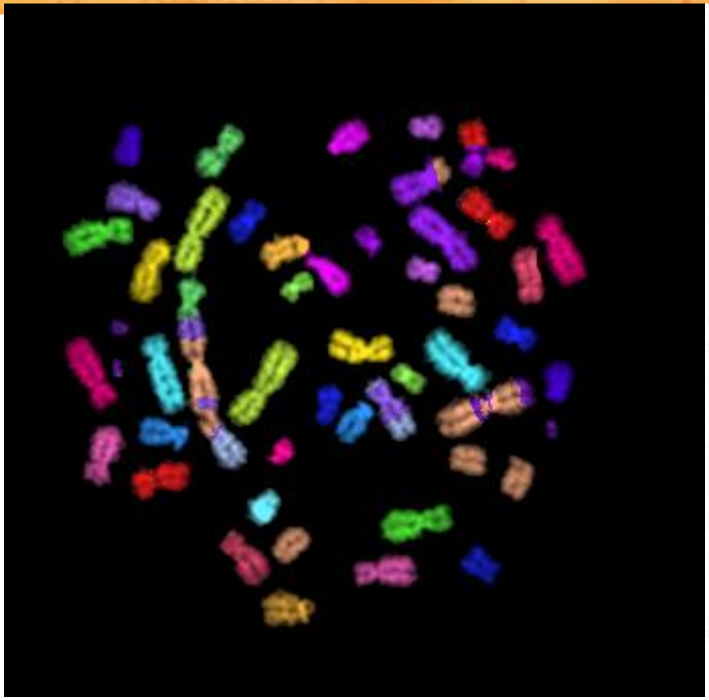
γ-rays

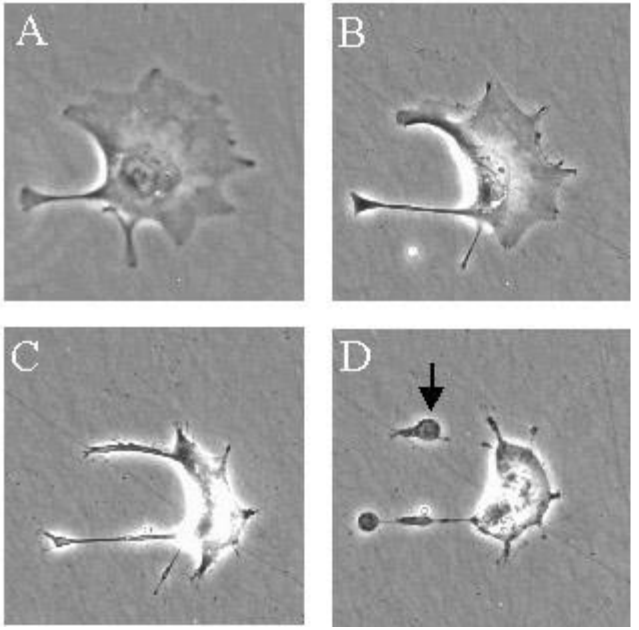


silicon



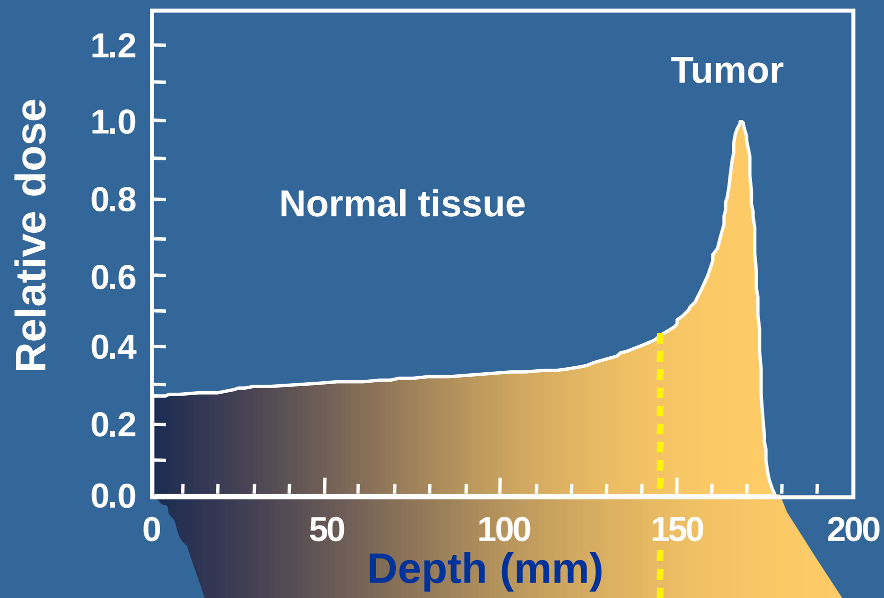
iron

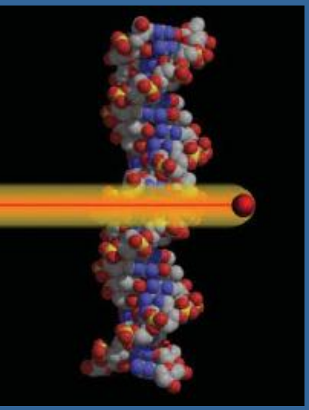




Durante & Loeffler,

***Nature Rev Clin Oncol* 2010**

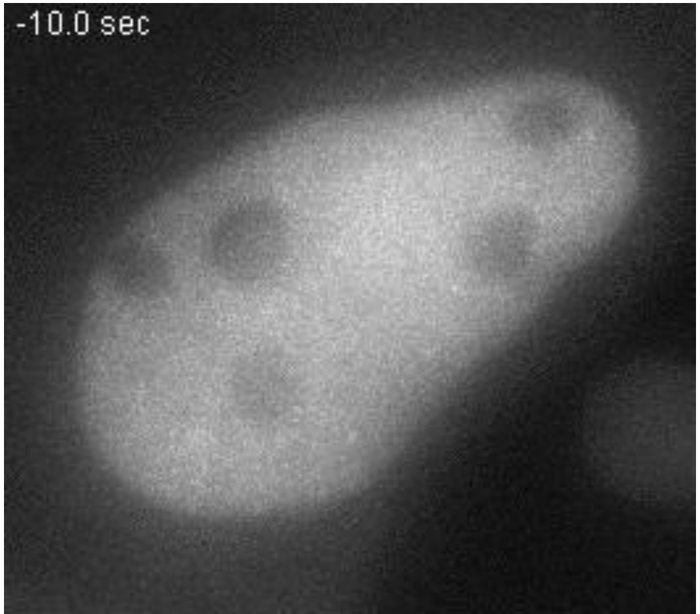


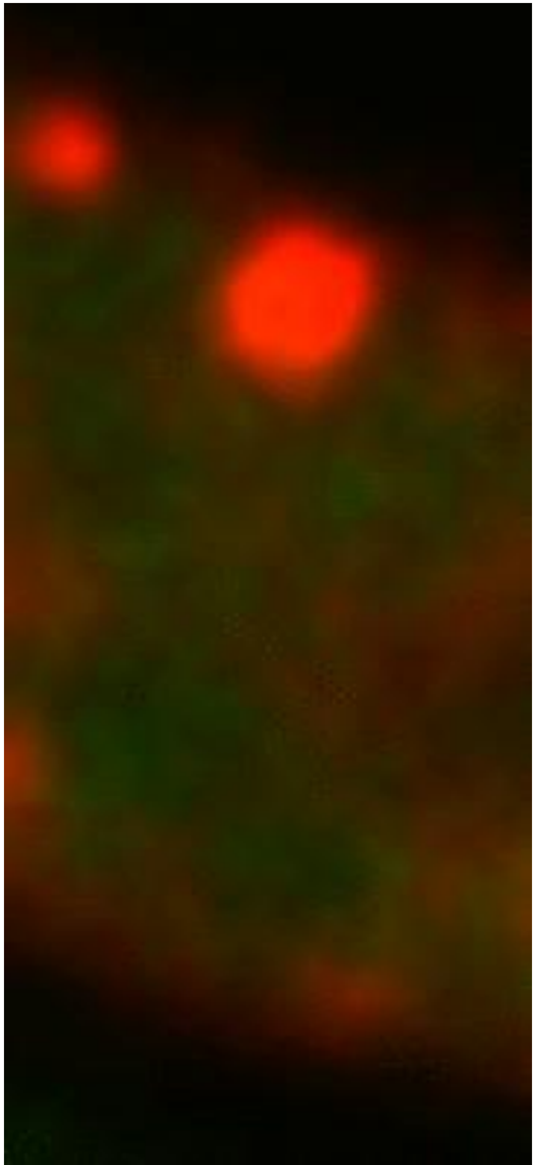


			Potential advantages
Energy	high	low	
LET	low	high	
Dose	low	high	High tumor dose, normal tissue sparing
RBE	≈ 1	> 1	Effective for radioresistant tumors
OER	≈ 3	< 3	Effective against hypoxic tumor cells
Cell-cycle dependence	high	low	Increased lethality in the target because cells in radioresistant (S) phase are sensitized
Fractionation dependence	high	low	Fractionation spares normal tissue more than tumor
Angiogenesis	Increased	Decreased	Reduced angiogenesis and metastatization
Cell migration	Increased	Decreased	

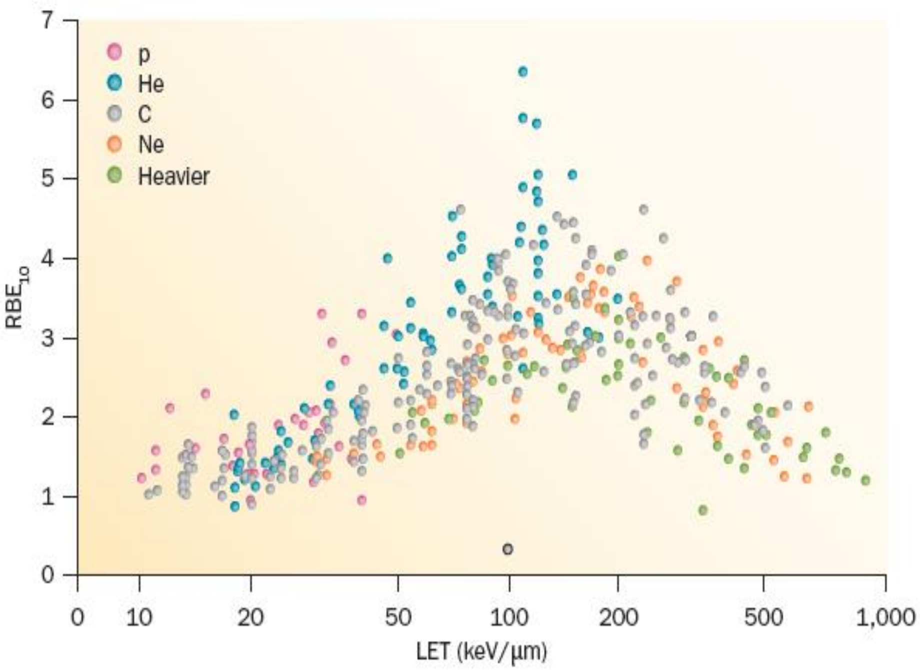
„Hot topics“ in clinical particle radiobiology

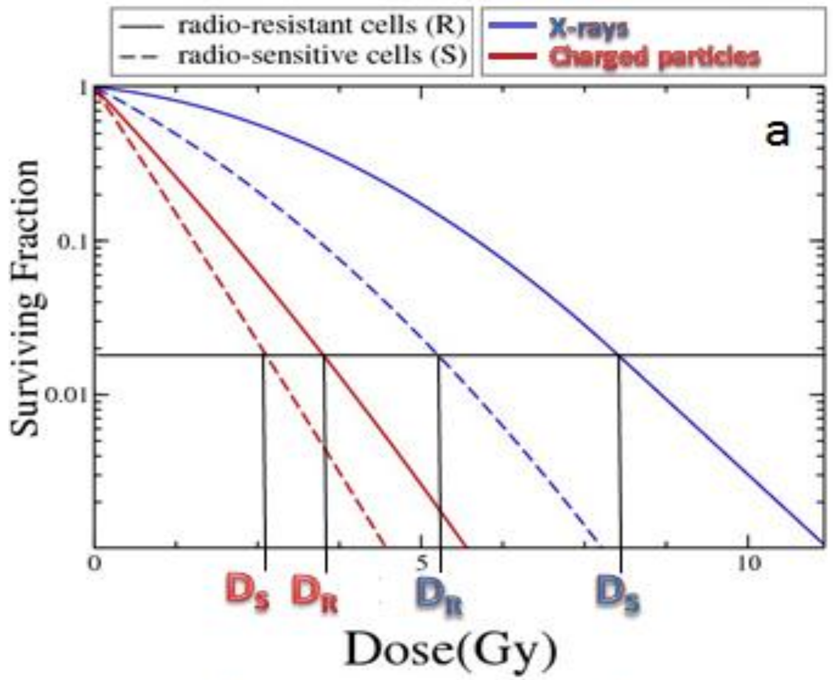
- RBE
- Cancer stem cells
- Hypofractionation
- Combined treatments
- Radiogenomics
- Intra-tumoral heterogeneity
- Second cancers





RBE – uncertainty or power?





$$RBE_R = \frac{D_{R(photons)}}{D_{R(ions)}} > RBE_S = \frac{D_{S(photons)}}{D_{S(ions)}}$$

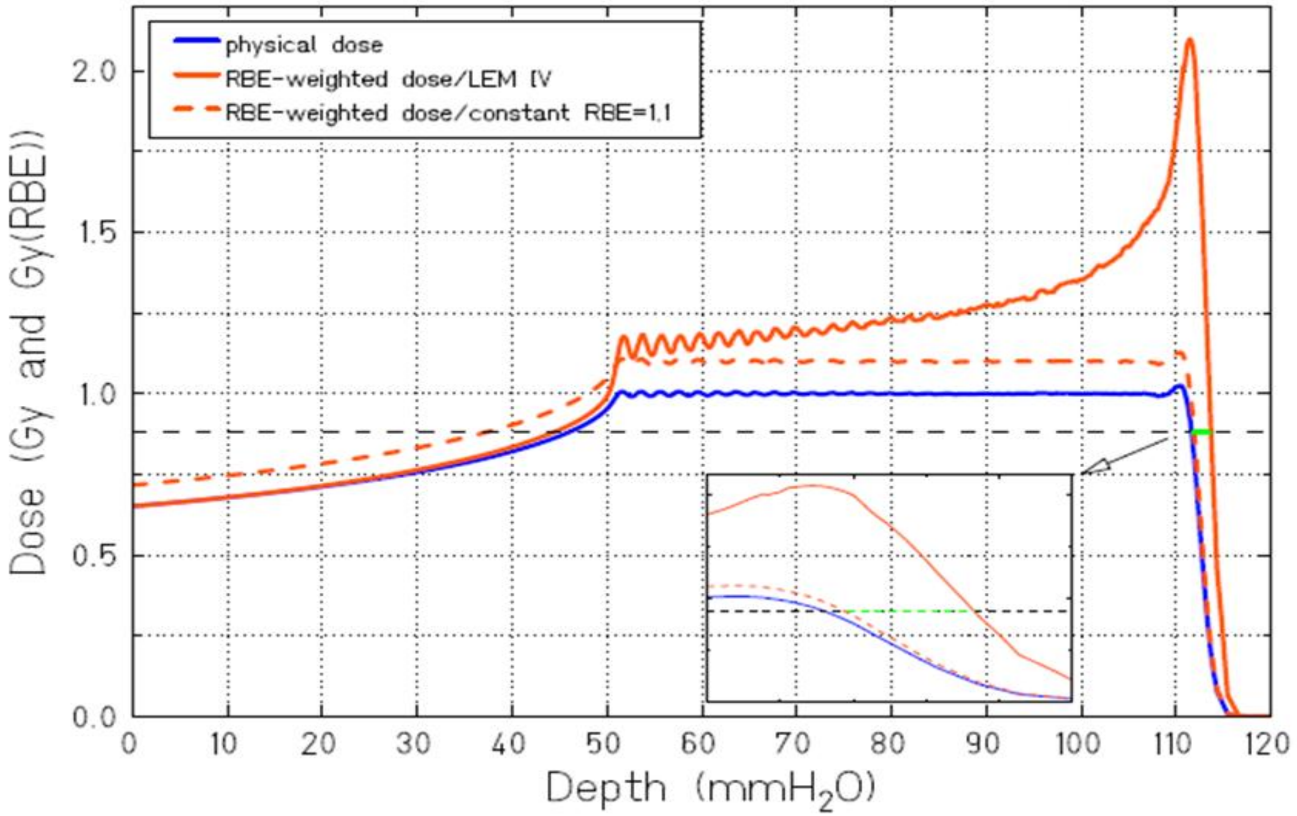
PIDE database – http://www.gsi.de/bio-pide
Friedrich *et al., J. Radiat. Res*. 2013

Non uniform target ... used in clinics (SRS, SBRT, ...

Overcoming resistance of cancer stem cells

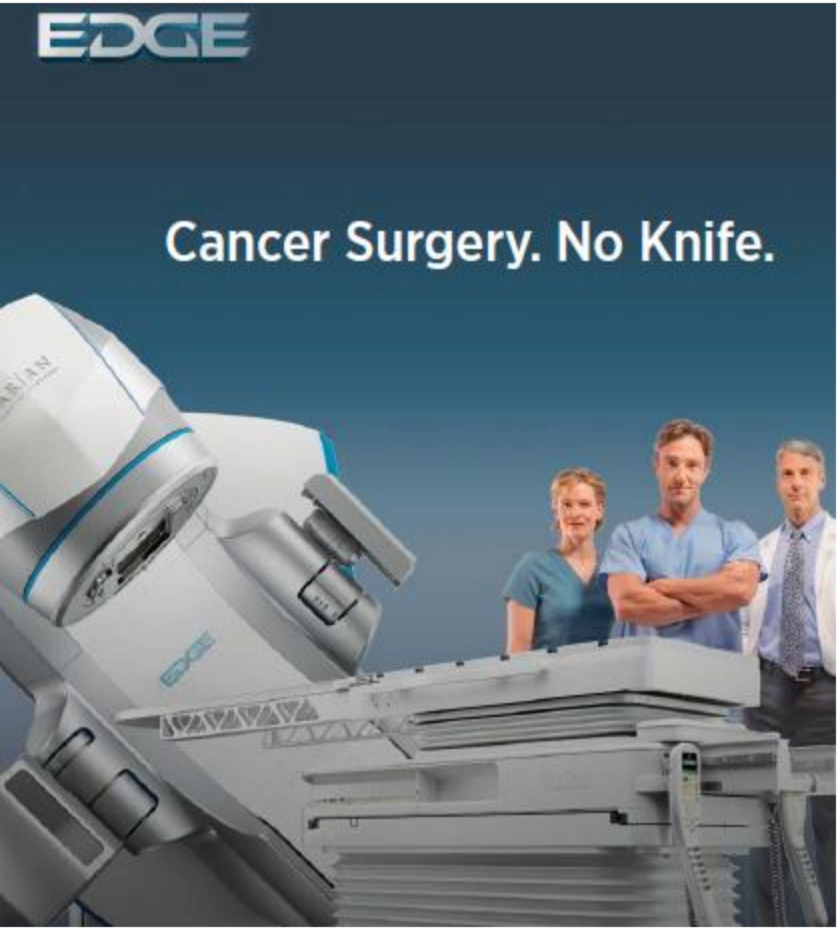
www.thelancet.com/oncology **Vol 13 May 2012**

RBE in protontherapy



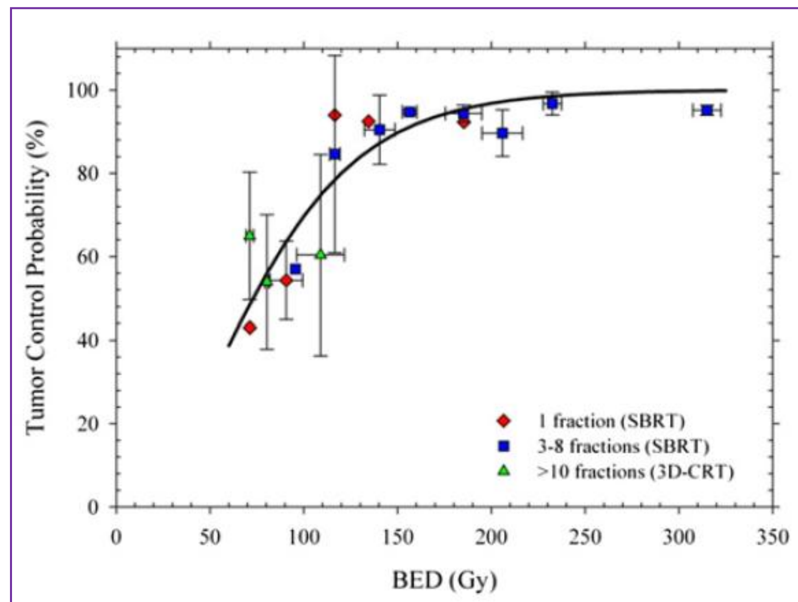
Grün *et al.*, *Med. Phys*. 2013

Radiosurgery (SBRT): the new frontier in stereotactic image-guided radiotherapy



- Stage I (T1N0M0) NSCLC
- Oligometastases
  - Hepatocellular carcinoma
  - Advanced (T2-T4; >3 cm) NSCLC
  - Localized tumors in kidney, prostate, pancreas, adrenal gland, pravertebal tumors etc.

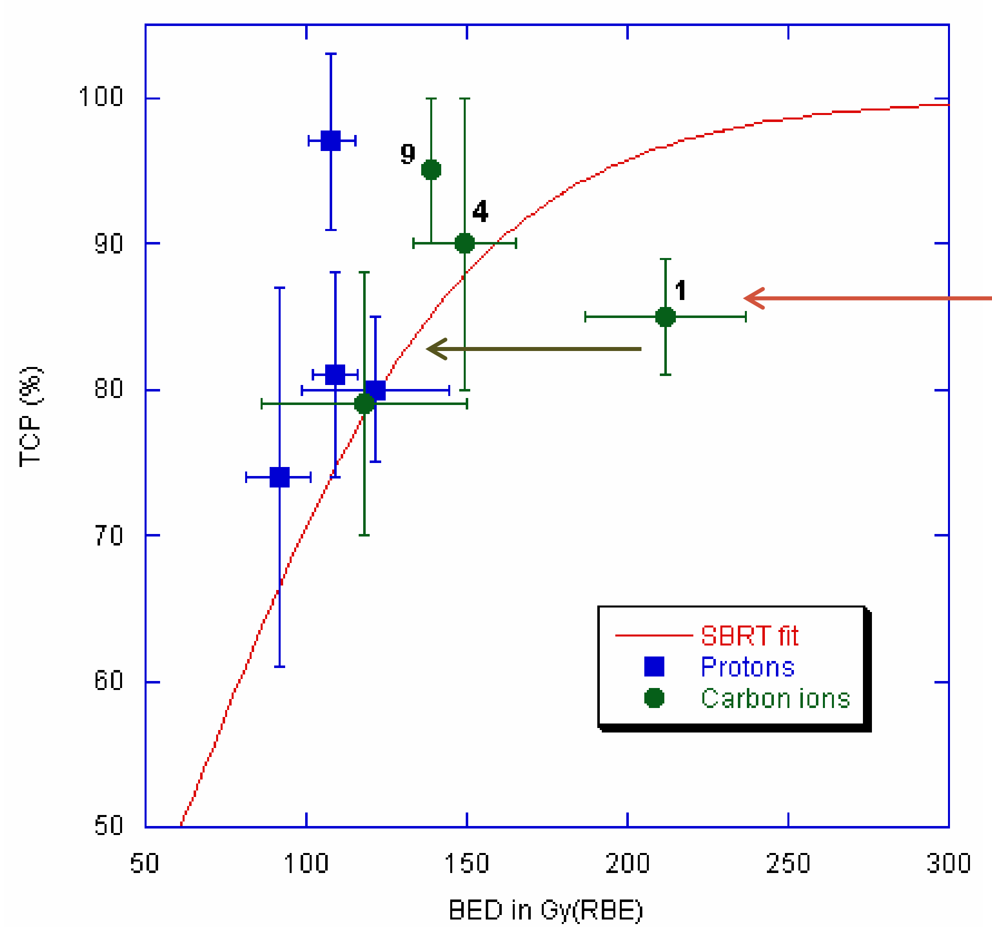
$$BED_{\alpha/\beta} = nd\,[1 + d/(\alpha/\beta)\,] \qquad \text{(LQ model)}$$



Brown *et al., Int. J. Radiat. Oncol. Biol. Phys*. 2013

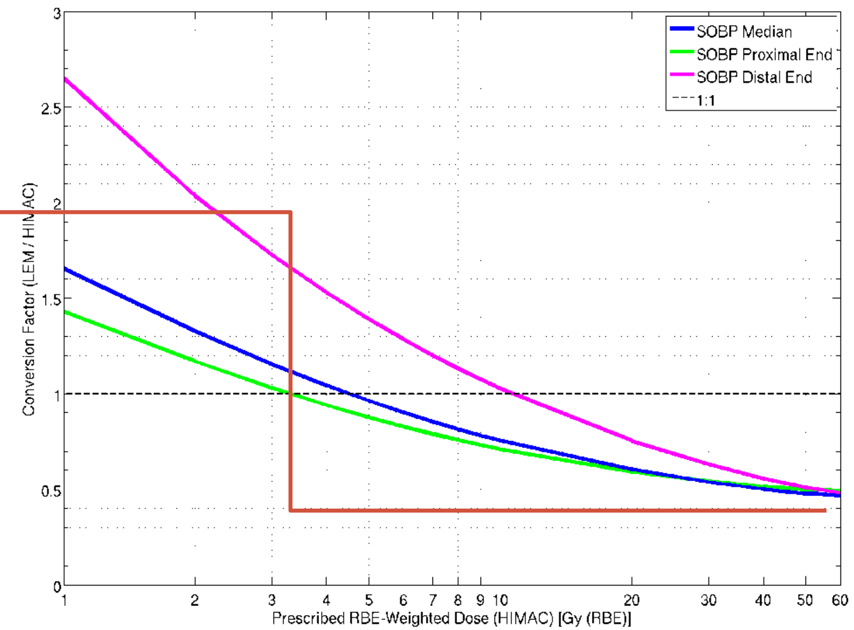
SBRT only possible thanks to IGRT and to the low *mean* dose to parallel organs

Ions vs. X-rays in SBRT for NSCLC



TCP vs. BED for Stage I NSCLC by X-rays or charged particles

Durante, *Br. J. Radiol*. 2013



HIMAC vs. LEM: dependence of the RBE on the dose/fraction *d*

Steinsträter *et al.*, *Int. J. Radiat. Oncol. Biol. Phys*. 2012

Re-oxygenation in radiosurgery

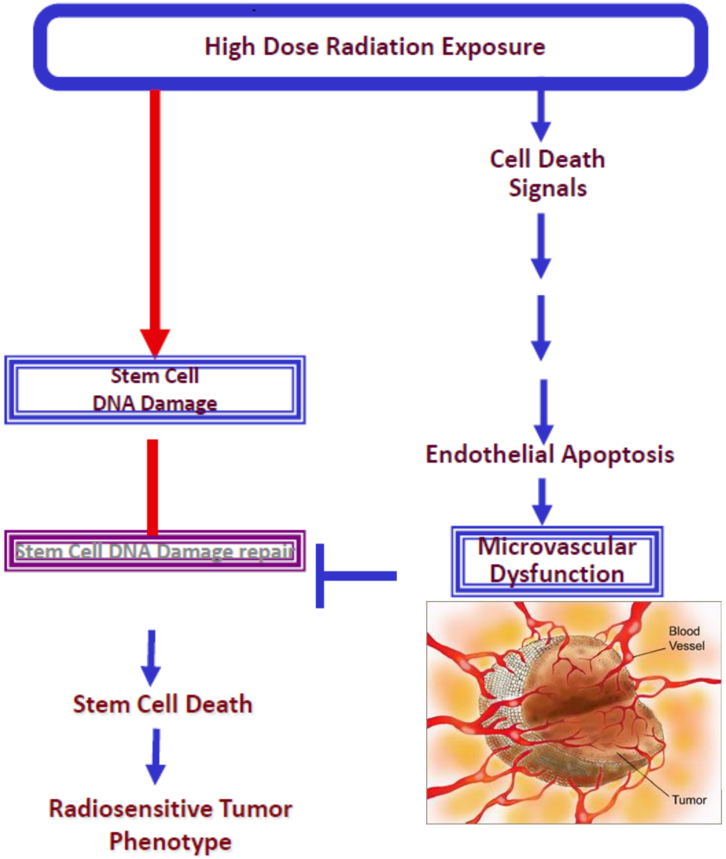
- Models of oligofractionation predict failure for hypoxic tumors
- re-oxygenation between fractions is in fact essential for local control for at least some tumors (H&N, cervix, pancreas, prostate).
- if the number of fractions is severely reduced then this vital process will be rendered less effective

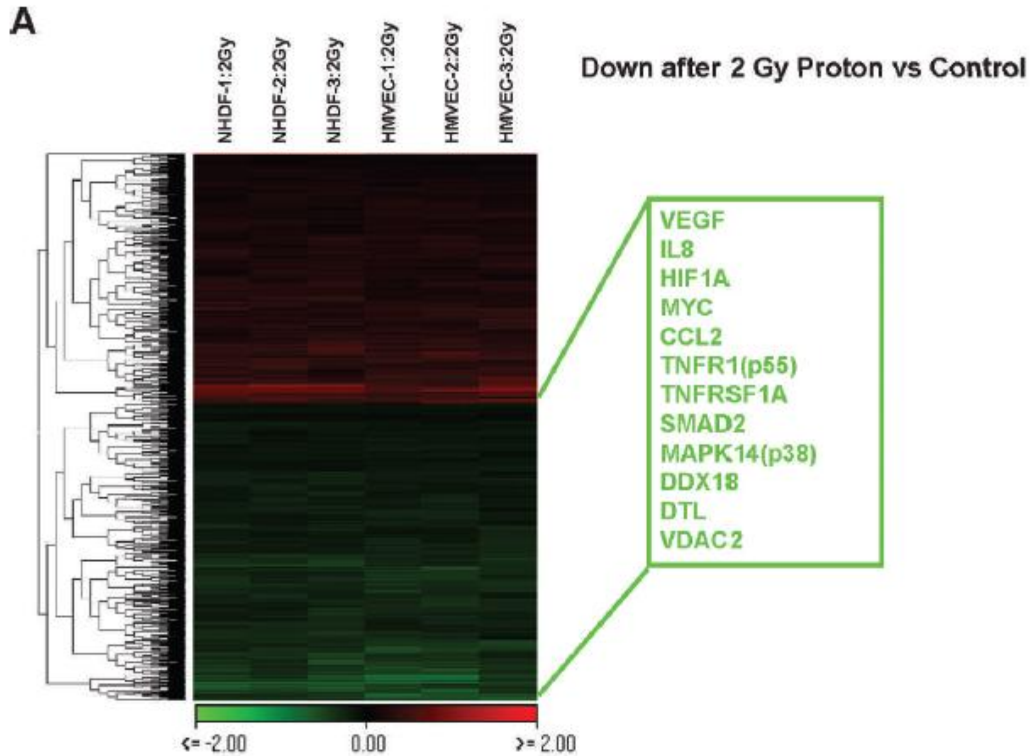
Published in final edited form as:
Int J Radiat Oncol Biol Phys. 2010 October 1; 78(2): 323–327. doi:10.1016/j.ijrobp.2010.04.070.

Stereotactic ablative radiotherapy should be combined with a ~~hypoxic cell radiosensitizer~~ heavy ions

J. Martin Brown, D.Phil., Maximilian Diehn, M.D., Ph.D., and **Billy W. Loo Jr., M.D., Ph.D.**
Department of Radiation Oncology

A new radiobiology for high-dose, single fraction stereotactic radiosurgery (hypofractionation, SBRT)?

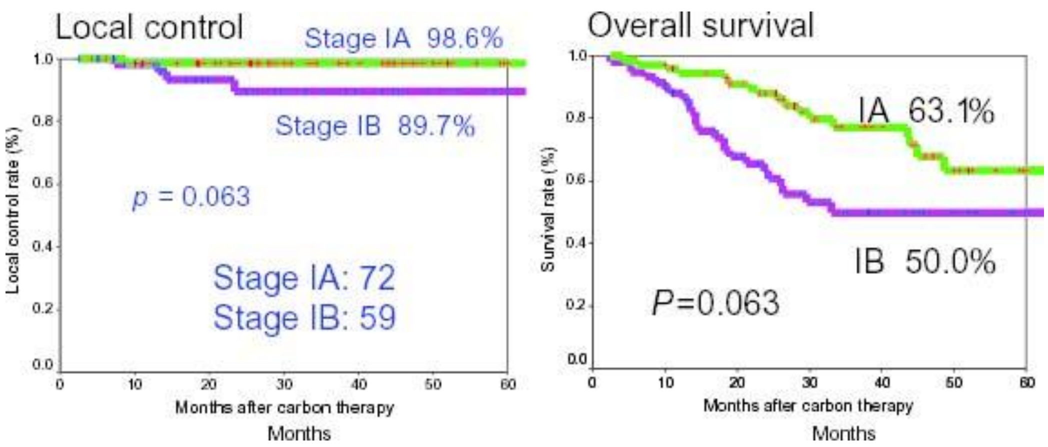




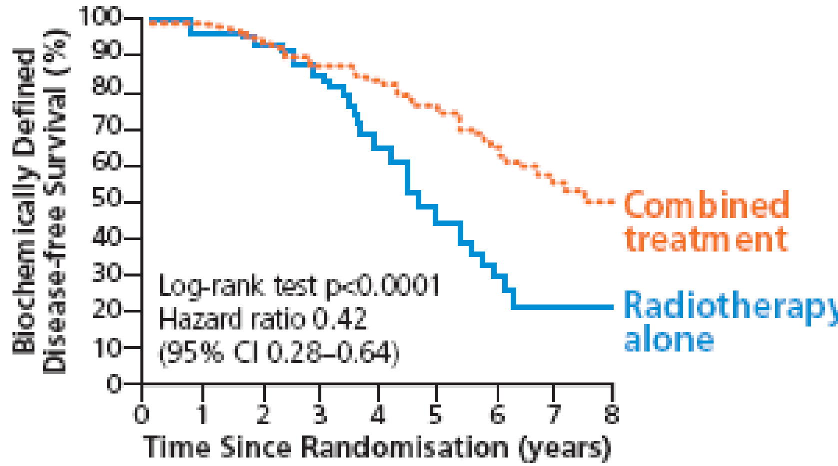
Girdhani *et al., Radiat. Res*. 2012

•Kolesnick *et al., Science* 2008

Combined treatments: beyond LC

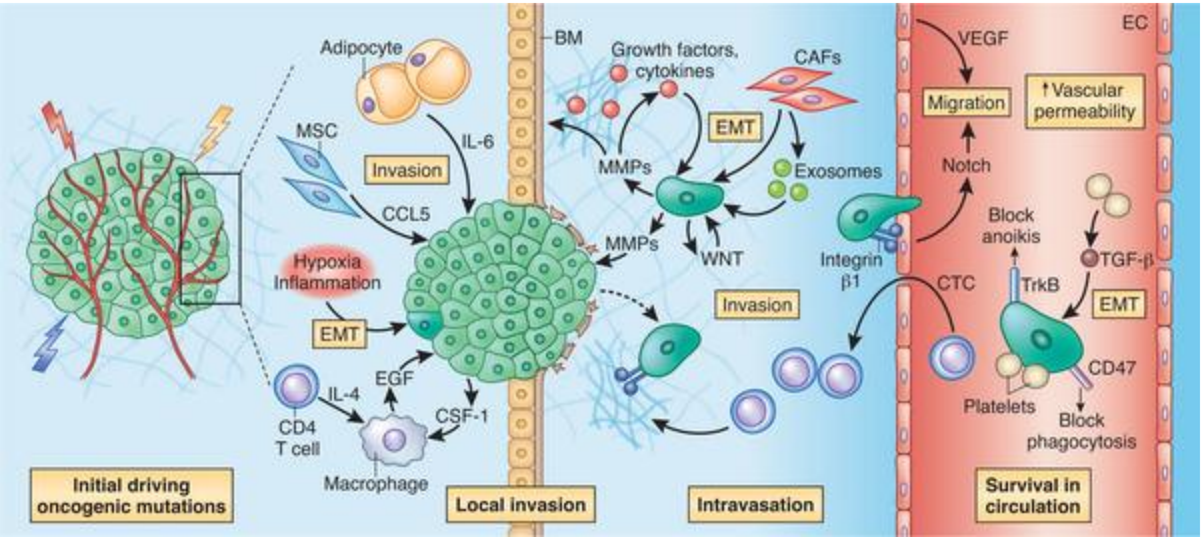


Tsujii *et al.*, *New J. Phys*. 2008



High risk prostate cancer patients RT + ADT

Bolla *et al.*, *Lancet* 2012



Wan *et al.*, *Nat. Med.* 2013

IGRT+immunotherapy

Melanoma – Ipilimumab (anti-CTLA4)

Postow et al.; Hiniker et al.

N.Eng. J. Med. 366; 2012

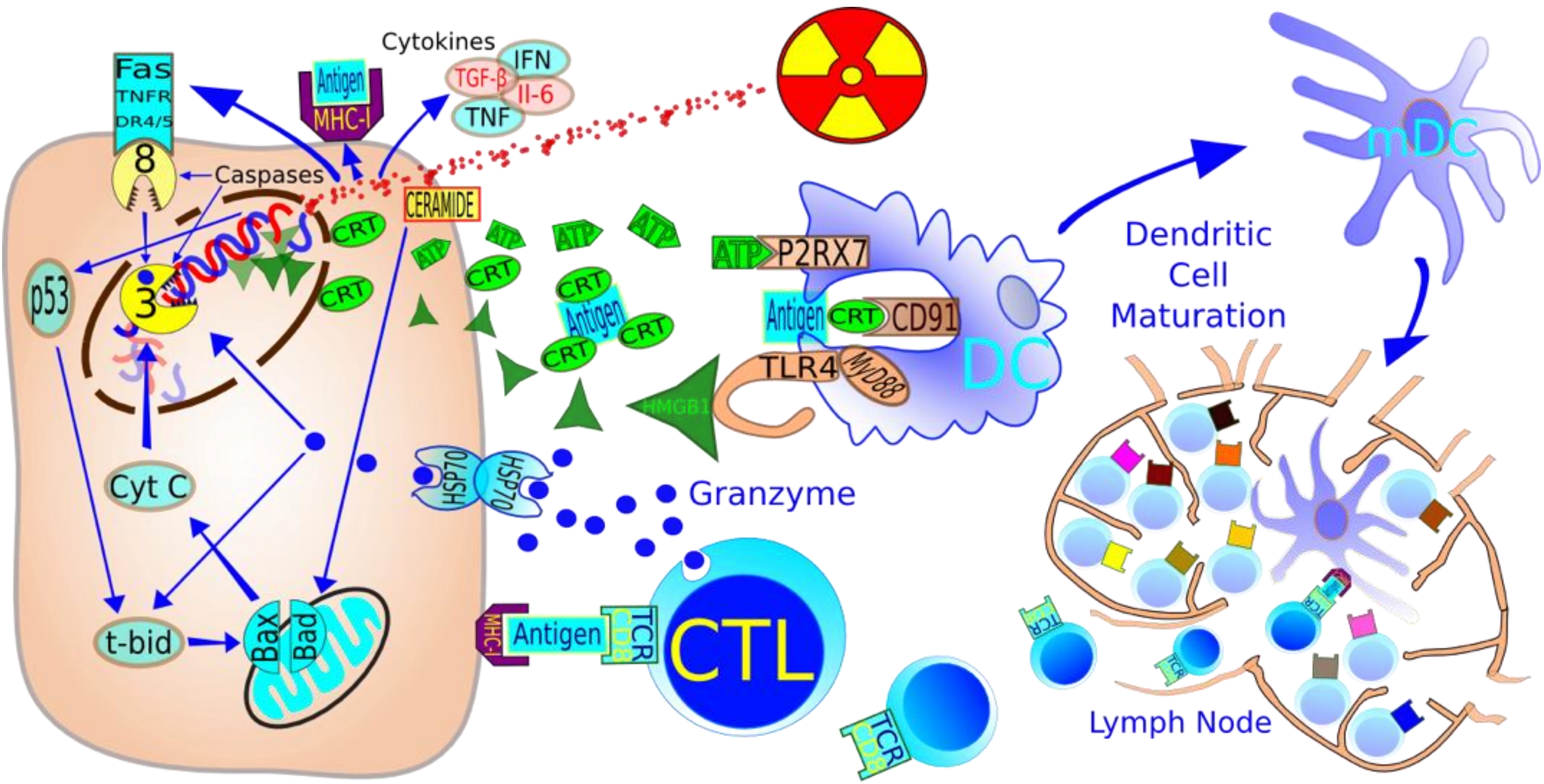
Oligometastasis – Sunitinib (anti-STAT3 and –VEGF)

Tong et al., *PLoS One* 7; 2012

Chondrosarcoma – **protons** + sunitinib

Dallas et al., *J. Med. Case Rep*. 6; 2012

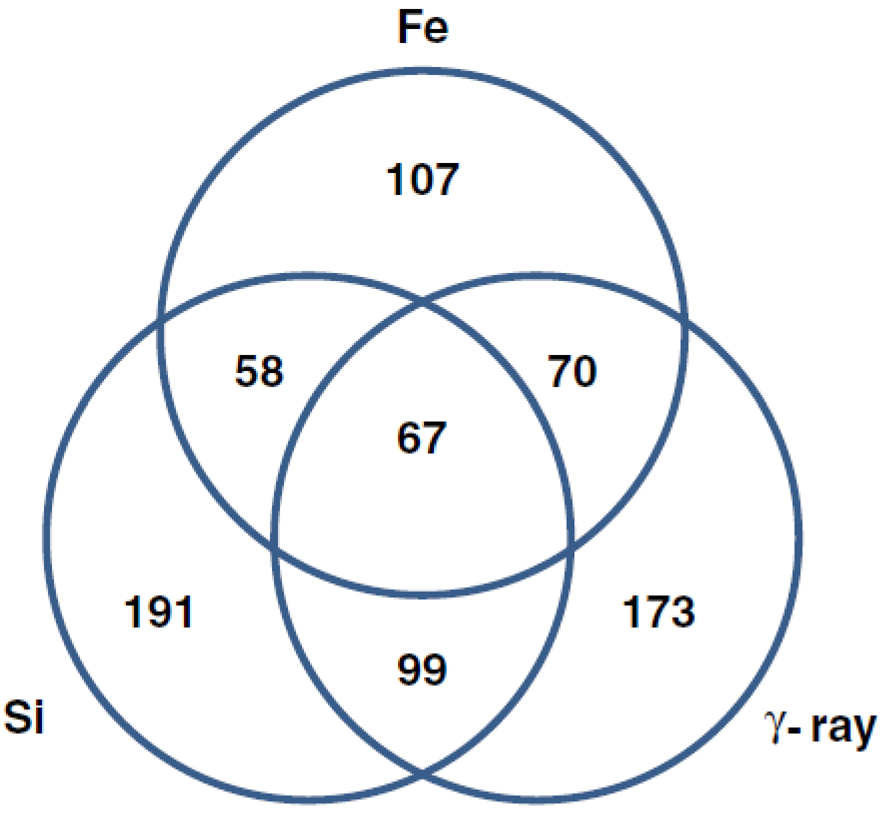
Radioimmunology mechanisms



Durante *et al.*, *Trends Mol. Med*. 2013

Radiogenomics in particle therapy

- To develop a genetic risk profile for individualization of radiation dose prescriptions
- Genetic variations include single nucleotid polymorphism (SNP), copy number variations (CNV), epigenetic changes
- Candidate-gene approach: DNA repair (BRCA1/2), cytokine production (TGFb), scavenging of free radicals (SOD2) etc.
- So far no association found between SNP and radiotoxicity (Barnett *et al.*, *Lancet Oncol*. 2012)
- Large differences in gene expression have been observed in vitro after γ-rays or charged particles



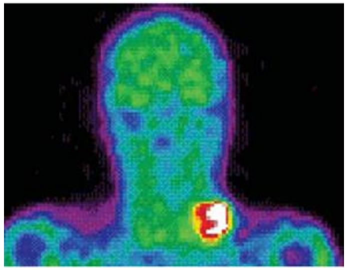
Differentially expressed genes in human bronchial epithelial cells exposed to γ-rays or heavy ions (Ding *et al.*, *BMC Genomics* 2013)

Intratumour heterogeneity in treatment planning

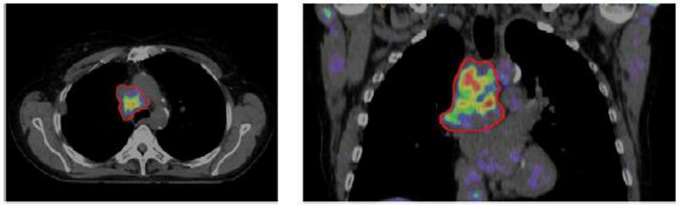
Is a complex issue, affecting different sensitivity or function

- Is normally responsible of treatment outcome
- Can be in principle detected by functional imaging (PET):

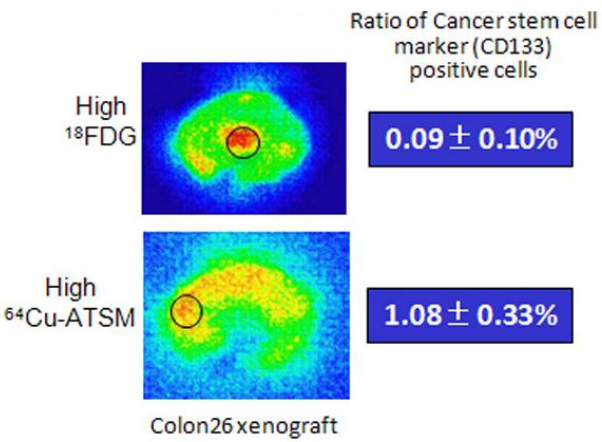
- ^{18}FDG-> areas with enhanced metabolism (recurrence?)
- ^{18}F-MISO or ^{18}F-HX4 → hypoxia
- γH2AX→ highly repairing subpopulations
- ^{64}Cu-ATSM-> niches of cancer stem cells



F-MISO:Mortensen *et al., Acta Oncol*. 2010

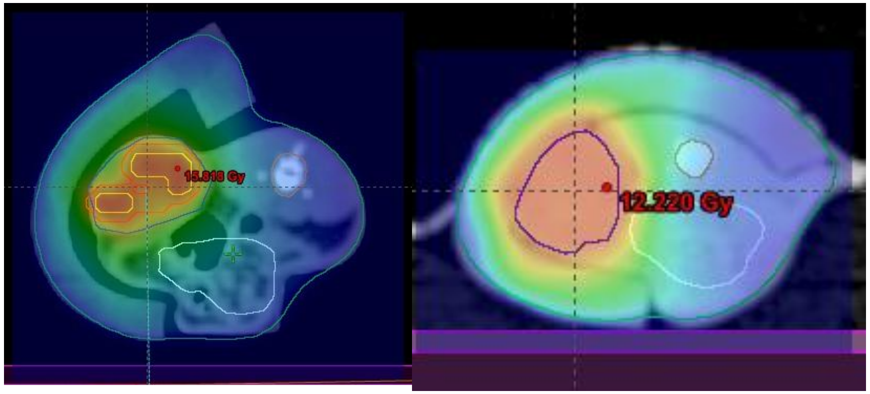


F-HX4:Dubois *et al., Proc. Natl. Acad. Sci. USA* 2011



^{64}Cu-ATSM

Yoshii et al., Nucl. Med. Biol. 2010



Heterogeneous (Left) and homogeneous(Right) irradiation plans of two rat rhabdomyosarcomas .
Heterogeneous (dose painted) plan was based on PET imaging of FDG tumour uptake at 2 hr post-injection.
(Courtesy of Daniela Trani , MAASTRO).

OER(pO_2, LET) model for adaptive particle treatment planning

$$OER(\overline{L},p) = \frac{b(aM+\overline{L}^3)/(a+\overline{L}^3)+p}{b+p}$$

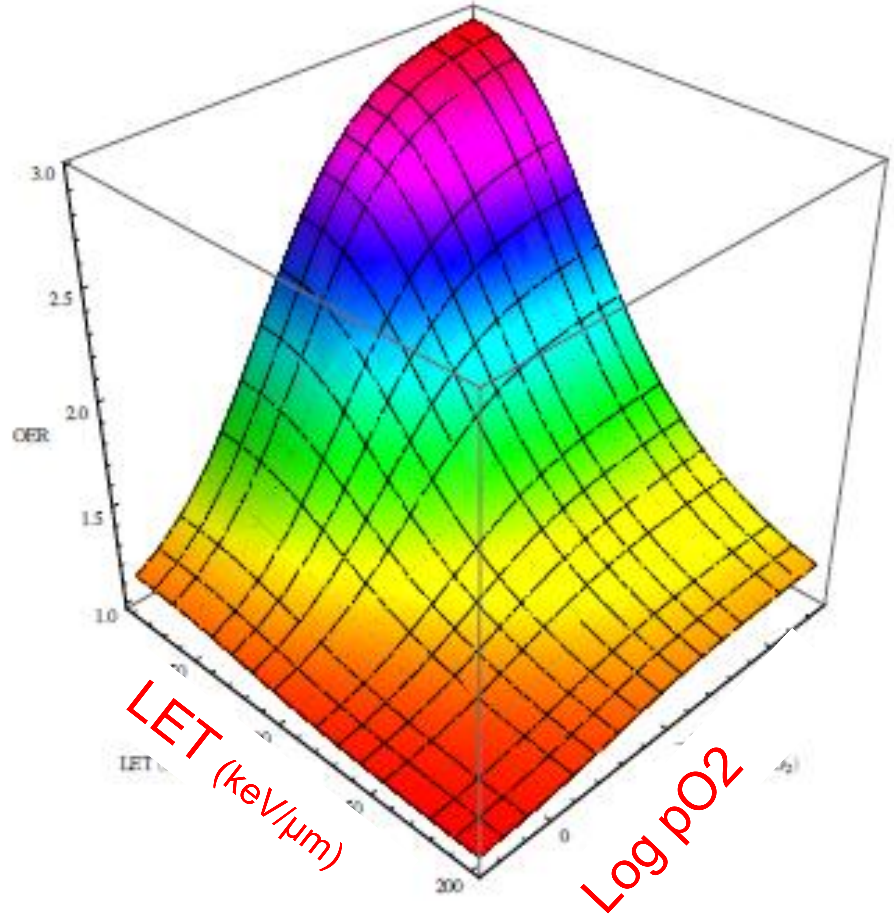
$$D^{i}_{bio}(\vec{N}) = \sqrt{\frac{\alpha_i \cdot \vec{c}_i^{\,T} \cdot \vec{N} + \beta_i \cdot (\vec{c}_i^{\,T} \cdot \vec{N})^2}{\beta_x} + \left(\frac{\alpha_x}{2\beta_x}\right)^2} - \frac{\alpha_x}{2\beta_x} \quad ;$$

Krämer & Scholz, *Phys. Med. Biol. 2006*

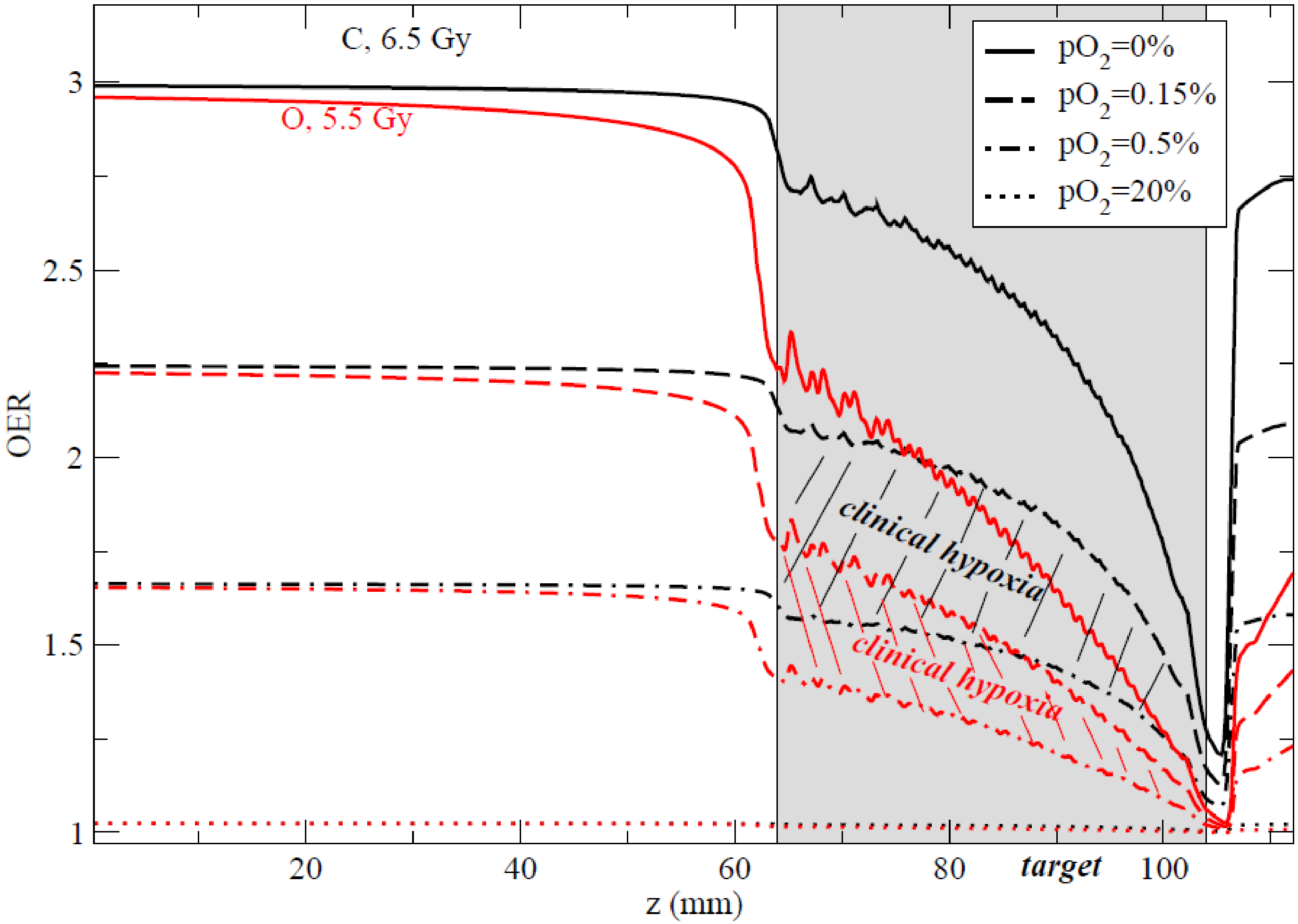
$$\alpha'_i(\overline{L}_i, p_i) = \alpha_i / OER(\overline{L}_i, p_i)$$

$$\sqrt{\beta'}_i(\overline{L}_i, p_i) = \sqrt{\beta_i} / OER(\overline{L}_i, p_i)$$

Scifoni *et al.*, *Phys. Med. Biol*. 2013



OER along an irradiated volume for different ions

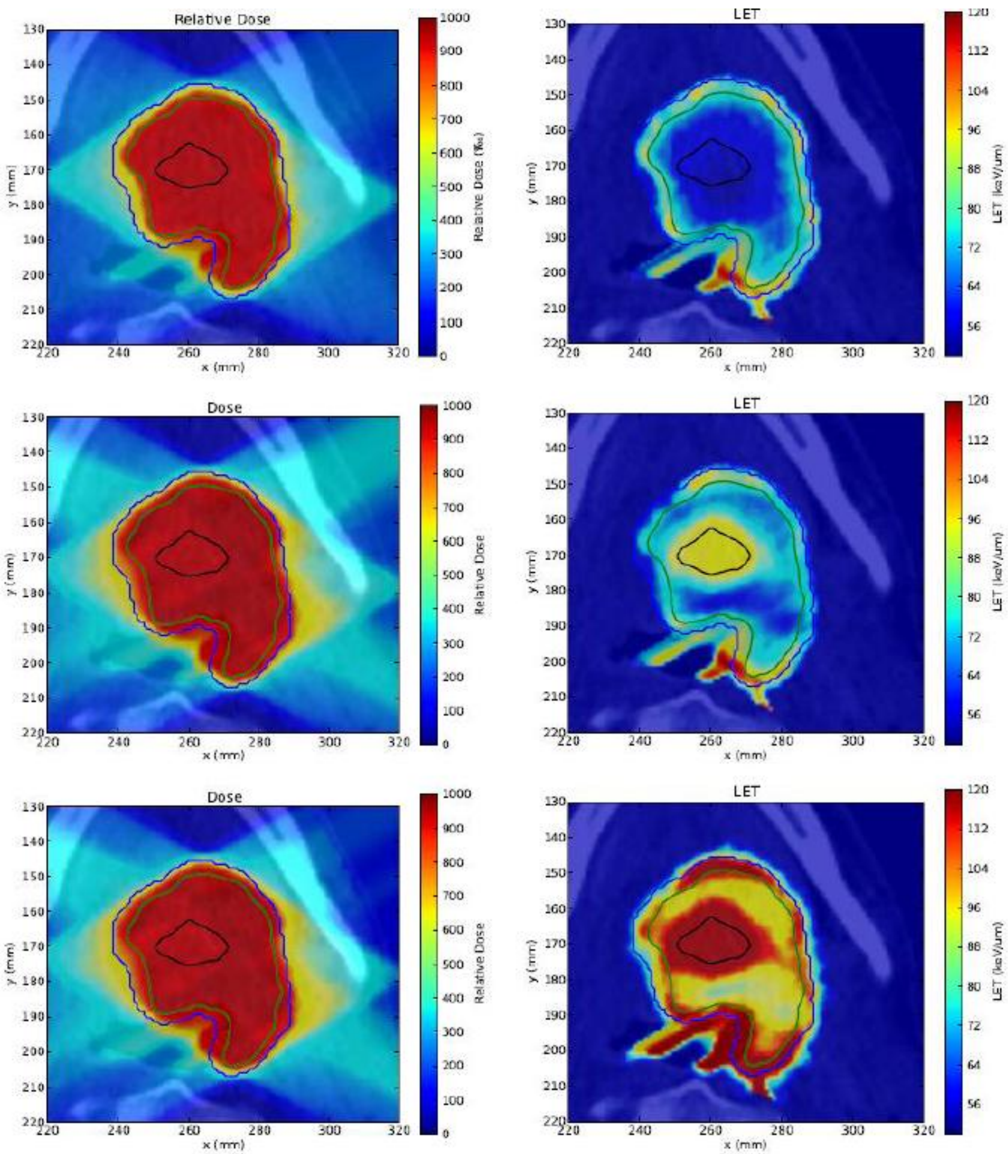


Krämer *et al., J. Phys. Chem. Solids* 2013

- C, O, p and soon He available @HIT
- Joining OER driven and Multiion modality in next TRiP release

LET painting

Bassler *et al.*, *Acta Oncol*. 2013

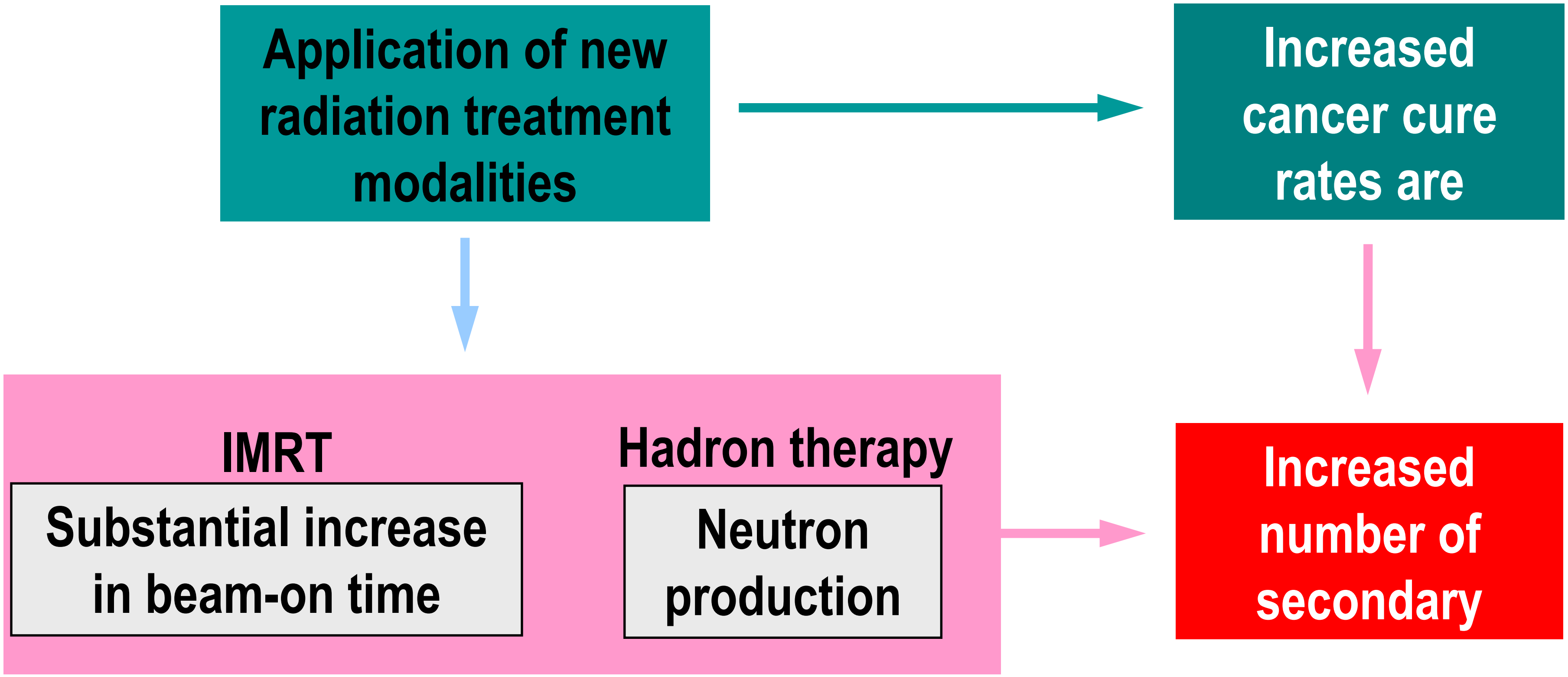


4 flat fields C-ions

4 ramped fields C-ions

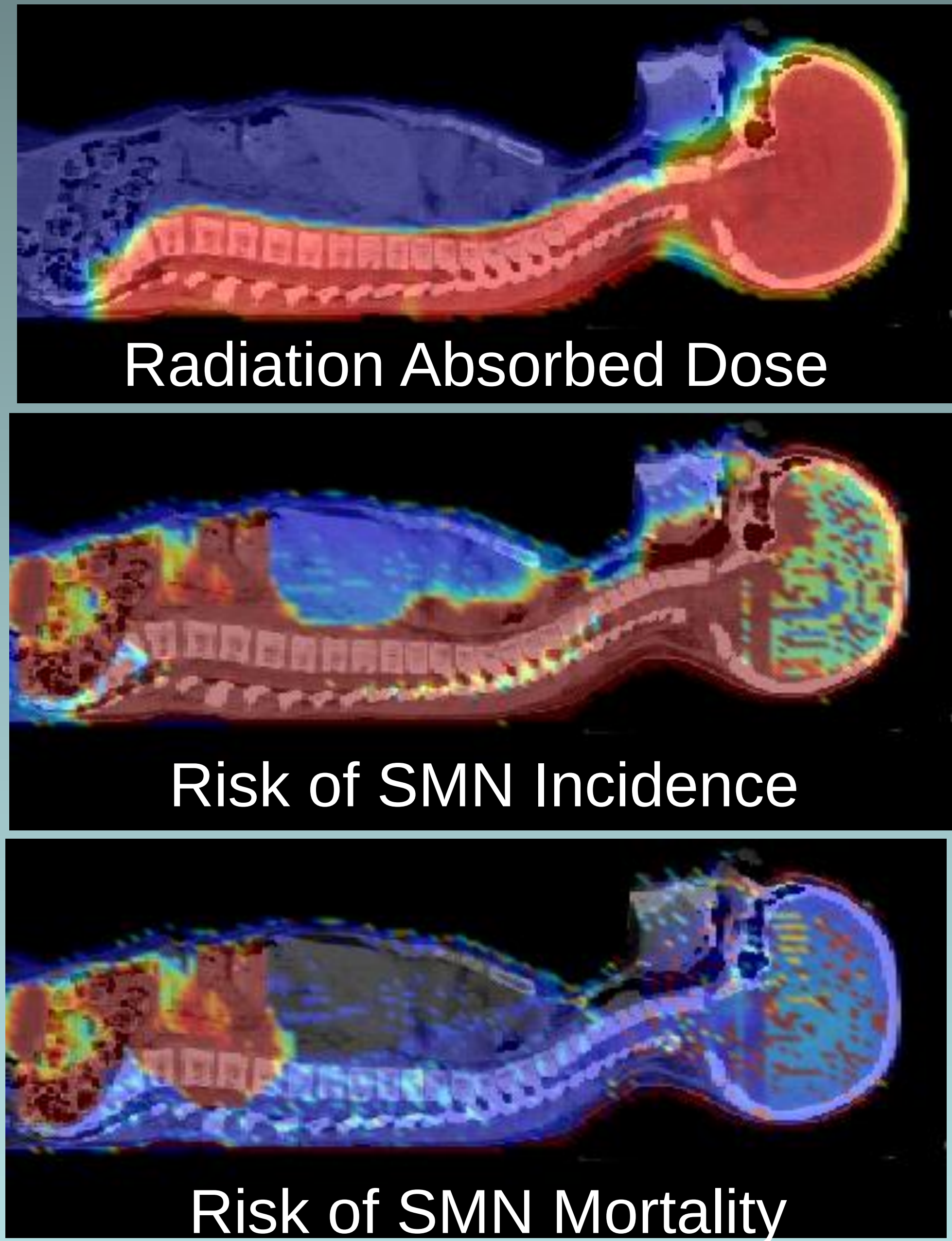
4 ramped fields O-ions

Second malignant neoplasias (SMN)



- Childhood cancer is 1% of cancer diagnosis, but 1st cause of disease-realted death in children
- Most common pediatric tumors are leukemia (34%) and CNS tumors (27%)
- Survival rate is now over 80%, but the incidence of SMN is close to 20%
- Most common SMN are breast, CNS, bone, soft tissue, AML

Secondary Malignant Neoplasms (SMN) in particle therapy



Comparison of relative radiation dose distribution with the corresponding relative risk distribution for radiogenic second cancer incidence and mortality. This 9-year old girl received craniospinal irradiation for medulloblastoma using passively scattered proton beams. The color scale illustrates the difference for absorbed dose, incidence and mortality cancer risk in different organs.

Newhauser & Durante,

Nature Rev. Cancer 2011

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What do we need?

1. Exploiting RBE against radioresistant subpopulations (CSCs, hypoxia...) using non-uniform dose target coverage and multi-ions
2. Modelling hypofractionation with charged particles (including tumor hypoxia and NTCP)
3. Animal models for vascular damage in tumors
4. Animal models for radioimmunotherapy at very high dose/fraction and STAT3/VEGF inhibition
5. Radiotoxicity in genetically modified animals
6. Inclusion of second cancer risks in pediatric TP

Biophysics Department

M. Durante (Director)

G. Kraft (Helmholtz Professor)

G. Taucher-Scholz (DNA damage)

S. Ritter (Stem cells)

C. Fournier (Late effects)

C. Hartel (Clinical radiobiology)

M. Scholz (Biophysical modelling)

M. Krämer (Treatment planning)

C. Graeff (Moving targets)

C. La Tessa (Dosimetry)

Thank you very much!

http://www.gsi.de/biophysik/