^{211}At production in LHE

G de France, GANIL

GANIL Scientific Council, January 17-18, 2023

Agenda

- REPARE
  - Motivations
  - CS measurements and inventory MC calcs
  - Solid target
  - Liquid target
  - Generator
  - Next steps for REPARE
- REPARE: part of more global project
- This overall project
  - Target/pathologies
  - Dosimetry
  - Collaboration
- Installation of REPARE in NFS
- Installation of REPARE in LHE
  - Location, cost, planning
- Summary

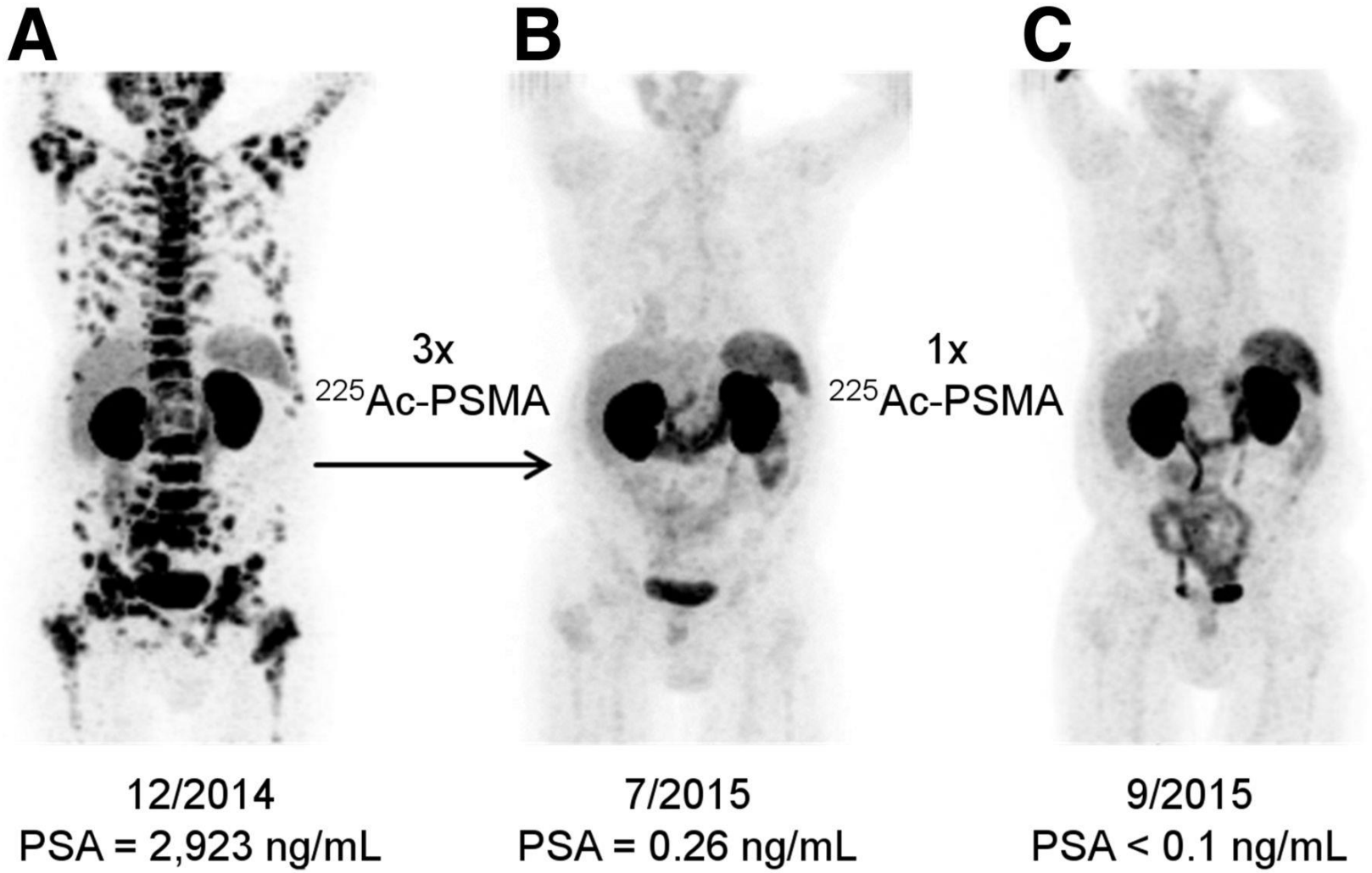
Motivations (TRT)

- **Targeted Radio-Therapy:**
  - Idea: determine the most effective therapy and tailor this therapy during the course of treatment based on radiation dosimetry and tumor response
  - Principle: target receptors that are present at the surface of the tumour cells or relevant biomolecules overexpressed in the development of a pathological process
  - Benefits: personalized medical care, optimized for patient and disease characteristics
  - Personalized: need various decay properties (radiation types, LET, half-life,…)
  - radiation to be delivered directly to the targeted site of disease => Spare the surrounding healthy tissues

Motivations (TAT)

- **Targeted α Therapy:**
  - High-LET α-particles promising to target single cells (range comparable to cancer cell)
  - Promising for numerous cancers (non solid like leukemia, lymphoma, micro metastasis,…)
  - Treatment of residual disease (individual or cluster of cancer cells circulating in the body after surgery or other therapies)
  - α-particles carried to cancer sites by appropriate vectors
  - Highly cytotoxic => high efficiency (DNA double-strand breaks)

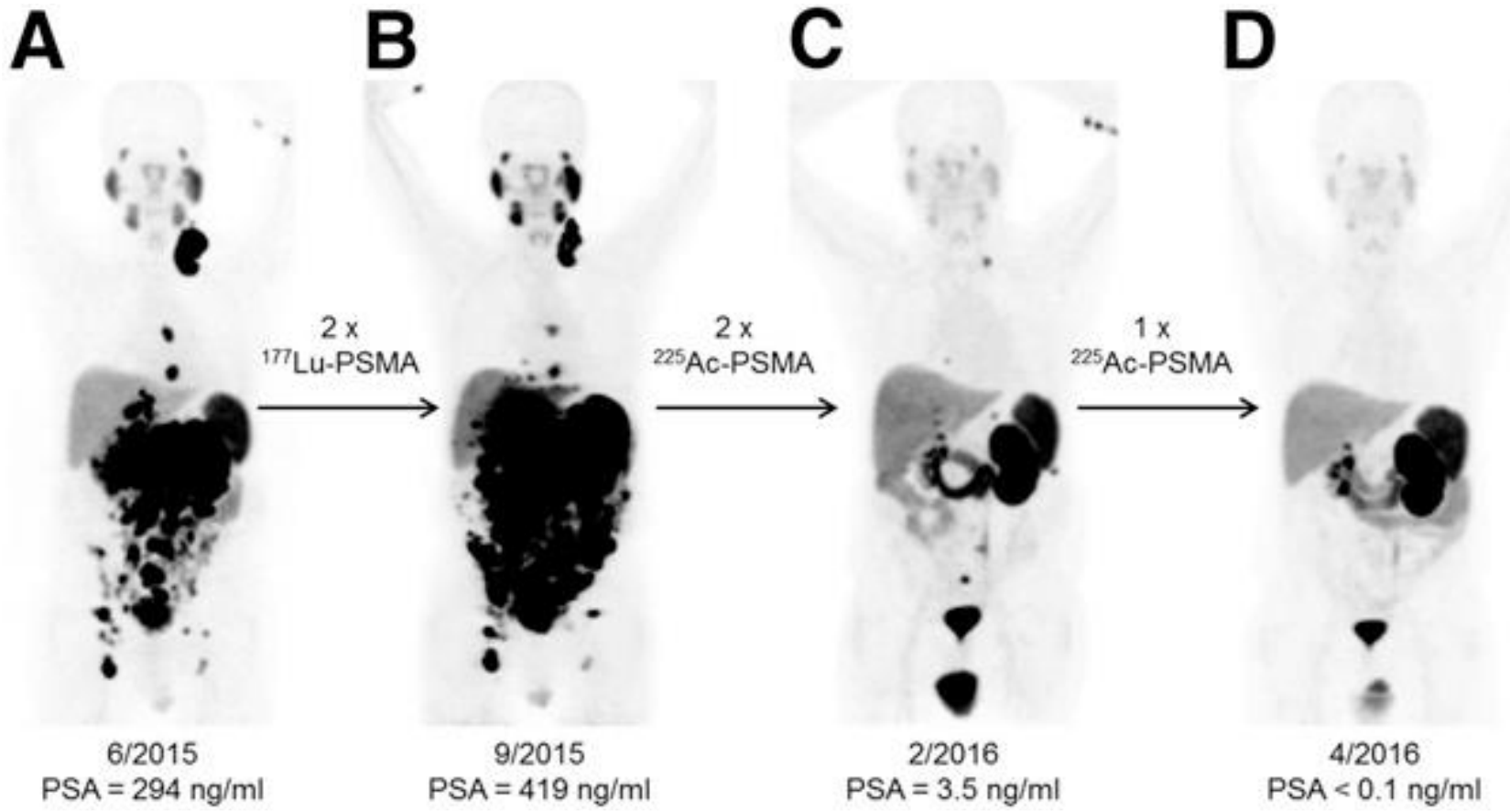
Promises of targeted α therapy



68Ga-PSMA-11 PET/CT scans of patient A. Pretherapeutic tumor spread (A), restaging 2 mo after third cycle of 225Ac-PSMA-617 (B), and restaging 2 mo after one additional consolidation therapy (C). Clemens Kratochwil et al. J Nucl Med 2016;57:1941-1944

JNM The Journal of NUCLEAR MEDICINE

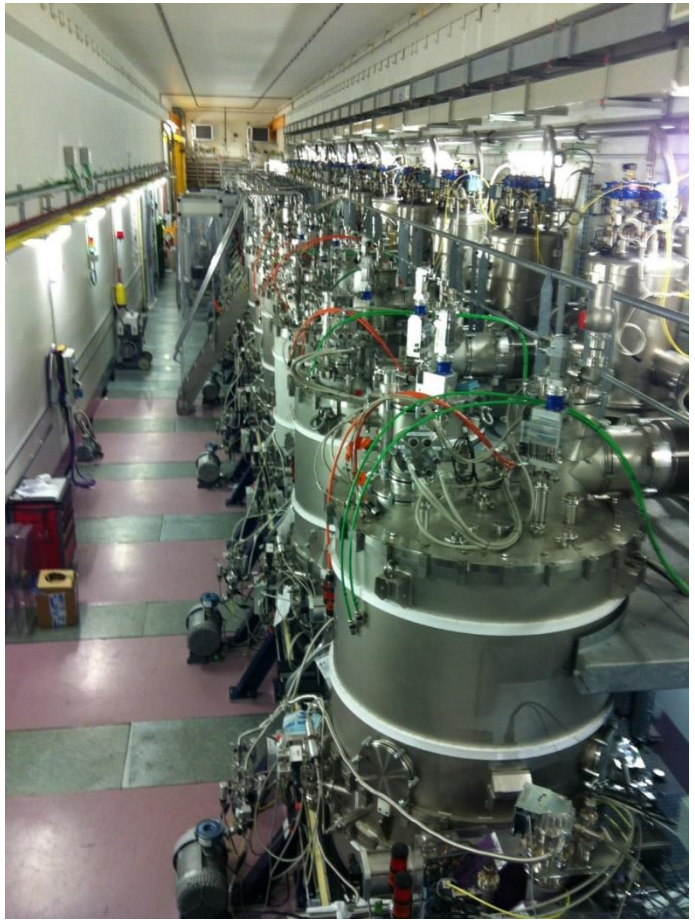
Promises of targeted α therapy

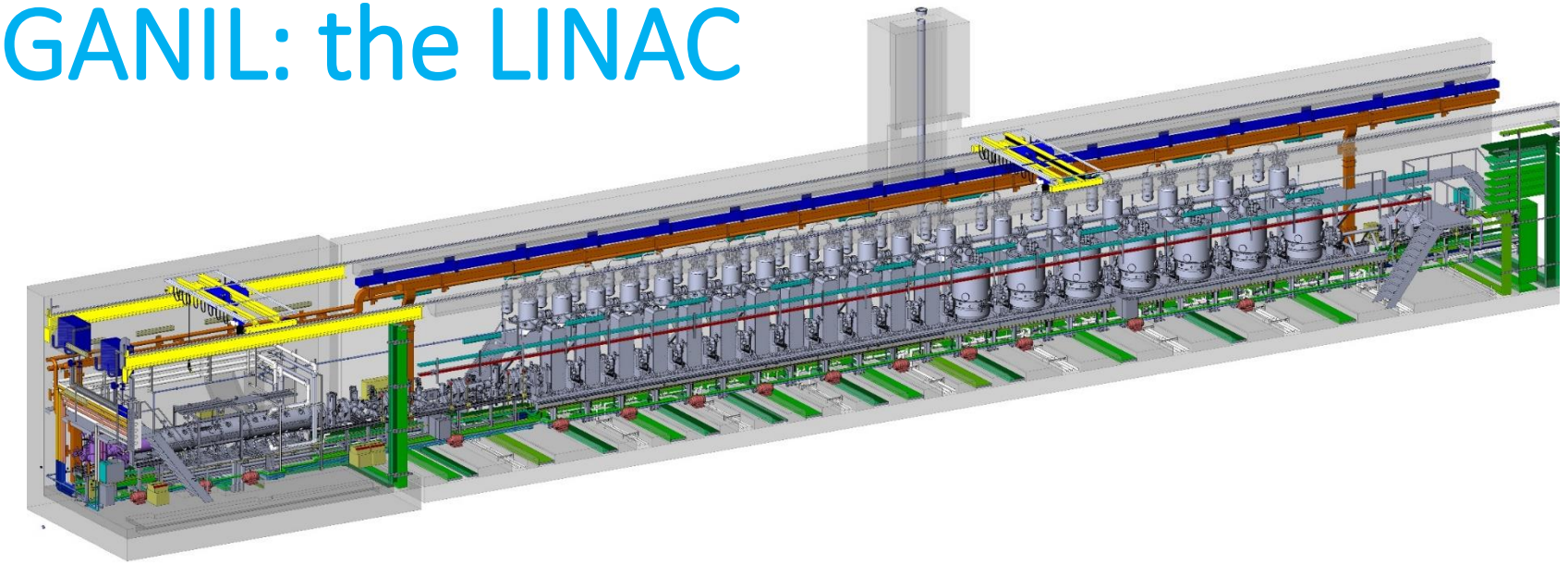


Very limited access to ^{225}Ac

JNM The Journal of NUCLEAR MEDICINE

Opportunities at GANIL: the LINAC





Particles	H+	$^{3}He^{2+}$	$^{4}He^{2+}/D^{+}$	ions	ions
q/A	1	3/2	1/2	1/3	1/6
Max. I (mA)	5	5	5	1	1
Min. Energy (MeV/A)	0.75	0.75	0.75	0.75	0.75
Max Energy (MeV/A)	33	24	20	15	9
Max beam power (kW)	165	180	200	45	54

➔ Opportunities for efficient production of radioisotopes (especially alpha beam)

➔ focus on ^{211}At: $^{209}Bi+\alpha$

Current limitations for ^{211}At

- Maximum alpha beam intensity available at accelerator centres (ARRONAX 70 eμA max).
- Energy loss of alpha particles in the bismuth target (90μm to absorb 8.3 MeV alphas from 29 MeV to 20.7 MeV, production threshold) => melting of bismuth.
- Production of ^{210}At decaying to ^{210}Po which concentrates in bones (for patients) and high energy gamma-rays in the decay of ^{210}At (radioprotection issue for the personnel).
- The half-life of 7.2 h, which limits the delivery zone.
- Uncertainty on allowable ^{210}At/^{211}At and production cross-sections of contaminants (Po, At)

Research and dEvelopements for the Production of innovAtive RadioElements

The REPARE Project

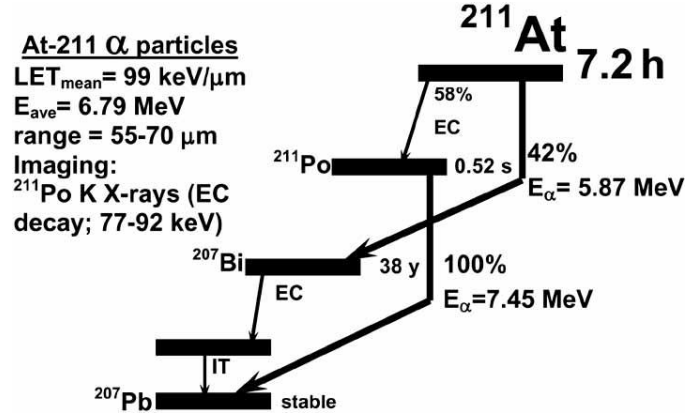
- Research and dEvelopements for the Production of innovAtive RadioElements
  - ^{211}At ($T_{1/2}$ = 7.2h): promising α-emitter for Targeted α Therapy
  - WP1: Inventory calculations and cross section measurements (α, Li induced reactions)
  - WP2: High power solid target
  - WP3: High power liquid target
  - WP4: ^{211}Rn generator
- **Our objectives are:**
  - To study ways to increase ^{211}At production through the **^{209}Bi(α,2n)** reaction
  - To take advantage of the characteristics of SPIRAL 2 beam (up to 80MeV and **mAe of α**)

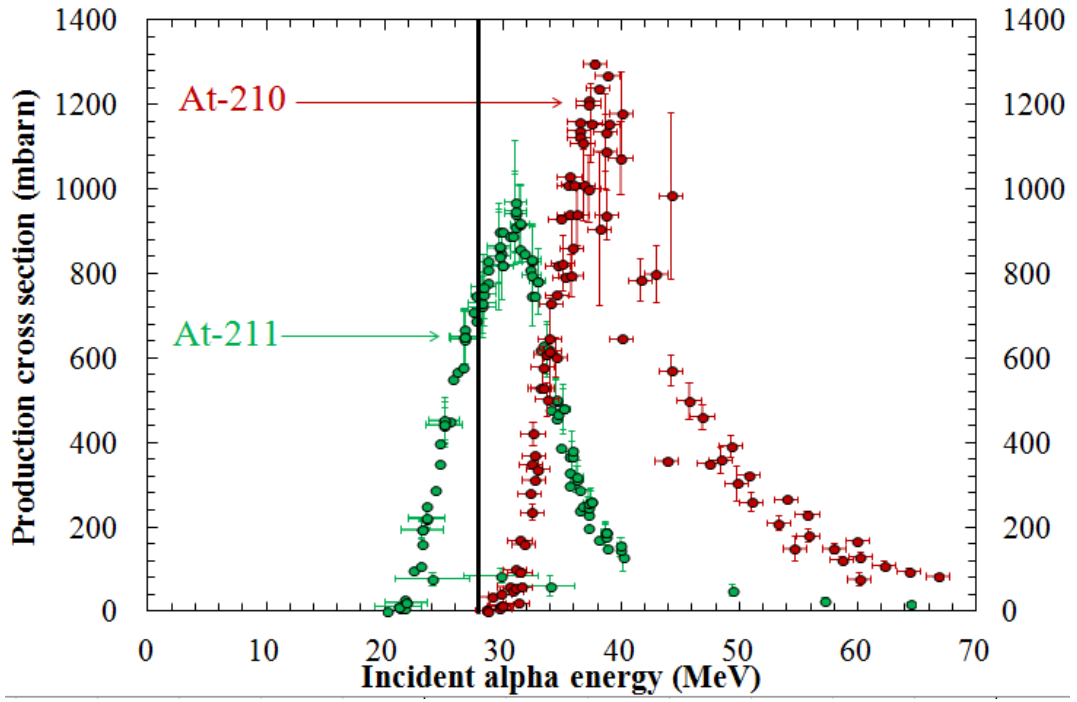
MC calcs and cross section measurements

- Monte Carlo calculations using Bi and Pb (LBE)
- Precise measurements of the relevant production cross-sections
  - Using alpha (ARRONAX, SP2)-Direct production of ^{211}At
  - Using ^{6,7}Li (SP2)-Generator
  - Collaboration with Czech Rep (expt Sep ’22)

^{209}Bi(α,2n)^{211}At, 20.7 MeV

^{209}Bi(α,2n)^{211}At, 28.6 MeV

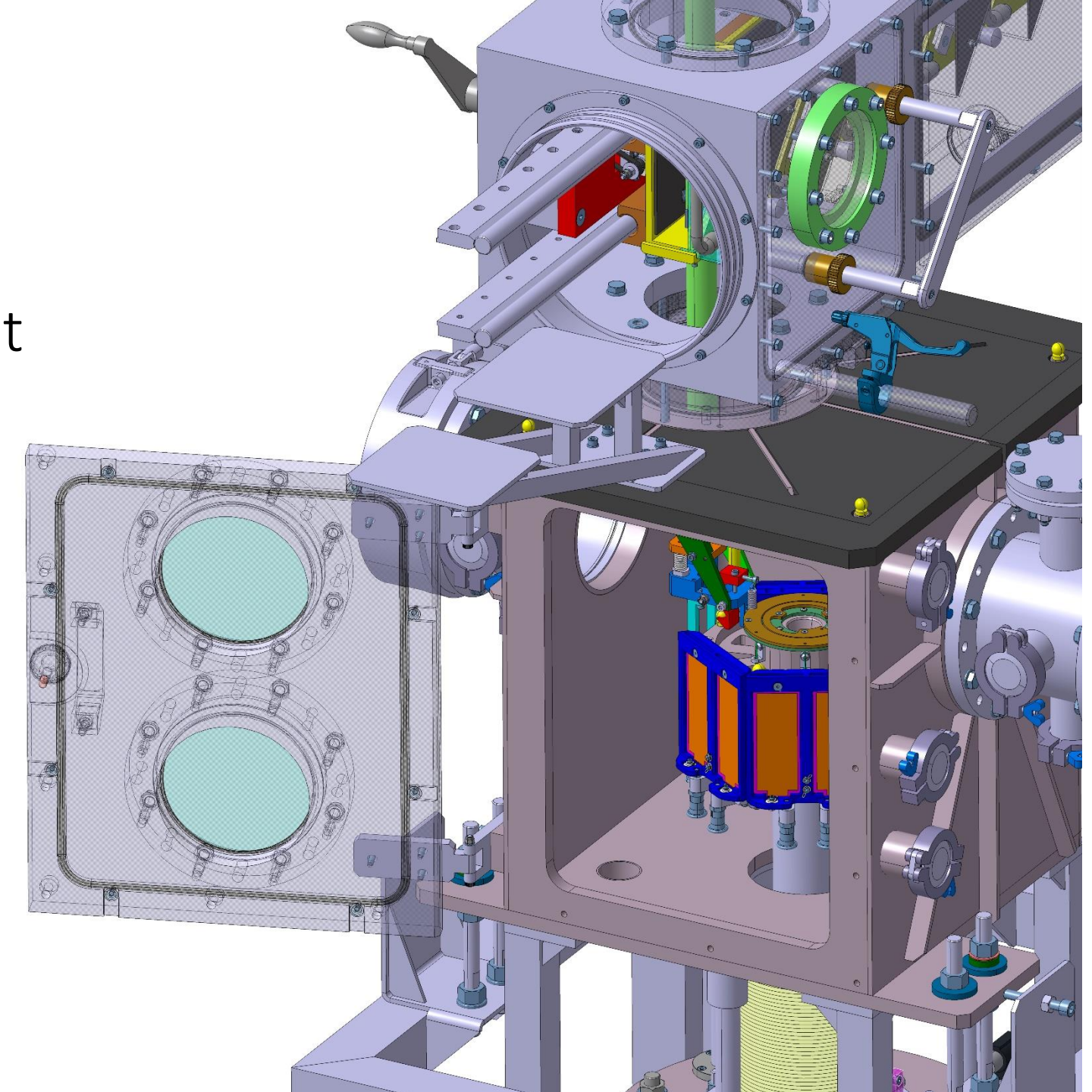




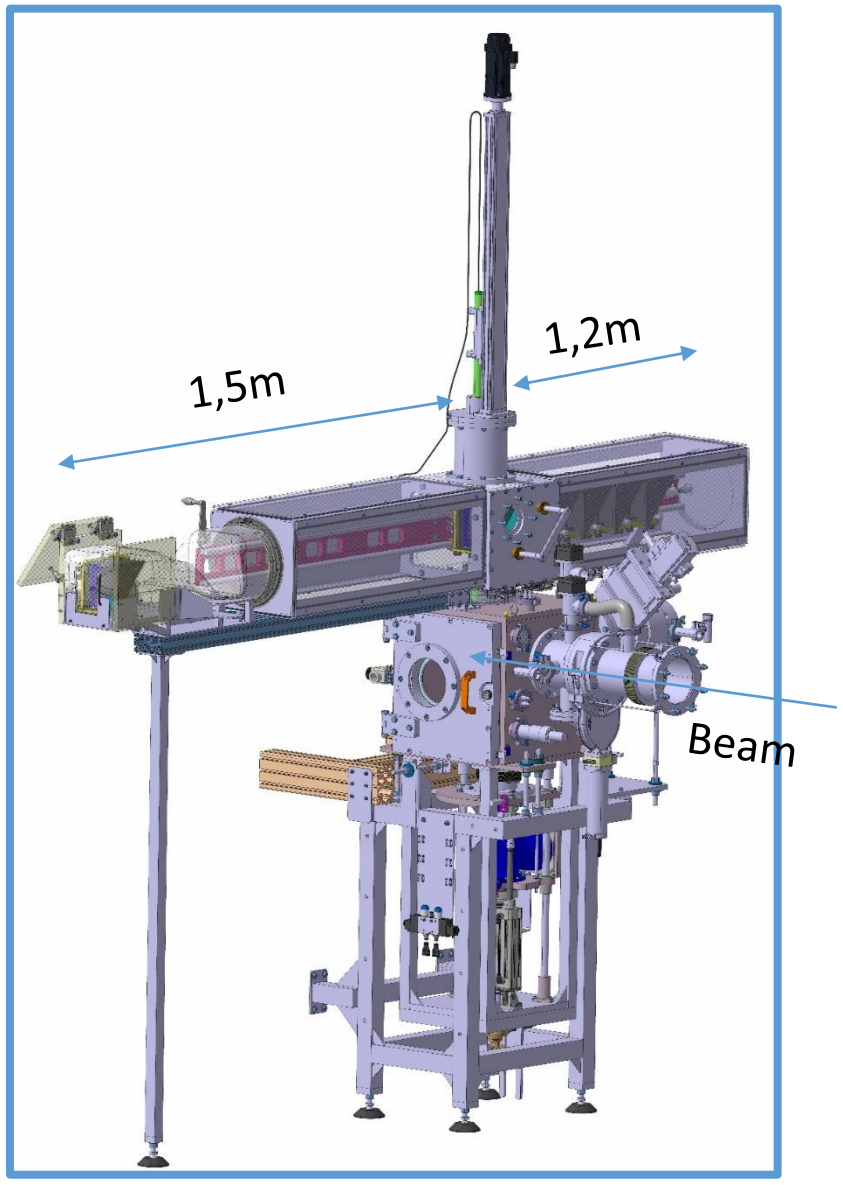
Solid Bi target

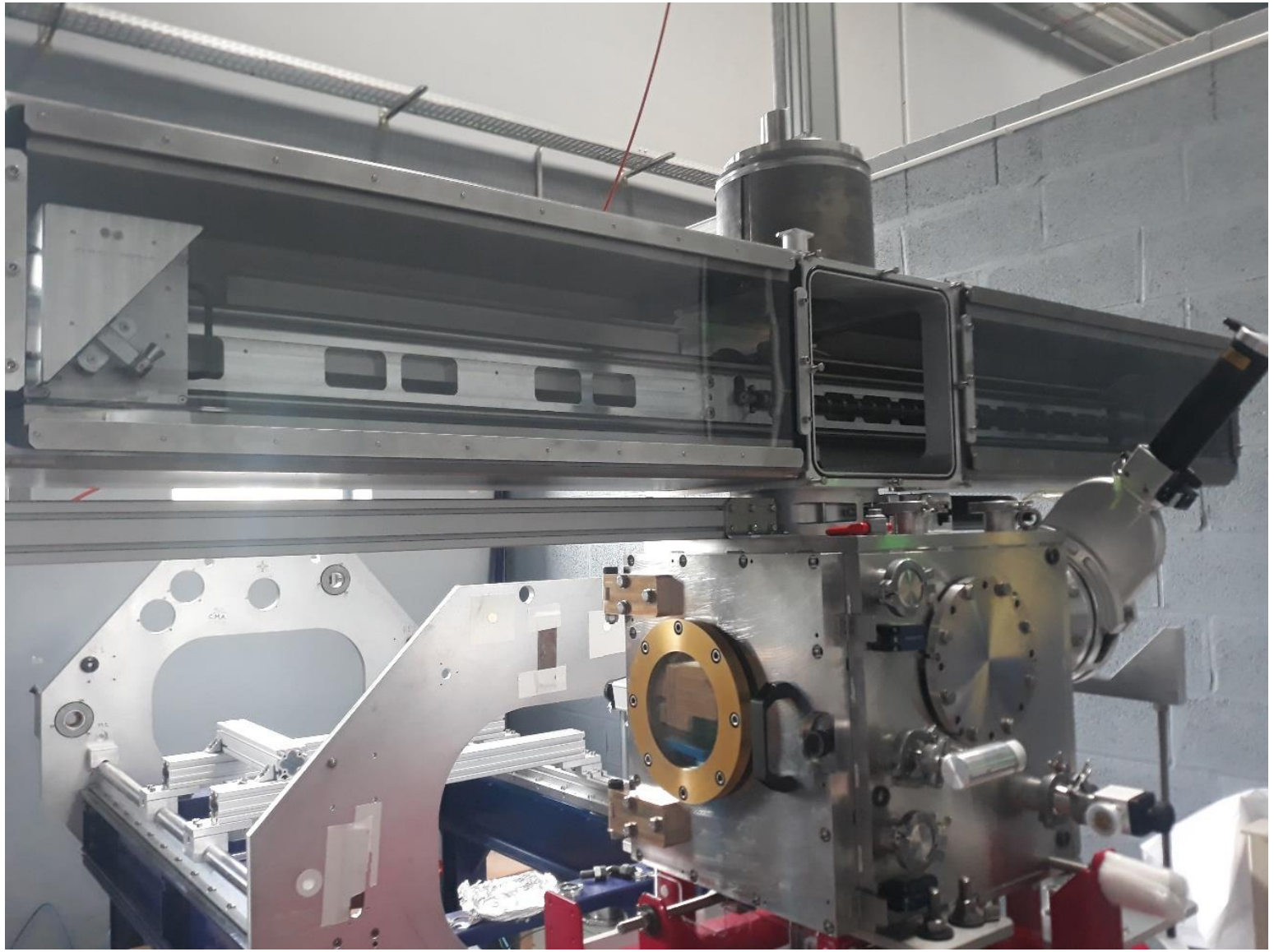
- High power rotating target

→ 2 targets/racket; 6 rackets/wheel
→ Target cooling (direct water cooling + rotation)
→ Monitoring (beam setting, current measurement)
→ Radioprotection/safety
→ Retractable



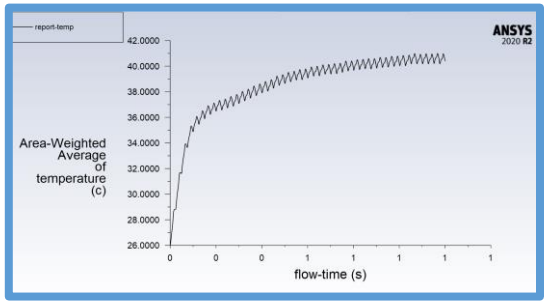
Solid Bi target



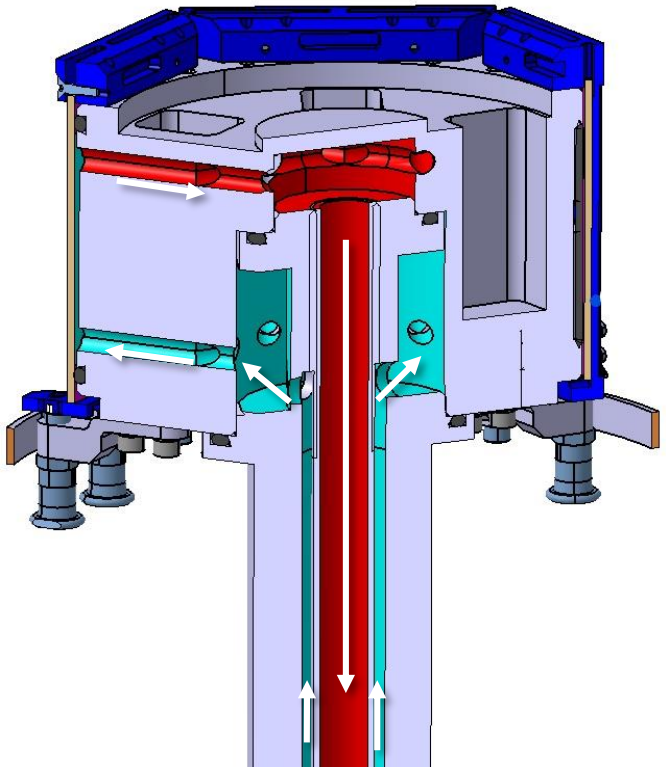


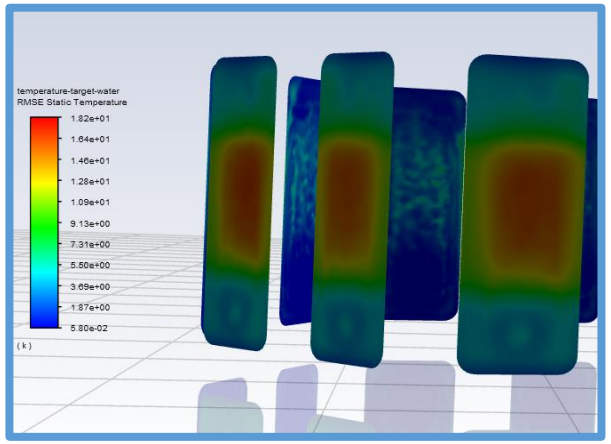
Target cooling (10 kW)

- Rotation speed to maintain Ttarget < 150°C:
  - Little impact (41°C @100tr/min, 31°C @400tr/min)
- Water velocity (>1m/s)/No air pocket
- Twater < 100°C → 18°C (simulation)
- Water pressure → 2 bars (input) (1,3 bars interface)

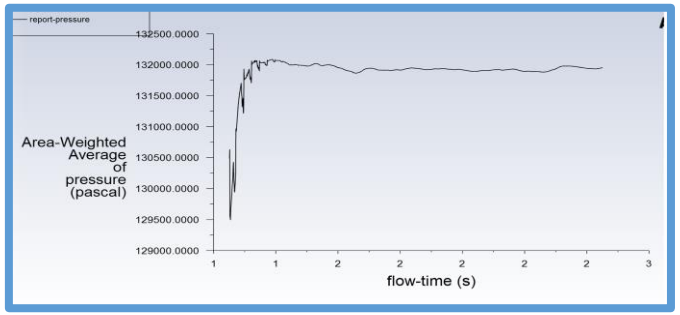


progression de la température @10KW 100 tr/min 2 bars

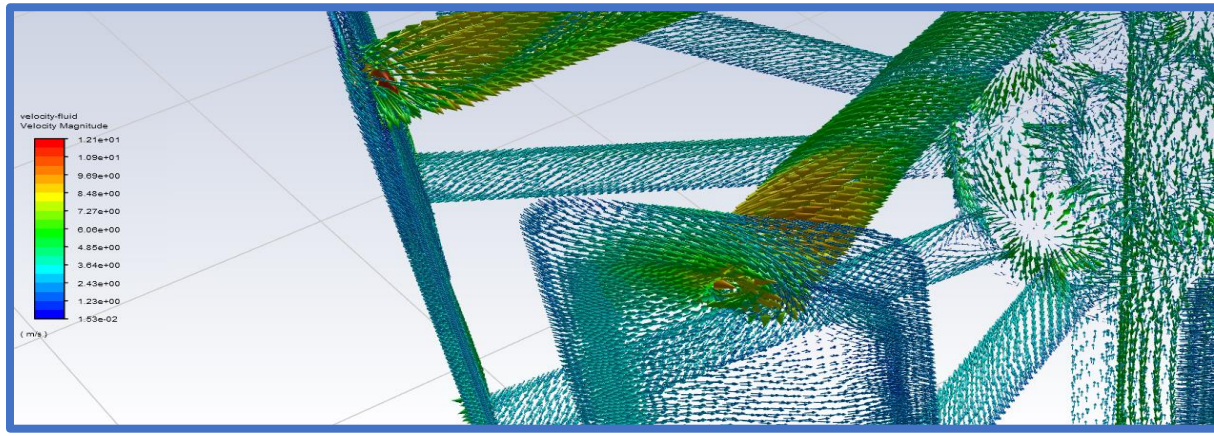




Température de l'eau @200tr/min, 2 bars



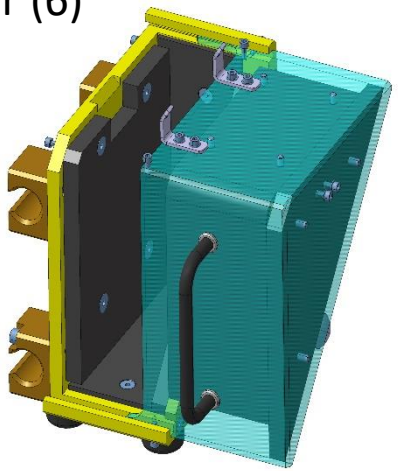
Pression l'eau interface @100tr/min, 3 bars



Vitesse @10KW 200 tr/min 2 bars

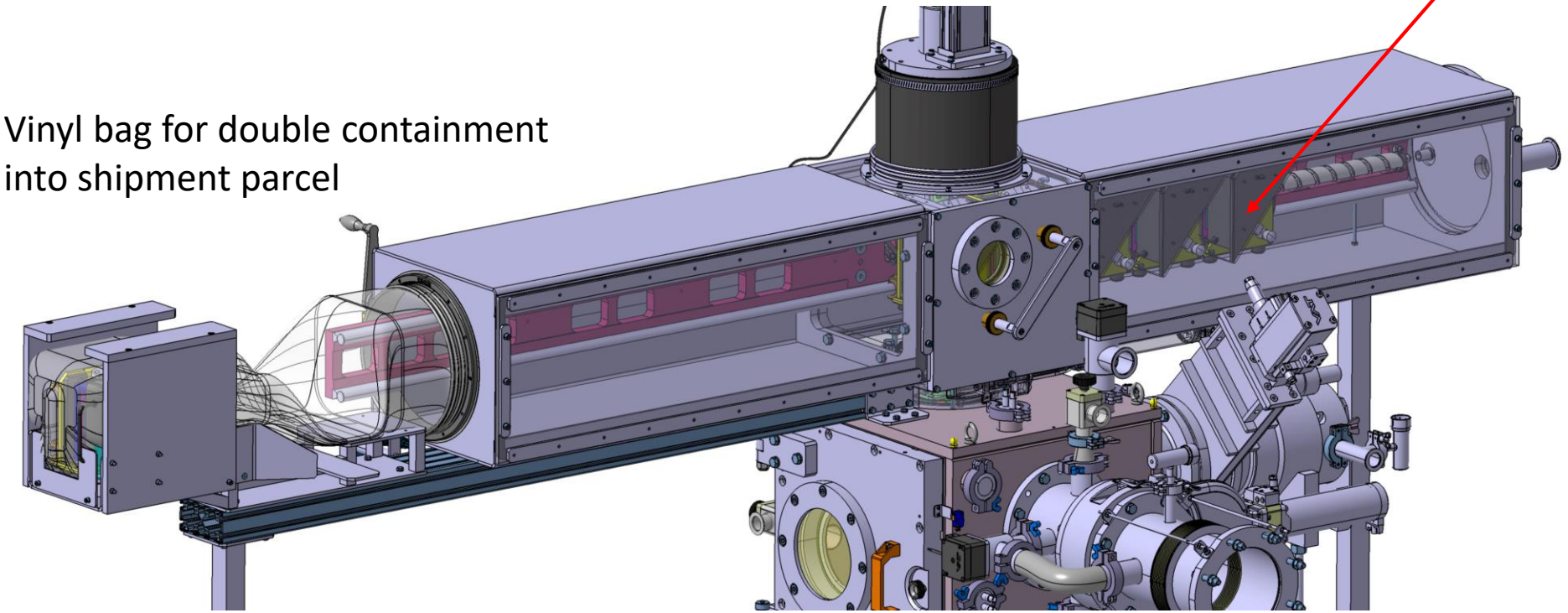
Radioprotection/safety

Lead target container (6)



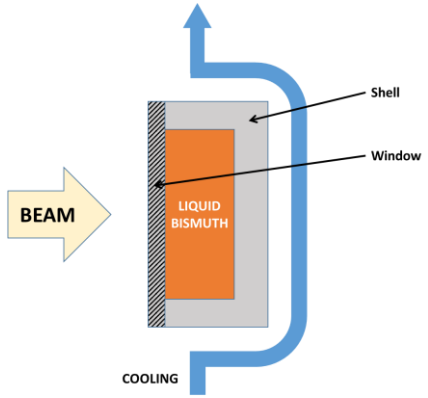
« racket » extraction system

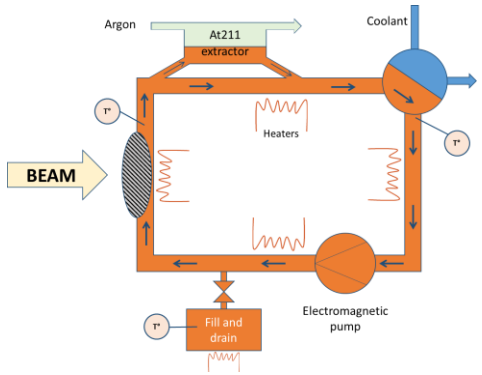
Vinyl bag for double containment into shipment parcel

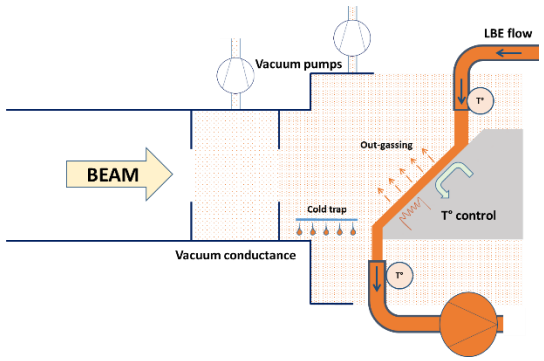


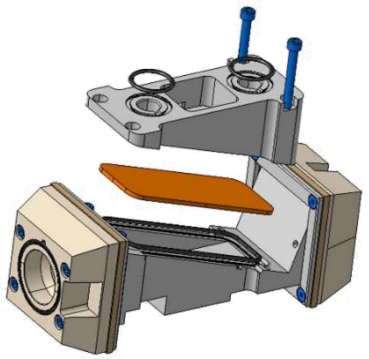
Thick target chamber

Liquid Target Concepts









Criteria	Bismuth Capsule	LBE loop	Windowless LBE loop	ARRONAX
Production	** 4.9 GBq - 1h	* 0.21 GBq - 1h	*** 11.5 GBq - 1h *(pending losses evaluation)*	* ~0.43 GBq – 1h TBC
Maturity	*** In service for other targets. Curved window not demonstrated.	** Feedback from MEGAPIE.	* Lack of experience on liquid LBE in the vacuum.	***** In service.
Exploitation	*** Manual extraction, easier transport.	** In line extraction as an option. Important volume of LBE.	* In line extraction. Important volume of LBE. Beam line losses.	*** Manual extraction, easier transport.
Cost	**** Simpler system.	** Pump, pipe, exchanger…	* Pump, pipe, exchanger, beam line modifications…	**** Simpler system.
Integration	**** Simpler system.	** Pump, pipe, exchanger…	* Pump, pipe, exchanger, beam line modifications…	**** Simpler system.

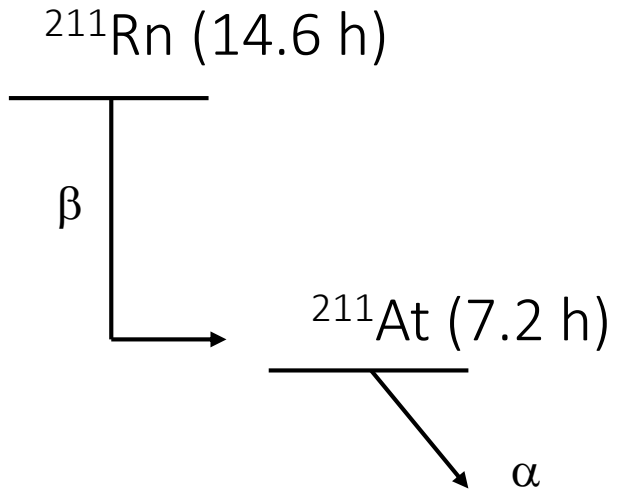
$^{211}Rn/^{211}At$ generator

Alpha

☺ Cross section gives large initial activity

☹ Targets must be dissolved each run

☹ Dry distillation or wet extraction



Lithium

☺ 14h half life: useful yield 1-3 days after EOB

☺ Continuous extraction of ^{211}Rn from target

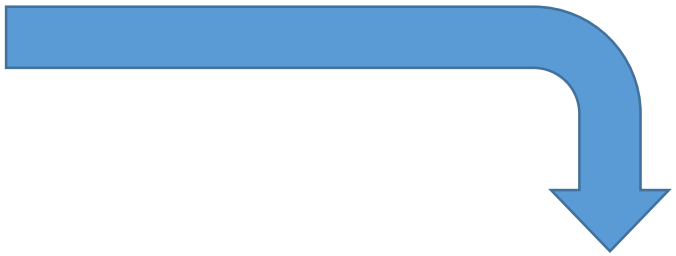
☺ Simple physical extraction of ^{211}At from the « generator »

☺ Less ^{210}Po

$^{211}Rn/^{211}At$ generator

Main tasks:

- Trapping Rn
- Elution of ^{211}At
- Tests at GANIL



Principle:

- ❑ Physi-sorption/condensation
- ❑ Solubilisation

Micro/nano-porous materials:

Physi-sorption/condensation: Zeolite / activated carbon / MOFs (519?) /Cyclodextrine/polycarbonates*; (pore sizes/ specific surface)

Solubilisation: impregnated resins*

*Labcom TESMARAC (SUBATECH/TRISKEM) 2020-2024

Nest steps for REPARE

- Data analysis of Sept ‘22 run
- In-beam test (cyclotron) of the solid Bi target station (July ‘23):
  - Mechanical aspects
  - Cooling
  - Beam synchronization and focusing
  - Current readings
  - …
- Installation in NFS and α beam from LINAC on Bi target (Sept ‘23):
  - Confirm previous controls
  - Radiological aspects (absence of contamination, easyness of extraction system)
  - At production and QC
- Generator: Rn adsorbtion measurements (Feb ‘23)
- Shipment of ^{211}At to ARRONAX

REPARE in a more general context

Steps from synthesis to clinical trials:

- Synthesis of ^{211}At
- Radiochemistry for extraction
- Radiolabeling and radiosynthesis of radiopharmaceuticals specific to targets of interest (PSMA, anti-VCAM-1, anti-TROP2, etc.) with ^{211}At
- Physicochemical and metabolic characterization of radiopharmaceuticals
- In vitro characterization of the response of tumor cells to treatments
- Dosimetry, biodistribution
- In vivo validation of treatments and first in Human phase 0 study (GMP/CYCERON, clinical research unit)

Installation of the REPARE target station in LHE → WP1

REPARE in LHE: the scientific project

Goal: install the high power irradiation station developped in the framework of the REPARE ANR project in the high energy hall of the SPIRAL2 building

To:

- comply with GANIL involvement in REPARE: deliver ^{211}At to ARRONAX
- contribute to develop the full value chain from the synthesis of ^{211}At up to clinical trials relying on local expertise and in collaboration with Nantes colleagues

Target choices and pathologies of interest

First thing to do: identify the most promising combination of target and pathologies in coherence with the local expertise and what is done elsewhere (Nantes)

1) Antibodies against VCAM for the treatment of brain metastases
2) PSMA ligands in metastatic prostate cancers
3) Antibodies against Trop-2 for the treatment of breast and ovarian cancers

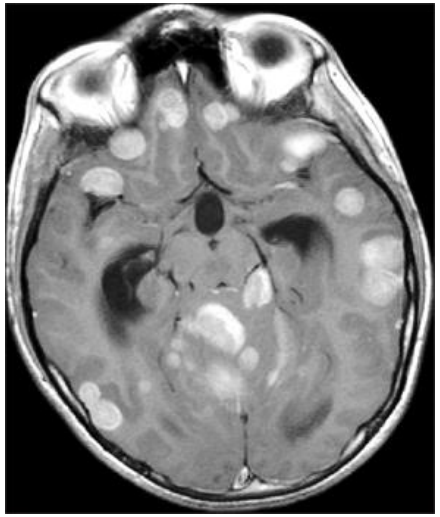
1/Antibodies against VCAM for the treatment of brain metastases

Brain metastases

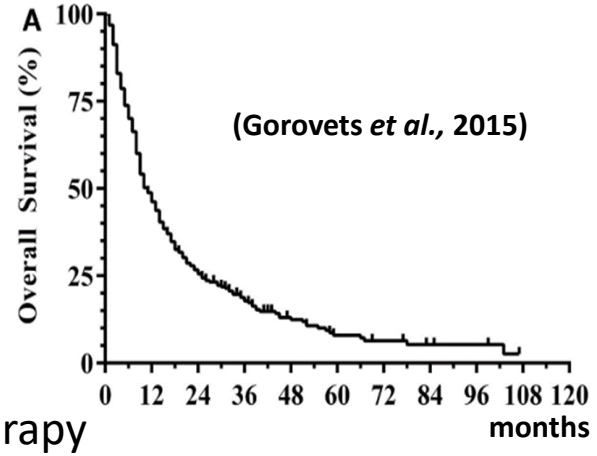
- Most frequent brain tumors (Takei *et al.,* 2016):
  - 10 times more frequent than primary brain tumors (Rudà & Soffietti, 2016)
  - Primary lung (40%) and breast cancers (20%) (Schuette *et al.,* 2004)

- Conventional treatments :
  - Surgery
  - External RT (whole brain) / radiosurgery => Median survival ~ 12 months
    - ➢ Cognitive decline

- Treatment too **late** *(Larkin et al., 2016)*
  - Late detection
  - Presence of the BBB prevents the efficacy of intravenously injected chemotherapy



Brain metastases MRI
Vide et al., 2011



(Gorovets *et al.,* 2015)

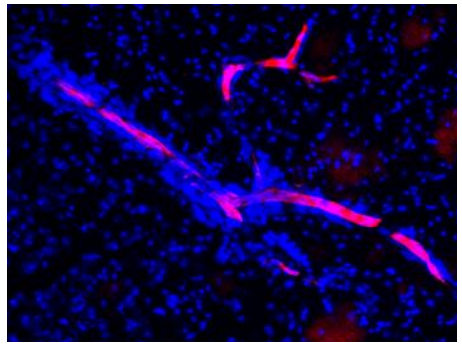
➔ Need new target of early brain metastases, reachable even with intact Blood Brain Barrier

1/Antibodies against VCAM for the treatment of brain metastases

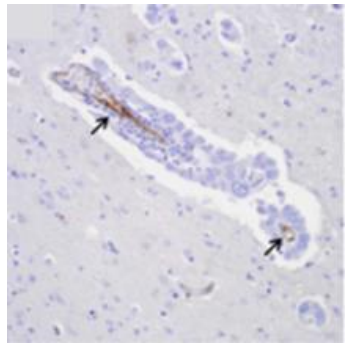
- VCAM: Vascular Cell Adhesion Molecule.
- Mediates adhesion of leukocites to vascular endothelium
- Inflammation of endothelial cells at early stage of cancer
- VCAM overexpressed in inflammatory cells

➔ Early biomarker of metastases

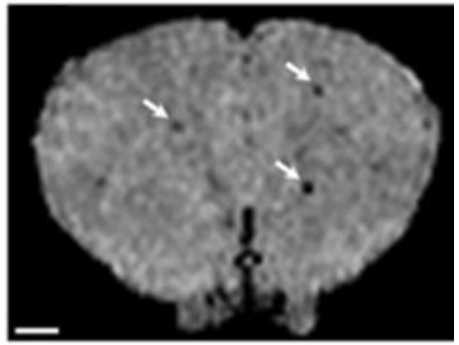
VCAM-1 : biomarker of **early brain metastases**

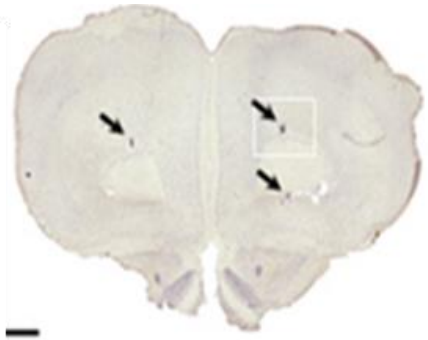


Corroyer-Dulmont et al., Neuro-Oncology (2020)



Serres *et al.*, 2012





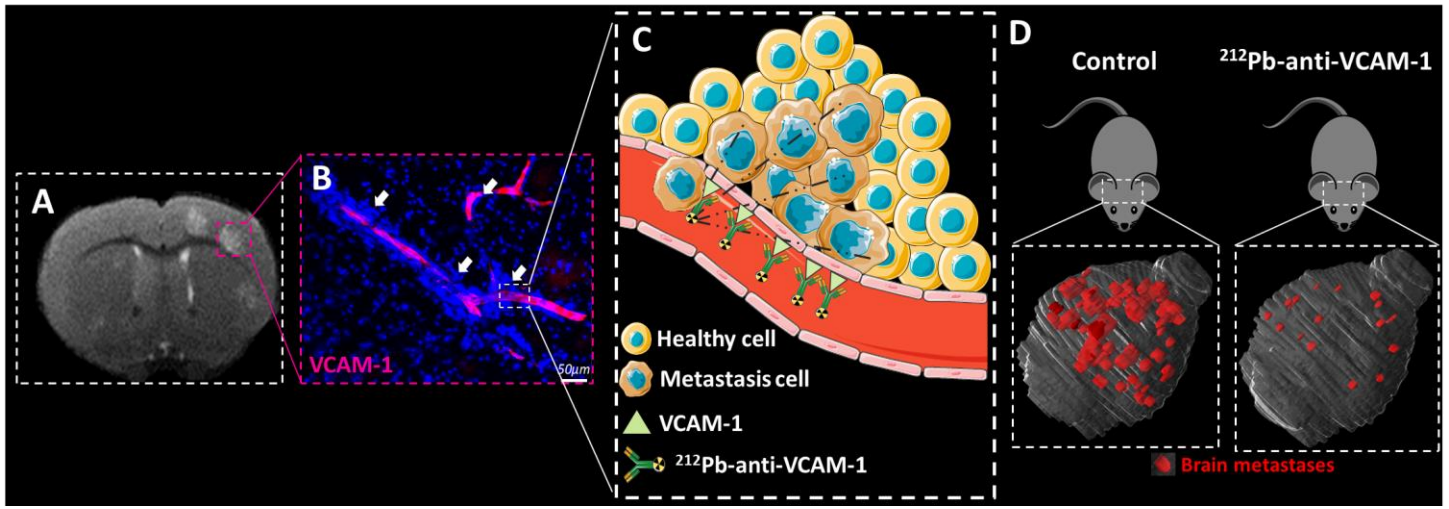
Serres *et al.*, 2012

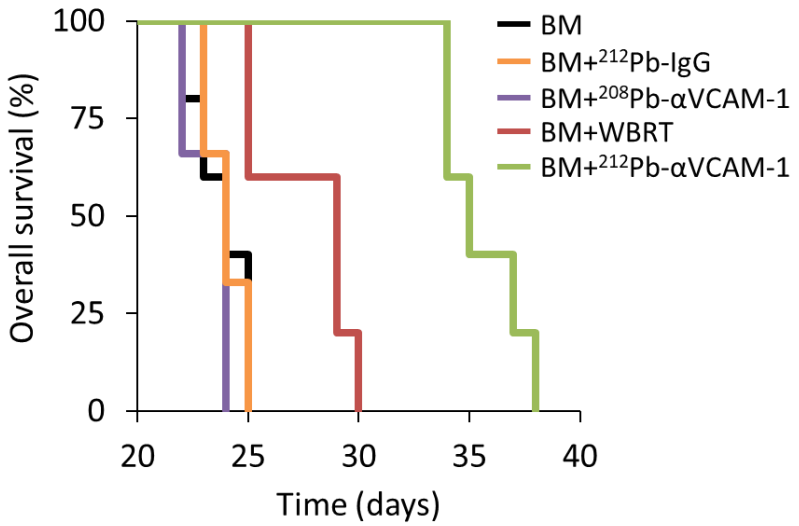
➔ Promising therapeutic Target

1/Antibodies against VCAM for the treatment of brain metastases

In vivo therapeutic study ^{212}Pb

- Using preclinical model of brain metastases with human tumor cell line primary breast cancer MDA-231-Br





Neuro-Oncology
XX(XX), 1–12, 2019 | doi:10.1093/neuonc/noz169 | Advance Access date 20 September 2019

VCAM-1 targeted alpha-particle therapy for early brain metastases

➢ Corroyer-Dulmont et al., Neuro-Oncology (2020)

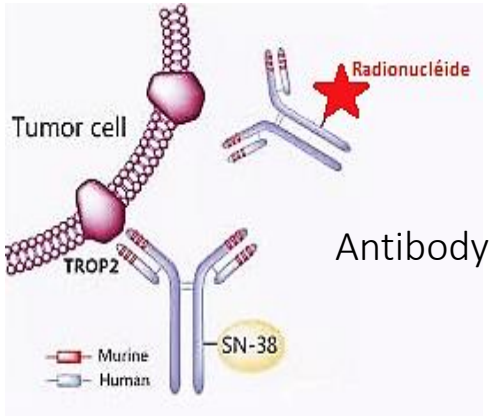
2/Antibodies against Trop-2 for the treatment of breast and ovarian cancers

Trophoblast cell-surface antigen-2 (Trop-2)

- Monomeric transmembrane glycoprotein
- Intracellular calcium signal transducer
- Stimulates self-renewal, proliferation, invasion, and survival
- Upregulated in a variety of epithelial tumors
- Membrane expression of Trop-2 is found in more than 85% of breast tumors, including triple negative tumors
- Moderate to high membrane expression of Trop-2 is found in about 50% of ovarian epithelial tumors

2/Antibodies against Trop-2 for the treatment of breast and ovarian cancers

- Possible labelling of an antibody directed against TROP2 with a radionucleide for imaging (γ or β^+) or therapy (β^- or α)



Antibody Drug conjugate

- Publications concerning other types of cancers have already demonstrated the feasibility of implementing such a strategy:

  Pretargeted Radioimmunotherapy of Prostate Cancer with an Anti-TROP-2×Anti-HSG Bispecific Antibody and a (177)Lu-Labeled Peptide.
  van Rij et al, Cancer Biother Radiopharm. 2014 Oct;29(8):323-9. PMID: 25226447;

  Pretargeted immuno-PET and radioimmunotherapy of prostate cancer with an anti-TROP-2 x anti-HSG bispecific antibody.
  van Rij et al., Eur J Nucl Med Mol Imaging. 2013 Sep;40(9):1377-83. PMID: 23674207.

- Could provide a new treatment option for poor prognosis cancers with a limited number of treatment lines, such as triple-negative (and RH+) breast cancers, or ovarian cancers.

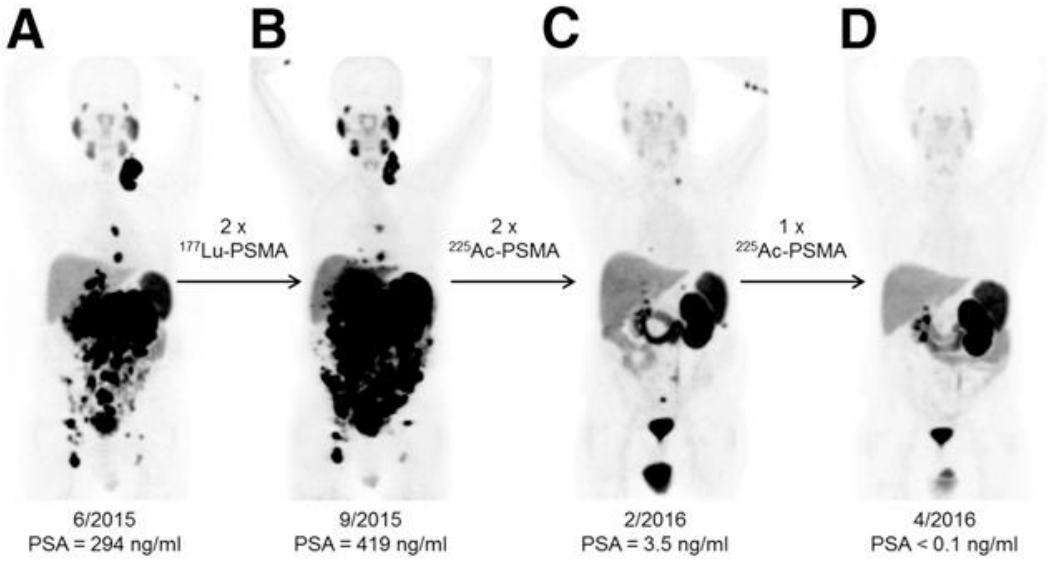
3/PSMA ligands in metastatic prostate cancers that escape PSMA-Lutetium

- PSMA ligands = molecule targeting compound that bind to cancer cells expressing PSMA
- Radioligand Therapy: combines ligand (targeting) and radioisotope (eg ^{177}Lu-PSMA-617 PSMA ligand+^{177}Lu)
- Use an α-emitter instead:
  - Coupled with PSMA-ligand PET/CT imaging for theranostics
  - Still experimental
  - Higher biologic effectiveness than the β-emitter ^{177}Lu
  - Strong potential to significantly benefit advanced-stage prostate cancer patients

3/PSMA ligands in metastatic prostate cancers that escape PSMA-Lutetium

- Clinical effectiveness demonstrated with ^{225}Ac-PSMA-617 (Kratochwil JNM 2016, Zacherl JNM 2021…)

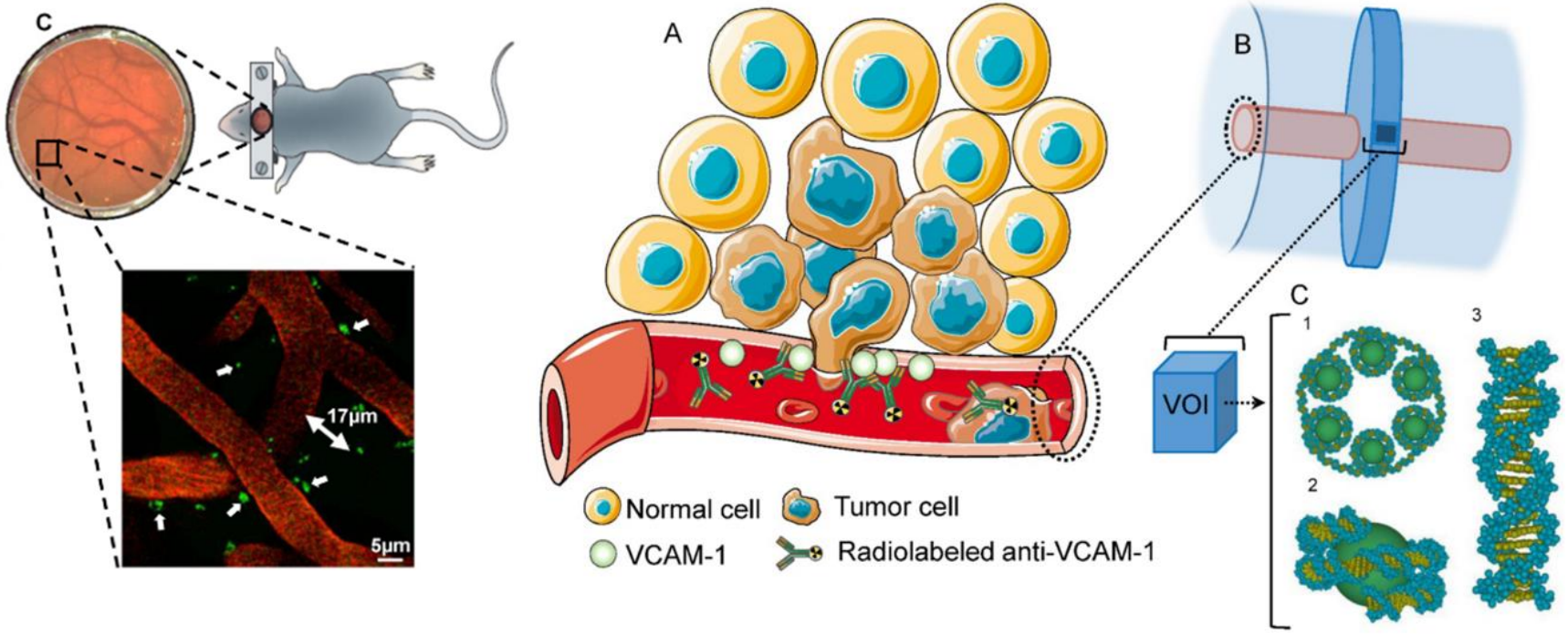
- Including ^{177}Lu-PSMA–refractory patients
- Feasibility of ^{211}At-PSMA (Mease JNM 2022)
- Progressive refractory thyroid cancers

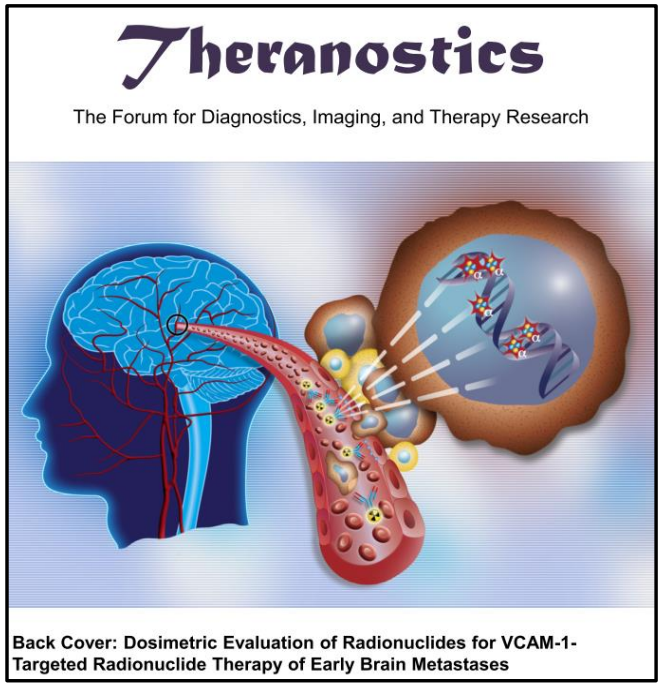


Kratochwil JNM 2016

In vitro-dosimetry, simulation studies

- Monte carlo simulation : dose-deposition and DNA damage (^{211}At, ^{212}Pb, ^{213}Bi, ^{225}Ac and ^{177}Lu, ^{161}Tb, ^{90}Y…)

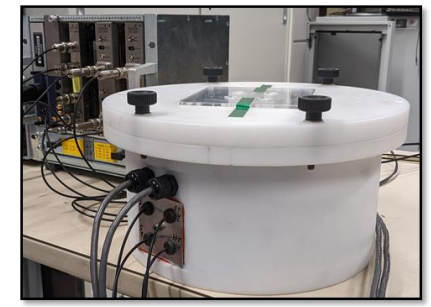


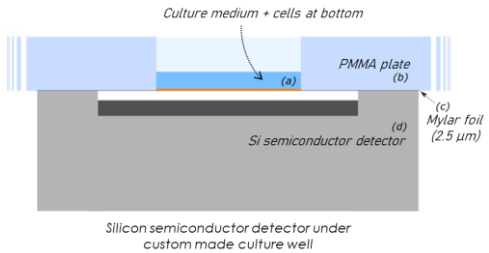


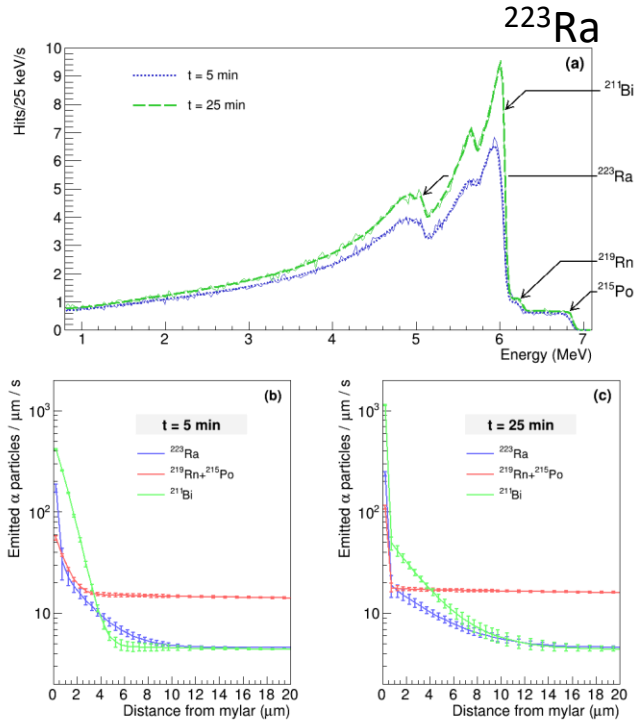
Falzone et al., 2018

In vitro-dosimetry, simulation studies

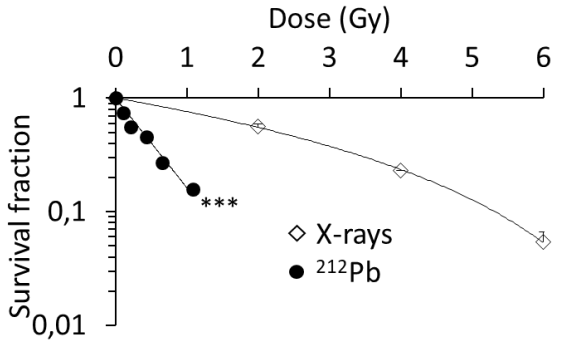
- ^{212}Pb *versus* X-rays therapeutic effect differences
- Need to develop of a new dosimetry system (MITI ISOTOP 2020) to enhance radiobiology results in *in vitro* experiments







Biological end point
e.g. double strand-break rate

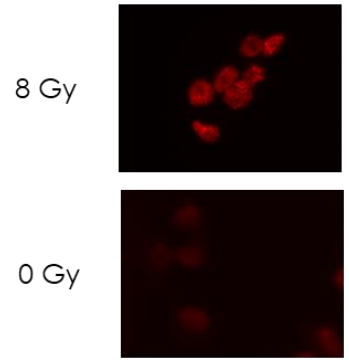


IN VITRO RADIOSENSITIVITY		
	SF2	D50
X-rays	0.60 (0.06)	2.41 (0.18)
^{212}Pb	0.026 (0.001) ***	0.382 (0.04) ***

Frelin et al., (2020) Medical Physics

Absorbed dose
(or other metrics)

DNA DSBs



MDA-MB (Br) cells seeded on a custom culture plate (2.5 µm mylar foil)

The collaboration

GANIL laboratoire commun CEA/DSM spiral2 CNRS/IN2P3

Centre Baclesse unicancer NORMANDIE - CAEN

CENTRE D'ÉTUDES ET DE RECHERCHE SUR LE MÉDICAMENT DE NORMANDIE

Subatech

ARRONAX

CHU CAEN NORMANDIE

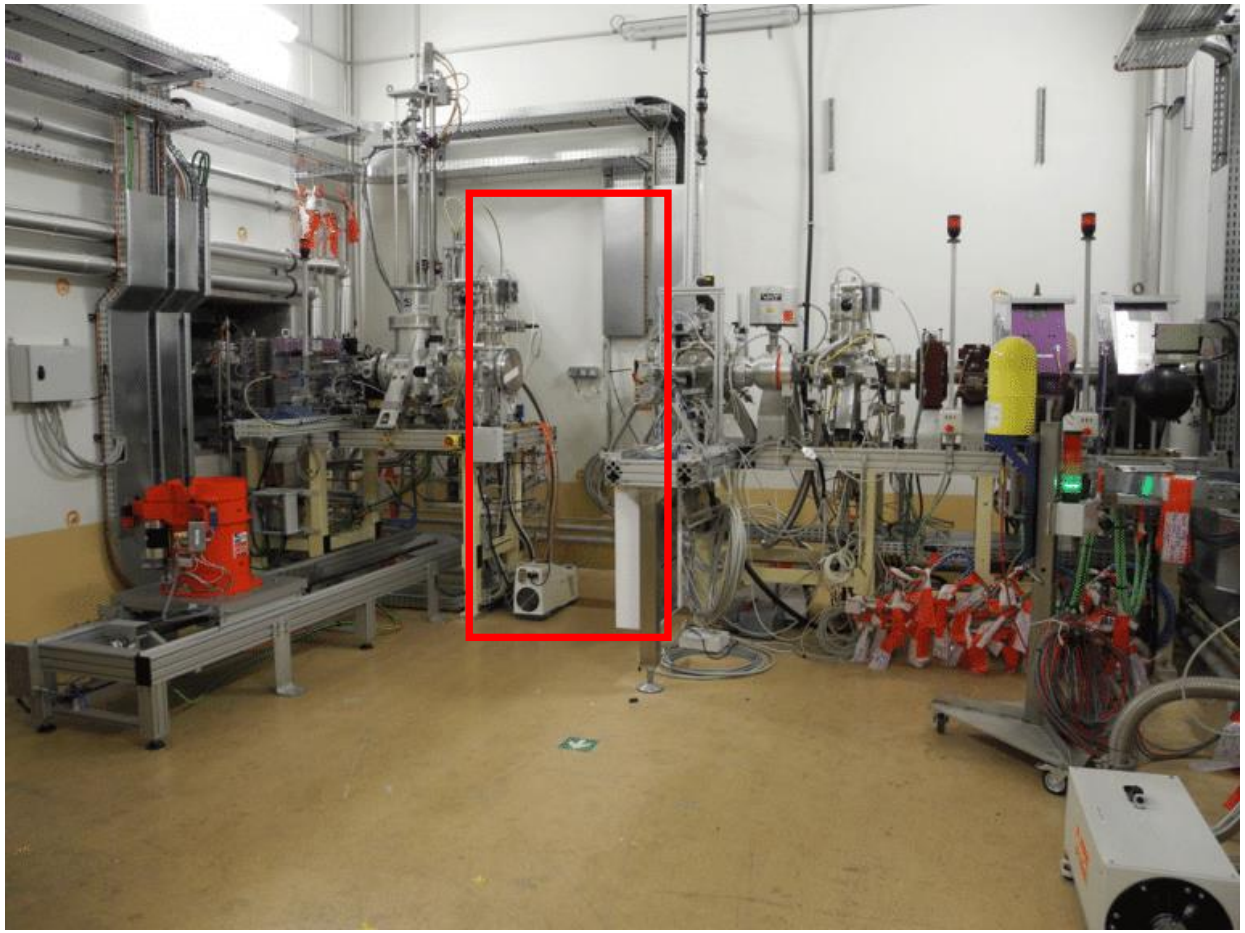
Anticipe

IST2

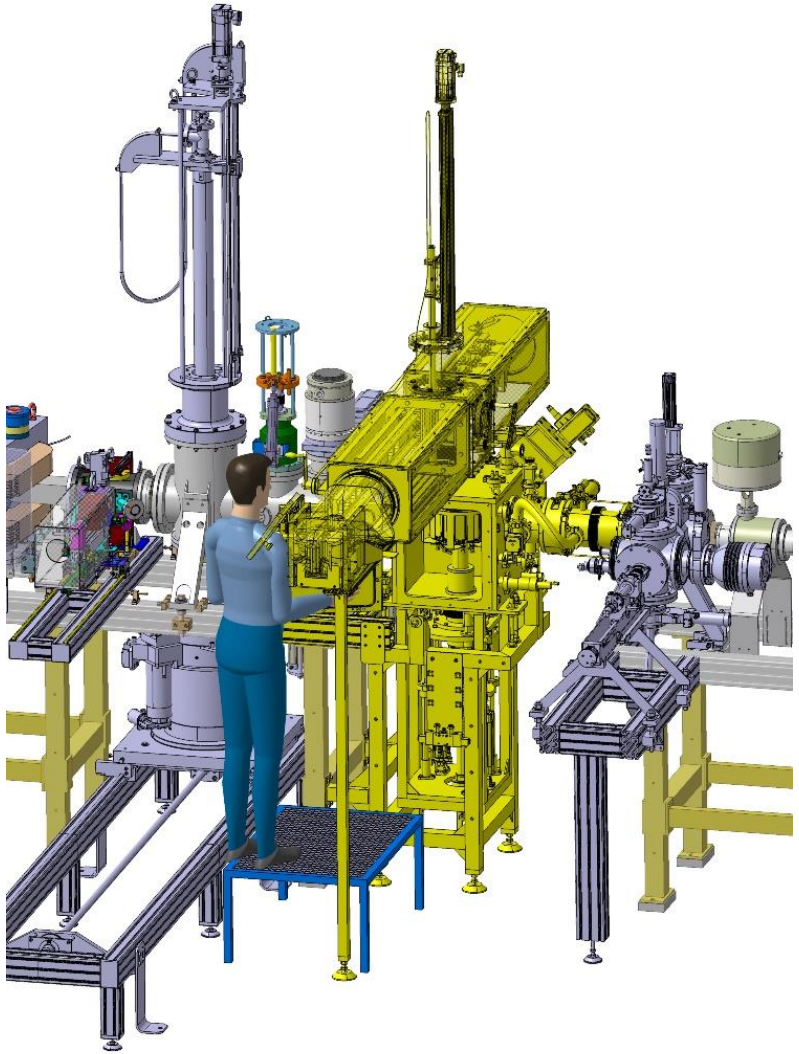
CERN

Cyceron PLATEFORME D'IMAGERIE BIOMÉDICALE

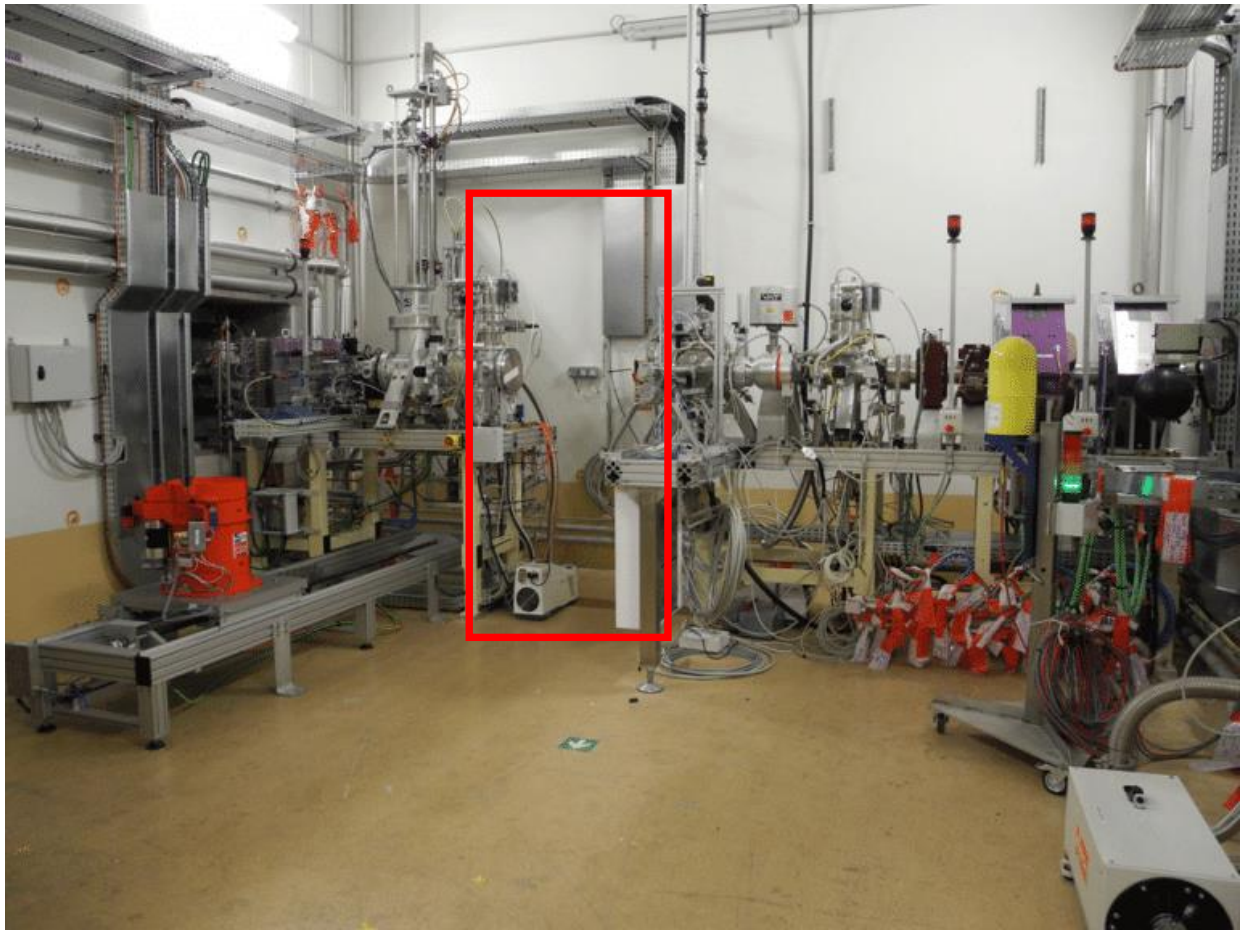
Installation of REPARE in NFS



NFS converter room



Installation of REPARE in NFS



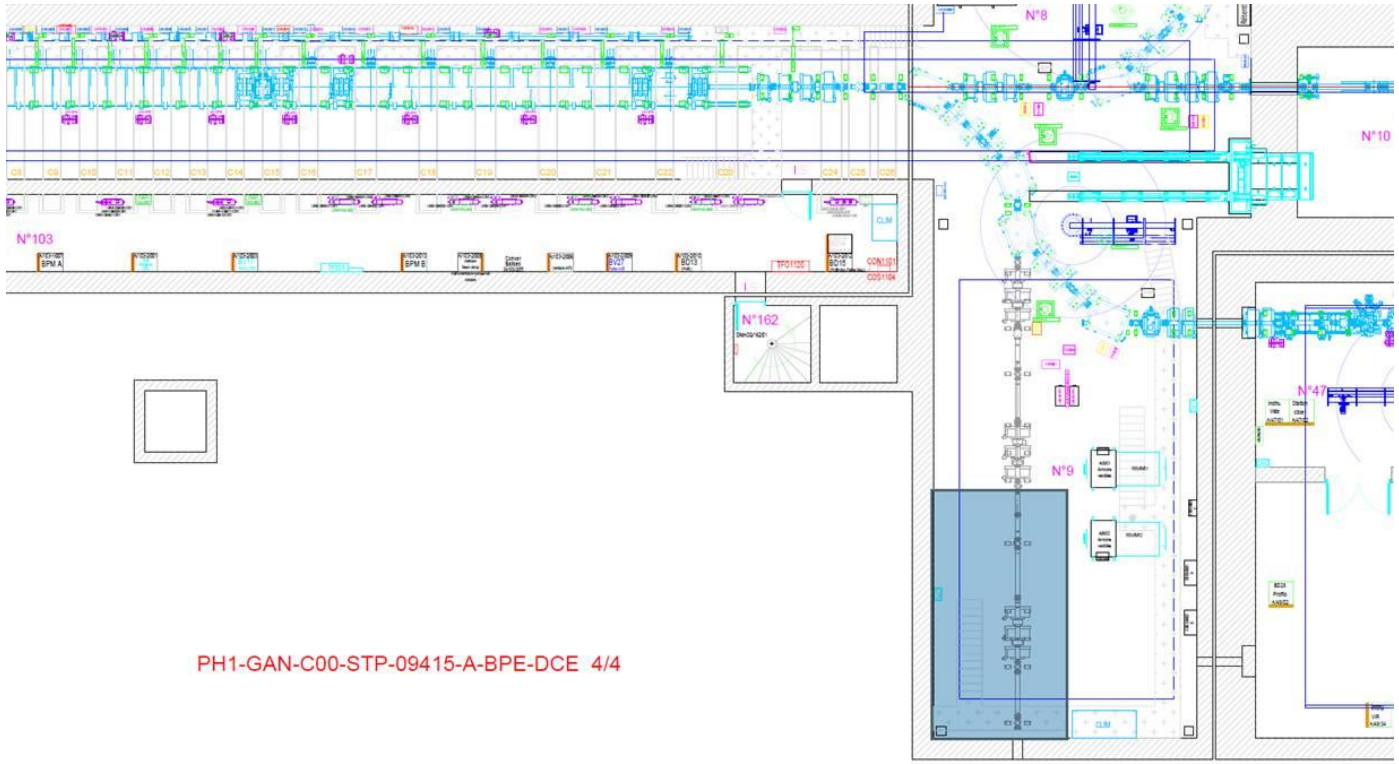
NFS converter room

- Very limited space!
- Need access to some room infrastructure devices (valves of the cooling system for several devices like magnet, Faraday cup, converters)
- Occupied by teams using the rabbit system
  ➔ only a temporary position…
- High neutron flux activates the station itself
- Using the station in the converter room prevent from running or preparing any experiment in NFS (and vice versa)

➔ Installation in LHE

Installation of REPARE in LHE

Location at SPIRAL2:



A new area at SPIRAL2 where we can use the high intensity of charged particle beams

Activity containment in case of fire ➔ casemate

➔ connection no Nuclear Ventilation System

➔ ASN authorization required

Costs

Casemate

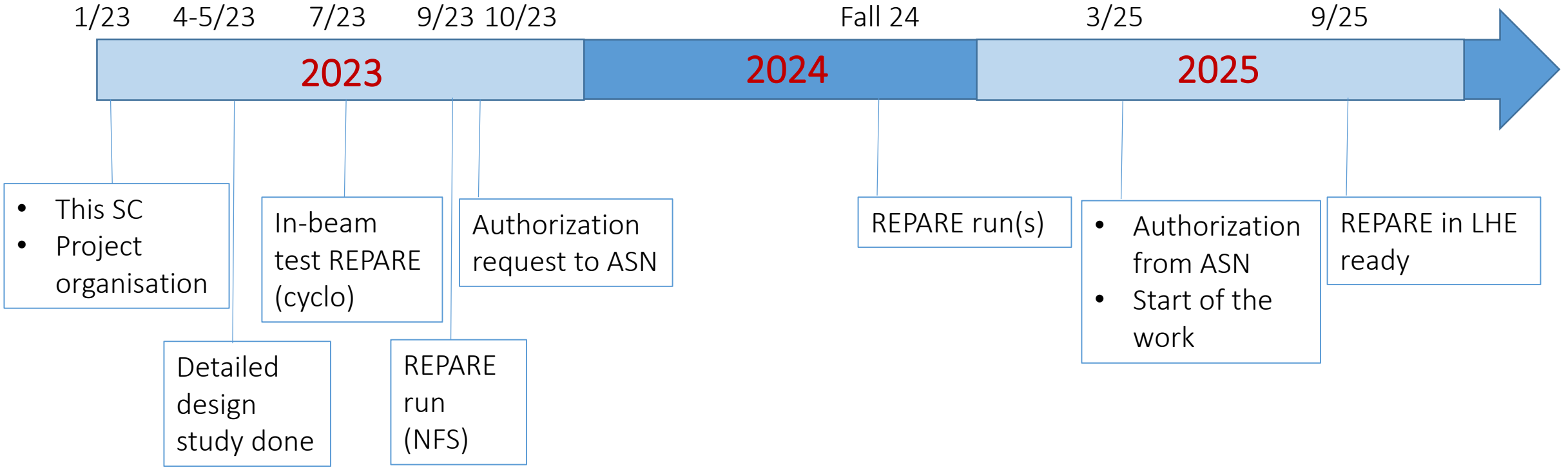
Local CF 2H et ventilé	Q	prix (€)
armature, cloison CF2H, Portes et 2 fenetres CF2H	140m2	100000
distri elec/eclairage		5000
résine au sol	40m2	3000
peinture 140m2 (X2 faces)		5000
VN équilibrage		2000
instrumentation VN		5000
dérivation VN A/R + registres		15000
clapets CF (non CTHEN)	2	3000
détection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

Beamline

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

- Target station self funded (ANR)
- Not specific to REPARE
- Mainly beamline => detailed design study to check length (maximum length considered)

Planning and beam time request



Beam time request: small amount but regularly (ideally a few hours/week)

Summary

- REPARE: ongoing project to optimally produce ^{211}At. High power targetry developments. Generator option. Temporary installation in NFS. ^{211}At delivery to ARRONAX.
- Much more global project involving local players (GANIL, hospitals, CYCERON, INSERM research units, CERMN,…). Elaboration of this project over the last 18 months. Targets and pathologies identified. Tasks and partners for the complete chain identified. Need to move forward (apply to project calls).
- REPARE in LHE: a unique opportunity to give flexibility and more efficient use of beam time. Of interest for other cases: a new experimental area at SPIRAL2.
- Recommended in the first Phase of the Spiro report (« A vision for GANIL »):

« The committee recommends a timely installation of a dedicated target station in the LHE2 (High Energy Line) area for production of medical radioisotopes to exploit the most intense high intensity LINAG beams for this important societal application"