Master Project « Targeted Radiation Therapies »

(2026-2029)

- **CNRS Nuclei & Particles**

IN2P3

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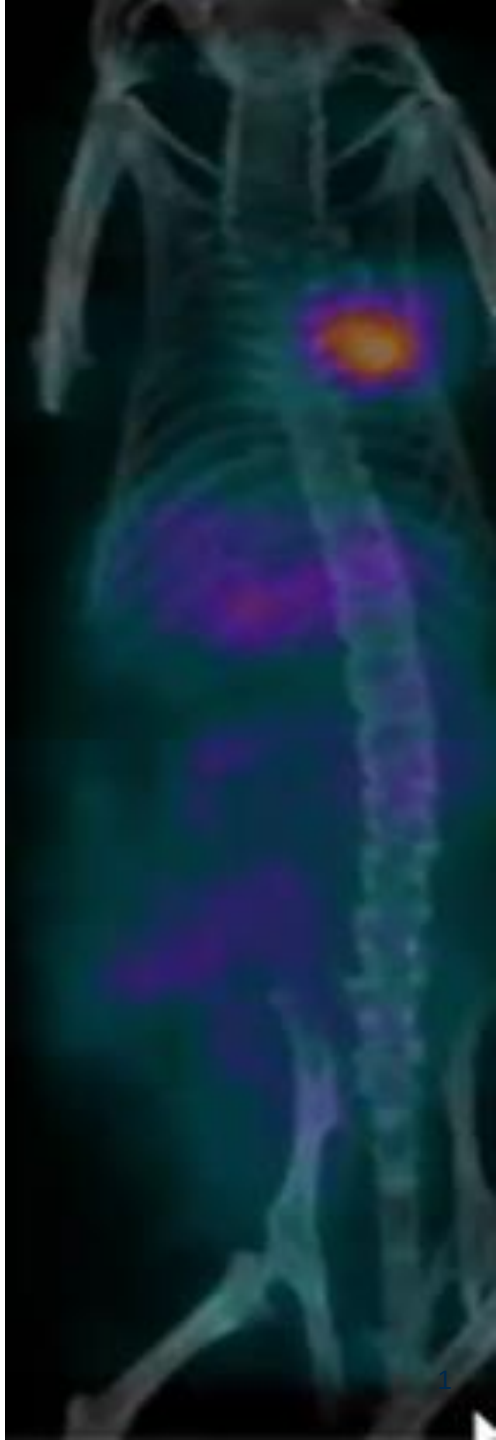
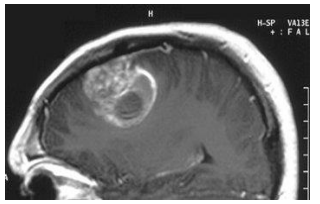
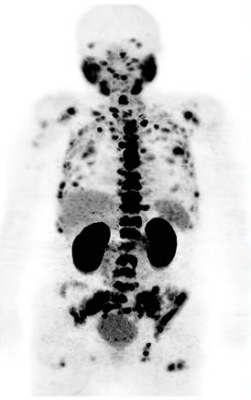


Context: Targeted Radiation Therapies

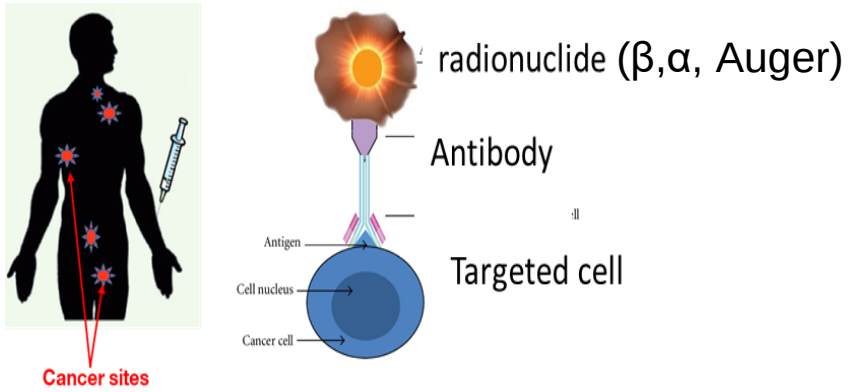




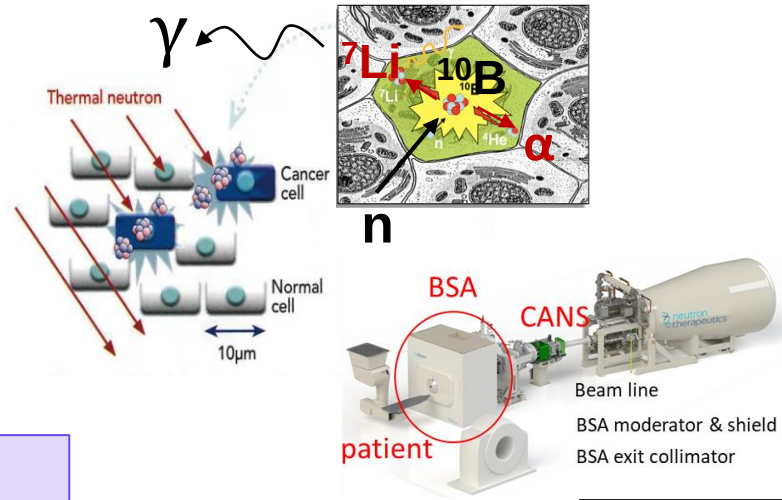
➢ **Therapeutic strategies for aggressive or systemic cancers**

= molecular targeting of cancer cells

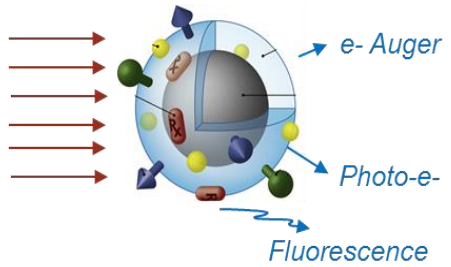
Targeted Radionuclide Therapy (TRT)



Accelerator-based Boron neutron capture therapy (BNCT)



NP-enhanced RT (radiosensitizers)



- **Internal irradiation** (full or secondary reaction)
- Need for a "**vector**" with specific targeting
- **Short range** of particles, potential **high-LET**
- **Dosimetry challenges**: imaging quantification, high heterogeneity, control → *adapted num & instru tools*
- **Neutron production / detection**
- **Biological mechanisms** may differ from EBRT

	α-TRT	BNCT	NP
Radionuclide/particle	^{223}Ra, ^{225}Ac, $^{212/213}$Bi, ^{211}At, ^{212}Pb…	^{10}B/^{11*}B	e- (PE, Auger)
Energies α (& ^{7}Li) or e-	5-9 MeV	0.8-1.7 MeV	0-100 keV
Range α (& ^{7}Li) or e-	40 –100 μm	5 –9 μm *(<cell)*	0-100 μm
LET *(keV/μm)*	60 – 100	≥ 200	0.5-20

MP Targeted Radiation Therapies: organization

Scientific Coordinators
R. Delorme – LPSC
AM. Frelin – GANIL
P. Vernet - LPCA

Technical Coordinators
A. Maia Leite – IJCLab

WP1 - Deciphering biological responses from molecules to cells in targeted radiotherapies

P. Vernet - LPCA

T1.1: Functional impact of alpha-emitters and nanoparticles on molecular targets

T1.2: Biological data production to feed and benchmark models

WP2 - Multiscale modeling of physical dose and theoretical biological response

R. Delorme – LPSC

T2.1: Modeling at the subcellular, cellular, and multicellular scales

T2.2: Preclinical and clinical modeling

WP3 - Optimization and control of dose delivery

AM. Frelin – GANIL

T3.1: Optimization and characterization of neutron fields in BNCT

T3.2: Dose delivery control in *in vitro* and preclinical radiobiology

T3.3: Clinical dose delivery control in internal radiotherapy

Related projects

- PCSI Picture
- MITI AlphaBioDose
- ANR IRHydroBRAIN
- PCSI OPTADOM

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- MITI AlphaBioDose
- ANR IRHydroBRAIN
- PCSI OPTADOM

- MP AB-BNCT
- MP BioALTO
- XEMIS
- THIDOS
- AIDER

MP Targeted Radiation Therapies: organization

& Partners

(academic, clinical, industrial)

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***coordinators**

WP1: Deciphering biological responses from molecules to cells in targeted radiotherapies

Characterize and quantify the biological specificity of targeted RT efficacy, through detailed radiobiological studies using **radionuclides**, **NP** or **high-LET** particles (relevant for α-IRT and BNCT).

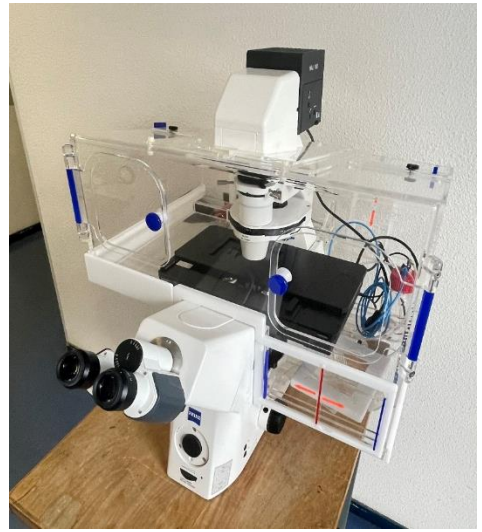
T1.1 Functional impact of α-emitters and nanoparticles on molecular targets

Molecular and functional analysis

- **Online analysis of molecular** and **functional damage** following **DNA metabolizing enzymes** exposure with α-emitters
- **Mitochondrial / metabolism** impact of dose enhancement due to **metal NPs.**

Follow-up of irradiation impact on cells *(instrumental dev. in WP3)*

- In Clermont-Ferrand: **Mini-X** prototype of an **epifluorescence microscope coupled with** a **mini-irradiator** (X-rays)
- In GANIL: **scintillator-based imaging setup + microscope** for **α-IRT** exp.



Hibernation: bio-inspired approach to radiosensitize human cells

- **Deciphering specific mechanisms involved in radiosentization**
- Characterization of bear serum specific compounds

WP1: Deciphering biological responses from molecules to cells in targeted radiotherapies

Characterize and quantify the biological specificity of targeted RT efficacy, through detailed radiobiological studies using **radionuclides**, **NP** or **high-LET** particles (relevant for α-TRT and BNCT).

T1.1 Functional impact of α-emitters and nanoparticles on molecular targets

T1.2: Biological data production to feed and benchmark models

Presentation Alicia Garnier (mardi 31 Juin)

In vitro biological effect of β-emitting isotopes *(IRHydrobrain)*

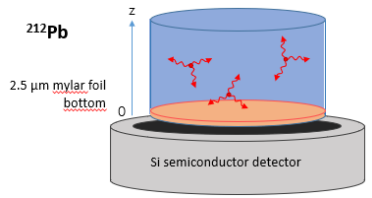
Strategy for **intraoperative TRT** in **glioblastoma** with **radiolabeled chitosan hydrogel with ^{90}Y or ^{177}Lu**.

- Radiobiological effects of hydrogel will be studied **on F98-spheroid model** in terms of **DNA damage** *(gH2AX foci)*, **cell depth**, **cell migration, ROS measurements**.

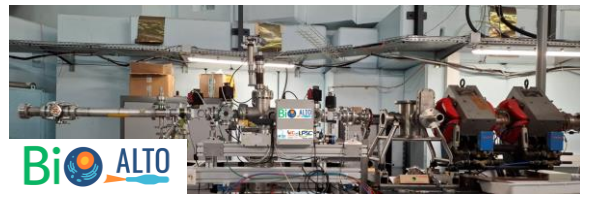
In vitro biological effect of α-emitting isotopes *(AlphaBioDose, OPTADOM)*

Application to breast cancer brain metastasis treated with α-IRT *(and other cell lines)*

- **Clonogenic cell survival** and **sub-cellular damage** *(DNA, mitochondria, membrane)* measurements, on various cell lines, with **α radionuclides** (^{223}Ra, ^{212}Pb…) thanks to **dosimetrically instrumented experiment**



- and with **low-energy ^{4}He and ^{7}Li ions** on **SiLab** and **BioALTO** plateforms



WP2: Multiscale modeling of physical dose and biological response

2.1: Modeling at the subcellular, cellular, and multicellular scales:

➔ Develop **advanced modeling tools** to reproduce TRT irradiation dose distributions with heterogeneity complexity and **predict biological damage** at **cellular**, and **multicellular scales**.

Main obj. 2026:
3 Master internship
Poster at PTCOG

Past and current developments:

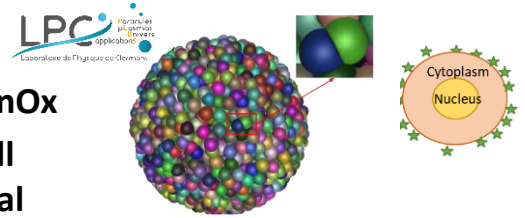
- **NanOx Biophysical model:** predict cell survival probability from physical dose distribution with mix of **nano- and micro-dosimetry and consideration of** oxydative stress.

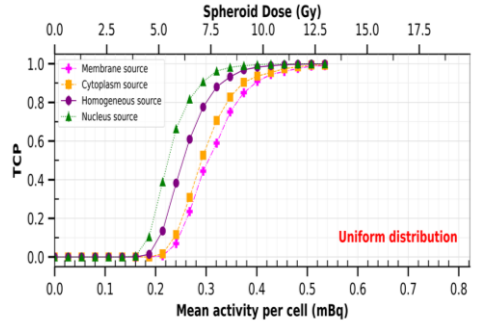
→ Recently **adapted** from hadrontherapy **to low-energy ion TRTs***

- **Application to α-TRT:**

Calculation pipeline: **CPOP - Geant4 - NanOx** to study impact of **intra-cell** and **inter-cell heterogeneities** of sources on **cell survival** and **tumor control probability** in spheroids.

→ **effect++ of inter-cell activity fluctuation****





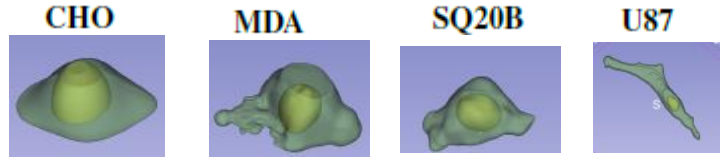
- **Preliminar application to BNCT:**

→ **Huge impact of intracellular heterogeneities**

**Alcocer-avila et al., 2024, Med. Phys. 51(12):9358.*
***Levrague et al., 2025, Med. Phys. 52:e17917*

Main perspectives (~4y):

1. **Benchmark of calculated cell survival to** biological in vitro experiments (in TRT & BNCT).
2. **Impact study of realistic cell morphologies**: microscopy-reconstructed numerical phantoms



3. **Intra-cell & intra-tumoral heterogeneity impact study for BNCT** (and GdNCT).
4. **NanOx extension to new cancerous cell lines** *(U87, SQ20, MDA…)* and **extra-nuclear damage**.
5. **GATE bio-dose actor developments** applied to αIRT and BNCT treatments

WP2 – Including LQD Cross Sections in G4-DNA

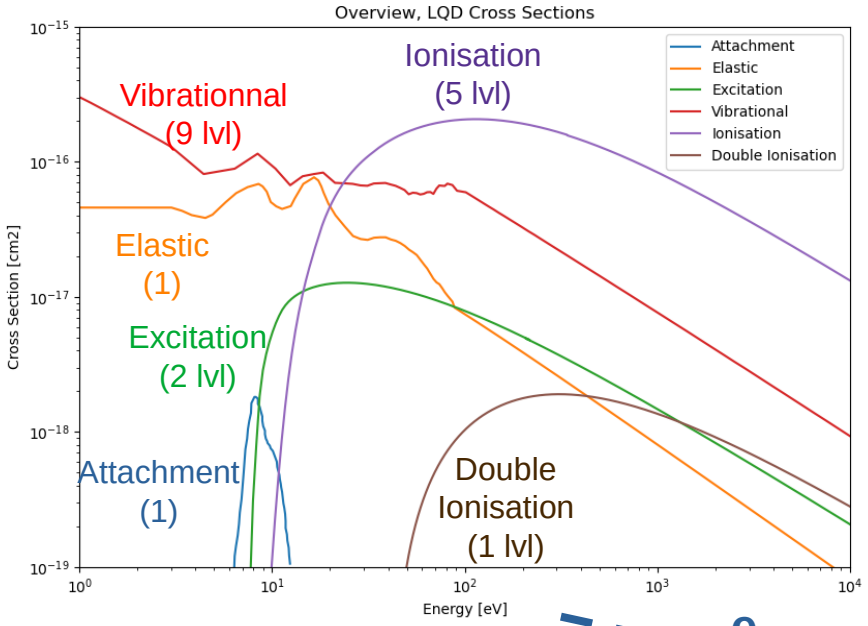
Presentation Loic COUSIN (mardi 31 Juin)

LQD Code : Monte-Carlo simulation of Ions transport in liquid water

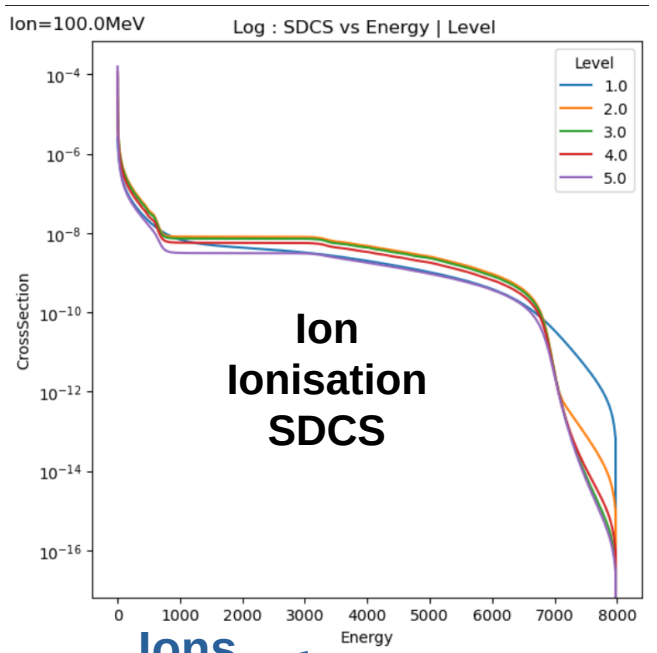
In collaboration with CIMAP (Caen), Rosario university (Argentine) and IP2I (Lyon)

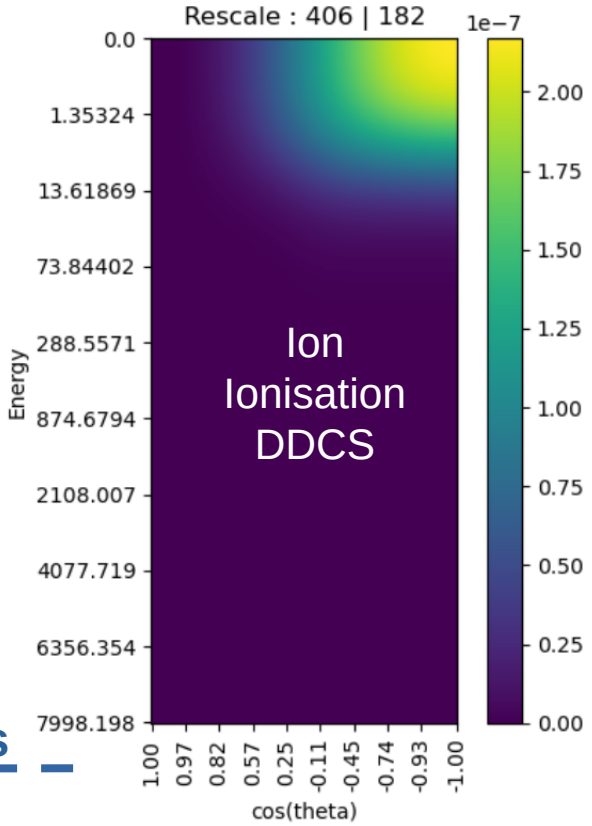
Objective : *Including LQD cross sections (CS) in a new Physic List of G4-DNA.*

LQD : Electron Cross Sections



LQD : Ion Cross Sections





e-

Ions

Ions

For Ions (H, He, C, ...) :

- **Ionisation :**
  - **CDW-EIS Model :**
  - ***Simple Diff and Double Diff CS : (Ei vs Esec, Angle)***
- **Multiple Ionisations**
- **Outlooks : Uses the new G4 LQD Physic List within the collaboration**

Ref : Gervais, M. Beuve, G.H. Olivera, M.E. Galassi,
Numerical simulation of multiple ionization and high LET effects in liquid water radiolysis,
https://doi.org/10.1016/j.radphyschem.2005.09.015.

WP2: Multiscale modeling of physical dose and biological response

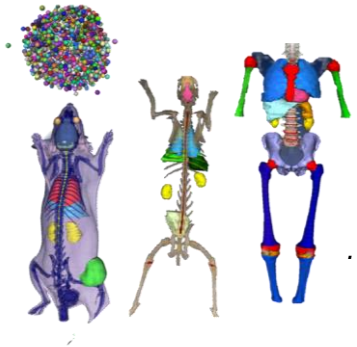
2.2: Preclinical dose and biological effect modeling

Presentation Alicia Garnier

➔ Aims at developing **modern dosimetry workflow** based on **multi-modal biodistribution imaging**, **Monte Carlo simulation** and **statistical approaches**, to optimize experiments and interpret preclinical results.

Development of GATE modeling tools to support innovative β-IRT strategy for intraoperative GBM *(IRHydrobrain)*:

GATE 10 used to support in vitro & in vivo experiments:



3D reconstruction (spheroid, mouse, rabbit and human) from microscopic or CT imaging. Geometries in GATE.

1. Calculate **dose to targets** with **rat digital twin** (*in vivo correlation)*
2. Implementation of a **spheroid digital twin** *(in vitro exp.)*

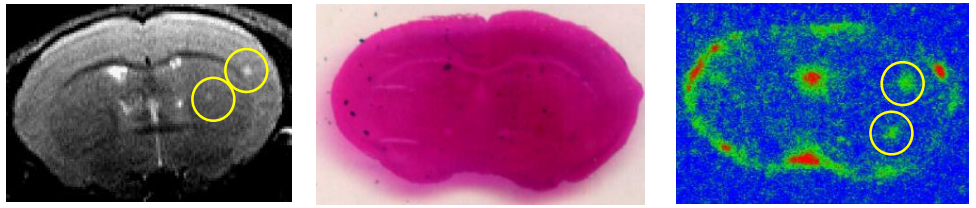
2.1 implementation of a **Chemistry actor**

2.2: **ROS quantification** and comparisons

2.3: **DNA damage** and comparisons

Application to breast cancer early brain metastasis treatment with α-IRT *(AlphaBioDose, OPTADOM)*:

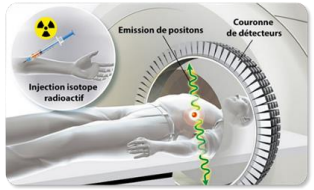
1. **Activity biodistribution determination** of antibodies in **mice** using **multimodal information**: PET imaging and autoradiography, vs anatomical MRI and histology.



2. **Dose rate and dose distribution calculation** using GATE
3. **3D biological dose maps calculations** *(from T2.1 TCP models)* and *in vivo* response comparison.
4. **Learning by statistical methods** for dose and bio-dose **reconstruction**

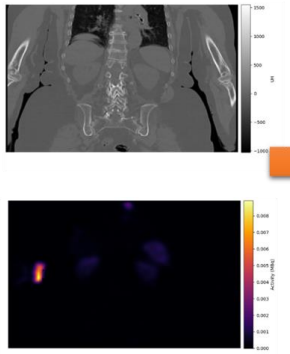
WP1/2/3 – 3D dosimetry in Targeted Radionuclide Therapy (TRT)

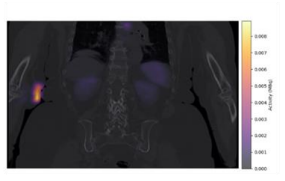
- ***Dosimetry workflow applied to a clinical case*** *(S. Lechien PhD thesis)*

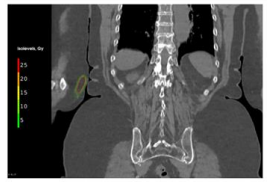


Anatomical imaging (CT/MRI)
+
Functional imaging (PET/SPECT)
at different times

Biodistribution
A(x,y,z,t)





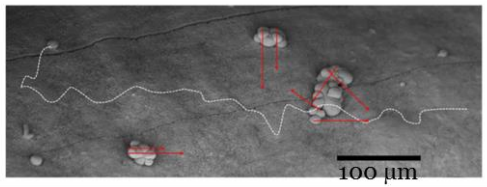


Monte Carlo simulation:
- Particle transport
- Deposited energy

Application to preclinical studies

Experiment performed in 2026 with ^{223}Ra

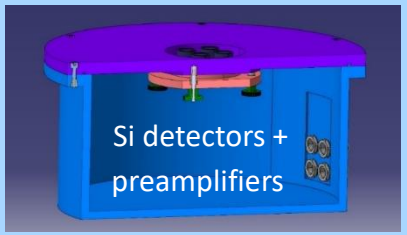
- ***Assessment and integration of biological effect of alpha particles*** *(A. Doudard PhD)*

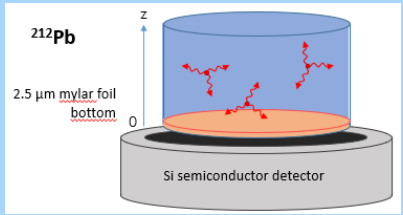


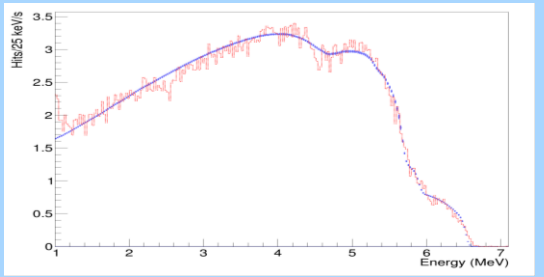
Scanning electron microscopy micrograph of micro-metastatic clusters and illustration of α and β⁻ particles

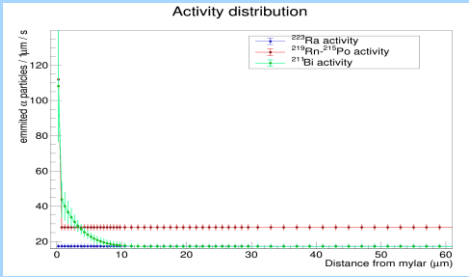
A emitters:
→ **Short range**
→ High LET
→ Hypoxia sensitivity

Main achievement: developed a **Si detector** for precise **dosimetry in *in vitro* α-emitter experiments**, using a **deconvolution of energy spectra** to reconstruct radionuclide z-position distribution in the wheel.









Major article: Doudard A et al., *Application of a new spectral deconvolution method for in vitro dosimetry in assessment of targeted alpha therapy.* Med Phys. 2023;50:3762–3772. https://doi.org/10.1002/mp.16279

WP3: Optimization and control of dose delivery

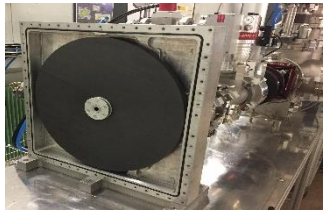
3.1: Optimization and characterization of neutron fields in BNCT

➔ Aims at proposing an **optimal set of accelerator-based BNCT systems**, including the study of **innovative targets** for the production of intense epithermal neutron field and their test system, the **design of optimized moderators**. and **instrumental developments for neutron field detection** and microdosimetry.

Main obj. 2026:
Experiment + ICNCT conf in Oct 2026 Buenos Aires

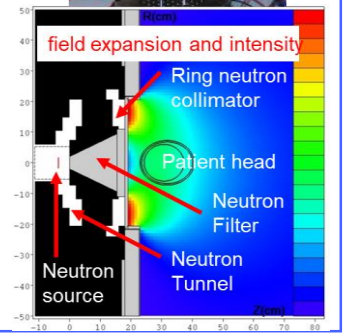
Past and current developments:

1. **Innovative targets for intense epithermal neutron:**
   - Developed a rotating target on a graphite wheel + ^{9}Be (or ^{13}C) deposit
   - e- thermal test beamline (3 kW/cm²)



2. **Neutron field detection**
   - NFM gas detector with ^{10}B-foil for **field monitoring**
   - MIMAC-FastN **neutron spectrometer in epithermal and fast ranges** *(angular distributions meas. legnaro)*

3. **Optimal moderator (BSA) design:**
   - Developed **new topology optimization** (**TopOpt**) method → deepest treatment depth achievable in the AB-BNCT community ***(~10 cm vs std ref ~7.6cm)***



Main perspectives

1. **Dev. of a rotating ^{13}C (d (1.5 MeV,n)) target** for the Buenos-Aires AB-NCT accel.
2. **BSA design: Optimal Moderator design** for the ^{13}C (d (1.5 MeV,n)) reaction + **for metrological epithermal neutron** *Cadarache (LMDN-ASNR)*
3. **Neutron spectro**: charac. The TANDAR field
4. Test MIMAC as **microdosimeter** with Tissue equivalent gaz
5. **NFM detector validation** on metrological ASNR neutron high flux & at GANIL
6. Ultimate goal: propose **optimal AB-BNCT facility design**

LMDN

Argentina TANDAR

WP3: Optimization and control of dose delivery

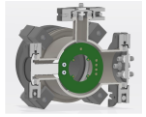
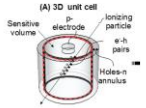
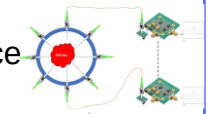
3.2: Dose delivery control in *in vitro* and preclinical radiobiology

➔ Aims at developing dedicated irradiation facilities and detectors enabling accurate and quantitative assessment of biological experiments, in full complementarity of WP1.

BioALTO irradiation platform *(~4y perspectives)*:

Aims to provide **multiple low- and medium-energy ion beams**, with irradiation quality **compatible with radiobiology studies**.

1. **Upgrade RG device** to improve ALTO interoperability
2. **Develop new beam diagnostics and dosimetry** tools:

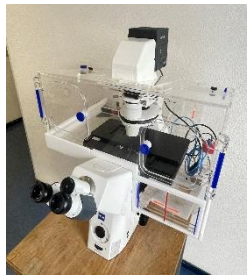
Diamond counter  Si-based µdosemeter  Air fluorescence Profiler 

3. **Creation and equipping a cell culture room** @ALTO
4. **Dosimetric and radiobiological** validation
5. **Feasibility studies for UHDR** irradiations

Presentation Louis Hardouin

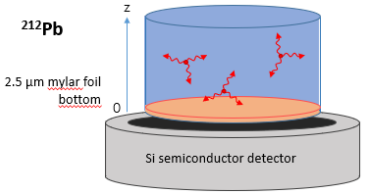
Mini-X for online functional analysis: Coupling between a **microscopy platform** and a **mini-irradiator** (X-rays)

- enables **real-time visualization** of the **early cellular responses to irradiation**.
- **Online dosimetric characterization system** under development



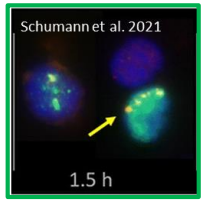
In vitro dosimetry of α-emitters:

Si-based dosimeter designed for use in cell culture incubator → determine real dose received to cells during exp.



Frelin-Labalme et al., Med Phys. 2020;47(3):1317.

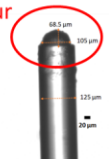
- dose information at the scale of the culture well
- **new system to enable microdosimetry** measurements at the scale of **individual cells**. Combines **scintillator-based imaging** *(α tracks visu)* setup with a **microscope** *(damage follow-up)*
- Complementary to mini-X



Preclinical dosimetry in IRT:

Development of a **customized biomimetic mouse phantom** instrumented with **miniature scintillating fibre dosimeters**

→ **for IRT dosimetry evaluation.**

Micro-scintillateur 

NUCLÉAIRE & PARTICULES

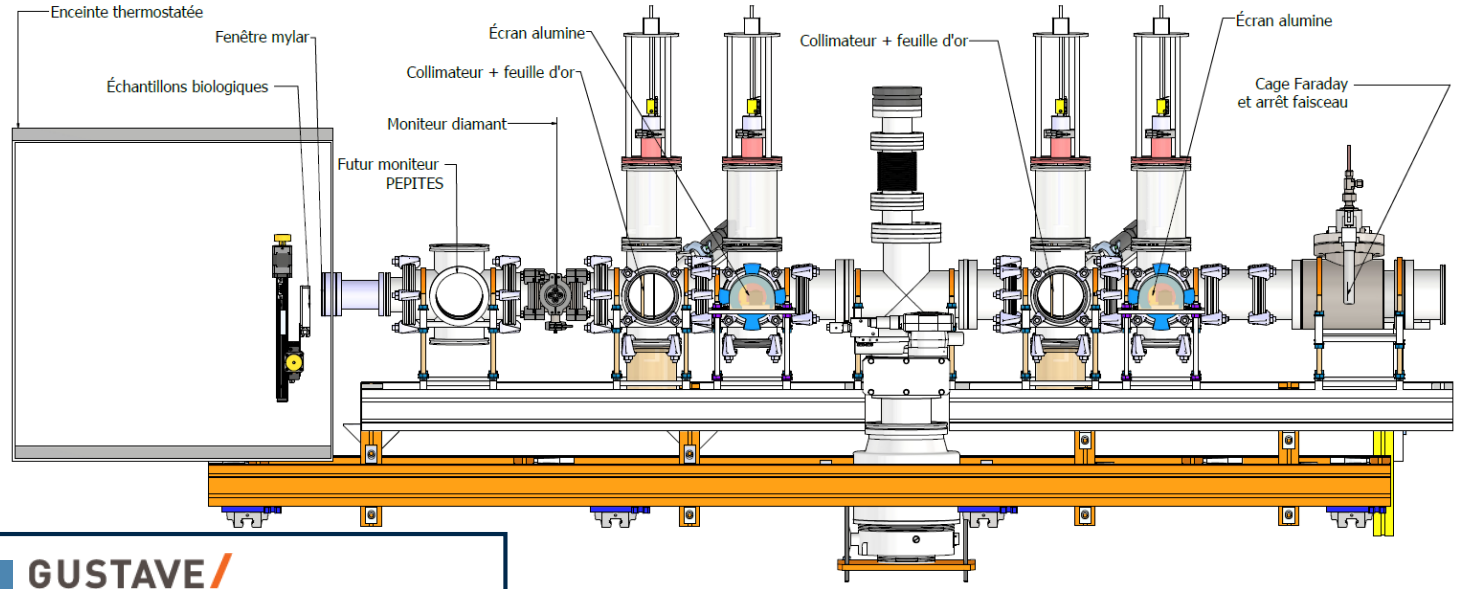
BioALTO

Hope first dosimetric exp. By end 2026 / begin 2027

Lauréat SESAME 2025 Région Île de France:

- Jouvence ligne BioALTO
- Jouvence ALTO
- Financement moniteur PEPITES dédié
- Financement microdosimetre dédié

Plan CAO de la nouvelle ligne BioALTO en cours de montage:



Équipes:

Physique des Accélérateurs
Accelerator Physics

PHYSIQUE SANTÉ
HEALTH

IJCLab Irène Joliot-Curie
Laboratoire de Physique des 2 Infinis

ALTO Accélérateur Linéaire et Tandem à Orsay

Partners:

LPSC Grenoble

IP2I

GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

CNM CENTRO NACIONAL DE MICROELECTRONICA

IMB

ISMO

Contact: Amélia Maia Leite, Quentin Mouchard
bioalto@ijclab.in2p3.fr

WP3: Optimization and control of dose delivery

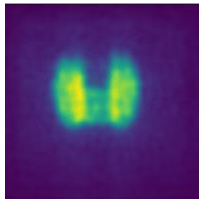
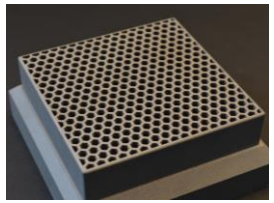
3.3: Clinical dose delivery control in internal radiotherapy (personalized dosimetry)

➔ Aims at developing advanced imaging technologies to enable the individual determination of absorbed doses to organs-at-risk and target regions.

THIDOS :

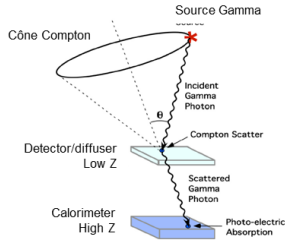
Clinical prototype of a mobile γ camera of 10x10cm field of view, to control the **dose delivered** during **^{131}I** (β 364 keV) treatment for thyroid diseases.

2025: First clinical evaluation at IUCT. And in 2 other clinical centers


Perspectives (~1-3y):

1. **Adaptation for dose-based treatment planning of thyroid diseases using ^{123}I** (160 keV, Cochin)
2. **Open use to medium-energy γ-emitters** *(200-400 keV, ^{177}Lu or ^{225}Ac)*
3. **Develop a DL-enhanced Compton camera** to allow dosimetric monitoring of **TAT** (Eg ≳ 400 keV). ^{149}Tb, ^{213}Bi, ^{225}Ac or ^{212}Pb



XEMIS2:

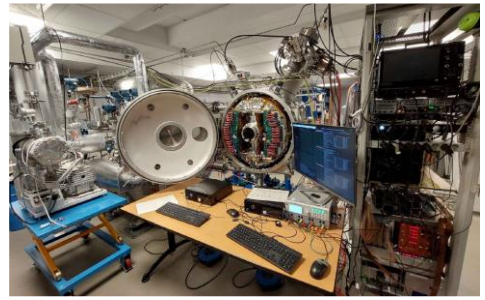
First liquid Xenon medical imaging system for small mammals

Installed @ Nantes Université Hospital

Dedicated to multimodal imaging (high-energy SPECT, PET, 3Ɣ)

Allow image acquisition with reduced activity

Main Perspective for TRT:
Explore it's use for IRT monitoring through images of gamma rays.
➔ **feasibility study with ^{212}Pb**



AIDER: European project (HORIZONEURATOM, Spain, Italy…):

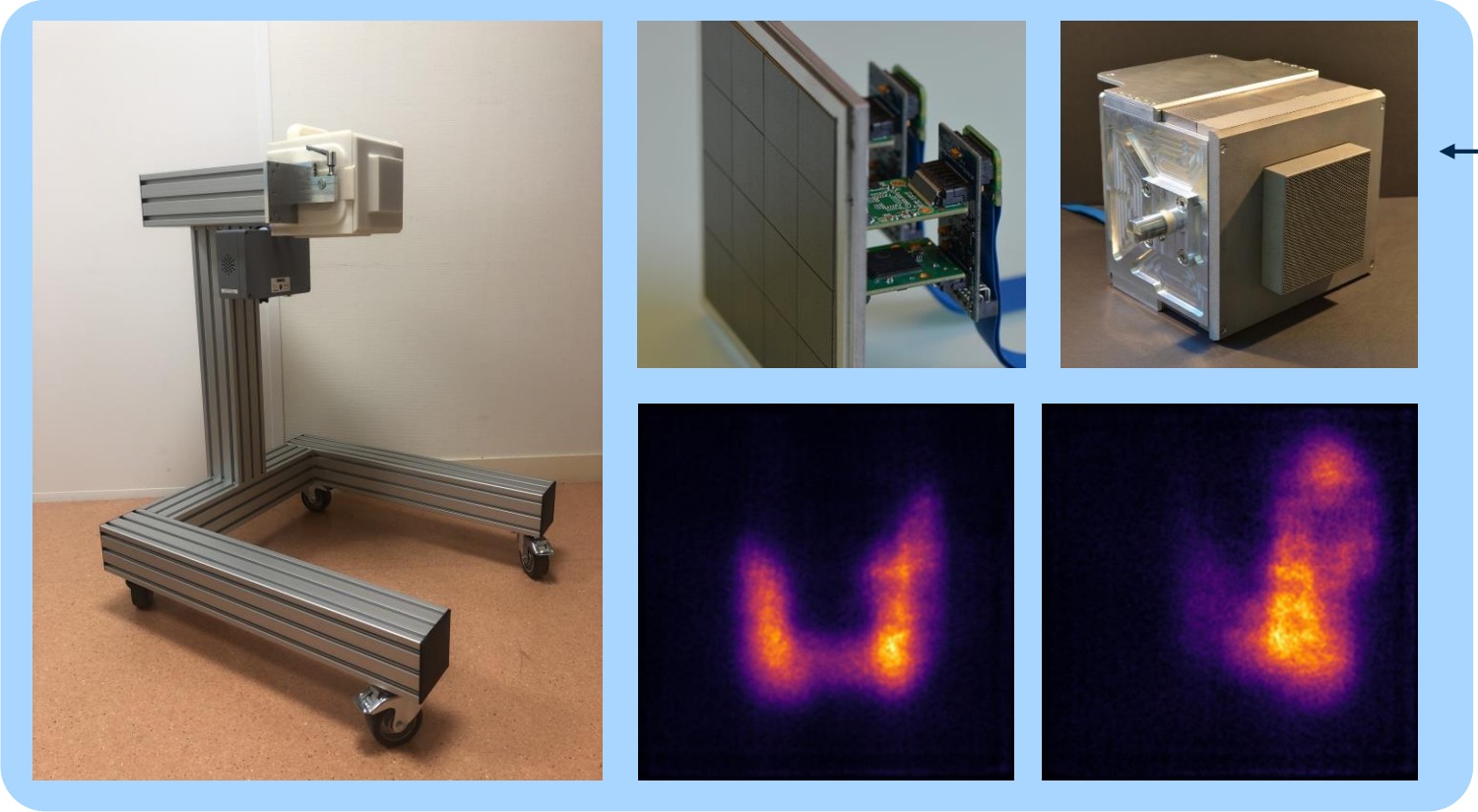
Development of a Compton Camera for TRT (α-IRT and BNCT):

@Lyon (CREATIS-IP2I) : Camera optimization using MC simulations + image reconstruction

WP3 – Clinical dose delivery control in TRT

- ***First clinical evaluation of the mobile THIDOS gamma camera:***

Finalization of the **first clinical evaluation of the THIDOS mobile camera** conducted on **20 patients with benign thyroid diseases** (Claudius Régaud Institute, Toulouse).
Preliminary results indicate **unprecedented image quality** at energies of approximately 400 keV.



Presentation Marc-Antoine Verdier (Lundi 29 Juin)

Principales réalisations 2025/2026

- **Fin 1er essai en ^{131}I sur patients en mars 26 avec ICR, Toulouse**
  → analyse dosi en cours

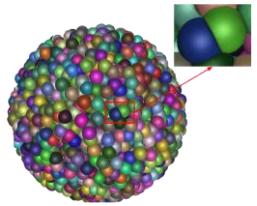
- **Design d'un nouveau collimateur pour le ^{177}Lu, essai prévu avec CHUV Lausanne**

Recent articles related to the THIDOS camera:

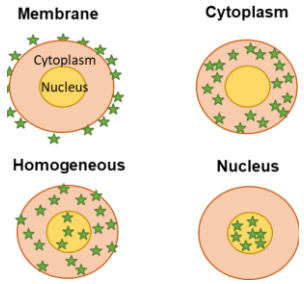
Bossis et al. (2024). *A high resolution portable gamma-camera for estimation of absorbed dose in molecular radiotherapy*. IEEE TRPMS, 8(5):556–570
Bossis, T. et al. (2023). *Optimized reconstruction of the position of interaction in high-performances γ-cameras*. NIM-A, 1048:167907

Some detailed projects & backup

WP2 – biophysical modeling at microscale in TAT and BNCT

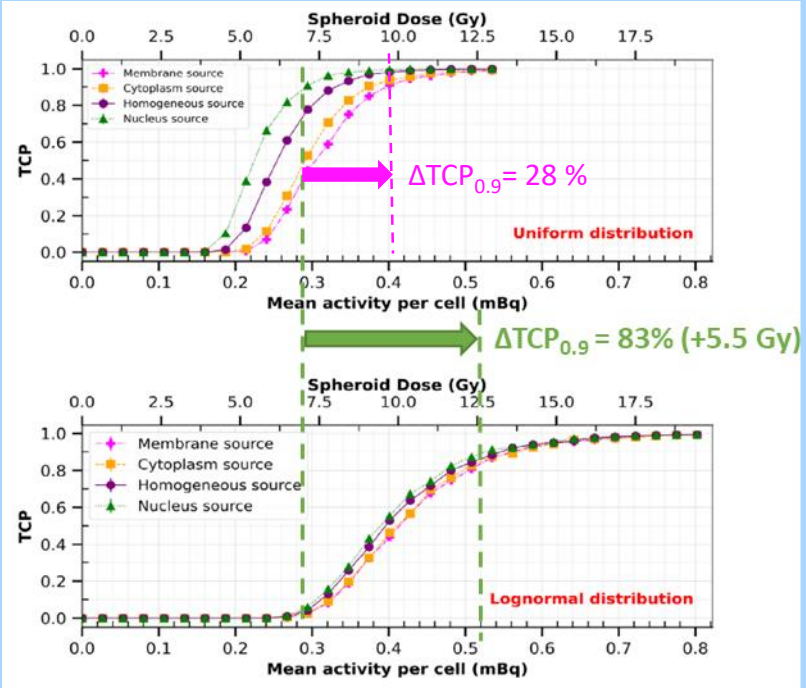


α-emitters or ^{10}B



Calculation pipeline:
*Spheroid modeling = **CPOP**.*
*Particle transportation = **Geant4**.*
*Cell survival & TCP conversion from deposited energies = **NanOx**.*

***TAT** : Tumor control probability (TCP) as a function of cell internalization and inter-cell fluctuations of* α emitters



- Main Results *(V. Levrague PhD thesis & PICTURE project)*:

Calculation pipeline: Objective to quantify the uncertainties on therapeutic effect predictions due to intracellular and intratumoral heterogeneities

TAT ➔ Lognormal α distribution at tumor scale have a major impact on efficacy. *Uniform hypothesis may cause overestimation of TAT efficacy*

2 major publications in Medical Physics :

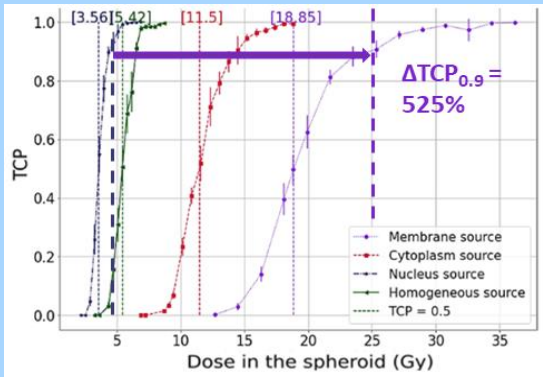
- ***Levrague** et al, Impact of intracellular radionuclide distribution in a Monte Carlo biophysical 3D multi-cellular model for Targeted Alpha Therapy. Medical Physics **2025**; 52:e17917, https://doi.org/10.1002/mp.17917*
- ***Alcocer** et al., Biophysical modeling of low-energy ion irradiations with NanOx. Med Phys. **2024;1-14**. https://doi.org/10.1002/mp.17407*

BNCT ➔ Larger impact of cell internalization of ^{10}B on TCP, compared to TAT.

Nuc ➔ Mem = + 500% on TCP

(preliminar results only for Boron dose component)

***BNCT** : TCP as a function of cell internalization of ^{10}B*



➔ Perspectives to benchmark model with ***in vitro*** **biological data for TAT** & **BNCT**.

Funds:

Design of AB-BNCT Beam Shaping Assemblies at LPSC

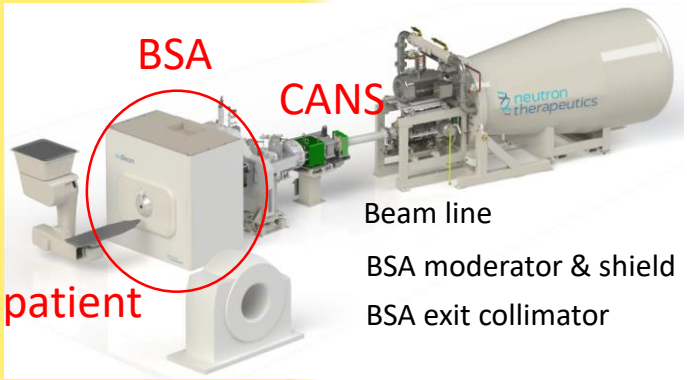
AB-NCT Challenges:

- To bring 10^9 $n_{ep}/(cm^2.sec)$ to the tumor (30' irradiation time) using a **compact and safe facility** installed at a hopital
- **To build a target** coping with 30-50 kW on 10 cm^2 (3-5 kW/cm^2)
- **Shaping and characterizing the neutron field** getting out the targets and the moderators = **Beam Shapping Assemblies (BSA)**

Beam Shaping Assemblies (BSAs) are key components of the therapy, positioned between the source and the patient, to shape and optimize the neutron field used for treatment. **Their design addresses a complex constrained optimization problem**, until now always solved by parametric optimization.

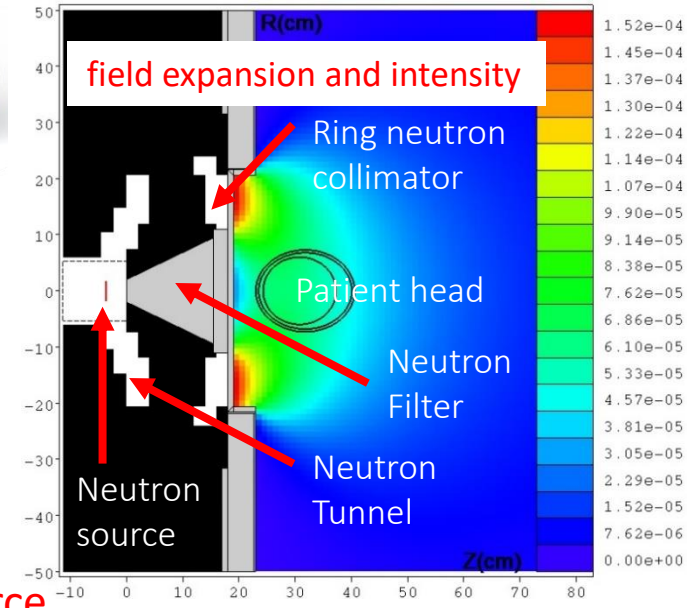
At LPSC, we have introduced a new design method, called topology optimization (TopOpt), developed internally. This method can compute with little or no approximation the best possible structure of a particle propagator. See S. Chabod et al., Phys. Med. Biol. 70(3) (2025) 035008.

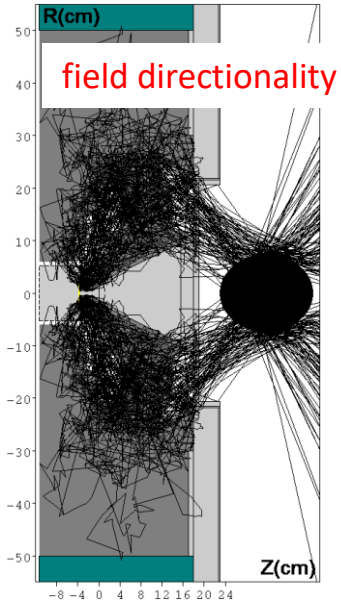
Topology optimized BSAs generate advanced neutron fields, $\varphi(\underline{r},E,\underline{\Omega})$, that combine neutron directionality ($\underline{\Omega}$), space expansion ($\underline{r}$) and energy distribution (E) to control tumors, generating treatment depths 30% greater than the best value achieved so far by the global AB-BNCT community.



Neutron Therapeutics®: scheme of the AB-BNCT treatment facility at Helsinki University Hospital. Left: treatment room, **with the BSA and patient bed.** Right: accelerator and beam line. The line ends with the target, inserted into the BSA.

CANS = Compact Acc. Neutron Source





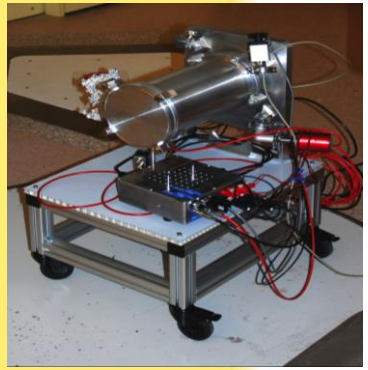
TopOpt introduces new and unique components into BSA design: neutron tunnels, filters and ring collimators that mimic the effects of multi-beam BNCT treatments.

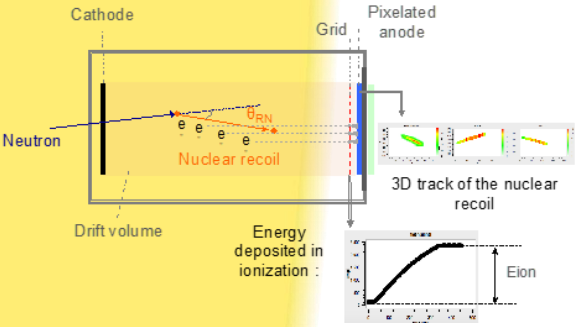
BNCT literature	Source	TD (cm)
Riley et al. 2003	MIT Reactor	7.8
Kononov et al. 2004	^{7}Li(p(2.3 MeV),n)	7.0
Kim et al. 2009	^{7}Li(p(2.5 MeV),n)	6.0
Inoue et al. 2014	^{9}Be(p(8.0 MeV),n)	5.0
Minsky et al. 2014	^{7}Li(p(2.3 MeV),n)	7.0
Capoulat et al. 2014	^{9}Be(d(1.45 MeV),n)	7.8
Capoulat et al. 2017	^{13}C(d(1.45 MeV),n)	7.8
Torres-Sánchez et al. 2021	^{7}Li(p(2.1 MeV),n)	7.85
Bae et al. 2022	^{9}Be(p(10 MeV),n)	7.2
Rong et al. 2024	^{7}Li(p(2.8 MeV),n)	6.5
Verdera et al. 2024	^{45}Sc(p(2.918 MeV),n)	7
Our work	**^{7}Li(p(2.5MeV),n)**	**10.3**

Compilation of BSA treatment depth (TD) performance data obtained by the global AB-BNCT community over the past 20 years. TD had progressed by only 0.05 cm in 20 years.

FastN
^{9}Be(d(1.45 MeV),n)- LPSC-Tandar (CNEA)

MIMAC-FastN = a fast neutron directional detector to characterize the neutron fields spectrally



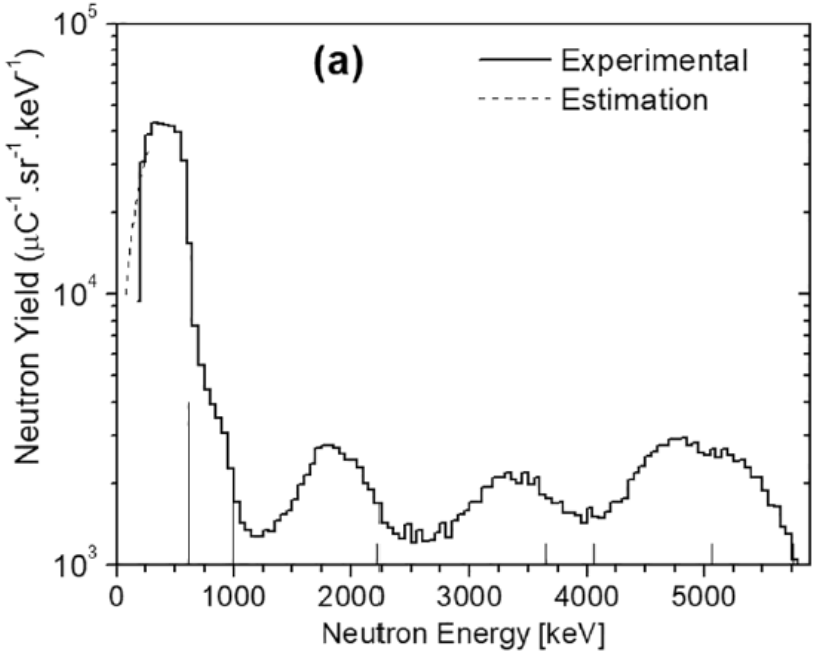


700 mbar
He/CO_2 (5%)

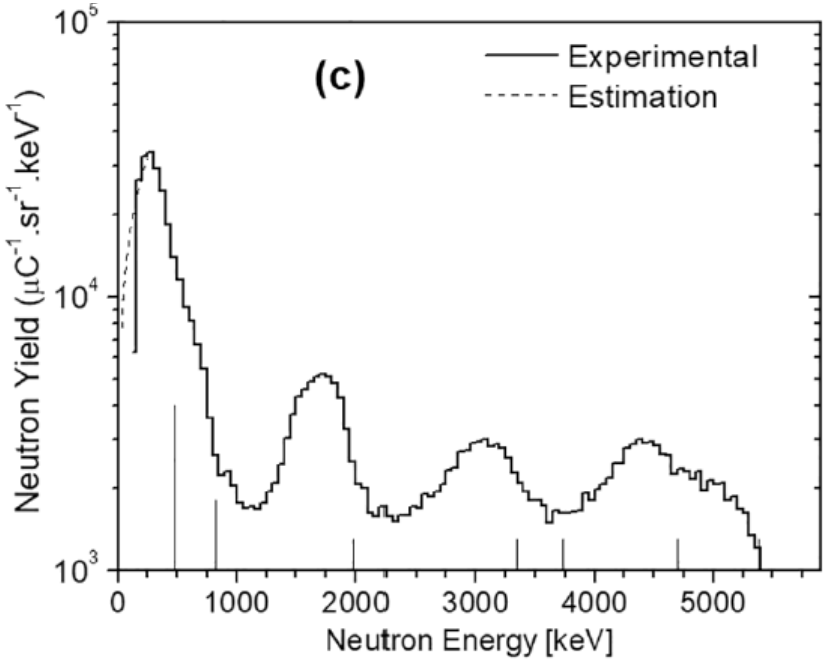
Angular distribution
for an AB-BNCT nuclear reaction

INFN LNL
(Legnaro - Italy)

Spectrum measured at **0 deg**



Spectrum measured at **60 deg**

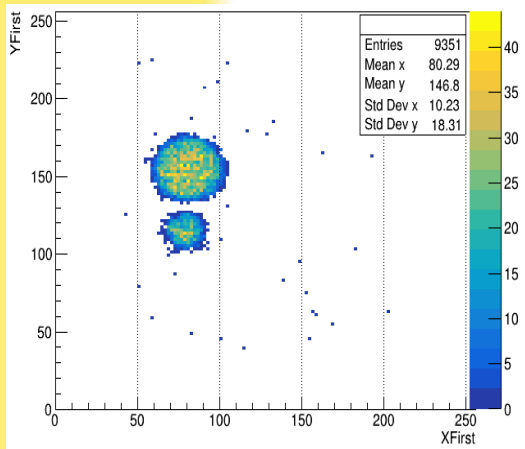


M.E. Capoulat, N.Sauzet *et al.*
« Neutron spectrometry of the ^{9}Be(d(1.45 MeV),n)^{10}B reaction for accelerator-based BNCT » NIM B, vol. 445, pp. 57-62, 2019

NFM (Neutron Flux Monitor) Detector

Giving the neutron flux (up to 10^{12}n/s) as a function of time, with an evaluation of the dead time

NUCLÉAIRE & PARTICULES

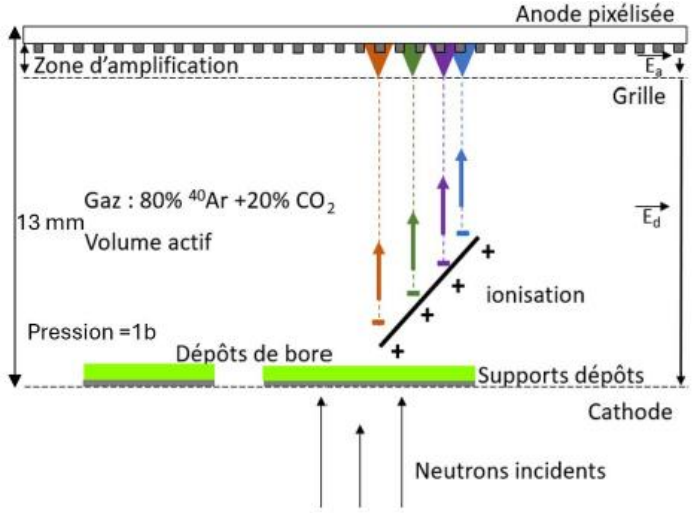


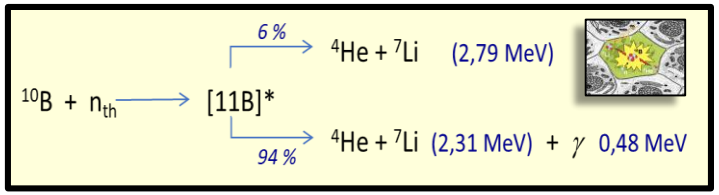
*Distribution of the first measurement of the 3D-tracks produced by an epithermal and thermal neutron field at AMANDE (Cadarache) in 2025, in The frame of the **CHEMIN project (ASNR – CNRS)***

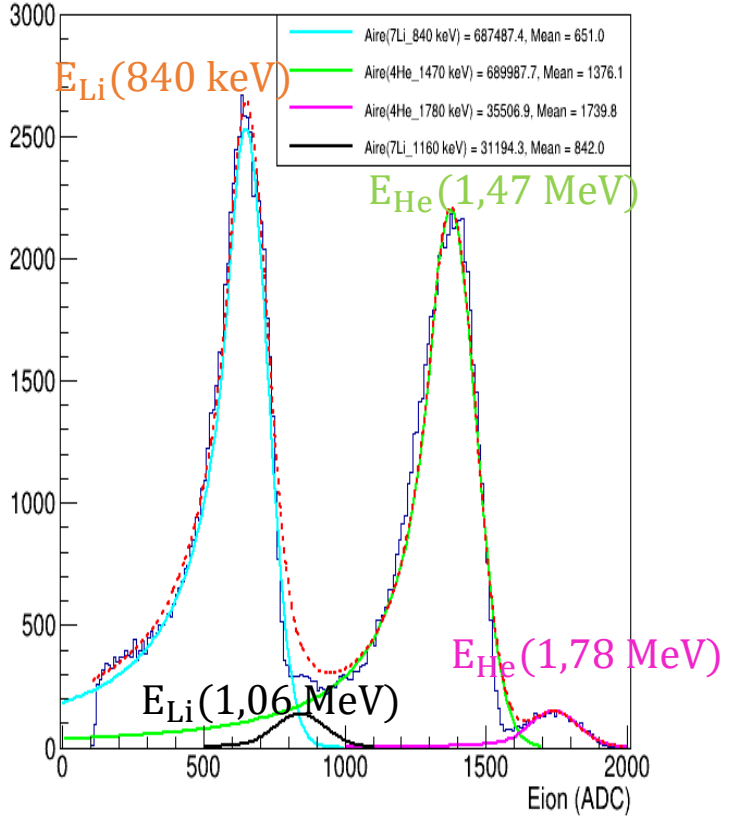
Multi-layer deposition PAPVD (plasma-assisted)

LPSC – Alexandre BES, Ana LACOSTE

Including a natural Boron layer well measured (thickness, surface and homogeneity)!!

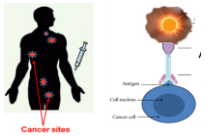






Context: TRT Dosimetry

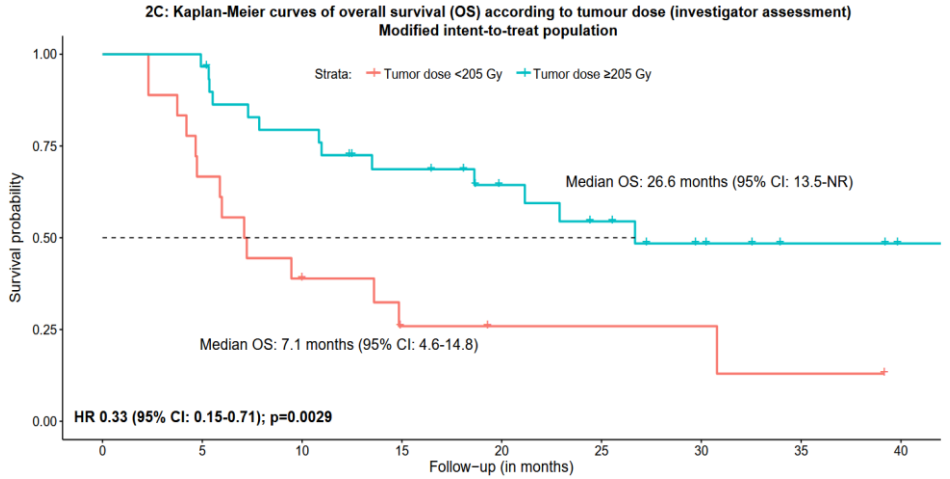
See Ali Ouadi talk for Radionuclides



➢ Radionuclide RT is increasing a lot in clinical practice.
But sub-optimal fixed activity is applied for curative treatment:

- **Dosimetry may guide personalization** to achieve durable complete response by adapting activity / cycle
- **Requires biokinetic imaging and dose calculation models**

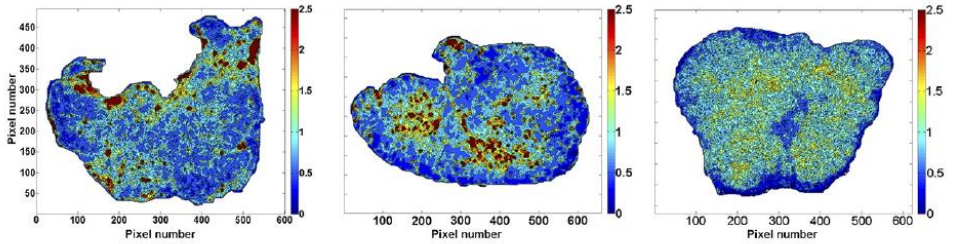
➔ Need to simplify dosimetry protocols with the improvement of imaging systems and reconstruction algorithms



Garin et al., SIRT using personalized dosimetry for locally advanced hepatocellular carcinoma (HCC) patients. Lancet, 6(1),2021

➢ Additional difficulties with high-LET/short range emitters:
Difficulty to observe clear "dose-effect relationship".

- **High heterogeneity** at micro/tissue scale, often unknown → *homogeneous hypothesis may lead to errors*
- **High** (and variable) **Relative Biological Efficacy (RBE).**
- **Complex cellular or systemic biological response**.

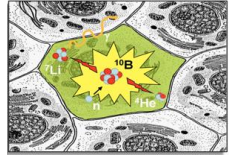


Example of heterogeneous activity distribution in tumor 7min, 7h, and 21h after injection in TAT. Bäck T et al. J Nucl Med. 2010;51(10):1616-23.

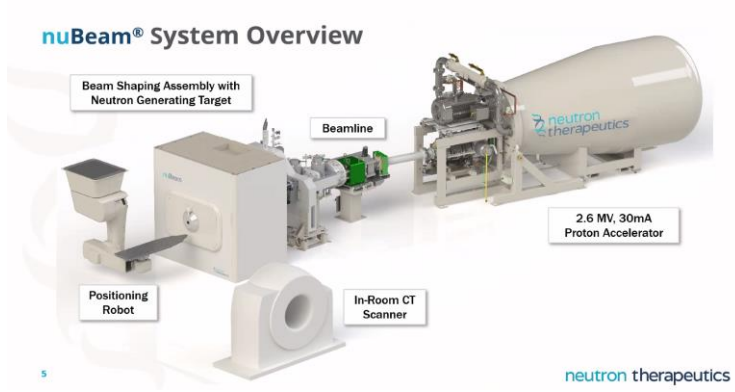
➢ We can work on some of the challenges:

- Efficient gamma cameras for personalized dosimetry (> 300 keV)
- Multiscale modeling tools to account for heterogeneities in bio-dose prediction
- Dedicated controlled radiobiological experiments (in vitro / in vivo) to deepen understanding of TRT biological effects

Context: Accelerator-Based NCT



- New era for clinical trials since compact accel. neutron sources (CANS) allow performing BNCT in hospital.
  - About **26 new AB-BNCT** facilities world-while. Clinical trial started **in Finland** 2025, **clinical routine** for **recurrent H&N cancers** in **Japan.**
  - Compagnies proposing integrated systems *(e.g. neutron therapeutics, TAE life science…)*
  - Improved patient care and **beam spectra** for **treating deeper tumors**



Ex. of NuBeam® system (ex. installed in Finland, Japan, UK…)

- Some challenges:
  - **Production targets**: High power (30-75 kW) degrades targets. Residual radioactivity with ^{7}Li, needs frequent change. → **Design optimal targets.**
  - **Online monitoring**: target aging (neutron flux ↘) and delivered dose → **Develop n & γ** (480 keV) **detectors.**
  - **Beam shaping assembly** → **Find optimal moderation to maximize penetration in tissue** with high-enough intensity.
  - **Lack of standardization** → **Neutron field spectral and fluence characterization**
  - **Complex bio-dosimetry**, several components.
    BNCT biologically-weighted dose based on fix RBE(or CBE) factors:

$$D_W = w_f D_f + w_t D_t + w_\gamma D_\gamma + w_B D_B$$

→ **Models to account for dose micro-heterogeneities & RBE variation**