Tumor Therapy with Ion Beams

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Outline

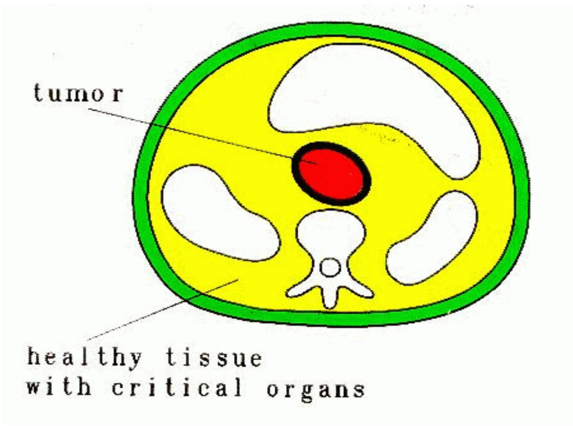
- Why ion beams?
  - Physics: Improved dose delivery
  - Biology: Increased effectiveness

- Pilot project at GSI Heavy Ion Research Center
  - Physical / technical aspects
  - Radiobiology / biophysical modelling

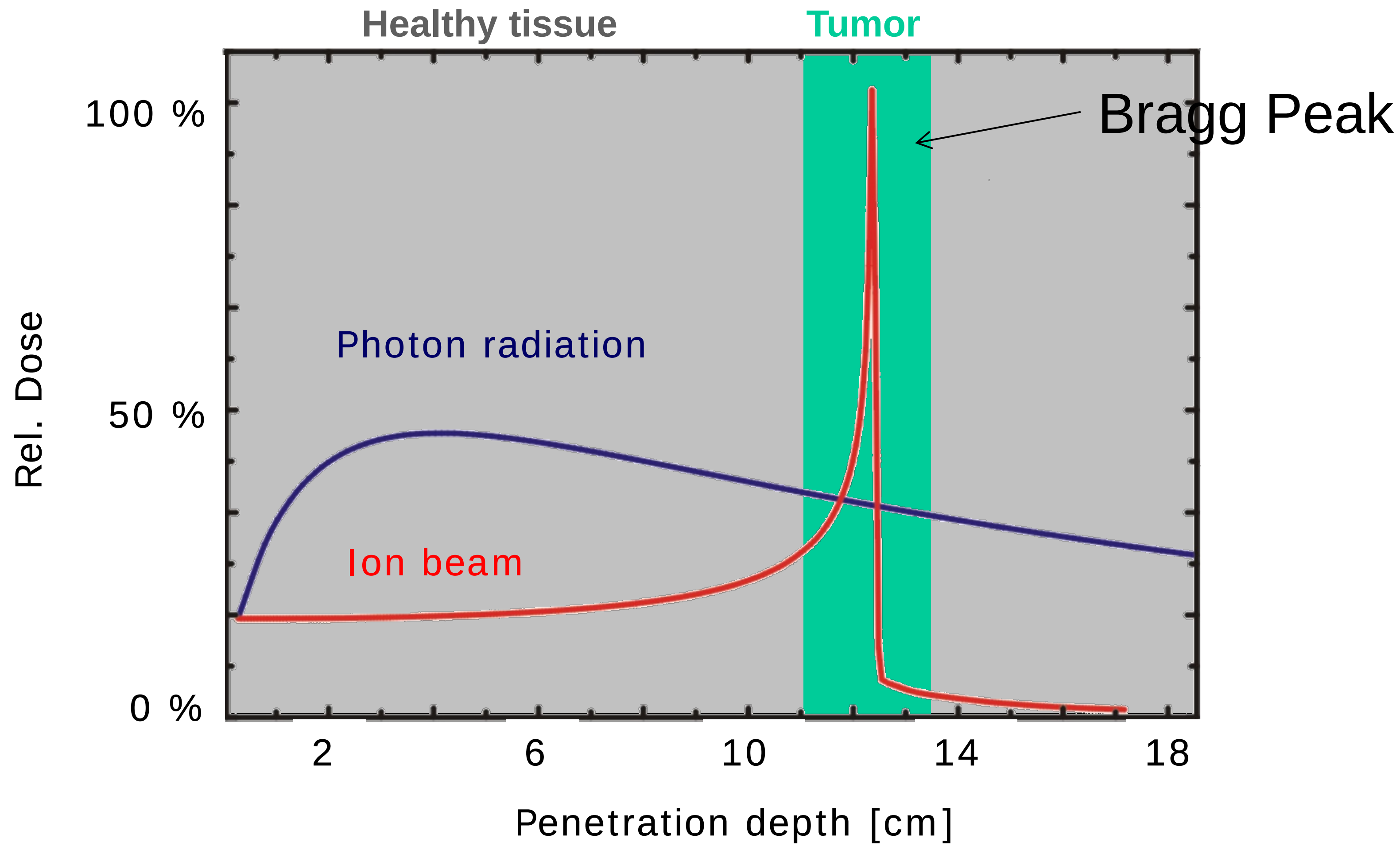
- Translation to clinical application: HIT Heidelberg

- Future perspectives

Limits of Conventional Photon Therapy

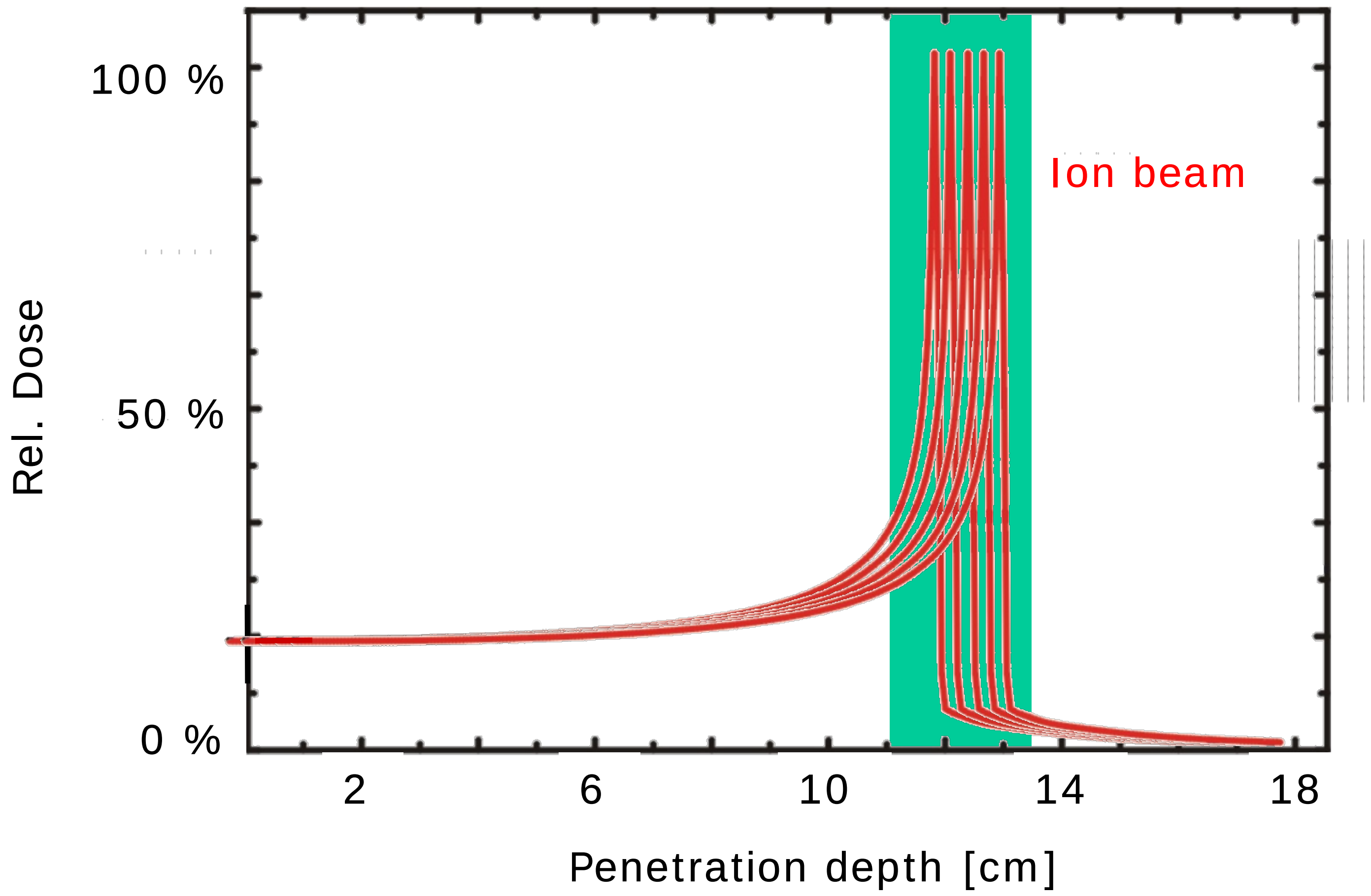


Advantage of Ion Beams: Physical



First proposal for clinical use of ion beams: Wilson 1946

Variation of Penetration Depth

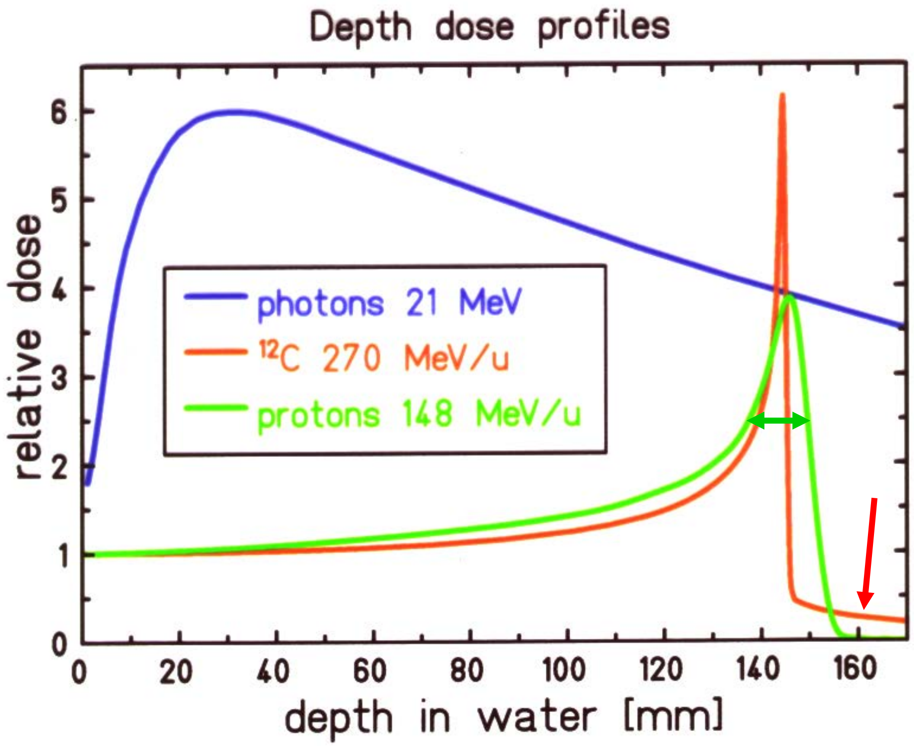


Range variation by energy variation:

Passive (cyclotron+synchrotron)

Active (synchrotron)

Comparison Proton – Carbon Ions



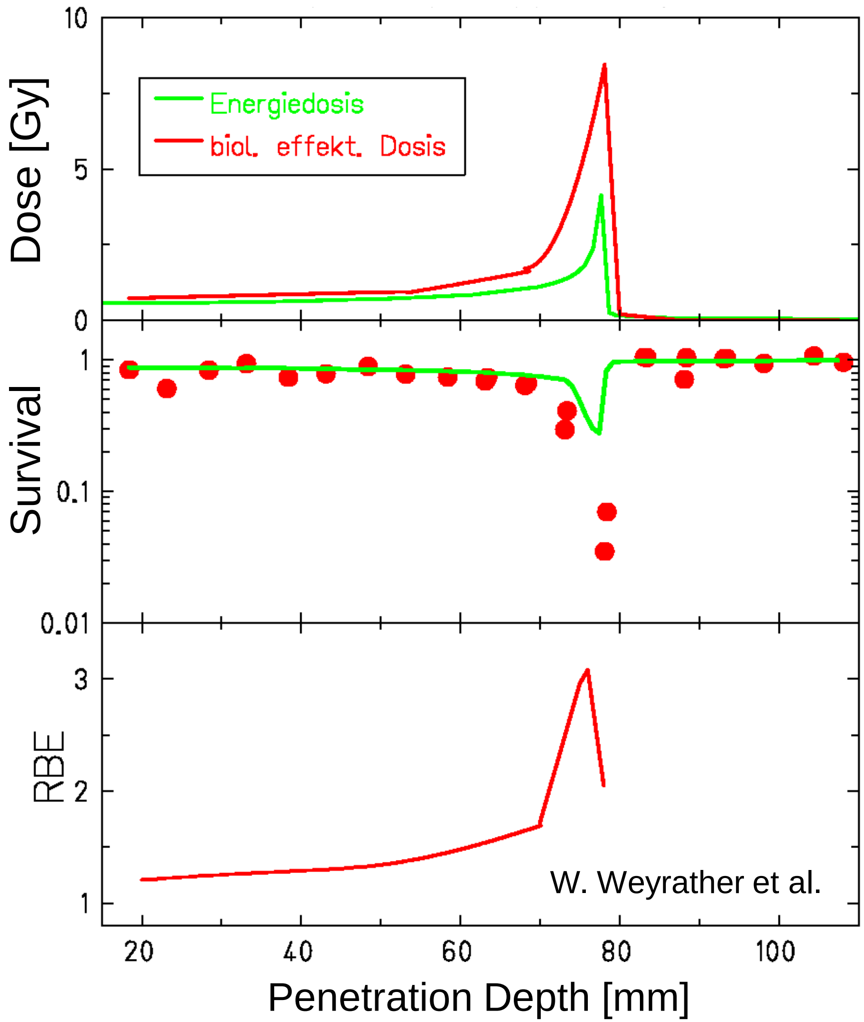
U. Weber, PhD Thesis 1996

Protons: more pronounced straggling

Carbon: fragmentation of primary ions

Biological Advantage: Increased Effectiveness

Carbon 195 MeV/u



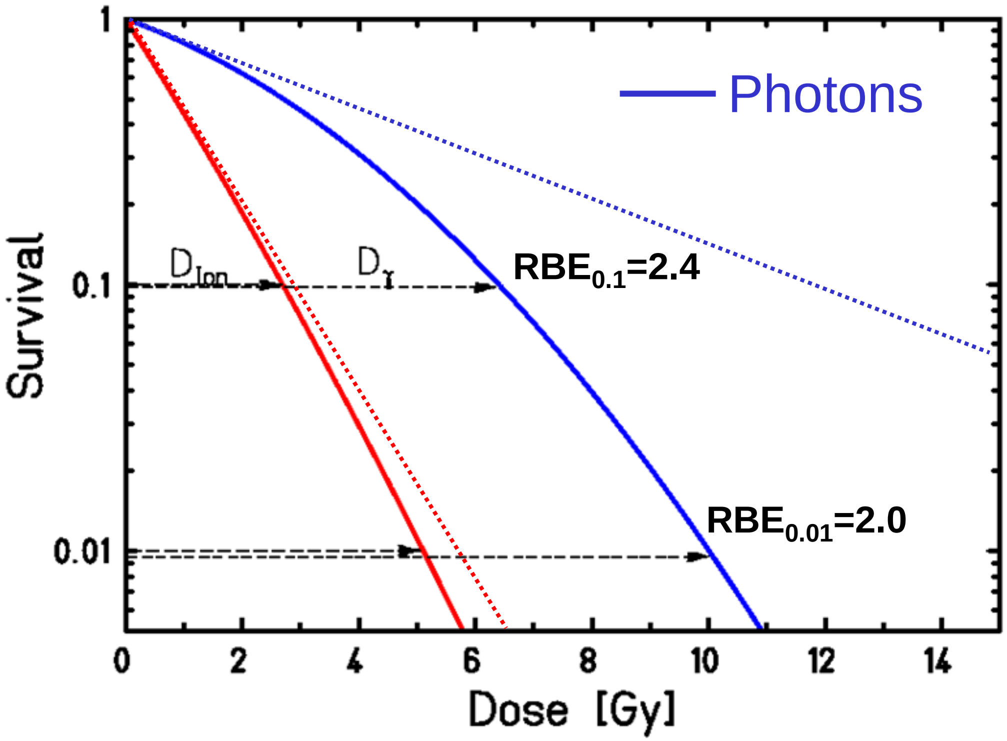
Relative Biological Effectiveness:

$$RBE = \frac{D_\gamma}{D_{Ion}}\Bigg|_{Isoeffect}$$

Differential Effect:

$RBE_{Depth} > RBE_{Entrance}$

Definition: Relative Biological Effectiveness (RBE)



$$S = e^{-(\alpha D + \beta D^2)}$$

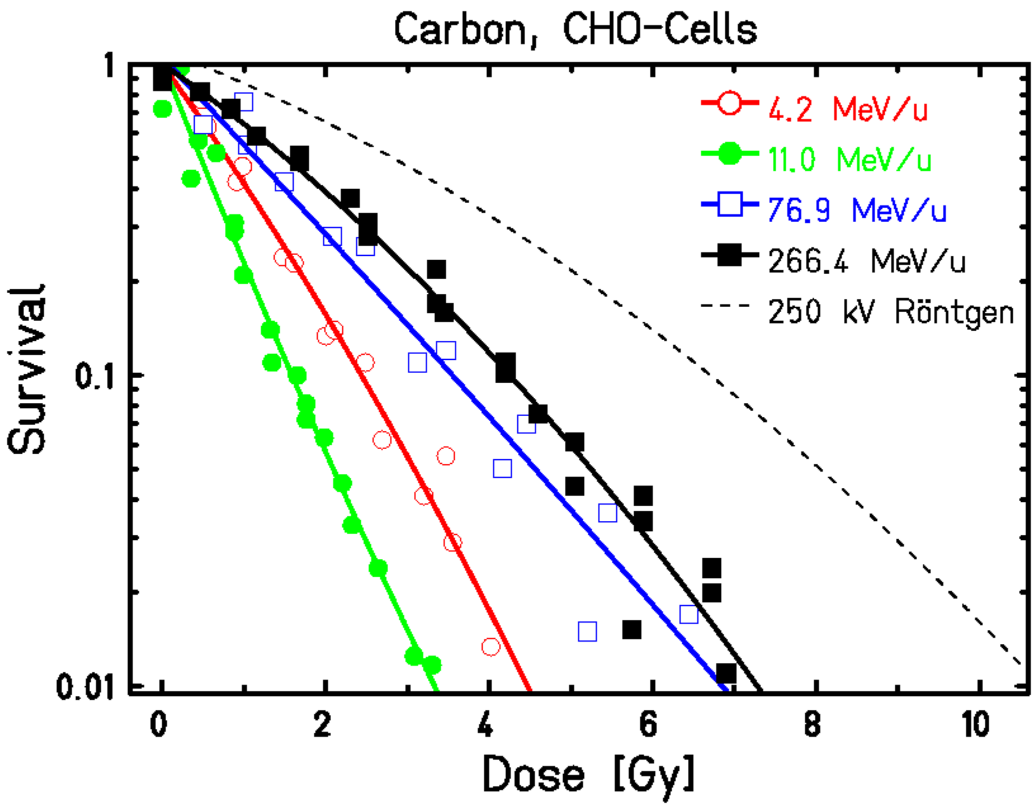
$$\alpha_{Ion} \geq \alpha_{Photon}$$

$$\beta_{Ion} \leq \beta_{Photon}$$

$$RBE = \left. \frac{D_{Photon}}{D_{Ion}} \right|_{Isoeffect}$$

$$RBE_{\alpha} = \frac{\alpha_{Ion}}{\alpha_{Photon}}$$

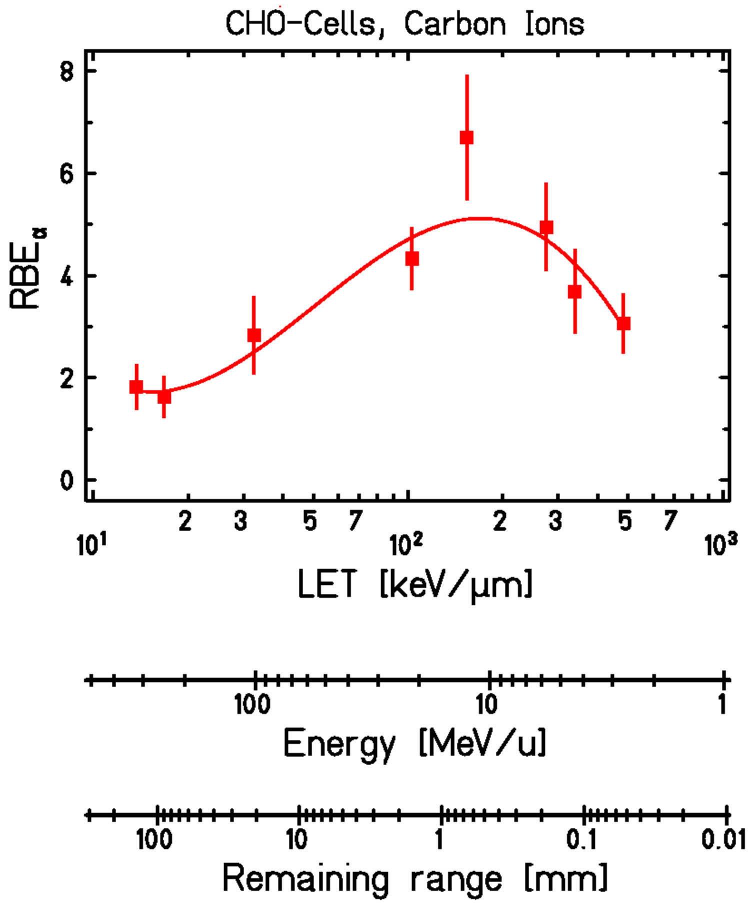
Survival after Carbon Ion Irradiation



W. Kraft-Weyrather
IJRB 1999

- Increasing effectiveness with decreasing energy
- Saturation effects at very low energies (<10 MeV/u)
- Transition from shouldered to straight survival curves

Linear Energy Transfer Dependence of RBE



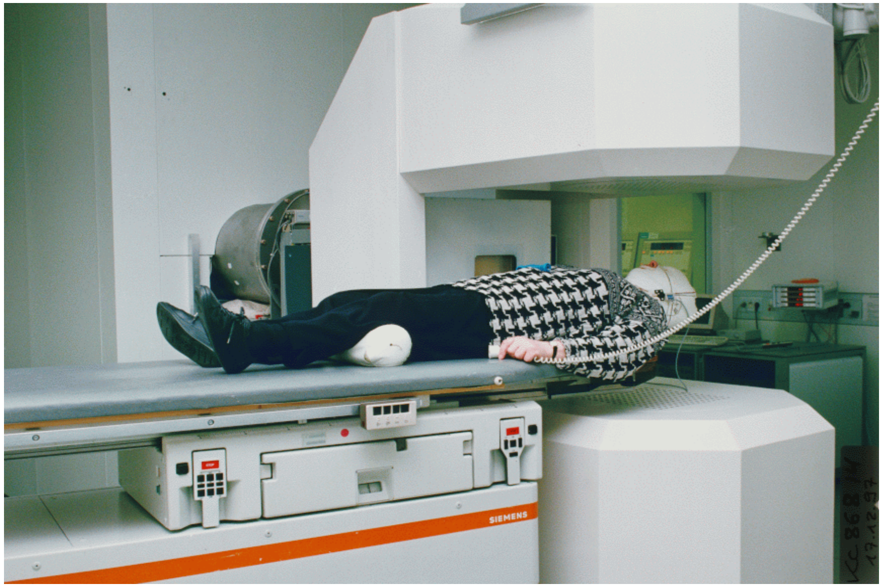
LET

≈

dE/dx

Weyrather et al. IJRB 1999

Pilot project for ion beam therapy at GSI



Cooperation partners:
Radiologische Klinik Heidelberg
Krebsforschungszentrum Heidelberg
Forschungszentrum Rossendorf

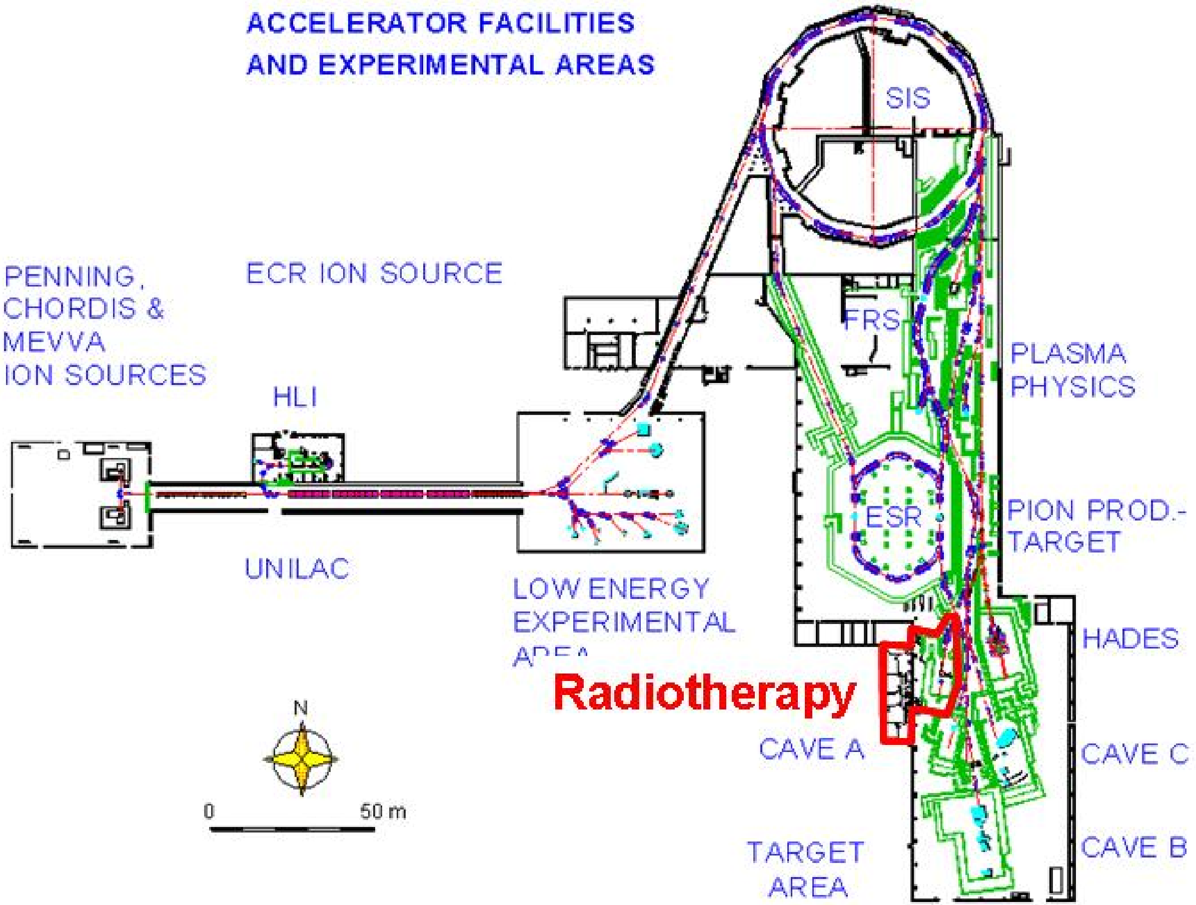
Special developments:

Active beam delivery (Rasterscan)

Positron emission tomograpy for range verification

Biologically optimized treatment planning

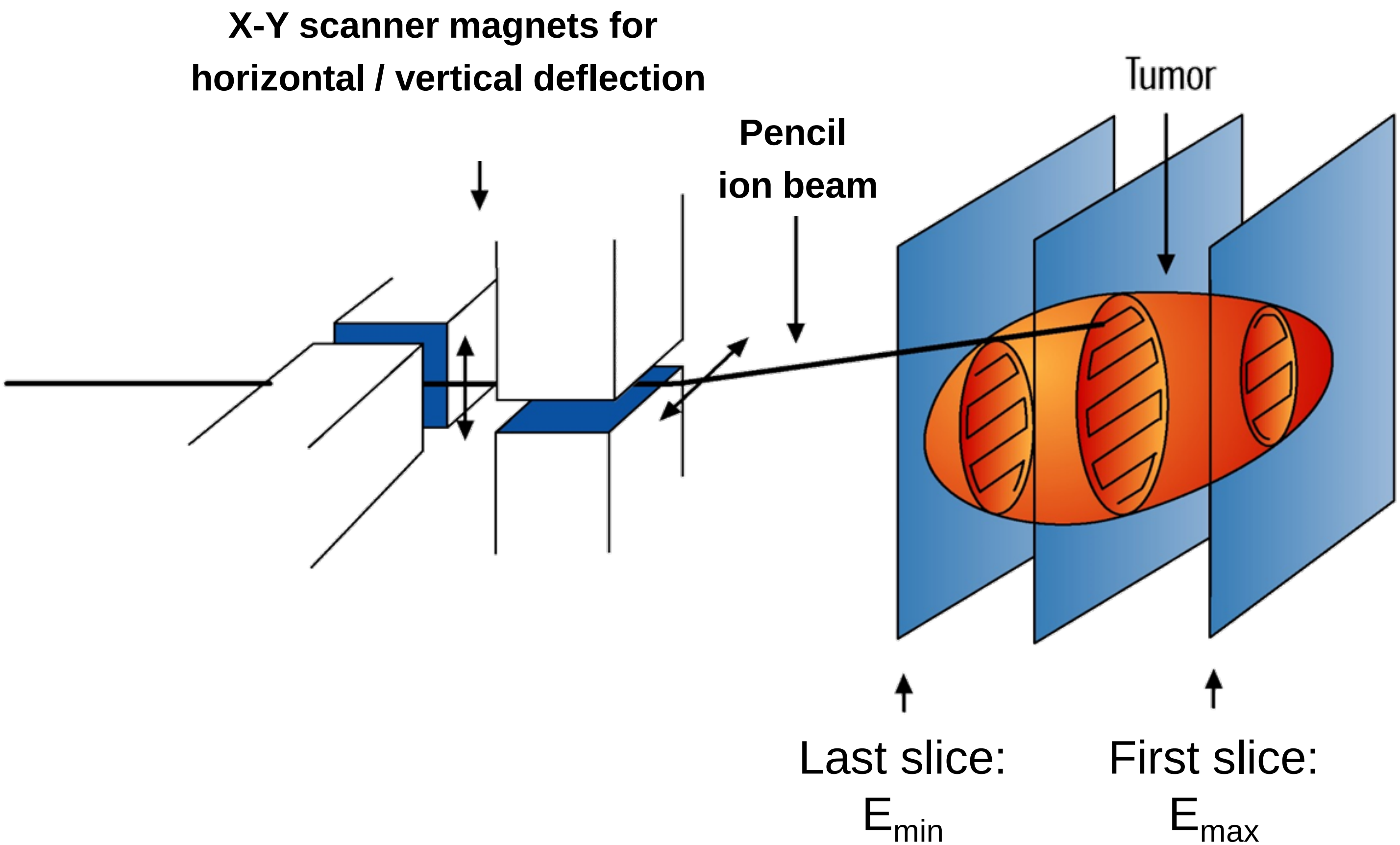
GSI Accelerator and Therapy Facility



Energies: < 15 MeV/u (UNILAC), < 2 GeV/u (SIS)

Ion species: Proton … Uranium

Active Beam Delivery

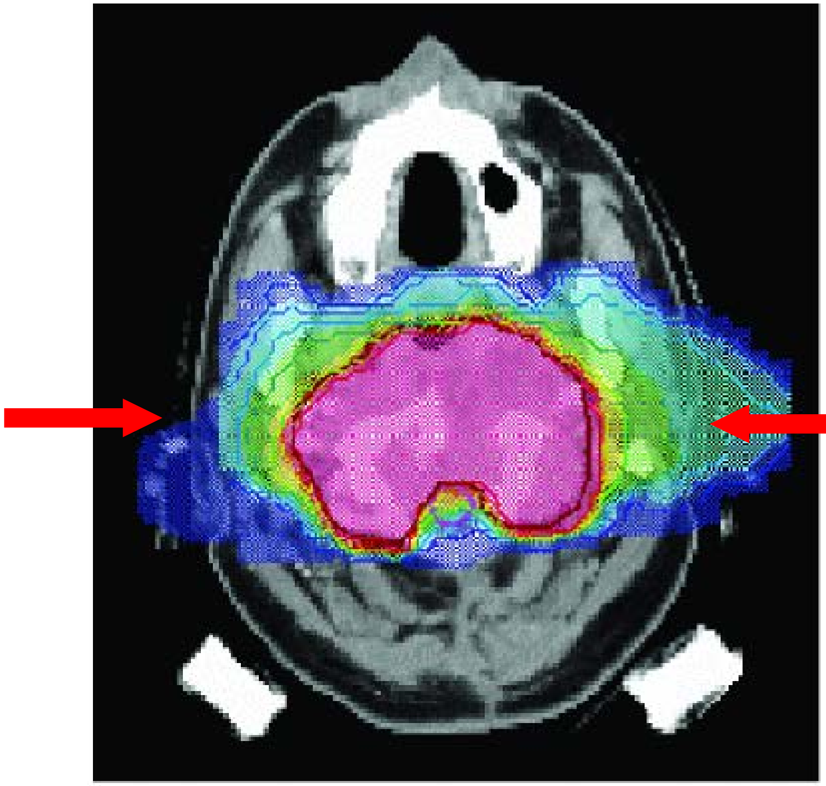


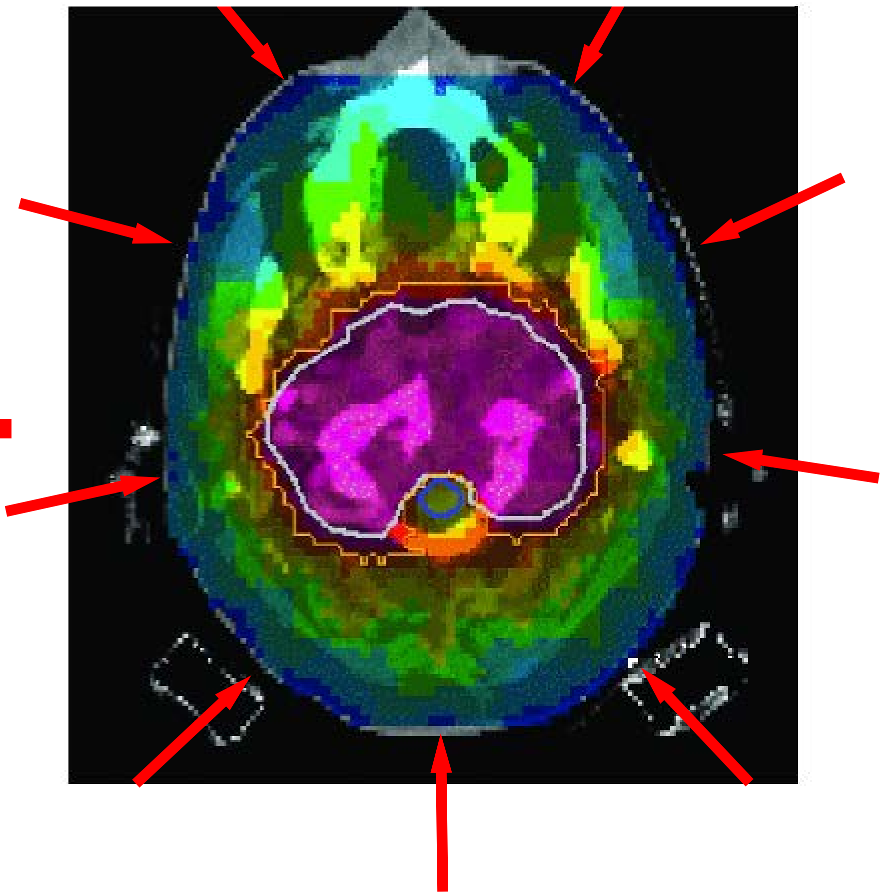
Intensity controlled raster scan

Accelerator Requirements

- Computer control of complete accelerator complex
- No manual interaction during irradiation
- Fixed accelerator parameters for library of 250 beam energies (5-35cm penetration depth)
- Slow extraction of beam for typically 5 sec.
- Variation of energy from pulse to pulse, i.e. within typically 2 seconds
- Library of 15 intensity steps and 7 focus steps chosen according to the dose level, size of the tumor and precision requirements
- Safety system for automatic abortion of beam in case of any failure

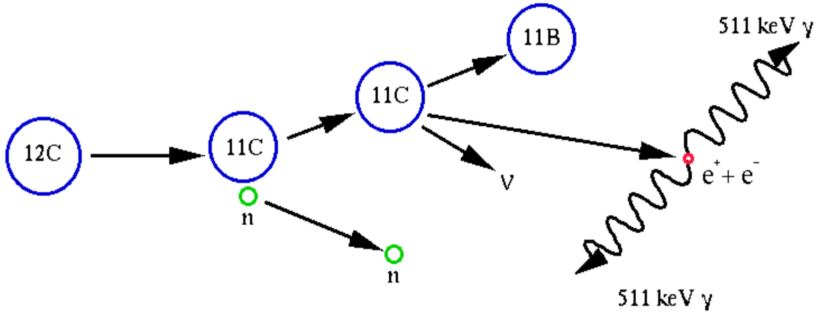
Comparison of Treatment Plans: Carbon Ions vs. Photons



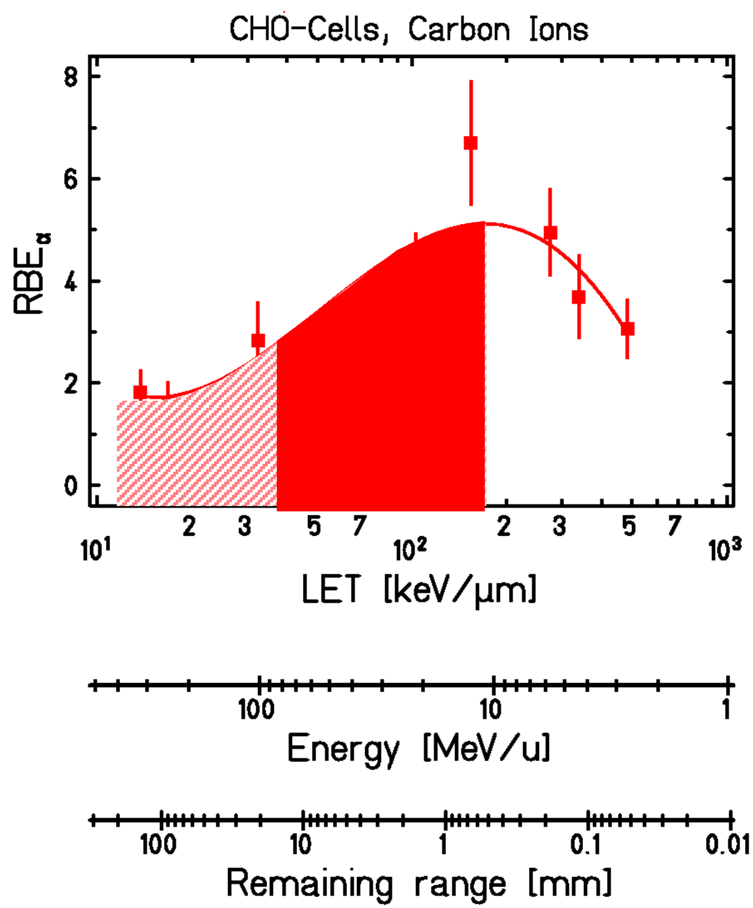


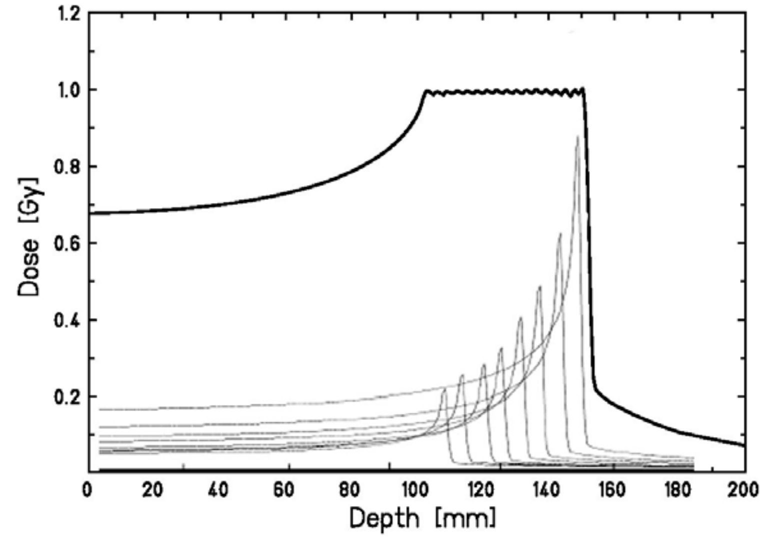
O. Jäkel et al.

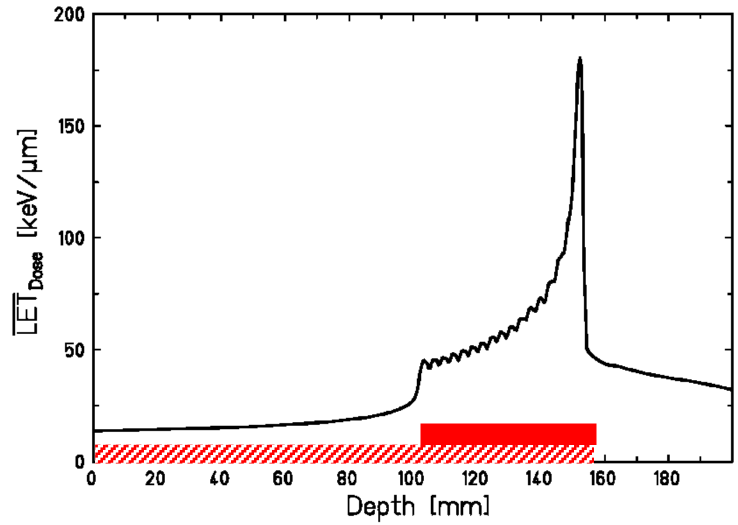
Positron Emission Tomography for verification of penetration depth



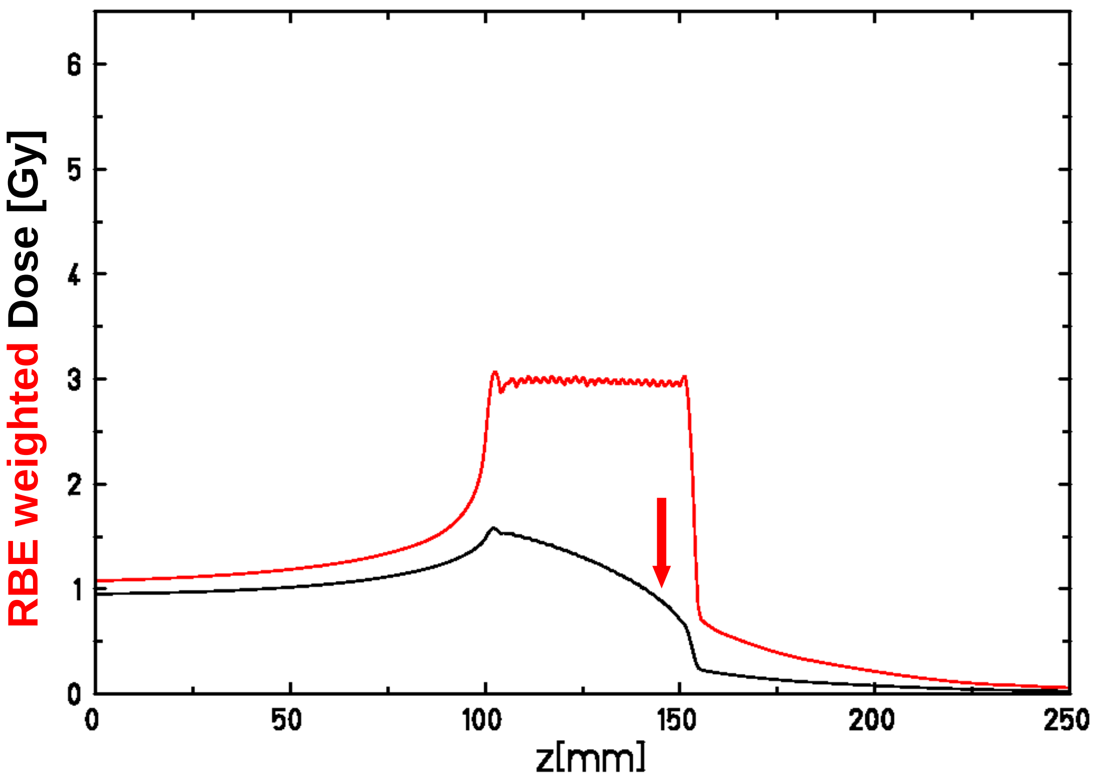
Depth Dependence of RBE







Depth Dependence of RBE



Goal of treatment planning: Homogeneous effect in target region

➡ Reduction of dose towards distal peakto account for increase of RBE

Treatment planning for carbon ions

Complex RBE dependencies: E, LET, D, cell type,…

Interpolation/extrapolation required for treatment planning in HI therapy

HIMAC

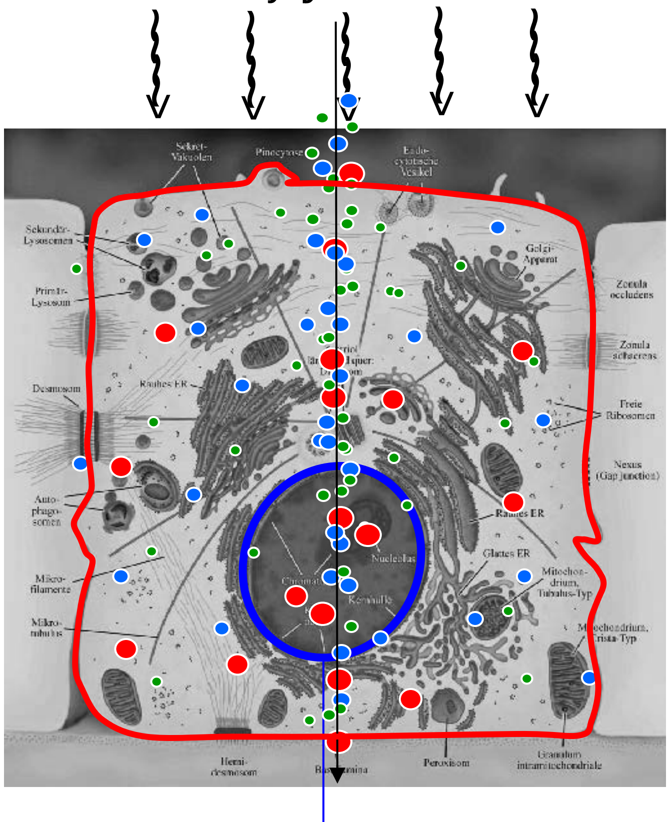
Experimental Data
+ Clinical Neutron Experience
(‚Fixed‘ RBE-scheme)

GSI / HIT

Biophysical Modelling
(Local Effect Model LEM)
(Variable RBE-scheme)

Radiation Biology: Basics

Energy deposition
by photons
by ions

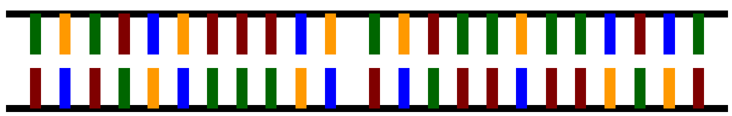


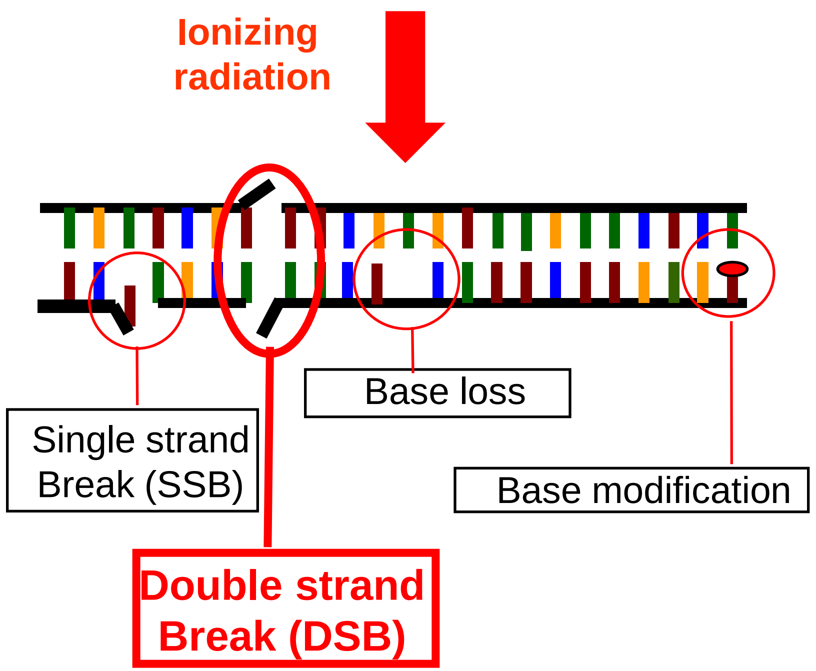
Cell nucleus represents the „critical target“, because it contains genetic information (DNA)

Genomic content of mammalian cell:

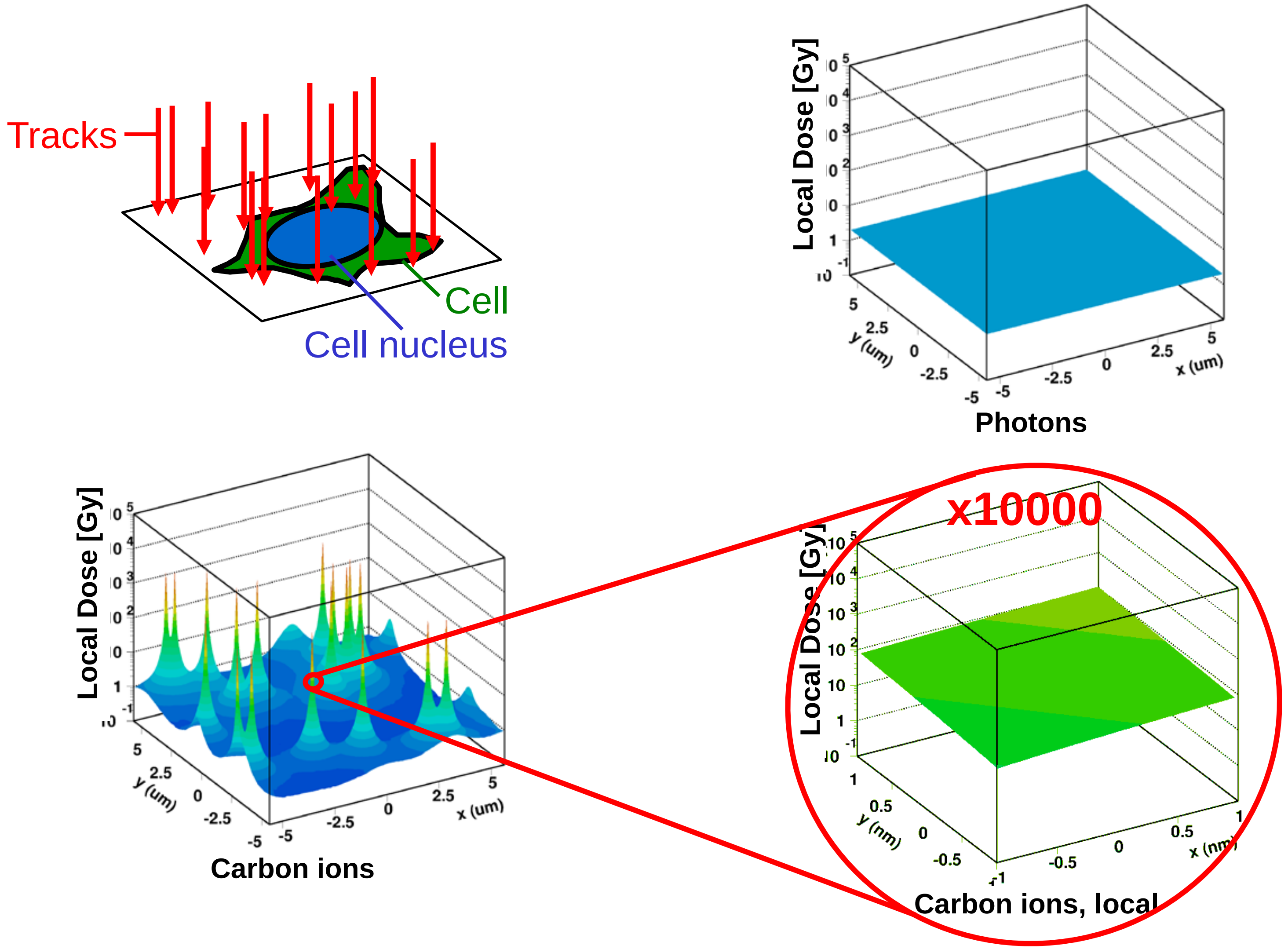
~ 3 x 10^9 base pairs

DNA double strand





Basics of Modelling

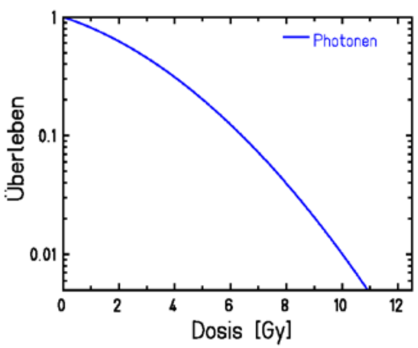


Local Effect Model LEM

Basic Assumption:

Increased effectiveness of particle radiation can be described by a combination of the photon dose response and microscopic dose distribution

Local Effect (Photons) = Local Effect (Ions)



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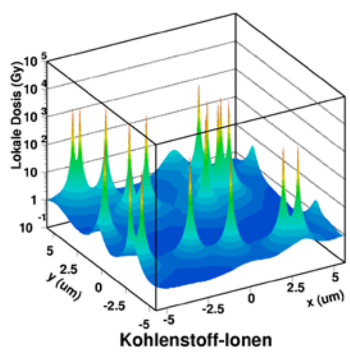
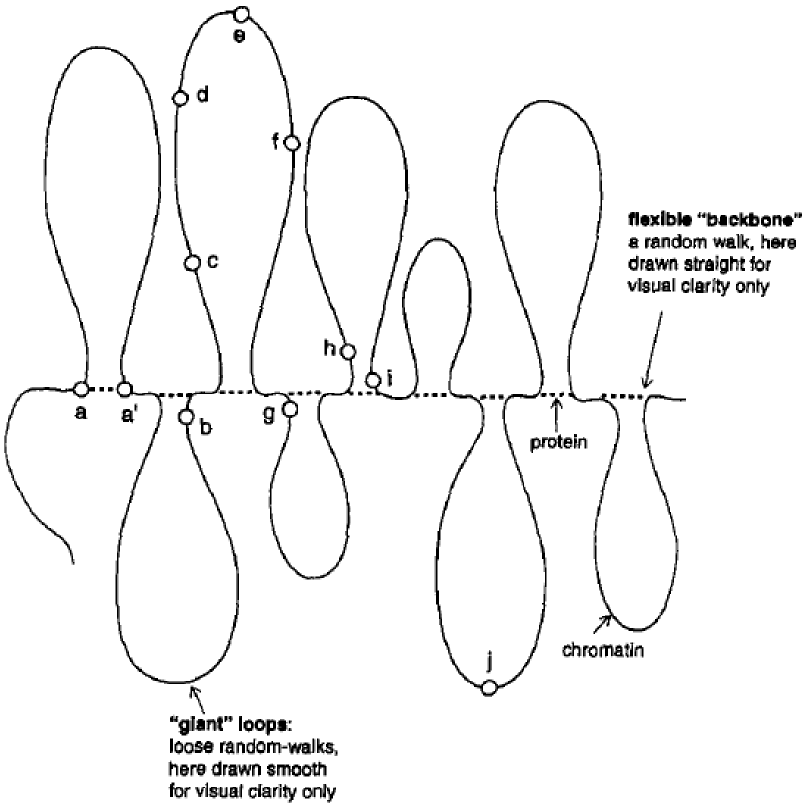


→ RBE !

LEM: Transfer of low-LET experience to high-LET

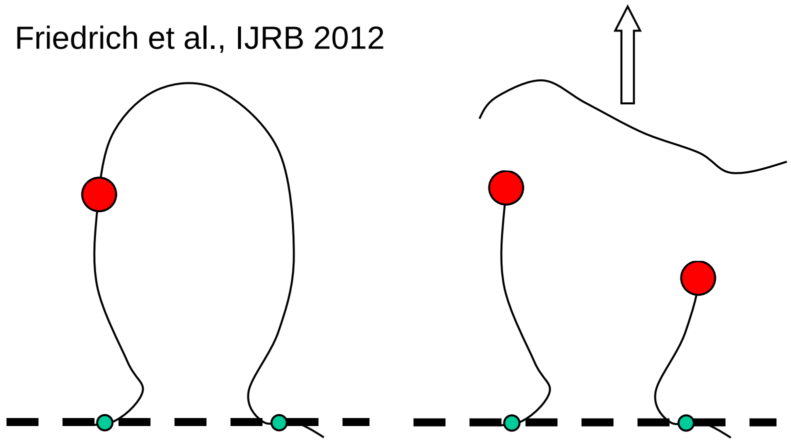
Basic Idea of LEM

Background: ‚Giant Loop Model‘ of DNA / chromatin organization



Yokota et al. JCB 1995

Friedrich et al., IJRB 2012



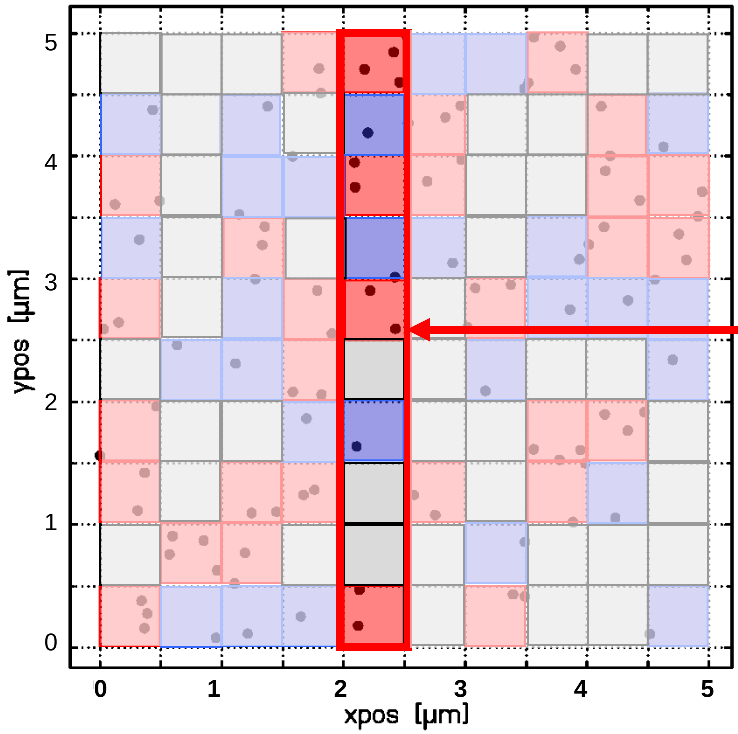
Isolated DSB:
easy to repair

clustered DSB:
difficult to repair

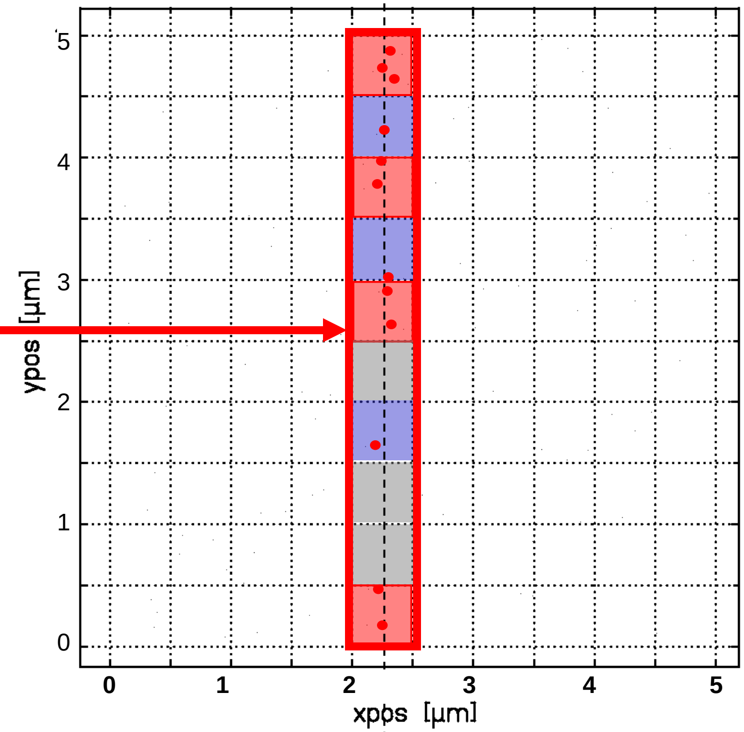
Genomic content of 1 loop
~ 1 x 10^6 base pairs
Volume covered by 1 loop:
typ. dimension 0.5 … 1 μm

Basic Idea of the LEM

Pattern of DSB distribution after X-irradiation in 2D



Pattern of DSB distribution after ion irradiation in 2D

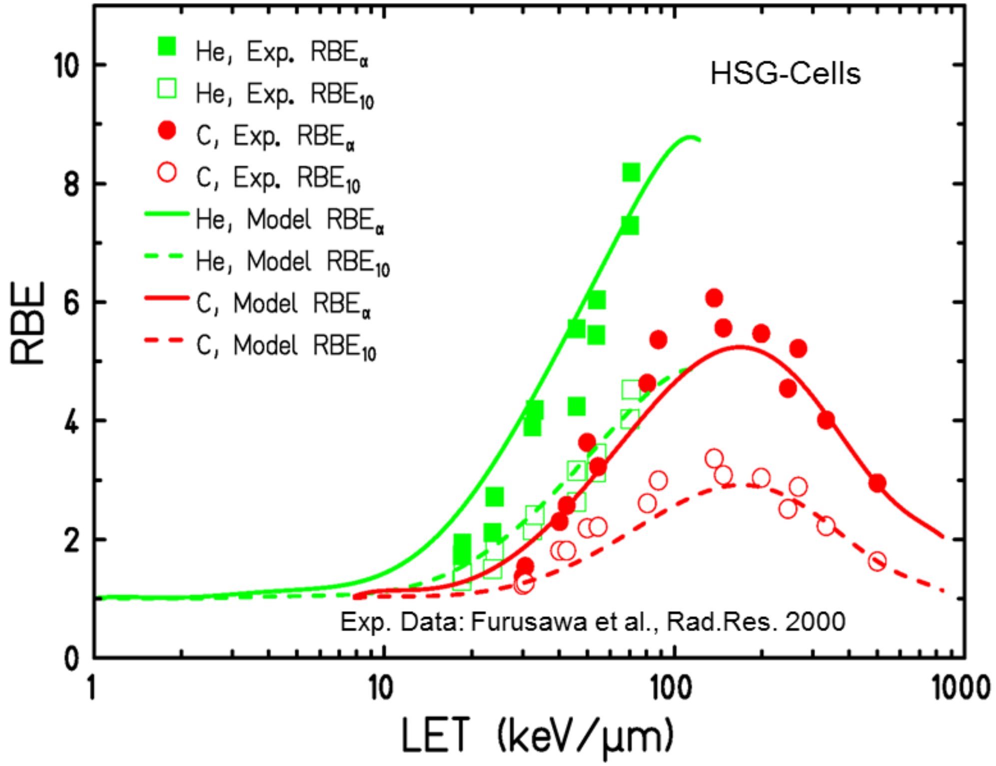


Friedrich et al., IJRB 2012

- $n_{DSB}=0$
- $n_{DSB}=1$: **i**solated DSB
- $n_{DSB}\geq 2$: **c**lustered DSB

DSB distribution in single track can be interpreted as cut-out of X-ray distribution!

Comparison LEM – Experimental Data



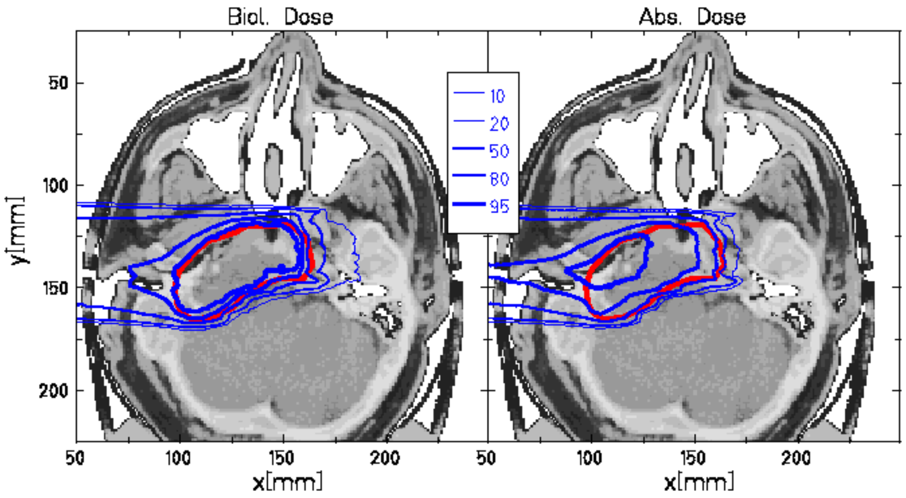
Elsässer et al., IJROBP 2010

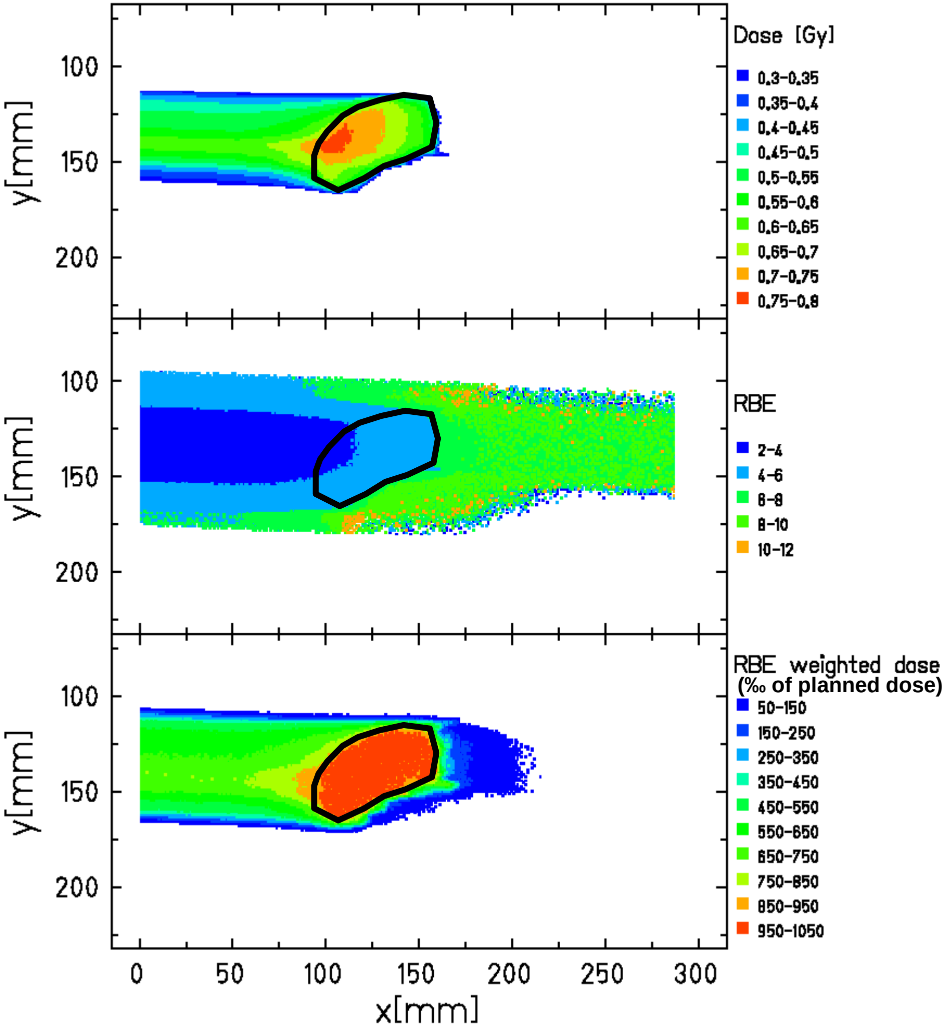
LEM is implemented in treatment planning for biological optimization; RBE is calculated in each individual voxel

Further Support for iDSB / cDSB Concept

- Modelling of photon dose response (GLOBLE)
  Friedrich et al., Rad. Res. 2012
- Kinetics of DSB rejoining after high-LET and low-LET
  Tommasino et al., Rad. Res. 2013
- Dose rate effects after low-LET
  Herr et al., PLOS ONE 2014
- Increased RBE of ultrasoft X-rays
  Friedrich et al., Rad. Res. 2014
- Cell cycle dependent radiosensitivity
  Hufnagl et al., under revision for DNA Repair (2014)
- Impact of DSB repair deficiencies
  Hufnagl et al., under revision for DNA Repair (2014)

RBE-Map

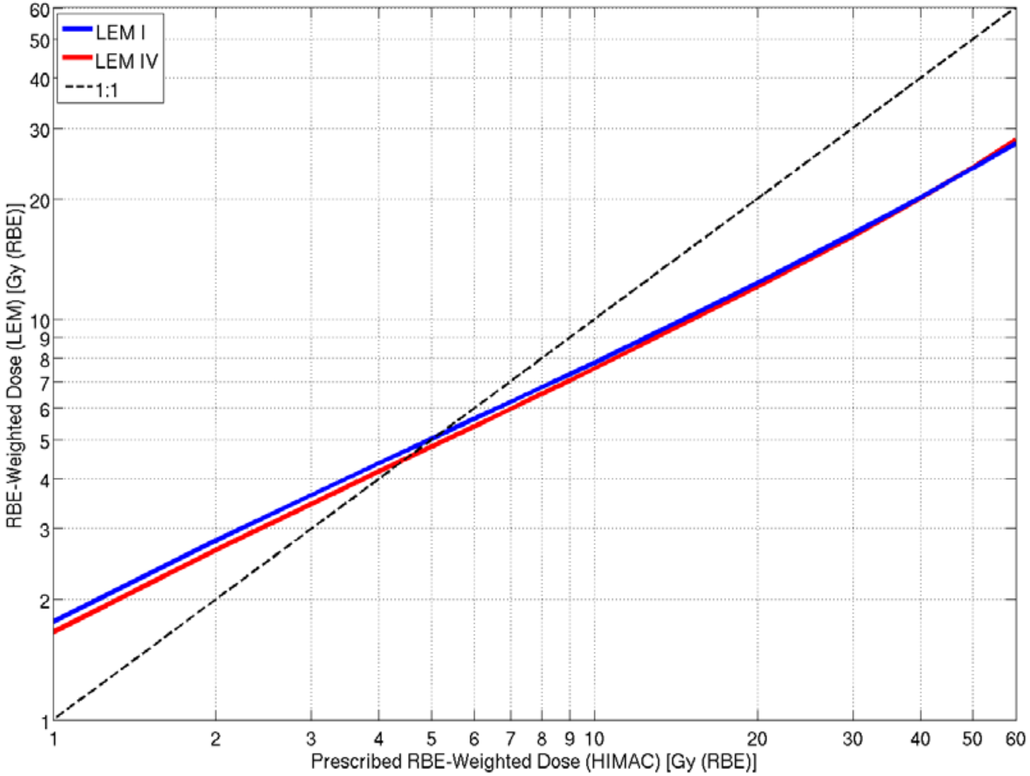




M. Krämer et al.
Phys. Med. Biol. 2000
Phys. Med. Biol. 2006

Comparison LEM – HIMAC approach

LEM-based RBE-weighted dose *vs*. HIMAC-based RBE-weighted dose



Steinsträter et al., IJROBP 2012

Identical numbers do not necessarily mean identical effect!

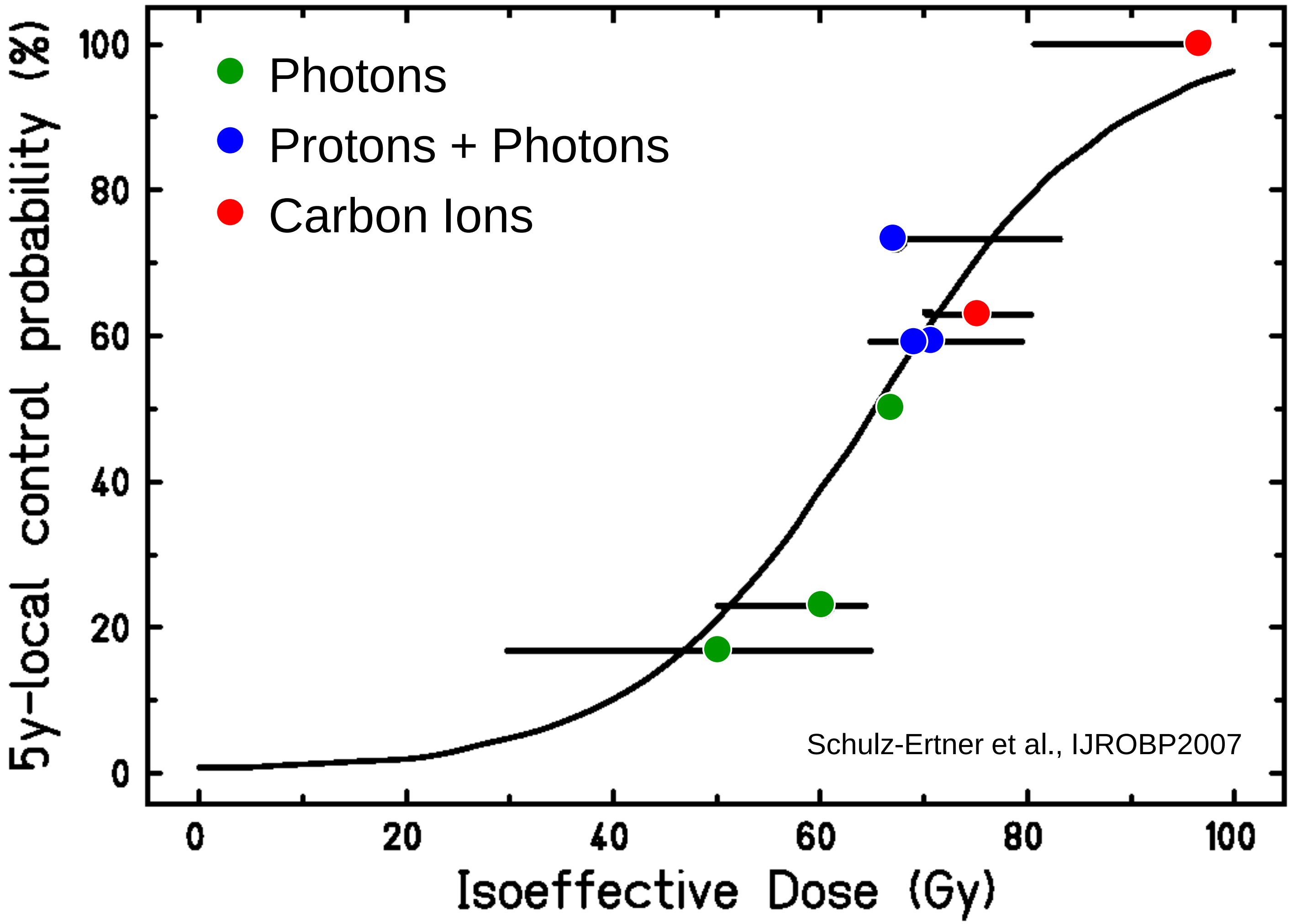
Clinical Results

- Tumor types: Chordoma, Chondrosarcoma, Adenoid-cystic carcinoma, (Prostate carcinoma)
- Treatment scheme: 20F Carbon ions
  6F Carbon ions + IMRT
- ~440 Patients 1997 - 2008
- Better tumor control, fast response
- Lower normal tissue complications

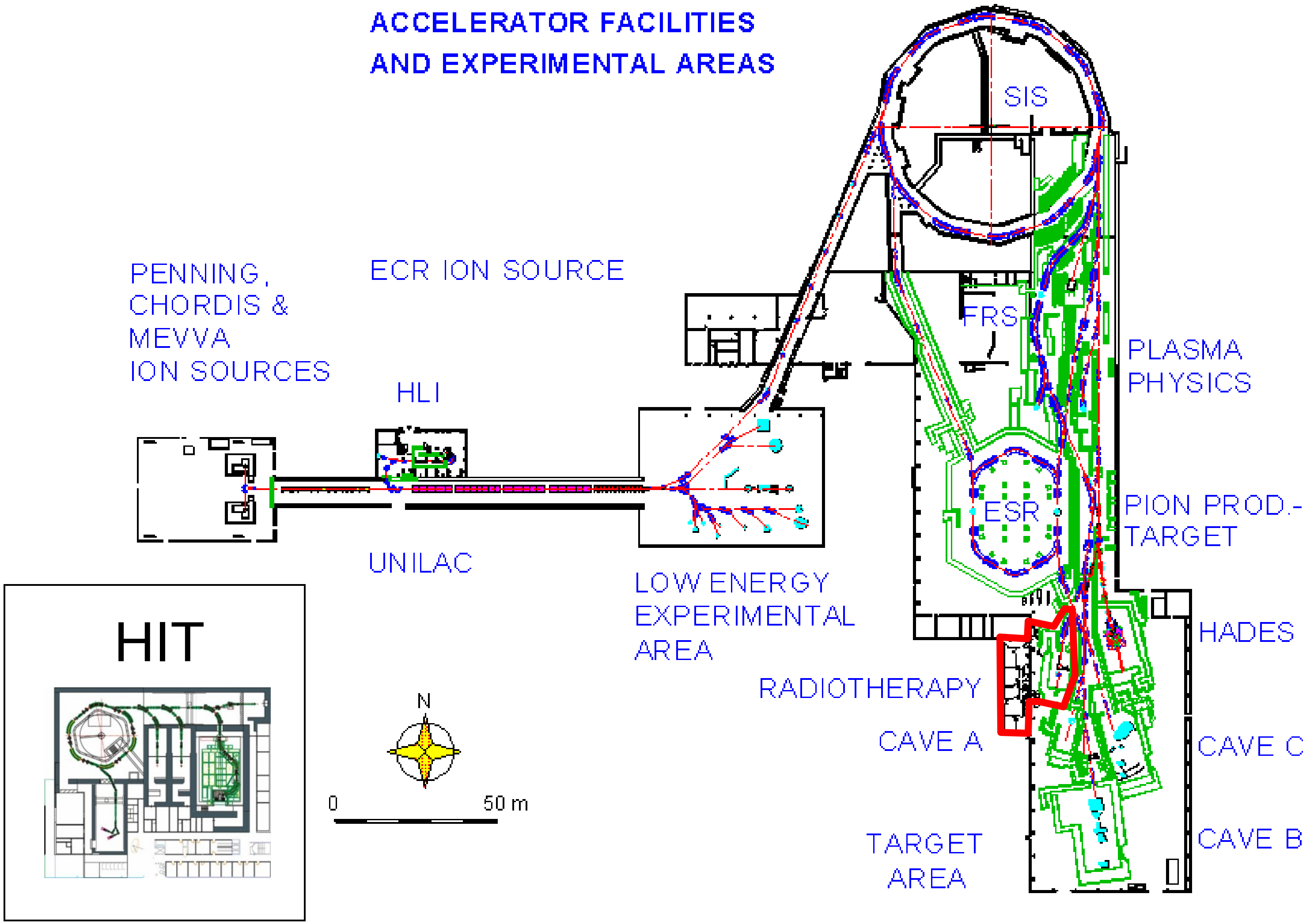
➡ Clinical based facility in Heidelberg

Comparison with other modalities

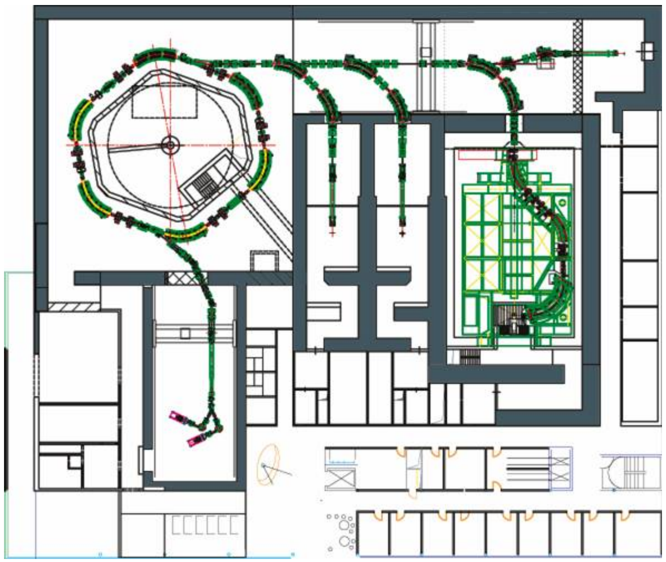
Skull Base Chordoma



Comparison HIT - GSI



Heidelberg Ion Beam Therapy Centre HIT



Start of patient treatments: 2009

~ 2000 patients treated up to now

(up to 750 patients / year)

Combined p / C (He / O planned)

Heidelberg Ion Beam Therapy Centre HIT

First Heavy Ion Gantry System

Treatment Room

© Univ. Clinics Heidelberg

Length: 25m Diameter: 13m
Weight: 670 t Precision: <1mm

Clinical Trials at HIT

- Chordoma / Chondrosarcoma
- Rectum carcinoma
- Recurrent Glioma, Glioblastoma
- Hepatocellular carcinoma
- Prostate carcinoma

Perspectives

- Facilities in operation (Oct. 2014):
  - 46 proton facilities
  - 8 carbon ion facilities

- Proposed facilities / under construction:
  - 24 proton facilities
  - 4 carbon ion facilities

- Major task for future applications of ion ions:

$\longrightarrow$ Reduce the number of fractions: „Hypofractionation“

$\longrightarrow$ Compare different ion species: p, He, C, O

Heavy-Ion Therapy at GSI Dec. 1997
Collaboration: FZ Rossendorf - GSI Darmstadt - Radiol. Klinik Heidelberg - DKFZ Heidelberg

Thank you!