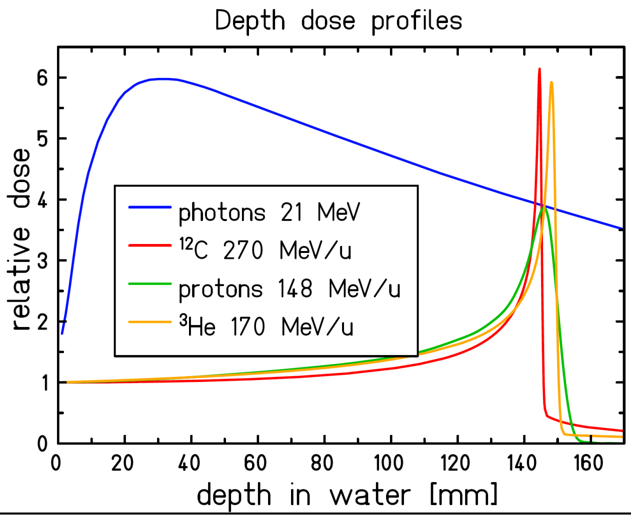
Hadrontherapy at in2p3

Marie Vanstalle (IPHC) on behalf of the community

IN2P3 Scientific Council – 08/07/2025

Why nuclear physics for health?

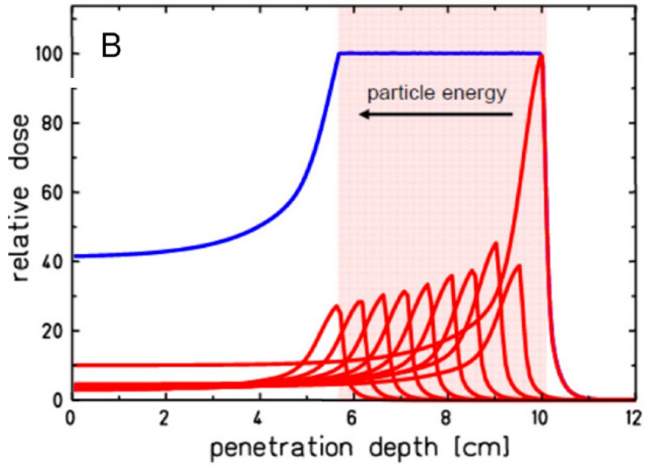
- **Hadrontherapy:** accelerated ion beams (cyclotrons or synchrotrons) for cancer therapy
- **Ion types**: ^{1}H, ^{4}He, ^{12}C, ^{16}O between 80 and 400 MeV/u
- **Interest**: ballistic advantage of charged particles (Bragg Peak) + potential biological advantage



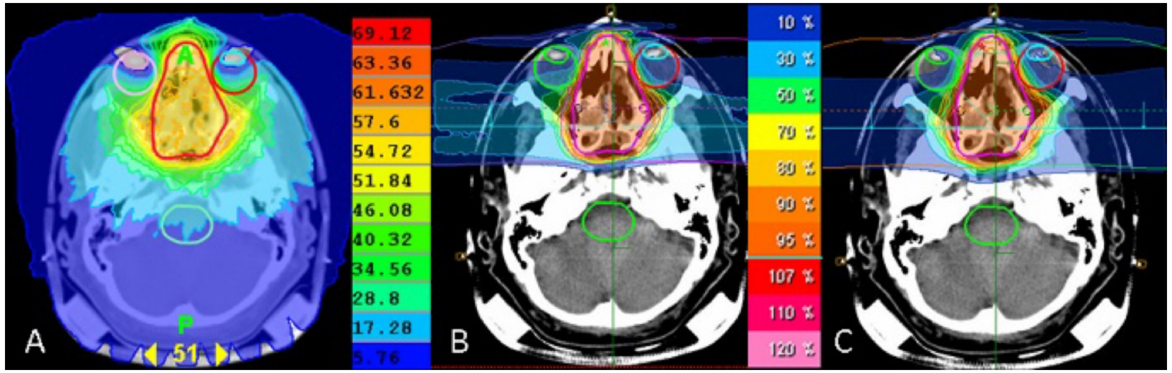
From **Kraemer et al.**, *Helium ions for radiotherapy? Physical and Biological verifications of a novel treatment modality*, Med. Phys. (2016).

What scientists see...

What patients see...



From **Durante and Paganetti**, *Nuclear physics in particle therapy: a review*, Rep. Prog. Phys. (2016).

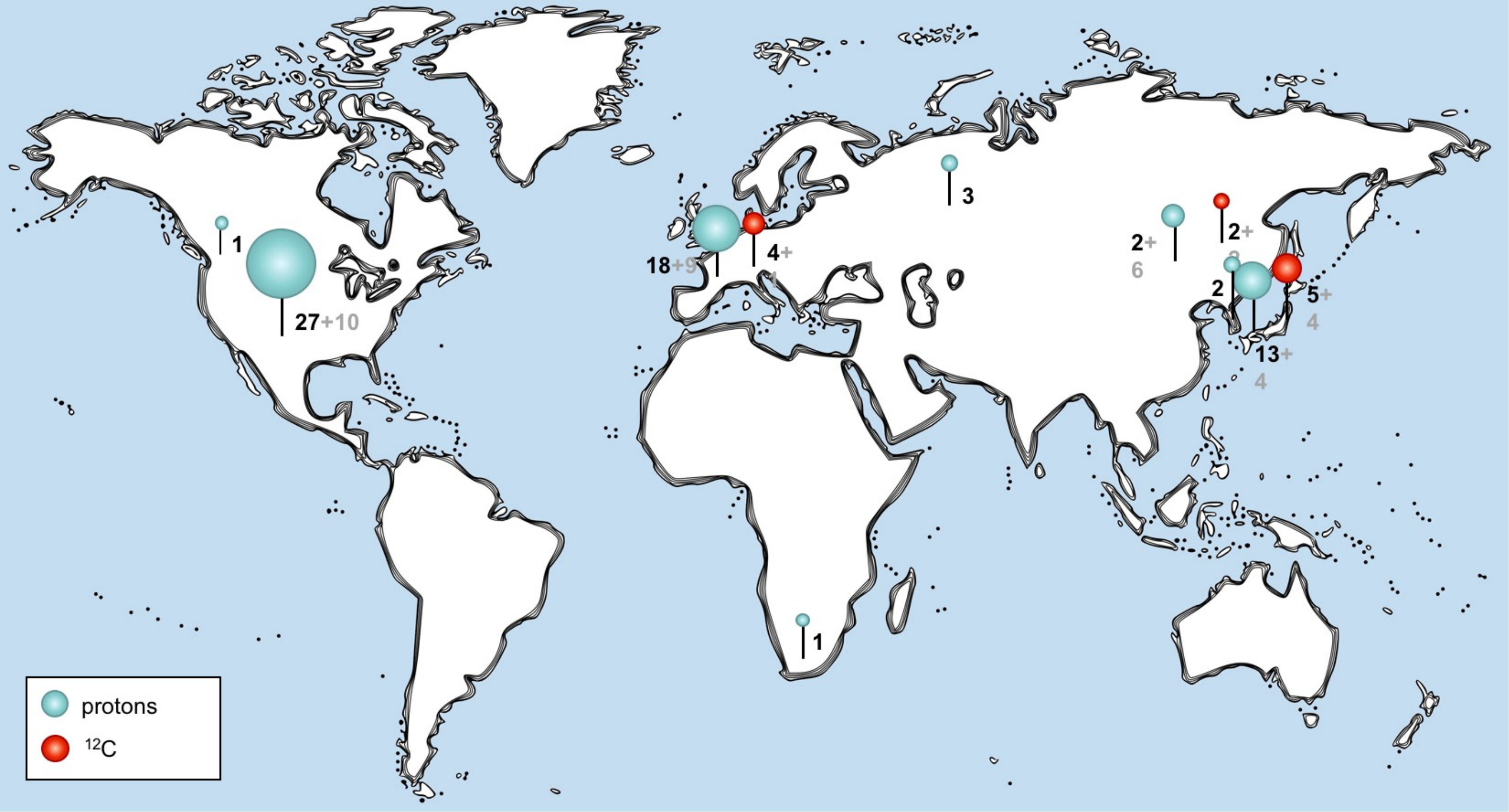


From **Kosaki et al.**, *Comparison of intensity modulated radiotherapy (IMRT) with intensity modulated particle therapy (IMPT) using fixed beams or an ion gantry for the treatment of patients with skull base meningiomas*, Rad. Onc. (2012).

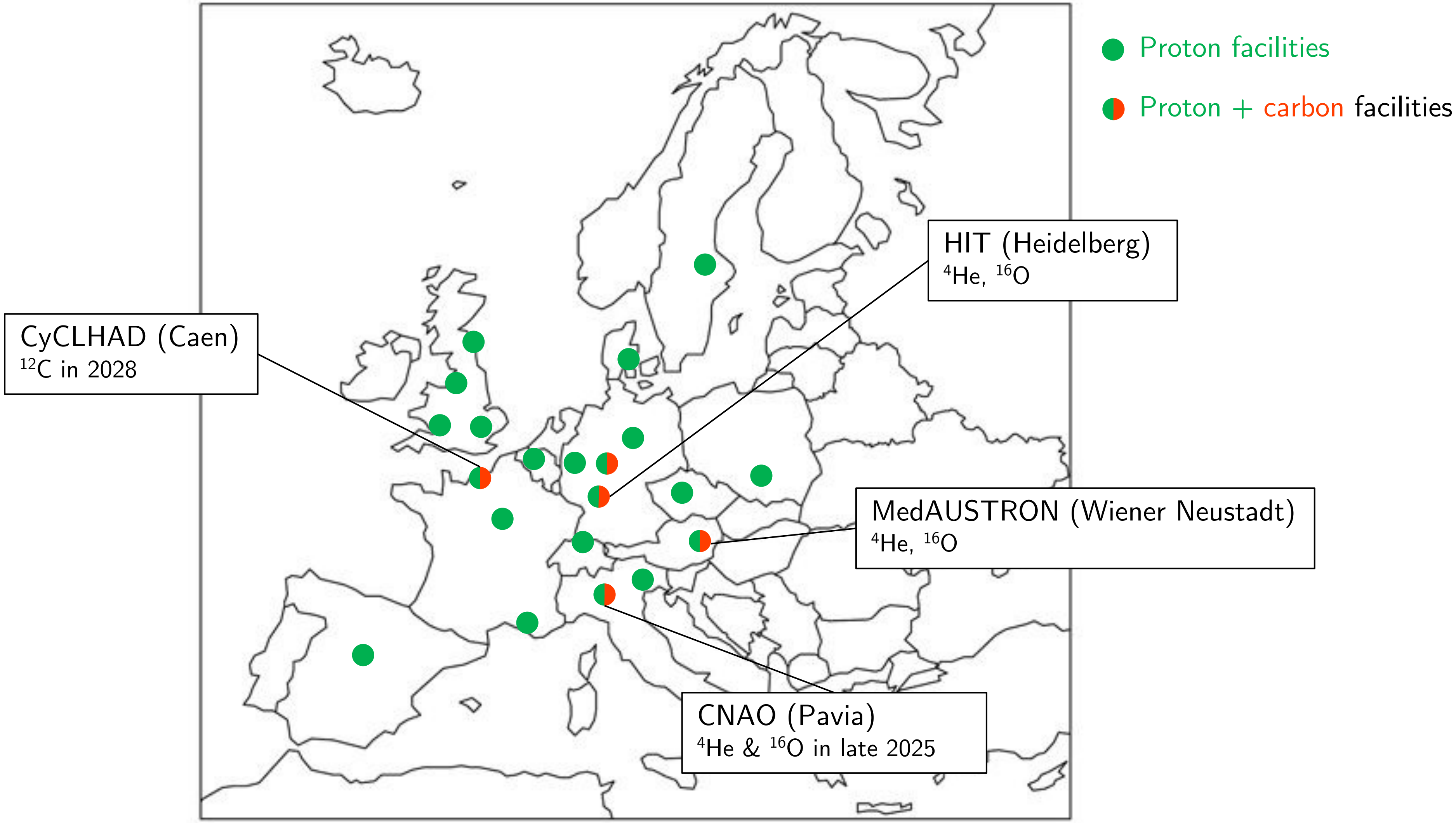
Hadrontherapy facilities in the world

More than 300,000 patients treated with protontherapy in the world
50,000 with ^{12}C therapy
(Statistics from PTCOG website, up to 2022)

Main indications: pediatric cancers, head & neck cancers, deep-seated tumors,…

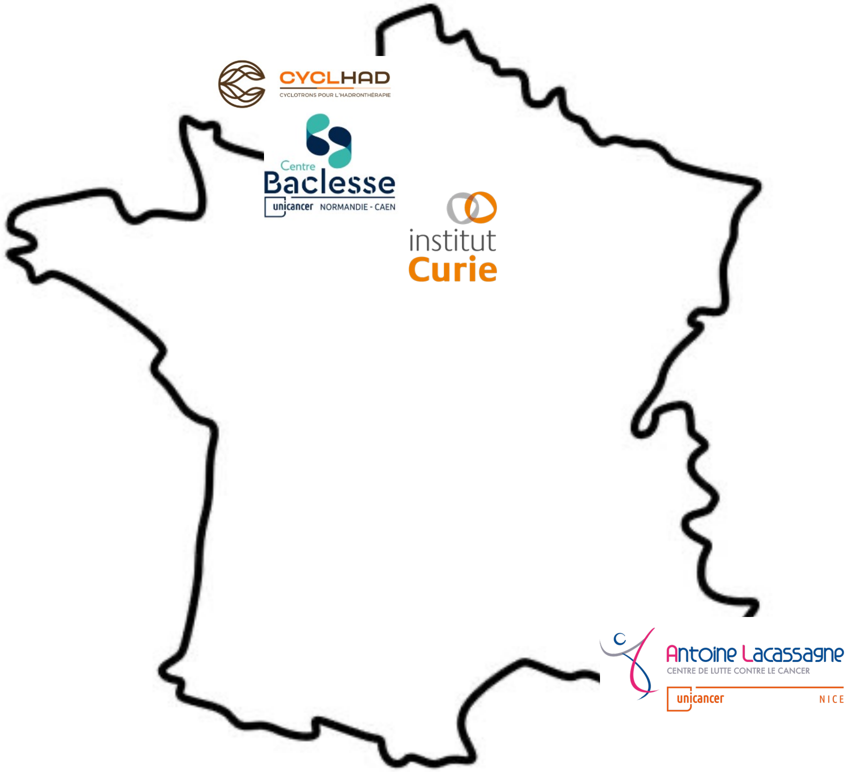


Hadrontherapy facilities in Europe



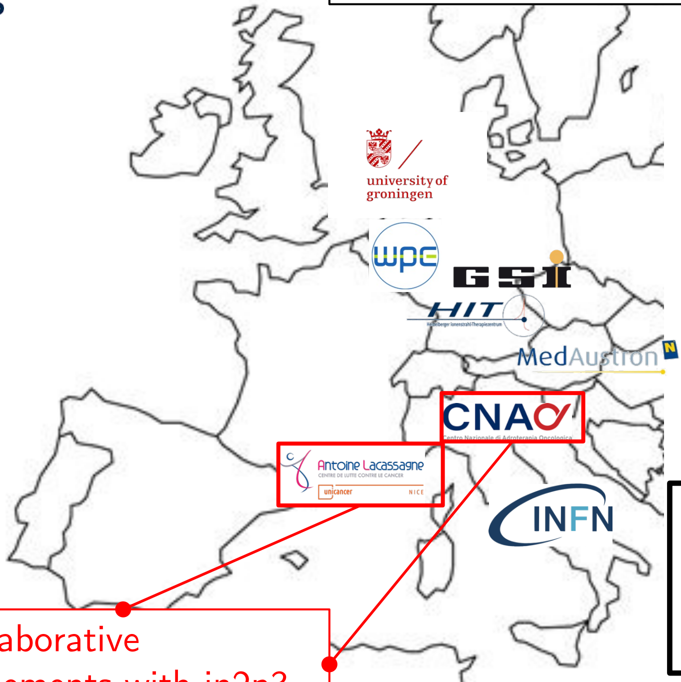
Hadrontherapy in France

Participation in international networks



Clinical facilities

IN2P3 laboratories & platforms



Collaborative agreements with in2p3

+ Japan

Collaborations (2025 status)

Hadrontherapy @ in2p3

Final goal: improvement of hadrontherapy treatments

NUCLÉAIRE & PARTICULES

Clinical applications

Control of the treatment

Beam monitoring

E.g., diamond detectors

Ion-range monitoring

E.g., prompt-gamma imaging

Dosimetry

Simulation codes/platforms

Fundamental research

Understanding of fundamental processes

Better understanding of physical processes

E.g., fragmentation, secondary particles

E.g., radiolysis measurements

Better understanding of chemical processes

Better understanding of biological processes

Dose & biological effects modeling

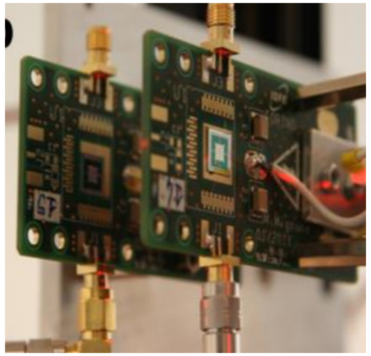
Clinical application

Control the dose delivery – beam monitor

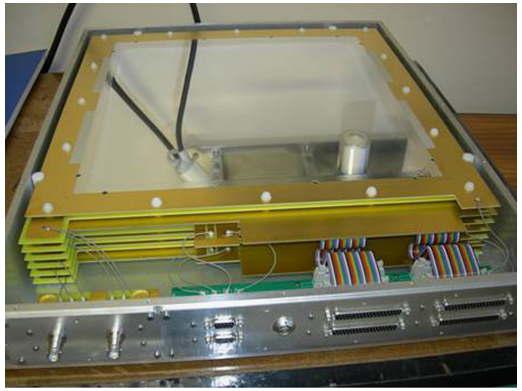
- **Beam monitoring** is crucial in hadrontherapy for beam control during treatment + for many experiments
- **Mostly used technology:** ionization chambers, usually integrated in the nozzle
- Limitations: aging of ionizing chambers + slow collection time of gaz detectors
  ⇒ difficult to use in fast mode, or for moving targets

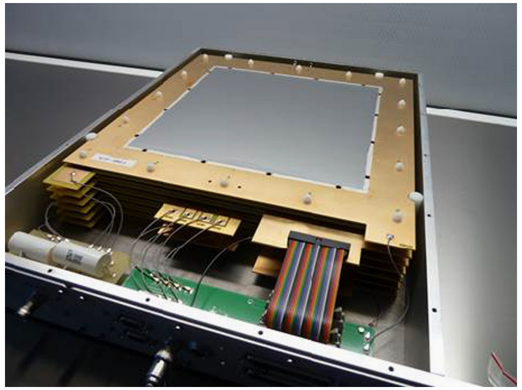
- **Challenges for beam monitoring in hadrontherapy**
  - Providing a direct information on the dose/energy/fluence of the in-coming beam
  - Radiation hardness
  - High fluences of FLASH therapy (>40 Gy/s), pulsed accelerators
  - Low material-budget

⇒ new implementations based on **solid-state detectors** (e.g., ultra-fast silicon detectors, diamonds,...)



UFSD developed by INFN (Torino)
Extracted from **Vignati et al.**, *A new detector for the beam energy measurement in proton therapy: a feasibility study*, Phys. Med. Biol, 2020.





Ionization chamber IC2/3 developed by LPCC in collaboration with IBA
Extracted from **Courtois et al.**, *Characterization and performances of a monitoring ionization chamber dedicated to IBA-universal irradiation head for Pencil Beam Scanning*, Nuclear Instruments and Methods A, 2014

Clinical application

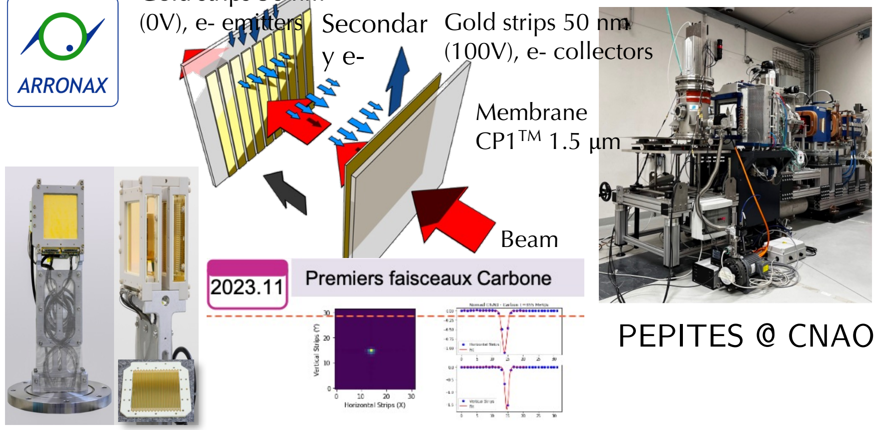
Beam monitoring @ in2p3

NUCLÉAIRE & PARTICULES

- **Beam monitoring projects:** PEPITES, DIAMANT, MATRIX
- Collaborative projects with clinical facilities (CAL, CNAO, WPE) and experimental facilities (ARRONAX)
- **5-years prospects**
  - Adaptation of the monitors on clinical facilities (e.g., PEPITES @ CNAO, DIAMANT @ CAL)
  - Possible installation of beam monitors on experimental platforms (BioALTO, ARRONAX)
  - Application to **FLASH conditions** (high dose rates)

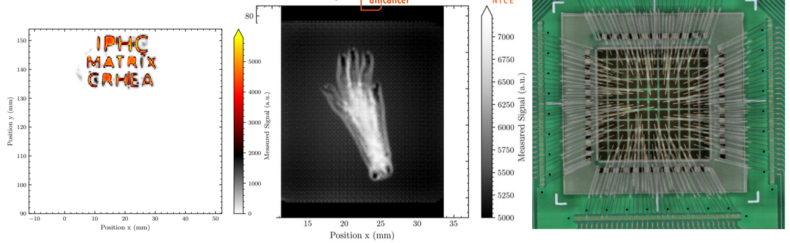
⇒ More details on technical developments in *Instrumentation* presentation from E. Testa

PEPITES



PEPITES @ CNAO

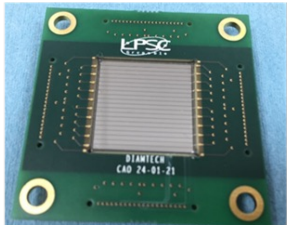
MATRIX

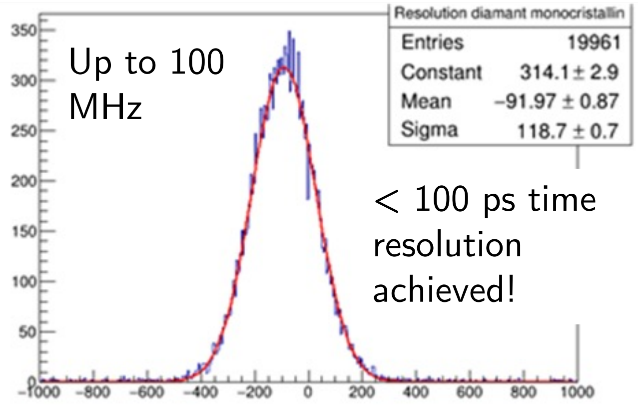


GaN for monitoring: radiation hardness, fast detectors, high efficiency, big surfaces achievable

DIAMANT

Diamond detector for monitoring: radiation hardness, fast detectors, high efficiency





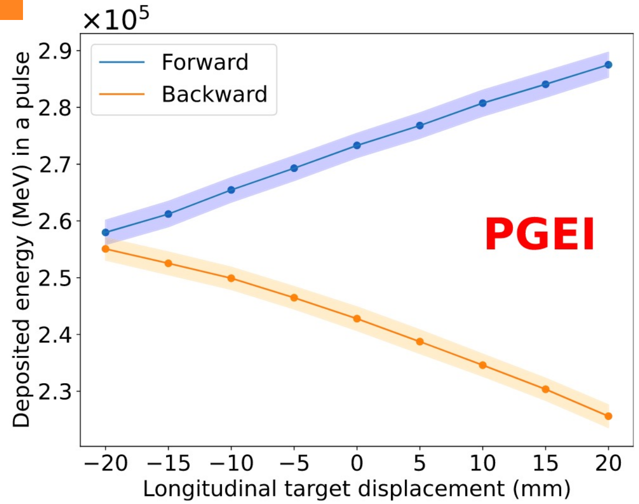
Up to 100 MHz

< 100 ps time resolution achieved!

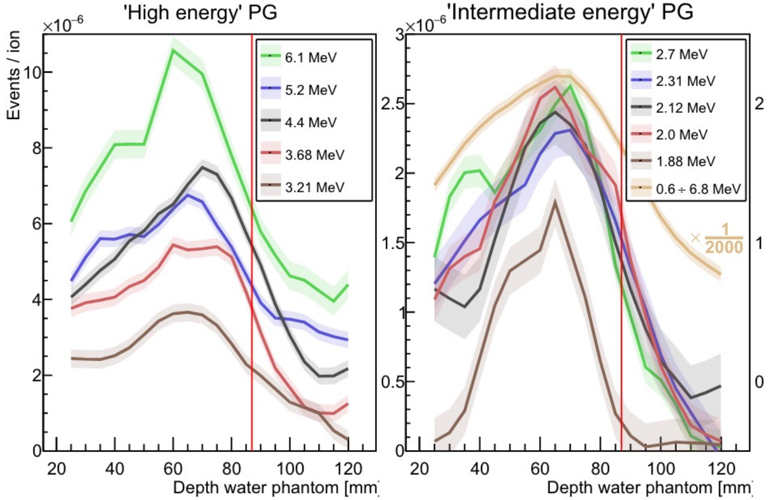
Control the dose delivery – ion-range monitor

- **Goal of ion-range monitoring:** to determine Bragg peak/SOBP position during irradiation to perform corrections in TPS if needed
- **Detection of secondary particles during treatment**
  - $\beta+$ emitters (^{11}C, ^{15}O)
  - **Prompt-gammas** ⇒ one of the most advanced monitoring technique: gamma imaging (collimated camera,...), prompt-gamme energy measurement, prompt-gamma timing
  - Secondary protons (IVI - Ion Vertex Imaging)

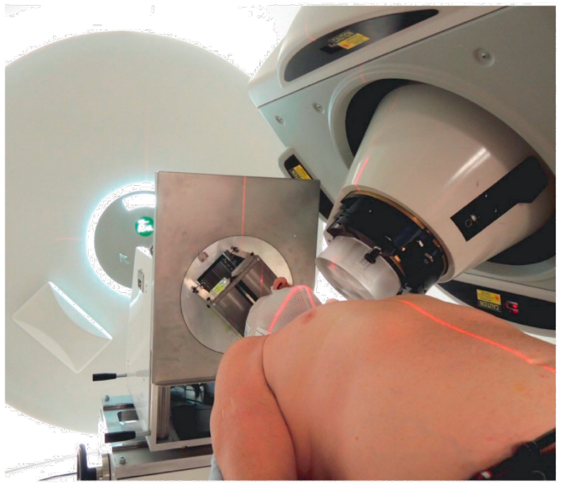
Clinical application



Extracted from **Everaere et al.**, *Prompt gamma energy integration: a new method for online-range verification in proton therapy with pulsed-beams*, Frontiers in Physics, 2024



Extracted from **Bello et al.**, *Prompt gamma spectroscopy for absolute range verification of ^{12}C ions at synchrotron-based facilities*, Phys. Med. Biol., 2020



Extracted from **Richter et al.**, *First clinical application of a prompt gamma based in vivo proton range verification system*, Radiotherapy and Oncology, 2016.

Ion-range monitoring @ in2p3

CNRS NUCLÉAIRE & PARTICULES

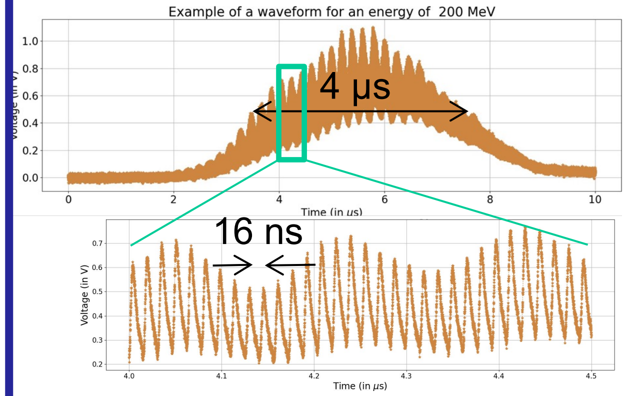
- Ion-range monitoring projects: TIARA, CLaRyS
- Collaborative projects with clinical facilities (CAL, CNAO)
- **5-years prospects:**
  - Tests of clinical feasibility of prototypes
  - Extension to larger projects on online control
  - Extension to carbon-therapy facilities (e.g. CNAO)
  - Potential collaboration with Cyclhad

⇒ More details on technical developments in *Instrumentation* presentation from E. Testa

Clinical application

CLaRyS

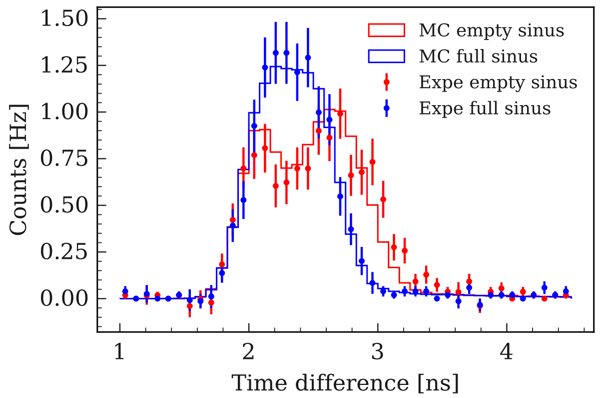
Online control of pulsed medical beam of synchrocyclotron Proteus One



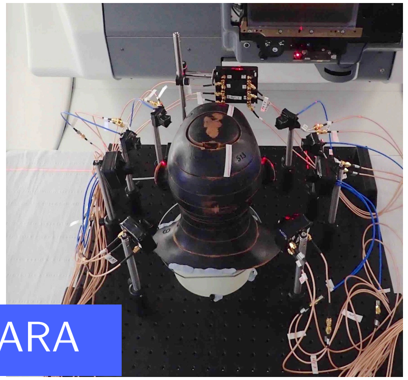
Beam measurement at CAL-Proteus One with diamond detector

Method: Use of integrated signals of small amount of detectors (adaptation of PGPI method) in $PbWO_4$

LABEX PRIMES Université de Lyon; MITI Mission pour les Initiatives Transverses et Interdisciplinaires; Antoine Lacassagne Centre de lutte contre le cancer, unicancer Nice; LPSC Grenoble | Modane; CREATIS; iP2i Les 2 infinis Lyon



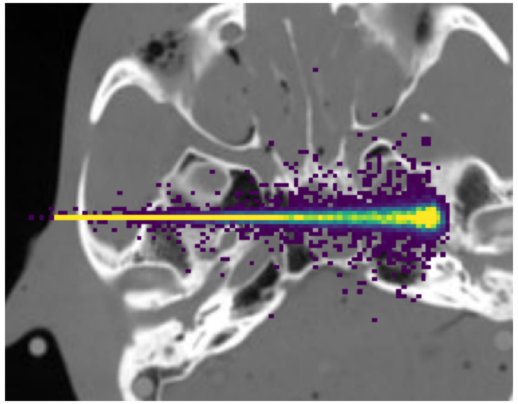
Detection of anatomical variations with the TIARA setup



TIARA

aviesan, Inserm, UGA Université Grenoble Alpes, erc

$$TOF = t_{stop} - t_{start} = T_{proton}(\mathbf{r}_v, \mathbf{v}_p) + T_\gamma(\mathbf{r}_v, \mathbf{r}_d)$$

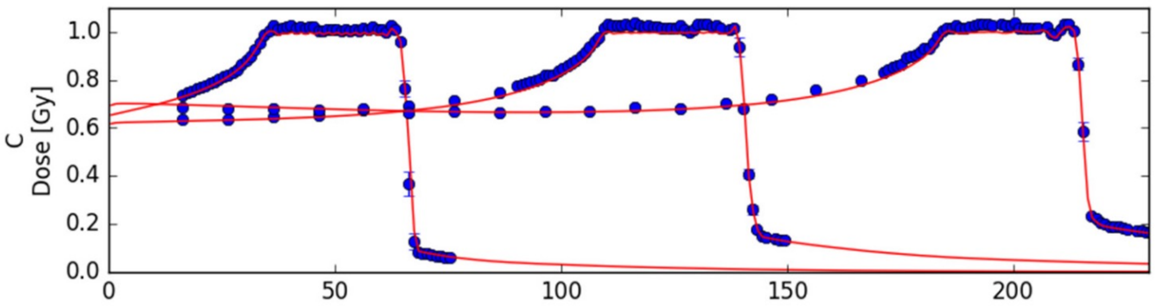


CPPM Centre de Physique des Particules de Marseille; LPSC Grenoble | Modane; Antoine Lacassagne Centre de lutte contre le cancer, unicancer Nice

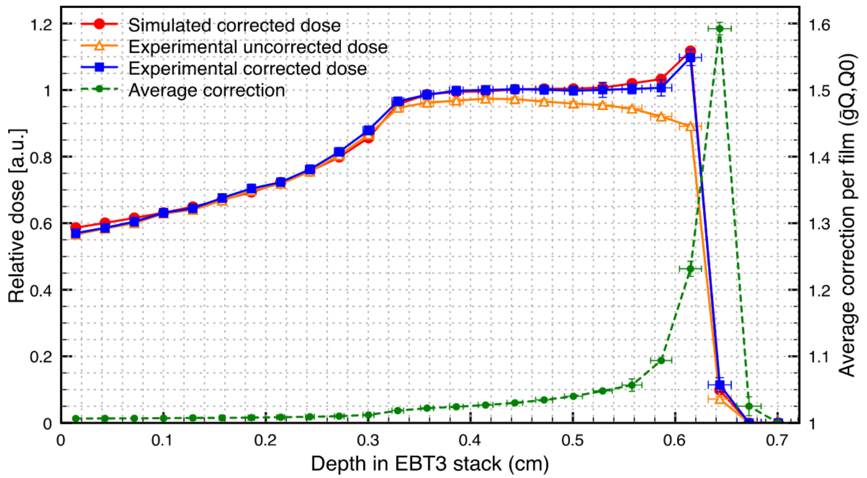
Control the dose delivery – dosimetry

- Dosimetry in hadrontherapy centers mainly performed with **ionizing chambers** and **passive detectors** (gafchromic films)
- **Challenges in dosimetry for hadrontherapy:**
  - Better understanding of the dose deposition both laterally and in depth
  - Control of the TPS simulation at the patient position
  - Dosimetry for low-energy beam lines (e.g. BioALTO, ARRONAX, Cyrcé…)

Clinical application



Measured carbon SOBP in water with PinPoint ionization chambers (from PTW)
Extracted from **Tessonnier et al.**, *Dosimetric verification in water of a Monte Carlo treatment planning tool for proton, helium, carbon and oxygen ion beams at the Heidelberg Ion Beam Therapy Center*, Phys. Med. Biol., 2017.



Measured proton SOBP with EBT3 films
Extracted from **Fiorini et al.**, *Under-response correction for EBT3 films in the presence of proton spread out Bragg peaks*, Physica Medica, 2014.

Dosimetry @ in2p3

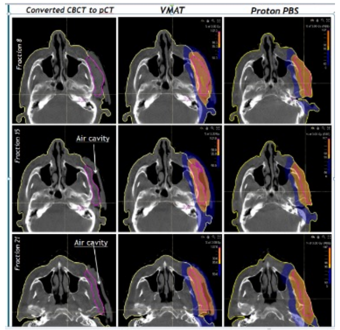
CNRS NUCLÉAIRE & PARTICULES

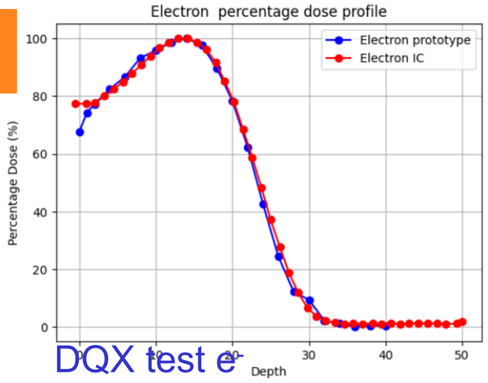
- Projects: SCICOPRO, DeCuPro
- 5-years prospects:
  - New tests @ ARRONAX facility
  - Finalizing the DeCuPro ionization chamber in 2026

Clinical application

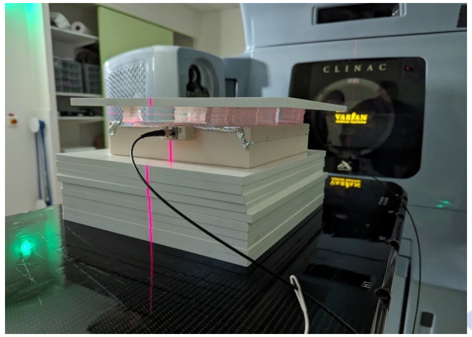
DeCuPro

Skin dose evaluation for the treatment of non-melanoma skin cancers (NMSCs) in conventional radiotherapy and proton therapy ⇒ DQX scintillation dosimeter ProtoV2 under e⁻/X-ray testing





DQX test e⁻

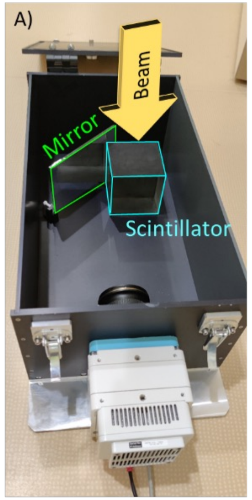


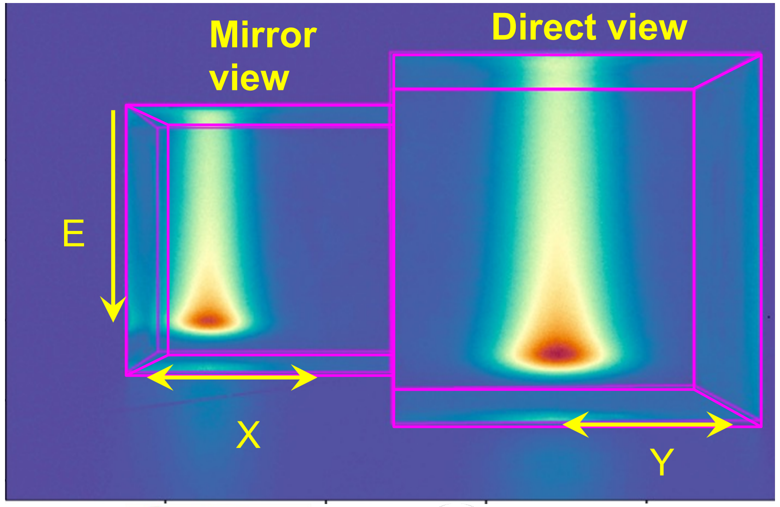
LPC CAEN

SCICOPRO

Measurements of dose rates for Pencil Beam Scanning (PBS) in protontherapy

- Spatiotemporal dose deposition in PBS and its correlation with biological effects
- Characterization of dose and dose-rate maps in PBS treatments
- Dose maps



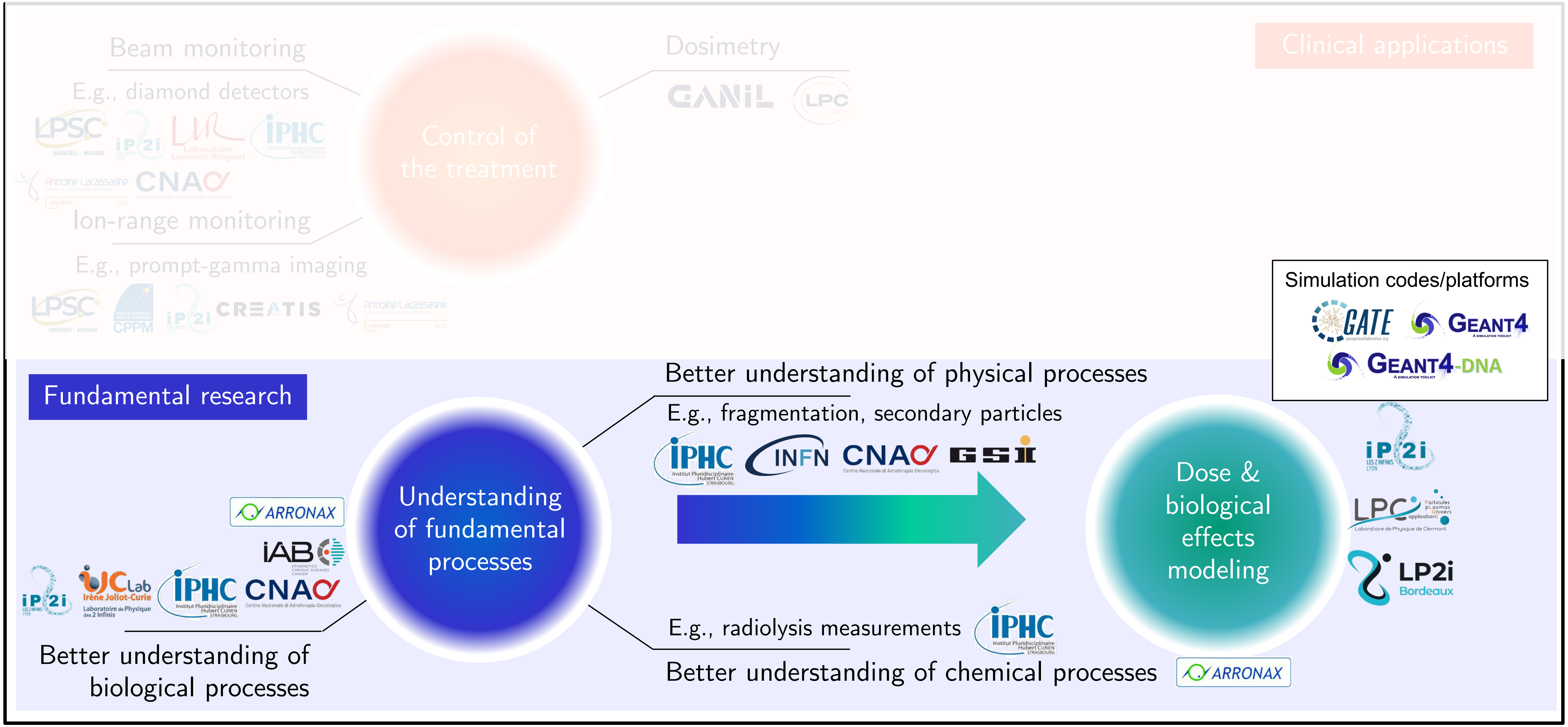


GANIL | LPC Caen Laboratoire de physique corpusculaire | Centre de Lutte contre le Cancer François Baclesse, unicancer Normandie - Caen | Le projet PMRT est financé par Région Normandie, Union Européenne Fonds européen de développement régional

Hadrontherapy @ in2p3

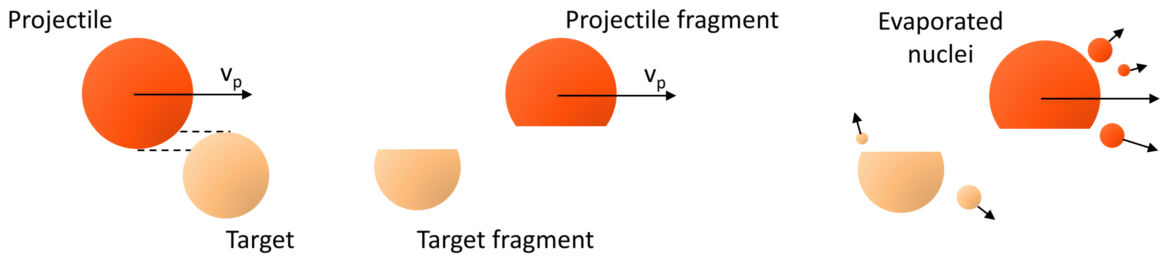
Final goal: improvement of hadrontherapy treatments

NUCLÉAIRE & PARTICULES



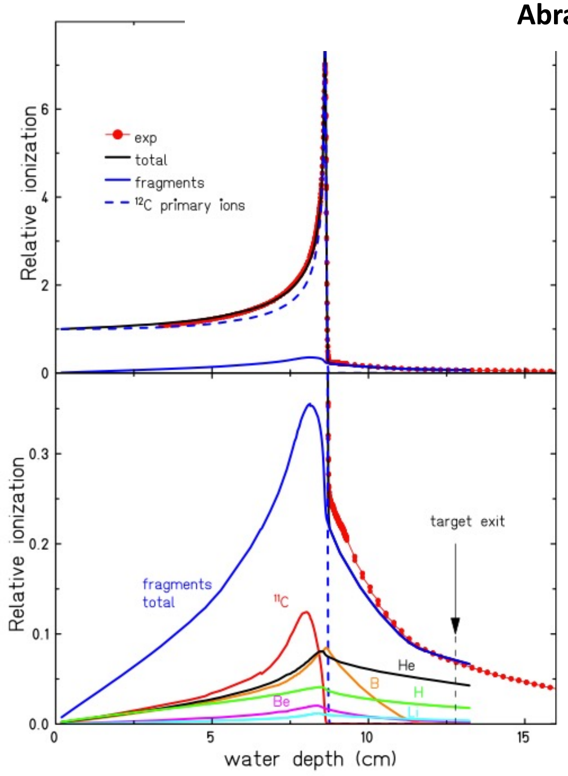
Nuclear processes for hadrontherapy

Fundamental research



Abrasion **Ablation**

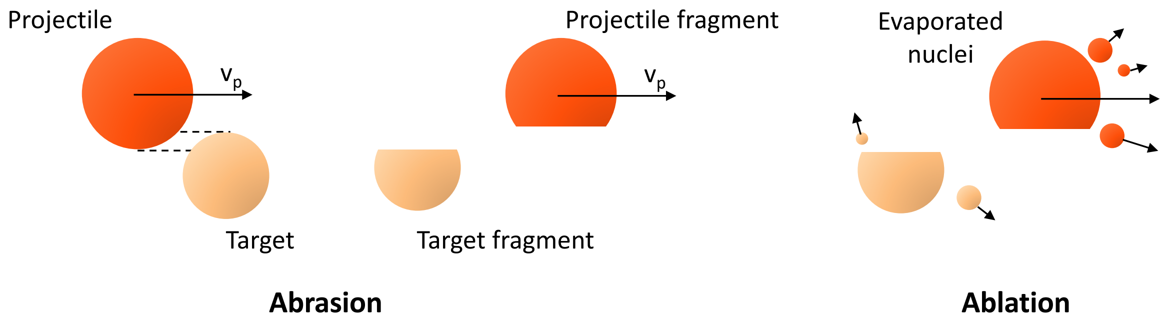
Fragmentation



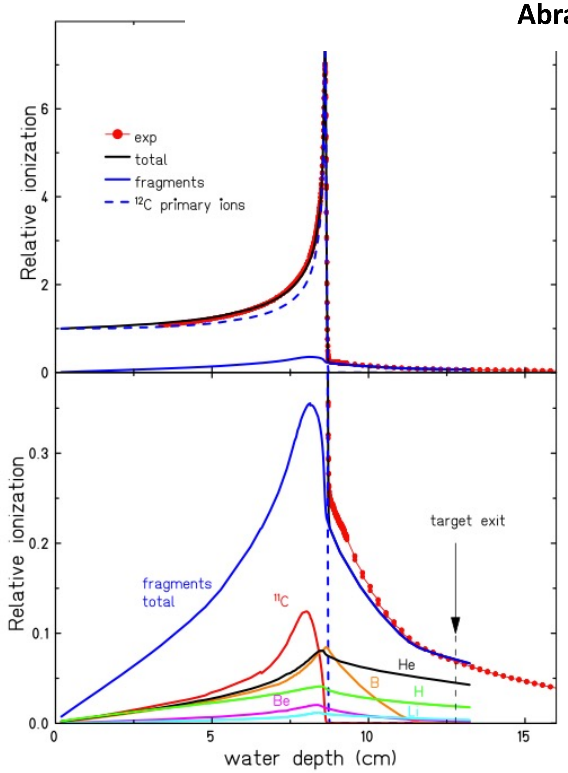
Bragg curve of a 200 MeV/u ^{12}C ion beam in water.
Extracted from **Gunzert-Marx et al.**, *Secondary beam fragments produced by 200MeV/u ^{12}C ions in water and their dose contributions in carbon ion radiotherapy*, New Journal of Physics, 2008.

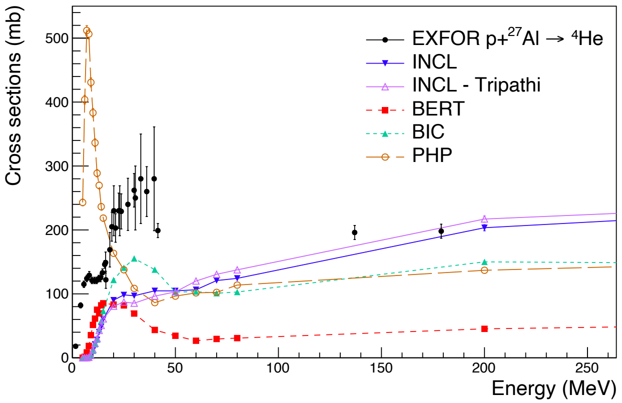
Nuclear processes for hadrontherapy

Fundamental research



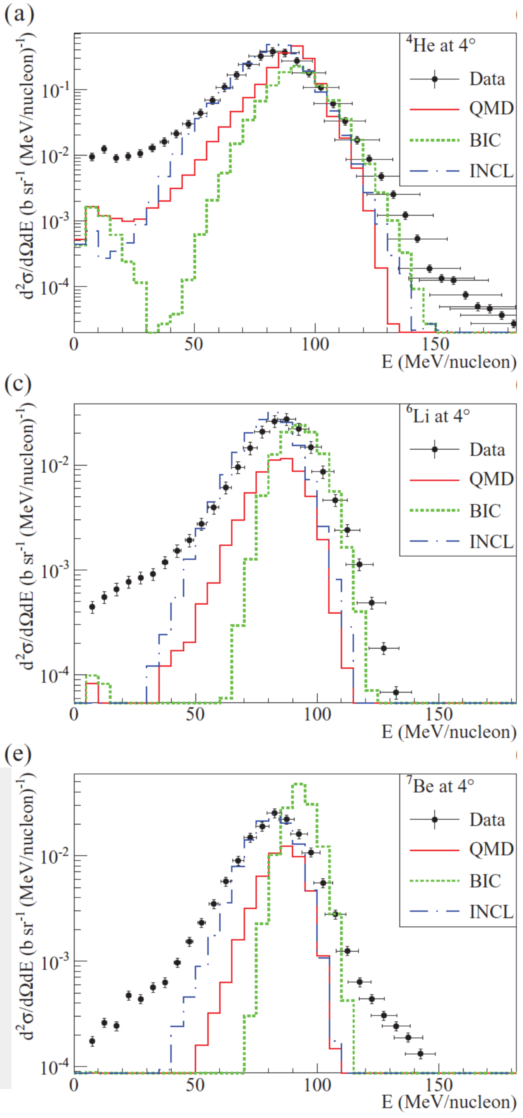
Fragmentation





Bragg curve of a 200 MeV/u ^{12}C ion beam in water. Extracted from **Gunzert-Marx et al.**, *Secondary beam fragments produced by 200MeV/u ^{12}C ions in water and their dose contributions in carbon ion radiotherapy*, New Journal of Physics, 2008.

Extracted from **Dudouet et al.**, *Benchmarking GEANT4 nuclear models for hadron therapy with 95 MeV/nucleon carbon ions*, Physical Review C, 2014



It doesn't matter how beautiful your theory is, it doesn't matter how smart you are. If it doesn't agree with experiment, it's wrong.

RICHARD FEYNMAN

Nuclear processes for hadrontherapy @ in2p3

NUCLÉAIRE & PARTICULES

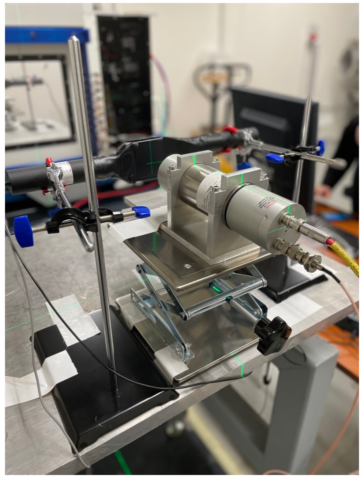
Fundamental research

- Projects: FOOT, CLINM
- 5-years prospects:
  - FOOT: Measuring **double differential cross-sections** for hadrontherapy with 5% accuracy
  - CLINM: measuring **secondary particles coupled with radiolysis** measurement
  - **Strengthenink links with the Geant4 collaboration**
  - Data in EXFOR database

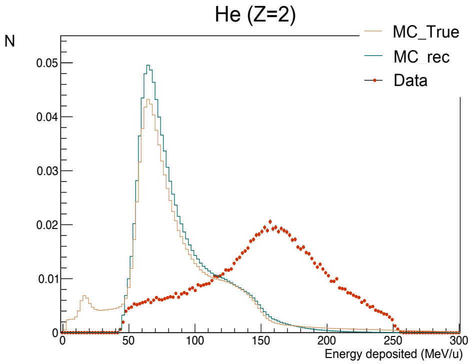
Types of beams: ^{4}He, ^{12}C, ^{16}O, (^{56}Fe)
Targets: C, C_2H_4, PMMA, Al

CLINM

Measurements of secondary particles physical properties (energy, charge)



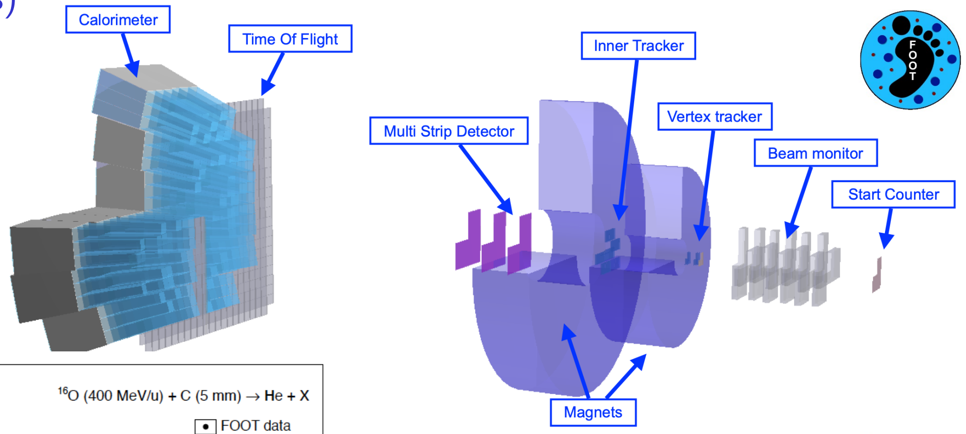
ΔE-E/ΔE-ToF setup for characterizing secondary particles produced in thick targets

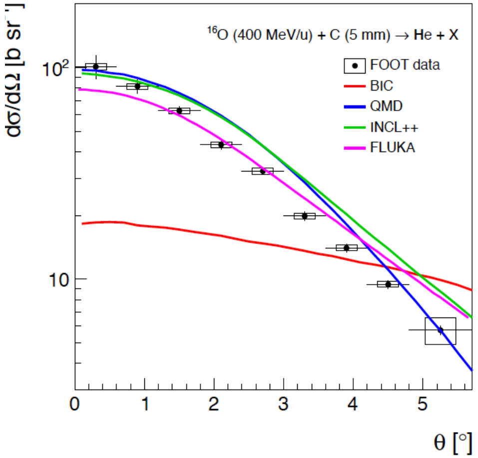


IPHC, cnes, CNAO Centro Nazionale di Adroterapia Oncologica, HITRIplus Heavy Ion Therapy Research Integration, anr

FOOT

Nuclear data for hadrontherapy (differential cross-sections)





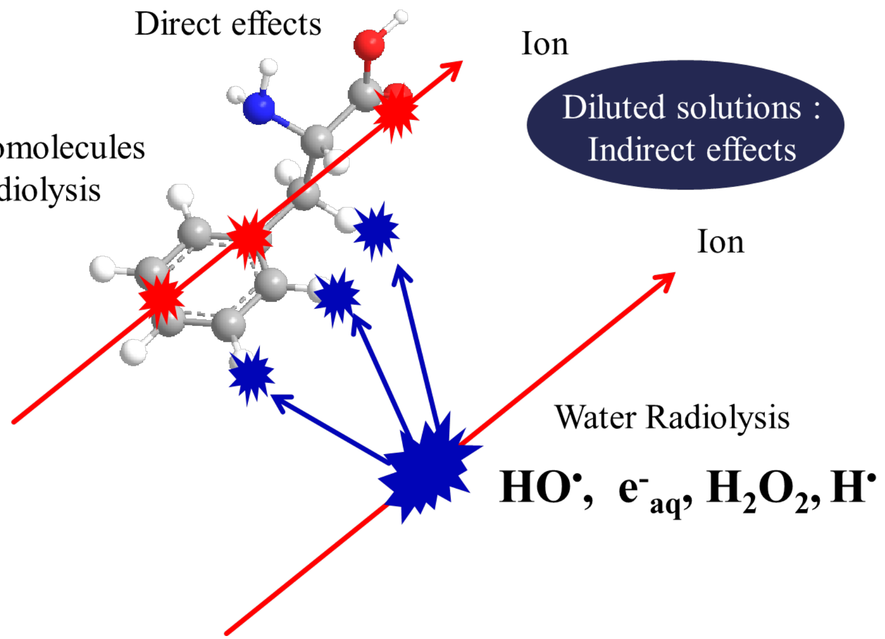
Multi-detector setup
International collaboration with INFN laboratories

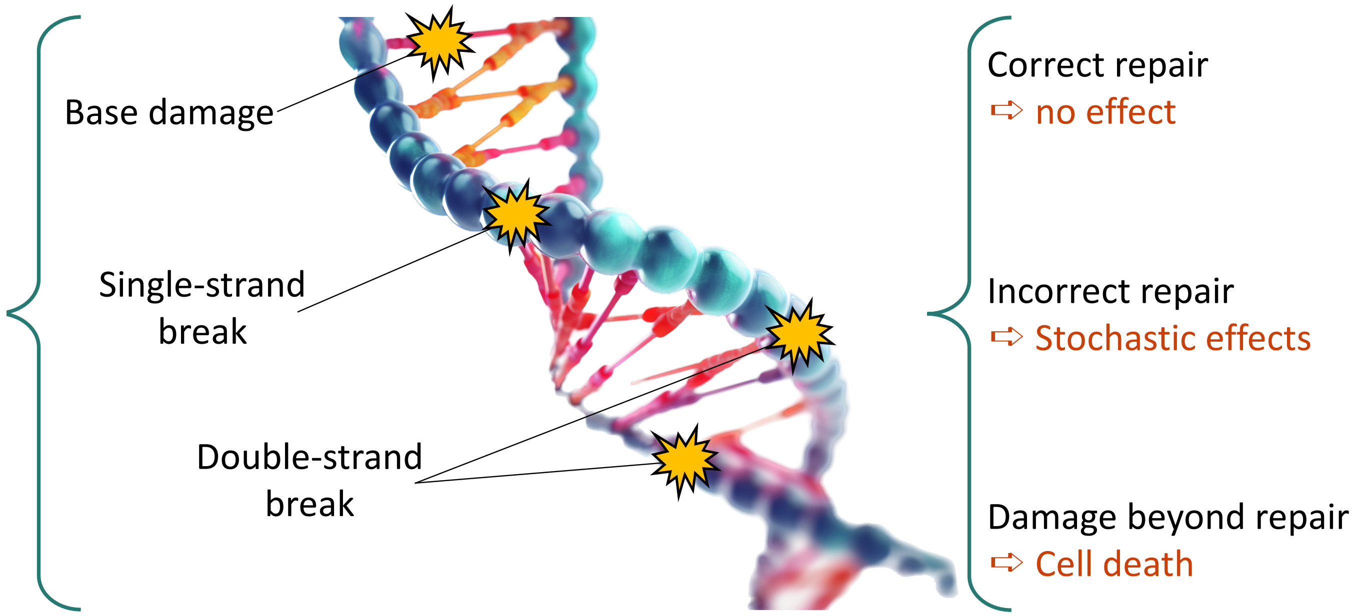
IPHC, GSI, INFN, CNAO Centro Nazionale di Adroterapia Oncologica

Chemical processes for hadrontherapy

Fundamental research

- **Indirect effects** responsible for an important part of damages on biomolecules inside the cells (between 30-70%)





Courtesy of L. Gesson

Chemical processes for hadrontherapy @ in2p3

CNRS NUCLÉAIRE & PARTICULES

- Projects: biomolecules radiolysis, CLINM
- 5-years prospects:
  - Fragments data with ^{4}He, ^{12}C, ^{16}O beams
  - Dose rates effects studies (FLASH) and oxygen effects
  - Experimental validation of Geant4-DNA

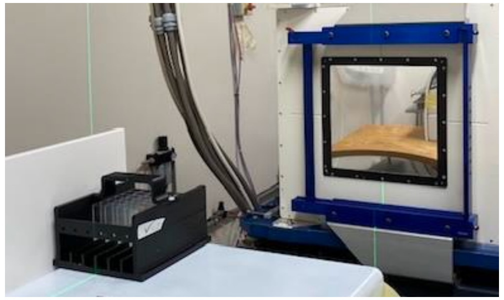
Types of beams: ^{4}He, ^{12}C, ^{16}O, (^{56}Fe)

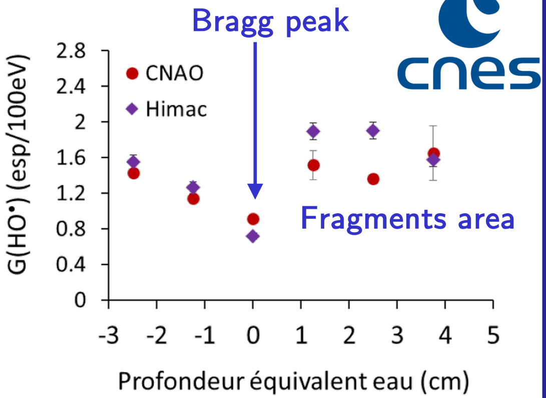
Fundamental research

CLINM

Study of radiolysis products in the fragments area (after the Bragg peak) and impact of secondary particles on indirect effects

IPHC Institut Pluridisciplinaire Hubert CURIEN STRASBOURG — anr — CNAO Centro Nazionale di Adroterapia Oncologica — cnes

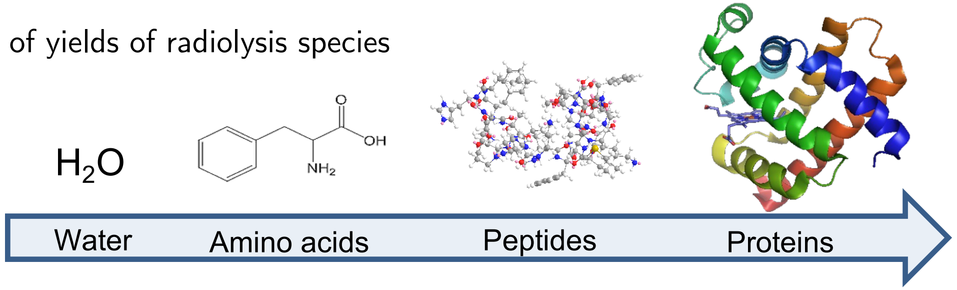


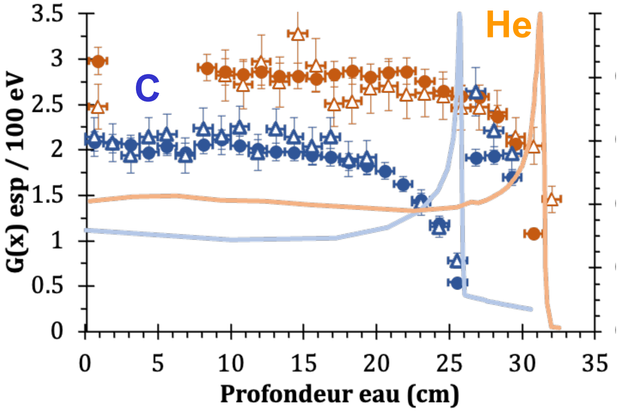


Radiolysis

Study of LET effects, dose rate effects, oxygen effects on radiolysis of biomolecules + comparison to simulations

⇒ Measurement of yields of radiolysis species

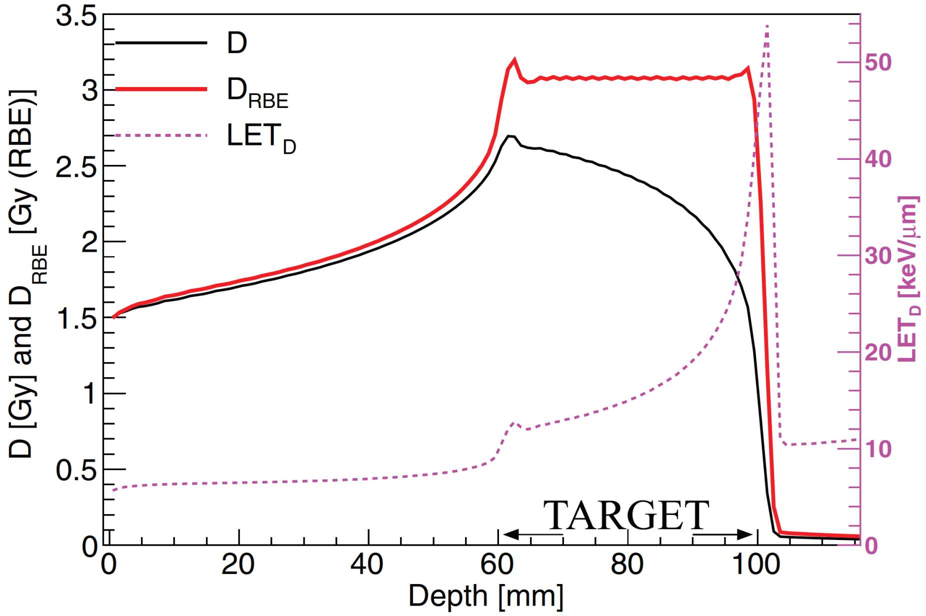




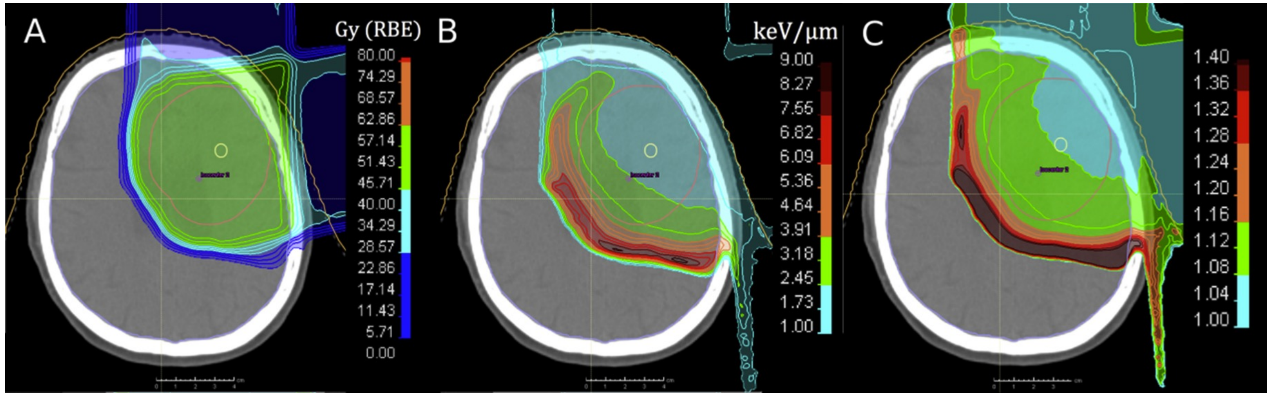
IPHC Institut Pluridisciplinaire Hubert CURIEN STRASBOURG — ICANS Institut de Cancérologie Strasbourg Europe — ICUBE — Aerial — CNAO Centro Nazionale di Adroterapia Oncologica — QST

Biological processes for hadrontherapy

- Understanding of biological response of cells to ionizing particles essential for hadrontherapy
- Optimization of TPS **regarding biological dose** ⇒ necessity to correctly modelize biological effects
- Better characterization of the **biological advantage** of ions for **radioresistant** and **hypoxic** tumors
- Potentialization of hadrontherapy with other treatments? (chemotherapy, immunotherapy,...)



Mairani et al. *Biologically optimized helium ion plans: calculation approach and its in vitro validation.* Phys. Med. Biol., 2016.



Extracted from Luehr et al., *Relative biological effectiveness in proton beam therapy: Current knowledge and future challenges.* Clinical and Translational Radiation Oncology, 2018.

Final goal: to deliver biologically-optimized treatments to patients

Fundamental research

Biological processes for hadrontherapy @ in2p3

NUCLÉAIRE & PARTICULES

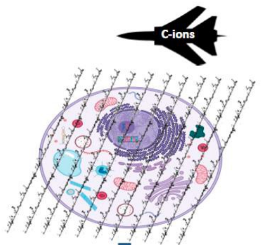
- Projects: BioHADRON, MODERATO, PROTOVEC
- 5-years prospects:
  - MODERATO: Tests in different environments (normoxia/hypoxia), with/without nanoparticles, 3D spheroids, irradiation with protons (BioALTO, Inst. Curie, Gustave Roussy)
  - BioHADRON: Impact of ion radiation on tumor metabolism, immune response, and metastasis ; validation of in-ovo cellular model
  - PROTOVEC: Impact of proton FLASH, potentialization with α-particle

Fundamental research

BioHADRON

Characterization of the biological responses of tumoral cells (2D and 3D models) and pre-clinical models (in-ovo or in-vivo irradiations) to ions (protons, heliums, carbons)

CLARA CANCÉROPÔLE LYON AUVERGNE RHÔNE-ALPES | Lyon 1 | iP2i



Main goals

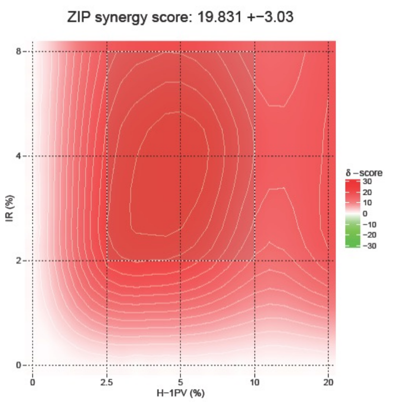
- Improvement **of biological dose calculations** in simulations (NaNOx, Geant4-DNA)
- **Better characterization** of biological advantage of particle therapy

CNAO Centro Nazionale di Adroterapia Oncologica | Antoine Lacassagne Centre de lutte contre le cancer | unicancer NICE | IAB Epigenetics Chronic Diseases Cancer

PROTOVEC

IPHC Institut Pluridisciplinaire Hubert CURIEN STRASBOURG

Potentialization of protontherapy with immunotherapy using protoparvoviruses on rodents



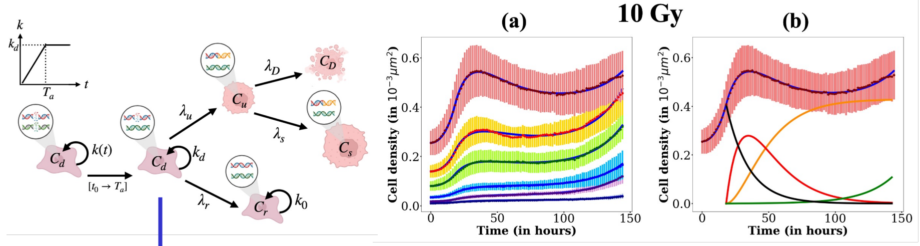
anr

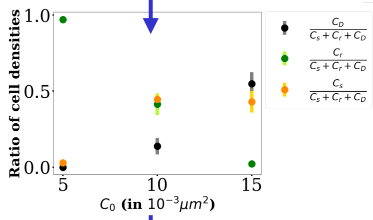
MODERATO

Multi-scale biophysical modeling of the effects of irradiation on cells in their environment

IJCLab Irène Joliot-Curie Laboratoire de Physique des 2 Infinis

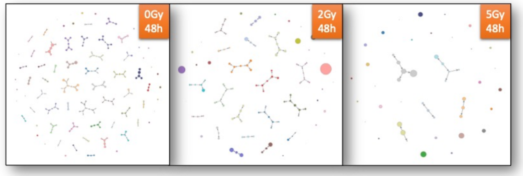
Mathematical models describing the modulation of the effects of radiation on cell populations





⇒ strong dependency on the initial cell density of the surviving fraction, C_r

Development of a tracking software to analyze the faith of individual cells: obtention of individual cell lineage trees.



Billoir M. et al (2025) The temporal response of a glioma cell population to irradiation: modeling the effect of dose and cell density, Royal Society Open Science, 12 (4), 241917

Dose modeling

- **Geant4/Geant4-DNA** platforms to reproduce physical/chemical/biological response to irradiation
- OpenGATE platform

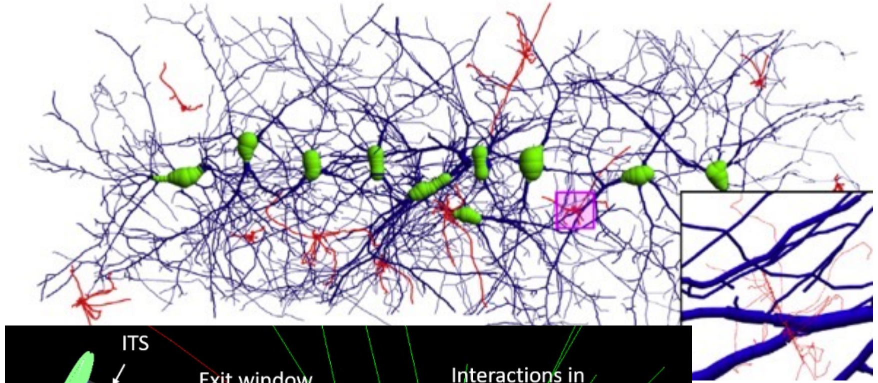
Open-access codes

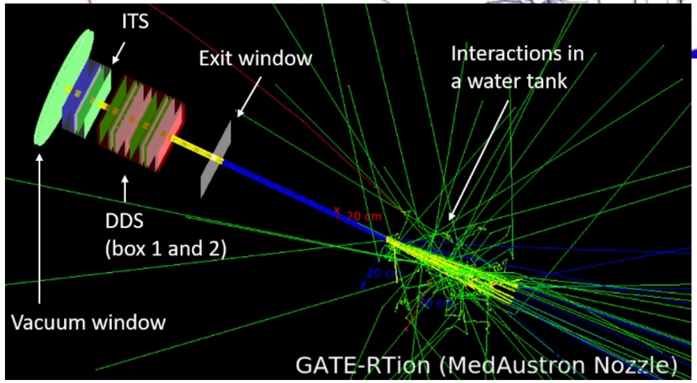
International Journal of Modeling, Simulation, and Scientific Computing | VOL. 01, NO. 02

THE GEANT4-DNA PROJECT

S. INCERTI, G. BALDACCHINO, M. BERNAL, R. CAPRA, C. CHAMPION, Z. FRANCIS, P. GUÈYE, A. MANTERO, B. MASCIALINO, P. MORETTO, P. NIEMINEN, C. VILLAGRASA, and C. ZACHARATOU

https://doi.org/10.1142/S1793962310000122





Numerical twins of the irradiation beam lines

GATE: important user community > 2000 users, 100 scientists trained each year

GATE The collaboration

23 laboratories, companies, clinics developing and validating an open source platform

Spokesperson: Lydia Maigne (LPCA)

Technical coordinator: David Sarrut (Creatis)

France — 10 labs — CNRS, CEA, Inserm

Europe

FH Aachen, University of Applied Sciences, Julich, Germany
Medisip, Ghent University, Belgium
Medical University of Vienna, Wiener Neustadt, Austria
MedAustron, Wiener Neustadt, Austria
Christie Medical Physics & Engineering, Manchester, UK
Institute of Nuclear Physics Polish Academy of Sciences, Poland
Univ. of Patras, Dept of Med. Phys., Greece
BioemTech, Athens, Greece
Paul Scherrer Institute (PSI), Switzerland

Elsewhere

MSKCC, New York, USA
UC Davis, Davis, USA
Sogang University, Seoul, South Korea
QST, Chiba, Japan

Modeling

Hadrontherapy @ in2p3 – Master-project

CNRS NUCLÉAIRE & PARTICULES

- Structuring hadrontherapy activities in **1 master-project Hadrontherapy**

WP1
Modeling physical dose and clinical-biological response

Coordinator:
Juliette Thariat (LPC, Caen)

- NanOx/GATE
- Moderato
- PMRT

WP2
Nuclear and chemical data measurements

Coordinator:
Marie Vanstalle (IPHC, Strasbourg)

Nuclear data
- CLINM
- FOOT

Chemical data
- Radiolysis

WP3
Dose delivery control

Coordinator:
Sara Marcatili (LPSC, Grenoble)

Ion-range monitoring
- CLaRyS-S2C2
- TIARA
- Xemis2

Dosimetry
- DOSADO
- Micro-dosimeter

Beam monitoring
- Diamant
- PEPITES
- Dose profiler BioALTO
- Matrix

WP4
Effects on living-tissues Experimental hadronbiology

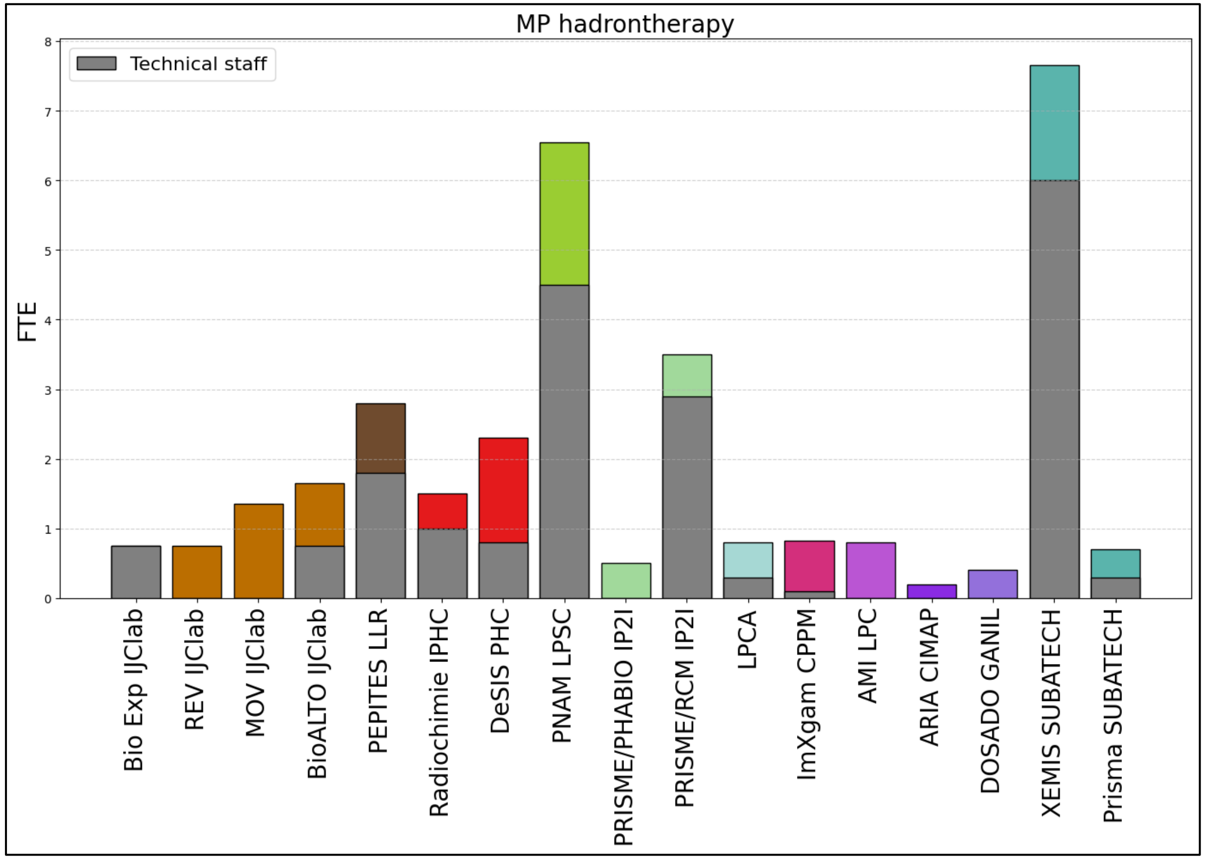
Coordinator:
Claire Rodriguez-Lafrasse (IP2I, Lyon)

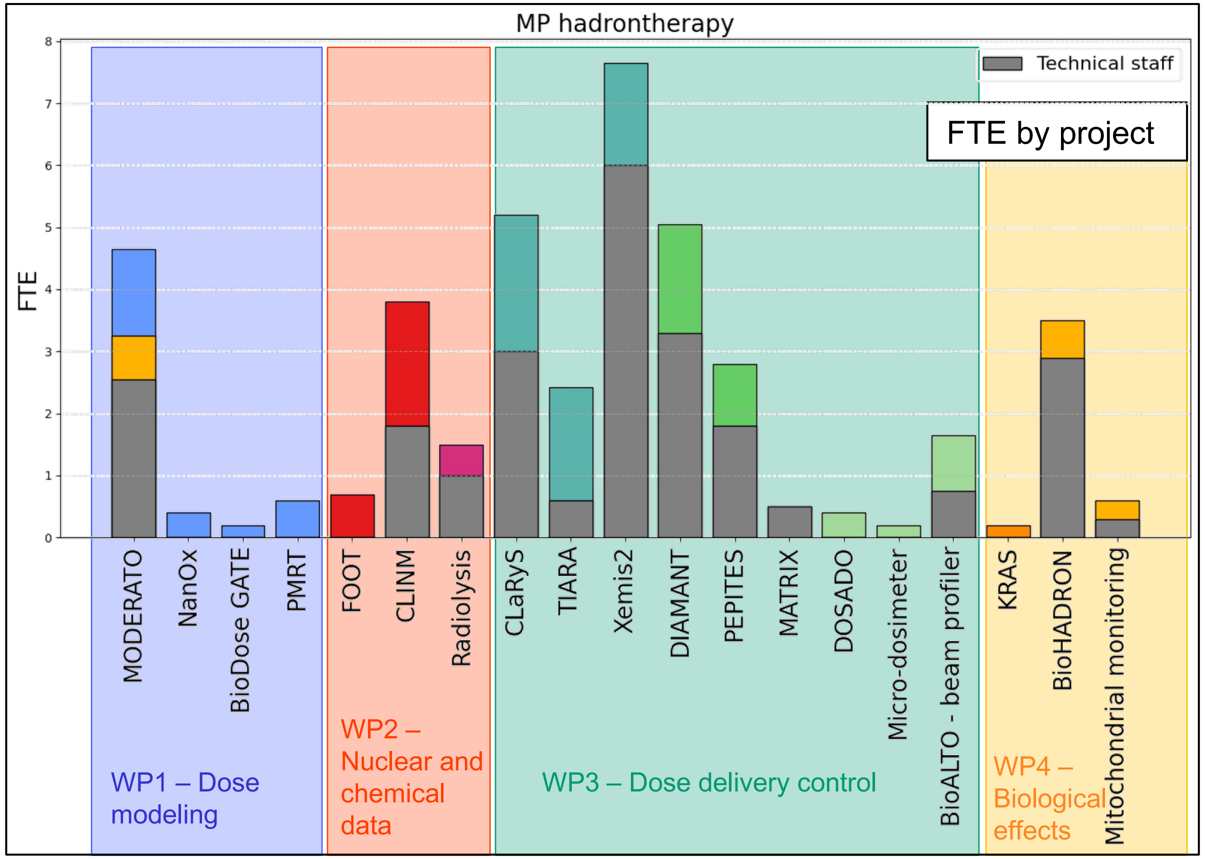
Radiosensitization
- KRAS inhibitor

Multi-scale radiobiology
- BioHADRON
- Moderato

Hadrontherapy @ in2p3 – Master-project

- FTE in the Hadrontherapy Master-project of **in2p3**



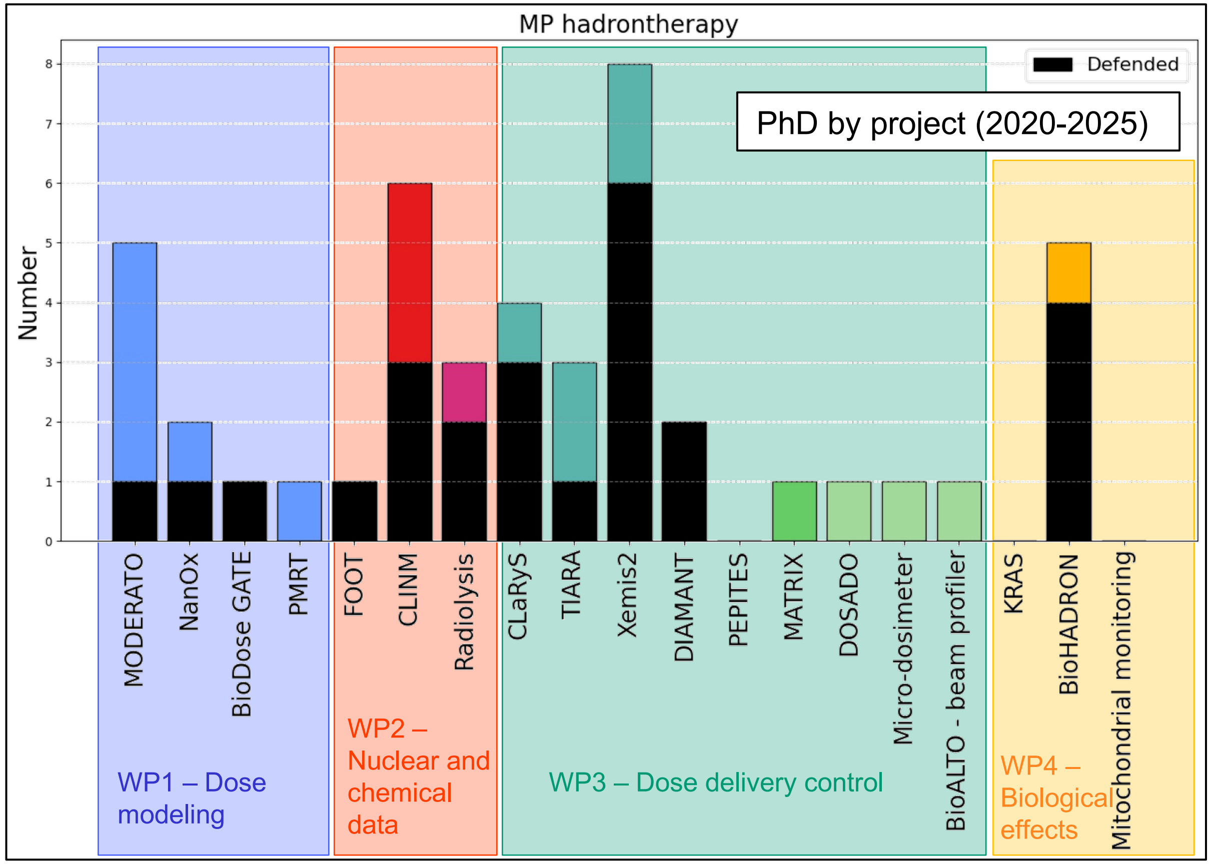


Total FTE in Hadrontherapy MP: 15.33 researchers, 19.60 technical staff

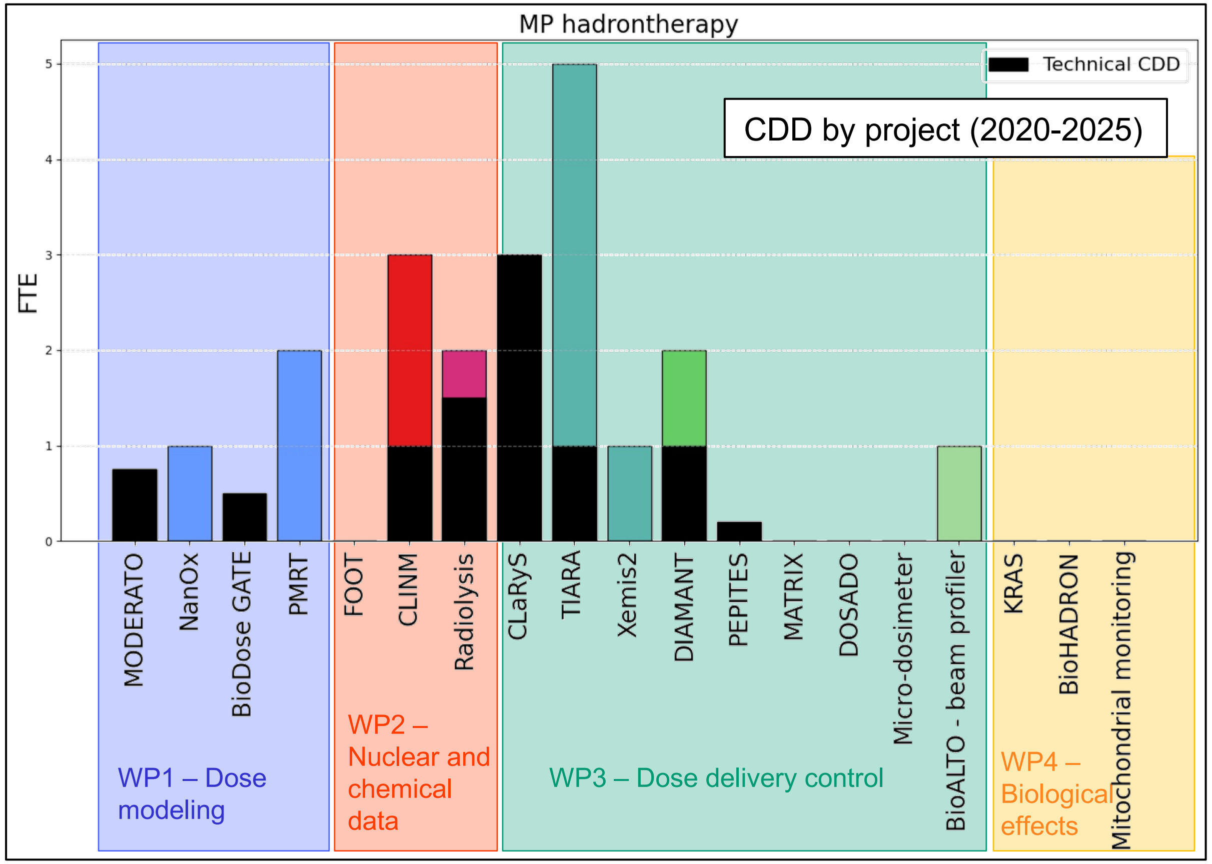
Hadrontherapy @ in2p3 – Master-project

NUCLÉAIRE & PARTICULES

- FTE in the Hadrontherapy Master-project of **in2p3**



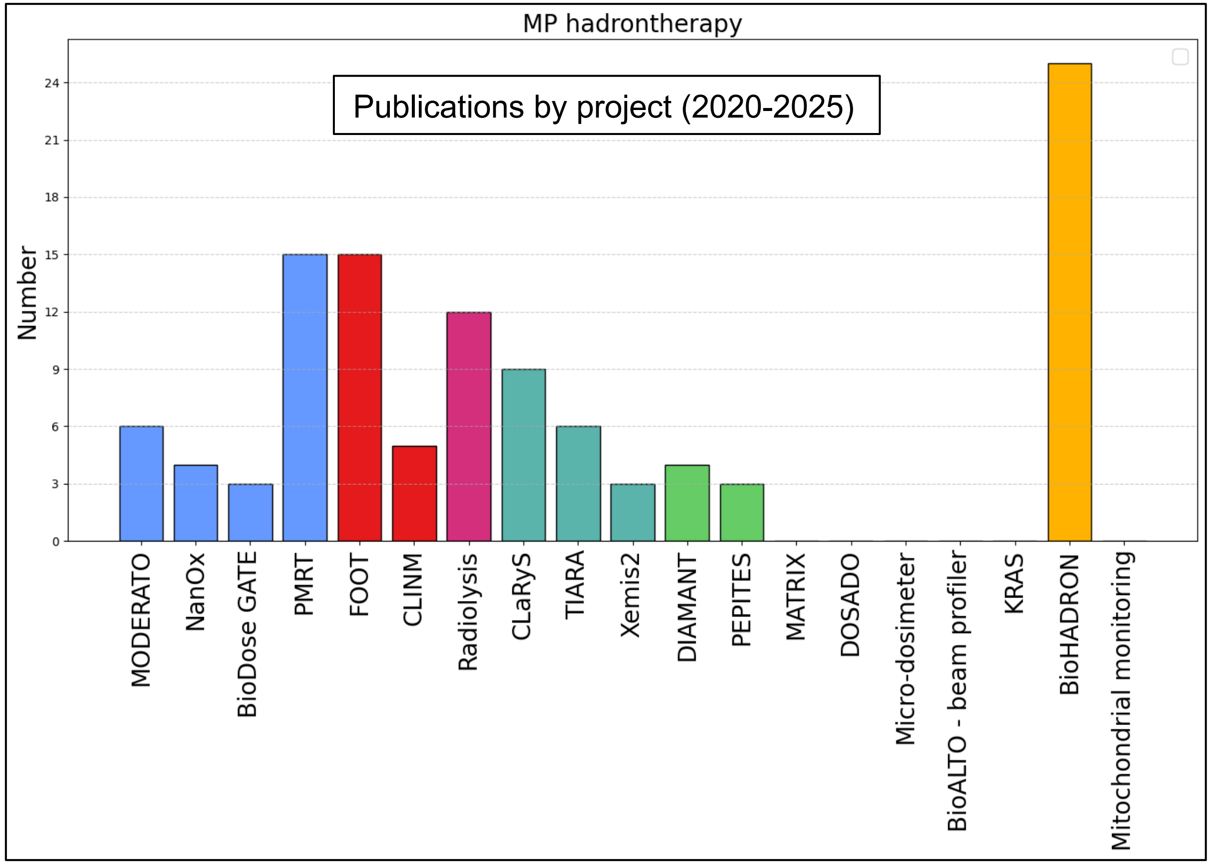
Total PhD in Hadrontherapy MP: 27 defended, 20 on-going

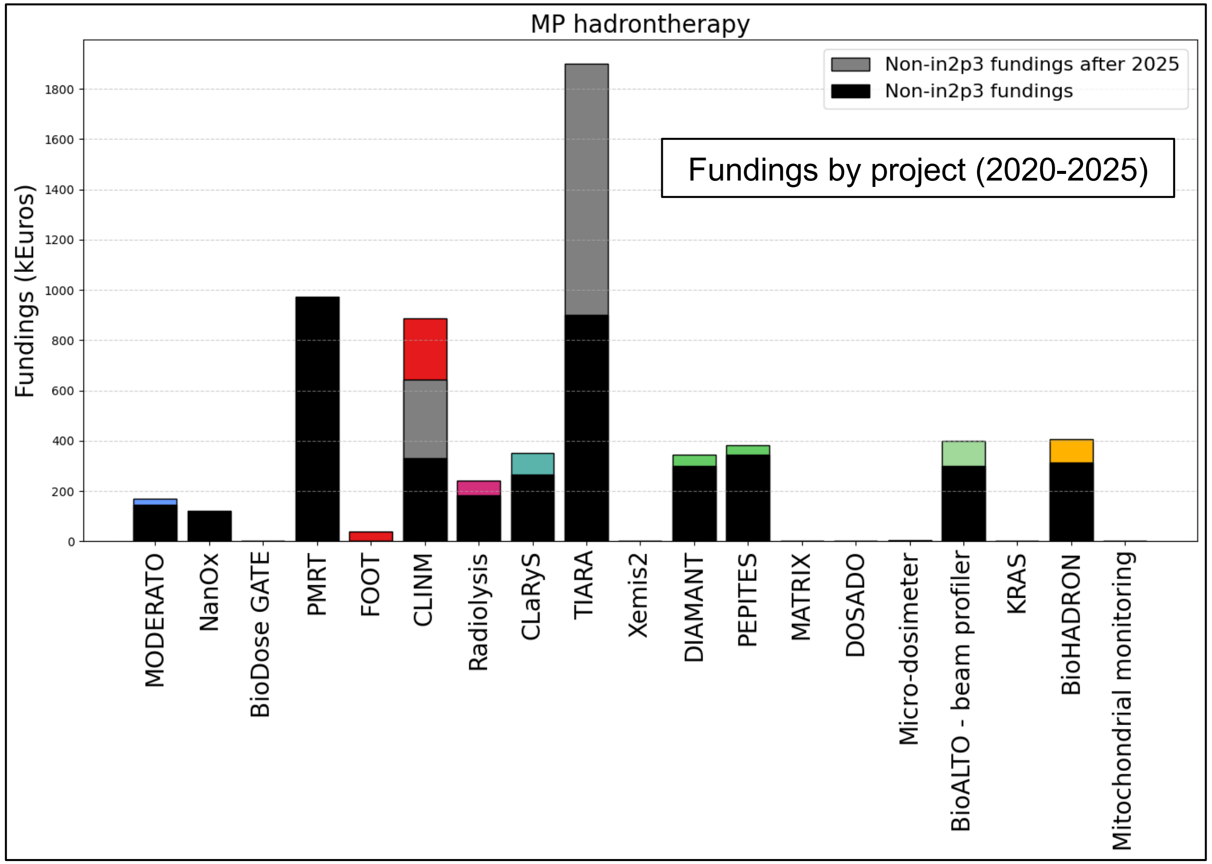


Total CDD in Hadrontherapy MP: 11.20 FTE researchers, 9 FTE technical staff

Hadrontherapy @ in2p3 – Master-project

- Publications and fundings





Total publications in Hadrontherapy MP: 111

Total fundings in Hadrontherapy MP: 1039 kEuros in2p3, 4058 kEuros non-in2p3

Hadrontherapy @ in2p3 - SWOT

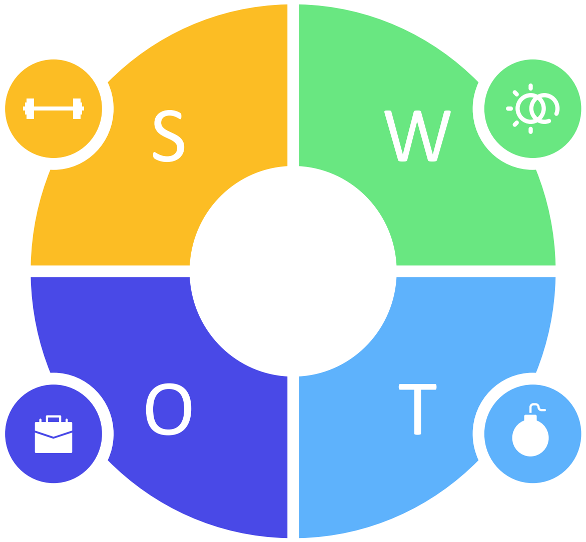
NUCLÉAIRE & PARTICULES

Strengths

- Highly interdisciplinary projects
- Unique set of irradiation platforms for multidisciplinary research
- Access to experimental and clinical facilities (CNAO, CAL, GANIL)
- **Strong partnerships with leading national and international institutions** (CNAO, INFN, GSI, GANIL…)
- **High success to competitive funding agencies**
- Important expertise of the teams in instrumentation and modeling
- Strong contribution and leadership in highly-used open-source code
- Strong links with INSERM

Opportunities

- Collaborative works with many national institutions (INSERM, CNES, clinical facilities) and regional structures
- Possible transfer to industry or clinical routine (e.g., online monitoring)
- Commissioning of the C-400
- New accelerators techniques (e.g. laser)



Weaknesses

- Difficulty securing external funding for long-term projects
- Human Resources
- Dependence on external irradiation facilities
- High dependence on radionuclide availability slowing-down TRT research projects

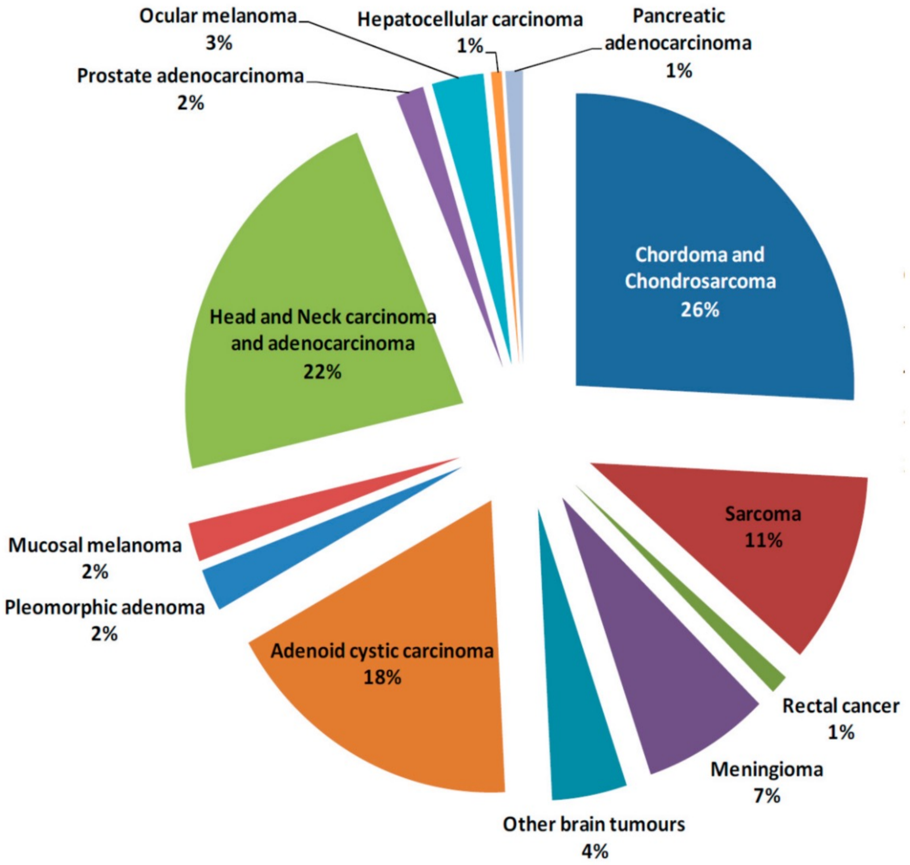
Threats

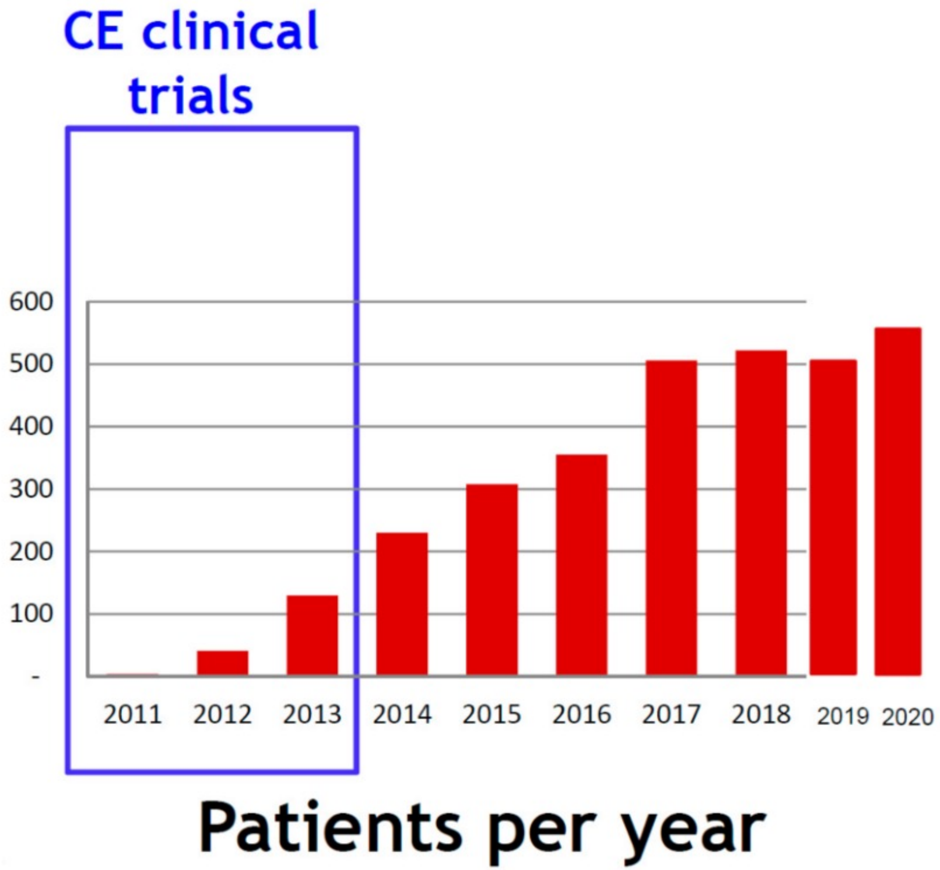
- Strong competition for fundings in the fields of radiation biology and radiotherapy
- Risk of project slow-down due to staff turnover or lack of recruitment
- Regulatory and logistical constraints associated with international beam time access
- Uncertainty in long-term institutional or political support for interdisciplinary research
- Lack of attractiveness due to low amount of permanent positions in the field
- Cost of access to clinical beam

Appendix

Hadrontherapy in Europe

- Which tumors are treated with hadrontherapy? ⇒ the CNAO example





Extracted from **S. Rossi**, *Hadron Therapy Achievements and Challenges: The CNAO Experience*, Physics, 2022.

How do we choose an ion for hadrontherapy?

Oxygen enhancement ratio

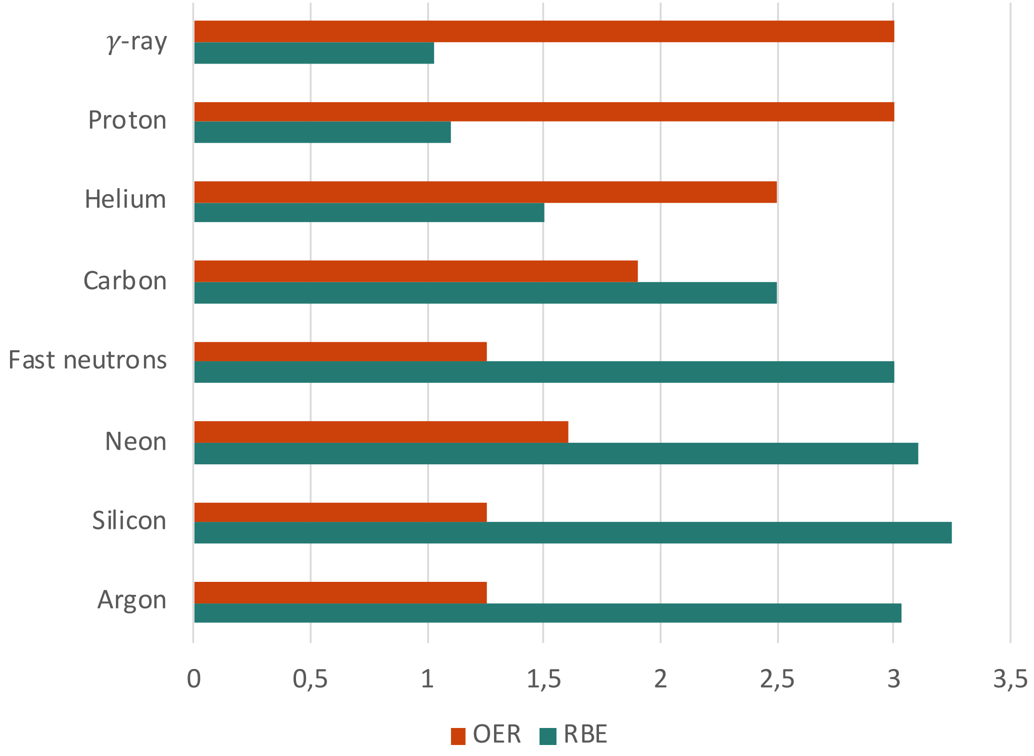
- Reduced oxygen concentration in cell (hypoxic cell) reduce radiation effectiveness
- $$\text{OER} = \frac{\text{radiation dose in hypoxia}}{\text{radiation dose in air}}$$

Relative biological effectiveness

- Take into account radiation type
- Based on cellular survival curves
- $$\text{RBE} = \frac{D_{\text{Xray}}}{D_{\text{ion}}}$$

Reference dose with X-ray therapy

Dose under investigation yielding equivalent cellular survival



High RBE = Lot of damages

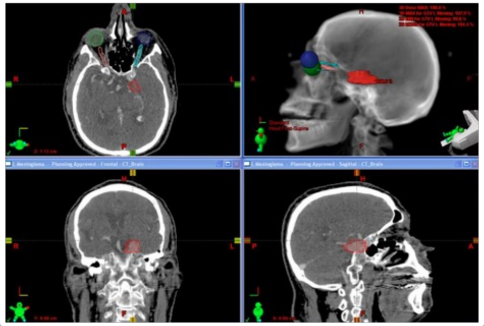
Low OER = Low resistance of hypoxic cells

Courtesy of L. Gesson

Why nuclear physics for health?

Imaging

Define tumoral/targeted volume



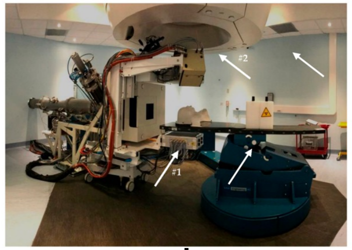
Treatment planning system (TPS)

Treatment

Irradiation control

PET, prompt-gamma

The INSIDE system in CNAO treatment room Extracted from **S. Rossi**, *Hadron Therapy Achievements and Challenges: The CNAO Experience*, Physics, 2022.



Dose calculation

Physical processes

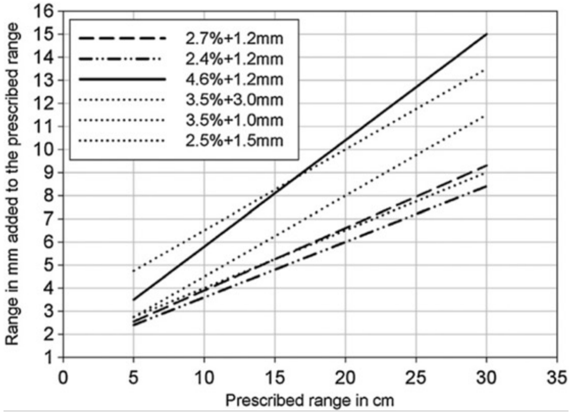
Biological processes

Chemical processes

NUCLÉAIRE & PARTICULES

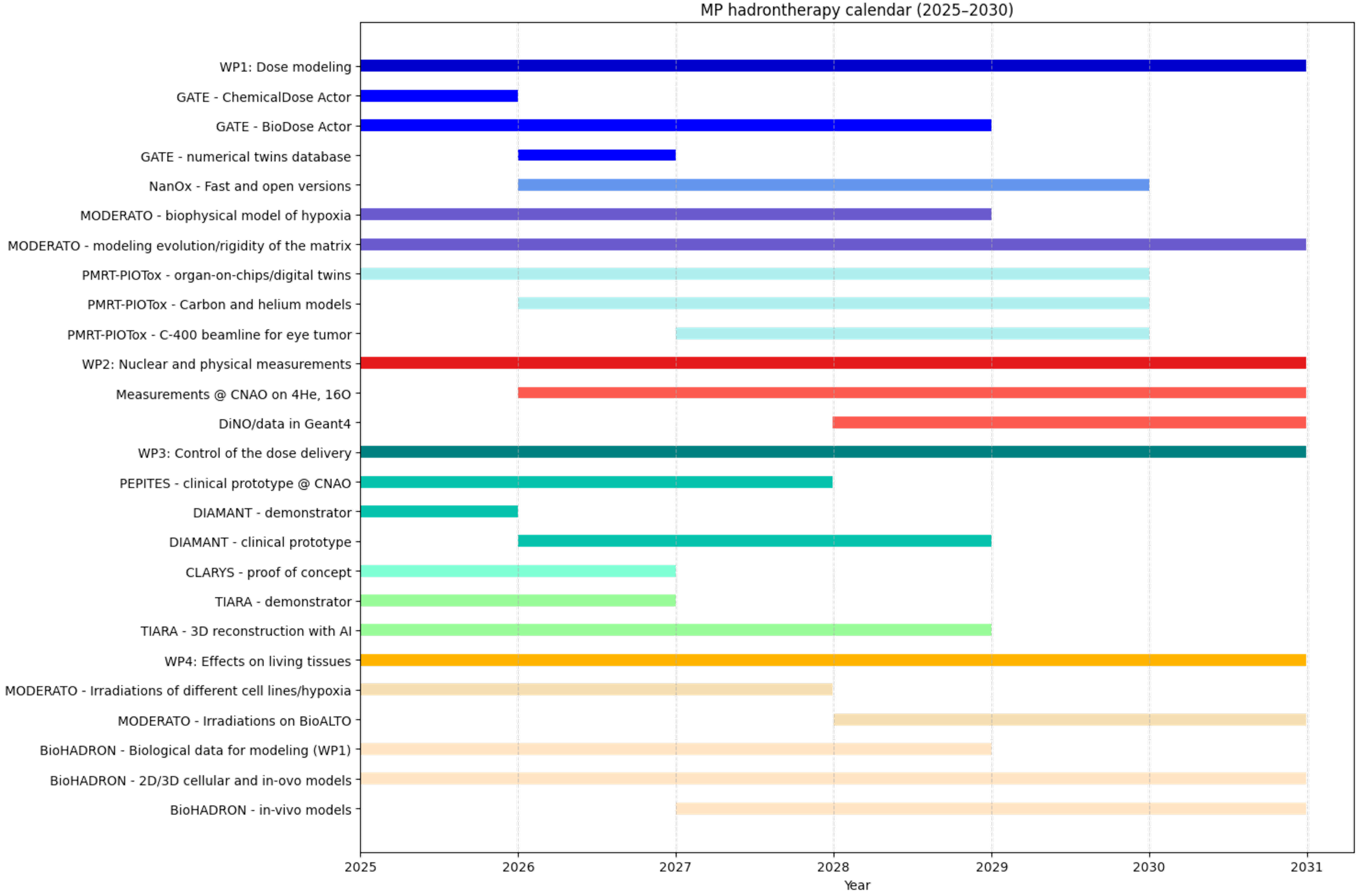
Corrections

Comparison between delivered and planned dose



From **Paganetti**, "*Range uncertainties in proton therapy and the role of Monte Carlo simulations*", Phys. Med. Biol. (2012).

Hadrontherapy @ in2p3 – Master-project



WP1 projects

Dose modeling

Resp.: Juliette Thariat (LPC Caen)

Modélisation Des Effets RAdiobiologiques in ViTrO (MODERATO)

NUCLÉAIRE & PARTICULES

Objective: Multi-scale biophysical modeling of the effects of irradiation on cells in their environment

Data production and image analysis

- Different cell lines
- Different irradiation (photons, protons, e- etc) at Inst. Curie, Bioalto, Inst. G. Roussy
- Different environment (high/low cell density, normoxia/hypoxia, different elasticity of the matrix, migration promoted or not etc)

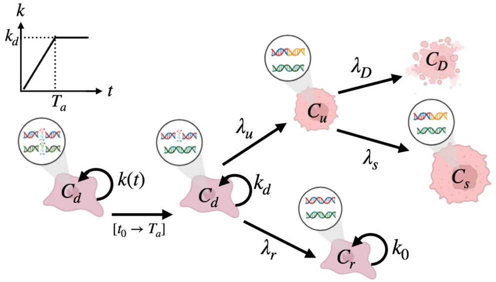
- With/without nanoparticules
- 2D and 3D (spheroïds)
- Cell transfection (nucleus or cytoplasm)
- Imaging (video microscopy)
- Image analysis (software development)

5 year-projection
Done already

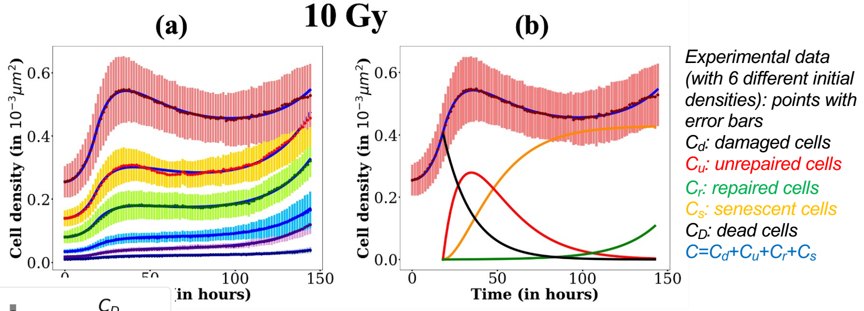
Modeling and tracking

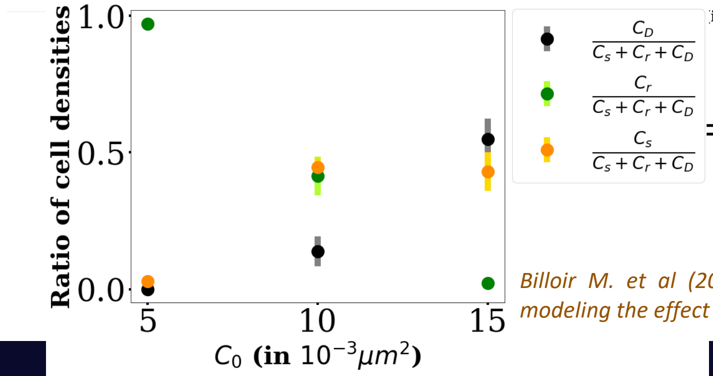
Mathematical models describing the modulation of the effects of radiation on cell populations

A simple compartmental model…



… that fits well the data.



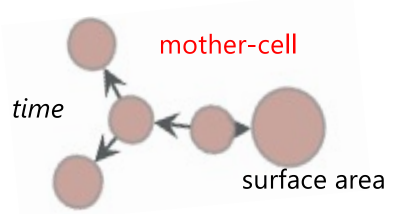


$\Longrightarrow$

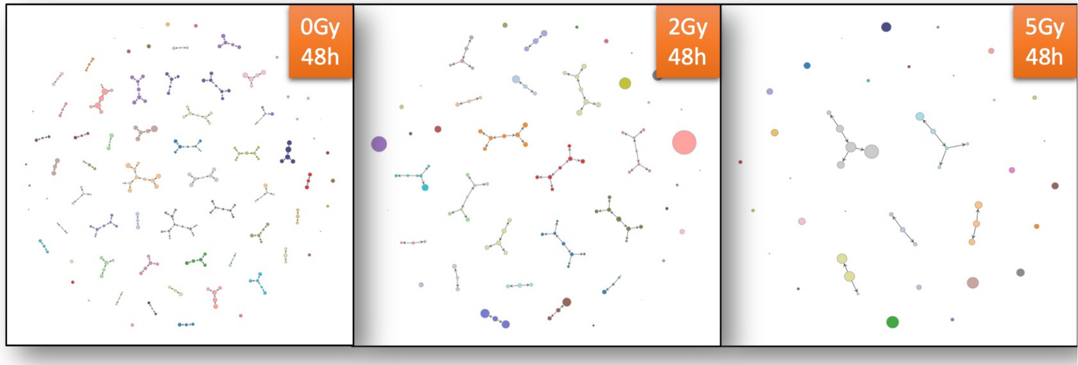
The model reveals **a strong dependency on the initial cell density of the surviving fraction**, C_r (but also C_s senscent and C_D death cells), 6 days after irradiation)

Billoir M. et al (2025) The temporal response of a glioma cell population to irradiation: modeling the effect of dose and cell density, Royal Society Open Science, 12 (4), 241917

Development of a tracking software to analyze the faith of individual cells: obtention of individual cell lineage trees.

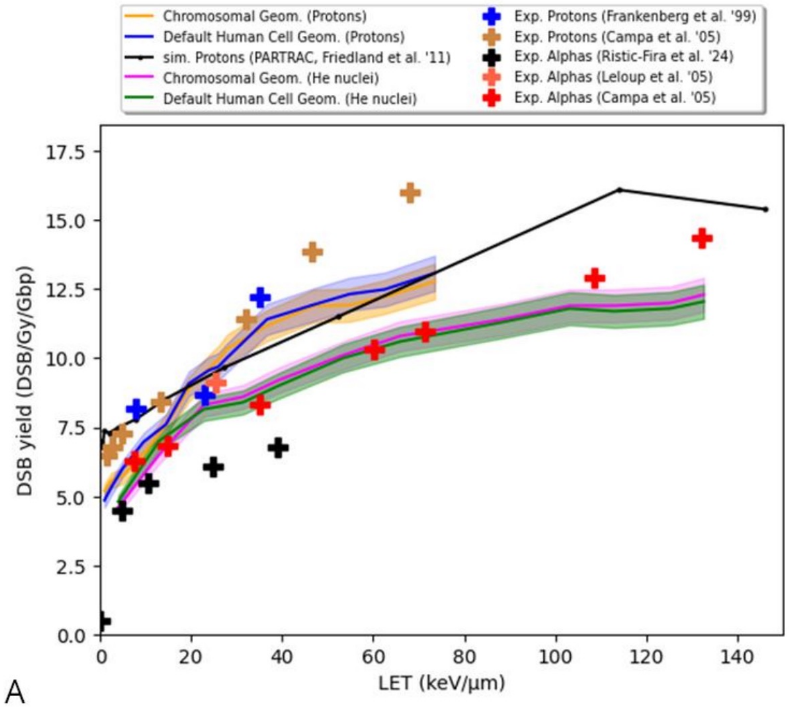


Exemples of lineage trees of MCF7 cells treated with different Xray doses

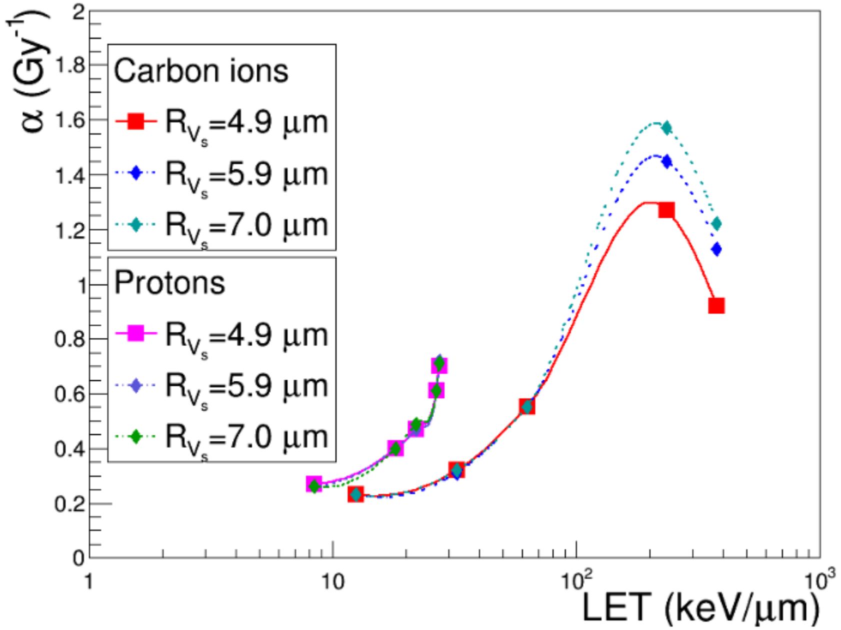


Dose modeling @ in2p3

- Important implication of IN2P3 in **Geant4/Geant4-DNA/GATE**
- Development of the **NanOx model**



From Chatzipapas et al., *Development of a novel computational technique to create DNA and cell geometrical models for Geant4-DNA*, Physica Medica, 2024.



From Monini et al., *Study of the Influence of NanOx Parameters*, Cancers, 2018.

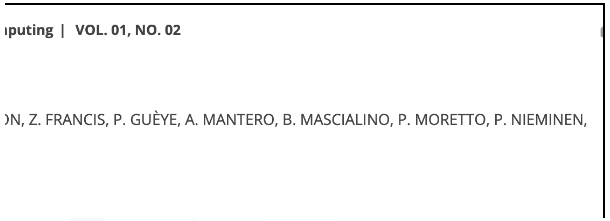
CNRS NUCLÉAIRE & PARTICULES | GEANT4-DNA | GEANT4 | GATE | IP2I | Laboratoire Leprince-Ringuet | LPC Laboratoire de Physique de Clermont | LP2i Bordeaux

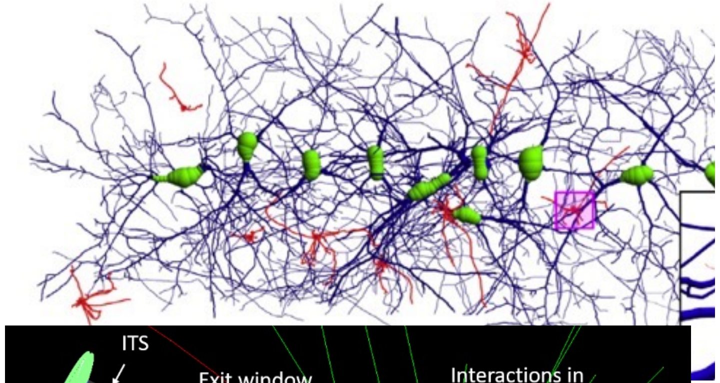
⇒ More details on simulation platforms in ***Instrumentation*** presentation from E. Testa

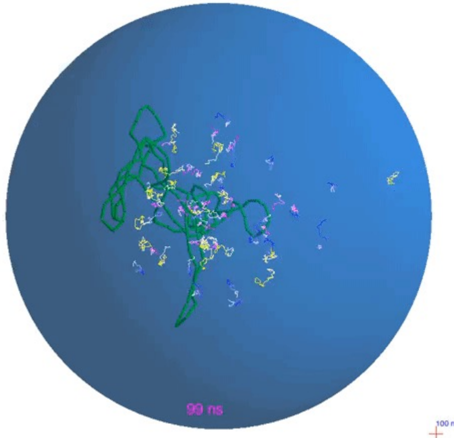
Dose modeling

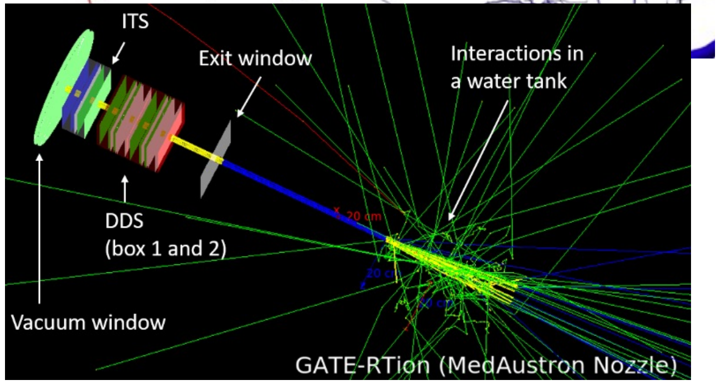
- **Geant4/Geant4-DNA** platforms to reproduce physical/chemical/biological response to irradiation
- OpenGATE platform

Open-access codes



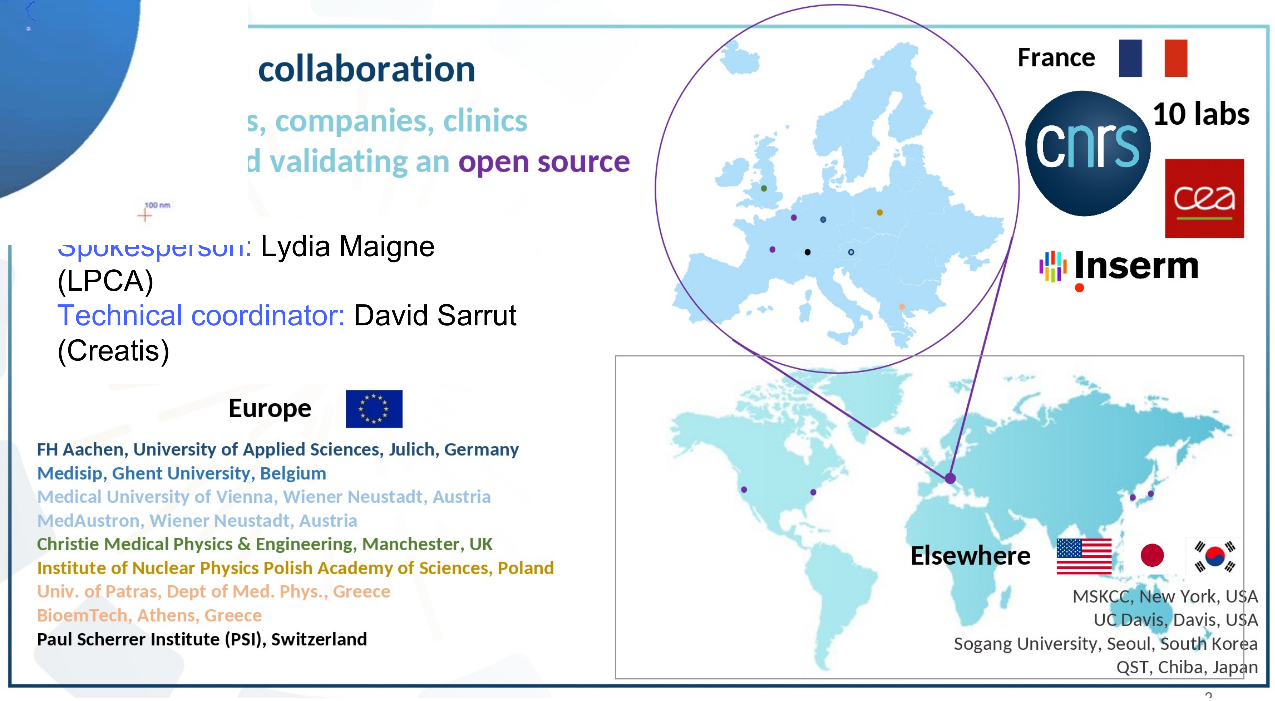






Numerical twins of the irradiation beam lines

GATE: important user community > 2000 users, 100 scientists trained each year



WP2 projects

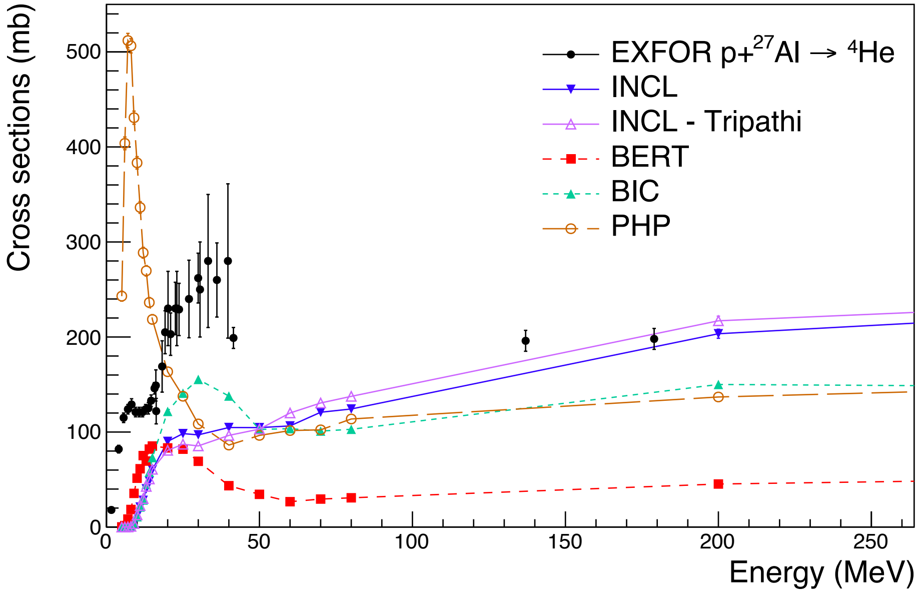
Nuclear and chemical data

Resp.: Marie Vanstalle (IPHC Strasbourg)

Nuclear processes for hadrontherapy

Fundamental research

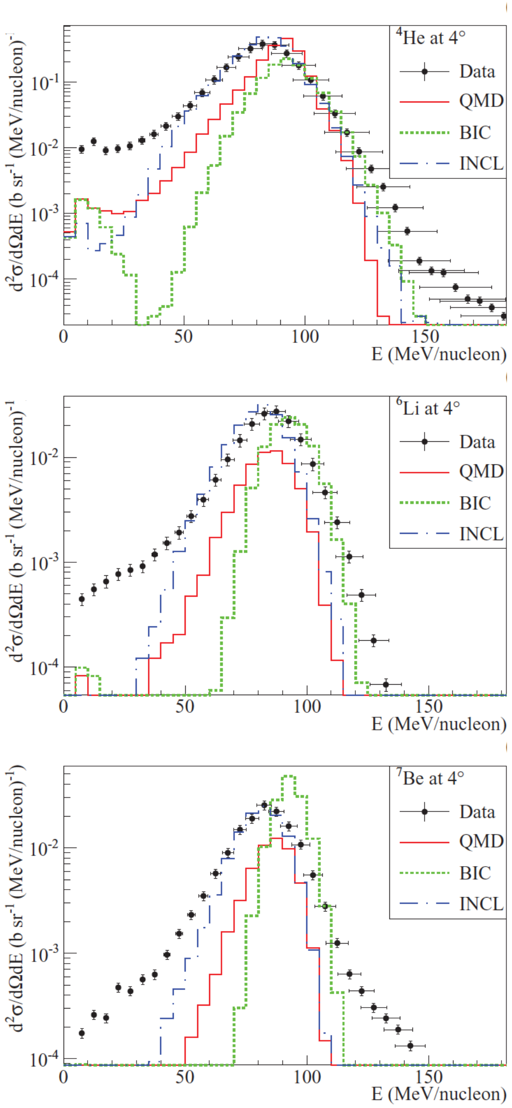
- Important discrepancies between models and data



What accuracy do we need on cross-sections for radiobiology & radiation protection?

$\frac{d\sigma}{dE} \sim 10\%$ $\quad$ $\frac{d^2\sigma}{dE d\Omega} \sim 5\%$

$\sigma_Z \sim 2\%$ $\quad$ $\sigma_A \sim 5\%$



Necessity to measure the missing cross-sections in order to improve constraints on the models

Extracted from **Dudouet et al.**, *Benchmarking GEANT4 nuclear models for hadron therapy with 95 MeV/nucleon carbon ions*, Physical Review C, 2014

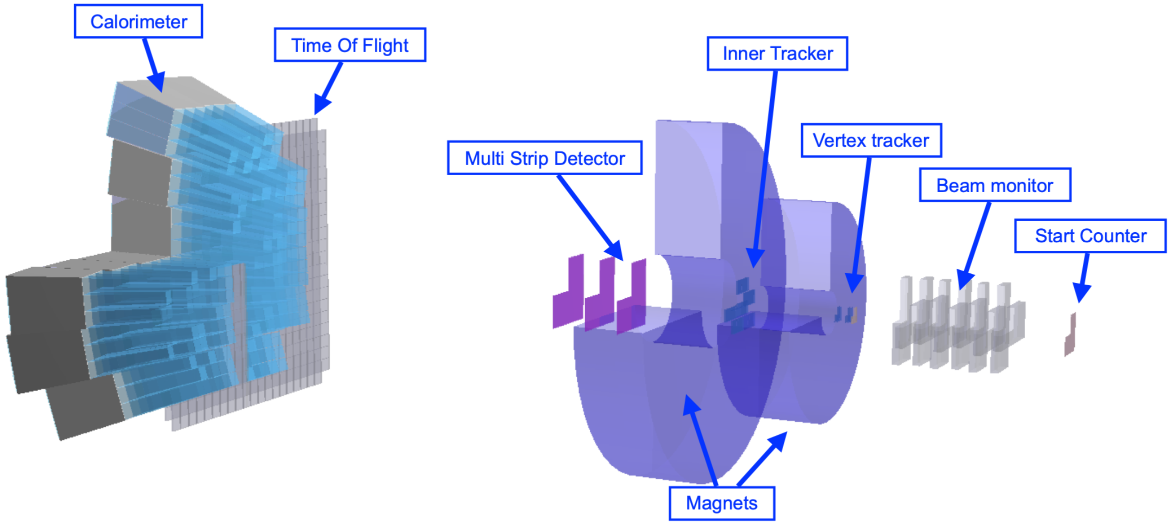
It doesn't matter how beautiful your theory is, it doesn't matter how smart you are. If it doesn't agree with experiment, it's wrong.

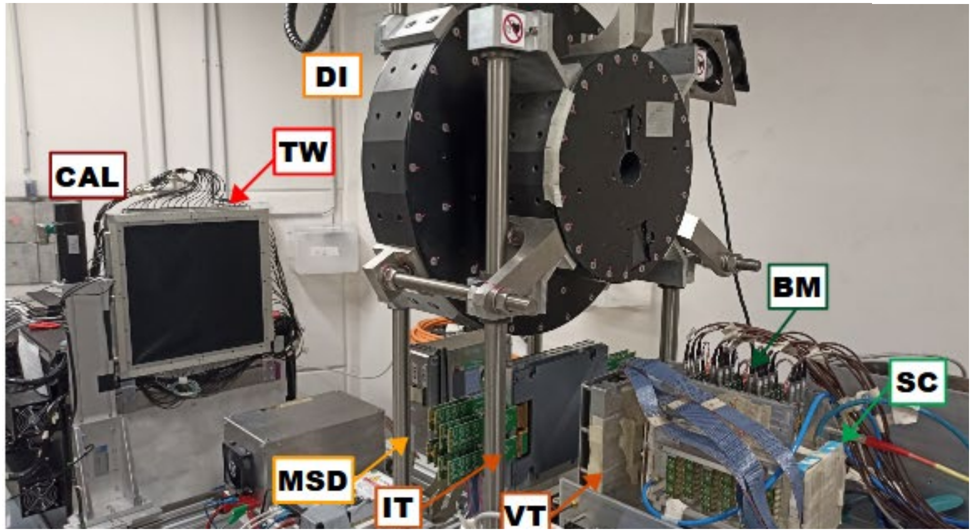
RICHARD FEYNMAN

The FOOT experiment

- FOOT (FragmentatiOn Of Target) : **double differential cross-sections measurements** of ^{12}C, ^{16}O, ^{4}He, ^{56}Fe @200-700 MeV/u on C, $(C_2H_4)_n$, PMMA target
  - Goal: cross-sections measurements with 5% of accuracy (double differential)
  - Ground-based experiments at GSI and CNAO
- Z identification ⇒ Start counter (SC) + ToF wall (TW)
- A identification ⇒ magnetic spectrometer: beam monitoring (BM) + vertex detector (VTX) + inner tracker (IT) + multi-strip detector (MSD)
- Total energy ⇒ calorimeter (CAL)

Direct + inverse kinematic approach





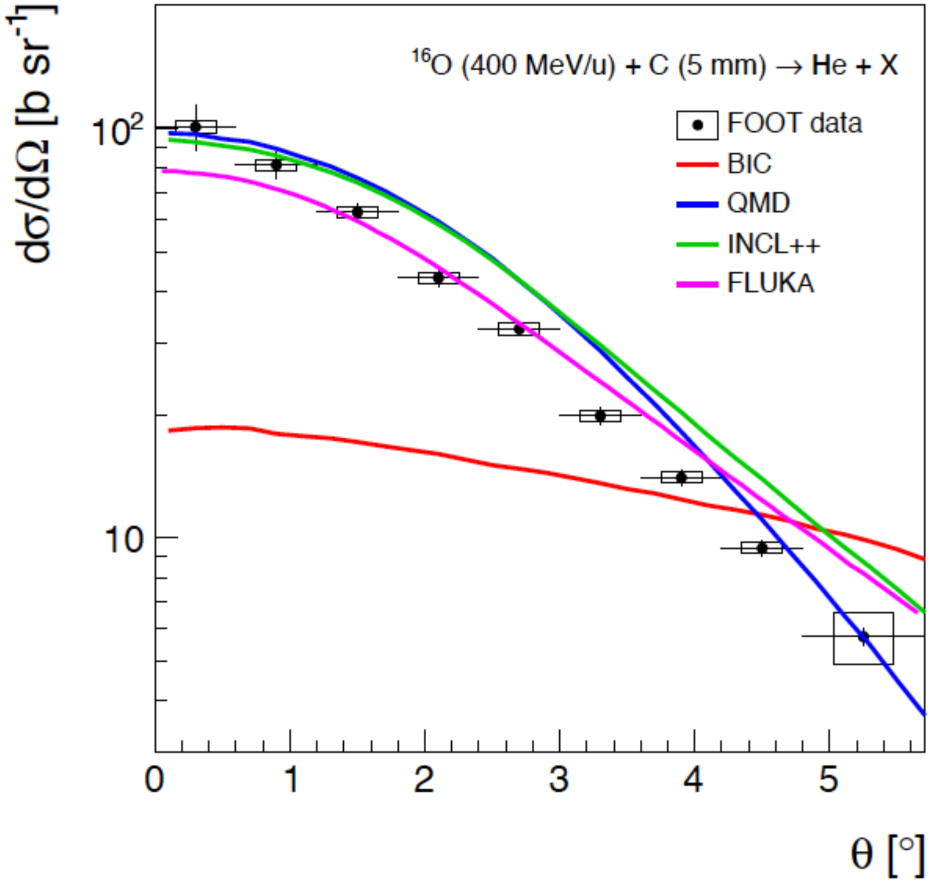
+ emulsion setup to measure fragments of Z<3 and up to 70º

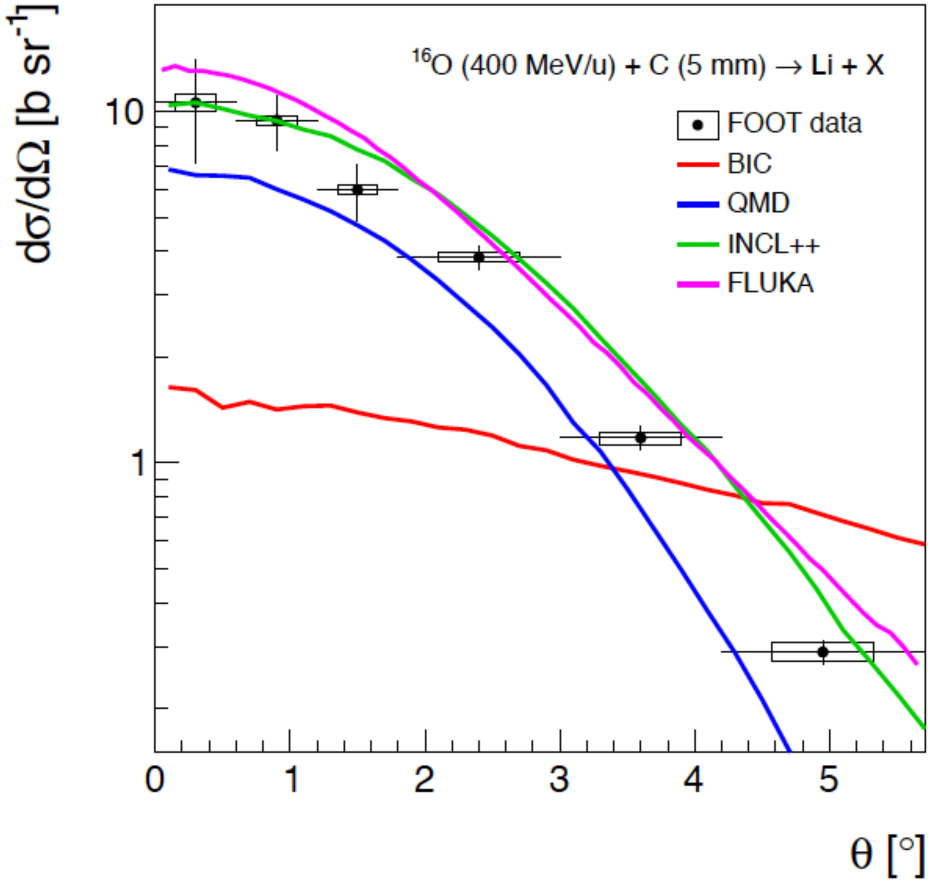
What performances do we want?

$$\frac{\sigma(p)}{p} < 5\% \qquad \frac{\sigma(\Delta E)}{E} < 5\% \qquad \sigma_{ToF} < 100\ ps$$

The FOOT experiment

^{16}O (400 MeV/u)+ $^{12}C \rightarrow$ ^{4He} + X, ^{16}O (400 MeV/u)+ $^{12}C \rightarrow$ ^{7}Li + X (GSI – 2021)
Angular differential and elemental fragmentation cross sections of a 400MeV/u ^{16}O beam on a graphite target with the FOOT experiment, accepted in Physical review C



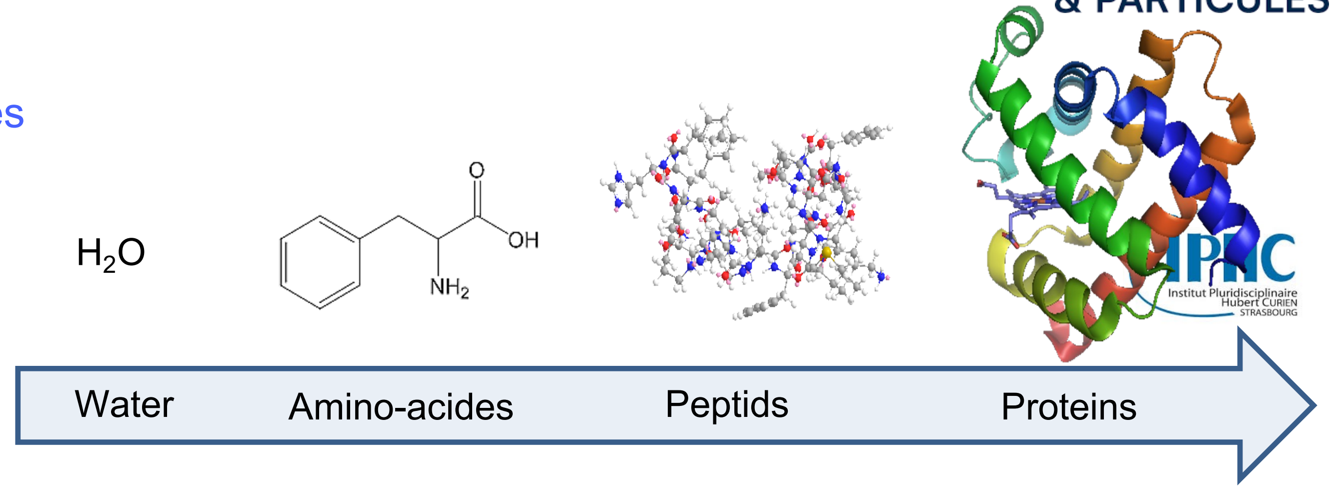


Radiolysis measurement

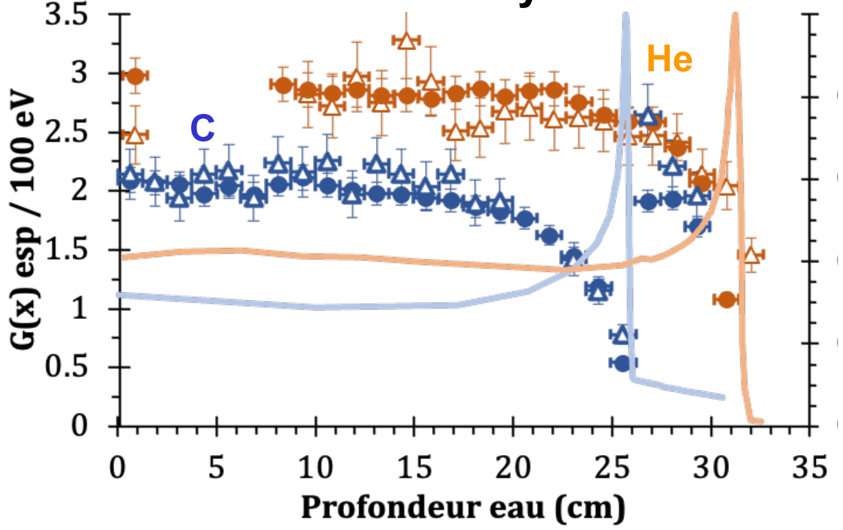
Radiochemistry team + DeSIS - IPHC, Strasbourg

Goal: to determine radiolysis mechanisms on biomolecules

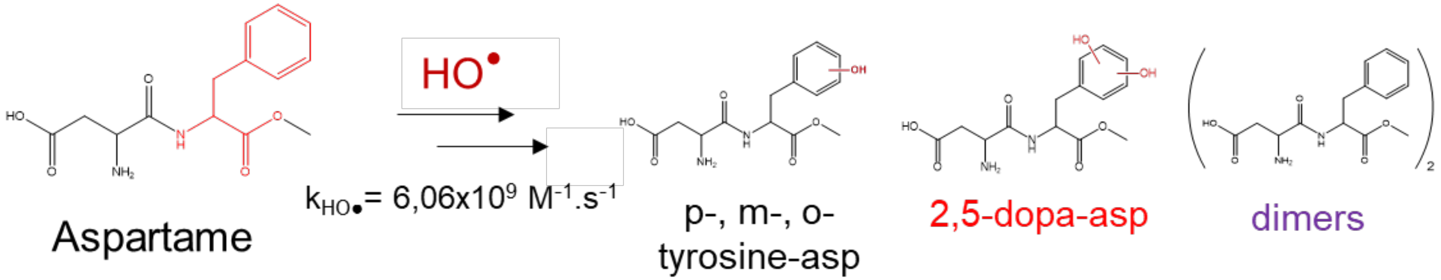
Molecular scale:
LET effects (ions/RX, e-)
Dose rate effects (FLASH)
Oxygenation effects
Simulations performed with Geant4-DNA (DeSIS team)



Water radiolysis



$HO^{\bullet}$ and e^-_{aq} yields along the ion path



- Determination of normalized yields via G(HO•) ⇒ independent of LET or dose rate effect on water radiolysis
- Identification and quantification of specific products at high LET and/or high dose rate
- Formation mechanisms

Nuclear & chemical processes for hadrontherapy @ in2p3

NUCLÉAIRE & PARTICULES

CLINM

- 4 IPHC researchers
  - **DeSIS team: N. Arbor, C. Finck, M. Vanstalle**
  - Radiochemistry team: Q. Raffy
- 5 IPHC technical staff
  - **DeSIS team: S. Chefson, S. Higueret, T.-D. Lê**
  - Radiochemistry team: C. Galindo, P. Peaupardin
- PhD:
  - **DeSIS team: 2 phD defended (2022, 2024), 1 ongoing (2024-2028)**
  - Radiochemistry team: 1 defended (2023), 1 ongoing (2022-2025)
- Post-doc: 2 from DeSIS team (2022-2024, 2024-2025)
- Fundings: IN2P3 (master-project FOOT-Xn), ANR (PRC), CNES (phD), HITRI+ (in-beam experiment)

cnes HITRI plus Heavy Ion Therapy Research Integration anr

FOOT

- 2 IPHC researchers: C. Finck, M. Vanstalle
- 1 phD student, defence in 2022 (A. Sécher)
- Non-in2p3 collaborators: 82 researchers from INFN, 3 from GSI
- Extension to more IN2P3 labs? (LPSC,...)
- Fundings: IN2P3 (master-project FOOT-Xn), INFN

INFN

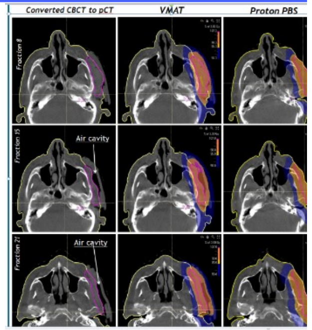
WP3 projects

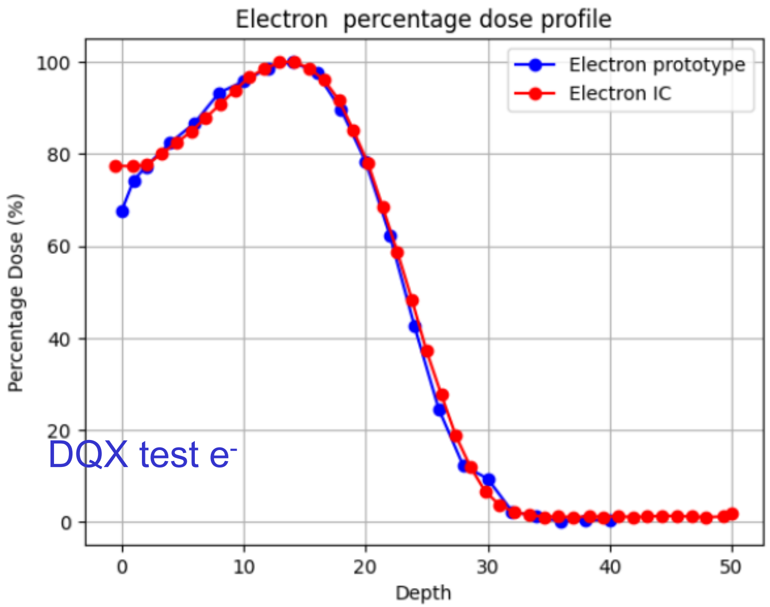
Control of the dose delivery

Resp.: Sara Marcatili (LPSC Grenoble)

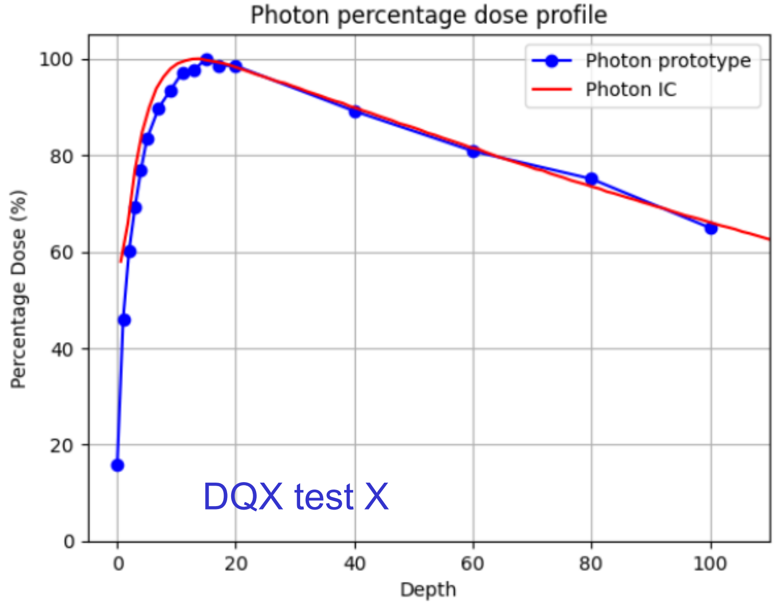
DeCuPro @ AMI LPC Caen

- Evaluation de la dose à la peau pour le traitement des tumeurs cutanées non mélanocytaire (*TCNMs*) en radiothérapie conventionnelle et protonthérapie
- Projet en collaboration avec 2 physiciens médicaux du *centre de traitement contre le cancer François Baclesse* (CFB, Caen)
- Dosimètre à scintillation DQX ProtoV2 en tests e^-/X
- Comparaisons avec mesures films (CFB) et détecteur diamant (Le Havre)
- Tests prévus à *ARRONAX* avec table XY+Z fin 2025
- Chambre Ionisation prévue pour 2026

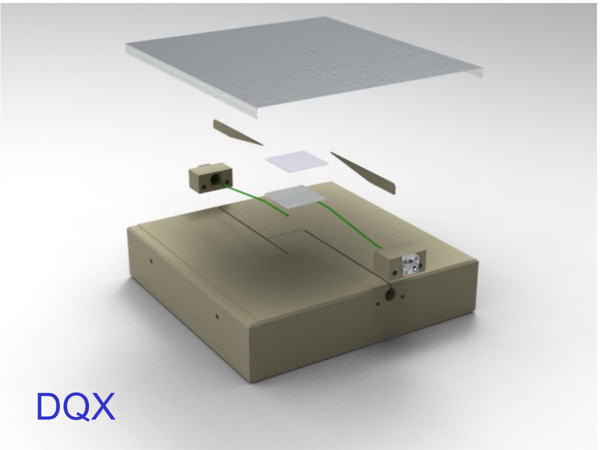




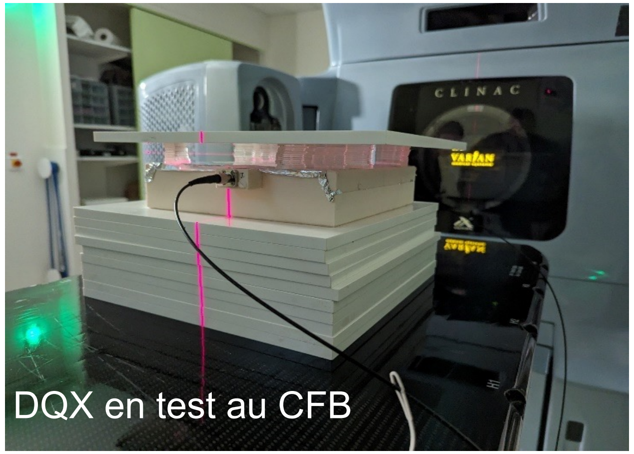
DQX test e⁻



DQX test X



DQX



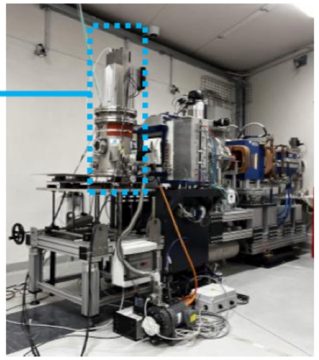
DQX en test au CFB

PEPITES

PEPITES @CNAO

Accord CNRS/CNAO (04.2024)

« Nomade »
Copie du PEPITES d'ARRONAX



PEPITES

CNAO

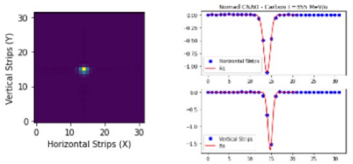
Moniteur 6.5 m en amont du patient : **budget matière crucial !**

- Evaluation de « faisabilité » ✓

Programme sur 3 ans envisagé pour un moniteur en clinique

- Étude d'adaptation (ligne et/ou PEPITES)
- Production d'un système complet (détecteur, readout, DAQ)
- Tests

2023.11 — Premiers faisceaux Carbone



2024.09 — Tests anodes hors axe (WET 10 µm → 5 µm)
DAQ avec trigger externe CNAO

2025.04 — Comparaison DAQ ARRONAX & Nomade
Mesure taux SEE pour carbone

INSTITUT POLYTECHNIQUE DE PARIS

Ion-range monitoring @ in2p3

NUCLÉAIRE & PARTICULES

TIARA

- 7 in2p3 permanent staffs
  - **LPSC:** S. Marcatili, M.-L. Gallin Martel, C. Hoarau, J.-F. Mouraz
  - **CPPM:** Y. Boursier, C. Morel, M. Dupont
- Non-in2p3 collaborators: D. Maneval, J. Hérault (CAL)
- 2 phD on-going (2022-2025), 1 phD to come (2025-2028)
- 3 post-doctoral contracts on-going
- **Fundings:** IRS from UGA (), PCSI (Physique cancer, 2020-2023), ERC (2022-2027)

aviesan alliance nationale pour les sciences de la vie et de la santé
Inserm
UGA Université Grenoble Alpes
erc

CLaRyS

- 11 in2p3 permanent staffs
  - **LPSC:** D. Dauvergne, M.-L. Gallin Martel, S. Marcatili, L Gallin-Martel, M. Marton, JF Muraz, Ch Hoareau
  - **CPPM:** Y. Boursier, C. Morel, M. Dupont
- Non-in2p3 collaborators: ??
- 3 phD defended (2020-2025),
- **Fundings:** MITI, Labex Primes

MITI Mission pour les Initiatives Transverses et Interdisciplinaires
LABEX PRIMES UNIVERSITÉ DE LYON

WP4 projects

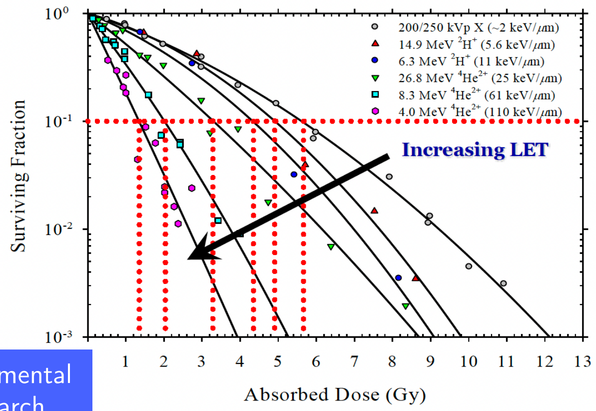
Effects on living tissues

Resp.: Claire Rodriguez-Lafrasse (IP2I Lyon)

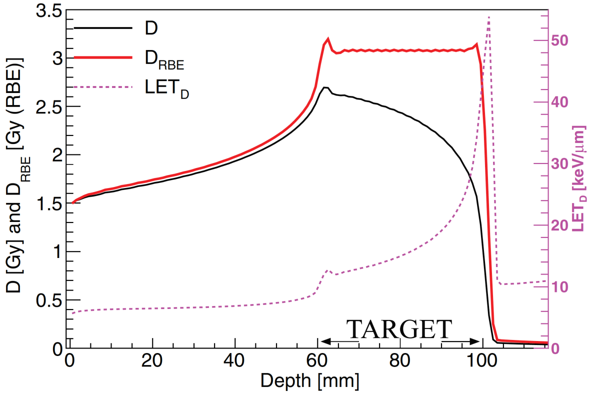
Biological processes for hadrontherapy

- Understanding of biological response of cells to ionizing particles essential for hadrontherapy
- Optimization of TPS **regarding biological dose** ⇒ necessity to correctly modelize biological effects
- Better characterization of the **biological advantage** of ions for **radioresistant** and **hypoxic** tumors
- Potentialization of hadrontherapy with other treatments? (chemotherapy, immunotherapy,...)

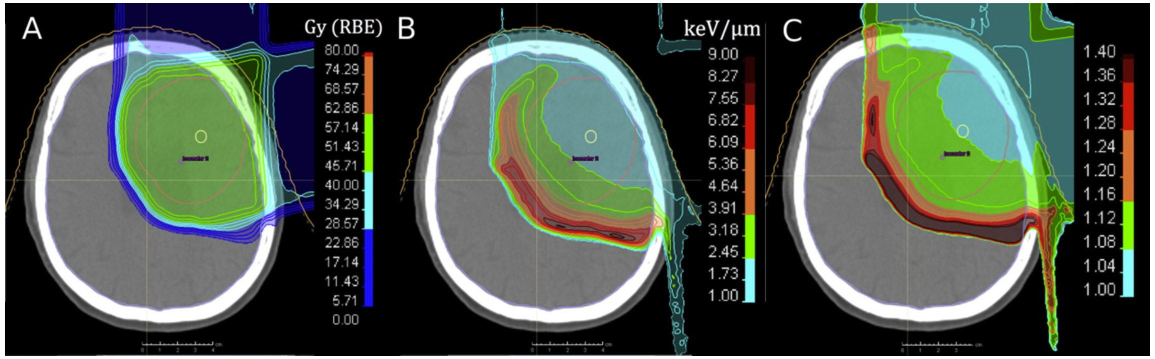
Fundamental research



Barendsen *et al.* (1960, 1963, 1964, 1966): *In vitro* cell survival data for human kidney T-1 cells



Mairani et al. *Biologically optimized helium ion plans: calculation approach and its in vitro validation.* Phys. Med. Biol., 2016.



Extracted from Luehr et al., *Relative biological effectiveness in proton beam therapy: Current knowledge and future challenges.* Clinical and Translational Radiation Oncology, 2018.

Final goal: to deliver biologically-optimized treatments to patients