

# Role of the CERN International Strategy committee in the LEIR initiative

## Biology

**P. Lambin on behave of the radiobiological subcommittee of the  
International Strategy Committee**

# Content



1. Introduction: the context
2. Biology does matter!
3. Motivation & Potential research questions
4. Experimental models
5. Wish list and the user model

# Statement:

**The knowledge of CERN should be used for medical applications**

*e.g. Specific Statement: We should investigate whether we could use different ions like we use different drugs (R. Orecchia)*

# Background and context

- 2012 brainstorming meeting:  
**“community call for a dedicated radiobiological research facility”**
- Concepts presented and discussed, e.g. in Brainstorming Meeting on LEIR in 2012 and a in global feasibility study (Abler et al.)
- Need to go beyond this initial work and establish a **coherent proposal** based on solid requirements and assumptions
- Should reflect the views of a **“community”** and not of a single institute



# The New CERN Initiatives



(Ghislan Roy, et al. Presentation of 2015-03-27)

## 1. Medical *Accelerator* Design

Coordinate an international collaboration to design a new compact, cost-effective accelerator facility, using the most advanced technologies

## 2. *Biomedical Facility*

Creation of a facility at CERN that provides particle beams of different types and energies to external users for radiobiology and detector development

3. *Detectors* for beam control and medical imaging
4. Diagnostics and *Dosimetry* for control of radiation
5. *Radio-Isotopes* (imaging and possibly treatment)
6. “*Big data*”: Large Scale Computing (simulations, treatment planning telemedicine etc)
7. Applications *other* than cancer therapy

# Content



1. Introduction: the context
2. Biology does matter!
3. Motivation & Potential research questions
4. Experimental models
5. Wish list and the user model

# Accelerators

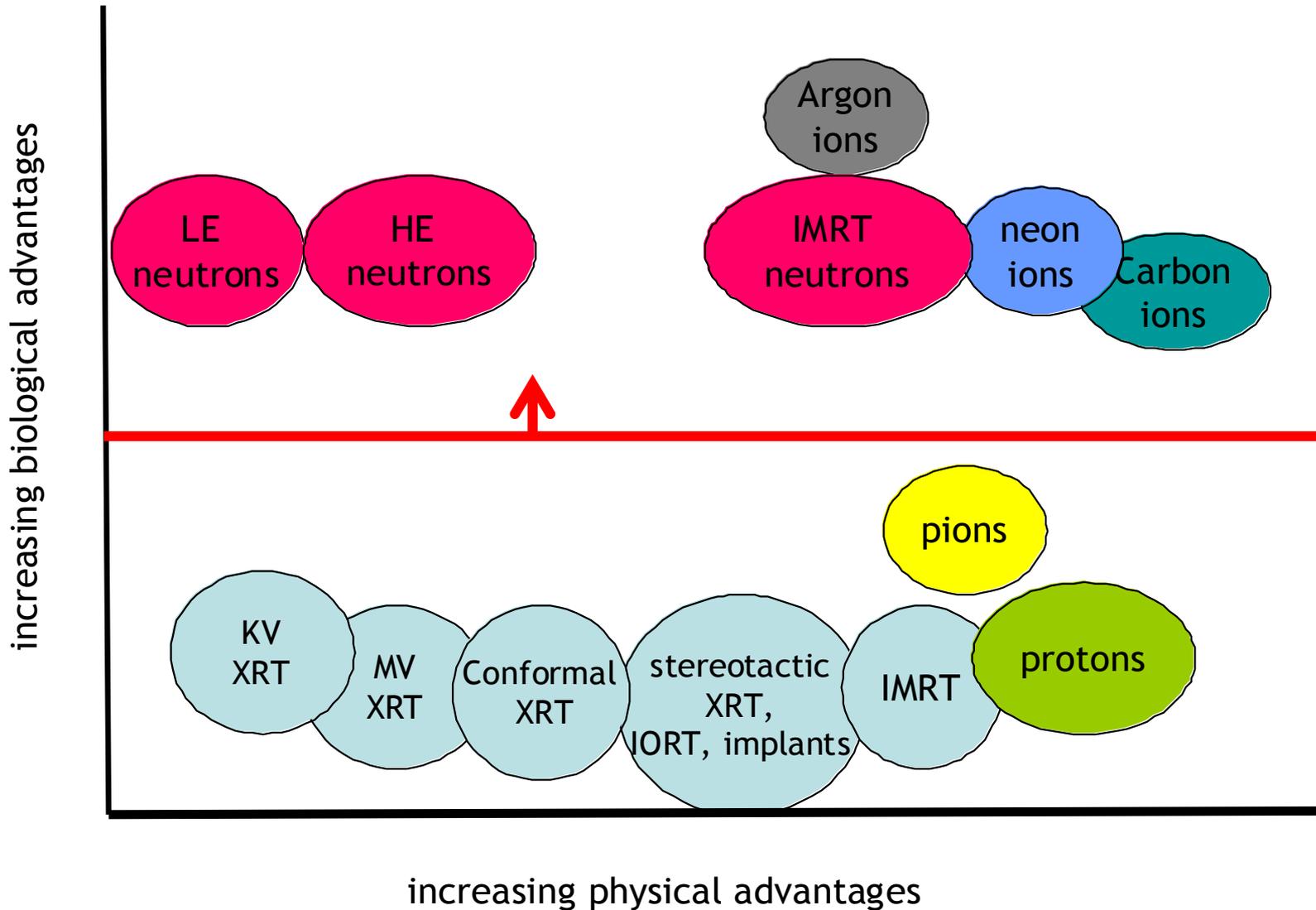


# Interactions

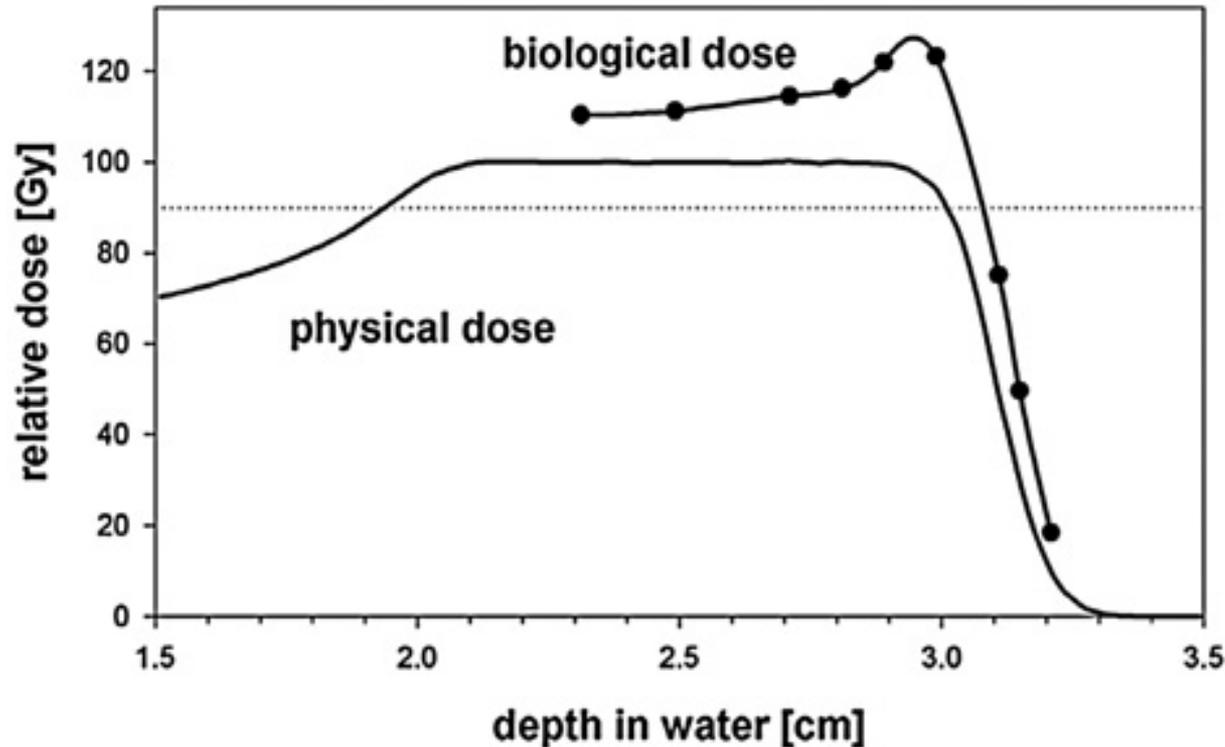
- The Stopping Power
- The Scattering Power
- The Biological effects



# Biology does matter!



# Calculation models including biological effects



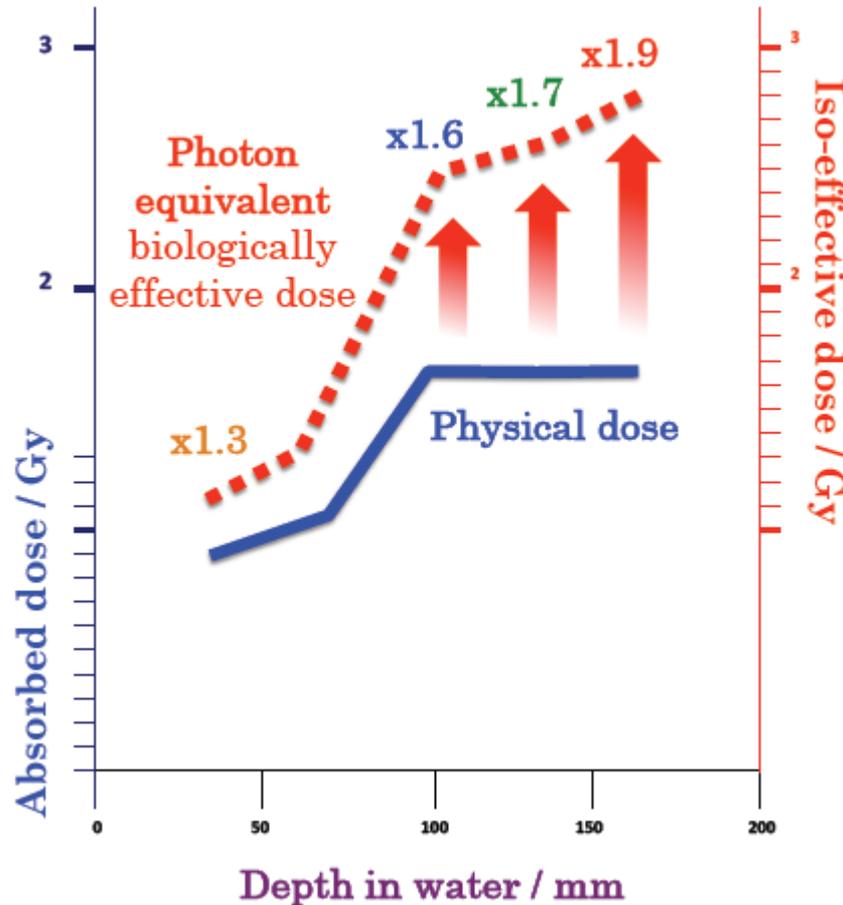
Physical dose and biological dose (physical dose times RBE; line with circles) simulated for one particular endpoint and dose. RBE varies significantly across the Bragg curve with strong dependency on **LET, Dose, and Radiosensitivity**

Adapted from Paganetti and Goitein (2000) and Paganetti (1998). *Courtesy of T. Lomax.*

# RBE - painting

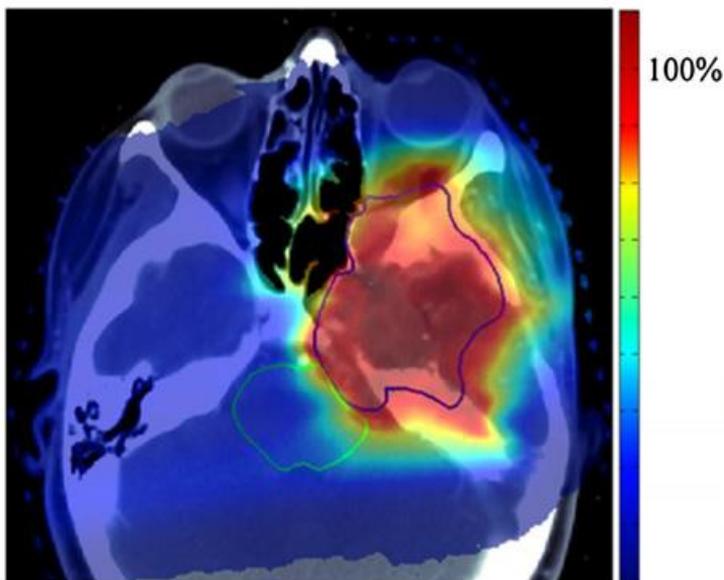
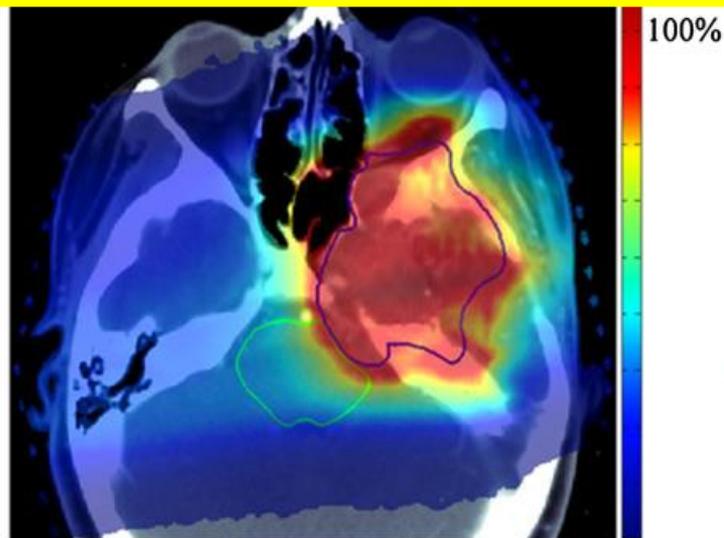


Carbon ions



Gueulette *et al* 2010

- A homogeneous biologically effective dose requires an inhomogeneous physical dose distribution – even for protons



Distal High RBE  
on critical organs

- Mitigation proposals:**
- Different beams
  - Different optimisation  
(up to 30% increase in the Bragg peak)

Two dose distributions (left; in %) and the corresponding dose averaged LET distributions,  $LET_d$ , (right; in  $\text{keV } \mu\text{m}^{-1}$ ) illustrating that clinically equivalent dose distributions can be achieved with quite different LET distributions steering dose falloffs away from critical structures in intensity modulated proton therapy. Based on Grassberger *et al* (2011) published by H.Paganetti Phys. Med. Biol. 57, R99-R107 (2012)

# Content



1. Introduction: the context
2. Biology does matter!
3. Motivation & Potential research questions
4. Experimental models
5. Wish list and the user model

# Motivation

(Ghislan Roy, et al. Presentation of 2015-03-27)

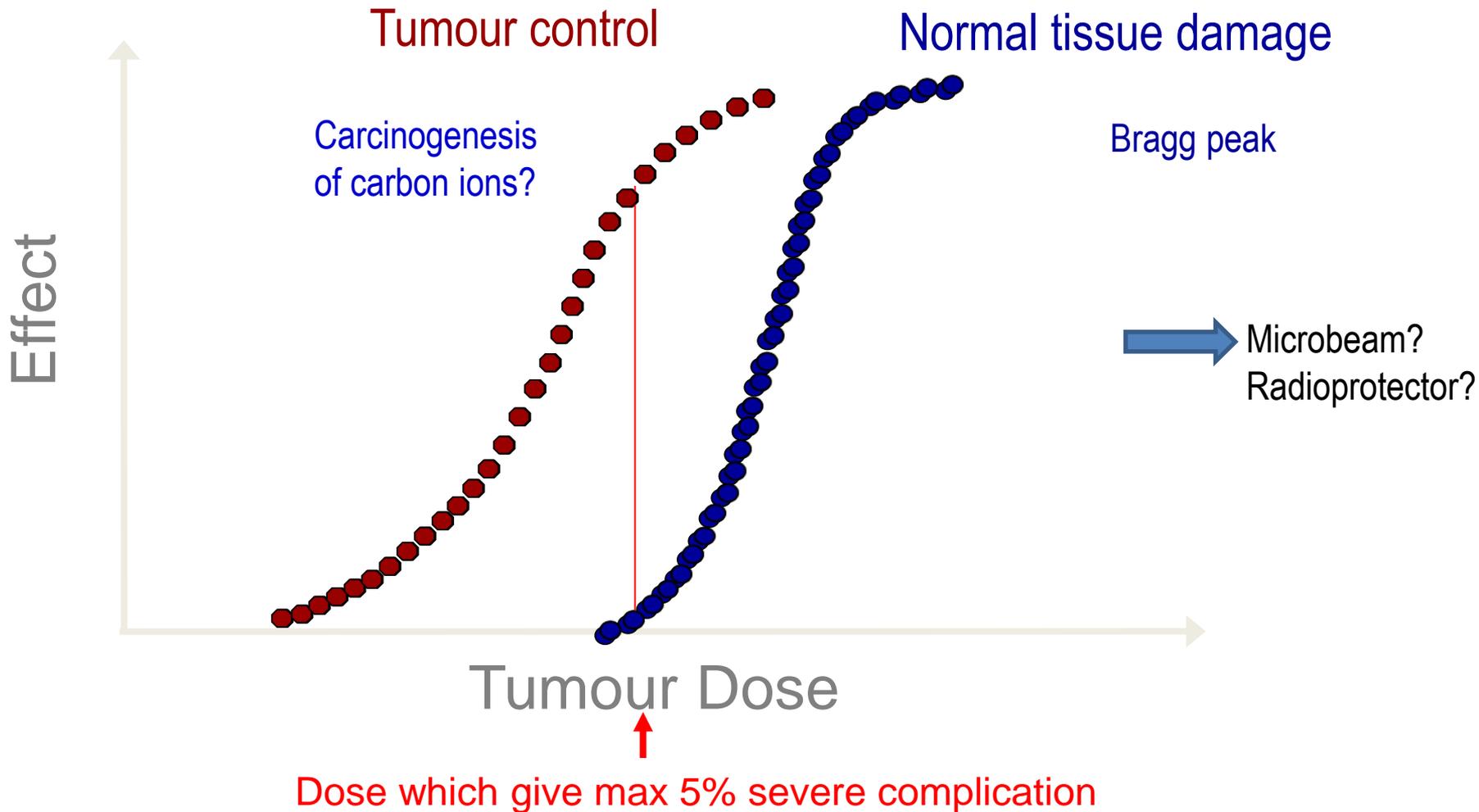


## Need for radiobiological research with ion beams:

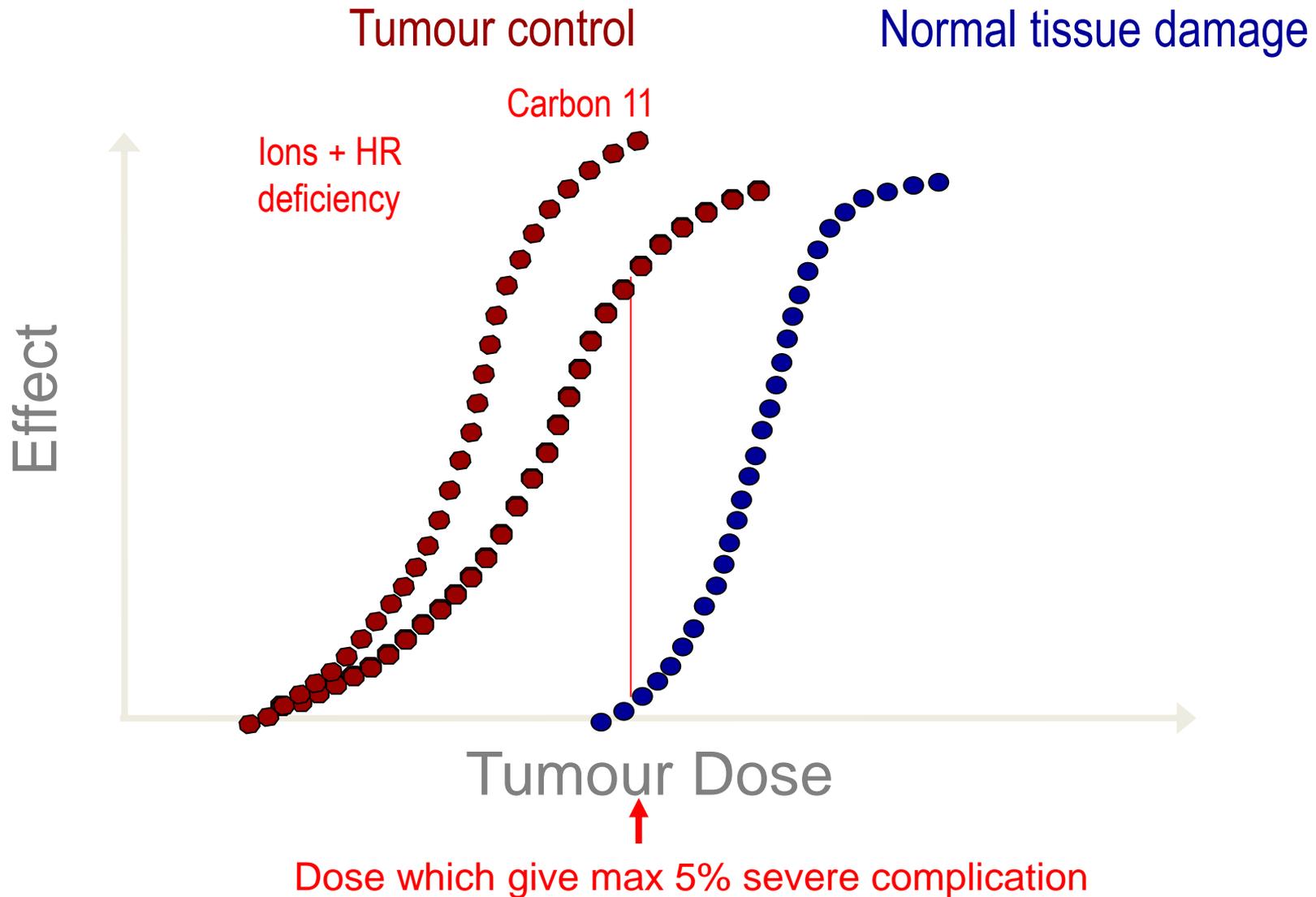
- Protons and Carbon ions *in clinical use*
  - Improved dose distribution, but limited understanding of all effects
  - Other ions than p and C could be better suited (for certain cases)
- **Radiobiology of new ions**: Incoherent sets of data (radiobiological and clinical) observed under different conditions: cell survival for **different ions**/LET/doses, bystander effects, RBE ...

1. “Provides particle beams of different types and energies: *Exotic ions*
2. Only for comparison: X-rays, protons carbon ions...

# Question 1: "The tolerance of normal tissues"



# Question 2: “The radiosensitivity of tumours”



# Question 3: “Descriptive & mechanistic Modelling”

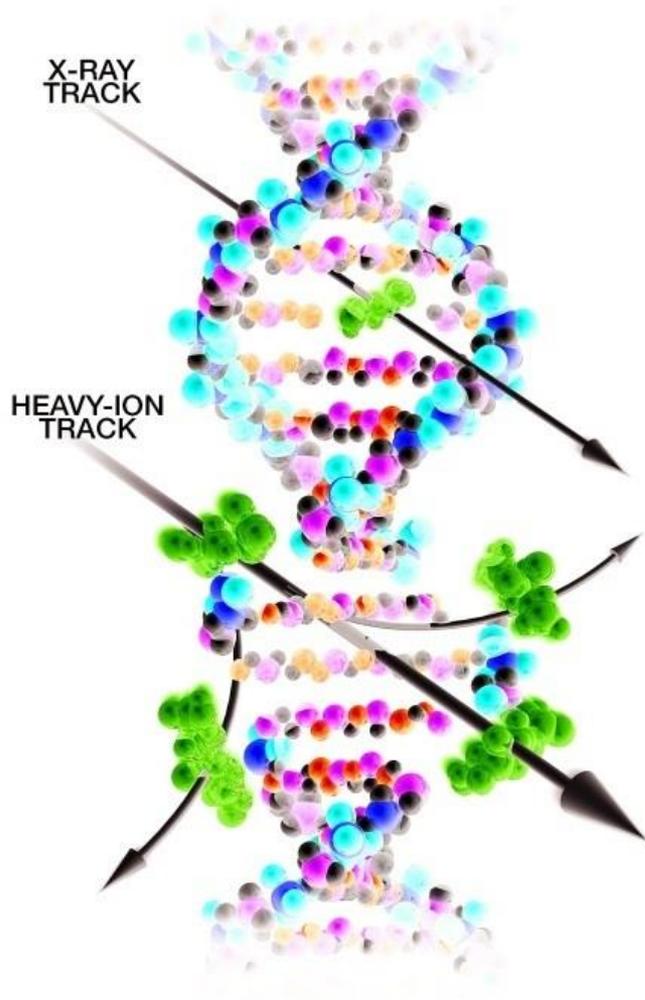
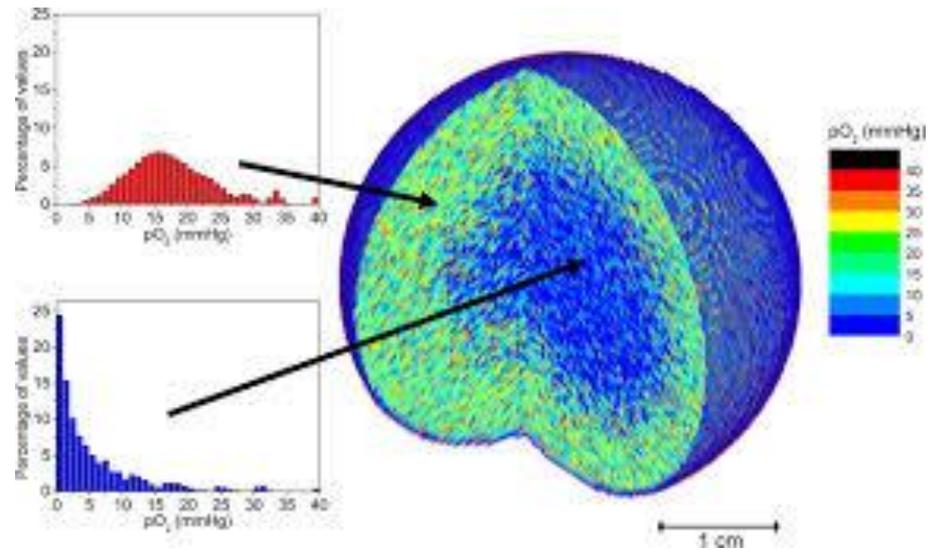


image credit: NASA

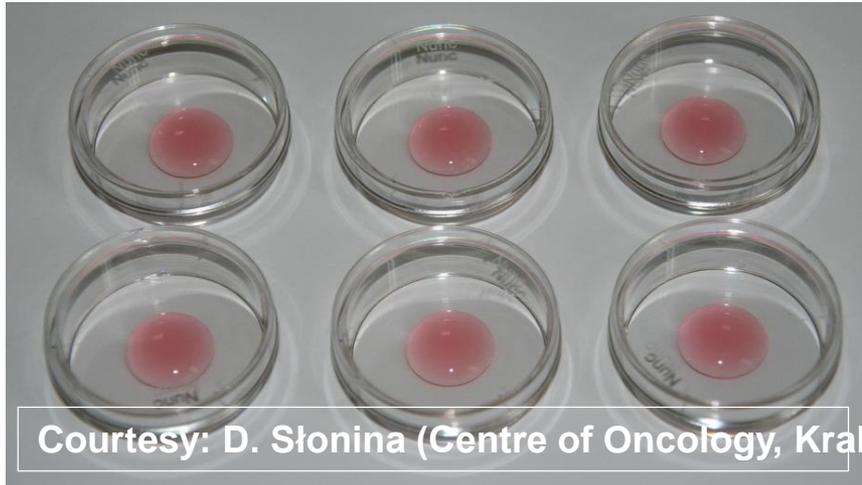


# Content



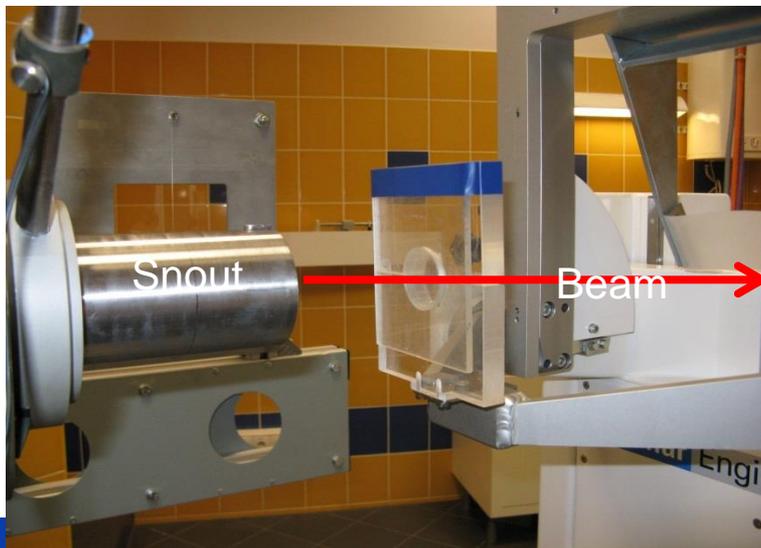
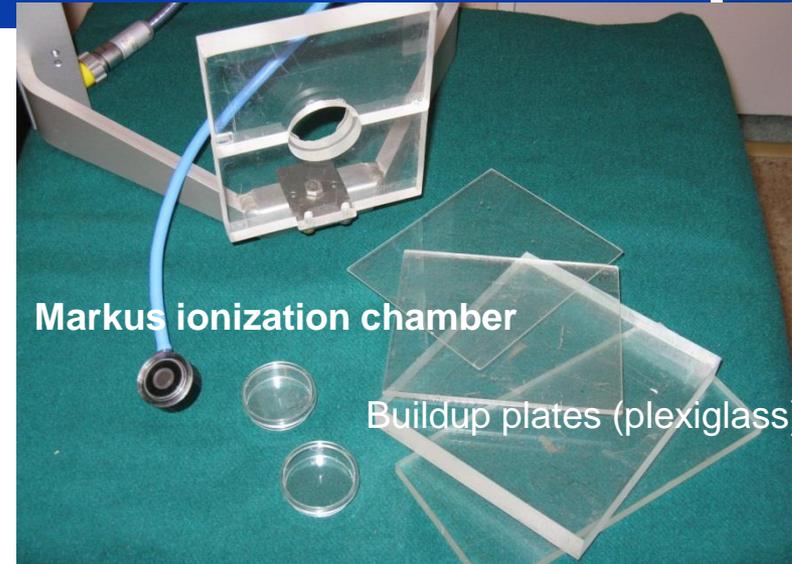
1. Introduction: the context
2. Biology does matter!
3. Motivation & Potential research questions
4. Experimental models
5. Wish list and the user model

# Classical monolayer cellular models



Courtesy: D. Słonina (Centre of Oncology, Krak)

Cells ( $1 \times 10^5$ ) in 400  $\mu$ l of medium, plated as a drop in the centre of a 35 mm Petri dish and left overnight to adhere (cells occupied an area  $\sim 1 \text{cm}^2$ )



- Ions: H, He, Li, Be, B, C, N, O, Ne, Ar, Fe, Pb, U ??
- Energy: 5 – 70 MeV/amu ??
- Range in water: 0.1 – 30 cm
- Beam c/s: 0.5 - 15 cm (flat dose distr.)
- Dose rates: 1-10 Gy/min.
- Horizontal and vertical (up) beams
- Dosimetry: protocol/to be developed

Courtesy of Prof. Waligorski

# Classical 2D cellular models

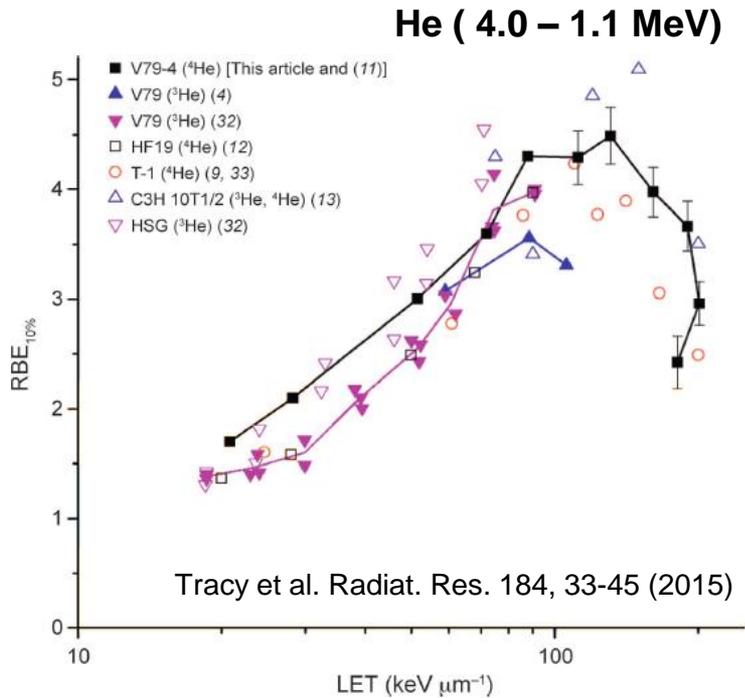


FIG. 8. Variation in RBE for 10% survival as a function of LET of helium ions (<sup>3</sup>He and <sup>4</sup>He) for a range of experimental data on V79 cells (closed symbols) and other cell lines (open symbols).

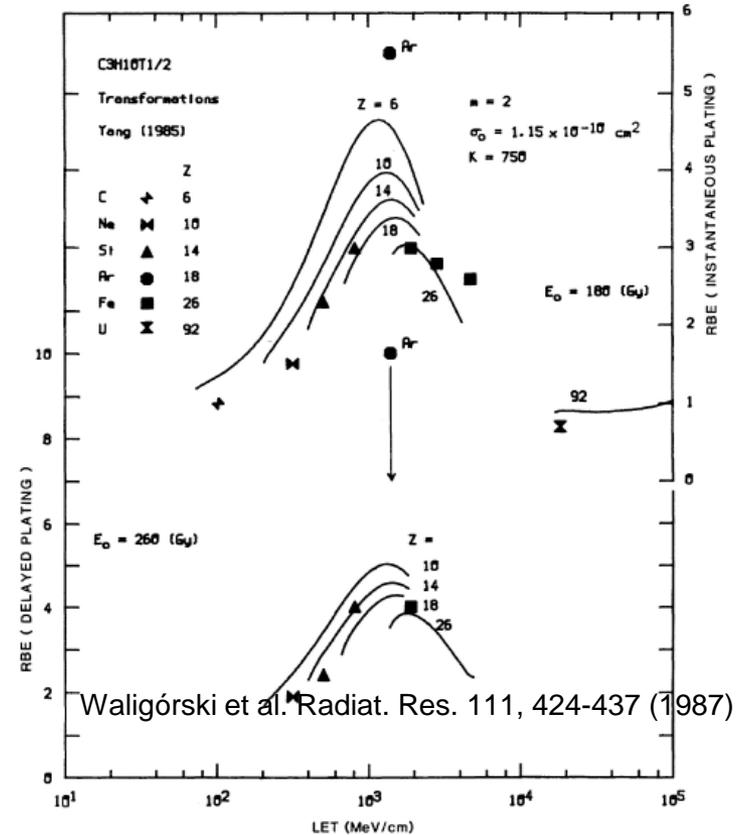
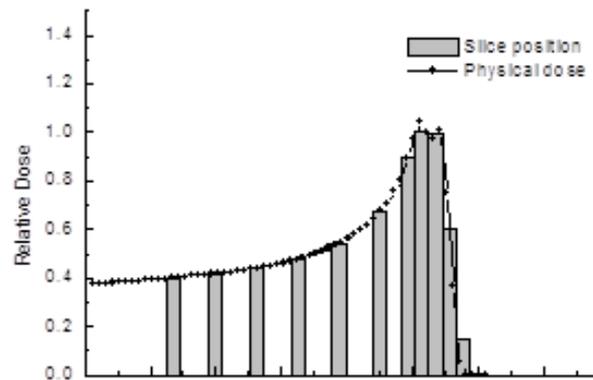
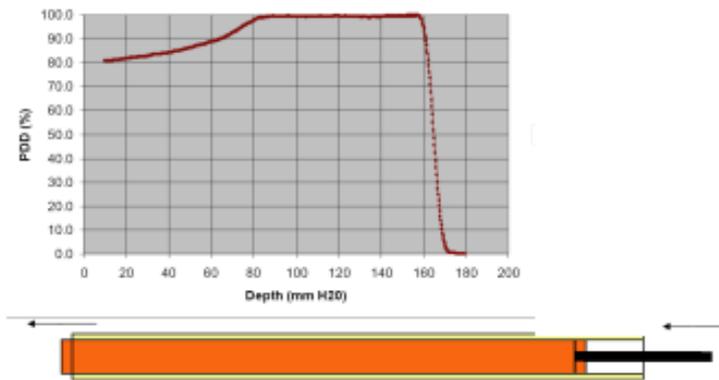


Figure 5. Measured (7) and calculated RBE for transformations in C3H10T1/2 cells at levels corresponding to 50% survival, indicated in Figure 4, for instantaneous (upper panel, upper right-hand ordinate) and delayed (lower panel, lower left-hand ordinate) plating.  $m = 2$  target parameters were used.

Ions: C, Ne, Si, Ar, Fe, U  
 Energy: 425 – 960 MeV/amu,

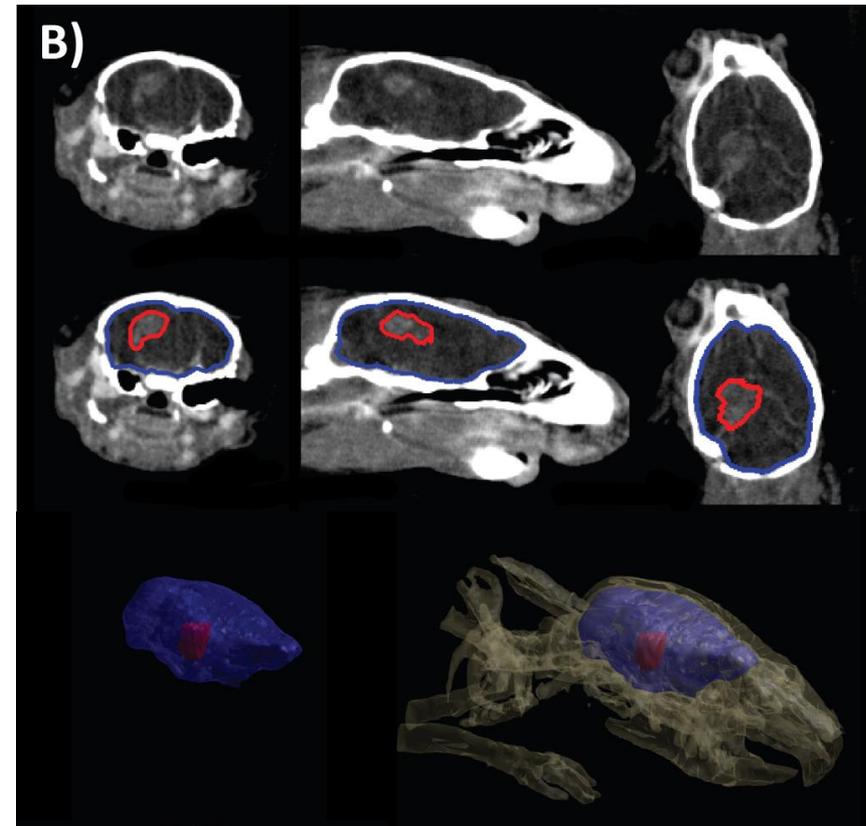
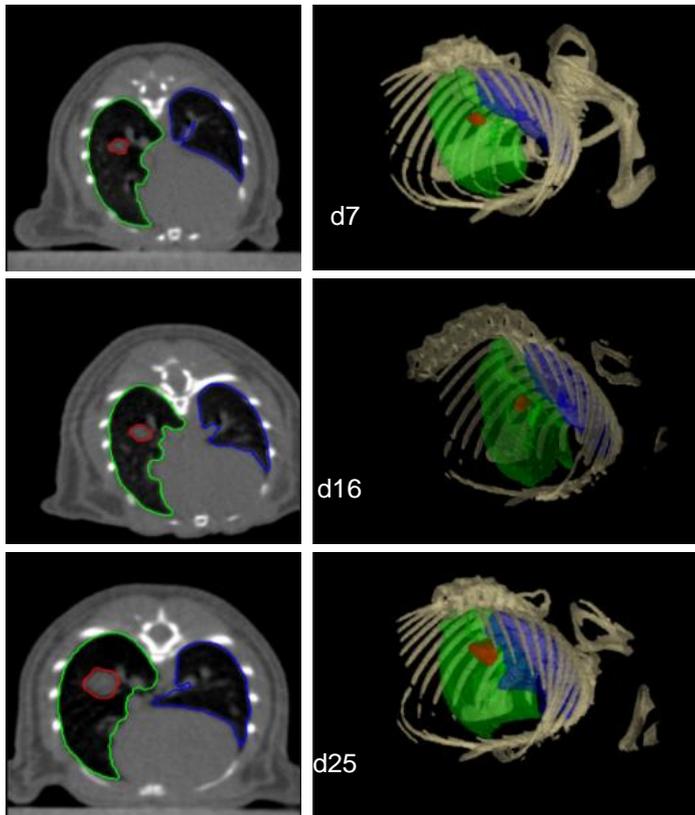
# 3D models “The radiobiological sausage”



# Animal experiments: Cancer models



- Subcutaneous murine, rat, syngeneic, human, PDX tumor models
- Orthotopic lung, brain human models (pneumonitis and fibrosis)

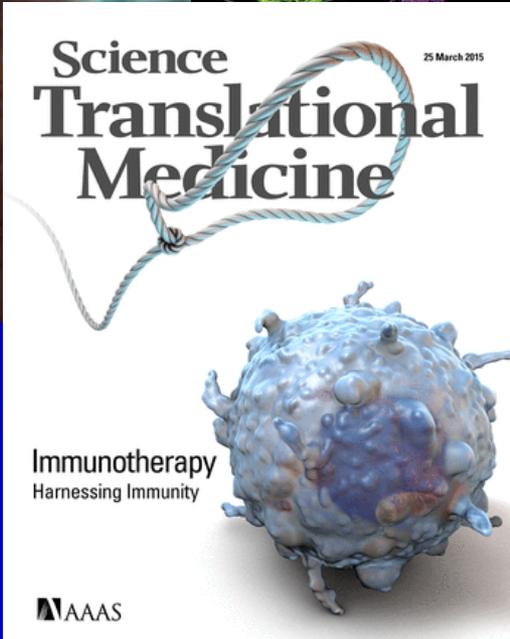


Test immunological effects, dose/RBE painting strategies, genetic defects...

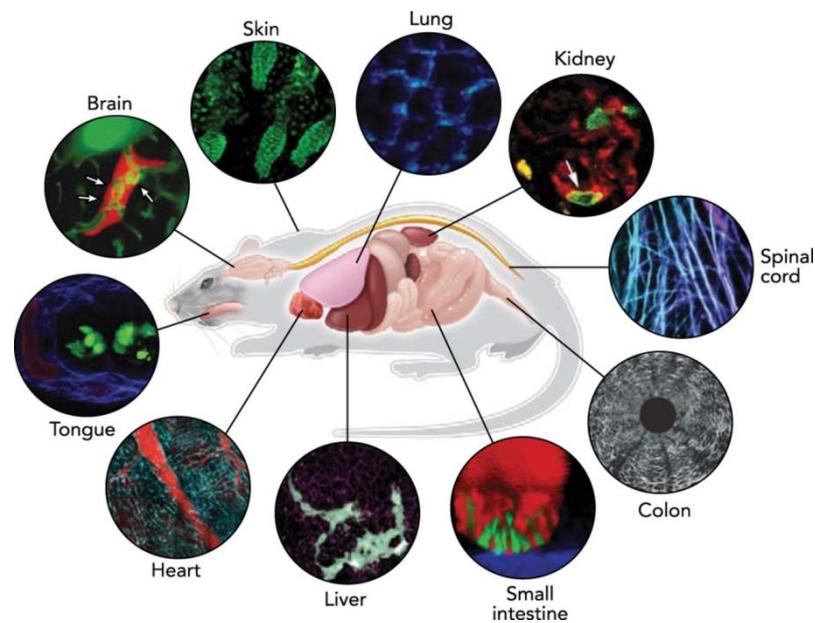
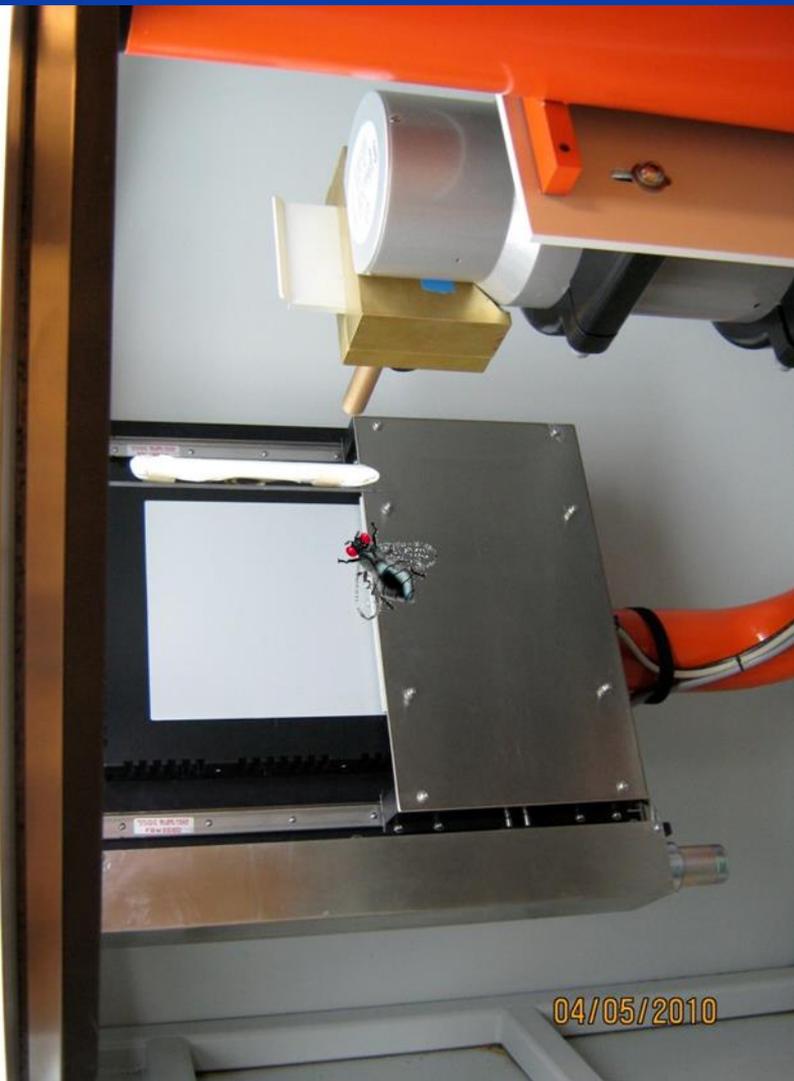


**2015 TOP CANCER DOCTORS**

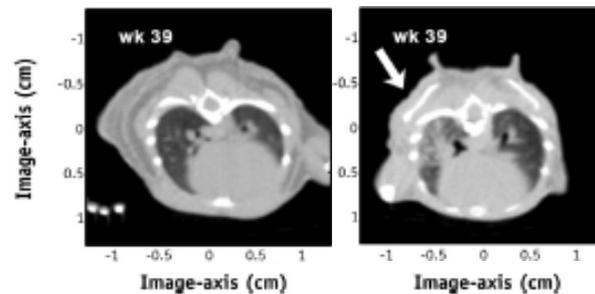
# Newsweek



# Normal tissues



- Normal tissue radiation-induced toxicity models (gut mucosa, lung pneumonitis and fibrosis)



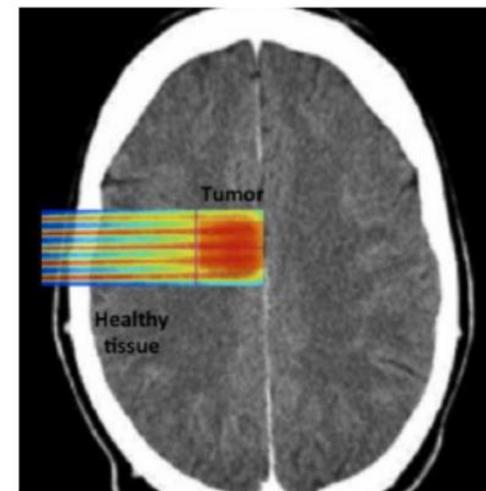
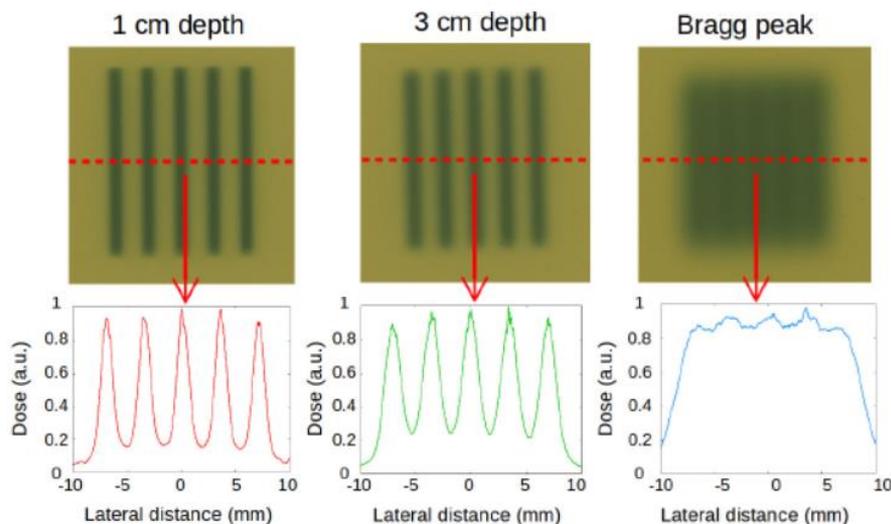
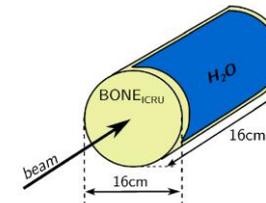
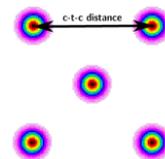
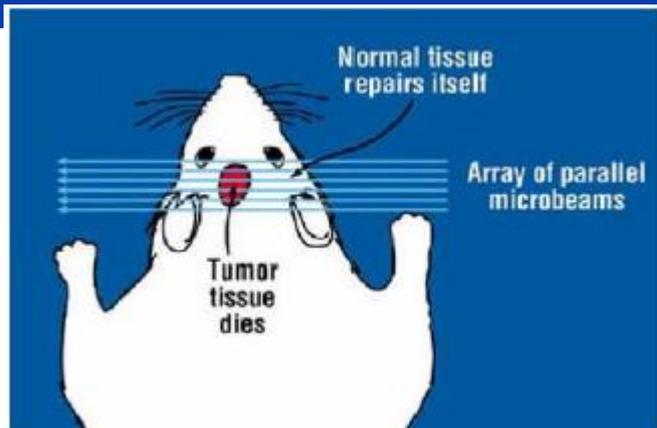
# Animal models e.g. microbeams



## Proton microbeams

(Kłodowska et al. Physica Med. 2015,

(FLUKA MC)



# Content



1. Introduction: the context
2. Biology does matter!
3. Motivation & Potential research questions
4. Experimental models
5. Wish list and the user model

## 1. Accelerator requirements

+ **Access to reference sources:** Co-60 reference unit (c. 2 Gy/min.), X-ray reference unit (e.g. 250 kVp, variable dose rate, 0.5 Gy/min – c.. 5 Gy/min);

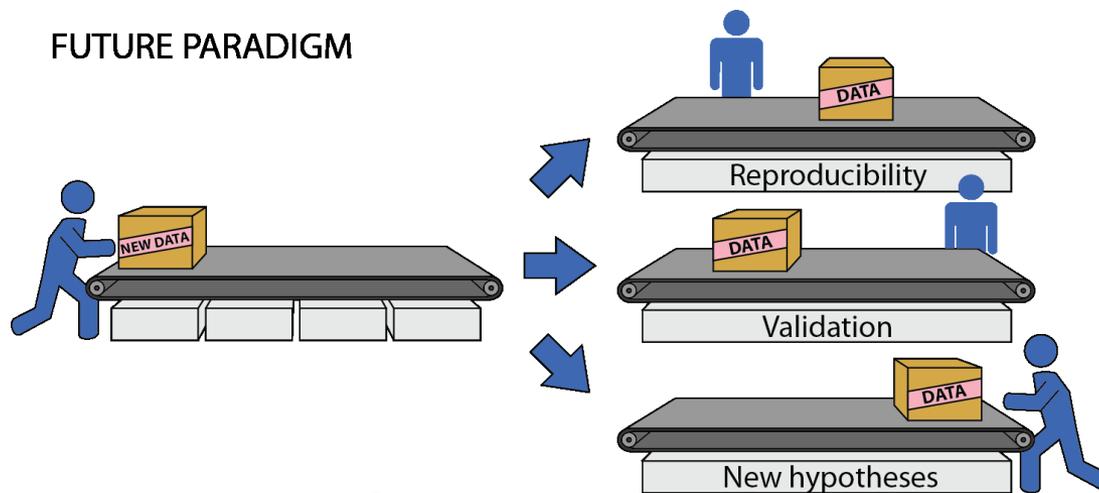
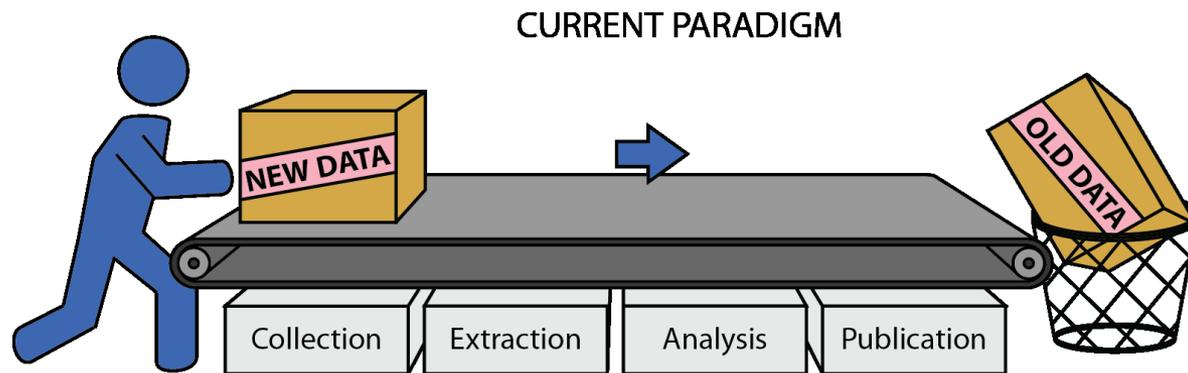
## 2. Equipment for biological experiments

- + **Electronic web-based recording system (« CERN invented internet »):** easier for external collaborators + facilitate to reuse the data
- + **State of the art Animal facility** (or access to animal facility with « transient hotel »).

# All data open source for reuse



e.g. [www.cancerdata.org](http://www.cancerdata.org)



Modified from  
Deasy et al.

# Models



1. User service- no active lab just a manager officer) – external scientists
2. Updated core facility with an active lab & experienced technicians, open to external groups (the GSI model)

# Conclusions



1. The context: CERN medical
2. Biology does matter!
3. Motivation & Potential research questions
  1. Normal tissue
  2. Tumor
  3. Mechanistic & descriptive modelling
4. Experimental models: cellular (2D-3D), animals (controversy)
5. Wish list and the user model

# Acknowledgements:

Mike Waligorski

Bleddyn Jones

Kevin Price

Marco Durante

Brad Wouters

Ludwig Dubois

***Thank you for your attention***

Reserve slides

# Summary:

## Role of the International Strategy committee in the LEIR initiative

In short: “Give input from the community”

- 1. Research questions (priority)**
- 2. Requirements for infrastructure**
- 3. Network**
- 4. Grant**

# A Wish List - Accelerator requirements (1/2)

(compiled with the help of Mike Holzscheiter, Niels Bassler, and Alberto Del Guerra)

**Ion species:** Lighter (H, He, Li, Be, B, C, N, O), heavier (Ne, Ar, Fe, Ar, Kr?, Xe?, Pb? U?) No need for a complete range. The lighter ions are for radiobiology and radiotherapy, the heavier for physics, dosimetry, detector studies, radiation protection and some radiobiology;

**Ion energy:** Lower (< 70 MeV/u), higher (50 -500 MeV/u) and highest (>1 GeV/u) Lower energies for radiobiology, higher for medical applications (radiotherapy, dosimetry), highest for physics and dosimetry. Physical data (for MC and therapy planning) to be gathered at all energies for all ion species;

**Beam Lines:** **Vertical** (50 or 70 MeV/u) for radiobiology and radiotherapy (animals); **Horizontal** (all energies);

**Extraction:** Fast uncomplicated energy switching (spill by spill), either directly in synchrotron mode, or by a range shifter;

# A Wish List – Equipment & Support

**At target area (isocenter):** XYZ translator, with sub mm precision; water phantom (PTW MP3 or similar); laser guides; video surveillance, data transfer systems & power supplies;

**Access to machine shop facilities:** tasks include building custom sample holders, custom phantoms, etc.;

**Access to reference sources:** Co-60 reference unit (c. 2 Gy/min.), X-ray reference unit (e.g. 250 kVp, variable dose rate, 0.5 Gy/min – c.. 5 Gy/min);

**On-site tissue culture laboratory, equipped** (see next slide);

**Dedicated office space for visiting groups (how large?) ;**

**Managing officer** (to instruct on use of equipment, collaborate with users, liaise with accelerator staff, workshop, to design and maintain dosimetry and control equipment, power supplies, communication networks, data transfer, etc.) Also to perform his own research on site.

**Flexible design of research area:** to incorporate future themes, research issues and technology development;

**Stable financing:** European/world collaboration programmes (Horizon 2020?)

# A Wish List – The Clean Room

The dedicated clean room for biology & radiobiology experiments should contain:

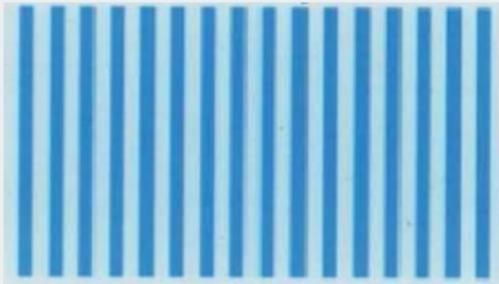
- 4 incubators, or more (bottleneck)
- 3 flowbenches for handling of sterile samples
- 1 fumehood
- refrigerators for and grow media
- freezer -20 for cell cultures
- freezer -80 for cell cultures
- 2 centrifuges
- cell counter
- autoclave
- special glassware dishwasher
- 2 standard microscopes
- 1 UV microscope (nice to have)
- Biohazard disposal?
- Gas supply (CO<sub>2</sub> for incubators)
- Water-sterilizer
- ~ 10 meters of bench space
- consumables (gloves, pipettes, etc.?) to be provided by visiting groups



[z5waligo@cyfronet.pl](mailto:z5waligo@cyfronet.pl)

## Minibeam radiation therapy

- Submillimetric field sizes (beam width: hundreds of  $\mu\text{m}$ ).
- Spatial fractionation of the dose.



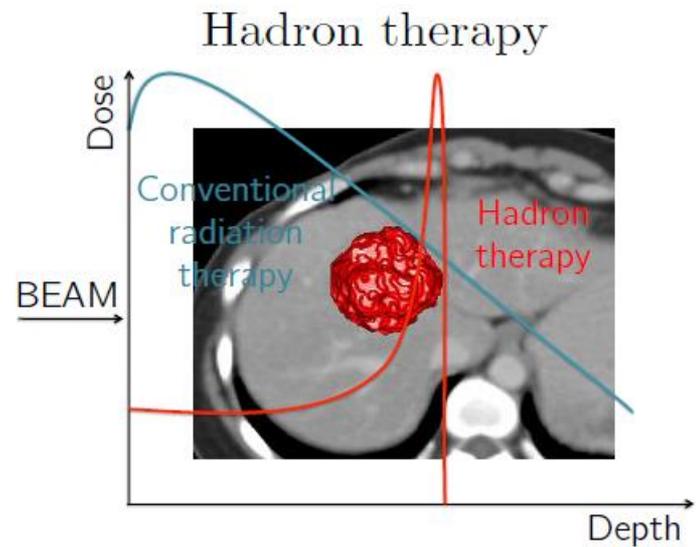
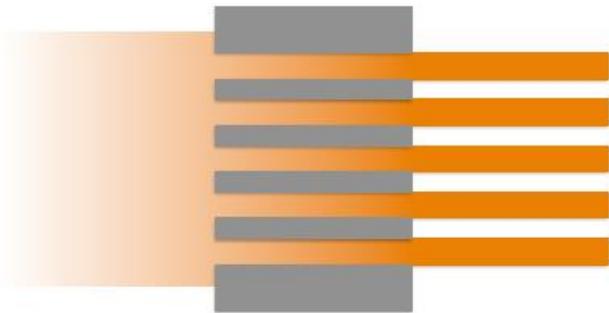
## Conventional radiation therapy

- Large field sizes (larger than  $1 \times 1 \text{ cm}^2$ ).
- Homogeneous dose distributions.

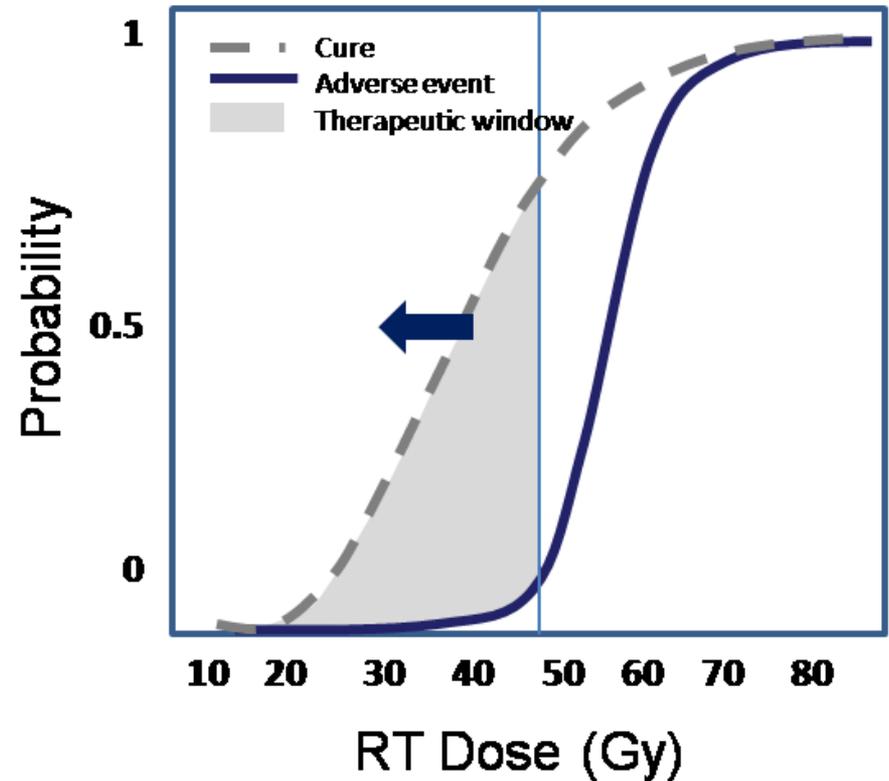
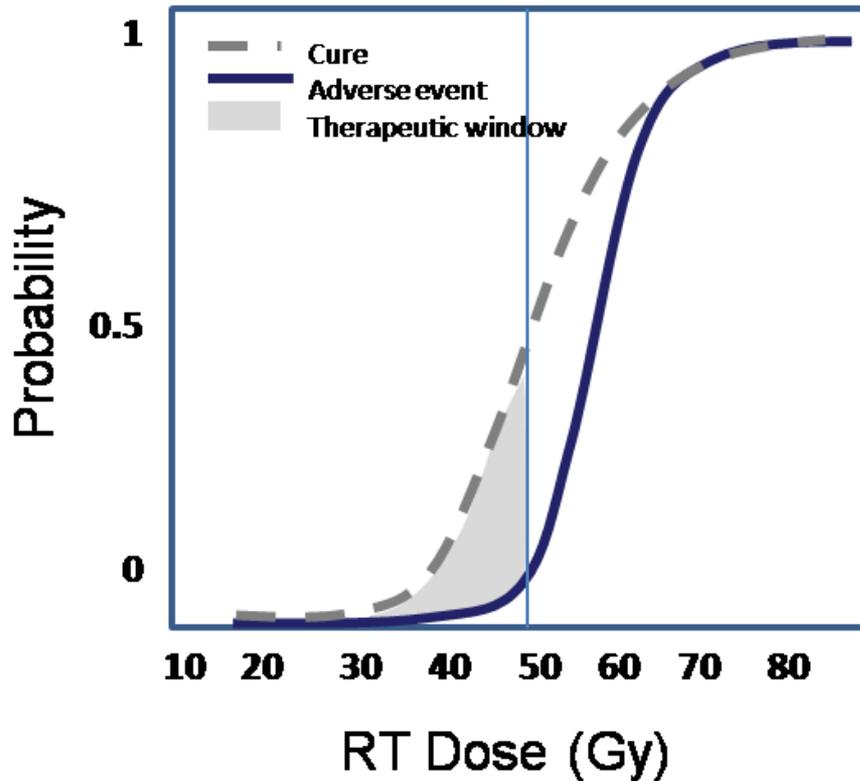


## Hadron minibeam radiation therapy

Spatially fractionated  
radiation therapy (MBRT)



# WHY? RADIOTHERAPY OPTIMIZATION



*Schematic representation of opening the radiotherapy therapeutic window provided by radiosensitizers (left: radiotherapy alone; right: radiotherapy in the presence of radiosensitizers).*

