OncoRay – National Center for
Radiation Research in Oncology, Dresden

# Does RBE depend on LET and ion type?

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# Motivation – Challenges with RBE

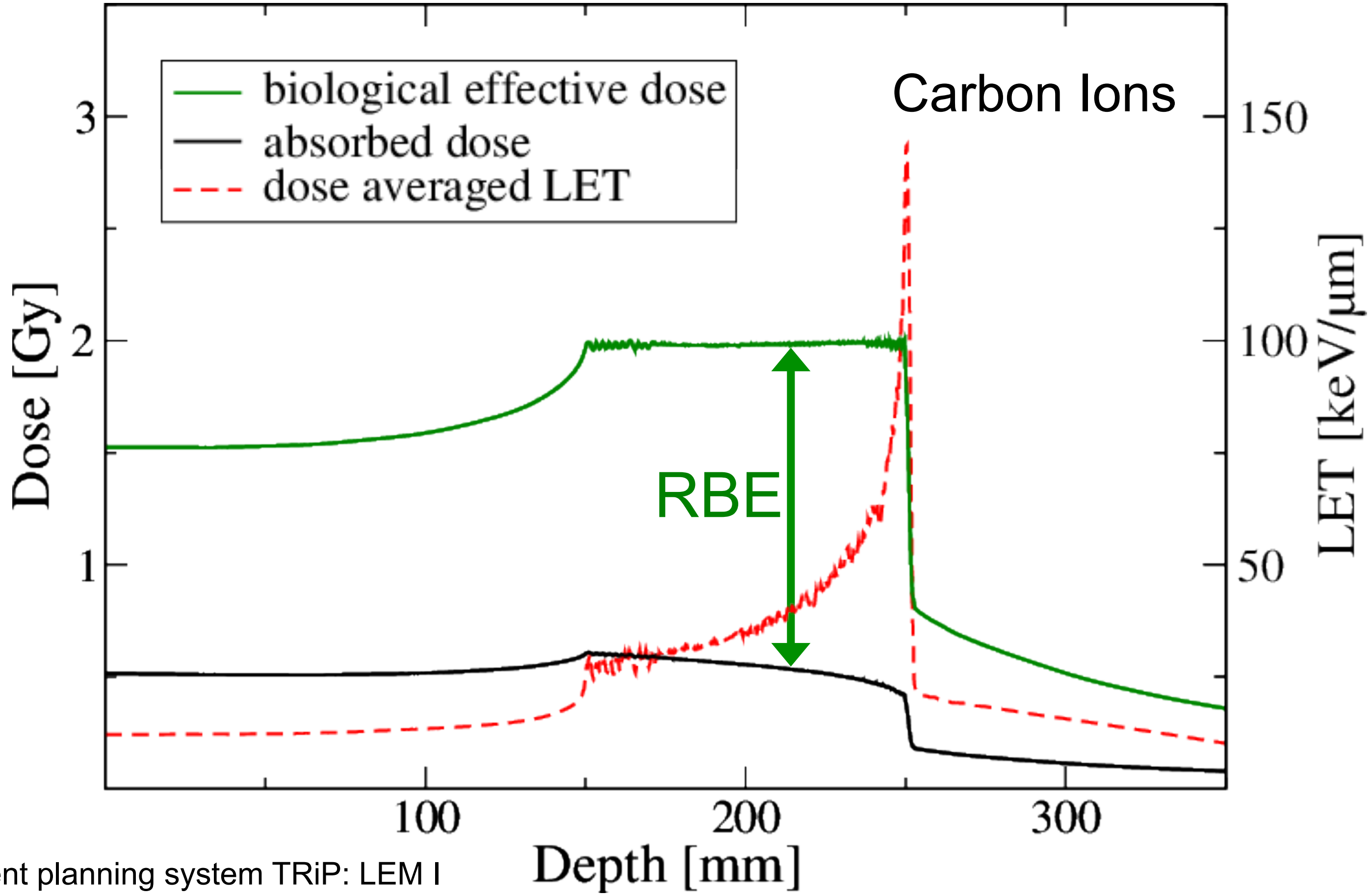
1. Difficult to compare prescribed dose values in carbon ion therapy

2. RBE prescription/description differs between proton and ion therapy

3. Interdisciplinary task – common communication

# Particle therapy

1. **Improved dose distribution**
2. **Higher relative biological effectiveness (RBE)**




Treatment planning system TRiP: LEM I

# RBE – dependence on physics and biology

**RBE depends on many factors, e.g.:**

- Cell line
- Ion energy
- Ion type
- *In vivo* and *in vitro*
- Endpoint
- Microenvironment
- Dose
- Track structure

**Physics**

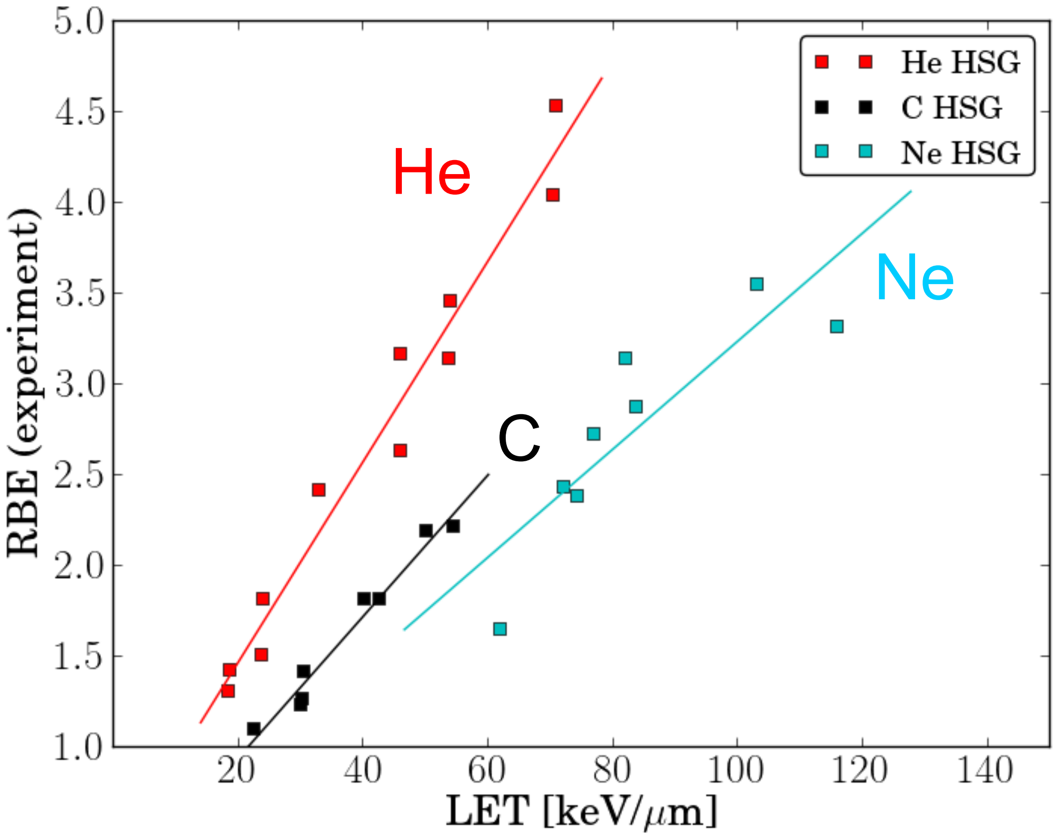
- Ion energy
- Ion type
- LET
- Dose
- Track structure

**Biology**

- Cell line
- *In vivo* and *in vitro*
- Endpoint
- Microenvironment

# RBE *in vitro* data – LET

**Linear energy transfer: LET**

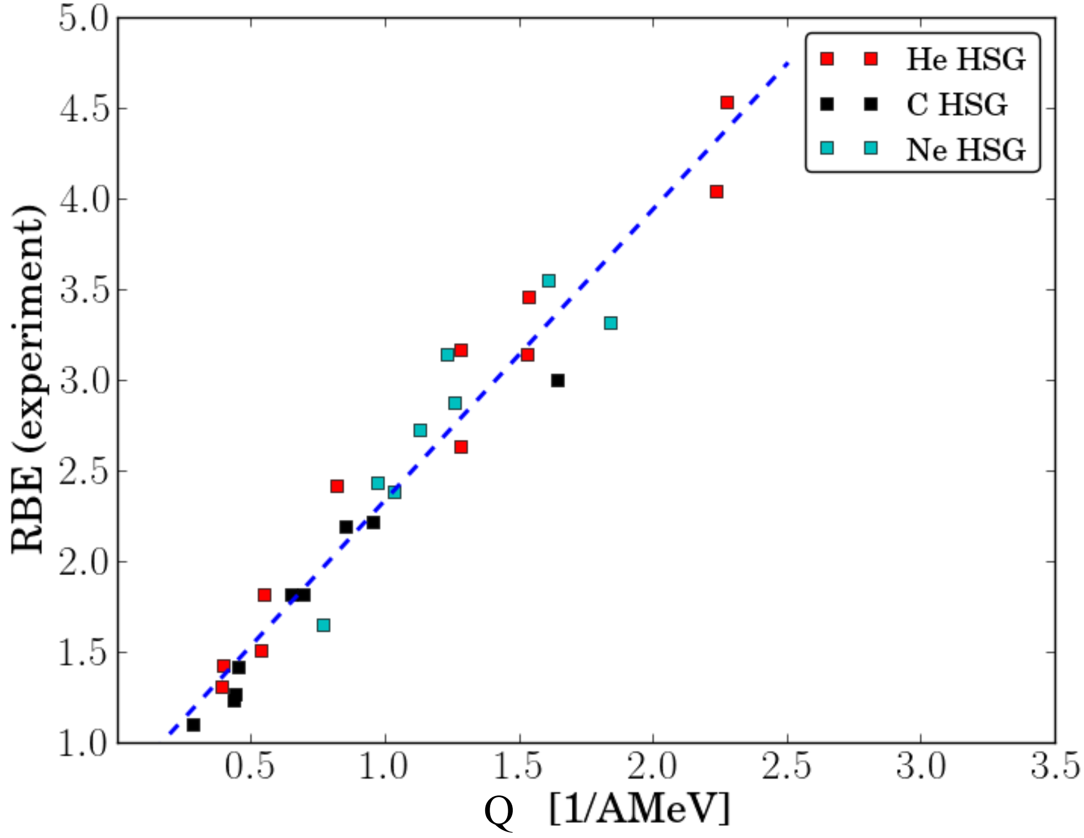



RBE for HSG cell lines, Furusawa et al. 2000

# RBE *in vitro* data – beam quality Q

**Beam quality:** **$Q = Z^2 / E$**

→ Z: charge of particle; E: kinetic energy of particle

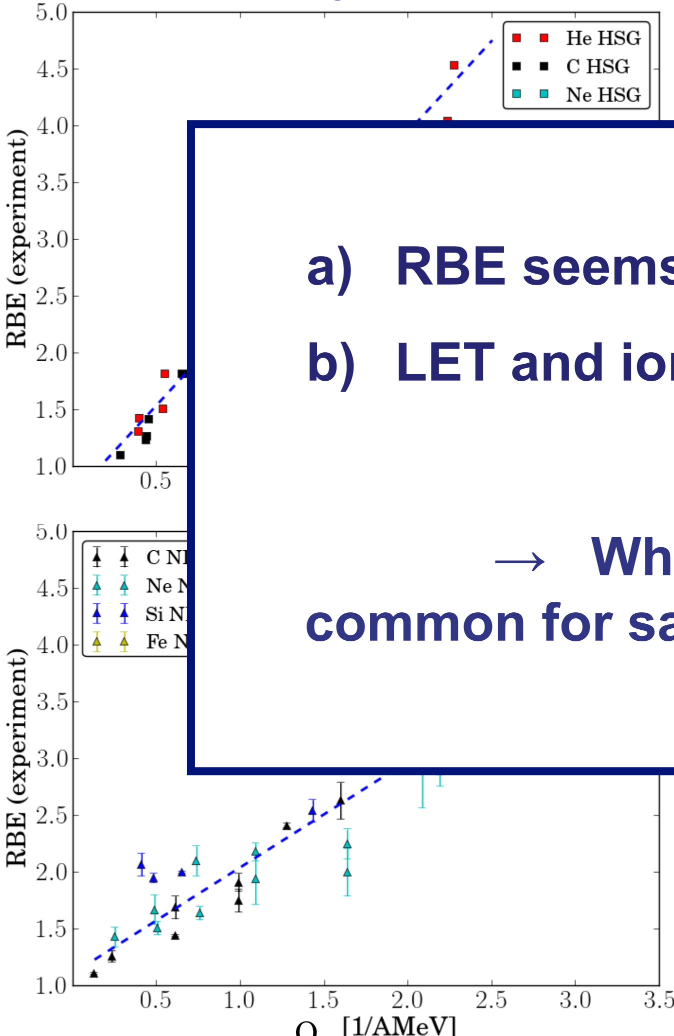


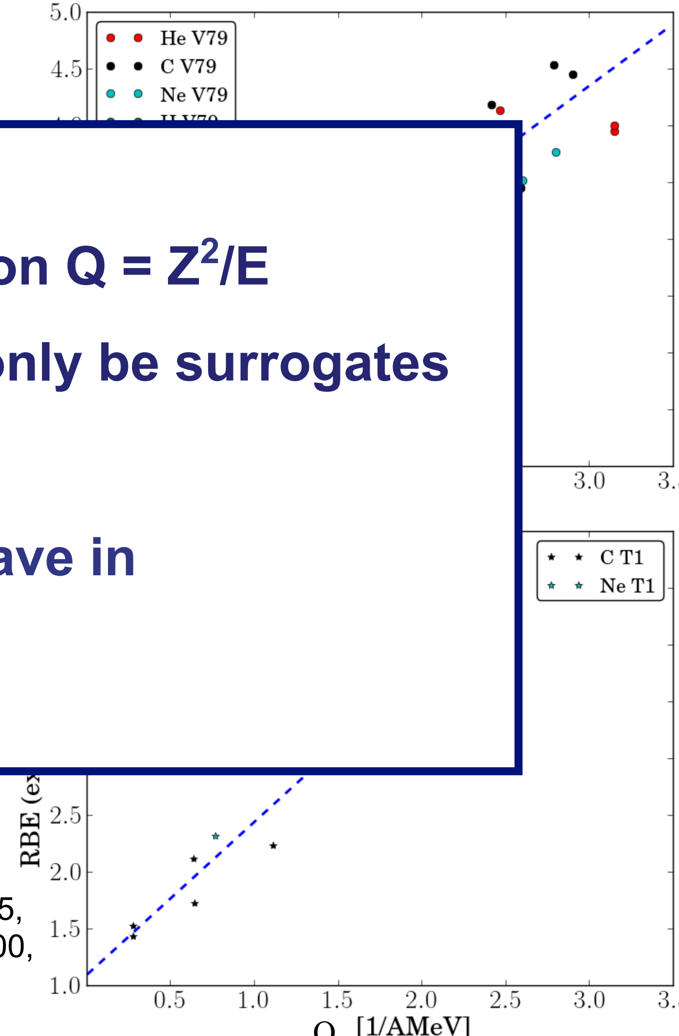

RBE for HSG cell lines, Furusawa et al. 2000

# RBE *in vitro* data – beam quality Q

**Beam quality:** $Q = Z^2 / E$

**6 ions:**
H He




a) **RBE seems to depend on $Q = Z^2/E$**

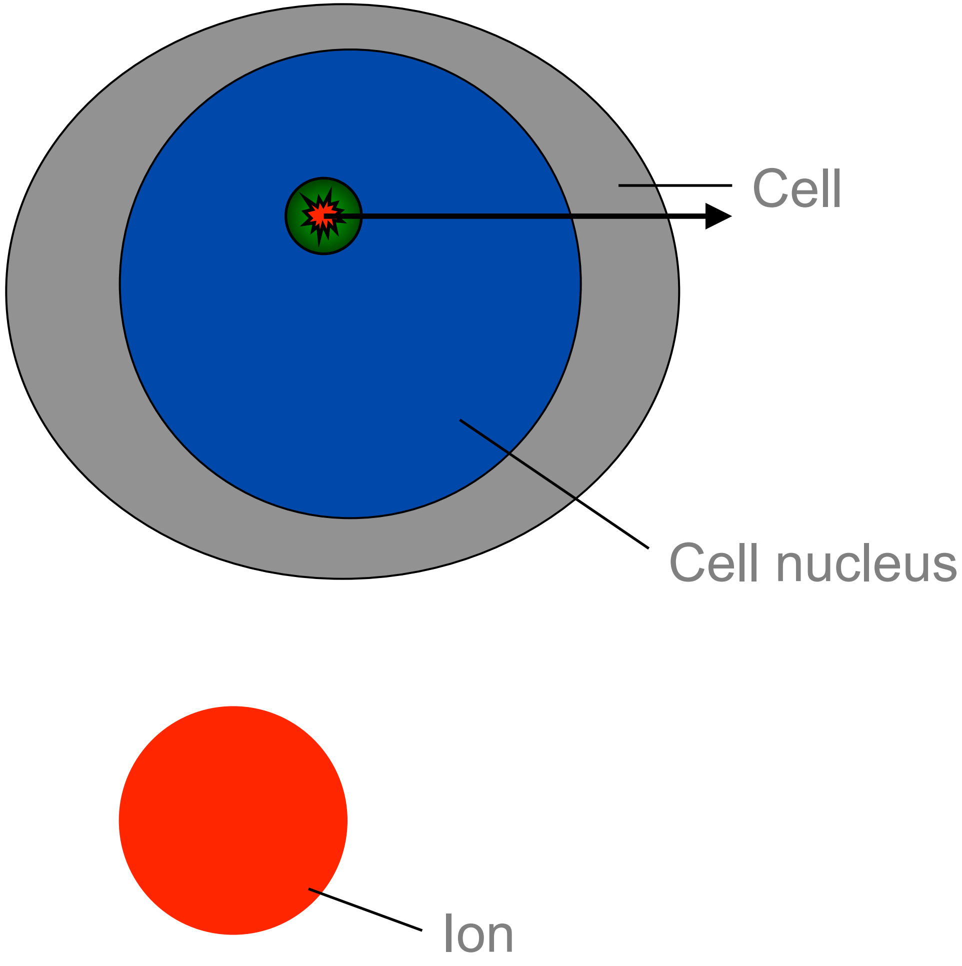
b) **LET and ion type may only be surrogates**

→ **What do ions have in common for same Q ?**

Tsuruoka et al. 2005,
Furusawa et al. 2000,
Folkard et al. 1996,
Belli et al. 1998

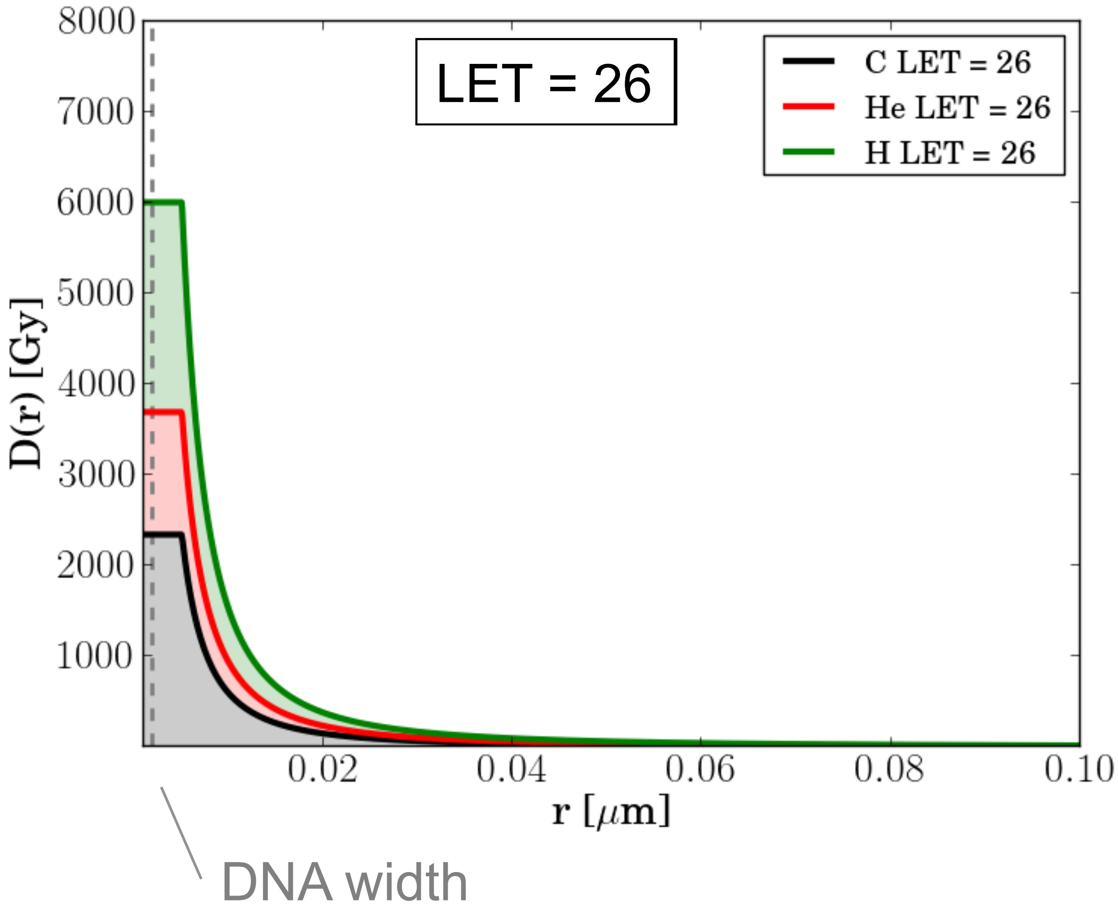
# Explanation – Track structure

## Dose distribution on the cellular level



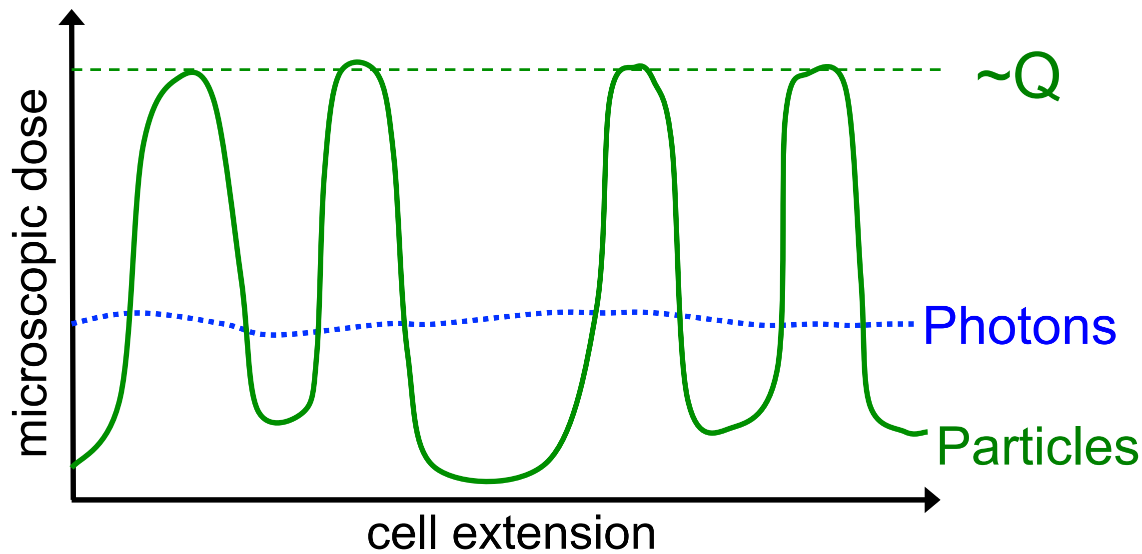
# Explanation – Track structure

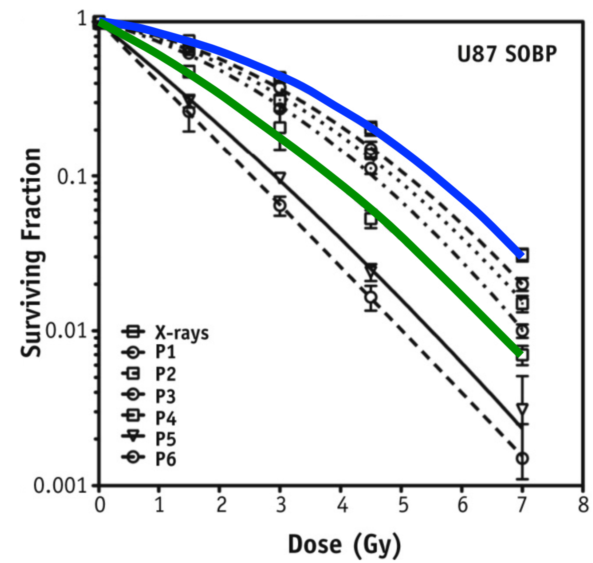
## Dose distribution on the cellular level: same beam quality LET



# Explanation – Track structure and LQ model

## Dose distribution on the cellular level → local effect




Radiation effect

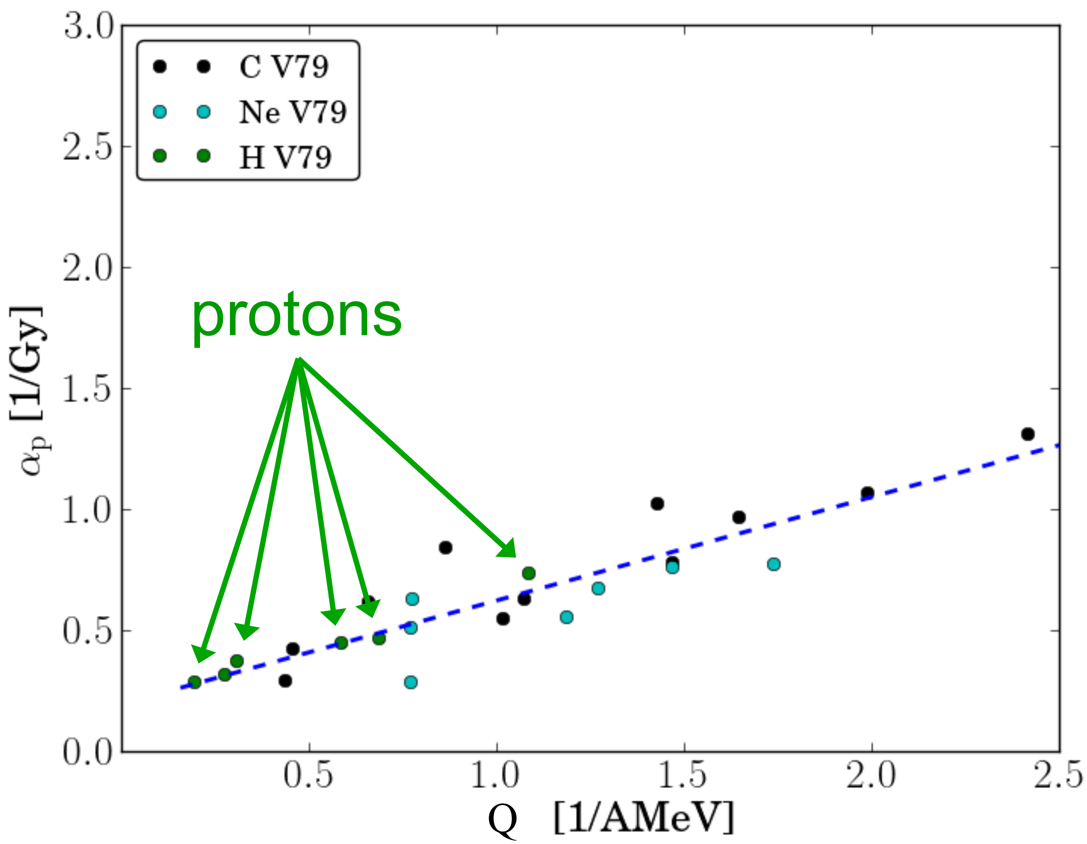
Photons: $E = \alpha D + \beta D^2$

Particles: $E = (\alpha + \beta m Q) D + \beta D^2 \Rightarrow$

$$\alpha_p = \alpha + \beta m Q$$

# LQ parameter $\alpha_p$: dependence on Q

$$\alpha_p = \alpha + \beta\, m\, Q$$

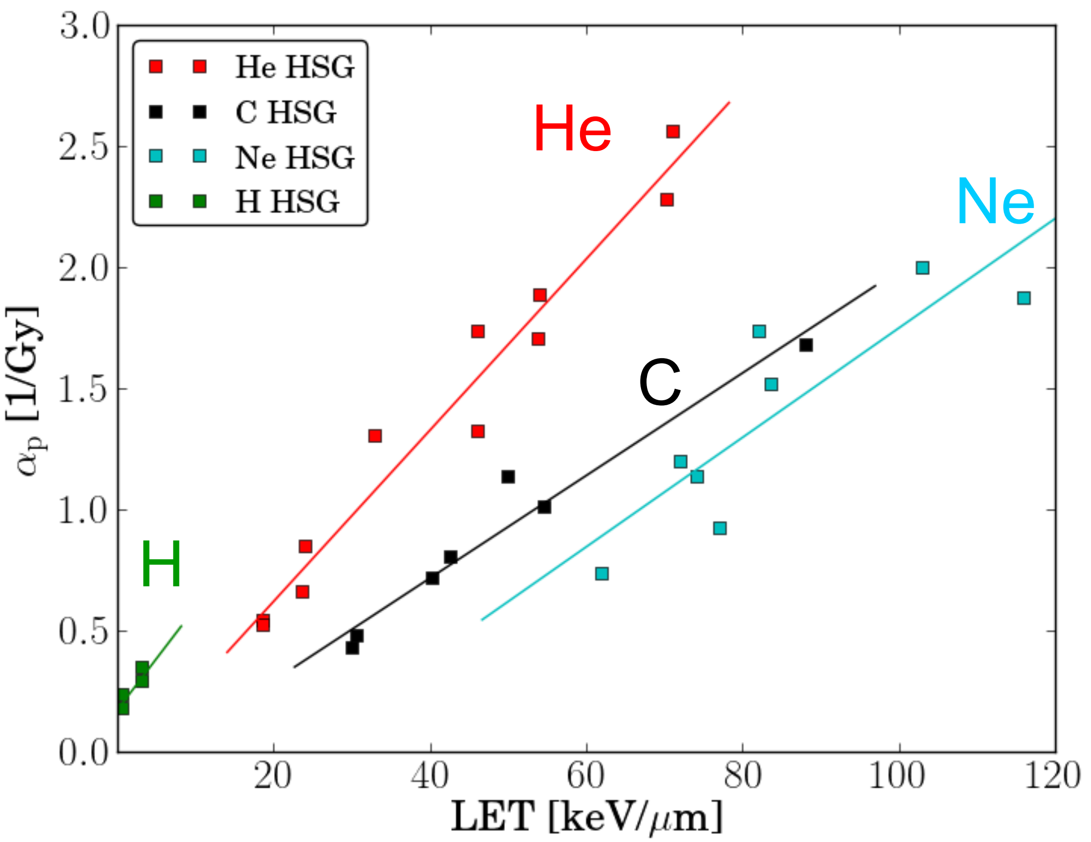



*In vitro* $\alpha_p$ for V79, Furusawa et al. 2000, Belli et al. 1998, Folkard et al. 1996

*In vitro* $\alpha_p$ for HSG, Furusawa et al. 2000, Matsuura et al. 2010

# LQ parameter $\alpha_p$: dependence on LET

$$\alpha_p = \alpha + \beta\, m\, \text{LET}$$

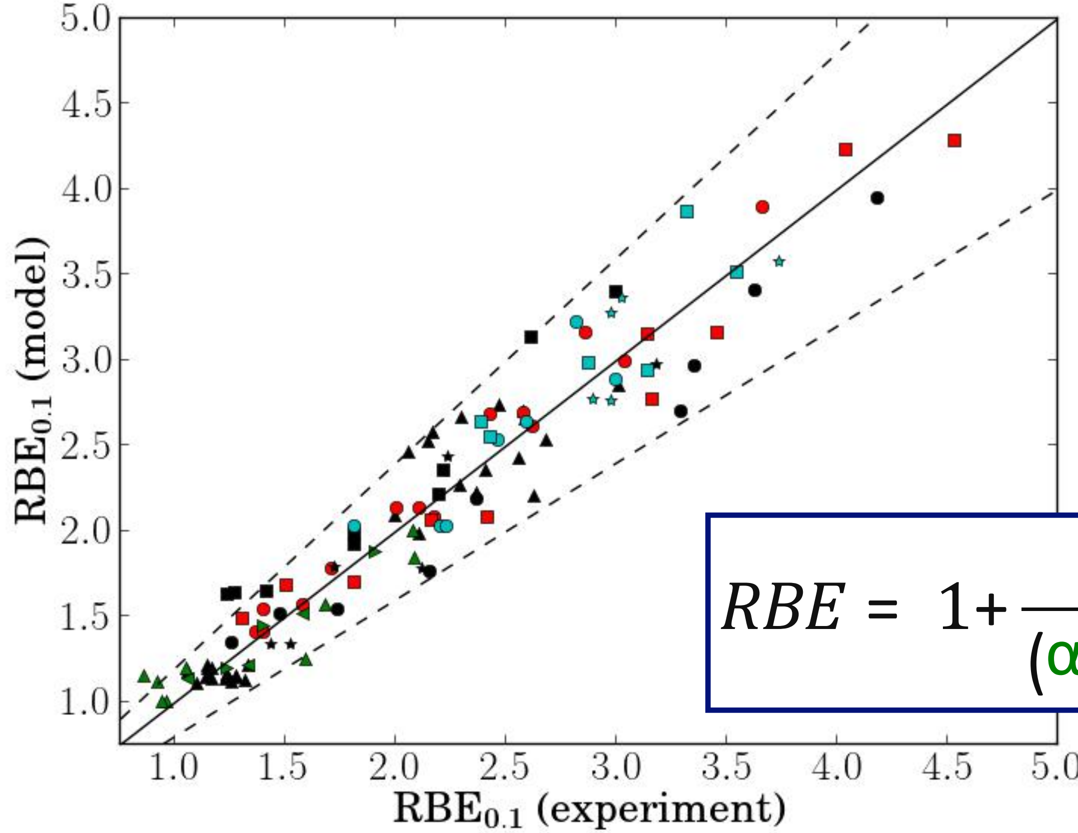



*In vitro* $\alpha_p$ for HSG, Furusawa et al. 2000, Matsuura 2010

# Modeling RBE – as function of Q

**RBE as function of Q and $\alpha/\beta$**

*m* = model parameter – fixed for all ions and cells; $D_t$ = threshold dose



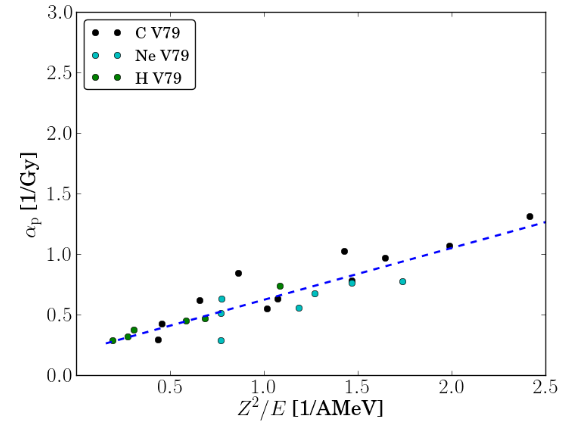

$$RBE = 1 + \frac{D_t\, m}{(\alpha_x/\beta_x) + 2D}\, Q$$

RBE: about 120 in vitro RBE data points

# Conclusions

- **RBE for same biological endpoint**
  - Seems to **depend on Q = $Z^2$ / E** (beam quality)
  - Ion type, i.e., **Z and LET** may **only** be **surrogates**

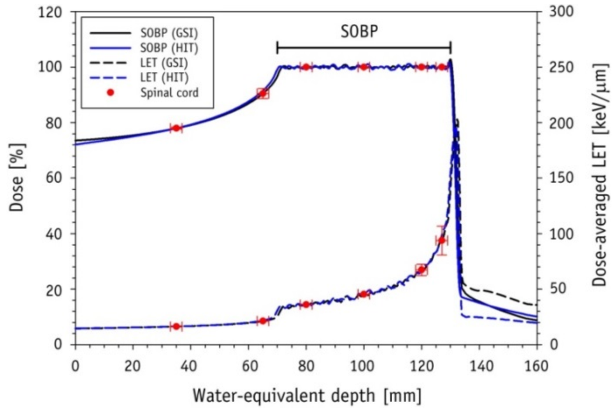
- **RBE and $\alpha_p$ increase linearly with Q**
  - Radial dose increases linearly with Q



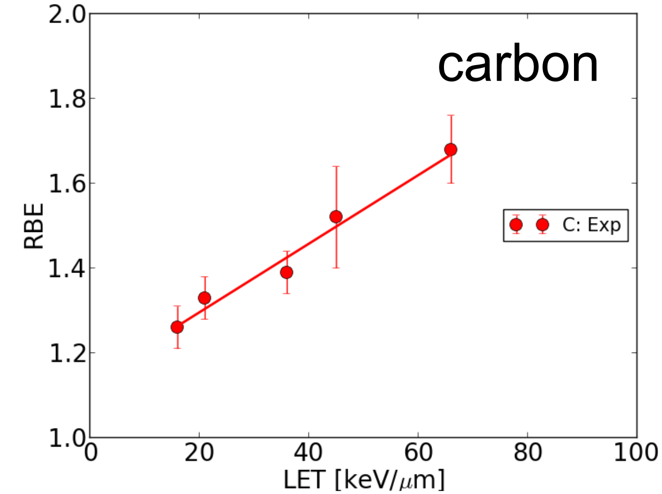

- **Impact on RBE description**
  - separation between biology and physics
  - linearity in Q allows for dose averaging in an SOBP
  - *E* convenient quantity → translation to treatment planning

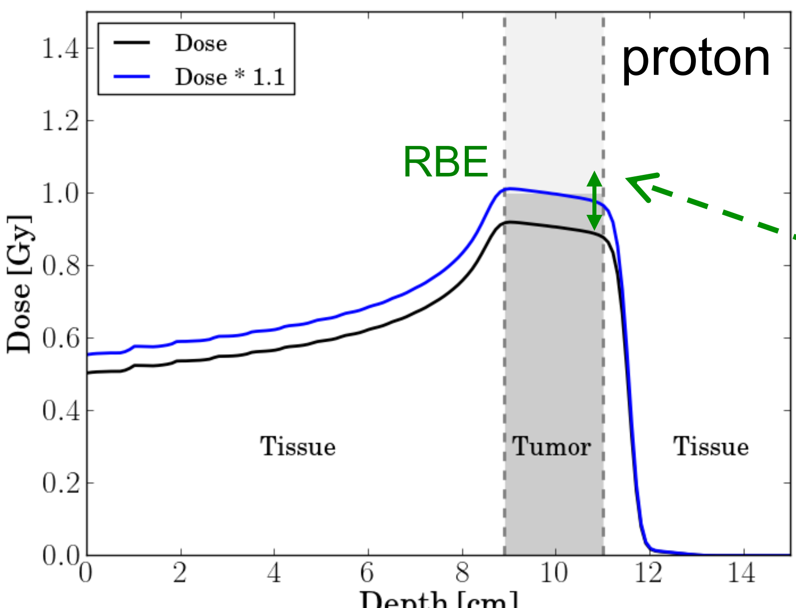
# Implication: Transfer C-ion RBE to proton therapy

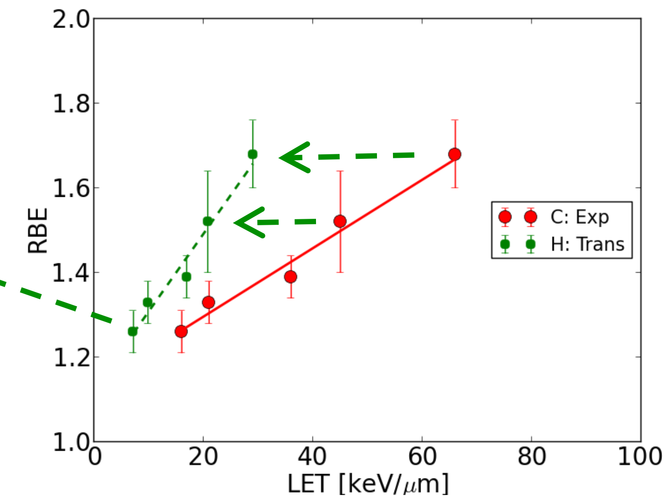
## Carbon ion irradiation of the rat spinal cord








cord, Saager et al. 2014

# RBE – dependence on physics and biology

**RBE depends on many factors, e.g.:**

**Physics**

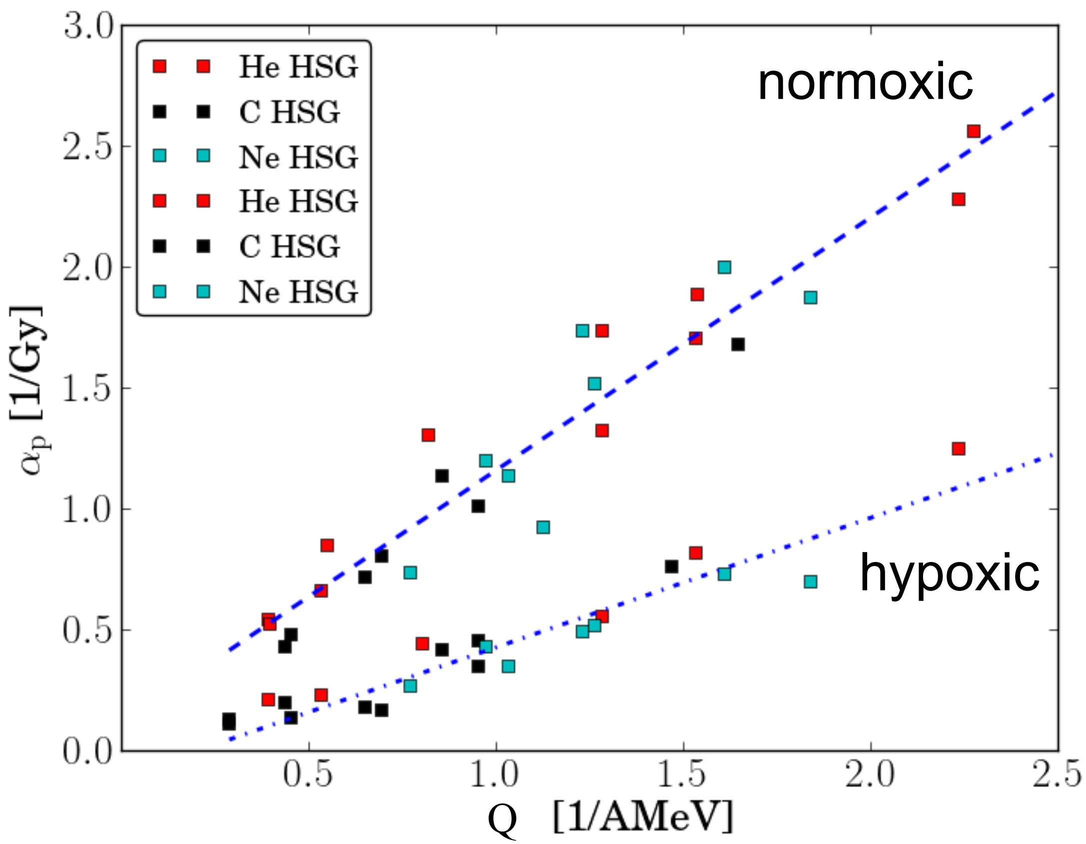
- Ion energy
- Ion type
- LET
- Dose
- Track structure

**Biology**

- Cell line
- *In vivo* and *in vitro*
- Endpoint
- Microenvironment

# LQ parameter $\alpha_p$: microenvironment

$$\alpha_p = \alpha + \beta\, m\, Q$$



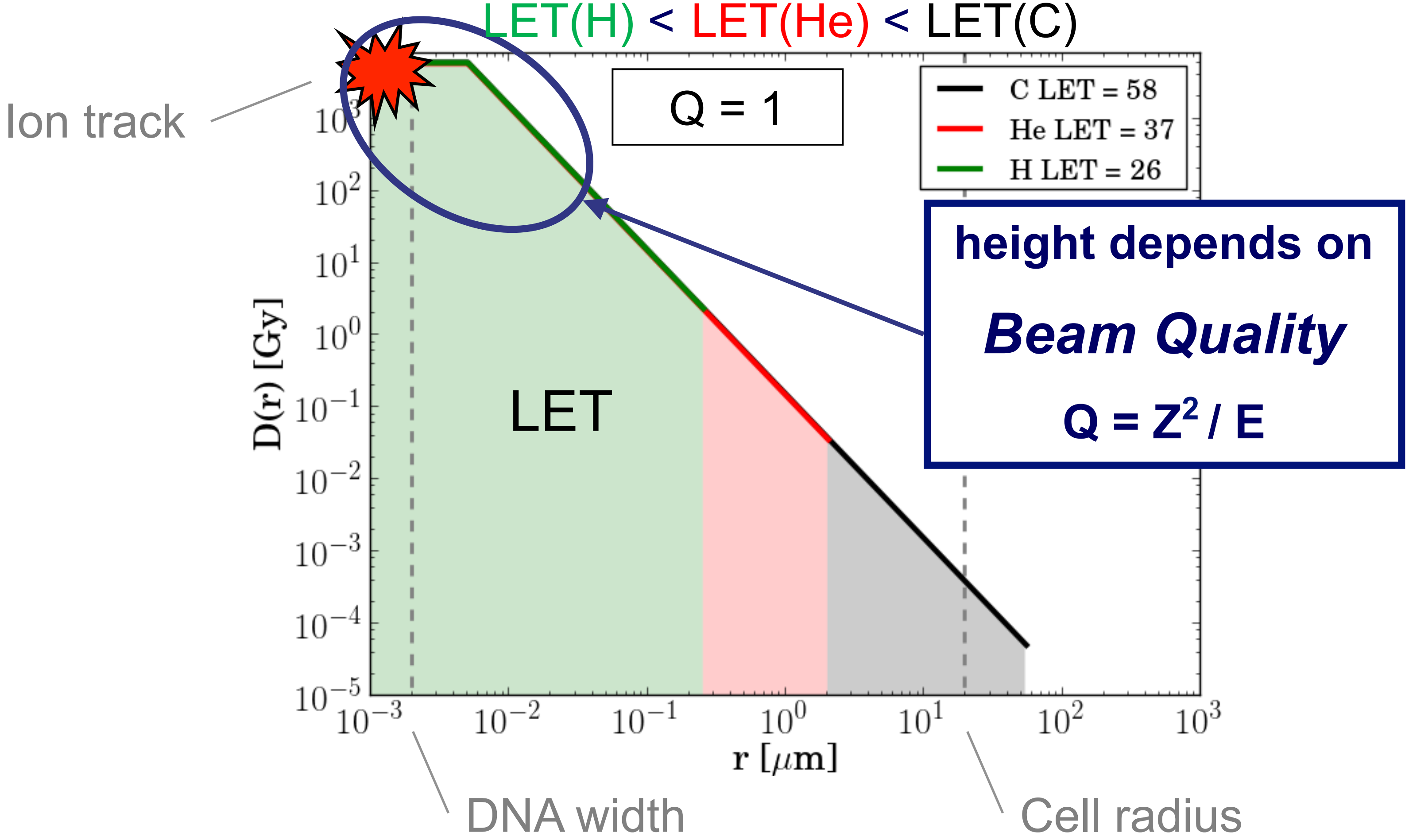

$\alpha_p$ for HSG cell lines, Furusawa et al. 2000

# Explanation – Track structure

**Dose distribution on the cellular level: same beam quality**

Q(H) = Q(He) = Q(C)

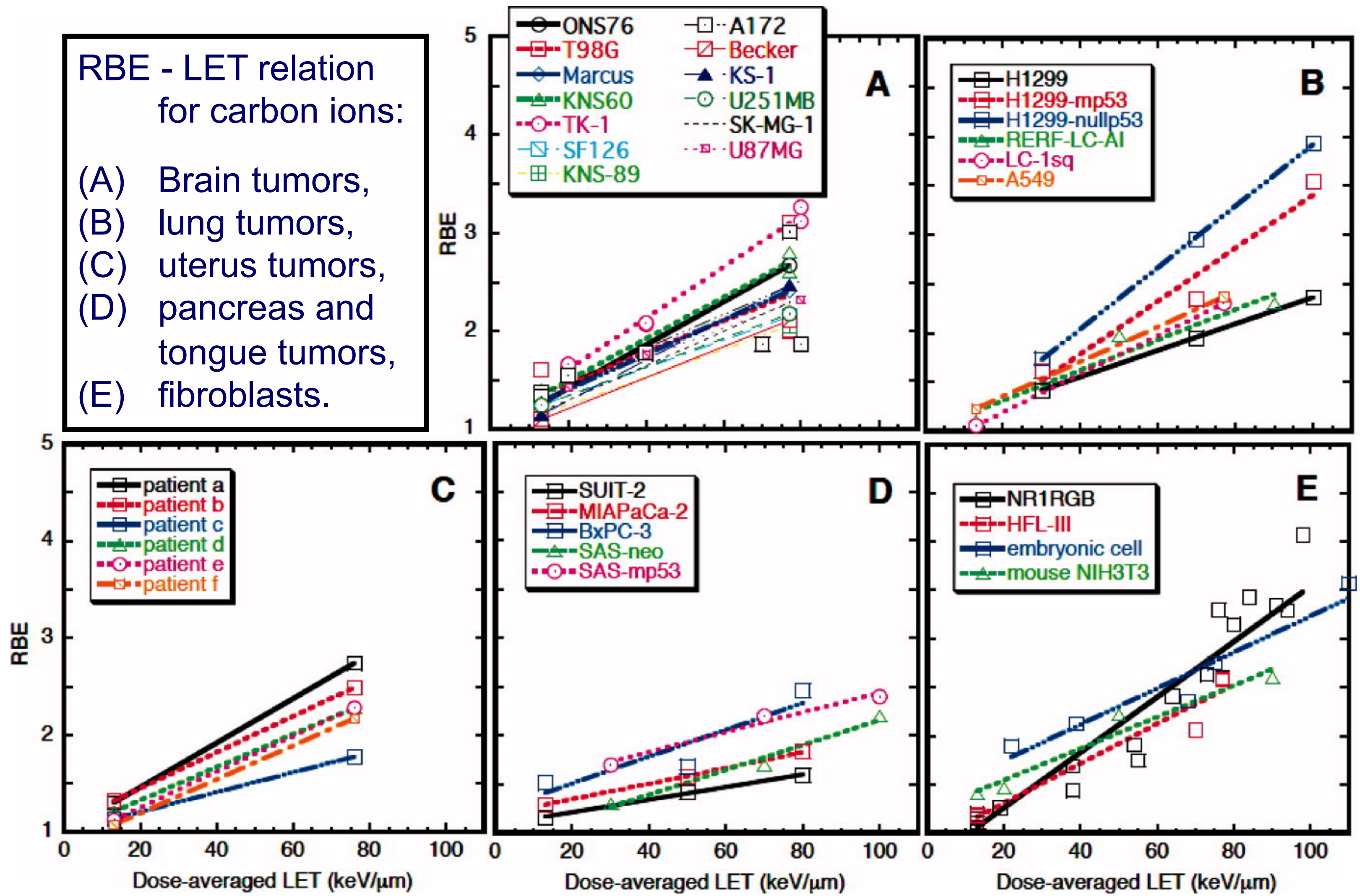
LET(H) < LET(He) < LET(C)



# RBE values for human cells: carbon

RBE - LET relation for carbon ions:

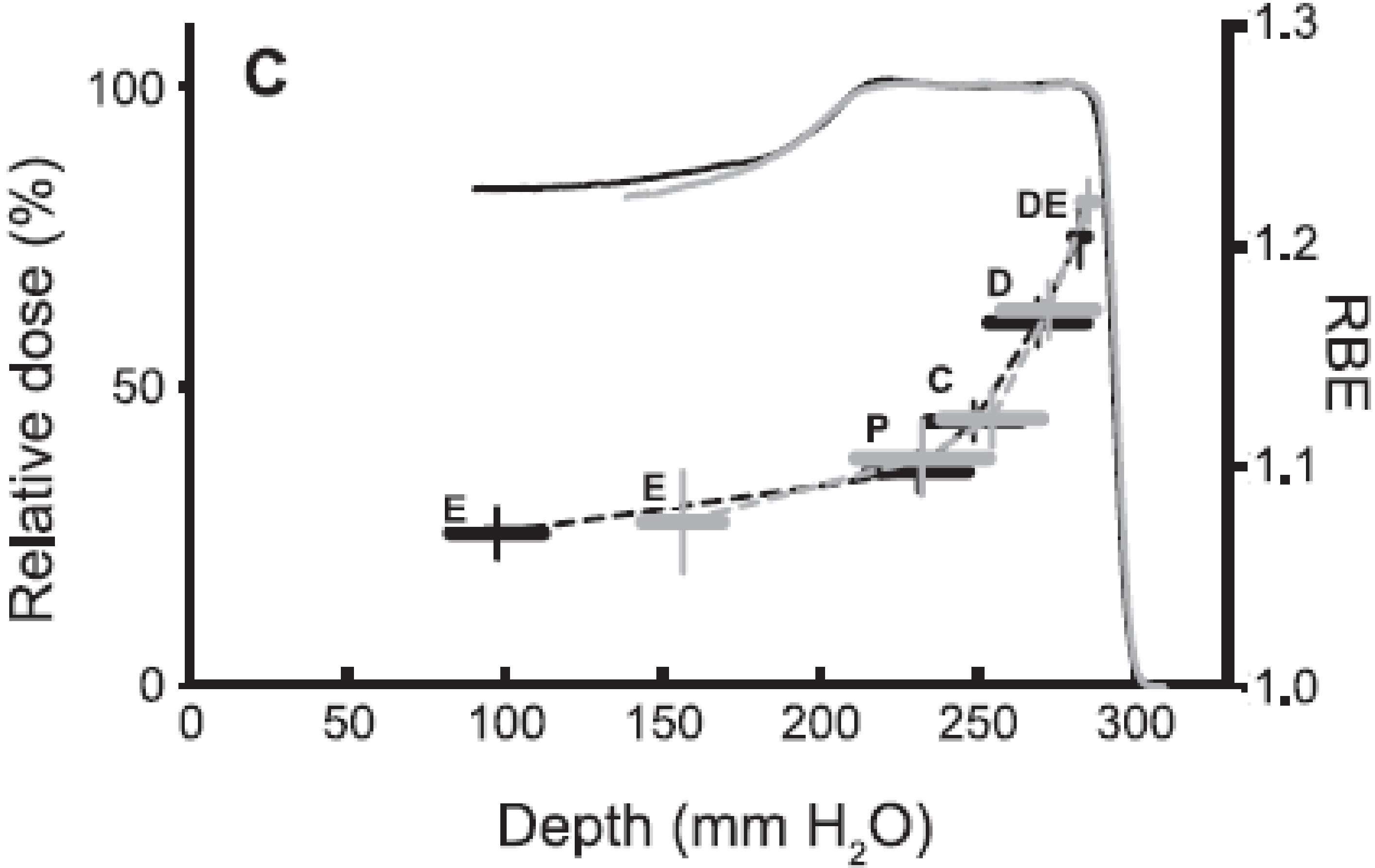
(A) Brain tumors,
(B) lung tumors,
(C) uterus tumors,
(D) pancreas and tongue tumors,
(E) fibroblasts.




RBE for human cells, Review on LET dependence, Ando and Kase 2009

# Clinical Significance

**Variable RBE → inhomogeneous cell kill with tumor**

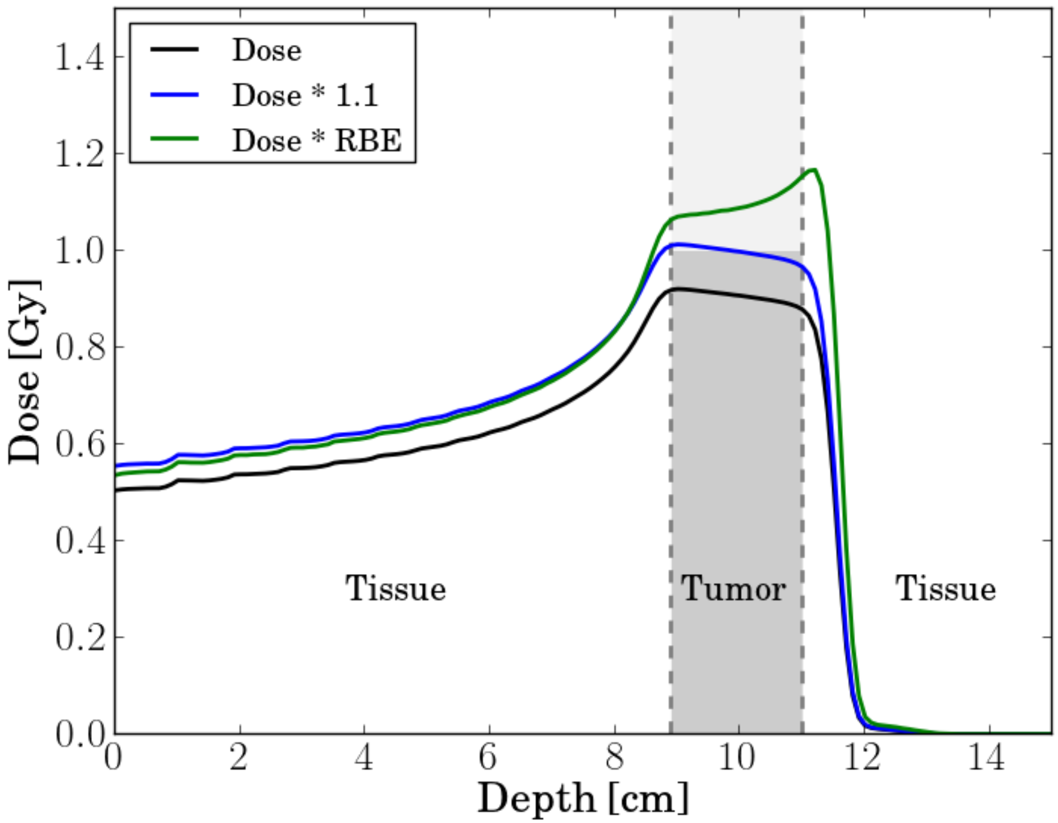



Proton RBE for V79 and two SOBP, Wouters et al. 2015

# Clinical Significance

**Treat entire tumor volume with tolerance dose**

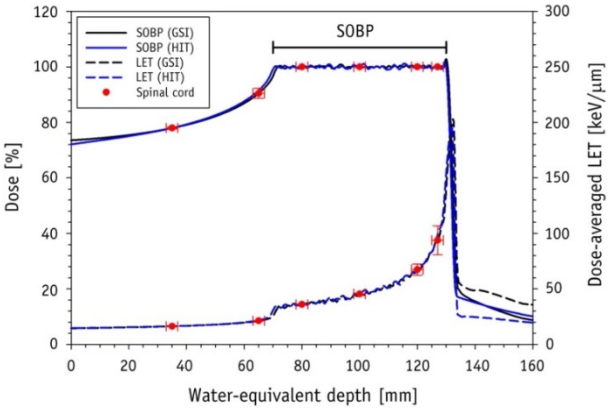
**→ Not only distal part of SOBP**



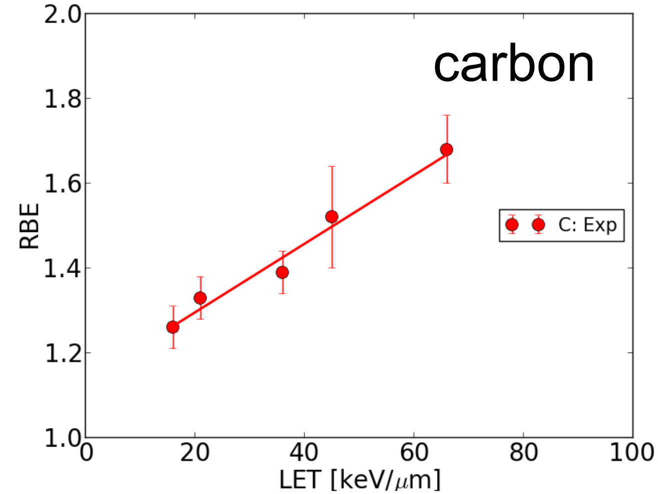

Proton RBE for glioma (U87) based on Chaudhary et al. 2014

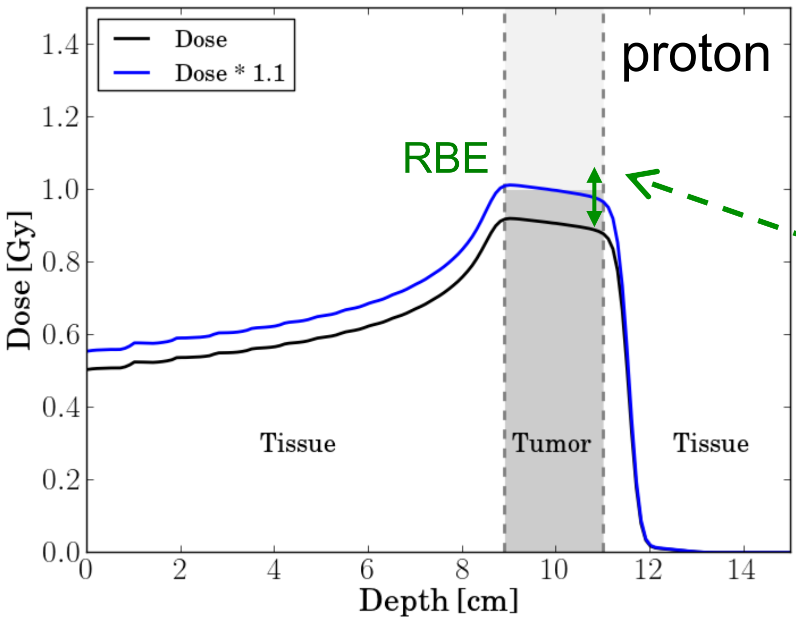
# Implication: Transfer C-ion RBE to proton therapy

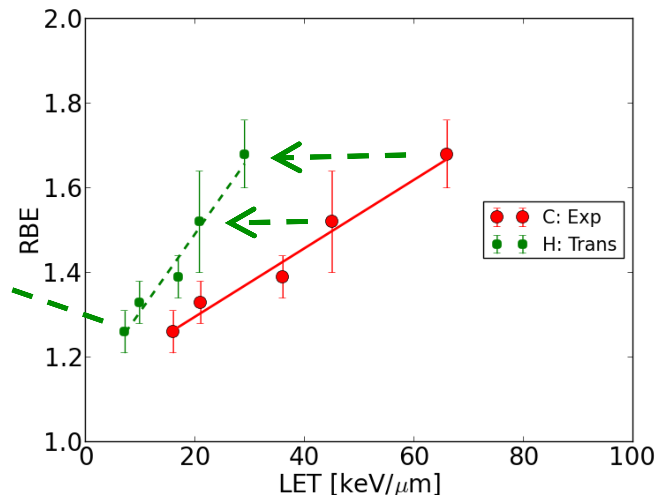
## Carbon ion irradiation of the rat spinal cord





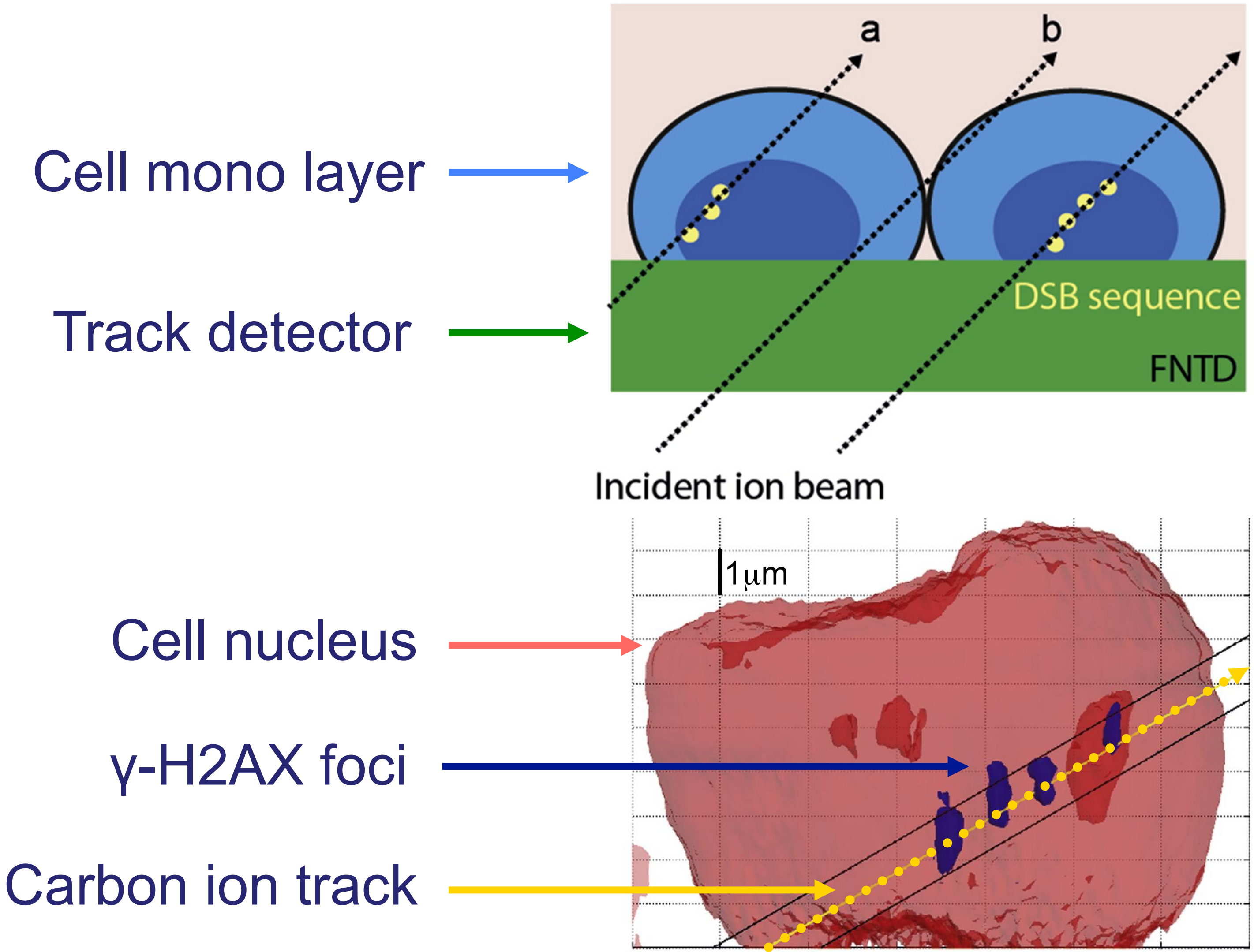



RBE for rat spinal cord, Saager et al. 2014

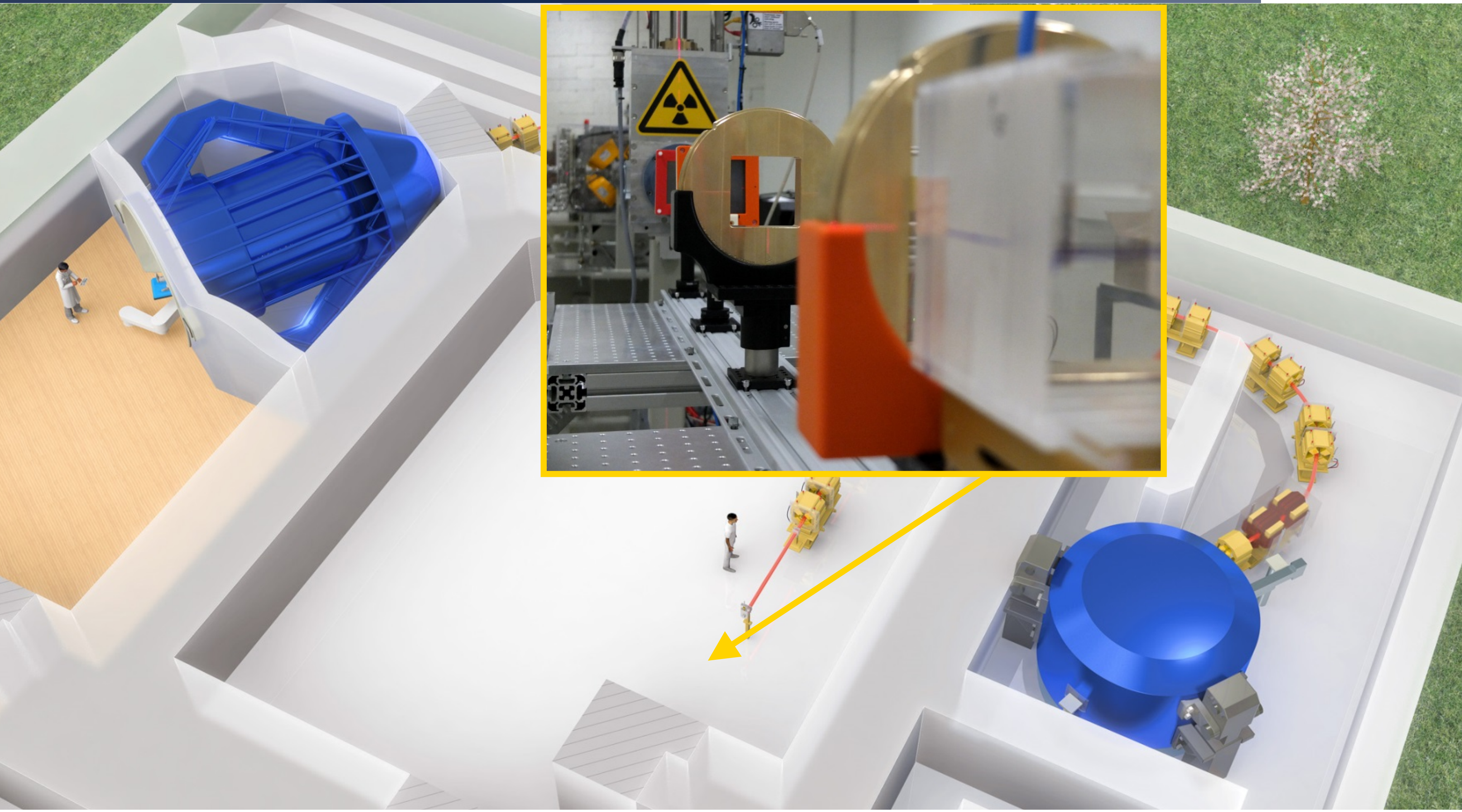
# Spatial correlation: ion track and cell response




- Human lung adeno-carcinoma (A549) cells
- Carbon ion:
  - Q = 0.66
  - LET = 42 keV/μm

Cellular response to ion traversal, Niklas et al. 2013

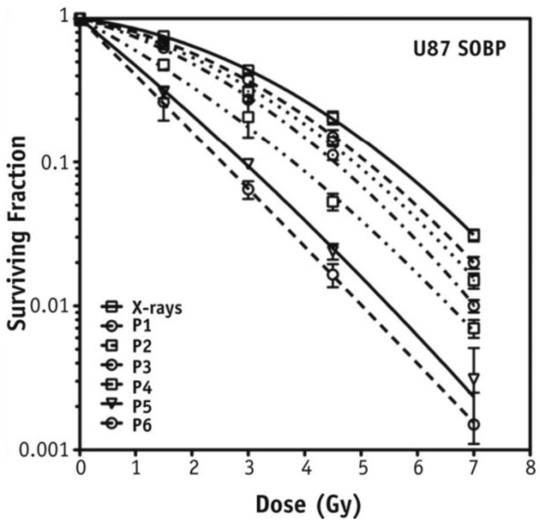
# Outlook: experimental verification




OncoRay 2015

# Background

- RBE is considered *constant* in **proton therapy: RBE = 1.1**
- Experimental ***in vitro*** data show that **this is not true**
- No debate on **variability of RBE for heavier ions**, e.g., He- and C-ions




Proton *in vitro* survival data at different depths in SOBP

**Why do we consider RBE differently for proton and ion therapy?**

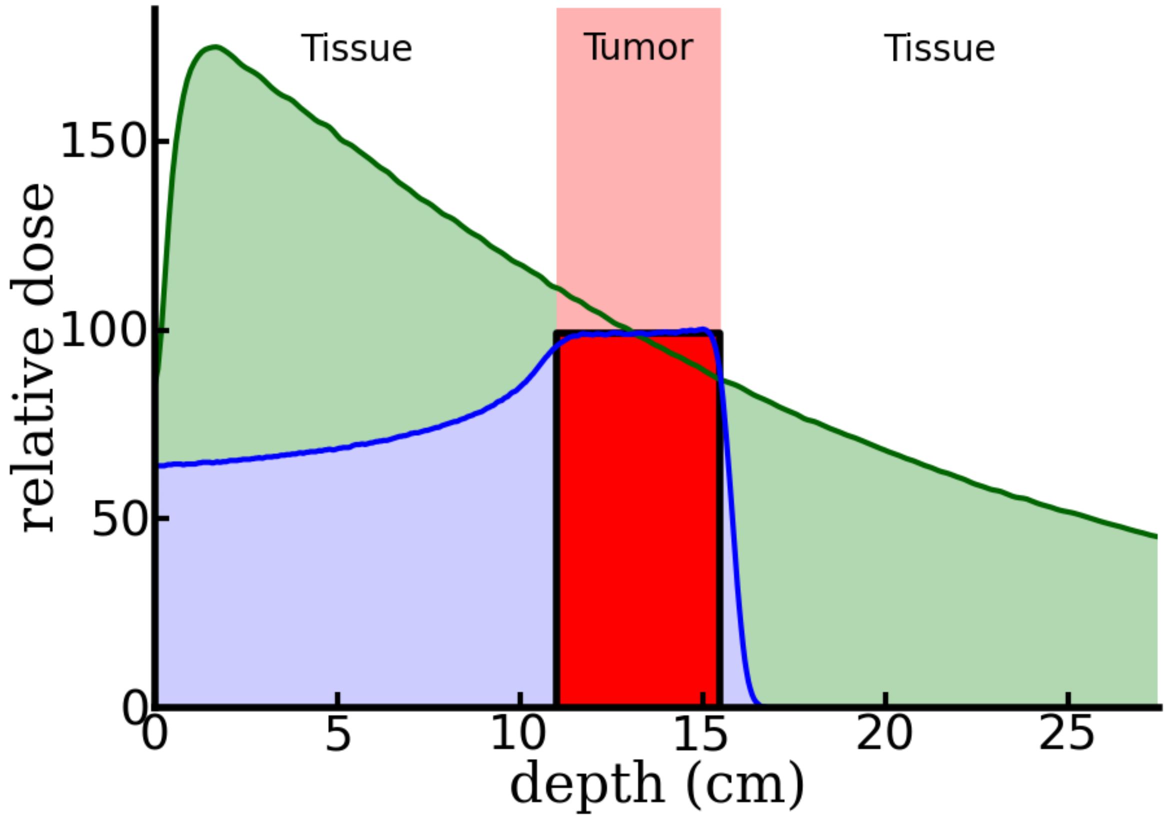
a) Relevant physics/biology for protons systematically different.

b) Better signal to noise ratio in RBE experiments with ions.

Proton *in vitro* survival data, glioma (U87): Chaudhary et al. 2014

# Particle therapy

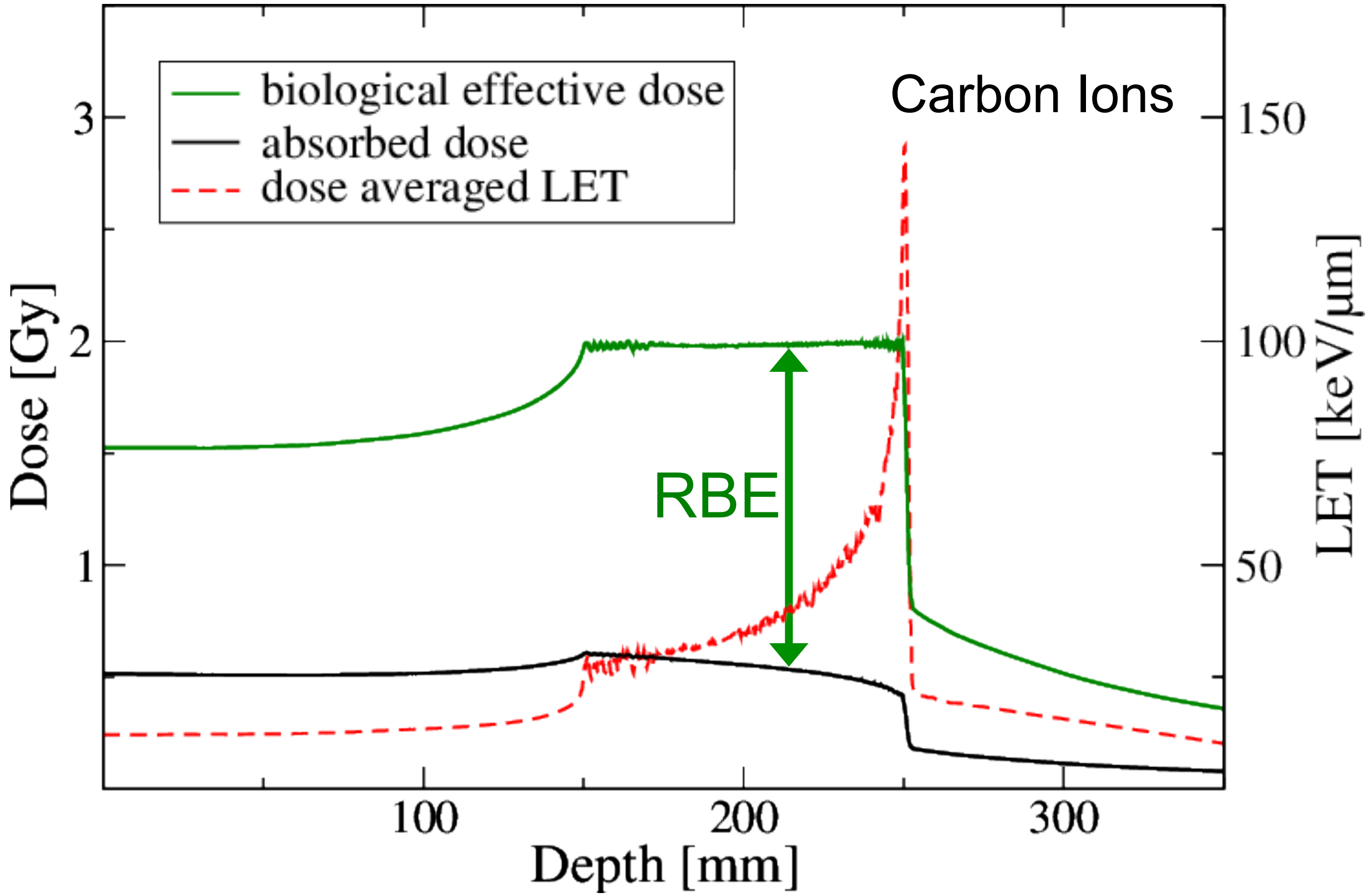
## 1. Improved dose distribution




measured depth-dose curves, Dresden

# Particle therapy

## 2. Higher relative biological effectiveness (RBE)




optimized depth-dose curves, treatment planning system TRiP