Activities on the production of ^{211}At at GANIL

G de France, GANIL, for the REPARE collaboration and beyond

Colloque du GANIL, Soustons, Sept. 25-29, 2023

Agenda

- Motivations
- The REPARE project
- Beyond REPARE
- Summary

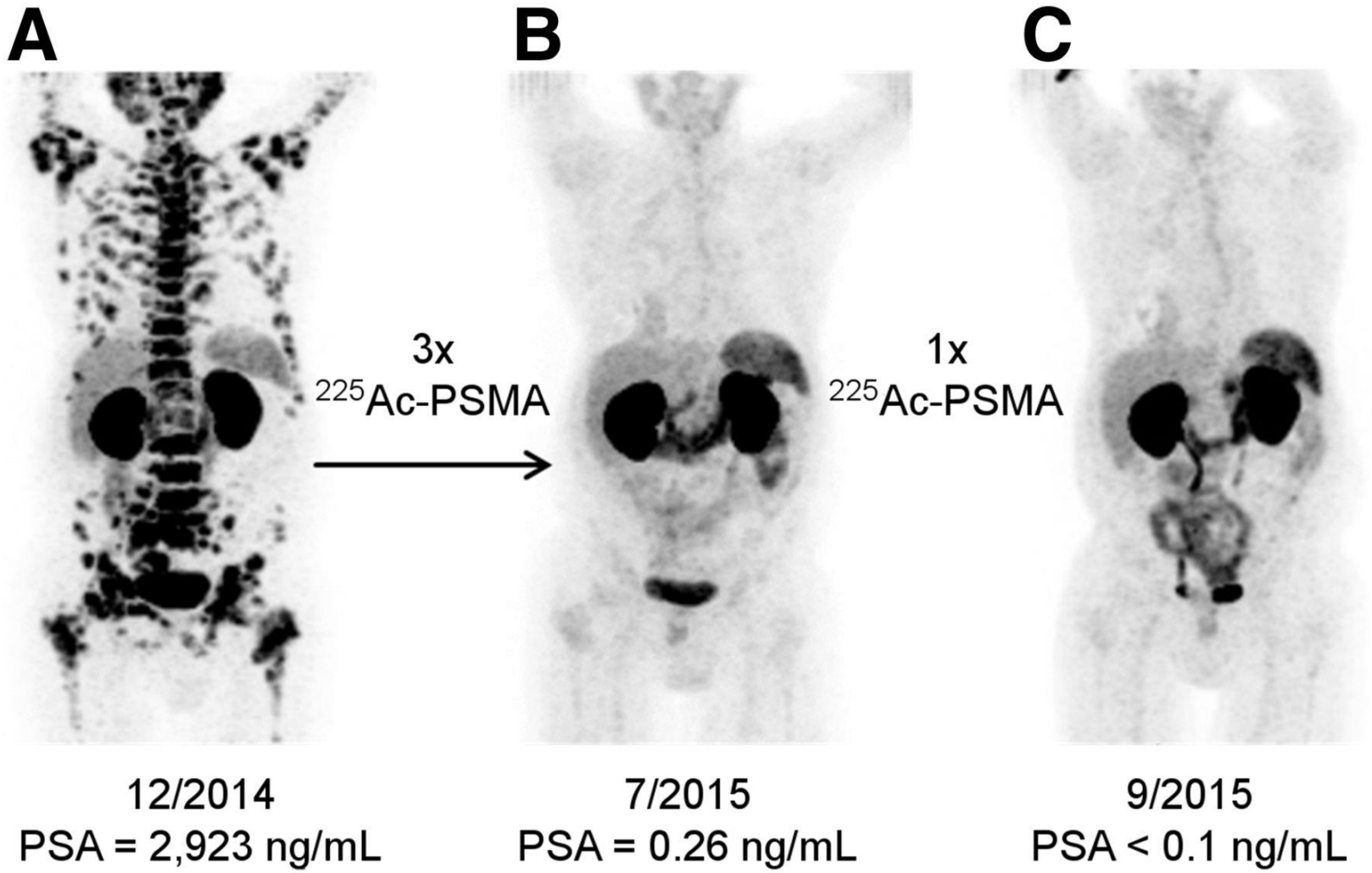
Motivations (TRT)

- **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)

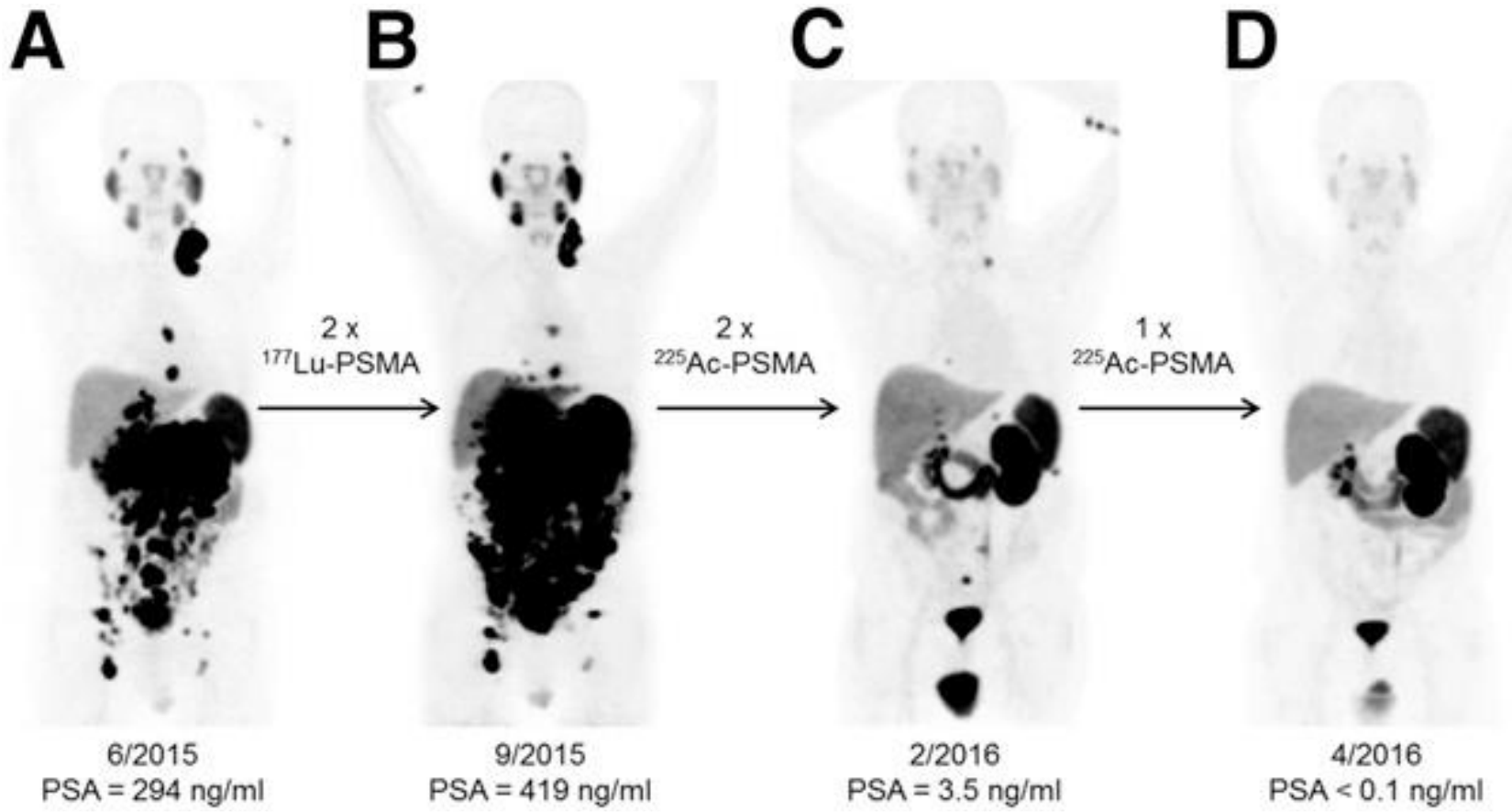
Promises of targeted α therapy



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



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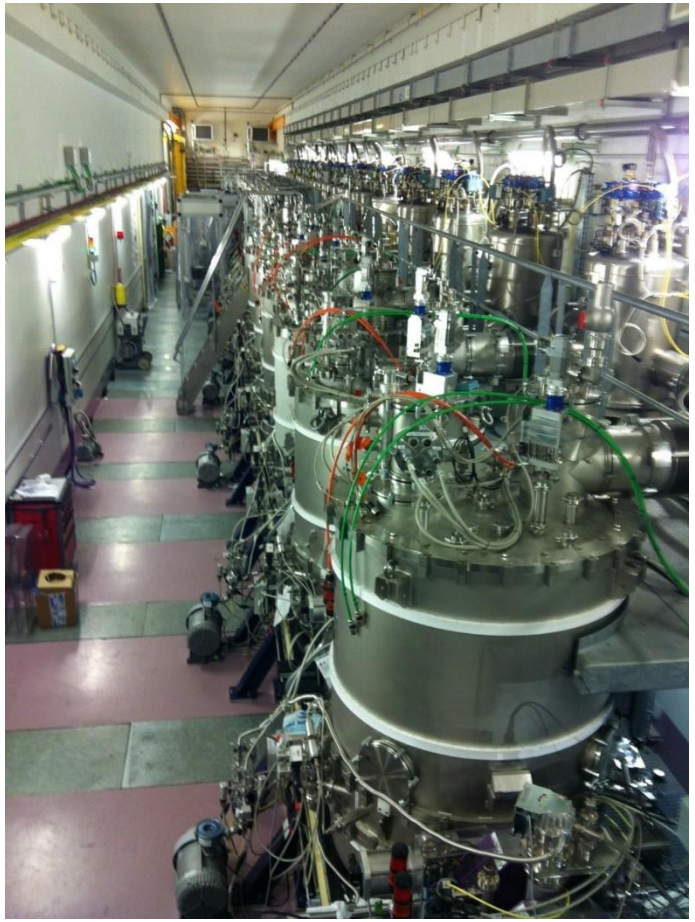
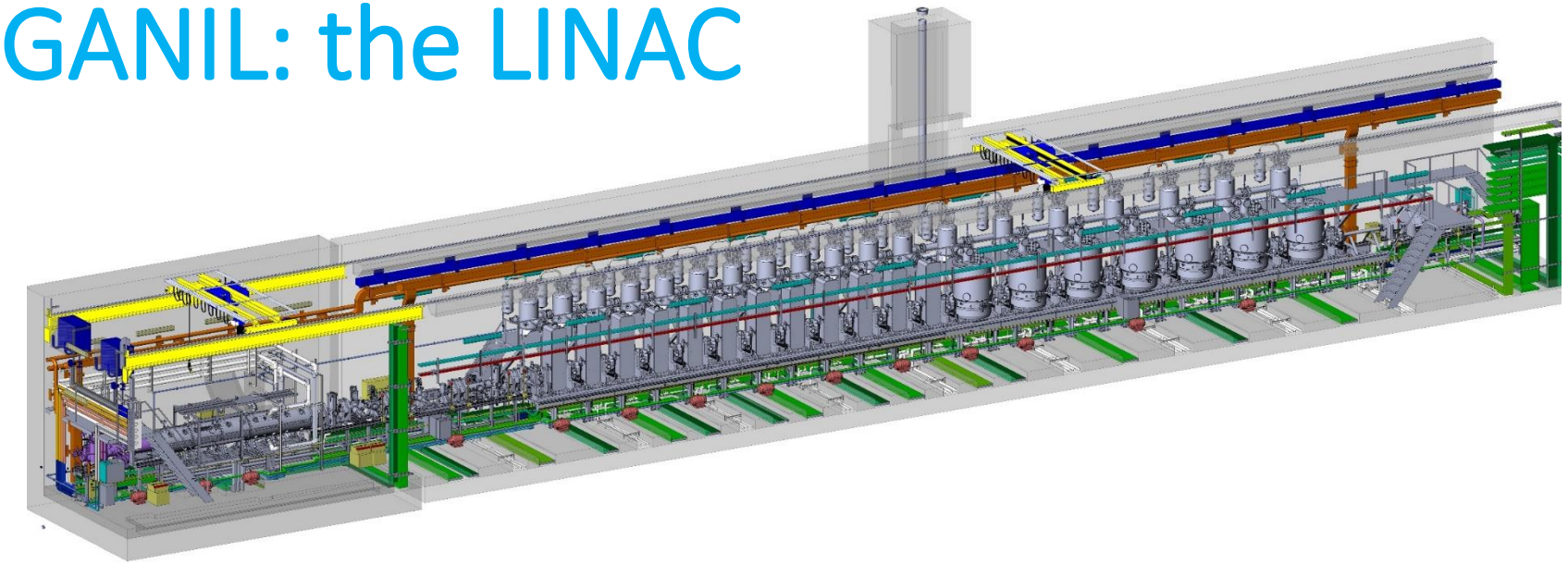
Opportunities at GANIL: the LINAC





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

1 mA ~ 10^{15} pps

➔ 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)

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**)

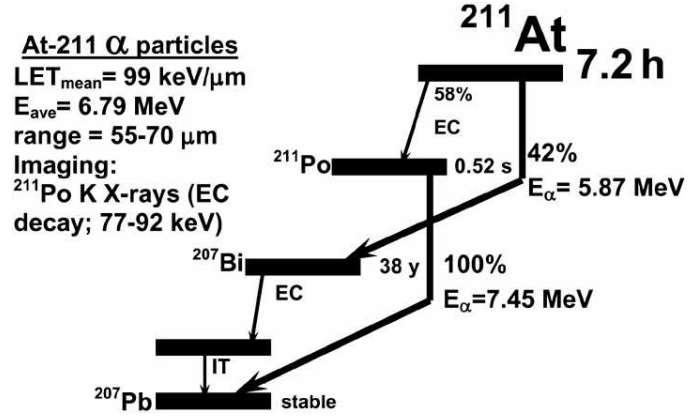
WP1: MC calcs and cross section measurements

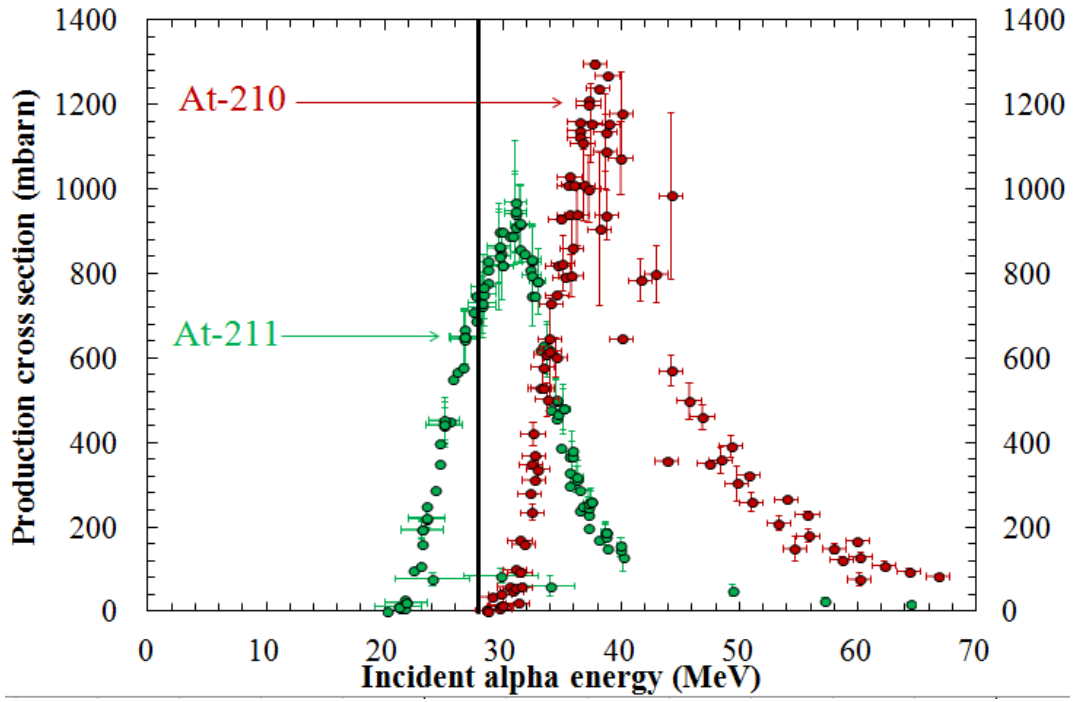
- Monte Carlo calculations using Bi and Pb (LBE) targets
- Precise measurements of the relevant production cross-sections
  - Using alpha (ARRONAX, SP2)-Direct production of ^{211}At
  - Using ^{6,7}Li (SP2)-Generator
  - Collaboration with Czech Rep (expt Sep ’22)

^{209}Bi(α,2n)^{211}At, 20.7 MeV

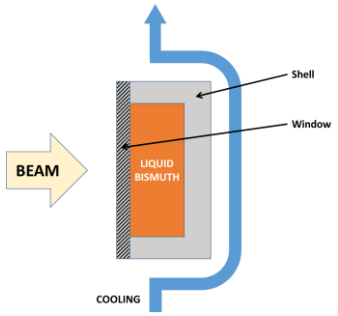
^{209}Bi(α,3n)^{210}At, 28.6 MeV

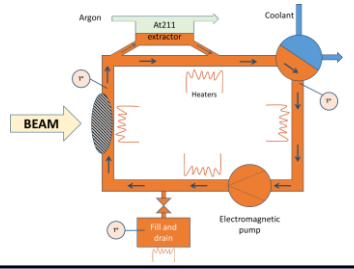
➔ **Talk Saba Ansari-Chauveau**

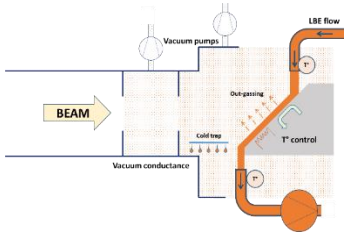


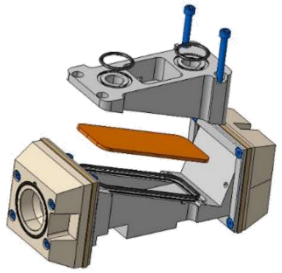


WP3: Liquid Target Concepts









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.

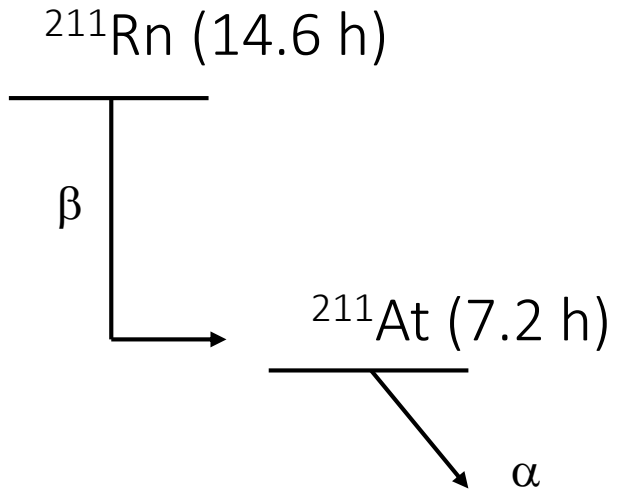
WP4: ^{211}Rn/^{211}At generator

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

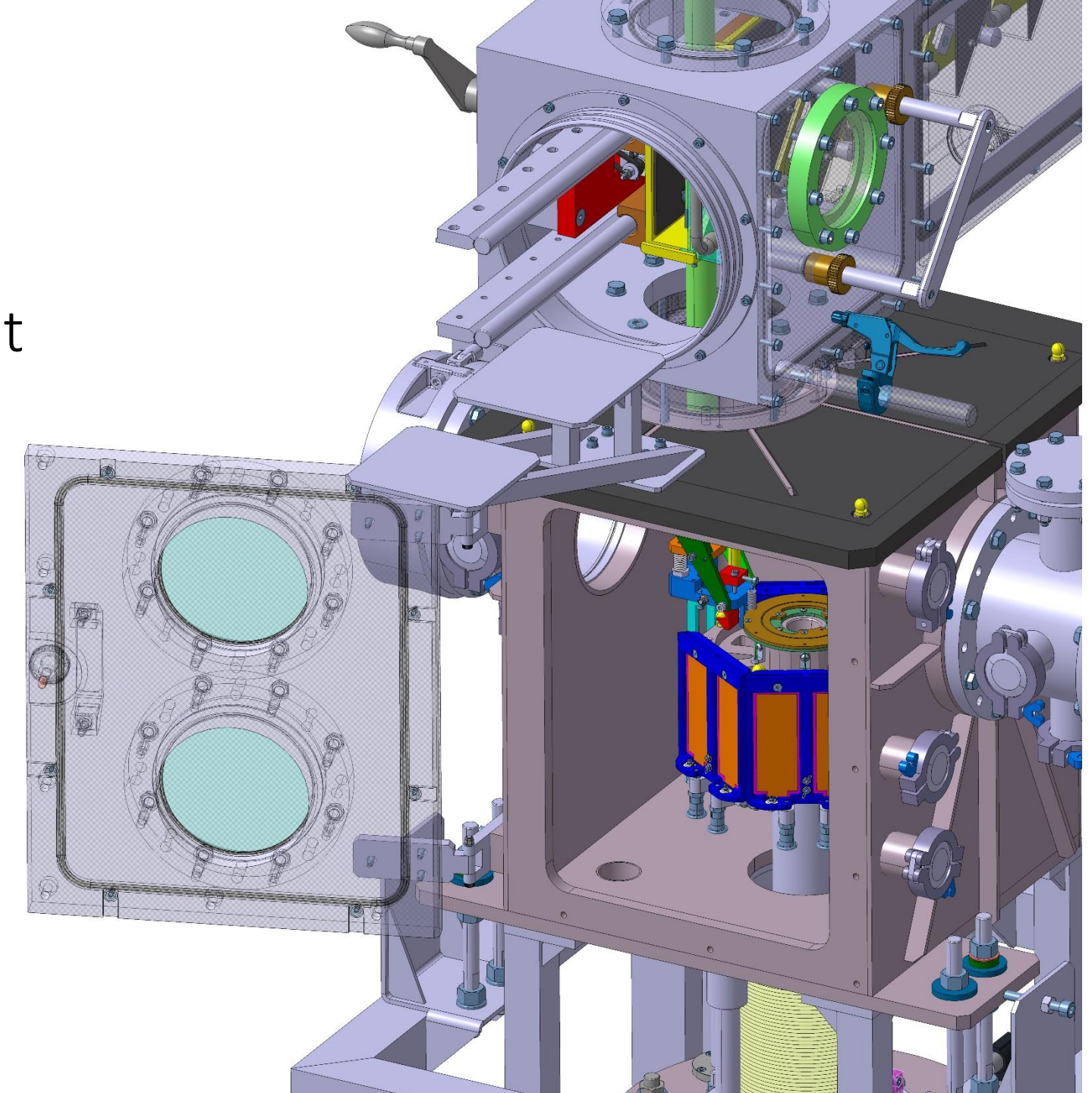
☺ Simple physical extraction of ^{211}At from the « generator »

☺ Less ^{210}Po

WP2: Solid Bi target

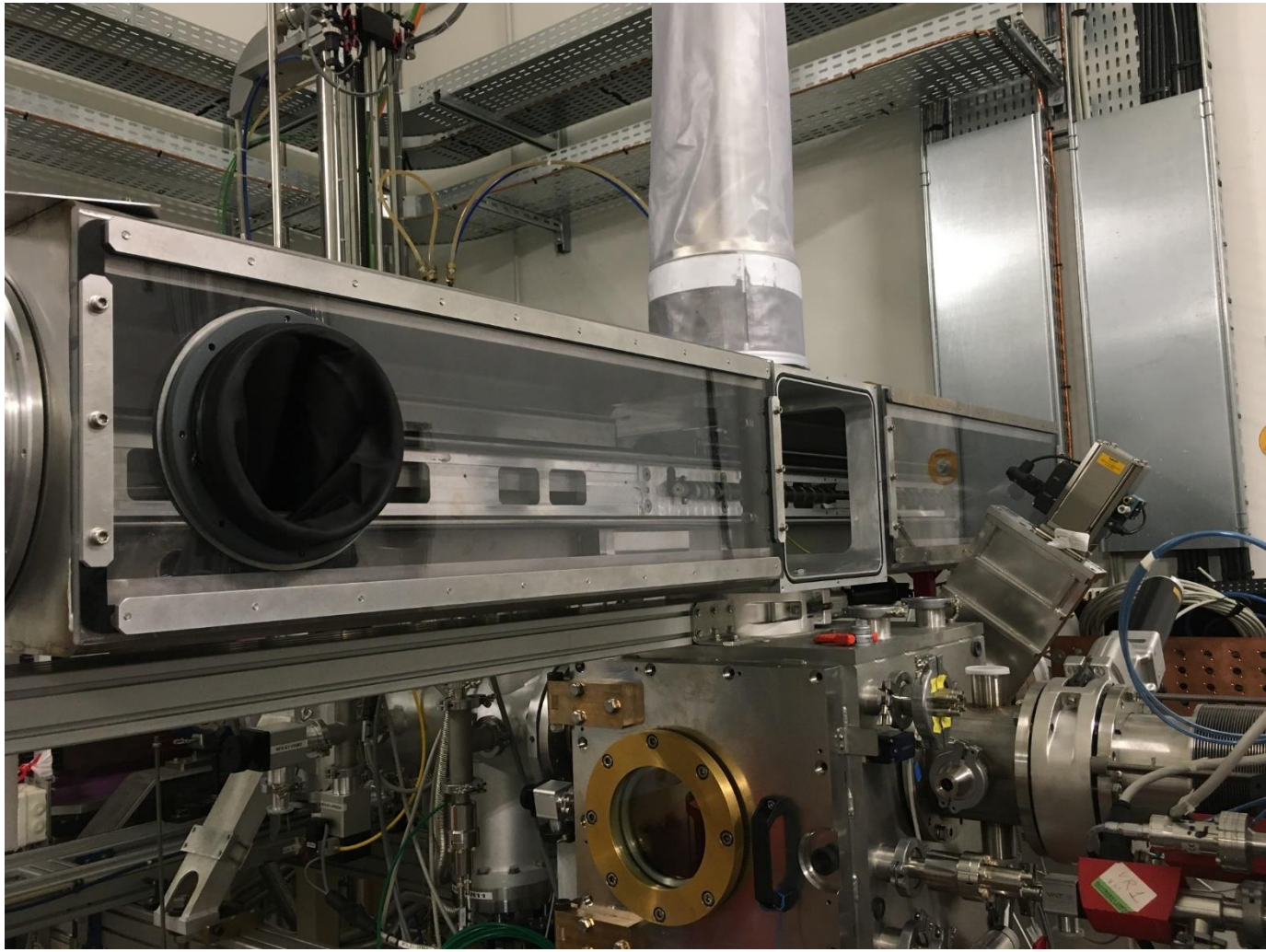
- High power rotating target

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



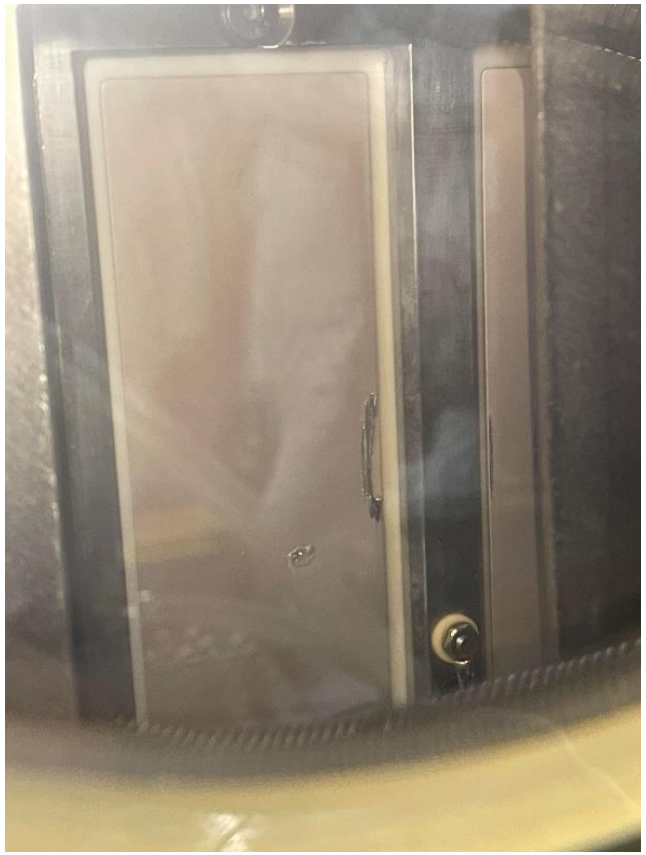
WP2: Solid Bi target

- Tests:
  - July: cyclo, ^{20}Ne, 4.5 MeV/A
  - Sept 3-4: α, 7MeV/A, low power (10W)
  - Sept 10-11: α, **7MeV/A**, high power



WP2: Solid Bi target

- Results:
  - Cyclo: Mechanics, cooling, current readings, vacuum, beam synchronization with wheel rotation, hard/soft of automatic system handling REPARE,…: OK
  - 10W:
    - no contamination (sputtering): validation of hypothesis of the safety file
    - no trace of ^{210}At: good energy
    - ^{211}At activity (~16 MBq) scaling well with beam current
    - no activity on collimator: beam synchro confirmed
  - 10 kW:
    - Wrong beam structure (3ms/s) => target damage while scanning target for precise adjustment of synchro (w/o rotation)
    - Loss of communication with automatic system (with human machine interface); failure of card handling rotation of the wheel => beam stop. Too large neutron flux?
    - Full analysis ongoing (restart of the automatic system)



WP2: Solid Bi target

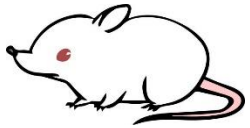
- Cure/Improvements identified :
  - Beam bunches on target as short as possible
  - No scan (ie no low power run needed)
  - Automatic system installed in TOF area (outside converter room)
  - Mechanical adjustment in NFS to ease target station installation
  - System to ease Pb container closing
  - Training of radioprotection people

Next steps

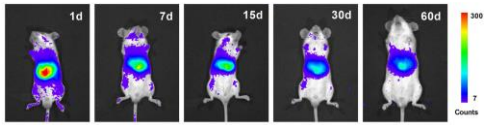
- Full analysis, feedback and improvements/upgrades following the observed issues
- Beam time request for next year to:
  - Finalize the high power test
  - Deliver ^{211}At to ARRONAX
  - And to CYCERON:
- Approved project with CYCERON and ISTCT: synthesis, extraction of ^{211}At from Bi irradiated targets, radiolabelling of antibody anti-VLA-4. Proof of concept. Would need more frequent beamtime for this.
- GANIL SC early 2023:
  - Proposal to setup an area in the high energy hall of the LINAC for R&D on radioelements as well as any other activity using charged particle (constraints from NFS converter room)
  - Positive feedback. Need to consolidate the collaboration and the involvements of partner around a more general project

Beyond REPARE: develop the full value chain at the regional level

Pre clinical trail/in vivo studies

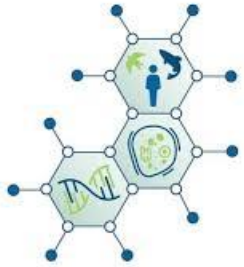


Dosimetry
Biodistribution



Clinical trials

Toxicology

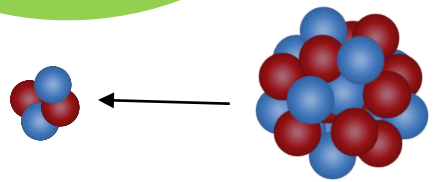


Targeted Alpha Therapy

Drug design/chelation

Regumation/paper work…

Synthesis/
Physicochemistry



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

Full project defined with the relevant local actors

Summary

- REPARE: ongoing project to optimally produce ^{211}At. High power targetry developments. Generator option. Temporary installation in NFS. Feedback of tests ongoing. ^{211}At delivery to ARRONAX and CYCERON.
- Much more global project involving local players (GANIL, hospitals, CYCERON, ISTCT, INSERM research units, CERMN,…). Targets and pathologies identified. Tasks and partners for the complete chain identified.
- Proposal to setup a dedicated area in the high energy hall of the LINAC (REPARE in LHE). Need ASN authorization.
- Gain in visibility and structuration: proposal to create a « Groupement d'Interêt Scientifique » on alphatherapy in Caen

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

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Anticipe

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