Trento Institute for
Fundamental Physics
and Applications

Istituto Nazionale
di Fisica Nucleare

OMA School – CNAO 2017

Radiobiology

of particle beams

- Basics & Hot Topics -

Emanuele Scifoni

TIFPA-INFN ,Trento (I)

Overview

- **Radiobiology: the basics**

- **Particle beam radiobiology (PR)**

- **RBE**
- **OER**
- **Radiosensitizers**

- **Biophysical Models**
- **Radiobiology based treatment planning**

- **Selected Hot Topics in PR**

Basics

Why is Radiobiology important?

SIMPSONS GUIDE TO RADIATION

Bequerel [Bq]
How brightly your
Cesium glows

ACTIVITY

Why is Radiobiology important?

SIMPSONS GUIDE TO RADIATION

Bequerel [Bq]
How brightly your Cesium glows

Gray [Gy]
How brightly Cesium will make you glow

ACTIVITY *ABSORBED DOSE*

Why is Radiobiology important?

SIMPSONS GUIDE TO RADIATION

Bequerel [Bq]
How brightly your Cesium glows

Gray [Gy]
How brightly Cesium will make you glow

Sieverts [Sv]
How many extra eyes will you have after glowing?

ACTIVITY

ABSORBED DOSE

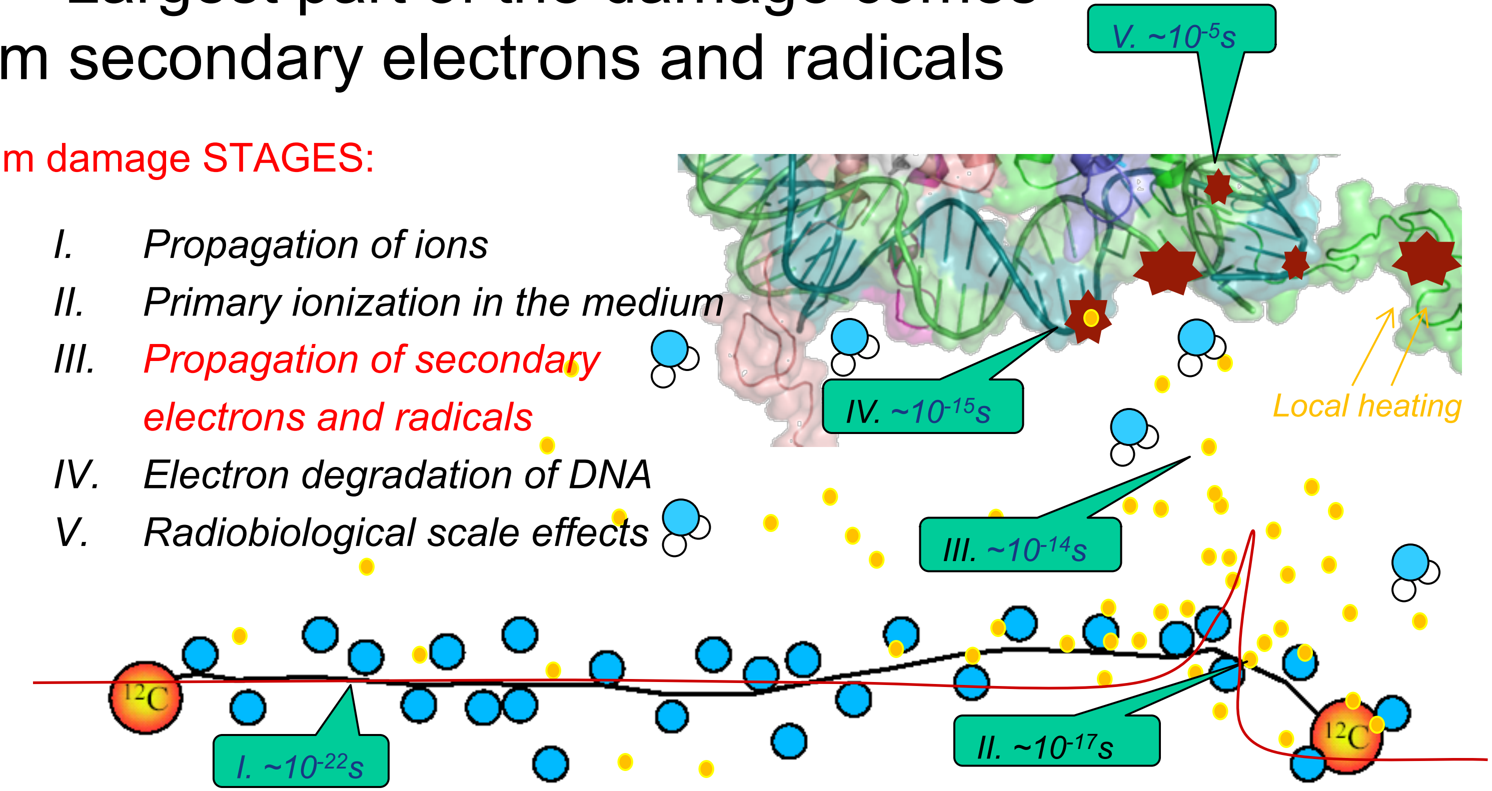
(BIOLOGICAL) EFFECTIVE DOSE

The mechanism of biological damage with ions

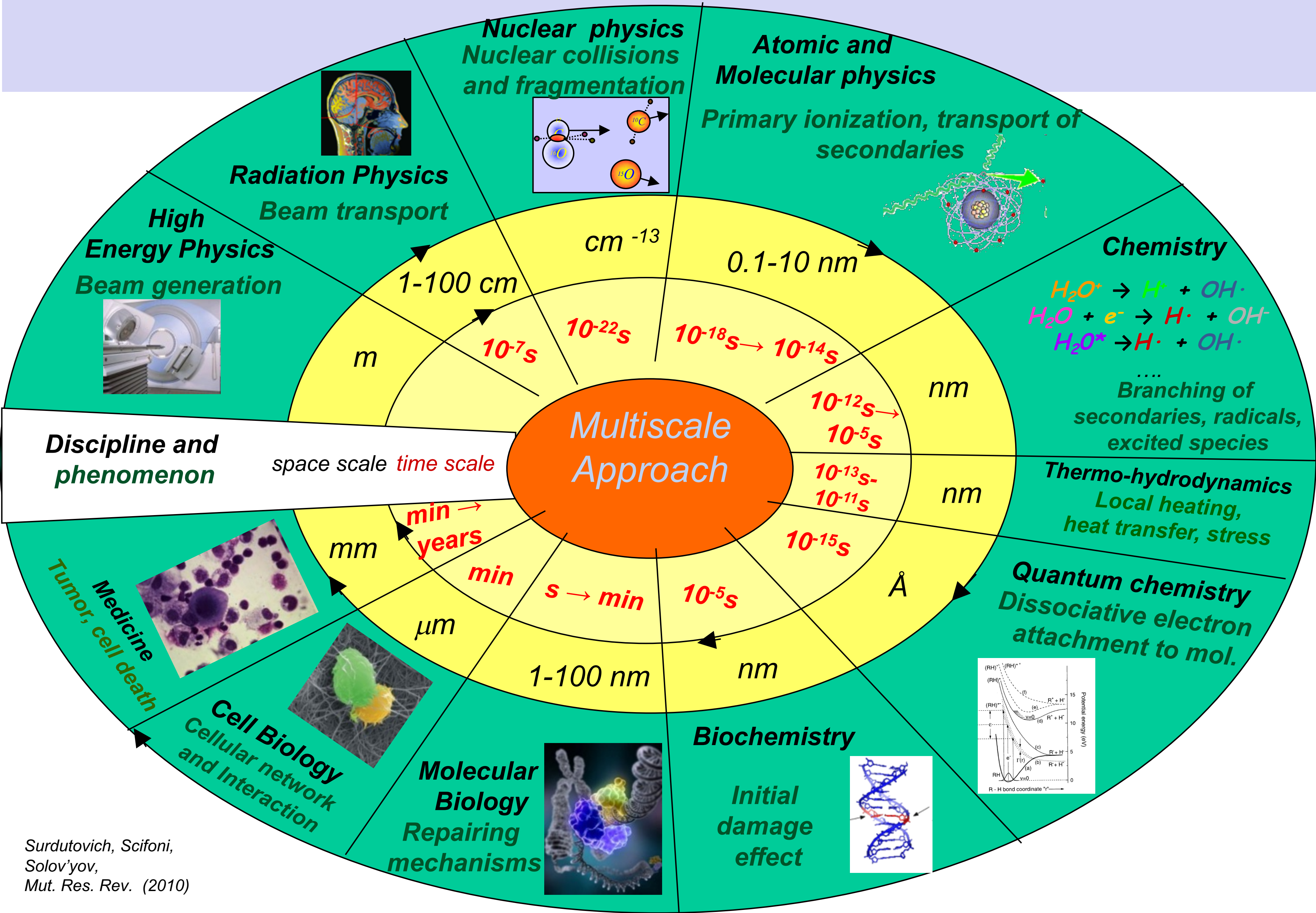
Largest part of the damage comes
from secondary electrons and radicals

Ion beam damage STAGES:

I. *Propagation of ions*
II. *Primary ionization in the medium*
III. *Propagation of secondary electrons and radicals*
IV. *Electron degradation of DNA*
V. *Radiobiological scale effects*



Spatiotemporal scales of Radiation Damage



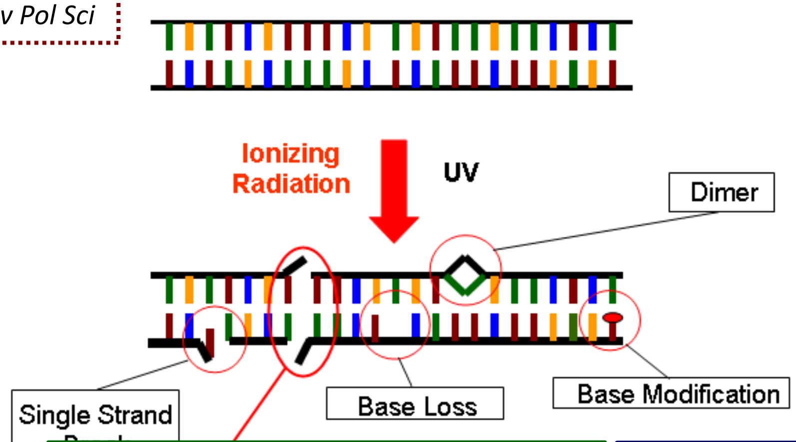
Multiscale Approach

Discipline and phenomenon	space scale	time scale
High Energy Physics Beam generation	m	
Radiation Physics Beam transport	1-100 cm	10^{-7}s
Nuclear physics Nuclear collisions and fragmentation	cm $^{-13}$	10^{-22}s
Atomic and Molecular physics Primary ionization, transport of secondaries	0.1-10 nm	10^{-18}s → 10^{-14}s
Chemistry $H_2O^+ \rightarrow H^+ + OH\cdot$ $H_2O + e^- \rightarrow H\cdot + OH^-$ $H_2O^* \rightarrow H\cdot + OH\cdot$ .... Branching of secondaries, radicals, excited species	nm	10^{-12}s → 10^{-5}s
Thermo-hydrodynamics Local heating, heat transfer, stress	nm	10^{-13}s- 10^{-11}s
Quantum chemistry Dissociative electron attachment to mol.	Å	10^{-15}s
Biochemistry Initial damage effect	nm	10^{-5}s
Molecular Biology Repairing mechanisms	1-100 nm	s → min
Cell Biology Cellular network and Interaction	μm	min
Medicine Tumor, cell death	mm	min → years

Surdutovich, Scifoni,
Solov'yov,
Mut. Res. Rev. (2010)

DNA Damage

Scholz 2006
Adv Pol Sci

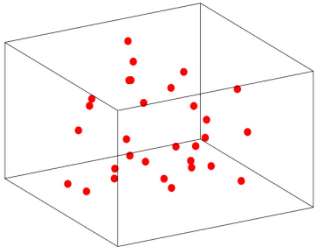


- *The DNA* ***Double Strand Break (DSB)*** *is considered the type of lesion most directly related to cell killing*
- *Different radiation qualities produce the same spectrum of DNA lesions*
- ***BUT*** *the distribution of lesions inside the target can be very different*

Photons

x-rays

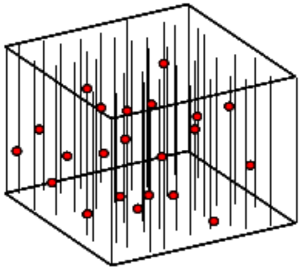
Random
DSB distribution



^{12}C Low LET

200 MeV/u, ≈ 16 keV/μm

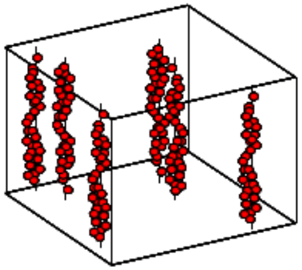
Random
DSB distribution
(photon-like)



^{12}C High LET

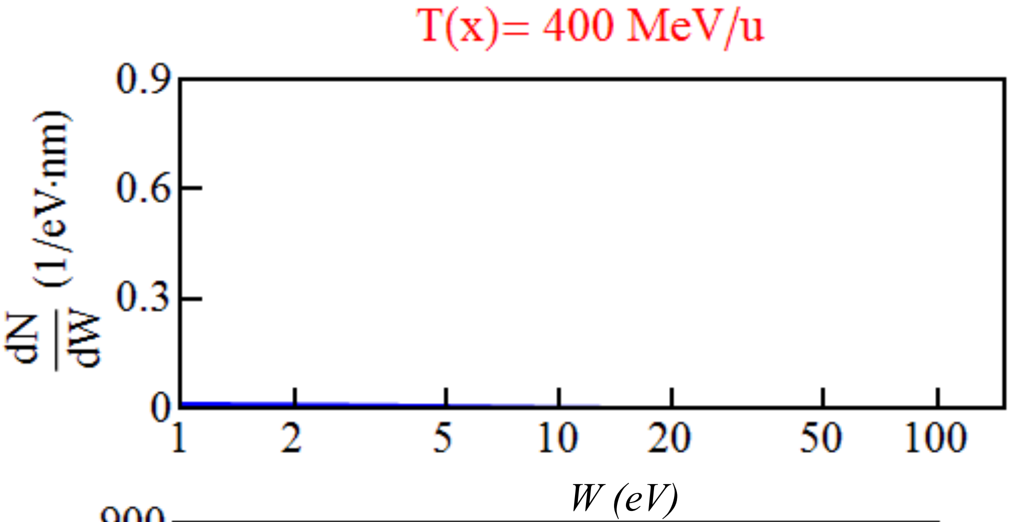
1 MeV/u, ≈ 690 keV/μm

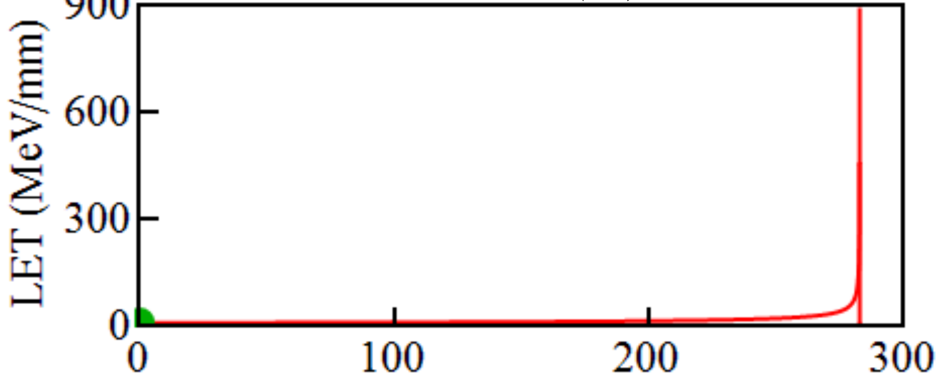
Non-random
DSB distribution
(RBE>>1)



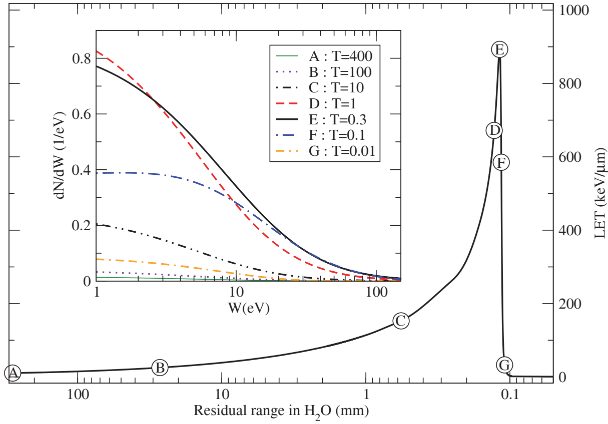
Courtesy of F. Tommasino

Secondary Electrons produced by an ion along a Bragg Peak



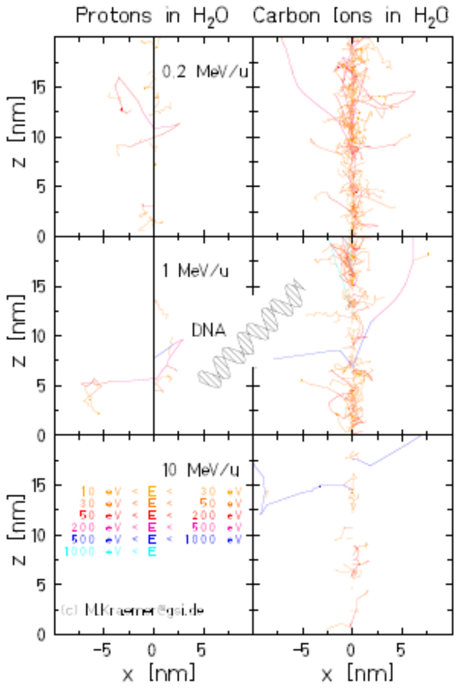


T_0=400 MeV/u *penetration depth, x(mm)*

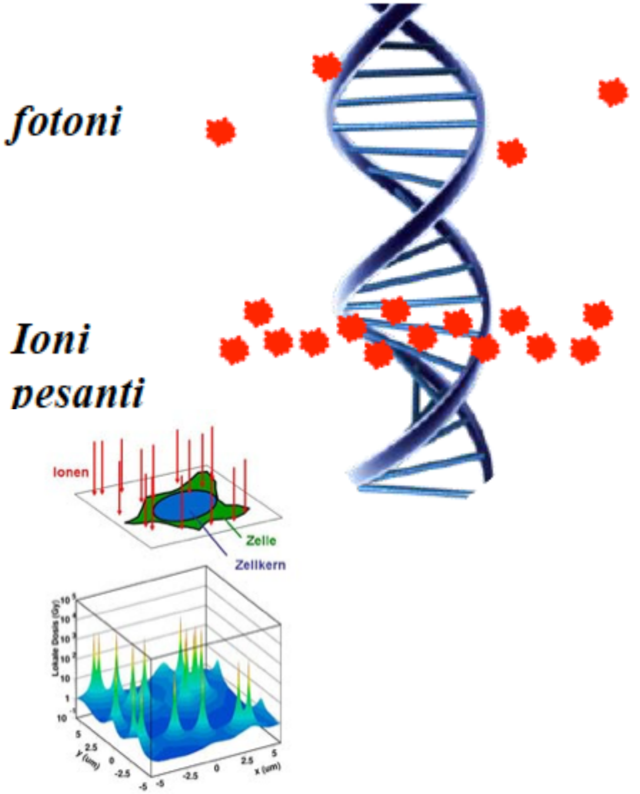


Scifoni, MPL 2015

Kraemer et al JPCS 2012



RBE: Relative Biological Effectiveness

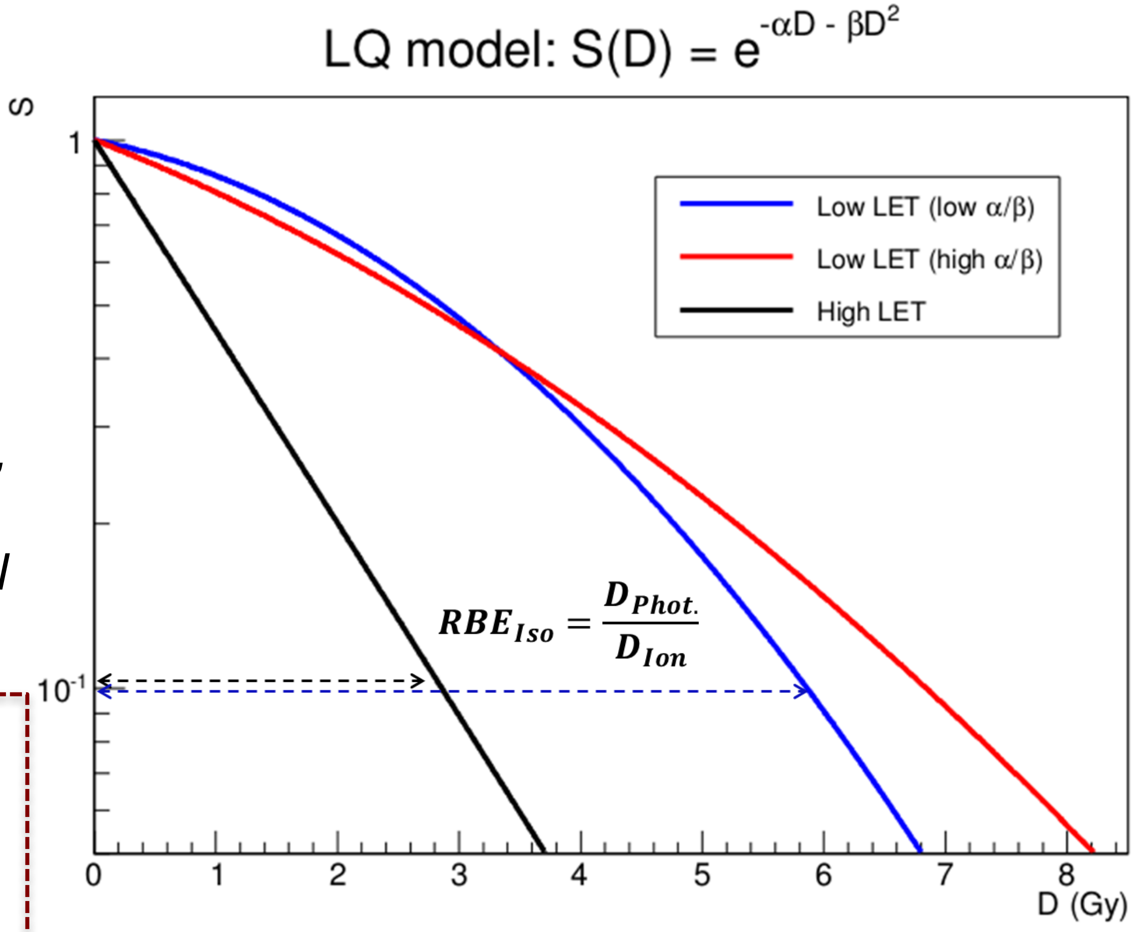


Photons

Ions

RBE: Relative Biological Effectiveness

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



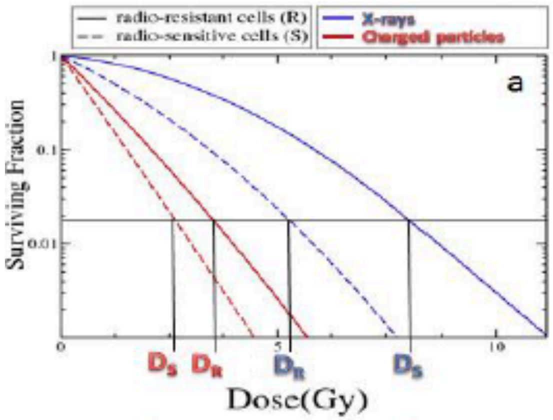
RBE depends on:

- *Physical parameters (dose, LET, fractionation).*
- *Biological parameters (cell cycle, oxygenation, end-point).*

$$RBE(\alpha_\gamma, \beta_\gamma, \alpha_I, \beta_I, S) = \\ = \frac{-(\alpha/\beta)_\gamma \pm \sqrt{(\alpha/\beta)^2_\gamma - 4(\ln\ S/\beta)_\gamma}}{-(\alpha/\beta)_I \pm \sqrt{(\alpha/\beta)^2_I - 4(\ln\ S/\beta)_I}}$$

Particle beams advantage with resistant tissue

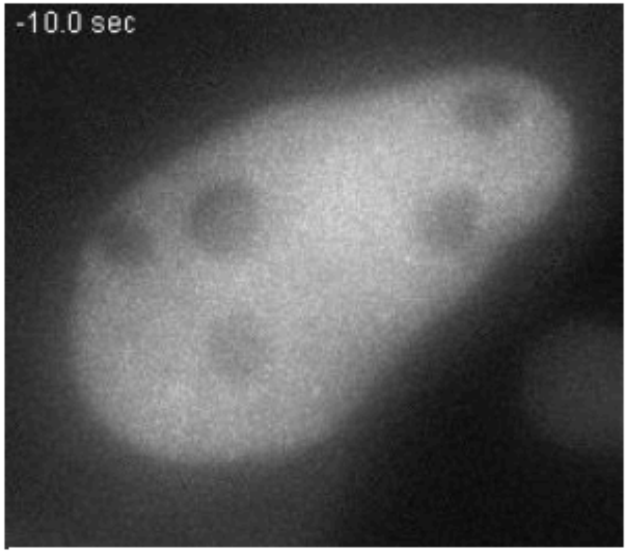
Jakob et al.,
PNAS 2009

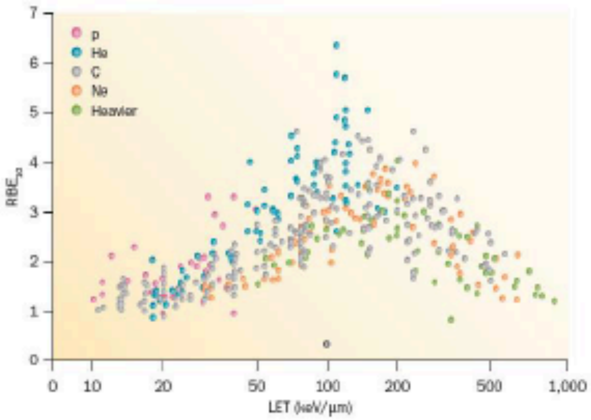


$$RBE_R = \frac{D_{R(photons)}}{D_{R(ions)}} > RBE_S = \frac{D_{S(photons)}}{D_{S(ions)}}$$

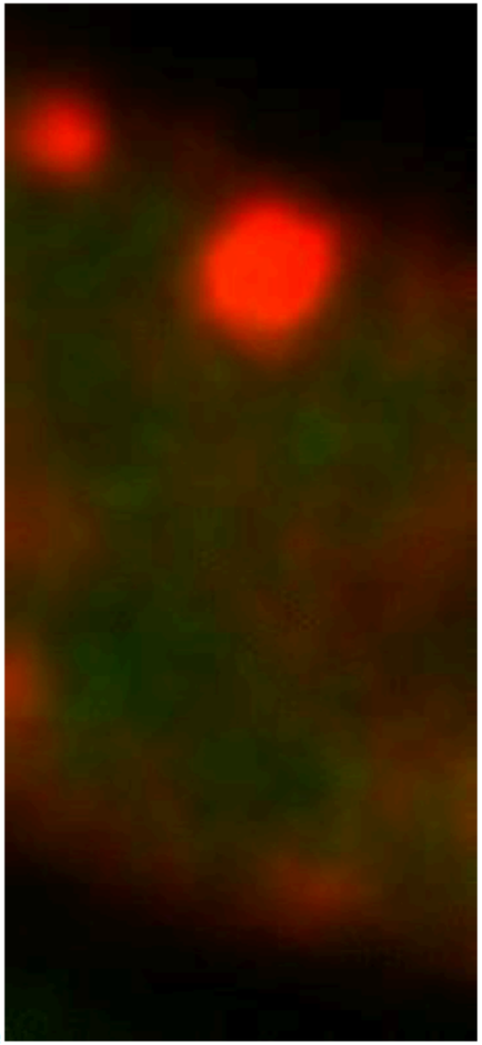
Overcoming resistance of cancer stem cells

www.thelancet.com/oncology **Vol 13 May 2**





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



Courtesy of M.Durante

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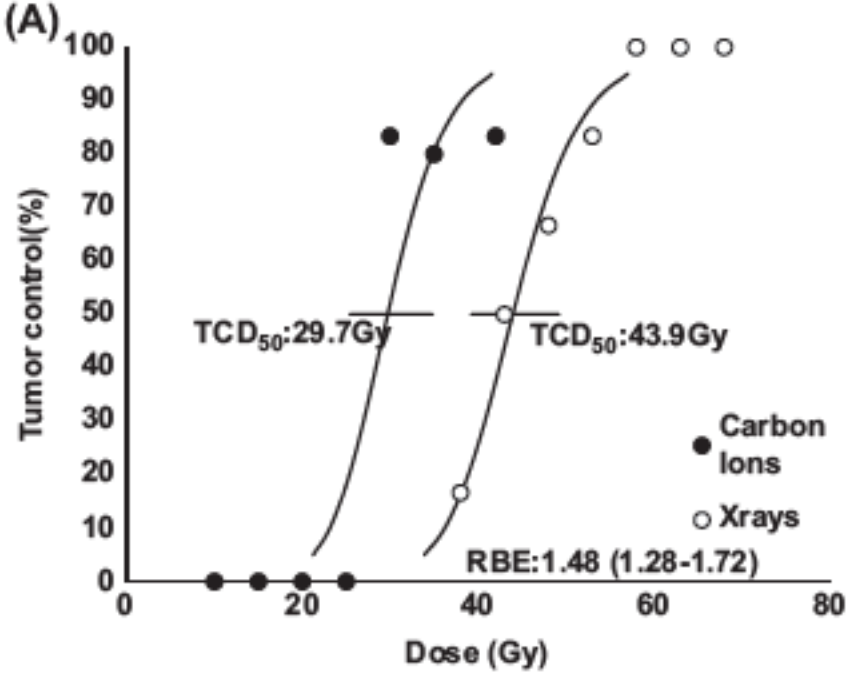
RBE in vivo

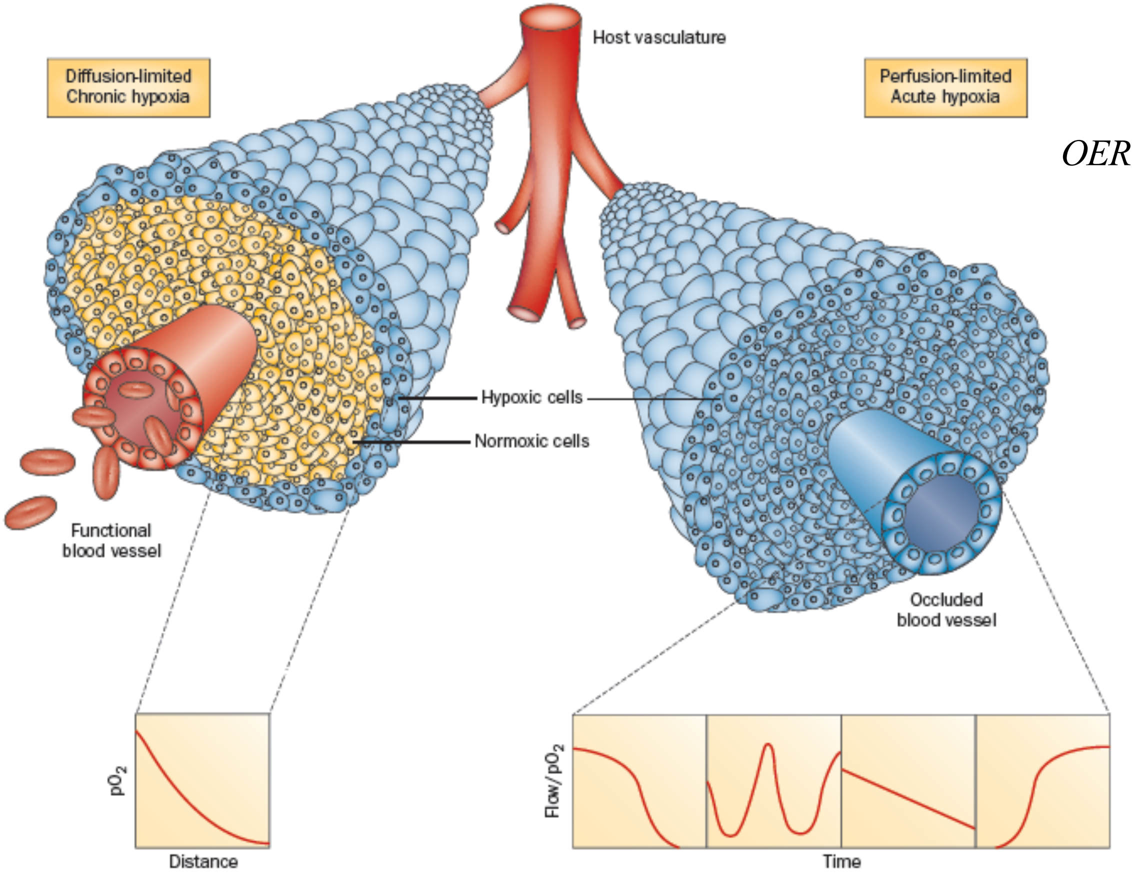


Sorensen Acta O 2016

Modifiers of radiation response

1. *Intrinsic (genetic) radiosensitivity*
2. *Fractionation/Dose rate*
3. *Cell-cycle*
4. *Oxygen/scavenger concentrations*
5. *Radioprotectors/radiosensitizers*

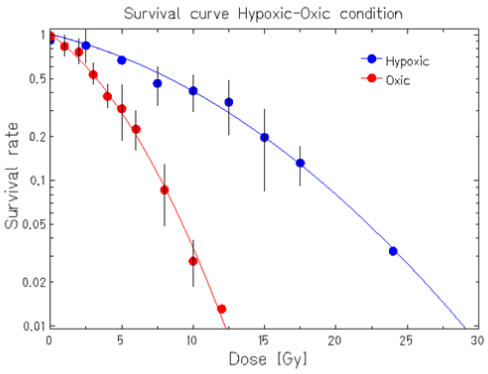
Hypoxia and OER

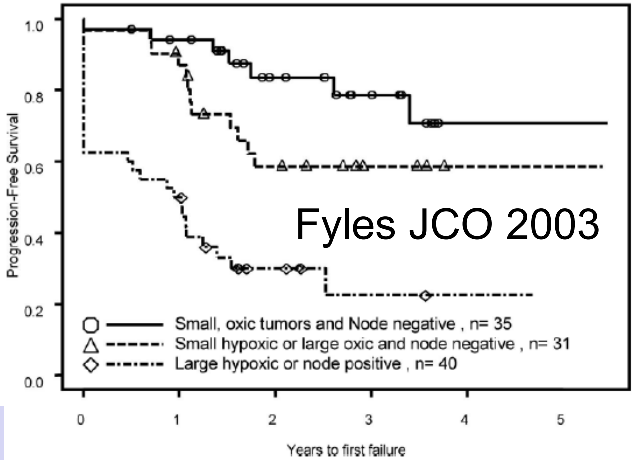


Horsman et al *Nat. Rev. Clin. Oncol.* (2012)

Oxygen Enhancement Ratio

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





Fyles JCO 2003

Radiosensitizers

- in general a dose enhancement factor (DEF) is defined as a ratio of doses compared to normal conditions (n.c.)

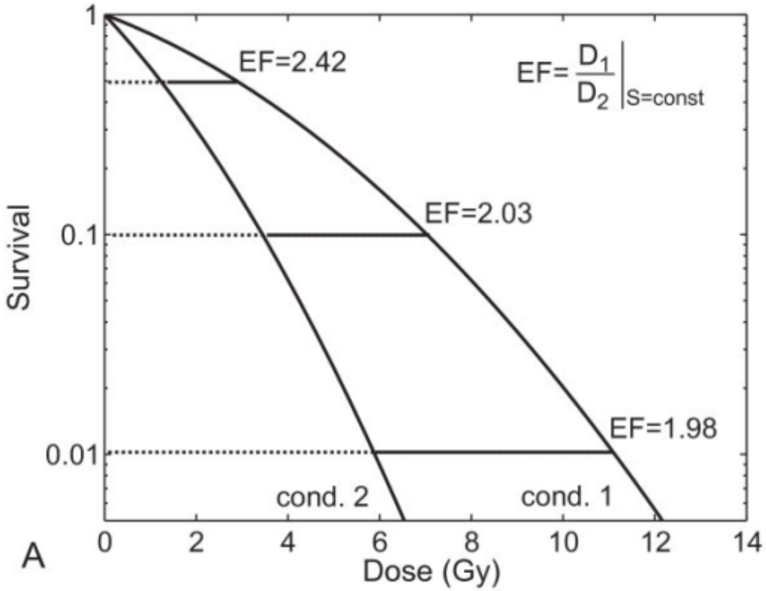
-also called Sensitizer enhancement Ratio (SER)-

$$DEF = \left.\frac{D_{special\,conditions}}{D_{n.c.}}\right|_{same\,effect(S)} \quad ; \quad DEF([C]) = \left.\frac{D([C])}{D_{n.c.}}\right|_{same\,effect(S)}$$

- instead of being a radiation quality related feature like RBE, it is more a *target* property (like e.g. OER)
- it is called a „*dose modifying factor*“ if independent on S (or D)

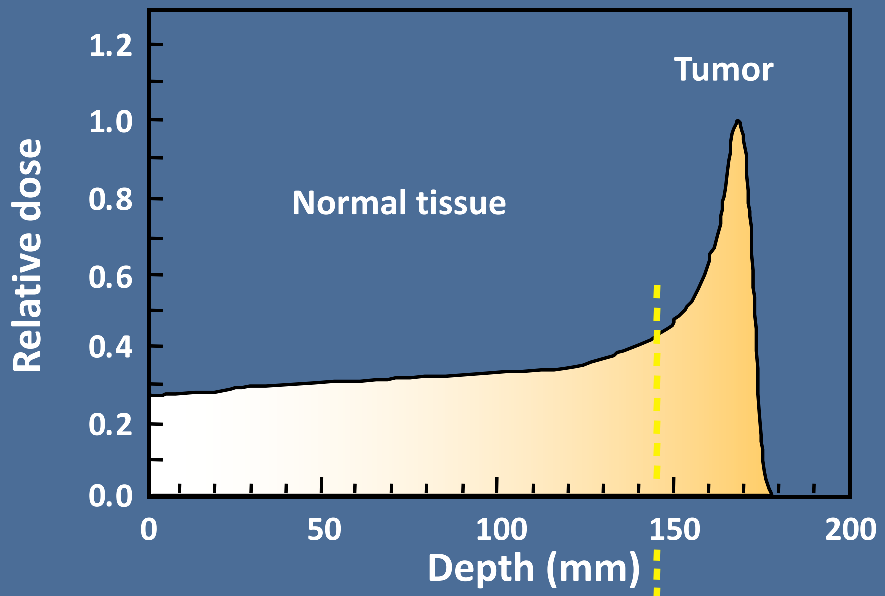
Relevant effects in low-LET radiation: what about high LET?

$$DEF(LET,[C]) = \left.\frac{D(LET,[C])}{D_{n.c.}}\right|_{same\,effect(S)}$$



Wenzl&Wilkens 2011

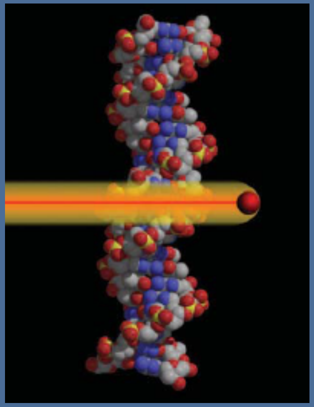
Charged particle therapy: improved physics and enhanced biological effectiveness



Durante & Loeffler,

Nature Rev Clin Oncol 2010

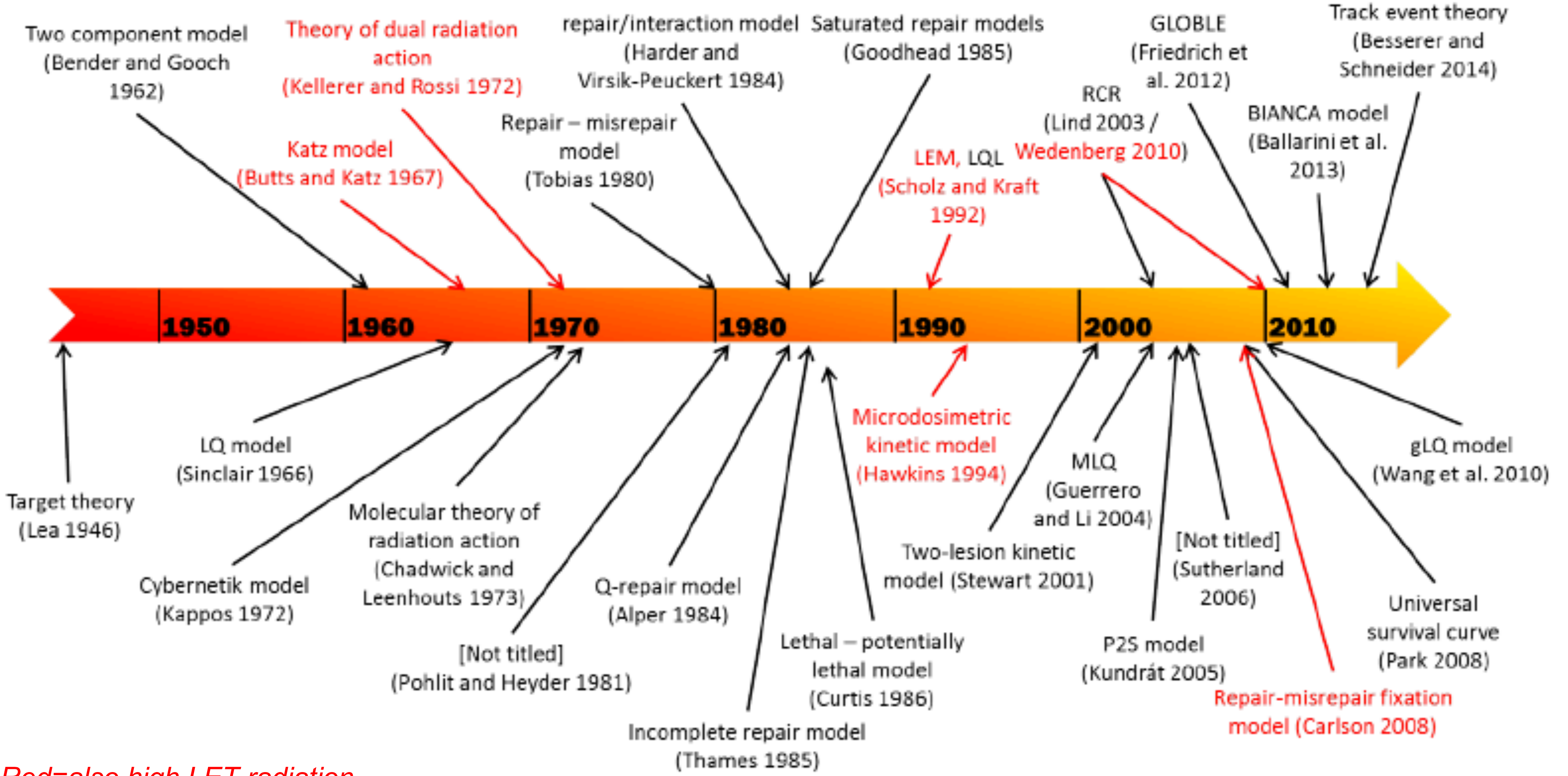
Potential advantages



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	

Biophysical Models

History of biophysical modeling



Two component model (Bender and Gooch 1962)

Theory of dual radiation action (Kellerer and Rossi 1972)

Katz model (Butts and Katz 1967)

Repair – misrepair model (Tobias 1980)

repair/interaction model (Harder and Virsik-Peuckert 1984)

Saturated repair models (Goodhead 1985)

LEM, LQL (Scholz and Kraft 1992)

RCR (Lind 2003 / Wedenberg 2010)

GLOBLE (Friedrich et al. 2012)

BIANCA model (Ballarini et al. 2013)

Track event theory (Besserer and Schneider 2014)

1950

1960

1970

1980

1990

2000

2010

Target theory (Lea 1946)

LQ model (Sinclair 1966)

Cybernetik model (Kappos 1972)

Molecular theory of radiation action (Chadwick and Leenhouts 1973)

[Not titled] (Pohlit and Heyder 1981)

Q-repair model (Alper 1984)

Incomplete repair model (Thames 1985)

Lethal – potentially lethal model (Curtis 1986)

Microdosimetric kinetic model (Hawkins 1994)

Two-lesion kinetic model (Stewart 2001)

MLQ (Guerrero and Li 2004)

P2S model (Kundrát 2005)

[Not titled] (Sutherland 2006)

Repair-misrepair fixation model (Carlson 2008)

Universal survival curve (Park 2008)

gLQ model (Wang et al. 2010)

Red=also high LET radiation

T. Friedrich (Habil Thesis) TUD 2016

Clinically applied models

- *MKM – Microdosimetric Kinetic Model (Japan)*
- *LEM– Local Effect Model (Europe)*

Amorphous Track Structure Model Assumptions

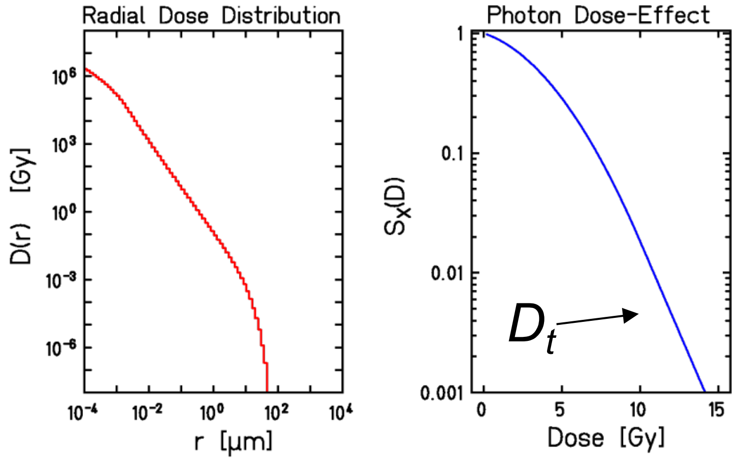
1. ***Simplification of Track Structure by neglecting the stochastic processes of secondary electron emission. The concept of an amorphous radial dose distribution is used.***

2. ***No general difference between high- and low LET radiation, since all damage is generated by secondary electrons***

3. ***Convolution of low-LET survival curve and radial dose distribution yields response to heavy ion irradiation.***

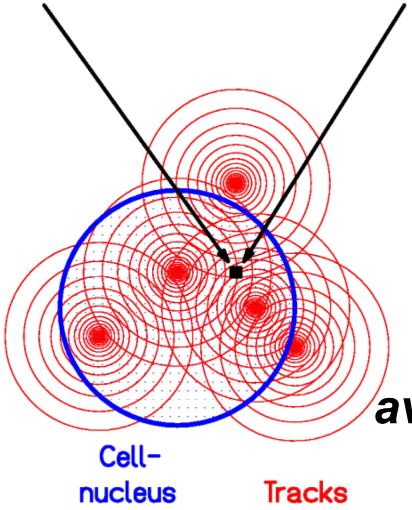
LEM I: Three Ingredients

Physics Radial Dose Distribution: *Monte-Carlo (Krämer), Experimental Data, Semi-empirical*



Radiobiology Photon Survival Curve: *large data base available linear-quadratic-linear: LQL*

Geometry Target (cell nucleus): *Experimental Data*



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

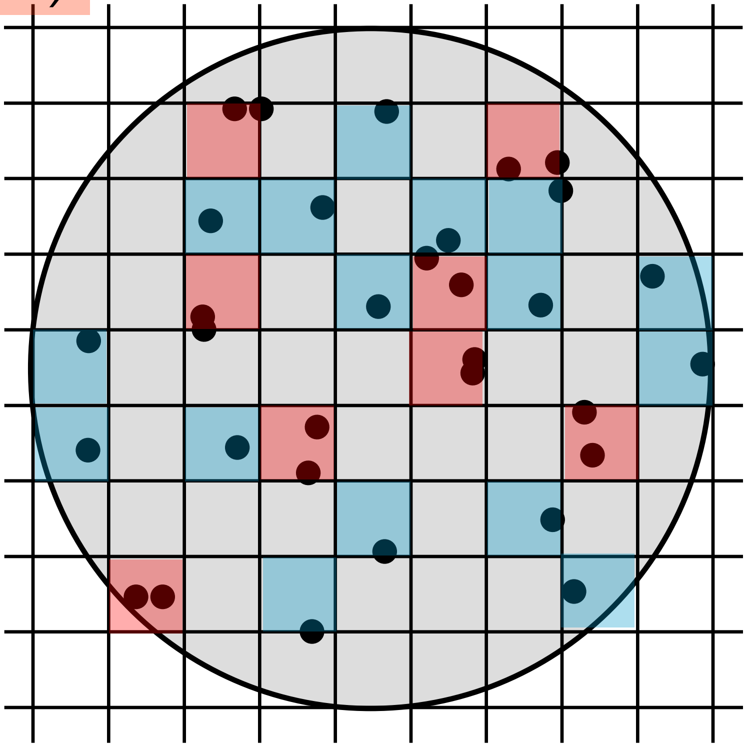
$$S = e^{-s_{\max}\eta(D - D_t)}, \quad D \ge D_t$$

average number of lethal events

LEM IV: Cluster Index

Distinguish between

- *Isolated DSBs (iDSB)*
- *DSB clusters (cDSB)*



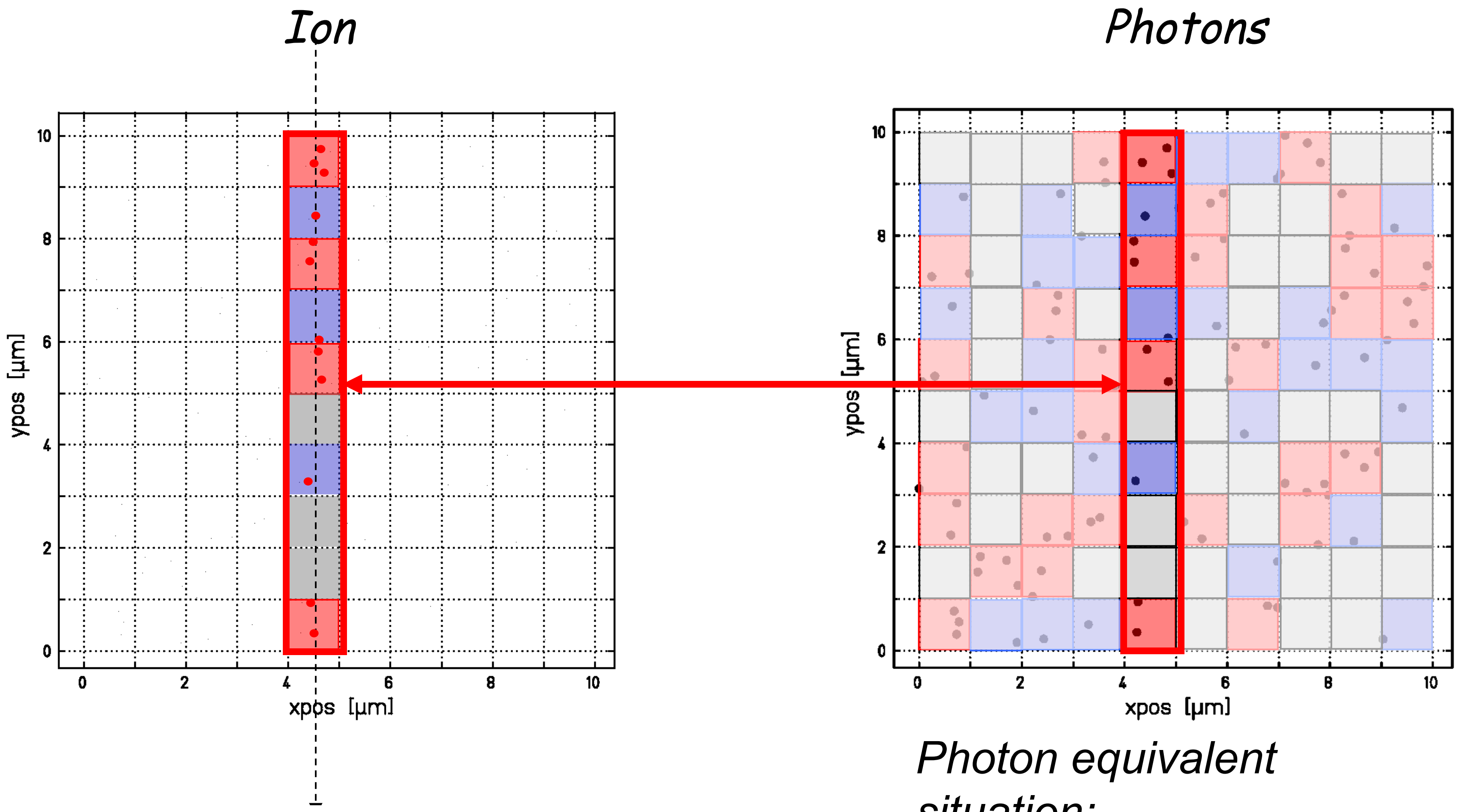
Measure for complexity of lesions: Cluster index

$$CI = \frac{\#(\mathrm{cDSB})}{\#(\mathrm{cDSB})+\#(\mathrm{iDSB})}$$

→ *Derive statistics of lesions*

Courtesy.of T. Friedrich

LEM IV: Ion-Photon Equivalence



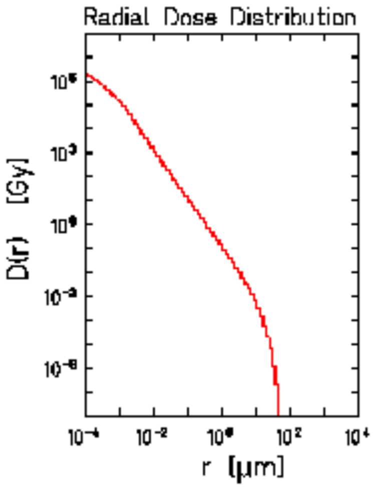
DSB distribution in single track = cut-out of X-ray damage pattern

Photon equivalent situation:

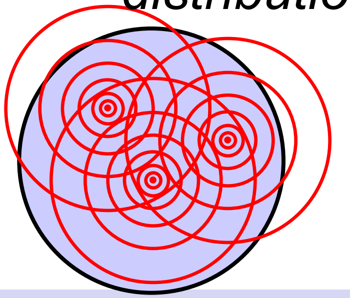
$CI_{Photons} = CI_{Ion}$ at dose D_{eq}

Courtesy.of T. Friedrich

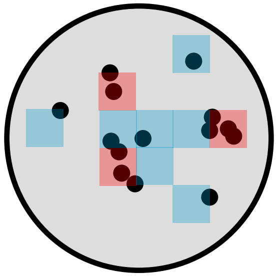
LEM IV: Calculation Path



Amorphous track structure



Local dose distribution

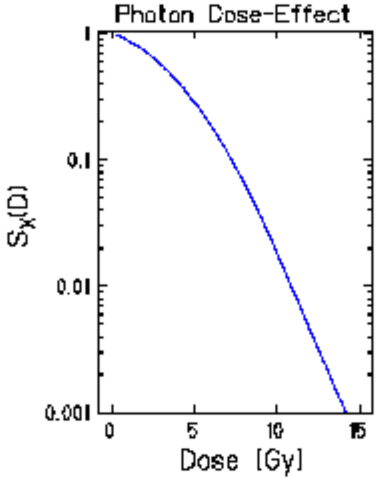


Local lesion distribution

Lesion statistics

🟦: *7*

🟥: *3*



Photon equivalent situation

RBE

Courtesy.of T. Friedrich

Microdosimetric Kinetic Model

Extension of the Dual Radiation Action Model.
Cell nucleus divided into a number q of microscopic sites called domains.
Survival fraction s_d of a domain after a dose z is absorbed:

$$\boxed{-\ln s_{\mathrm{d}} = Az + Bz^2}$$

Independent of the radiation quality.

Number of hits to a domain: Poisson distribution.
Survival fraction of a cell: S.
A cell survives if all domain survive.

Biologically based Treatment planning

Advancing clinical prescription for Particle therapy

optimized quantity:

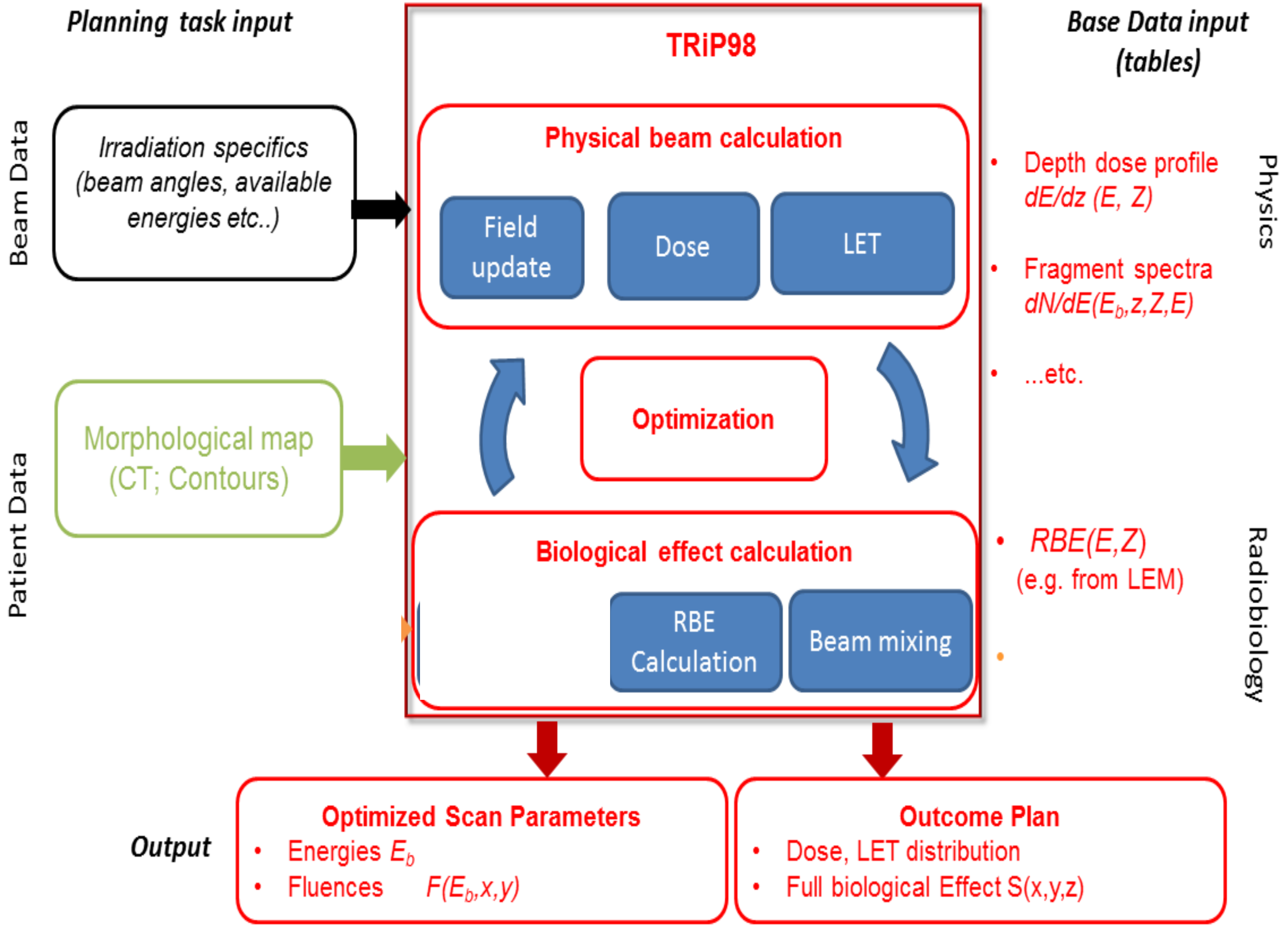
- Absorbed Dose

⬇

- Biologically effective Dose (RBE weighted)

TRiP98 – Treatment planning for Particles

Clinical use in pilot project, Research use in GSI, HIT, Aarhus, Lyon etc.
Reference for: Siemens SynGo/PT, RayStation Carbon



Planning task input

Beam Data

Irradiation specifics (beam angles, available energies etc..)

Patient Data

Morphological map (CT; Contours)

TRiP98

Physical beam calculation

Field update

Dose

LET

Optimization

Biological effect calculation

RBE Calculation

Beam mixing

Base Data input (tables)

Physics

- Depth dose profile *dE/dz (E, Z)*
- Fragment spectra *$dN/dE(E_b,z,Z,E)$*
- ...etc.

Radiobiology

- *RBE(E,Z)* (e.g. from LEM)

Output

Optimized Scan Parameters

- Energies E_b
- Fluences $F(E_b,x,y)$

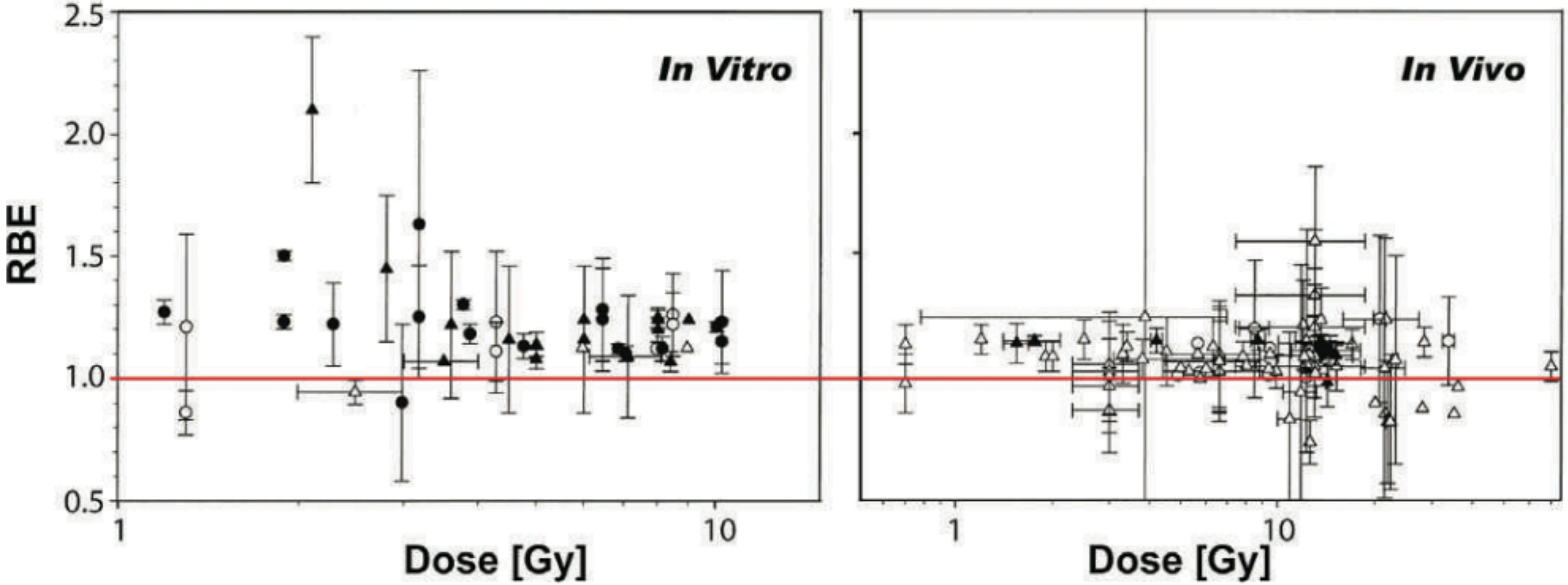
Outcome Plan

- Dose, LET distribution
- Full biological Effect S(x,y,z)

Proton RBE

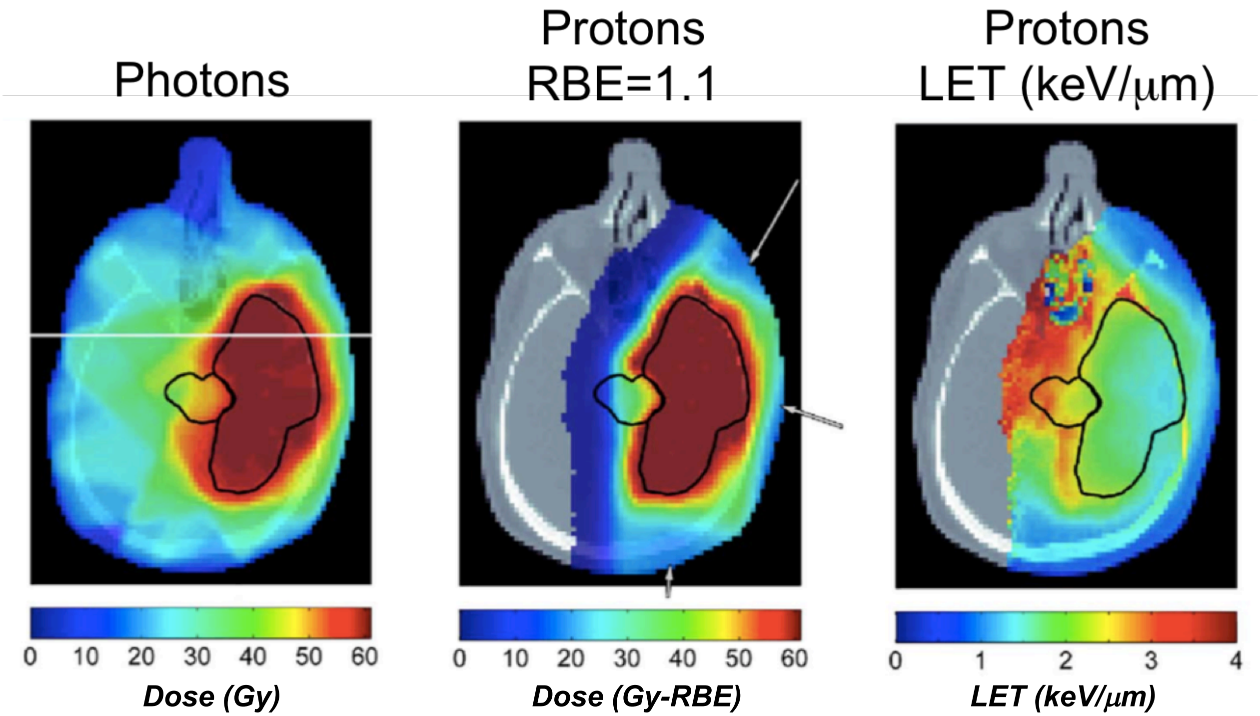
RBE=1.1 for protons in radiation therapy

(ICRU recommendations)



Paganetti 2002 PMB

…are deviations from 1.1 of ***clinical relevance***?



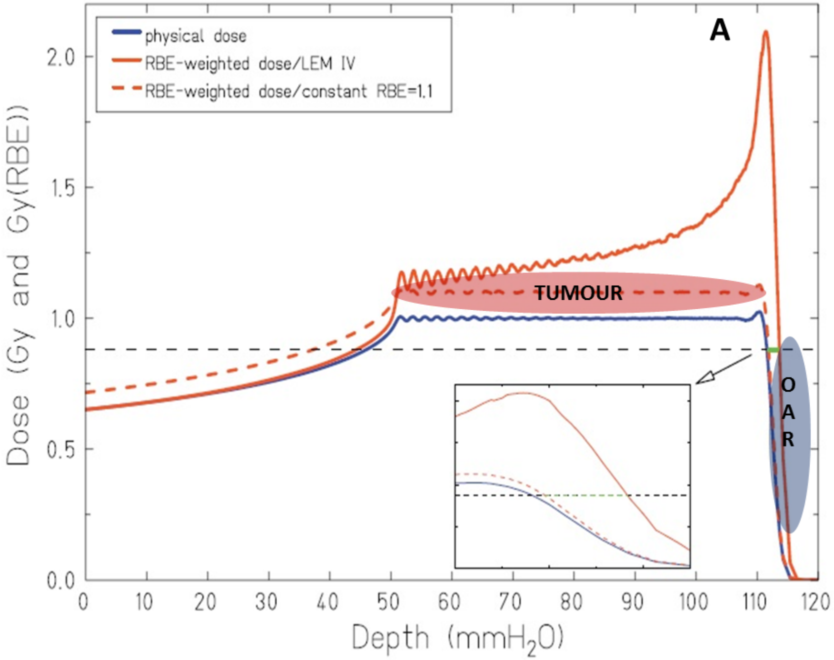
Wedenberg 2014 Med Phys

- ***Potential improvements offered by biological optimization***
- ***Possible bias when neglecting variable RBE***
- ***Sensitivity to RBE model***
- ***Only 3 patients considered!***

Courtesy of F. Tommasino

Biological Range uncertainty

(additional to physical range uncertainty!)

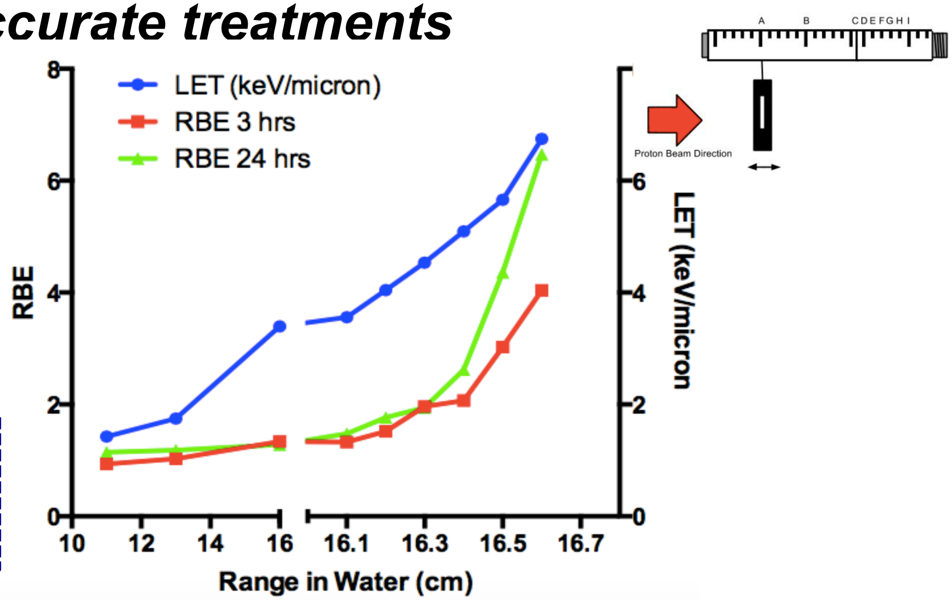


Grün 2013 Med Phys

Range defined as distal D80

Distal SOBP:

- *Parallel decrease of dose and increase in LET*
- *RBE is highly uncertain*
- ***RBE can be >>1 in OAR!!***
- ***Better characterization -> more accurate treatments***

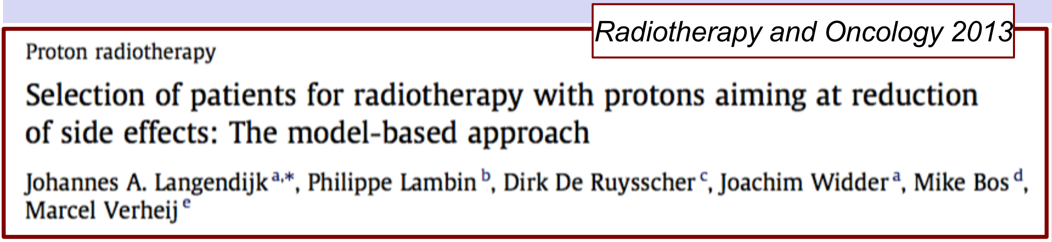


Cuaron 2016 IJROBP

DSB induction and repair

Chasing a Clinical Impact

Radiotherapy and Oncology 2013

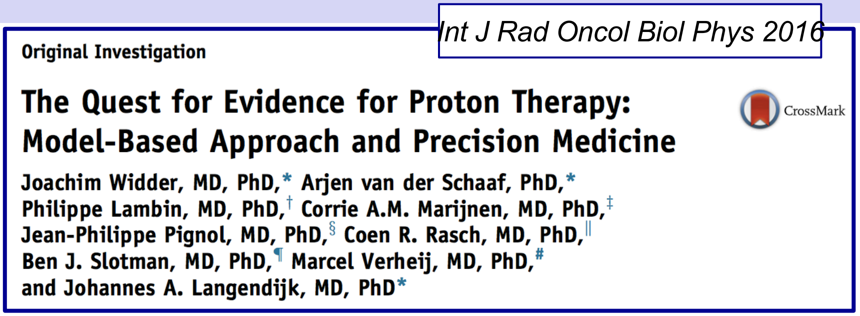


Proton radiotherapy

Selection of patients for radiotherapy with protons aiming at reduction of side effects: The model-based approach

Johannes A. Langendijk[a,*], Philippe Lambin[b], Dirk De Ruysscher[c], Joachim Widder[a], Mike Bos[d], Marcel Verheij[e]

Int J Rad Oncol Biol Phys 2016

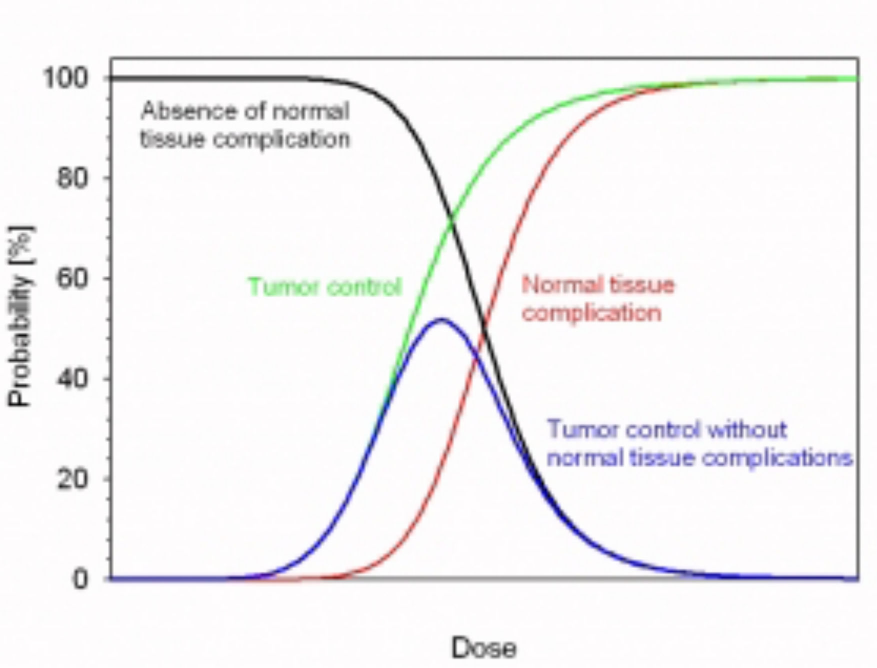


Original Investigation

The Quest for Evidence for Proton Therapy: Model-Based Approach and Precision Medicine

Joachim Widder, MD, PhD,[*] Arjen van der Schaaf, PhD,[*] Philippe Lambin, MD, PhD,[†] Corrie A.M. Marijnen, MD, PhD,[‡] Jean-Philippe Pignol, MD, PhD,[§] Coen R. Rasch, MD, PhD,[‖] Ben J. Slotman, MD, PhD,[¶] Marcel Verheij, MD, PhD,[#] and Johannes A. Langendijk, MD, PhD[*]

Physical Dose ← ***NTCP models*** → ***Clinical Outcome***

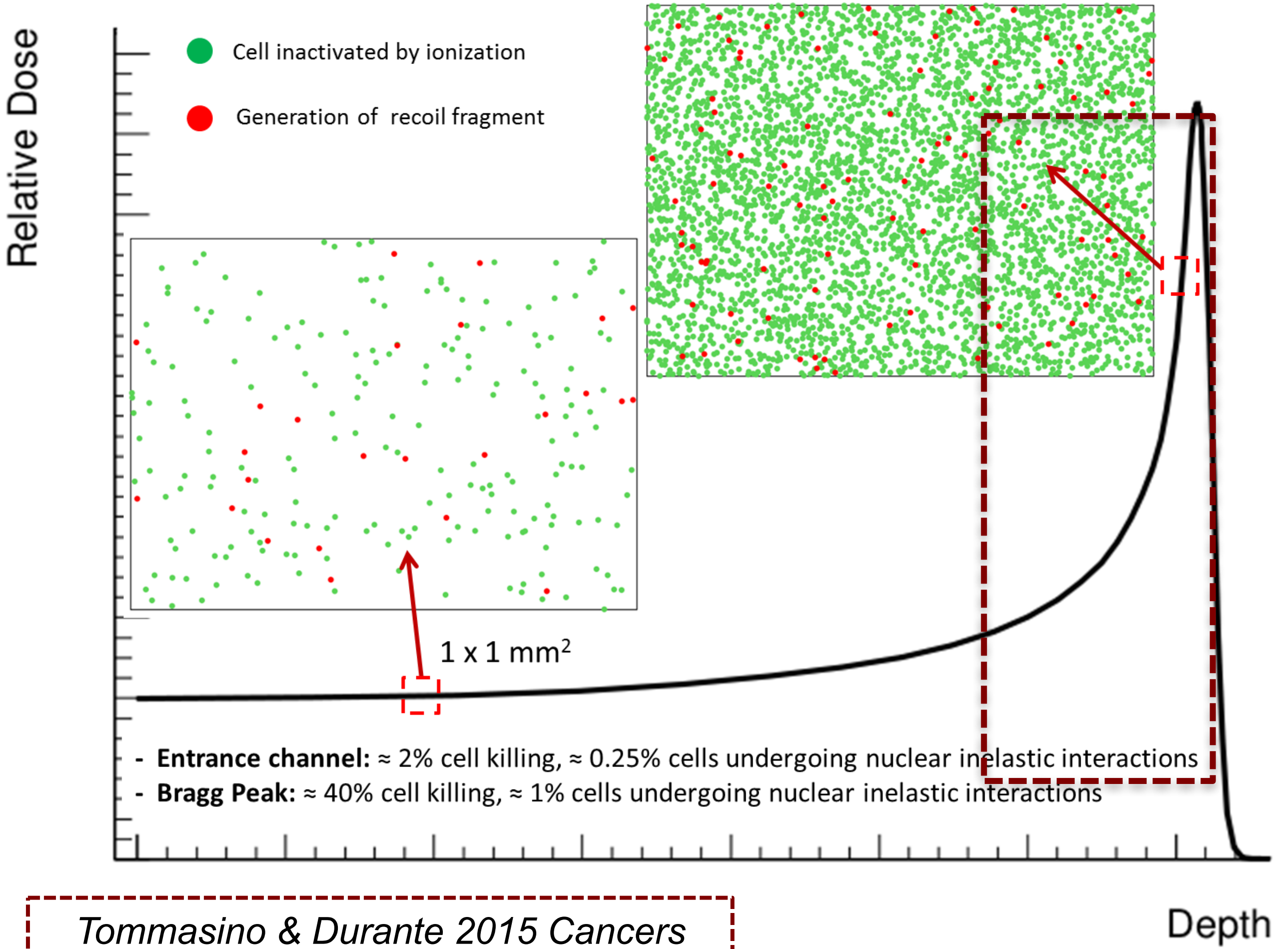


Protons will lead to improved clinical outcomes (less serious toxicity) if:

1. ***Normal tissue sparing can be obtained (Δdose)***
2. ***Δdose will result in lower clinically significant complication risks (ΔNTCP)***

Courtesy of F. Tommasino

Target fragmentation in proton therapy



- **Entrance channel:** ≈ 2% cell killing, ≈ 0.25% cells undergoing nuclear inelastic interactions
- **Bragg Peak:** ≈ 40% cell killing, ≈ 1% cells undergoing nuclear inelastic interactions

About 10% of biological effect in the entrance channel due to secondary fragments

↓

Largest contributions of recoil fragments expected from

He, C, Be, O, N

↓

Heavy fragments have low residual energies and release low doses -> high RBE!!

Tommasino & Durante 2015 Cancers

Courtesy of F. Tommasino

Target fragmentation in proton therapy

Fragment	E (MeV)	LET (keV/μm)	Range (μm)
^{15}O	1.0	983	2.3
^{15}N	1.0	925	2.5
^{14}N	2.0	1137	3.6
^{13}C	3.0	951	5.4
^{12}C	3.8	912	6.2
^{11}C	4.6	878	7.0
^{10}B	5.4	643	9.9
^{8}Be	6.4	400	15.7
^{6}Li	6.8	215	26.7
^{4}He	6.0	77	48.5
^{3}He	4.7	89	38.8
^{2}H	2.5	14	68.9

About 10% of biological effect in the entrance channel due to secondary fragments

↓

Largest contributions of recoil fragments expected from

He, C, Be, O, N

↓

Heavy fragments have low residual energies and release low doses -> high RBE!!

Tommasino & Durante 2015 Cancers

Courtesy of F. Tommasino

BioTPS with New ions

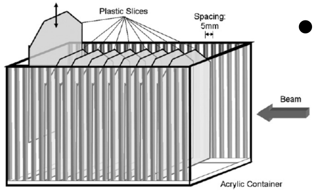
(Re)introducing new ions

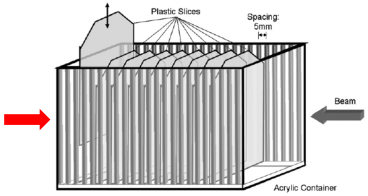
•**O** and **He** available @HIT with full active scanning capabilities and potentially in future at CNAO and Med-AUSTRON

- Comparative TPS studies between different ions require an advanced modeling of the physics and radiobiology
- Such biological characterization in same cases should go beyond the concept of RBE-weighted dose.
- Biological dosimetry *in vitro/in vivo*, not only on monoenergetic but on extended targets
- Treatment planning tests on several levels

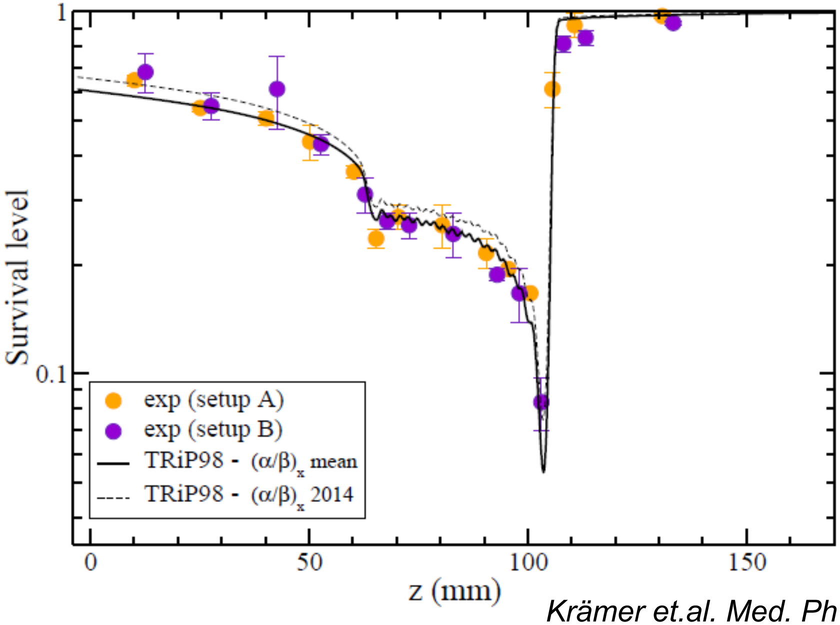
^{4}He biological verification

- New Beam model + LEMIV
  - CHO cells Survival on a He planned extended volume
  - spatial resolution : 2.5 mm



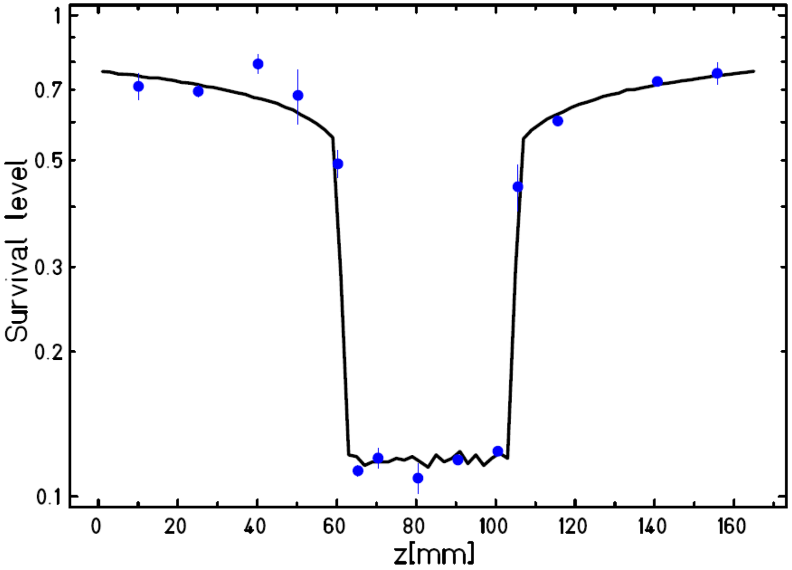


- Single field, optimized on flat physical dose =4Gy



Krämer et.al. Med. Phys. 43, 2016

- 2 Fields bio-optimized (MFO) on uniform survival



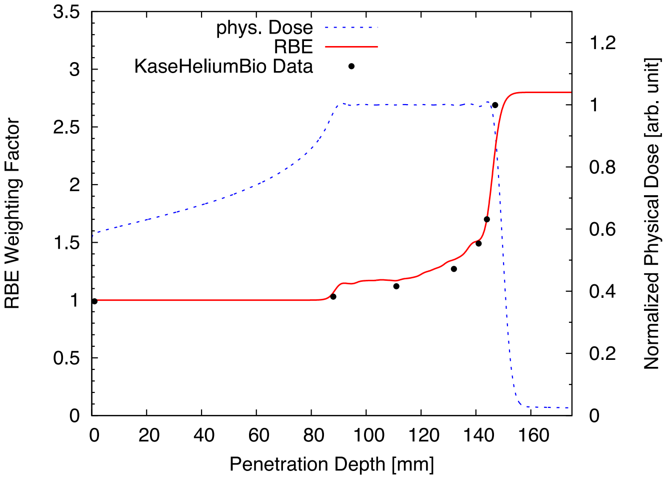
Sokol et. al. in prep for Med Phys.

^{4}He Med AUSTRON model

Fuchs et al Med Phys (2015),

- empirical “zonal” depth-dependent RBE model, independent from dose level and cell type.
- 1.0 in the plateau, then increasing RBE up to a value of 2.8 at the Bragg peak region and constant in fragmentation

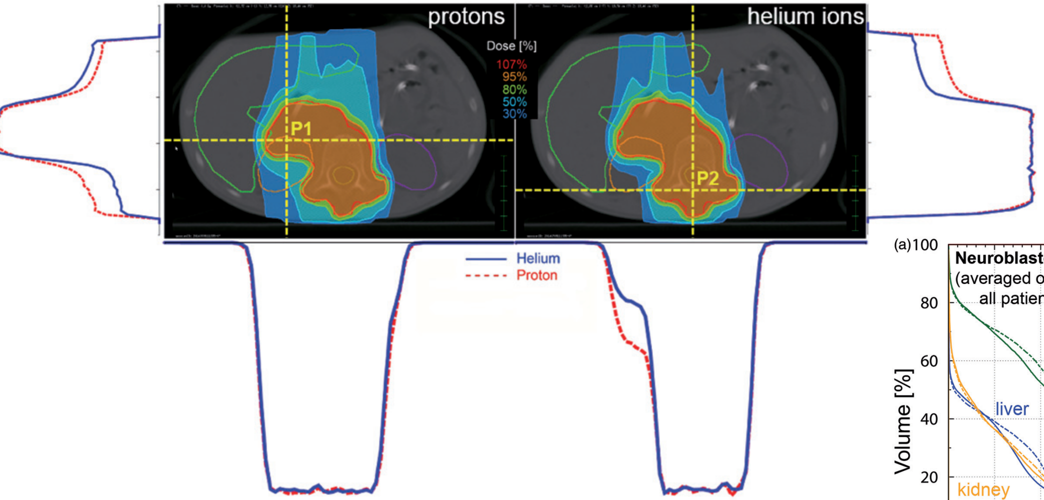
TPS: HYPERION



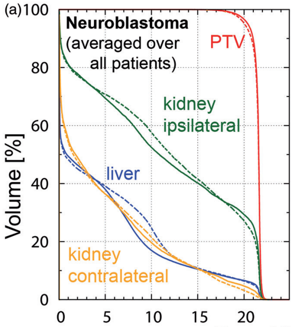
(b)

Treatment plan quality slightly improved with ^{4}He compared to proton plans, but advantages in OAR sparing were depending on indication and tumor geometries.

High sensitivity to beam model



Knaüsl et al. Acta Oncol. 2016



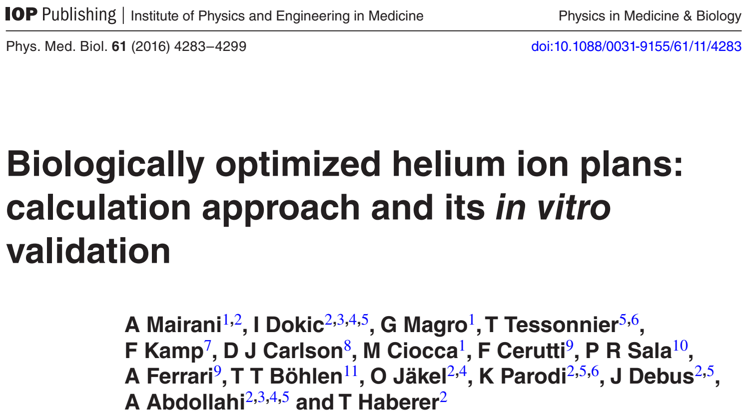
^{4}He CNAO/HIT model

Mairani et al. PMB 2016 A,B

Phys Med Biol. 2016 Jan 21;61(2):888-905

Data-driven RBE parameterization for helium ion beams.

RBE(dose, LET, $(\alpha/\beta)_{ph}$)



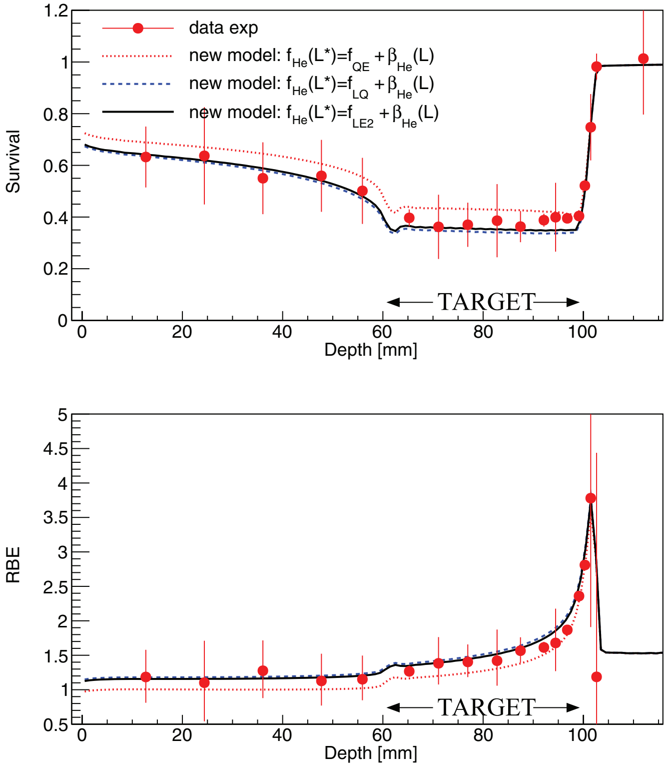
IOP Publishing | Institute of Physics and Engineering in Medicine   Physics in Medicine & Biology

Phys. Med. Biol. **61** (2016) 4283–4299   doi:10.1088/0031-9155/61/11/4283

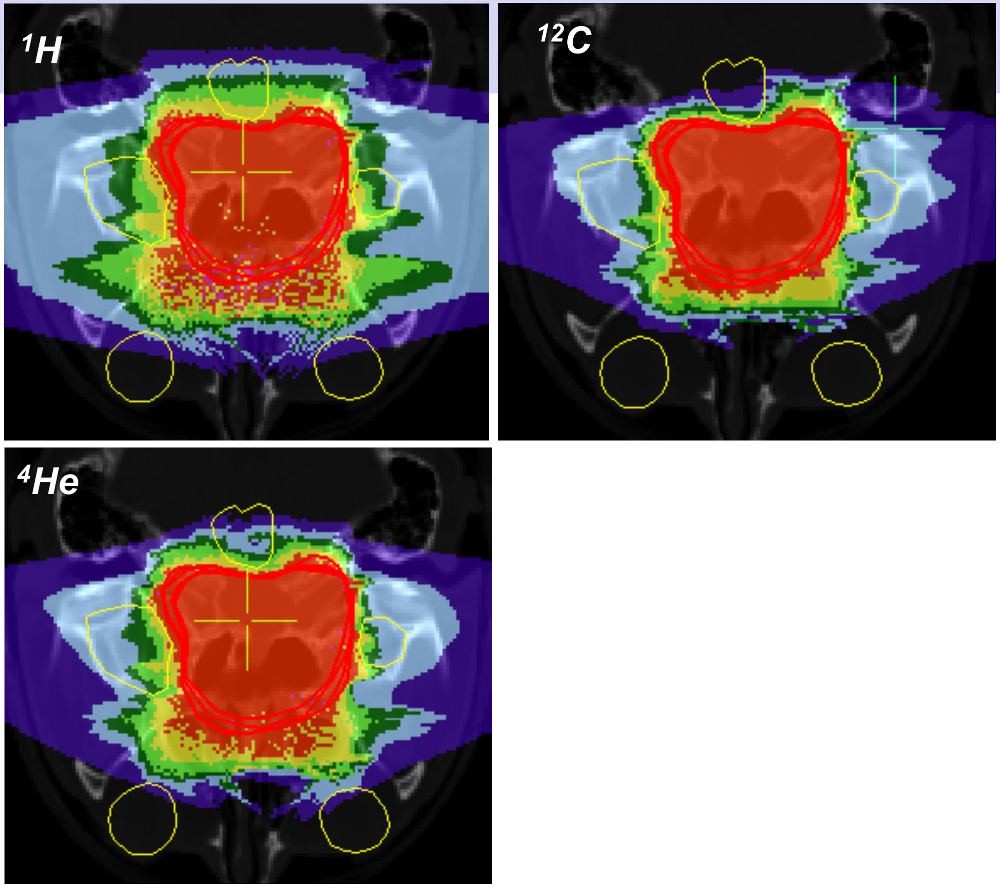
Biologically optimized helium ion plans: calculation approach and its *in vitro* validation

A Mairani[1,2], I Dokic[2,3,4,5], G Magro[1], T Tessonnier[5,6], F Kamp[7], D J Carlson[8], M Ciocca[1], F Cerutti[9], P R Sala[10], A Ferrari[9], T T Böhlen[11], O Jäkel[2,4], K Parodi[2,5,6], J Debus[2,5], A Abdollahi[2,3,4,5] and T Haberer[2]

TPS: MCTP->FLUKA



TRiP98 treatment plans comparison - a patient example

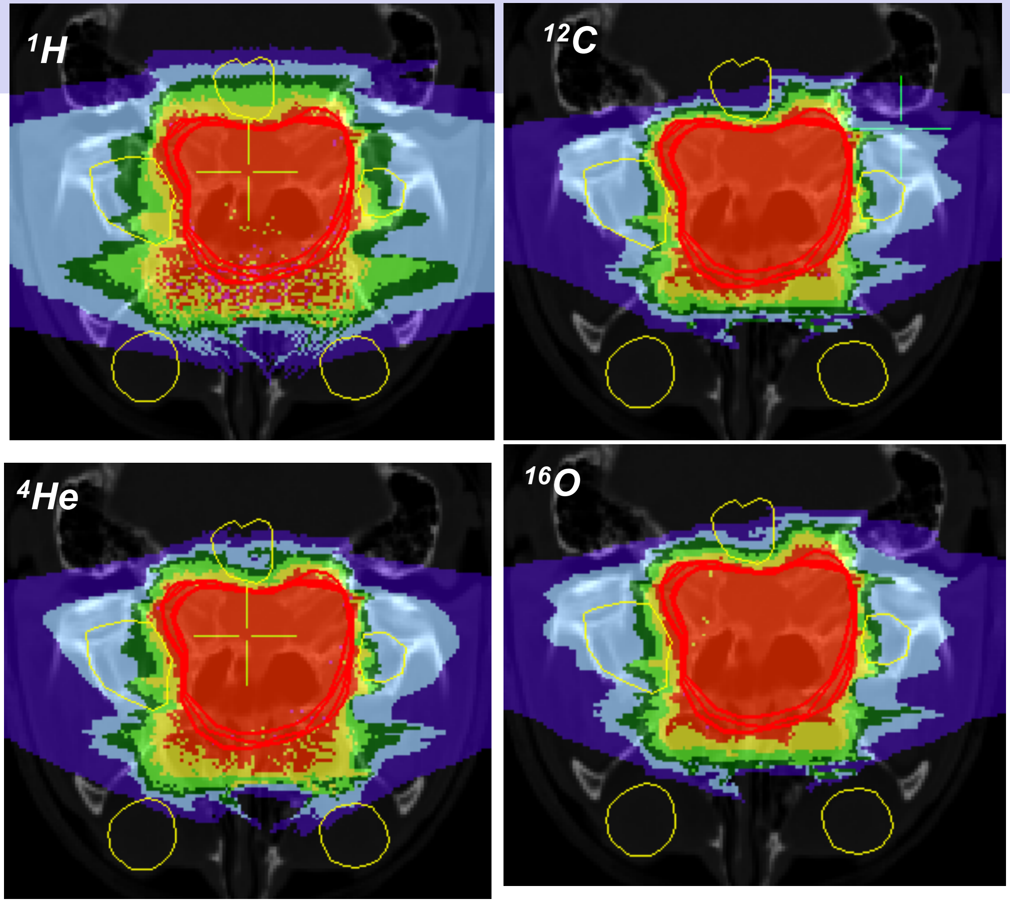


Two-dimensional dose distributions for GSI pilot project patient CT slice Plans for double-field irradiation of chordoma with ^{1}H, ^{4}He, ^{12}C

R. Grün et al, Med.Phys. 42, 1037 (2015)

Helium: a promising alternative for carbon and protons

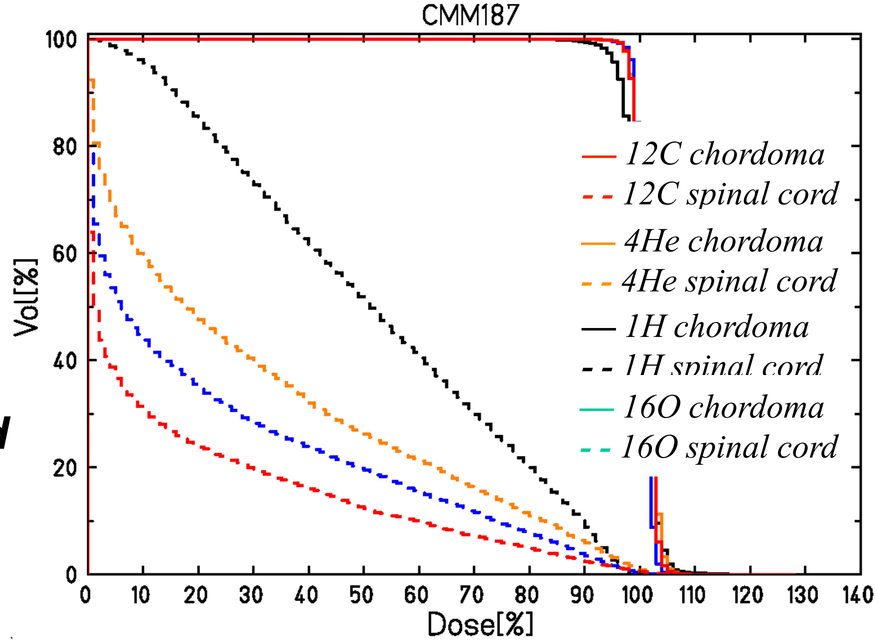
TRiP98 treatment plans comparison - a patient example



Two-dimensional dose distributions for GSI pilot project patient CT slice
Plans for double-field irradiation of chordoma with ^{1}H, ^{4}He, ^{12}C

R. Grün et al, Med.Phys. 42, 1037 (2015)

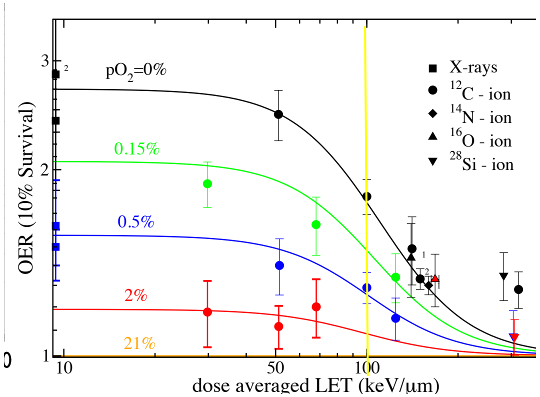
*Extended + ^{16}**O** (Sokol et al. unpub)*

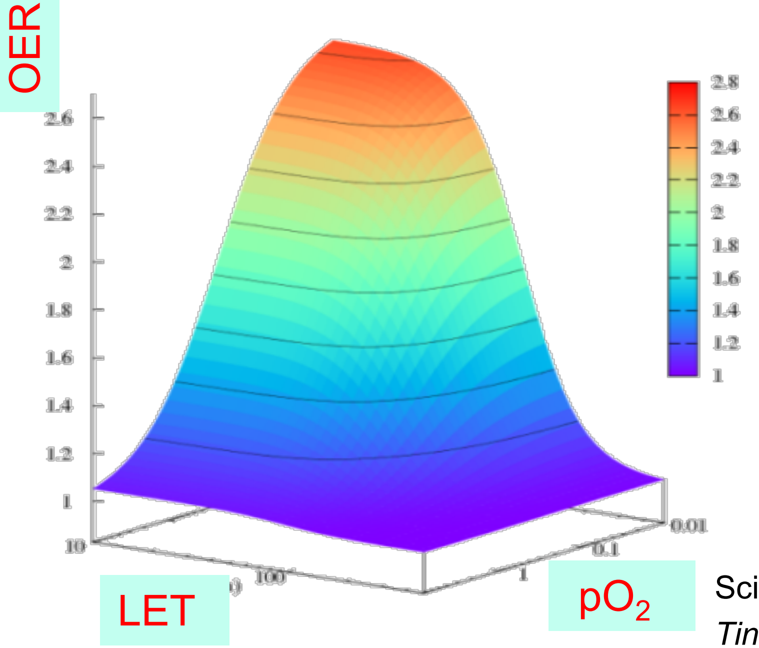


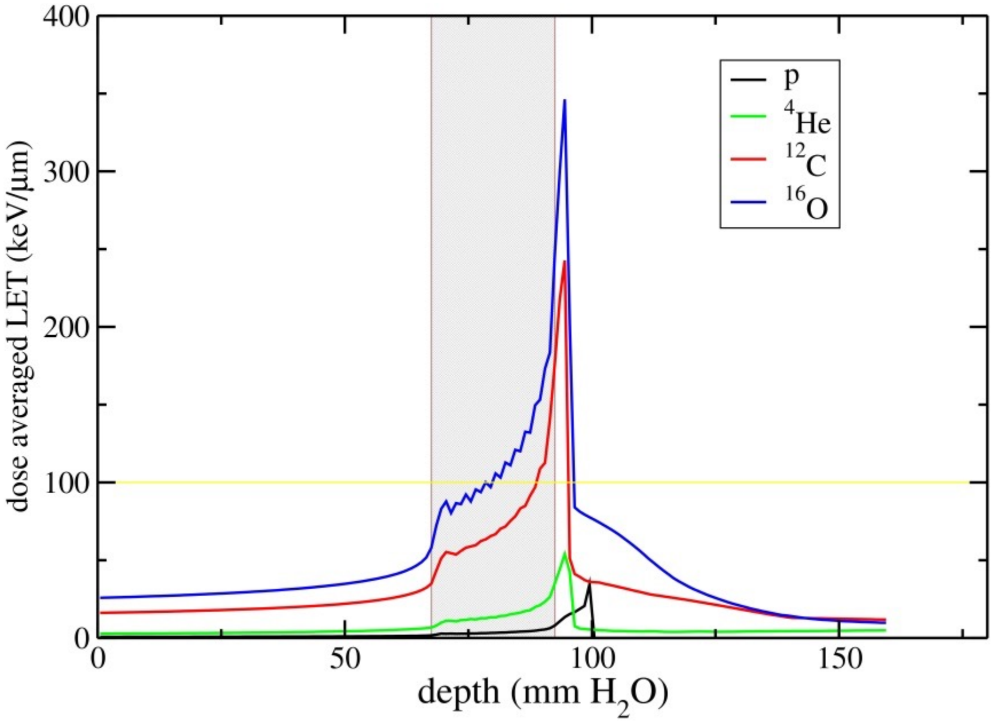
Helium: a promising alternative for carbon and protons

Special cases for using oxygen?

OER (pO2,LET)





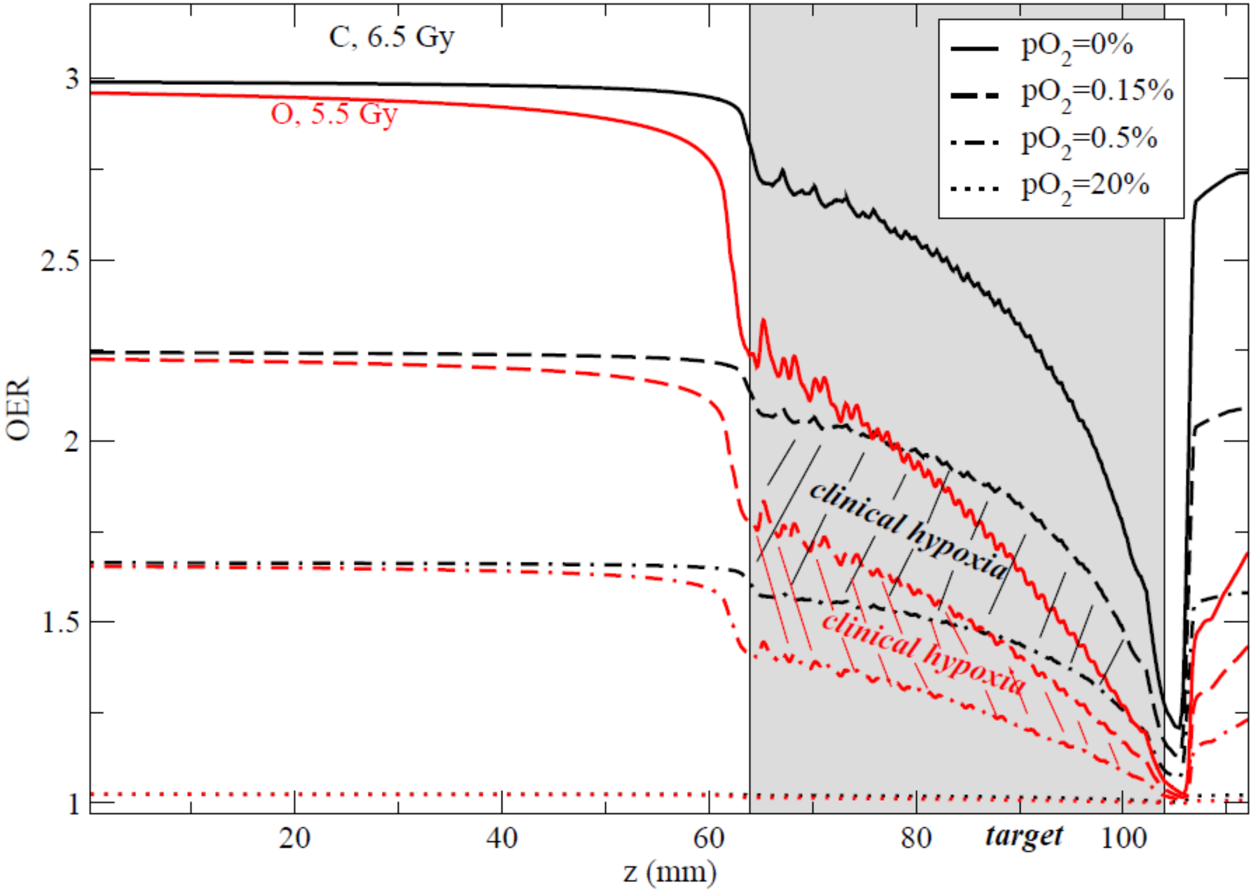


Tommasino Scifoni Durante Int J Part Ther 2015

Scifoni et al PMB 2013

Tinganelli et al. Sci Rep 2015

OER profile O vs C



Scifoni et al PMB 2013

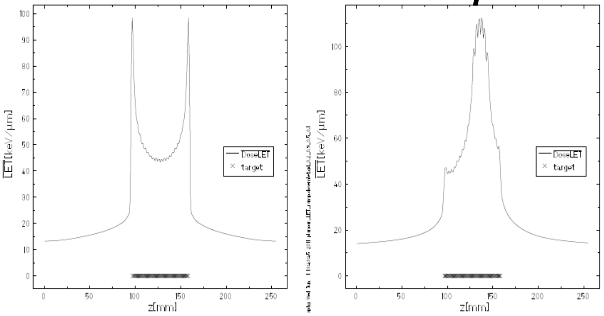
- OER along the irradiation depth for different ion and pO2

-selective advantage of O beam

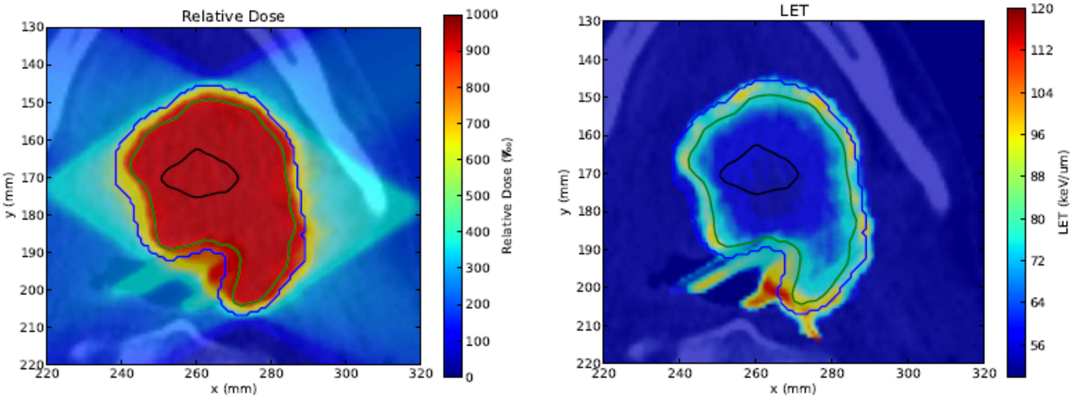
LET painting

- Redistribution of LET,
to be maximized
in a target volume,

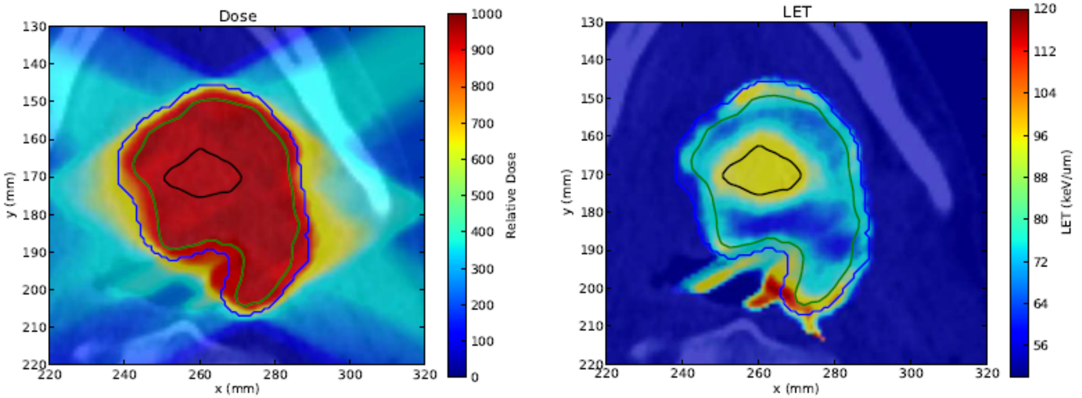
using TRiP98
with dose ramps



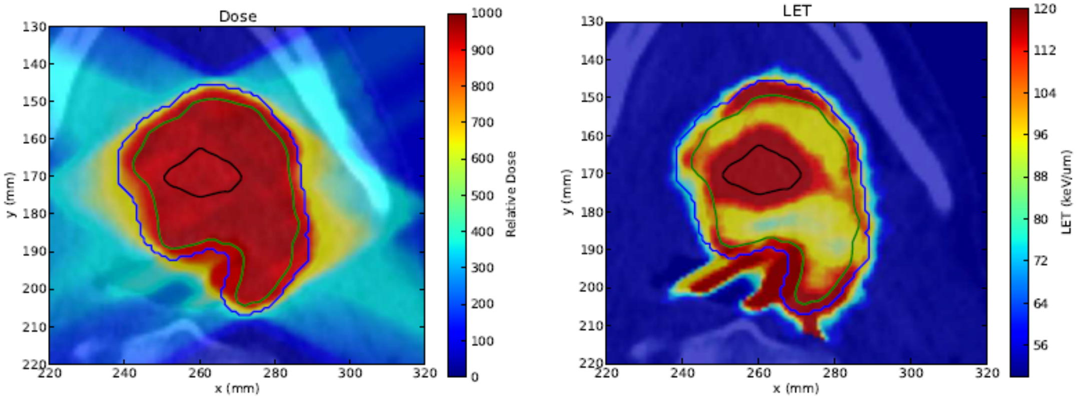
4 Flat
C fields



4 Dose
ramped
C



4 Dose
Ramped
O



Bassler et al. Acta Oncol 2014

The kill painting basic idea

optimized quantity:

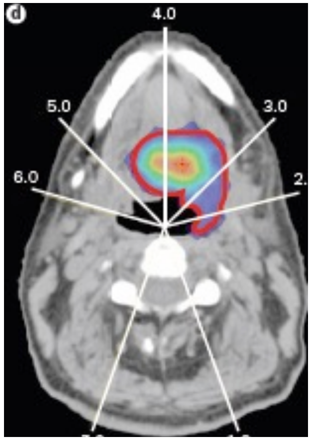
- Absorbed Dose

⬇

- Biologically effective Dose (RBE weighted)

⬇

- Biologically isoeffective Dose in the local microenvironment

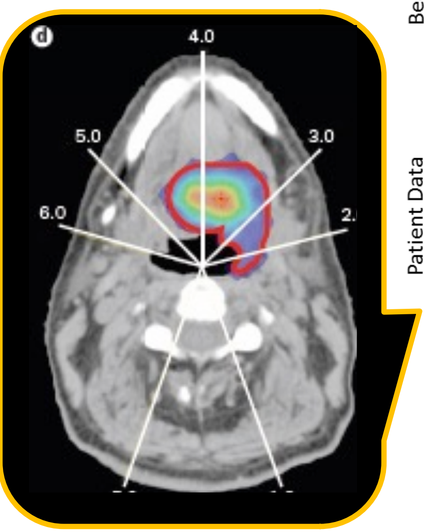


Intra-tumour
Heterogeneity
revealed by functional imaging
e.g. CT/PET(FMISO)
Horsman NRCO 211

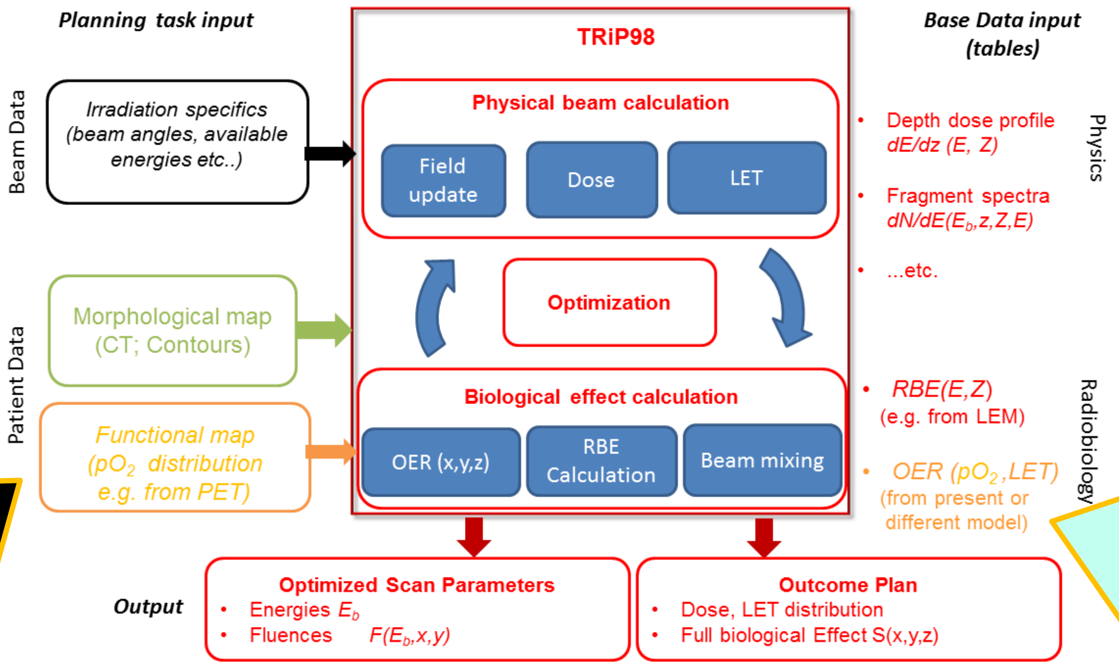
What is needed:

- ✓ Physical beam modeling
- ✓ RadioBiological modeling
- ✓ Implementation in TPS
- ✓ Experimental Verification

Kill painting implementation in TPS



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



Planning task input

TRiP98

Base Data input (tables)

Beam Data

Irradiation specifics (beam angles, available energies etc..)

Physical beam calculation

Field update | Dose | LET

- Depth dose profile *dE/dz (E, Z)*
- Fragment spectra *$dN/dE(E_b,z,Z,E)$*
- ...etc.

Physics

Patient Data

Morphological map (CT; Contours)

Functional map (pO_2 distribution e.g. from PET)

Optimization

Biological effect calculation

OER (x,y,z) | RBE Calculation | Beam mixing

- *RBE(E,Z)* (e.g. from LEM)
- *OER (pO_2,LET)* (from present or different model)

Radiobiology

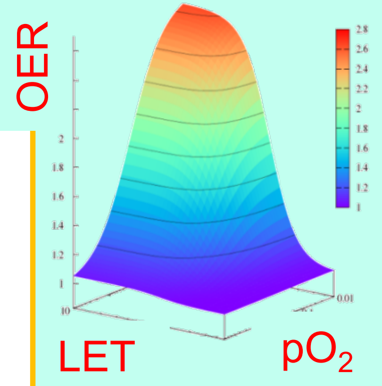
Output

Optimized Scan Parameters
- Energies E_b
- Fluences *$F(E_b,x,y)$*

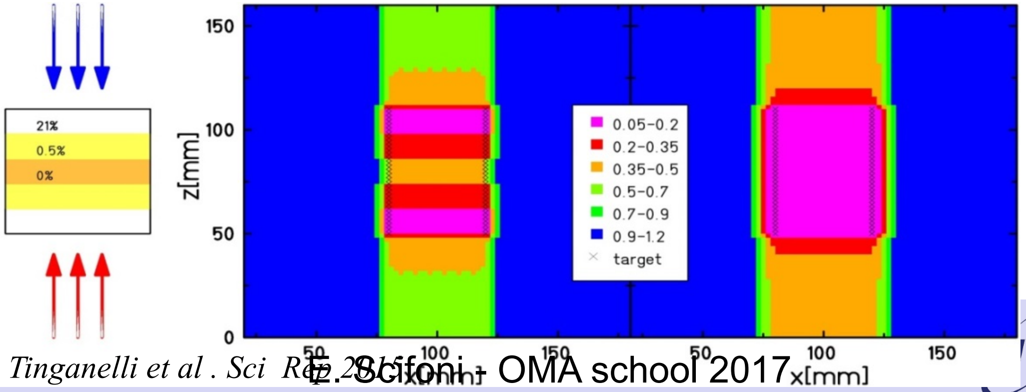
Outcome Plan
- Dose, LET distribution
- Full biological Effect S(x,y,z)

Semi-empirical model for OER (pO_2,LET)

Scifoni et al . Phys Med Biol 2013



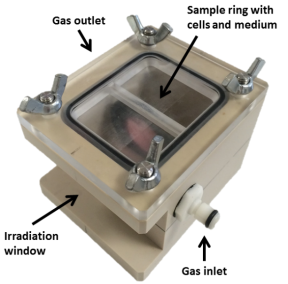
LET and dose distribution of the particle fields automatically adjusted from the optimization to the oxygen distribution

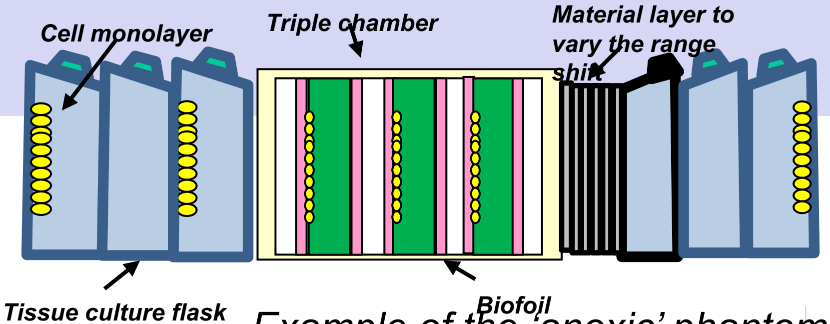


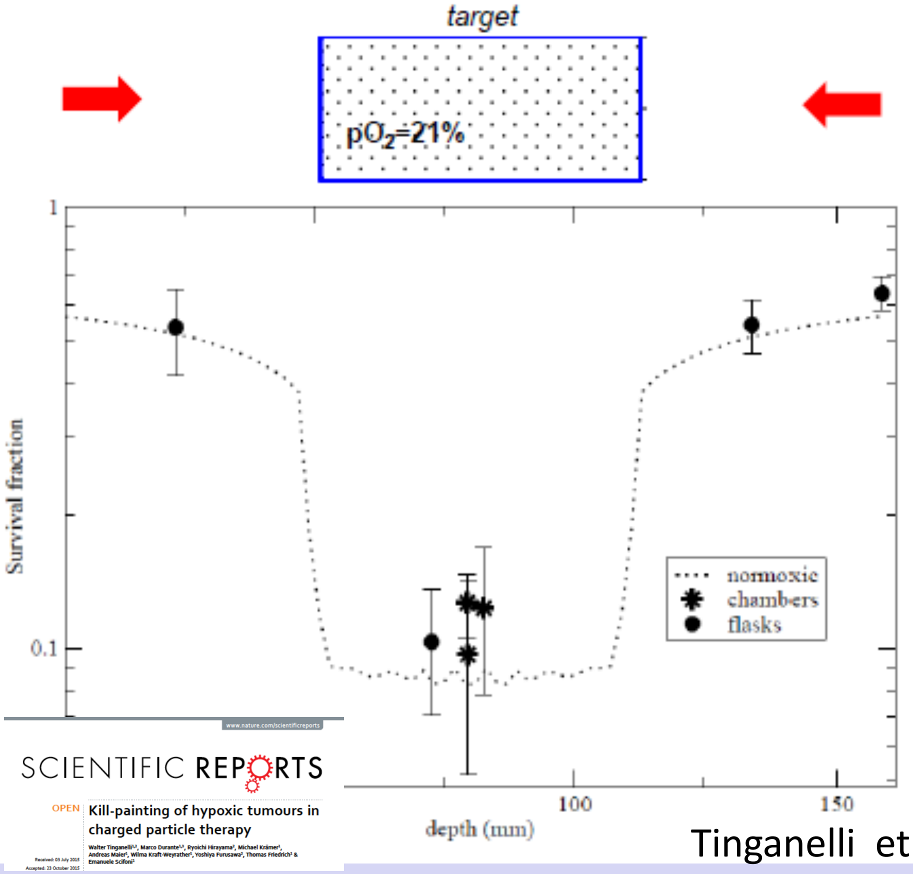
Tinganelli et al . Sci Rep 2015

Experimental verification: Hypoxic cell chambers

2 Fields C ions@GSI







www.nature.com/scientificreports

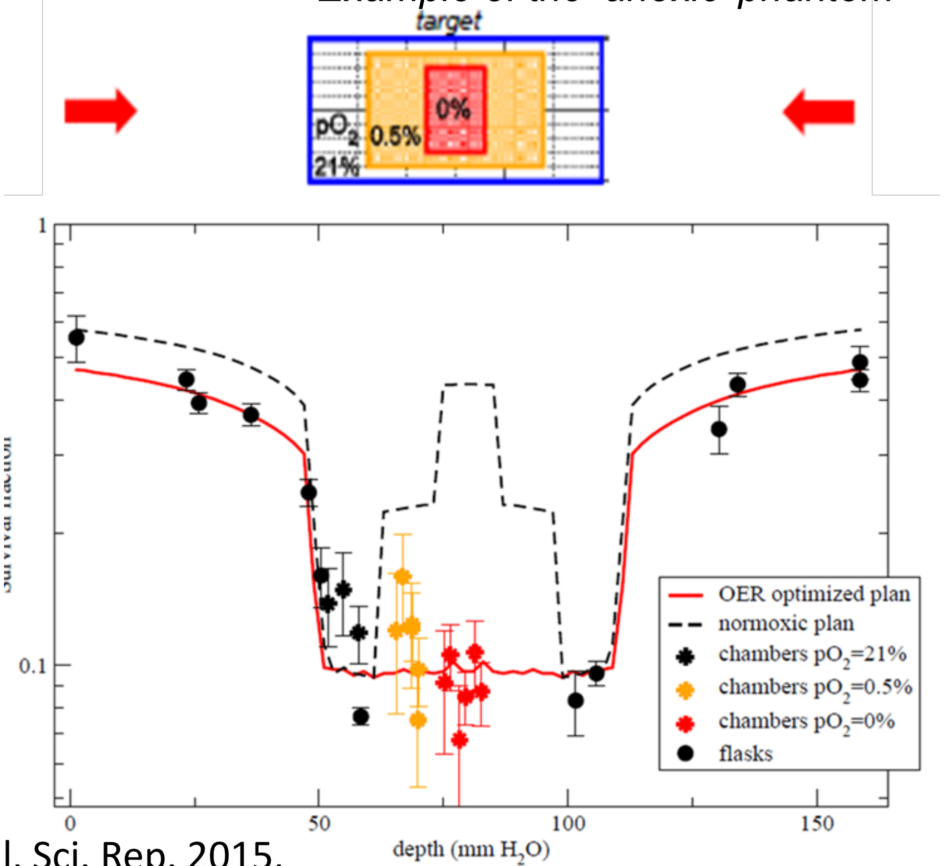
SCIENTIFIC REPORTS

OPEN **Kill-painting of hypoxic tumours in charged particle therapy**

Walter Tinganelli[1,2], Marco Durante[1,3], Ryoichi Hirayama[2], Michael Krämer[1], Andreas Maier[1], Wilma Kraft-Weyrather[1], Yoshiya Furusawa[2], Thomas Friedrich[1] & Emanuele Scifoni[1]

Received: 03 July 2015
Accepted: 23 October 2015

Example of the 'anoxic' phantom

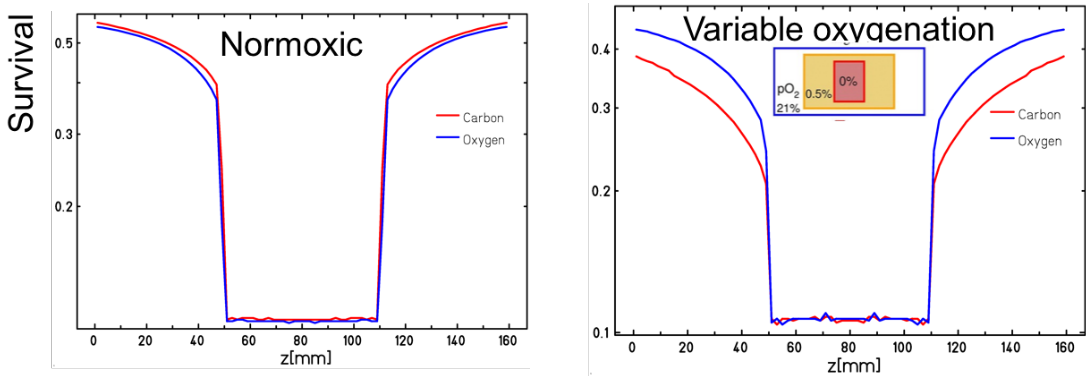


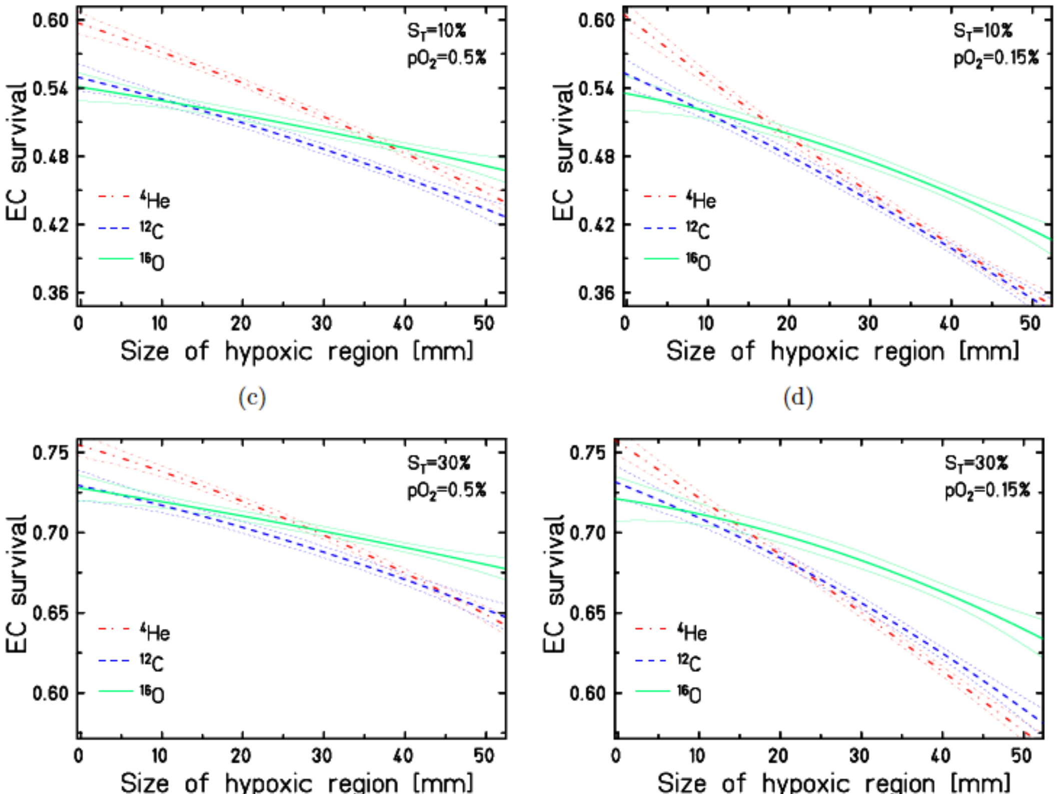
Tinganelli et al. Sci. Rep. 2015.

OER optimized plans with O (kill painting)

Sokol et al. subm to PMB (minor rev.)

- *In case of hypoxia, proper optimization accounting for OER may lead to **Inverted peak-to-entrance ratios** as compared to a normoxic case*
- *According to actual oxygenation, O beam may overcome the price of larger entrance channel with the LET advantages*
- *Trade-off analysis between better **LET distribution** and worse **Fragmentation** in entrance and tail*

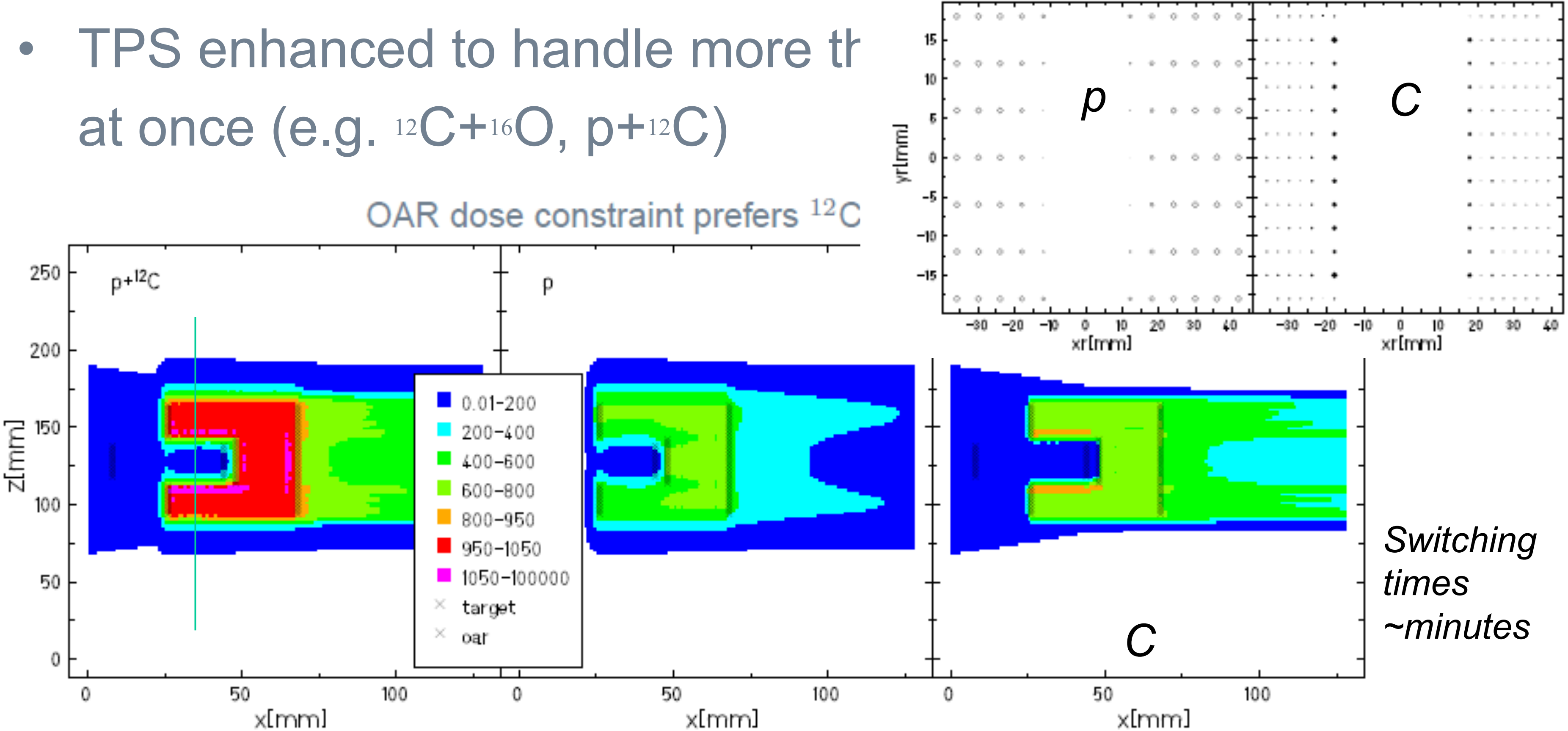




(c) (d)

Multi-ion treatment planning

- TRiP version for a biologically optimised multi-ion treatment plan
- TPS enhanced to handle more t
  at once (e.g. $^{12}C+^{16}O$, p+^{12}C)



Switching times ~minutes

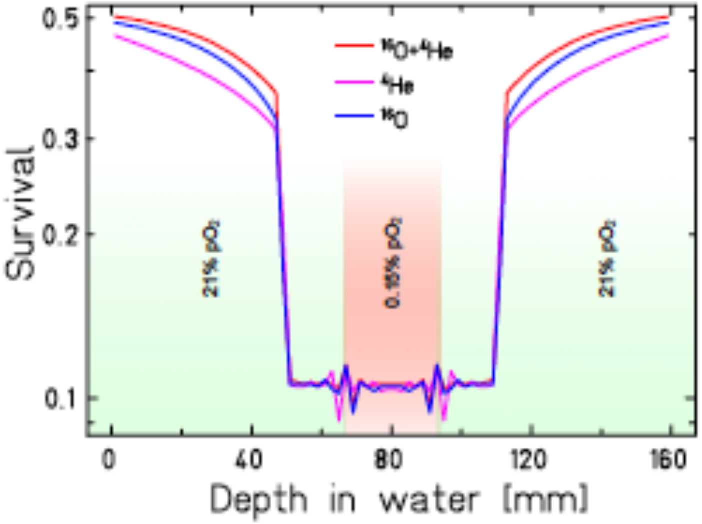
Krämer, Scifoni, ,Schmitz, Sokol, Durante, *EPJD 68 (2014)*

Multi-ion plans + OER driven optimization

Towards the multi-ion treatment planning with ^{16}O beams

O. Sokol[*1,2], *E. Scifoni*[1,3], *S. Hild*[1,3], *M. Krämer*[1,2], *and M. Durante*[2]

GSI Sci Rep. (2017)
Sokol et al. PTCOG '17



Survival distributions for single-ion double-field optimizations (^{4}He + ^{4}He and ^{16}O + ^{16}O), and multiion quadruple-field optimization (^{16}O + ^{16}O + ^{4}He + ^{4}He).

pO_2 =20%: $z < 6.6$ & $z > 9.4$
pO_2 = 0.5%: $6.6 < z < 9.4$

Depth	Entrance channel survival, %		
	^{16}O	^{4}He	^{16}O + ^{4}He
5 mm	48.4	45.4	49.9
45 mm	34.3	32.4	37.7

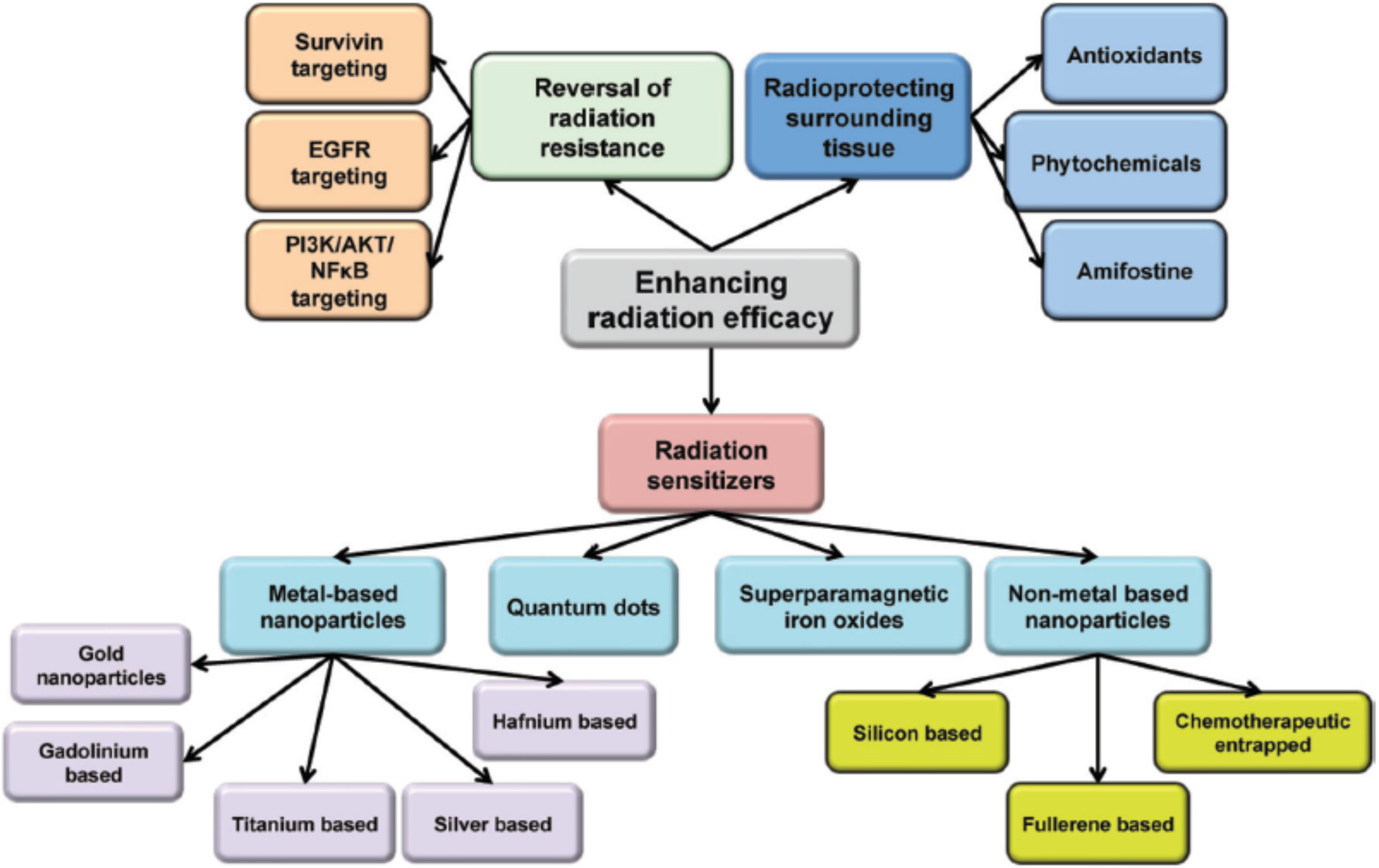
Research based TRiP98 version Including both features

The aim is let the optimization choose the ion at different Spots also according to the local oxygenation

4 Fieds (2He +2O) MF optimized

Nanoparticles as dose enhancers

Radiation sensitizers



Survivin targeting

EGFR targeting

PI3K/AKT/ NFκB targeting

Reversal of radiation resistance

Radioprotecting surrounding tissue

Antioxidants

Phytochemicals

Amifostine

Enhancing radiation efficacy

Radiation sensitizers

Metal-based nanoparticles

Quantum dots

Superparamagnetic iron oxides

Non-metal based nanoparticles

Gold nanoparticles

Gadolinium based

Titanium based

Silver based

Hafnium based

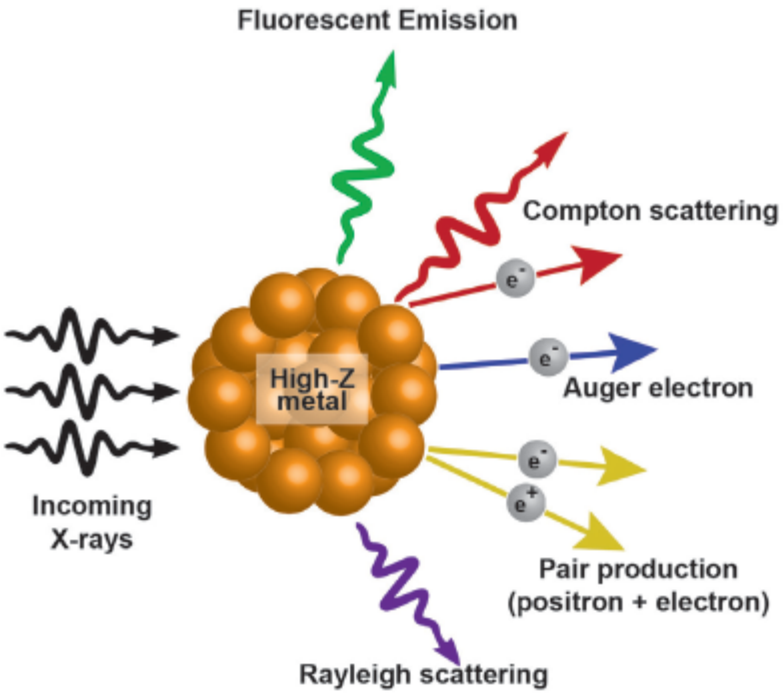
Silicon based

Chemotherapeutic entrapped

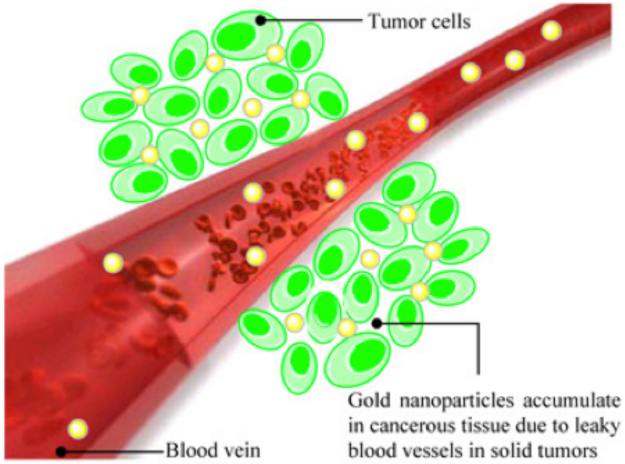
Fullerene based

Kwatra et al. Transl. Cancer Res. 2013

High Z Nanoparticle sensitization



Kwatra et al. Transl. Cancer Res. 2013



http://www.nanomedicine.dtu.dk

NP: high cellular uptake in tumours

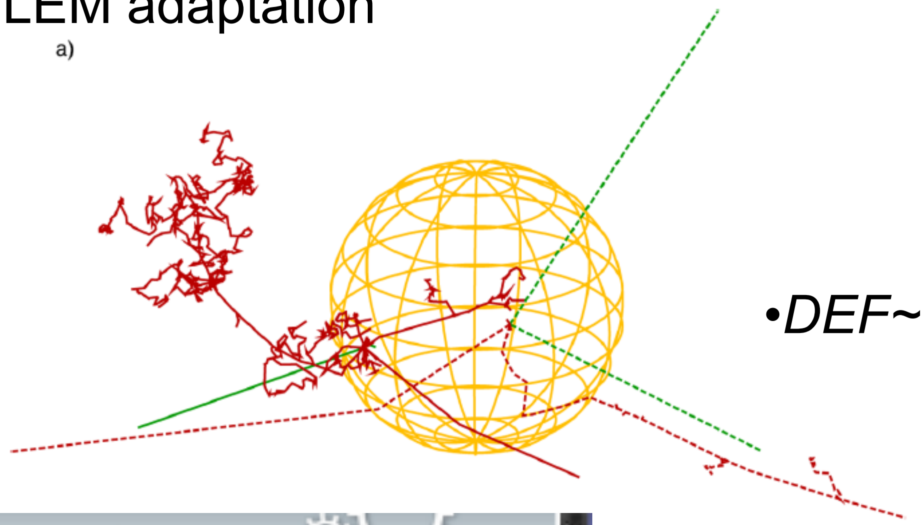
well known adavantage for photons;
high Z ➔ high e^- emission vs. high absorption

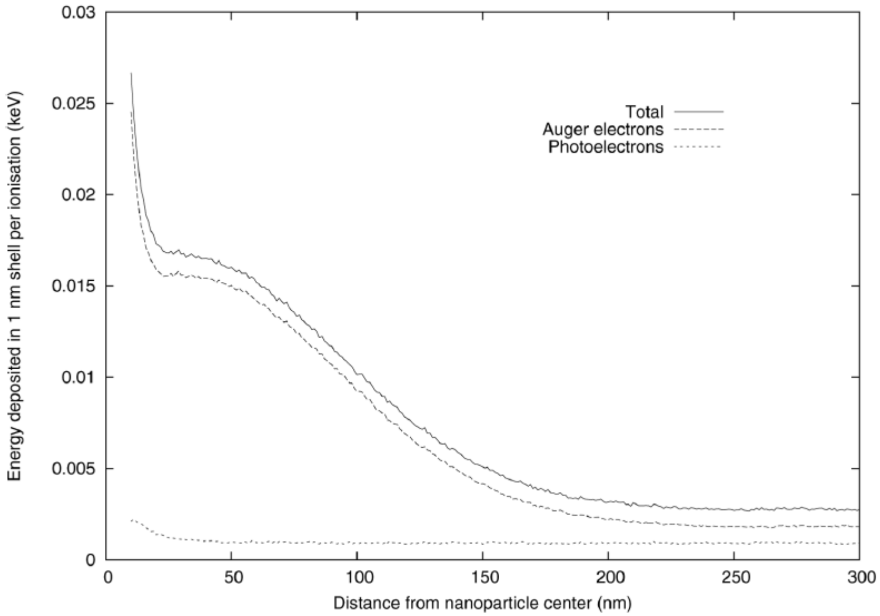
advantage with ion irradiation?

Au NP with photons – Mechanistic insight

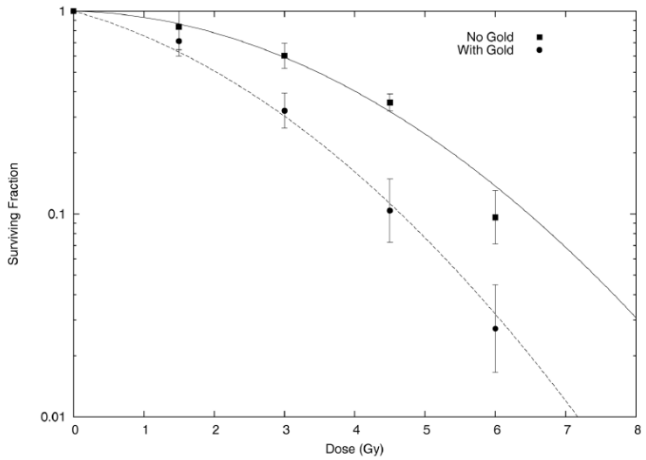
- Auger electrons play a crucial role for photons
- local dose enhancement

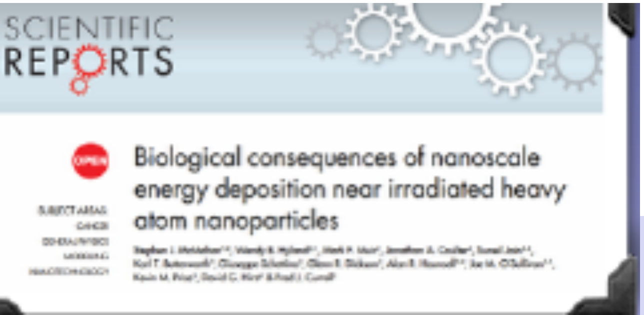
analysis based on track structure and LEM adaptation





- *DEF~1.5*





SCIENTIFIC REPORTS

OPEN

Biological consequences of nanoscale energy deposition near irradiated heavy atom nanoparticles

Mc Mahon et al.
Sci. Rep. 2011

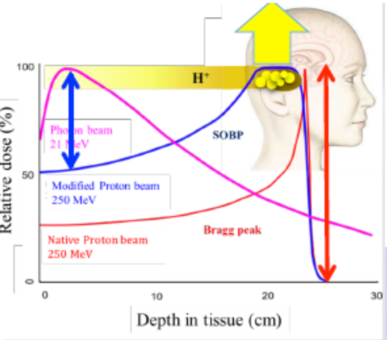
Local dose enhancement?

(Courtesy of Fred Currell)

- photon +NP ≈ Ion ?

Then, what about:

- Ion+NP= ??

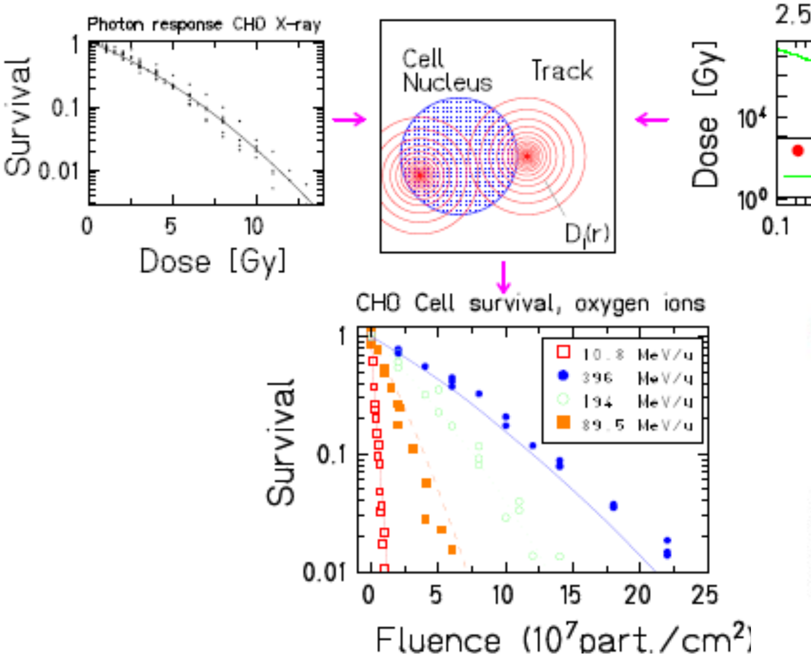


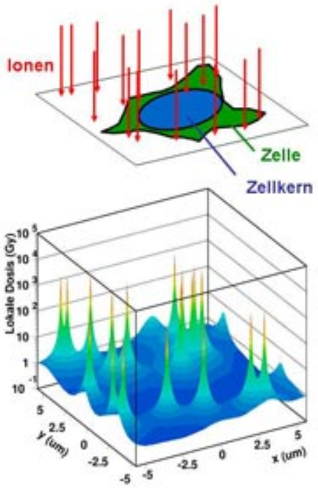
(Courtesy of S. Lacombe)

cal Effect Model (LEM)

oton Dose-Effect $\propto \alpha_x D + \beta_x D^2$

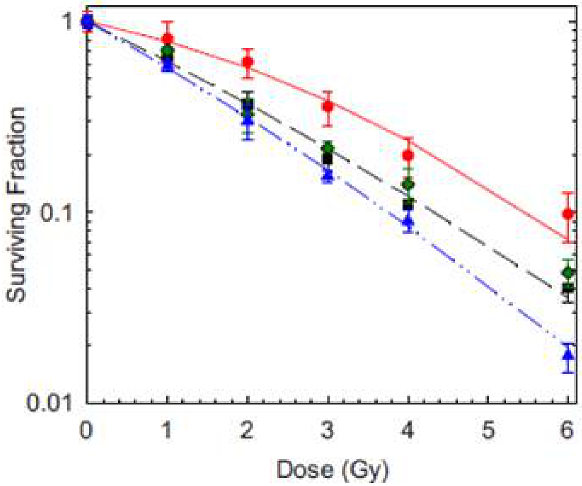
for single particles (RBE base data set)





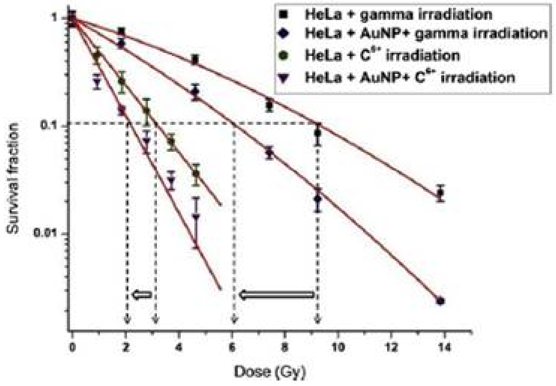
Elsaesser,Scholz 2008

NP sensitization with ion beams



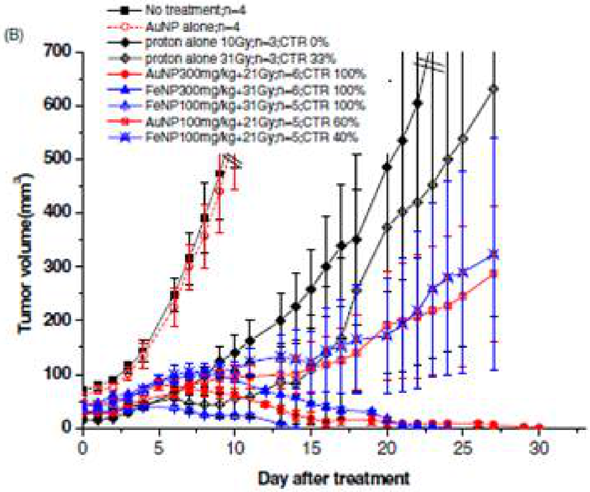
p+NP, pc, 15% enhancement

Polf et al., Appl.Phys.Lett. 98(2011)



C 5 MeV/u +NP, HeLa, 40% enhancement

Kaur 2012



p+NP, mouse tumour,

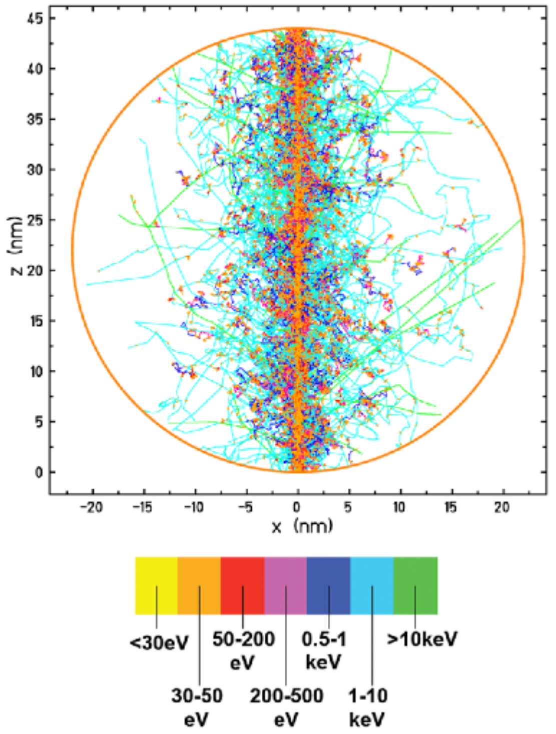
Kim et al. PMB 57(2012)

Preclinical data evidence, no explanation

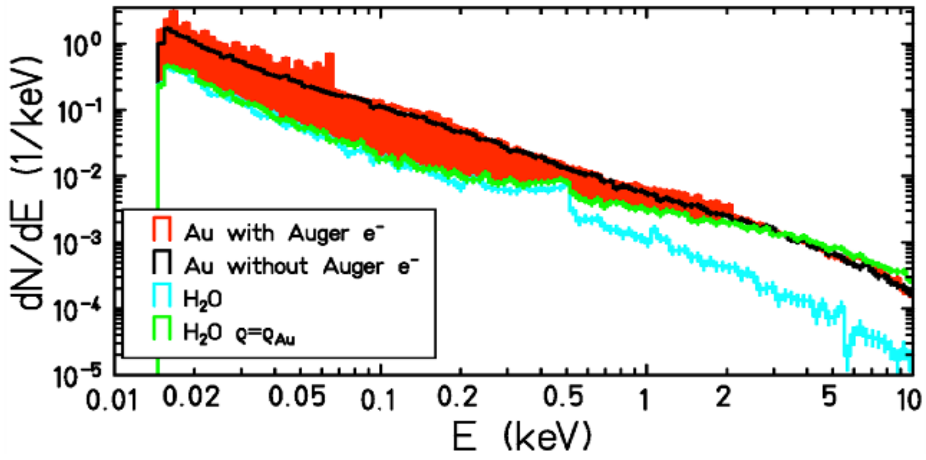
$\rightsquigarrow$ dependence on cell line, NP conditions, ...

$\rightsquigarrow$ sensitive target $\neq$ cell nucleus?

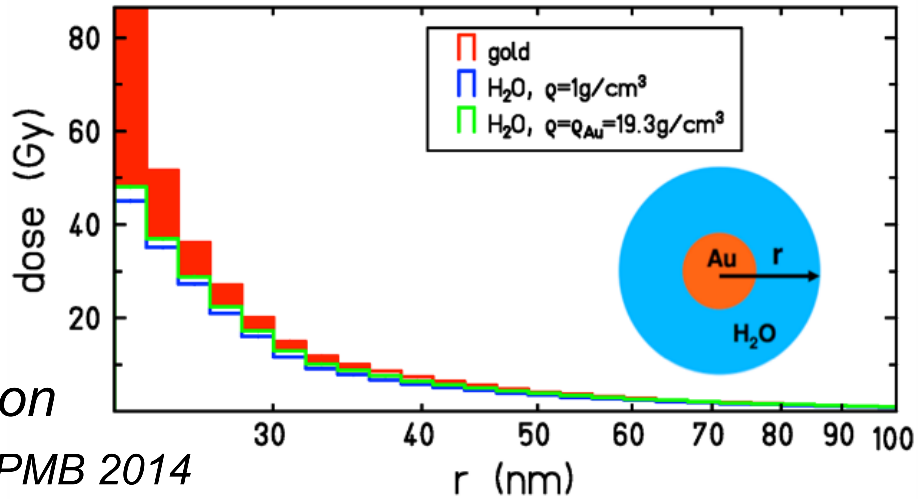
Track structure analysis (TRAX)



secondary electron spectra outside NP



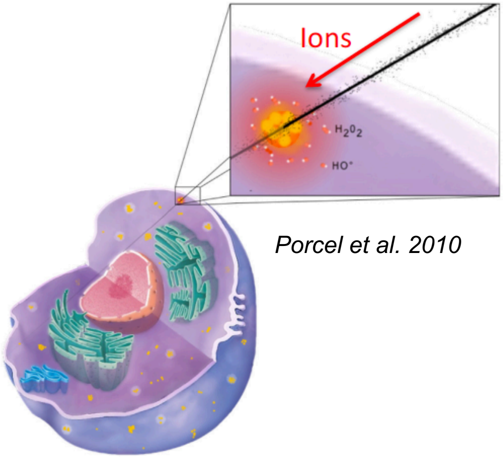
spherical dose of 1E6 80MeV p (disk source) around r=22nm Au NP



Direct traversal not enough to justify relevant sensitization

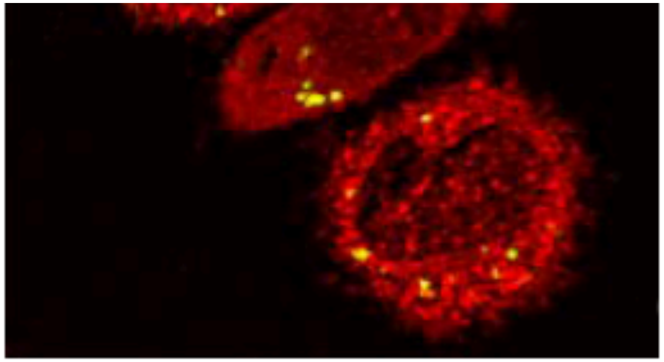
Waelzlein, Scifoni, Kramer, Durante PMB 2014

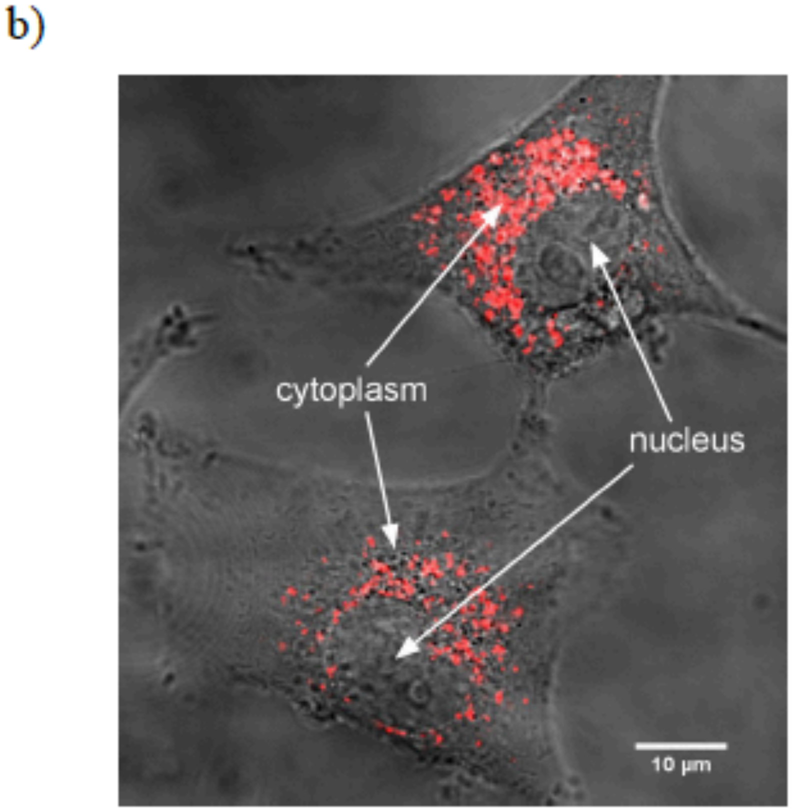
Cellular Localization



Porcel et al. 2010

Figure 3: Sketch of nanoscale impact initiated by nanoparticles in the cytoplasm. Adapted from





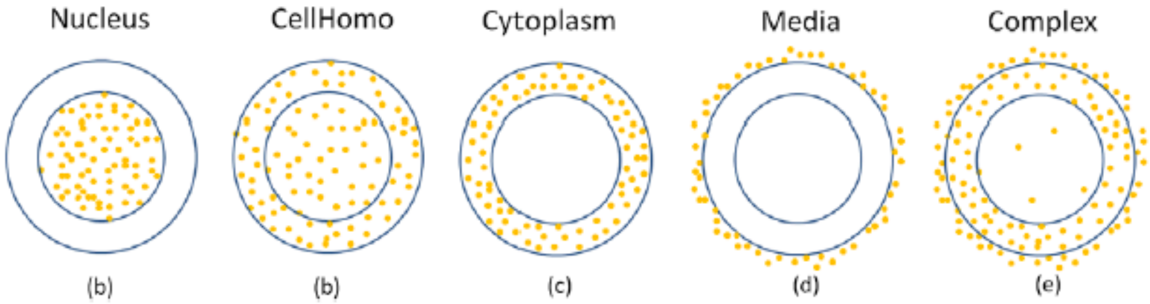
Confocal microscopy show evidence of localization in the citoplasm

Usami et al. 2010
Stefancikowa et al 2015

Impact of Cellular localization

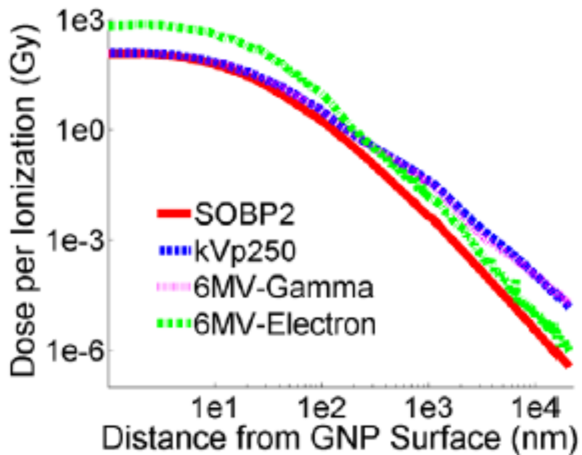
Lin et al. PMB 2015

GNP-LEM, pure dose enhancement study at differerent concentrations



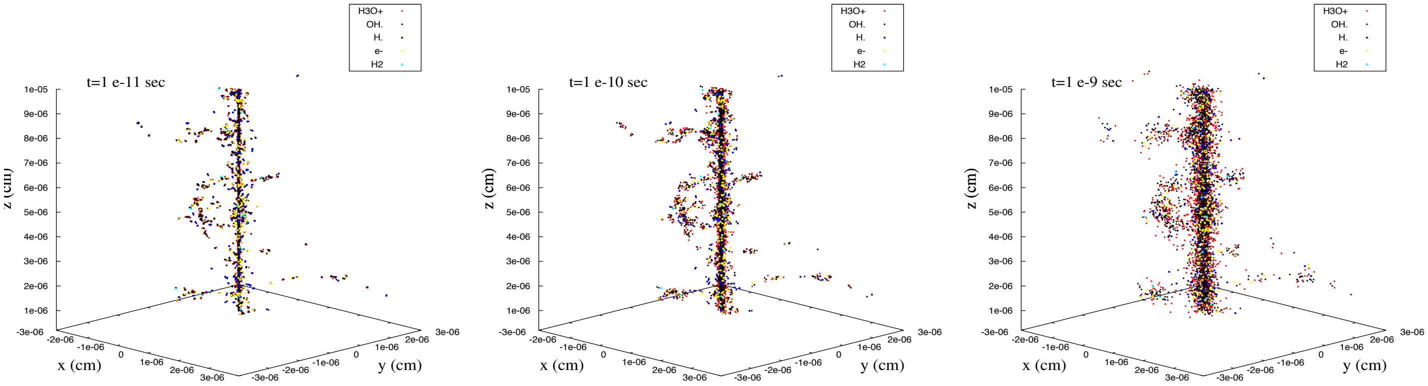
- GNPs no internalized, no DEF
- GNPs In the cytoplasm, a smaller sensitization ~1.1 after a given dose from proton treatment than when photons
- GNPs into the cell nucleus, significant effect (~1.3) for all beams

Protons induced Secondary electrons range in water much shorter compared to photons, dose enhancement ~1/30 vs kV photons at 10 μm from the GNP surface.

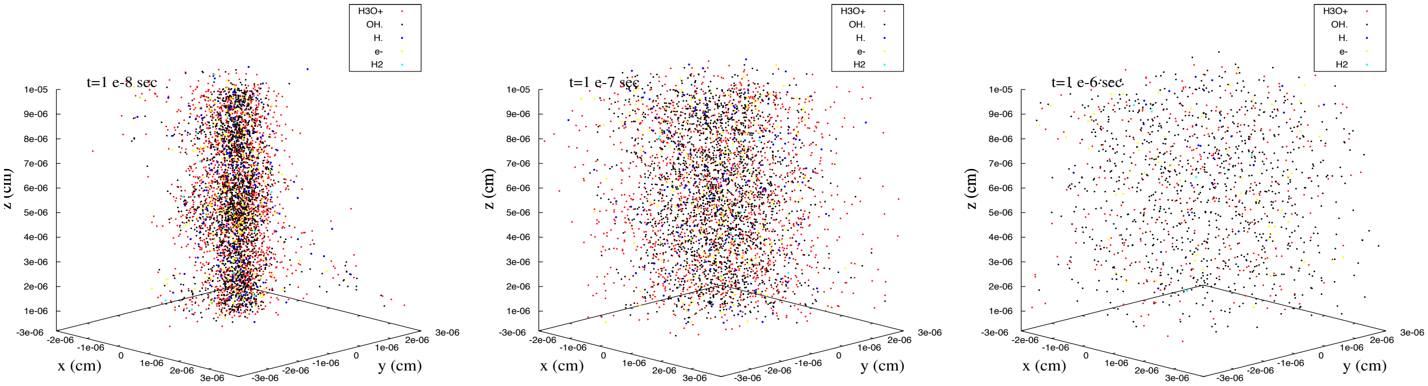


Direct effect + Radiation Chemistry

radical diffusion ^{12}C 3 MeV/u (TRAX simulation, D.Boscolo)



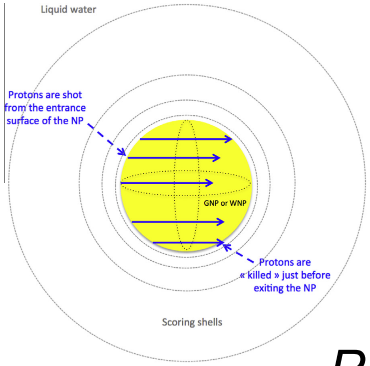
Boscolo et al GSI Sci Rep.(2016)

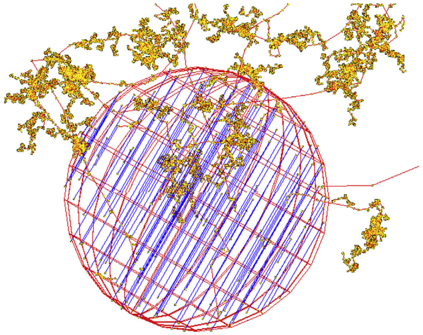


Radiolysis enhancement factor

$$REF = \frac{G(OH)^{NP}}{G(OH)^{H_2O}}$$

H.N. Tran et al. / NIMB 373 (2016) 126–139
GEANT4+GEANT4DNA





Protons 2 to 170 MeV

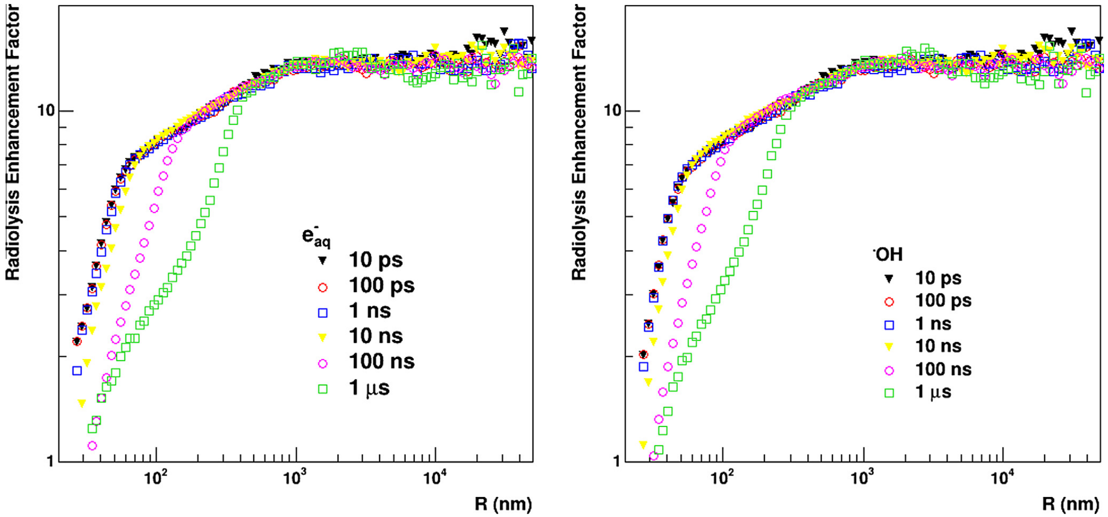


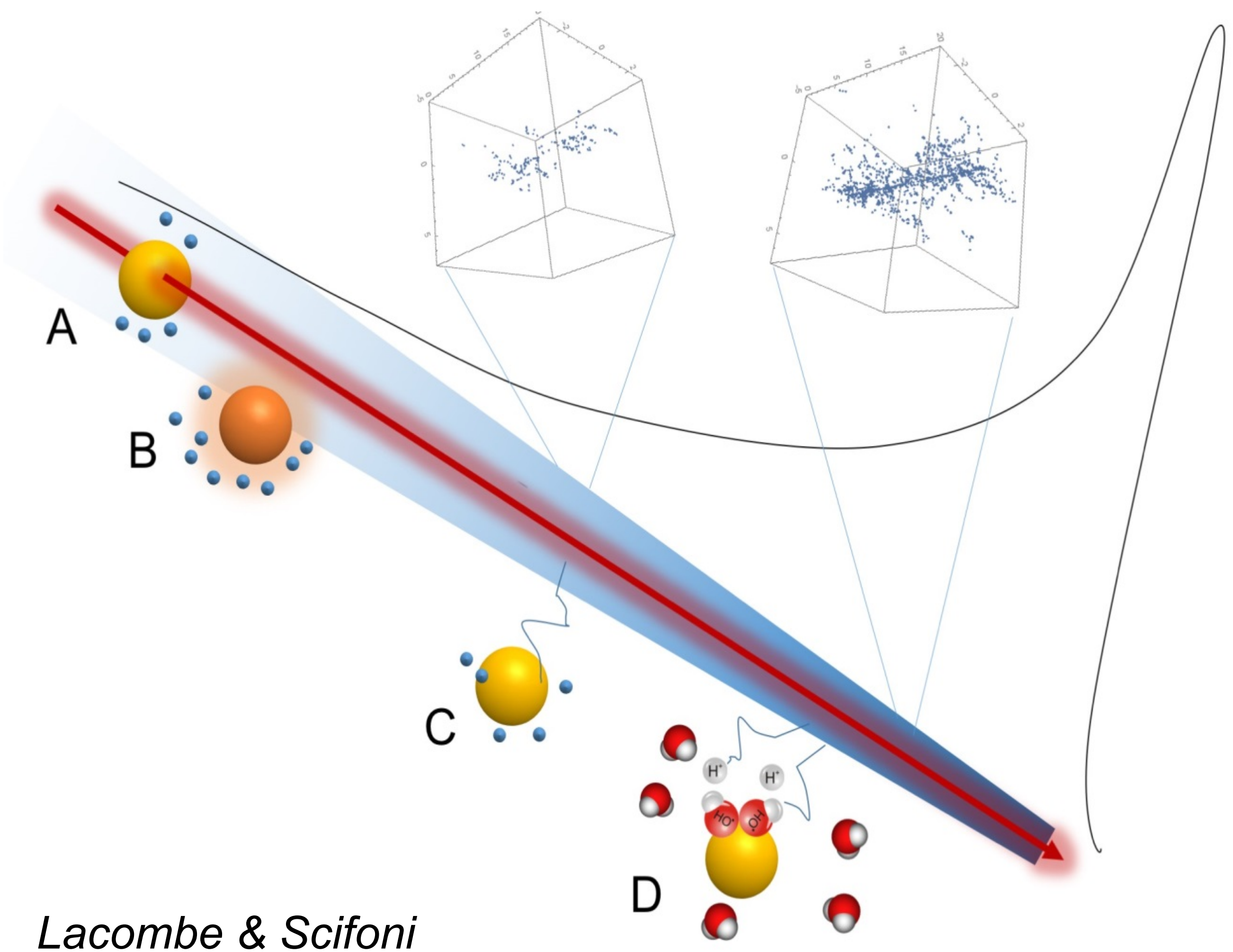
Fig. 19. Radiolysis Enhancement Factor of the distribution of chemical species (e^-_{aq}, ·OH) produced by incident 100 MeV protons as a function of radial distance from the NP. Results are shown at six different times after irradiation (10 ps, 100 ps, 1 ns, 10 ns, 100 ns, 1 µs).

Relevant enhancement of radical products

Decreasing for higher LET, in contrast to higher absolute dose deposition

Limits: cutoff in delta electrons

Possible sensitization mechanisms



Lacombe & Scifoni
Cancer Nanotech. 2016 (Review subm.)

A) *Direct traversal: enhanced electron production from Auger processes*

B) *Plasmon excitation coupling with strong electron production.*

C) *Secondary electrons on the NP, produces additional electron emission*

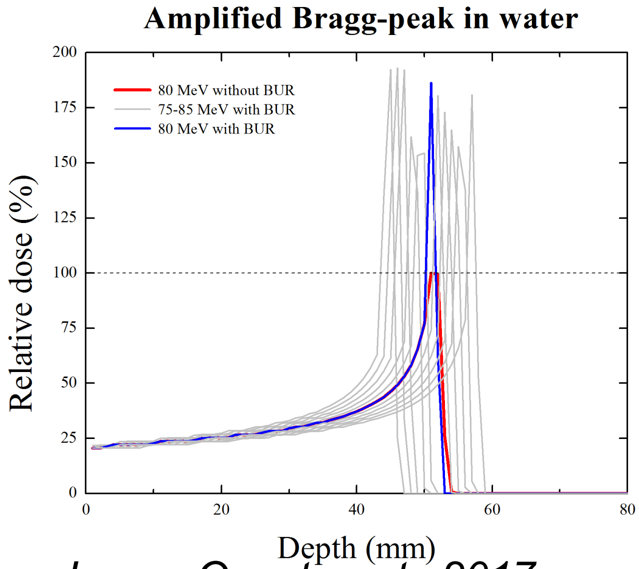
D) *Catalytic effect on radiolytic species*

Other Hot Topics in Particle Radiobiology :

- Radioimmunotherapy: Is carbon ion more immunogenic than photons?

- Proton Boron Fusion Therapy. Feasible? Relevant dose enhancement? Better than BNCT?

- Particle radiosurgery (hypofractionation)



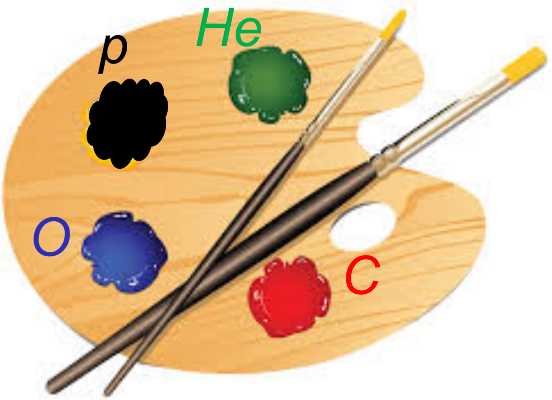
Jung – Oncotargets 2017

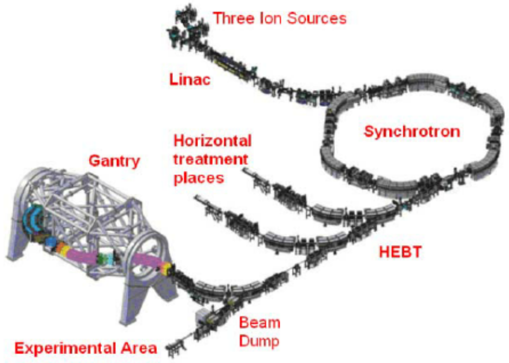
Summary

- Radiobiology of charged particles developed a lot, but still several open questions are pending
- **Proton RBE** is clearly differing from a constant. But the clinical impact of considering this variation seems negligible.
- **Biologically optimized** TPS is needed for exploiting new ions and different merits
- **Helium ions** are promising alternative to protons, their implementation in TPS has been advanced in latest years from some groups. Biology seems consistent between different models. Variable RBE is a must
- **Oxygen ions** are mostly useful when hypoxia is accounted via proper adaptive TP tools, so that O beam may overcome the price of larger entrance channel with the LET advantages
- **Multi-ion** optimization may exploit combination of different ions peculiarities for specific biological/geometrical scenarios. Mixed **He/O** plans promise to be a powerful combination of low/high LET.
- **Nanoparticles** may act as sensitizers also for ion beams , increasing the selectivity, but their mechanistic comprehensive description is still missing

Challenges for OMA

Towards the dream „ion palette“





- Optimized Accelerators and beamlines are relevant for allowing better research on these biological effects
- New Ions are attracting interest and possibly their combination: Design of optimized ion sources and their transport is crucial.
- Future accelerators may offer fast switching time between different ions allowing combined treatments

...in case you didn‘t get enough:

(a few) ***References***

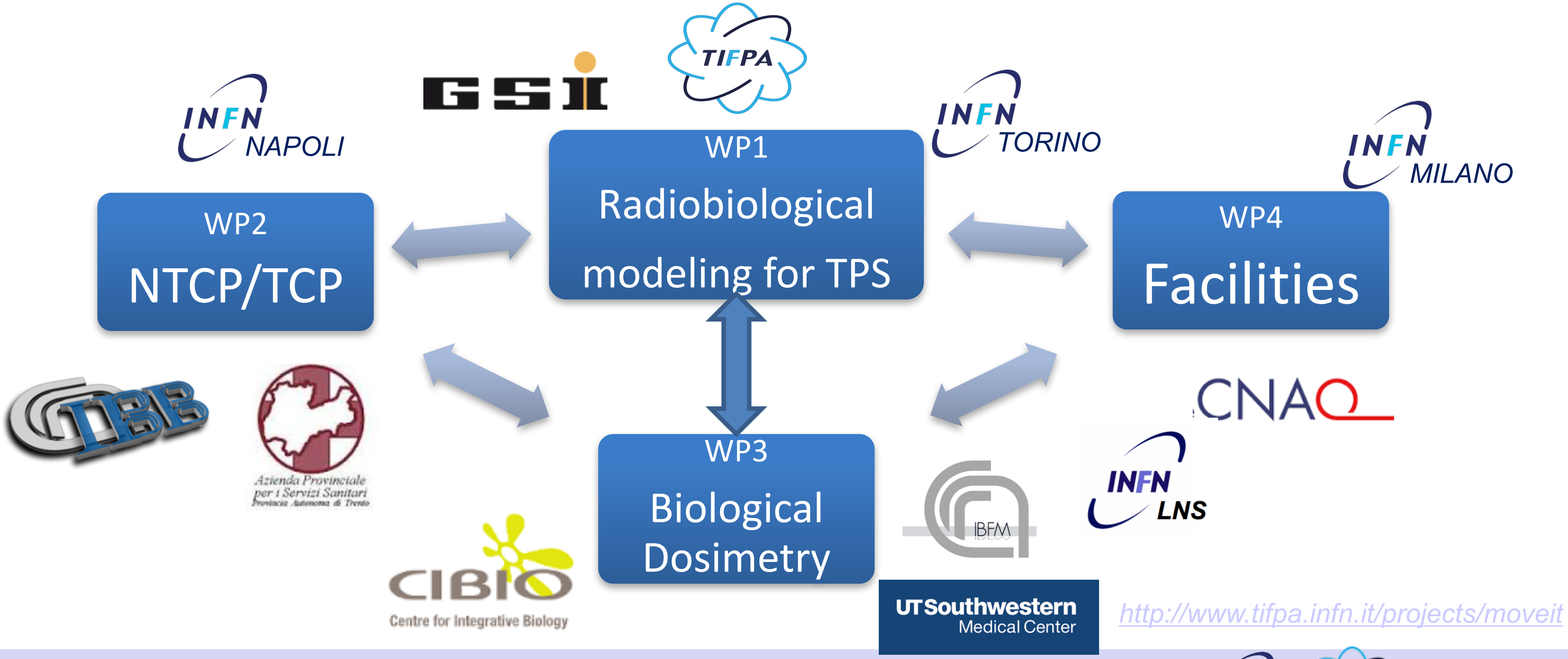
- *Durante M, New challenges in high-energy particle radiobiology. Br J Radiol 2014;87:20130626.*
- *Schardt D, Elsässer T, Schulz-Ertner D (2010) Heavy-ion tumor therapy: Physical and radiobiological benefits. Rev Mod Phys 82:383–425.*
- *Scifoni E (2015) Radiation biophysical aspects of charged particles: From the nanoscale to therapy. Mod Phys Lett A 30:1540019.*
- *Friedrich T Biophysical modeling of effects of ionizing radiation and associated uncertainties (Habilitation Thesis) TUD 2016*
- *Tommasino F, Durante M (2015) Proton radiobiology. Cancers (Basel) 7:353–381.*
- *Paganetti H, Relative biological effectiveness (RBE) values for proton beam therapy. Variations as a function of biological endpoint, dose, and linear energy transfer, Phys. Med. Biol. 59 R419 (2014).*
- *Tommasino F, Scifoni E, Durante M (2015) New Ions for Therapy. Int J Part Ther IJPT-15-00027.1*

MoVe IT

Modeling and **Ve**rification for **I**on beam **T**reatment planning

INFN Network - Call group V - funded 2017-2019- Coordinator: E. Scifoni

- Advancing biolological treatment planning (e.g. impact of full nuclear spectra (including target fragments) on RBE, hypoxia, intra-tumour heterogeneities)
- Developing new systems and tools for biological verification



WP1
Radiobiological modeling for TPS

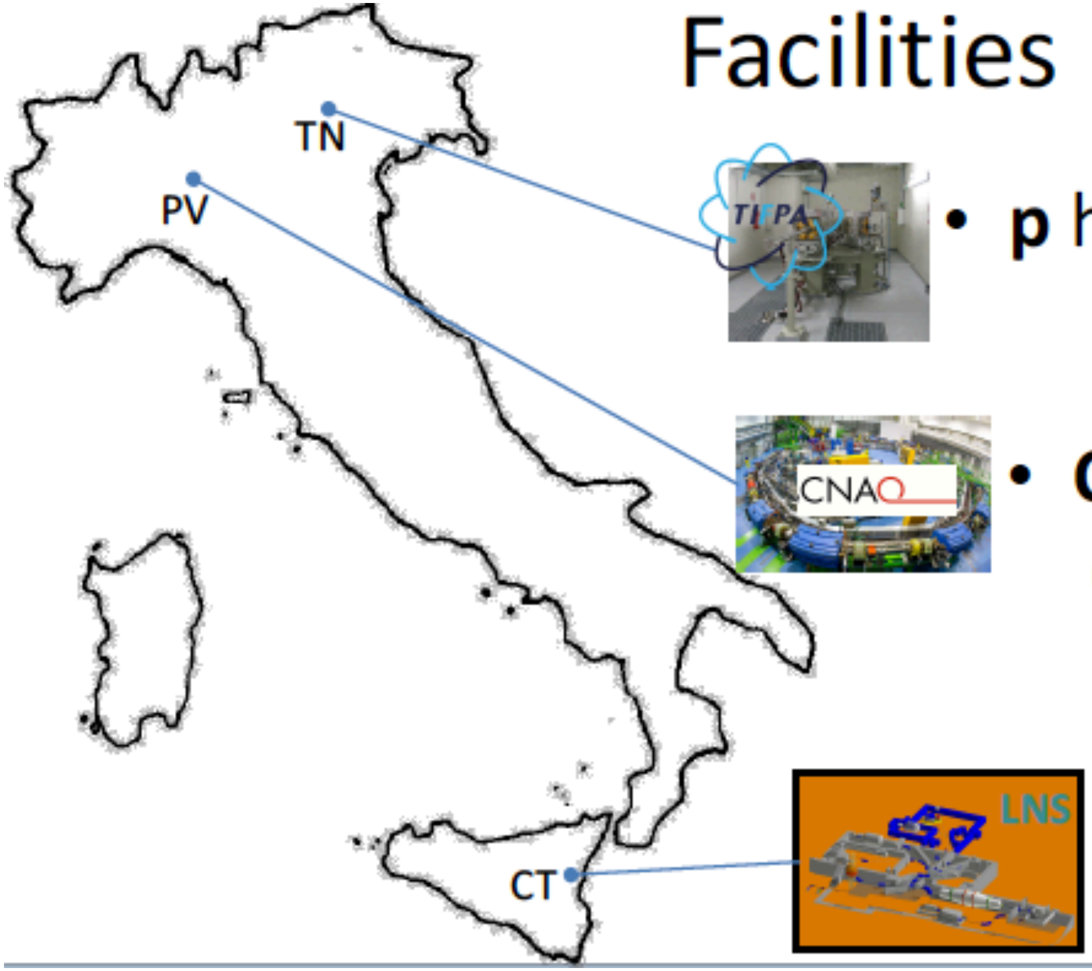
WP2
NTCP/TCP

WP3
Biological Dosimetry

WP4
Facilities

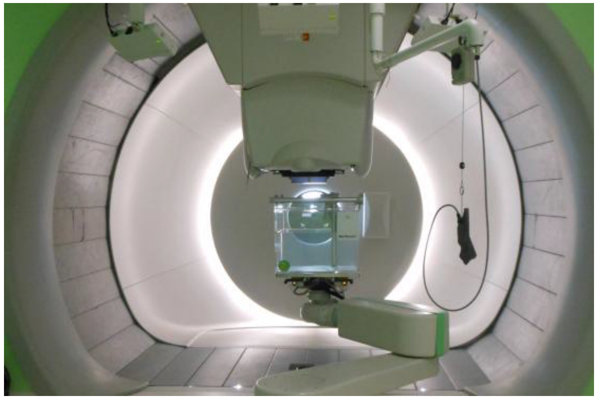
http://www.tifpa.infn.it/projects/moveit

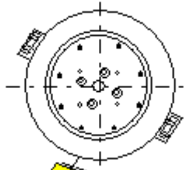
Facilities

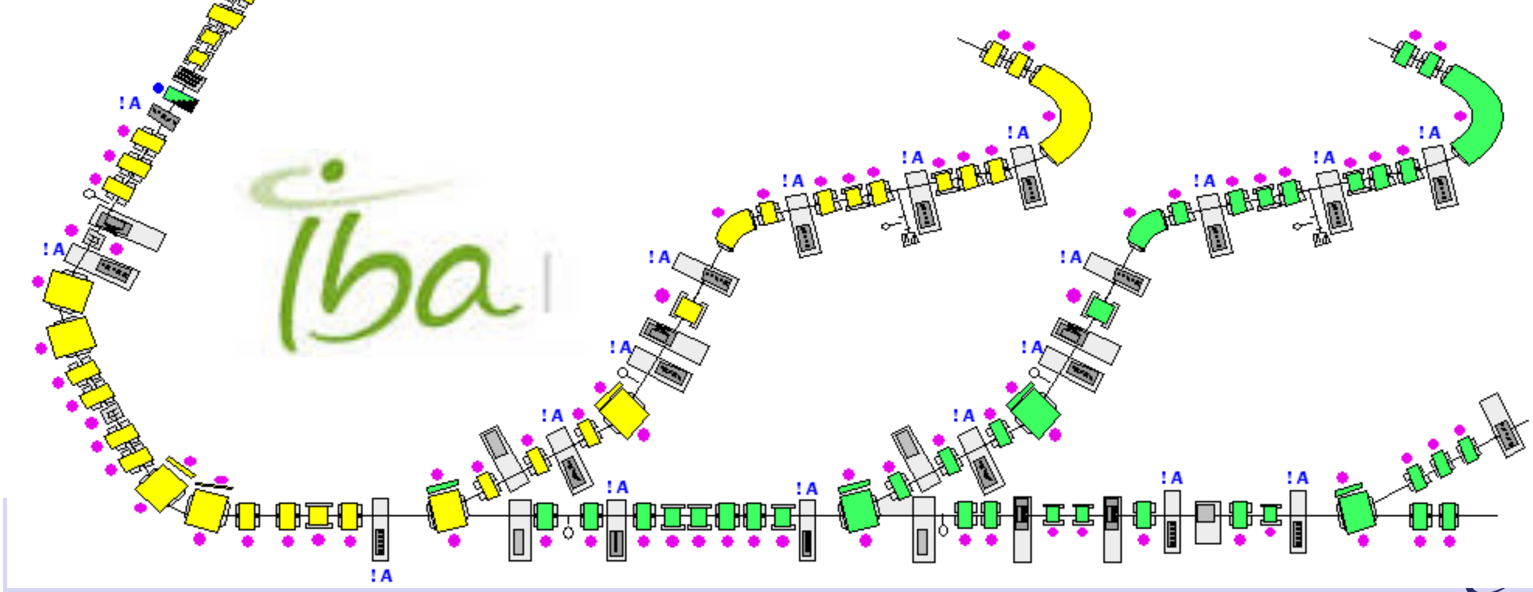


- **p** high E (70-235 MeV)
- **C,He,O** high E
  (80-400 MeV/u)
- **p,C,He,O** low E
  (20-80 MeV/u)

TIFPA Experimental beam facility @Trento protontherapy center



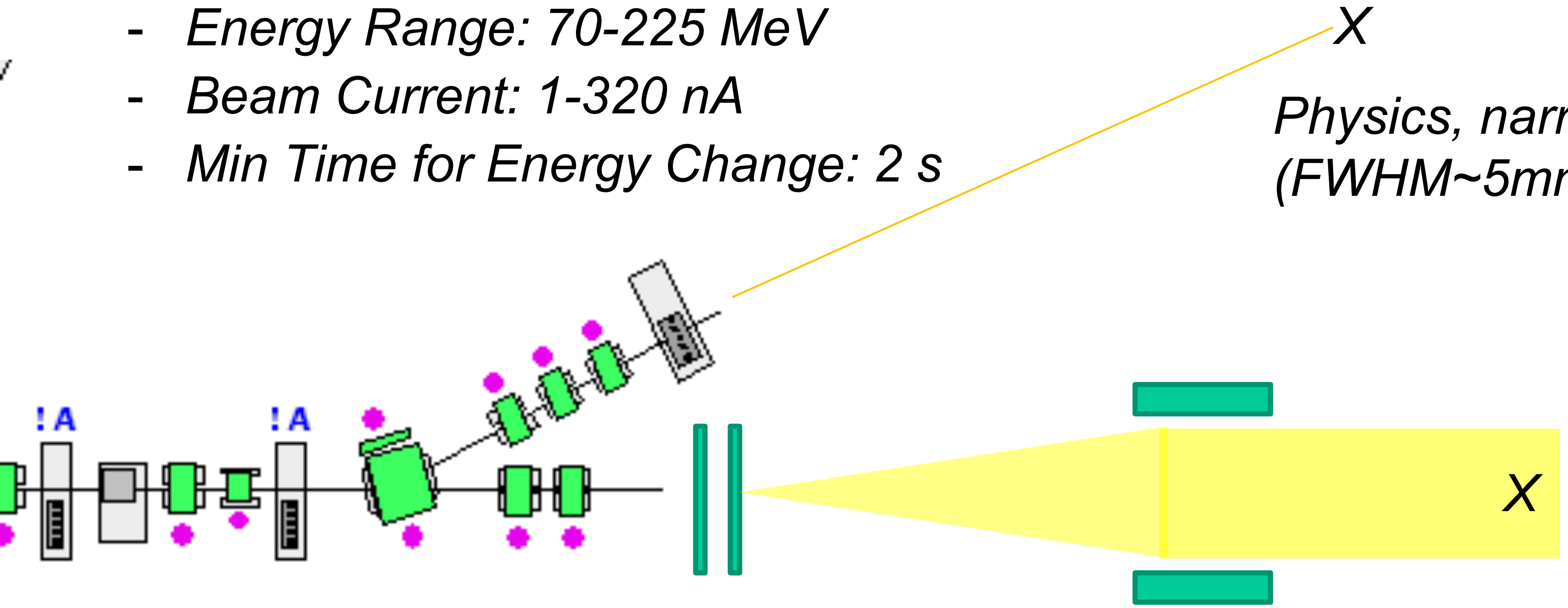




Lines details

Beam Production:

- *Isochronous Cyclotron*
- *Energy Range: 70-225 MeV*
- *Beam Current: 1-320 nA*
- *Min Time for Energy Change: 2 s*



Physics, narrow beam (FWHM~5mm)

Radiobiology, broad beam 5-10 cm
Via Passive Scattering
Or Scanning Nozzle

PAC open for BT proposals at :

http//www.tifpa.infn.it/sc-init/med-tech/p-beam-research/

- ***Mon/Fri 19:00-22:30***
- ***Sat 6:00 – 14:30***

Thanks to

Trento Institute for
Fundamental Physics
and Applications

M. Kraemer
O. Sokol
W. Kraft-Weyrather
D. Boscolo
T. Friedrich
M. Scholz

M. Durante
W. Tinganelli
F. Tommasino
M. Rovituso
S. Hild
C. La Tessa

S. Brons

S. Lacombe
E. Porcel

Y. Furusawa
R. Hirayama

Thanks for your attention!