Health-related activities at IN2P3

IN2P3 scientific committee report

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with the contributions of the whole community

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Abstract This report provides an overview of the health-related activities within IN2P3, along with their future prospects, following the agenda planned for the IN2P3 Scientific Council meeting in July 2025. It begins with a general overview of health activities, highlighting in particular their organization within the GDR MI2B and the Master Projects currently under development. This is followed by the three thematic areas: “Hadrontherapy”, “New Approaches in Radiation Therapy”, and “Instrumental and Numerical Developments”. We have made a point of emphasizing the links between the activities described in the sections “Hadrontherapy” and “New Approaches in Radiation Therapy” and the associated technical developments detailed in the final section, “Instrumental and Numerical Developments”.

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Overview of health-related activities at IN2P3 (CNRS - Nucléaire & Particules)

1.1 Introduction

The growing convergence between nuclear physics and biomedical sciences is opening new and promising avenues for addressing major health challenges. Within this context, the IN2P3 (Institut National de Physique Nucléaire et de Physique des Particules) plays a significant role in developing interdisciplinary approaches.

This chapter presents a comprehensive overview of the scientific efforts conducted within IN2P3 in the field of Health, focusing on the interdisciplinary framework provided by the GDR MI2B (Groupe de Recherche – Nuclear Methods and Tools for Cancer Research). The first sections are dedicated to identifying key scientific challenges such as the development of innovative radiotherapies, advances in biomedical imaging, modeling approaches for radiobiology, the use of radionuclides, and the physicochemical characterization of radiation-matter interactions.

These challenges are followed by a detailed presentation of the main research projects and activities currently underway, supported by human and financial resources mobilized for their realization. In addition, this chapter highlights scientific output through international collaborations, publications and PhD defenses, demonstrating the vitality and academic productivity of the field.

The latter part of the chapter is devoted to the role of the GDR MI2B as a structuring tool for coordination, collaboration, and scientific animation. It also outlines the current deployment of Master Projects (MPs) across various Health-related topics such as hadrontherapy, FLASH therapy, targeted radiotherapies, and the development of radionuclides for both diagnostic and therapeutic purposes.

Through this multi-dimensional analysis, the chapter aims to provide a clear picture of the strategic scientific positioning of IN2P3 in the Health sector and its contributions to advancing medical innovation through nuclear science.

1.2 Radiation physics for Health

The research activities follow four main axes: **imaging, radiobiology, radiotherapy and radionuclides.**

The CNRS is widely involved in life-sciences research. IN2P3 contributes significantly to this effort with 11 laboratories, around 75 permanent researchers and 60 PhDs and post-docs involved (average number over the past decade 2015 - 2024). Within this frame, the research teams carry out a wide variety of activities that share a common goal: the use of ionizing radiation to observe and understand living organisms and use this radiation notably for therapeutic purposes (e.g. in the fight against cancer). These activities rely on the unique skills of the teams and services of the IN2P3 laboratories: on the modelling of fundamental interactions between the elementary constituents of matter and the biological environment, on the production of beams and radionuclides, and on the associated instrumentation for radiation detection (imaging) and monitoring (dosimetry). Several teams of biologists and clinicians have joined IN2P3 laboratories (e.g. LP2IB in Gradignan, IP2I in Lyon, LPC in Clermont-Ferrand and Caen, IPHC in Strasbourg...) and reinforce the available expertise to conduct relevant research related to health. All research projects are today brought together in a single IN2P3-research program, entitled ”Innovative Nuclear Techniques for Health (INTH)”.

Regarding **imaging**, the main achievements include preclinical molecular imaging and portal clinical imaging, new techniques for X-ray, gamma-ray and particle imaging: photon counting, time-of-flight Positron Emission Tomography (ToF-PET) and Single Photon Emission Tomography (SPECT) including Compton imaging, proton radiography, and novel approaches for quantitative reconstruction.

Radiobiology activities are dedicated to the development of tools and methods for biological data acquisition within a network of national irradiation facilities, and to the development of biophysical models to understand and predict the effects of irradiation, in relation to clinical applications.

Radiotherapy-related activities aim at optimizing the therapeutic efficiency, by means of beam monitoring, dose control and prediction. In particular, new challenges have raised during the last decade, concerning radiation delivery modes (FLASH therapy, Targeted therapies, and various ions for particle therapy). Online control and appropriate evaluation of the physical dose require innovative instrumentations and models.

Last, **radionuclide research activities** have emerged with the launch of ARRONAX, CYRCé, Ganil, IJClab and other platforms outside IN2P3 in particular for the production of new radiotracers, and study of their use for imaging and/or therapy.

The IN2P3 teams'activities are part of the national **GDR MI2B (Nuclear Tools and Methods for Cancer Treatment, formerly Instrumentation and Modeling for Biomedical Imaging) under CNRS governance**. The MI2B Research Group (GDR MI2B) was created in 2004 at the initiative of IN2P3, with the aim of clearly identifying interdisciplinary research within the Institute. Since then, it has been structured around scientific divisions, and **now extends beyond the boundaries of IN2P3, with the participation of laboratories from CNRS-Biologie (with its deputy director), CNRS-Informatique, CNRS-Ingénierie, CNRS-Physique, and Inserm, the National Institute for Medical Research. Connections also exist with societies such as the French Society of Medical Physics (SFPM) and the French Society of Radiation Biology (SFBR)**.

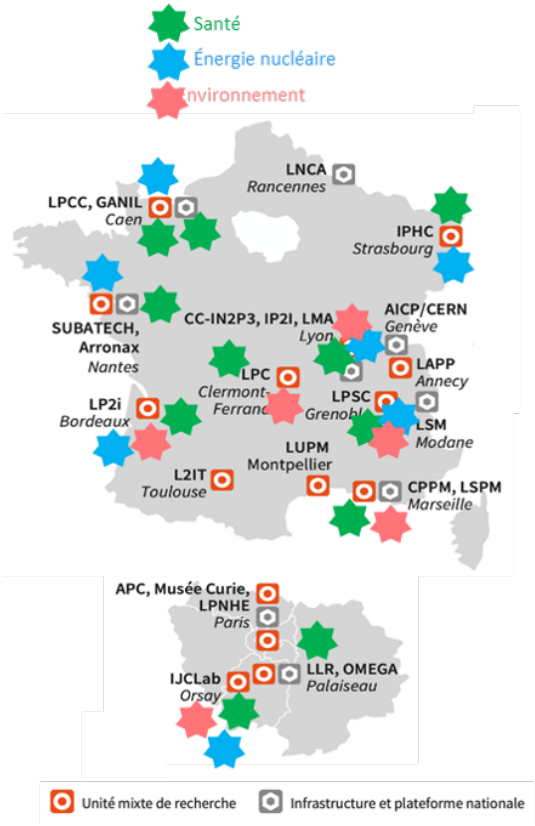


Figure 1.1: IN2P3 laboratories involved in interdisciplinary research

Locally, teams are part of University division, Labex (PRIMES, IRON), IDEX, EQUIPEX (RECHadron).

1.2.1 Scientific challenges

The wide range of scientific expertise of IN2P3 research teams makes possible to meet major challenges covering the fields of physics for innovative radiotherapies, biomedical imaging, models and methods for radiobiology and medicine, and radionuclides for imaging and radiotherapy.

1.2.1.1 Physics for innovative radiotherapies

The main objective is to infer new irradiation modalities in order to improve the therapeutic efficiency of radiotherapy, and develop related tools for dosimetry and treatment control.

The challenges addressed by novel radiotherapy modalities are connected to:

- temporal fractionation (FLASH irradiation) and associated radiobiology;
- spatial fractionation: micro- and mini-beams and associated radiobiology (Micro or Mini Beam Radiation therapy);
- tumour targeting and dose optimization: targeted radionuclide radiotherapy, ballistic precision in hadrontherapy, neutron-capture therapy, radio-sensitising nanoparticles, radioactive ion beams;
- the radiation quality: France will propose a unique offer for various irradiation modalities: protons and light ions (in particular carbon), photons from synchrotron X-rays to high-energy, pulsed beams of

very high energy electrons, alpha- and beta-radioisotopes, neutron sources. Each of these modalities presents challenges for radiobiology and for a versatile dosimetry;
- the prediction of the radiobiological effectiveness of radiation through multi-scale simulations and models: Geant4 and their dedicated toolkits Geant4-DNA and GATE, biophysical models as NanOx;
- the need for online, and possibly real-time control of the treatment quality;
- the development of strategies for patient-data based models for personalized treatment efficiency modelling;
- the acquisition of nuclear data to improve the precision of the effective dose during hadrontherapy treatments.

Such questions are addressed worldwide. IN2P3 teams are strongly involved in the ENLIGHT European network (European Network for LIGht ion Hadron Therapy coordinated by CERN) for ion therapy, and participate in the newly emerging International Biophysics Collaboration. There is a favorable national context with irradiation facilities favoring a research organization including clinicians, biologists, instrumentalists, physicists, imaging scientists...

1.2.1.2 Biomedical imaging

Imaging in medicine is nowadays an essential tool in the diagnosis, interventional medicine and follow-up of patients towards an increasingly personalized medicine. Research in the field aims at improving existing techniques (e.g. using scintillators and photosensors, by improving detection, acquisition and reconstruction strategies), or developing innovative ones, by exploiting the expertise acquired in core-experiments of the Institute.

At the international level, technological developments in PET imaging aim at increasing the field of view of cameras, improving time-of-flight measurement and measuring the depth of interaction in crystals to improve the image reconstruction. Various teams at IN2P3 are bringing important impact on improving the sensitivity and reducing the doses received by patients in clinical and preclinical PET and SPECT scans, or by innovative 3-gamma imaging (XEMIS). The search for better coincidence time resolution (CTR) in PET, will improve the signal-to-noise ratio, and ultimately allow a direct 3D volume representation of the distribution of a radiopharmaceutical activity at the millimeter level. Compton imaging can improve detection efficiency with respect to conventional SPECT cameras, which deserves further investigation. A positron probe (MAPSSIC project) for functional imaging of the brain of vigil rats answers both challenges of dose reduction and miniaturization: it will provide pharmacological and physiological information related to neuroscience by combining behavioral analysis and imaging in free-moving rodents.

The developments of new imaging techniques result in most cases from local collaborations. The ClearMind project has been dedicated to improving the CTR of PET detectors. France has also participated in the European FAST (Fast Advanced Scintillator Timing) action on costs, and part of the R&D carried out in this area was discussed within the CERN Crystal Clear collaboration, which involves a number of French laboratories, including the CPPM at IN2P3.

1.2.1.3 Models and methods for radiobiology and medicine

The study of the mechanisms involved in the interactions of ionizing radiation with the biological medium remains a major challenge in current radiobiology, particularly in the context of studying new approaches in radiation therapy, but also for space radiation protection purposes.

Significant efforts are made at IN2P3 to develop tools, methods, models and simulations to help biologists in their quest to understand the effects induced by ionizing radiation on living matter. Over the past years, modalities of action were based on two topics: (i) the acquisition of physical, chemical and biological data, with common protocols but under multiple conditions (dose delivery mode, environment, cell lines);

(ii) the development of biophysical models to synthesize, understand and predict the effects as a function of irradiation (dose, particle, energy, dose rate), in individuals or cell lines.

Radiation biology experiments are deeply transdisciplinary and require access to ion beams, electron beams (VHEE - Very High Energy Electrons), Laser Plasma accelerators ... for experimentation on cells and even more on animals with dedicated facilities:

- for light ions, **access to research platforms** at Bordeaux (AIFIRA), Orsay (ALTO), Nantes (ARRONAX), Strasbourg (PRECY), and clinical platforms such as Nice and Orsay (Institut Curie); for carbon ions at GANIL (Caen, cells only), CNAO (Italy, cells and animals) and NIRS (Japan, cells and animals); complementary reference irradiations with X-rays are performed via **long-term collaborations between IN2P3 and local medical facilities** (Bordeaux, Caen, Grenoble, Lyon, Nantes, Nice, Orsay, Strasbourg, . . .);

Several national and international initiatives for coordination are emerging with ongoing (CAL, CNAO, ASNR) or planned framework agreements (Inserm):

- the International Biophysics Collaboration through the future availability of the FAIR accelerator at GSI, in coordination with European facilities. In this context, the European Space Agency (ESA) wants to complete nuclear databases for space, through especially the IBER (Investigations into Biological Effects of the Radiation) project, in collaboration with the GSI Biophysics department. The FOOT (FragmentatiOn Of Target) collaboration is planning to measure cross-sections of interest for space and hadrontherapy at low energies. Complementary beam-time for hadrontherapy may be available when the carbon and light-ion beams of ARCHADE (C400) will be accelerated. Coordination of experimental efforts, data evaluation, model improvements and clinical/radioprotection applications will be undertaken.
- for simulation an international collaboration has developed the first toolkit for early DNA damage prediction — the Geant4-DNA toolkit — which is fully open-source and seamlessly integrated into the general-purpose Monte Carlo platform Geant4. Additionally, GATE, also built on Geant4, provides advanced simulation tools for medical imaging, radiotherapy, and radiation physics.

  At the national level, IN2P3 supports irradiation facilities through their networking thanks to their complementary and original performances (AIFIRA, ALTO, ARRONAX, CYRCé); in addition, IN2P3 will follow in details the developments around ARCHADE center (carbon and light ion beams up to 400 MeV/u).

1.2.1.4 Radionuclides for imaging and radiotherapy

The **theranostic approach** aims at developing personalized treatments based **on the vectorization of nuclear medicine probes** to address new targets by using vectors (e.g. peptides, antibodies, etc.) carrying radiation emitting isotopes (alpha, beta, positrons, Auger electrons) used for therapy (e.g. Lutathera developed by the AAA company, which combines ^{68}Ga for imaging and ^{177}Lu for therapy). It is then interesting to develop combinations of pairs or triplets of isotopes allowing to combine therapy with low / high Linear Energy Transfer (LET) radiation emitters and imaging with positron / gamma ray emitters. This implies **to develop new radioisotopes with high purity** and to produce those in large quantities. For this, one needs to develop **high-power, high-intensity target systems** for beam irradiations.

French teams are involved at ARRONAX, CEMHTI, CYRCé, ILL and Medicis at CERN, which are acting together in the field of producing emerging radioisotopes (e.g. ^{44}Sc, ^{64}Cu, ^{89}Zr, ^{149}Tb, ^{211}At, etc.). At the European level, there is an emerging community focusing on radioelements production for research called PRISMAP. As an example, ARRONAX, Subatech, CERN and GANIL are already working on astatine, in connection with Inserm units and hospitals. As a complement to accelerators, neutron beams are useful for radioelement production as what can be imagined at SPIRAL2 (CANS project for compact accelerator neutron source).

1.2.1.5 Biophysical and chemical characterization

The long-standing expertise of IN2P3 research teams around light-ion beams has strongly encouraged the emergence of areas of research ranging from fundamental measurements to healthcare and environmental problematics.

Irradiation of biomolecules: data on biomolecules (e.g. ionization and fragmentation cross-sections, radiochemical yields) under irradiation by ions are necessary to implement Monte Carlo models (e.g. Gean4-DNA) and to cross-check the predictions of theoretical models used in hadrontherapy and radioprotection (e.g. for future space missions).

Nuclear microprobe analysis: one of the main applications of nuclear microprobe is the ability to reveal in routine the two-dimensional elemental maps of a sample by scanning a highly focused ion beam and monitoring the X-rays produced by the chemical elements. The interaction of charged particles and matter provides quantitative information on its chemical composition. **These characteristics make the nuclear microprobe analysis a multi-elemental, quantitative, sensitive, and non-destructive powerful tool to investigate the composition techniques at the cellular scale of biological specimens**. Nuclear microprobe analysis has led to a better understanding of the role and/or toxicity of metals in neurobiology, the impact of intracellular metal/metal-oxide nanoparticle homeostasis on living organisms, their potential use as radiosensitizers and the optimization of biomaterials. Finally, the fine analysis of geochemical analogues has led to a better description of the conditions of formation of primitive life on Earth.

1.2.2 Main scientific projects and activities

Health-oriented research projects are more specifically often driven by short-term grants (2-4 years) and local multidisciplinary collaborations. However, the scientific strategy of IN2P3 makes possible to identify longer-term objectives, in particular thanks to the development of common tools and equipments.

1.2.2.1 Physics for innovative radiotherapies

New dose-delivery modalities are emerging, among which IN2P3 teams play a leading role: spatial fractionation with the use of microbeams of synchrotron radiation; **high dose-rate temporal fractionation** (FLASH therapy with X-rays, electrons, ions) has proven efficient healthy tissue sparing. It is rapidly developing, but still requires extensive understanding of the underlying biochemical mechanisms, both theoretically and experimentally, and dedicated instrumentation for dosimetry: the development of FLASH irradiation is one of the objectives of ARRONAX and CYRCé platforms. Similarly, **hadrontherapy** with protons, alpha and carbon ions, require **basic physical data** (fragmentation cross sections) and radiobiological data for implementing **biophysics models** such as NanOx and Geant4-DNA, and improving the precision of online range verification by secondary emission. Various irradiation modes will be studied in a complementary and comprehensive way: external with protons, alpha particles (Arronax, next BioALTO, AIFIRA), carbon ions (presently in GANIL, CNAO and Japan, next at ARCHADE), radioactive ions at GANIL (alpha, beta+/- emitters for dose enhancement and theranostics), **VHEE**, and internal with **targeted radionuclide therapies**, stimulated by innovative radioisotope production at ARRONAX and other sources, **accelerator-based Boron Neutron Capture Therapy (AB-BNCT)**, for which improvement in intense neutron production and dose modeling is being developed at LPSC, and nanoparticle radiosensitizers that are studied by several groups. Combined therapies (immuno- and radiotherapy, radio and hadrontherapy...) are studied in the frame of collaborative projects with clinicians and biologists.

Specific instrumental and model developments are required:

- **beam monitors:** several strategies are studied at ARRONAX (air fluorescence technique using photomultiplier tubes – PMTs), LPC-Caen (in collaboration with CPO), LLR (Pepites project,) LPSC (DIAMANT projects) to meet the requirements of **FLASH irradiation:** a few Gy delivered within short time,

from 40 Gy/s up to 1MGy/s in less than 1 s, whatever the type of radiation. They concern detector material and electronic issues. These studies involve the ARRONAX and CYRCé irradiation platforms. Additional challenges arise from **spatial fractionation** (microbeams at X-ray synchrotrons), and **fast timing** for treatment verification (diamond detectors: DIAMANT project). Microdosimeters for particle therapy are under development at IJCLab (3D-silicon arrays) and LP2I Bordeaux (thin diamond arrays);
- **online control of innovative radiotherapies:** the **THIDOS project** (IJCLab) consists of a gamma camera for iodine-131 beta targeted therapy. For hadrontherapy, prompt-gamma **range verification** (CLaRyS collaboration IP2I, CPPM, LPSC) explored several prompt-gamma detection modalities (Compton and collimated cameras, integral counting), which led to new projects like **TIARA - ERC PGTI** (LPSC, CPPM CAL Nice - 3D time-of-flight-based imaging) and CLARYS-S2C2 (LPSC, IP2I, CAL, CREATIS) dedicated to pulsed-synchrotron beams.

1.2.2.2 Biomedical imaging

For the improvement of CTR in PET imaging, special attention must be paid to each link in the detection chain (crystal sensitivity, light collection, photodetectors, detection of Cherenkov light, development of metamaterials with quantum dots or nano-chips and scintillation properties...). A dedicated R&D program in the field of **instrumentation for fast timing applications**, making use of the IN2P3 technical knowledge, should be stimulated by the ongoing "10 ps challenge".

The **IMOP project** for interventional imaging launched in 2012, had led to a clinical trial starting in 2020 and the complete prototype will be delivered in 2025.

The XEMIS2 camera for small animals is now constructed and installed at the CHU of Nantes. It should be operational by the end of 2025 (commissioning). In the longer term, it is envisaged to build a **XEMIS3 camera for diagnostic imaging of humans** in cancerology.

A strategic reflection of interdisciplinary research with **Compton imaging**, stimulated by medical applications, should be undertaken at IN2P3 with partners from the medical imaging community, involving instrumentation, reconstruction and application aspects.

1.2.2.3 Models and methods for radiobiology and medicine

The proposed scientific program must favor strong interactions between fundamental researchers at IN2P3 (physics, biology, mathematics, computing sciences, chemistry...) and clinicians (medical physics and oncology) and will offer the opportunity to:
- **characterize the energy deposit at different biological levels** (from macromolecules, mitochondria, cell, tissue to the whole organism), and time scales using new and emerging numeric simulation codes and model organisms; simulation of the physical, physicochemical and chemical stages of radiation-induced damage at multiscale levels using multimodal approach (GATE, Geant4-DNA, Nanox,...);
- **optimize predictive capabilities that would improve both the accuracy of radiation therapy as well as the estimation of their risks** (side-effects, cancer) and **radioprotection models**. It will include biological and clinical data modeling, statistical physics and algorithms development to deal with high data volume from biological or clinical applications;
- improve **the radiation dose response within different dose delivery modalities** (from low to high dose, Bragg peak, vectorized alpha therapies ...) **and also help understand their consequences in oncogenesis**;
- **validate a multidisciplinary and multimodal approach integrating the chain of physical, chemical and biological events** triggered by well-characterized irradiation conditions within emerging cancer models (such as spheroids-3D models, C. elegans...);

- test the molecular basis of **new emerging radiation therapy protocols** (hadrontherapy with various light ion species, FLASH, high-Z nanoparticles, targeted alpha therapy, immunotherapies).

1.2.2.4 Radionuclides for imaging and radiotherapy

The development of radioisotopes for new theranostic approaches can be subdivided into five research and development activities:

- research for **alternative production pathways of theranostic pairs** (e.g. ^{64}Cu/^{67}Cu, ^{44}Sc/^{47}Sc, ^{152}Tb/^{149}Tb, ^{203}Pb/^{212}Pb, etc.).
- identification and production of **high LET radioactive emitters** (e.g. alpha-emitters ^{225}Ac, ^{211}At, etc. or Auger electron-emitters ^{97}Ru, ^{103}Re, etc.).
- study of the **chemical properties** of these radionuclides in view of their absorption in molecular vectors
- development of **high power targetry**.
- development and exploitation of **isotope mass separator** (e.g. ISOLDE at CERN) and **laser ionization** techniques to get high purity isotopes.

1.2.2.5 Biophysical and chemical characterization

IN2P3 expertise in light ion-beam analysis will contribute to the emergence of healthcare problematics.

Radiolysis of biomolecules: It is proposed to develop an experimental setup based on mass spectrometry and molecular jets to study radiolysis of biomolecules by accelerated ions operated at ARRONAX and then later on the IN2P3 platforms.

Nuclear microprobe: Despite the routine use of nuclear microprobe analysis methods, a number of points are under development to improve the data acquisition in terms of quality and quantity:

- correlative and 3D imaging methods need improvement both in terms of sample preparation, data recording and image reconstruction accuracy. These developments will have potential future medical applications (protontherapy);
- data processing, analysis and archiving need to move towards greater possibilities of meta-analysis and data archiving compatible with international standards;
- to elucidate the impact of inorganic physiology on cellular processes, the aim is to associate in the future the chemical element quantitative composition, the tissue-specific functionality with genomic information by taking advantage of well-characterized multicellular organisms (such as C. elegans).

1.2.3 International collaboration

Table 1.1 gives the results of a survey conducted in 2024 by S. Incerti (IN2P3 teams) on international collaborations.

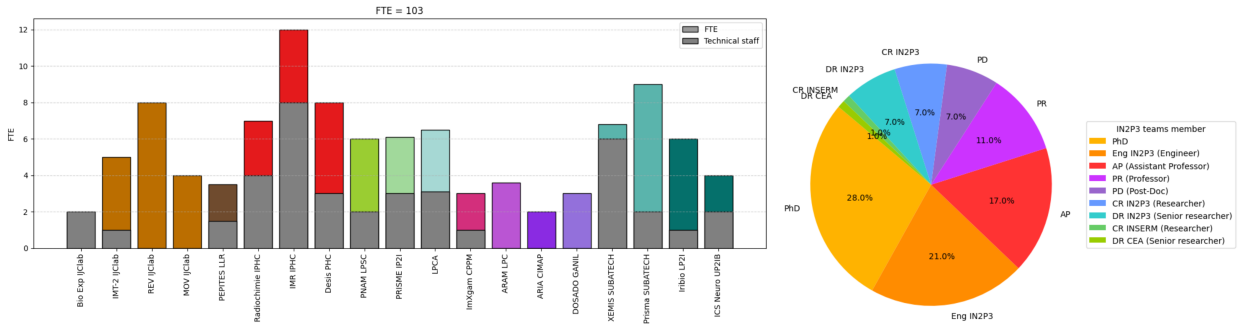
1.2.4 Human and financial resources

1.2.4.1 Human ressources

This distribution by professional category reveals, among permanent staff, a notably high proportion of technical personnel, highlighting the strong engagement of teams in detector instrumentation and software development. These aspects will be further explored in Chapter 4. Additionally, the number of teaching and research faculty is observed to be twice that of CNRS research staff. Lastly, the significant presence of non-permanent members, such as PhD students and postdoctoral researchers, reflects the dynamic and evolving nature of our field.

Country	Institution	Topic
EU	PRISMAP, EURADOS	Radionuclide production, dosimetry
Italy	INFN	FOOT-Xn (FOOT collaboration), radionuclide production
	CNAO	FOOT-Xn, ANR CLINM, carbon ion radiobiology
Switzerland	CERN	imXgam: R&D detectors
	Transmutex	
Spain	University of Granada	Radionuclide production
	University of Seville	BNCT modeling
	CSIC Valencia	R&D Compton camera
Belgium	Univ Leuven	Proton FLASH
UK	Imperial College	Lhara: laser acceleration for medical use
Germany	GSI	Hadrontherapy monitoring with CMOS sensors
Argentina	University of Rosario	Atomic and molecular theoretical physics
	CNEA Buenos Aires	BNCT
Australia	Ansto	Microbeam radiotherapy
Japan	NIRS	Radiobiology
	AIST – Tsukuba	Diamond detectors
USA	NASA	IEA project: DNA break modeling

Table 1.1: Institutions and projects related to radiobiology and associated therapies



(A) **(B)**

Figure 1.2: FTEs for Health Teams across IN2P3 laboratories – permanent staff only (A); staff distribution across teams (B).

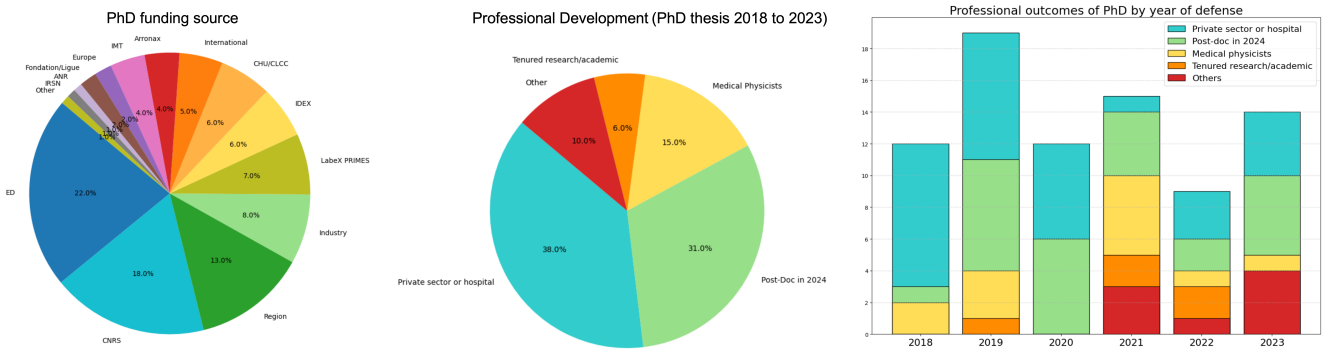
1.2.4.2 Financial ressources

Aside from funding from CNRS (MITI), IN2P3 (mostly core funding for teams), LabEx (PRIMES, IRON...), and Universities (IDEX, doctoral school), **most of teams' resources come from responses to various CfPs** (e.g ANR, PCSI, ERC, ...). This facilitates collaborations at local, national, and international levels, often across multiple disciplines, bringing together various areas of expertise. However, this also leads to the individualization of projects and challenges in maintaining long-term strategies. Funding supports the development of detectors, modeling software, beamline testing, and enables the recruitment of PhD students, postdocs, and contract engineers, providing the human resources necessary to support both research teams and technical services within the laboratories.

All of the projects are driven by a common objective: the development of innovative tools and methodologies to enhance the fight against cancer. Since each project is limited in time due to funding mechanisms, specific scientific objectives and development requirements are defined at the time of proposal submission in collaboration with clinical representatives (university hospitals, hadron therapy centers, veterinary clinics, etc.) and major research facilities. As highlighted later in this overview, some projects run concurrently without dedicated CfPs, while others interconnect. Some continue through successive CfPs

as part of a strategic approach, each time progressing based on achieved milestones. The ultimate goal is to demonstrate the real added value of teams' research compared to existing solutions in clinical settings. In some cases, this effort extends to patent filings which is particularly complex in healthcare due to strict facility certification standards.

1.2.5 Publications, PhD Defense



(A) **(B)** **(C)**

Figure 1.3: PhD funding sources (A) and Professional outcomes of PhD's over 2018-2023 (B) and by year of dissertation defense (C). Source: survey conducted in 2024 through the GDR MI2B.

The number of publications by all the teams working on the Health theme at IN2P3 has reached ∼700, led to more than 80 PhD defenses, with about thirty currently in progress, and 10 habilitation defenses (HDR – Habilitation à Diriger des Recherches) on the last 10 years.

In 2024, the GDR MI2B conducted a survey (focus on years 2018-2024) on the future prospects of PhD students affiliated with the GDR. This survey aimed to identify a talent pool in the challenging recruitment context at IN2P3, characterized on one hand by abundant PhD funding opportunities, and on the other by a low number of PhD graduates remaining in academia, with some postdoctoral positions extending over unusually long durations.

This survey is therefore not limited to IN2P3 teams alone (whose members account for approximately 53% of the entire GDR), but includes all the groups that make up the GDR (see Figure 1.4 in the next section dedicated to GDR MI2B to have an overview of the distribution according to research Institutes). Nevertheless, it provides an overview of the distribution by PhD funding sources and future employment sector of PhD students in our research theme illustrated in Figure 1.3.

1.3 The GDR MI2B, a structuring animation tool for research in the field of Health at the CNRS in conjunction with other research organizations.

1.3.1 Mission and Objectives

The primary objective of the GDR is to foster dialogue and promote new methodological and instrumental approaches in the field of nuclear health for diagnosis and therapy. It also aims to encourage the creation of interdisciplinary collaborations, support and train young researchers and engineers, and strengthen the connections between research stakeholders and irradiation platforms.

The main scientific topics addressed include molecular imaging, innovative therapies (both external and internal), radionuclides related to theranostic approaches, and key challenges in radiobiology.

To maintain national coherence and a shared ambition, The mission of the GDR , initiated by IN2P3, the is to animate a broad scientific and interdisciplinary community working in the field of

nuclear methods for health, including all the research in this field at the Institute. The GDR fosters the community engagement, animates scientific interaction to promote new methodological and instrumental approaches in the field of radiation physics for diagnosis and therapy.

Throughout the year, the GDR MI2B organizes meetings that bring together researchers from various backgrounds to discuss and debate scientific issues related to nuclear physics for Health. In this way, **the GDR sets up a national scientific framework to intensify research efforts in this field**.

Through its unifying role, the GDR aims to stimulate the emergence of new collaborative projects. **These go beyond the boundaries of IN2P3, which is why the GDR has, since its inception, opened widely to teams from the CNRS-Biologie (with its deputy director),CNRS Ingénierie, CNRS-Informatique, CNRS-Physique, as well as Inserm and ASNR. Connections also exist with the SFPM and SFRB.**

1.3.2 Scientific organization

IN2P3, founding member of the GDR, contributes to technological and knowledge advancement in nuclear applications for Health. The current challenges—tackled by teams often in multidisciplinary collaboration with other CNRS Institutes or Research organizations—aim primarily at early disease diagnosis and increasingly personalized therapies.

The GDR is organized into four thematic divisions:

- Methods and Instruments in Biomedical Imaging
- Physical Tools and Methods for Innovative Radiotherapies
- Radiation Effects on Living Organisms
- Radionuclides for Imaging and Therapy

And five cross-cutting themes:

- Biology
- Clinical Application
- Computing
- Instrumentation
- Irradiation Platforms

1.3.2.1 Methods and Instruments in Biomedical Imaging

Current clinical imaging challenges focus on early diagnosis and personalized patient treatment. In preclinical imaging, the focus is on accelerating the development of new theranostic agents. The development and widespread adoption of quantitative, multi-parametric molecular imaging techniques are key solutions. This requires significantly improving the sensitivity of molecular imaging, reducing associated doses, developing integrated multimodal systems, and specialized imaging devices tailored to specific organs (heart, breast, prostate, etc.) or applications (surgical/radiotherapy treatment guidance, small animal models), and improving patient accessibility.

The GDR MI2B imaging division addresses these major challenges through:

- high-sensitivity multimodal diagnostic imaging (Time-of-Flight PET, hybrid PET/CT and PET/MRI, 3-gamma imaging, photon-counting and spectral CT),
- treatment planning (proton tomography),
- image-guided therapy (prompt gamma imaging in hadrontherapy, intraoperative imaging),
- preclinical imaging (demonstrators, multimodal platforms, hybrid imaging, intracranial probes for imaging in awake animals).

These developments are driven by technical challenges in nuclear and particle physics such as tracking, calorimetry, data acquisition, processing, and Monte Carlo simulations. Strong synergies emerge with IN2P3's core activities. These projects often require interdisciplinary collaborations due to their complexity.

1.3.2.2 Physical Tools and Methods for Innovative Radiotherapies

This division focuses on improving the therapeutic index of radiation treatments—maximizing tumor control while minimizing damage to healthy tissue. Healthy tissue tolerance remains a limiting factor in delivering curative doses. Topics include:

- quality control of dose delivery,
- innovative dose delivery modes (energy, position, timing),
- optimization of treatment planning.

Quality control involves improving the dose differential between tumor and healthy tissue. Beam monitors for therapy and radiobiology are being developed, as well as in-line dose deposition monitoring in hadrontherapy using secondary particles (beta+, gamma, protons, etc.).

Innovative dose delivery modes explore spatial and temporal fractionation and ultra-high dose rates. This requires beam production studies (small fields with high intensity) and suitable dosimetry tools and protocols. Treatment planning optimization aims to reduce safety margins by improving physical/anatomical input data. This includes pre-treatment imaging and basic data collection (cross-sections, dosimetry) to refine or develop models.

1.3.2.3 Radiation Effects on Living Organisms

This GDR pole is driven by biologists for the experimental part, the physicists of IN2P3 intervene on the control of irradiations and biophysical modeling.

Technical platforms and multidisciplinary collaborations have been built. Current radiobiology themes include:

- optimizing radiotherapy protocols (proton/hadrontherapy), and developing innovative therapies (e.g., nanomedicine); including studies on radiosensitivity and tumor radioresistance mechanisms, and identification of biomarkers for estimating individual/population-specific radiation risks.
- understanding the mechanisms (physical, chemical, biological, epigenetic) at low dose exposure levels across individuals, populations, and generations (transgenerational effects, epigenetics). These studies involve controlled exposures and analysis across various organisms and dose levels.
- contributing to predictive modeling of biological responses using ”Big Data” from imaging, biomarkers, irradiation parameters, chemical agents, and tumor microenvironment information.
- estimating molecular to whole-body effects based on different dose delivery modalities.
- understanding therapeutic exposure mechanisms and associated side effects from low doses.
- risk assessment of various radiotherapy protocols.

1.3.2.4 Radionuclides for Imaging and Therapy

Radionuclides are crucial in molecular imaging (PET, SPECT) for neurology and oncology, and in cancer therapy. This requires developing innovative radiopharmaceuticals and transitioning them to clinical use. These contribute to precision medicine by tailoring therapy to disease stage and patient response. The division seeks to:

- stimulate research on innovative theranostic radionuclides,
- increase radionuclide and radiopharmaceutical availability for early-phase clinical trials.
  Key research questions include:
- which innovative radionuclides to promote?
- which biological agents for selective targeting?
- how to stably attach radionuclides to biological vectors? Availability depends on partners’ capacity to produce sufficient quality/quantity.

The five transversal themes—biology, clinical applications, computing, instrumentation, and irradiation platforms—are addressed across all divisions. With the GDR's renewal on January 2025, focus will be made on:

- computing: data storage, patient data ethics, open-source deployment, AI.
- instrumentation: innovation and transition of research tools into clinical practice.
- irradiation Platforms: partnerships with IN2P3 and external centers like ARCHADE, CLCCs, or CHUs to enhance access.

1.3.3 Governance

Over the period 2015 (date of the previous evaluation of Health activity by the Scientific Council of IN2P3) - 2025, the governance of the GDR was ensured by Dr David Brasse (IPHC Strasbourg) until 2020 then by Dr Denis Dauvergne (LPSC Grenoble) until 2024.

The Steering Committee manages scientific divisions and cross-cutting themes. It includes the GDR director, her deputy, and division heads.

Role	**Name(s) and Affiliation(s)**
Director / Deputy Director	Marie-Laure Gallin-Martel (LPSC – IN2P3), Lucie Sancey (IAB – CNRS-Biology)
Division Heads	
Imaging	Marc-Antoine Verdier (IJClab – IN2P3), Mathieu Dupont (CPPM – IN2P3)
Radiotherapy	Rachel Delorme (LPSC – IN2P3), Jean Michel Létang (CREATIS – CNRS-Engineering)
Radiation Effects	Mathilde Badoual (IJClab – IN2P3), Michael Beuve (IP2I Lyon – IN2P3), Patrick Vernet (LPCA – IN2P3), Lucie Sancey (IAB – CNRS-Biology)
Radionuclides	Ferid Haddad (SUBATECH – IN2P3 / GIP ARRONAX), Ali Ouadi (IPHC – IN2P3)
Cross-cutting Themes	
Biology	Lucie Sancey (IAB – CNRS-Biology), François Paris (Inserm)
Clinical Applications	Juliette Thariat (LPC – IN2P3 CHB – Caen)
Computing	Lydia Maigne (LPCA – IN2P3), Jean Michel Létang (CREATIS - CNRS - Engineering)
Instrumentation	Mathieu Dupont (CPPM - IN2P3)
Irradiation Platforms	Charbel Koumeir (SUBATECH – IN2P3 / GIP ARRONAX)
External Relations	
SFPM	Ludovic Ferrer
SFBR	Julie Costanzo
Inserm	Jean-François Paris

Table 1.2: Organizational Structure: Roles and Responsibilities in GDR MI2B

1.3.4 Budget, members, links with other Institutes, Academic Societies and Network in the field of Health

The annual budget amounts 20k€ financed, up to 2024, solely by IN2P3.

The GDR has 123 permanent members when it is renewed in January 2025.

More than 53% of the GDR MI2B members are from IN2P3 teams, illustrating their central role in the group's activities. In addition, a broad range of partner research institutes are represented, either through framework agreements between IN2P3 and other organizations—such as ASNR (formerly IRSN), Inserm, and others—or through interdisciplinary collaborations initiated by the CNRS Mission for Cross-disciplinary and Interdisciplinary Initiatives (CNRS-MITI) with other CNRS institutes (e.g., CNRS-Biology, CNRS-Chemistry, CNRS-Engineering, CNRS-Computer Science). Finally, the high proportion of non-permanent members (PhD students and postdoctoral researchers) relative to permanent staff reflects both

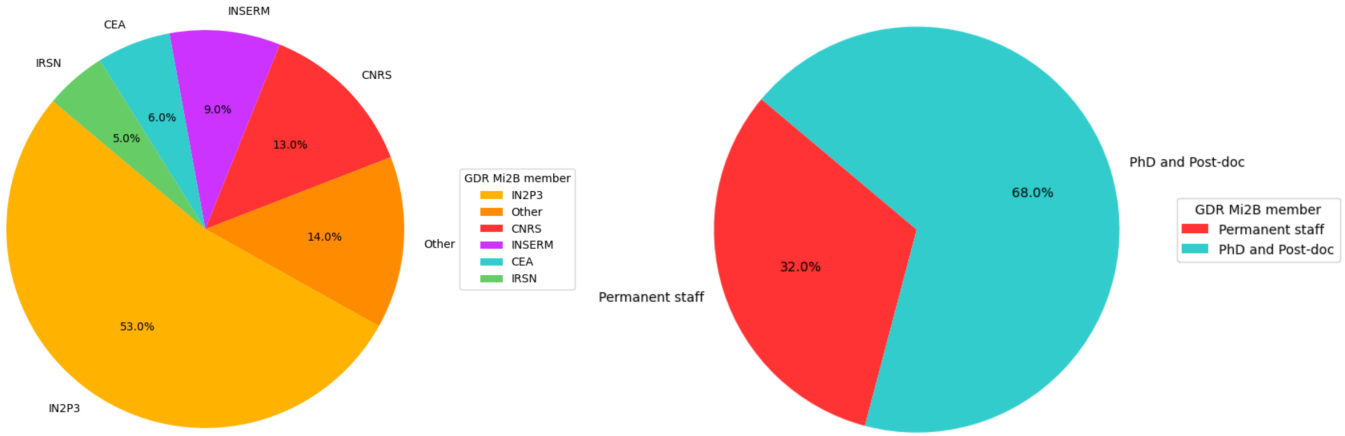


Figure 1.4: Distribution of members belonging to GDR MI2B: (left) by Research Institute, (right) between permanent and non-permanent staff (all Research Institutes merged).

a strong interest in our research domains and the key role played by our teams in training the next generation of scientists.

1.3.5 Communication, educational program and outreach

1.3.5.1 Website and Mailing Lists

Mailing list (280 members) shares:

- PhD, internship, job opportunities
- announcements: calls, seminars, workshops, defenses (online)
- separate list for MI2B group at CCIN2P3 and one in progress for RESPLANDIR

Website:

- hosts announcements
- links to INDICO event sites
- articles contributed by GDR members

1.3.5.2 Annual General Assembly, Symposium, and Workshops

In addition to the annual assembly, scientific meetings throughout the year allow cross-disciplinary discussion on nuclear-health topics.

1.3.5.3 Education and Training

Young researchers present at AGs (oral/poster), including with SFPM. Thematic school “Physics for Radiobiologists” (2024) is to be repeated every two years. A similar initiative is being considered for “Radiobiology for Physicists,” inspired by the 2024 Joliot-Curie school in Oléron. Potential partners: RADIOTRANSNET, SFBR.

1.3.5.4 Communication and Outreach

Links established with:

- **National:** learned societies (SFPM, SFBR), CNRS institutes, Inserm (e.g., alpha therapy group), ASNR (via framework agreements) and GDRs (e.g., SciPac, SciNEE, DI2I for instrumentation) with

IN2P3 governance but as well with GDR AIM (Molecular Imaging Agents) with CNRS-Chimie governance.

The GDRs SciPac (Science of Particle Accelerators) and SciNEE (Nuclear Sciences for Energy and the Environment), both established more recently than MI2B, share several common areas of interest. These include the development of irradiation platforms (networks, access conditions, digital twins, etc.) as well as the design of future accelerators (such as Laser Plasma Accelerators, PERLE, etc.). To foster synergies between their respective teams, a joint scientific workshop is planned for March 25–27, 2026, at LPSC Grenoble. This event will serve as a key starting point for structuring our future collaborative actions.
In the case of the GDR DI2I (Detectors and Instrumentation for the Two Infinities), the connection with MI2B lies primarily in instrumentation development. These activities—whether aimed at specific applications, demonstrations of emerging technological breakthroughs, or simply maintaining technological vigilance and expertise within IN2P3 research units—are enriched by the significant technical challenges of nuclear and particle physics: tracking, calorimetry, data acquisition, processing, and Monte Carlo simulations. As such, they have strong potential to generate synergies with the Institute's core scientific programs.
Regarding the GDR AIM, a convergence is underway, as common themes have been identified, notably the production of radionuclides and their use in targeted internal radiotherapy. Two joint workshops are planned in 2025, in the form of presentations at the respective annual meetings: in early July in Nantes for the GDR AIM, and in mid-November for the GDR MI2B. In the longer term (within three years), the GDR AIM could merge with the GDR MI2B. Discussions on this potential integration are currently ongoing between the leadership teams of both GDRs.

- **Local:** LabEx (PRIMES, Lyon 1), Federations (OLIMPICS, UGA), cancer centers (Institut Curie, CLB Lyon, CAL Nice, ...). The LabEx have been strongly supporting the GDR-related activities over the last deacade-and half. Although new LabEx were extended, in particular at IDEX sites, their financial support is significantly decreasing.
- **International:** CNAO (carbon therapy, Pavia), with potential expansion under IN2P3 bilateral agreements; other collaborations include Japan's NIRS and possibly INFN.

To summarize, the GDR advances nuclear-health technologies and knowledge. It is identified as the tool recognized by the IN2P3 to interact with the community. IN2P3's technical and scientific expertise drives its laboratories to contribute to life-science research. They offer knowledge in instrumentation, radiation and particle detection, beam monitoring, imaging, simulation, dose prediction, and accelerator technology. The 2020 contract opened cooperation with CNRS-biologie; since then, ASNR teams joined under framework agreements. Future partnerships may include Inserm, CEA, or ARCHADE.

The primary goals are early disease diagnosis and increasingly personalized therapies. To ensure national coherence and shared ambition, GDR MI2B supports IN2P3 and CNRS-biologie by uniting the community and promoting new methodological and instrumental approaches in nuclear-health for diagnosis and therapy. Its unifying role also encourages collaborative projects beyond IN2P3.

1.4 The current deployment of Master Projects (MP) in Health activities at IN2P3 through the GDR MI2B

At the beginning of 2025, following the renewal of the Institute's management, the research teams working on interdisciplinary topics (health, energy, environment) were invited to structure themselves at the national level into larger *Master Projects* (only 4 for Health). These projects are to be defined with clear scientific objectives, a strategic framework, key milestones, and a five-year timeline.

To better define the notion of a *Master Project* as understood within the IN2P3 for readers unfamiliar with the concept, we refer to an excerpt from the decree of April 29, 2016, concerning the IN2P3, cited in the ATRIUM document 390030 titled *"IN2P3 Project Governance"*:

"The Institute designs, coordinates, and leads national and international research programs within its fields of expertise." In practice, these research programs are implemented through research projects, some of which can be grouped into *Master Projects (MPs)*.

This definition can be further specified using excerpts from the document *"IN2P3 Project Handbook"*, ATRIUM reference 282506. It highlights that:

"A Master Project is generally managed by a Scientific Lead and a Technical Lead. This duo has complementary tasks and responsibilities. They are responsible for steering all the constituent research projects (or MP work packages). A project always involves contextual stakes, a clearly defined goal, expected outcomes (scientific, economic, societal, etc.), and a defined duration. It always brings together a consortium of teams around a shared objective. In addition to physicists, the project team also includes individuals from various professional backgrounds (especially for interdisciplinary topics), as well as technical services (IT, electronics, detectors, instrumentation, mechanics, etc.) from different and often multiple laboratories (at least two)."

In this context, the GDR MI2B organized two workshops in the form of general assemblies — on March 20, 2025 (https://lpsc-indico.in2p3.fr/event/4048/) and May 16, 2025 (https://lpsc-indico.in2p3.fr/event/4066/) — gathering all IN2P3 teams involved in the health domain (around 40 permanent members attending). The first workshop aimed to define four priority thematic areas to be structured and associated with existing or to-be-established partnerships. This discussion was based on the current and future relevance (particularly with the arrival in France of new infrastructures such as the C400 at the ARCHADE site in Caen) of deploying combined therapies and imaging in clinical settings for cancer treatment:

- External therapies using different ion types in hadron therapy: protons, carbon, alpha, oxygen...
- External therapies (e.g., X-rays or hadron therapy) with spatial (micro- or mini-beams) and/or temporal fragmentation (FLASH).
- Internal radiotherapy within the theranostic approach
- Combined external (X-ray or hadron therapy) and internal therapies (e.g. radionuclide therapy, BNCT...).

With the following scientific objectives:

- Significantly improving the effectiveness of treatments for cancers that are radioresistant, recurrent, therapeutically unresponsive, metastatic or diffuse, or detected at an advanced stage due to the absence of early biological markers, by combining particles with low and high LET.
- Enabling dose hypofractionation to achieve effective tumor volume reduction while minimizing damage to surrounding healthy tissues, improving treatment tolerance for patients.
- Moving toward evolving medical practices through theranostic approaches that combine therapy and diagnostics.

As a result, four research projects have been proposed:

- Hadrontherapy
- FLASH Therapies
- Targeted Radiotherapies
- Radionuclides for Therapy and Diagnostics

These would represent a vertical thematic structuring of our activities (MPs), complemented by a horizontal, matrix-based structuring into work packages (WPs). These WPs are aligned with our research domains (imaging, radiobiology, radiotherapy, radionuclide development, etc.) and supported by our expertise in nuclear physics and chemistry, in computing, instrumentation, irradiation platforms, as well as biology and clinical applications, both within IN2P3 and in our partner organizations. These collaborators, many of whom are part of the GDR MI2B and its associate leadership, already have established partnerships with us.

The second workshop, held recently, allowed for a refinement of these Master Projects, including the definition of their scope, stakes (via MP structuring), strategic approach, governance, and partner teams. This structuring is currently in progress at the time of writing and is expected to be finalized by the end of summer 2025, with a third workshop to be planned as part of the GDR MI2B's general assembly. This final phase will include the drafting of four scientific dossiers, each presented by their respective MP leads, featuring detailed schedules and milestones. These will be reviewed and discussed collectively in plenary session before submission to the IN2P3 management.

To conclude this first section, which provided an overview of Health-related activities at IN2P3, the outlines of these four master projects are summarized below to highlight the future direction of the organization.

1.4.1 MP Hadrontherapy

Challenges in hadrontherapy :

Treatment Planning
- Beam modeling: experimental characterization using monitors.
- Patient anatomy: HU-to-stopping power conversion.
- Dose calculation: physical dose (requiring knowledge of cross sections) and biological dose (radiobiological models, radiolysis).
- Dose calibration: measurements of dose and dose rate in water.

Treatments
- Beam monitoring: detector development
- Online control of hadron path: detector development and cross-section data acquisition

The overall objective is to gather data, develop models, and design detectors to enhance the precision of hadron therapy treatments.

Figure 1.5: The IN2P3 laboratories participating to the MP Hadrontherpy

Scientific objectives of the research program: this program aims to span from preclinical development ("bench to bedside") to clinical applications (in collaboration with Healthcare Institutions), within the framework of national and European protocols and translational research ("bedside to bench"), producing data to feed physical and biological models. Strong collaborations are underway between IN2P3 and CNRS-biologie, with a growing presence in Caen (C400 accelerator, multi-ion capabilities including FLASH hadron therapy; see the following chapter in present document), supported by national and international partnerships (e.g., "Hadrontherapy for Life" workshop in Caen, March 2025).

Multidisciplinary and multi-laboratories coordinating team:
- Sara Marcatili (LPSC Grenoble, Instrumentation),
- Claire Rodriguez-Lafrasse (IP2I Lyon, Radiobiology),
- Juliette Thariat (LPCC Caen, Clinical),
- Marie Vanstalle (IPHC Strasbourg, Phenomenology – cross sections).

MP structure (see figure 1.5 for list of involved IN2P3 teams):
- **WP1: Modeling of physical dose and clinicobiological response** (lead: Juliette Thariat, LPC Caen): use of NanOx for cell survival prediction from micro- and nanometric energy deposition maps and development of a BioDose Actor in GATE adapted to hadron therapy.
- **WP2: Measurement of nuclear and physico-chemical data** (lead: Marie Vanstalle, IPHC): includes secondary particle (charged and neutral) yield measurements in thick targets for hadron therapy and

space radioprotection (DeSIs, IPHC), measurements of radiolysis product yields (radioChemistry, IPHC), aiming to implement these data in Geant4-DNA/Geant4, and cross-section measurements for incident beam fragmentation.

- **WP3: Control of irradiation delivery** (lead: Sara Marcatili, LPSC): development of instrumentation and reconstruction methods to monitor the beam delivery, image the ion path via detection of secondary particles (e.g., prompt gammas) and provide absolute measurements of absorbed dose and dose rate in water.
- **WP4: In vivo measurements** (lead: Claire Rodriguez-Lafrasse, IP2I): biological response characterization to ion beams (protons, carbon, helium) in 2D and 3D tumor cell models and preclinical models (e.g., embryonated eggs or murine models), supporting biological validation of physical concepts. Objectives include improving biological dose calculations in simulations (e.g., Nanox, Geant4-DNA) and better characterizing the advantages of hadronic treatments for resistant and hypoxic tumors.

Transversal Task to all MPs (lead: M. Rousseau, LPC Caen, RESPLANDIR network manager): **coordination with the platform network** (see figure 1.6, non-exhaustive list).

External and international collaborations:

- WP1: CREATIS, LIRIS.
- WP2: QST-HIMAC (Japan), CNAO, INFN, GSI (Darmstadt, Germany).
- WP3: CAL Nice, CNAO, upcoming CYCLADE.
- ALL: CNAO (IN2P3-CNAO framework agreement), CNES, QST-HIMAC (Radiochemistry module), AERIAL-CRT, ICube, ICANS.

Figure 1.6: Map of platforms (not exhaustive)

Timeline: under development (initial proton beams for commissioning on the C400 are expected by late 2026).

1.4.2 MP FLASH therapies

Challenges in FLASH therapy: since the discovery of the Flash effect in 2014, which involved reduced toxicity to normal tissue at dose rates exceeding 40 Gy/s, research has continued to explore the factors that protect normal tissues. These investigations have combined different disciplines, including physics, chemistry, and biology, to establish the fundamental mechanisms involved.

Scientific Objectives of the Program: in the objective of explaining the mechanisms underlying FLASH effects. Radiobiological and radiolysis experiments will be developed mainly in ARRONAX (Nantes) for H^+ and He^{2+}, GANIL (Caen) for C-ion and Feerix (Strasbourg) for e^- and X-rays. The monitoring and the dosimetry will be developed in parallel to ensure the quality control process on all the beam lines. The development of the digital twins of the beam lines will be performed with the GATE Monte Carlo simulation platform. At the micro- and nano-scales the development and validation of the Geant4-DNA toolkit will be ensured.

Figure 1.7: The IN2P3 laboratories participating to the MP FLASH

Coordination Team: Lydia Maigne (LPCA), [Co-lead to be confirmed]

MP structure (see figure 1.7 for list of involved IN2P3 teams):

- **WP1: Quality control and dosimetry for UHDR beam lines (H^+, He^{2+}, C, e^-, X-rays)** (leads: Charbel Koumeir, GIP ARRONAX; Ziad El Bitar, IPHC): control of beam time structure, development of UHDR-specific instrumentation, dosimetry protocol validation for ions and electrons.
- **WP2: Effect of dose rate on experimental water radiolysis** (leads: Quentin Raffy, IPHC; Guillaume Blain): study of dose rate effects as a function of LET, the influence of the beam time structure, pH and O_2, until the study of the radiolysis of biomolecules.
- **WP3: Irradiation of cell populations** (leads: François Chevalier, CIMAP; Claire Rodriguez-Lafrasse, IP2I Lyon): analysis of dose rate effects based on LET and beam time structure, with attention to the influence of pH and O_2.
- **WP4: Multi-Scale Digital Twins** (leads: Lydia Maigne, LPCA; Nicolas Arbor, IPHC): simulation of beam lines using GATE 10, radiolysis chemistry with Geant4-DNA, biological damage with biophysical models, and creation of an open-access database.

Transversal Task to all the MPs (lead: M. Rousseau, LPC Caen): shared with the hadron therapy program – **coordination with platform networks.**

External and international collaborations:

- **Physics:** CNAO (Italy), ASRN (ex-IRSN, PIANOFORTE call), IFJ-PAN (Poland), C400 (Caen).
- **Chemistry:** QST-HIMAC (Japan), DKFZ (Germany), IBA (Belgium), Aerial-CRT (France).
- **Biology:** IFIN-HH (Romania), Institut Gustave Roussy, Institut Curie, DKFZ (Germany), IBA (Belgium).
- **Computing:** Geant4-DNA and OpenGATE collaborations.

Timeline: currently being defined at the time of writing this report.

1.4.3 MP Targeted Radiotherapies

Promising approaches for non-localized cancers

What is meant here by “Targeted RTs” are approaches that implies the intraveneous injection of a chemical vector enabling molecular targeting of cancer cells and produce either a fully internal irradiation, or a combination of external irradiation with an internal boost. This offers a solution for radioresistant, diffuse, micro-invasive, or metastatic cancers, where the ballistic precision of external radiotherapy alone is insufficient or not appropriate. We explore the following therapeutic strategies in this MP:

- Targeted Radionuclide Therapy (TRT): especially with α particles,
- Accelerator-Based Boron Neutron Capture Therapy (AB-BNCT): $^{10}B(n,^7Li)$ α,
- Photoactivation of high-Z nanoparticles (NPs) (Au, Pt, Gd...) and use of radiosensitizers

Figure 1.8: The IN2P3 laboratories participating to the MP Targeted Radiotherapies

Potentially highly aggressive internal irradiation, due to the local emission of high-LET particles, and heterogeneous distribution of the dose deposition (short range, vector distribution) could be achieve with such approaches, both aspects that have to be considered in modeling tools. Some of these therapies are already at the stage of clinical use, or tested in several clinical trials, but much remains to be understood and improved regarding

implementation in clinical routine, efficacy optimization and treatment control.

Overall objectives: the MP's contributions aim at optimizing therapeutic efficacy and improve personalized dosimetry through four main points: visualize vector biodistribution at macro and micro-scales, optimize dose delivery and irradiation control, determine the physical dose delivered and predict the biological response to treatment, understand the mechanisms underlying therapeutic efficacy, and how to quantify them.

Coordination Team: Rachel DELORME (LPSC) and Anne-Marie FRELIN (GANIL) [Biological co-lead to be confirmed]

Multidisciplinary collaborations: physics, informatics, biology, chemistry, and clinical fields.

MP Structure (see figure 1.8 for list of involved IN2P3 teams):

- **WP1: Multiscale modeling of physical dose and biolological response:** this include modeling tool developments to allow reproducing irradiation dose and damage predictions at the sub-cellular, cellular, and multicellular levels (2D and 3D), as well as preclinical and clinical modeling (in vivo, patient) to link biophysical modeling with clinical practice.
- **WP2: Optimization and control of dose delivery (preclinical and clinical):** this include optimization and characterization of neutron fields in BNCT by means of instrumental and modeling developments, control of dose delivery in in-vitro and preclinical radiobiology studies in TAT, control of clinical dose delivery in TRT to improve personalized dosimetry.
- **WP3: Understanding the Biological Mechanisms:** this aims to identify and quantify the specificity of targeted RTs in terms of therapeutic efficacy, passing by radiobiology studies for low-energy ions (involved in TAT and BNCT) under low-energy ion beams or in TAT/BNCT conditions, to study sub-cellular (nucleus, mitochondria, membrane...), cellular, and multicellular damage responses (immunogenicity, bystander...) to identify the relevant level of mechanisms to be considered (in models for example) for each therapies.

External and International Collaborations:

We are still at the stage of MP construction, the following gives a global idea of the already identified ones. At the national level, active collaborations were developed with several Inserm laboratories (e.g. LITO, LEDI, IRCM, IMoST, CRCI2NA...), especially around TAT, with other CNRS institutes as CNRS-Biologie (IAB, ISTCT...), CNRS Ingénierie et CNRS Sciences informatiques (CREATIS, LIRIS...), CNRS-Physique (CINaM, ISMO, CRAN), with ASNR (LMDN, LEDI), several clinical centers (Centre François Baclesse (Caen), CLCC Centre Jean Perrin (Clermont), CHUGA (Grenoble), Hopital Lyon Sud, IGR (Villejuif), Institut Cochin (Paris), IUCTO (Toulouse)...) and with industry (NanoH SAS...). At the international level, collaborations are active with CNAO (Italy), CNM-IMB and University of Granada (Spain), IFJ-PAN (Pologne), Korea, Sherbrooke and Melbourne Universities, Tandar (CNEA) and university of Buenos Aires (Argentine) and global networks as the BNCT-Global and the Open GATE collab.

Timeline: currently being defined.

1.4.4 MP Radionuclides for therapy and diagnostic

Challenges: in the recent years, there have been new developments in nuclear medicine with the approval of 2 radionuclide targeted therapies using lutetium-177 (neuro-endocrine tumors and prostate cancer) the rise interest on alpha emitters and more generally on high linear energy transfer radiation that may be more effective in cell killing and finally the new paradigm of theranostics that combine imaging and

therapy. In this approach, what you see is what you treat. These applications rely on radiolabeled vectors designed to selectively target tumor cells. Used in imaging this technique allow for better patient stratification and treatment planning. To tackle these challenges, a multidisciplinary approach across physics, chemistry, radiobiology, and clinical sciences is needed.

Scientific objectives of the research program:

The MP sets out to:

- **Innovate in radionuclide production** (high LET particles, theranostic pairs, rare isotopes, radionuclides allowing new imaging modalities etc.), exploring a broad landscape of projectiles (neutrons, photons, charged particles) and target configurations across various production platforms (reactors, accelerators, laser-plasma accelerators), while addressing nuclear cross-section data, purity, specific activity, and contaminant control.
- **Advance separation chemistry**, developing selective, fast, and robust chemical processes (including mass separation) compatible with radiopharmaceutical use, and exploring novel ligand frameworks with improved thermodynamic and kinetic properties over existing standards like DOTA.
- **Improve radiolabeling and vectorization**, optimizing bioconjugation methods and injectable formulations for diverse vectors (antibodies, peptides, small molecules), with a focus on stability, bioavailability, and therapeutic efficacy.
- **Integrate preclinical and clinical evaluation**, combining multimodal and multi-isotope imaging with (micro)dosimetry, modeling, and instrumentation to better understand and predict biological responses, minimize off-target effects, and inform regulatory strategies.

Figure 1.9: The IN2P3 laboratories participating to the MP Radionuclide

Multidisciplinary and multi-laboratory coordinating team:

The Master Project is coordinated by a multidisciplinary team bringing together complementary expertise in instrumentation, nuclear physics, and radiochemistry.

- Ferid Haddad (ARRONAX) oversees the physics dimension, including beam development and radionuclide production strategies for theranostic approaches.
- Ali Ouadi (IPHC) coordinates radiochemistry activities, focusing on separation chemistry, complexation, and radiolabeling.
- Frédéric Boisson (IPHC) leads instrumentation-related developments, particularly in imaging and detection systems.

Together, they ensure scientific integration across the work packages, strategic alignment with national and international priorities, and coordination with clinical and technological partners.

Project Structure:

The MP is organized into six Work Packages (WPs), each addressing a specific domain:

- **WP1: High-LET particles**: study of alpha and Auger emitters, focusing on production routes, vectorization strategies, and dosimetric modeling at cellular and subcellular levels.
- **WP2: Theranostic approaches**: development of diagnostic/therapeutic radionuclide pairs, with emphasis on chemical compatibility and personalized treatment strategies.

- **WP3: Innovative radionuclide production** : exploration of emerging technologies (e.g., laser-plasma acceleration), optimization of high-yield and high-purity production chains, and integration of mass separation processes.
- **WP4: Separation chemistry and formulation:** design of innovative ligands and separation methods for key isotopes, including complex media radiolysis, speciation, and injectable formulation stability.
- **WP5: Vectorization and radiolabeling**: development of efficient and specific coupling between radionuclides and biological vectors, ensuring therapeutic performance and compliance with radiochemical and safety standards.
- **WP6: Preclinical and post-clinical imaging and dosimetry**: evaluation of biodistribution and dosimetry through advanced imaging techniques and integration of dual-tracer and multi-isotope strategies for comprehensive biological insight.

External collaborations:

Most of the IN2P3 labs have developped strong local collaborations with research laboratory in chemistry (CNRS) and biology (Inserm, CNRS-biologie) as well as nuclear medicine research teams in hospitals. As an example, in Nantes, the DHOLMEN project financed by the ISITE NExT have been financed end 2024 for 4 years and gather 20 teams (13 research teams and 7 clinical teams).

International collaboration: CERN-MEDICIS, PRISMAP infraia project, COST NOAR project on astatine-211

Timeline under construction

The time allocated to the collective preparation of the Master's Projects was very limited (starting in spring 2025). In this section, we have done our best to present our research activities and the scientific priorities of these master's projects as clearly as possible.

1.5 Summary

This first chapter has outlined the broad landscape of health-related research at IN2P3, with a focus on interdisciplinary developments in radiation physics, imaging, radiobiology, and radiotherapy. It also highlighted the structuring role of the GDR MI2B in coordinating these activities and fostering national collaborations. Building on this foundation, the following chapters will delve deeper into key thematic areas: Chapter 2 will explore the advances and challenges in hadrontherapy, Chapter 3 will focus on emerging approaches in radiation therapy, and Chapter 4 will present the latest instrumental and numerical developments supporting these innovations.

2 Hadrontherapy

2.1 Introduction

Hadrontherapy was first proposed by Robert Wilson in 1946 [Wilson, 1946], as a way to treat deeply located tumors. Wilson highlighted the ballistic advantage of charged particles: unlike X-rays, these particles deposit most of their energy at the end of their path, as presented on Figure 2.1. The first clinical trials with protons began in the early 1950s but were soon limited by the low energy of the accelerators at that time. The expansion of proton therapy has been slow compared to conventional X-ray radiotherapy. Technical difficulties, higher costs, and the lack of clinical evidence showing a clear advantage over X-ray photon therapy have all contributed to the long-standing stagnation of proton therapy. However, since the early 2000s, there is a renewed interest for hadrontherapy, and particularly protontherapy.

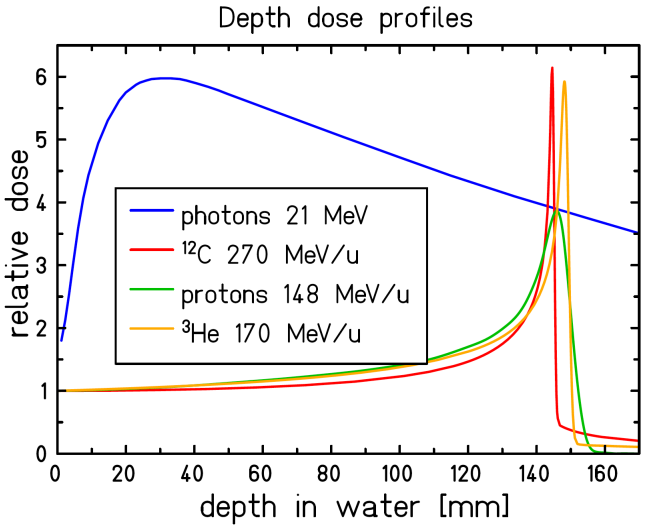


Figure 2.1: Dose deposition profiles of 21 MeV photons, 270 MeV/u ^{12}C ions, 170 MeV/u ^{3}He ions, and 148 MeV protons [Krämer et al., 2016].

2.1.1 International context

Currently, there are 67 operational centers that deliver proton treatments and 11 centers delivering treatments with carbon-12 ions. The global distribution of these facilities is shown in Figure 2.2. Since 1954, more than 400,000 patients have been treated with protons, and over 50,000 patients with ^{12}C since 1994 [PTCOG, Particle therapy co-operative group,].

Other charged particles, such as helium and oxygen ions [Tommasino et al., 2015, Krämer et al., 2016, Mairani et al., 2016, Tessonnier et al., 2017, Mairani et al., 2022], are also currently being studied for therapeutic use. Some treatment centers, such as CNAO in Pavia (Italy), HIT in Heidelberg (Germany) and MedAustron (Austria), are equipped with sources capable of producing beams from these particles.

Currently, the therapeutic indications for hadrontherapy mainly concern eye cancers, brain tumors located in sensitive regions, and pediatric tumors. The detailed list of these indications for each relevant country is provided in Table 2.1. Nevertheless, studies have demonstrated the potential benefits of charged particles in the treatment of certain gastrointestinal cancers. For example, the work published by [Terashima et al., 2012] and [Shinoto et al., 2016] shows that combining gemcitabine-based chemotherapy with proton or ^{12}C radiotherapy can increase the 2-year survival rate of patients to nearly 50%. By comparison, 2-year survival rates for treatments combining gemcitabine with X-ray radiotherapy are around 25% [Hong et al., 2008, Crane et al., 2009, Ch'ang et al., 2011].

Figure 2.2: Geographical distribution of treatment centers using protons (blue) and ^{12}C (red). The number of centers under construction is indicated in grey (data extracted from the PTCOG website [PTCOG, Particle therapy co-operative group,]).

2.1.2 National context

Hadrontherapy in France has experienced steady development over the past two decades, positioning the country as a significant player in the field of particle therapy in Europe. Two clinical centers currently provide proton therapy treatments: the Institut Curie – Orsay Proton Therapy Center, one of the oldest in Europe, and the Centre Antoine Lacassagne (CAL) in Nice, which has adopted an innovative cyclotron for eye and pediatric tumors. In 2018, the CyclHAD hadrontherapy center was inaugurated in Caen. This new hadrontherapy facility is currently delivering proton therapy treatments, and will be able to deliver carbon ion beams with the C-400 cyclotron in 2027. A map of the existing french hadrontherapy facilities and the irradiation platforms is presented on Figure 2.3.
Research in hadrontherapy is mainly supported by IN2P3, but is also carried out in strong collaboration with INSERM, university hospitals and other CNRS institutes. The support from IN2P3 has allowed to build collaborations with hadrontherapy facilities, such as CAL and CNAO in Pavia (Italy), through collaborative agreements. These agreements provide IN2P3 teams with ongoing access to clinical-quality beams. In parallel, several low-energy irradiation platforms were also set-up, such as Bio-ALTO (Paris), AIFIRA (Bordeaux), Cyrcé (Strasbourg), or ARRONAX (Nantes), as presented on the map 2.3.

Figure 2.3: Geographical distribution of hadrontherapy facilities, IN2P3 laboratories implied in hadrontherapy projects in France and associated platforms or accelerators in Europe (courtesy of Sara Marcatili).

Country	Group 1 (main indications)	Group 2 (potential indications)
USA	• Ocular tumors • Chordomas and chondrosarcomas • Spinal tumors • Hepatocellular carcinomas • Pediatric tumors • Patients with genetic syndromes	• Head and neck cancers • Thoracic tumors • Abdominal cancers • Pelvic cancers
UK	• Skull base and spinal chordomas • Skull base chondrosarcomas • Soft tissue sarcomas • Pediatric tumors	
Italy	• Skull base and spinal chordomas and chondrosarcomas • Adenoid cystic carcinomas of the salivary glands • Mucosal melanomas • Ocular melanomas • Osteosarcomas • Pediatric tumors	
France	• Skull base and spinal chordomas and chondrosarcomas • Primary eye tumors • Pediatric tumors	
Netherlands	• Skull base and spinal chordomas and chondrosarcomas • Meningiomas • Pediatric tumors	• Re-irradiations • Paranasal sinus tumors • Nasopharyngeal carcinomas • Retroperitoneal sarcomas
Canada	• Chordomas and chondrosarcomas • Ocular melanomas • Pediatric tumors	• Benign central nervous system tumors • Paranasal sinus and nasal cavity tumors

Table 2.1: Recommended indications for hadrontherapy in different countries (from [Durante and Paganetti, 2016]).

2.1.3 Major stakes

The ballistic advantage of hadrontherapy also comes with a greater sensitivity to uncertainties related to the irradiation of tumor volumes. Indeed, the steep dose gradient at the Bragg peak implies that even a slight deviation in the particle range within matter can result in over-irradiation of healthy tissues or under-irradiation of the tumor volume.

The accuracy of the particle range is influenced by several factors, including uncertainties in imaging, patient positioning errors, tumor volume changes, and variations in the patient's anatomy. As a result, depending on the treatment center, margins ranging from 1 to 3 mm must be added to the target volume [Paganetti, 2012].

In addition to these uncertainties in the incident beam path, there are also uncertainties in the actual dose delivered to the tumor. These arise in part from corrections made in the treatment planning process to account for biological effects, as well as from secondary particles generated by nuclear reactions along the

beam path. Indeed, inelastic interactions between the incident ions and the target tissue produce lighter secondary particles, which follow a different trajectory and, consequently, can deposit dose outside of the targeted volume, in surrounding healthy tissues.

The reduction of treatment margins and the improved assessment of the impact of secondary particles are thus major challenges in hadrontherapy, as the associated uncertainties currently prevent full exploitation of the ballistic advantage of ions. Therefore, enhancing treatment planning in hadrontherapy, and thereby improving dose delivery to the patient, depends on addressing these issues.

2.1.3.1 Modeling

Modeling physical and biological dose in hadrontherapy is essential in order to provide accurate treatment planning system to correctly deliver the dose to the tumoral volume. Indeed, treatment plans are generally computed using analytical algorithms, or Monte Carlo-based planning approaches are beginning to emerge [Paganetti, 2012, Perl et al., 2012, Parodi, 2012, Mairani et al., 2016].
Numerous studies focus on optimizing the **biological dose** rather than the physical dose in treatment planning [Wilkens and Oelfke, 2005, Frese et al., 2011, Mairani et al., 2016]. This optimization involves accounting for the variability of the **Relative Biological Effectiveness (RBE)** along the path of charged particles. Considering this effect is particularly important for high-**LET** particles, such as α-particles or ^{12}C ions [Mairani et al., 2016]. Figure 2.4 shows survival data of human adenocarcinoma cells irradiated with ^{4}He ions, compared to a constant RBE model (RBE = 1.3) and a variable RBE model. In the latter case, cell survival near the distal edge, corresponding to the high-LET region, is better reproduced.

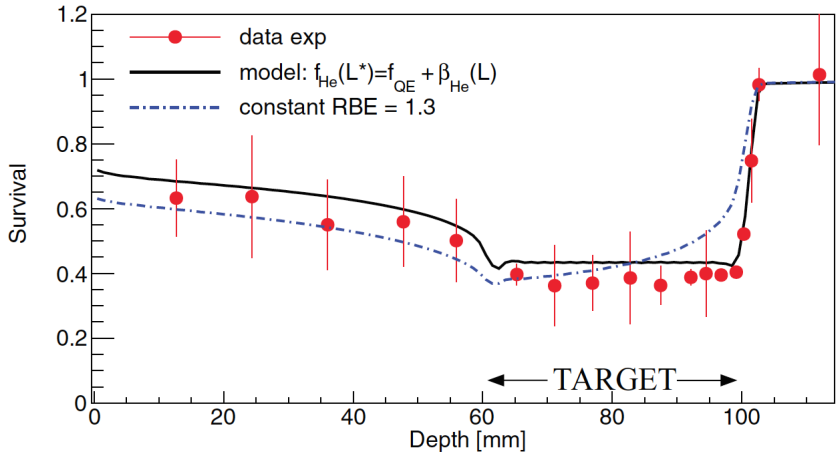


Figure 2.4: Cell survival of A549 cells irradiated with ^{4}He as a function of depth [Mairani et al., 2016]

2.1.3.2 Ion-range verification

The high sensitivity of dose deposition by charged particles to the composition of the traversed medium raises the question of verifying the conformity of the delivered dose to the target volume. Since secondary particles produced by nuclear reactions of the incident beam can potentially exit the patient's body, it is possible to envision monitoring of the tumor irradiation by exploiting the correlation between the production of these particles and the trajectory of the primary beam. The detection of prompt radiations (prompt gamma rays and secondary charged particles) as well as PET imaging (detection of β^{+}-emitting isotopes) can be considered [Krimmer et al., 2018, Parodi and Polf, 2018]. However, these techniques are not yet implemented in clinical routine.
Several verification methods were proposed for monitoring the beam range, including:

- **Prompt gamma monitoring**, which relies on the detection of prompt γ-rays emitted during the de-excitation of nuclei produced by nuclear interactions between the incident particles and the target;
- **Secondary charged particle tracking** (also called *Interaction Vertex Imaging*, IVI), primarily used for range verification in heavy ion therapy, where particles heavier than protons are employed;
- **PET imaging** (Positron Emission Tomography), which takes advantage of the production of β^+-emitting isotopes along the beam path [Parodi, 2012]. This method can also be performed *offline*, i.e., after treatment;

In addition to these techniques of ionizing radiation detection, two other modalities have been investigated:

- The **detection of the acoustic waves** generated by the energy loss of incident ions within tissues [Assmann et al., 2015].
- The **detection of the electromagnetic field** generated by the propagation of the incident ions in the patient [Rädler et al., 2021, Albert et al., 2018].

2.1.3.3 Secondary particles measurements

Light secondary particles (charged and neutrals) produced by inelastic interactions between the ion-beam and the target have different paths and dose deposition profiles compared to the primary beam. These particles can contribute up to 5% of the total physical dose at the Bragg peak, and their biological impact on surrounding tissues may increase the toxicity of hadrontherapy treatments on healthy tissues, as they typically exhibit high LET. For instance, secondary particles produced by the interaction of 160 MeV protons in a tissue-equivalent phantom have LET values ranging from 100 to 160 keV/µm, while the LET of the incident beam varies between 1 and 12 keV/µm [Grassberger and Paganetti, 2011]. Furthermore, one of the main indication for hadrontherapy is to treat pediatric cancers, for which the radio-induced cancer risks must be considered more carefully. The contribution of secondary particles to the dose received by healthy tissues must therefore not be neglected, both in terms of physical and biological dose estimation. Accurately accounting for nuclear reactions in dose calculations requires precise measurements of the cross-sections of these reactions, which typically exhibit uncertainties ranging from 5% to 15% [Dudouet et al., 2014]. Although several experiments have already been carried out using thick targets [Schall et al., 1996, Haettner et al., 2013] and thin targets in the energy range used in hadrontherapy (80 to 400 MeV/u) [De Napoli et al., 2012, Dudouet et al., 2014, Divay et al., 2017, Horst et al., 2019], the fragmentation cross-section data remain incomplete, especially for incident particles with atomic number greater than that of protons, such as carbon or oxygen. It is therefore necessary to conduct dedicated measurement campaigns for these cross-sections.

2.2 Hadrontherapy projects within IN2P3

Many instrumental realizations were carried out within laboratories involved in the presented projects. All will be developed and presented in detail in Chapter 4.

2.2.1 Modeling the effects on living organisms

In the research field, the modeling biological effects relies on coupling Monte Carlo particle transport codes with biophysical models. Among the most widely used tools, Geant4 and its extension Geant4-DNA [Kyriakou et al., 2021] allow detailed simulation of energy deposition from the nanoscale to the macroscopic scale. The GATE platform [Sarrut et al., 2022], built on Geant4, is commonly used in clinical settings and supports 3D biological dose maps using anatomical data. Other codes like FLUKA [Ballarini et al., 2024] can compute LET distributions and are often coupled with models like LEM [Scholz et al., 1997]. MCHIT,

also based on Geant4, has been used in combination with MKM to assess RBE in ion beam therapy [Burigo et al., 2015].

2.2.1.1 Geant4-DNA

A mechanistic understanding of the biological effects of ionizing radiation remains a major challenge in current radiobiology. The computational (in silico) approach is currently favored [Emfietzoglou et al., 2005, Nikjoo et al., 2006, Nikjoo et al., 2016] to address this challenge, in particular to meet the need for accurate tools for radiotherapy treatment planning, or to better estimate the risk to human health during long-term exposure to ionizing radiation in manned space missions. Numerous simulation tools have been developed worldwide over the past decades. They can simulate the damage induced to the DNA of the cell nucleus, which is still considered the primary site sensitive to ionizing radiation in cells, following a "bottom-up" approach (from DNA to macroscopic biological effects). Many such ≪proprietary≫ codes still exist and continue to be developed (see a detailed list in Table 1 of [Kyriakou et al., 2022]), highlighting the dynamics within this research field. Unfortunately, none of them are currently available to users, which prevents their widespread use and adaptability to different user needs.

Instead, in an open science approach, Geant4-DNA (https://geant4-dna.org) is the first fully accessible platform developed for the mechanistic modeling of biological effects of ionizing radiation at the (sub)cellular scale. The project was initiated in 2001 by Petteri Nieminen of the European Space Agency (ESA). It provides to the scientific community the possibility to simulate track structures using various physics models in liquid water (the main component of biological medium) and other materials, as well as several chemistry models for the simulation of radiolysis. These can be combined with a variety of geometries of biological targets to predict, in particular, the induction of damage at the (sub)cellular scale. Being a full component of the Geant4 Monte Carlo toolkit (https://geant4.org), Geant4-DNA functionalities become accessible to other codes based on Geant4 (e.g. GATE, TOPAS/Topas-nBio, GAMOS).

An example of significative result obtained by the Geant4-DNA collaboration is presented on Figure 2.5, where it can be observed that the Monte Carlo simulation is able to reproduce the double strand breaks yields experimentally measured with protons and alpha-particles.

2.2.1.2 GATE

GATE is an open-source Monte Carlo simulation platform, based on Geant4 and dedicated to applications in medical physics (imaging and therapy). The OpenGATE collaboration (www.opengatecollaboration.org) includes 25 international laboratories, of which 6 are IN2P3 laboratories (LPCA, JCLab, CPPM, IPHC, IP2I, and LPSC). Lydia Maigne (LPCA - IN2P3) is the current spokesperson of the collaboration and David Sarrut (CREATIS CNRS) is the technical coordinator. More than 2,000 users are registered worldwide. Over the past five years, the number of publications has been approximately 15 per year. Two publications from the OpenGATE collaboration received the "most cited publication" award in the journal Physics in Medicine and Biology, in 2009 and 2015 respectively [Jan et al., 2004, Sarrut et al., 2014], demonstrating the platform's impact at the interface of physics, medicine, and biology; then, we continued to showcase our developments with collaboration papers [Grevillot et al., 2020, Winterhalter et al., 2020, Sarrut et al., 2022]. Every year, an international scientific meeting is organized to present the last developments and validations performed by the collaboration developers and the user community [Ali et al., 2022b].
To keep the GATE platform competitive, structural developments were necessary. The code, written in C++, needed to be updated and partially rewritten. Modifications of the platform have been performed since 2023 to encapsulate parts of the code in Python to facilitate platform installation and usage, as the current macro

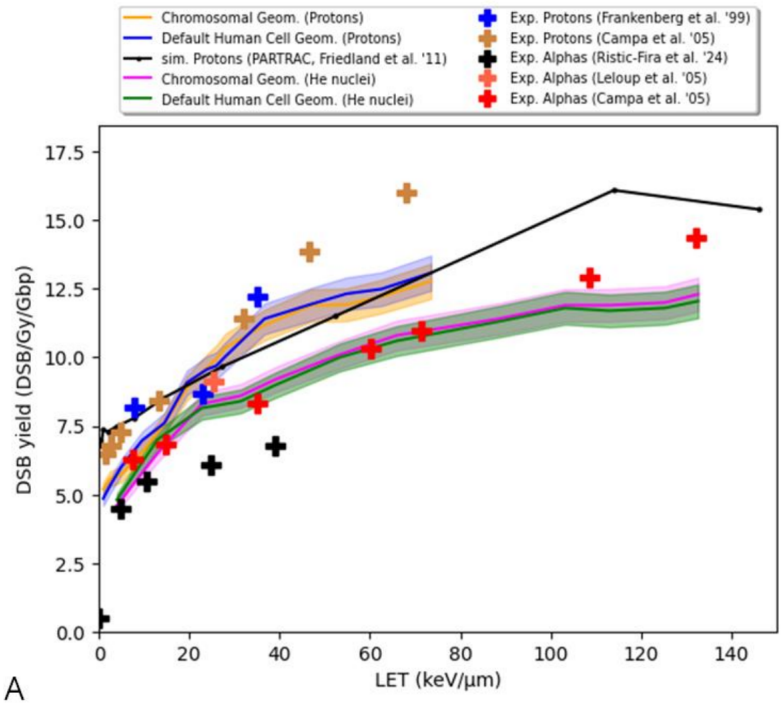


Figure 2.5: Quantification of Double Strand Breaks yields for several Geant4-DNA human cell models, irradiated by protons and alphas for several values of LET (lines: Geant4-DNA and PARTRAC simulations; crosses: experiments), extracted from [Chatzipapas et al., 2024]

system (text files interpreted in C++) is no longer sufficient for managing increasingly complex simulations. The GATE 10 version was officially released in November 2024 and is continually updated since this date.

2.2.1.3 NanOx

More recently, the NanOx model was developed to predict cell survival following irradiation by accounting for both local lethal events at the nanometric scale and global damage processes at the cellular (micrometric) scale. It is compatible with outputs from Geant4 and GATE, and has shown improved predictive performance over standard models [Monini et al., 2019].
The primary goal of this research axis is to develop a dedicated module in GATE (the BioDoseActor) to compute biological dose in the context of hadron therapy. This module will be implemented in successive versions, progressively integrating improvements in both technical performance and biological realism. In parallel, we aim to initiate a broader effort toward the development of a fast implementation of the NanOx model, suitable for integration into treatment planning systems, as well as the creation of an open-access version of the code to support wider use within the scientific community.

Both Geant4-DNA and GATE will be detailed in sections 4.6.2 and 4.6.3 of Chapter 4.

2.2.1.4 5-year prospects

IN2P3 is aligning its research efforts with emerging trends in medical physics, notably the integration of artificial intelligence (AI) and the development of digital twins—virtual patient models that simulate biological and physiological responses to predict treatment outcomes and optimize therapies. A coordinated strategy will be established across IN2P3 teams to define AI-related priorities, including modeling of patients, experimental setups, and instrumentation. The LPCA will play a leading role in modeling radiobiological experiments, particularly for studying the FLASH effect and innovative internal radiotherapy (IRT) techniques.

In parallel, IN2P3 teams will continue to drive core developments in the Geant4-DNA simulation toolkit. Priorities include improving physics models for electrons and ions in water and other materials, extending radiolysis modeling to ultra-high dose rates, and validating biological damage predictions across multi-scale geometries. Future directions also include AI integration and potential GPU implementation. Application efforts will focus on building a modular, multi-scale simulation platform with initial use cases in space radiation, advanced radiotherapy (e.g., FLASH, VHEE), and environmental radiation modeling.

2.2.2 Online monitoring and dose control

The precision required for dose delivery in hadrontherapy imposes a rigorous control of the beam during treatment. In-beam monitoring focuses on measuring and verifying beam parameters—such as position, intensity, energy, and timing—during irradiation, directly within the beamline or at the treatment nozzle. In addition to in-beam monitoring, other techniques were proposed to monitor the dose delivered inside the tumor volume using secondary particles produced during treatment, as listed in section 2.1.3.2.
Several online monitoring systems have been proposed in recent years in France (CLaRyS collaboration) and across Europe [Krimmer et al., 2017] to measure the ion range with an accuracy of a few mm for large beam spots (i.e. 10^8 particles in proton therapy). The CLaRyS collaboration, during the CLaRyS-UFT project (2017-2021) studied the assets of fast timing ($\sim$ 100 ps) for online control of treatments [Dauvergne et al., 2020]. An example of simulated setup and result of the Compton camera for Prompt-Gamma imaging is presented on Figure 2.6, which demonstrates the interest of a highly time-resoluted measurement of prompt-gamma.

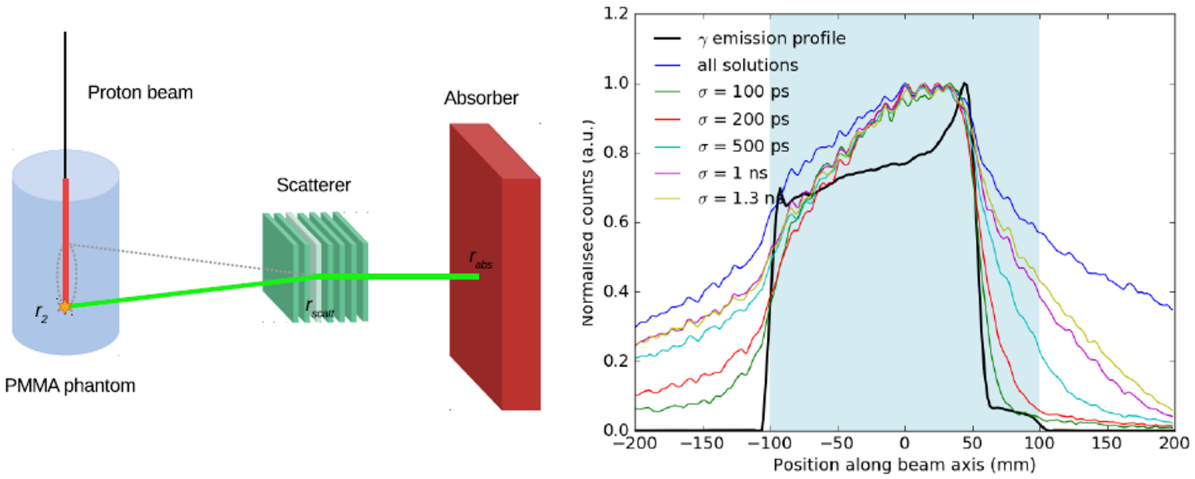


Figure 2.6: Simulation of prompt-gamma detection using a Compton camera with a 150 MeV proton beam incident on a PMMA cylinder (15 cm range). Top: detection scheme; bottom: comparison of profiles obtained through cone-line reconstruction with selection of solutions compatible with the measured time-of-flight [Livingstone et al., 2021]

This idea of adapting prompt-gamma detection to the beam structure (single projectile mode or pulsed beams) was further pursued in two IN2P3 projects, which essentially aim at enhancing the sensitivity of ion-range monitoring (TIARA project) and proposing a detection system compatible with the specific time-structure of synchro-cyclotrons (e.g. the S2C2 of the IBA Proteus One in the Centre Antoine Lacassagne in Nice).

In parallel, accurate beam monitoring during the treatment is crucial, as it supports quality assurance protocols, and facilitates the clinical translation of advanced irradiation modalities such as Pencil Beam

Scanning (PBS), FLASH therapy, or multi-ion approaches. As hadrontherapy expands worldwide, the development of robust, high-resolution, and clinically compatible monitoring systems becomes increasingly essential to harness its full therapeutic potential. Several IN2P3 teams are working on developing new monitoring techniques, such as diamond (MP DIAMANT) or GaN detectors (MATRIX), or ultra-thin monitors (PEPITES), to address the emerging challenges of the field.

2.2.2.1 TIARA

Launched in 2020, the TIARA project aims to enhance the sensitivity of ion-range monitoring by introducing a novel device that combines an original data reconstruction method - Prompt Gamma Time Imaging (PGTI) - with an innovative type of prompt gamma detector (TIARA Time of flight Imaging ARrAy). A set of gamma modules is placed around the patient and read in time coincidence with a dedicated beam monitor located upstream of the patient. The total time-of-flight (TOF) measured corresponds to the proton transit time within the patient up to the prompt gamma emission vertex, plus the PG TOF from the vertex to the gamma detector. When these measurements are combined, they constrain the location of the prompt gamma vertex, which is retrieved by solving an inverse problem. The PGTI reconstruction method enables the combination of data from detectors placed at various angular positions, which is not feasible with conventional PG timing techniques, thus enhancing detection efficiency. Moreover, the use of Cherenkov detectors (PbF_2) instead of conventional scintillators provides high time resolution and an improved signal-to-noise ratio, due to their inherent insensitivity to neutron background.
The TIARA project was supported by different competitive funding grants: IRS (Initiatives de Recherche Stratégiques) from the UGA (Université Grenoble Alpes) between 2020 and 2021, the PCSI (Physique et Cancer) program between 2020 and 2023, and by an ERC starting grant from 2022 to 2027. TIARA regroups researchers from LPSC, CPPM and the CAL protontherapy facility, and discussions with the CNAO facilities have started to build a collaboration based on the existing collaborative agreement between CNAO and IN2P3. The technical developments around this project are detailed in 4.2.1.1.

2.2.2.2 CLaRyS-S2C2

The proton beams delivered by the Proteus-One synchro-cyclotron accelerator at CAL-Nice or Cyclhad-Caen have a structure with pulses of a few microseconds every millisecond, with a very low duty cycle, of the order of 1/1000, and therefore a very high peak intensity. A first challenge is therefore to acquire a sufficient number of gamma-ray photons associated with these short pulses, with a detection system having a sufficient dynamic range. A second issue is related to the ability to predict and model by fast Monte Carlo simulations the emitted radiation with their temporal and energy distribution [Kanawati et al., 2015, Létang et al., 2024]. Finally, a third issue lies in the comparison between the signal obtained with a prediction from a treatment planning, if possible in a very short time in order to consider a possible adaptation of the treatment in case of detected deviation. Everaere *et al.* proposed to use a small set of large detectors and integrate the prompt signals accumulated during each pulse [Everaere et al., 2024a]. The ability to detect millimetric range deviations at a pencil beam spot level is further investigated, experimentally and by simulations, in the frame of a 80 PRIME thesis.

The technical developments around this project are detailed in 4.2.1.2

2.2.2.3 Beam monitors

Diamond detectors Unlike post-treatment imaging or secondary particle detection, in-beam monitoring provides immediate, real-time feedback on the characteristics of each individual particle spot or spill. This is particularly crucial for pencil beam scanning (PBS), where accurate control of each scanned position is essential for dose conformity. Key technologies in this domain include beam current monitors,

position-sensitive detectors (e.g., multi-wire ionization chambers), and time-of-flight systems, all integrated upstream of the patient. These devices enable fast quality assurance, adaptive beam control, and improved reliability of dose delivery, especially in complex or hypofractionated treatment scenarios.
In order to overcome the technological barriers related to the deployment of innovative radiation therapies, studies on the use of diamond were initiated in 2015 by the PNAM team at LPSC. The scientific objective is to use diamond for particle detection in extreme conditions either in intense radiation environments, with high particle flux or fluence for use in clinical beam delivery modes, or at very low fluxes where high transparency to high-LET particles is required, as in radiobiology applications.
More specifically, a beam hodoscope for hadron therapy was developed through two PhD [Curtoni, 2020, Everaere, 2023]. In addition, two other prototypes were developed in the framework of FLASH therapy (DIAMMONI [Molle, 2024]) and MRT (IDSYNCHRO [Rosuel, 2021a, di Franco et al., 2023]). DIAMMONI is now definitely installed in ARRONAX whereas IDSYNCHRO is temporarily installed on the medical line of the Melbourne synchrotron at the occasion of preclinical experiments. The technical developments around this project are detailed in 4.2.2.1.

PEPITES The PEPITES activity (LRR) started more than a decade ago following contact from the IBA company regarding the need for distant beam profilers to be used continuously during therapeutic irradiation. This requirement implies that the monitor must have a very low water equivalent thickness (WET) to minimize its impact on beam divergence, and must also be radiation tolerant. In the case of IBA, the WET had to be below 15 µm (monitor-to-patient distance $\sim$2 m), and the system had to withstand annual doses of 10^{7-8} Gy.
Low-pressure ionization chambers are typically used in this context, but prolonged exposure leads to frequent replacements. The membranes of these chambers, whose thickness must balance minimal WET with mechanical strength, suffer from radiation damage and gas leaks due to the vacuum environment of the beamline.
PEPITES addresses both limitations by using Secondary Electron Emission (SEE) as the detection mechanism. SEE requires only $\mathcal{O}$(10 nm) of metal thickness to be effective, enabling ultra-thin sensitive areas. Since the membranes supporting the metal deposits are not under mechanical stress, they can be as thin as technology (and cost) allow. Radiation damage is less consequential, resulting in improved monitor lifetime.
Furthermore, SEE is a highly linear process. In recent years, FLASH irradiation has become a major research focus, but its high instantaneous intensities challenge ionization chambers due to saturation effects. SEE does not suffer from these limitations up to at least $\mathcal{O}$(A) instantaneous intensities, as demonstrated in neutrino experiments where SEE-based profilers are used to monitor the proton spills generating the neutrinos. The technical developments around this project are detailed in 4.2.2.2.

MATRIX The development of GaN-based detectors for proton therapy beam monitoring started 7 years ago between the CRHEA-CNRS (Valbonne) laboratory and the Centre Antoine Lacassagne in Nice. Based on promising first results this activity was enlarged through the years in the framework of the National project NECTAR founded by the INSERM and the international ANR-DFG project called MATRIX.
This project implied new collaborations with the University of Bochum, the Proton Therapy center of Essen and the IPHC (Strasbourg). The goal is to develop a beam monitor for hadrontherapy that could sustain the extreme conditions required by FLASH therapy. The technical developments around this project are detailed in 4.2.2.3.

2.2.2.4 Dosimetry

Treatment delivery techniques in hadrontherapy are very different from conventional treatments, and adapted commercially available dosimeters are scare and make Quality Assurance (QA) time consuming. To overcome this limitation, scintillation detectors have advantageous properties and with the progress in image acquisition and processing, studies have shown the possibility to perform 3D dosimetry [Rilling et al., 2020], as well as their adequation with fast delivery of Pencil Beam Scanning in protontherapy [Goddu et al., 2022, Rahman et al., 2020, Clark et al., 2023]. A few studies have also tested scintillator dosimeters in clinical Carbon ion beams [Yogo et al., 2021].
In this context, the LPC Caen and GANIL, in collaboration with the CLCC François Baclesse, are developing a new dosimetry system named SCICOPRO. It was developed to perform 3D dosimetry in PBS proton therapy. It is based on a $10\times10\times10$ cm^3 scintillator cube and a fast camera. Unlike existing detectors, the system can be used to verify pencil beam (PB) characteristics or reconstruct 3D dose distribution in a single acquisition. This development led to a publication in Medical Physics in 2024 [Frelin et al., 2024].

2.2.2.5 DeCuPro

Unlike conventional photon radiotherapy, proton therapy does not require a bolus for skin tumors due to proton properties. High-energy photons exhibit a significant “build-up” effect near the surface, needing a bolus to ensure proper dose delivery at skin depth (usually 0 to 3 mm, with ICRU recommending 0.07 mm). Protons deposit energy locally, sparing underlying tissues better than photons, which pass through tissue. To determine if proton therapy’s advantage is due to a lack of skin dose in conventional radiotherapy, a study was conducted by the Centre François Baclesse Team of Medical Physicists using the RayStation treatment planning system (TPS) with a Monte Carlo algorithm on a photon VMAT case that experienced recurrence. Daily CBCT scans were used to recalculate the skin dose for each session. Despite significant air gaps (up to 12 mm), especially late in treatment, calculations showed no deficiency in target coverage. However, the potential dose reduction caused by air gaps between the bolus and skin in cutaneous tumors requires further investigation through measurements, as TPS results do not fully align with published literature. Since TPS calculations are not well suited for this location, a thin plastic scintillator detector was developed at LPC Caen during a Master’s internship to improve dose measurement. This study is being continued with an IN2P3 funded PhD grant, in collaboration with LDRI (ASNR, Fontenay-aux-Roses) in charge of the modeling of the PBS beamline at the Normandy Proton Therapy Center using Gate.

The DeCuPro project was initiated in collaboration with the Medical Physics team at the François Baclesse Cancer Center. An agreement was signed between LPC Caen and the François Baclesse Center to integrate the CFB team with the LPC AMI department for joint research. Subsequently, the DeCuPro MITI project was approved, involving the LDRI ASNR team. There are currently 1.5 FTE working on this project, in addition to one PhD student and 4 medical physicists.

2.2.2.6 5-year prospects

The CLARYS project is paving the way toward a clinically viable Prompt-Gamma monitoring system tailored for protontherapy with medical synchro-cyclotrons. Its detection system, based on scintillators coupled with photomultiplier tubes (PMTs), offers a cost-effective, robust, and modular solution using a limited number of detection units. The ongoing developments are expected to provide key design inputs for future clinical implementation.
In a similar fashion, the TIARA project also aims to develop a full-scale prototype by 2027. If spatial resolution proves sufficient, the project will move toward demonstrating TOF-based proton radiography, thus broadening the clinical potential of the TIARA system.
Similarly, many beam monitors developed by IN2P3 teams for hadrontherapy aims to be installed in clinical

(e.g. CAL, CNAO) and experimental (e.g. ARRONAX) facilities and target to be able to sustain extreme fluences that will be required for FLASH therapy.
The detailed prospects for each specific technical projects will be developed in 4.2.

2.2.3 Secondary particles measurements

Several IN2P3 teams are involved in secondary particle measurements in hadrontherapy through international collaborations. The different projects are detailed in the following sections.

2.2.3.1 The FOOT collaboration

The FOOT (FragmentatiOn Of Target) collaboration is one of the biggest collaboration for secondary particles measurements in applied physics in the world. It regroups different laboratories from INFN (Roma, Bologna, Pisa, Torino, Perugia, Frascati, Milano, Napoli,...), the CNAO hadrontherapy center, IPHC (DeSIS team) and GSI laboraboratory. Discussions are on-going to integrate LPSC (Grenoble) in the collaboration, on prompt-γ particle measurements. FOOT is mainly funded by INFN, but some support was provided since 2017 by the IN2P3, within the FOOT-Xn master-project.
The experiment aims to measure the double-differential cross sections of nuclear reactions occurring during hadrontherapy treatments, using ^{16}O and ^{12}C beams with energies ranging from 150 to 400 MeV/u, on targets of interest such as carbon or polyethylene. The experimental setup is designed to measure the characteristics of fragments with $Z \geq 2$ within an angular acceptance between 10 and 20^o, corresponding to the preferred emission directions of fragments as predicted by Monte Carlo simulations. The experiment also aims to evaluate the cross sections of reactions involving proton beams on ^{12}C and ^{16}O targets using inverse kinematics.

Since 2021, several campaigns of data taking were performed with partial or total setup (since 2023). The first charge-changing cross sections measured by the collaboration were published in [Toppi et al., 2022]. The full setup campaigns that were performed at CNAO (2023,2024) are presently under analysis. The characterization, the alignment or the calibration of the last added detectors (Inner-tracker, Calorimeter) is under investigation. Meanwhile, more than 25 papers have been published, mostly proceedings and more than 25 talks at conferences have been presented. One Phd was defended in 2022 at IPHC on software development associated to SHOE (for *Software for Hadrontherapy Optimization Experiment*) [Sécher, 2022]. First results of differential cross-sections of 400 MeV/u ^{16}O beam fragmentation on graphite target were obtained at CNAO in 2024, and the associated publication is currently under review [Ridolfi et al., 2025]. An example of the obtained cross-sections for helium and lithium fragmentation products, with associated simulations performed with Geant4 and FLUKA, is presented on Figure 2.7.

Even if IPHC is currently the only french laboratory involved in the FOOT experiment, its contribution is crucial within the collaboration. Indeed, an important part of the software development for the data analysis of the FOOT collaboration (SHOE) was performed by a researcher of the DeSIS team (Christian Finck), who was the software deputy from 2018 to 2021, and then software coordinator of the experiment for 4 years from 2021 to 2025. Furthermore, the CMOS sensors (MIMOSA-28) used in the FOOT experiment are also produced by IPHC. This unique expertise is essential for the FOOT project, as the vertex tracker and inner tracker are based on this technology. These sensors were widely used in hadrontherapy applications in different collaborative projects with different laboratories, such as GSI (Darmstadt, Germany) [Reidel et al., 2019, Reidel et al., 2020, Reidel et al., 2021, Reidel et al., 2025], the Frascati laboratory [Spiriti et al., 2017] and LP2I (Lyon) [Finck et al., 2017]. The instrumentation developed within these projects will be detailed in the chapter 4.

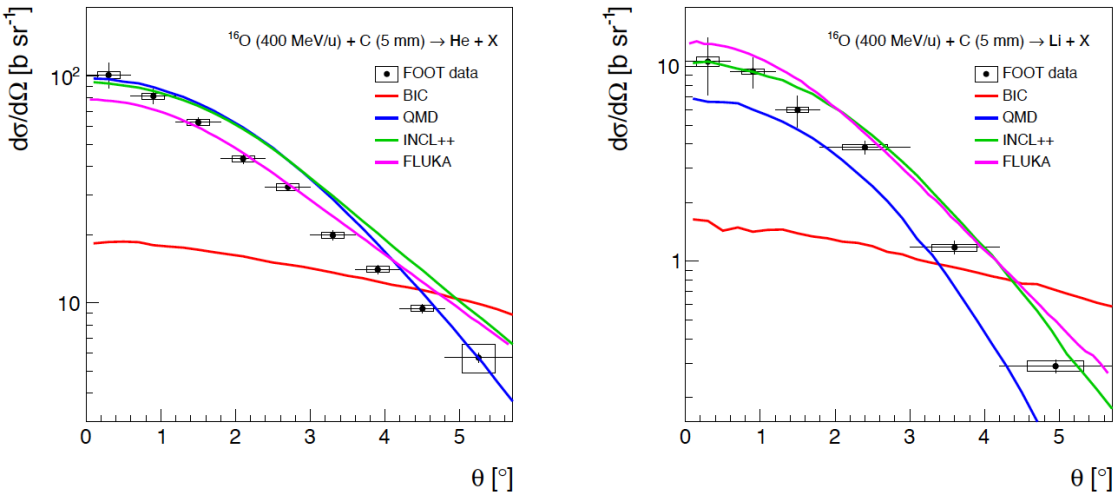


Figure 2.7: Angular differential cross sections for the production of He and Li fragments in the interaction process of a ^{16}O beam of 400 MeV/nucleon on a graphite target together with FLUKA and GEANT4 predictions with four different models (see insert), extracted from [Ridolfi et al., 2025].

2.2.3.2 The CLINM project

The CLINM project aims to characterize both the nuclear fragmentation products and their chemical effects, notably water radiolysis. Indeed, in hadrontherapy, an important part of the energy is deposited in water, which constitutes approximately 65% of the cell content. This induces water radiolysis and the formation of reactive species (such as HO· and H_2O_2), responsible for so-called indirect effects, which account between 30 and 70% of total radiation-induced cellular damage, depending on the type of particles used. While the molecular effects of radiation on water and proteins have been extensively studied with X-rays, gamma rays, and electrons, fewer data are available for accelerated ions, and even less for the fragments produced by their interaction in matter. These ions, characterized by a high linear energy transfer (LET), create dense local radical populations, significantly influencing the radiolysis mechanisms. Characterizing secondary particle production and their radiochemical consequences is thus crucial for treatment planning improvement in hadrontherapy and mission safety in space radiation protection.

Since 2020, the full setup of CLINM was characterized, both on clinical facilities (CNAO, CAL) and experimental accelerators (GANIL, GSI, Cyrcé). This resulted in a publication that was submitted to JINST in 2025, and that is currently in review [Gesson et al., 2025]. A first experiment was carried out at CNAO in May 2023, where the first measurements including both physics and chemistry part of the setup were performed with clinical ^{12}C ions. This experiment allowed to highlight an important discrepancy between the data and the simulation of the ^{12}C break-up in 2-3 α (Figure 2.8-left, that presents the reconstructed energy spectra of secondary helium ions from 400 MeV/u ^{12}C fragmentation in a 23 cm tissue-equivalent target). Chemical measurements, performed in the very same conditions, showed a significant increase in the quantities of HO· and H_2O_2 in the fragment region with the depth traversed by ions. The first publication of these results is currently in the writing process. All these results were also presented during the PhD defense of Levana Gesson in 2024 [Gesson, 2024].

All collected data of the CLINM project will be used to improve nuclear physics models that are currently used in Monte Carlo codes such as Geant4, which are widely used within the subatomic physics community. For example, radiolysis measurements are crucial to improve the Geant4-DNA code. Two researchers of the CLINM project (Quentin Raffy and Nicolas Arbor) are already members of the Geant4-DNA collabo-

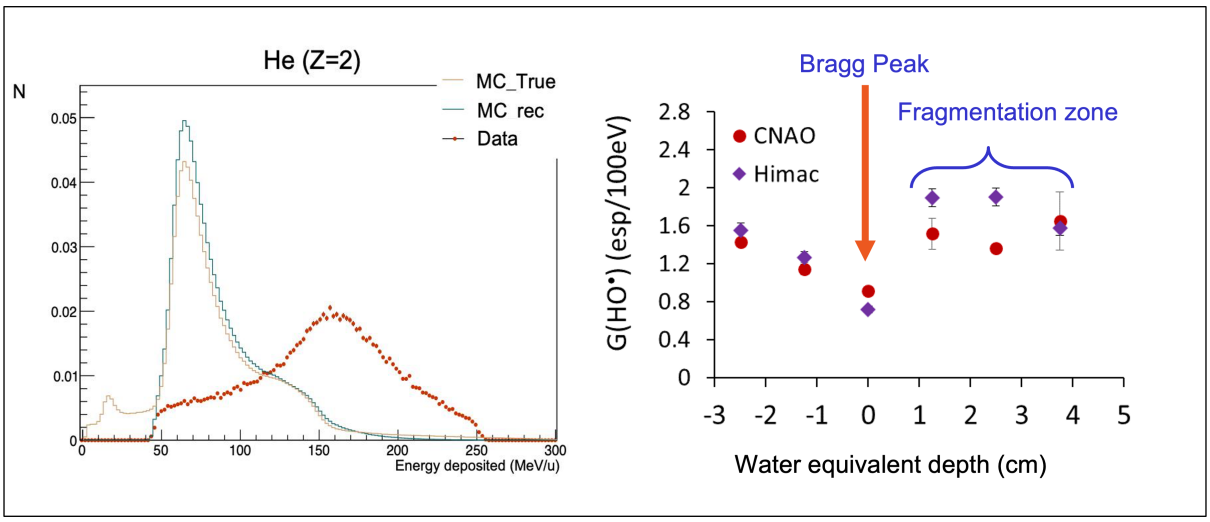


Figure 2.8: Left: Comparison between simulated (green line) and measured (red dots) energy distributions of Z=2 produced by a 400 MeV/u carbon ion beam interacting by 23-cm RW3 phantom. Right: Evolution of the number of $HO^{\cdot}$ radicals formed per ion ($N(HO^{\cdot})$/ion) with the depth traversed by C ions, performed with 400 MeV/u ^{12}C ions in HIMAC and CNAO.

ration. This project is part of the collaborative agreement that was signed between CNAO and IN2P3, and therefore measurements are mainy performed in the experimental room of the CNAO facility.

The CLINM project was supported by IN2P3 by different ways: first, through the FOOT-Xn mater-project of IN2P3 from 2020 to 2024, and also through one post-doctoral contract (Arshiya Sood, 2022-2024) and the PhD contract of Lévana Gesson (2021-2024) that was half-funded by the Institute. In 2024, an ANR-PRC was obtained and should last until 2028. This last funding allowed the recruitment of a new PhD student (Giovanna Rezende, 2024-2028), whose contract is co-funded by the CNES.

2.2.3.3 Radiolysis measurements

In addition to the CLINM project, the Radiochemistry team of IPHC is also performing a systematic study, at the molecular scale, of the radiolysis of protein biomolecules by accelerated ions, as well as low LET radiations (X-Rays and electrons), for comparison. Dose-rate effect is also studied, in a context of FLASH radiotherapy, and will be detailed in Chapter 3.2.2.1.2. One purpose of these measurements is to provide original robust experimental data for the improvement of simulation codes, such as Geant4-DNA (see 2.2.1.1). To do so, measurement of radiolytic yields of main water radiolysis species are performed in the very same conditions, to help constraining simulation results.

In this project, the radiolysis of amino acids and small peptides was studied, protein building blocks, as well as whole native proteins. It involves several associate professors and engineers from IPHC. Four PhD students have been involved, among which two will defend in 2025.

Initial studies on amino acid radiolysis, led by Nicolas Ludwig [Ludwig, 2018], demonstrated that 2,5-dihydroxyphenylalanine (2,5-DOPA) and phenylalanine dimers—products of phenylalanine radiolysis—form preferentially under irradiation with accelerated ions, as opposed to low-LET radiation. During her PhD (2022–2025), Aurélia Arnone showed that similar effects occur when phenylalanine is part of the peptide aspartame, representing a step closer to protein behavior.
Radiolytic yields of hydroxyl radicals (HO·), hydrated electrons (e^-_{aq}), and hydrogen peroxide (H_2O_2) were quantified along the tracks of 230 MeV/u He and 400 MeV/u C ions at various scavenging times (Figure 2.9).

These data enabled the reconstruction of reaction kinetics and were accurately reproduced by Geant4-DNA simulations (PhD work of Séverine Chefson). Additional measurements were performed using ^{8}Li beams at GANIL (LISE line), within the scope of the CLINM project. Radiolytic yields of phenylalanine and aspartame under He and C ion beams revealed that, unlike HO· and e^-_{aq}, the yields of their main products—tyrosine isomers—did not depend on LET.

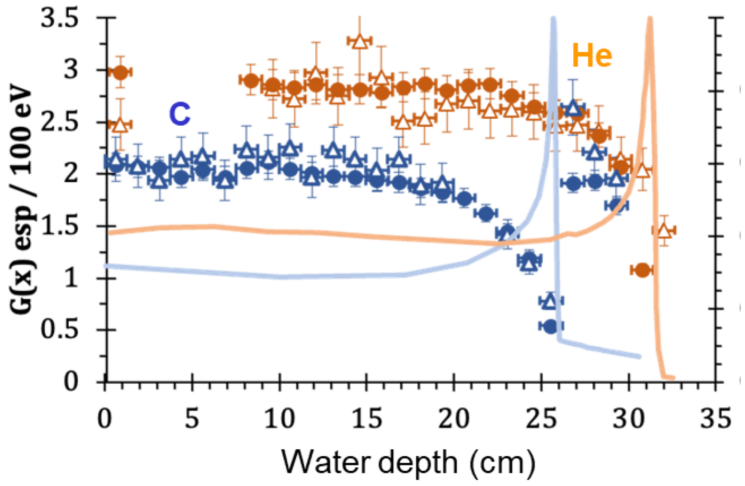


Figure 2.9: Radiolytic yields of HO· (left) and e^-_{aq} (right) along the track of 400 MeV/u C and 230 MeV/u He ions, measured for a scavenging time of 74 ns.

2.2.3.4 5-year prospects

The FOOT collaboration will soon enter an upgrade phase, with MIMOSIS sensors that will replace the MIMOSA-28 sensors in the vertex tracker (see Chapter 4). On a long term prospect, it is planned to extend the collaboration to other IN2P3 laboratories, such as LPSC, which has suggested the addition of prompt-γ measurement in the FOOT experiment. Indeed, the measurement of the γ-spectra could provide additional information on the type of nuclear reactions that occur within the target.
The CLINM project will be extended to the study of other ions than ^{12}C in collaboration with the CNAO hadrontherapy center, as they are currently commissioning new ion sources. A collaboration with the CNES regarding the space radiation protection measurement is currently being built, through a new PhD contract between IPHC and CNES.

2.2.4 Biological effects

2.2.4.1 BioHADRON

Context As previously stated, hadrontherapy provides superior dose precision through the Bragg peak and greater biological effectiveness. Recent biological insights highlight the *stealth-bomber paradigm* [Wozny and Rodriguez-Lafrasse, 2023], a concept describing the highly localized damage caused by carbon ion tracks via reactive oxygen species (ROS), which effectively destroy tumor cells while minimizing off-target effects. This contrasts with conventional photon therapy, which often induces pro-tumorigenic mechanisms such as angiogenesis or metastasis through more diffuse ROS production.

At the current state of the art, treatment planning for carbon ion therapy relies on predictive models of biological dose deposition (e.g., LEM, MKM), though these models remain imperfect and are continuously refined through new biological and physical data. Ongoing international clinical trials are comparing the

therapeutic benefits of carbon ions versus protons or photons, but a lack of long-term data—particularly regarding toxicity and secondary cancers—remains a limitation to broader adoption [Nitta et al., 2022].

Parallel preclinical and translational research is therefore essential to address these gaps. There is also growing interest in other ions such as helium, which may offer a balance between the benefits of protons and carbon ions, but require further biological validation [Chew et al., 2019].

In response to these challenges, the **BIOHADRON** project aims to provide a detailed biological characterization of the response to different ions (protons, carbon, helium) using advanced cellular and preclinical models. The main objectives are:

- Improving biological dose calculations in simulation models (e.g., NanOx, Geant4-DNA);
- Better characterizing the therapeutic advantages of hadronic treatment modalities for radioresistant and hypoxic tumors;
- Ultimately, contributing to improved patient care.

Status A collaboration has been initiated with CNAO, involving Marco Pullia and Angelica Facoetti, to carry out experimental studies using carbon ion beams. The first *in vitro* irradiation experiments on tumor cells were conducted in March 2024, leading to the acquisition of biological data, such as cell survival curves, which will be integrated into the NanOx model (see section 2.2.1.3).
In addition, experiments were conducted to quantify oxidized proteins as biomarkers of oxidative stress, with the aim of validating the *stealth-bomber paradigm*, which focuses on the spatial and temporal distribution of ROS to explain the enhanced relative biological effectiveness (RBE) of carbon ion irradiation. A new experimental series has also been launched to investigate whether the cytosolic DNA cGAS-STING pathway—an essential component of the innate immune response—is activated following carbon ion irradiation, and whether this response differs from that observed after conventional photon irradiation. This study aims to better understand the immunological consequences of high-LET radiation.

In parallel, a collaboration with Dr. Lucie Sancey (Université Grenoble Alpes) has been established to develop the *in ovo* technique as a preclinical model. This approach uses fertilized chicken eggs in which tumors are grafted onto the chorioallantoic membrane (CAM), a highly vascularized structure that enables rapid tumor growth. The CAM model provides an ethical and practical alternative for intermediate radiobiological investigations. The first *in ovo* irradiation using carbon ions was successfully performed at CNAO in April 2025, marking a significant milestone toward validating this model for particle therapy research.

To conduct this work at the IP2I laboratory, a PhD student was recruited in September 2023 (1 FTE, funded by CNRS). The researchers involved are A.-S. Wozny (0.3 FTE) and C. Rodriguez-Lafrasse (0.2 FTE) for the biological part, and M. Beuve (0.1 FTE) and E. Testa (0.1 FTE) for the physical part. For technical support, one engineer (0.3 FTE) and two technicians (2×0.5 FTE) are also contributing to the project.

5-year prospects The project aims to explore the role of cytosolic DNA, small fragments released from the nucleus and mitochondria, in triggering immune responses in tumor cells following irradiation with different ion types (carbon, protons, helium). These studies will help clarify how tumor cells interact with their immune environment under high-LET radiation.
A second objective is to investigate the effects of ion irradiation on tumor cell metabolism and mitochondrial function, including mitophagy, respiratory chain integrity, mitochondrial DNA, and redox status. The goal is to understand how these alterations influence metastatic potential under various oxygen conditions (hypoxia, physioxia).
To support these investigations, biological data such as cell survival curves and confocal microscopy images will be collected and used to refine predictive simulation models for radiotherapy.

Finally, results will be validated using a preclinical model based on tumor xenografts in embryonated chicken eggs, enabling assessment of ion effects in a more physiologically relevant context.

2.2.4.2 Protovec

Context Glioblastomas (GBM) and Pancreatic Ductal Adenocarcinomas (PDAC) are highly aggressive tumors with a very poor prognosis, showing a 5-year survival rate of less than 5%. They are often unresectable and, moreover, resistant to all current therapies (radiotherapy, chemotherapy, and immunotherapy). In this context, it is crucial to develop new therapeutic tools and strategies to more effectively combat these tumors. These neoplasms are notably characterized by a ”cold” tumor microenvironment, in which effector immune cells—such as cytotoxic T lymphocytes and natural killer (NK) cells—are either non-functional or absent. As a result, the immune system is unable to fulfill its natural role of surveillance and control, which normally enables it to detect and eliminate transformed or malignant cells from the body. Oncolytic viruses (OV) like natural rodent protoparvoviruses MVMp (mouse) and H-1PV (rat) are considered a novel form of immunotherapy and clearly represent a new hope in the fight against cancer. They are capable of specifically infecting and destroying tumor cells, such as GBM and PDAC cells, while sparing the normal (healthy) cells of the host. Infection of malignant cells by these viruses triggers immunogenic cell death (ICD). This form of cell death is characterized by the production, release, or secretion of immunostimulatory molecules (PAMPs, DAMPs, tumor antigens) by the infected malignant cells into the tumor microenvironment (TME). This immunostimulatory cocktail promotes the recruitment, infiltration, and reactivation of immune cells—particularly T lymphocytes and NK cells—within the tumors, thereby theoretically enabling the immune system to destroy all malignant cells through the activation of an antitumor immune response. Unfortunately, this response, tested using H-1PV in patients with GBM or PDAC, is currently not strong enough to be curative.

Status This research, conducted within the IMR team of IPHC, investigates the ability of natural rodent protoparvoviruses (PVs), MVMp (mouse) and H-1PV (rat), to convert the ”cold” tumor microenvironment (TME) of glioblastomas (GBM) and pancreatic ductal adenocarcinomas (PDAC) into a ”hot” or inflamed environment where immune cells can once again exert antitumor activity (antitumor immune response).
The aim of my project is to enhance the immunostimulatory potential of PVs by combining their administration with ionizing radiation. I first investigated whether DNA damage induced by ionizing radiation (IR)—specifically, proton beams delivered by the Cyrcé cyclotron at IPHC—could increase the production of parvoviral PAMPs (nucleic acids and viral proteins). The production of these molecules during a standard infection relies on natural DNA lesions (breaks) that occur during the S phase of the cell cycle. These breaks serve as entry points where PVs insert their genome and hijack cellular repair mechanisms to enable viral replication. Applying IR prior to infection is therefore expected to significantly increase the number of DNA breaks and extend their presence beyond the S phase. Using in vitro 2D (IPHC) and 3D (NCT/DKFZ) cellular models of GBM and PDAC, we observed that this strategy effectively enhances PV replication, PAMP production, and even synergizes the cytotoxic effects of IR and viral infection (Figure 2.10). Ongoing studies are currently aiming to confirm these findings in an in vivo GBM model. At present, two full-time equivalents (FTEs) at IPHC and four FTEs at NCT/DKFZ are involved in the project.

This project was funded since 2021 through an ANR PRCI grant, that will end in March 2026, in collaboration with the National Center for Tumor Diseases (NCT), led by Dr. Guy Ungerechts, and the German Cancer Research Center (DKFZ), both located in Heidelberg, Germany. , and lead by an INSERM researcher within the IMR team of IPHC. With the support of E. Santiago (Engineer assistant within the IMR team), a complete cell culture laboratory was equipped and an animal facility was adapted within the Cyrcé platform at IPHC in order to meet the standards required for Biosafety Level 2 (BSL-2). Approvals were

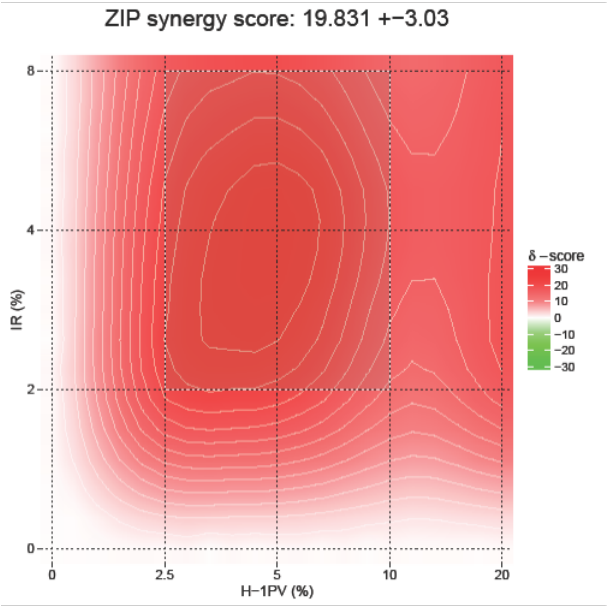


Figure 2.10: Synergy (Score>10) between the cytotoxic effects—measured by MTS assay after 4 days—of proton beam irradiation at various doses (0, 2, 4, 8 Gy) and infection with different doses (MOI; multiplicity of infection of 0, 2.5, 5, 10, and 20 PFU/cell) of H-1PV parvovirus in a 2D culture of U251 human glioblastoma cells.

obtained from the Ministry of Research to conduct BSL-2 experiments in both the laboratory and the animal facility.

5-year prospects New projects will be developed based on the results obtained in the PROTOVEC project, with the goal to study the impact of proton FLASH and α-particle irradiation on the therapeutic potential of protoparvoviruses (PVs) in glioblastoma (GBM) and pancreatic ductal adenocarcinoma (PDAC) models. It explores how these irradiation modalities influence PV-induced oncosuppressive and immunostimulatory responses in both in vitro systems (2D cultures, spheroids, organoids) and in vivo tumor-bearing rodents. A key objective is to assess whether combining irradiation with wild-type or genetically enhanced PVs improves antitumor immunity. The project will also focus on how radiation affects the DNA damage response (DDR) pathways that PVs exploit to replicate, particularly at sites of DNA breaks, potentially revealing new insights into virus-radiation synergy or interference.

2.3 Summary

The growing interest in hadrontherapy, both internationally and nationally, highlights its potential as a powerful cancer treatment modality. As this field evolves, it faces several scientific and technological challenges, particularly in accurate modeling, dose delivery, and understanding biological effects.

IN2P3 has positioned itself as a major player in addressing these challenges through a comprehensive and multidisciplinary approach. Its contributions span from detailed modeling of radiation-matter interactions—using tools like Geant4-DNA, GATE, and NanOx—to the development of innovative solutions for real-time monitoring and dosimetry, as demonstrated in the TIARA and CLaRyS-S2C2 projects.

Moreover, IN2P3 is actively involved in measuring secondary particles and understanding their implications, notably through its participation in the FOOT collaboration and the CLINM project. Its commitment to exploring biological responses at the cellular and molecular levels, via programs such as BioHADRON and Protovec, further underlines the institute's pivotal role in bridging physics and biomedical research.

Altogether, these initiatives illustrate IN2P3's strong engagement in advancing hadrontherapy, not only by contributing to current clinical capabilities but also by paving the way for future therapeutic strategies. The current roadmap implemented through the MI2B GDR and presented in chapter 1 with the implementation of the Hadrontherapy Master Project for the coming years confirms a strategic vision by bringing together the expertise of the IN2P3 teams.

3

New approaches in radiation therapy

3.1 Introduction

3.1.1 Current advances and limitations to treat some cancers

Clinical Radiation Therapy (RT) is currently mostly delivered by external beams (EBRT) with mega-voltage X-ray beams (∼90% to 95%). Over the past two decades, substantial technological advances have revolutionized EBRT, enhancing both its precision and clinical outcomes [Citrin, 2017]. Among these, the advent of intensity-modulated RT (IMRT) and volumetric-modulated arc therapy (VMAT) techniques has allowed highly conformational dose distributions, particularly beneficial in anatomically complex regions (e.g., head and neck (H&N) cancers), resulting in reduced acute and chronic toxicity without compromising tumor control (see Figure 3.1 illustrating very conformal RT treatment isodoses). In addition, Image-guided RT (IGRT) incorporates real-time imaging modalities, such as cone-beam computed tomography (CBCT) or Magnetic Resonance Imaging (MRI), to account for inter- and intra-fractional anatomical variations and facilitate margin reduction. It is essential for hypofractionated regimens, where the biological equivalent dose per fraction is higher. The total treatment dose being delivered sometimes in only 1 to 5 fractions, it was shown highly effective for oligometastatic disease resulting in similar tumor control while gaining significantly in patient comfort and savings by reducing the treatment duration [Rodin et al., 2021].

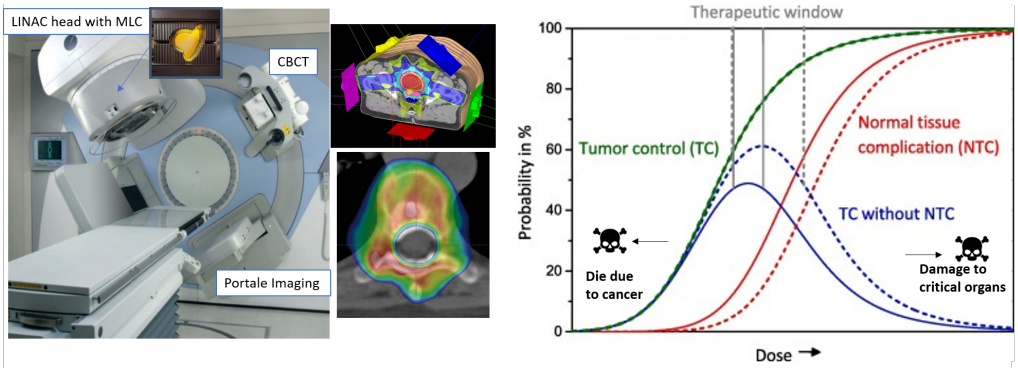


Figure 3.1: Left: typical clinical linear accelerator used in most RT treatment centers, with embedded imaging tools (CBCT, portal imaging...) and the use of multileaf-collimators (MLC) for dose conformity to target volumes. Center: examples of very conformal doses delivered thanks to IGRT and IMRT/VMAT techniques. Right: illustration of the therapeutic window concept, a clinical tool driving dose prescription choices using TCP and NTCP models.

Despite these technological advances, EBRT presents curative limitations especially for highly diffuse, non-localized (e.g. leucemia, multi-metastatic...) and radioresistant cancers. New solutions can play on increasing the efficacy on tumor tissue, clinically modeled by the Tumor Control Probability (TCP), and/or decreasing the damage to healthy tissue, represented by the Normal Tissue Complication Probability (NTCP) models. Proposing a ”new approach in RT” for a certain kind of cancer treatment means increasing its therapeutic window (illustrated Fig.3.1-right).

Among others, targeted RTs bring promising solutions for general cancers by allowing a molecular targeting of cancer cells using a chemical vector injected intravenously. This is the case of targeted radionuclide therapy (TRT), that uses a radiopharmaceutical, i.e. a radioactive isotope attached to a specific chemical vector, producing an internal irradiation only. Other targeted approaches combine both an external irradiation with an internal targeting by a ”neutral” vector, that will act as a contrast agent having higher interaction cross section with the radiation to produce an internal ”boost” of energy deposition where the vector has accumulated. This is the case of Boron Neutron Capture Therapy (BNCT) and of high-Z nanoparticle (NP)-enhanced RT. Another approach allow increasing normal tissue tolerance by playing on

dose delivery modes. This is the case of Ultra-High Dose-Rate (UHDR) therapy (often called ”FLASH” therapy) and spatially fractionated therapy (SFRT) that deliver very heterogeneous doses in target regions. These innovative therapies explore the full spatio-temporal space of treatments and question the standard paradigms of RT history.

IN2P3 has a crucial role to play in these new therapies to help their clinical transfer. The following sections gives a brief context, state of the art and main stakes to be addressed for each approach, and have been grouped into 3 main categories:

- **targeted radiotherapies**: including TRT, BNCT and NP-enhanced RT,
- **new dose delivery modes**: including FLASH and SFRT,
- developments related to the **Understanding of biological mechanisms and patient-data based models**.

3.1.2 Principle, context and main stakes

3.1.2.1 Targeted RT

3.1.2.1.1 Targeted Radionuclide Therapy (TRT)

Nuclear medicine uses unsealed sources for both imaging and treatment of patients, in contrast to radiology and radiotherapy, which utilize external or sealed (brachytherapy) sources. The objective is to selectively target cells of interest using a radionuclide whose emissions enable either visualization (gamma rays, X-rays, β^+) or destruction of the cells (Auger electrons, internal conversion electrons, β^-, alpha particles). A recent paradigm, *theranostics*, combines imaging and therapy within a personalized approach [Filippi et al., 2020, Arnold, 2022]. It relies on using the same targeting vector or chelator, while switching only the radionuclide: one isotope for imaging (e.g., Cu-64) and another for therapy (e.g., Cu-67), or pairs such as I-123/I-131 and Ga-68/Lu-177. This dual functionality paves the way for innovative strategies, including dual-tracer injections, three-photon imaging [Lainé et al., 2024], or whole-body imaging, and enables the potential use of isotopic triplets (for imaging, beta therapy, and alpha or Auger therapy). Applications can be tailored to disease presentation: diffuse tumors may benefit from the crossfire effect of beta emitters, whereas residual or isolated tumors can be more effectively targeted with alpha particles. Certain radionuclides exhibit a natural affinity for specific organs (e.g. iodine for the thyroid, rubidium for the heart [Chatal et al., 2015], radium-223 for the bones [Parker et al., 2013]). However, most applications require a specific targeting vector (such as a chemical molecule, a peptide like PSMA [Sartor et al., 2021], or an antibody or antibody fragment like girentuximab [Shuch et al., 2024]), a suitable chelator, and a radionuclide. Together, these components form a radiopharmaceutical. Two therapeutic radiopharmaceuticals labeled with Lutetium-177 were approved for routine use: ^{177}Lu-DOTATATE for neuroendocrine tumors in 2018 [Strosberg et al., 2017] and ^{177}Lu-PSMA for metastatic prostate cancers (2021) [Sartor et al., 2021]. Currently, over 45 radiopharmaceuticals are in clinical trials using novel therapeutic radionuclides (e.g., ^{177}Lu, ^{225}Ac, ^{212}Pb/^{212}Bi) and imaging isotopes (e.g., ^{68}Ga, ^{64}Cu, ^{203}Pb) [Zaidi, 2017], with growing interest in targeting the tumor microenvironment and exploring Auger emitters. Targeted Alpha Therapy (TAT) showed especially spectacular therapeutic response for

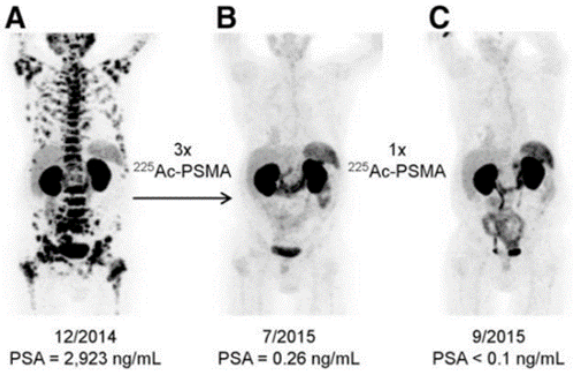


Figure 3.2: Spectacular response of Metastatic Castration-Resistant Prostate Cancer patient using 225Ac-PSMA-617 TAT [Kratochwil et al., 2016]

metastatic prostate cancers (Fig. 3.2 [Kratochwil et al., 2016]), boosting the interest in the field, but also adding challenges in practical use [Eychenne et al., 2021].

Radiolabeling, the process of attaching the radionuclide to the vector, requires high radionuclidic and chemical purity, as the presence of impurities (whether radioactive or stable) can negatively impact labeling efficiency and compromise biological specificity. Therefore, the specific activity must be as high as possible, as well as the extraction efficiency and the plurality of production modes, to meet the growing demand for medical radioisotopes throughout the country. A critical but often overlooked issue is **radiolysis**, where the radiation emitted by radionuclides alters the physicochemical properties of their surrounding medium. This can affect the stability and yield of radiopharmaceuticals. Understanding these effects is essential to ensure reliable formulations.

Another important challenge in the use of TRT is the individual determination of absorbed doses to organs-at-risk and target regions, which relies primarily on the accurate quantification of the radiopharmaceutical biokinetics [Flux et al., 2018, Kesner and Bodei, 2018]. At present, and despite its obvious interest, dosimetry-based treatment personalization is rare, with most therapies relying on fixed activity protocols [Chiesa et al., 2017]. The inability of current gamma cameras to image photons above 300 keV (necessary for therapeutic radionuclides) is one of the reasons for this limitation.

The use of high-LET radionuclides in TAT adds uncertainty to the dose–effect relationship due to highly heterogeneous dose distributions at the micrometer scale, resulting from the vector's tissue distribution, short ion range ($<$ 80 µm), and increasing RBE with energy loss. To improve dose estimation and therapeutic predictions, models should incorporate at least microdosimetry [Tronchin et al., 2022]. This requires thorough characterization of radiobiological mechanisms, potentially distinct from EBRT, due to vector–cell and microenvironment interactions. Extensive in vitro/in vivo experiments are needed, including instrumental and numerical means to assess precisely the deposited dose in biological samples with unsealed sources. IN2P3's detection technologies (Micromegas, SiPMs, advanced scintillators, ...) enable the development of highly sensitive tools for measuring low activities in biological matrices, such as the digital beta-imager developed at Subatech. Then, monte Carlo simulations (e.g., Geant4-DNA) as well as biophysical models can model dose deposition at microscale and integrate the biological-data to better consider dose heterogeneity, RBE, and relevant TRT-specific mechanisms.

To summarize, the main challenges in TRT align with those outlined in the introductory chapter 1 with the two developing Master Projects (*Targeted Radiotherapies* and *Radionuclides for Therapy and Diagnostic*). This broad research initiative aims to advance radionuclide-based therapies through:

- **Innovations in radionuclide production**: identifying high-LET radionuclides of interest, including alpha and Auger emitters and theranostic pairs. Evaluating optimal and alternative production routes based on projectile types, target materials, and irradiation facilities: accelerators of charged particles, reactors, decay chains, and innovative approaches such as laser–plasma acceleration, notably for isotopes like Cu-67 and Ac-225. Scaling up production also involves addressing high-power target issues, particularly thermal effects. Contributing in nuclear metrology with nuclear data acquisition and modeling (e.g. XFOR [Otuka et al., 2014]), and in separation and characterization methods using advanced techniques.
- **Chemical/biological transformations**: developing innovative ligands with enhanced stability and kinetics, where selective separations, radiolabeling strategies, and site-specific bioconjugation is emphasized. Mass separation is considered to complement chemical purification, enabling high specific activity products.
- **visualization and dosimetry control in clinical TRT**: developping advanced imaging to track radiopharmaceutical biodistribution and online gamma detection solutions to allow personalized dose quantification.
- **instrumental development for radiobiology**: to monitor in vitro and preclinical experiments

- **radiobiology to understand and predict clinical efficacy**: investigating biological mechanisms of action — such as DNA, mitochondrial, and membrane damage, immune response, and the impact of vector heterogeneity — both in vitro and in vivo. Develop biophysical models across cellular and multicellular scales to help predicting treatment outcomes for high-LET radionuclides, especially TAT.

3.1.2.1.2 Accelerator-based boron neutron capture therapy

Boron Neutron Capture Therapy (BNCT) is a targeted radiotherapy technique that leverage the unique nuclear reaction between ^{10}B stable isotope and thermal neutrons to produce high-LET alpha particles and ^{7}Li nuclei. Such ions travel less than a cell-size ($< 9\,\mu m$) and may induce lethal damage primarily within boron-containing cells, offering a highly selective approach to tumor treatment. Currently, the main boron compounds used in clinical BNCT are: Boronophenylalanine (BPA), the most widely used in clinical trials, and sodium borocaptate (BSH), that passively accumulates in tumors but has limited cellular uptake compared to BPA. Both compounds have regulatory approval and are under continued investigation for improved delivery, uptake, and selectivity. The clinical potential of BNCT have been demonstrated in the treatment of recurrent, inoperable, or radioresistant malignancies such as glioblastomas, H&N cancers, and melanomas [Shen et al., 2024]. Historically dependent on nuclear reactor-based neutron sources, recent advances in accelerator technology have revitalized interest in BNCT as a hospital-based modality [Kreiner et al., 2016]. Currently, Accelerator-Based-BNCT (AB-BNCT) facilities are being designed and constructed at medical centers around the world, and some are already being used clinically [IAEA, 2023]. Figure 3.3 gives an overview of the world distribution of planned or operational BNCT treatment facilities [1]. Japan, is by far the country devoting the largest effort with 9 AB-BNCT facilities, including one system that was approved as a medical device in 2020 for the treatment of unresectable locally advanced or locally recurrent head and neck carcinoma. In Europe, the first AB-BNCT center has opened at the Hospital of Helsinski (Finland) where the first patient was treated in May 2025 as part of a clinical trial[2].

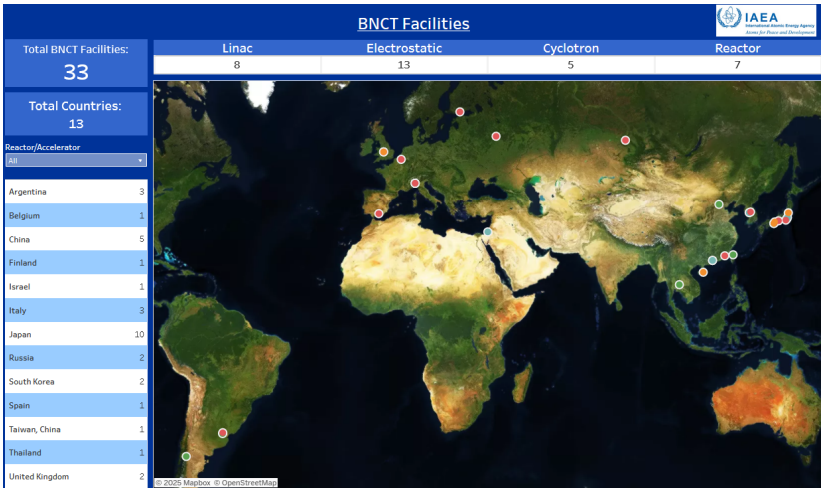


Figure 3.3: Visualization of the IAEA BNCT database showing the distribution of operational research reactors and the planned and operational accelerator based neutron facilities involved in BNCT. Colour code: red = electrostatic; orange = cyclotron; cyan = linac; green = reactor [IAEA, 2023].

As technical solutions progress, the integration of BNCT into routine oncologic practice will depend on coordinated interdisciplinary efforts bridging nuclear physics, radiobiology, pharmacology, and clinical oncology. In terms of AB-BNCT facilities, several technical problems remain. For example target systems struggle to withstand the required beam power (30–75 kW), and frequent automated replacement is needed

1 https://nucleus.iaea.org/sites/accelerators/Pages/default.aspx
2 https://www.hus.fi/en/newsroom/bnct-treatments-cancer-patients-have-started-part-clinical-trial

due to residual radioactivity (e.g., ^{7}Be in lithium targets). Neutron moderation is not yet optimized for producing an ideal epithermal neutron field, and precise spectral and fluence characterization of the neutron field is lacking, limiting accurate dose assessment and clinical comparison. Furthermore, real-time monitoring of neutron production is currently unavailable, making system performance highly sensitive to target conditions and thus unreliable. Dosimetry in BNCT also constitute challenges due to the complexity of the mixed radiation field of various LET. The dose calculation is often separated in four main components: the thermal neutron dose (capture on 14N), the fast dose (elastic scattering of epithermal neutrons on hydrogen), the gamma dose and the boron dose. To account for the biological dose calculation in patients, current protocols are based on either fixed RBE and compound biological effectiveness (CBE) factors [Coderre and Morris, 1999] or isoeffective dose models [Gonzalez et al., 2017] applied for each contributions. These are imprecise as they take little or no account of ion energy loss and heterogeneities at both organs and cellular scales. The use of adapted biophysical models integrated with simulation protocols may play a crucial role in BNCT by providing a framework to predict the biological effects of the radiation dose delivered in cases when experimental data are not available. Finally, to improve both boron-compound developments and relevant biophysical modeling, it is mandatory to better understand and quantify the main biological processes involved in BNCT. In particular, the fact that boron-compound sometimes don't internalize the cells (e.g. BSH) but still can induce very efficient damage when irradiated, despite the very low range of the ions produced, question the DNA damage as the main cause of the radiation efficiency and requires exploring other avenues.

To summarize, several challenges remain to help the clinical transfer success of AB-BNCT. These include:

- Achieving clinically sufficient neutron fluxes with appropriate energy spectra using accelerator-based systems by developing innovative production targets and optimized moderators;
- Developing detectors for online dosimetry control and clinical neutron field characterization;
- Developing and validating new boron delivery agents with high tumor specificity and cellular uptake as well as understanding their radiobiological effects.
- Standardizing treatment planning systems and improve dosimetry models tailored to BNCT's unique biophysical characteristics.
- Demonstrating consistent clinical efficacy through large-scale, multicenter trials;

IN2P3 teams can contributes in most points by providing unique knowledge in detector, neutronics and modeling.

3.1.2.1.3 Nanoparticle-enhanced radiation therapy

Nanoparticle(NP)-enhanced radiation therapy (NERT) is an emerging modality that uses high atomic number (Z) NP to amplify the effects of ionizing radiation within tumors. By interacting with the primary radiation beam, these high-Z NP (composed most often of gold (Au), hafnium oxide (HfO_2), or gadolinium (Gd)) first allow their use as imaging contrast agent, opening the door to theranostic, and can at high dose produce a cascade of secondary electrons and reactive oxygen species, leading to enhanced local dose deposition. First shown in 2004 [Hainfeld et al., 2004], the radiosensitization effect of NPs have been supported by extensive experimental validation, showing NPs efficacy in both in vitro and in vivo systems with either kilovoltage or megavoltage X-rays as well as charged particles [Schuemann et al., 2016]. Recent advances have translated into clinical trials. Hafnium oxide NPs (NBTXR3, Hensify®) have demonstrated safety and efficacy in a phase II/III trial for soft tissue sarcoma and are currently being investigated in multiple cancers including head and neck, liver, and rectal cancers [Bonvalot, 2019, Nanobiotix, 2024]. Gadolinium-based NPs (AGUIX®) are also under clinical evaluation for theranostic applications, combining MRI contrast enhancement with radiosensitization for brain metastasis and glioblastoma [Verry et al., 2021, Biau et al., 2024]. However, the radiosensitization process of NERT is still misunderstood, the field suffering from a

wide range of particle sizes, shapes and preparations resulting in various cell uptake mechanisms that prevent from clear identification of NP efficiency processes. In addition, previous modeling studies [Delorme et al., 2017, Poignant et al., 2021] aimed at characterizing the local high-dose and biological effects impact of the Auger-electron cascade caused by the irradiation of NPs in cells. The conclusions were that the physical boost of energy deposition due to the secondary electrons could not explain alone the larger efficiency observed experimentally in vitro, suggesting an additional radiosensitization effect due to the NPs alone that remain to be elucidate.

Main challenges that have to be addressed:

- **Develop efficient NP for theranostic:** studying biological efficiency according to irradiation type and NP type (coating, material, targeting...)
- **Understand radiosensitization processes**: study biological responses induced by NP-enhanced RT and radiosensitization processes, need for instrumentally equipped irradiation platforms and microscopy analysis
- **Develop multiscale dosimetry models and biological effect modeling** that have relevant outcomes for the application of NPs

In the past 15 years, several IN2P3 teams worked on the subject of NERT. Among them the LP2IB work on understanding the radiosensitization mechanisms in vitro of metal-oxide nanoparticles thanks to the AIFIRA platform unique capability of online imaging at micro-scale during radiation and elemental metal identification in biological samples. The IP2I C. Rodriguez team worked in collaboration with the NHTheraguix company in the development of new generation of theranostic NPs (AGUIX®) for NERT, in order to characterize the influence of the high-Z material used, the surface coating as well as studying radiosensitization mechanisms in vitro. The LPCA developed their own metallic NP to target mitochondria, test their efficacy and study their radiosensitization mechanism of action. Theses radiobiology projects have in common the study of extra-nuclear mechanisms of radiosensitization, on mitochondria, membrane or reticulum stress. Targeted therapies may trigger much complex damage than DNA breaks that are usually only considered in simplified EBRT radiobiology. Besides, as mentioned in section 3.2.1.3.3, other NP-based studies are in progress at Clermont but used for TRT, the NP acting as a functionalized vector of the radiopharmaceutical. Finaly, former modeling activities from LPSC-member and IP2I were done to model nano and micro-dosimetry around Gd and Au nanoparticles (PhD thesis of R. Delorme (2013) and F. Poignant (2019)). These NP-modeling activities are not active anymore at IN2P3, waiting from new insights on the mechanisms on the radiobiological side, except for a perspective work planed in the Moderato project at IJCLab, a more integrated model focused on tumor response (section 3.2.3.2). Only the LPCA project will be described in more details in the ”IN2P3 project section” (section 3.2.1.5).

3.1.2.2 New dose delivery modes

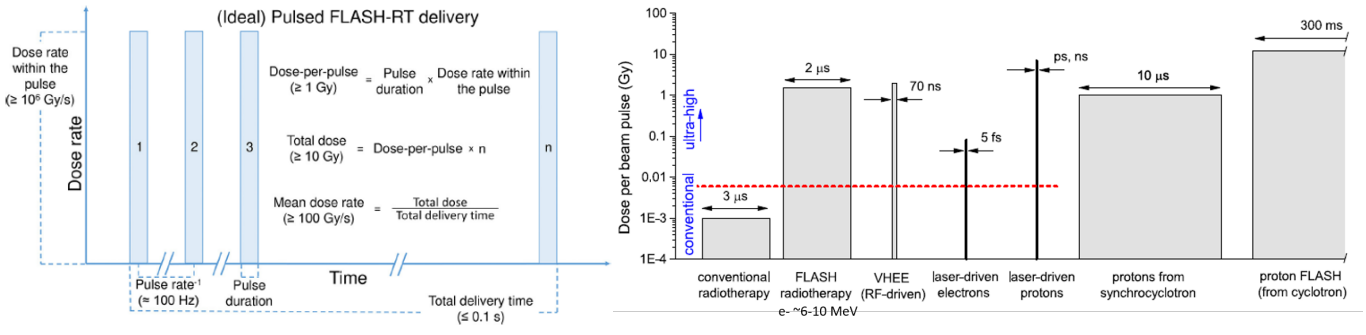
Playing on dose-delivery mode will allow to increase the differential effect between tumor and normal tissue responses. Historically, dose fractionation, i.e. the manner to deliver the total dose in several sessions, was introduced in X-rays radiotherapy to decrease the normal tissue complications because for most of cancers (but not all) normal tissues recover better from radiation damage from a session to another than cancer tissues. A typical fractionation scheme used clinically as a ”standard” is to deliver 1 session of 2 Gy per day, 5 sessions per week, up to the required curative total dose to be delivered as homogeneously as possible with mean dose rate on the order of the Gy/min. A lot of the radiobiological knowledge in terms of organ dose constraints or tumor to normal tissue response ratio for example were empirically based on this typical scheme. However, with the advances in IGRT and EBRT technologies, the dose deposited in normal tissues were drastically reduced, allowing margin reductions. These ”standard” fractionation scheme are not necessarily needed to optimize the tumor response. There is a tendency in clinical practice to go in hypofractionation scheme, that may induce a higher toxicity to tumors now that the potential increased

early toxicity response in normal tissues is manageable with the technical advances. In addition, an evolution of the concept of homogeneous dose in the tumor delivered by either brachytherapy or EBRT extreme intensity modulation techniques has been observed. With these accelerating change of practices, the radiobiological references that were historically acquired are now to be extended and probably redefined to optimize treatment efficacy in a safe way.

Pushing these tendencies to extreme concepts, the ultra-high dose-rate (UHDR) therapy, able to induce a FLASH effect or the spatially fractionated Radiation therapy (SFRT) are both very innovative approaches that have demonstrated preclinical very impressive results in terms of normal tissue tolerance for a same tumor response and are currently increasingly studied to help clinical transfer. Both are on the way of clinical trials but there is still a lot to do to optimize the therapies.

3.1.2.2.1 FLASH Therapy, or Ultra-High Dose Rate (UHDR) therapy

Ultra-high Dose-rate (UHDR) therapy, able to induce a *FLASH effect*, consists of a reduction in toxicity to healthy tissue with equivalent tumor control for the same doses when these are delivered at UHDR ($\succ$ 40 Gy/s on average, typically delivered in milliseconds) compared to the conventional dose rate (CDR, a few Gy/min). Since its discovery in 2014 [Favaudon et al., 2014], it have been an accumulation of biological evidences demonstrated normal tissue protection in lung, skin, and brain [Montay-Gruel and et al., 2017], on various kind of in vivo models including veterinary trials on cats or mini-pigs [Vozenin et al., 2019a]. First-in-human treatments using FLASH was performed for a cutaneous lymphoma in 2019 [Bourhis et al., 2019], demonstrating technical feasibility and clinical safety, which open the way to to translate this to clinical practice. Most of the experiments were conducted on low energy ($\leq$ 10 MeV) electron beams coming from modified LINAC tuned for UHDR, limiting the application of FLASH therapy to surface tumors, but several evidence are now available with protons, either demonstrated with scattered and PBS proton beams [Diffenderfer et al., 2022], and some on X-rays. However, the underlying mechanisms causing the FLASH effect are still under investigation. Hypotheses include reduced production of reactive oxygen species, oxygen depletion, inflammatory processes and altered immune responses [Vozenin et al., 2019b, Friedl et al., 2021]. Some negative FLASH results were reported in the literature showing e.g. unexpected osteoradionecrosis on dog trials [Børresen et al., 2023], showing the limit in fast clinical transfer of this still unknown therapy. It turns that specific time structure and some limits in irradiation parameters may be required. For example, the review of Wilson et al. [Wilson et al., 2020] reports conservative parameters to produce a FLASH affect, with minimal dose per pulse of 1 Gy, total dose of $\geq$ 5 to 10 Gy, mean dose-rate $\geq$ 100 Gy/s and dose-rate within the pulses $\geq 10^6$ Gy/s (see fig. 3.4-left).



(A) **(B)**

Figure 3.4: (A) Important physical parameters to trigger a FLASH effect [Wilson et al., 2020] ; (B) Time structure characteristics according to accel types [Schüller et al., 2020]

There is a multitude of accelerator types capable of delivering UHDR but having very different pulsed time structure that need to be carefully studied in terms of radiobiological impact (see Fig 3.4-right). One

good candidate to allow FLASH treatments of deep-seated tumors are the very-high energy electrons (VHEE) that can be produced by compact RF accelerators or laser-plasma technologies, having extreme time structures with pulses of few fs. All these facilities would require adapted detector systems for absolute dose measurements and beam monitoring without recombination, as is the case with the current smaller ion chamber on the market [Schüller et al., 2020, Cavallone et al., 2022]. If some solutions start to come commercially for punctual FLASH dose measurement in electron beams, as the FlashDiamond system of PTW[1] that can be used up to about 1 kGy/s, solutions are still needed for ion beams, especially for ultra-high dose rates as those possible at ARRONAX (up to 1 MGy/s), and others to provide online and 2D profilers to monitor experimental beams.

In summary, FLASH-RT has the potential to revolutionize radiotherapy by widening the therapeutic window. The major stakes lie in understanding its underlying mechanisms, needing adapted irradiation facilities allowing the exploration of various beam structures, with radiolysis species measurements capability and robust biological models to predict outcomes, optimizing treatment parameters through investigation of various beam structure and particle types, and scaling up to treat deep-seated tumors in clinical settings with adapted online dose monitoring tools.

Main challenges to address in FLASH:

- **Provide irradiation platforms for FLASH radiobiology:** allow studies with different type and energies of ions, and other particles (VHEE, X-rays...) at UHDR regime, with various time-structure of the pulse irradiation. Platforms need equipments for radiochemistry and biology studies (in vitro and in vivo).
- **Detector developments:** develop reliable instrumentation for platforms and clinical facilities for quality assurance, dosimetry and online beam monitoring operational without (charge recombination) at all UHDR regimes
- **Understand chemical mechanisms of FLASH**: effect of UHDR on water radiolysis, according to particle type, time-structure of beam, cell or tissue type (influence Ph, O2...)
- **Understand biological mechanisms of FLASH**: same + study different biolgical models (cell 2D, 3D...)
- **Develop digital twins for FLASH effect prediction as a function of irradiation config**: need for full inclusion of chemical processes in codes and understanding and quantification of biological mechanisms that can be modeled.

3.1.2.2.2 Spatially fractionated radiotherapy (SFRT): micro or mini-beam therapy

Spatially Fractionated Radiation Therapy (SFRT) represents a paradigm shift from conventional uniform dose delivery in radiotherapy to a non-uniform, high-dose pattern—typically delivered in arrays such as grids or lattices [Billena and Khan, 2019]. The core concept behind SFRT is the delivery of high radiation doses in very small beamlets to increase the peak-dose in it exploting the dose-volume effect, separated to get minimum doses between them (valleys) that lead to a reduced toxicity on normal tissues and potentially enhanced anti-tumor immune responses [Cunha et al., 2021].

Originally introduced as GRID therapy for bulky tumors [Myerson and et al., 1995], SFRT has evolved into advanced forms like Lattice Radiotherapy (LRT) and Microbeam Radiation Therapy (MRT, having beam sizes of only 50 to 200 micrometers) or MiniBeam RT (MBRT, with beams of $\geq$ 400 micrometers), supported by modern imaging, treatment planning, and delivery technologies. Preclinical studies and early-phase clinical trials have shown promising results, particularly in treating radioresistant and large tumors, with encouraging normal tissue sparing and immune modulation effects [Wu and et al., 2021, Asur and et al., 2012]. Among new propositions are also the use of proton minibeam [Bertho et al., 2024] or grid-therapy

[1] https://www.ptwdosimetry.com/en/products/flashdiamond-detector

using VHEE beams, to further combine FLASH and SFRT effects [Clements et al., 2023], that may allow easier clinical transfer than MRT. While clinical adoption is still limited, SFRT is gaining attention as a potential complement to immunotherapy, FLASH radiotherapy, and particle therapy due to its ability to reshape the tumor microenvironment and induce bystander and abscopal effects. As for the previous therapies, all is still to do to explore the biological mechanisms explaining the sparing effects and problem the heterogeneous dose deposition can pose in cancer treatments, as well as a need for dedicated dosimetry instrumentation capable to cope with the high resolution of the beam structure.

Main challenges to address in SFRT:

- **develop technical means to provide such irradiation possibilities**: adaption of collimators for X-ray/proton facilities, and propose compact sources (e.g. compact light sources to replace synchrotron beams).
- **Provide detectors to monitor SFRT beams and provide experimental dosimetry:** high spatial resolution, radiation-hard as potential high dose-rate used (synchrotron)...
- **Optimize treatment parameter by simulation:** particle type, energy, beam divergency, etc., provide specific dosimetry metrics (PVDR, peak and valley doses, equivalent uniform dose concepts)
- **Explore biological effects according to irradiation parameters** in terms of in vitro and preclinical response, understand cause of normal tissue tolerance, role of vasculature, immuno response triggered by microbeams...

3.1.2.3 Understanding of biological mechanisms and patient-data based models

A common point in all innovative RT deployment is the need for better understanding the link between physical dose delivery and final clinical response on the entire spatio-temporal space of the treatments in order to propose relevant models to assist the clinical practice for treatment optimization. Some challenges to address (non-exhaustive) can be listed as follows:

- **produce biological data (in vitro, preclinical) to improve relevance of biophysical modeling**: e.g. membrane or cytoplasmic damage can have a role in cell death, especially in targeted RT [Pouget et al., 2015]. Distant effects due to tumor microenvironment and cell-signaling (bystander, abscopal, immuno-response) may also play various importance in targeted RT compared to EBRT or according to particle type. It is important to properly characterize radiobiological mechanisms and quantify their relative importance in order to guide the development of effective vectors and provide relevant biophysical modeling.
- **develop irradiation platforms and instrumentation allowing radiobiological experiments:** having the ability of providing stable and uniform irradiation, with a good control of irradiation parameters, and of accommodating for radiochemistry studies and different biological models (*in vitro* 2D, 3D, *in vivo*)
- **bridge the gap between radiobiological studies with clinical application:** by providing multi-scale modeling tools, or numerical developments for patient-data and image analysis to develop response or toxicity models for personalized treatment efficiency modeling (as TCP/NTCP).

This, by essence, need an interdisciplinary effort of research at the meeting point of physics, informatics, chemistry, biology and clinics. IN2P3 have a crucial role to play by providing unique irradiation facilities, top of the art instrumentation knowledge, and modeling and data analysis capacity to help optimizing the clinical treatments.

3.2 Projects in which IN2P3 is involved

3.2.1 Targeted radiation therapies

3.2.1.1 Radionuclide production, separation and chelation

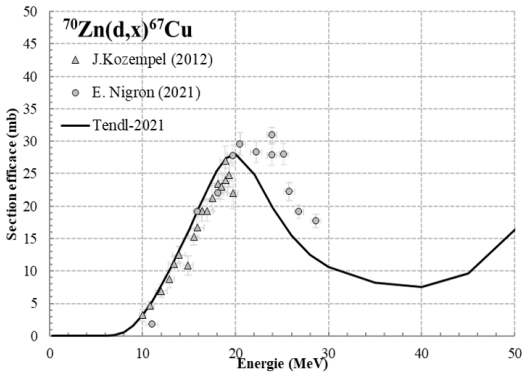
3.2.1.1.1 Radionuclide production at Nantes - ARRONAX

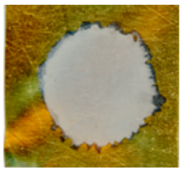
Context : For many years, nuclear medicine focused primarily on imaging with Technetium-99m and limited therapy using Iodine-131 for thyroid cancer. In the 2000s, PET imaging with ^{18}F-FDG revolutionized cancer diagnostics [Zhou et al., 2024], though early therapeutic agents like Zevalin (^{90}Y-labeled antibody) showed limited market success [Doyle et al., 2020]. Since 2013, a third wave has emerged, emphasizing theranostics—combining imaging and therapy—particularly peptide receptor radionuclide therapy [Filippi et al., 2020]. This led to the approval of ^{177}Lu-DOTATATE (2018) for neuroendocrine tumors [Strosberg et al., 2017] and ^{177}Lu-PSMA (2021) for prostate cancer [Sartor et al., 2021]. Currently, over 45 radiopharmaceuticals are in clinical trials using novel therapeutic radionuclides (e.g., ^{177}Lu, ^{225}Ac, ^{212}Pb/^{212}Bi) and imaging isotopes (e.g., ^{68}Ga, ^{64}Cu, ^{203}Pb) [Zaidi, 2017], with growing interest in targeting the tumor microenvironment and exploring Auger emitters.

Status : The PRISMA team (SUBATECH) is involved in radionuclide production since 2004 and the identification of radionuclides of interest to be produced using the unique capabilities of the ARRONAX cyclotron. Many production cross sections data have been generated over the years with a particular interest for deuteron beam, alpha beams and high energy proton beams (above 30 MeV). PET imaging radionuclides were first investigated: Sr-82 and Cu-64 as well as At-211 for which little was known on the chemistry. Works cover cross section data, targetry for high current operations (150 µA on target) as well as chemistry to extract and purify the isotope of interest. Then other radionuclides that may benefit from ARRONAX beam characteristics (Cu-67, Sn-117m, Re-186 . . .) were studied. The goal was to generate new nuclear database and compare different production routes in terms of yields but also purity. A focus was put on deuteron reaction and now alpha particle beam on a wider scale. In parallel, work is shared with the instrumentation's team to identify 3–photon emitters and with chemists to provide element for their studies as for example polonium radionuclides.
In addition, the team is working on target development, in particular on electroplating that provide efficient deposit for high current irradiation. This method was adapted to produce an alloy target of Ni_2Ga_3 that have better thermal properties than Ga targets. Recently, other methods were investigated for lanthanides for which electroplating in water solution does not work. A co-deposition method was set-up and the team is currently developing molecular plating of Gadolinium and plan to look to molten salts. They have experiences on pelletizing.
Finally, they worked with AI4R's device to develop a methodology that allows to differentiate the alpha emission of all daughters of a decay chain as in Ac-225 Figure 3.5.

The team's collaboration includes: INFN Milano (Italy), INFN Legnaro (Italy), CEA (projet ICONE), CEMHTI Orléans, Universitad de Granada (Espagne), CERN MEDICIS, GANIL, IJCLab, ORANO, AI4R, CRCI2NA (INSERM, CNRS, univ-nantes), Services de médecine nucléaire du CHU Nantes et ICO Nantes. Discussions ongoing to collaborate with the Norvegian Center for nuclear research in Oslo (Norway).

In the last 5 years, the team supervised 5 PhD students and published more than 30 journal articles and 2 patents. The researchs were/are funded through MITI (2024-2025) - production of TM165, ANR REPARE (2020-2024) and TTRIP (2021-2025), ISITE NExT; TransForMed (ended in 2024), Dholmen (2025-2028), France relance (AI4R, ORANO) ended in 2024 and Prismap project.





Thickness = 13 µm
(50-µm-thick gold substrat)

Figure 3.5: Left: work done on Deuteron reaction to produce new nuclear data. Right: example of target with Gd deposit obtained by codeposition of Gd–$2O_3$ on a Ni matrix

5-year prospects : In the next 5 years, several challenges will be adressed:

- Perform new cross-section measurements for key medical radionuclides and their contaminants using the stacked foils technique. Key questions include: Can Lu-177 be produced with a deuteron beam? What is the best route for high-purity Tb-155?
- Evaluate stacked foil reactions, such as ^{nat}Ni(d,x)^{61}Cu or ^{nat}Al(α,x)^{24}Na, in light of updated nuclear data.
- Constrain nuclear codes with data on stable product radionuclides by exploring Mass separation—potentially via SMILES.
- Study alpha-induced reactions and production cross sections opened by new alpha accelerator opportunities.
- Explore molecular plating and alternatives (molten salts, co-deposition) for producing enriched and dense targets with favorable thermal properties, starting with lanthanides.
- Study production routes for promising Auger emitters (Ge-71 and Hg-197m).
- Explore the possibility of producing Generator systems for alpha (U-230/Th-226) and Auger (Ru-103/Rh-103m, Pd-103/Rh-103m) emitters, to facilitate the logistics for short-life radionuclides.

3.2.1.1.2 The EUROPA project

Context Conventional radioisotope (RI) production facilities are increasingly unable to meet the growing demand for innovative isotopes in medical research. Although laser-driven particle sources produce average fluxes that are orders of magnitude lower than conventional accelerators [Leemans et al., 2014, Higginson et al., 2018, Modena et al., 1995, Shaw et al., 2021], they are gaining attention for societal applications. Notably, several initiatives have explored their potential for external beam radiotherapy, such as ELIMED, LhARA, LAIA, and the eBeam4Therapy project. While only a few efforts have focused specifically on RI production, promising results have already been reported [Ledingham et al., 2010, Maffini et al., 2023], particularly within the LaserPET and ENSURE projects. These efforts highlight the importance of developing broader collaborative frameworks. In this context, the EUROPA project (lasEr-driven Universal Radio-isOtope Production Accelerator) was recently launched and submitted to the EIC Pathfinder Open call. Led by Subatech (IMT Atlantique), it brings together 25 researchers from 11 institutions across six European countries. French partners include LP2i Bordeaux (CNRS/IN2P3), INCIA (CNRS/INSB and Bordeaux CHU), CELIA (CNRS/INP and CEA), and industrial stakeholders such as Thales Laser and Amplitude. A related initiative, IRABEL, supported by CNRS/MITI and launched in April 2025, investigates bremsstrahlung production from laser-accelerated electrons for RI generation, in collaboration with CELIA

and INCIA. A doctoral project funded by IMT will begin in October 2025 to support these experimental efforts.

EUROPA also involves key collaborations at the European level, including CLPU (Spain), GSI and Focused Energy (Germany), IFIN-HH (Romania), Laser-Lab Europe (Belgium), and the University of Strathclyde (UK). Notably, Dana Niculae (IFIN-HH), a leading expert in radiopharmaceuticals, is actively involved.

5-year prospects : The project aims to demonstrate the feasibility of RI production using laser-driven sources for medical applications. Key challenges—such as limited average flux and broad energy spread—will be addressed through optimized isotope selection strategies and novel purification methods co-developed with domain experts.

3.2.1.1.3 SMILES

Context : Isotopic analysis, while crucial for environmental studies, is also key in nuclear medicine to distinguish isotopes of the same element, as prioritization of an element from another done by the production route is sometimes insufficient [Palenzuela et al., 2021, Gadelshin et al., 2020]. To meet these needs, the SUBATECH laboratory is developing mass separation devices using electrostatic or magnetic fields coupled to laser ionization, as part of the SMILES project (Mass Separation Coupled with Selective Laser Ionization at Subatech). Different kinds of source will be used to desorb neutral species from their backing before laser ionization and mass separation, either through laser desorption or thermal source. These new facilities will be located in a dedicated building at the SUBATECH laboratory on the IMT Atlantique campus in Nantes.

Status : The design and construction of the mass separator system, initiated in 2023, is organized into three phases, with completion expected by 2028:

1. **Charged particle optics simulations:** Using SIMION software [Dahl, 2000], simulations conducted as part of Keerthana Kamalakannan's PhD (2020–2024) helped optimize the setup by analyzing the effects of parameters such as Einzel lenses, voltages, and electrode geometries.
2. **Analytical mass separator development:** A time-of-flight (TOF) system was constructed, first in a linear configuration, then with a reflectron to improve the isotope separation resolution. The separator was successively coupled with desorption laser ionization and thermal ionization sources, using a laser model developed by the LARISSA group (Germany) [Schneider,]. First experiments are scheduled before June 2025.
3. **Magnetic mass separation:** The final phase involves implementing magnetic separation combined with laser and thermal ionization in the newly constructed facility.

In addition, a prototype thermal source was designed to test possible materials, their shaping and the measuring equipment to be used, depending on the temperatures reached, and will be used to validate the ANSYS simulations.

The project include collaborations with GANIL (CNRS), PRISMAP European consortium, Larissa Group University Johannes Gutenberg in Mainz, Germany, MEDICIS (CERN). It was funded by the CPER 2021-2027, supported by IMT Atlantique, with a share of CNRS funding.

5-year prospects : Objectives for the next 5 years are:

- for 2025: an operational linear TOF and oven prototype for thermal study, SMILES lab set-up in new building and magnet call for tenders.

- for 2026: coupling reflectron TOF coupled with laser ionization source and integration of thermal source to start analyses of copper and actinide and to elaborate magnetic separator transport line.
- for 2027: mass separator with operational magnet and test on copper isotopes.
- for 2028: cross section measurements of stable copper isotopes during Cu 61, 64 or 67 productions, mass separation and collection of radium isotopes for realization of a Ra 228 source.
- for 2029: Creation of new research collaboration projects with external partners.

3.2.1.1.4 The PRALINE project

Context : The need for new medical radiopharmaceuticals for more personalized treatments is sometimes hampered by the difficulty of producing radionuclides in sufficient quantity and purity, and of synthesizing bifunctional ligands compatible with a wider range of biological vectors. As part of these studies, terbium (Tb) is an appealing element, offering four clinically interesting radioisotopes with complementary physical decay characteristics [Müller et al., 2012]: 149 Tb ($T_{1/2}$ = 4.12 h, α therapy), 152 Tb ($T_{1/2}$ = 17.5 h, PET), 155 Tb ($T_{1/2}$ = 5.32 d, SPECT and Auger therapy), and 161 Tb ($T_{1/2}$ = 6.9 d, β^- and possibly Auger therapy). Another theranostic pair of interest is 43 Sc ($T_{1/2}$ = 3.9 h, PET) and 47 Sc ($T_{1/2}$ = 3.3 d, β^- therapy).

The **PRALINE** project (Production of Radionuclides and Ligand for Dosimetry and Nuclear Imaging), a continuation of the **PRISM** project (funded by ANR-21-CE19-0037-01 2022-25), aims to optimize 155 Tb production and to develop a proof-of-concept alternative production route for isotopes that are difficult to obtain by usual methods. In addition, the second challenge addressed by the project is to develop previously unavailable terbium-specific bifunctional chelators that are compatible with the use of monoclonal antibodies as biological vectors.

Status : The ^{155}Gd(p,n) reaction has been identified as a promising alternative route for the production of ^{155}Tb. This approach aims to determine the optimal conditions (target purity and beam energy) for maximizing the ^{155}Tb to contaminant production ratio. This is made possible by the production of highly purified ^{155}Gd targets (purity $>$ 99.9%) [Dellepiane et al., 2022] at IJCLab. First results obtained using pure ^{155}Gd targets and complete ^{155}Tb excitation functions are partially published [Bouteculet et al., 2024] and full cross section data for the production of other Tb isotopes will be available in the PhD thesis of M. Bouteculet[1]. Additionally, the maximum contamination level of ^{156}Tb compatible with clinical applications is currently being evaluated through quality imaging studies[2]. Functionalized chelator specifically designed for conjugation to Trastuzumab (Herceptin) were synthetized as suitable for bio-conjugation with Tb. In vivo tests on mice with ^{161}Tb (a β^- theranostic partner of ^{155}Tb) are currently ongoing. Furthermore, a new project proposed by Bordeaux University Hospital (CHU) is being launched, focusing on similar challenges related to the production and chelation of ^{43}Sc, along with the evaluation of ^{44}Sc contaminant [Lima et al., 2021].

PRALINE is a multi-collaborative project, lead by IJCLab (C.O. Bacri), that involved more than 30 permanent researchers, 10 technical staff and 5 PhD Thesis within the last 5 years distributed accross IN2P3 laboratories (IJCLab, Subatech, Arronax, Ganil), CNRS-Chimie (ICMub, ICUNISTRA) and clinical institutes (CHUV, Lausanne; CHU Bordeaux and UJF-Rez-Czech Republic). These researches were/are funded by ANR, grants from European program PRISMAP, CNRS/IN2P3 and MITI, IRSN collab. and LEA (NuAg).

[1] to be defended on September 15th, 2025

[2] This second subject is part of the PhD thesis of M. Hussein, at IJCLab.

5-year prospects : The new PRALINE project will finalize these studies through quantitative dosimetry studies related to contaminant, and added value study of the 155Tb use to image and prepare a treatment with ^{161}Tb vectorized by antibody. Clinical trials using the new bioconjugate ^{161}Tb may also be possible. The ^{43}Sc (PET imaging) will be then investigated with the same methodology in order to study the feasibility of the use the theragnostic pair 43Sc-^{47}Sc [Carzaniga et al., 2017] along with new Sc bioconjugates to be tested in vitro/in vivo. In parallel, the project will take the opportunity of the results obtained in the THIDOS project (see section 3.2.1.2.2) to open-up its use to clinical applications using medium-energy gamma-emitters (200-400 keV).

3.2.1.1.5 The REPARE project @GANIL

Context : Radio-isotopes are used routinely in medicine for both diagnostic and treatment purposes. The potential interest of a given radio-isotope in medicine depends on a number of different factors: specific decay properties, radiological decay half-life, transport constraints, chemical properties and ease of production. Apart from a few exceptions, the required radio-isotopes have to be artificially produced in nuclear reactors or in accelerator centres. A strong limitation of the development of targeted radiotherapy is the supply of medical radioisotopes. A challenge for nuclear physics is to find ways to provide the most promising radionuclide for such applications. The REPARE project (Research and dEvelopements for the Production of innovAtive RadioElements) aims at bringing together research laboratories to develop innovative technologies, adapted at a later stage to industrial production of medical radioisotopes using ^{211}At as a pilot project.

Status : REPARE was an ANR project started late 2029 and which ended in March 2024. It gathered teams from GANIL, ARRONAX, SUBATECH, CYCERON and CERN. Different production methods have been investigated. The main outcome is a high power target using a solid bismuth target. This station has been built and tested at GANIL (see figure). Two targets irradiated at GANIL have been shipped to ARRONAX (1 GBq each).

The liquid bismuth target route has been investigated in detail and the conclusion was a no go for a prototype. Another work package was dedicated to the ^{2}11Rn/^{211}At generator. A test setup has been built to evaluate the physico-chemical properties of several materials for radon. The ^{210}At production cross-section in the alpha+^{209}Bi reaction was measured at threshold energies (S. Ansari-Chauveau, submitted). This measurement is important since ^{210}At beta-decays to ^{210}Po which is a poison.

The team collaborate with GANIL, ARRONAX, SUBATECH, CYCERON, CERN. Research was funded by ANR (2019-2024) and a little from the PRISMAP H2020 project. Apart from the 3 hired persons, it is estimated that about 15 FTE from the collaboration worked for REPARE over the 4.5 years of the project.

5-year prospects : The perspectives for R&D works on the production of innovative radioelements at GANIL is large. Of course this research line is interdisciplinary in essence and GANIL is the starting point: no development of new radiopharmaceutical without regular availability of radioisotopes. GANIL cannot be a production center but it must accompany the research at each level of the process and up to (pre)-clinical studies. Beyond 211At, new isotopes should be investigated (eg other alpha emitters, Auger emitters).

3.2.1.2 Develop detector solutions for TRT personalize dosimetry

Three main projects developing gamma-cameras with complementary technical solutions, are being developped in in2p3 teams, with an ambition of contributing in personalized dosimetry for TRT, working at

high-energy gammas (300 keV). Those are the XEMIS 3-photon camera project, the portable THIDOS gamma-camera and the European AIDER project on optimal design of compton cameras for TRT monitoring. The section gives a brief context for each solution but the technical details on the instrumental developments (XEMIS and THIDOS) are given in the dedicated Chapter 4.

3.2.1.2.1 XEMIS

Context The XEMIS (XEnon Medical Imaging System) projects aim to propose new cameras technology for high energy gamma rays Compton imaging. In the health sector, it is planned to use this new generation of camera firstly in the fields of gamma nuclear imaging at the Nantes University Hospital, then gradually in order to strengthen the role of imaging in internal radiotherapy and, also, in therapies performed with hadron beams. The technologies put forward to achieve this objective are those of time projection chambers (TPC) combined with a liquid xenon (LXe) detection medium. From 2025, the first images should be obtained at the small animal scale using high-energy SPECT, PET and 3-photon imaging. By combining high geometric acceptance with excellent angular resolution, the deployment of new imaging modalities is targeted.

The technical developments achieved and prospects within XEMIS project are described in details in the section 4.4.1.

3.2.1.2.2 THIDOS

Context : Current limitations to propose dosimetry-based treatment personalization are primarily due to the fact that most clinical gamma-cameras used to image the distribution of radionuclides from their gamma emissions are based on Anger's principle, which becomes ineffective when photon energies exceed 300 keV (e.g., ^{131}I, ^{90}Y, ^{177}Lu, ^{225}Ac, ^{227}Th, ^{213}Bi, ^{211}At, ^{212}Pb) [Ljungberg and Gleisner, 2018].

In that context, the objective of the THIDOS project is to propose new instrumental and methodological approaches aiming to strengthen the control of the dose delivered during TRT by reducing the uncertainties related to dose calculation.

The technical developments achieved and prospects within THIDOS project are described in details in the section 4.3.1

3.2.1.2.3 The AIDER project

The AIDER project is a European HORIZON-EURATOM project (2025-2029) that aims at developing a Compton camera (CC) prototype to measure the radiopharmaceutical biodistribution in the body and control the dose administered to the tumour and organs at risk. It gathers partners in France (IP2I and CREATIS in Lyon), Spain, Italy and Germany. In France, the CREATIS-IP2I collaboration is in charge of optimizing the CC prototype by means of Monte Carlo simulations and reconstructing the images. It is based on a former long-term collaboration on CC within the Master Project CLaRyS (2016-2022), the development of the GATE module dedicated to CC modeling (CCmod actor) [Etxebeste et al., 2019] and the "CoReSi" image reconstruction software [Lequertier et al., 2025].

The following funding has been obtained: European HORIZON-EURATOM project (2025-2029), CSIC (Valencia, Spain), IMT (Lübeck, Germany), CREATIS-IP2I-CLB (Lyon, France), Politechnico di Milano (Italy), DAMAVAN Imaging (France), 2 PhD students in Lyon.

3.2.1.3 Improve dosimetry protocols and biological effect modeling

3.2.1.3.1 Microdosimeters for TRT radiobiological experiments

Context and status : The biological effects of alpha particles in TAT must be characterized and considered to predict and understand treatment outcomes. Unfortunately, there are very few dosimetry methods that can accurately quantify the biological effect at the cellular level. In that frame, the GANIL DOSADO team developed a project for dosimetry in TAT. It is part of a program that studies multiscale biological effects for the treatment of brain metastasis [Corroyer-Dulmont et al., 2021, Corroyer-Dulmont et al., 2020]. It began in 2018 with the development of a new dosimetry method adapted for two-dimensional (2D) in vitro irradiations, which was funded by the MITI in 2019 [Frelin-Labalme et al., 2020]. The prototype developed is shown in Figure 3.6.

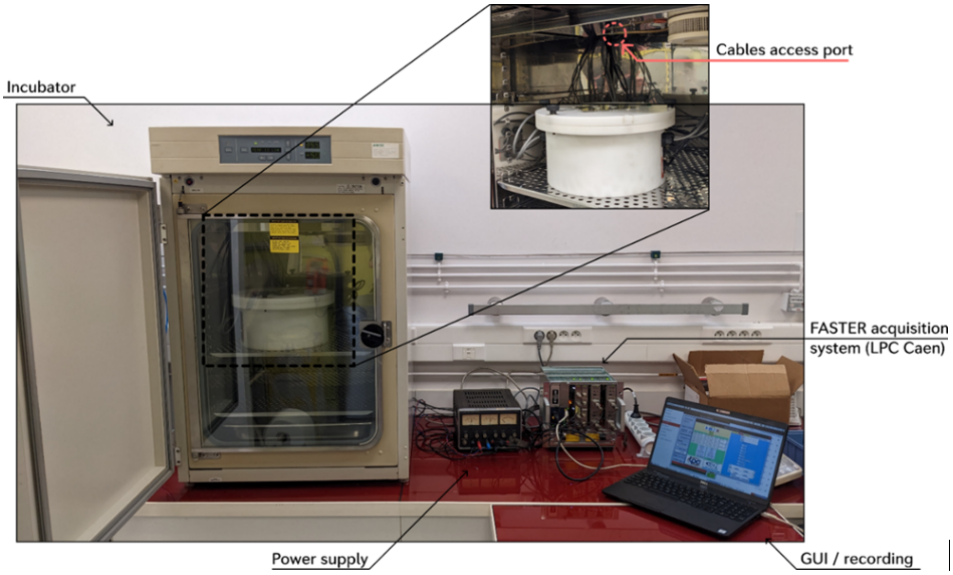


Figure 3.6: Experimental setup of in vitro experiments with alpha radionuclides performed at Caen with the prototype of alpha dosimeter containing four silicon detectors in a waterproof chamber.

From 2020 to 2023, Alexis Doudard developed and evaluated a new deconvolution method for alpha energy spectra for his Ph.D. thesis [Doudard et al., 2023]. In 2024, the project expanded to include collaboration with the LPSC and LITO laboratories to provide experimental data for constraining biological effect models (see next section for more details in modeling developments). In this frame, preclinical in vivo dosimetry implementation has started to evaluate treatment efficiency and toxicity at the small animal scale.

5-year prospects : TAT treatments imply large ranges of dose rate and dose deposition which may necessitates either dosimetry or micro-dosimetry measurements to characterize irradiation effect at the cellular level. To conduct this study, a 2D dosimeter system based on a scintillator and a microscopic system will be developed. This system development and characterization will be part of a PhD. thesis beginning in October 2025. In the long term, the data measured in this experimental program will supplement dose treatment plans (the dosimetry process that is currently implemented) to improve the prediction of TAT treatment outcomes.

This project involved 0.25 eq. FTE permanent/year over 8 years + a PhD at Ganil, and about 10 permanent researchers are involved in the collaboration distributed between GANIL, ISTCT (INSB) – CLCC François Baclesse, LPSC, LITO (INSERM). The project was funded by a PhD grant, and 2 CNRS/MITI

project (Défi ISOTOP, PI: AM Frelin, GANIL in 2019; PIB CNRS/MITI-INSERM PI: R. Delorme, LPSC in 2024). Next funds are expected from A PhD thesis request at the Normandy Region and an INSERM PCSI AAP submitted.

3.2.1.3.2 Biophysical modeling in TAT and BNCT

Context : TAT and BNCT both rely on the biological effects of low-energy ions, with RBE values that can exceed 4. As in hadron therapy, treatment planning requires biophysical modeling to predict biological dose maps. Dosimetry protocols in TAT is the subject of extensive ongoing research [Tronchin et al., 2022, Sato et al., 2021]. In BNCT, treatment planning typically relies on fixed weighting factors that may be dependent on cell type and ion energy and the most advanced model currently in use employs microdosimetry [Inaniwa et al., 2020, Sato et al., 2018]. However, it appears necessary to move down to the nanometric scale to accurately represent the structure of ion tracks, which for low-energy ions laterally extend only a few nanometers. It is also crucial to quantify the impact of unresolved heterogeneities on therapeutic efficacy predictions when these are unknown during the course of treatment. Developing flexible models capable of accounting for such parameters may help defining the range of errors made in treatment prediction efficacy were there are not considered or unknown.

Status - TAT In a multiscale modeling approach, this challenge was addressed by leveraging a suite of tools developed within IN2P3, through a LPSC-IP2I collaboration, and externally with LIRIS and IFIR (Rosario, Argentina). Specifically, for Targeted Alpha Therapy (TAT), the biological dose and the tumor control probability (TCP) was computed for microtumors, as detailed in the PhD thesis of Victor Levrague (2021–2024). To achieve this, the implementation of the NanOx model was extended to accommodate low-energy ions, as NanOx was initially develop and efficiently implemented for medium- and high-energy ions used in hadron therapy. This extension is detailed in the work by Alcocer-Ávila et al. (2024) [Levrague† et al., 2024]. An enhanced version of the CPOP code [Maigne et al., 2021] was used, with developments available in a public GitHub repository [1], to generate geometries of multicellular systems (spheroids). By coupling low-energy Geant4 simulations with the NanOx model through the creation of efficient algorithms, cell survival rates were calculated as well as biological doses within spheroids. These predictions, when combined with a tumor control model, enabled them to forecast TCP with various modeling parameters, as a function of the activity of injected radiopharmaceuticals and intra-cellular and tumor heterogeneities [Levrague et al., 2024a, Levrague et al., 2024b]. The Figure 3.7 illustrate one of the main result obtained in the Victor Levrague's thesis work.

The project involved 6 permanent researchers in the core of the project from LPSC, IP2I and LIRIS (2.5 FTE), + 2 postdocs and 1 PhD student, with in addition the staff members linked to the BioAlto project (see section 4.5.2) that is linked to the project because the beamline was first developed to perform precision biological data at low-energy ions in order to feed the models.

5-year prospects - TAT : The next steps involve generating experimental data to assess the validity of these predictions. The team also aims to extend these calculations to macroscopic tumors and, if feasible, develop a new version of the "BioDoseActor" within GATE (in collaboration with LPCA) to produce biological dose maps and TCP estimates for patients treated with TAT. This work has commenced under a MITI collaboration initiated in 2024 between LPSC/IP2I and GANIL, the J.F. Baclesse Center, ISTCT, and LITO (AlphaBiodose project, continued within the MP Targeted RT program). The objectives include: 1) Producing in vitro (2D and 3D) data of cells irradiated with low-energy alpha particles (SI-Lab@IP2I and

[1] https://github.com/lpc-umr6533/cpop

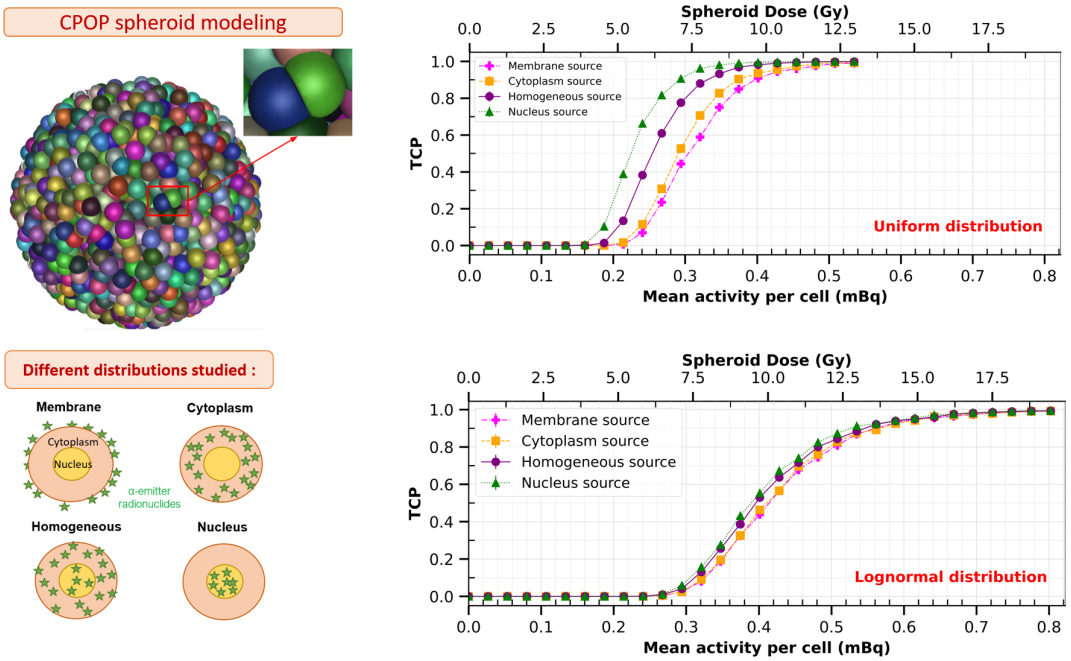


Figure 3.7: Left: Schematic representation of CPOP generated spheroid and heterogeneous intracellular alpha radionuclide distributions studied; Right: results of TCP calculations according to these heterogeneities and cell-to-cell fluctuations of activities (uniform vs lognormal) [Levrague et al., 2024a]

BioALTO@IJCLab platforms) and with alpha-emitting radionuclides (Cyceron), under dosimetric control using the microdosimeter developed at GANIL (see section 3.2.1.3.1); 2) Characterizing and quantifying sub-cellular lethal mechanisms (DNA, mitochondrial, membrane damage) to integrate extra-nuclear damage into the NanOx model; 3) Studying the impact of realistic cell geometry by creating digital twins of the studied cell lines based on microscopy images; 4) Investigating in vivo (mouse models) the intratumoral biodistribution of alpha-emitting radionuclides through multimodal imaging and reconstructing dose maps using AI; 5) Grouping previous data in a multiscale approach to determine biological dose maps.

Furthermore, within the INSERM-CNRS FANTASTIC consortium (French Alpha Network for Targeted and Innovative Cancer Therapy), and subject to funding, its is aimed to standardize physical dosimetry protocols and characterize the biological effects of promising radiopharmaceuticals in a multicenter preclinical study.

3.2.1.3.3 Preclinical and clinical dosimetry of innovative TRT treatments

Context : For over 15 years, the LPCA has collaborated with medical partners and radiobiologists to study the dosimetric and microdosimetric impact of innovative targeted radionuclide radiotherapy treatments or radiopharmaceuticals dedicated to SPECT or PET imaging using the GATE simulation platform (see section 4.6.3). The LPCA has coordinated or participated in several research projects focused on various theranostic molecules and has been involved in clinical translation efforts. The studied radiopharmaceuticals included ^{131}I-ICF01012 for SPECT imaging and treatment of melanoma, ^{177}Lu-Tz for SPECT imaging and treatment of peritoneal carcinomatosis, and ^{99m}Tc-NTP15-5 or ^{68}Ga-bifunctional chelators for targeted SPECT or PET imaging of cartilage. Preclinical studies on rodents (mice or rabbits) were conducted in strong partnership with INSERM IMOST 1240 unit of Clermont-Ferrand while the clinical trials were set up by the Jean Perrin cancer centre.

Status : Until now, two major collaborative projects with INSERM and the Jean Perrin Center enabled dosimetric studies to be conducted first in small animals and then in humans. The first project led to the clinical translation of the ^{131}I-ICF01012 molecule for melanoma treatment [Thivat et al., 2022b, Jouberton et al., 2018, Chanchou et al., 2021], while the second enabled the use of ^{99m}Tc-NTP15-5 for cartilage imaging [Fois et al., 2020, Thivat et al., 2022a]. Absorbed doses to critical organs have been calculated with the GATE Monte Carlo simulation platform from bio-distribution data obtained by organ sampling and by SPECT/CT imaging at different times after injection. S-factors were calculated from rodent and/or human CT scans before the calculation of the doses to organs at risk and targets.

5-year prospects : At the beginning of 2025, the IRHydroBRAIN project was launched to develop an innovative strategy for intraoperative TRT of glioblastoma, based on radiolabeled chitosan hydrogel functionalized with ^{90}Y or ^{177}Lu. Supported by a complementary consortium—including two CNRS research groups (CRAN, UMR7039 Nancy) and the company Nano-H S.A.S. (Lyon)—the goal is to demonstrate improved local control and reduced post-surgical recurrence in vivo. Dosimetry modeling will compare theoretical and experimental results to optimize treatment based on tumor volume and hydrogel diffusion/degradation. Simulations will help optimize the activity deposited in the resection cavity, estimating dose rate and total dose both at the margin and in surrounding brain tissue. In vitro and in vivo models will characterize the hydrogel's conformation, local distribution, influence on tumor cell invasiveness, and degradation over time. Dosimetry will incorporate both physical parameters and in situ radiobiological responses.
LPCA will continue to take in charge innovative dosimetry studies for preclinical and clinical treatments in the objective to support the market introduction of new radiopharmaceuticals. The GATE 10 simulation platform and the Geant4-DNA toolkit will be developed and validated to perform accurate treatment plans. Even if, until now, LPCA worked essentially with beta-emitters, its is aimed at working on the testing of new radiopharmaceuticals based on alpha emitters in a near future.

This activity has been, and still is, financed thanks to various successful ANR projects.

3.2.1.4 BNCT

A BNCT activity has been developed at LPSC for more than 10 years in a multi-disciplinary project team bringing together extensive experience in neutron physics, particle detection (potentiating experience from dark matter measurements) and medical physics to propose relevant developments for BNCT. On a second hand, an activity carried out in collaboration with IP2I concerns the development of multi-scale simulation tools using the NanOx biophysical model to improve predictions of biological efficiency in BNCT, taking into account the great heterogeneity of energy deposit distribution at the micrometric scale. The main achievements and medium-term projects for these projects are detailed in the following 2 sections.

3.2.1.4.1 Optimize beam production in Accelerator-based BNCT and characterize neutron fields

Context : This project 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. This started in the frame of previous Master projects named "AB-nCT", first evaluated in 2015 and reconducted from 2024. The following summarize the main developments performed the last 5 years and those planned in the next 3 in the frame of AB-nCT project, separated in 4 main contributions:

1. **Target Development and Thermal Testing**.

Producing intense neutron fluxes for accelerator-based BNCT (AB-BNCT) requires high-intensity (10–30 mA), low-energy (1–3 MeV) ion beams focused onto small surface areas. Critical criteria for BNCT neutron field production are that a minimal 5.10^8 n/cm^2/s is to achieve to limit the treatment time, and with an optimal spectral epithermal component to treat tumors of few cm deep but of maximum energy of 10 keV to limit the undesirable dose due to fast neutrons. Due to nuclear and material constraints, target options are limited to three materials: beryllium (^{9}Be), lithium (^{7}Li), and carbon (^{13}C).

- Beryllium-9: can be used in solid form due to its high melting point (1287, ℃). However, it's vapor form is highly toxic.
- Lithium-7: is used already in the recently opened AB-NCT center in Helsinski for ex., but the target can age rapidly and need frequent change. Due to its lower melting point (180, ℃) it would be better suited for use in liquid form.
- Carbon-13: offers the double advantage that the neutrons produced have lower kinetic energies—therefore simpler to moderate—than in the case of ^{9}Be, while offering greater mechanical robustness and no toxicity.

All the targets studied by the LPSC team share the use of a rotating system that distributes the power transmitted by the beam over an area larger than its section. A rotating target design on a graphite wheel was developed in the last years (small-scale prototype shown in Figure 3.8-right), on which the reactive material (initially planned for ^{9}Be) must be deposited using a sputtering method integrated into the system, to be able to regenerate the material without changing the target beyond a degradation threshold. In addition, another innovative ^{7}Li-based target with recycling of material was designed and patented in 2020 [Ghetta et al., 2020]. A dedicated 3 kW.cm^{-2} electron-beam test bench was used for thermal resistance validation (Figure 3.8 left) [Muraz et al., 2019]. Graphite-based prototypes achieved 500, ℃ stability under 2.9 kW (Figure 3.8 right). This thermal beamline is maintained at LPSC at the technical platform "Directional detection of dark matter and neutrons for Science and Society" (D2S2) and can be used for material testing in different application fields.

Figure 3.8: Left:3 kW electron-beam test bench. Right: Graphite-based rotating target.

2. **Moderator optimization (BSA)**. The aim is to maximize the treatment depth (TD) for epithermal neutron beams (under treatment time and OAR dose constraints) and propose optimal beam shaping assembly (BSA) systems for BNCT treatment installations. This uses OptTop, a very efficient algorithm based on inverse topological optimization developed by S. Chabod (LPSC) [Chabod, 2019, Chabod et al., 2022]. In the Frame of the CHEMINS IRSN-CNRS project, an optimal BSA solution was found achieving top of the art performance with a TD improved from 7.6 cm (standard) to 10.1 cm while respecting dose constraints on skin and brain (see Fig. 3.9). This involved replacing traditional conical collimators with annular neutron guides, mimicking multi-angle exposure [Chabod et al., 2025].
   Moderators use heterogeneous materials as air, AlF_3 moderating body with neutron "guide" and a LiFPE+LiF filter cone for optimized neutron shaping, supported by detailed Monte Carlo simulations.
3. **Neutron Field Characterization**.

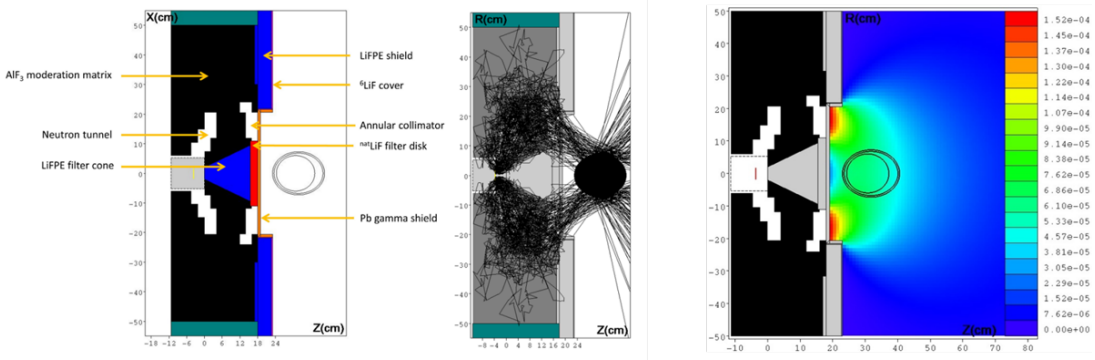


Figure 3.9: Example of topological optimization simulations to design a moderator for AB-BNCT facilities (based on Li target and accel. system as those of the AB-NCT installation of Helsinski) allowing to propose an optimal neutron moderation for beam intensity and spectrum [Chabod et al., 2025]

Tree detector prototypes has been developed in the last 5 years to allow precise measurement of neutron fields in a wide range of energy (thermal, epithermal, fast):

- Neutron Field Monitoring (NFM): Gas detector (Ar/CO_2) with 10^B-coated foil; enables time-resolved neutron flux and alpha/^{7}Li separation (Figure 4.11) [Muraz et al., 2019]. It was developed and used in the frame of E. Mobio PhD thesis and CHEMINS project.
- Microdosimetry with MIMAC-FastN: Measures 3D ion tracks in tissue-equivalent gas. Enables comparison with Geant4 and Geant4-DNA simulations. Will require ionization quenching factor (IQF) measurements at COMIMAC [Sauzet et al., 2020, Beaufort et al., 2024].
- Spectral Characterization: MIMAC-FastN to map neutron spectra in epithermal and fast energy ranges [Santos et al., 2019].

4. **Demonstrator design of optimal AB-BNCT facility**. Finally, these developments are potentiated to define an optimal solution for AB-BNCT, with an objective of standardizing epithermal neutron fields used in clinical treatments and monitor neutron field for clinical intercomparison centers. In recent years, many attempts and discussions with THALES have been made to develop a first demonstrator in France, but these efforts have so far been unsuccessful. The best current option seems to be a collaborative effort with Professor Kreiner's team in Argentina, who developed electrostatic accelerators without moving parts or SF6, and are finalizing their AB-nCT installation in Buenos Aires. Such an optimal system may be potentially hosted at CHU Grenoble or other sites. Components include:
   - Compact deuteron accelerator (1.45 MeV, $>$10 mA). Argentina design.
   - Rotating or fixed 30 kW ^{9}Be or ^{13}C target (WP1)
   - Optimized moderator for epithermal neutrons (WP2)
   - Neutron detection and dosimetry systems (WP3)

Project collaborators include BNCT-Global (W. Sauerwein), IAB-Grenoble (L. Sancey), CHU Grenoble (C. Verry), and TANDAR lab (Prof. A. Kreiner). The project involve about 1.6 FTE (per year) in 9 persons from LPSC, 1.3 FTE from LMDN-Cadarache (including a PhD student E. Mobyo in co-supervision LPSC) and 0.3 FTE from Argentina. It is mainly fund by IN2P3 through the Master project, and other budgets from dark matter activities concerning the instrumental detector developments.

5-year prospects : apart from the global design of optimal AB-BNCT facilty, some specific advances will be adressed. In terms of target design, the mid-term next developments planed in the AB-nCT MP will be to design and develop a demonstrator of ^{13}C based target, to be deposited on the graphite wheel, in collaboration with Prof. Kreiner's group (TANDAR, Argentina). Neutron angular distributions will be measured using MIMAC-FastN [Capoulat et al., 2019]. It will also enable exploratory microdosimetry measurements with a tissue-equivalent gas mixture in France. The new prototype of the NFM detector will be characterized in a high-flux neutron field first at GANIL and then at TANDAR in 2026. in terms of moderation, next

objectives will be to design an optimal moderator and construct it for the Argentina accelerator solution, with possibly the newly designed ^{13}C target and another one to produce the epithermal neutron field of the new T400 accelerator at ASNR-Cadarache, that will be the first metrological epithermal neutron beam in France.

3.2.1.4.2 Biophysical modeling in BNCT

This project, lead by LPSC and IP2I, is related to the previously described project for TAT modeling in section 3.2.1.3.2, as our multiscale modeling approach was designed to be applicable to any therapy involving low-energy and high RBE ions, such as BNCT.

Regarding BNCT an initial estimation of biological dose mapping is proposed by combining Geant4/GATE simulations with data from the NanOx model, following an approach similar to that used for the "BioDoseActor" in hadron therapy. Initiated through the postdoctoral work of Maria Pedrosa Rivera and followed by a collaboration with Prof. I. Porras's team at the University of Granada, this effort compared current BNCT dosimetric methods with our NanOx-based approach, leading to a manuscript in preparation. It is planned to extend the modeling strategy developed for TAT to BNCT to quantify the impact of vector distribution heterogeneities, which are expected to be more significant in BNCT. The goal is to design a BNCT-specific "BioDoseActor" in the coming years. Additionally, the team seeks to expand collaboration with IAB (pending funding) to experimentally validate our calculations on in vitro and in ovo models and study the effects of various innovative boron compounds developed by IAB, with planned experiments at ILL and CNAO (once the BNCT facility becomes accessible).

3.2.1.5 Radiobiology of radiosensitization processes with nanoparticles

Context : This project explores radiobiology with an emphasis on radiosensitization and radio-modulation strategies, which are rapidly evolving to enhance radiotherapy [Gong et al., 2021]. High-Z elements, used with X-ray irradiation, offer increased local energy deposition near tumors [Schick et al., 2024]. Additionally, radio-modulation opens promising avenues for developing protective strategies against radiation-induced side effects, with hibernation-based mechanisms showing particular potential [Cerri et al., 2021, Puspitasari et al., 2021].

Status : Two complementary research axes were initiated through PhD projects launched in 2020 and 2022. The first project focused on the development of mitochondria-targeted gold nanoparticles synthesized via green chemistry, aiming to enhance local dose deposition. Despite effective mitochondrial targeting, no significant radiosensitizing effect was observed on prostate tumor cells. The second project adopts a bio-inspired strategy based on hibernation, using the brown bear model to investigate potential radioprotective effects on human cells exposed to X-rays. Unexpectedly, incubation with bear serum exhibited a radiosensitizing effect on human cells. In parallel, a collaboration was established with an INSERM team in Nantes (Dr. F. Paris) to design a coupled epifluorescence microscope and mini-irradiator system (max 50 kVp), enabling real-time observation of radiation-induced cellular damage. Thanks to top-of-the-art instrumentation development and image analysis, it has bee possible to elucidate the molecular mechanisms underlying mitochondrial DNA maintenance, a critical factor in the emergence of mutations linked to severe pathologies. By leveraging single-molecule biophysical techniques using a spectroscopy equipment, the team has advanced the understanding of DNA compaction dynamics and protein interactions, notably identifying functional consequences of mutations in key mitochondrial proteins such as TFAM and mtSSB, leading to 4 published articles [Martucci et al., 2023, Martucci et al., 2024, Debar et al., 2023, Mehmedović et al., 2022]. In parallel, with the Dutch company (1NA), it develops DNA curtains technology helping to analyze populations of DNA molecules at the same time on TIRF microscopy.

Current project staff includes about 2.7 FTE permanent + a PhD student from the university, in addition to one PhD student (MITI 80PRIME) and an engineer (0.8 FTE) from CNRS. Collaborations include CEA Paris Saclays, INSERM Angers and Nantes, INSB (iGReD), IPHC, IP2I (LabEx PRIMES), INRAe (Human Nutrition Unit) and Gotenburg Univ. (Pr. Falkenberg). This is funded thank to LabeX PRIMES, MITI80Primes, an Emergence Program, Dutch fundings, AFM-telethon and completed by lab fundings. Over the past five years, 4 PhD theses have been defended on the 3 projects (Eguida J. (2021) and Tabanou T. (2024), Martucci M 2023; Debar L 2023).

5-year prospects : The radiosensitization integrated project will consists of three partially independent tasks. Task 1 focuses on investigating the radio-sensitizing effects of hibernating bear serum on human cells, aiming to identify the underlying mechanisms and active compounds. Task 2 explores nanoparticle-mediated dose enhancement through mitochondrial pathways, in collaboration with IN2P3, with emphasis on metabolic effects. Task 3 involves the development of a prototype system coupling an epifluorescence microscope with a mini X-ray irradiator, enabling real-time monitoring of radiation-induced cellular changes and associated dosimetry. On the DNA maintenance side, future research will focus on the interplay between mitochondrial DNA compaction and repair mechanisms, and on elucidating the impact of specific protein mutations on mtDNA stability.

3.2.2 New dose delivery modes

3.2.2.1 FLASH

3.2.2.1.1 Understanding mechanisms of FLASH therapy

Context : Since the discovery of the FLASH effect in 2014 and despite accumulation of biological evidences, underlying mechanisms causing the FLASH effect are still unknown. Exploring UHDR requires suitable beams, specific dosimetric tools, radiolysis species measurement skills, strong links with biologists and models able to reproduce experiments and predict the effect. Monte Carlo track structure (MCTS) codes are used for micro and nanodosimetry (molecular level) by estimating the detailed clustering of individual energy depositions (mainly by atomic ionizations and excitations) along the track of ionizing particles and subsequent free chemical species diffusion and interactions in liquid water or with DNA molecules. Over the past five years, the LPCA has been committed to the development and validation of water radiolysis under ultra-high dose rate (UHDR) irradiation conditions to understand the role that certain radiolytic species may play under varying pH, oxygen concentration, dose rate, or LET conditions in explaining the 'FLASH' phenomenon. In the same way, Subatech developed innovative beam monitoring tools, validate UHDR dosimetry system onto Arronax cyclotron beam lines. FLASH community first gathered mainly biologists and physicist while chemistry issues were pointed. In this context, based on its radiochemistry skills, Subatech decided to investigate UHDR chemistry, providing experimental insight to biologists and dataset to challenge models. In addition to Geant4-DNA, other simulation codes such as TOPAS-nBio, gMicro-MC, and others are also being developed and validated to address this question. The challenge lies in comparing these codes with one another, as well as confronting them with experimental results.

Status : In 2020, the LPCA partnered with the Subatech laboratory on the FLASHMOD (PCSI) project led by the ICO-Subatech in Nantes. This project aimed to develop a comprehensive environment around the ARRONAX proton beam to study the FLASH effect [Koumeir et al., 2019]. It included the technical implementation of pulsed irradiation modes allowing dose rates ranging from 1 mGy/s to 1 MGy/s, their physical dosimetry, as well as in silico and in vitro studies of water radiolysis (including the study of H_2O_2 production) and biological damage on endothelial cells and zebrafish.

Subatech developed innovative beam monitoring dedicated to UHDR: photomultiplier is daily used to perform time resolved dosimetry, while Bremstrahlung effect and othrochromic OC1-films have been validated for in-vivo dosimetry. For this project, the LPCA fully simulated the irradiation beam using GATE and validated its dosimetry with experimental measurements. This work led to a first publication in the journal Medical Physics [Fois et al., 2024] and additional papers in collaboration with Subatech and IP2I [Blain et al., 2024, Maigne et al., 2022, Ali et al., 2022a].

Since 2021, Subatech started water radiolysis investigation under both UHDR and conventional dose-rate, showing a drecrease in H_2O_2 production under protons beams with increasing dose rate, thanks to a post-doc position funded by FLASHMOD (PCSI) project [Bongrand et al., 2021].

In 2022 and up to now, the effect of hydrated electron (e^-_{aq}) scavenging and oxygen content onto H_2O_2 production yields was performed [Blain et al., 2022]. Up to know, a PhD student funded by Subatech and Nantes-University is studying microsecond transient hydrated electron yields Vs oxygen content and pH, taking advantage of the pulsed radiolysis system developed during the last decade, using Arronax pulsed beams. At the same time, biological studies onto zebrafish embryos and endothelial cells were achieved in collaboration with biologist from US2B laboratory trying to link chemical measurement to biological observations [Ghannam et al., 2023].

In 2023, LPCA obtained from IN2P3 a PhD grant to continue the work of simulation started in 2020. LPCA has continued its collaboration with ICO, Subatech, ARRONAX and LP2I to validate the Geant4-DNA code under proton and alpha beams to consolidate previous results by new comparisons involving other radiolytic species, such as e^-_{aq} and $\cdot O_2^-$ to further study the mechanisms underlying the FLASH effect [Terfas et al., 2025]. Proton and alpha beams are now simulated with GATE 10 and different dose rates, pH and oxygen levels are tested with a beta version of the Geant4-DNA code to reproduce experimental measurements of H_2O_2 and e^-_{aq}. A paper showing comparisons between experiments and simulations should be submitted this summer.

In 2024, a dedicated small animal holder for both imaging and UHDR irradiation was build by subatech, coupled to associated dosimetry validation, opening the way to further studies [Evin et al., 2024]. In 2025, LPCA, LP2IB and Subatech strengthen their collaboration onto GATE and G4-DNA model validation by new experimental results using recently obtained chemical yields under fractionated UHDR beams, using pulsed radiolysis as well, starting time structure effect onto radicals and H_2O_2 yields.

5-year prospects : The fruitful and highly interdisciplinary collaborations that have been established between several IN2P3 teams are intended to be expanded to lead to studies on the production of reactive oxygen species in more complex cellular environments. The simulation work should be extended to bio-equivalent media and not only to pure water. LPCA will continue the validation of Geant4-DNA on different types of ion beams and will integrate all relevant Geant4-DNA developments into GATE 10 through a ChemistryActor. Subatech will keep on investigating experimental chemistry of FLASH, targeting LET influence using He^{2+}, time structure effect and superoxide as key species for biological effect using pulsed raiolysis in water and biomedia.

The FlashDanze project have been submitted to the PIANOFORTE call, it will be led by ASNR and LPCA activities will be included in the WP3 concerning the mechanistic simulation at the sub-cellular scale, while Subatech will provide experimental data in WP2.

Subatech will also start some studies about opportunity to couple UHDR to Spatially Fractionated Radiotherapy (SFRT) in collaboation with Team Innate Immunity and Cancer & InGenO laboratory (INSERM $CRCI_2NA$, Pierre Vidi).

This work was funded mainly through the PCSI FLASHMOD project (including 5 Postdoc positions) and by 2 PhD grants (1 IN2P3 and one form Nantes univ.). In the future, application to an ANR and the Pianoforte call. The full collaboration include 3 IN2P3 labs (Subatech (lead), LPCA and LP2IB), CLCC

ICO Nantes, Nantes-Université-INSERM US2B, Dredse Flash team (Germany, Elke Beyreuther et Joerg Pawelke) and will integrate soon IPHC and CIMAP/GANIL whithin the next MP dedicated to FLASH that will start next year (see also next section about radiolysis work for FLASH).

3.2.2.1.2 Radiolysis of Biomolecules for FLASH irradiation

This is part of the activity on radiochemistry for ion beams of the IPHC team, already described in section 2.2.3.3. This section focus on the FLASH-related developments of the team.

Status : In a context of FLASH therapy, there is an interest in better understanding the dose-rate effects on the radiolysis of water and biomolecules, as well as the impact of oxygen. Using specific probes, the IPHC team has shown that the radiolytic yields of ·OH and e^-_{aq} remain unaffected by dose rate under 24 MeV proton (H^+) irradiation, from conventional dose rates (0.1 Gy/s) up to 200 Gy/s, for scavenging times up to 300 ns. With the same probes, it was determined that the radiolytic yields of these species decrease with helium (He) and carbon (C) ions for dose rates above several kGy/s.

As for protein biomolecules, it has been noticed that under conditions where no dose-rate effect was observed on water radiolysis, a clear dose-rate effect appeared on 2,5-DOPA and an aspartame analog. Their relative yield increases significantly with dose rate, suggesting that this effect originates from radical–radical recombination occurring within and between ion tracks (Figure 3.10). The formation of tyrosine isomers and analogs remains unaffected by dose rate.

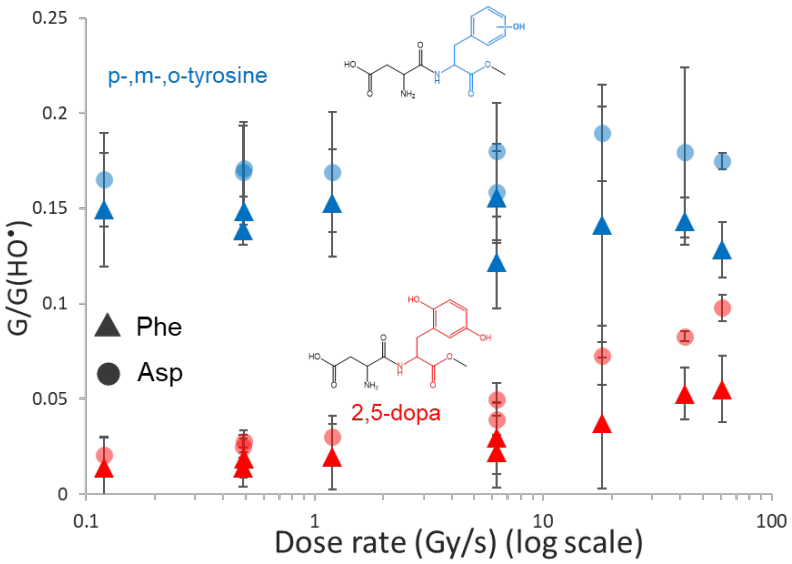


Figure 3.10: Dose rate effect on the radiolysis products of phenylalanine and aspartame, under 24 MeV H^+ irradiation.

The scientific developments of this project have led to an applied project focused on the development of thin dosimetry films for skin dose measurement during treatment. This project was funded by CNRS Innovation (CNRS Prématuration, Q. Raffy, 2023–2025), and continues through a new prematuration phase funded by SATT (2025, Q. Raffy and L. Huart). Collaborations include Icube and the platform Acacia, NIRS-QST (Japan) and CNAO (Italy), ICANS, Aerial-CRT (Illkirch) platform as well as G4-DNA collab and CEA Saclay with G. Baldacchino.

5-year prospects :

- Study of the impact of O_2 concentration on dose-rate effects observed in biomolecule radiolysis.
- Comparison of results obtained using probes (IPHC) and by μs-pulsed radiolysis with experiments at Arronax, in collaboration with Subatech.
- Measurements of water radiolysis species and biomolecule radiolytic yields under ultra-high dose-rate H^+ irradiation at HIMAC.

- Dose-rate effects on radiolysis of water and biomolecules under electron and X-ray irradiation, within the joint laboratory with Aerial-CRT.
- Study of more complex peptides to identify potential intramolecular radical–radical transfer processes that may occur in proteins.
- Investigation of the evolution of radicals formed in proteins under irradiation, using low-temperature (26 K) irradiation conditions.

3.2.2.1.3 Dose monitoring for FLASH therapy experiments

Several developments are done at IN2P3 to find innovative solution for UHDR beam monitoring, that are described in more details in the Chapter 4.

A diamond based solution to monitor proton and alpha beams have been developed by LPSC, with the DIAMMONI prototype currently installed on the ARRONAX beamline (see section 4.2.2.1). Besides, several ultra-thin and portable PEPITES prototypes (see section 4.2.2.2) are been developed to monitor FLASH beams either in terms of intensity (SPLIF) than in profile (SPLAF). They also have a new project in collaboration with LOA to work on monitoring of ultra-FLASH beams as such produced by laser-plasma with few fs of pulse-length that brings additional measurement constraints. Such Laser-plasma beams are of particular interest for FLASH as there are high candidates to produce VHEE beams, that may be the best solution to treat deep-seated tumors with UHDR.

Finally, an important effort is done on instrumenting the IN2P3 ion beam platforms to allow various FLASH experiment with a high precision on the delivered dose. This is the case on ARRONAX ion beams, as previously described in the section 3.2.2.1.1, as well as the BioALTO platform that should evolve, after the commissioning phase and first radiobiological experiments at conventional dose rates (planned 2026), to UHDR regimen with dedicated instrumental diagnostic developments: a new prototype of the already-installed diamond detector monitor (on the model of the DIAMMONI system) and an innovative solution of non-interceptive detector based on air fluorescence (see section 4.5.2).

3.2.2.2 SFRT

3.2.2.2.1 Diamond detectors for microbeam dose monitoring

Context : The advent of synchrotron radiation (SR) has significantly expanded the use of X-rays in imaging and radiotherapy (RT) [Suortti and Thomlinson, 2003]. In RT, although SR beams have relatively low penetration energies (102 keV), this is offset by: (i) high dose rates to exploit the FLASH effect [Favaudon et al., 2014]; (ii) high coherence enabling submillimeter fields and spatial dose fractionation used in microbeam radiation therapy (MRT, e.g., 50 µm wide beams separated by 400 µm) [Eling and , 2019]; and (iii) combination therapies with high-Z radiosensitizers [Bort and , 2020].

A phase I/II clinical trial of SR-RT was recently conducted at ESRF with a dose-escalation protocol on 15 patients [Adam and , 2016]. MRT is progressing toward clinical application [Eling and , 2021]. It is particularly promising for treating radioresistant tumors, including pediatric brain cancers, due to its ability to spare healthy tissue while delivering high tumor doses. Preclinical MRT research has been carried out at ESRF and the Australian Synchrotron (AS) [Davis and , 2021], including translational work on veterinary patients [Adam and , 2022] and mini-pigs [Coquery and , 2019].

Accurate dosimetry of SR X-rays remains a challenge and a key factor for safe clinical implementation [Smilowitz and , 2015, Verhaegen and , 2018]. Diamond detectors are a promising solution due to their radiation hardness, high carrier mobility, and tissue-equivalent atomic number.

Status : A diamond-based microstrip detector (with 153 strips equipped with individual charge integration channels (ASIC)) for MRT beam monitoring and portal dosimetry was developed at LPSC and tested at the ESRF and at the Australian Synchrotron. The technical achievement is described in section 4.2.2.1 and illustrated in Figure 4.7. The detector demonstrated linearity over a wide range of doses and dose rates relevant to MRT (1 Gy/s to 10 kGy/s) [Rosuel, 2021b, Di Franco et al., 2023]. Dosimetric measurements in solid water phantoms also showed good agreement with theoretical and Monte Carlo calculations (see Figure 3.11).

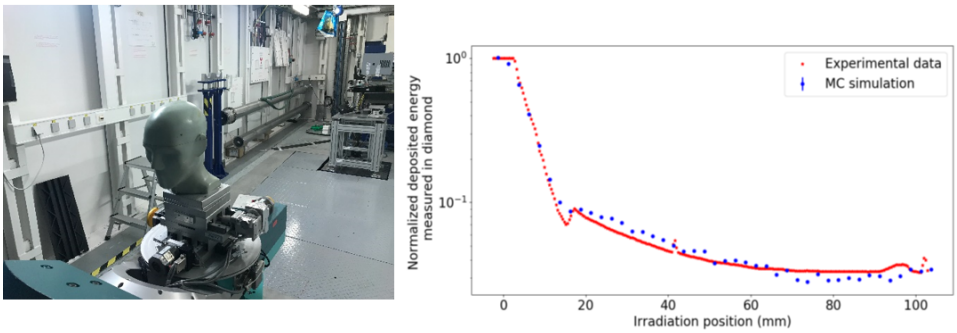


Figure 3.11: Left: irradiation of an anthropomorphic phantom at ESRF/ID17. Right: measurement with the diamond detector of the response to a single microbeam during a vertical translation of the phantom, compared to a GATE simulation (N. Rosuel Thesis)

5-year prospects : The use of research synchrotron accelerators is hardly compatible with routine hospital-operation, and more adapted solutions for clinical environment are necessary. Compact light sources, such as the Munich one [Dombrowsky et al., 2020], provide an alternative and promise to fulfill the demand for more affordable and accessible hospital-sized sources with very high brightness and tunability compared to x-ray tubes. A new perspective of the project is to design, manufacture and characterize a large area, diamond-based pixelated detector for beam monitoring in medical and biological studies, quality assurance and transit dosimetry at compact light sources, small-animal irradiator and if feasible clinical state of the art machines such as the cyberknife®.

This work is performed in collaboration between LPSC, the STROBE team (INSERM), and INL (INSIS), with 1 FTE permanent per lab involved + 1 PhD and 1 post-doc at LPSC. In addition, there is collaboration with the CHUGA hospital for clinical trials, and with Néel institute (NanoFab platform) for the diamond developments. This research was mainly funded by a PCSI project and the Labex PRIMES for a PhD grant and equipment and beam access costs solicitation. A PhD, funded by LabEx GIMED (UGA), will start in 2025 for the realization of a new upstream detector.

3.2.2.2.2 Exploring new approaches in SFRT

Context : Very High Energy Electrons (VHEE) are promising due to their dosimetric advantages compared to conventional X-rays, as well as their potential combination with FLASH dose rates or spatially fractionated dose delivery for the treatment of deep-seated tumors [Clements et al., 2023]. Prior to clinical application, it is essential to thoroughly characterize their biological impact on tissues and to develop appropriate dosimetric tools for these high-intensity beams delivered in ultra-short pulses (ns – fs range).

Status : This work aimed to characterize by Monte Carlo simulations, in terms of physical and radiobiological figures of merit, different SFRT approaches with various particles, including VHEE, to optimize they use in preclinical experiments. It also include experimental dosimetry measurements for MBRT in vivo

experiments [Gonzales et al., 2020], and at UHDR electron-beam facility, as well as laser-plasma beams, to explore dosimetry solutions for future VHEE beams in combination or not with grid therapy.

Using Monte Carlo simulation with GATE and the Microdosimetric Kinetic Model (MKM), the theoretical RBE, microdosimetric characteristics, and the number and types of DNA strand breaks induced by VHEE microbeams were determined, comparison with other established clinical beams (clinical electrons < 20 MeV, X-rays, protons, and carbon ions) was done. Notably, it was shown that the RBE of VHEE should be comparable to that of clinical electrons, despite exhibiting a higher LET, which could facilitate the rapid clinical implementation of these beams [Delorme et al., 2021, Dos Santos et al., 2020]. In addition, a radioprotection study was conducted to evaluate radiation constraints for a possible VHEE treatment room [Masilela et al., 2021].

Besides, experimental campaigns conducted on intense electron beams aimed to assess cellular responses under fs laser-plasma electron beams with dosimetric control, performed at LOA [Cavallone et al., 2021], and to determine recombination correction factors for the use of a commercial ionization chamber under FLASH dose rates [Cavallone et al., 2022].

This work was initiated at IMNC (now "pole Santé" at IJCLab) in the Y. Prezado team from 2016 to 2019, and continued in 2020 - 2022 at LPSC in collaboration with Institut Curie, LOA, and the Lausanne University Hospital (CHUV). This VHEE/SFRT activity is not anymore active at IN2P3, due to a lack of manpower and time, but may be restarted in few years in case of collaborative opportunities, and if available VHEE platforms to assess radiobiological experiments would open in Europe to test the grid and/or UHDR combination with VHEE.

3.2.3 Understanding of biological mechanisms and patient-data based models

3.2.3.1 Correlation of MRI data analysis to predict tumor response to RT

Context : The Lyon University Hospital hosts France's first MRI-Linac (Unity) enabling real-time MRI-guided radiotherapy (RT) for adaptive, personalized treatment based on tumor and tissue characteristics. While quantitative MRI has been linked to clinical and genomic data, its correlation with spatial biological data remains unexplored. This project aims to combine MRI with multispectral microscopy in a mouse model of oropharyngeal cancer, to identify radioresistant tumor regions and build a tumor control prediction model (TCP). A retrospective clinical study will then validate these MRI parameters using patient data treated with MRI-Linac.

Status : It cannot be carried out in humans without the completion of a pre-clinical study on a mouse model of oropharyngeal cancer. In first phase, the mouse model will be used to correlate MRI (quantitative/radiomic) with spatial biological data (multispectral microscopy), enabling the identification of reliable MRI markers of radioresistance (Figure 3.12). Started in 2025 with funds from the Ligue contre le cancer,

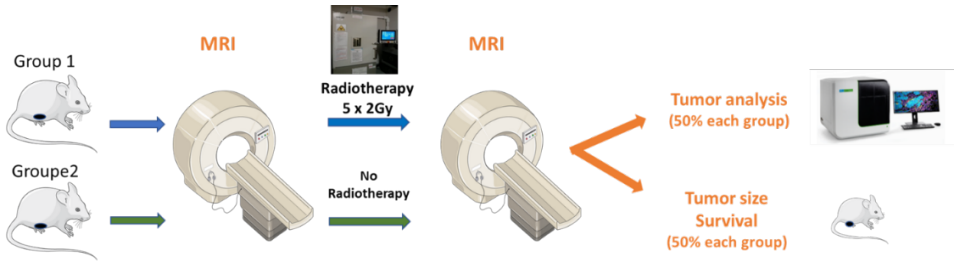


Figure 3.12: Experimental protocol for, 1) the validation of the mouse model, calibration of MRI images and tumor sections, 2) the correlation of radiobiological data and radiomic parameters (shown)

the project began with the recruitment of a Labex PRIMES-funded postdoc and the animal study will start in July 2025. It involves an interdisciplinary team of radiobiologists, imaging experts, clinicians, and physicists

from UMR CNRS 5822 IP2I and LabEX PRIMES (CREATIS, in collaboration with radiotherapists from the Lyon-South Hospital Group.

5-year prospects : The goal is to create MRI-based maps of tumor radioresistance to enable adaptive radiotherapy and improve tumor control by the end of 2015. After a preclinical study, parameters will be validated on surgical specimens from 15 patients with oral/oropharyngeal cancer by correlating biological data with pre-surgical imaging (end 2027). This will adapt the mouse-derived models to human tumors before launching a phase II clinical trial of daily adaptive RT with targeted dose escalation (2028-2029). The final clinical objective will be to enable dose adaptation at each RT session, allowing to improve survival, reduce toxicities, and enhance patient quality of life.

3.2.3.2 MODERATO

Context : The new MODERATO project aims to develop increasingly complex biological models to study cellular responses to radiation and integrate these findings into predictive mathematical models of tumor growth. This interdisciplinary effort combines experimental work (2D to 3D cell models and time-lapse imaging) with theoretical modeling (beyond the linear-quadratic (LQ) model), led by two IJCLab teams (P.I M. Badoual). Current clinical LQ-based models does not consider key factors like cell-cell interactions, hypoxia, and 3D growth [McMahon, 2018]. MODERATO seeks to address these gaps by generating experimental data to inform multiscale models, eventually linking subcellular radiation effects (e.g., via GEANT4-DNA) to tumor-scale behavior. To build the model, videomicroscopy will be used thanks to fluorescent-labeled cells enable real-time tracking of post-irradiation responses, supporting standardized, quantitative analysis for model development.

Status : The preliminary MODERATO project, launched in 2023 for three years, involves two main research axes through two PhD theses. Marianne Billoir's work (defense Oct. 2025) focuses on modeling glioma tumor population behavior to refine the LQ model for radiation response, successfully fitting data with only three parameters [Billoir et al., 2025]. Joséphine Courouble's thesis (defense Oct. 2026) analyzes individual mammary tumor cells using machine learning and lineage tracking to correlate cell fate (proliferation, senescence, arrest) with radiation dose, aiming to understand how resistant clones emerge post-treatment.

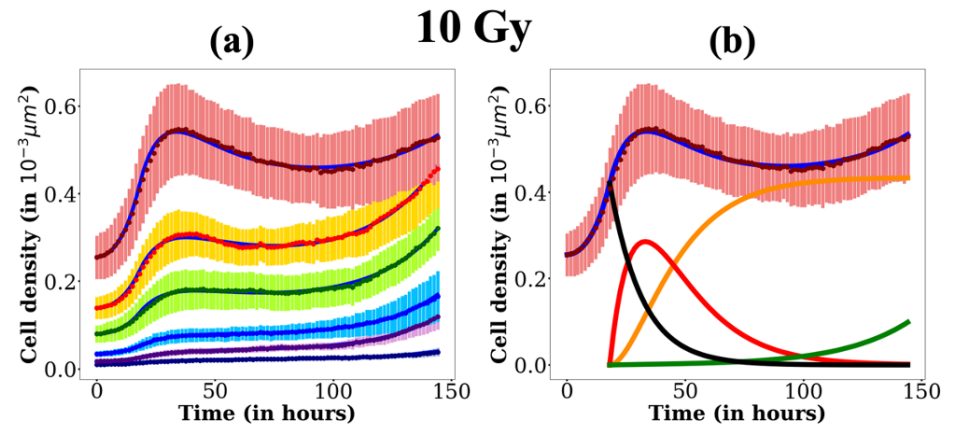


Figure 3.13: (a) Experimental cell density versus time, with different initial cell densities (data points with error bars) and the model (blue curve); (b): for the largest cell density, the different cell populations predicted by the model (orange: senescent, green: proliferating, black: initially damaged cells; red: unrepaired cells)

about 5.7 FTE mainly from IJCLab are involved, with collaborations with ISMO (INC CNRS), IFJ-PAN (Krakow, Poland), ALBA Synchrotron (Barcelona, Spain), and CEA-LIDYL. It is fund mainly through an MITI project and IJCLab internal Call. ANR submission is forecast.

5-year prospects : The MODERATO project, initially planned for 3 years, aimed to assess the feasibility of using videomicroscopy to study the effects of ionizing radiation in vitro. The population study explores several variables: multiple cell lines, tumor/normal cell co-cultures, and various irradiation types (X-rays, protons, ions), with experiments already planned on the BioAlto platform. Additional investigations include the impact of hypoxia (linked to the Metamod project), spatially structured irradiation (mini-beams), and irradiated spheroids. The algorithm developed for single-cell tracking has generated substantial data using X-rays. Further optimization is planned with support from a new PhD/postdoc in the upcoming ALLEGRO project. ALLEGRO will expand to include diverse irradiation modalities (protons, electrons) and radiosensitizing nanoparticles, in collaboration with ISMO-Orsay and IFJ PAN Krakow.

3.2.3.3 Numerical tool developments for patient-data analysis and treatment choice

Context : In the continuity of former PMRT project, that aimed at facilitating patient-data storage and analysis for retrospective clinical studies, the LPC Caen developed in the last years 2 numerical tools to ease patient-data extraction and analysis for clinical studies: ESPADON and SPaM (using ESPADON).

Status : **ESPADON**: As part of radiotherapy research, the open-source R library ESPADON, was developed to analyze diagnostic and control imaging, delineations, as well as data produced by Treatment Planning Systems (TPS) [Fontbonne et al., 2023]. This library, downloaded approximately 350 times per month by radiotherapists, medical physicists and their students from around the world, offers numerous possibilities for calculation, analysis and automation of studies. Espadon has enabled various comparative studies of practices or accelerators in France, Switzerland, and Belgium. For example, it enabled a multicenter study analyzing the dosimetric performance of VMAT in breast radiotherapy in twenty-two cancer treatment centers (ARPHYCO network, SFPM 05/06/2025). It was extensively use during the PhD of Nathan Azemar to model optical nerve toxicities induced by protontherapy [Azemar et al., 2024]. The library's development phase is now complete [1] and availiable on CRAN [2]. It is now in its maintenance phase, with occasional improvements being made. About 1 FTE from 3 LPCC persons involved during 5 years were needed to this achievement. **SPAM**: Medical records are often fragmented and in formats that hinder digital processing, making it difficult to trace a patient's medical journey. The SPaM (Specification of the Medical Pathway) software addresses this by offering an abstract medical model to formally define clinical activities, enabling easier patient selection for studies and supporting personalized treatment through integrative digital tools. Developed in ADA for reliability, SPaM aims to become the "GEANT4 of medicine." A fully functional first version of SPaM is expected by summer 2025 and has been tested since January 2024 in collaboration with the François Baclesse Cancer Center (PREFERANCE project). The goal is to create a digital tool comparing toxicities from X-ray and proton therapy, with models refined as patient data grows. Ultimately, radiation oncologists will have a decision-support tool to optimize treatment choices for each patient. In addition, the "Worm Model" toy was created to validate SPaM's core concepts and guide the development of user-friendly tools for defining medical protocols and visualizing medical pathways, especially for non-programmers. The project involved 2 persons from LPCC (1.9 FTE 1DR + 1 IR) and is developed for and in collaboration with the François Baclesse radiation oncologists.

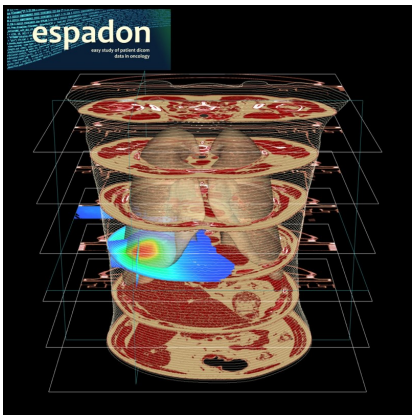


Figure 3.14: ESPADON R library

[1] https://espadon.cnrs.fr/
[2] https://cran.r-project.org/web/packages/espadon/index.html

5-year prospects : The first version of SPaM will be finalized by the end of summer 2025, with key developments including a DICOM import/export library, container-based deployment, and comprehensive user documentation and training tools. Ongoing efforts also focus on strengthening the collaboration with the François Baclesse Cancer Center and exploring new partnerships and valorization opportunities.

3.3 Summary

The growing complexity and diversity of cancer types, as well as the limitations of conventional radiotherapy, have driven the emergence of innovative therapeutic strategies. This chapter has highlighted how new approaches—ranging from targeted radionuclide therapies (TRT) and boron neutron capture therapy (BNCT), to nanoparticle-enhanced radiosensitization and novel dose delivery modes like FLASH and SFRT—are reshaping the landscape of radiation oncology.

IN2P3 is deeply involved in these developments through a broad array of multidisciplinary projects. Its contributions span the entire TRT chain: from radionuclide production at ARRONAX and chelation chemistry (EUROPA, PRALINE, SMILES, REPARE), to the development of advanced detectors for personalized dosimetry (XEMIS, THIDOS, AIDER), and the refinement of biophysical and microdosimetric models.

In BNCT, IN2P3 teams work on optimizing accelerator-based beam production, characterizing neutron fields, and improving biological modeling to better predict therapeutic outcomes. Research on nanoparticle-induced radiosensitization is also advancing, with a focus on understanding underlying radiobiological mechanisms.

For new dose delivery modes, particularly FLASH and SFRT, the institute plays a key role in elucidating the fundamental processes (such as radiolysis under high dose-rates), developing adapted detectors, and establishing reliable dose monitoring techniques.

Finally, by integrating biological data and imaging (e.g., MRI analysis, MODERATO project), IN2P3 contributes to the creation of predictive tools and personalized treatment planning models.

These efforts illustrate IN2P3's strategic commitment to advancing the science and application of innovative radiation therapies, reinforcing the bridge between nuclear physics and clinical oncology.

4

Instrumental and numerical developments

4.1 Introduction

Instrumental developments and numerical simulation platforms are key components of the research conducted by IN2P3 teams in the field of health, whether in the context of hadron therapy, innovative radiotherapies, radionuclide production, or medical imaging. This section of the report aims to provide a detailed overview of the developments mentioned in the first two parts of the report.

4.2 Hadrontherapy

4.2.1 Ion-range monitoring

4.2.1.1 TIARA

Status The first 3 years of the project (2020-2023) were dedicated to the R&D of the TIARA block detector [Jacquet et al., 2023] and beam monitor [André et al., 2025]. Through recurrent experiments carried out at CAL ($\sim$ 2/year), their response in terms of time resolution and detection efficiency was optimized. For the beam monitor, a spatial resolution $<$ 2 mm was measured for the single proton and a time resolution below 100 ps RMS for protons up to 230 MeV. The coincidence time resolution for the two detectors is of 114 ps RMS at low beam intensity (single proton regime). According to MC simulations [Jacquet et al., 2021], this time resolution is sufficient to reach a 1 mm (at 2 σ) accuracy on the proton range with 10^8 protons. In 2024, with a simplified geometry consisting of PMMA targets separated by an air gap, we have measured a 3.3 mm (at 2 σ) accuracy with an approximate statistic of 10^7 protons (paper in progress). Overall, the TIARA detection principle has been experimentally validated with protons from cyclotrons (MEDICYC), synchro-cyclotrons (S2C2) and synchrotrons (CNAO) at low intensities, and with carbon ions at clinical intensities. At the end of 2024, the TIARA prototype has been tested with an anthropomorphic phantom (Figure 4.1) at S2C2 accelerator operated at low intensities. The TOF profiles obtained when irradiating one of the phantom sinuses (either empty or filled with gel) demonstrated that the system is not only capable of measuring the hadron range (from the profile width), but also to detect variations in the tissues traversed by the projectile (from the different PG yield), thus paving the way for the use of TIARA for proton tomography. In 2025, the first experiments at S2C2 was carried out, at clinical intensity, observing no saturation of TIARA modules.

The following fundings have been obtained:

- 2020–2021. IRS (Initiatives de Recherche Strategiques)
- 2020–2023. PCSI, Physique-Cancer, funded by InCa/INSERM (LPSC, CPPM and CAL)
- 2022-2027. ERC Starting Grant (CPPM, CAL, LPSC)

$\sim$ 12 FTE (IN2P3) are working on this project.

5-year perspectives By 2027, the TIARA prototype will be scaled up to include $\sim$ 30 channels. To do so, the design of the mechanical support has alreday started and a dedicated acquisition system based on a fully digital TDC implemented on an FPGA is currently under development. The board should be ready in 2026. Given the experimental results obtained, one should consider the feasibility of the approach validated at low beam intensity and the TIARA team will focus its future experimental campaigns on the clinical intensities. So far an approximate (and biased) solution of the data reconstruction algorithm has been developed, but the TIARA team is also working towards an unbiased PGTI reconstruction for which they expect first results by the end of 2025. At the same time, a fully AI-based reconstruction approach will be developed (postdoc starting in October 2025) with the goal of producing 3D images of the delivered dose, directly from the measured TOF profiles. For this a patient image database is to be built in collaboration with CAL. If the results obtained with the different reconstruction methods are satisfying in terms of spatial

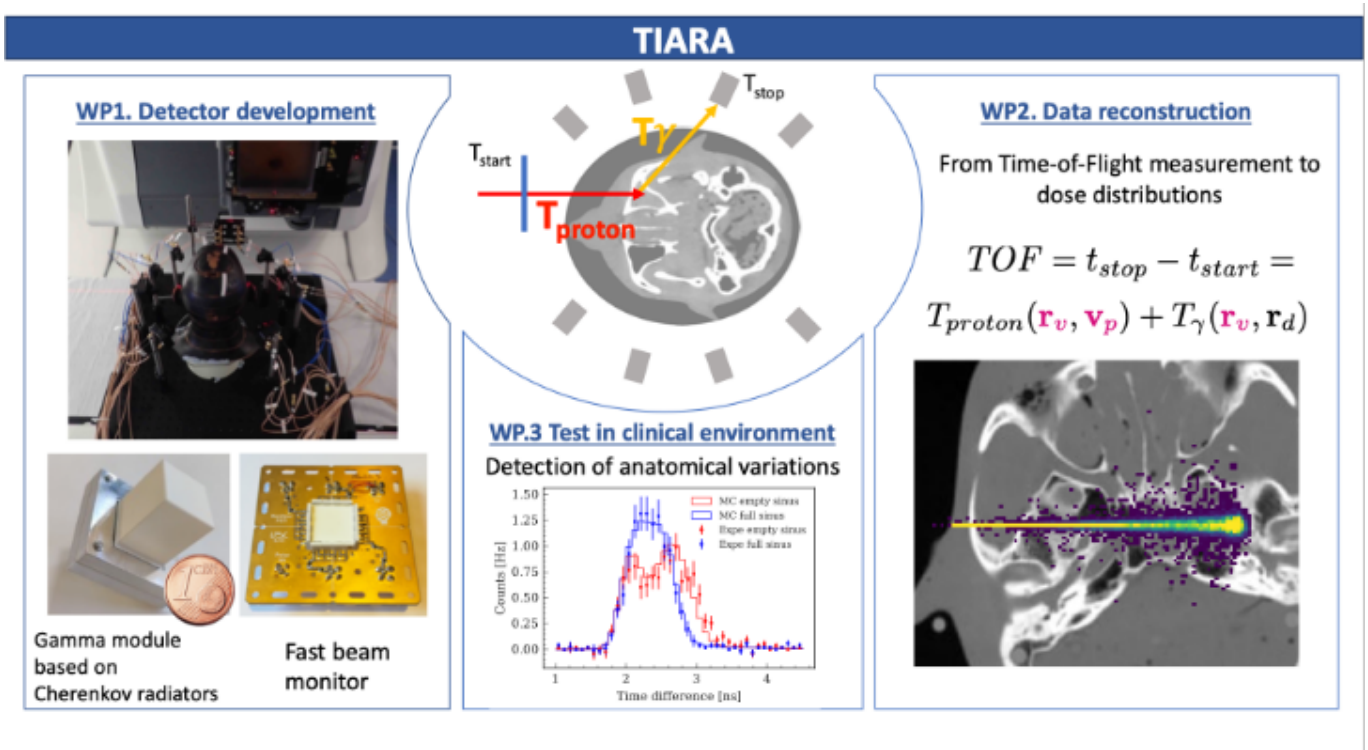


Figure 4.1: Left: TIARA prototype. One of the gamma modules and the beam monitor are shown in the insets. Centre: Detection principle (top) and example of TOF distributions obtained with TIARA (bottom). Right: PGTI reconstruction equation and expected output of the reconstruction algorithm.

resolution (at low intensity), TIARA will focus part of its effort to demonstrate the experimental feasibility of TOF-based proton radiography with TIARA.

4.2.1.2 CLaRyS-S2C2

Status This project, also introduced in section 2.2.2 is undertaken in collaboration between IP2I, LPSC, CREATIS and CAL-Nice.

Preliminary simplified simulations were carried out using the GATE tool (Pierre Everaere's thesis, defended in December 2023). These simulations were able to demonstrate the sensitivity of the PGEI (Prompt Gamma Energy Integration) method in detecting a displacement of a spherical plastic target, using two groups of detectors, symmetrically placed upstream and downstream of the target. The evolution of the integral of the signals measured by the two groups of detectors for a 160 MeV spot beam of 1.5×10^7 protons, shown in Figure 4.2, shows a significant variation (at 1 sigma) for a target displacement of 3 mm [Everaere et al., 2024b].

Tests on proton beams at CAL-Nice and ARRONAX-Nantes enabled the team to study the response of several types of scintillator coupled to a photomultiplier tube (PMT) under conditions close to those of the synchro-cyclotron targeted by this project. The measurements quickly converged on the use of a $PbWO_4$ scintillator, which is very faint but very fast. A very short transit-time PMT has been chosen (Hamamatsu R11265-U100). A LPSC-made acquisition board with a charge-integration ASIC has been adapted for this development (Figure 4.3).

Systematic detector characterization and calibration was performed at ESRF using well-energy-defined photon bunches. Measurements were performed at ARRONAX and CAL-Nice using homogeneous plastic targets, whose positions were translated. In parallel, GATE 9.3 simulations were carried out and compared with the results. The results are presented in Figure 4.4 for 68 MeV protons, irradiating a target as a

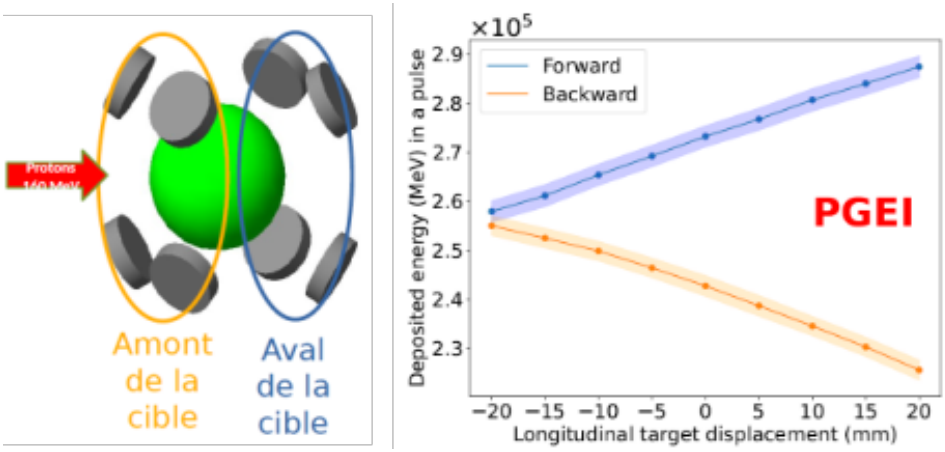


Figure 4.2: GATE simulations of the PGEI integral method with a 160 MeV proton beam incident on a spherical PMMA target capable of longitudinal displacement. Colored bands correspond to measurement uncertainties (at 1σ) for a beam spot of 1.5x10^7 protons.

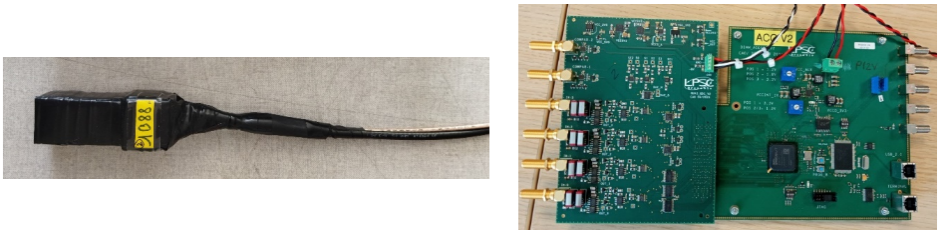


Figure 4.3: Left: 2.5x2.5x5 cm^3 $PbWO_4$ scintillator coupled to PMT; right: 4-channel acquisition board.

function of the longitudinal target position, for three observation angles, showing very good agreement between measurements and simulations.

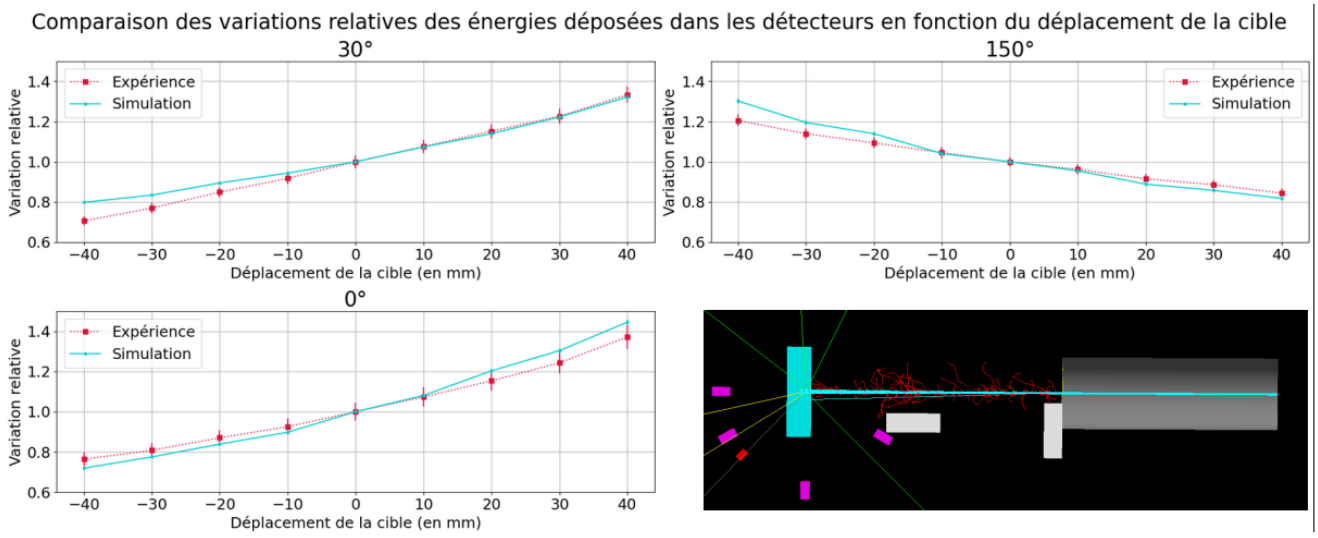


Figure 4.4: PGEI yields measured for proton beams stopped in a movable PMMA target at ∼ 1 µA pulse-current, for 3 observation angles (0°=forward direction). Comparison with GATE simulations (illustrated bottom right).

The next step is to perform such measurements at higher energy on the CAL-Proteus One (only preliminary measurements were performed so far), and complete this study with realistic treatment-planned irradiations on anthropomorphic phantoms.

This project is supported by CNRS/MITI (80PRIME: thesis Sarah Otmani 2023-2026 + environment 2023-2024), LabEx PRIMES (Thesis Pierre Everaere 2020-2023, access to beam time, equipment).

$\sim$ 3 FTE (IN2P3) are working on this project.

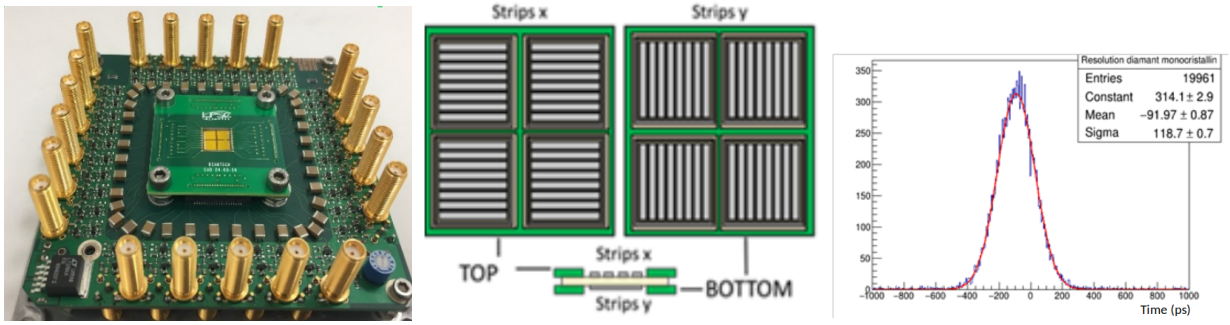
5-year perspectives This project is a necessary step for the design of a clinical setup for Prompt-Gamma monitoring of protontherapy with medical synchro-cyclotrons. This scintillator+PMT detection solution is simple, cheap and robust, coping with a relatively small number of detection units, easily modulable and versatile. This study will provide valuable inputs for such a design.

4.2.2 Beam hodoscopes

4.2.2.1 Diamond detectors

Status Several R&D efforts have been conducted, leading in 2024 to the development of three distinct prototypes:

- a beam hodoscope for hadron therapy [Curtoni, 2020, Everaere, 2023] (Figure 4.5)
- the DIAMMONI detector for FLASH therapy (ANR DIAMMONI 2020-2024 [Molle, 2024]) (Figure 4.6)
- the IDSYNCHRO detector for MRT (Microbeam Radiation Therapy) (IDSYNCHRO [Rosuel, 2021a, di Franco et al., 2023]) (Figure 4.7)



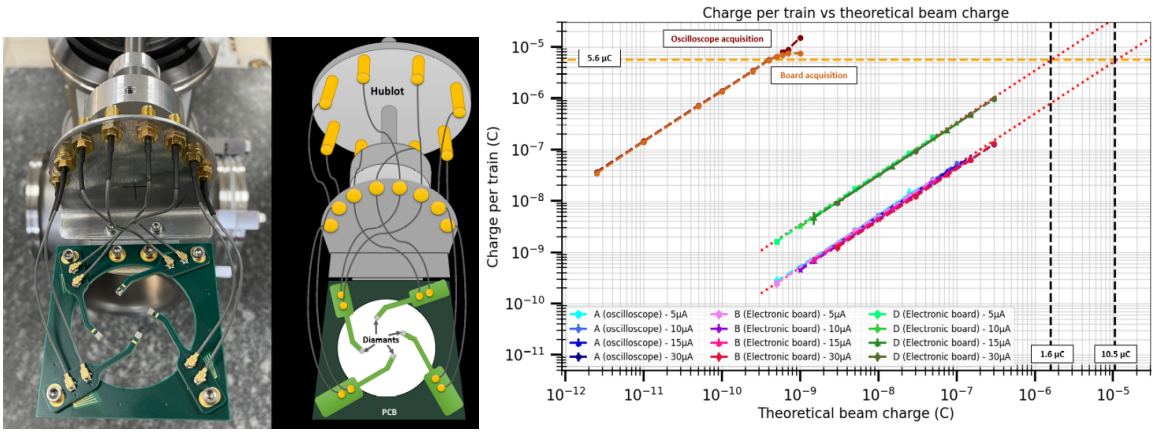
(A) **(B)** **(C)**

Figure 4.5: The Diamond beam hodoscope for on-line monitoring of the hadrontherapy (A), the stripped diamond detector mounted on its FE electronic board that consists in fast preamplifiers, details of the diamond metallisation (B) and time measurement (C) operated on the MEDICYC beamline at Centre Antoine Lacassagne that demonstrates a time resolution of less than 100 ps on a (x,y) couple of orthogonal strips crossed by a 70 MeV proton beam.

The latter two prototypes are now being used in preclinical applications for small animal experiments - respectively at the ARRONAX cyclotron (research line, PhD thesis of R. Jbara, in collaboration with medical physicists at Nantes University Hospital) and at the Melbourne synchrotron, following the 2022 closure of the ID17 medical beamline at ESRF. In addition to the design of these beam monitors, dedicated characterization tools have been developed to simulate radiation–matter interactions and better understand charge collection mechanisms in diamond (e.g., trapping, polarization effects). Notably, a Time-of-Flight eBIC (electron Beam Induced Current) system was developed at Institut Néel [Portier, 2023], as well as a ToF XBIC (X-ray Beam Induced Current) setup on beamline BM05 at ESRF [Lafont et al., 2023].

These tools have brought our understanding of charge collection in diamond to a state-of-the-art level [Portier et al., 2023], paving the way for international collaborations (CNRS-JSPS France–Japan, [Portier, 2023]) and national ones (CNRS MITI 80 PRIME, [Léonhart, 2025]), all within a highly interdisciplinary context. Ultimately, these developments open avenues for applications beyond the medical field, including nuclear physics (ILL – [Gallin-Martel et al., 2021]) and high-energy physics (CERN RD42 and DRD3).

The following fundings have been obtained:



(A) **(B)**

Figure 4.6: (A) The DIAMMONI detector for FLASH therapy monitoring 4 small diamonds are positioned at the ends of articulated arms which allow them to be positioned in the center of the beam or in the halo. A dedicated read-out electronics (measurement of the charge in each train of particles of the pulsed beam) have also been designed at the LPSC. (B) Diamond charge measurements (bottom) as a function of beam charge for different positions: top left: the 4.6×4.6×0.55 mm² diamond centered on the beam axis; bottom right: diamonds named A, B, and D (2.2×2.2×0.15 mm²) off-center and positioned closer to the halo.

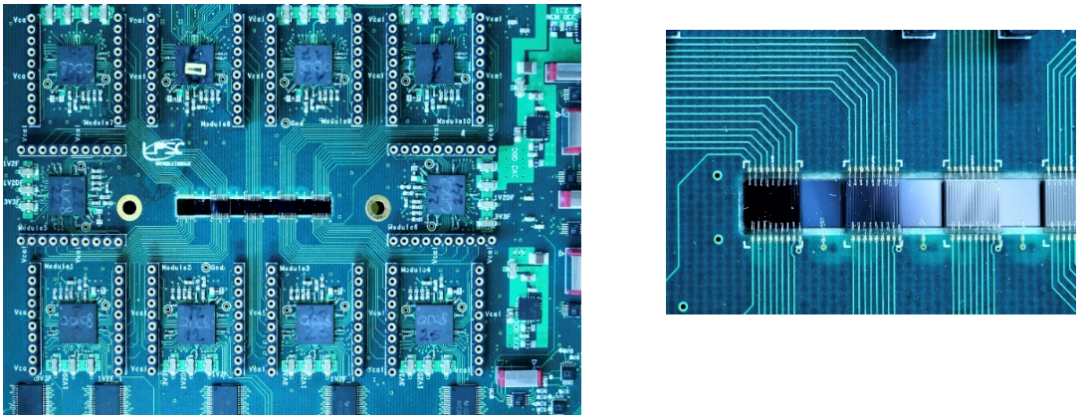


Figure 4.7: IDSYNCHRO detector for MRT monitoring (left: collaboration between the Detectors and Instrumentation (SDI) and Electronics Design (CAO) departments of LPSC), with an active surface (detail on the right) composed of 8 diamonds arranged in a linear array (17 micro-strips per diamond – collaboration with Institut Néel, NanoFab platform, and LPSC), read out by integrated QDC electronics developed by the Electronics Department at LPSC.

- Master projet DIAMANT IN2P3
- ANR DIAMMONI
- PCSI IODA Master + PCSI MRT Clintra
- IDEX UGA (1 PhD funded) + CNRS MITI 80 PRIMES (1 PhD funded)

$\sim$ 25 FTE (IN2P3) are working on this project.

5-year perspectives Two beam monitors (DIAMMONI and IDSYNCHRO) have been designed for pre-clinical applications on small animals (ARRONAX and ANSTO synchrotron in Melbourne). Their porting to the clinic remains to be considered (CAL MEDICYC beamline). In addition, the proof of concept for the manufacture of an active diamond membrane used as an extraction window on microbeam installations for radiobiology applications is currently being demonstrated. Decisive manufacturing steps have already been validated as part of the CNRS MITI 80 PRIMES DéFI DiaMs project (2023-2025). The major objective of this project is to improve the existing technology on the AIFIRA microbeam platform [Barberet et al., 2021] from LP2I Bordeaux to IN2P3, adapted to protons, with the production of even thinner diamond detectors ($\leq$ 1 µm) with the aim of enabling ion counting at high beam intensity ($\sim 10^4$ s^{-1}) but also of extending the use of such monitors to heavier ions such as carbon, available on the MIRCOM microbeam facility [Vianna et al., 2022] of IRSN, in Cadarache. Proof of concept of operation should be achieved in 2025 for process improvement in 2026-2027 with a view to their valorization.

4.2.2.2 PEPITES

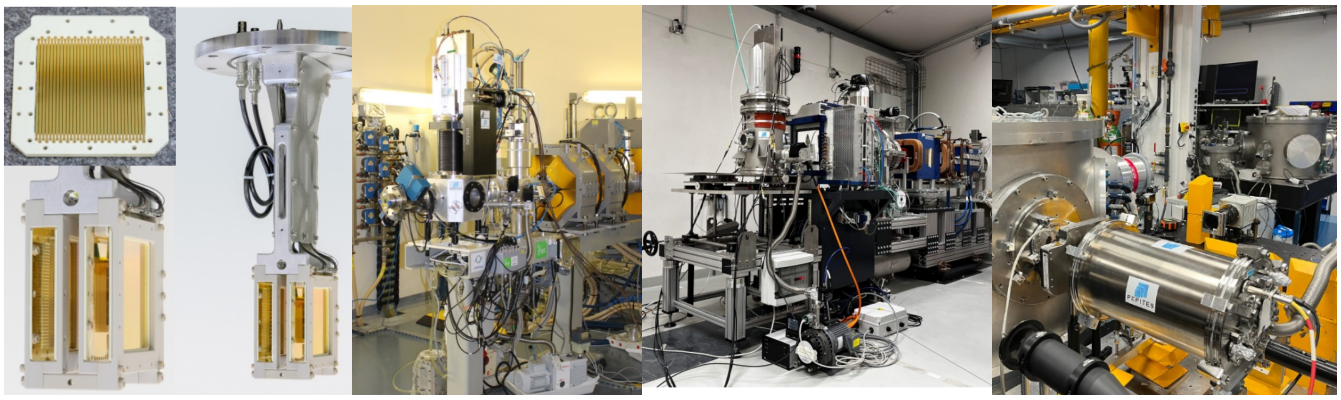
The context of the PEPITES project is described in the “Hadrontherapy” chapter at section 2.2.2.3.

Status We can distinguish two main topics with PEPITES: PEPITES as a thin monitor and PEPITES for FLASH.

1. PEPITES as Thin Monitor
   The PEPITES ANR project (2017–2022) ended with the permanent installation of a fully functional prototype, 10 µm WET, at ARRONAX (Figure 4.8B) in May 2022, with the strategy of obtaining feedback on the technique from routine operations. The consortium was composed of:
   - ARRONAX: radiation damage studies and prototype hosting,
   - CEA/DEDIP: design and production of low-noise and high dynamic range ASIC current readout, and host board,
   - LLR: sensitive area, mechanics, high-quality connectivity, acquisition, management.

   The project involved up to $\sim$ 15 persons, with $\sim$ 3 outside IN2P3, and about 50% engineers.
   The second topic for PEPITES as thin monitor is CNAO, started in 2023, where the monitor-patient distance is 6.5 m, imposing stricter limits on the material budget (Figure 4.8C). At this point, a 5 µm WET is used as working hypothesis. PEPITES has shown to work properly with carbon ion beams in the therapeutic range (energy and intensity). Discussions have started for the definition of the monitor. The CNAO team is about 4 persons (plus some additional help). The LLR team devotes 8 persons to the project, including 5 engineers and one postdoc.
2. PEPITES for FLASH
   Two X/IPP pre-maturation projects have been funded: SPLIF for intensity (2023–2024, one year), SPLASH for profile (2025–2026, one year). These projects are purely LLR and involved/involve $\sim$ 4 persons, including one CDD engineer funded by the project. These projects are mentioned but are not funded by IN2P3.
   The last project is UltraFlash MITI (2023–2024, two years), in collaboration with the LOA, which studied the applicability of SEE for beam monitoring of ultra-short beams (30 fs) produced by laser-plasma acceleration. A simple monitor (PUFF) with two parallel plain planes and adjustable gap was

developed to measure the SEE rate under these conditions (Figure 4.8D). Using this monitor at LOA, and also at Orsay with the ElectronFlash machine (1 µs e^- pulses) and ELYSE (10 ps e^- pulses), strong signal attenuation was observed with shorter pulse durations. One person from LOA was involved (with some help), and LLR provided the same team as for CNAO.



(A) (B) (C) (D)

Figure 4.8: (A) PEPITES sensitive area: The strip plane is 7×7 cm^2. The planes are (anode)-(strip)-(strip)-(anode).; (B) PEPITES at ARRONAX: Vacuum chamber inserted on AX3 beam line; above in black is the translation system and its engine to move PEPITES in/out of the beam; on top, the metallic box is the readout electronics. (C) PEPITES at CNAO: "NOMAD" version hosted in a vacuum chamber independent of the beam line. The chamber includes entrance and exit Kapton windows. The same readout electronics are placed on top. (D) PEPITES UltraFlash (PUFF): Monitor with two plain planes and adjustable gap, placed at the exit of the ZITA LOA vacuum chamber where the plasma is created.

5-year perspectives

- PEPITES as Thin Monitor: At ARRONAX, the PEPITES prototype continues to be operated, with valuable feedback being collected on electronics and acquisition. Notably, ARRONAX also tests PEPITES with ms-scale flash beams. At CNAO, a decision is expected soon regarding the construction of a dedicated clinical PEPITES monitor. If confirmed, this would be the first clinical deployment of the device. Discussions are also ongoing with the BioAlto team for a possible dedicated system.
- PEPITES for High-Intensity (Flash) Beams: The SPLIF and SPLASH projects explore the development of portable systems compatible with both conventional and flash modalities. Active components of PEPITES may be directly integrated into beam lines. For ultra-short beams, the PUFF prototype is used to investigate the cause of SEE signal attenuation and its implications for beam monitoring. LhARA has expressed strong interest in the technology, especially if compatibility with fs-scale beams is demonstrated.
- Technology Transfer Outlook: PEPITES and related systems hold potential for industrial applications, particularly in medical contexts. Demonstrations at ARRONAX and CNAO could be pivotal for validating ultra-thin performance. The linearity of the SEE-based technique under flash conditions is a strong asset, and combining ultra-thinness with high linearity may offer a unique advantage for technology transfer.

4.2.2.3 MATRIX

Status The development of GaN-based detectors for proton therapy calibration was initiated seven years ago through a collaboration between CRHEA-CNRS (Valbonne) and the Centre Antoine Lacassagne in Nice. Following encouraging results, this activity expanded under the national NECTAR project funded by INSERM and the international ANR-DFG MATRIX project [Duboz et al., 2019, Duboz et al., 2021].

This collaborative effort brought together the University of Bochum, the Proton Therapy Center in Essen, and IPHC (IN2P3 Strasbourg), creating an interdisciplinary team of 7 researchers and engineers, 3 PhD students, and one postdoc.

The suitability of GaN diodes for proton dosimetry, even for low-dose beams has been recently demonstrated: a linear array of GaN detectors successfully monitored the non-collimated, Gaussian-like 64.8 MeV proton beam at the Lacassagne Center [Duboz et al., 2019, Duboz et al., 2021]. Thanks to developments at IPHC, a 128-pixel linear array combined with commercial electronics enabled object imaging at the CYRCE proton facility. Recently, an 11×11 GaN matrix (Figure 4.9) has demonstrated real-time beam calibration capabilities for quality assurance.

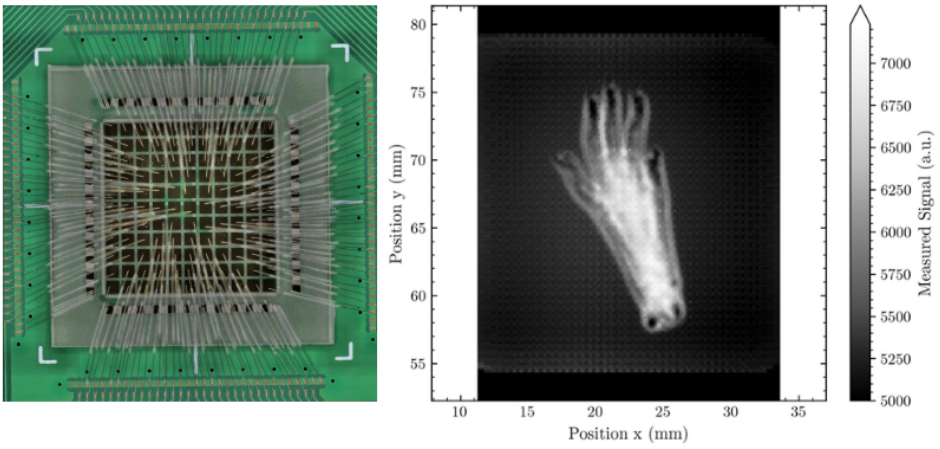


Figure 4.9: Left: 11x11 MATRIX array; left: Image of mouse foot.

The following fundings have been obtained: the national project NECTAR founded by the INSERM and the international ANR-DFG project “MATRIX”.

$\sim$ 3 FTE (IN2P3) are working on this project.

5-year perspectives The final system aims to address three core needs: i) High-resolution spatial beam imaging, ii) Temporal structure analysis for FLASH therapy and iii) Real-time energy/dose characterization.

- Phase 1 (18 months): Development and validation of 32×128 and 128×128 matrices with associated electronics.
- Phase 2 (18 months): Clinical validation using medical beams, system refinement.

A collaboration with CNAO (Italy) will ensure clinical relevance and help define future European hadrontherapy protocols. The compact, robust system may lead to industrial technology transfer for use in medical physics, aerospace, and nuclear security.

4.2.3 Trackers for measurements of fragmentation cross-sections

Over the past decades, the Picsel team has established itself as a leader in the development of CMOS sensors, initially for high-energy physics and more recently for medical applications.

The MIMOSA-28 sensors, developed by this group, currently form the vertex detector of the FOOT experiment (see section 2.2.3.1). However, their relatively long readout time (200 µs) leads to significant pile-up effects. To mitigate this limitation, the MIMOSIS sensor—featuring a much faster readout time of approximately 5 µs—was selected as a replacement.

Originally developed for the CBM Micro-Vertex Detector at FAIR-GSI [Arnoldi-Meadows et al., 2023], the MIMOSIS sensors will be integrated onto the experiment’s motherboards this summer. A dedicated test campaign is scheduled for the autumn, during which tracking efficiency and other key performance metrics of the chip will be thoroughly evaluated.

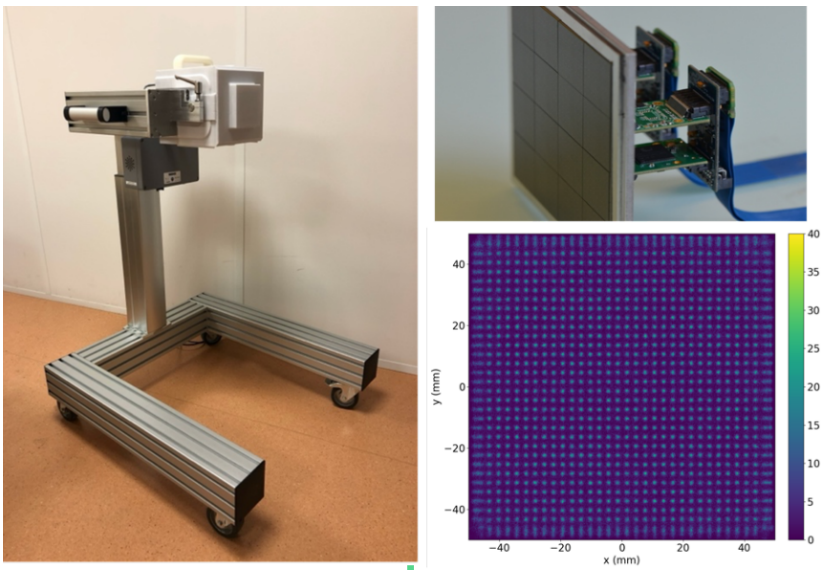


Figure 4.10: The mobile gamma-camera for estimation of absorbed dose in molecular radiotherapy (left); photodetection module consisting of a silicon photomultiplier array and reading electronics (top right); Intrinsic spatial performance of the camera (133-Ba, 356 keV) [Bossis et al., 2023].

4.3 New approaches in radiation therapy

4.3.1 Nuclear Imaging for Theranostics in Targeted Radiotherapies (THIDOS project)

The context of the THIDOS project is described in the previous chapter describing TRT-related in2p3 projects, at section 3.2.1.2.2.

Status The first approach was focused on the treatment of benign and malignant thyroid diseases with ^{131}I (365 keV). The project was carried out in collaboration with ARSN (formerly IRSN) and Institut Claudius Régaud, and funded by the Cancer Plan (AAP Physicancer, INSERM, 2019–2023). A high spatial resolution mobile gamma camera specifically designed to improve the quantitative assessment of ^{131}I biokinetics in the thyroid and organs at risk, before and after treatment administration, was first developed (see Fig. 4.10).

The first prototype of the camera was commissioned in November 2021. All the objectives in terms of spatial and energy resolution, image quality, and compactness were achieved. Pre-clinical studies based on precise calibration of the camera and measurements on 3D thyroid phantoms demonstrated its ability to quantify activity with a high degree of accuracy (maximum bias of less than 5%, even for small radioactive sources).

These promising results are due both to the very high spatial resolution of the camera compared with conventional devices (4–6 mm versus 1.5 cm at 365 keV), and to the implementation of accurate and robust quantification methods (segmentation of the source image, correction for the partial volume effect, and scattering correction).

The first clinical evaluation of the mobile camera involving 20 patients with benign thyroid diseases was completed in March 2025. Results are currently being analyzed. A detailed assessment of the sources of uncertainty in the quantification process was also carried out using Monte Carlo simulations.

The second axis of the project focused on the reliability and quality of dosimetric calculations through the implementation of innovative error propagation methods based on a Bayesian network to estimate dose uncertainties. This method will soon be evaluated using clinical data acquired by the mobile camera.

The whole project was carried out as part of three doctoral theses [Trigila, 2020, Bossis, 2023, Bensiali, 2022] and resulted in several papers published in peer-reviewed scientific journals [Bossis et al., 2023, Bossis et al., 2024, Trigila et al., 2022].

13.6 FTE are involved in this project in IN2P3. This project was mainly funded by the THIDOS PCSI project (AAP Physicancer, INSERM, 2019-2023).

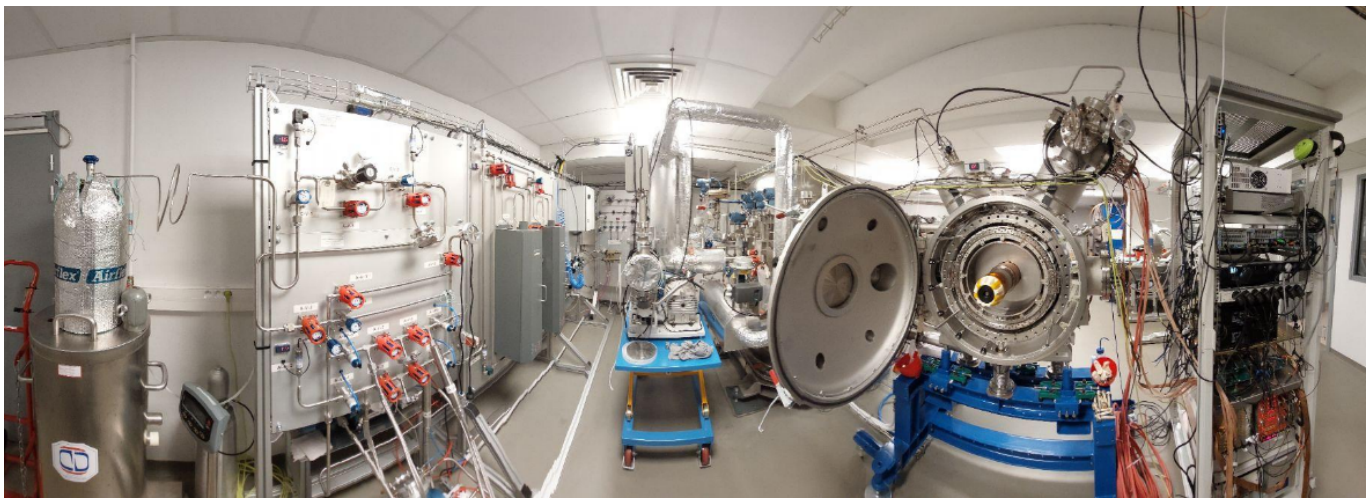


Figure 4.11: Photograph of the XEMIS2 camera installed at the Nantes University Hospital.

5-year perspectives Beyond setting up an extended clinical protocol of the mobile gamma camera for the treatment of thyroid diseases (including differentiated thyroid cancers and benign thyroid conditions), the next steps involve adapting this system for dose-based treatment planning using ^{123}I, in collaboration with the Cochin Institute. The camera is also expected to be extended to support clinical applications involving medium-energy gamma emitters (200–400 keV), such as ^{177}Lu, ^{225}Ac, ^{211}At, and ^{90}Y.

In the longer term, a new international collaboration with South Korea has been initiated to develop a dedicated Compton camera for real-time dosimetric monitoring using high-energy gamma rays (>400 keV), specifically for targeted alpha therapy with ^{225}Ac in colorectal tumors. This future device will rely on AI-based image reconstruction techniques to enhance detection performance and enable robust clinical use.

4.4 Imaging and Endomicroscopy

4.4.1 XEMIS

As for Thidos, the context of the Xemis project is described in section 3.2.1.2.1.

Status The XEMIS projects represent a technological breakthrough compared to the cameras currently marketed for medical imaging: they are directly inspired by the experiments deployed for fundamental research in rare events physics involving liquid xenon Time Projection Chamber. Many embedded technologies were initially developed to adapt the detection scheme to medical imaging, in particular to offer a satisfactory solution for high flows and limited exposure time. A first version dedicated to small animal imaging was entirely designed in this context as part of the XEMIS2 project. The studies, construction and installation of this camera represented around ten years of work and mobilized a team composed of engineers and technicians from IN2P3 and members of the Subatech Xenon research team. The XEMIS2 camera is now fully installed at the Nantes University Hospital and its first observations will begin in the fall of 2025. At IN2P3, around ten Subatech engineers and technicians built, installed and implemented the XEMIS2 camera during this period. The development of the embedded solutions also involved the electronics departments of LPC and IP2I, which developed one of the ASICS used (XTRACT) in collaboration with Subatech staff. The camera is planned to be operated until 2031 with a rich and collaborative research program to investigate the characteristics of the observations in the context of nuclear imaging and high-energy SPECT, PET and 3-photon modalities. Rapid upgrades of the on-board photodetection and the xenon purification system are in preparation and should also occur during this period.

5-year perspectives The objectives for this first demonstrator on a small animal scale are firstly to demonstrate the feasibility of images with very low injected activity (of the order of 20 kBq in the animal in 3 gammas imaging mode), then to also show the capacity of the camera to procure precise SPECT and TEP images and finally to produce fast images with lower exposure time in the order of a few ten of seconds. During this period, it is also planned to initiate activities strengthening the role of imaging in the therapies currently practiced in RIV α and β, and for the control of treatments with hadron beams.

4.4.2 MAPSSIC

Context The MAPSSIC project involves the development of a pixelated intracerebral probe dedicated to small animal imaging. Its goal is to provide radiation-sensitive detection tools that enable the local measurement of radiolabeled molecule concentrations while the animal is awake and free to move. Until now, standard techniques such as microPET required the animal to be anesthetized and immobilized, which significantly limited their use in studies of brain function [Patel et al., 2008, Schulz et al., 2011]. This is why we are aiming to overcome this limitation by proposing a miniaturized tool implanted directly in the brain, promoting both autonomy and increased detector sensitivity. The autonomous nature of the probe has been patented [Delpierre et al., 2007]. Following two probe versions, we are currently developing a sensor based on CMOS technology, which offers many advantages for our setup (sensitivity to positrons, transparency to gamma rays, mechanical robustness, and integrated electronics within the sensor).

Status This project is being carried out jointly by three IN2P3 laboratories (IJClab, IPHC and CPPM), with the support of 1 INSB partner: BIORAN from CRNL in Lyon, associated with CERMEP in Lyon (a reference center for PET imaging), who are providing all the specific expertise required for handling and implanting intracerebral sensors, and for biological validation of the new device. The project, which requires the involvement of 5 C/ECs and 20 ITs from all the laboratories, has been the subject of 3 theses [Heymes, 2018, Ammour, 2018, El Ketara, 2024].

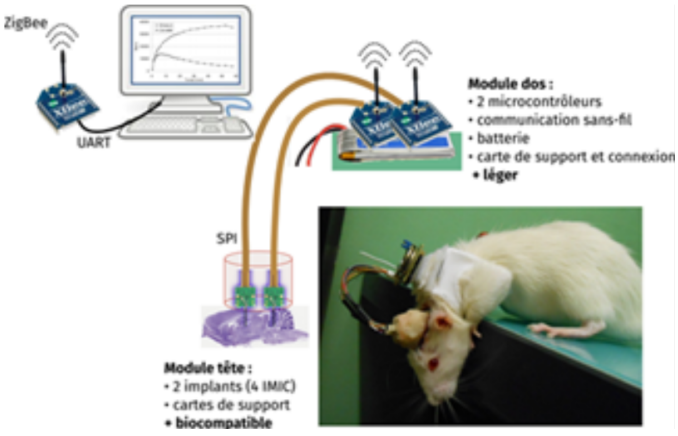


Figure 4.12: The detection system includes three main components: (i) a head module with probes on a mini PCB implanted stereotactically and secured with a cemented cap; (ii) a backpack module containing a microcontroller, RF system, and microbattery, connected to the head via a flexible link and held by a harness; and (iii) an acquisition module with a console and RF receiver for data transmission.

After several prototype tests on the IPHC's PICSEL platform and Monte Carlo simulations on the GATE platform, we were able to identify a suitable probe configuration and complete the feasibility stages by developing a 3D probe optimized for sensitivity and ergonomics. In this configuration, the detector is based on an assembly of two 200 µm thin CMOS sensors glued back-to-back and mounted by wiring and gluing on a PCB that holds the probes to be implanted on the rodent's skull and links them to the interface connector to the backpack containing the telemetry control electronics (CPPM). As with previous sensors, the whole system is biocompatible thanks to a 6 µm film of parylene (IJClab). The physical development of the project ended with a sensor characterization based on two prototypes and the use of 18F phantoms, and showed that the probes were globally functional for our application [Ammour et al., 2019, El Ketara et al., 2024].

21 people are involved in this project that was funded with IN2P3 support, CNRS/MITI and France Life Imaging (programme d'investissement d'avenir)

5-year perspectives The MAPSSIC project has reached an advanced development stage, with 70 intracerebral pixelated probes produced and 80 more underway. These probes are intended for large-scale physical and biological validation. They must first be characterized on radioactive phantoms to optimize noise, thresholds, and polarization, then calibrated before implantation. Development of acquisition software is ongoing to integrate pharmacological and behavioral data in animal models.

The next steps include evaluating probe biocompatibility via cerebral inflammation markers and validating in vivo radiotracer kinetic measurements through microPET comparison, especially in neurobehavioral studies. A major application involves assessing dopamine release triggered by cocaine-related stimuli using ^{11}C-raclopride PET. MAPSSIC could surpass microdialysis by enabling real-time monitoring in awake animals.

The use of CMOS sensors paves the way for multimodal imaging by combining radioactive detection with optical techniques such as fluorescence and membrane potential imaging. Their low power and flexibility also support implantable use. Portable β^+ cameras for surgical applications are in development. If validation proves successful, technology transfer may follow through Beams, an IJCLab spin-off, based on a patent for wireless in vivo β detection.

4.4.3 ClearMind

Context Positron emission tomography (PET) has revolutionized molecular imaging since the 1970s due to its sensitivity at the picomolar level [Cherry, 2017]. Yet, further performance improvements are necessary. Increasing the axial field of view boosts sensitivity, improving both signal-to-noise ratio (SNR) and enabling lower dose imaging [Snyder, 1981]. Time-of-flight (TOF) techniques, which utilize the arrival time difference between the two annihilation photons, offer another path forward [Budinger, 1983]. The precision of TOF is governed by the coincidence time resolution (CTR), with current systems achieving $\sim$220 ps FWHM [van Sluis, 2019], leading to an SNR improvement of about 3.5.

Pushing toward a CTR of 10 ps FWHM could enable direct positron emission imaging (dPEI), removing the need for image reconstruction [Lecoq, 2017, Lecoq and Morel, 2020, Lecoq et al., 2020]. The ClearMind project (2020–2025), funded by ANR and coordinated by CEA-IRFU in collaboration with CPPM and IJCLab, targets sub-100 ps CTR using an innovative "scintronic" detector concept [Yvon, 2020]. The module features a $PbWO_4$ monolithic scintillator optically coupled to a $5\times5\,cm^2$ MCP-PMT, with a photocathode deposited directly on the inner face and passivated by a thin optical coating (Figure 4.13(A)). This configuration enhances photon extraction efficiency by suppressing total internal reflection due to refractive index matching [Sung, 2023].

Status Technical developments include Monte Carlo modeling of light transport incorporating thin-film interfaces in Geant4 [Cappellugola, 2021]. Experimental work is conducted at CPPM using the tomXgam system (Figure 4.13(B)) for coincidence evaluation with ^{18}F phantoms. A first module delivered by Photek Ltd. was characterized [Galindo-Tellez, 2024], but fabrication issues led to a new collaboration with Incom Inc. (USA). Additional contributions include AI-based event reconstruction [Sung, 2023] and SiPM modeling in GATE [Mehadji, 2022a, Mehadji, 2023a].

The following fundings have been obtained or are pending approval:

- ClearMind, Development of a "scintronic" crystal for ultrafast gamma-ray imaging applications (CEA-IRFU, CPPM, IJCLab), ANR 2020-2025 (24 months post-doc)
- AAIMME, Machine Learning for molecular imaging and future medicine (CEA-DM2S, CEA-IRFU, CEA-BioMaps, INRIA, CPPM), ANR 2025-2029 (12 months post-doc)

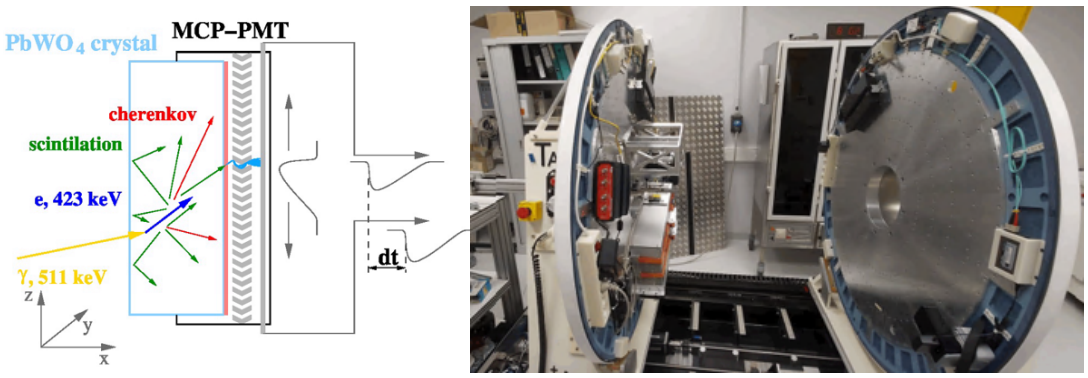


Figure 4.13: (A) Scheme of the ClearMind detection module. Transmission lines are read at both ends and analysed using delay lines to determine the interaction position and time ; (B) Picture of tomXgam, a double rotating mechanical test bench for experimentation in tomograph.

- Chronos, Cherenkov and cross-luminescence timing for low-dose TOF-PET clinical imaging (CEA-IRFU, CEA-BioMaps, U-Tartu, FZU (Prague), DKZ (Berlin), CERN, CPPM, 2026-2029) EIC Pathfinder Open (3 yrs PhD), submitted May 2025

5-year perspectives

- Carry on work on the development and characterization of “scintronic” detection modules within AAIMME as a follow-up of ClearMind until end 2029
- Contribute to the development and characterization of new fluoride crystals with cross-luminescence and index of refraction within Chronos (tbc).
- Contribute to model multilayer optical coating and crystal anisotropy for Geant4 and to extend the SiPM model developed for GATE to SiPM arrays within MP ModOp (tbc).

4.4.4 Photon-counting CT

Context The development of X-ray photon counting-computed tomography (PC-CT) covers both the development of prototype scanners using hybrid pixels that were originally developed for charged particle trajectography at the LHC [et al., 2021a] and the development of methodology for material basis decomposition in the frame of spectral-CT [Alvarez and Macovski, 1976]. Hybrid pixel X-ray detectors represent a technological breakthrough for medical imaging compared to charge-integration detectors of the CCD or CMOS pixel type. The suppression of dark noise thanks to photon-by-photon thresholding allows operation at very low flux and enables access to the energy of each detected photon. This improves image contrast significantly [Taguchi and Iwanczyk, 2013, et al., 2016].

Status Capitalizing on the development of the PIXSCAN PC-CT prototype [Kronland-Martinet, 2014, et al., 2013] and the ClearPET/XPAD PET/CT prototype [Hamonet, 2015], the PIA France Life Imaging (FLI) funded the construction of PIXSCAN-FLI (Fig. 4.14) at CPPM, which includes an XPAD camera delivered by the CPPM startup imXPAD. The camera comprises 8 modules of 7 XPAD3.2 chips developed at CPPM (arrays of 80 × 120 pixels of 130 µm × 130 µm), whose charge amplifier linearity has been extended to 60 keV, hybridized with more than 500,000 silicon pixels of 500 µm thickness. This setup allows whole-body mouse scans within 4 minutes with a delivered dose below 100 mGy per scan [et al., 2007, et al., 2014].

The PIXSCAN-FLI PC-CT prototype was exploited to carry out longitudinal imaging of spontaneous liver tumours in mice labelled with barium nanoparticles. Thanks to the barium nanoparticles, which are

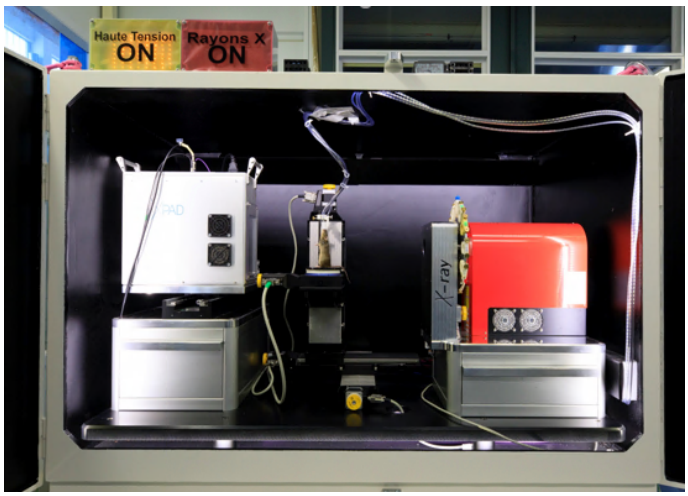


Figure 4.14: Picture of the PIXSCAN-FLI PC-CT prototype.

absorbed by the Kupffer cells of the liver, the absorption of X-rays is enhanced in the liver. Tumours, which do not absorb barium nanoparticles, then appear in negative contrast. The follow-up of mice with hepatocellular carcinoma over one month revealed exponential tumour growth with a doubling period of 22 days. Longitudinal studies were then used to monitor the response to a hepatospecific therapy over 40 days [Cassol and et al., 2019, Cannet and et al., 2025].

ProMeSCT, a variable metric proximal algorithm for material basis decomposition, was also developed. This algorithm can quantify basis material concentrations while modulating beam filtration and/or pixel energy thresholds, requiring one scan per target material. Based on a precise Monte Carlo model of detector response and interaction cross-sections, ProMeSCT was evaluated using *in vivo* spectral data from a mouse labelled with barium nanoparticles and imaged with a prototype XPAD3/CdTe camera with 700 µm thick CdTe pixels [et al., 2021b].

The following fundings have been obtained or are pending approval:

- DePIcT: A project focused on deep learning-based processing of spectral photon-counting CT (PC-CT) data from longitudinal liver cancer studies in mouse models. The aim is to design and optimize combination immuno-anticancer therapies. The project involves CPPM and the IBDM team and was funded by CNRS MITI 80|Prime in 2020. *PhD thesis of Floriane Cannet*.
- SELF PorTrait: A project aiming to identify vulnerabilities in both early and late stages of liver cancer to target tumor and immune cells. Partners include CRCM, CPPM, and I2M. Funded by Fondation ARC (2024–2026).
- FLAP*VAP: A study of [^{18}F]-fluorinated apelin for PET-based vasculomonitoring of APJ receptor expression. Partners include C2VN, CERIMED, ICR, CRCM, CPPM, and iDEAL. Funded by the AMIDEX Interdisciplinary Program (2024–2026).
- CdTe Detector Study: A CIFRE-funded project (2023–2026) in collaboration with Detection Technology and CPPM, aiming to develop and characterize a novel cadmium telluride (CdTe) detector array for X-ray photon counting using Monte Carlo modeling.

5-year perspectives

- Possibly start a new collaboration with Detection Technology on the characterization of a novel CdTe detector array for spectral CT.
- Carry on our collaboration with the PI of the research team Signalling networks for stemness and tumorigenesis and the Institute of Mathematics of Marseille (I2M) on the characterization of immuno-anticancer treatments in liver cancer mouse models through longitudinal spectral PC-CT studies using the PIXSCAN-FLI PC-CT prototype.
- Continuation of PIXSCAN-FLI exploitation for actual (SELF PorTrait and FLAP*VAP) and future preclinical research at CERIMED.

4.4.5 Molecular imaging and Radiobiology @IPHC

Context : The IMR team project aims to investigate tumor characterization at both molecular and functional levels (including volumetry, vascularization, metabolism, etc.) through an integrated theranostic approach. It relies on the development and optimization of dedicated preclinical imaging systems (PET, SPECT, CT), for which our expertise in instrumentation represents a major asset. The goal is to provide high-performance tools for diagnosis and therapeutic monitoring, tailored to the specificities of biological studies, through cellular, organoids and animal models. This approach will combine advanced imaging capabilities with dedicated reconstruction and quantification algorithms based on AI approaches.

Status : The team's expertise has enabled various instrumental developments over the past decade, particularly in PET and SPECT imaging. Notably, FPGA developments were registered with the SATT (Technology Transfer Office), leading to a collaboration with the company Inviscan to design next-generation PET modules. In partnership with this industrial collaborator, we proposed a PET detector design project titled **digiPET**, which was endorsed by the Biovalley cluster and funded by the Alsace Region, the Eurometropolis of Strasbourg, and BPI France. As part of the CPER I2MT program, we also worked on the design of a PET insert for a high-field preclinical MRI system. Additionally, we successfully completed a project funded by the French National Cancer Institute (INCa): the **rpPET** project. This innovative approach aimed to demonstrate the relevance of PET imaging in a macroscopic radiobiology context, following tumor irradiation using a proton beam [Brasse et al., 2021]. Our developments in SPECT also opens interesting perspectives [Boisson et al., 2016]. Finally, our developments are also part of a translational approach, specifically in the context of clinical brain PET imaging, supported by ANR fundings and an ongoing PhD research. The team joined the Laboratory of Excellence (LabEx) Médalis, through what it receive support from the Institut du Médicament de Strasbourg. We work with clinical actors with strong connections with the Paul Strauss Cancer Center, and maintain collaborations with the compagny Inviscan, as well as an ongoing CIFRE PhD project with Smiths Detection

5-years prospects : The next 5 years will be supported by the improvement of molecular imaging modalities that enable a more refined and comprehensive tumor characterization at both molecular and functional levels. The integration of these advanced techniques will not only enhance diagnostic capabilities but also open new avenues for data processing and interpretation. By enabling richer, multidimensional datasets, the project aims to support the development of personalized therapeutic strategies and contribute to the emergence of next-generation imaging-based decision-making tools.

4.4.6 Compton imaging and Compton Collimated Probe

Context The concept of gamma-ray imaging using the Compton effect was first introduced in the 1970s [Todd et al., 1974]. It has since evolved into a versatile technique, applicable in nuclear medicine to localize tumors marked with radio-tracers [Krimmer, 2015], in dose monitoring for hadrontherapy [Muñoz, 2017], and in environmental mapping following nuclear incidents such as the Fukushima disaster [Jianyong, 2016]. Compton Cameras (CC) are built using a scatterer, where the incident gamma ray undergoes a Compton interaction, and an absorber, where the scattered photon deposits its residual energy. By recording the positions and energies of both interactions, a cone of possible directions is reconstructed. The intersection of these cones identifies the radioactive source location.

Status The TEMPORAL project (2016–2024, PIA ANDRA) aimed at designing a portable Compton camera for nuclear waste characterization, using $CeBr_3$ monolithic scintillators coupled with SiPM arrays [Iltis

and Snoussi, 2015, Iltis, 2016, Iltis, 2018]. The same detector design is used for both scatterer and absorber. By analyzing the distribution of scintillation photons within the first 100 ns, depth-of-interaction (DOI) information is extracted.

Our team contributed by modelling the system with GATE, developing a polyenergetic list-mode MLEM reconstruction algorithm [Mehadji, 2018], and implementing realistic SiPM response models in GATE [Mehadji, 2022b, Mehadji, 2023b].

As a spinoff, we developed a Compton-Collimated Probe (CCP) for beta$^+$ radio-guided surgery. The CCP consists of two aligned detectors; coincidences imply a Compton interaction followed by full absorption. Setting an upper threshold on the first detector's energy enables electronic collimation based on Compton kinematics.

This probe is currently being developed at UC Davis by B. Mehadji, now funded by NIH [Mehadji, 2025]. Telix Pharmaceuticals expressed interest following a 2024 NSS/MIC presentation [Mehadji, 2024b]. A PCT patent was filed [Mehadji, 2024c].

Several prototypes using Philips dSiPMs have been tested at CPPM with ^{18}F and ^{68}Ge sources. An angular resolution (ARM) of $23.1^\circ \pm 0.4^\circ$ and intrinsic efficiency of 8‰ were achieved, close to the simulated 11.2‰ [Mehadji, 2024a].

The following fundings have been obtained:

- TEMPORAL, Temporal spectrometric imager for the dismantling of nuclear equipment (Damavan Imaging, WEEROC, CPPM) PIA ANDRA (RTSCNADAA160019) 2016-2024 (42 months CDD IR)
- CCP, Compton collimated probe (CPPM, AP-HM), CNRS DECLIC 2023-2024

5-year perspectives SATT has expressed an interest in financing a one-year post-doctorate and providing the resources needed to develop CCP on condition that we collaborate with a French industrial partner, yet to be identified, who would become the exclusive operator.

4.4.7 Opalis

Context Over the past decade, intraoperative imaging has emerged as a critical tool for enhancing the precision of surgical procedures, particularly in oncology and neurosurgery. However, real-time, high-resolution, and label-free imaging modalities remain limited. Recent advances in nonlinear optical imaging, including multiphoton microscopy, second harmonic generation (SHG), and stimulated Raman scattering (SRS), offer promising avenues for label-free, high-contrast visualization of tissue architecture and biochemical composition [Cheng and Xie, 2015, Campagnola et al., 2020]. Despite these advances, miniaturization, integration of multimodal signals, and real-time data interpretation remain major technical challenges. Our project aims to address these limitations by developing a compact, fiber-based nonlinear endomicroscope integrating spectral, lifetime, and structural contrast for neurosurgical guidance.

Status The OPALIS project aims to deliver real-time optical guidance during brain tumor surgeries by developing tools for immediate intraoperative diagnosis and accurate delineation of infiltrative tumor margins. The project is structured around four main pillars: OGINS, a multimodal nonlinear endomicroscope; OPTIPEN, a clinically tested bimodal prototype; a comprehensive, multiscale tissue database (DATAbank); and AI-powered analytical tools (DATAuse). OPTIPEN operates in the visible spectrum and enables quantitative assessments of endogenous fluorescence using spectral and fluorescence lifetime measurements. Validated in neurosurgical settings, it serves as a proof-of-concept for real-time optical interrogation. OGINS, based on near-infrared nonlinear excitation, has thus far focused on quantitative contrasts. Between 2020 and 2023, the project achieved key milestones, including optical characterization of brain metastases, development of a custom bimodal fiber-optic probe, and early clinical validation of OPTIPEN. Over the next

five years, the priority will be full system integration, notably through the development of qualitative contrast modalities (such as fluorescence and second harmonic generation imaging) and the incorporation of a scanning system to OGINS, enabling high-resolution real-time imaging.

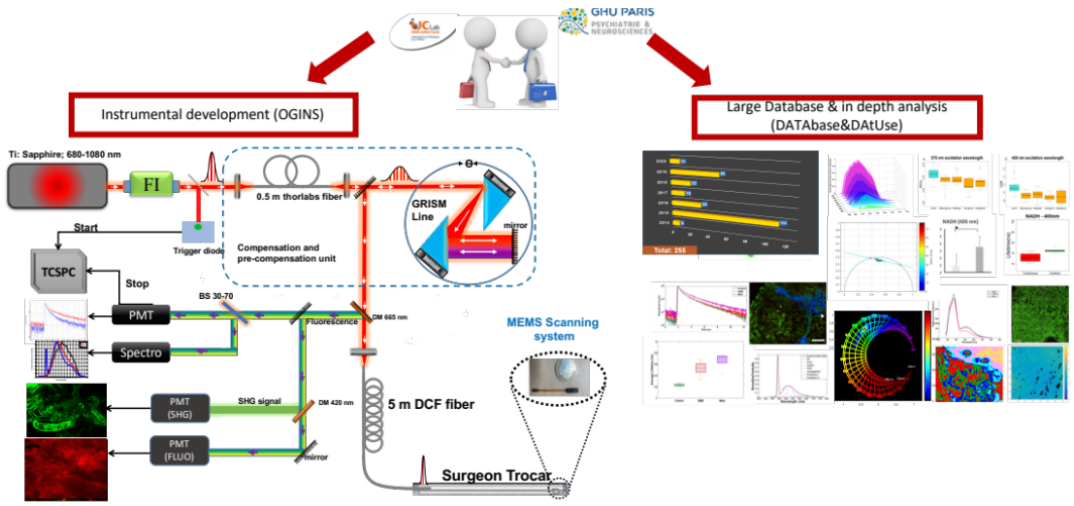


Figure 4.15: The two main components of the project are built on close collaboration between clinicians and researchers: on the right, the architecture of the endomicroscope currently under development; on the left, an illustration of the various qualitative and quantitative analyses performed within the database.

Two ongoing PhD theses (2024–2027) are dedicated to the optimization of the scanning module and the AI-based classification of multimodal signals. Collaborations include CREATIS, Sainte-Anne Hospital, Lariboisière Hospital synchrotron SOLEIL and Beijing Institute of Technology. Our team comprises 2 CNRS researcher, 1 faculty members, and 2 PhDs.

The project currently involves 3.3 full-time equivalents (FTEs), including optical engineers, data scientists, and clinical partners.

Over the last 15 years, the project has received more than €1.5 million in funding. Major and strategic funding sources include:

- 3 PCSI projects
- CNRS Programs:
  - 80PRIME: PhD fellowship
  - MITI Transverse Program: One PhD fellowship focused on interdisciplinary innovation.
  - Pre-maturation Program
- Augusta Foundation
- SATT Paris-Saclay (POC'UP Program)
- Université Paris-Saclay and Associated Labs:
  - LabEx P2IO: One-year postdoctoral fellowship.
  - IdEx Paris-Saclay: One PhD fellowship (2015–2018).
- Ligue contre le cancer: PhD fellowship (2017–2020)

5-year perspectives Our goal is to deliver a clinically usable, CE-mark-ready multimodal endomicroscope for neurosurgical guidance. We aim to expand its application to other surgical specialties (e.g., urology, ENT), develop automated AI-assisted diagnosis, and establish a startup for commercialization in collaboration with the SATT Paris-Saclay. Recruiting a full-time optical engineer remains a strategic priority to support this translational development.

4.5 Irradiation platforms

4.5.1 The Resplandir network

The Resplandir network (Réseau des Plateformes Nationales pour la Dosimétrie, l'Instrumentation et la Radiobiologie) is an informal network created under the aegis of the GDR MI2B in 2013. The network brings together a number of X-ray and hadron irradiation platforms. Table 4.1 provides the list of platforms that is currently being updated and will evolve over time. It includes both clinical and preclinical systems from IN2P3, but also from CEA, INSERM, ASNR, various universities and CLCCs.

Ions			X-rays and e^-
Centers	Ions	Energy (MeV/n)	Centers
CPO (Orsay)	p	76–201	ICO (Nantes)
CAL (Nice)	p	65	CERVO (Lyon)
GANIL (Caen)	C, O	up to 95	PARMIVA (Clermont)
Arronax (Nantes)	p, α	70	RadeXp (Orsay)
CYRCé (Strasbourg)	p	25	IRCM (Fontenay aux roses)
AIFIRA (Bordeaux)	p	3	Cyceron (Caen)
BioAlto (Orsay)*	p, O	8–25	CGFL (Dijon)
SILab (Lyon)*	α	~ 3	CREFRE (Toulouse)
			Gustave Roussy, (Villejuif)
			CRAN (Nancy)
			IRCM (Montpellier)
			STROBE (Grenoble)

Table 4.1: Irradiation platforms within the Resplandir network (Réseau des Plateformes Nationales pour la Dosimétrie, l'Instrumentation et la Radiobiologie), categorized by particle type. On the left: ion beam facilities using protons (p), alpha particles (α), and heavier ions such as carbon (C) and oxygen (O). On the right: facilities delivering X-rays and electrons (e). Platforms marked with an asterisk (*) are currently under development. All ion irradiation platforms are accelerator-based, except for SILab, which uses a radioactive Americium-241 source.

2013	Dosimetric comparison of X-ray generators (Orsay)
2013	High-LET irradiation platforms (Orsay)
2014	ResPlaNDIR workshop on the PRECy project (Strasbourg)
2017	Radiobiology division meeting (Lyon)
2018	X-ray platforms (Dijon)
2019	ResPlaNDIR meeting (Dijon)
2023	ResPlaNDIR meeting (Dijon)
2024	Dedicated session at the SFBR congress (Porquerolles)

Table 4.2: List of the Resplandir meetings organized since 2013.

The network aims to bring together a variety of irradiation platforms and to foster regular exchanges between users and those responsible for the platforms' development and metrology. Regular meetings are held, typically gathering between 40 and 70 participants (Table 4.2).

Key topics of discussion include the development of standardized irradiation protocols, the harmonized use of metrology and dosimetry tools across platforms, and the intercomparison of both physical and biological dosimetry practices.

In 2024, the network received a €5,000 allocation from IN2P3. As it does not have a dedicated operating budget, joint equipment development is currently not undertaken within this framework. The available

funding was used to initiate a physical intercomparison program based on alanine pellet irradiation. Measurements were conducted at various dose rates and LET values, under both in vivo and in vitro conditions, across several sites: Arronax, Cyrcé, CPO, CAL, and GANIL (for hadron beams), as well as around ten X-ray irradiators. Alanine analysis is centralized at ASNR in Fontenay-aux-Roses.

In parallel, a LET characterization campaign has been launched in collaboration with C. Guardiola's team (Barcelona). A first experiment took place at Arronax in September 2024, with a second planned at GANIL in June.

The network also supports emerging platforms by providing feedback and assistance in drafting specifications for the procurement of commercial equipment (e.g., X-ray irradiators).

Looking ahead, the network intends to continue its intercomparison activities, particularly by developing shared phantoms and restraint systems usable across all platforms. In the longer term, biological intercomparison efforts will be pursued through the creation of a master cell bank and the definition of standardized biological and dosimetric protocols. However, due to current budget constraints, the development of shared equipment and material exchanges is not yet feasible.

Formalizing the network through a collaboration agreement remains challenging, given the number of institutions involved. Establishing a dedicated association could provide a more viable structure for sustaining and expanding the network's activities.

4.5.2 The BioALTO project

status : The BioALTO project (IN2P3 Master Project, 2024-2027), aims to establish an experimental platform at the ALTO facility (IJCLab, Orsay) dedicated to advanced preclinical research in hadron therapy and radiobiology of low-energy ions, within the national Resplandir network. The project involves the optimization of a dedicated ion beamline, the installation of an irradiation station suitable for radiobiology experiments, and the setup of a nearby cell culture room for the preparation, storage, and analysis of biological samples.

The BioALTO platform addresses the growing demand for ion beams from the scientific community working on innovative cancer therapies, particularly in the Île-de-France region. Following the closure of the Van de Graaff accelerator at IP2I in 2020, the RadioGraaff device [Constanzo et al., 2014] was transferred to ALTO. Initial post-transfer tests in 2022 revealed the need for modifications and repairs to integrate the system into the new environment.

In 2023, the BioALTO project was officially launched as a collaboration between IJCLab, IP2I, and LPSC to adapt the RadioGraaff system for use with ALTO's wide range of ion sources, including protons, helium, lithium, carbon, and oxygen, all of which are relevant to radiobiological studies.

In 2024, the final chassis housing the irradiation line and the RadioGraaff device was installed in Room 320 at ALTO. By the end of the same year, the line was equipped with a diamond monitor developed by LPSC (see section **??**), enabling particle counting and accurate dose measurement. Several beam diagnostics and cameras were added on the beamline, and an analytical model of the beam transportation across the 2 diffuser and collimators of the beamline was developed to determine optimal diffuser thicknesses for each ion type and energy to be used, and ease the future operation of the experiments to optimize beam homogeneity and intensity (an article describing the model will be submitted by the end of the year).

This project was primarily supported by the PCSI PICTURE project and the IN2P3 funding associated with the Master Project. 13.65 FTEs distributed among approximately 30 people are involved on this project.

5-year prospects : The platform is expected to be operational by end-2025, including an upgrade with a Faraday cage for beam adjustment and stopping during irradiation. The first biological irradiation is planned for 2026. After this commissioning phase, the platform will be made available to external research teams. In addition, new beam diagnostic adapted to low-energy ions, without interfering in the beam, is

expected. IJCLab is developing a compact detector using air as a scintillating medium, leveraging UV emission from nitrogen molecules (300–480 nm). A ring of optical fibers around the beam, near biological samples, will collect the light and transmit it to SiPMs. This system will allow fluence, geometry, and temporal beam structure measurements near the sample. This may work to control UHDR irradiation, which is one of the evolution perspective of the platform (beyond 2027) to propose another site to perform FLASH radiobiological studies.

4.5.3 A multidisciplinary research room at Cyclhad

Planned Beam Capabilities The CyclHAD C400 accelerator is designed to deliver proton, helium, and carbon ion beams at energies up to 400 MeV/nucleon. In the longer term, with the installation of a new ion source, lithium and oxygen beams may also be considered.

Accelerator Status

- The installation of the accelerator is currently in progress.
- The first carbon beam from the C400 is expected in June 2026.
- Clinical qualification of proton and carbon beams is scheduled between mid-2026 and the end of 2027.
- A collaboration with NHa (Normandie Hadronthérapie) and LPC Caen is planned to evaluate beam purity.

Infrastructure Status

- A dedicated but currently **empty experimental room (”physics room”) is available and ready to be fully equipped.
- Laboratory space for cell culture and molecular biology is already in place.
- An X-ray irradiator is also available on-site.

Project Vision The goal is to develop a multidisciplinary irradiation beamline in the physics room to support the following applications:

- GDR-related research (dose control, cross-section measurements, radiobiology – in collaboration with INSB)
- Solid-state physics experiments (INP)
- Sensor testing (for CNRS and CNES)
- Industrial irradiations, as part of the regional initiative ”Normandie Accélérateur” involving local industry, the University of Caen, GANIL, and LPC as partners.

Technical Specifications The facility must be designed to be compatible with all intended applications. For health-related research in particular, the following capabilities are required:

- Scanning system: Based on the GANIL model, suitable for wide-field *in vitro* applications.
- Passive irradiation systems: Based on Arronax and CYRCé models, for small-field, *in vitro* experiments. Includes the capability to vary LET and dose rate.
- SOBP (Spread-Out Bragg Peak) generation systems
  - Rotating wheels (Arronax, CYRCé models) for *in vitro* and *in vivo* small-field irradiations.
  - Ridge filters (GANIL model) for *in vitro* and *in vivo* FLASH-like applications.
- Microbeam systems: For MRT (Microbeam Radiation Therapy) studies.
- Irradiation timing control systems: Kicker system based on the Arronax model.

Validation and Metrology A comprehensive validation plan will be required, including metrology and dosimetry to ensure precise and reproducible irradiation conditions across all platforms and applications.

4.6 Numerical simulation platforms

4.6.1 National Efforts in Multi-Scale Modeling for Innovative Radiotherapies

Modeling the biological effects of ionizing radiation is a complex, multidisciplinary challenge, particularly relevant to innovative radiotherapies such as hadrontherapy, Targeted Alpha Therapy (TAT), and Boron Neutron Capture Therapy (BNCT). These effects depend on energy deposition at the nano- and micrometer scales, varying with particle type, energy, delivery mode, and combined agents. Long-term clinical outcomes further emphasize the need for robust modeling frameworks.

A comprehensive and realistic approach must integrate physics, chemistry, biology, and clinical insights across multiple scales, from atomic interactions to whole-body effects. Rather than relying on a single model, this requires a network of interconnected simulation tools. Reliable experimental data are essential to validate these models at all scales.

Initial modeling starts at the microscopic level with Monte Carlo codes (e.g., Geant4-DNA, LPChem), which simulate interactions and energy deposition in water and other biomolecules, as well as the production of free radicals. These tools can incorporate molecular structures like DNA and simulate repair mechanisms.

To extend modeling to cellular and tissue levels, biophysical models such as NanOx are used to predict cell survival, supported by biological data and geometric representations (e.g., CPOP digital phantoms). For preclinical and clinical use, models must be scaled to the macroscopic level using platforms like GATE, which generate 3D biological dose maps from physical and biological data.

Ultimately, these models enable simulation of tumor control and healthy tissue complications, offering powerful tools for optimizing and personalizing radiotherapy treatments.

4.6.2 Geant4-DNA

Status IN2P3 is currently involved at different levels in Geant4-DNA:

- Coordination activities: scientific, technical, collaboration, short-term Geant4-DNA related projects (funded externally),
- Software development: physics, chemistry, biological damage at the DNA scale,
- Counseling in other research projects (such as experimental validation of Geant4-DNA simulations).

The scientific workplan is established and reviewed by the Geant4-DNA collaboration during the annual collaboration meeting. A selection of the main achievements performed at IN2P3 during the last 5 years follows this timeline:

- 2020: New optimised “Independent Reaction Times” alternative approach (IRT)
- 2020: First “integral” chain for the simulation of early DNA damage in the full genome of bacteria and cells (“molecularDNA” Geant4-DNA example) – see Figure 4.16,
- 2021: New “mesoscopic” approach for the long-term simulation of water radiolysis,
- 2023: Inclusion of DNA damage repair & survival models in the “molecularDNA” simulation chain,
- 2023: New electron models for track structure simulations in DNA-related material,
- Regular development of several user applications showcasing Geant4-DNA features (Geant4 “extended” or “advanced” examples – see this link for the full list): e.g. for physics (dnaphysics, microdosimetry, microprox, microyz, mfp, range, slowing, spower, svalue, wvalue, AuNP), chemistry (chem1 to 6, UHDR), geometries (microbeam, cellularPhantom, pdb4dna, wholeNuclearDNA), biological damage (moleculardna),
- Regular Geant4-DNA tutorials (22 since 2011),

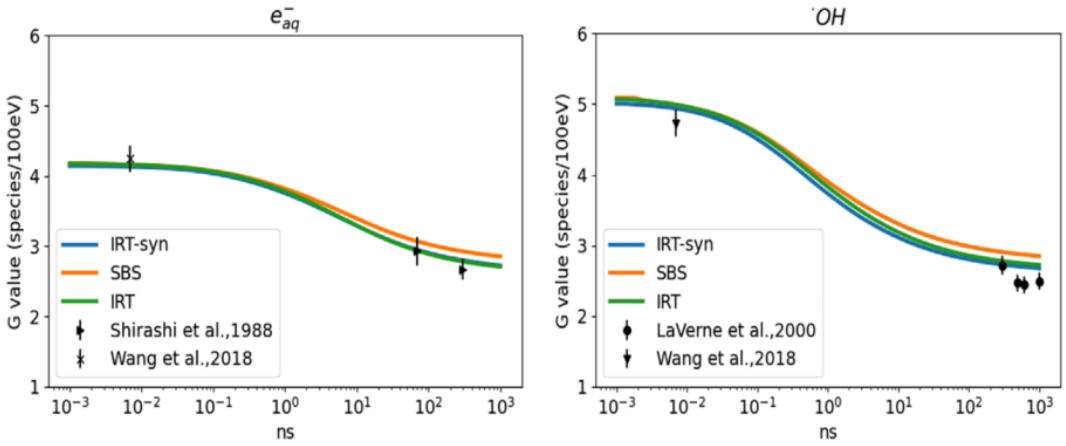


Figure 4.16: Quantification of DSB yields for several Geant4-DNA human cell models, irradiated by protons and alphas for several values of LET (lines: Geant4-DNA and PARTRAC simulations; crosses: experiments) (from https://doi.org/10.1016/j.ejmp.2024.104839)

- Regular (co)-organisation of the series of conferences "Geant4 International User Conference at the Physics-Medicine-biology Frontier" (5 since 2005). This series was initiated by IN2P3 (plenary sessions only, associated publications are available in Special Issues of the European Journal of Medical Physics / Physica Medica).

Over the past five years, the Geant4-DNA project, developed within IN2P3 and as part of the Geant4 collaboration, has received sustained support through the CNRS/IN2P3 Master Project *Geant4* (2022–present), which coordinates national development activities. Additional funding has come from several international and bilateral programs, including:

- CNRS/IN2P3 IEA France–Vietnam (2025–2026)
- CNRS/MITI & ASNR *INSIGHT-DNA* (2025–2026)
- CNRS/MITI & Inserm *Flash'Atlantic* (2023–2024)
- Campus France STAR France–Korea 47407QG (2023–2024)
- Campus France Pavle Savić France–Serbia (2023–2024)
- CNRS/IN2P3 IEA France–Serbia (2023–2024)
- CNRS/IN2P3 IEA France–USA (2023–2024)
- European Space Agency: *BioRad III* (4000132935/21/NL/CRS, 2021–2023)
- Swiss National Science Foundation: *MAGIC* project (2019–2023)

Additionally, a new IN2P3-funded postdoctoral fellowship at LP2i Bordeaux is scheduled for 2025–2027. Two prior postdocs were supported in 2020–2021 and 2009, respectively. No PhD fellowships have been directly funded by IN2P3 to date, although 14 PhDs were supported through alternative sources.

5-year perspectives The priorities we will be focusing on at IN2P3 are the following:

1. Core development of Geant4-DNA
   - Physics
     - extension of the energy coverage of electron inelastic models up to 10 MeV in liquid water,
     - collaboration with NASA: inclusion of a new physics list (electrons, ions) for liquid water based on the RITRACKS code for space applications,
     - improvement of accuracy of ion models at low energy (Li, C, . . .) in liquid water, considering in particular charge-exchange and multiple ionisation processes,
     - development of new models for track-structure simulations other materials (e.g. solid gold, O_2, N_2, CO_2),

  - possibly, inclusion of other alternative physics models, after approval by the Geant4-DNA collaboration.
- Chemistry
  - extension of radiolysis modeling for ultra high dose rate irradiation, taking into account the variety of beam structures,
  - experimental validation of radiolysis under various beam qualities and dose rates.
- Geometries of biological targets
  - completion of multi-scale library of biological models (bacteria, cells, 3D multi-cellular assemblies, DNA packing. . .) for the molecularDNA application,
  - corresponding experimental validation of damage prediction.
- Computing
  - possibly GPU porting & AI R&D (both within the workplan of the Geant4 collaboration)

2. Geant4-DNA applications
   - generic multi-scale (in space and time) and easy-to-use simulation platform for a variety of complex radiation fields, starting with a $\ll$ space mission $\gg$ use case,
   - development of new example applications & counselling to IN2P3 teams (if time permits):
     - simulation of innovative radiotherapy approaches (e.g. hadrontherapy with a variety of ions, Flash irradiation, VHEE, TRT. . .),
     - radiation protection in space,
     - environmental applications (e.g. track-structure simulations in the atmosphere).

4.6.3 GATE

Status

- Training sessions.
  Since 2019, LPCA has been responsible for trainings on the GATE simulation platform. These training sessions are conducted on behalf of the OpenGATE scientific collaboration as a “turnkey” learning approach. To achieve this, a shared computing infrastructure has been deployed that allows on-demand creation of user accounts for participants. The computing and software environment is fully controlled on dedicated resources, enabling the setup of directories with educational content (practical exercises) tailored to each participant’s level and specialization (e.g., imaging, dosimetry, radiation protection).
  A partnership agreement has been established with CNRS Formation Entreprises to organize one training session per year—a three-day remote session open to a maximum of 15 participants—dedicated to GATE simulations. Additional on-demand sessions are proposed, often in collaboration with scientific societies such as IEEE-NPSS, and target international Master’s students. In 2021 and 2022, two remote training sessions were held with Asia and Africa, each attended by 30 students.
  Furthermore, LPCA offers customized trainings for private companies or industries involved in detector development for dosimetry, imaging, environmental, or military applications. In 2025, LPCA will begin organizing training sessions for medical physicists and physicians, in collaboration with UNICANCER, with the goal of training 10 to 20 clinicians per year.
- Research
  - In 2022, LPCA received 3-year funding from IN2P3 to hire an engineer dedicated to simulation platform development. Contributions to the GATE version 10 included:
    * Implementation of a generic interface for energy spectra (discrete, histogram) and integration of predefined ICRP107 sources;
    * Development of a proof-of-concept for generic filters on GATE actors via metaprogramming (Abstract Syntax Tree processing and code generation);
    * C++ code optimization and maintainability improvements.

- Since 2022, LPCA has developed two new GATE modules (“actors”) aligned with its scientific projects, aiming to consolidate multiscale simulation capabilities.
  * The IP2I-CREATIS-LPCA collaboration implemented and validated the `BioDoseActor` to address biological dose calculations for preclinical and clinical hadron therapy using various biophysical models (e.g. mMKM, NanOx). An optimized voxel-compatible version of the `BioDoseActor` will be included in GATE 10.
  * The LP2I-LPCA collaboration also implemented and validated the `ChemistryActor`, allowing simulations of the chemistry of water radiolysis under different conditions (pH, O_2 levels, dose rates, LET, scavengers).

  Additional GATE modules have been developed within the framework of the collaboration. For example, the `vpgTLE` actor enables fast and accurate simulations of prompt gamma emissions in the context of hadron therapy, facilitating the design and performance assessment of prompt gamma detection systems for ion-range verification [Kanawati et al., 2015, Huisman et al., 2016, Létang et al., 2024].

  In 2024, the OpenGATE collaboration launched a new focus collection entitled “Advances in GATE Monte Carlo Simulations for Medical Physics Applications”, currently published in *Physics in Medicine & Biology*, with guest editors Lydia Maigne, Emilie Roncali, Nils Krah, Christian Morel, and David Sarrut.

The GATE collaboration has received funding from several sources in recent years, including the *SIRIC LYriCAN* grant (INCa-INSERM), the *LABEX PRIMES* of Université de Lyon and the *POPEYE ERAPerMed 2019* project. Developments related to optical modeling were supported by NIH grants and the work related to STL was carried out within the *MRTDosimetry* project, funded by the EMPIR programme, co-financed by the participating states and the European Union’s Horizon 2020 programme.

5-year perspectives Medical physics is being transformed by the growing use of artificial intelligence (AI) in personalized medicine. One promising area is the development of digital twins, virtual models of patients that replicate physiological and pathological processes in silico to predict treatment outcomes and optimize therapeutic strategies. A joint discussion will need to be conducted among all IN2P3 groups involved in the development and validation of the platform on the use of AI, to define our priorities for modeling digital twins of instruments, patients, or radiobiological experiments. The LPCA will be particularly involved in the latter aspect, as its main research activities are linked to the development of predictive tools for the understanding of the FLASH effect or innovative IRT treatments.

4.7 Summary

This section highlights the critical role of instrumentation and simulation in supporting innovative research in health physics at IN2P3. Major developments in hadrontherapy instrumentation, including ion-range monitoring, beam hodoscopes, and particle trackers, demonstrate IN2P3’s capacity to design and implement advanced detection systems, such as TIARA, ClaRyS, PEPITES, and MATRIX, tailored for real-time therapeutic monitoring and precision measurement.

The emergence of new approaches in radiation therapy, particularly through projects like THIDOS, underlines the integration of nuclear imaging into theranostic strategies. Similarly, advances in imaging and endomicroscopy technologies (e.g., XEMIS, MAPSSIC, ClearMind, and Photon-counting CT) reflect the Institute’s commitment to pushing the boundaries of medical diagnostics and visualization techniques.

Robust irradiation platforms, such as Resplandir, BioALTO, and the Cyclhad multidisciplinary research room, provide essential experimental environments for testing new concepts and validating therapeutic models. These facilities play a foundational role in bridging instrumentation with biological validation.

Finally, the section emphasizes IN2P3's leadership in numerical simulation platforms, with flagship efforts in Geant4-DNA, GATE, and multi-scale modeling. These tools are crucial for accurate dose calculation, radiobiological modeling, and optimizing new therapeutic protocols.

Conclusions

Document summary This report aims to provide a comprehensive overview of the health-related research activities conducted within IN2P3 (CNRS – Nuclear and Particle Physics), highlighting the interdisciplinary efforts and scientific innovations that drive the community's contribution to health and medical applications.

The first section outlines the broad scope of IN2P3's involvement in radiation physics for health, emphasizing scientific challenges and ongoing projects in areas such as innovative radiotherapies, biomedical imaging, radiobiology, and the development of radionuclides. The GDR MI2B emerges as a pivotal structure that fosters coordination, collaboration, and visibility of CNRS research across multiple institutions, supporting both scientific activities and training initiatives.

Subsequent sections delve into key research themes, including hadrontherapy, emerging approaches in radiation therapy (e.g., FLASH, SFRT, TRT, and BNCT), and the understanding of biological effects and modeling. These parts underline the strategic importance of IN2P3's expertise in instrumentation, simulation, and data analysis to support cutting-edge medical technologies.

The last chapter highlights the development of advanced tools and platforms: from beam monitoring systems and endomicroscopy to molecular imaging and multi-scale simulation frameworks like Geant4-DNA and GATE. These instrumental and numerical efforts significantly enhance the precision, safety, and effectiveness of future therapies.

Overall, the report demonstrates IN2P3's strong commitment to tackling major societal health challenges through fundamental research, technological innovation, and cross-disciplinary collaboration. This strategic investment not only strengthens the CNRS position in medical physics, but also lays the foundation for future breakthroughs in diagnosis and treatment.

Positioning summary IN2P3's involvement in therapeutic applications is strategic.

Teams contribute with essential expertise in Monte Carlo–based treatment planning, hadrontherapy beam monitoring, and the characterization of secondary particles. Notably, experiments like FOOT and CLINM rely on IN2P3's nuclear detection techniques and benefit from direct access to irradiation platforms such as Cyrcé or external facilities through formal partnerships (e.g., with CNAO and CAL).

On the modeling side, IN2P3 leads national efforts in developing simulation tools like Geant4-DNA, GATE, and NanOx, which are central to understanding radiobiological effects at various scales. These tools are reinforced by experimental data and enable precise predictions crucial for therapy optimization. Thus collaborations with biologists are essential. For instance, the BioHADRON project (IP2I/PHABIO) exemplifies the strength of IN2P3's interdisciplinary approach, integrating physics and biology to develop advanced, biologically-informed therapeutic strategies.

Similarly, the Institute supports cutting-edge innovation in online dosimetry, detector development, and gamma spectroscopy through projects such as TIARA, ClaRyS, SCICOPRO, and MATRIX. IN2P3 laboratories design and develop dedicated instrumentation (e.g., diamond detectors, advanced dosimetry systems, nuclear imaging devices) that are critical for clinical and preclinical applications. In this context, engineering teams (in mechanics, electronics, computing) provide essential support to meet high-level technological demands.

Furthermore, projects such as PRISMA activities at SUBATECH / Arronax, EUROPA, SMILES, PRALINE, and REPARE illustrate IN2P3's critical positioning in radionuclide production, including isotope separation, target design, and high-power accelerator operation. These initiatives benefit from the Institute's solid infrastructure and skilled technical workforce, offering an environment where complex nuclear techniques can be developed and applied to societal challenges in health and environment. The Institute pro-

vides access to unique experimental platforms (such as ARRONAX, Cyrcé, GANIL, IJCLab) that support a full R&D chain from target fabrication to irradiation, isotope separation, and characterization.

Finally, projects benefit from close collaborations with university hospitals, treatment centers, national networks (e.g., GDR MI2B), and doctoral schools, fostering training and integration of new researchers in health-related fields.

In summary, IN2P3's unique combination of scientific expertise, technological infrastructure, and interdisciplinary integration makes it an essential actor in the advancement of innovative health technologies. It brings a coherent and original scientific vision that complements and enhances national and international collaborations, reinforcing its leadership in nuclear applications for health.

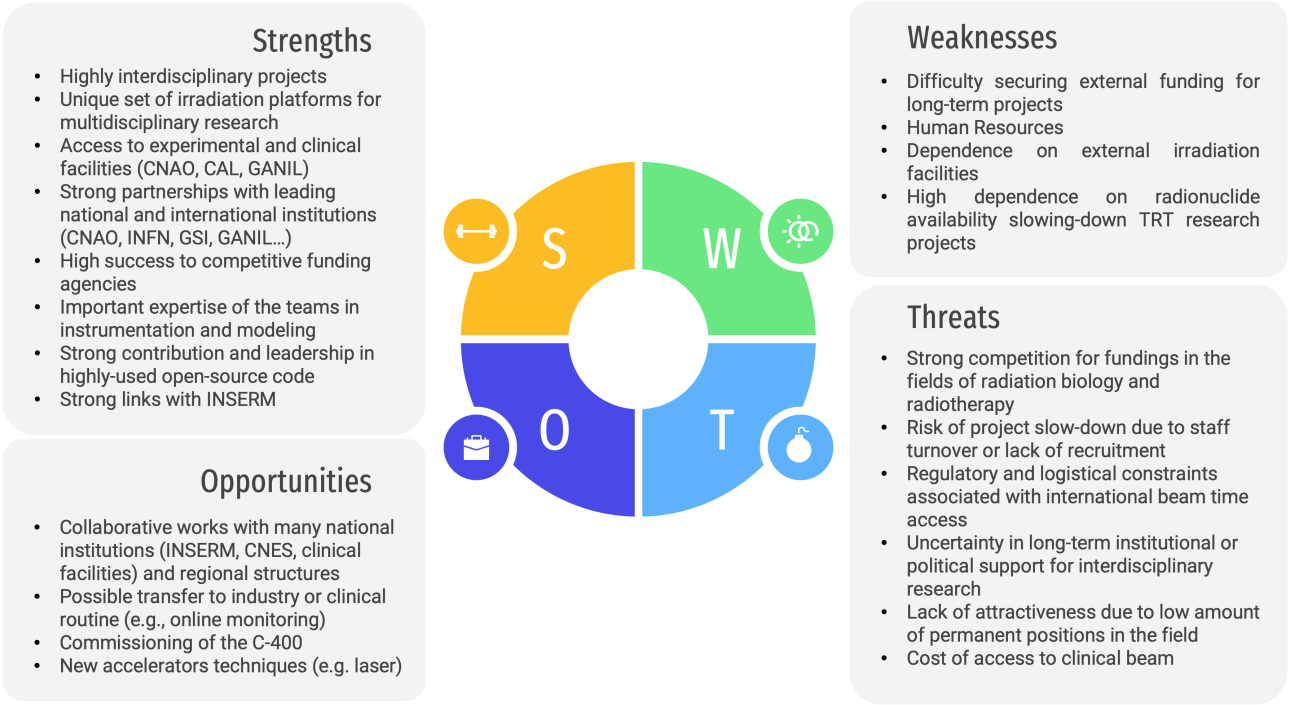


Figure 4.17: SWOT analysis of the IN2P3 activities for health.

SWOT analysis

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