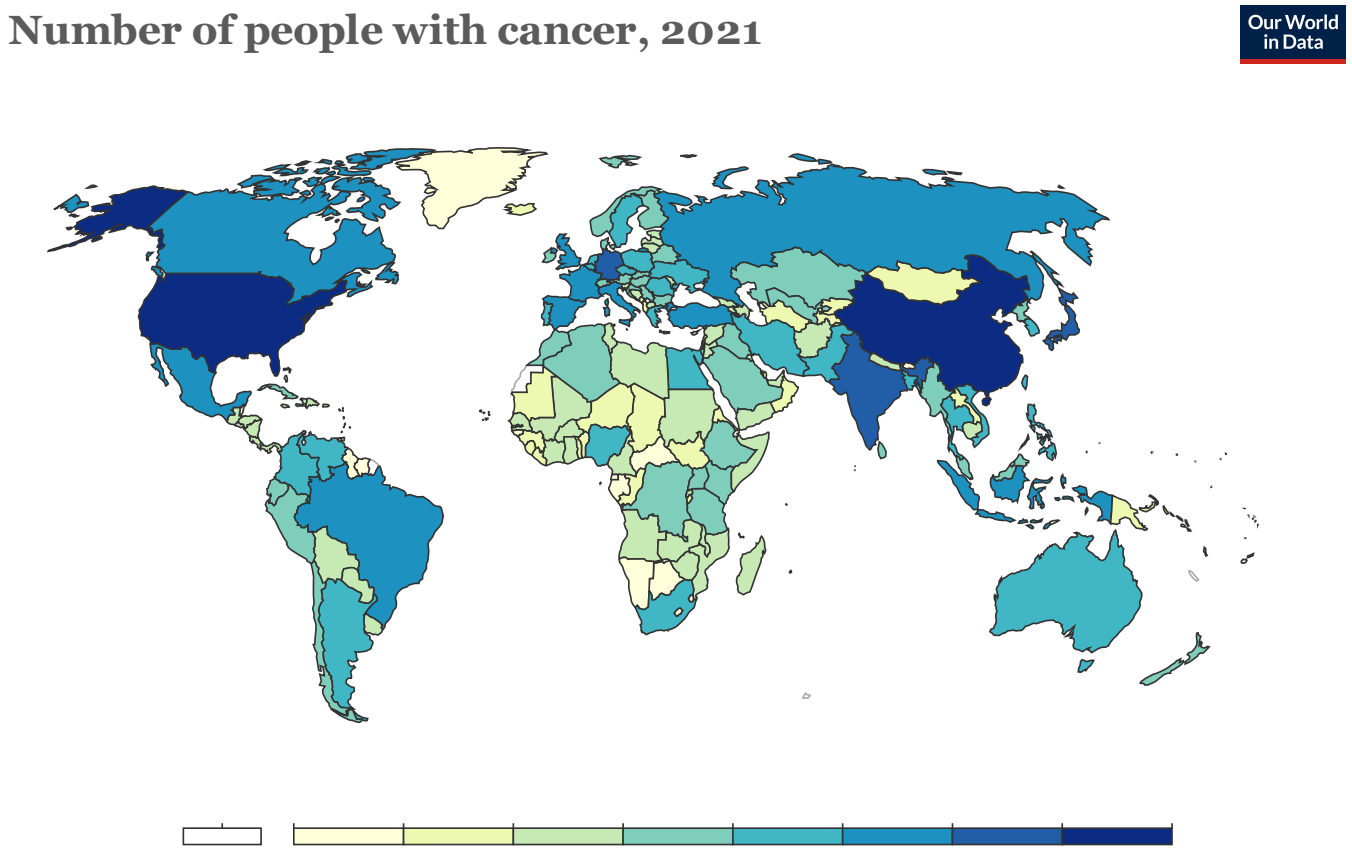
Applications de la physique pour la radiothérapie

Amélia Maia Leite

IJCLab, Pôle Physique des accélérateurs

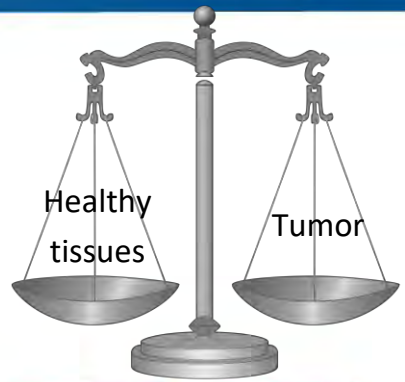
Why care about cancer?



World Health Organization: Cancer **2nd leading cause of death** worldwide.

Why care about cancer?

20 million new cases and 9.7 million deaths related to cancer in 2022
1 out of 5 men and **1 out of 6** women develop **cancer** in the course of their lives*

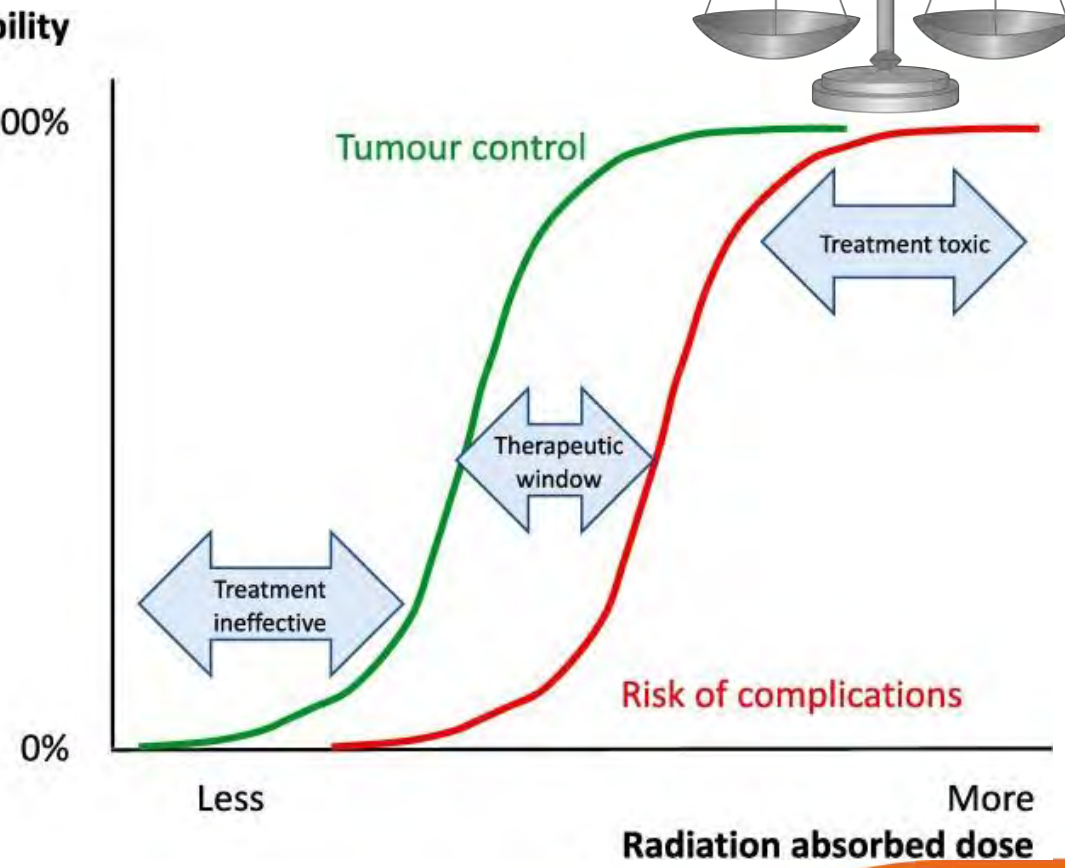


First cause of death in France **157 400 deaths** in 2018
(over ~430 000 new cases per year, https://www.e-cancer.fr/

Main treatments against cancer:
- Surgery (~ 80%)
- Chemotherapy
- Radiotherapy (~ 60%)

Radiotherapy: use ionizing radiation to kill tumour cells

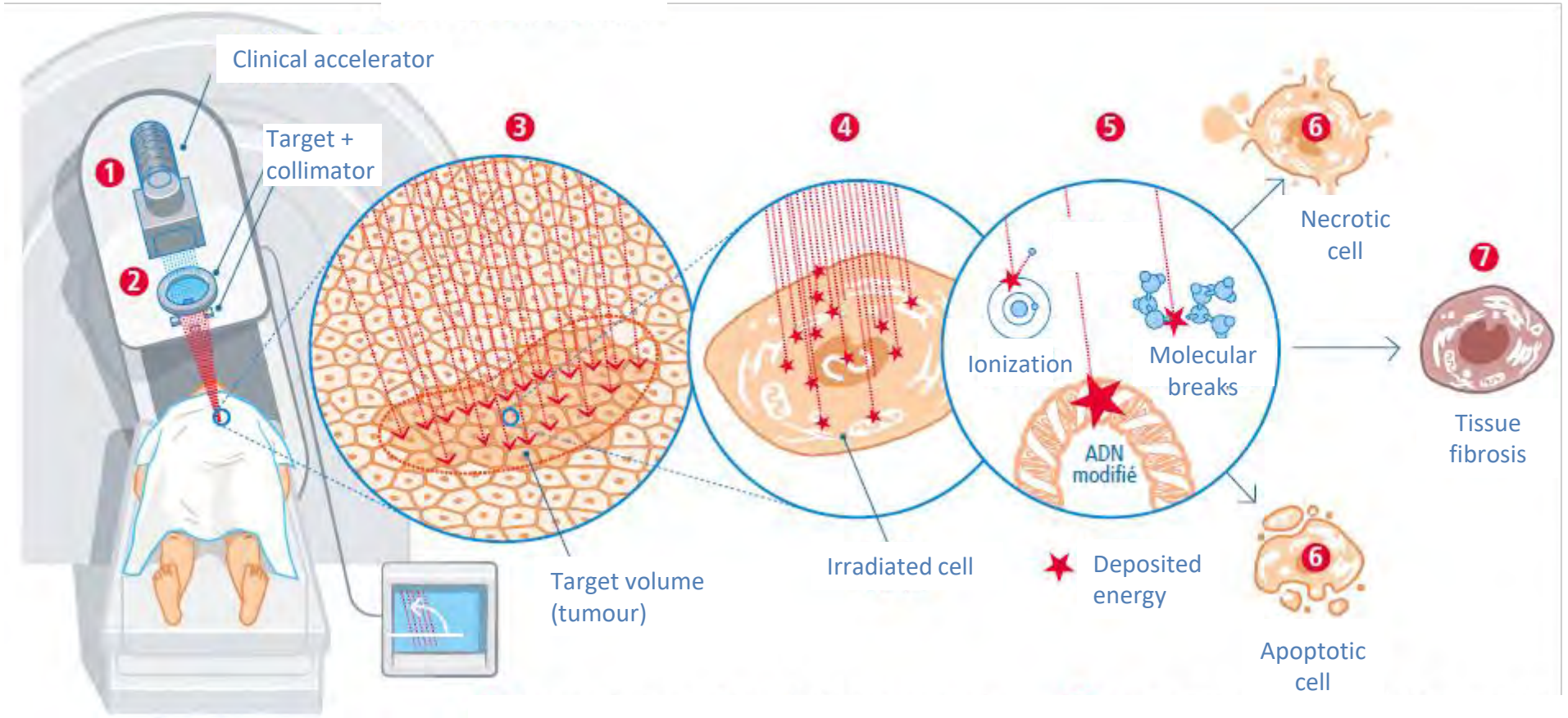
The challenge: **destroy** the tumour and **protect** the surrounding healthy tissues -> **Therapeutic window**

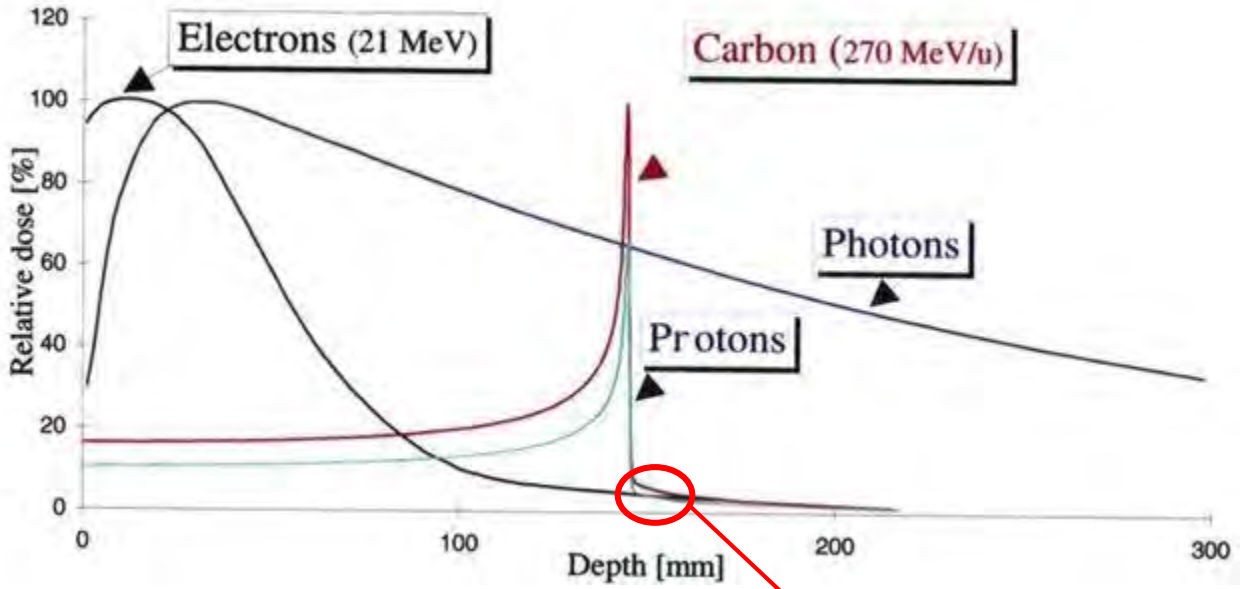


*World Health Organization

External radiotherapy - how it works

Using ionizing radiation (X-rays, p, n, e-) to kill tumor cells.





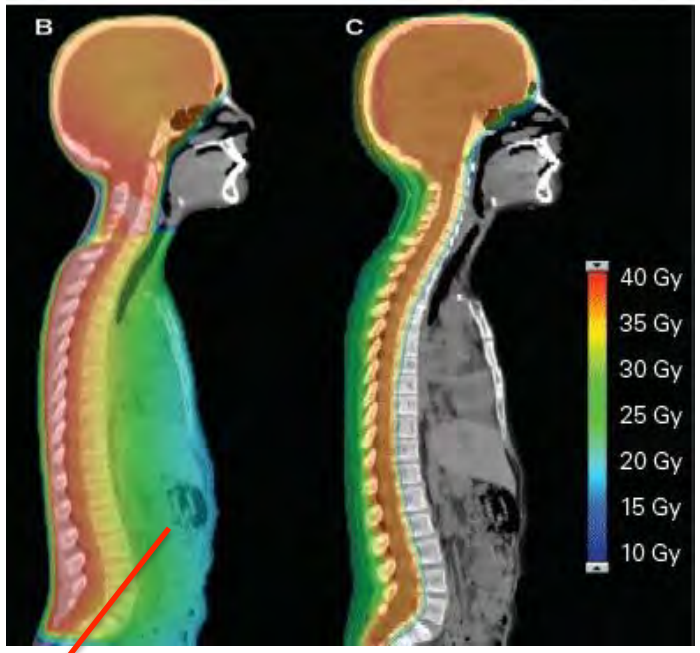
Dosimetric properties of light ions:

- Steep dose gradient
- Limited dose to the surrounding healthy tissues
- Toxicity reduction with comparable target coverage with respect to X-rays

Nuclear fragmentation! What are the consequences?

Ions have **better ballistic properties.**

Radiotherapy vs hadrontherapy



Dose distribution in a patient

X-rays don’t stop!

Dosimetric properties of light ions:

- Steep dose gradient
- Limited dose to the surrounding healthy tissues
- Toxicity reduction with comparable target coverage with respect to X-rays

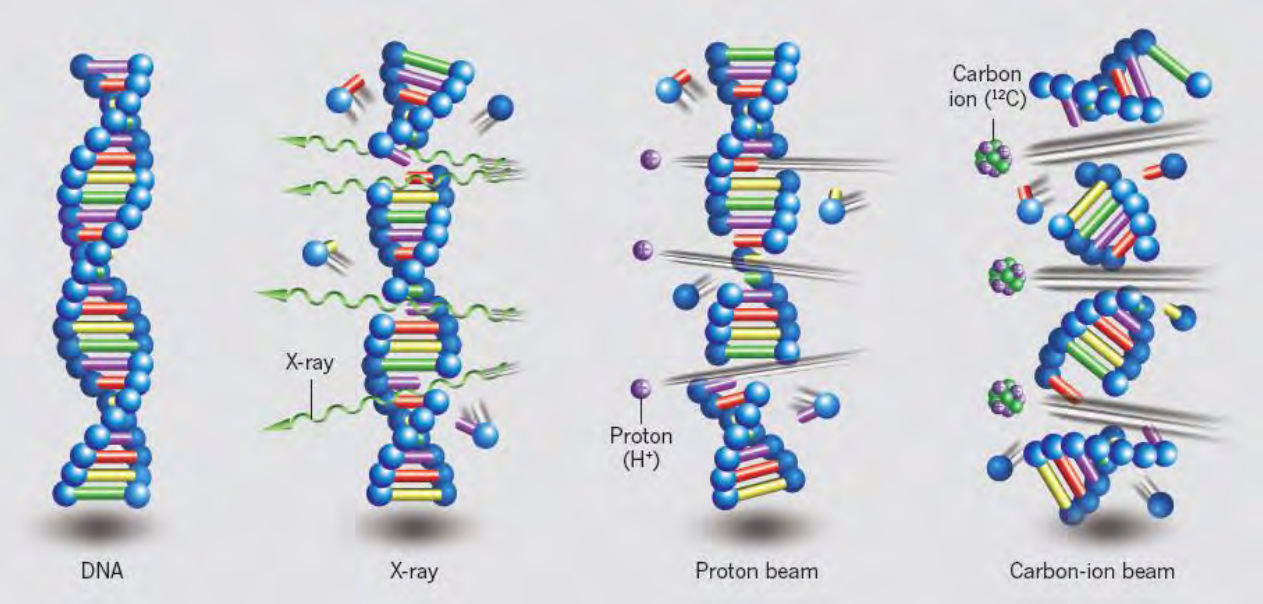
Therapeutic recommendations:

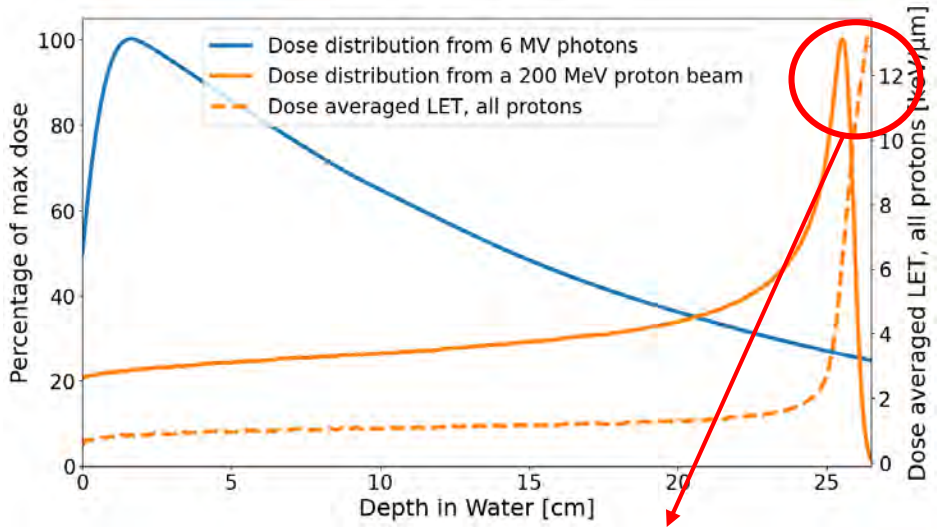
- Deep seated tumours
- Pediatric tumours

Radiobiological properties of light ions

- Higher **Linear Energy Transfer (LET)**: energy delivered per unit length keV/um
- More serious DNA damage induced
- Higher relative biological effectiveness (RBE)
- Higher efficacy on radioresistant tumours

The same dose not lead to the same **biological effect.**

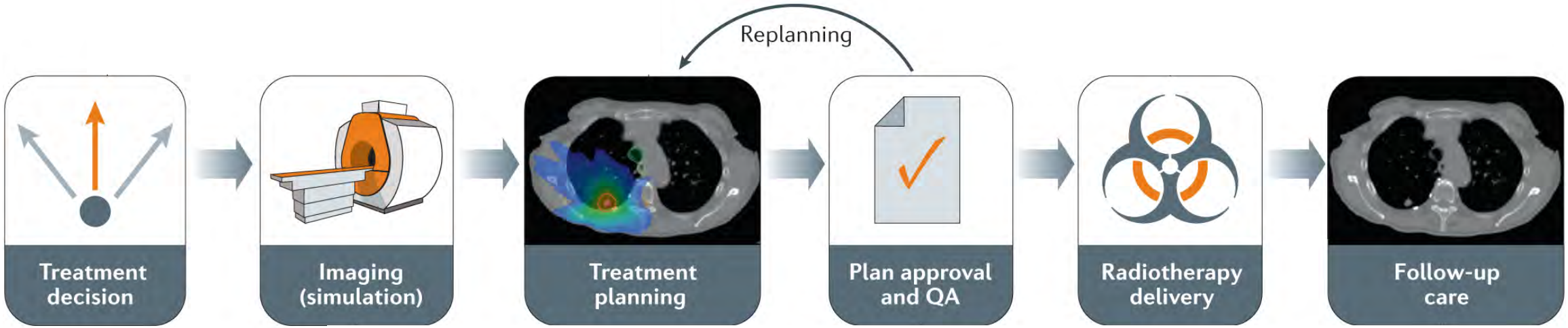




The highest LET is after the Bragg peak! What are the consequences?

Marx, V. Sharp shooters. *Nature* **508**, 133–138 (2014). https://doi.org/10.1038/508133a

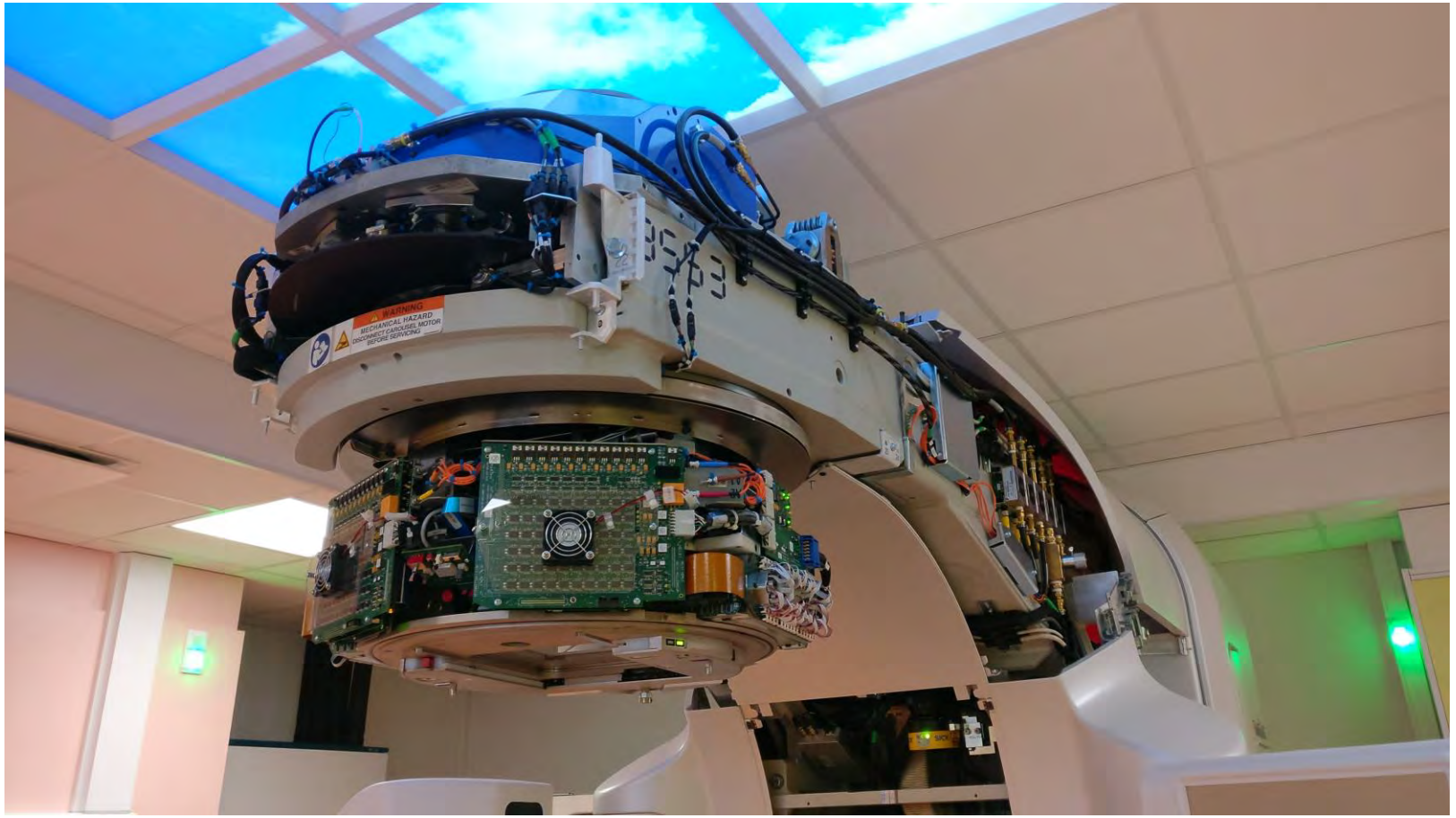
Radiotherapy – typical clincal workflow



Muldisciplinary team to cure cancer.

~ 1 MEur investment

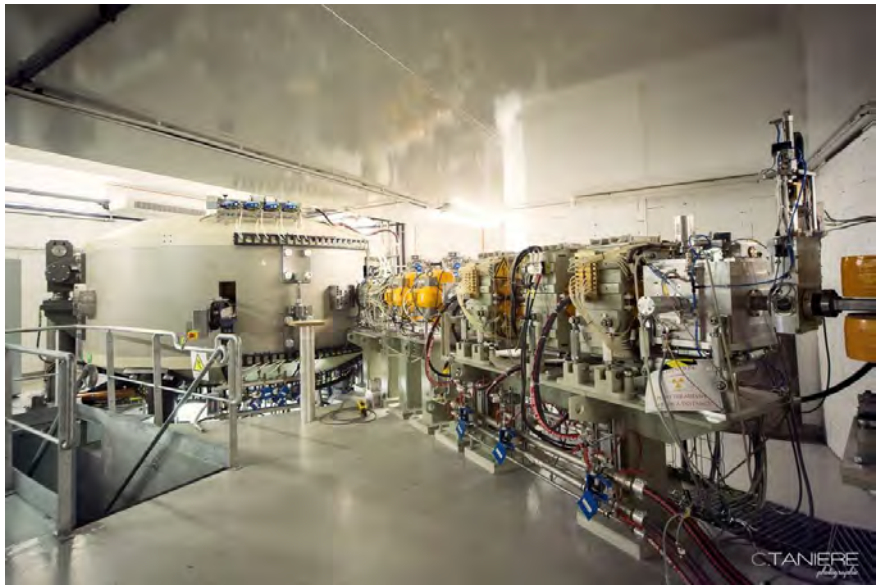
Typical radiotherapy treatment room.



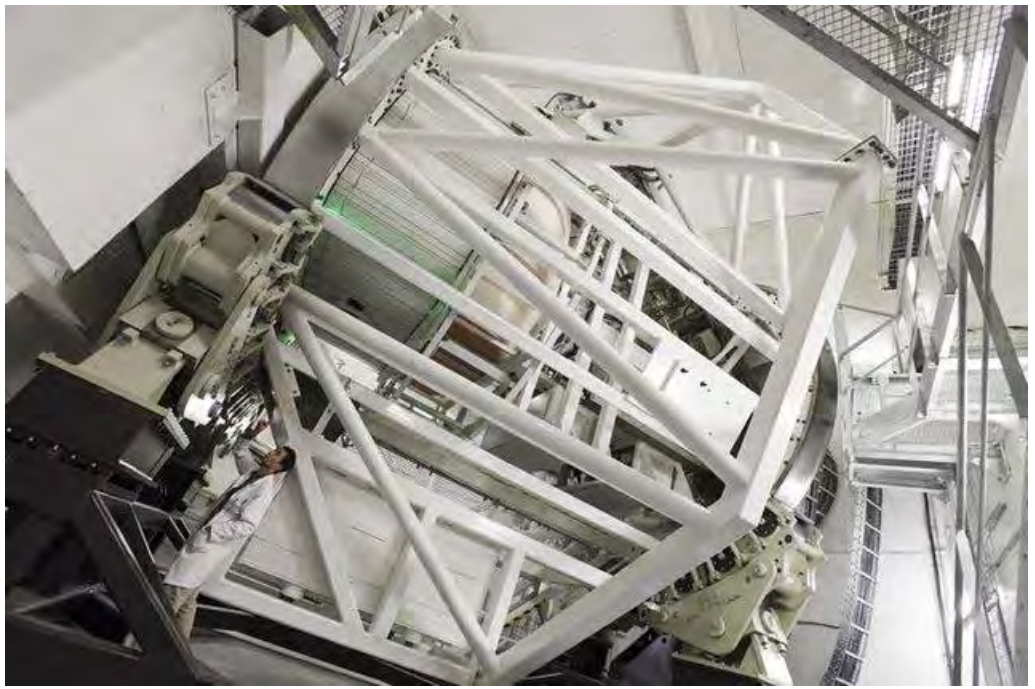
Typical X-ray machine: compact e- LINAC < 20 MeV

Hadrontherapy: Centre de Protonthérapie d'Orsay

At the Centre de Protonthérapie d'Orsay a cyclotron delivers proton beams to treat patients and to perform research activities.



Proton cyclotron, up to 230 MeV, 4m diameter.



A 360° rotating beam delivery system (gantry) delivers proton beams to patients.

Hadrontherapy: Centre de Protonthérapie d'Orsay

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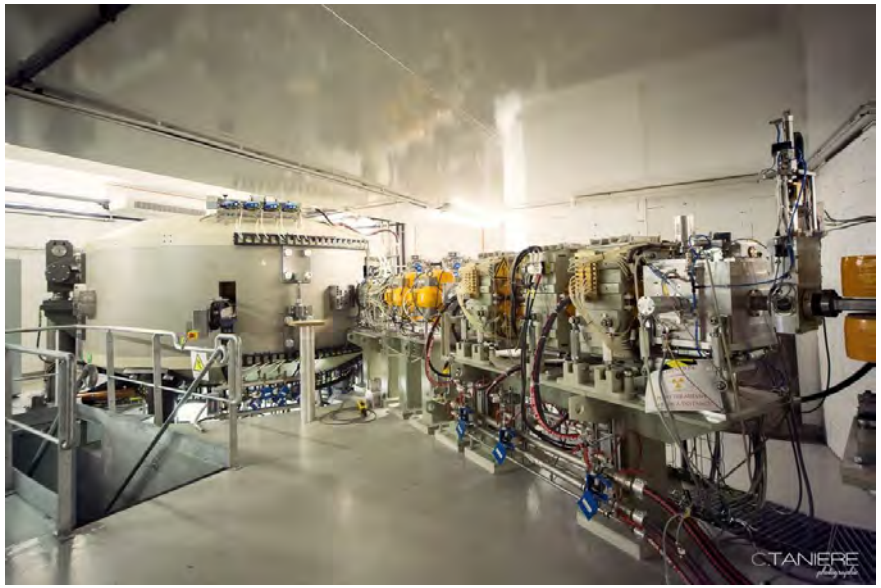
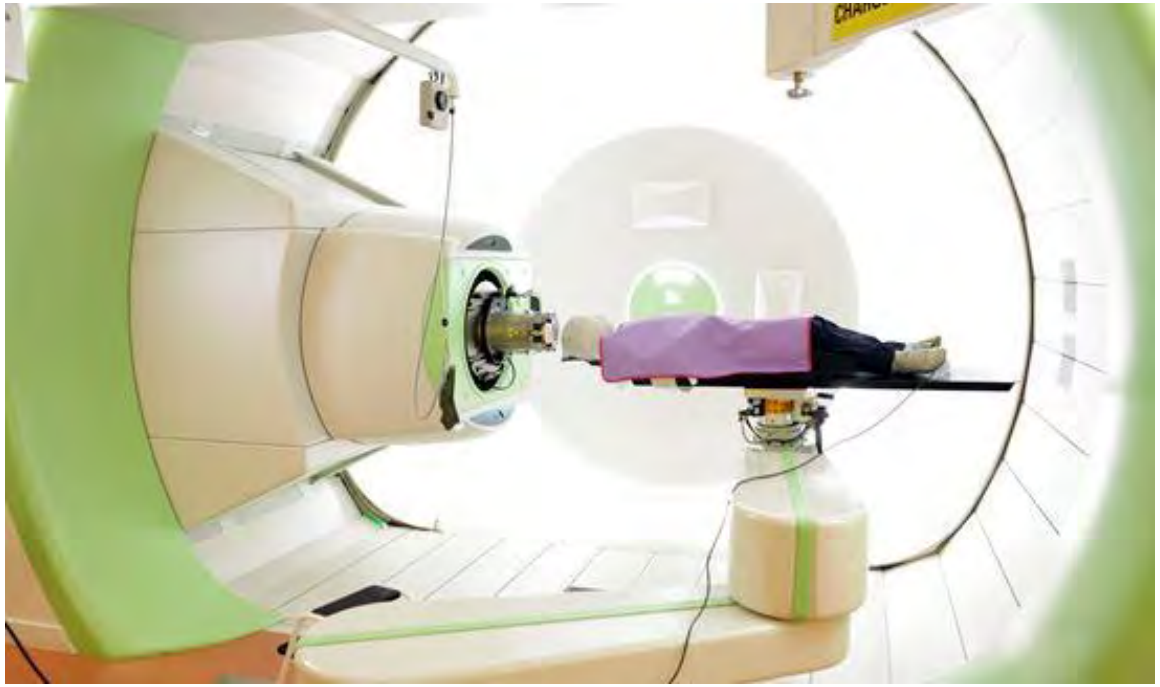


IBA proton cyclotron, up to 230 MeV, 4m diameter.



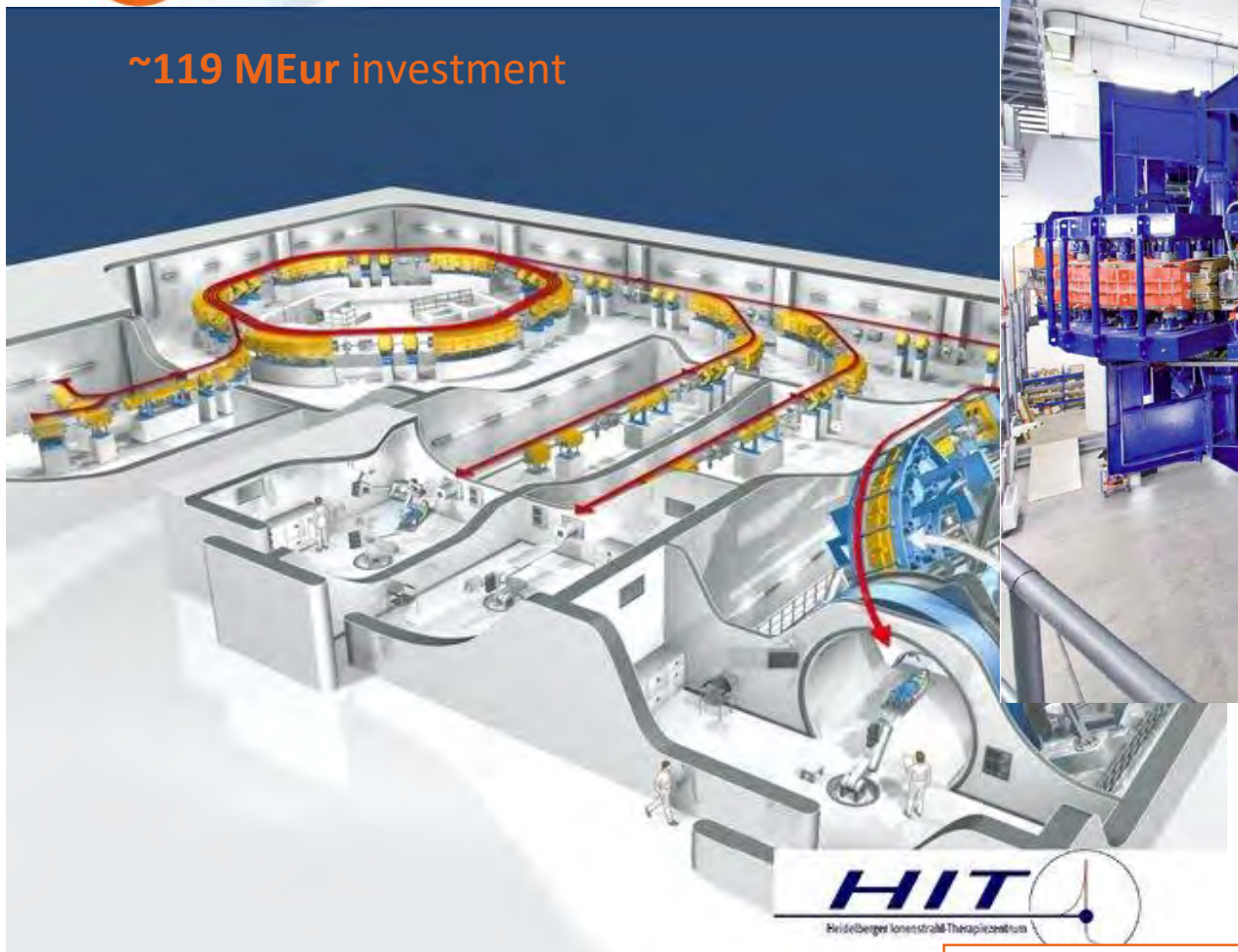
A 360° rotating beam delivery system (gantry) delivers proton beams to patients.

~ 40 MEur investment

Hadrontherapy: Heidelberg Ion-Beam Therapy Center

Protons + carbon ions

~119 MEur investment



Expensive and **huge footprint**!

LINAC combined synchroton and 3 treatment rooms

Gantry weighs as much as 600 tons.

Hadrontherapy: Heidelberg Ion-Beam Therapy Center

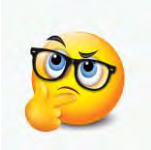
Gantry treatment room.

Extraordinary *claims* require extraordinary *evidence.*

Extraordinary *prices* require extraordinary *evidence!*

+120 hadrontherapy centers in operation worldwide, 3 in France!

+ what's the **best ion** for each tumour type/position?
+ what's the effect of the **nuclear fragmentation**?
+ what's the **biological effect** of ions?
+ can we make smaller/**cheaper machines**?
+ how can we **increase therapeutic index**?
+ …



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BioALTO Accélérateur Linéaire et Tandem à Orsay

Experimental platform for <u>pre-clinical</u> hadrontherapy research at ALTO

BioALTO

Accélérateur Linéaire et Tandem à Orsay

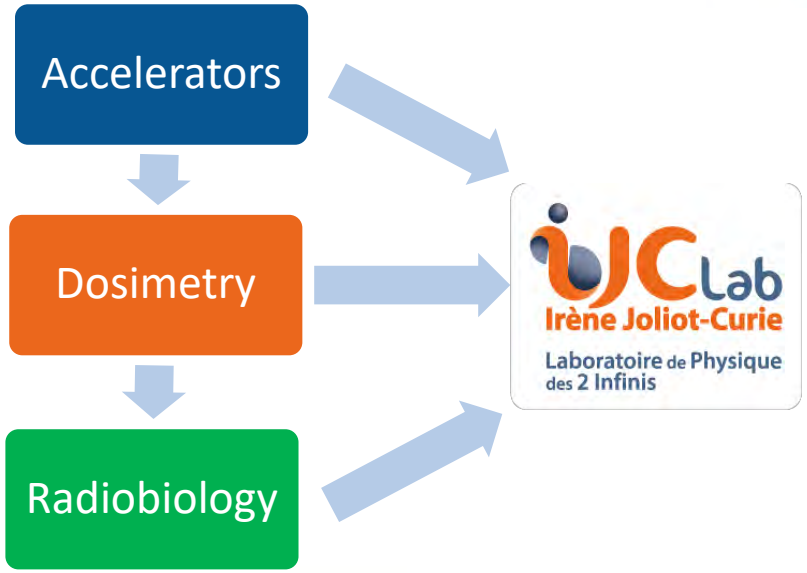
Goal of this project: Develop experimental **platform dedicated to cutting-edge pre-clinical research for hadrontherapy**

- Optimization of an **accelerator for radiobiology**.
- Equip an **irradiation station** to conduct radiobiology experiments.
- Installation of a **cell culture room** near the beamline for the preparation, storage, and analysis of biological samples.
- Open to **external users**.

BioALTO: unique experimental platform for pre-clinical hadrontherapy research

Coordinating Laboratory:

A. Maia Leite, Q. Mouchard, P. Laniece



Physique des Accélérateurs
Accelerator Physics

PHYSIQUE SANTÉ
HEALTH

ALTO
Accélérateur Linéaire et Tandem à Orsay

The creation of IJCLab offers a **unique opportunity** to develop such an **multidisciplinary project**.

BioALTO: unique experimental platform for pre-clinical hadron therapy research

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Physique des Accélérateurs
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Accélérateur Linéaire et Tandem à Orsay

Collaborators:

LPSC Grenoble

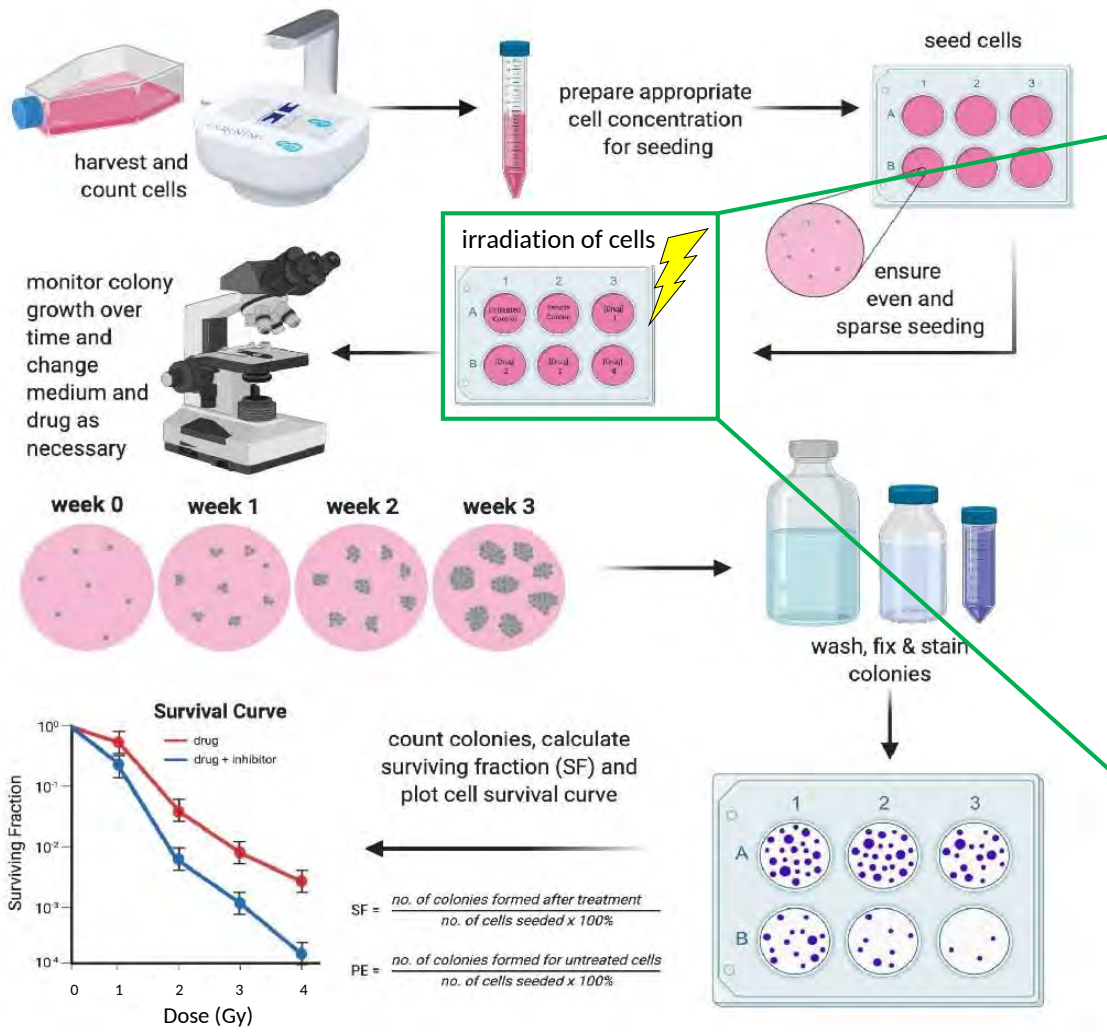
iP2i LES 2 INFINIS LYON

GUSTAVE ROUSSY
CANCER CAMPUS GRAND PARIS

CNM CENTRO NACIONAL DE MICROELECTRONICA IMB

ISMO

What is a radiobiological experiment?



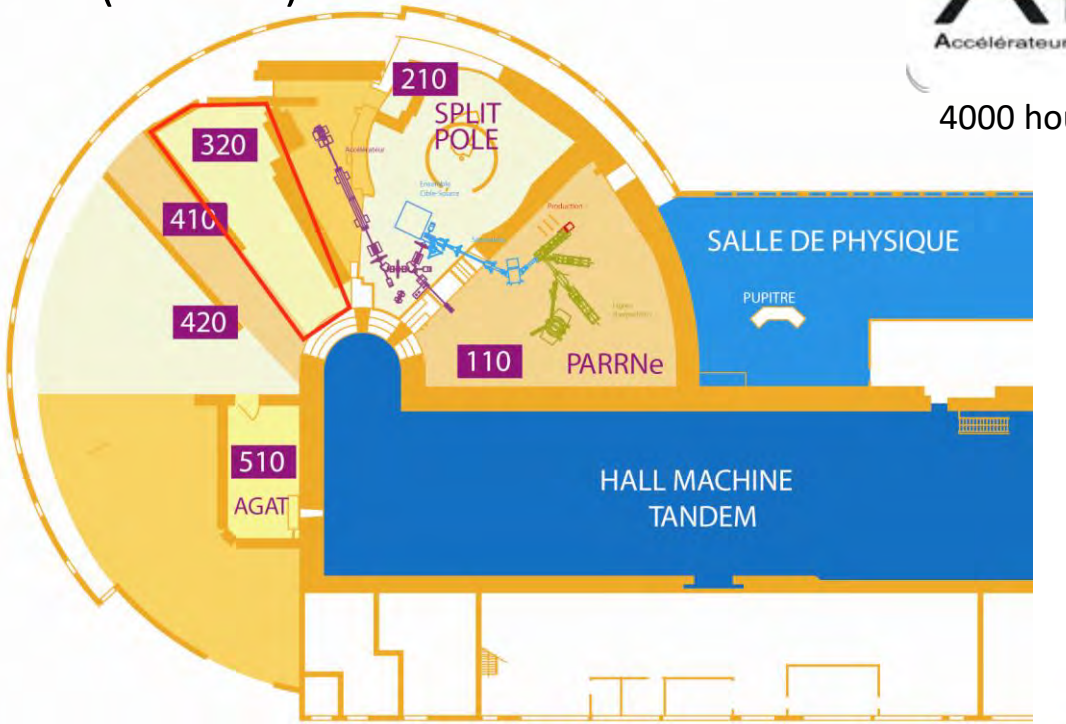
Radiobiological experiments requirements:

- ✓ Monoenergetic beams
  resolution better than 0.1 MeV
- ✓ Homogeneous irradiation field
  within 2% over ~cm^2
- ✓ Precise dose
- ✓ Precise dose rate
- ✓ Reproducibility
- ✓ Strict irradiation calendar

Accélérateur Linéaire et Tandem d'Orsay

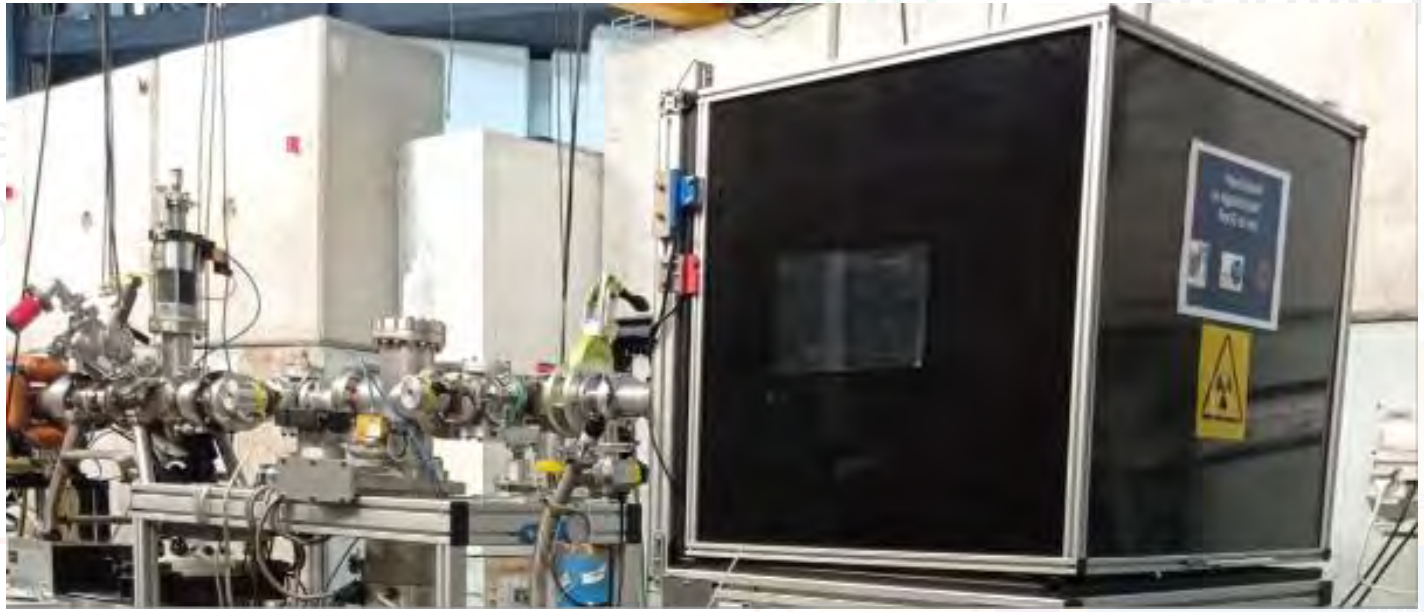
- 14.5 MV Tandem accelerator
- Wide range of intense (up to µA) ion beams (^{1}H – ^{127}I)

Ions	Max Energy (MeV)
p	25
α	43
^{7}Li	50
^{12}C	87



4000 hours per year of beam

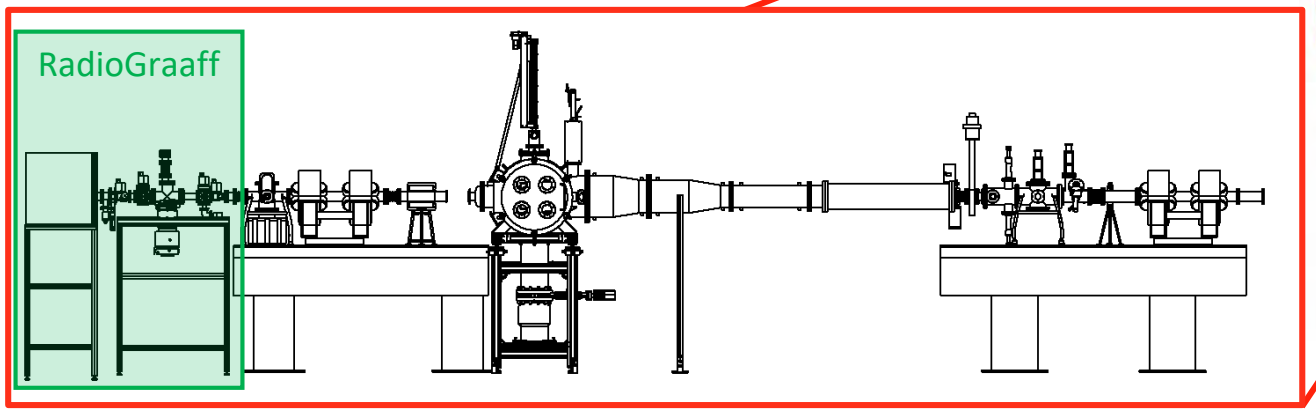
BioALTO beamline

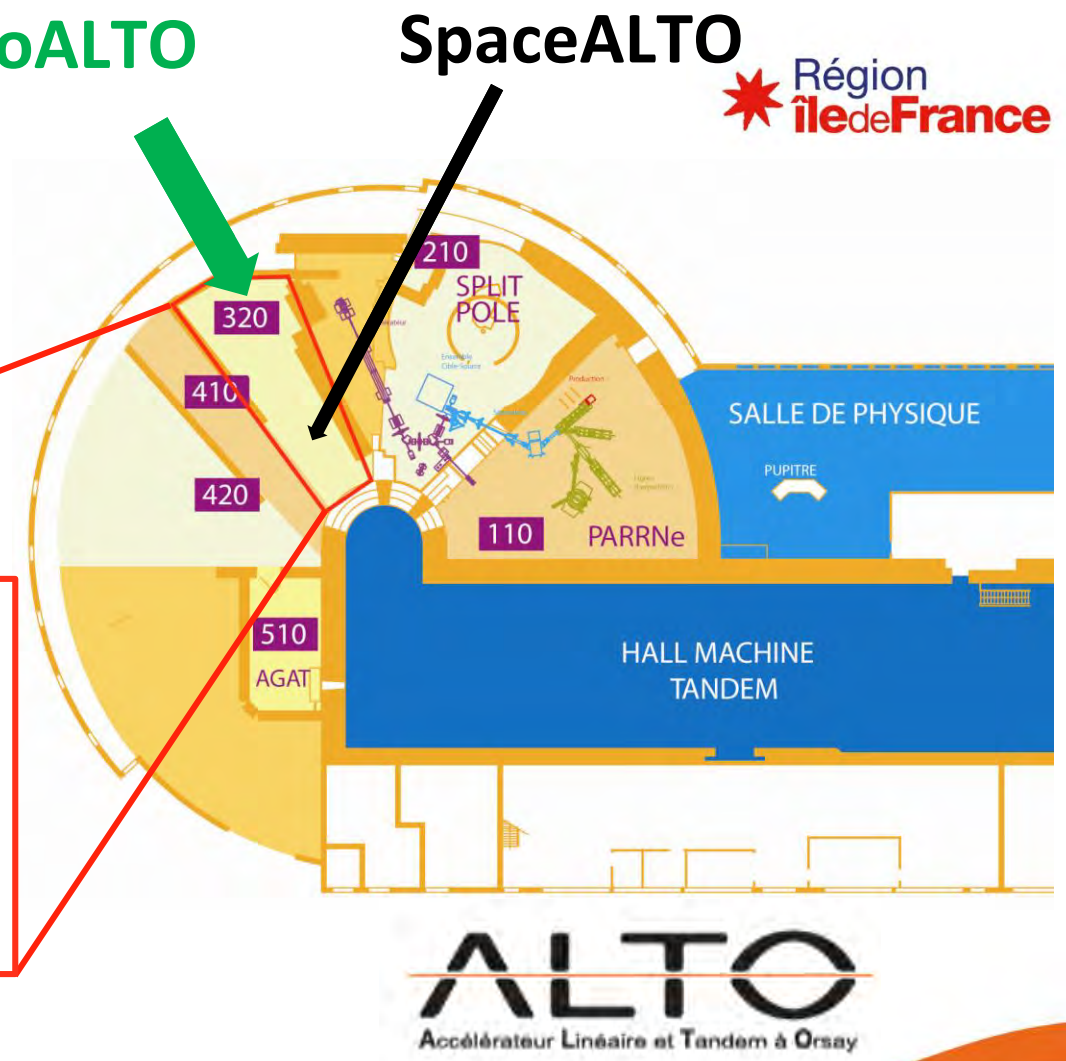


Picture of RadioGraaff setup @ALTO during preliminary dosimetry tests.

RadioGraaff made for 3 MeV protons.

- Permanent set-up of RadioGraaff at ALTO's 320 beamline.





BioALTO beamline

From ~ mm beam to 2 cm diameter homogeneous beam.

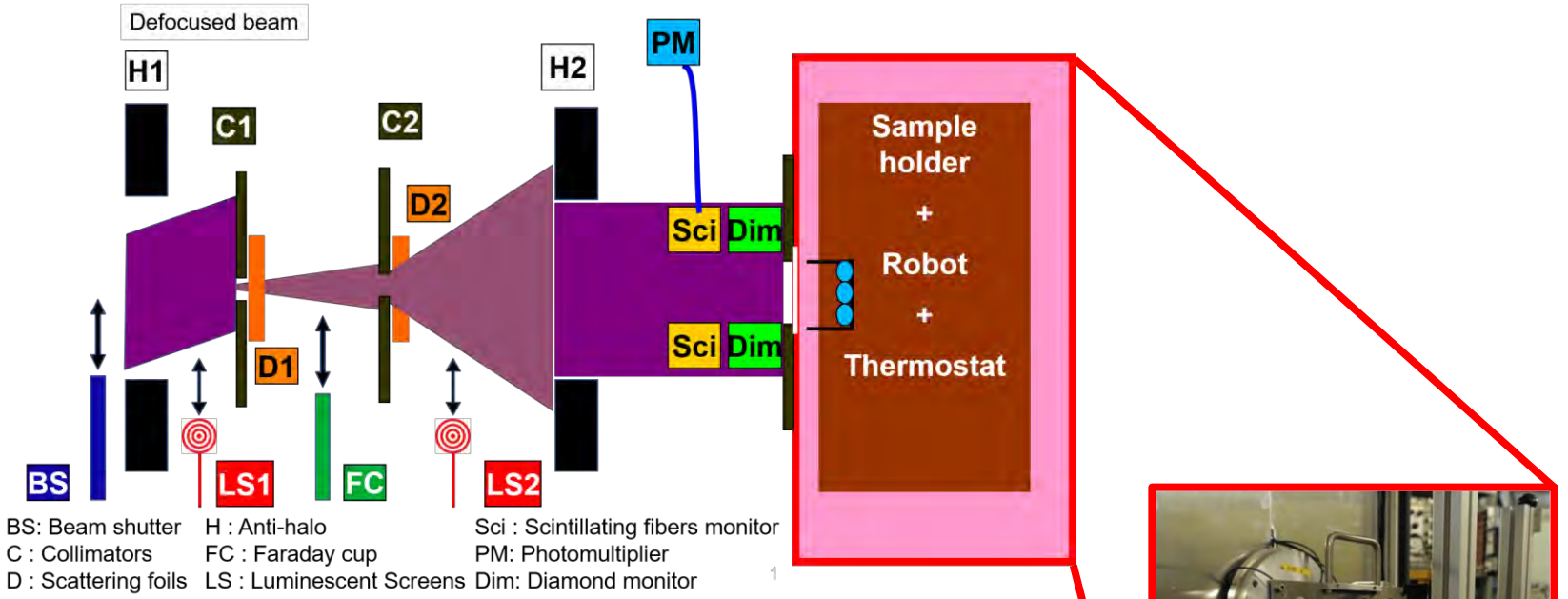
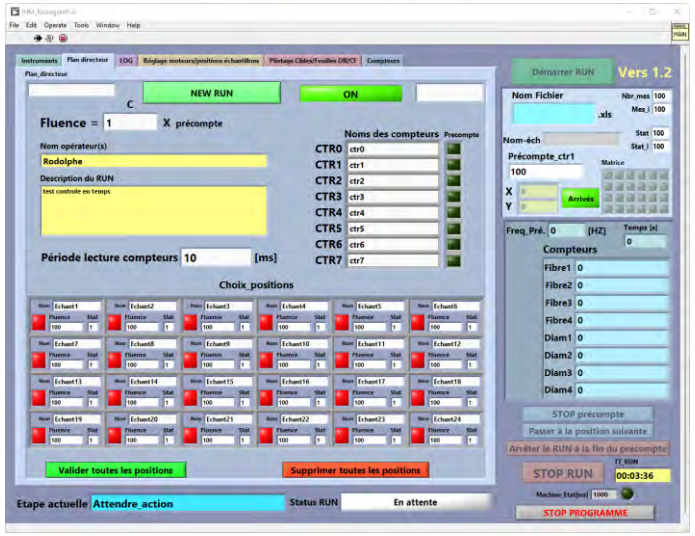


Diagram of beam line.

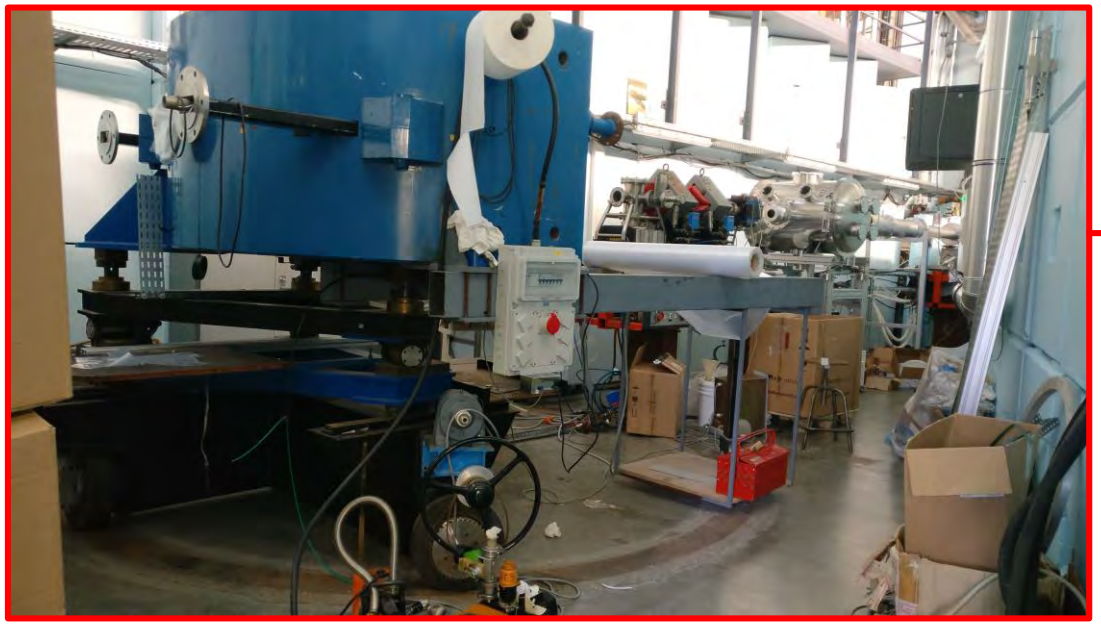


LabVIEW remote control and DAQ software.

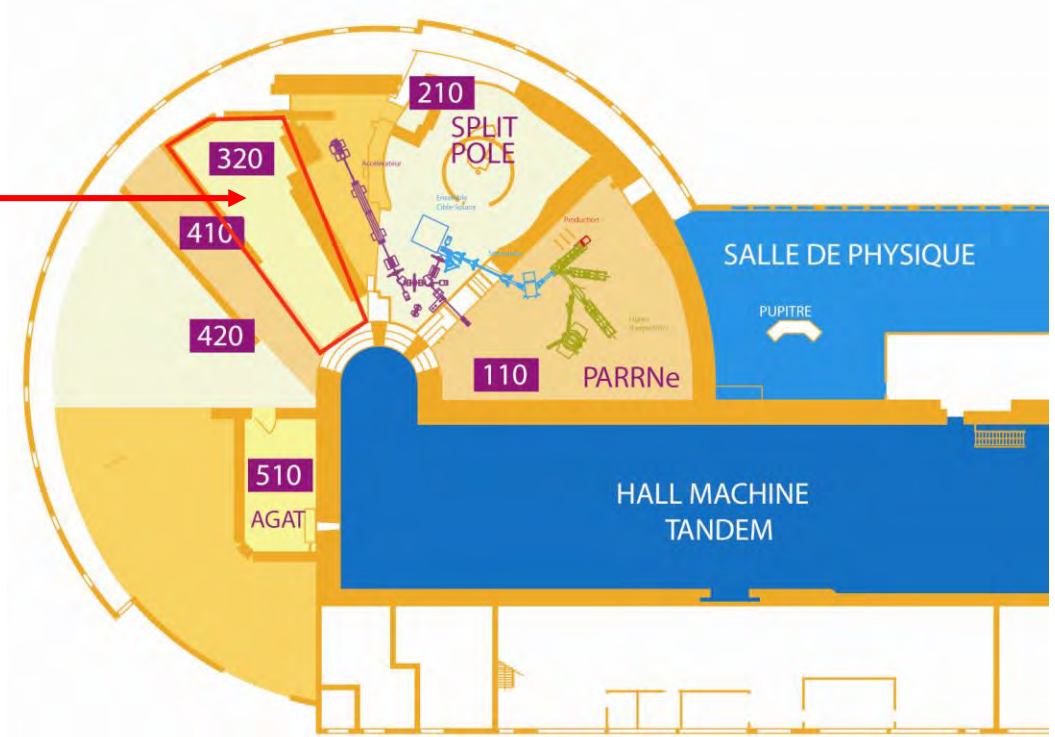
- Temperature-controlled enclosure
- XY motorized sample holder
- Automated sample changing

Cell samples/detector holder and robotic arm.

Making some space for BioALTO



Removed Bachus magnet from ALTO.



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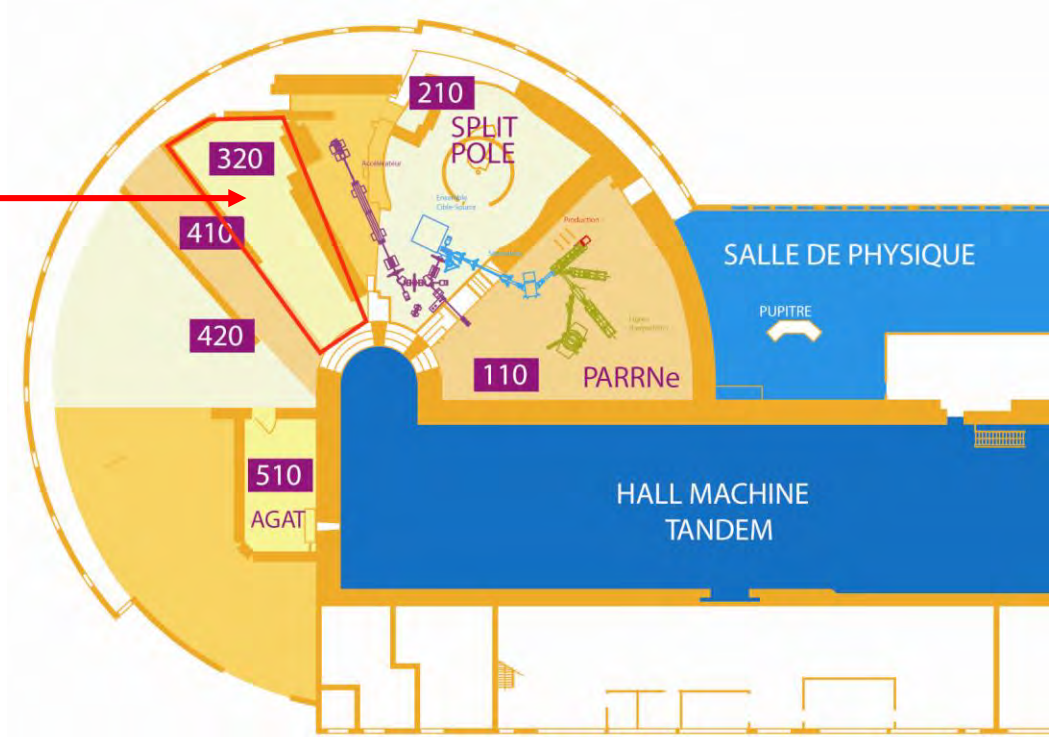
Accélérateur Linéaire et Tandem à Orsay

Making some space for BioALTO

Removed Bachus magnet from ALTO.



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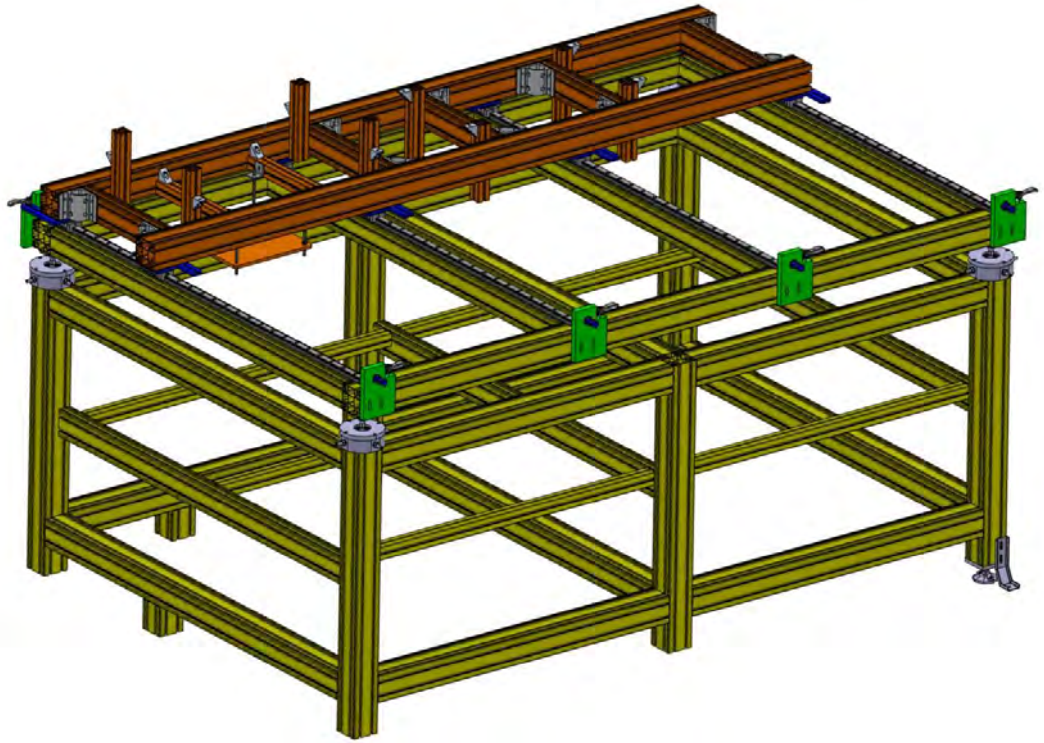
Installation at ALTO



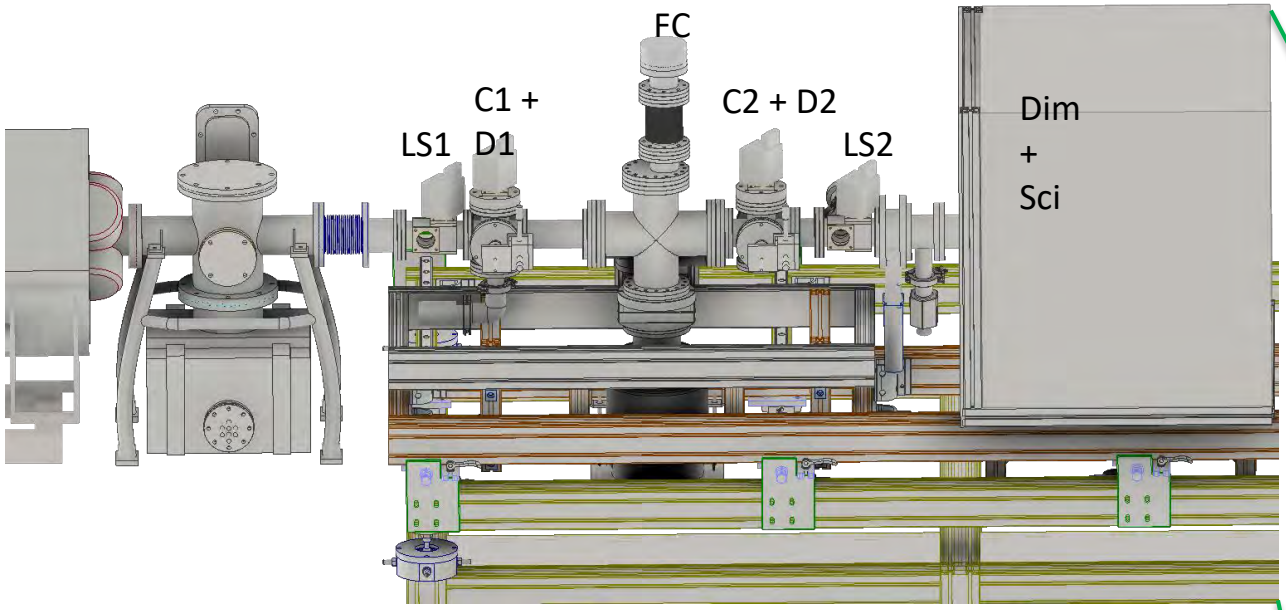
Chassis designed by bureau d'études IJCLab
Function: moves the beamline off the beam axis for experiments with Licorne (neutrons) for SpaceALTO

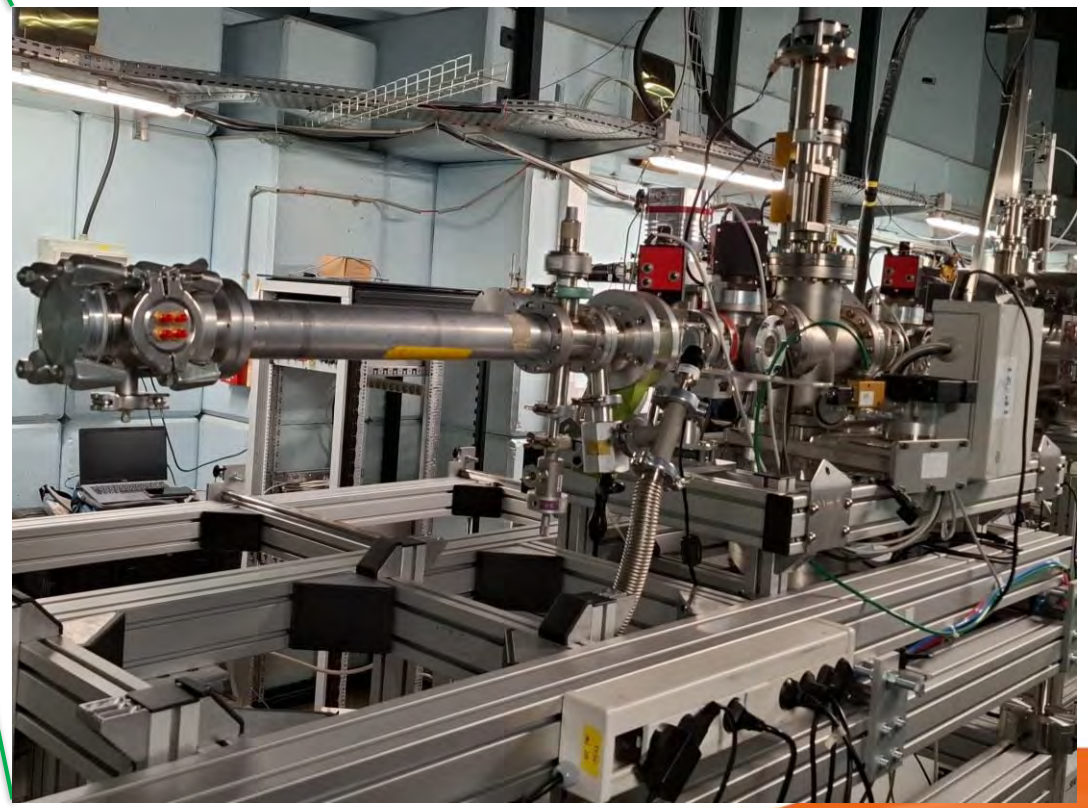
Installation in February 2024

Installation at ALTO

ALTO beam line

BioALTO beam line

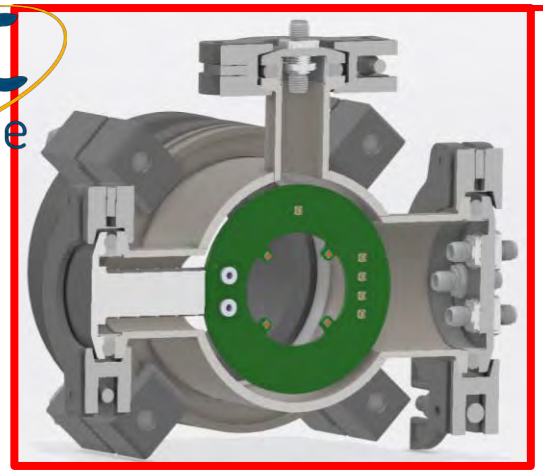


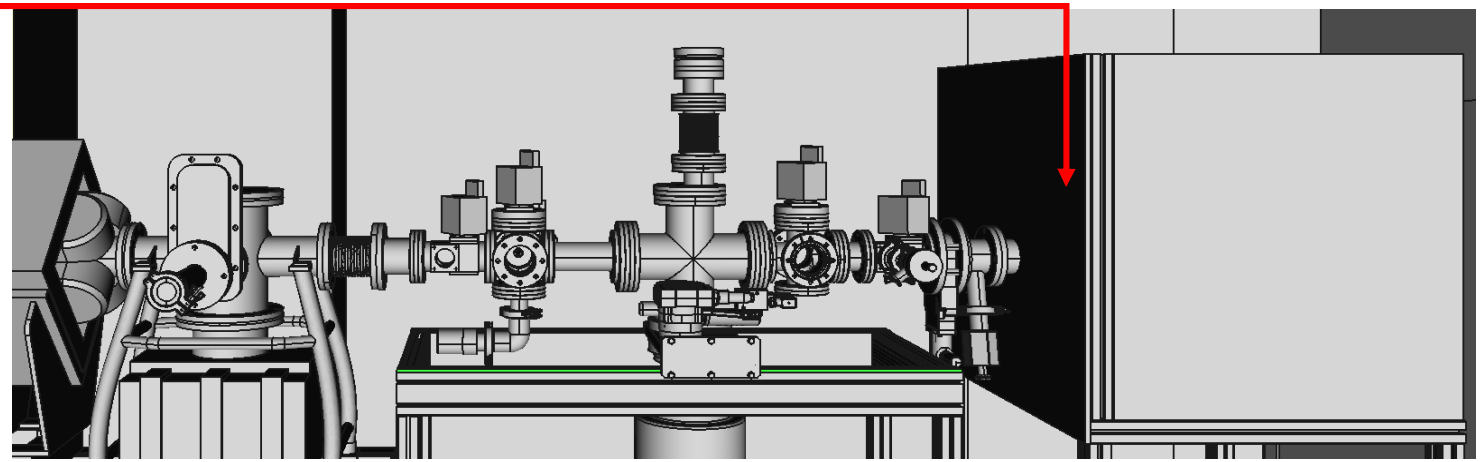


Installation of RadioGraaff on chassis.

Beam diagnostics – diamond counter

- **Online beam monitor** consisting on **diamond detectors** + dedicated electronics developed at **LPSC**, Grenoble
- The **4-diamond counter** is mounted at the end of RadioGraaff as close as possible to the mylar window -> **beam halo measurement**.

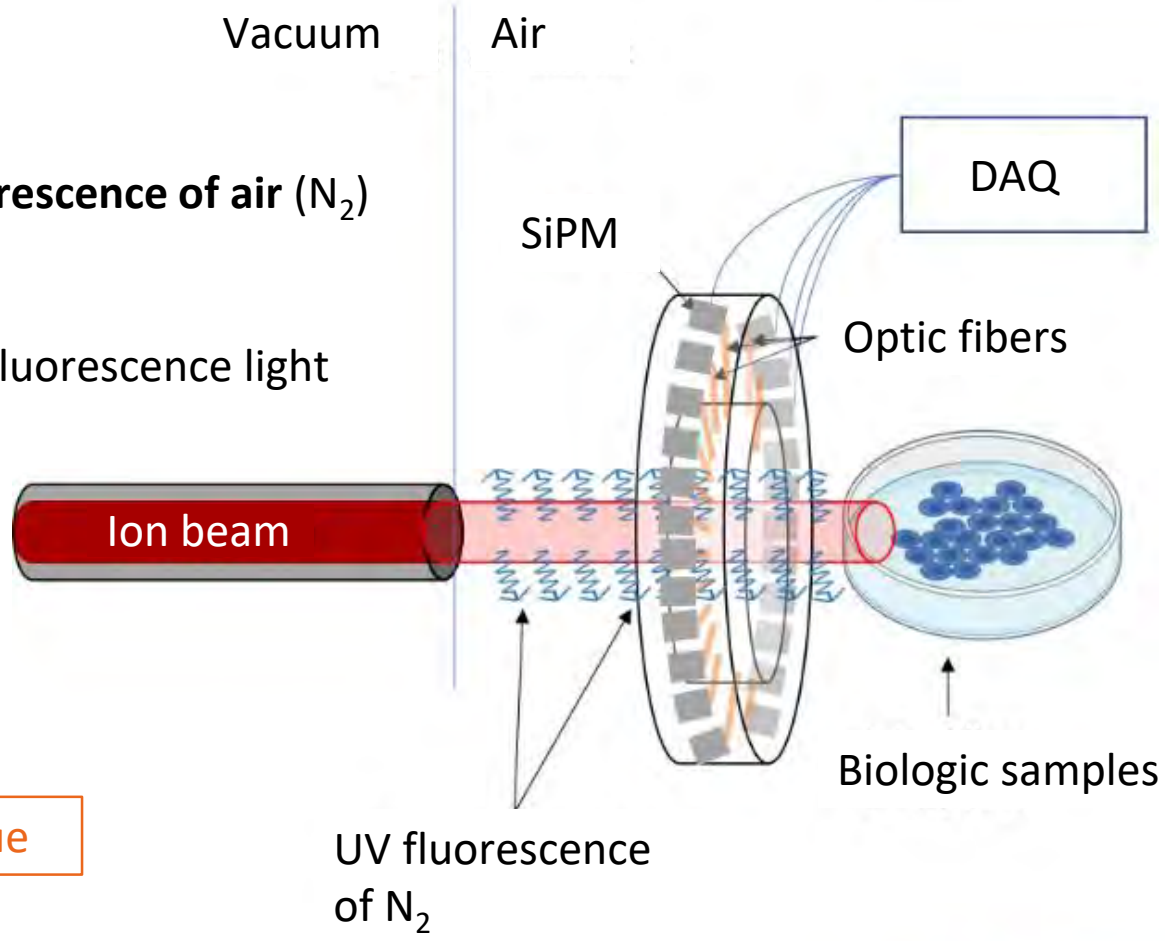




Rachel Delorme, Jean-François Muraz, Denis Dauvergne Marie-Laure Gallin-Martel.

Beam diagnostics – beam profiler

- Development of **non destructive beam profiler** based on **fluorescence of air** (N_2) induced by the ion beam.
- **Optical fibers** disposed radially around the beam axis collect fluorescence light until **silicon photomultipliers** (SiPM).
- **Assure beam homogeneity** with mm/sub mm precision. over 5 cm diameter.
- Tomographic reconstruction of the fluorescence image.



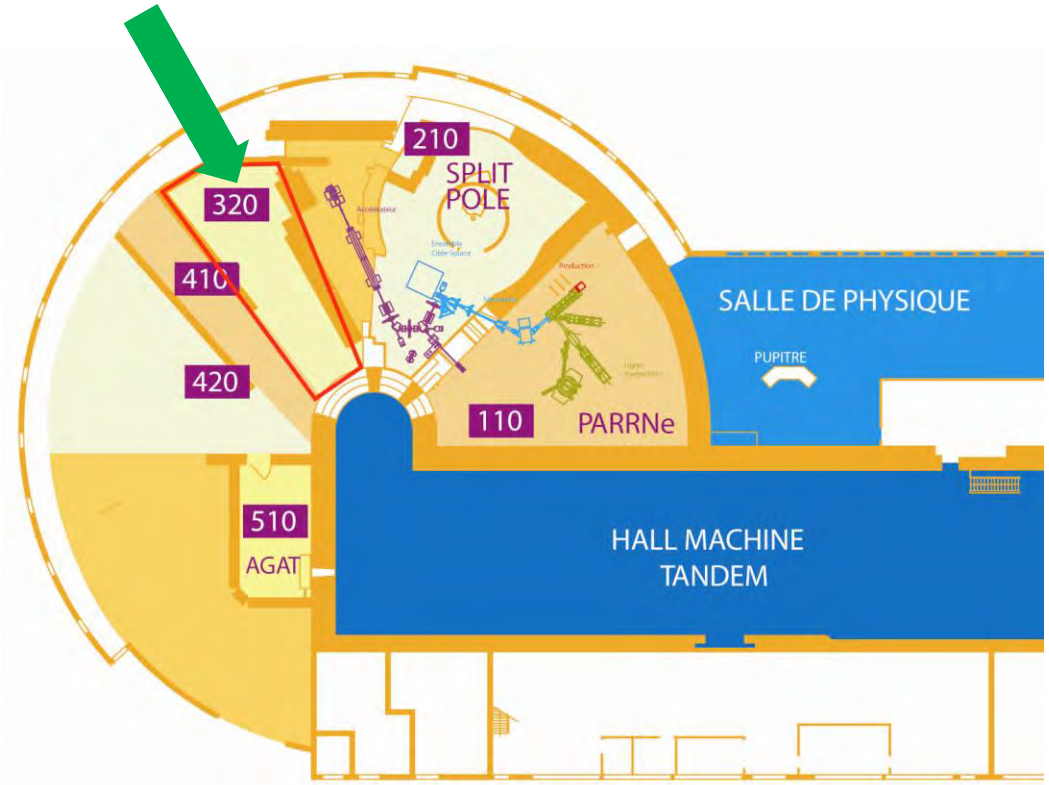
AAP Actions transverses 2025 Graduate School de Physique

Quentin Mouchard (IJCLab, Pôle Physique santé), ARRONAX

Biology room at ALTO to support users

Picture of a biology room showing a class II microbiological safety cabinet, a microscope and a CO_2 incubator.

BioALTO



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BioALTO
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What kind of research will we carry out with BioALTO?

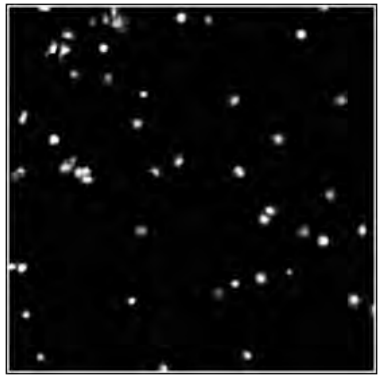
1) Biological effect of ions: ^{4}He, ^{12}C, ^{16}O, and others

@ Pôle Santé, IJCLab: **Modélisation Des Effets RAdiobiologiques in ViTrO (MODERATO)**

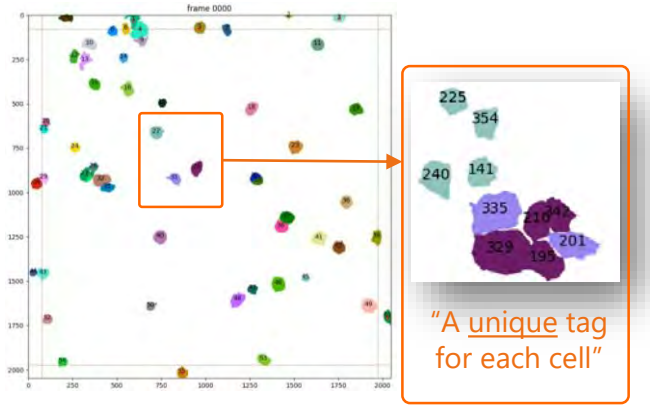
Goal: Identify **interactions** between **individual cells** inside cell populations, when they are subjected to ionizing radiation and/or mixed with other cells types (normal or tumour cells).

Analysis of individual cellular dynamics after irradiation

Development of a novel high-potential cell tracking algorithm for image sequences (films) obtained by videomicroscopy experiments.



MCF7 cells growth (experimental film)



Individual cell tracking

- **Single cell identification**
- **Track** cells over time
- Detect **mitosis** (**division** events)
- Characterize **individual behavior**
- Understand **bystander effect**

Videomicroscope

https://gitlab.in2p3.fr/josephine.courouble/celltrack

GitLab python

IJCLab Irène Joliot-Curie Laboratoire de Physique des 2 Infinis

PHYSIQUE SANTÉ HEALTH

J. Courouble, S. Plaszczynski, D. Crépin, O. Seksek

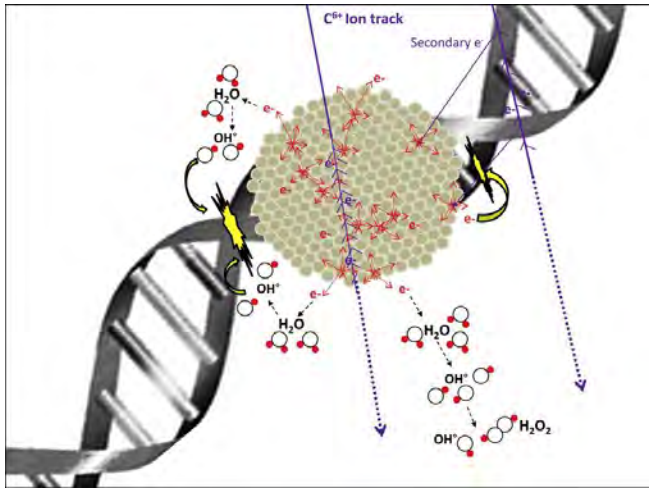
2) Nanoparticle-Enhanced Hadron Therapy

Study of the combination of hadron therapy with the use of **nanoparticles**.

Effects of nanoparticles:

- Improvement in **tumor targeting** due to **differential cell internalization**.
- Local **increase of ionization density** and dose deposition.

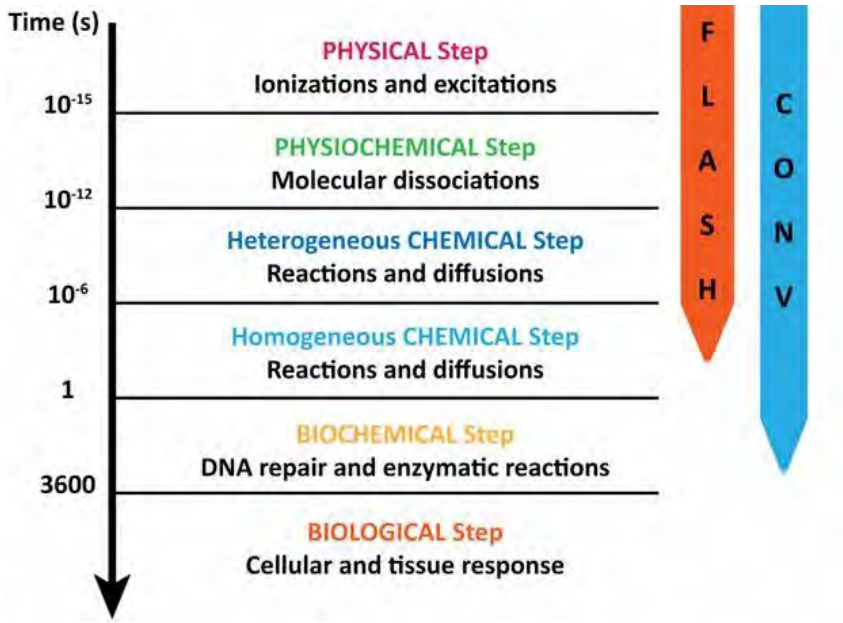
Goal: improve the efficiency of hadron therapy.
Widen Therapeutic index



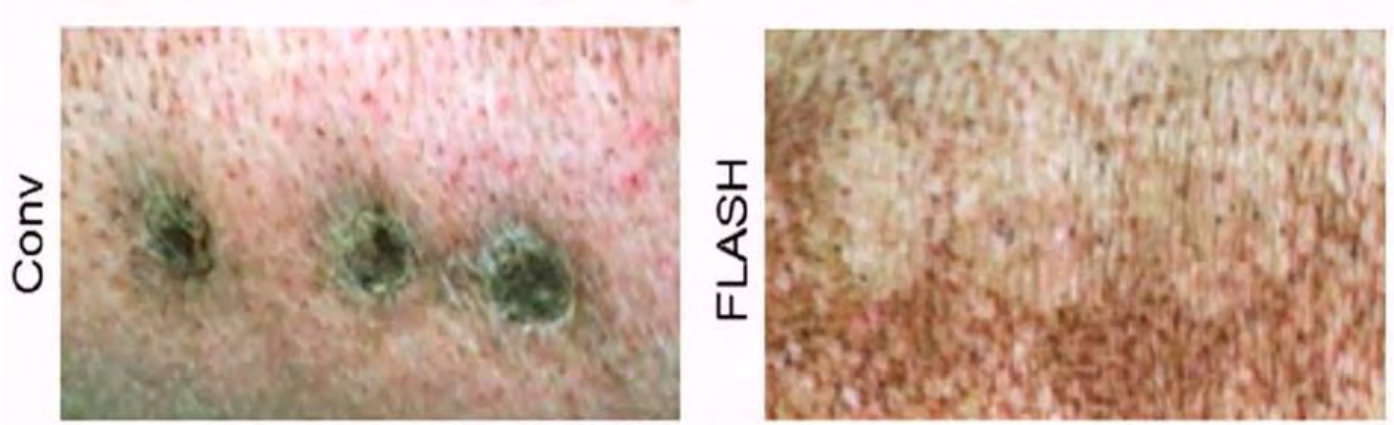
Platinum nanoparticles bound to DNA and excited by ionizing radiation.
Erika Porcel *et al* 2010 *Nanotechnology* **21** 085103

@ Institut des Sciences Moléculaires d'Orsay, group of Erika Porcel: development of radio-amplifying **metallic nanoparticles** to potentiate the effects of radiotherapy and in particular of hadron therapy (carbon ions).

3) FLASH Radiation Therapy



"Freeze" in time the biological or biochemical mechanisms.



Vozenin, MC et al. (2019) ClinCancerRes 25(1): pp. 35–42 (e⁻, 300 Gy/s)

Irradiated pig skin

Conventional irradiation (CONV):

- Dose rate ~ 0.02 Gy/s
- Irradiation duration: a few minutes

FLASH irradiation:

- Dose rate > 40 Gy/s
- Irradiation duration: ~ 100 ms

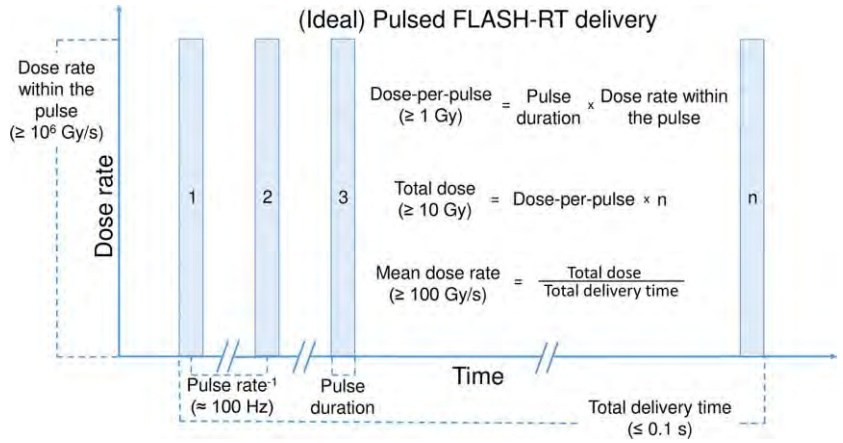
Equal lethality of tumor cells and substantial increase healthy tissues sparing.

Paradigm change for radiotherapy.

3) FLASH Radiation Therapy

Parameters to explore:

- Mean dose rate
- Dose per pulse
- Total delivery time
- Number of fractions
- Type of particles
- …

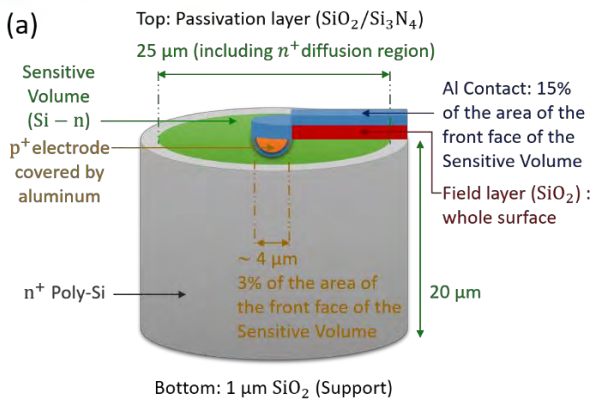


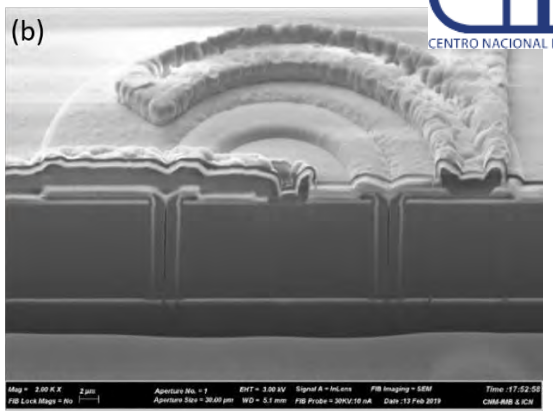
Discovered at Institut Curie **in 2014** but **first patient treated** in Lausanne in **2019!** Clinical trials ongoing...

Underlying mechanism is unknown. Research is urgent!

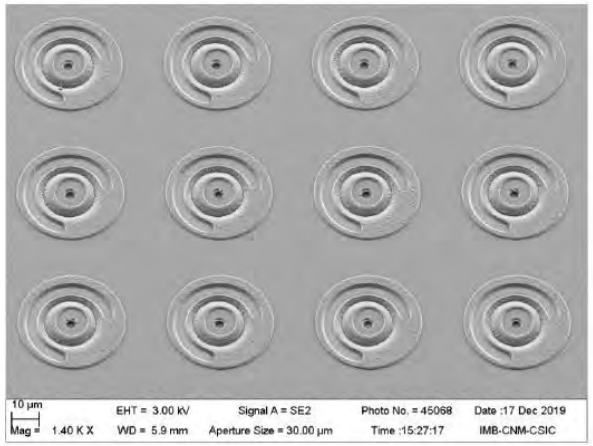
@ Institut Curie, C. Fouillade: *ex-vivo* model of thin **organotypic lung sections** to quantify the effect of FLASH irradiation of healthy murine and human lung.

4) Characterize new detectors for clinical hadrontherapy





3D silicon microdetectors mimic mammals cells



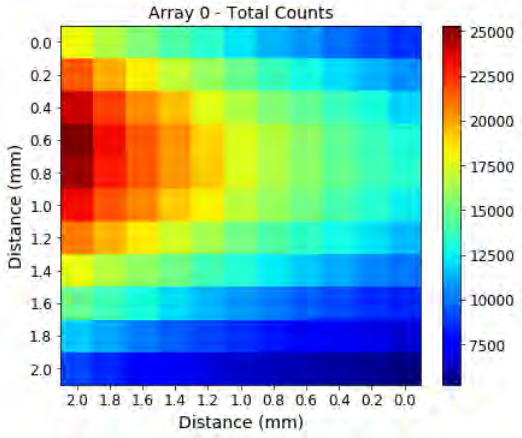
Multi-arrays of silicon microdetectors

Microdosimeter detector

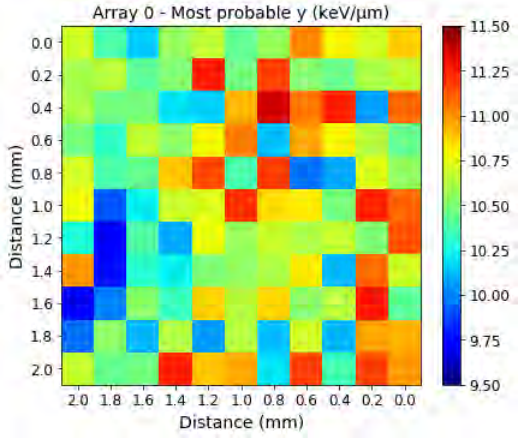
- Beam intensity
- **LET maps** -> Biological dose

Treatment plans that take into account biological effect.

Beam Intensity



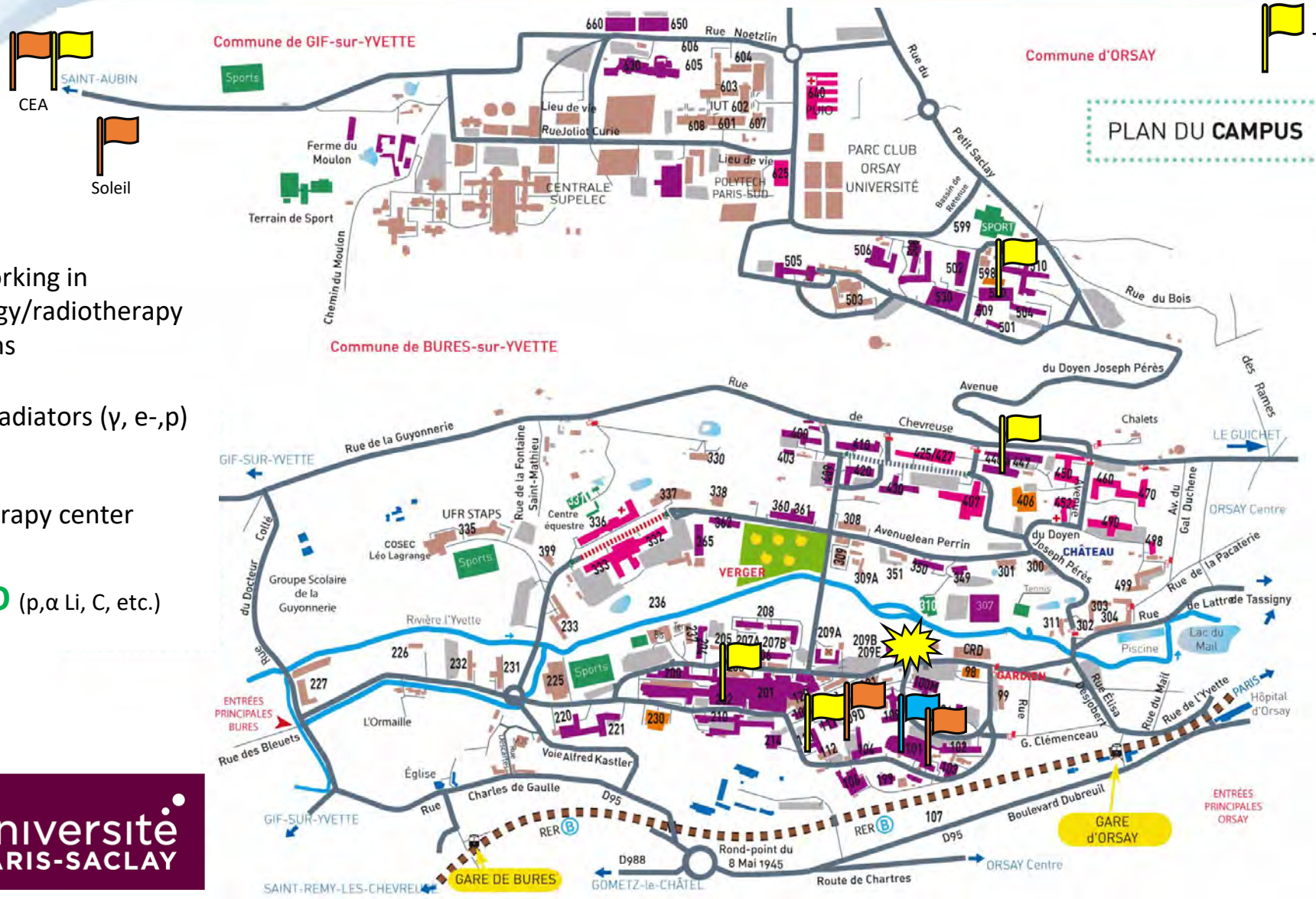
Energy Deposited



Ongoing collaboration with publication already submitted.

Y. Zhu, C. Guardiola

Positioning of the project in the region



+ Institut Gustave Roussy

Groups working in radiobiology/radiotherapy applications

Existing irradiators (γ, e-,p)

Proton therapy center

BioALTO (p,α Li, C, etc.)

Concluding remarks

- **Multidisciplinary approach** to treat cancer and widen therapeutic index.
- **BioALTO** is an opportunity to develop a **national platform** for radiobiology research for **hadrontherapy**.
- Meet **growing demand for ion beams** by the large community engaged in the research of **innovative therapies** and **R&D for cancer treatment** at Université Paris-Saclay .
- **Commissioning and biological validation in 2025!**

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Thank you!

Amélia Maia Leite