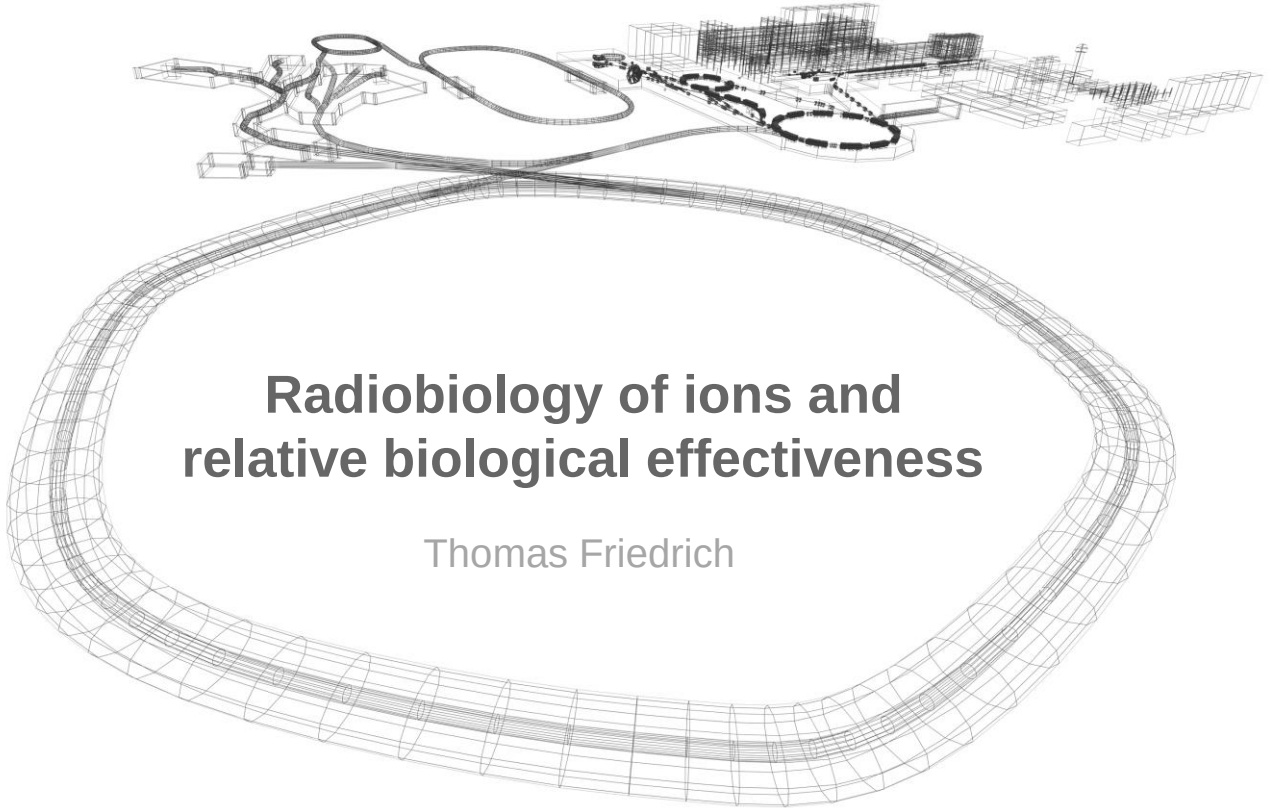
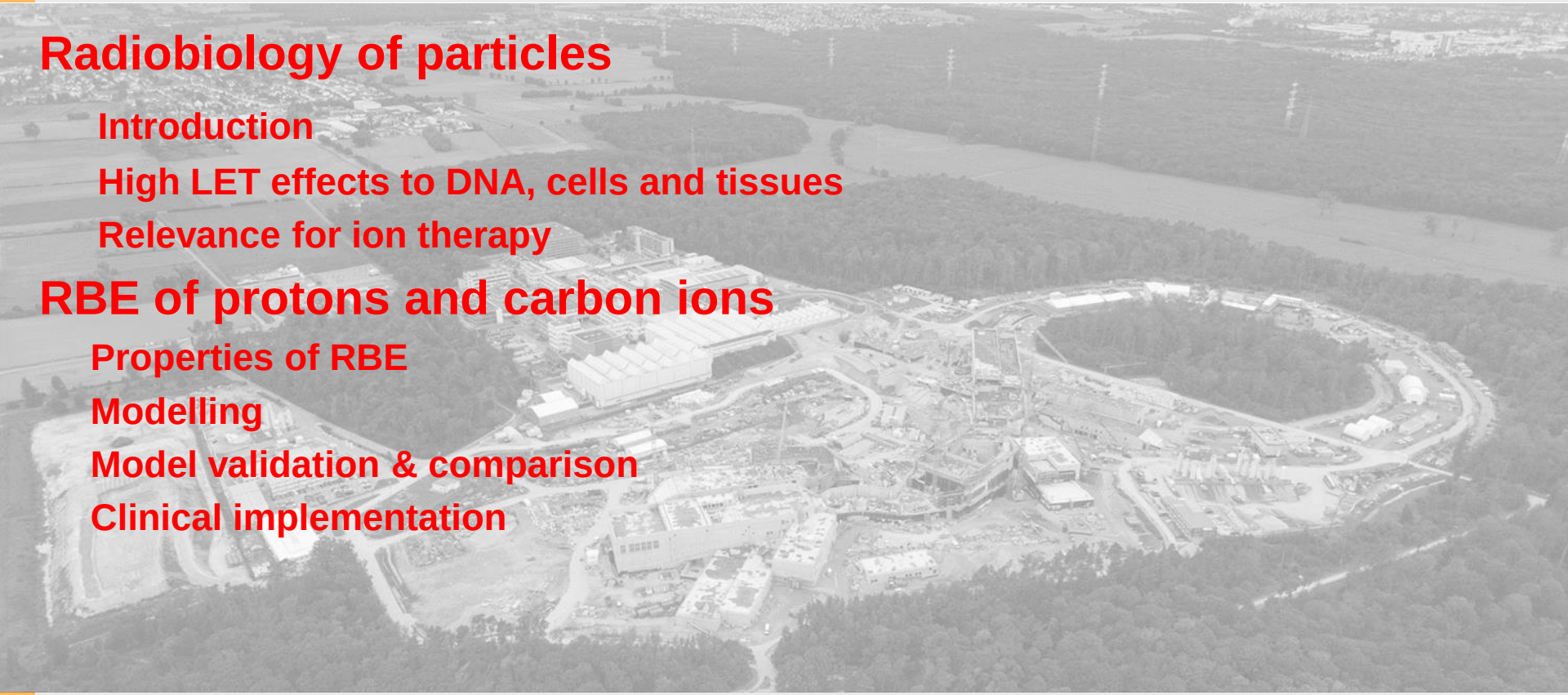


Radiobiology of ions and relative biological effectiveness

Thomas Friedrich

Agenda



Radiobiology of particles

- Introduction
- High LET effects to DNA, cells and tissues
- Relevance for ion therapy

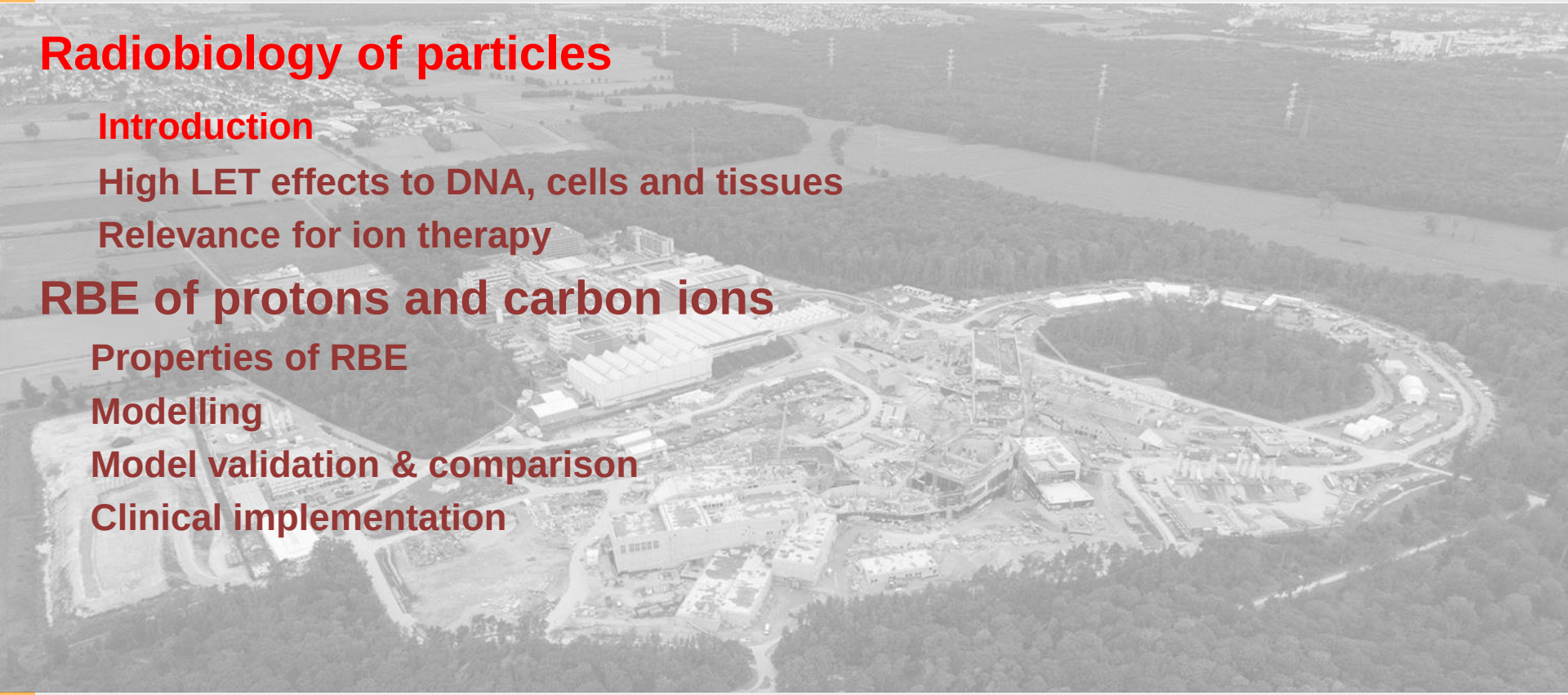
RBE of protons and carbon ions

- Properties of RBE
- Modelling
- Model validation & comparison
- Clinical implementation

Disclosure / Disclaimer

- Nothing to disclose
- Particles are not simply “better” than photons – some properties may be beneficial
- I here use often in-vitro considerations for didactical reasons. Next step would be extrapolation to in-vivo / clinical context.

Agenda



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What's so special about radiation?

Lethal dose
4 Gy = 4 J/kg

vs

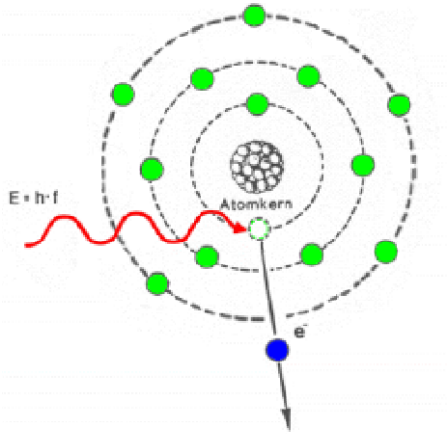
Heat energy to body
~70 J/kg

F. Dessauer
1881 - 1963

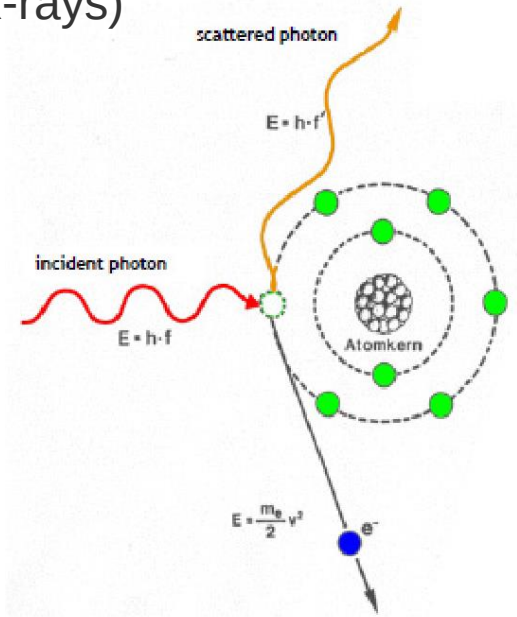
- How that?
  - Must be extreme concentration of energy on small scales
  - Radiation deposits energy very inhomogeneously
    → Ionizations of secondary electrons

Interactions: Photons

- Interaction of photons with matter (γ- or X-rays)



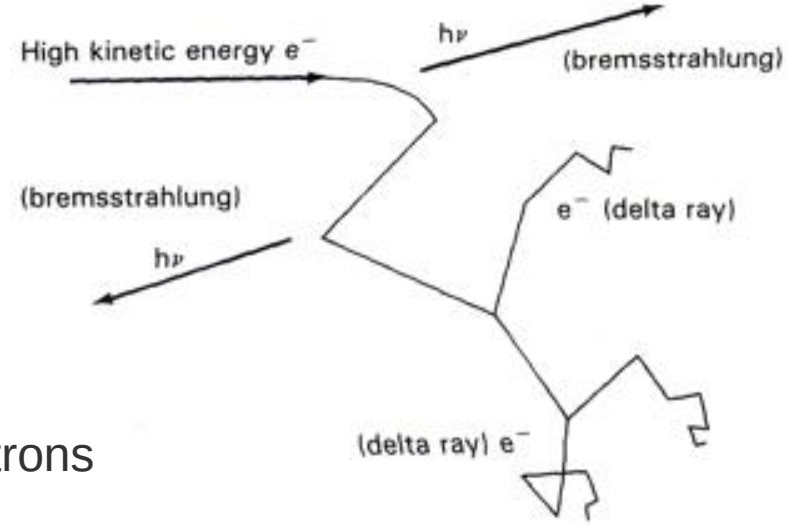
Photoionisation



Compton effect

Interactions: Electrons

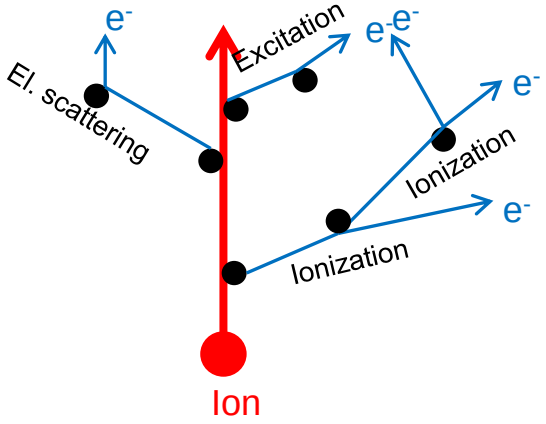
- Interaction of electrons with matter
  - Inelastic collisions
    - Ionization
    - Excitation
    - Bremsstrahlung
  - Nuclear reactions

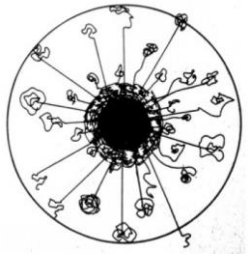


- Typical scenario:
  100 keV X-Ray photons
  → Compton scattering, secondary electrons
  → ~ 1000 – 3000 ionisations
  → Broadly scattered „sparsely ionising radiation“

Interactions: Ions

- Interactions of ions with matter (e.g. α particles)
- Again: Ionization, Excitation
- Typical scenario:
  → Ion moves straight
  → gradual deceleration
  → secondary e^-: “track structure”
  → “densely ionisinig radiation”

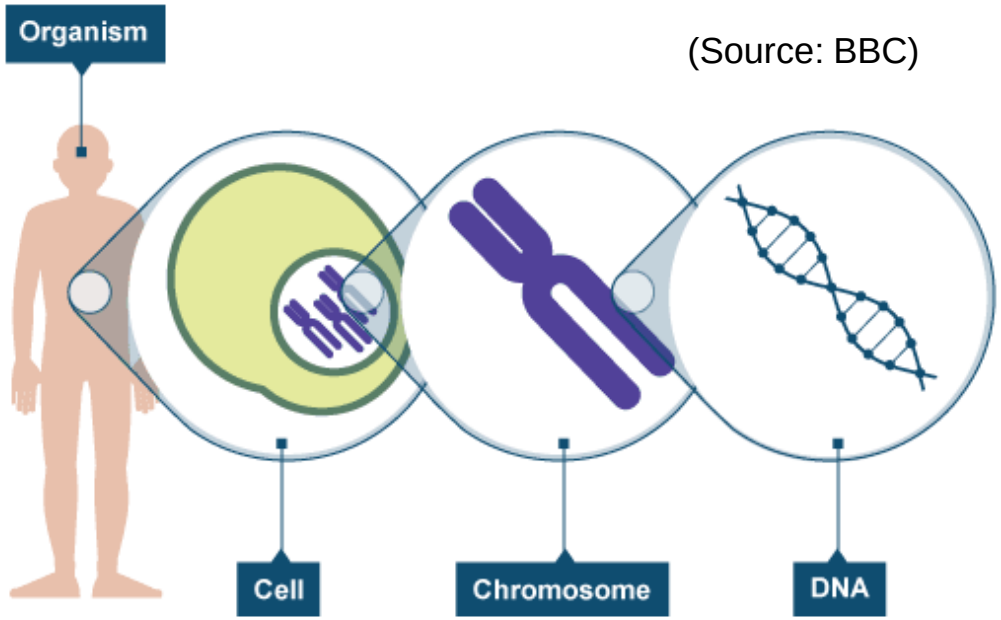




(A. Chatterjee)

Radiation damage on different levels

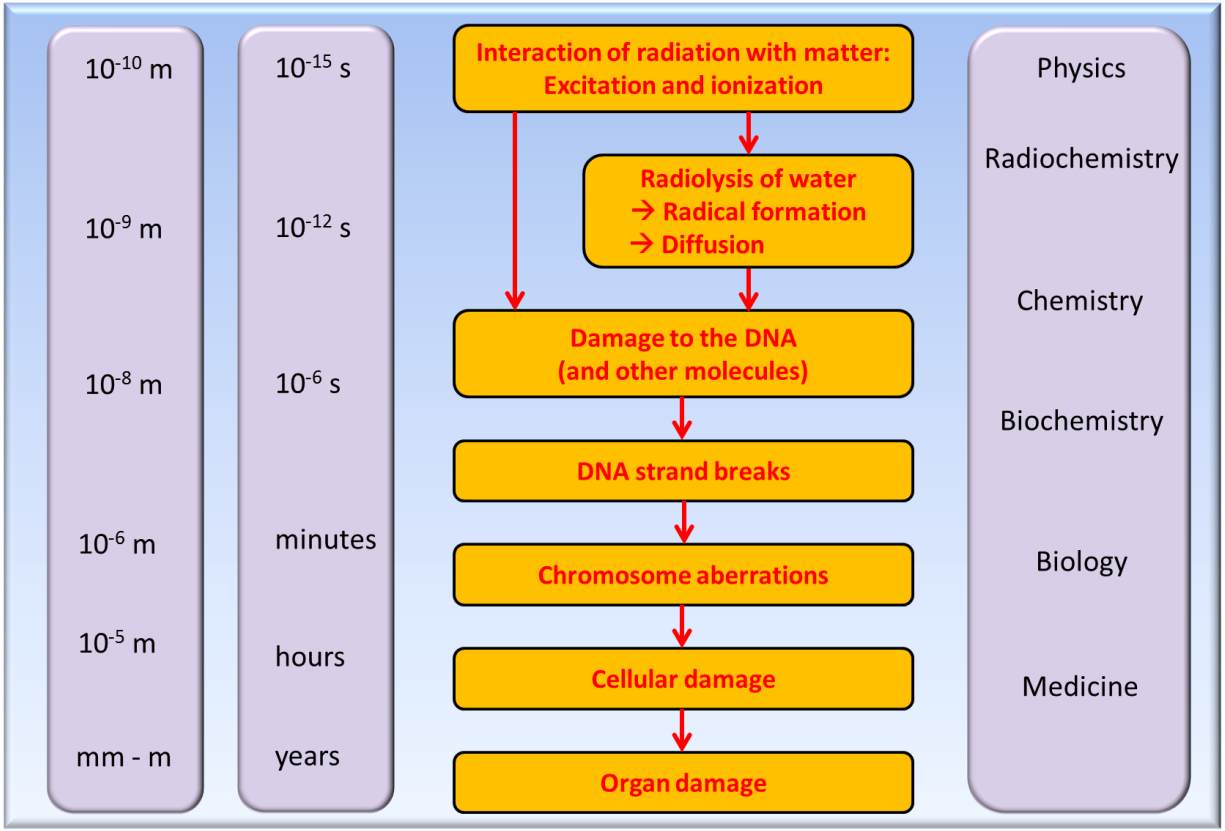
- Humans:
  - → 10^{14} Cells
  - → 46 Chromosomes
  - → 6 x 10^{9} DNA base pairs



(Source: BBC)

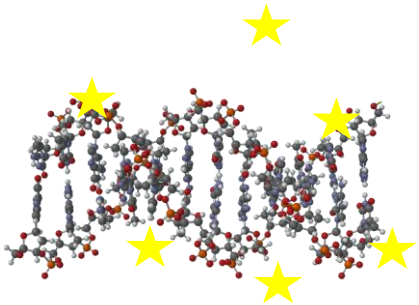
Radiation damage: Cell death Aberrations DNA damage Mutations

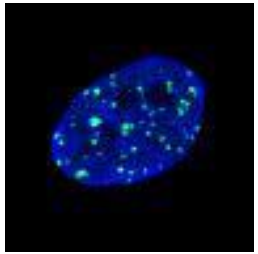
The big picture

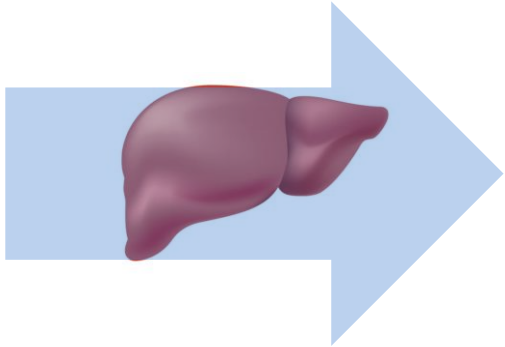


It’s all about inhomogeneity

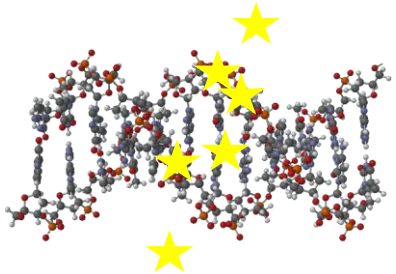
Homogeneous exposure

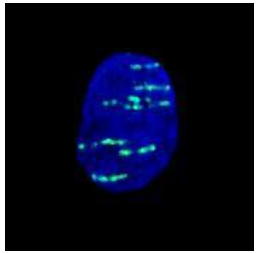


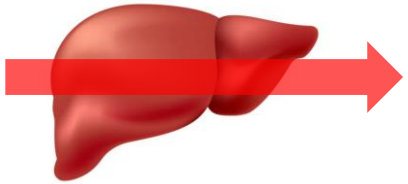




Inhomogeneous exposure



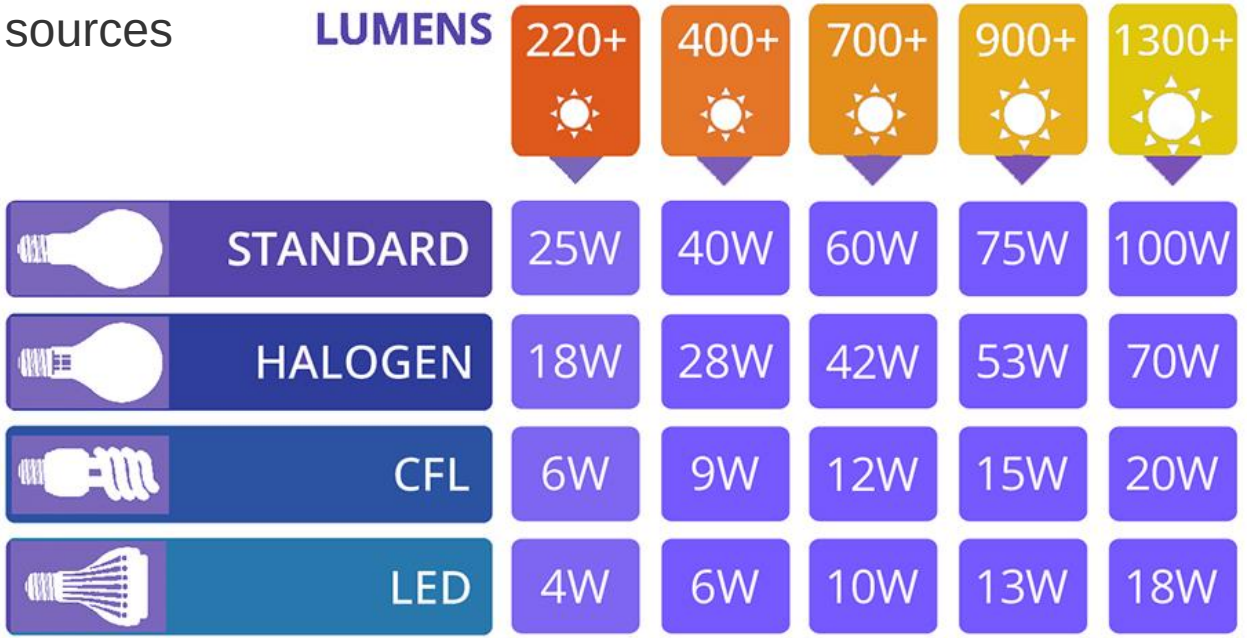




Inhomogeneous dose exposure is usually (but not always) more effective!

Same energy – more effect

- Analogy: light sources



lampsone.com

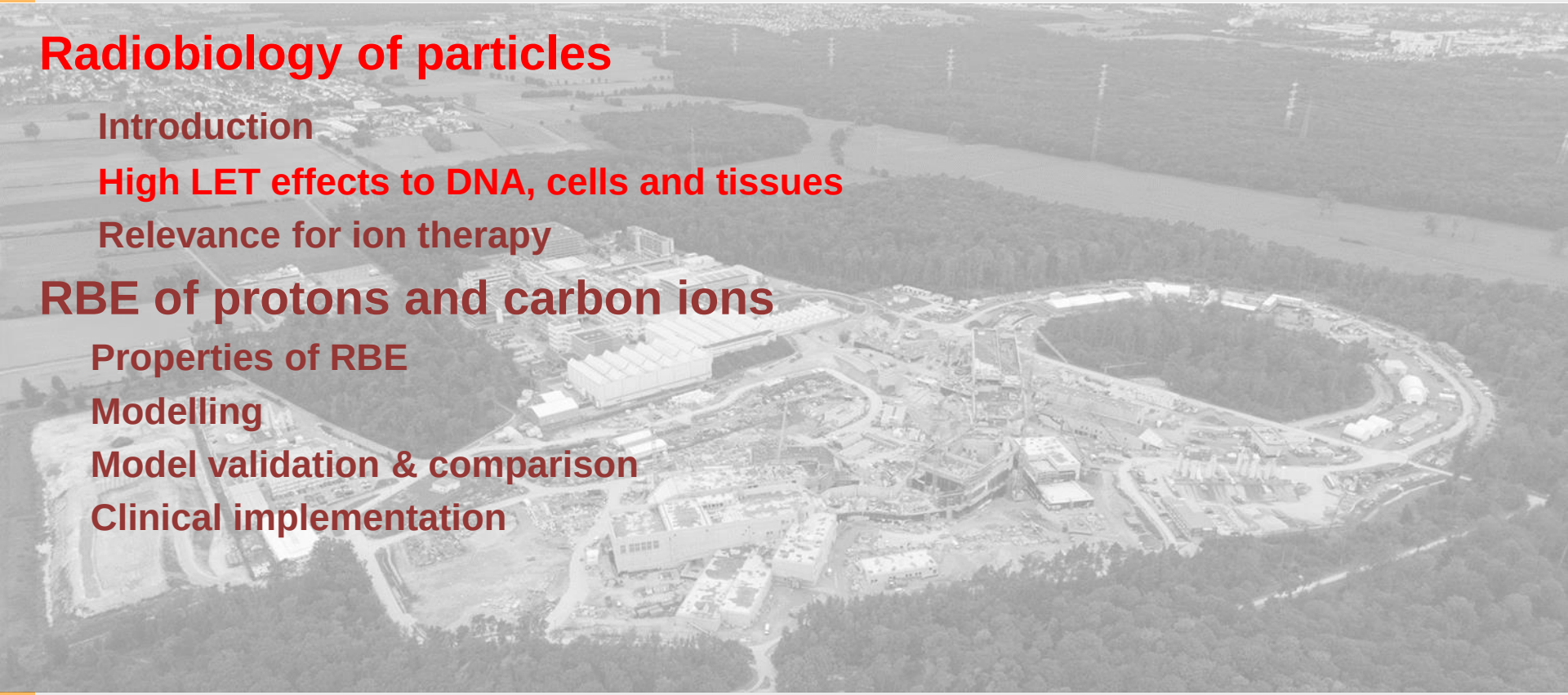
Relative Biological Effectiveness (RBE)

- Ions: Typically less dose needed to achieve the same effect as photons

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

- Example: Some cells are typically inactivated with 5 Gy of photons, but only 2.5 Gy are needed with 20 MeV/u carbon ions → RBE = 2
- Q: Why is this important?
  A: Per Gy we deliver more damage to the tumor in carbon ion radiation therapy.

Agenda



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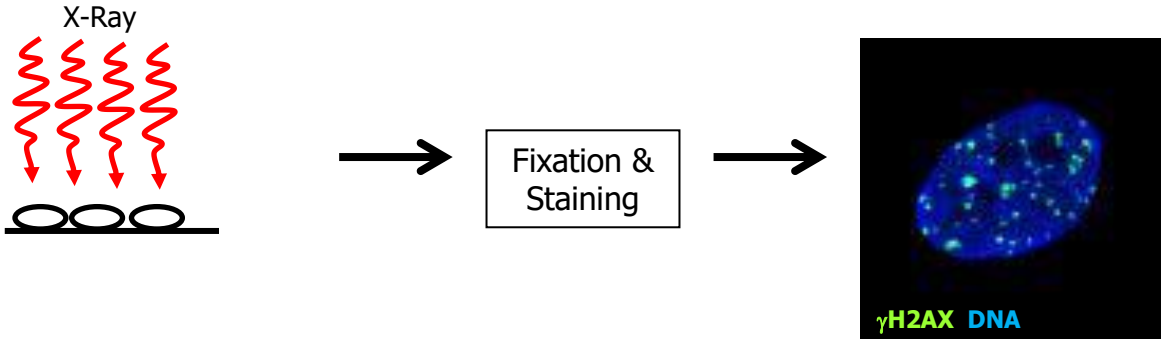
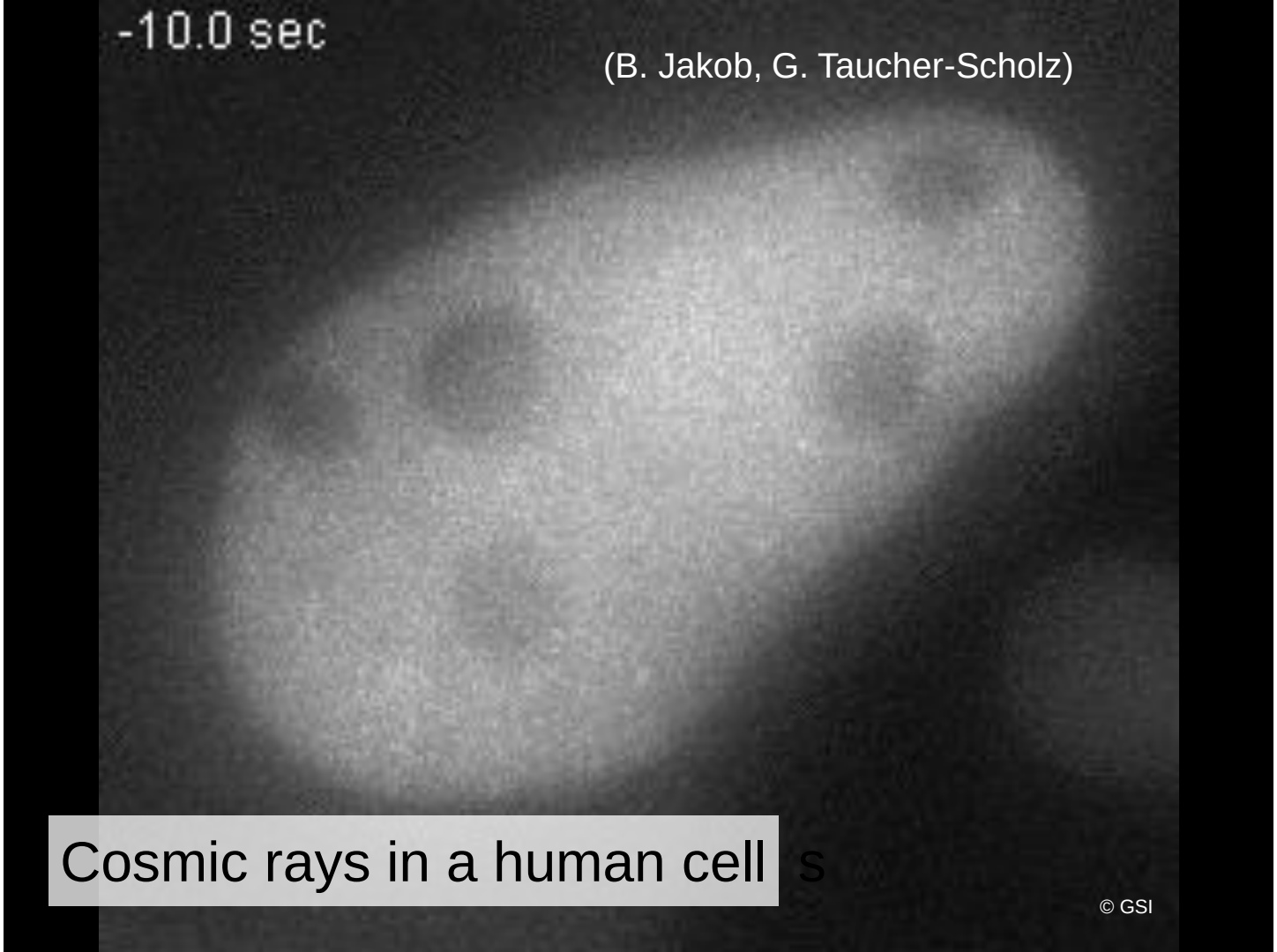
DNA damage


X-Ray
Fixation & Staining
γH2AX DNA
Ion beam
Fixiation& Staining
53BP1 DNA


-10.0 sec
(B. Jakob, G. Taucher-Scholz)
Cosmic rays in a human cell
s
© GSI

Damage induction

- DNA fragment size distribution:
  In particular more small fragments for high LET
- Moderate RBE values
- More unresolved fragments?

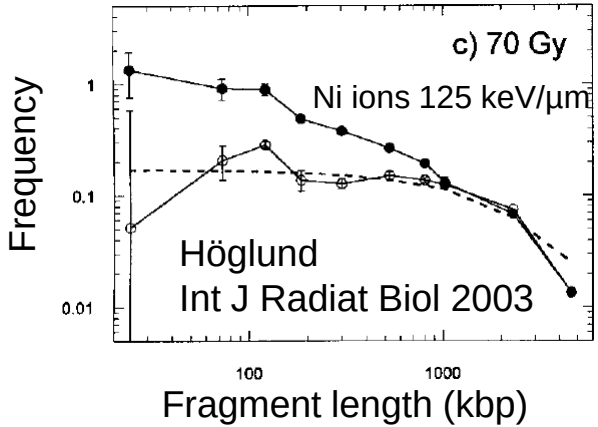
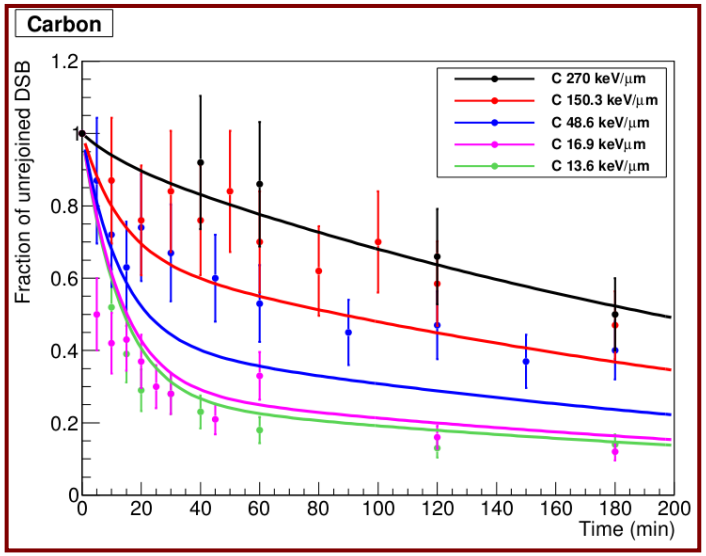


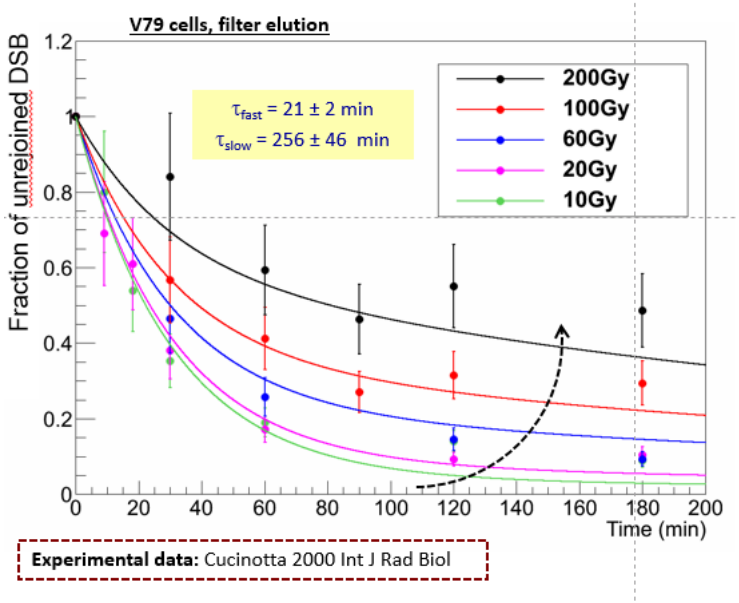
Table 2. DNA double-strand break induction yields after irradiation at different LET values.

Radiation quality	LET (keV/μm)	Yield ± SE[a] (10 × dsb/bp per Gy)	Random yield ± SE[b] (10 × dsb/bp per Gy)	RBE[c] dsb induction
^{60}Co photons	< 0.5	5.8 ± 0.1	5.2 ± 0.1	–
He ions	40	8.8 ± 0.2	5.0 ± 0.3	1.5
N ions	80	8.6 ± 0.9	4.8 ± 0.2	1.5
N ions	125	8.6 ± 0.3	4.3 ± 0.2	1.5
N ions	175	7.6 ± 1.0	3.8 ± 0.2	1.3
N ions	225	6.9 ± 0.7	3.3 ± 0.1	1.2

Damage repair

Tommasino, Radiat Res 2013

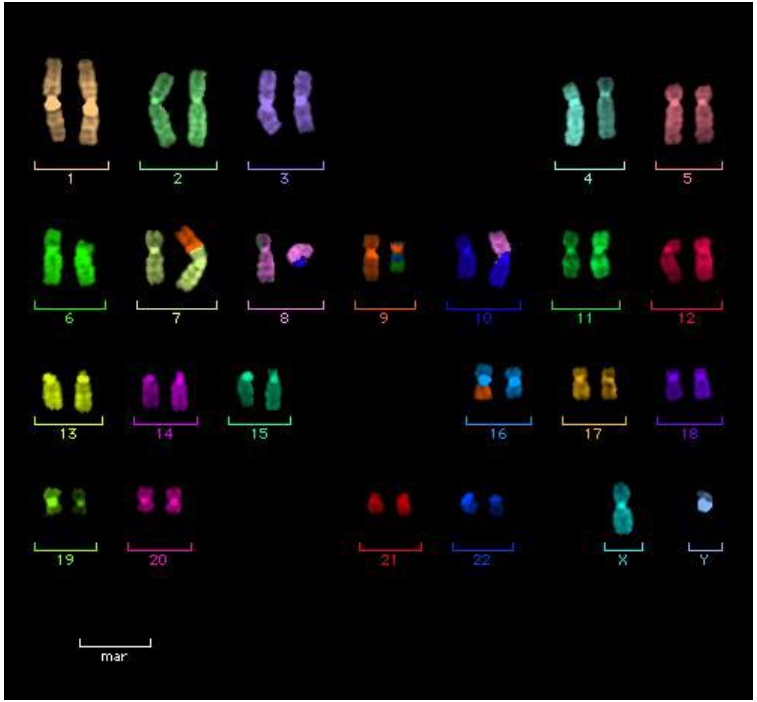




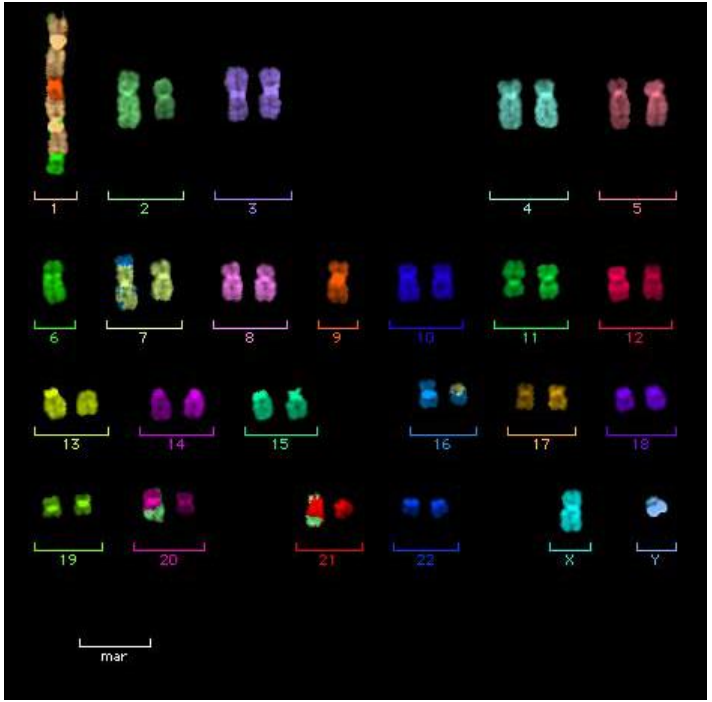
- Persistent damage at high LET and high doses → repair failure
- At least two components of repair (fast vs slow)

High LET cytogenetics

3 Gy γ-rays



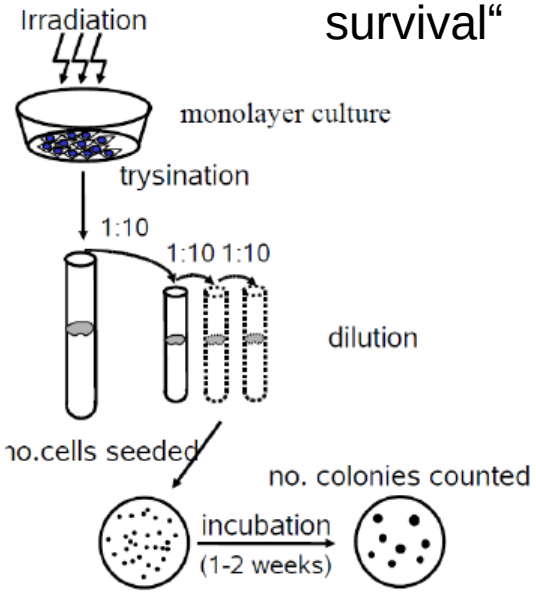
0.3 Gy Fe ions

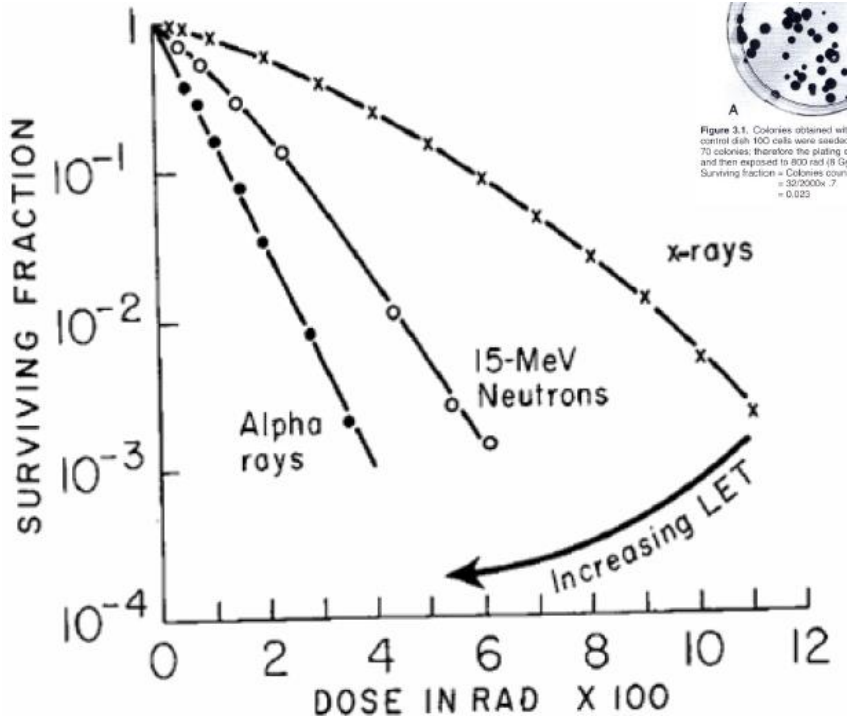


Durante et al., Radiat. Res. 2002

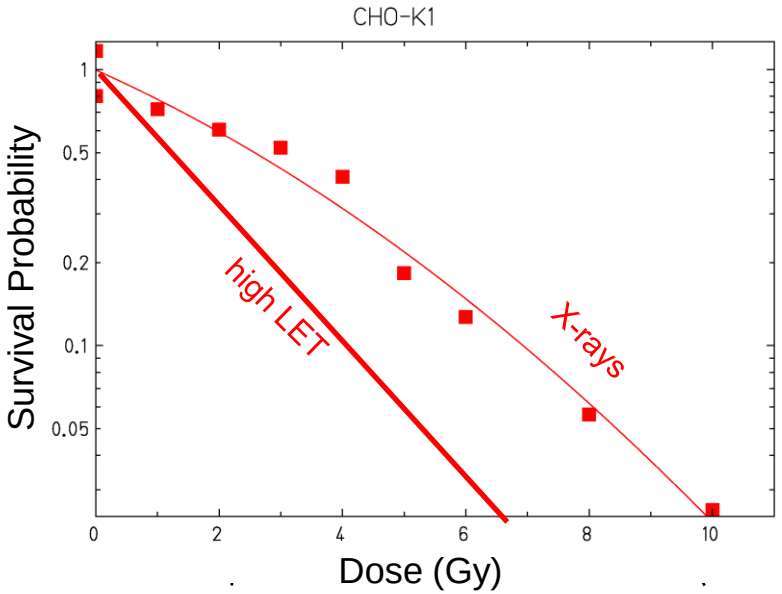
Cell survival

„clonogenic survival“





Linear quadratic model



αD
Intratrack-lesions

+

βD^2
Intertrack-lesions

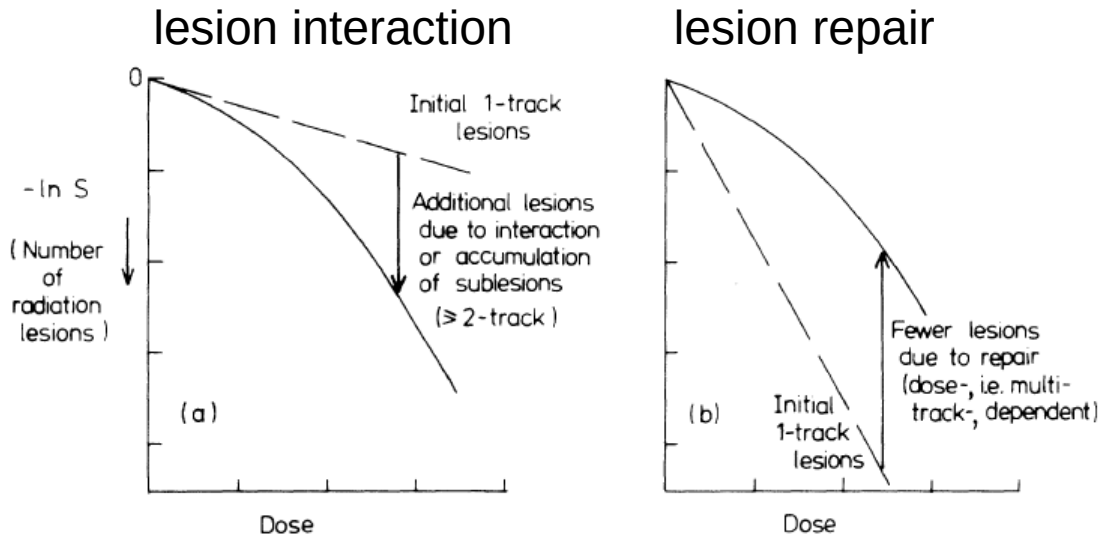
- Survival = Probability for no lethal event
  → Use Poission statistics

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

- Radiation is self-synergistic
- Two types of lesions
  (lethal vs sublethal)
- High LET: more lethal lesions per Gy
  (as for high doses)

Mechanistic interpretation of LQ model

- What are lethal lesions induced nonlinearly?
  Why is radiation more effective per Gy at high doses?

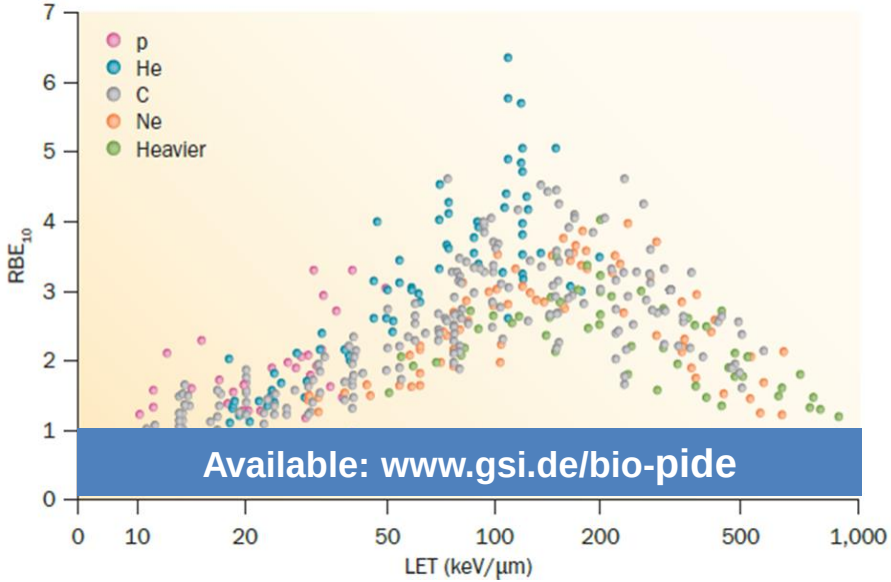


Goodhead, Radiat Environ Biophys 1985

Consider many data

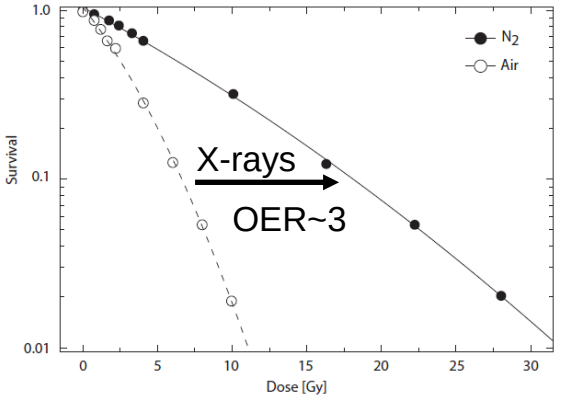
- Particle irradiation data ensemble (PIDE)
  - Collection of in-vitro survival data
  - > 1100 photon and ion effect curves
  - Different cell lines, radiation qualities, …
  - Suitable for model validation

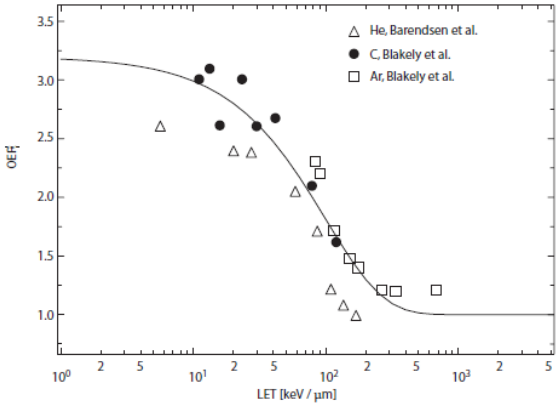
Friedrich et al., J. Radiat. Res. 2013
Friedrich et al., J. Radiat. Res. 2021



Hypoxia

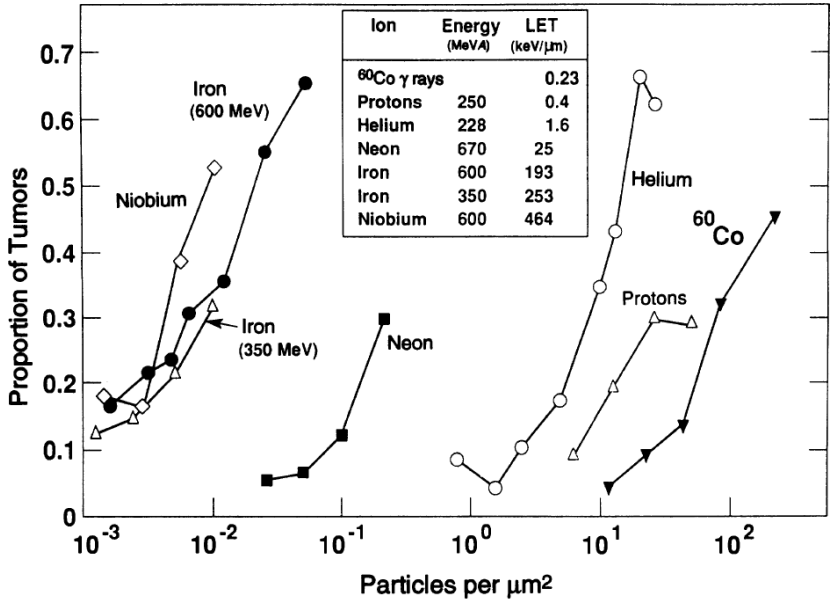
- Hypoxic cells (lacking oxygen atmosphere) are very resistant
- Reason: Oxygen can “fix” damage and make it less repairable
- OER: Dose ratio between aerobic and hypoxic conditions
- Tumors are often hypoxic in the core (e.g. pancreatic tumors)
- Hypoxia makes tumors resistant
- High LET radiation overcomes this resistancy





Kraft & Scholz, Adv. Space Res. 1994

Carcinogenic risk

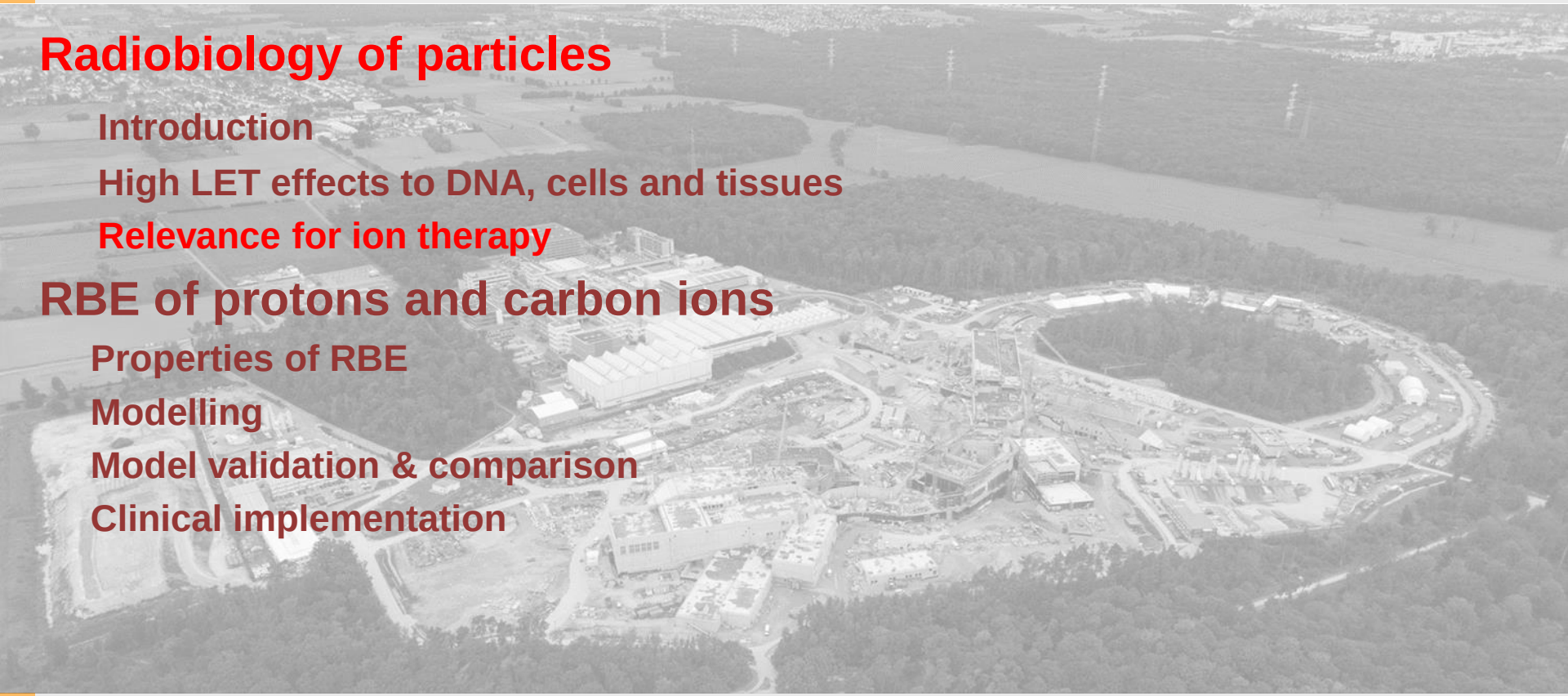


Alpen et al., Radiat Res 1993

Radiation	Initial slope ± SE (Δ% Prevalence/ΔGy)	RBE ± SE
^{60}Co γ rays	5.4 ± 1.7	—
Helium (228*A* MeV)	12.8 ± 1.8	2.3 ± 0.3
Iron (600*A* MeV)	214 ± 63.3	39.6 ± 11.5
Iron (350*A* MeV)	110 ± 29.7	20.3 ± 8.3

- High RBE also for carcinogenesis (here: Harderian gland data)
- Likewise: Mutation induction, cell transformation, micronucleus induction, …

Agenda



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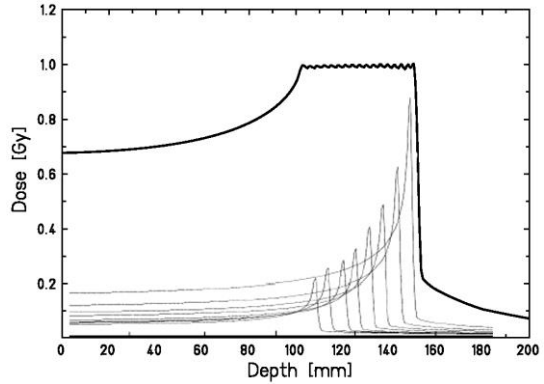
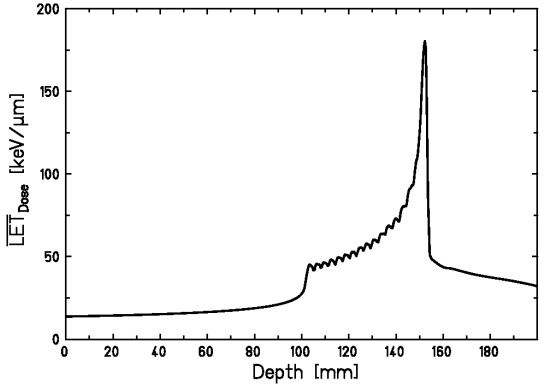
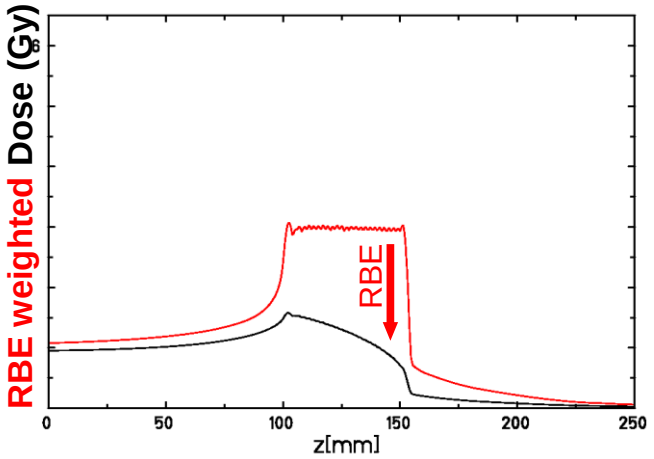
Effectiveness in carbon ion therapy

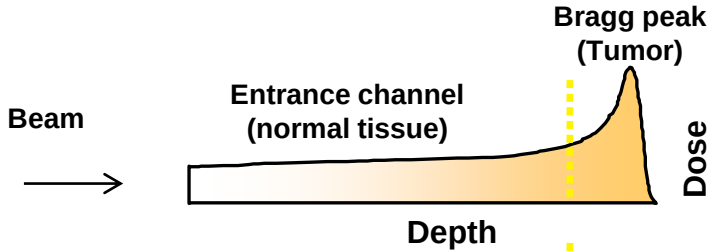






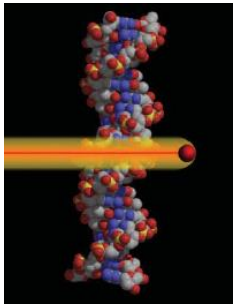
- RBE must be known in order to deliver the correct physical dose
- Radiation quality is different between entrance and SOBP, but also across the SOBP

Application to carbon ion therapy



Durante & Loeffler,

Nature Rev Clin Oncol 2010



Energy	high	low
LET	low	high
Dose	low	high
RBE	≈ 1	> 1
OER	≈ 3	< 3
Cell-cycle dependence	high	low
Fractionation dependence	high	low

Potential advantages

High tumor dose, normal tissue sparing

Effective for radioresistant tumors

Effective against hypoxic tumor cells

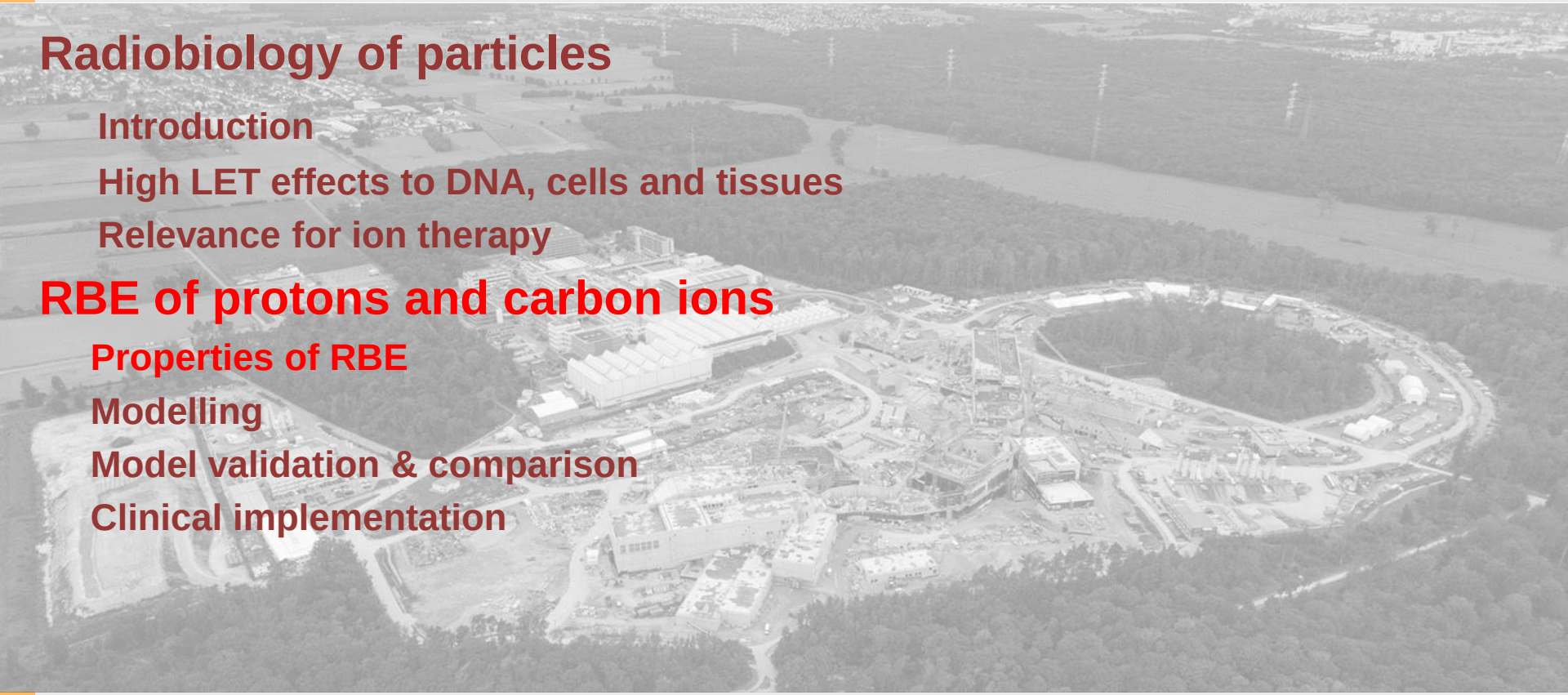
Increased lethality in the target because cells in radioresistant (S) phase are sensitized

Fractionation spares normal tissue more than tumor

Lessons learned

- Ions are more effective than photons, i.e. induce more damage per Gy
- Effectiveness is quantified by the RBE
- Ions induce more DSB damage, presumably much more small fragments
- They induce more complex DNA damage – it is less efficiently repaired, and repair takes more time
- Cell division is hence more likely to fail – hence ions cause more cell kill per Gy
- Ions are also more effective for later endpoints: tissue damage, tumor control, carcinogenesis
- High LET effects are similar to high dose effects
- At very high LET, effectiveness decreases due to “overkill” – less deposited energy per particle would have been sufficient
- Also other advantages: OER, cell cycle, ... → exploited in ion therapy

Agenda



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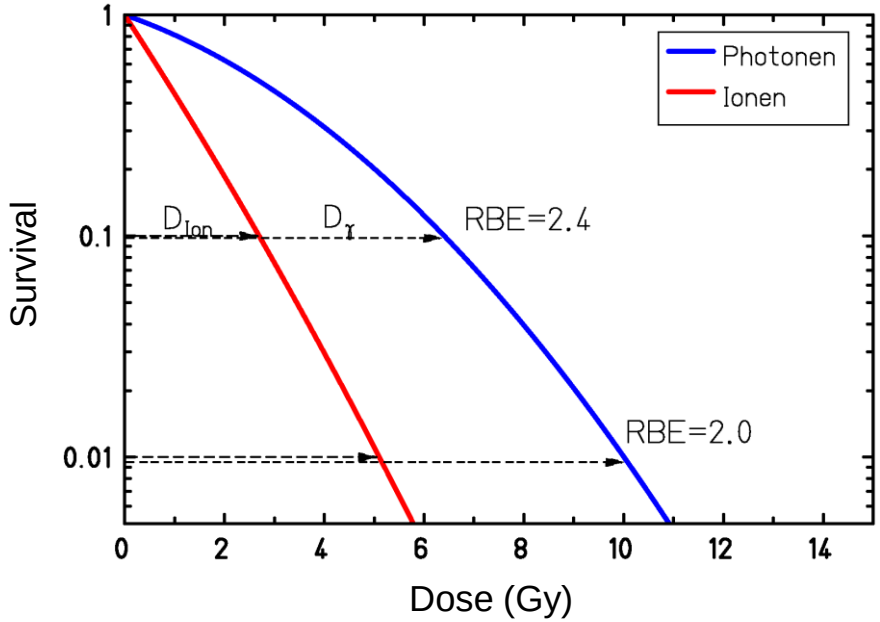
Relative biological effectiveness



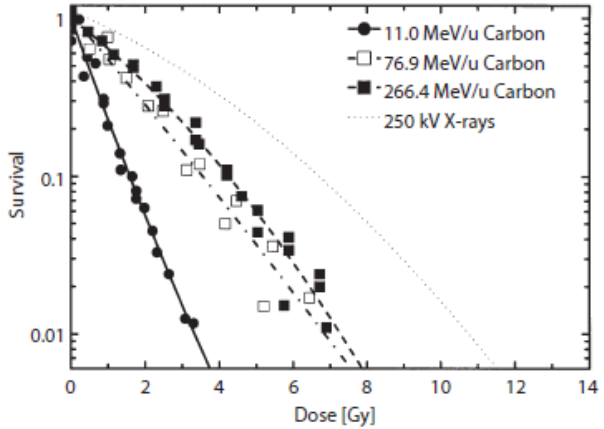
$$RBE = \frac{D_\gamma}{D_{Ion}}\Bigg|_{Isoeffect}$$

- RBE depends on:
  - Endpoint
  - LET
  - Dose
  - Particle type
  - Radiosensitivity

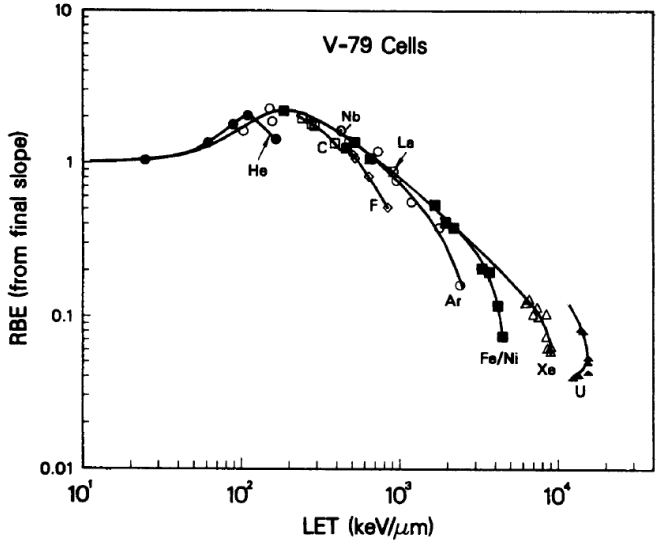
  → complex quantity

- Challenges
  - RBE systematics
  - RBE in complex radiation fields

RBE: LET dependence



Scholz, Adv. Polymer Science 2003

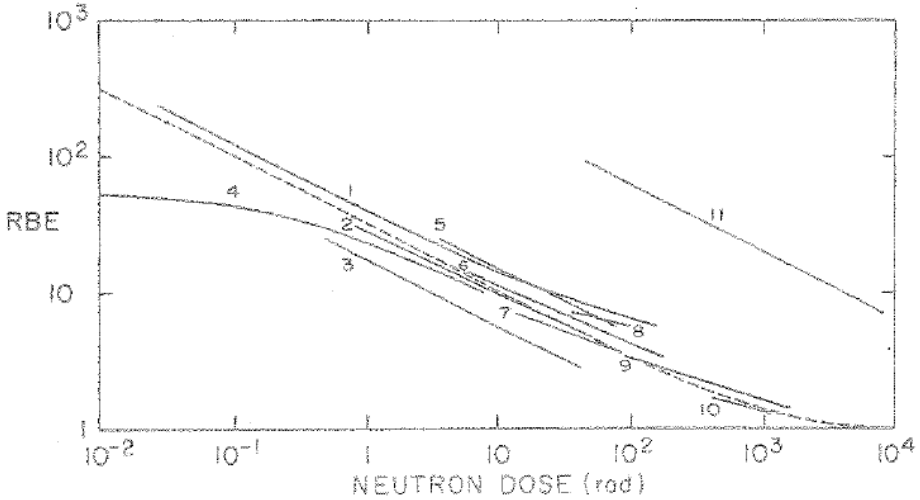


Kraft & Scholz, Adv. Space Res. 1994

LET↑	→	RBE↑ (RBE↓)
D ↑	→	RBE↓
Z↑	→	RBE↓
α/β↑	→	RBE↓

- RBE increases with LET
- At some point it decreases (overkill)

RBE: Dose dependence

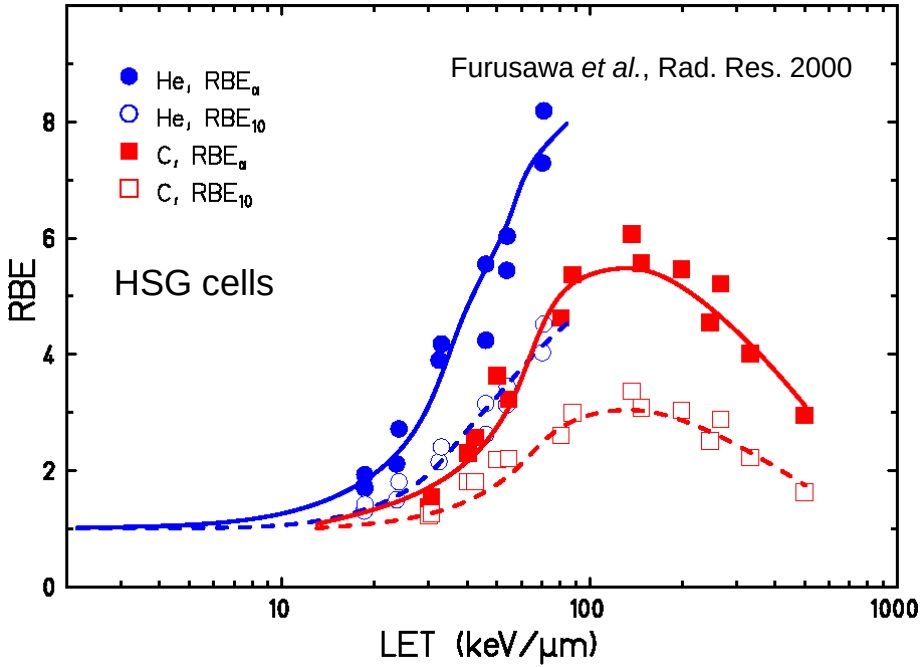


Kellerer, Curr. Top. Radiat. Res. Quarterly 1972

LET↑	→	RBE↑ (RBE↓)
D ↑	→	RBE↓
Z↑	→	RBE↓
α/β↑	→	RBE↓

- RBE decreases with dose

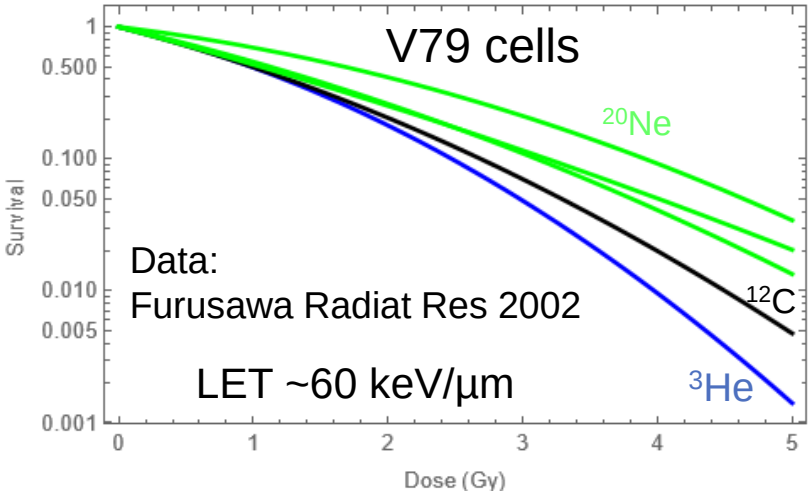
RBE: Particle type dependence

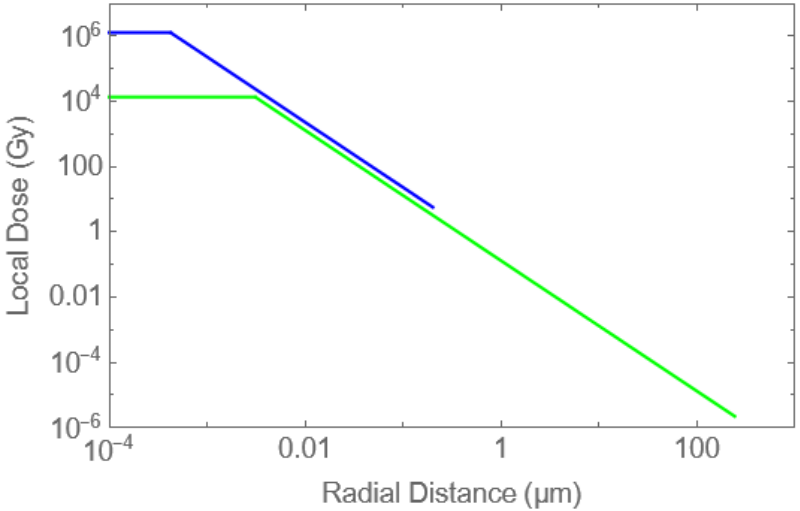


LET↑	→	RBE↑ (RBE↓)
D ↑	→	RBE↓
Z↑	→	RBE↓
α/β↑	→	RBE↓

- RBE decreases with increasing Z

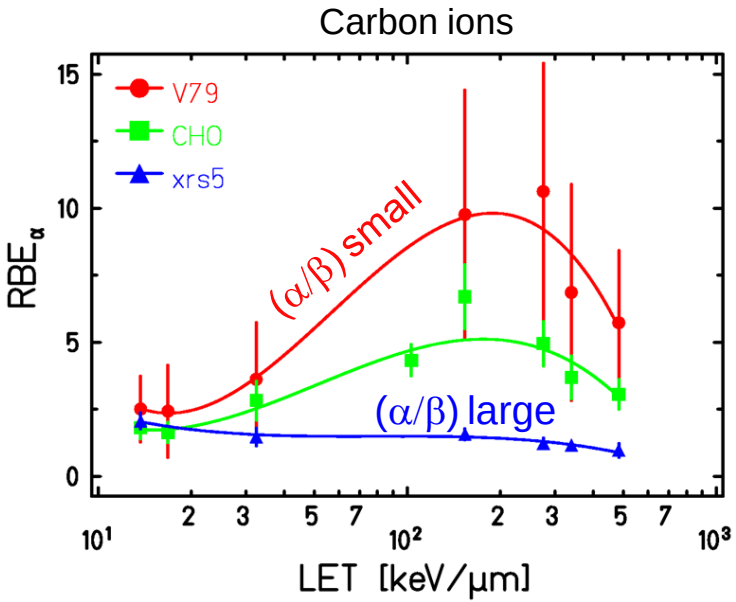
Same LET – different effects





- Neon ions have larger energy at 60 keV/µm than Helium ions
- Hence track structure is broader and shallower → less effect
- LET does not uniquely define radiation effects

RBE: Cell type dependence



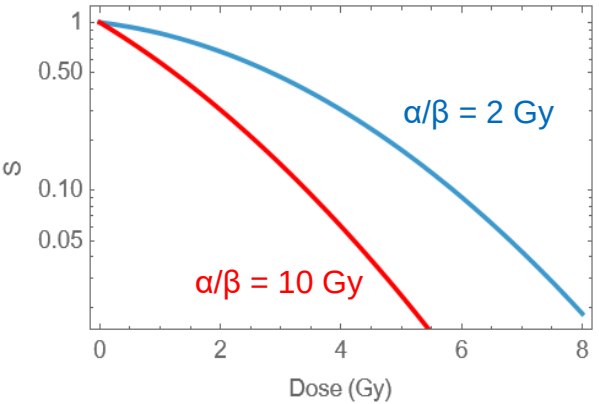
Weyrather *et al.* IJRB **75**, 1357 (1999)

LET↑ → RBE↑ (RBE↓)
D ↑ → RBE↓
Z↑ → RBE↓
α/β↑ → RBE↓

- RBE decreases with increasing α/β

Relevance of the α/β- ratio

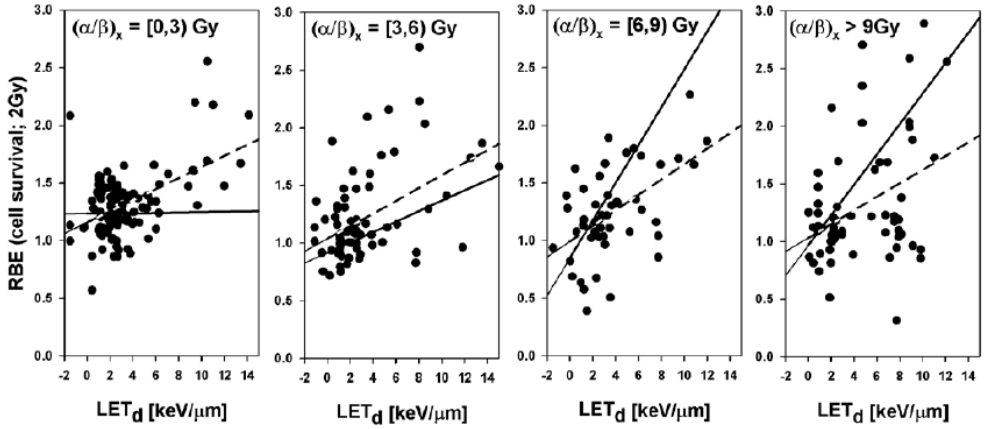
- Above α/β, the β component is more important than α
- Photon α/β: Scaling parameter for responsiveness of cells or tissues



	α/β small	α/β large
Survival curves	Shouldered survival curves → repair takes place	Straight survival curves → less repair or more complex lesions
Radiosensitivity	radioresistant	radiosensitive
Tumors	Slowly growing tumors	Quickly growing tumors
Normal tissues	Late responding tissue	Early responding tissue
RBE effects	Large RBE effects	Moderate RBE effects
Fractionation sensitivity	High	low

Proton RBE

- Protons are no exception
- LET remains fairly small (<<20 keV/µm)
- Lower RBE, hard to detect characteristics
- But: RBE > 1 is evident on average – also for low LET



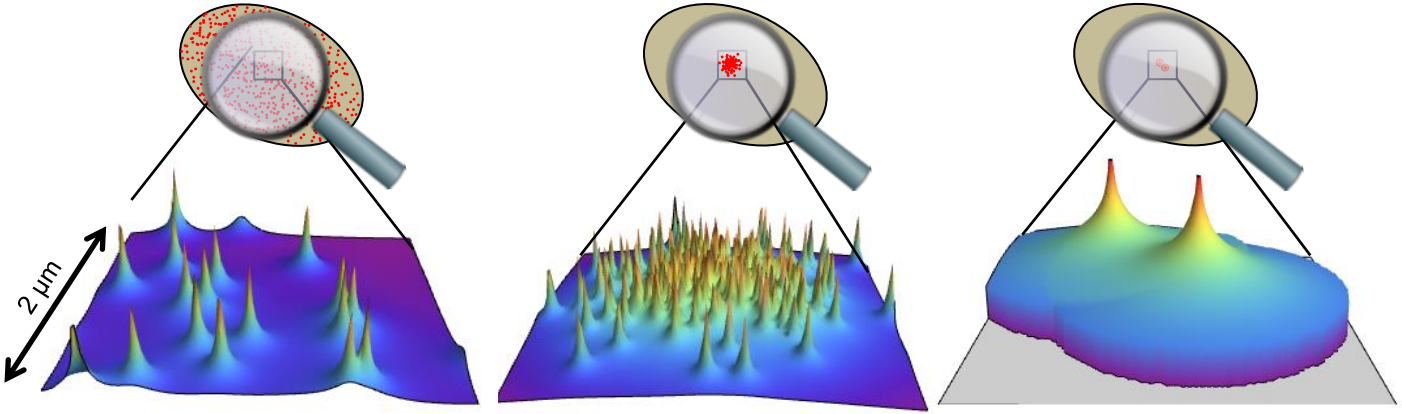
Paganetti PMB **59**, R419 (2014)

Fit including uncertainties

Fit ignoring uncertainties

Why are ions so effective?

A dose of 1.7 Gy could mean...

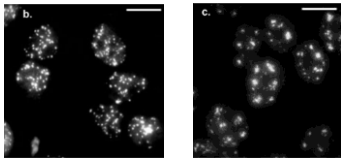


234 protons (20 MeV), homogeneous irradiation

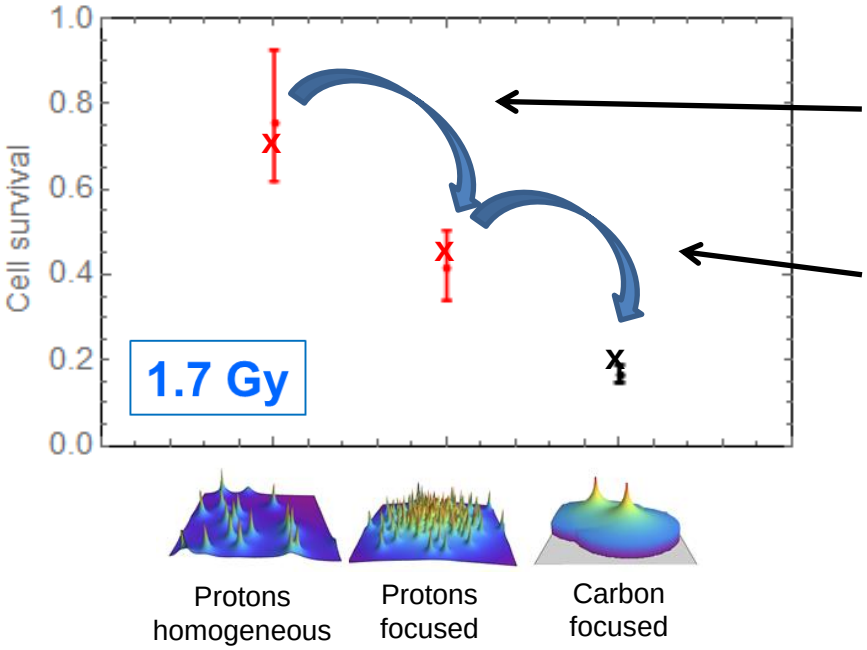
234 protons (20 MeV), focused to sub-µm spot

2 carbon ions (4.5 MeV/u), focused to sub-µm spot

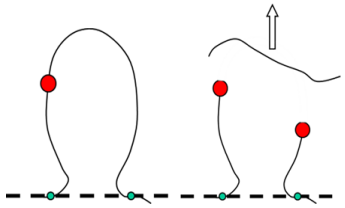
→ Test biologic response with microbeam



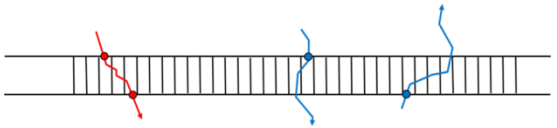
Radiation targets at different levels



µm lesion interaction (DSB proximity)



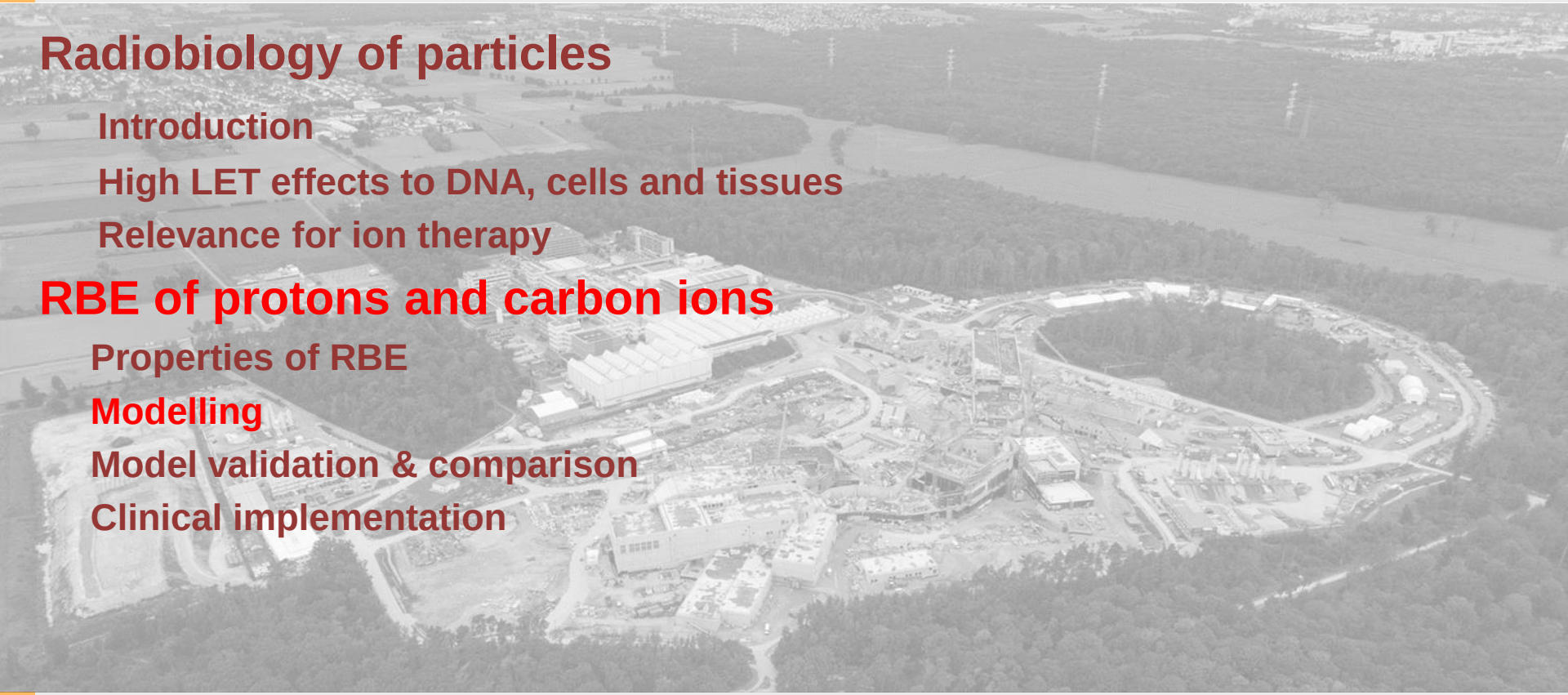
nm lesion interaction (DSB number)



Friedrich et al., Sci. Rep. 2018

→ Coexistence of lesion interaction mechanisms

Agenda



Radiobiology of particles

- Introduction
- High LET effects to DNA, cells and tissues
- Relevance for ion therapy

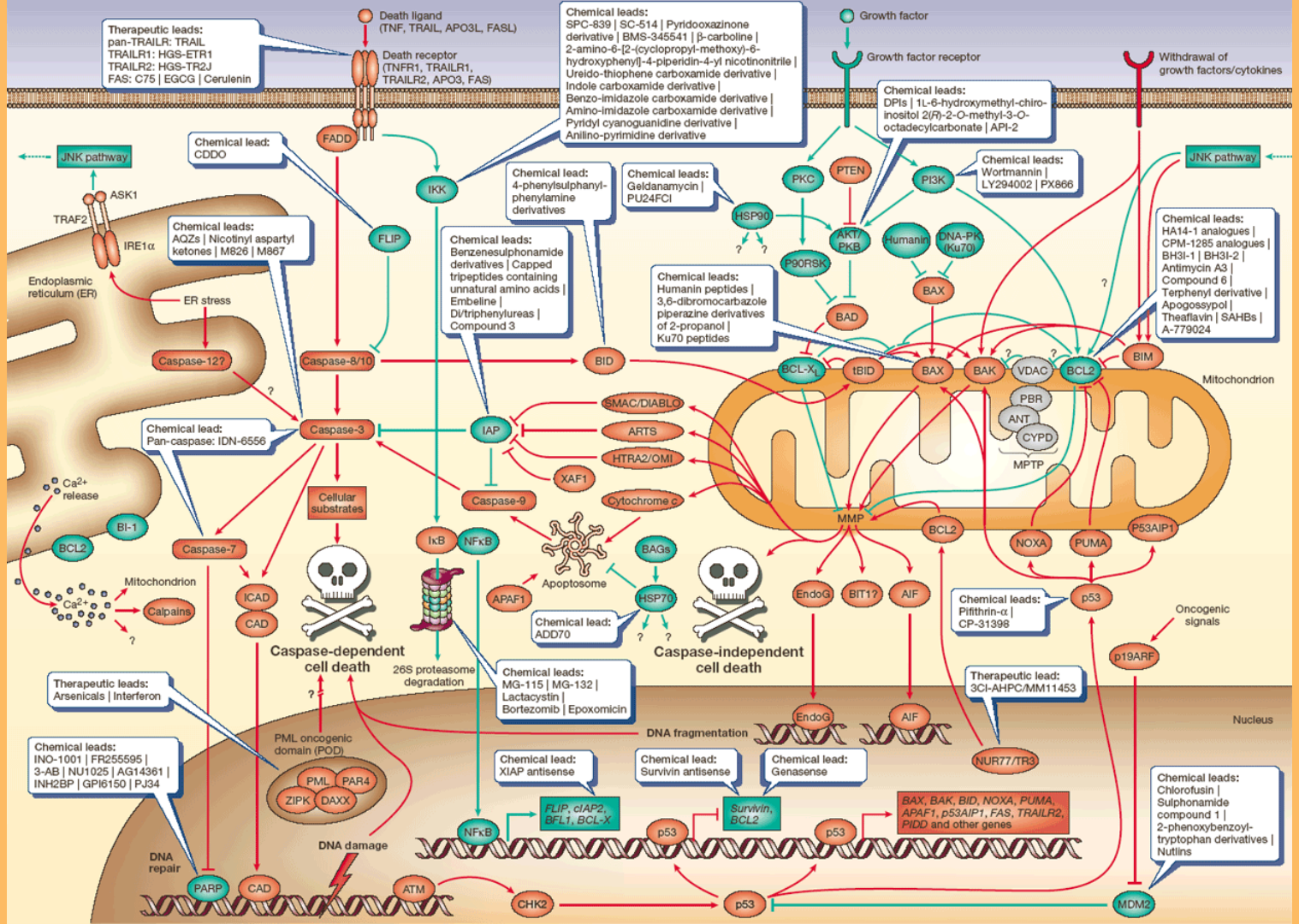
RBE of protons and carbon ions

- Properties of RBE
- Modelling
- Model validation & comparison
- Clinical implementation

“Essentially, all models are wrong,
but some are useful!”

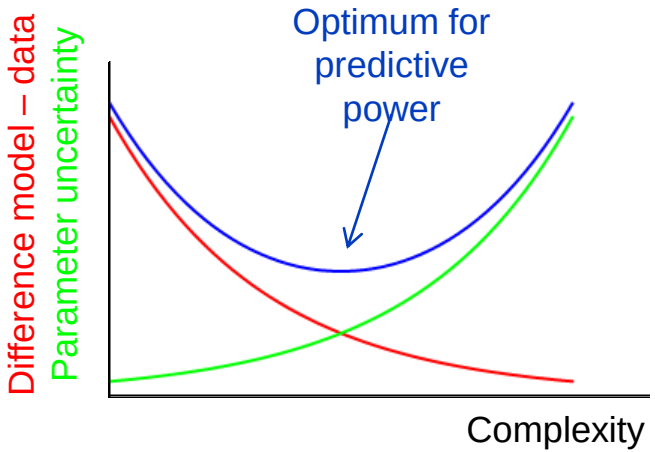
George E.P. Box, statistician

→ Models have limitations

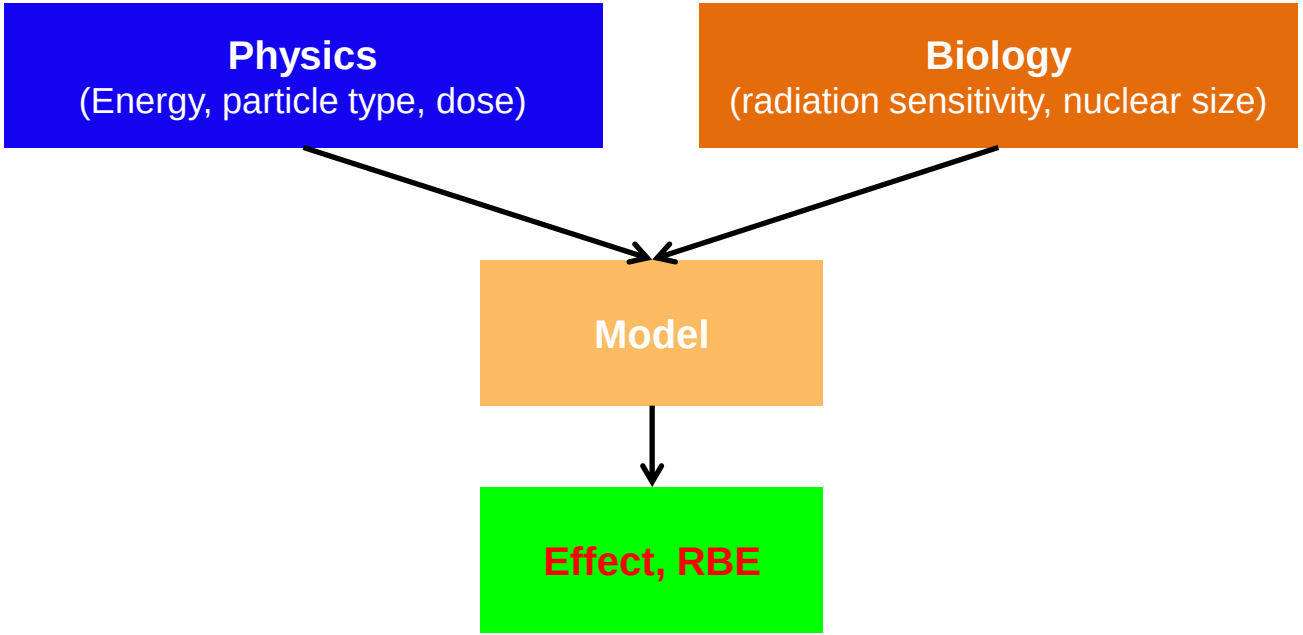

Therapeutic leads:
pan-TRAILR: TRAIL
TRAILR1: HGS-ETR1
TRAILR2: HGS-TR2J
FAS: C75 | EGCG | Cerulenin
Death ligand
(TNF, TRAIL, APO3L, FASL)
Death receptor
(TNFR1, TRAILR1,
TRAILR2, APO3, FAS)
Chemical leads:
SPC-839 | SC-514 | Pyridooxazinone derivative | BMS-345541 | β-carboline | 2-amino-6-[2-(cyclopropyl-methoxy)-6-hydroxyphenyl]-4-piperidin-4-yl nicotinonitrile | Ureido-thiophene carboxamide derivative | Indole carboxamide derivative | Benzo-imidazole carboxamide derivative | Amino-imidazole carboxamide derivative | Pyridyl cyanoguanidine derivative | Anilino-pyrimidine derivative
Growth factor
Growth factor receptor
Withdrawal of growth factors/cytokines
Chemical leads:
DPIs | 1L-6-hydroxymethyl-chiro-inositol 2(R)-2-O-methyl-3-O-octadecylcarbonate | API-2
JNK pathway
Chemical lead:
CDDO
FADD
IKK
Chemical lead:
4-phenylsulphanyl-phenylamine derivatives
Chemical leads:
Geldanamycin | PU24FCl
HSP90
PKC
PTEN
PI3K
Chemical leads:
Wortmannin | LY294002 | PX866
JNK pathway
ASK1
TRAF2
IRE1α
Chemical leads:
AQZs | Nicotinyl aspartyl ketones | M826 | M867
FLIP
Chemical leads:
Benzenesulphonamide derivatives | Capped tripeptides containing unnatural amino acids | Embeline | Di/triphenylureas | Compound 3
AKT/PKB
Humanin
DNA-PK (Ku70)
Chemical leads:
HA14-1 analogues | CPM-1285 analogues | BH3I-1 | BH3I-2 | Antimycin A3 | Compound 6 | Terphenyl derivative | Apogossypol | Theaflavin | SAHBs | A-779024
P90RSK
BAX
Chemical leads:
Humanin peptides | 3,6-dibromocarbazole piperazine derivatives of 2-propanol | Ku70 peptides
BAD
Endoplasmic reticulum (ER)
ER stress
Caspase-12?
Caspase-8/10
BID
BCL-XL
tBID
BAX
BAK
VDAC
BCL2
BIM
Mitochondrion
PBR
ANT
CYPD
MPTP
SMAC/DIABLO
ARTS
HTRA2/OMI
XAF1
Cytochrome c
Chemical lead:
Pan-caspase: IDN-6556
Caspase-3
IAP
Caspase-9
Cellular substrates
Ca2+ release
BI-1
BCL2
Caspase-7
MMP
BCL2
NOXA
PUMA
P53AIP1
IκB
NFκB
BAGs
Apoptosome
APAF1
HSP70
Chemical lead:
ADD70
EndoG
BIT1?
AIF
Chemical leads:
Pifithrin-α | CP-31398
p53
Oncogenic signals
p19ARF
Mitochondrion
Ca2+
Calpains
ICAD
CAD
Caspase-dependent cell death
26S proteasome degradation
Caspase-independent cell death
Chemical leads:
MG-115 | MG-132 | Lactacystin | Bortezomib | Epoxomicin
Therapeutic leads:
Arsenicals | Interferon
Therapeutic lead:
3Cl-AHPC/MM11453
Nucleus
DNA fragmentation
EndoG
AIF
NUR77/TR3
Chemical leads:
INO-1001 | FR255595 | 3-AB | NU1025 | AG14361 | INH2BP | GPI6150 | PJ34
PML oncogenic domain (POD)
PML
PAR4
ZIPK
DAXX
Chemical lead:
XIAP antisense
Chemical lead:
Survivin antisense
Chemical lead:
Genasense
FLIP, cIAP2, BFL1, BCL-X
Survivin, BCL2
BAX, BAK, BID, NOXA, PUMA, APAF1, p53AIP1, FAS, TRAILR2, PIDD and other genes
NFκB
p53
p53
DNA damage
DNA repair
PARP
CAD
ATM
CHK2
p53
MDM2
Chemical leads:
Chlorofusin | Sulphonamide compound 1 | 2-phenoxybenzoyl-tryptophan derivatives | Nutlins

Basic properties of models

- Models are a compromise between oversimplification and overdetailed descriptions of reality
- Big challenge in modelling
  - Often simple phenomenon…
  - …but very complex biology
- Keep models simple
  → make them practical
  → meaningful parameters
- … but not too simple!

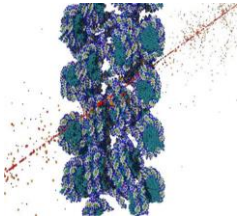


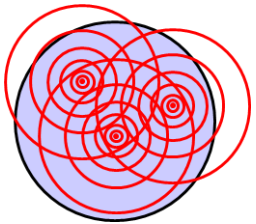
Model logic


Physics
(Energy, particle type, dose)
Biology
(radiation sensitivity, nuclear size)
Model
Effect, RBE

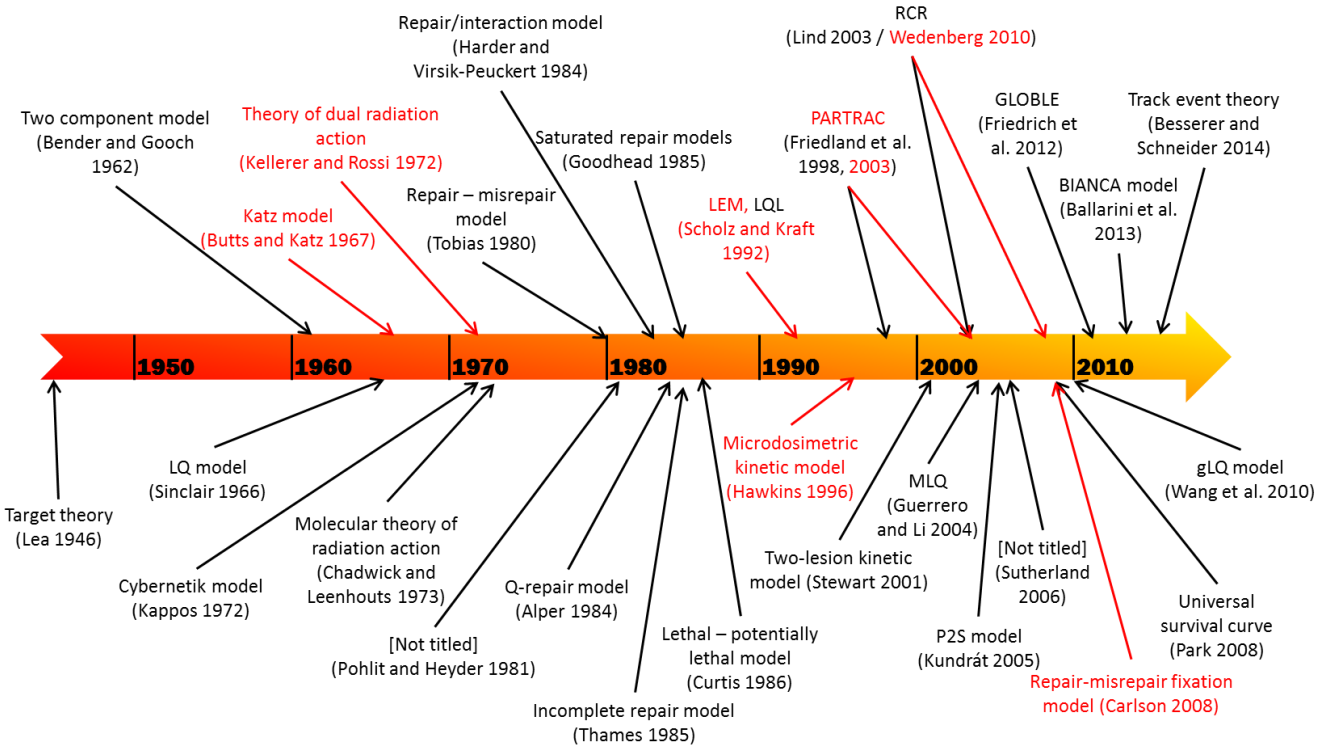
Model categories

- Generally different approaches
  - **„Ab initio“ models:** detailed and complex
    - Tools to investigate mechanistic aspects
    - Limited predictive power for late endpoints due to parameter accumulation
    - Example: Geant-DNA, PARTRAC
  - **Pragmatic models:** Empirically based, simple
    - Low number of free parameters, good predictive quality
    - Simple for applications
    - Limited mechanistic basis
    - Example: LEM, MKM





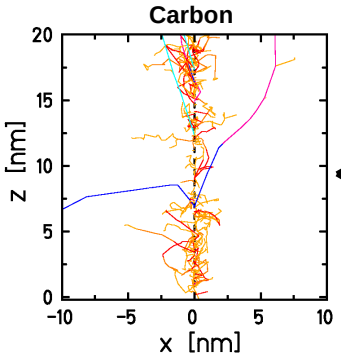
History in effect modelling



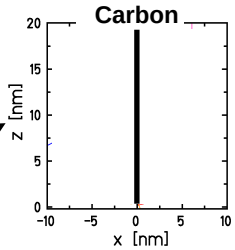
Red: High LET models

Track structure representation

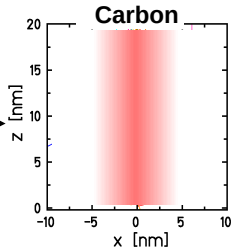
Track structure of high LET ions



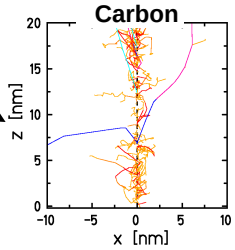
Model representation



1-dimensional
„LET-approximation“

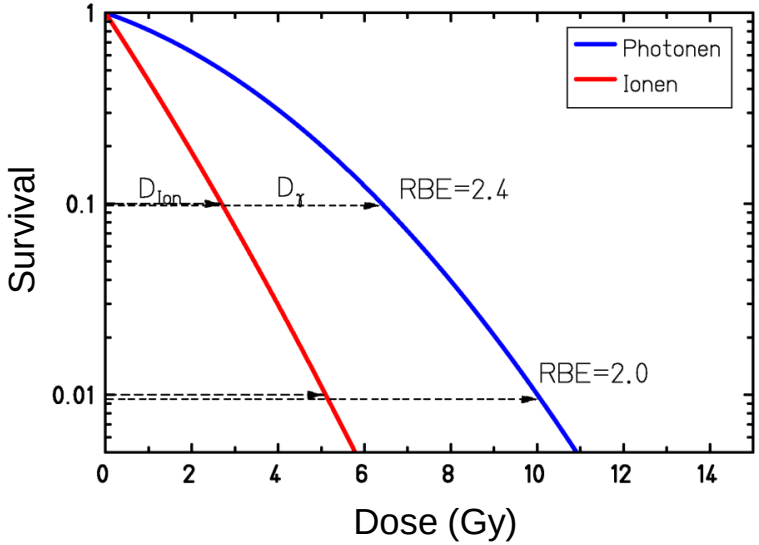


2-dimensional
„amorphous track“



3-dimensional
Full reconstruction

Modeling RBE



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

"Relative biological effectiveness"

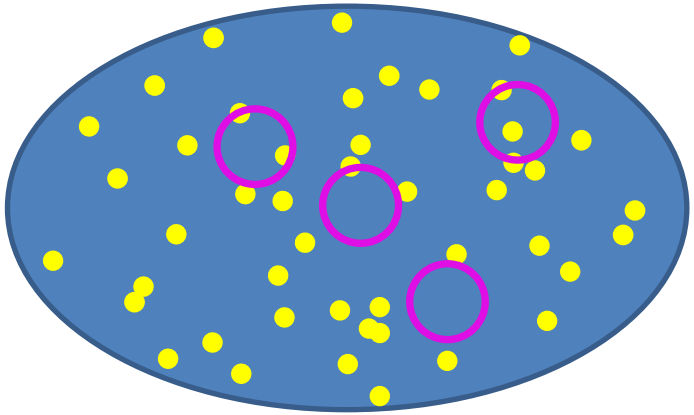
- RBE depends on:
  - reference radiation
  - endpoint
  - LET
  - Dose
  - Particle type
  - Radiosensitivity

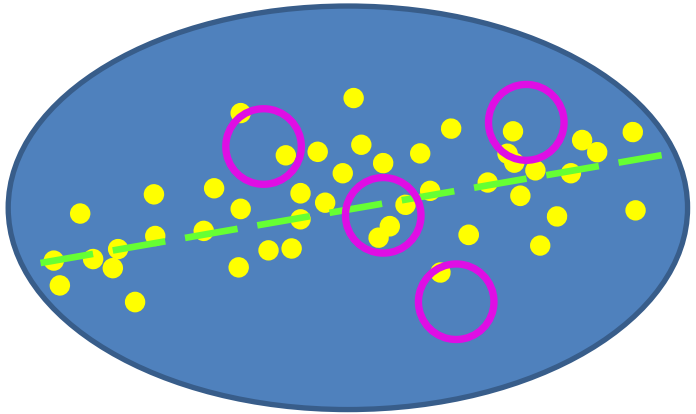
  → complex quantity!

- Goal of modelling: Describe and predict RBE (or LQ parameters)
  - for complex radiation fields, i.e. in particle therapy or space radation
  - for investigating mechanisms of high LET effects

Microdosimetry

- Dose of 1 Gy ~ 10^5 ionizations in a cell nucleus
- But: Microscopically, dose fluctuates
- Microdosimetry: Consider biologic relevant microdosimetric domains
  → Specific energy z is random variable equivalent of dose
  → Determine distribution of z

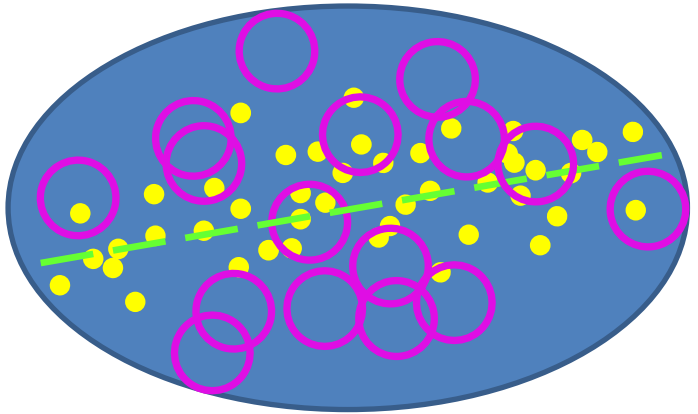




Microdosimetric Kinetic Model

- Consider survival s_d of domains
  (by sampling from the distribution of specific energy z)

$$-\ln s_d = Az + Bz^2$$



- Cell survives, if all domains survive
- Number of hits to a domain:
  Poisson distribution
- Survival fraction of a cell: S

$$-\ln S = (\alpha_0 + \beta z_{1,D})D + \beta D^2$$

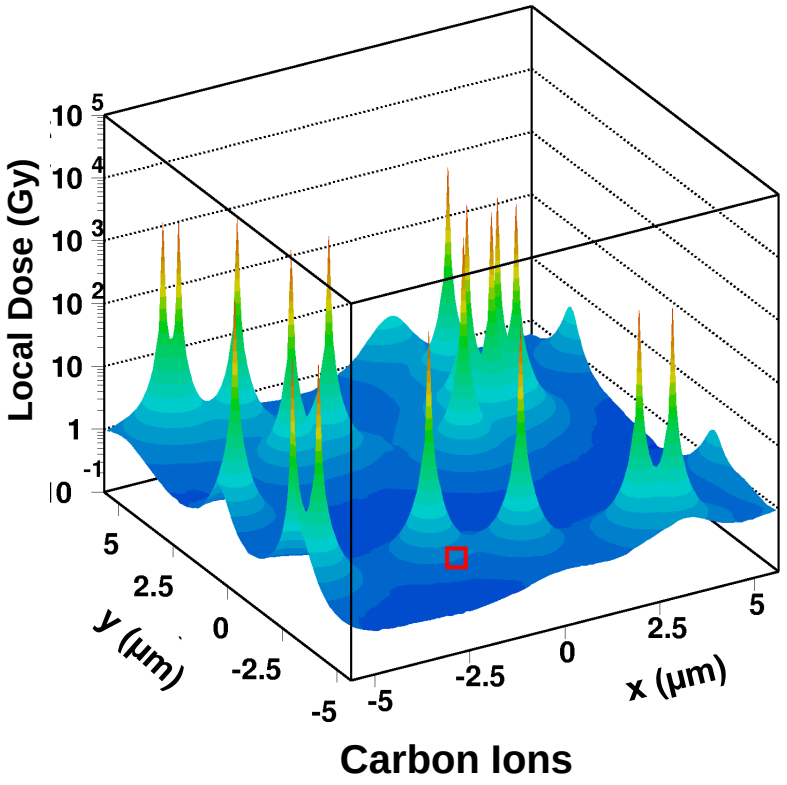
- Note: β drives up the effect!

Used as part of treatment planning in some Carbon ion facilities (Japan, Korea, Taiwan)

Local effect model: General concept

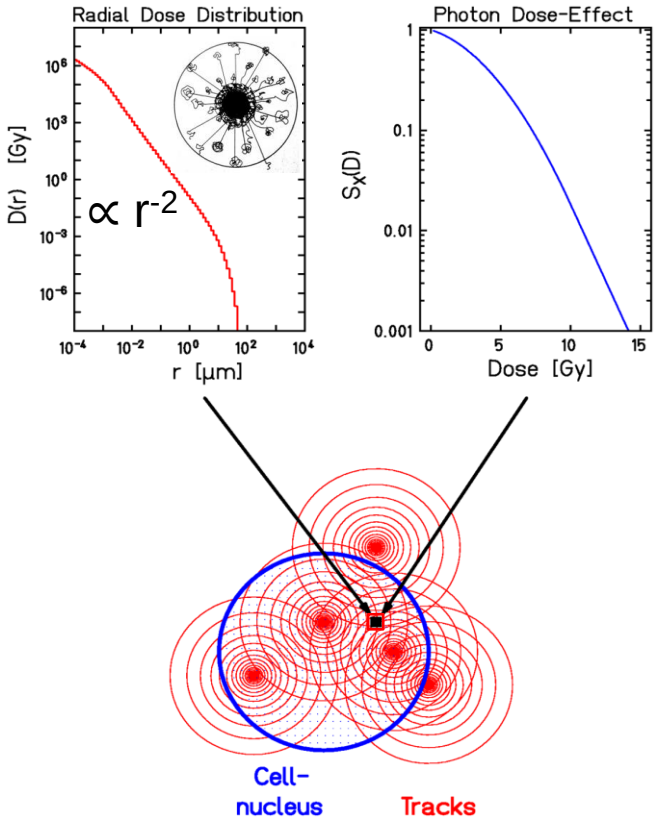
- Main idea of LEM (all variants):
  - Consider local energy concentration within amorphous track structure
  - Same effects establish as for photon exposure

→ Need
  - Track structure model
  - Photon dose-effect curve



Scholz & Kraft, Radiat. Prot. Dosim. 1994
Scholz & Kraft, Radiat. Environ. Biophys. 1997

LEM I Concept - Overview



LEM I

Sum over local effects

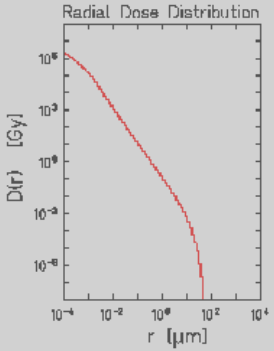
$$-\ln S_X(D) = \begin{cases} \alpha D + \beta D^2 & \text{for } D < D_t \\ \text{linear tail} & \text{for } D > D_t \end{cases}$$

$$S = \mathrm{V_n}^{-1} \exp\left\{ -\int \ln S_X\left(D(\vec{r})\right) d^3r \right\}$$

→ Adapted for carbon ions
→ Predictions valid in high LET (target) region

Used as part of treatment planning in some Carbon ion facilities (Europe + Shanghai)

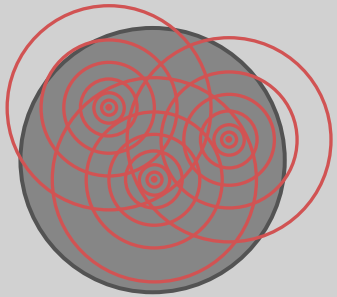
LEM IV concept – overview

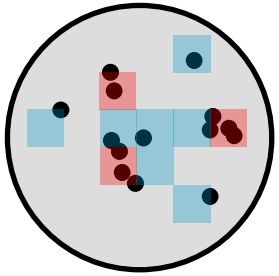


Amorphous track strucure

LEM IV

Local dose distribution

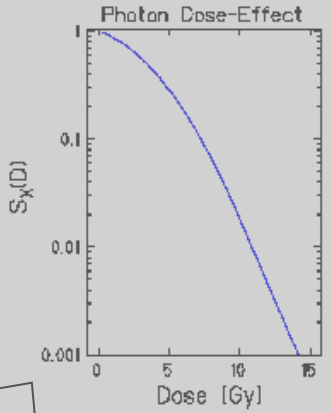




Local lesion distribution

Lesion statistics

iDSB	:	7
cDSB	:	3



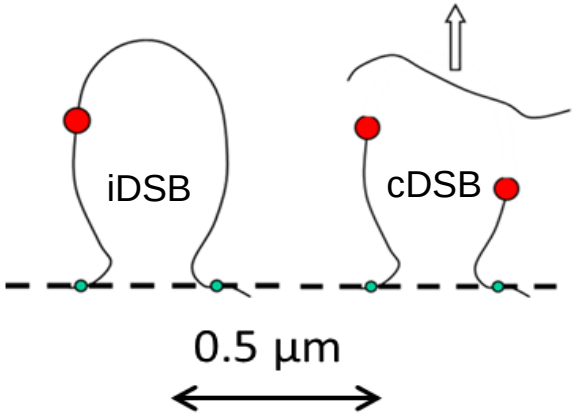
Equivalent photon dose

RBE

LEM IV concept

- Average over local damage concentration
- Include DSB distribution: Distinguish DSB in 2 Mbp chromatin loops
  - isolated DSB (iDSB)
  - clustered DSB (cDSB)

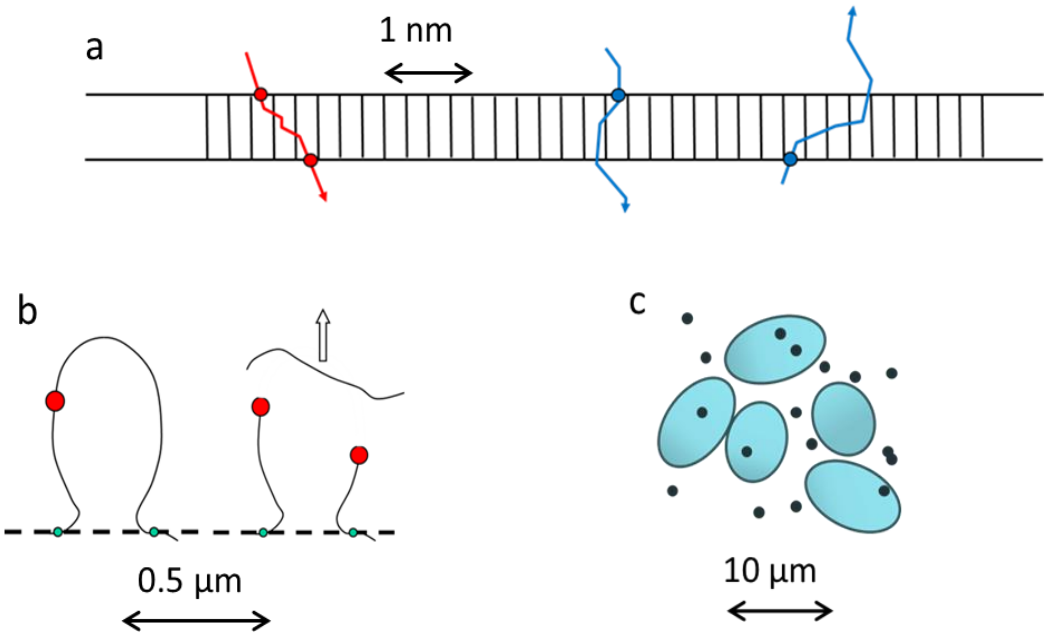
Elsässer et al., Red J 2010
Friedrich et al., Int J Radiat Biol 2012
Friedrich et al., Phys Med Biol 2013



→ Determine effect from photon exposure with same local DSB concentration
→ Valid for all ion species (validated up to ^{20}Ne)
→ Reasonable predictions for broad range of energies

LEM IV scales of radiation damage

- Lesion formation on three scales



"Mediators" of damage:
a. Number of DSB
b. Proximity of DSB
c. Presence of hits

LEM IV has elements of:
a. Nanodosimetry
b. Microdosimetry
c. Target theory

Proton RBE modeling

- Protons have less expressed RBE effects
- Simplest proton RBE model:

RBE = 1.1

Used as part of treatment planning
in all proton facilities

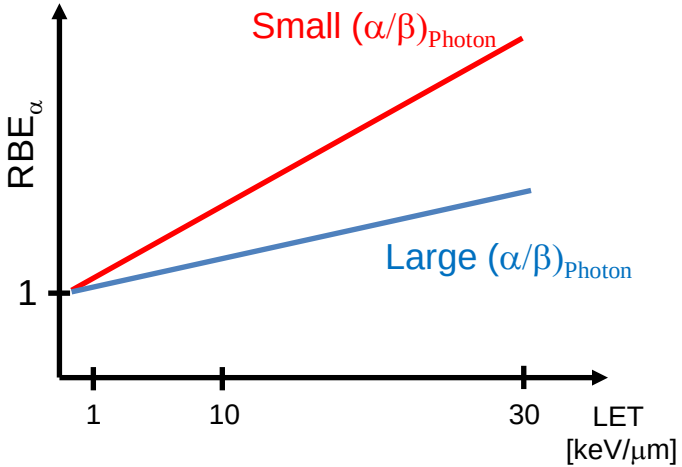
Proton variable RBE modeling

- Empirical RBE models for protons: RBE is linear in LET

$$RBE_{max} = RBE_{\alpha} = \frac{\alpha}{\alpha_{\gamma}} = 1 + q\frac{LET}{\alpha_{\gamma}/\beta_{\gamma}}$$

Wedenberg et al.
Acta Oncol. 2013

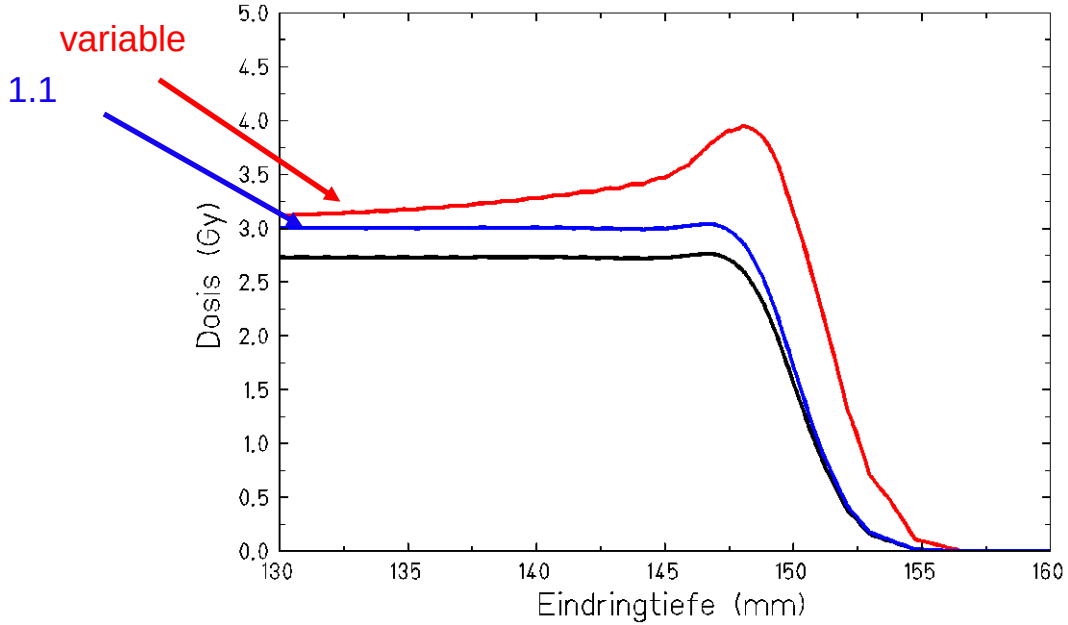
- Similar approach for β: $RBE_{min} = RBE_{\beta}$
- LQ model: Obtain RBE for any dose



- Restriction to protons
- Dose dependence debatable
- Low mechanistic rationale
- But: simple !

Why variable proton RBE?

- Extended range: RBE enhances irradiated target size



Grün et al. Med Phys 2013

- At distal end of a SOBP, high LET patterns may induce normal tissue effects (meanwhile we have clinical evidence)
- Likeweise, for hypofractionated regimens, RBE = 1.1 could result in underdosage

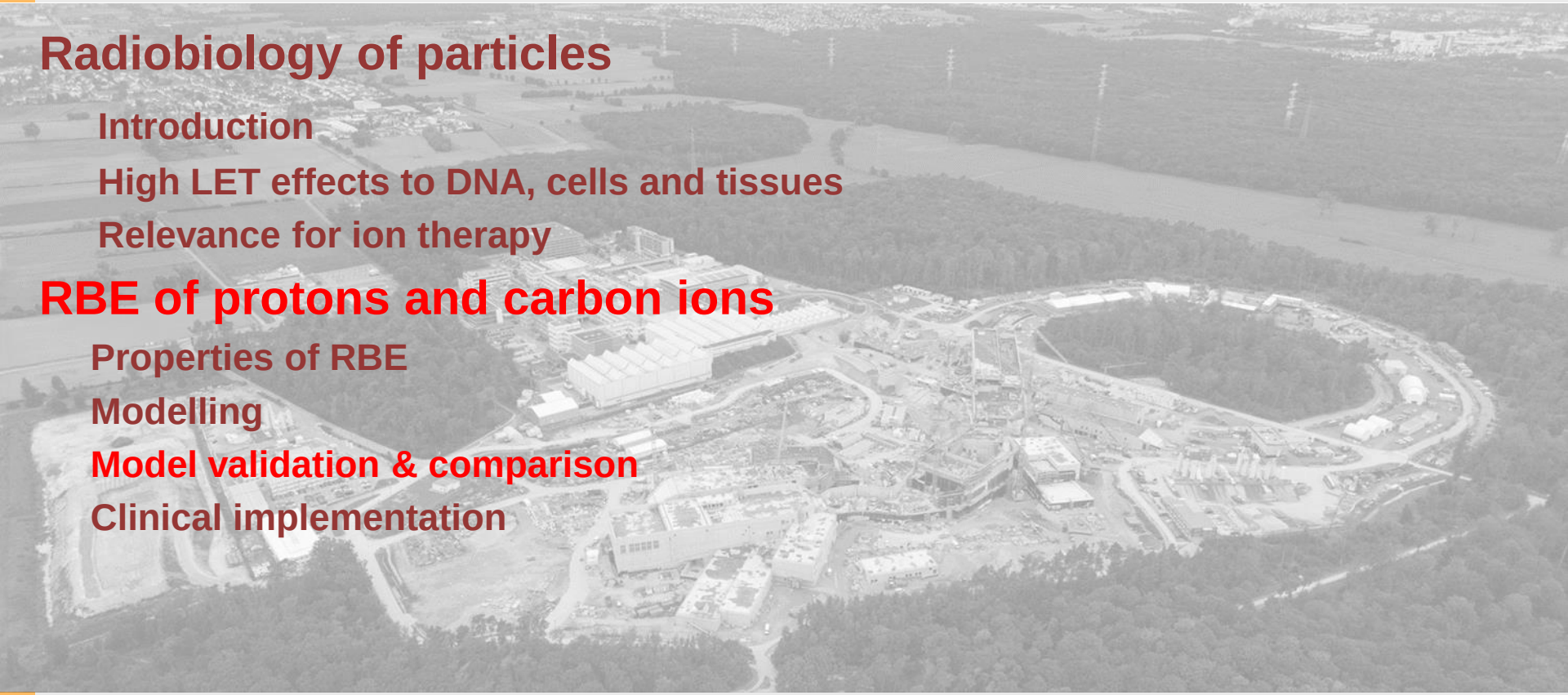
Agenda

Radiobiology of particles

- Introduction
- High LET effects to DNA, cells and tissues
- Relevance for ion therapy

RBE of protons and carbon ions

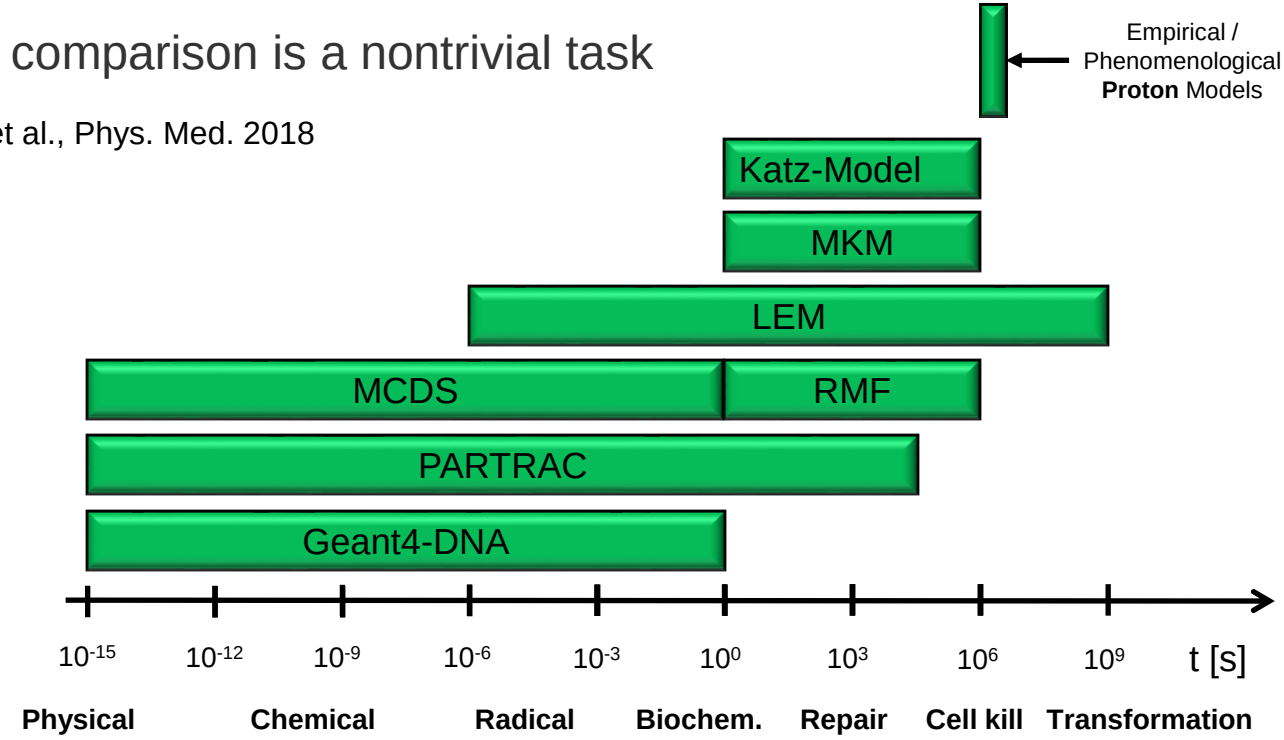
- Properties of RBE
- Modelling
- Model validation & comparison
- Clinical implementation



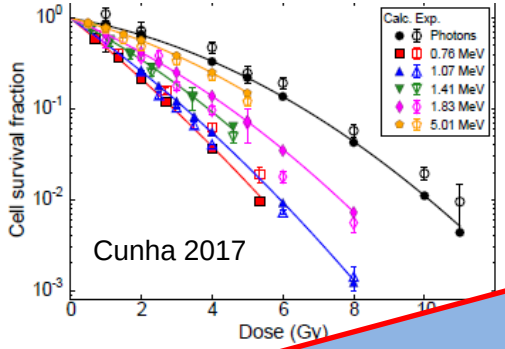
Many RBE models exist

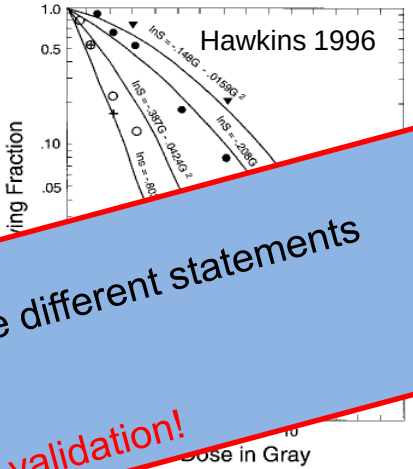
- Model comparison is a nontrivial task

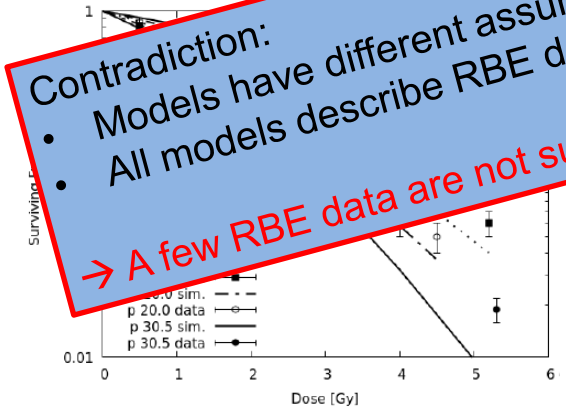
Stewart et al., Phys. Med. 2018

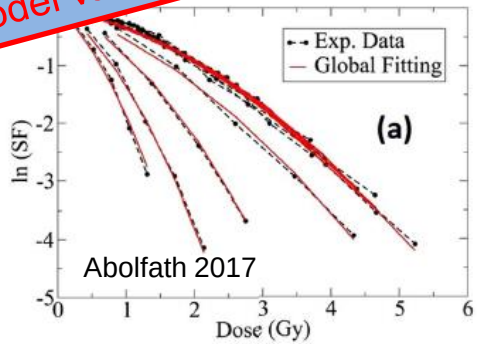


Who's right









Contradiction:

- Models have different assumptions and make different statements
- All models describe RBE data well

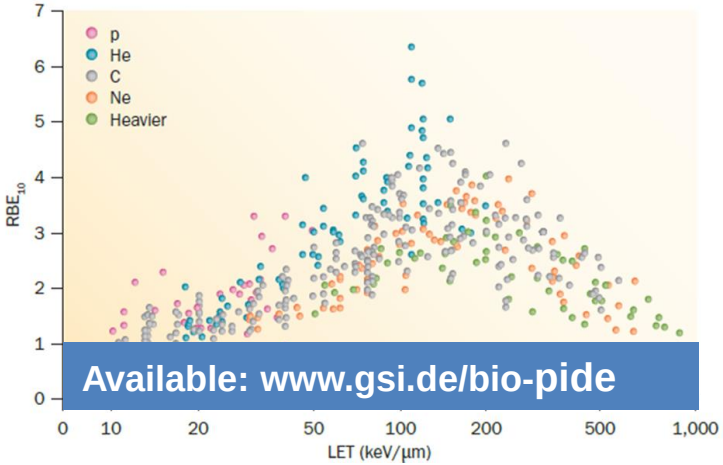
→ A few RBE data are not sufficient for model validation!

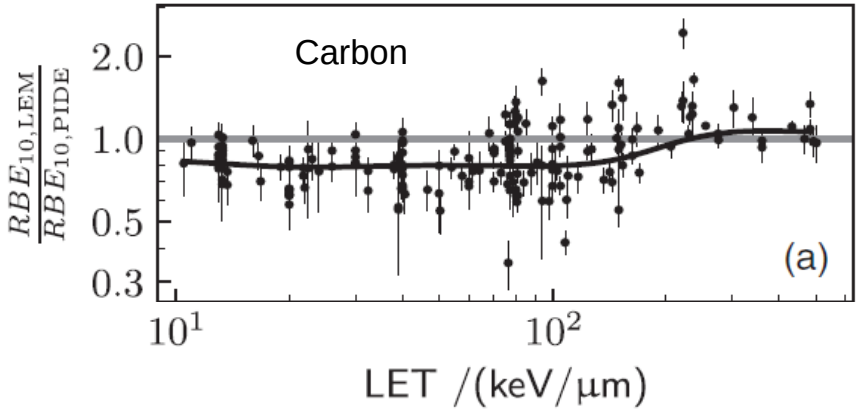
Model benchmarking

- Particle irradiation data ensemble (PIDE)
  - Collection of in-vitro survival data
  - > 1100 photon and ion effect curves
  - Different cell lines, radiation qualities, …
  - Suitable for model validation

Version 3.4
ParticleIrradiationDataEnsemble
www.gsi.de/bio-pide
A GSI biophysics project

Friedrich et al., J. Radiat. Res. 2013
Friedrich et al., J. Radiat. Res. 2021

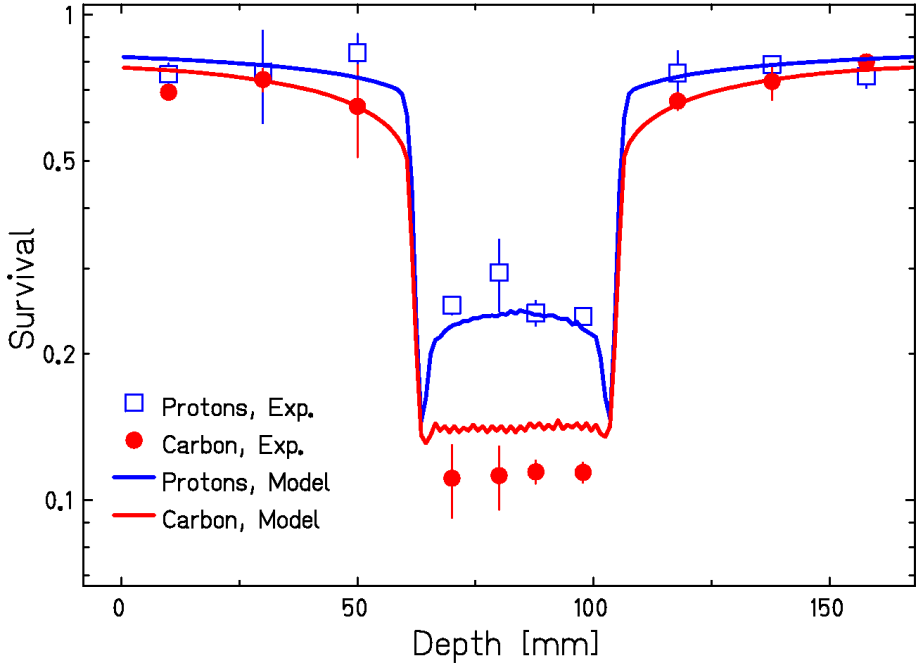




Pfuhl et al., Med. Phys. 2022

Model benchmarking

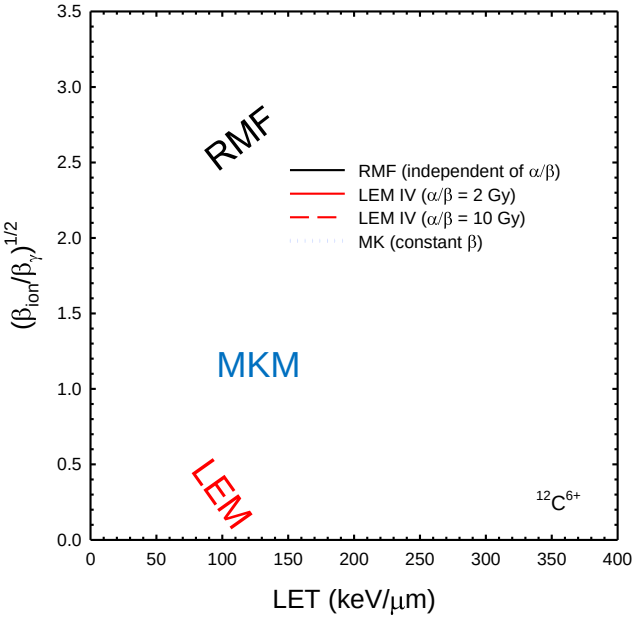
Extended Bragg peaks for therapy



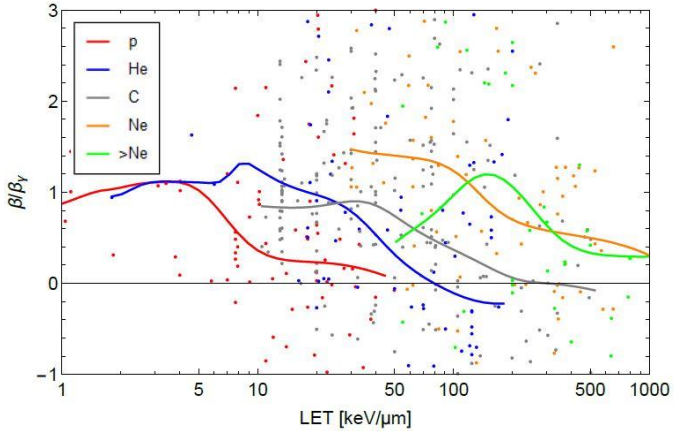
LEMIV (Elsässer et al., IJROBP 2010)

Check model predictions

- Different models make different predictions
- Example: Course of the β term with LET



Stewart et al., Phys. Med. 2018



Friedrich et al., J. Radiat. Res. 2013

Friedrich et al., J. Radiat. Res. 2021

Rat spinal cord irradiations

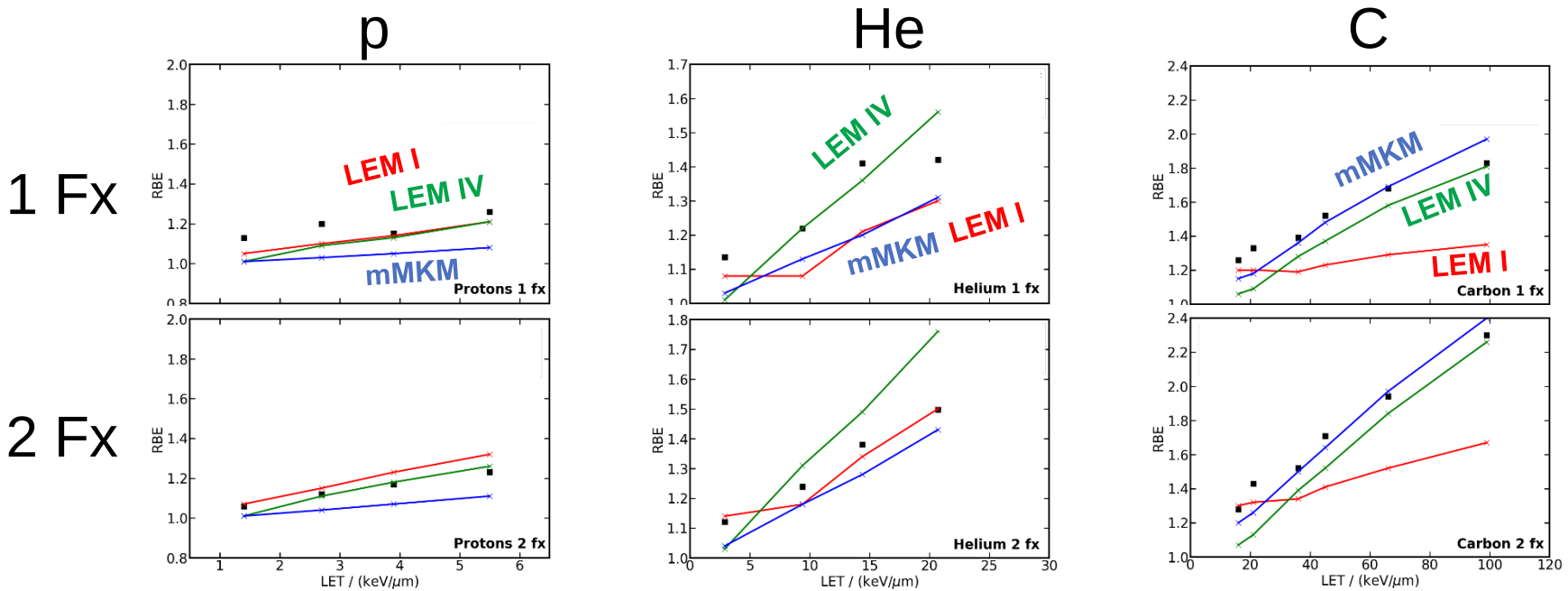
- Comprehensive experiment: Irradiation of rat spinal cord
  - In different positions of SOBP (physically optimized)
  - For p, He and C
  - 1 and 2 Fx
- Endpoint: myelopathy
- Detect RBE for tolerance dose TD50
- Modeling:
  - LEM I, LEM IV, mMKM
  - Same linear-quadratic parameters used

Debus et al., Radiat. Res. 2003
Karger et al., IJROBP 2006
Mein et al., JROBP 2020
Scholz et al., Front. Phys 2020
Hintz et al., Radiother Oncol 2022

Rat spinal cord: Model predictions

- Implementation of LEM versions and mMKM
- (Re)calculations courtesy K. Hilt / C. Deglow

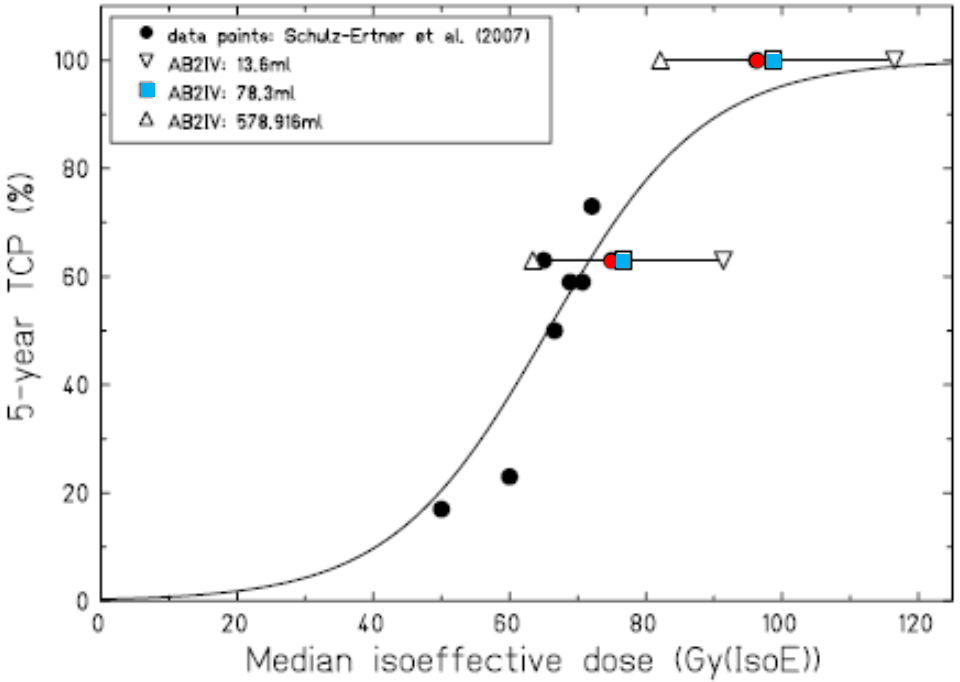
Mein et al., JROBP 2020
Scholz et al., Front. Phys 2020
Hintz et al., Radiother Oncol 2022



Skull based chordoma

- 96 patients, 1997-2005
- 20 x 3 Gy(RBE)
  EQD2 = 75 Gy
- LEM I with α/β = 2 Gy used for treatment planning

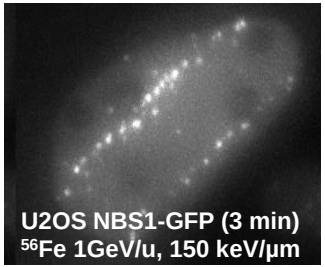
  Schulz-Ertner et al., IJROBP 2007
- LEM I: In agreement with prior data
- Forward calculation with LEM IV: In agreement as well

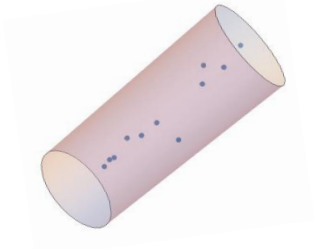


Grün et al., PMB 2012

Modeling across endpoints: Consistency

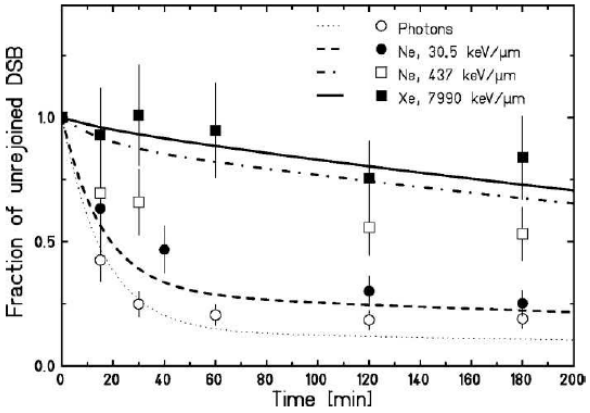
DSB induction





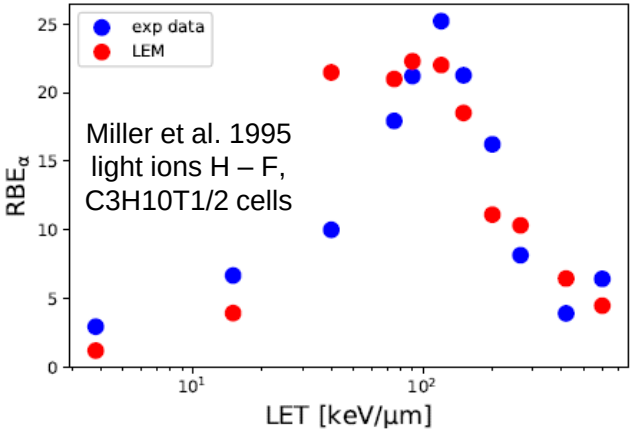
Baiocco et al., REB 2022

DSB rejoining kinetics



Tommasino et al., Radiat. Res. 2013

Cell transformation



A. Hufnagl et al., Radiat. Res. 2021

- Also: Temporal effects (split dose, …), mixed fields (e.g. fragmented beams)

Agenda

Radiobiology of particles

- Introduction
- High LET effects to DNA, cells and tissues
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RBE of protons and carbon ions

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- Modelling
- Model validation & comparison
- Clinical implementation

Effects of complex radiation fields

- Coexistence of different radiation qualities
  - SOBP is composed of multiple pristine Bragg peaks
  - Remaining particle energy and LET vary for each beam
    → Biologic effect different for each beam
  - Superposition? Response calculated by a microdosimetric method (Zaider / Rossi)

$$\bar{\alpha} = \frac{\sum_i D_i \alpha_i}{\sum_i D_i} \quad \text{and} \quad \sqrt{\bar{\beta}} = \frac{\sum_i D_i \sqrt{\beta_i}}{\sum_i D_i}$$

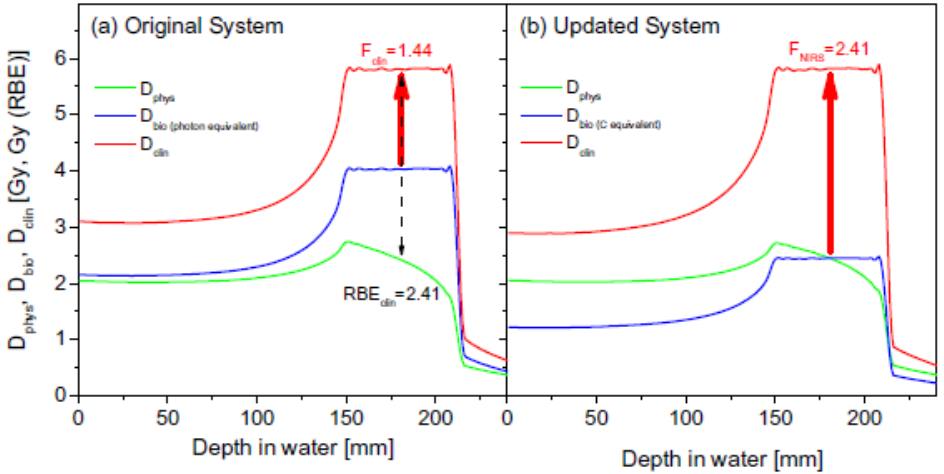
LEM I application in clinical application

- RBE tables: Provide single particle RBE values ('single particle approximation')
  - Relevant ions p-C
  - Relevant energies

- Treatment planning system:
  - Calculate mixed beam properties (Zaider-Rossi)
  - Include hit statistic correction to account for overkill
- Clinical use (EM I): Mostly photon α/β = 2 Gy table (designed for skull based chordoma)
- Problems:
  - Exploitation of photon reference to very high doses
  - Overestimation of RBE with LEM I for low LET (~entrance channel)

MKM application in clinical application

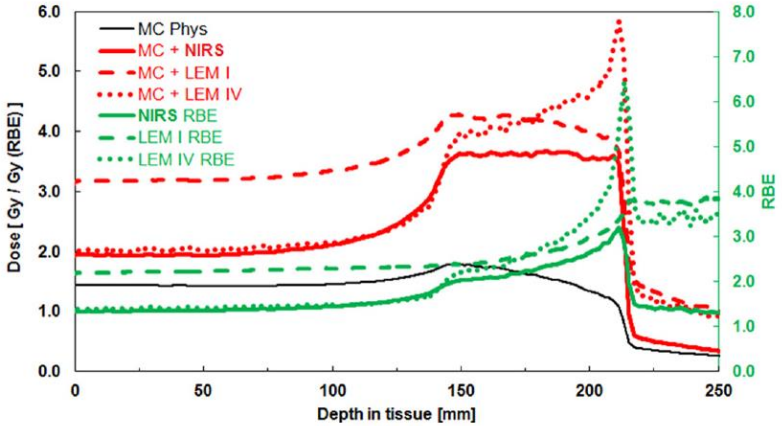
- Assume Human Salivary Gland (HSG) as representing tumor tissue
- Calculate RBE for 10% HSG survival (a/b ~ 6 Gy, blue)
- Optimize physical dose (green)
- Fix RBE in mid SOBP
  → Scale to „clinical dose“ used for describing and reporting
- Since 2015: Carbon ions as reference



Inaniwa, PMB 2015

Different models, different predictions

- Compare shape of model predictions:
  NIRS approach optimization
  → Recalculation with LEM I / LEM IV



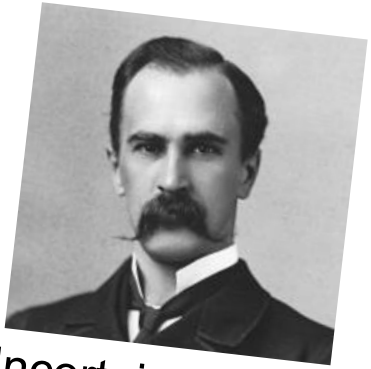
Magro et al., PMB 2017

Switching between models means

- Different RBE weighted doses
- Different LET patterns
- Inhomogeneous dose profiles

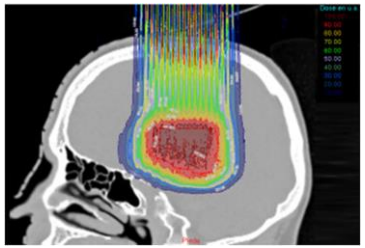
Sources of uncertainties

- Model selection
- Model application (a/b ratio, ...)
- Tissue radiobiology (hypoxia, vascularization,...)
- Cancer radiobiology (stem cells, ...)
- Positioning
- Interindividual deviation

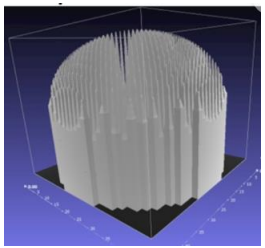


„Uncertainty is the rule in medicine“ (W. Osler)

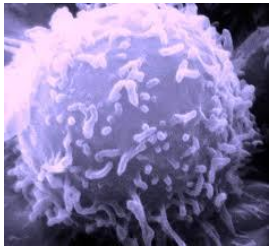
Current hot topics relating to RBE



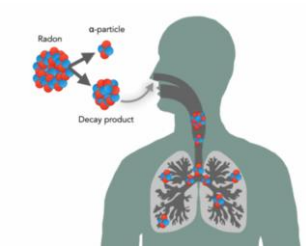
Spatial Fractionation



Flash



Radioimmunotherapy



High LET carcinogenesis

...

... and upright positioning!

Lessons learned

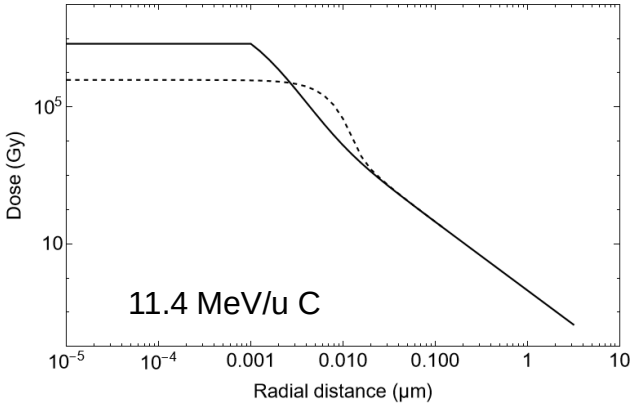
- For particle radiation, RBE has to be accounted for
- Despite simple definition, complicated quantity
- Typically RBE higher in SOBP than in entrance channel due to LET
  → exploitable in therapy
- Protons: 1.1 used in clinics, models predict higher RBE at distal end of SOBP
- Modeling is always a tradeoff between detailedness and oversimplification
- Two classes of RBE models: MKM and LEM based
- Further assumptions involved for clinical implementation (biologic system)
- Predictions vary between models
- RBE predictions have uncertainty for many reasons

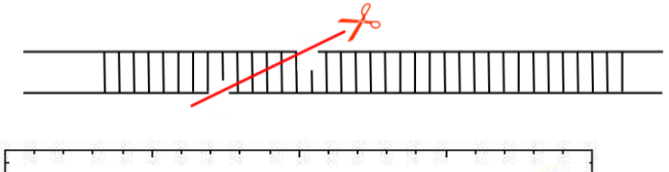
Contact: t.friedrich@gsi.de

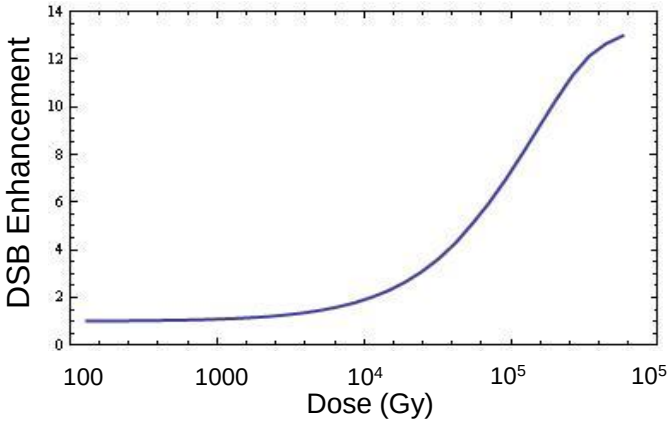
Spare Slides

LEM II and LEM III: Improvements

- LEM II
  - Get more DSB by clustering of single strand breaks
  - Dispersion of energy by free radical diffusion







- LEM III
  - Core radius becomes energy dependent

➢ Get better RBE description in entrance channel

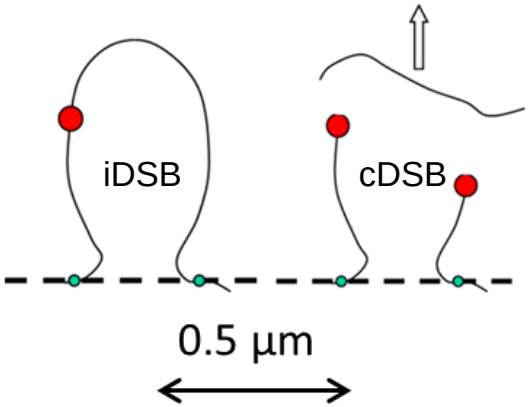
Elsässer et al., Radiat. Res. 2007

Elsässer et al., IJROBP 2008

Elsässer et al., New J. Phys. 2008

LEM IV: Towards mechanistic consistency

- Include DSB distribution
- Distinguish DSB in 2Mbp chromatin loops
  - isolated DSB (iDSB)
  - clusteres DSB (cDSB)



LEM IV

Average over local damage concentration

Elsässer et al., IJROBP 2010
Friedrich et al., IJRB 2012
Friedrich et al., PMB 2013

→ Determine effect from photon exposure with same local DSB concentration
→ Valid for all ion species (validated up to ^{20}Ne)
→ Reasonable predictions for all energies

LEM IV vs PIDE

- Particle irradiation data ensemble (PIDE)
  - Collection of in-vitro survival data
  - > 1100 photon and ion effect curves
  - Different cell lines, radiation qualities, …
  - Suitable for model validation

Version 3.4
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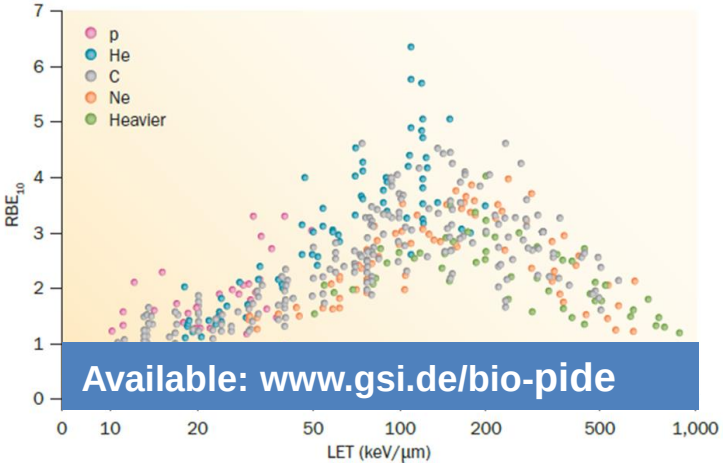
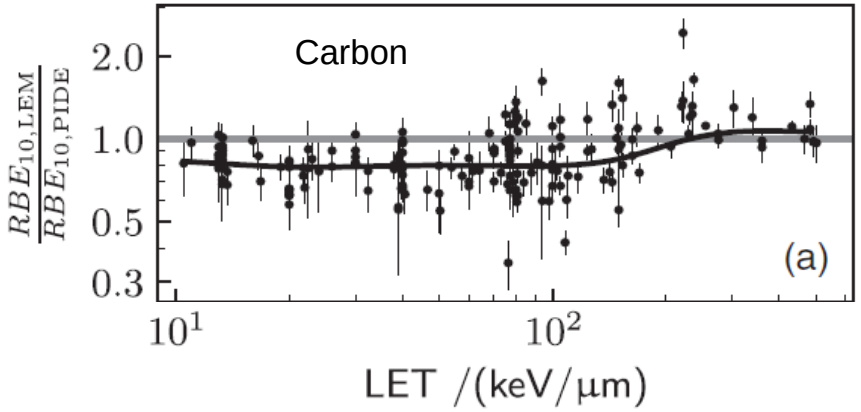
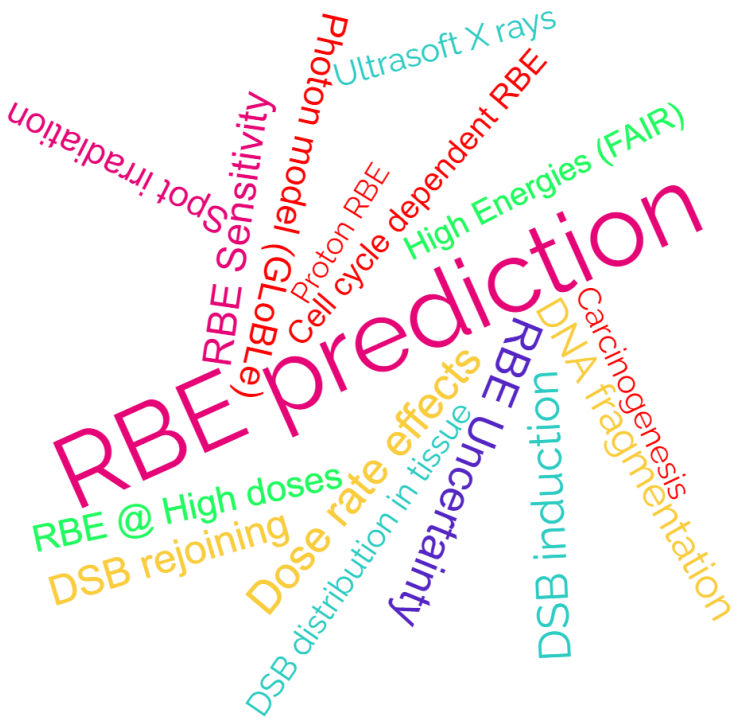




Pfuhl et al., Med. Phys. 2022

In vitro validation: the big picture



- LEM IV limitations quantified
- Model agreement for many situations
  - Endpoints
  - Applications
  - Radiation types & deliveries
- Model is consistent
  - Reflects numerous experimental findings
  - Allows for mechanistic interpretations

Rat spinal cord irradiation

- Comprehensive experiment: Irradiation of rat spinal cord
  - In different positions of SOBP (physically optimized)
  - For p, He and C
  - 1 and 2 Fx
- Endpoint: myelopathy
- Detect RBE for tolerance dose TD50
- Modeling:
  - LEM I, LEM IV, mMKM
  - Same linear-quadratic parameters used

Debus et al., Radiat. Res. 2003
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Mein et al., JROBP 2020
Scholz et al., Front. Phys 2020
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- Implementation of LEM versions and mMKM
- (Re)calculations courtesy K. Hilt / C. Deglow

Mein et al., JROBP 2020
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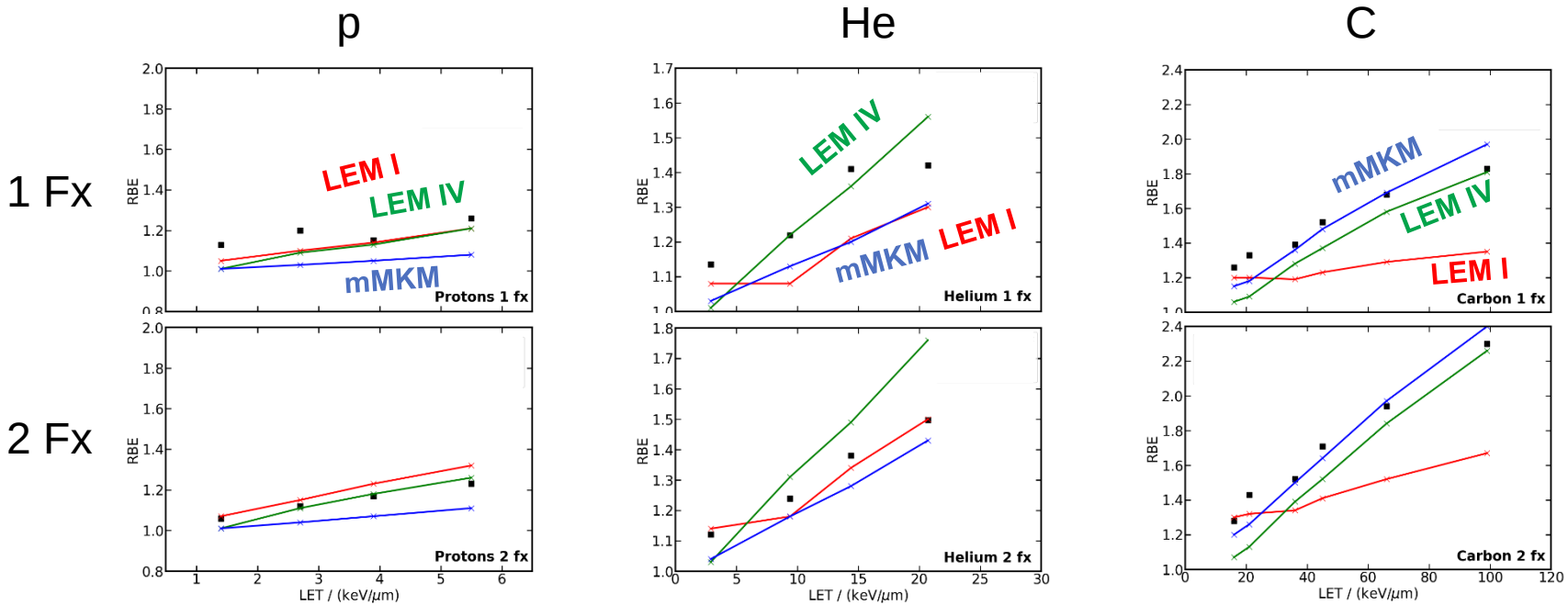
Hintz et al., Radiother Oncol 2022



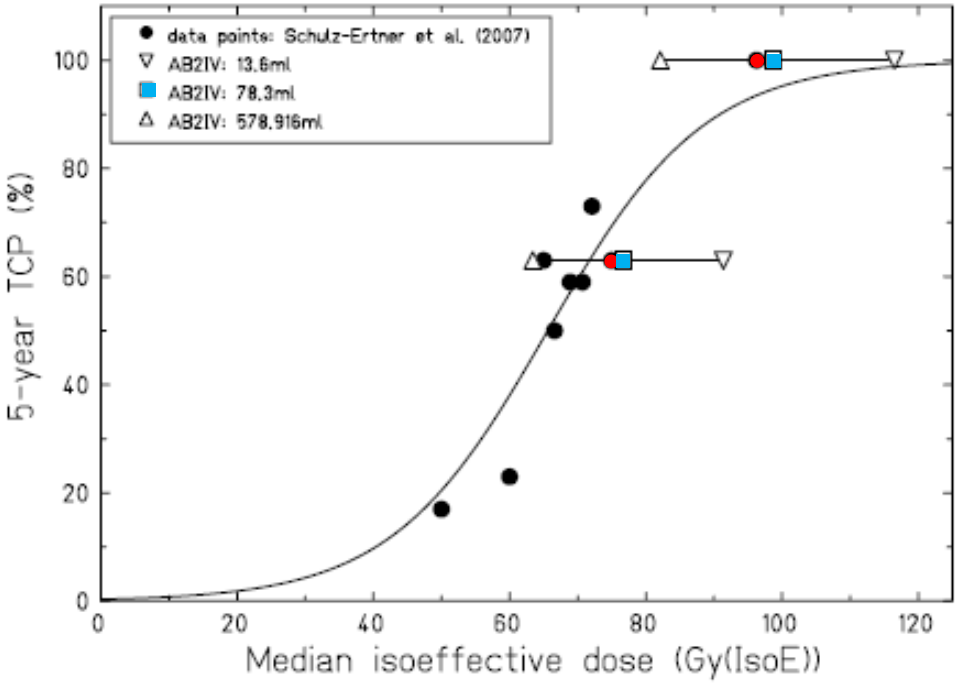
Skull based chordoma

- 96 patients, 1997-2005
- 20 x 3 Gy(RBE)
  EQD2 = 75 Gy
- LEM I with α/β = 2 Gy used for treatment planning

Schulz-Ertner et al., IJROBP 2007

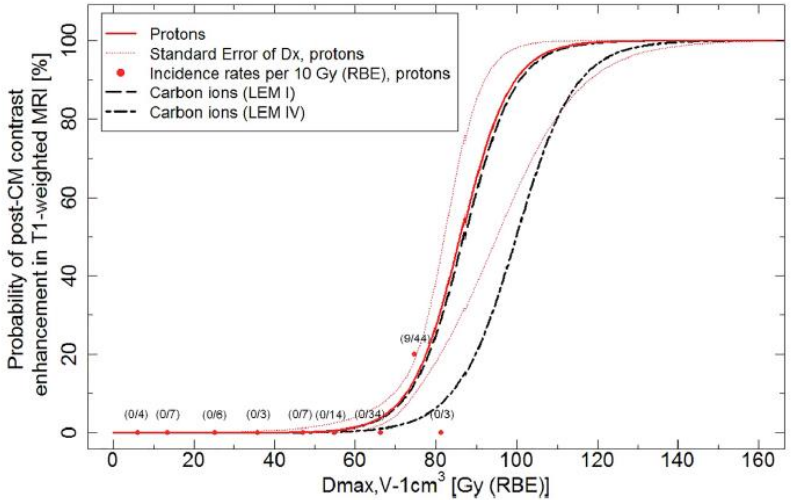
- LEM I: In agreement with prior data
- Recalculation with LEM IV: In agreement as well

"[...] the transition to LEM IV is not expected to lead to significant differences of the TCP dose-response relationship for chordoma as compared to the analysis based on LEM I."



Grün et al., PMB 2012

Temporal lobe reactions



Gillmann et al., Radiother. Oncol. 2018

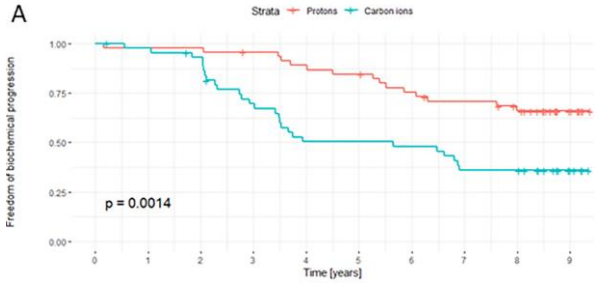
- Skull base tumors
- Temporal lobe reactions detected as image change
- Carbon doses calculated by LEM I coincides with proton curve, provided
  - Dosimetric variable D_{max} in V-1 cm^3
  - α/β = 2 Gy
  - Proton RBE = 1.1

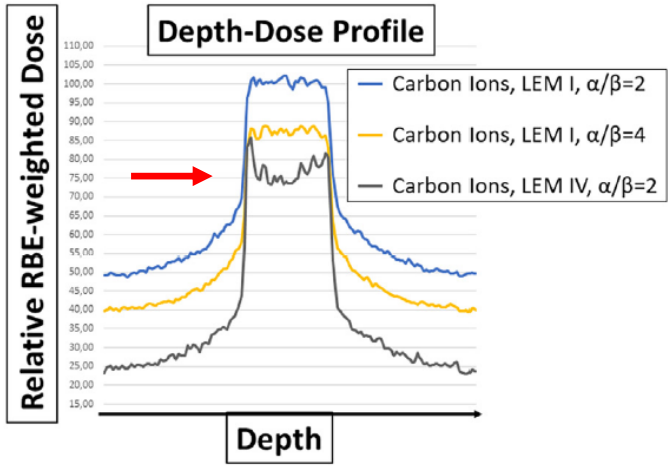
➢ Assumptions crucial for assessment

➢ Large uncertainty due to assumptions
→ No clear conclusion on model

Prostate tumors: LEM I overestimates RBE

- Carbons & protons @ prostate cancer
- Carbon inferior to protons (!)
- NIRS experience:
  88 Gy(RBE) ‘clinical dose’
- Optimization with LEM I
  → Only as effective as ~66 Gy(RBE)
  → LEM I overestimates RBE
- Possible alternatives
  - Retune LEM I with α/β = 4 Gy
  - LEM IV





Eichkorn et al., Radiother. Oncol. 2022

Comparison of RBE approaches

- Comparison of NIRS/HIMAC and European approach
  → Translate doses

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Physics Contribution

Mapping of RBE-Weighted Doses Between HIMAC– and LEM–Based Treatment Planning Systems for Carbon Ion Therapy

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Steinsträter et al., IJROBP 2012

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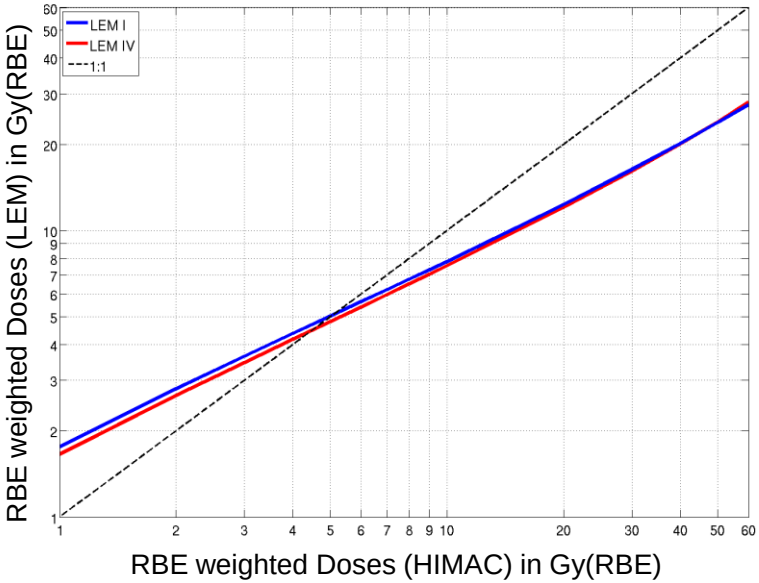
Dose prescription in carbon ion radiotherapy: a planning study to compare NIRS and LEM approaches with a clinically-oriented strategy

Piero Fossati[1,2,4,5], Silvia Molinelli[1], Naruhiru Matsufuji[3], Mario Ciocca[1], Alfredo Mirandola[1], Andrea Mairani[1], Junetsu Mizoe[1,3], Azusa Hasegawa[3], Reiko Imai[3], Tadashi Kamada[3], Roberto Orecchia[1,2,4] and Hirohiko Tsujii[3]

Fossati et al., PMB 2012

Translation of doses



Steinsträter et al., IJROBP 2012

- HIMAC approach (clinical dose) vs LEM based RBE weighted dose
- Turnover at ~5 Gy
- Further studies: TP and tolerance doses

Molinelli *et al.*, Radiother. Oncol. 2016
Wang *et al.*, Radiother. Oncol. 2020
Molinelli *et al.*, Radiother. Oncol. 2021

Report exactly how RBE is obtained. Say what you do!

ICRU Report **93** (2016)

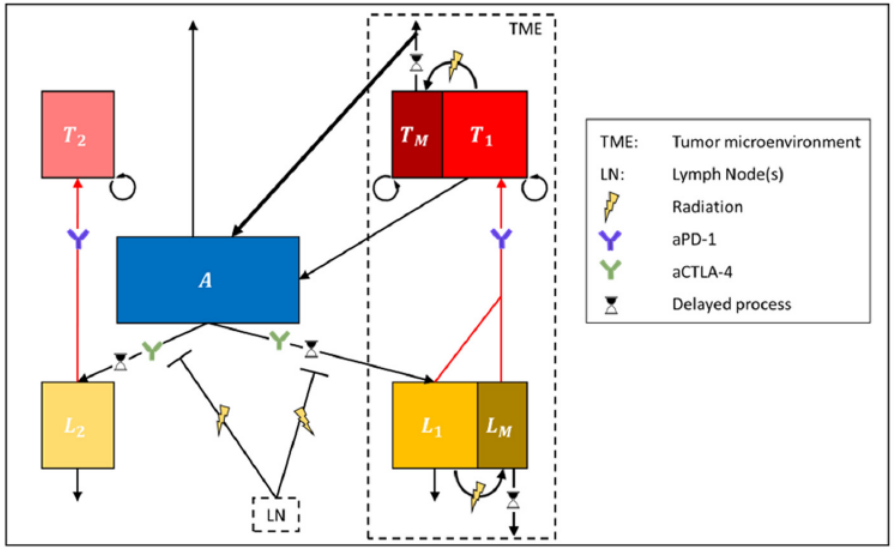
The COSMIC Proposal

- We have multiple models
  - LEM I (α/β = 2 Gy), mMKM + scaling
  - MCF-MKM, LEM IV
  - We may have more in future
- Pragmatic solutions needed for comparison
- Proposal to PTCOG for small consortium:
  Consensus statements on modelling in carbon ion therapy (COSMIC)
  - Experts in carbon RBE modelling
  - Pragmatic strategies to facilitate model application and comparison
  - Define situations of maximum model deviations
  - Find consensus statements about strategies to avoid misconceptions

Particle Therapy Co-Operative Group

GSI Radioimmunotherapy Model

- Consider
  - Compartments: Tumor cells, lymphocytes, damage signals
  - Agents: Radiation, immune checkpoint inhibitors



Friedrich et al., IJROBP 2022

$$\dot{T}_1 = \mu_1 T_1 - f_P(L_1 + L_M) - (1 - S_T)\sum_k \delta(\tau_k)\, T_1 \quad (1)$$

$$\dot{T}_M = (1 - S_T)\sum_k T_1(t_k) e^{\int_{t_k}^{t} \mu_1(t')dt'} \left(\mu_1 I(\tau_k) - D_K(\tau_k)\right) + (1 - S_T)\sum_k \delta(\tau_k)\; T_1 \quad (2)$$

$$\dot{T}_2 = \mu_2 T_2 - f_P a L_2 \quad (3)$$

$$\dot{A} = \rho(T_1 + T_2) - \lambda A + \psi(1 - S_T)\sum_k T_1(t_k) e^{\int_{t_k}^{t} \mu_1(t')dt'}\, D_K(\tau_k) \quad (4)$$

$$\dot{L}_1 = \mu_L L_1 + d - f_P L_1 - (1 - S_L)\sum_k \delta(\tau_k)\, L_1 \quad (5)$$

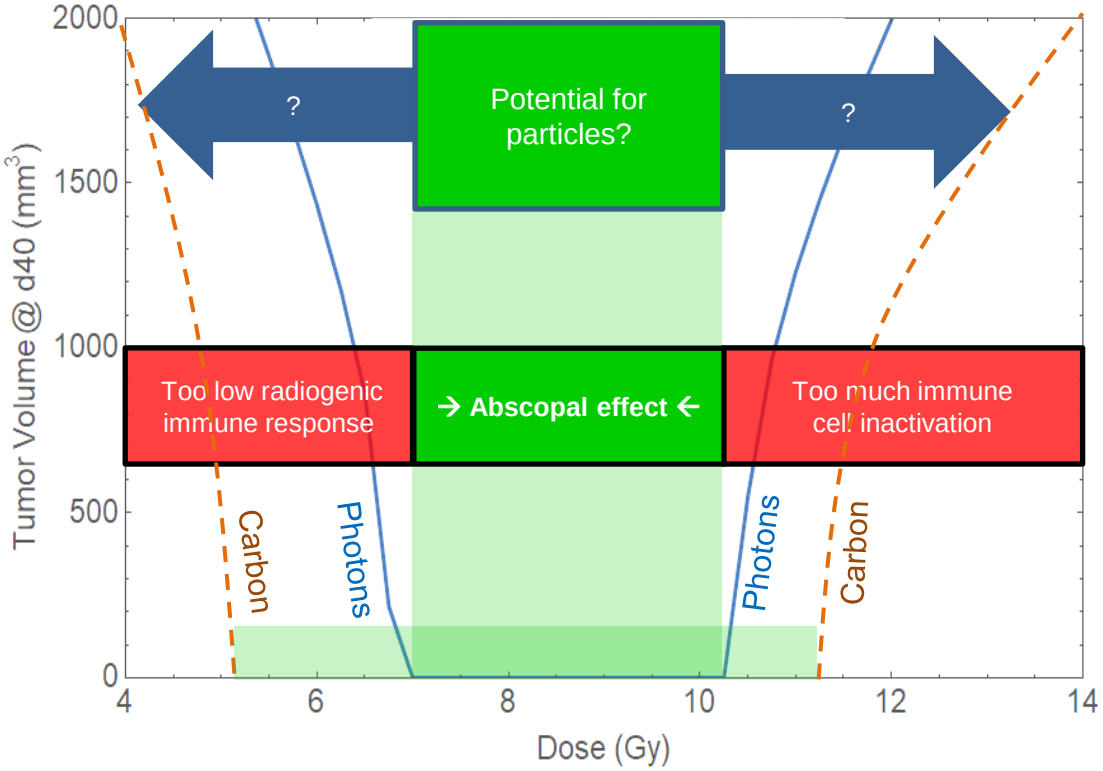
$$\dot{L}_M = -f_P L_M + (1 - S_L)\sum_k \delta(\tau_k)\, L_1 + (1 - S_L)\sum_k L_1(t_k)\, e^{\mu_L \tau_k} (\mu_L\, I(\tau_k) - D_K(\tau_k)) \quad (6)$$

$$\dot{L}_2 = \mu_L\, L_2 + d \quad (7)$$

$$d = \int_0^t S_{LN}{}^{n(t')} A(t') f_c(t') D_R(t - t')\, dt' \quad (8)$$

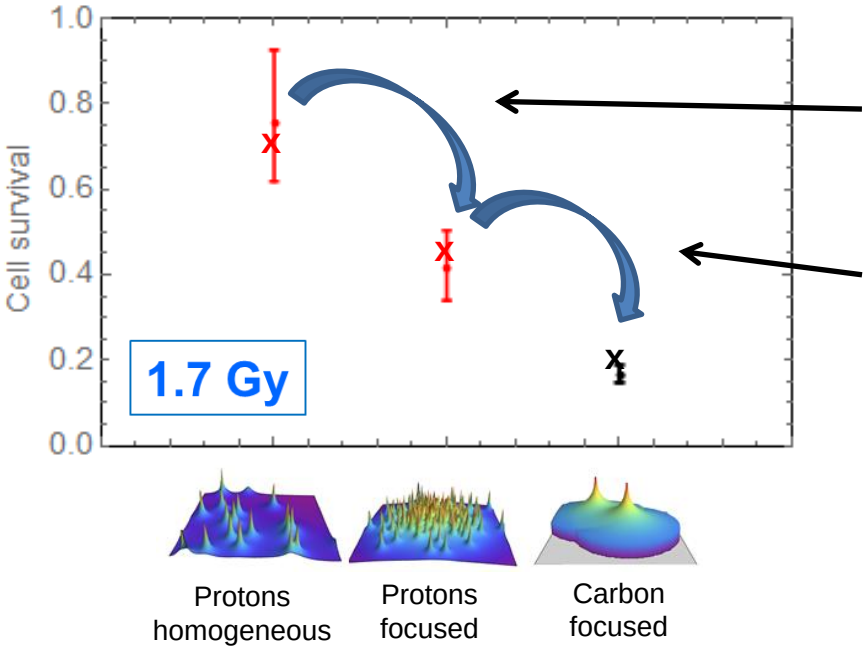
Potential for ions

- Prospective calculations for synthetic tumors
- Irradiate primary tumor, consider abscopal response
- Abscopal effect is expected only under certain conditions
- Can we broaden the dose window with particles?
- Preliminary calculation: Yes

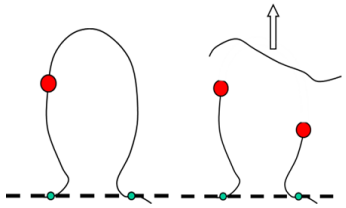


LEM IV vs spot irradiation experiment

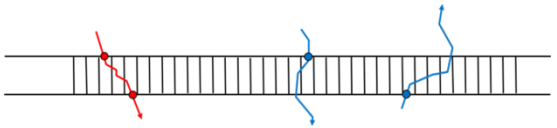
- Microbeam focused particle spots were used to investigate RBE



µm lesion interaction (DSB proximity)



nm lesion interaction (DSB number)

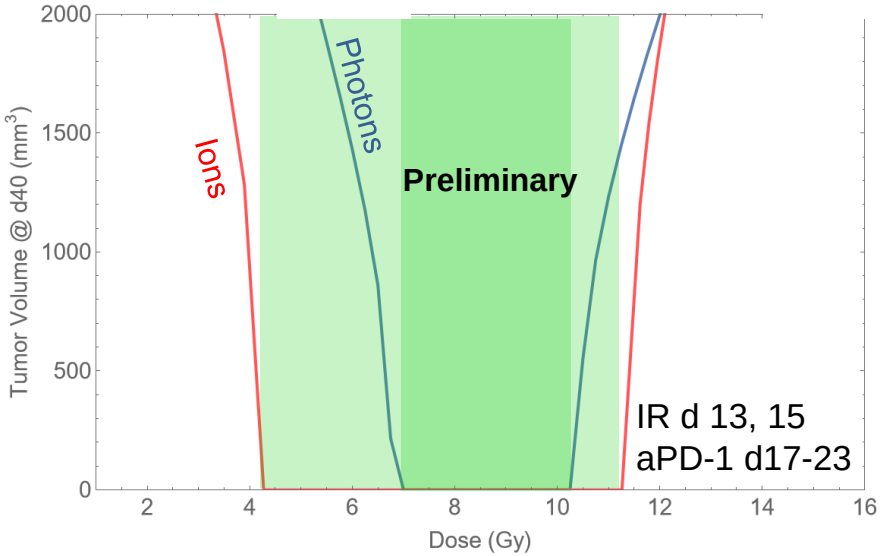


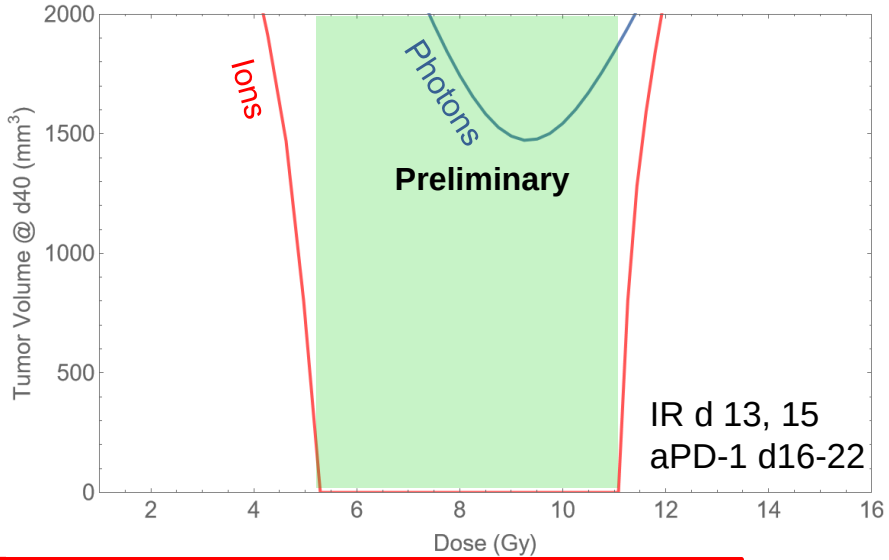
Bundesministerium für Bildung und Forschung
KVSF Kompetenzverbund Strahlenforschung

Friedrich et al., Sci. Rep. 2018

→ Coexistence of lesion interaction mechanisms

Prospective effects of Carbon Ions





Carbon ions are predicted to

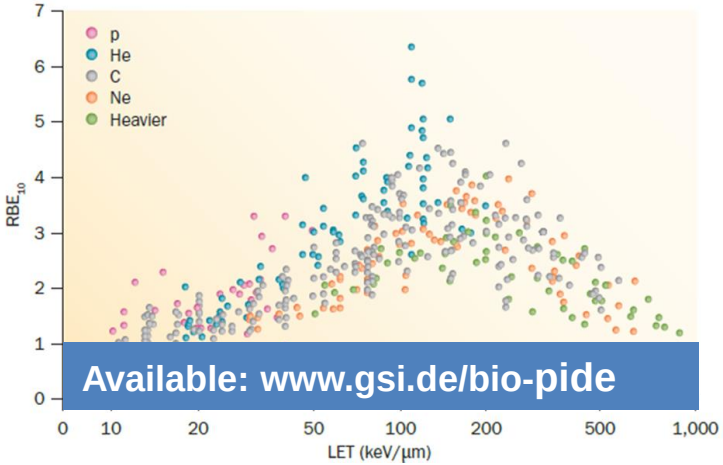
- broaden or open the dose window for abscopal effects (more immunogenic, less immunosuppression by lymphocyte kill)
- overcome strong sensitivity on scheduling

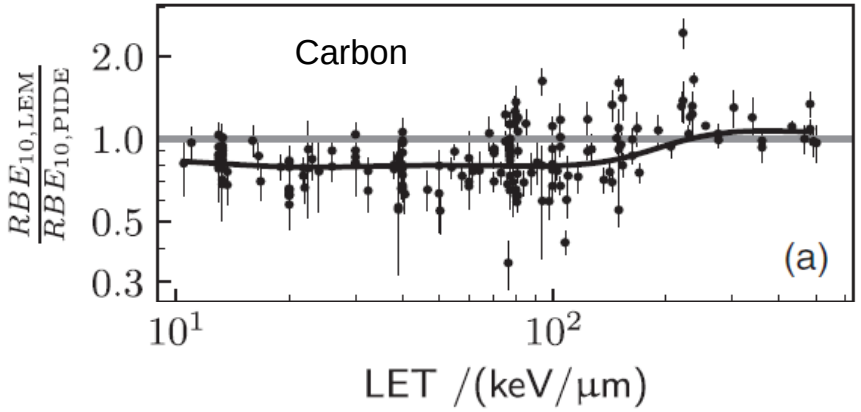
Lem iv vs pide

- Particle irradiation data ensemble (PIDE)
  - Collection of in-vitro survival data
  - > 1100 photon and ion effect curves
  - Different cell lines, radiation qualities, …
  - Suitable for model validation

Version 3.4
ParticleIrradiationDataEnsemble
www.gsi.de/bio-pide
A GSI biophysics project

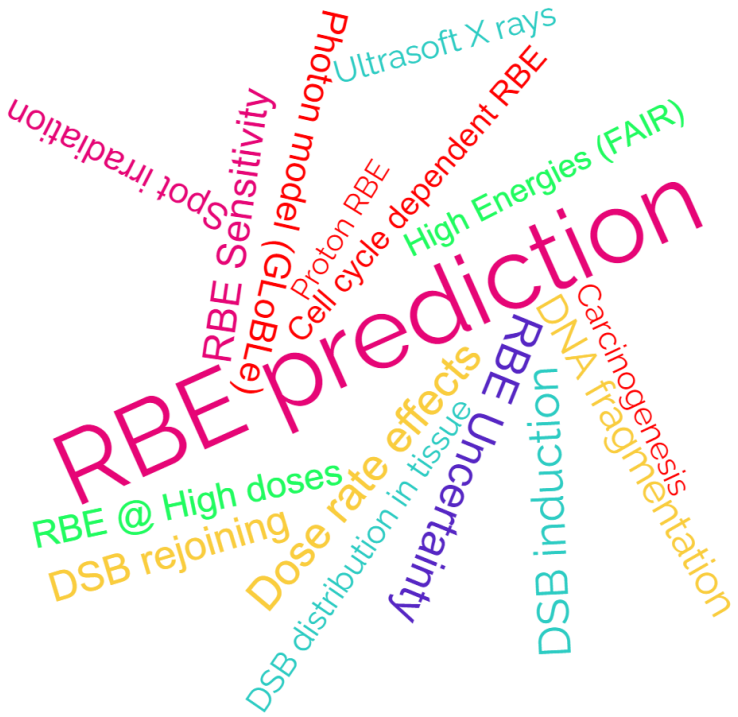
Friedrich et al., J. Radiat. Res. 2013
Friedrich et al., J. Radiat. Res. 2021



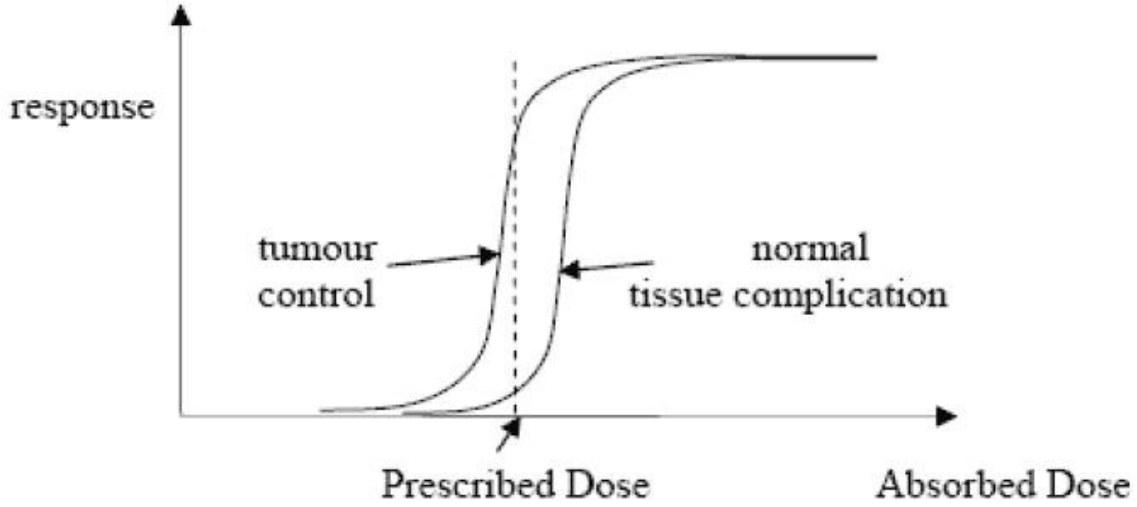


Pfuhl et al., Med. Phys. 2022

IN-VITRO VALIDATION: THE BIG PICTURE



- LEM IV limitations quantified
- Model agreement for many situations
  - Endpoints
  - Applications
  - Radiation types & deliveries
- Model is consistent
  - Reflects numerous experimental findings
  - Allows for mechanistic interpretations

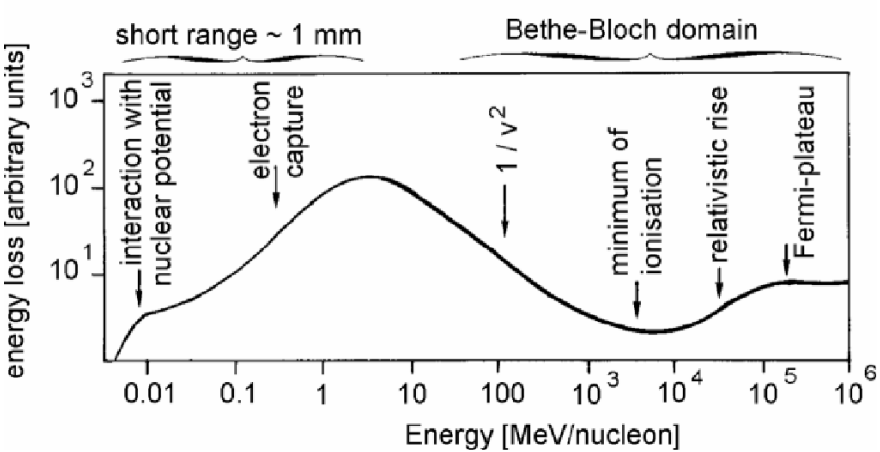


Ziel jeder Therapie: Maximierung der Fensterbreite

Interactions: Ions

- Bethe's eqution

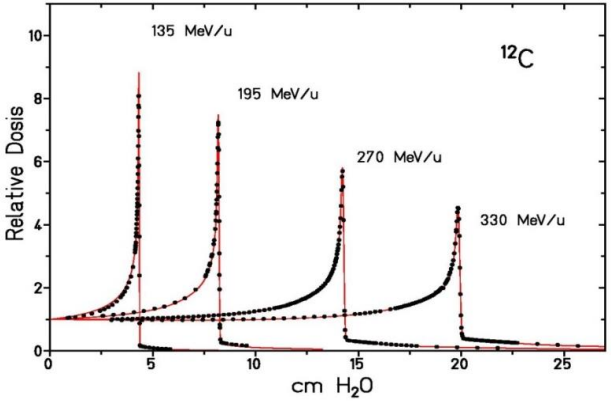
$$-\frac{dE}{dx} = \frac{Z_p^2 e^4 n_e}{4\pi\varepsilon_0^2 v_p^2 m_e}\left\{\ln\left(\frac{2m_e v_p^2}{\langle E_B^e \rangle}\right) - \ln\left(1-\beta^2\right) - \beta^2\right\}$$



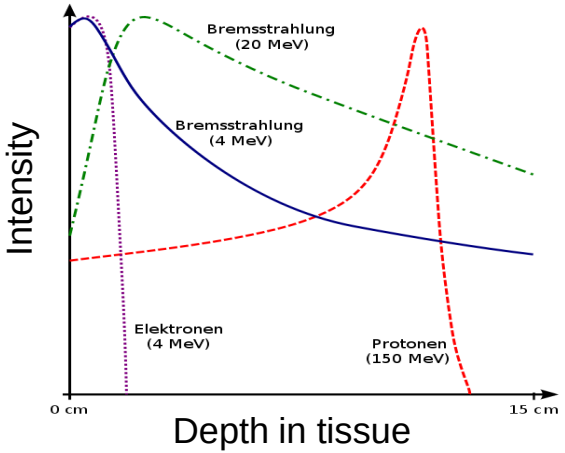
Energy loss per path length
=
"Stopping Power"
=
Linear Energy Transfer (LET)

→ Ions deliver most of their energy where they stop, in the "Bragg peak"

Bragg peak and ion therapy



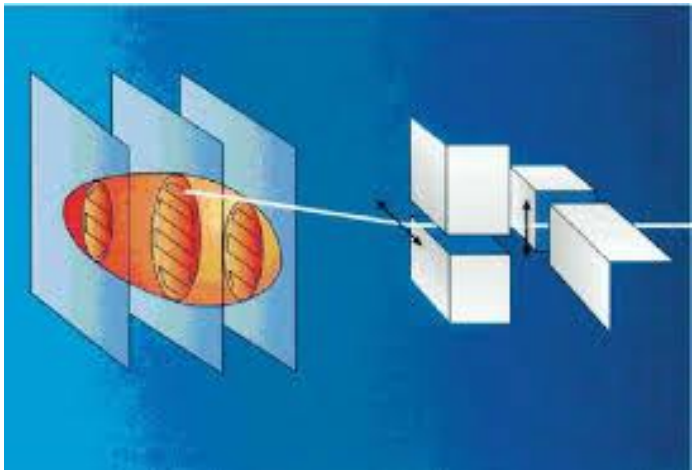
Schardt et al., Rev. Mod. Phys. 2010



- Conventional radiation therapy: Photons
- Ion therapy has two main advantages:
- - “Bragg peak”: Most of dose in tumor volume
  - Extreme high energy concentration
    → more severe lesions → increased biologic effect

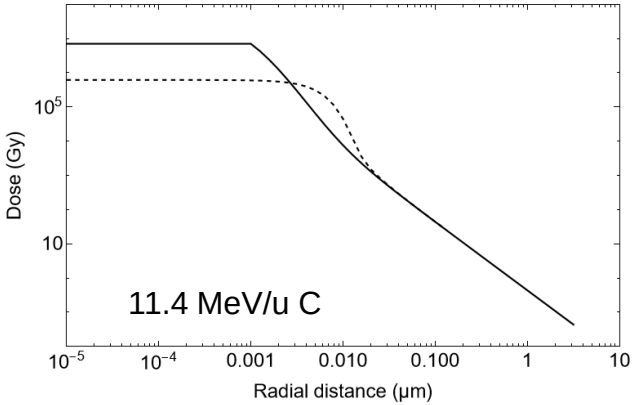
Particle therapy

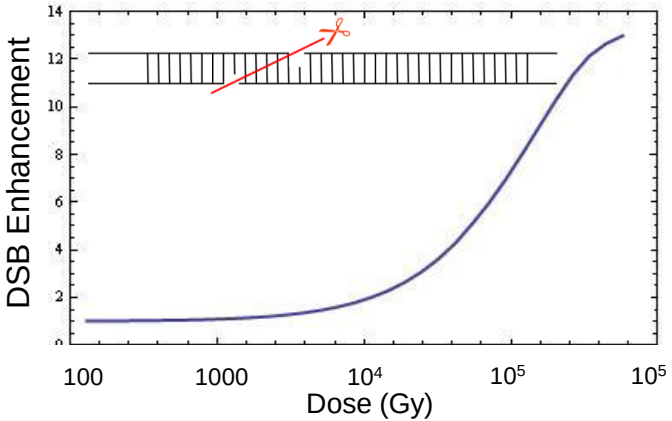
- Particle therapy of cancer
  - Many proton centers worldwide, protons in Trento
  - Carbon facilities in Japan and Europe, soon in the US



Lem ii and lem iii: Improvements

- LEM II
  - Get more DSB by clustering of single strand breaks
  - Dispersion of energy by free radical diffusion





Elsässer et al., Radiat. Res. 2007

Elsässer et al., IJROBP 2008

Elsässer et al., New J. Phys. 2008

- LEM III
  - Core radius becomes energy dependent

Get better RBE description in entrance channel

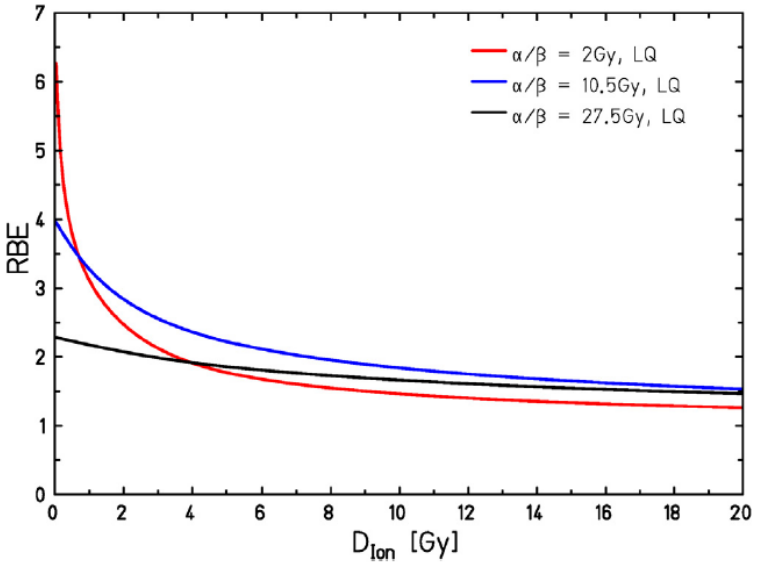
Proton RBE

- General procedure: RBE = 1.1 (ICRU78) in radiation field, including entrance channel
  - Possible reasons: High LET target fragments, more weight for low energetic electrons as compared to photons
  - Motivation: Old in-vivo data (Tepper, Urano: skin reactions, jejunal crypts, …)
- RBE is commonly regarded as a burden rather than as chance in protons: Try to avoid high LET regions
- First deviations from this ‘dogma’: Use LET_D as surrogate for RBE
  - This deserves a RBE that depends linear on LET
  - Try to homogenize LET distribution, avoid high LET in risk organs

Proton RBE

Hypofractionation

- Sparing effect of normal tissue allows hypofractionation
- However, only few studies with protons (all use RBE = 1.1)
- Probably no RBE effects visible on sound statistical basis
- But: if RBE goes down to zero, the 1.1 dogma implies underdosage!



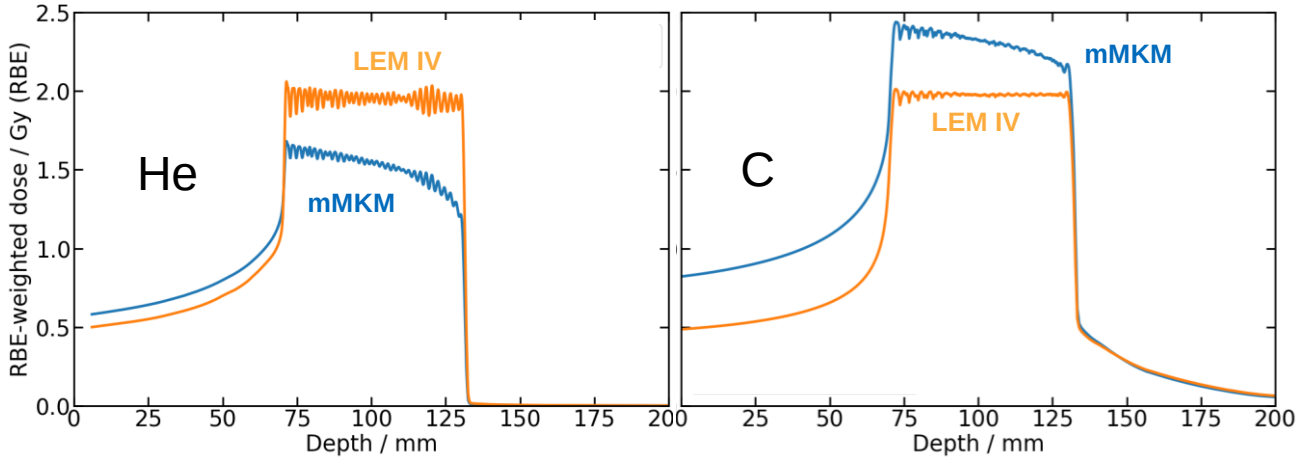
Friedrich et al. Phys. Med. 2014

Planning approach comparison: Conceptual

	mMKM + Scaling	LEM I (α/β = 2 Gy)	LEM IV
Biologic reference	HSG cells (α/β ~ 6 Gy)	α/β = 2 Gy	To be specified
Gy → Gy(RBE)	Mid SOBP: RBE = 2.4 → Scaling factor	Direct dose dependent evaluation	Direct dose dependent evaluation
Track structure model	Kiefer-Chatterjee	Kiefer-Straaten	Kiefer-Straaten
Relevant damage scales	µm	-	µm and nm
Overkill	Saturation correction	Hit statistic correction	Hit statistic correction
β(LET)	Constant	Decreasing	Decreasing

Model comparison: Pure models

- Even comparison for same biologic parameters can be complicated
- Development of a comparison platform
  - Example: LEM IV optimization
    mMKM forward calculation
    → Different systematics for He and C



Courtesy
K. Hilt, C. Deglow