REPARE in LHE

G de France on behalf of the REPARE collaboration (GANIL, ARRONAX, SUBATECH, CYCERON, CERN) and CLCC F Baclesse, CHU, CERMN, ANTICIPE (INSERM), CYCERON, ISTCT

1. Introduction

The project called « REPARE in LHE » aims at installing a high power target system designed to optimize the production method of innovative radioelements in the LHE (for Ligne Haute Energie) hall of the SPIRAL2 building. This target system is developped in the framework of an ANR project called REPARE (REsearch and developments for the Production of innovAtive RadioElements) led by GANIL. The first radioisotope of interest is the 211At alpha emitter. This installation is the starting point of an ambitious project, under construction since 15 months and involving the main actors involved in cancer treatment and located on the northern Caen area. Therefore, the final goal is to develop the full chain from the synthesis of 211At (to start with) up to the clinical trials. This would be possible if, and only if, some beam time is dedicated to this activity. The installation of a high power target in a dedicated zone would offer this possibility and give flexibility in planning and preparing other research experiments in the NFS area or elsewhere in the future. Finally, it will also offer the possibility of particle irradiation to other teams. Indeed, the only place where this is today possible is the converter room of NFS where space is extremely limited and constrained as it will be detailed later in the document.

In the following, and in order to have the complete picture, a summary of the full project is described including motivations, content of the project and its organization.

2. Motivations

While the use of radionuclides for diagnostic purposes (single photon emission tomography, SPECT and positron emission tomography, PET) is a mature field in nuclear medicine, the therapeutic use of radionuclides (Vectorized Internal Radiotherapy, VIR) is still today less advanced. Using basic clinical and imaging assessments, it is possible to determine the most effective therapy and to adjust that therapy during treatment based on radiation dosimetry and the tumoral response. Among the different treatment strategies that apply to the theranostic approach, the "targeted therapy" and in particular the VIR is a type of cancer treatment, which specifically targets the receptors present on the surface of tumor cells or overexpressed relevant biomolecules in the development of a pathological process. One of the most attractive advantage of targeted therapies is the possibility of personalized medical treatment, optimized for the characteristics of the patient and the disease.

Unlike conventional systemic chemotherapy, targeted therapies, which can also be systemic, allow radiation to be delivered directly to the targeted site of the disease with potentially less toxicity of normal tissue. Once in the vicinity of the cancer cells, treatment efficacy resides in the specific radioactive decay properties. Hence, in order to pave the way to a more personalized treatment strategy, radiation types which span different energy deposition ranges within the human body and different associated Linear Energy Transfers (LET) are required.

Improved overall response rates, survival benefit and a better safety profile have already been demonstrated for VIR compared to standard care including chemotherapy (ref). New applications are currently being developed with new new vectors (antibodies, peptides, folates, etc.) targeting more frequent types of cancer such as prostate cancer, melanoma, etc. which kill more than 100,000 patients in Europe every year. These new developments open up

the possibility of combining the new vector with a radionuclide with optimized decay properties at an early stage.

Internal radiotherapy: the hopes of alpha particles

When single cells need to be targeted (non-solid cancers such as leukemia or lymphoma, micro-metastases), and also for adjuvant treatment of minimal residual disease (i.e. single cancer cells or clusters of cells circulating in the body after surgery, or other therapies) or the targeting of chemo- and radio-resistant cancers (e.g. glioblastoma), high linear energy transfer (LET) particles such as alpha particles are very interesting because their ranges are comparable to the diameter of cancer cells. A few particles can be enough to destroy even a radio-resistant cancer cell. Recent developments using alpha emitters such as 211At, 212Pb, 213Bi or 225Ac have progressed from early in vitro studies to clinical trials and in vivo experiments. Targeted alpha therapy (TAT) seeks to achieve this goal by using highly cytotoxic alpha particle radiation delivered to specific cancer sites by appropriate carriers. Targeted radiation therapy is promising for many cancers with greater efficacy against the tumor while sparing surrounding healthy tissue and minimizing the treatment cost.

Molecular biology is a powerful tool for biological vectors such as monoclonal antibodies, specific proteins and peptides, and a variety of other molecules, to serve as specific carriers to deliver cell-killing radiation into tumors in a very localized manner. The majority of radiopharmaceuticals result from the combination of a radioisotope and a vector. Direct labeling via covalent bonds is only possible in certain cases with, for example, 18F, 11C or 123I. For the other radioisotopes, it is necessary to use chelators, which trap the radioisotopes and act as a bridge with the vectors.

There are two families of vectors:

- small organic molecules, including peptides. These vectors are designed from natural ligands which have a specific affinity for certain receptors that are expressed on the surface of cells. PARP inhibitors and PSMA ligands belong to this family.
- antibodies and antibody fragments can be labeled (Radio-Immunotherapy, RIT) by binding a radioisotope to groups of amino acids or to carbohydrate fragments of heavy chains. Iodine radioisotopes were the first to be used to label antibodies. However, iodine randomly binds to the antibody and can interfere with its biological properties. This is why other isotopes are currently used for labeling via a chelator. In this context, a promising avenue is the targeting of VCAM-1 with an antibody coupled to an alpha emitter. Targeting TROP2 with specific antibodies is another avenue of interest.

In this project, we propose to develop a continuum in TAT, from the synthesis of the 211At alpha emitter to the characterization of the response of tumor cells to treatments. To achieve this, we will explore the best possible target for optimal radiolabelling with 211At, using our local expertise and testing some specific therapeutic indications.

To achieve this objective, several areas of development must be carried out:

- Synthesis of 211At
- Radiochemistry for extraction
- Radiolabeling and radiosynthesis of radiopharmaceuticals specific to targets of interest (PSMA, anti-VCAM-1, anti-TROP2, etc.) with 211At
- Physicochemical and metabolic characterization of radiopharmaceuticals
- In vitro characterization of the response of tumor cells to treatments
- In vivo validation of treatments

- First in Human phase 0 study (GMP/CYCERON facility and ASN authorisation, clinical research unit)
- Dosimetry, biodistribution

Caen's northern plateau hosts many leading laboratories and facilities dealing with these different aspects, which makes it unique for setting up such an interdisciplinary project. For all of these developments, the project is organized in work packages, which are described in more detail later in this document.

3. Project summary

Target choices and pathologies of interest

We have chosen a few proteins for the implementation of the alphatherapy strategies. The targeting of these proteins (on the surface or intra-cellular) responds to clinical needs (ten-year cancer strategy) and concerns one or more of the pathologies for which the local teams have expertise, and/or for which in-depth models vitro, ex vivo or in vivo are available on the Caen site. For the concerned cancers, the chosen targets are overexpressed compared to normal tissues, and the targeted tumors will be those for which the expression of the chosen target will be the strongest and the most homogeneous within the tumor.

Targeting may involve the use of specific antibodies (VCAM, TROP2) or ligand molecules (PSMA ligand) coupled in both cases to the radioelements of interest for imaging or for treatment. These targets are presented below in the context of the pathology concerned by this approach, and the work packages then describe the approaches for synthesizing and evaluating these radioligands in the appropriate models.

One of the current limitations to the use of alpha therapy is the availability of the alpha emitter as well as obtaining biodistribution data to assess toxicity to healthy tissues and dosimetry. In this project, we propose to focus on 211At. The choice of this radioelement is based on several factors:

- The energies of alpha particles are similar to those of other alpha emitters (on the order of 5 to 6 MeV) and therefore they all have a similar biological efficiency per particle emitted.
- The production of 211At is done with an accelerator either directly by nuclear reaction or by decay in a generator. These production methods are well mastered and the difficulty lies mainly in the design of high power targets.
- The Caen site has, with GANIL ant its high intensity LINAC, a unique tool to promote transversal R&D as we propose it. The REPARE ANR project aims at optimizing these production methods and is already underway. The REPARE collaboration includes laboratories from the Nantes region (ARRONAX, SUBATECH) who are very active in promoting astatine. It is clear that the scale of the project is the France west region and we actively share our ideas and plans to progress in a coherent way.
- The chemistry of astatine extraction by dry or wet distillation is known and can probably be automated. The RadioPETT team from CYCERON has some expertise in this chemistry and a strong link with the experts in the Nantes region.

a) Use of antibodies against VCAM for the treatment of brain metastases.

Brain metastases are frequently detected during follow-up of patients with malignant tumors including lung, breast and melanoma tumors (Mao et al., 2016). Despite the progress made in cancer treatments, the average overall survival of these patients remains limited (6

months from diagnosis). In addition, cognitive decline is very regularly reported for patients treated with whole-brain external radiotherapy (Lawrence et al., 2010).

External irradiation techniques more targeted on metastases that are visible by imaging better preserve brain functions but do not prevent intracranial recurrences. These recurrences require sometimes complex re-irradiations which expose brain tissue to toxic doses.

Thus, more effective treatments allowing to target the microscopic disease at risk of recurrence, and to limit the doses in the healthy tissues to preserve them remain necessary. Radioimmunotherapy (RIT), the combination of a radionuclide with a specific antibody, seems to be a promising tool.

Inflammation is a biological process involved early in the development of brain metastases and a certain number of proteins will be expressed to allow the tumor cells to enter the brain. Among the proteins involved, VCAM-1 appeared to be very interesting because detected in a universal way for several primary tumors at the preclinical level as well as at the clinical level (Cheng et al., 2019). VCAM expression is then found on cells in direct contact with tumor cells only, in the case of brain metastases, no VCAM expression is found in healthy brain tissue.

Recently, we have shown that it is possible to target VCAM-1 with an antibody coupled to an alpha emitter, 212Pb (Falzone et al., 2018; Frelin-Labalme et al., 2020; Corroyer-Dulmont et al., 2021). In a preclinical model of cerebral metastases, the intravenous injection of an anti-VCAM-1-212Pb antibody significantly reduces the number of metastases, in turn significantly lengthening animal survival. In addition, we have shown that the dose deposition profile is very favorable for this targeted approach compared to external RT on the whole brain and this results in the preservation of healthy tissues (Corroyer-Dulmont et al., 2019). In parallel with this work, other studies have shown the interest of another integrin ligand similar to VCAM-1, VLA-4 (Soto et al., 2013, Cheng et al., 2019). The advantage of this integrin ligand, in addition to those already present with VCAM-1, is the availability of its antibody in an already humanized version, “natalizumab”, this point could notably facilitate the setting up of clinical trials. Eventually, it could be considered to treat patients with cerebral miliary in a clinical trial.

By developing a companion imaging biomarker specific to the target of interest, our project will allow it to be visualized in vivo. Used in animal models, this companion imaging biomarker will make it possible to compare the affinity for the target of the drug candidates identified during exploratory research (screening) and, thus, to finance preclinical and more expensive studies only for the most promising ones.

We also plan to radio-label the drug candidate and measure its bio-distribution and pharmacokinetics in a human subject by PET imaging. As the drug candidate is injected as a tracer, these studies present a low risk and their authorization application file is light. This "phase 0" optimizes phase 1 by eliminating drugs with unsuitable bio-distribution or pharmacokinetics. In phase I, the use of the companion imaging biomarker makes it possible to measure the attachment of the drug candidate to its target (“target engagement”).

This approach could then be tested in a situation of less advanced disease in the context of a phase II study, by TAT with immediate or delayed stereotactic (targeted) external radiotherapy in a salvage situation, for patients with one to 10 detectable metastases not operable. Considering the difficulties related to 212Pb and the advantages presented by

211At in the strategy of developing a continuum bringing together in a coherent way local skills that largely already exist, it is only natural that we propose to extend studies conducted with 212Pb to 211At.

Since astatine is not a metal like lead, its introduction into the molecules of interest will involve the formation of a carbon-astatine bond. Thus, to insert a 211A atom on an antibody, a boronic acid function will first be introduced, the boron will then be replaced by astatine. Similarly, this strategy will allow the introduction of iodine (123I or 124I) to perform SPECT or PET imaging studies respectively.

b) Use of antibodies against Trop-2 for the treatment of breast and ovarian cancers.

Trophoblast cell-surface antigen-2 (Trop-2) is a transmembrane monomeric cytoplasmic calcium-transducing glycoprotein that is up-regulated in a variety of epithelial tumors. This protein stimulates cancer growth by promoting cell proliferation, survival and invasion. Considerable amounts of Trop-2 are also retained in intracellular compartments, in a largely heterogeneous manner in different tumors. High levels of membrane expression of Trop-2 are associated with poorer prognosis in a variety of solid tumors, including breast cancer. In contrast, intracellular retention of Trop-2 is associated with less frequent disease relapses and better survival. Although Trop-2 membrane expression is reported in more than 85% of breast tumors, including triple-negative tumors, there is heterogeneity in expression profiles in virtually all histological subtypes. On the other hand, one study also reported moderate to strong membrane expression of Trop-2 in approximately 50% of ovarian epithelial tumors. Various antibodies directed against Trop-2 are currently in clinical development, in particular in the framework of breast cancers cares. We wish to look into the study of the interest of anti-Trop-2 antibodies in the context of the alpha-therapy approaches presented here.

The Anticipe Unit knows how to assess the effect of these cold molecules *ex vivo* or *in vivo*, and can support the assessment of the biological effect of radiolabeled molecules at the different stages of their development, in collaboration with the Cyceron teams. Currently applied to ovarian cancers, this strategy could later be applied to other types of cancers such as certain breast cancers.

c) Use of PSMA ligands in prostate cancers that escape PSMA-Lutetium and in thyroid cancers (under evaluation).

These ligands are also of interest, in particular in the context of cancers which over-express this surface antigen. PSMA (prostate-specific membrane antigen) is a type II transmembrane glycoprotein that was originally shown to be expressed in prostate epithelial cells. This protein is overexpressed in almost all prostate cancers and is currently widely exploited for imaging and VIR treatment of prostate cancer. It has also long been demonstrated that PSMA is not specific for prostate cancer and is expressed in the neovascularization of a wide variety of solid cancers, thus constituting a potential target for the development of an anti-neovascular treatment. In addition, a literature review recently summarized the current status of non-prostatic cancer imaging/therapy using PSMA-targeted radiotracers. In this context, a collaboration has already been established between the CERMN and the nuclear medicine department of the CLCC F. Baclesse, on two distinct aspects concerning the development of radiolabeled PSMA ligands on the one hand, and on the study of the expression of PSMA in cancers other than the prostate on the other hand. It is therefore the most advanced project for which many necessary tools or methodologies have been developed.

PSMA is abundantly expressed in 85-90% of metastasized prostate cancers. 177Lu-PSMA-617 is a molecule that binds to PSMA and thus delivers a VIR based on a beta emitter. This medicine is indicated for the treatment of adults with progressive, metastatic, castration-resistant prostate cancer overexpressing prostate-specific membrane antigen (PSMA) who have been treated with taxane chemotherapy and at least an anti-androgen hormone therapy. Phase III studies have confirmed that 177Lu-PSMA-617 treatment is a well-tolerated treatment option that improves progression-free survival and overall survival. These results are encouraging but the control remains limited and the hypothesis can be made that it is not a problem of vectorization but a problem of the efficiency of the radiation used. In this perspective, the coupling of PSMA with 211At will make it possible to verify this hypothesis. The therapeutic possibilities being limited after failure of 177Lu-PSMA-617, we will conduct a phase I study.

Refractory thyroid cancers and anaplastic cancers seem particularly interesting in the context of targeting PSMA on tumor neovessels. These cancers are rare, but responsible for the majority of the 400 deaths linked to thyroid cancer observed each year in France. They are generally rapidly progressive, with an unfavorable prognosis. They cannot be treated by 131I (historic model of VIR and of the concept of theranostics). Despite the recent arrival of targeted therapies, in particular tyrosine kinase inhibitors, the therapeutic possibilities remain limited and require the search for new therapeutic alternatives.

Recently, work carried out in the Nuclear Medicine Department of the François Baclesse Center with the INSERM Anticipe U1086 unit showed that the expression of PSMA, evaluated by immunohistochemistry, is increased in the neovascularization of metastatic lymph nodes in differentiated thyroid cancers, and that this expression is correlated with poor prognostic factors (Ciappuccini et al. JCEM 2021). In parallel with the clinical development of PSMA ligand imaging by positron emission tomography (PET) in this indication, it seems relevant to also explore PSMA under a therapeutic approach, by TAT. Preclinical studies are necessary and initially justify the identification and use of cell lines and mouse models of refractory thyroid cancers and anaplastic cancers.

This α-labeled PSMA therapy could also be studied in combination with cytotoxic chemotherapy molecules or tyrosine kinase inhibitors. This collaborative work could also benefit from a contribution by the researchers and clinicians of the national network TUTHYREF (refractory thyroid tumours, labeled INCa) in which the nuclear medicine department and the thyroid UCP of the François Baclesse Center participate.

Finally, as part of the chair of excellence requested by Elie Besserer-Offroy from the Normandy Region, an approach to identifying original targets is also planned, and will be integrated into this collaborative project. Other developments may therefore be proposed over the next few years in the context of an astatine alpha therapy approach.

4. Organization

In addition to a management work package (WP0), the project is organized in 6 work packages.

WP1 : 211At synthesis

This work package is the one directly concerned by this Scientific Council and therefore will be more elaborated than the other ones, see after the summary of the WPs.

WP2 : extraction radiochemistry

The work will include the implementation and optimization of extraction and purification processes for 211At from irradiated targets supplied by Ganil. The two types of process currently developed, namely distillation and separation on a solid support will be set up, optimized and compared in terms of extraction yield, nature and purity of 211At, and subsequent radiolabeling efficiency of the ligands of interest.

WP3 : Radiolabelling with 211At and iodine isotopes

There is no stable isotope of astatine. It will therefore be necessary in this project to objectify radiosynthesis by comparison with radioactive iodine isotopes (e.g. 125I). Iodine is the element that has the most similarity with astatine, whether from a physico-chemical point of view or a radiolabelling method. In addition, the use of 124I will make it possible, by the same radiochemical methods, to obtain PET tracers and 123I from SPECT tracers.

Thus, for the astatine labeling of small aromatic molecules (PSMA, PARPi ligands), recently described cupro-catalyzed deboronation reactions will be implemented (Reilly et al, Org lett 2018, 1752). For each molecule to be labeled, a non-radioactive iodine analogue will be synthesized. This molecule will serve as a non-radioactive reference in analysis and will also allow the synthesis of the boronic radiolabel precursor via a Miyaura borylation reaction. Once the boronic precursor has been obtained, cupro-catalyzed deboronation reactions will make it possible to obtain molecules labeled with radioactive iodine or astatine isotopes depending on the radioisotope chosen. For the labeling of biomolecules (antibodies, proteins), the same cupro-catalyzed deboronation reaction will be implemented as recently described (Chem. Sci. 2021, 1458). Here, a small molecule carrying both a boronic acid function and an activated ester function is synthesized beforehand and makes it possible to introduce a boronic prosthetic group on the substrate to be marked. The boron will then be exchanged with radioactive iodine or astatine using copper catalysis. The radiolabeling studies and the optimization of radiopharmaceutical radiosynthesis (including purification, formulation and automation) described above will be developed jointly by the RadioPETT (astatine) and CERMN (iodine) teams.

WP4 : Physicochemical characterization of radiopharmaceuticals

The in vivo evaluation of radiopharmaceuticals includes, in addition to studies of biodistribution, pharmacokinetics and specificity, physicochemical and metabolic characterizations in vitro and in vivo. Thus, the hydrophilicities (cLogP and LogD), the plasma and blood stabilities (in vitro by incubation at 37°C, and ex vivo after injection of the radiotracer then blood sample from the healthy and/or pathological animal) will be systematically determined for each labeled molecules developed.

WP5 : in vitro characterization of tumor cells response to treatment

In vitro studies: exposure of cell lines derived from lung or breast cancer with high metastatic potential for the brain in normoxia and hypoxia to increasing doses of 211At in order to determine the radiobiological parameters of 211At (in particular the absence impact of hypoxia on the therapeutic efficacy of alpha particles).
Characterization of the response of tumor cells (ovarian, mammary or thyroid cancers) to treatments, on 2D models cultured in vitro (lines), 3D models ex vivo (tumoroids derived from patients [or PDT]) and in vivo (xenografts derived of patients [or PDX]).

WP6 : dosimetry, biodistribution

Internal radiotherapy vectorized by α emitters is of major interest for the treatment of diffuse and metastatic cancers. In this context, the therapeutic interest of 212Pb-VCAM-1 has previously been shown, but also the need for precise dosimetry in order to assess the biological effect of treatments, including during in vitro studies.

Indeed, during in vitro studies, the biological effects are generally correlated with the activity injected into the culture medium. Hypotheses on the spatial distribution of the radioisotopes as well as on the geometry of the cells are then used to estimate the absorbed dose in the cells. If this method can give acceptable results for β- emitters, it is not satisfactory in the case of α emitters. Indeed, the path of the particles is very small compared to the dimensions of the culture medium (generating a significant uncertainty on the activity "seen" by the cells), but greater than the dimensions of the cells (generating an uncertainty on the fraction of energy transmitted by radiation to the cells). Determining the absorbed dose in the cells therefore requires knowing the spatial and temporal distribution of the isotopes as well as the thickness of the cells. A previous study showed that the lack of knowledge of the spatial and temporal distribution of the radioisotopes in the sample studied could lead to a 42% error in the estimation of the dose absorbed by the cells.

In response to this problem, an innovative in vitro dosimetry system (funded by the Mission for Transversal and Interdisciplinary Initiatives of the CNRS – ISOTOPE 2020 project) has been developed in order to provide an experimental dose for the in vitro tests carried out in Alpha Therapy. Preliminary evaluations have already been carried out for 223Ra solutions (without cells, at ambient temperature and humidity) and an in vitro evaluation of 212Pb-VCAM-1 will be carried out in November 2021.

The 123I imaging step (in SPECT imaging) and 124I (in PET imaging) will allow us to go back to biodistribution profiles and a dosimetric evaluation. The latter is essential for a transition to the clinical level because it allows a better understanding of the effects of the treatment, whether in terms of therapeutic efficacy on tumors or toxicity on healthy tissues.

WP7 :in vivo validation of treatments

In vivo efficacy study: Mouse brain metastasis models already developed and mastered by ISTCT will be used (Corroyer-Dulmont et al., 2019). For this, tumor cells will be inoculated intracardiacally into mice and the formation of metastases will be objectified by T2w MRI imaging. Binding of the anti-VCAM-1 antibody on cerebral metastases will also be visualized using MPIO labeling as described by Serres et al (Serres et al., 2012). Once the metastases have been detected, the Anti-VCAM-1-211Astate antibody will be injected intravenously, then the survival of the animals as well as the fate of the metastases will be monitored by MRI imaging. Similar approaches will be implemented on models of xenografts derived from patient tumors (PDX) already in place (ovary) or accessible (breast: implementation, collaborations), for anti-TROP2 antibodies, the PSMA ligand or even PARPi, in collaboration between the Anticipe unit and the ISTCT.

Phase 0: In our translational medicine approach, we will use the products of preclinical models adapted to phase 0 microdosing, which initially consists of injecting very low doses. As part of the pharmacodynamic study, the antibodies will be coupled to 124I. These radiopharmaceuticals cannot create drug interactions with other therapies and the dosages used are harmless. The clinical study will benefit from the clinical research unit of the Center François Baclesse. The implementation will be facilitated by the existence of existing radio-pharmaco-imaging circuits.

5. 211At synthesis (WP1) and installation in LHE

Radioisotopes are commonly used in medicine for diagnostic and treatment purposes. The potential interest of a given radioisotope in medicine depends on several factors: specific decay properties, radiological decay half-life, transport constraints, chemical properties, ease of production, etc.

With few exceptions, the necessary radioisotopes must be produced artificially in nuclear reactors or in centers with accelerators. Production mechanisms should be studied to assess potential production yields. Large production is required, which implies, in the case of accelerator-based production, the use of intense particle beams and the development of high-power target systems. The radionuclidic purity mainly depends on the chosen reaction (projectile/target combination, energy range) and on the separation process (both physics and chemistry can be used).

The molar activity describes the dilution of the radionuclides sought by the isotopes of the same element. In particular, receptor-targeted therapies require a high molar activity of the radiopharmaceutical to avoid saturation of the limited number of receptors per cancer cell by stable ligands. However, a strong limitation to 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. This requires defining and optimizing production processes, and participating in the proof of concept of innovative radioisotopes. In the coming months, SPIRAL2 [2] will deliver intense beams, which will allow breakthroughs in R&D for the production of innovative radioisotopes and in particular 211At one of the promising alpha emitters for medical applications.

Today, several factors prohibitively limit the production and use of 211At:

- The maximum intensity of the beam available from the accelerators (the most intense beam for this purpose is the one available at ARRONAX with 70 emA).
- The energy loss of the a particles in the bismuth target (90mm is enough to absorb the 8.3 MeV of a particles between the 29 MeV of incident energy for the production of 211At, which is the optimal energy, at 20.7 MeV, which is the production threshold below which 211At is no longer produced). This can cause the temperature to rise rapidly and the bismuth to melt as the beam current to the target increases.
- The production of 210At decaying into 210Po which concentrates in the bones (for patients) and the presence of high energy gamma rays in the decay of 210At (a potential radiation protection problem for personnel).
- The half-life of 7.2 h which limits the delivery zone.

At GANIL, the REPARE project, funded by the ANR, is underway and aims to remove the scientific and technical barriers linked to these limitations. This project involves the RadioPETT team for the extraction and the production route by generator in particular (see WP2).

To do this, we plan to:

- Use the high-intensity beam of alpha particles from SPIRAL2: the expected intensity is around one mAe, about 20 times more than at ARRONAX.
- Develop dedicated high power targets capable of maintaining available beam intensity. One option is a rotary system while an even more complex but potentially more efficient design would be a liquid target.
- Accurately measure the production of contaminants and in particular 210At and 210Po.

- Study of radon chemistry and possibly design of a 211At generator. This would make it possible to use the decrease in 211Rn (T1/2 = 14.5 h) to produce 211At, thus very significantly increasing the delivery zone. For this, the 6,7Li(209Bi,xn)211Rn reaction must be used and precisely characterized (in particular contaminants such as 210,211Po which are weakly produced but which have never been measured in these reaction pathways).

In practice, the target station developed under REPARE will be used to synthesize 211At for the proposed project. This station will initially be installed in the NFS room (see Fig. 1) and in the longer term, on the high-energy line (LHE2), an installation which requires an adaptation of the area. This installation is therefore a necessary condition for the development of the project and is the focus of this document.

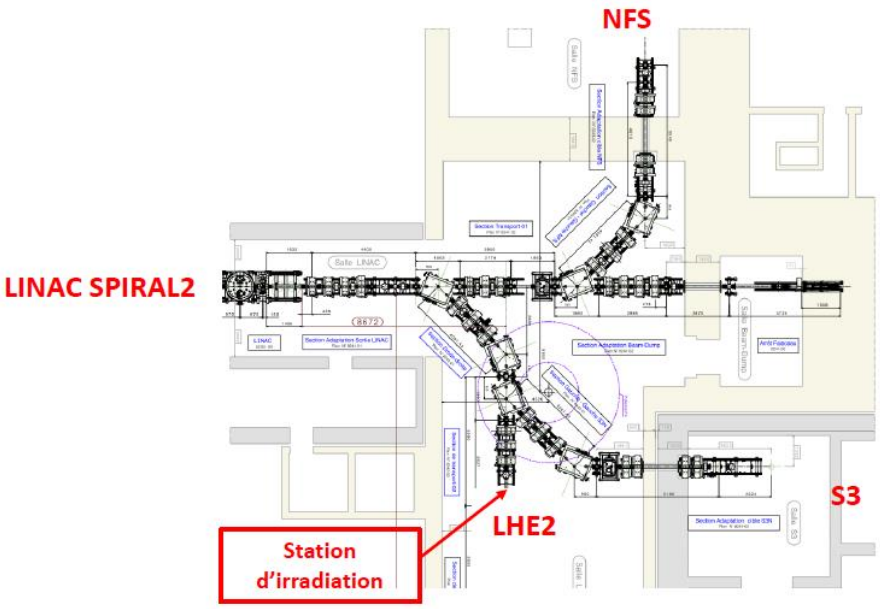

Fig. 1 : layout of the high energy part of the SPIRAL2 hall

To proceed with this installation some prerequisites are necessary :

- Readiness of the REPARE irradiation station
  Detailed fluidic calculations have been performed to ensure the capability of the station to handle 10 kW of beam power (for 211At production, the optimal energy is close to 29 MeV) in routine operation (see Fig. 2-5).

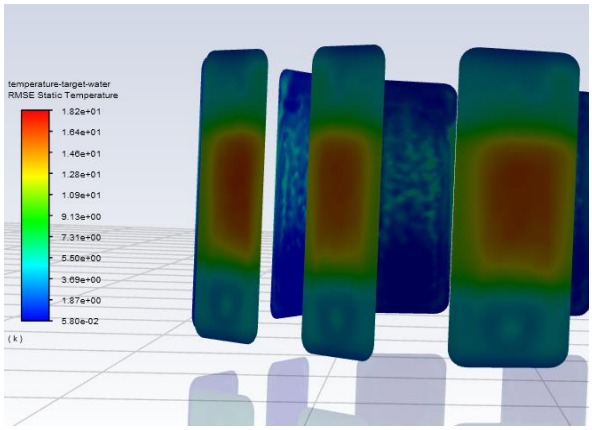

Fig. 2: simulation of water temperature (10 kW beam power, 200 rpm, 2 bars input pressure)

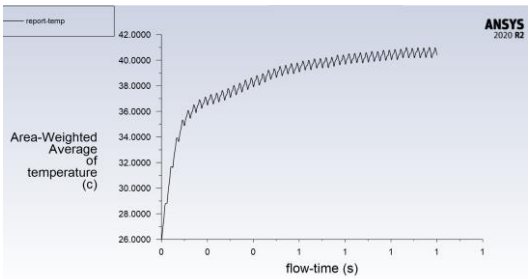

Fig.3 : simulation of temperature as a function of water flow (10 kW beam power, 100 rpm, 2 bars input pressure)

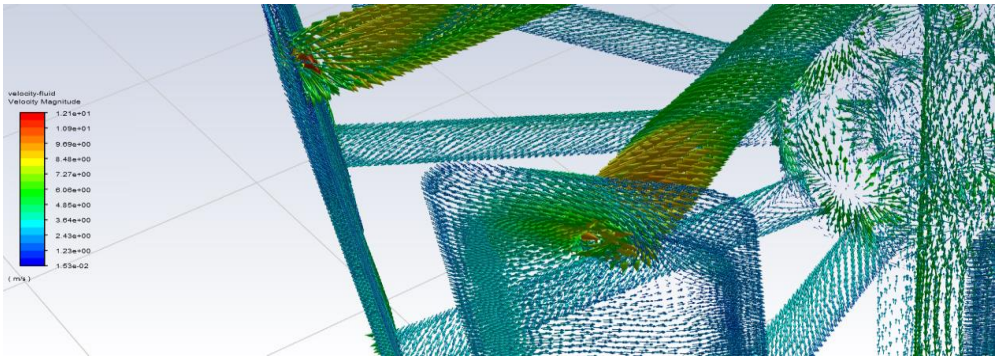

Fig. 4 : simulation of water velocity (10 kW beam power, 100 rpm, 2 bars input pressure)

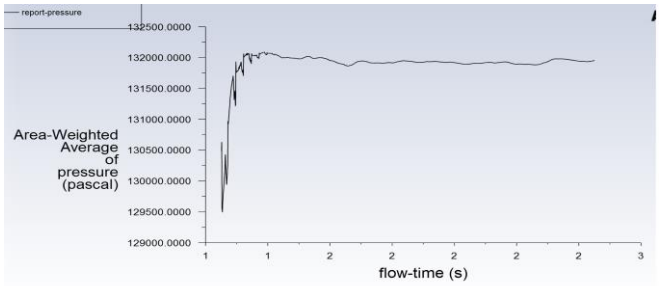

Fig. 5 : simulation pressure at the interface water-backside of target (100 rpm, 2 bars input pressure)

The target station is built (see Fig. 6) and various sub-systems have already been tested off beam as far as it was possible.

In 2023, it is planned to first test the functionalities (cooling, current reading, synchronization with beam pulses, etc.) using a 22Ne beam from the cyclotron (July 2023). Then a first installation will be made in the NFS area for a first 211At production run in the second semester of 2023. According the ANR project, one day per month of SPIRAL2 beam time is given to REPARE. This project will end mid 2024.

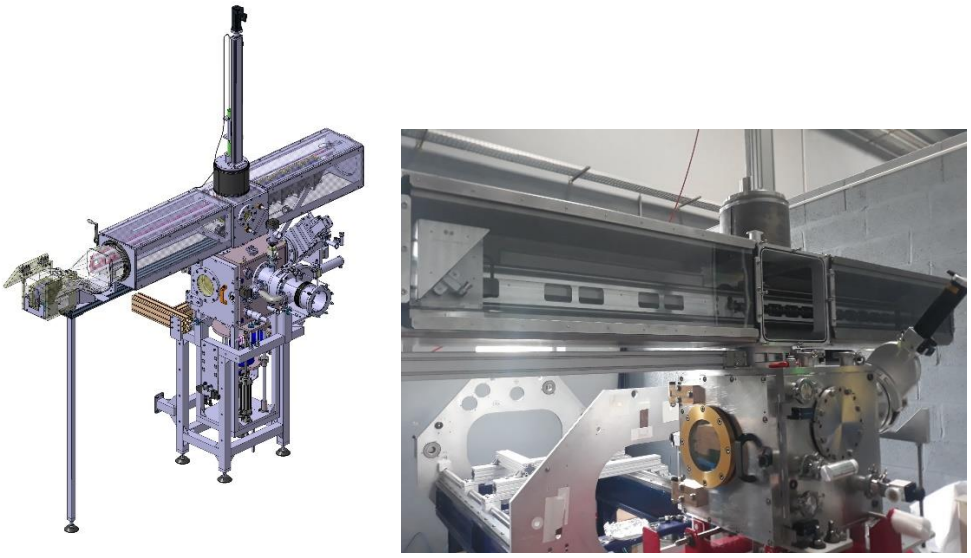

Fig. 6 : (left) CAD of the complete REPARE irradiation station. (Right) picture of the top part (the long horizontal part is the unloading system and the cubic part below hosts the rotating target wheel).

- Condition of the installation
  The installation of the REPARE irradiation station in NFS cannot be envisaged over long periods for several reasons :
  - The space available on the beam line in the converter room is extremely constrained (see figure) and the access to some room infrastructure devices (valves of the cooling system for several devices like magnet, Faraday cup, converters) located on the wall behind the beam line is hardly accessible.
  - This space is also the one used by all the teams using the rabbit system. Therefore it could only be a temporary position.
  - In the converter room the high neutron flux activates the station itself which might be not acceptable
  - Using the station in the converter room prevent from running or preparing any experiment in NFS

  For all these reasons and in order to optimize the use of the LINAC beam time it is proposed to install the REPARE station in the LHE part of the LINAC building. However this has a significant impact. The activity generated at the target point is important (of the order of 1 GBq/h). In case of fire this activity must be confined and a specific casemate must be built around the station. As a consequence, the new casemate must be connected to the nuclear ventilation system. This modification requires an authorization from the Nuclear Safety Authority (ASN). This implementation in LHE must be carefully evaluated and an estimate for this analysis is estimated to 6 months of work.

- Authorization from the safety authority
  As explained above the impact of the implementation of the irradiation station in LHE implies an authorization request to the ASN. Once the internal GANIL analysis has been transmitted to the ASN, it is estimated that 18 months are necessary before getting the final approval.

6. Role of the partners in the collaboration

Radioisotope production : GANIL
Synthesis of radio ligands : RadioPETT and CERMN
Clinical aspects (nuclear medicine, radiophysics, radiotherapy, clinical research): CLCC F Baclesse and CHU
Dosimetry : GANIL
Targets, biological evaluation of radioligands in vitro, ex vivo and in vivo : ISTCT, Anticipe

7. Beam time request, plannning and funding

a) Beam time request

The project is viable only if beam time is attributed on a regular basis to this activity. Ideally, this would be 4 hours a week or so. Of course, it has to be compatible with the exploitation of the LINAC beam for fundamental research. However precisely because the installation would be in a specific area, distinct from NFS and S3, this gives flexibility for beam scheduling and will optimize the use of beam time : when an experiment is being setup in NFS, the beam can be directed to the irradiation station instead of being lost in the beam dump.

Beyond the current project focusing on 211At, other radioisotopes of interest will be investigated.

Finally and it is an important aspect of this installation in LHE, the future casemate will also be available for other purposes (using or not the irradiation station) including experiments for astrophysics, detector tests, etc.

b) Planning

As mentioned earlier, the irradiation station will be tested and if successful used in 2023. The main constraints in terms of planning will then be the internal analysis to build the request to the ASN. The key dates are therefore :

- January 2023 : this Scientific Council which is a key for the full project
- January 2023 : if a GO is given, create a project structure at GANIL for the implementation of the irradiation station in LHE. This will involve various Divisions and Groups of GANIL
- April/May 2023 : detailed design study done
- July 2023 : in-beam test using 22Ne from CSS1
- Fall 2023 : first in-beam production test of 211At at NFS
- October 2023 : finalization of the internal analysis and authorization request to the ASN
- March 2025 : expect answer from ASN
- March 2025 : start of work in LHE. Construction of the casemate, connection to the nuclear ventilation system
- September 2025 : casemate with the irradiation station installed

c) Funding

The installation of the REPARE irradiation station implies various adjustments of the LHE area itself. These are :

- Construction of the casemate itself.

- There is a need for a quadrupole triplet for beam optics. These quadrupoles exist but the power supplies are to be purchased
- Modification of the nuclear ventilation system
- Infrastructure items

The implementation could be made as shown in Fig. 7.

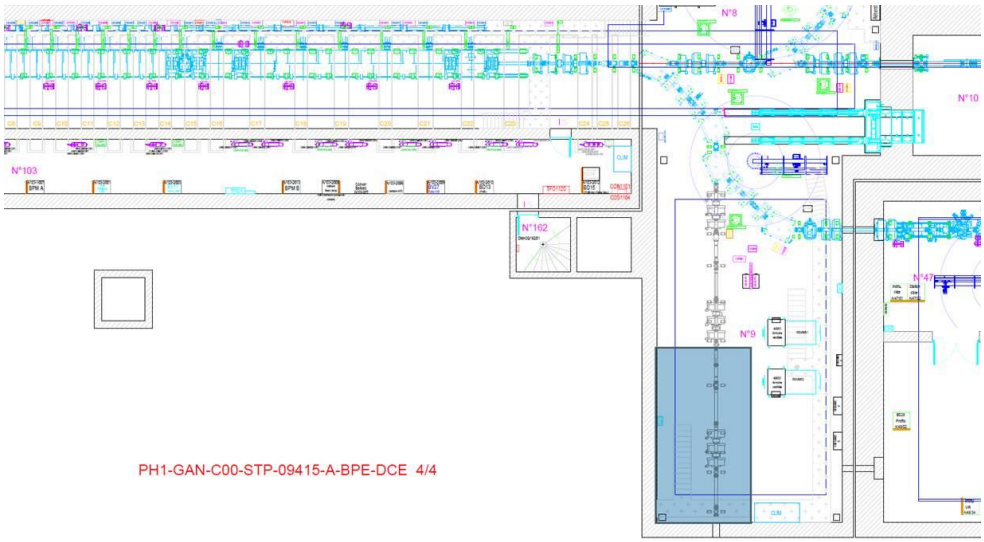

Fig. 7 : possible implementaion of the new casemate in the LHE area of SPIRAL2

The total area would be of the order of 40 m². The cost estimate is as follows :

For the casemate itself including connectio to the nuclear ventilation and various items, with 30% uncertainty and 25% of aleas :

Local CF 2H et ventilé	Q	prix (€)
armature, cloison CF2H, Portes et 2 fenetres CF2H	140m2	100000
distri elec/eclairage		5000
résine au sol	40m2	3000
peinture 140m2 (X2 faces)		5000
VN équilibrage		2000
instrumentation VN		5000
dérivation VN A/R + registres		15000
clapets CF (non CTHEN)	2	3000
détection incendie		5000
somme		143000
incertitude	30%	42900
marge	25%	35750
total avec incertitude et marge pour aléas		221650

For the beam line, and with the same uncertainty and alea :

ligne LHE2	Q	prix (€)
6 Qpoles LHE2	existant	0
tube faisceau, mécanique+Alim+vide+instru+diag	8ml à 90000€/ml	720000
somme		720000
incertitude	30%	216000
marge	25%	180000
total avec incertitude et marge pour aléas		1116000

The overall cost estimate including uncertainty and aleas is therefore 1.34 M€.

The project has already benefited from the ANR REPARE project (~550 k€ in total) and we plan to apply to various project calls for the funding of the whole project, including the installation costs mentioned here.