Physics and radiobiology in hadrontherapy

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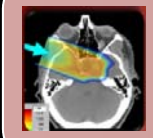
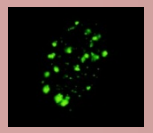
(CNRS/IN2P3 & Université Blaise Pascal)

Outline



1. The basic principles of hadrontherapy

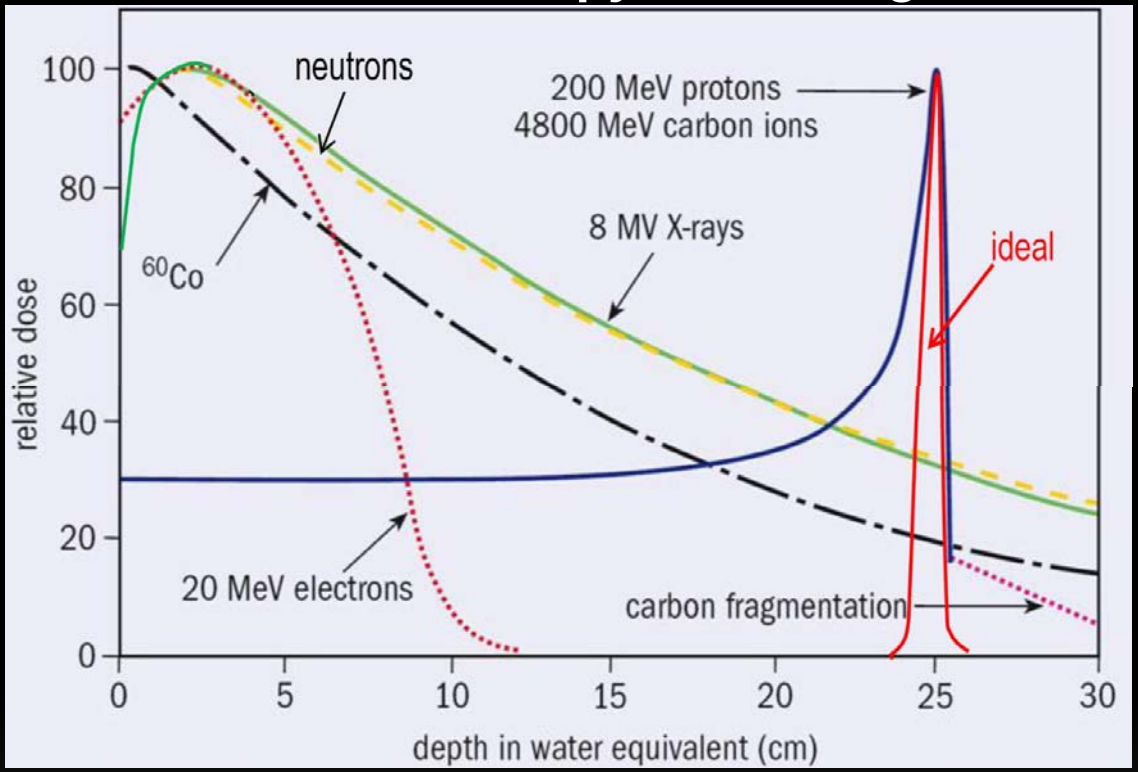
2. Physics for radiobiology



3. The structuration of the reseach for hadrontherapy

Physical basis of hadrontherapy

The icon of radiation therapy with charged hadrons



Radiation beam in matter

First idea : Bob Wilson, 1946
[R.R. Wilson, Radiology 47 (1946) 487]

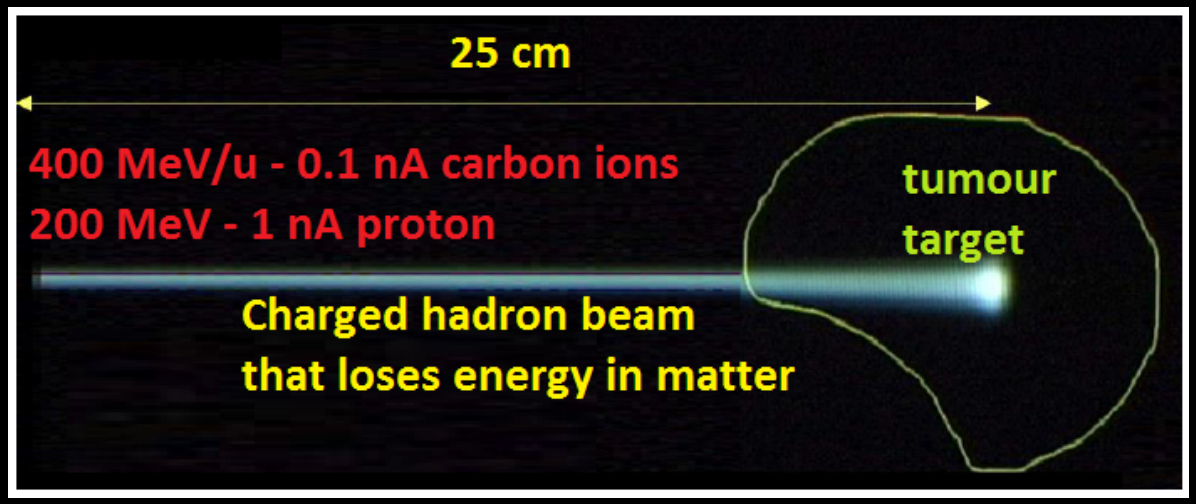
Bragg peak
Better conformity of the dose
To the target
→ healthy tissue sparing

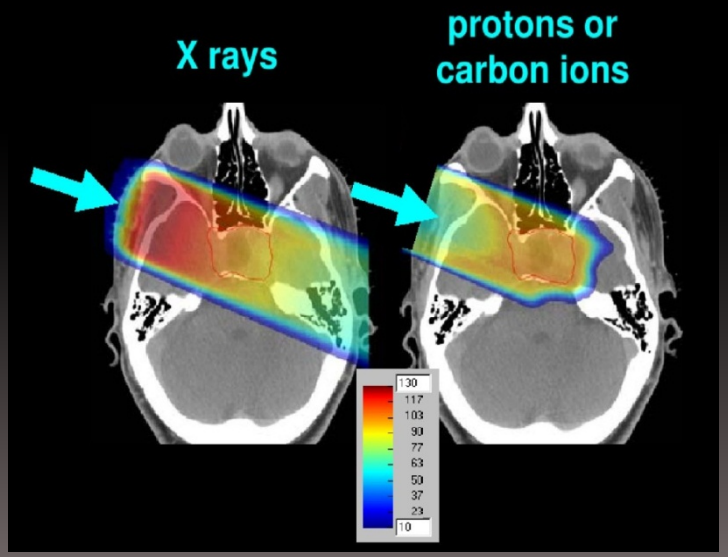
Hadrons are charged
→ Beam scanning for dose distribution

Heavy ions
→ Higher biological effectiveness (RBE)

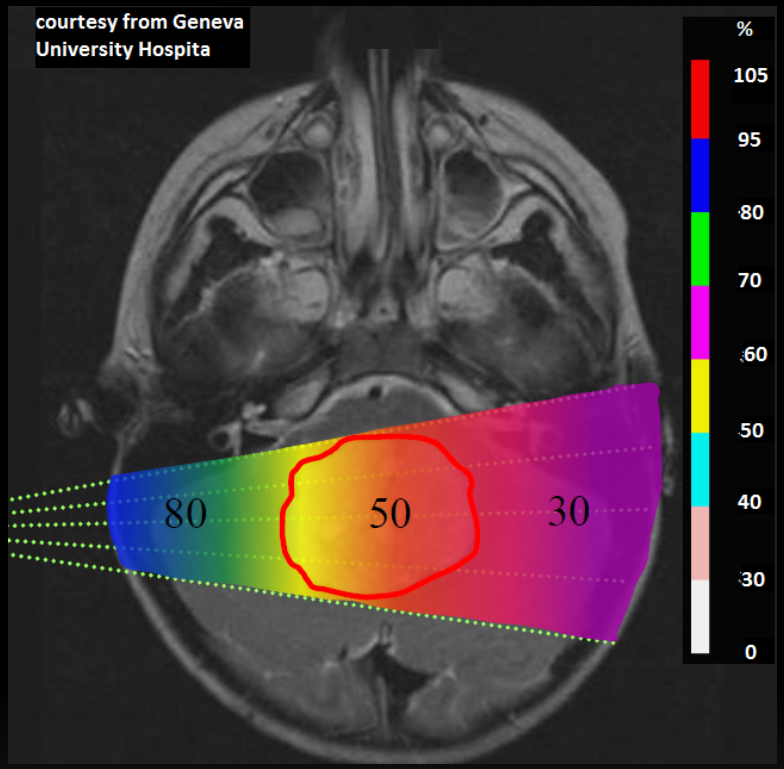
Physical basis of hadrontherapy

Protons and ions spare healthy tissues

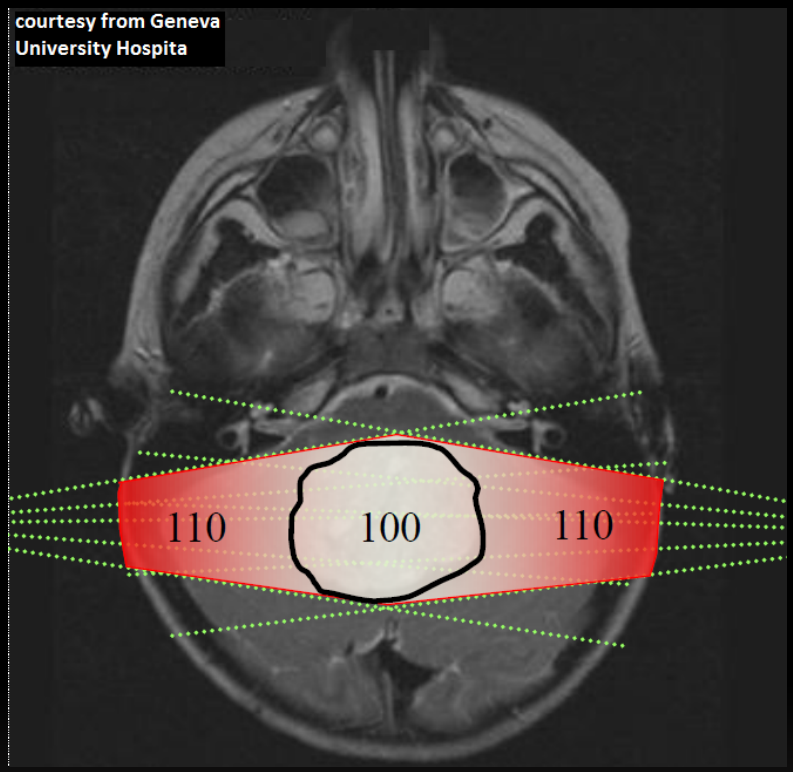




X-rays radiotherapy



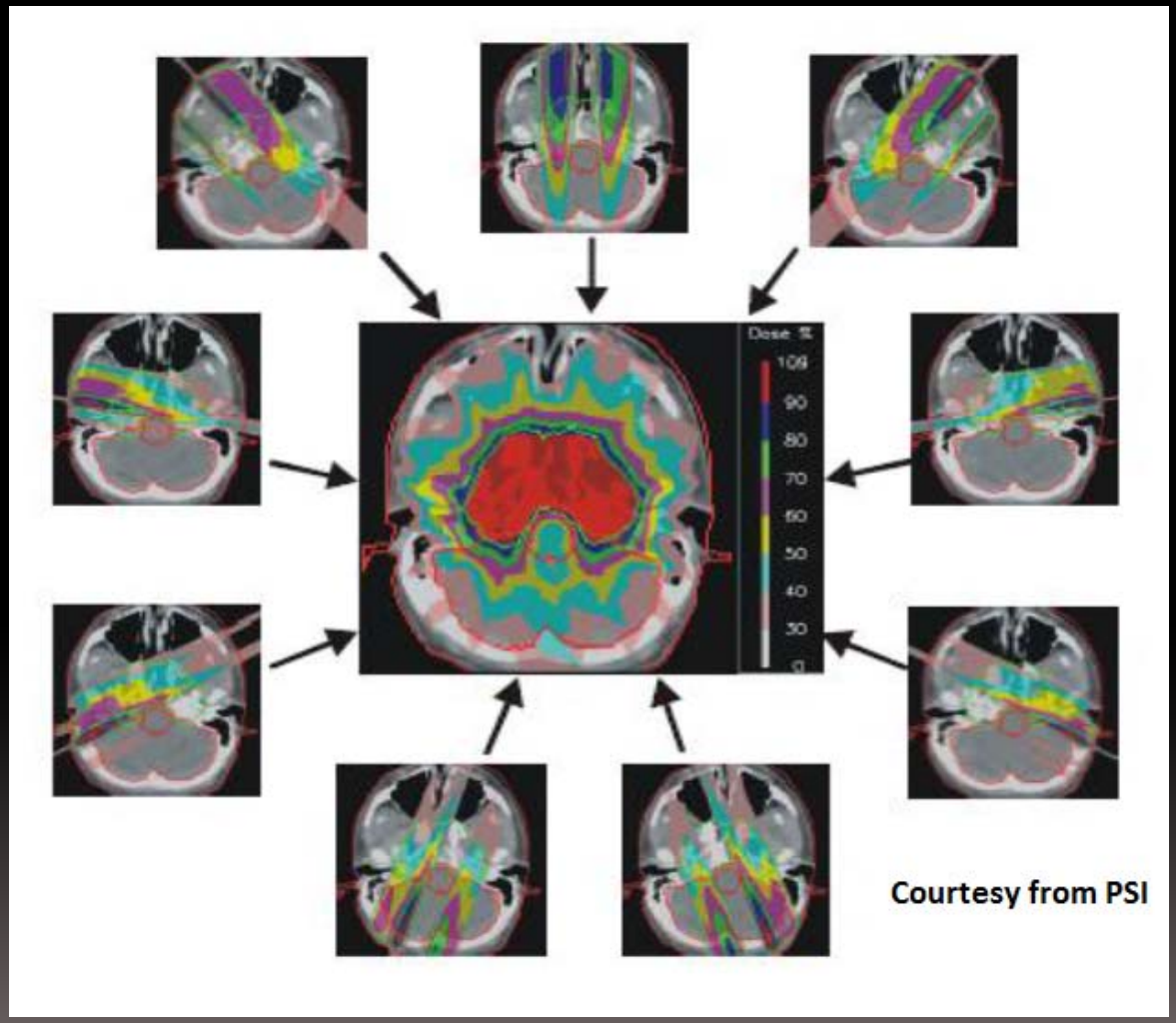
One lateral photon beam deliver a non conformal dose



Two opposite photon beams are not enough to deliver a conformal dose

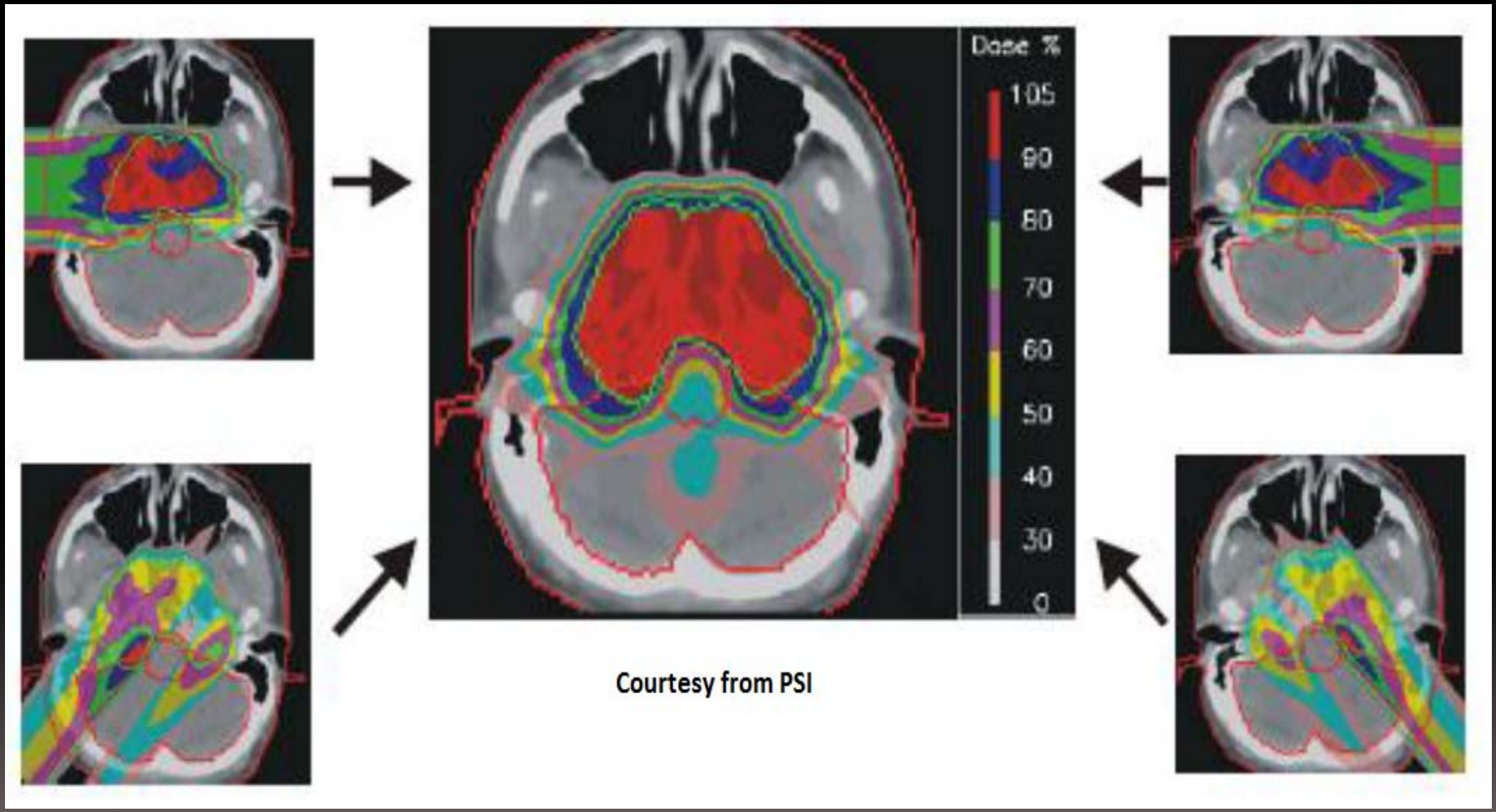
IMRT = Intensity Modulated Radiation Therapy with photons

9 non uniform fields



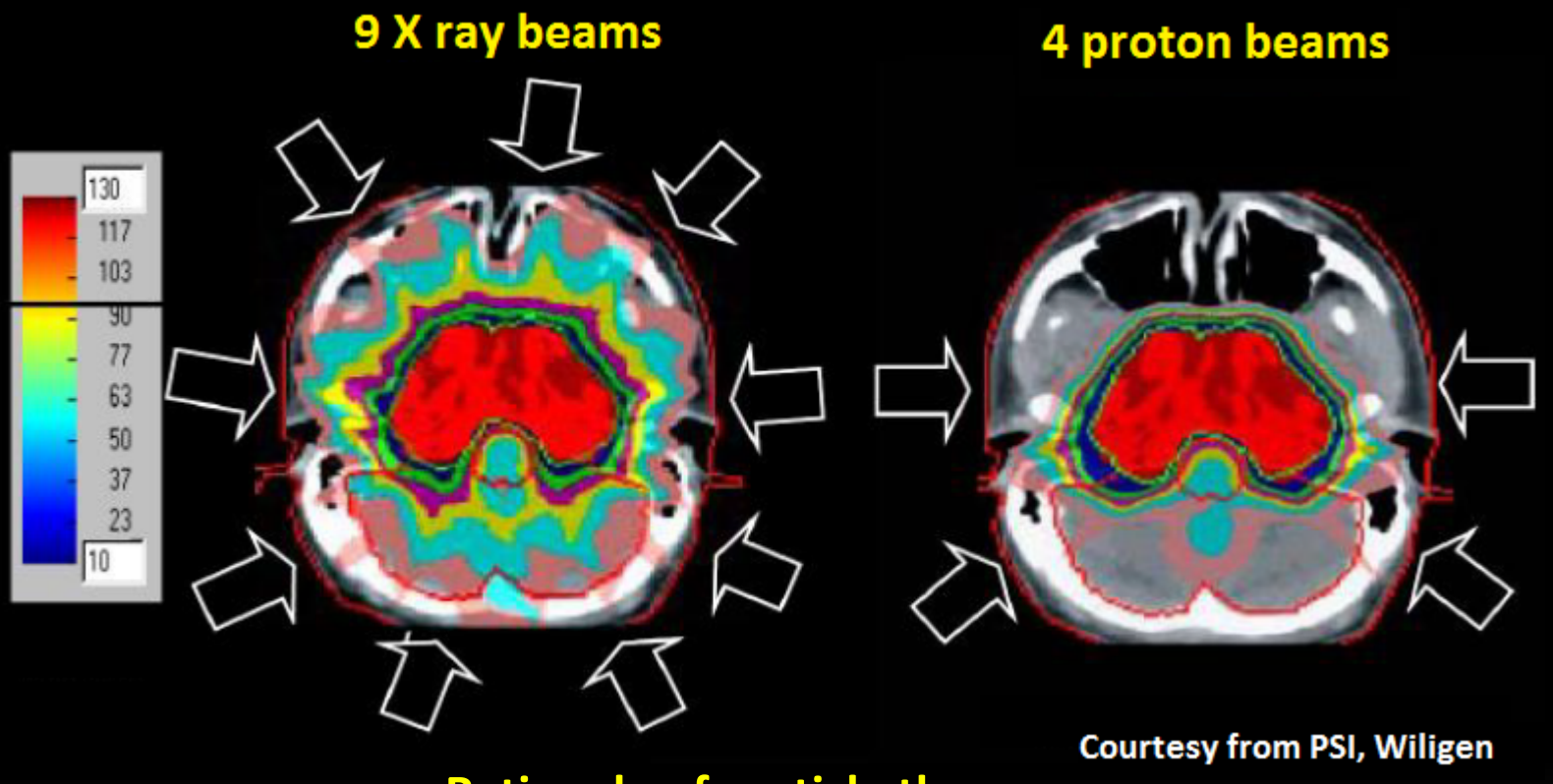
IMPT = Intensity Modulated Particle Therapy with protons

4 non uniform fields



Courtesy from PSI

Hadrons are quantitatively different from X-rays



Courtesy from PSI, Wiligen

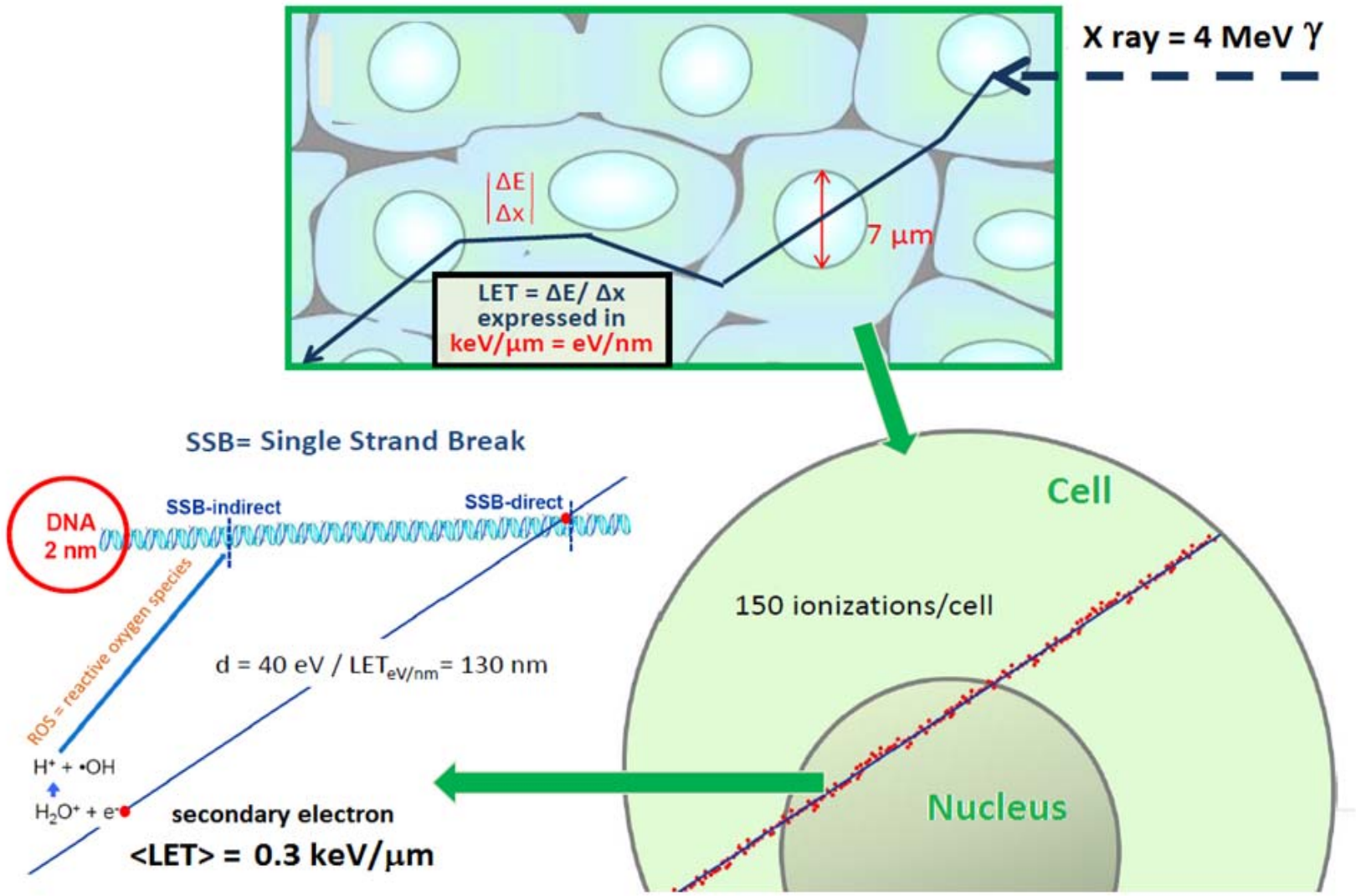
Rationale of particle therapy (proton, carbon ions)

Specific dose distribution for hadrons (Bragg peak)
Better conformity of the dose to the target → healthy tissue sparing

Higher biological effectiveness (RBE) to kill tumoral cells

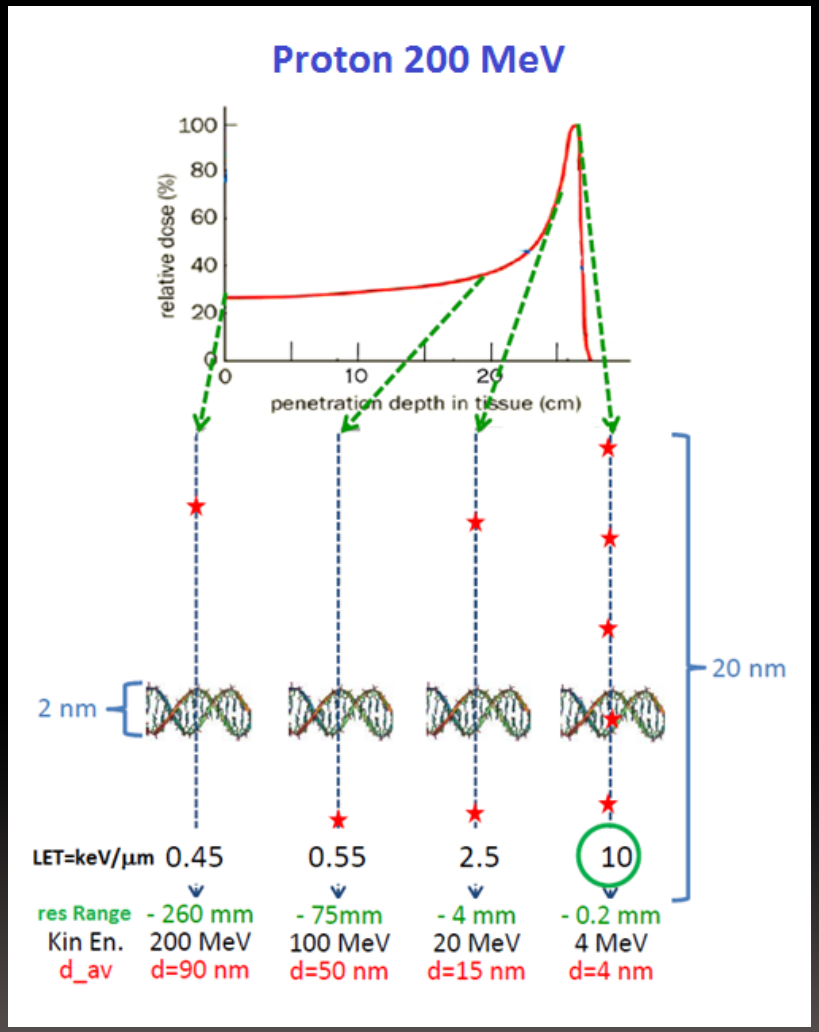
Insight of dose distribution at microscopic level

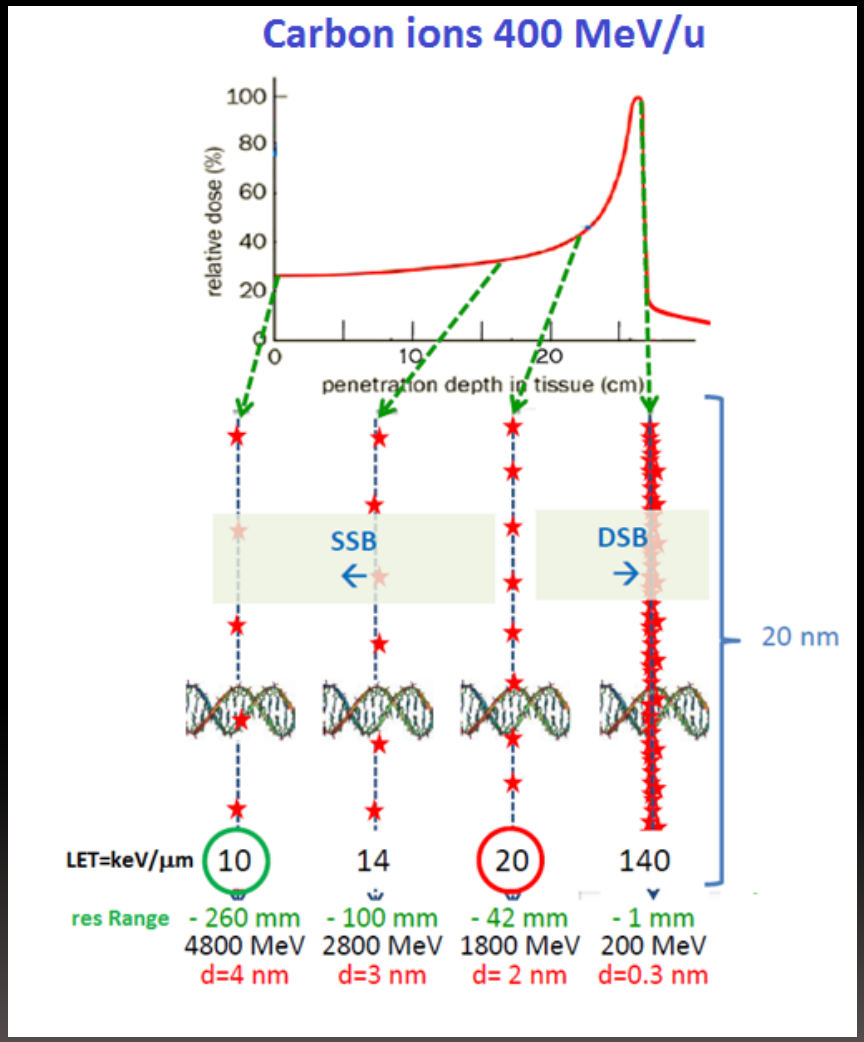
Microscopic distribution of the X-rays dose



Insight of dose distribution at microscopic level

Microscopic distribution of the hadronic ionization



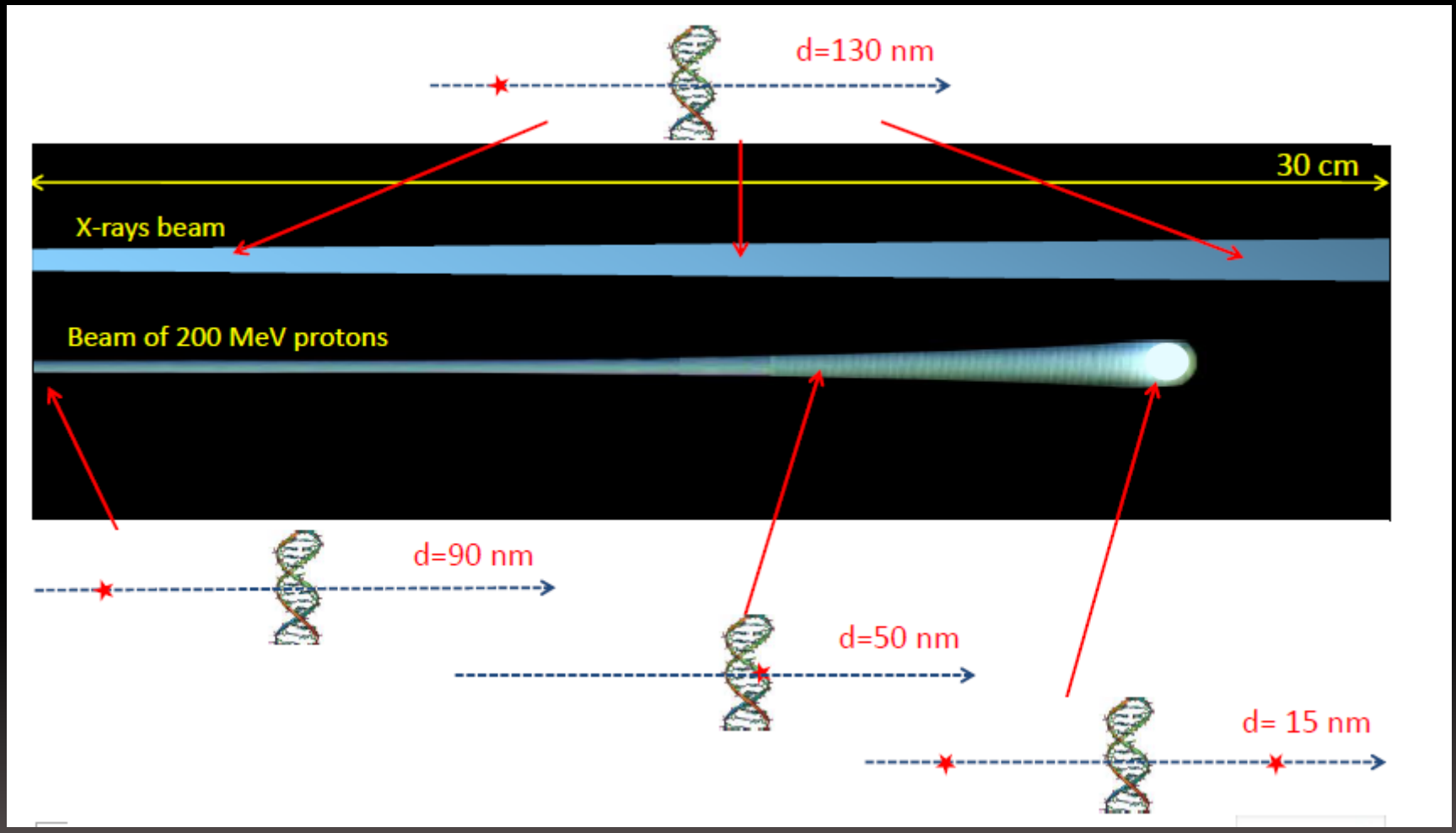


Protons are SPARSELY IONIZING

Carbon ions are DENSELY IONIZING (higher biological effectiveness

Insight of dose distribution at microscopic level

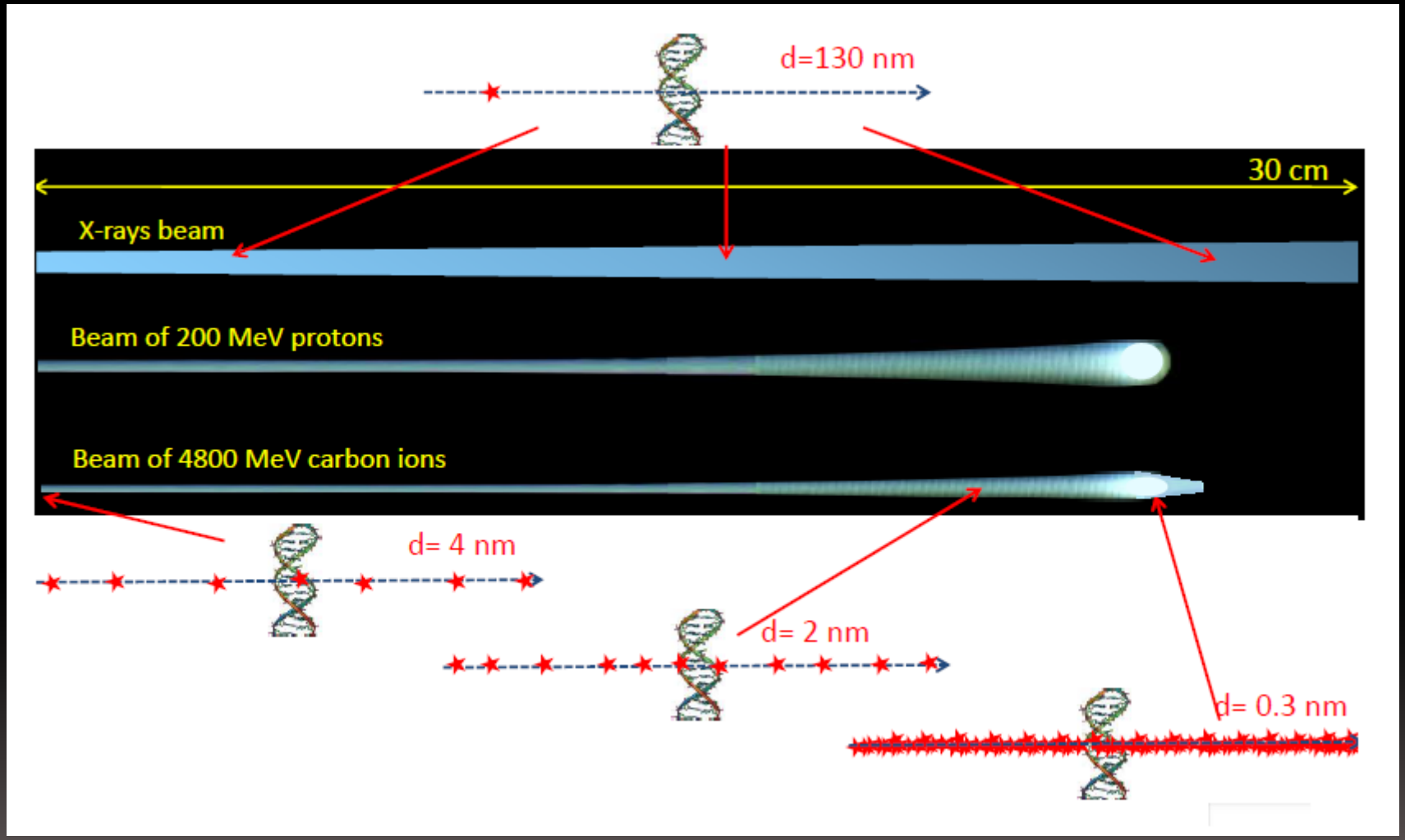
Protons: 1. more favorable dose 2. same '**indirect effects**'



Protons are SPARSELY IONIZING

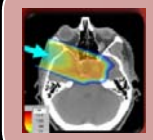
Insight of dose distribution at microscopic level

Carbon ions: 1. more favorable dose 2. '**direct effects'**



Carbon ions are DENSELY IONIZING (higher RBE)

Outline



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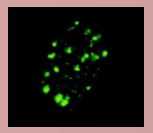


3. The structuration of the reseach for hadrontherapy

Scientific programs for hadrontherapy

Four Different domains of R&D:

1. **Clinical research in hadrontherapy**
2. **R&D to Improve treatment planning in hadrontherapy**
3. **Radiobiology for hadrontherapy**
4. **R&D in instrumentation for treatment quality**

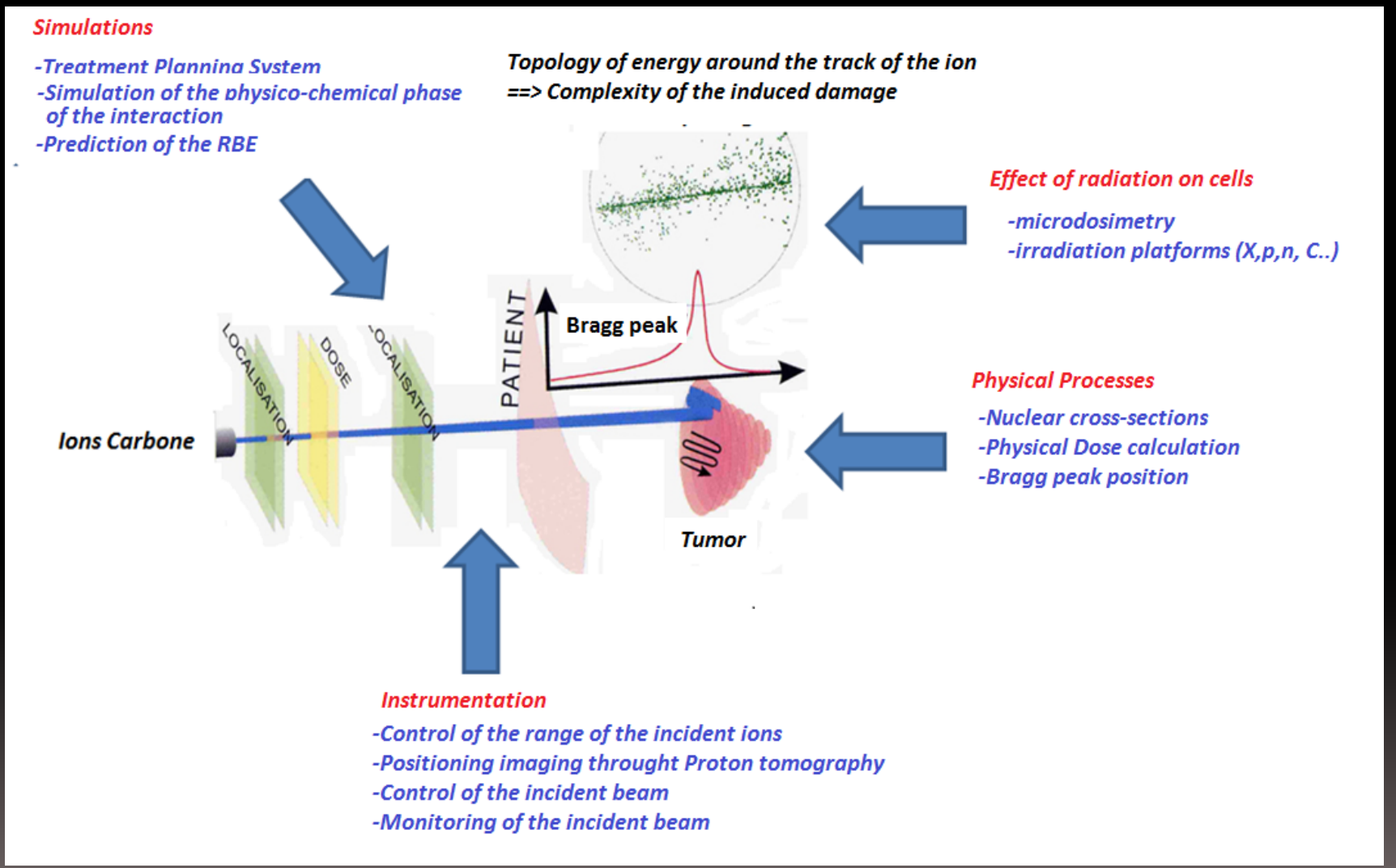
Multidisciplinary reseach involving clinicians and physicians, biologists, physicists, engineers.

I will adopt the point of view of a physicist and highlight some examples to show what the physics brings to item #2 and #3

The contribution of physics can be summarized in two main fields

- **Multiscale simulations of the interaction of radiation with biological matter**
  - ✓ **Simulation of the early physico-chemical effects of irradiation in cells at microscopic and nanometric scale**
  - ✓ **Biophysical prediction model of the RBE for treatment planning**
- **Instrumentation and development of specific tools**
  - ✓ **tools for i*n-vitro* and in-vivo irradiation platforms**
  - ✓ **instrumentation for microdosimetry and nanodosimetry**

Scientific programs for hadrontherapy



Scientific programs for hadrontherapy

In particle radiation therapy, it is essential to calculate not only the absorbed dose but also the biological effect, which is often expressed as following

Bragg peak

Physical Dose D_{phys}

$$RBE = \frac{D_{X-ray}}{D_{particle}}\Big|_{same\ effet}$$

Relative Biological Effectiveness

$$D_{Biol} = D_{Phys} \times RBE$$

Determination of D_{phys} and RBE are rather complex tasks since both depends of many parameters

D_{phys} depends

- ✓ *on the quality of the radiation fields at target*
- ➔ *du to carbon fragmentation*
- ➔ *rather complex fields*

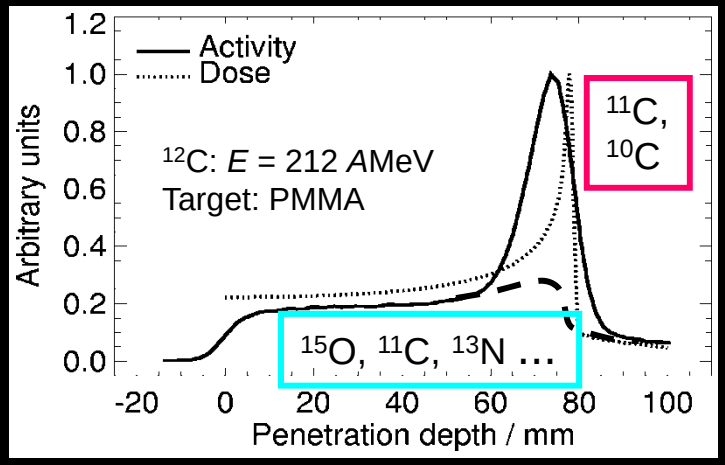
RBE depends

- ✓ on cell lines,
- ✓ *increase of RBE is also connected to a decrease in the radioresistance in oxygen depleted tissue*
- ✓ *RBE depends also of the LET of particles*

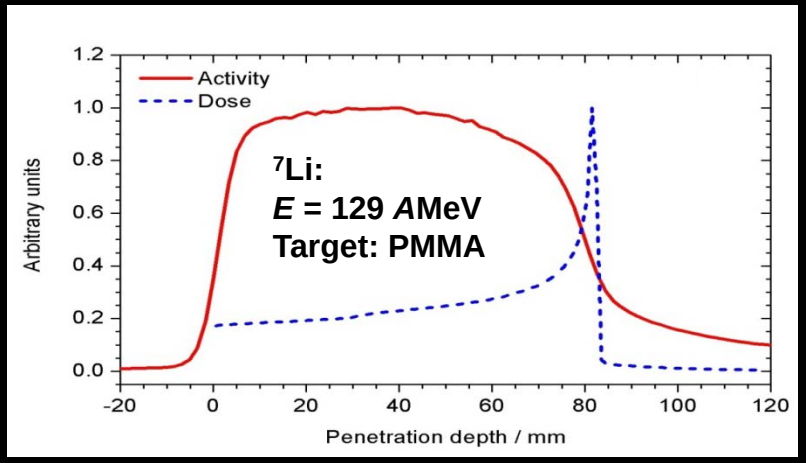
Scientific programs for hadrontherapy

Interaction of carbon ions by nuclear fragmentation or electromagnetic interaction imply a degradation of the incident beam, with productions of secondary particles (light fragments and radioactive nuclei)

$Z \geq 6$ **Projectile fragments** **Target fragments**



$Z < 6$ **Target fragments**



W. Enghardt et al.: Phys. Med. Biol. 37 (1992) 2127

Need to know exactly the physical interactions of 12C in heteregeneous tissues

- ***Simulations do not reproduce fragmentation of 12C with sufficient accuracy***
- ***~2.5% & ~1-3 mm on Bragg peak***
- ***Definition of the radiation field composition at tumour position***

- ***Need of experimental nuclear data specific of this application***
- ***Improve and constraint physical dose simulation codes***
- ***Integration of simulation in TPS***

Scientific programs for hadrontherapy

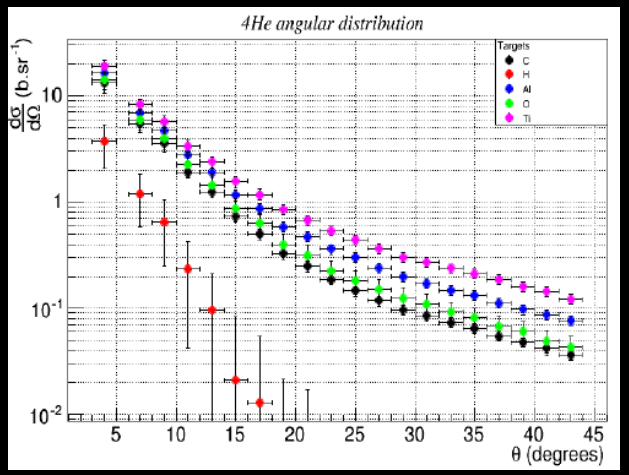
Experimental measurements of fragmentation cross-sections
= fundamental data for dose simulation and TPS

Experiments in GANIL

➔ experiments on thick PMMA targets (2008: LPC Caen, IPHC, IPNL)

➔ experiments on thin targets (2011: LPC Caen, IPHC, IPNL, SPhN, GANIL)

Projectiles : 95 MeV/u ^{12}C on different target (~50mg/cm-2) C, CH_2 ,Al,Al_2O_3 ,Ti

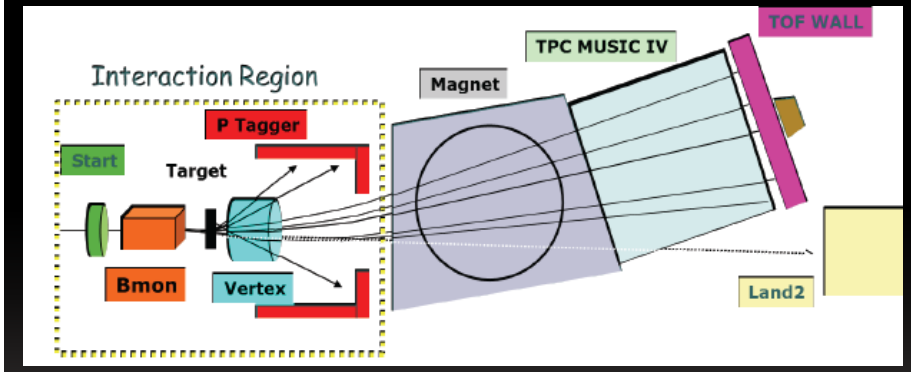


Differential cross-section $d^2\sigma(dEd\Omega)$
of ^{12}C on H, C, O, Ca from 4 to 43°

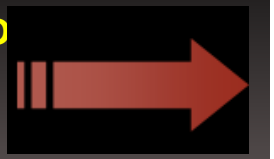
➔ 93% of the body composition

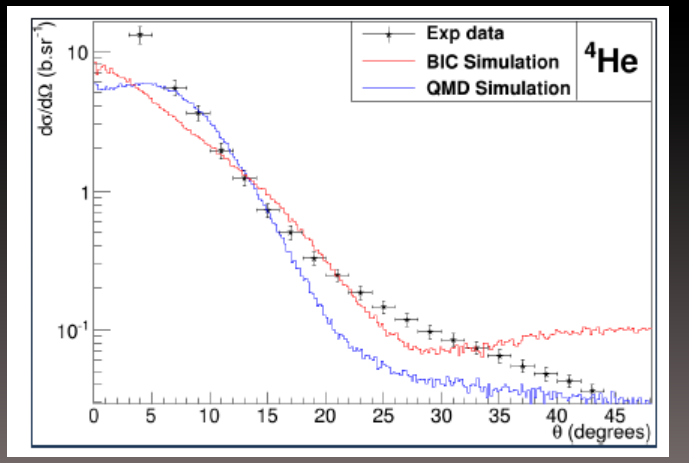
Experiment FIRST at GSI en 2011 (Allemagne,Italie,France):

Differential cross-section $d^2\sigma(dEd\Omega)$
of C+C, C+Au at 400MeV/u. (IPHC, SPhN, LPC Caen, IPNL)



Comparison of theoretical physical models (BIC, QMD INCL) shows disagreement with experimental data

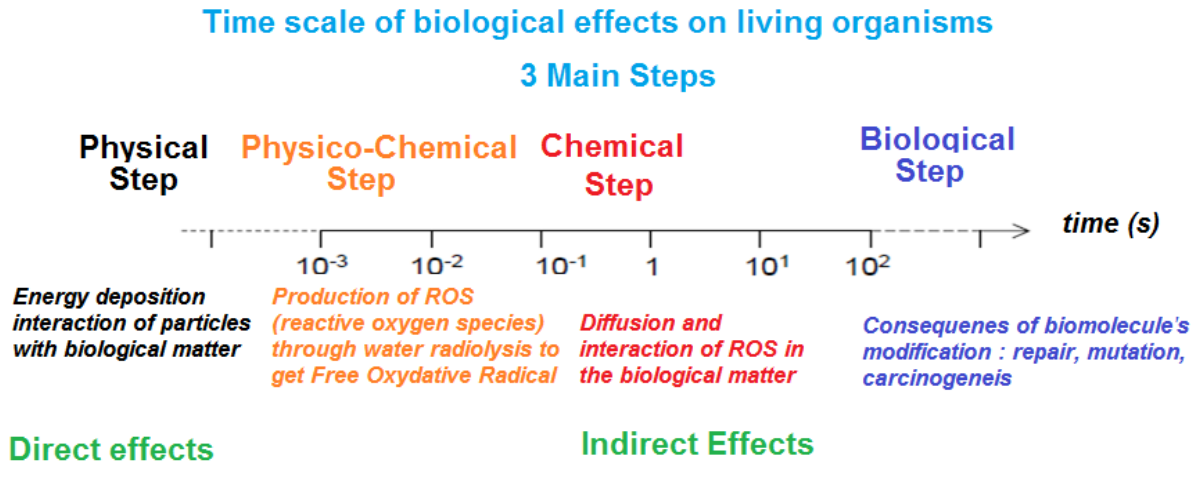


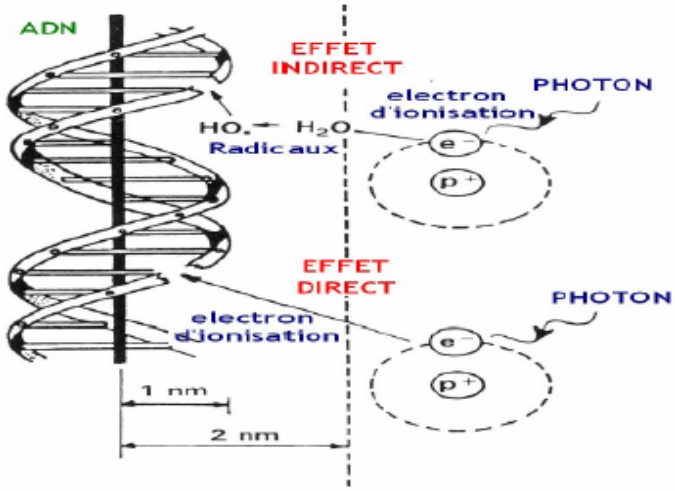


➔ Development of a dedicated model if necessary and/or generation of specific experimental databases

The shematic of the irradiation effects on cells

Modelisation to understand the early effects of Irradiation of cells
➔ Correlation with some biological endpoints





Design of simulation tools able to :

- ➔ *Simulate transport and physical early energy deposition at the correct scale (microscopic scale)*
- ➔ *Take into account the stochastic behavior of energy deposition at microscopic scale*
- ➔ *Take into account production and transport of main Reactive Oxygen Species*

As function of fluence, dose, LET of incident particle

Compare Monte Carlo prediction with biological observables

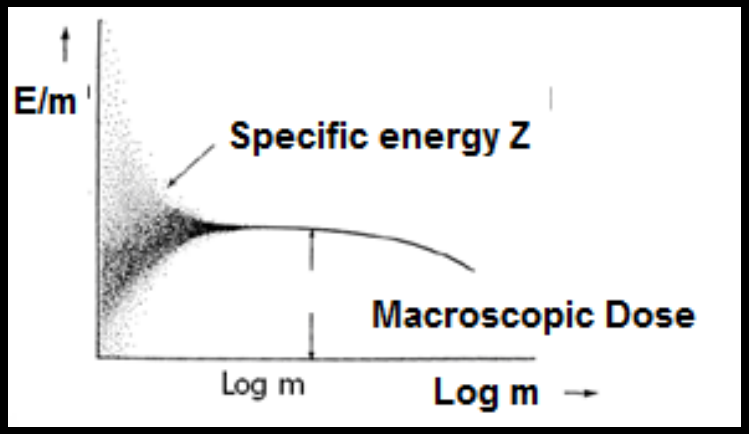
➔ from usual survival curves to foci analysis through immunofluorescence confocal microscopy

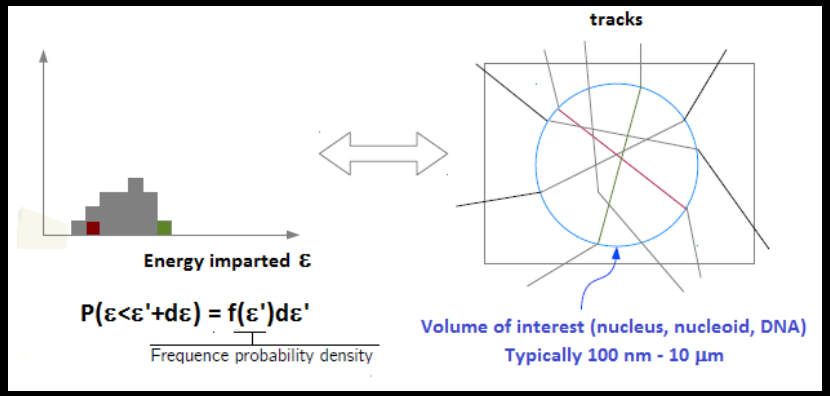
- ✓ GeantDNA project (*http://geant4-dna.org/*) ➔ From physical to chemical phase *S. Incerti et al.*
- ✓ LQ/Phychem/Chem ➔From physical to chemical phase *B. Gervais, M. Beuve et al.*
- ✓ PARTRAC project (*http://www.helmholtz-muenchen.de*) ➔From physical to early biological phase *W. Friedland et al.*

The Modelisation of the irradiation effects on cells

At small scale one should take into account the stochastic behavior of energy deposition

Use of the concepts of microdosimetry
(AM Kellerer and D Schmelevsky 1975)





Other quantities can be used to quantify the dose at microscopic scale :

➔ *Specific energy*, z, *equivalent to the dose, with mass* m *of the volume of interest where* ε *is the energy imparted in the volume of intererest*

$$z = \frac{\varepsilon}{m}$$

➔ *Lineal energy*, y, *equivalent to the Lineic Energy Transfert (LET) where* $\bar{l}$ *is the mean chord length in the volume of interest*

$$y = \frac{\varepsilon}{\bar{l}}$$

z *and* y *are stochastic quantities that are characterized by their probability distribution*

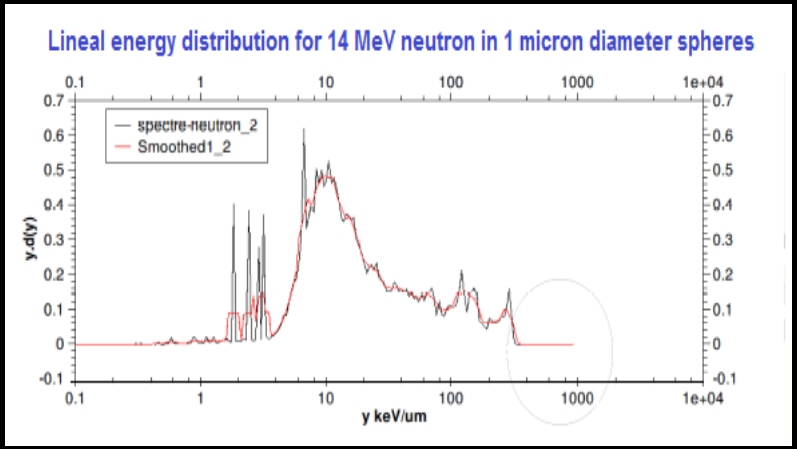
$f_1(z)$ *and* $f(y)$ *are the distributions for a "single" events (one energy deposition by only one track in the volume)*

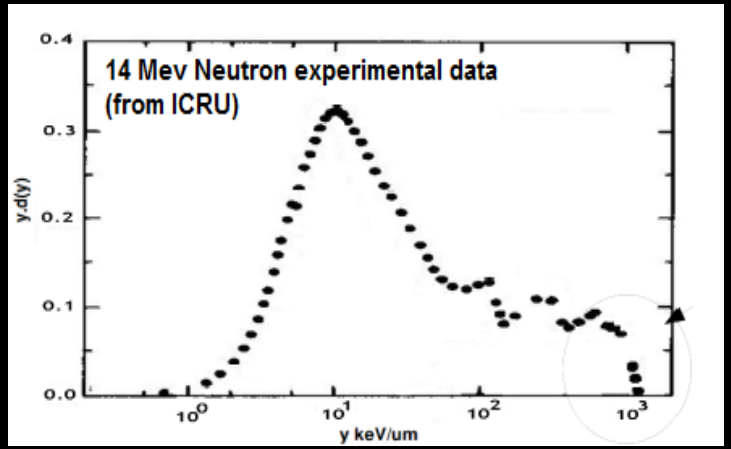
$f(z)$ *is the distribution for a "multiple" events*

Frequency mean specific energy $\overline{y_F} = \int_0^\infty y f(y)\,dy$

Dose mean specific energy $\overline{y_D} = \frac{1}{\overline{y_F}} \int_0^\infty y^2 f(y)\,dy$

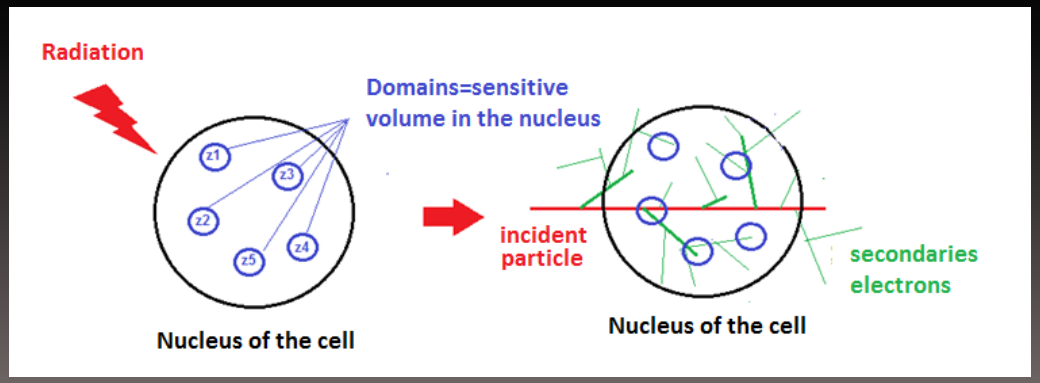
Use of the microdosimetry concepts





Simulation using Geant4 DNA for 14 Mev neutron lineal energy spectra in one micron sphere of liquid water ➔ to be compared with ICRU data

Application of the microdosimetry concepts to biophysics simulation of cell's survival fraction ➔ Biophysics prediction of the RBE using microdosimetric spectra as input data



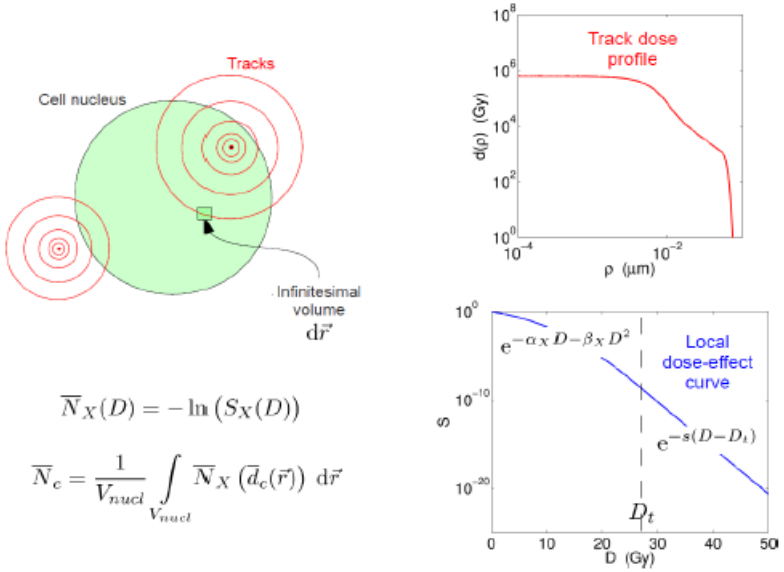
Prediction of the RBE using biophysics models

Different radiobiological model used in clinical centres for RBE prediction:

- ✓ **The Local Effect Model (Scholz & Elsasser) at GSI**
- ✓ **The Micro Kinetic Microdosimetric model (RR Hawkins)**
- ✓ **The « Nanox » model (M. Beuve et al.) developed in Lyon**

LEM model used at GSI

(Scholz et al. 1996, Elsasser et al. 2008)

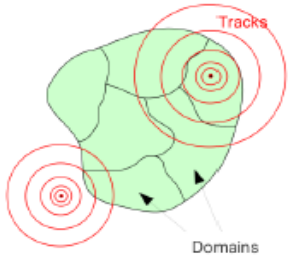


$$\overline{N}_X(D) = -\ln\left(S_X(D)\right)$$

$$\overline{N}_c = \frac{1}{V_{nucl}} \int_{V_{nucl}} \overline{N}_X\left(\overline{d}_c(\vec{r})\right)\, d\vec{r}$$

MKM model used in Japan

(RR Hawkins 2003, 2006, Kase et al 2006)



$$\overline{N}_d = \alpha_d z_d + \beta_d z_d^2$$

z_d : Specific energy in a domain

n : Number of domains

$$\langle \overline{N} \rangle_c = \langle n\, \overline{N}_d \rangle_c = \alpha_0 \langle z_d \rangle_c + \beta_0 \langle z_d^2 \rangle_c$$

$$\langle z_d \rangle_c = D$$

$$\langle z_d^2 \rangle_c = \gamma D + D^2$$

γ : Dose-weighted average of single-track specific energy

$$\langle \overline{N} \rangle_c = \underbrace{(\alpha_0 + \beta_0 \gamma)}_{\alpha_P} D + \underbrace{\beta_0}_{\beta_P} D^2$$

$$\alpha_X = \alpha_0 + \beta_0 \gamma_X \simeq \alpha_0 \qquad \alpha_P \simeq \alpha_X + \beta_X \gamma$$

$$\beta_X = \beta_0 \qquad \beta_P = \beta_X$$

$$\alpha \simeq \frac{1 - \exp\left(-\alpha_P \frac{LET}{\varrho\, \sigma}\right)}{\frac{LET}{\varrho\, \sigma}}$$

σ : Nucleus cross section

$$\beta = \beta_P$$

The Micro Kinetic Microdosimetric model (RR Hawkins) had been improved by japan groups at HIMAC

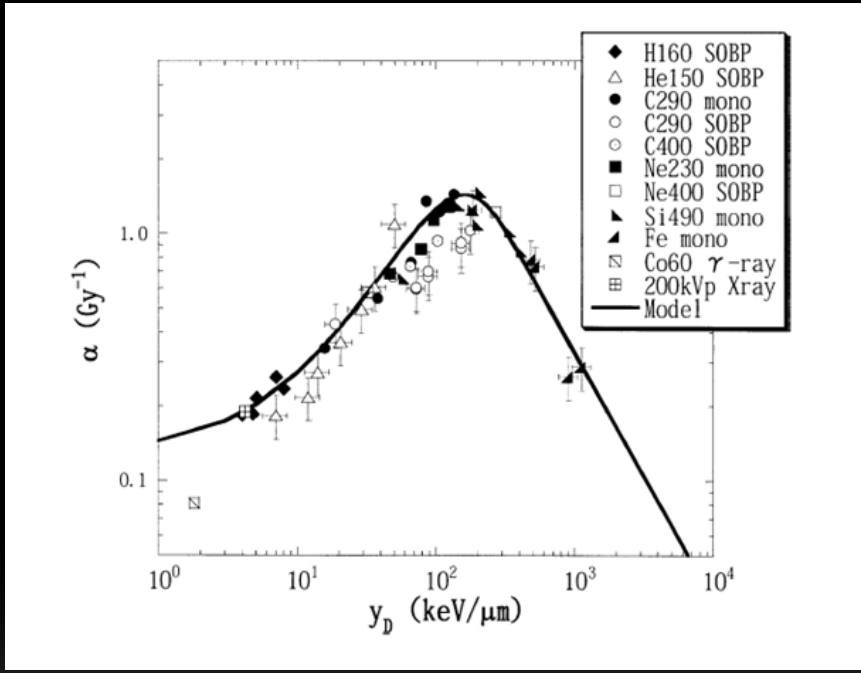
➔ **DMSK (Doubled Stochastic MKM) and SMK (simple Stochastic MKM)**

T Sato and Y Furusawa, Rad Res 178, 341–356 (2012)

Prediction of the RBE using biophysics models

The Surviving fraction of irradiated cells is parametrized through the Linear-Quadratic model

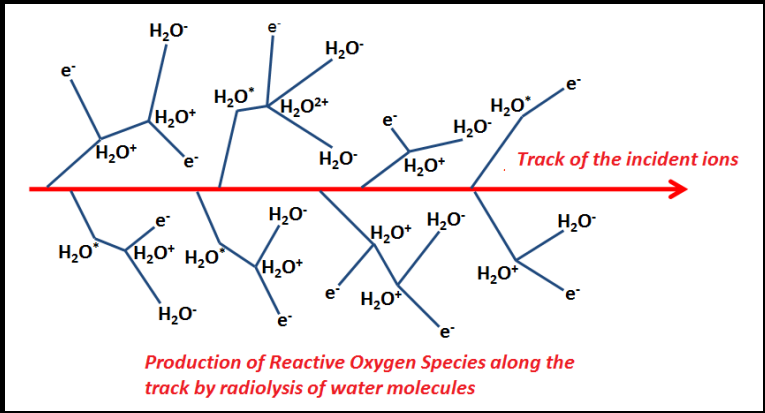
$$\ln\left(SF\left(D\right)\right) = -\alpha D - \beta D^2$$



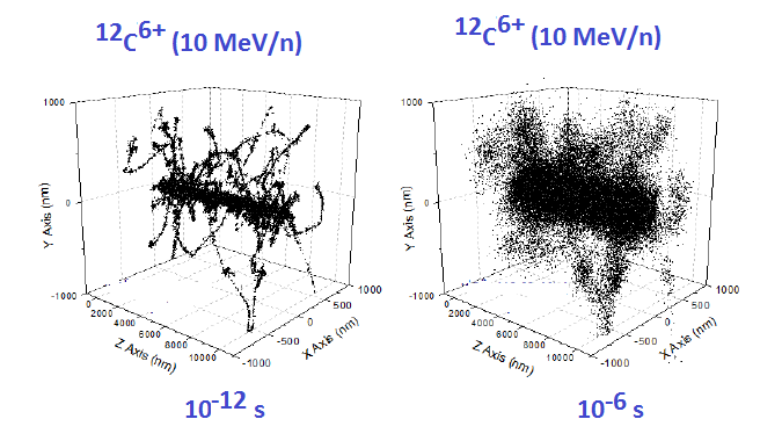
Experimental value of α with β fixed to 0.05 Gy^{-2} for HSG tumor cells based on the dose mean specific lineal energy y_D .The values of y_D were measured with a TEPC simulating a volume of diameter 1.0 μm. The solid line shows the calculated values of α using MKM model

Simulation of ROS Production

Physico-Chimical phase of LQD/Phychem/Chem model to simulate water molecule radiolysis
(A Colliaux Lyon PhD 2002)



Chimical phase of LQD/Phychem/Chem model to simulate in time evolution of produced radicals
(A Colliaux Lyon PhD 2002)



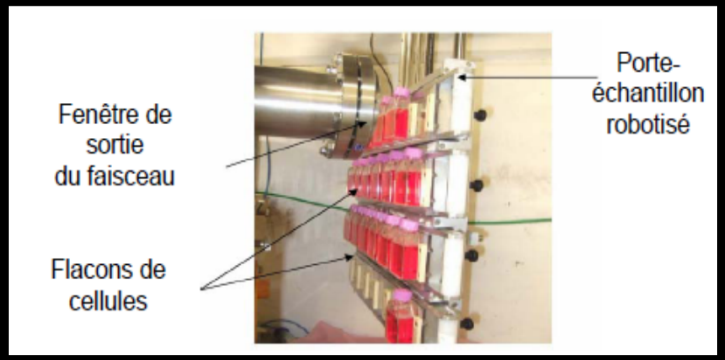
Evolution in time (between 10-12s and 10-6s) of
produced radicals along the track of an incident 12C ion with energy 10 MeV/n (LET~168 keV.µm-1)
(A Colliaux Lyon PhD 2002)

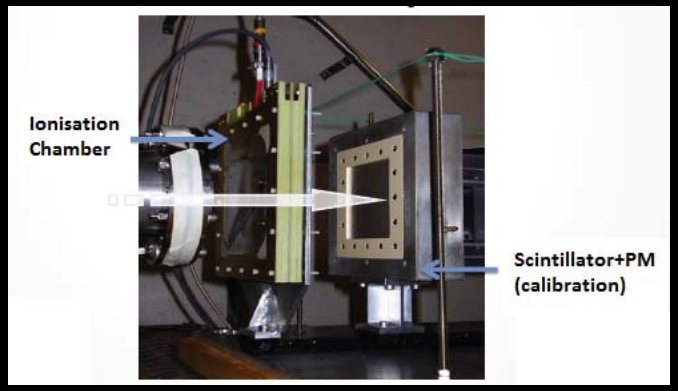
Cell's Irradiations facilities

Macrobeams

1°) Beam line D1 at GANIL (C12 of 75 and 95 Mev/u)

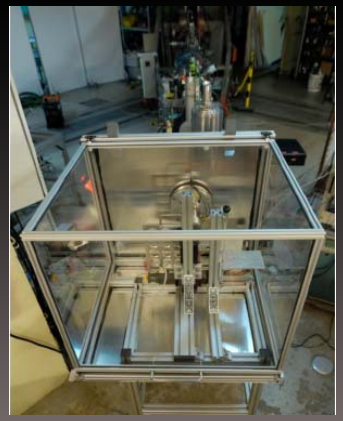
In-vivo Irradiation of cells with the measure of the delivered dose and fluence of incident ions during the irradiation through generic intrumentation





Detector for producing fluence map during carbone irradiation of cells (DOSION III) (LPC Caen)

2°) Radiograaf = Low energy proton (2.4 MeV) beam line at IPNL Lyon

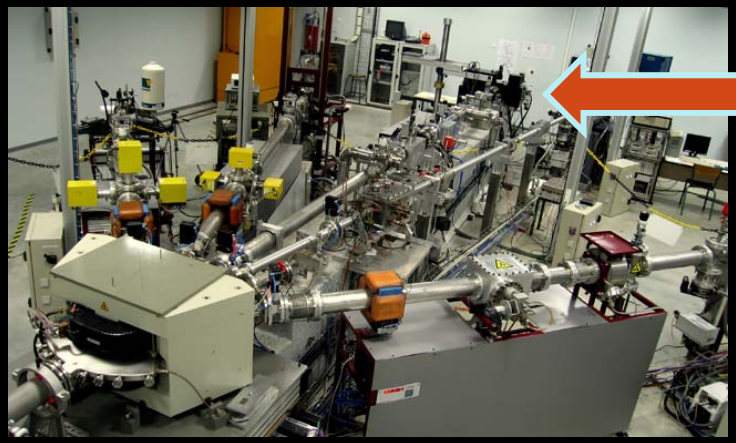


Use of a low energy Van de Graaf accelerator to provide low energy (2,4 MeV) proton irradiation facility

Cell's Irradiations facilities

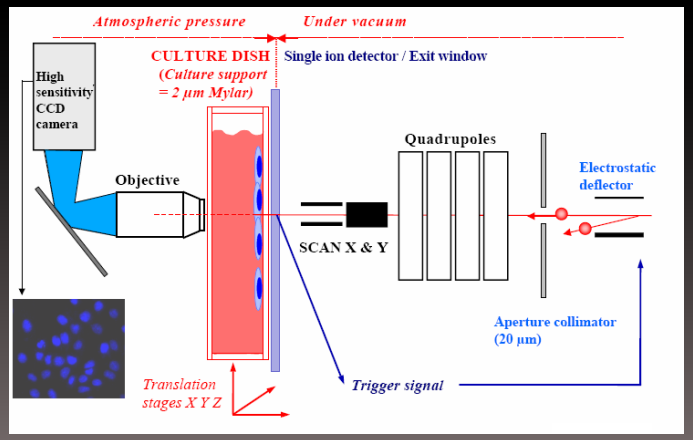
Microbeams

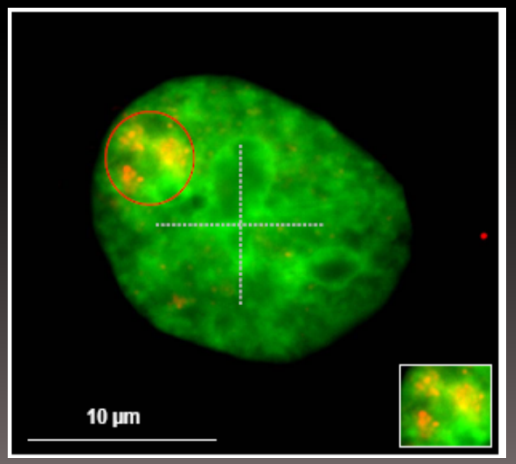
AIFIRA stands for « Applications Interdisciplinaires des Faisceaux d'Ions en Région Aquitaine ». This recently developed ion microbeam facility is equipped with a single stage electrostatic accelerator (HVEE 3.5 MV Singletron) delivering bright beams of light ions ($^{1}H^{+}$, $^{2}D^{+}$, $^{4}He^{+}$) with currents up to 100 mA



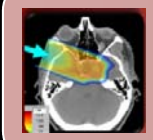
AIFIRA is used to target very precisely some part of the irradiated cells (CENBG Bordeaux)

Microirradiation of cells producing localy distributed foci



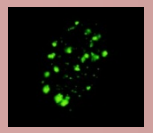


Outline



1. The basic principles of hadrontherapy


2. Physics for radiobiology



3. The structuration of the reseach for hadrontherapy

Structuration of Hadrontherapy related research in France

All these developments are in the framework of multidisplinary collaborations

➔ GDR CNRS/IN2P3 2917 « Outils et méthodes nucléaires pour la lutte contre le cancer »

➔Multidisciplinary Network *France Hadron* (Curie, Nice, Toulouse, Caen, Lyon)

The main objectives of the *France Hadron* network are :

➔ Provide beam time to research groups involved in Hadrontherapy to allow them to perform their research program

➔ To provide to the research groups generic equipment on irradiation platforms

➔ Allow valorization of results through translanational activities, scientific animation, publication

France Hadron

5 irradiation platforms (node) : ICPO, Nice, GANIL/ARCHADE, ETOILE, Toulouse

➔ Each node will contribute with its current and future equipments to provide a framework for scientific program to the research groups

➔Today only the active clinical centers of protontherapies (ICPO & Nice) and GANIL are capable of providing beam time and facilities

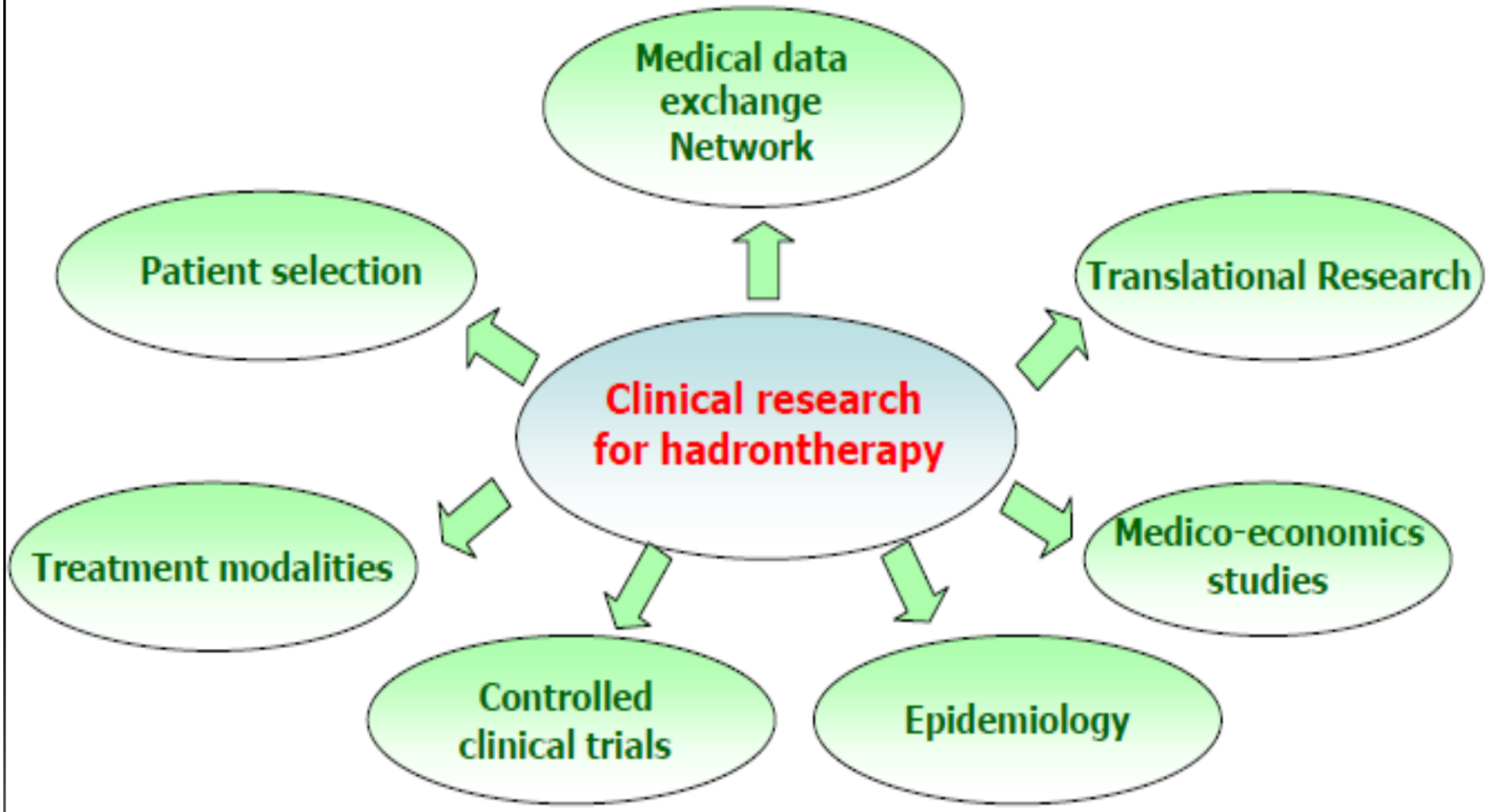
➔ Then new equipment will complement the offer in beam time and specific equipment:

ICPO (2014), Nice (2014-2015), Toulouse (2016-2017) and finally the Carbon ETOILE (?) and ARCHADE (2017-2018)

23 research groups (biologist, physicist, physicians…) leads research activities in the field of hadron distributed throughout France (Universities, CNRS, INSERM, IRSN, CEA

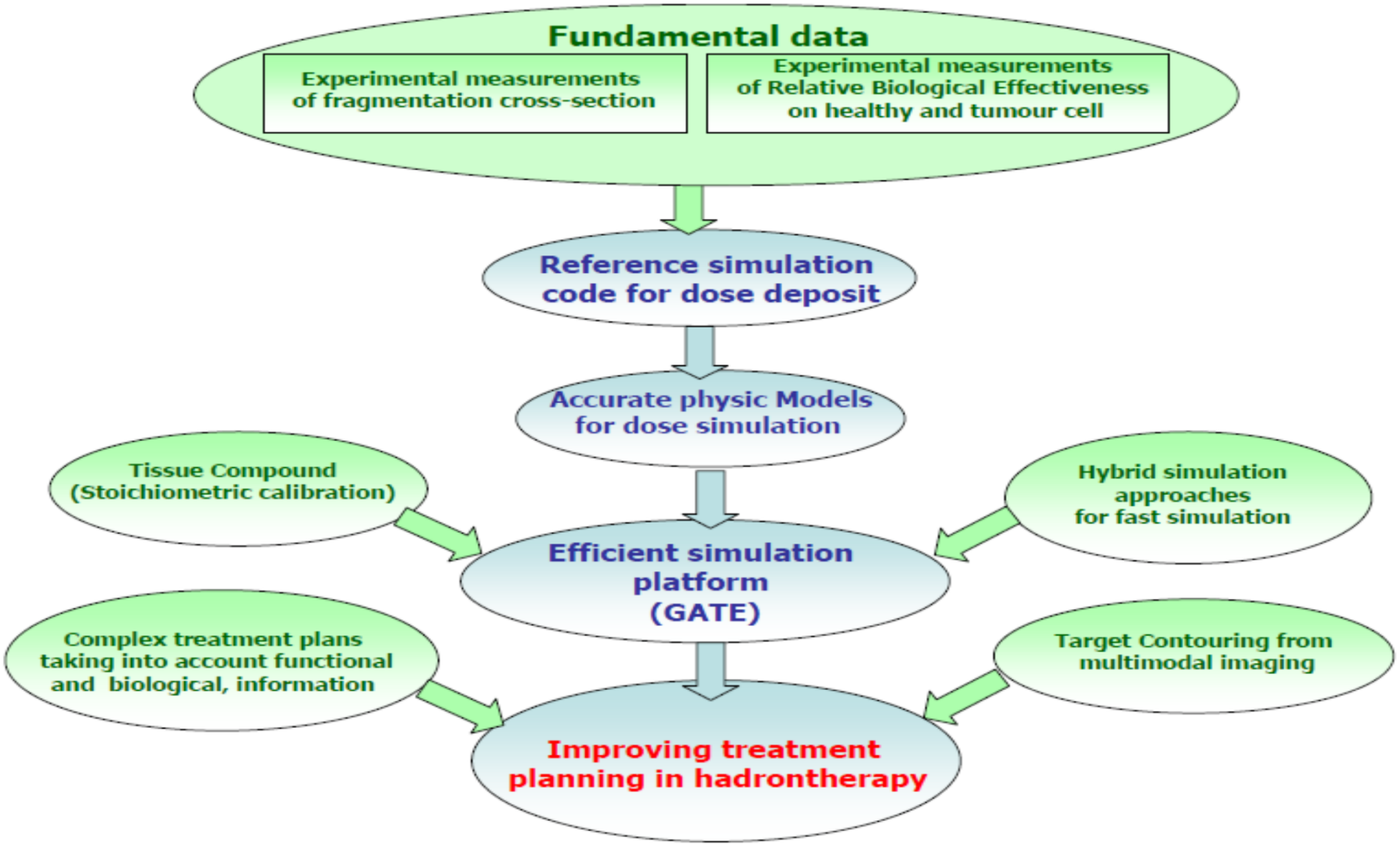
France Hadron Working Package #1

Clinical research in hadrontherapy

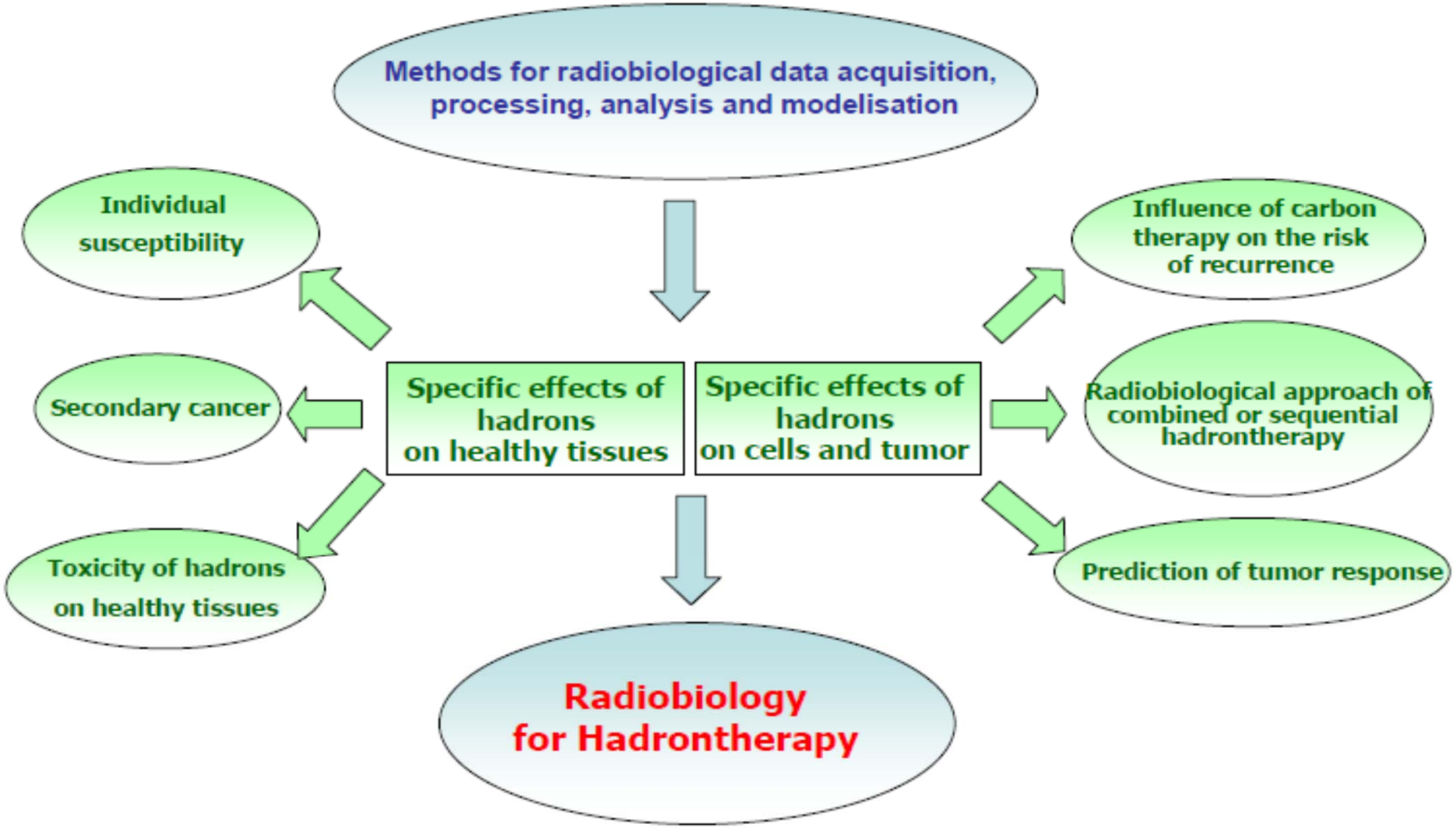


France Hadron Working Package #2

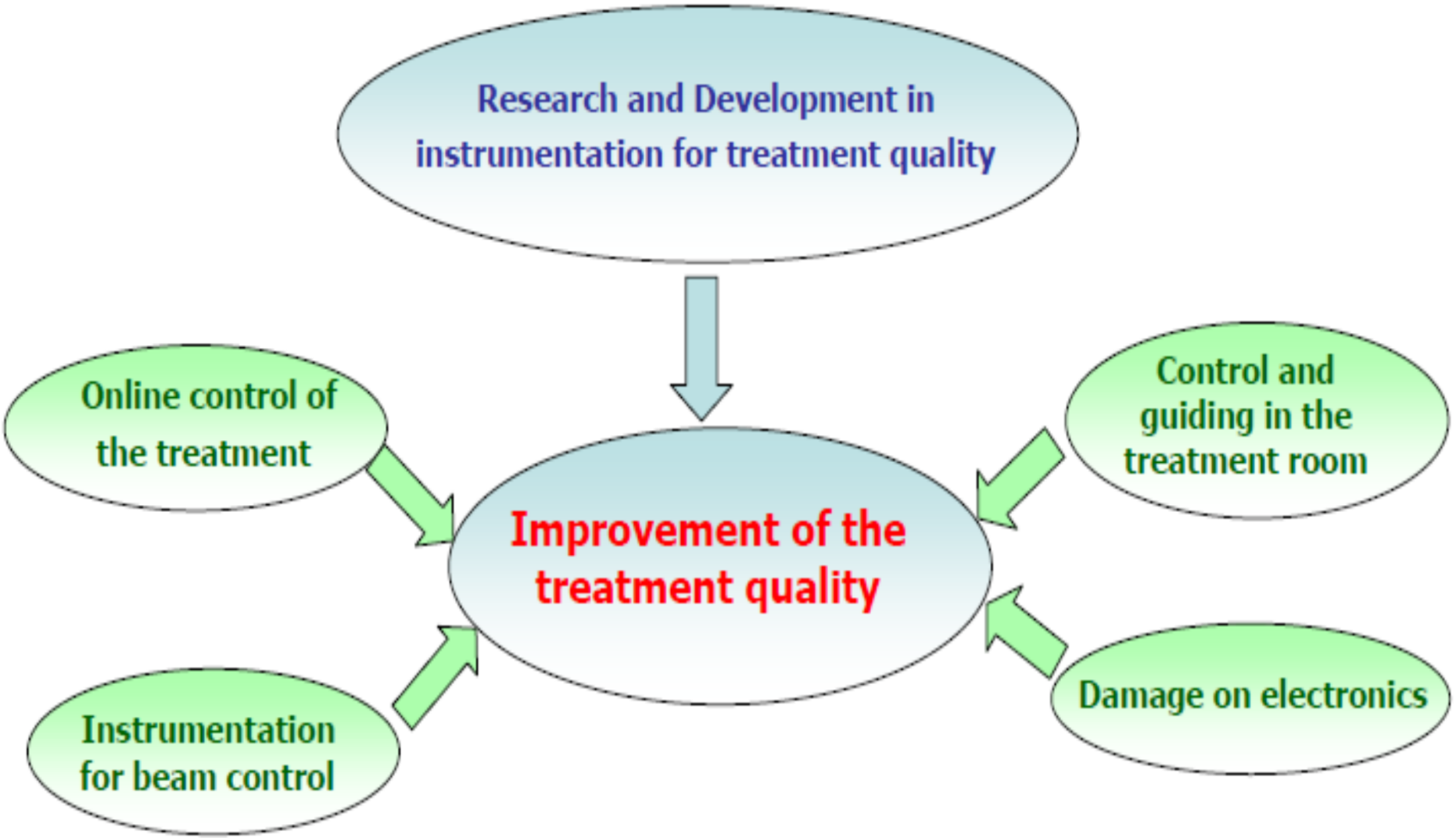
Improving treatment planning in hadrontherapy



France Hadron Working Package #3
Radiobiology for hadrontherapy



France Hadron Working Package #4
Research and Development in instrumentation for treatment quality



ENLIGHT network

The European Network for LIGht ion Hadron Therapy

Coordinator: Manjit Dosanjh (CERN)

Projects in FP7: ULICE, PARTNER, ENVISION , ENTERVISION for a total of 22 M€

http://enlight.web.cern.ch/

In H2020 programs, up to now:

ASTARTE: Applications of Nuclear Science and Technology for the Advancement of Radiation Therapy Detectors

➔ **Proposal for a Networking Activity within ENSAR-2 Dedicated to Research on Detector Instrumentation for Radiation Therapy**

➔ **Proposal for a Networking Activity within ENSAR-2 Dedicated to Nuclear tools for ion beam therapy**

Merci pour votre attention !!!

Numbers of potential patients

Combining studies made in Austria, Germany, France and Italy in the framework of ENLIGHT
Coordinator: Manjit Dosanjh (CERN)
Projects in FP7: ULICE, PARTNER, ENVISION , ENTERVISION for a total of 22 M€

X-ray therapy
every 10 million inhabitants: **20'000 pts/year**

Protontherapy
12% of X-ray patients **2'400 pts/year**

Therapy with Carbon ions for radio-resistant tumour
3% of X-ray patients **600 pts/year**

TOTAL every 10 M about 3'000 pts/year