Radiobiological aspects of proton and light ion therapy

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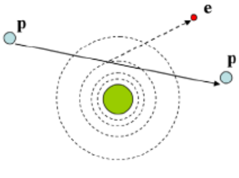
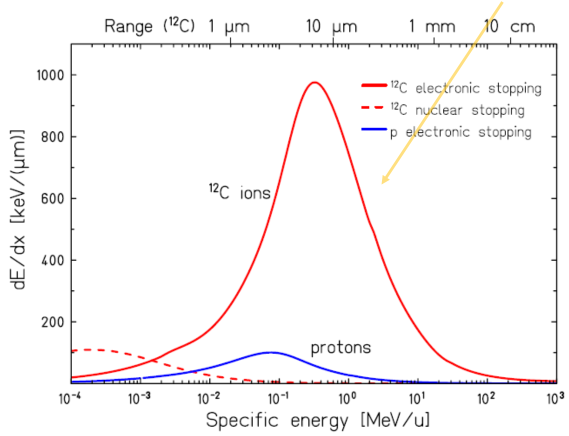
2021 AAPM Annual Meeting

Linear Energy Transfer (LET)



Energy loss with electrons (S_{el} = dE/dx $\propto Z^2 / v^2$) is related to **unrestricted Linear Energy Transfer (LET)**



LET is only defined for monoenergetic beams

In a realistic field LET typically refers to the dose-averaged value over the *i*-th particle energy spectrum

$$\mathrm{LET_d}(z) = \frac{\sum_i \int_0^\infty S_{\mathrm{el}}^{\mathrm{i}}(E)\, D^{\mathrm{i}}(E,z)\, \mathrm{d}E}{\sum_i \int_0^\infty D^{\mathrm{i}}(E,z)\, \mathrm{d}E}$$

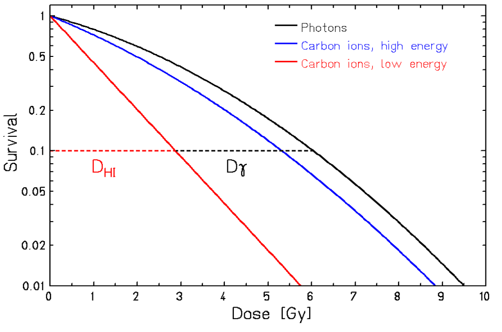
Schardt and Elsässer, Rev Mod Phys 82 (2010) *Karger and Scholz, PMB 01TR02 (2018)*

Relative Biological Effectiveness (RBE)

High LET radiation is more efficient in cell killing

Increased effectiveness expressed in terms of ***R***elative ***B***iological ***E***ffectiveness

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

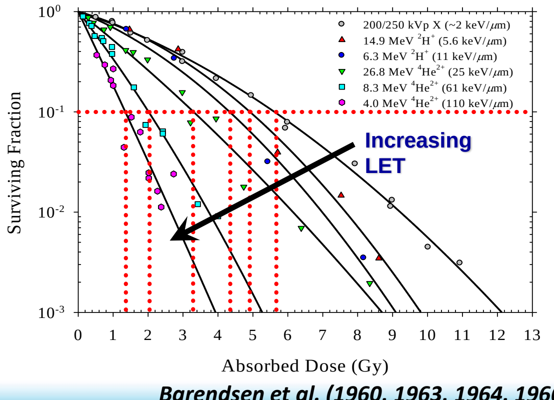


Pronounced increase at low energies, while small effect at high energies

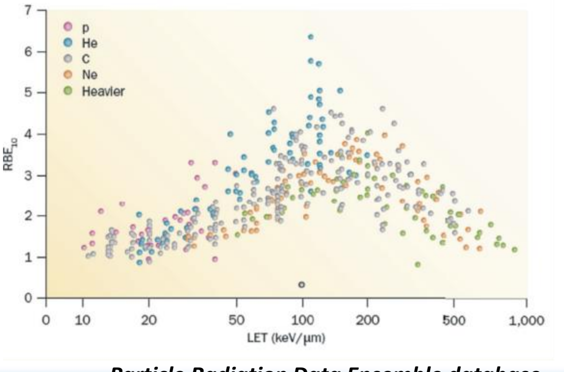
M. Scholz, GSI, Darmstadt

RBE dependence on radiation quality

- RBE generally increases with LET
- For too high LET, RBE decreases because of saturation and overkilling



Barendsen et al. (1960, 1963, 1964, 1966):
In vitro cell survival data for human kidney T-1 cells (courtesy D. Carlson)

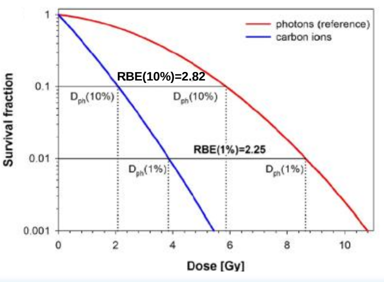


Particle Radiation Data Ensemble database (www.gsi.de/bio-pide)

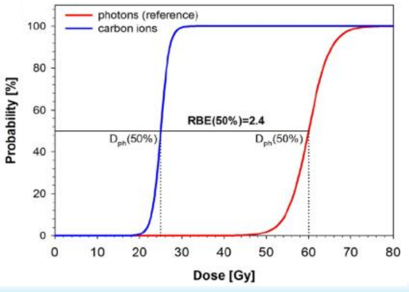
Additional RBE dependences

RBE is a complex quantity depending on
- particle type and energy (LET)
- dose
- cell type (e.g. α/β ratio) and cycle
- biological endpoint
- …

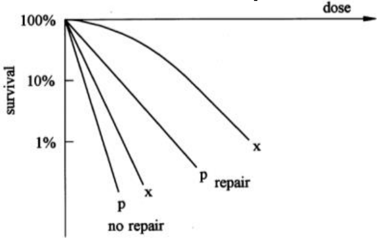
Dose dependence

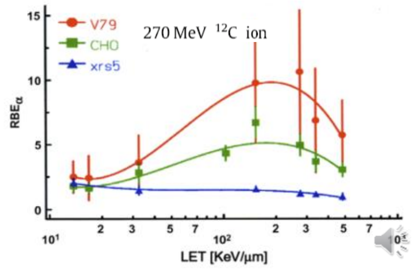


Biological endpoint



Tissue/cell dependence

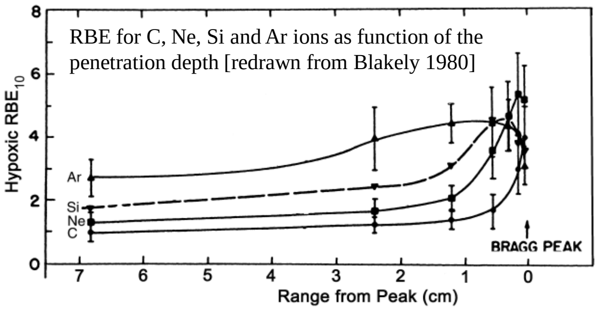


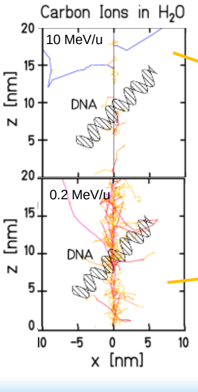


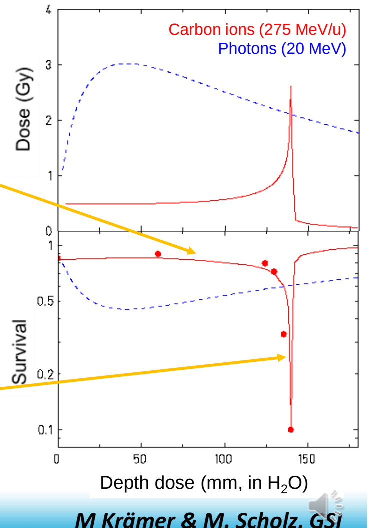
Karger and Scholz, PMB 01TR02 (2018) *G. Kraft, M. Scholz, GSI Darmstadt*

The motivation for carbon ions

Pioneering radiobiological and clinical (H, He, Ne, Ar, Si) studies suggested ^{12}C ions to offer optimum RBE increase from entrance channel to tumor (for radioresistant tumours)







G. Kraft, Progress in Particle and Nuclear Physics 45 (2000) S473-S544 *M Krämer & M. Scholz, GSI*

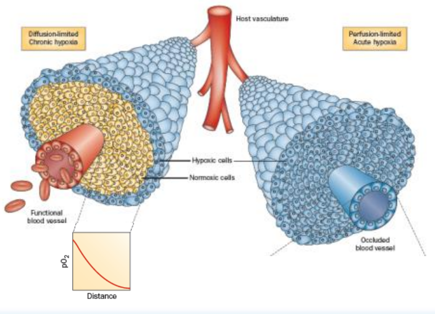
Oxygen Enhancement Ratio (OER)

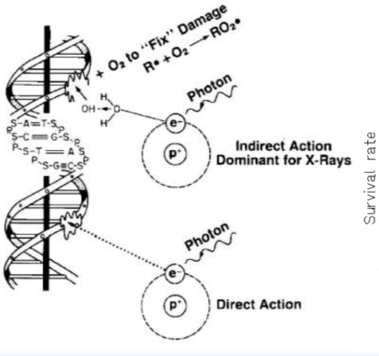
Tumour tissue can be scarsely vascularised

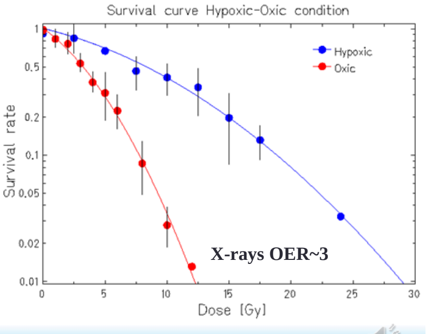
- Less oxygen content (chronic/acute hipoxia)
- Increase dose to the tumour to achieve desired effect

Oxygen **E**nhancement **R**atio

$$OER = \left.\frac{D_{hypoxic}}{D_{normoxic}}\right|_{same\,effect} \qquad OER(p) = \left.\frac{D(p)}{D_{normoxic}}\right|_{same\,effect}$$





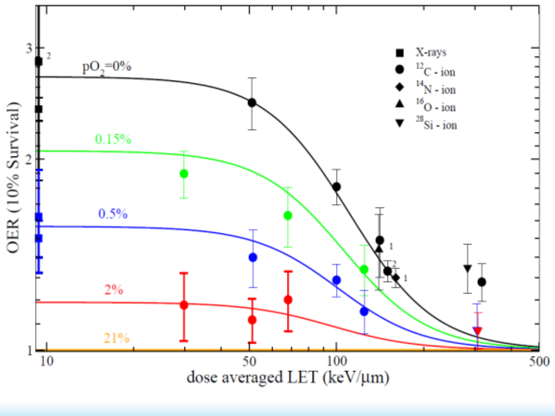


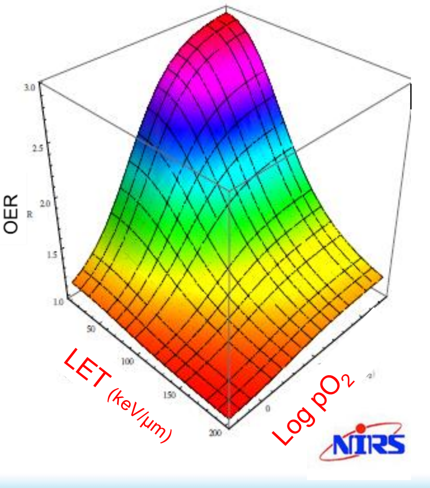
Horsman et al Nat. Rev. Clin. Oncol. (2012)

Courtesy M. Durante, GSI Darmstadt

Heavier ions can be effective against hypoxic tumors

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

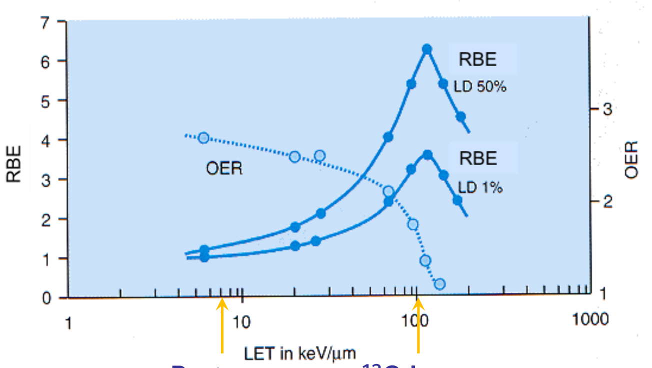




Tinganelli et al., Sci. Rep. 2015

Biological modeling for treatment planning

How to account for biological effects in particle therapy?



Modelling of RBE variations

Empirical LET-based RBE models (esp. protons)

- Wilkens and Oelfke (2004)
- Carabe *et al.* (2012)
- Wedenberg *et al.* (2013)
- McNamara *et al.* (2015)

Mechanistic RBE models

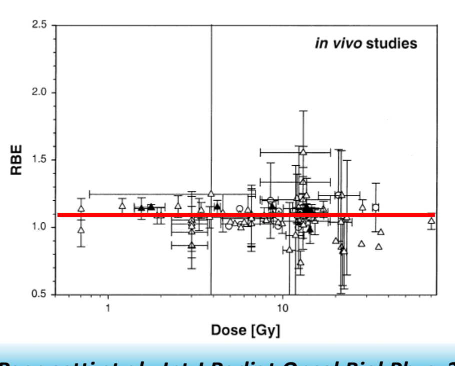
- Local effect model (LEMI-LEMIV)
- Microdosimetric kinetic model (MKM)
- Repair-misrepair-fixation model (RMF)

Other physical surrogates such as LET_d (may provide a reasonable approximation for protons)

Courtesy of C. Karger and D. Carlson

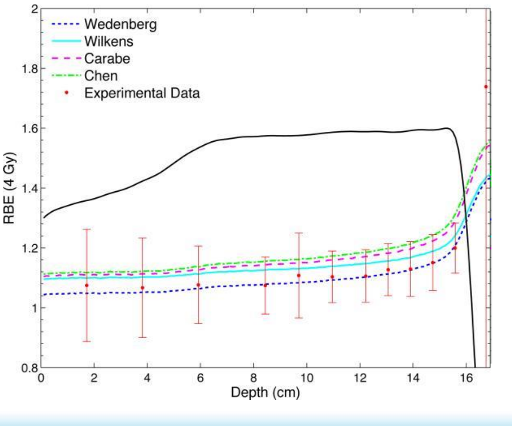
Biological modeling for treatment planning - protons

- Constant RBE = 1.1 clinically used
- Known RBE variations with LET
- Uncertainties of different models



Proton SOBP with 160 MeV max. E

RBE values for clonogenic survival of V79 cells



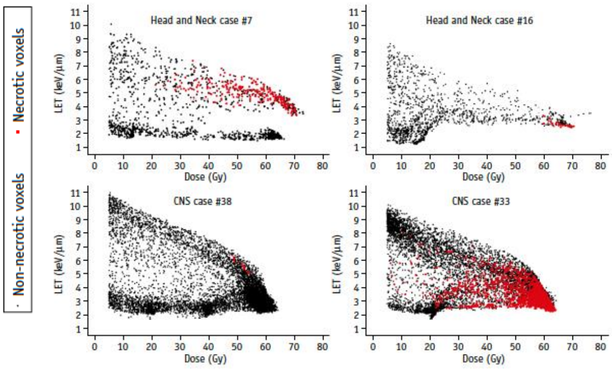
Paganetti et al., Int.J.Radiat.Oncol.Biol.Phys. 2002

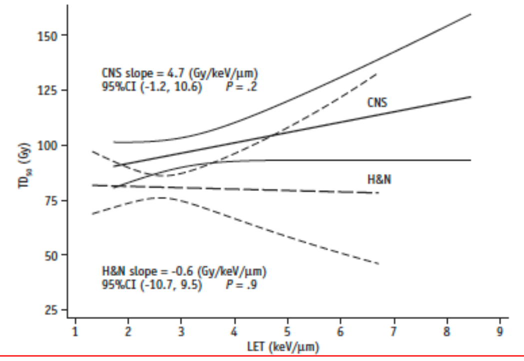
Polster et al.. PMB 60: 5053–5070 (2015); Courtesy of D. Carlson

Biological modeling for treatment planning - protons

- Unclear correlation of RBE/LET variations to outcome

Higher interpatient variability in radiosensitivity!





Results: In this patient cohort, LET adjusted for dose was not found to be associated with risk of brain necrosis.

Nienierko et al., Int. J. Radiat. Oncol. Biol. Phys. 2021

Biological modeling for treatment planning – carbon ions

- Variable RBE scheme (accounting for mixed radiation field)
- Different models used in the clinics (LEM, MKM) based on different underlying assuptions connecting survival *S* to average number of lethal lesions $\overline{N(D)} = -\ln S\,(D)$

LEM combines track structure model of radial dose *d*, cell nucleus size / volume *V* and photon survival curves *S:*

$$\overline{N(D)} = \int \frac{-\ln S\,(d\,(x,y,z))}{V} \mathrm{d}V$$

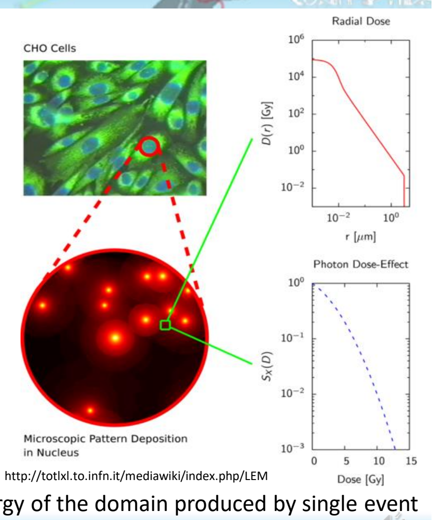
MKM links *S(D)* for macroscopic ion dose *D* to specific energy absorbed by a microscopic subnuclear structure 'domain':

Indep. of radiation quality

$$\overline{N(D)} = -\ln S = (\alpha_0 + \beta z^*_{1\mathrm{D}})D + \beta D^2$$

Initial slope of *S(D)* curve for LET→0

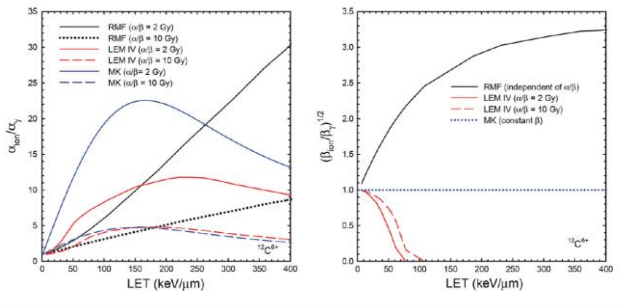
Saturation-corrected dose-mean specific energy of the domain produced by single event



Karger and Scholz, PMB 01TR02 (2018); Scholz et al Radiat. Environ. Biophys. 36 (1997); Inaniwa et al, PMB 55 (2010)

Biological modeling for treatment planning – carbon ions

- Uncertainties of model predictions
- Unclear correlation to outcome
- Importance of establishing relationship between model-dependent prescriptions



Stewart…Scholz, MedPhys 2017, Special issue PT

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Radiotherapy and Oncology 153 (2020) 272–278

Dose-averaged linear energy transfer *per se* does not correlate with late rectal complications in carbon-ion radiotherapy

Noriyuki Okonogi, Shinnosuke Matsumoto, Mai Fukahori, Wataru Furuichi, Taku Inaniwa, Naruhiro Matsufuji, Reiko Imai, Shigeru Yamada, Nobuyuki Kanematsu, Hiroshi Tsuji

Conclusion: We demonstrated that severe rectal toxicities were related to the rectal D_{2cc} of the clinical dose in C-ion RT. However, no correlations were found between severe rectal toxicities and LETd alone or physical dose *per se*.

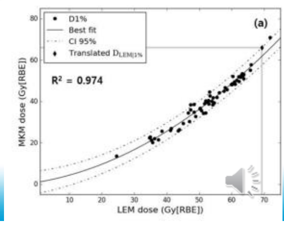
RBE-weighted dose!

Rectum Dose Constraints for Carbon Ion Therapy: Relative Biological Effectiveness Model Dependence in Relation to Clinical Outcomes

Kyungdon Choi, Silvia Molinelli, Stefania Russo, Alfredo Mirandola, Maria Rosaria Fiore, Barbara Vischioni, Piero Fossati, Rachele Petrucci, Irene Turturici, Jon Espen Dale, Francesca Valvo, Mario Ciocca and Andrea Mairani

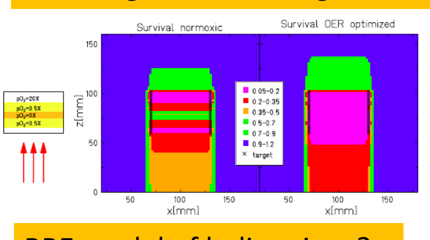
cancers MDPI

Cancers **2020**, *12*, 46; doi:10.3390/cancers12010046



New horizons in biological modeling

Including OER modeling for cell killing painting

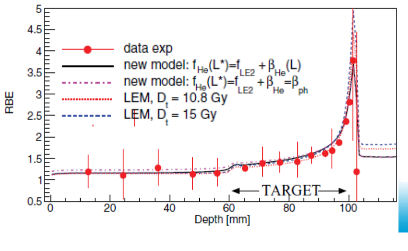


Phys. Med. Biol. **58** (2013) 3871–3895

Including oxygen enhancement ratio in ion beam treatment planning: model implementation and experimental verification

E Scifoni, W Tinganelli, W K Weyrather, M Durante, A Maier and M Krämer

RBE model of helium ions?



Phys. Med. Biol. **61** (2016) 4283–4299

Biologically optimized helium ion plans: calculation approach and its *in vitro* validation

A Mairani, I Dokic, G Magro, T Tessonnier, F Kamp, D J Carlson, M Ciocca, F Cerutti, P R Sala, A Ferrari, T T Böhlen, O Jäkel, K Parodi, J Debus, A Abdollahi and T Haberer

Toward multi-ion treatment

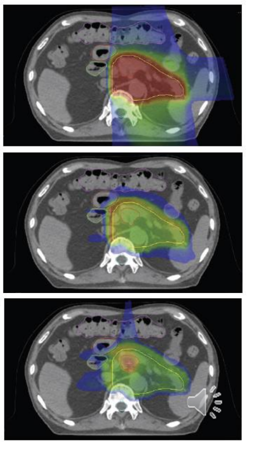
The Emerging Potential of Multi-Ion Radiotherapy

frontiers in Oncology — February 2021 | Volume 11 | Article 624786

RBE-weighted dose
(^{12}C ion treatment)

LET distribution
(^{12}C ion treatment)

LET distribution
(^{4}He, ^{12}C, ^{16}O mixed ion treatment at same biol. dose)



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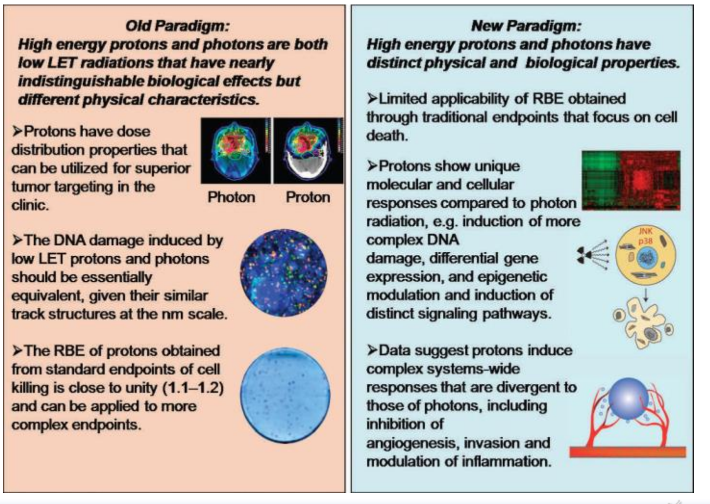
New horizons in radiobiology

Higher complexity beyond physico-chemical processes …



Girdhani et al., Radiat. Res. 2013

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New horizons in small animal research

Bridging the gap: small animal radiotherapy research

Emerging irradiation platforms for protons and heavier ions

PARTICLE THERAPY | RESEARCH UPDATE

Small-animal irradiation platform performs preclinical proton studies

physicsworld

23 Jul 2019 Tami Freeman

The Penn research team with the SARRP-on-rails. (Courtesy: Eric Diffenderfer)

Physics in Medicine & Biology — IPEM Institute of Physics and Engineering in Medicine

PAPER

Design and commissioning of an image-guided small animal radiation platform and quality assurance protocol for integrated proton and x-ray radiobiology research

Michele M Kim, Peyton Irmen, Khayrullo Shoniyozov, Ioannis I Verginadis, Keith A Cengel, Costantinos Koumenis, James M Metz, Lei Dong and Eric S Diffenderfer

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XSTRAHL LAUNCHES THE NEW SARRP BEAMLINE FOR PROTON, PHOTON, CARBON AND FLASH PRE-CLINICAL EXPERIMENTS

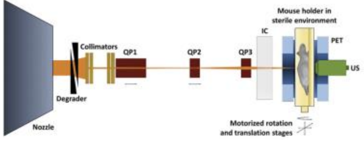
August 26th, 2019

ACTA ONCOLOGICA
https://doi.org/10.1080/0284186X.2019.1630752

Taylor & Francis

ORIGINAL ARTICLE

Towards a novel small animal proton irradiation platform: the SIRMIO project



https://www.lmu.de/sirmio

erc SIRMIO

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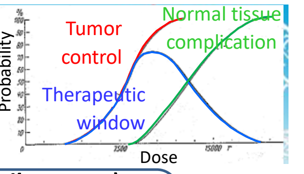
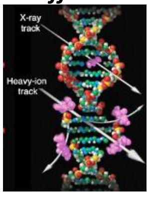
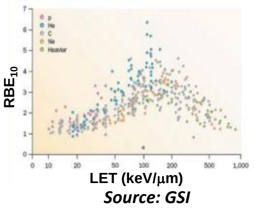
New frontiers to widen therapeutic window?



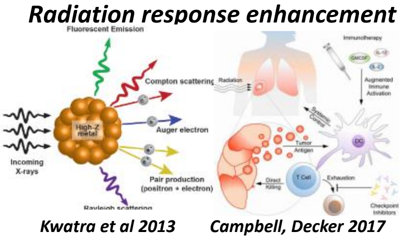
Different radiation qualities





Source: NASA *Source: GSI*

Radiation response enhancement

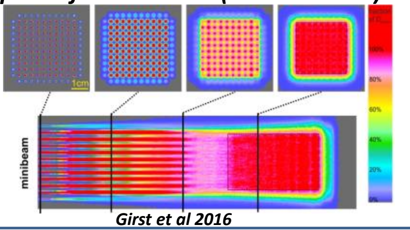


Kwatra et al 2013 *Campbell, Decker 2017*

Increased tumour cell killing

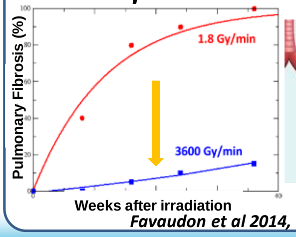
Reduced damage of normal tissue

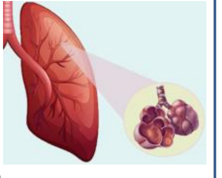
Spatial fractionation (minibeam RT)



Girst et al 2016

Temporal fractionation (FLASH)





Favaudon et al 2014, Durante et al 2017

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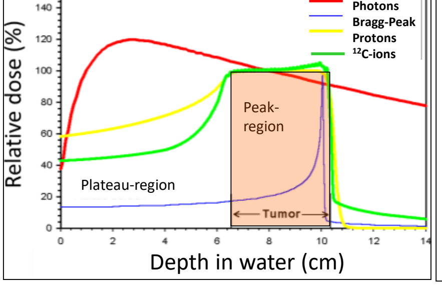
Conclusion and outlook

Physical selectivity

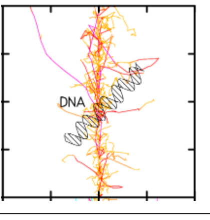
- Depth-dose profile (Bragg-Peak)
- ↓ lateral scattering *(Z>1)*



Radiobiological aspects

- Clinical proton RBE = 1.1
- Higher LET of heavier ions may
  - ↑ Biological effectiveness
  - ↓ Influence of tumour oxygenation

Carbon Ions in H_2O



Optimal differential effect Z ≈ 6 (^{12}C ions)

Outlook

- Account for RBE, LET and OER variations in treatment planning
- Toward multi-ion treatment optimization
- More translational research to understand in-vivo mechanisms
- Paving the way toward new treatment schemes & personalized medicine

Karger and Jäkel, DKFZ Heidelberg *Krämer et al, Adv Space Res 1994*

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Acknowledgement

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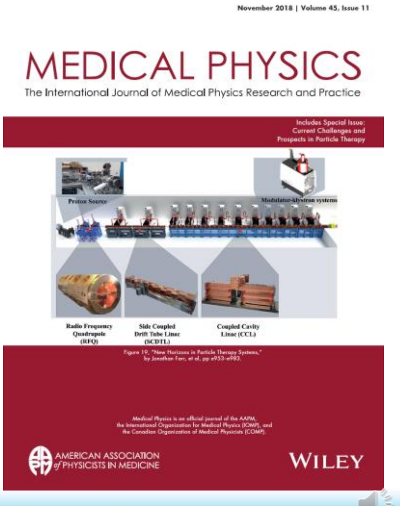
C. Orton & C. Borrás for organizing this session

M. Durante (GSI) & D. Carlson (UPENN) for material

Further reading:

Medical Physics Special Issue
"Current Challenges and Prospects in Particle Therapy"
(edited by J. Farr & K. Parodi, 2018)



Thank you for your attention