Production of non standard medical radionuclides

F. Haddad

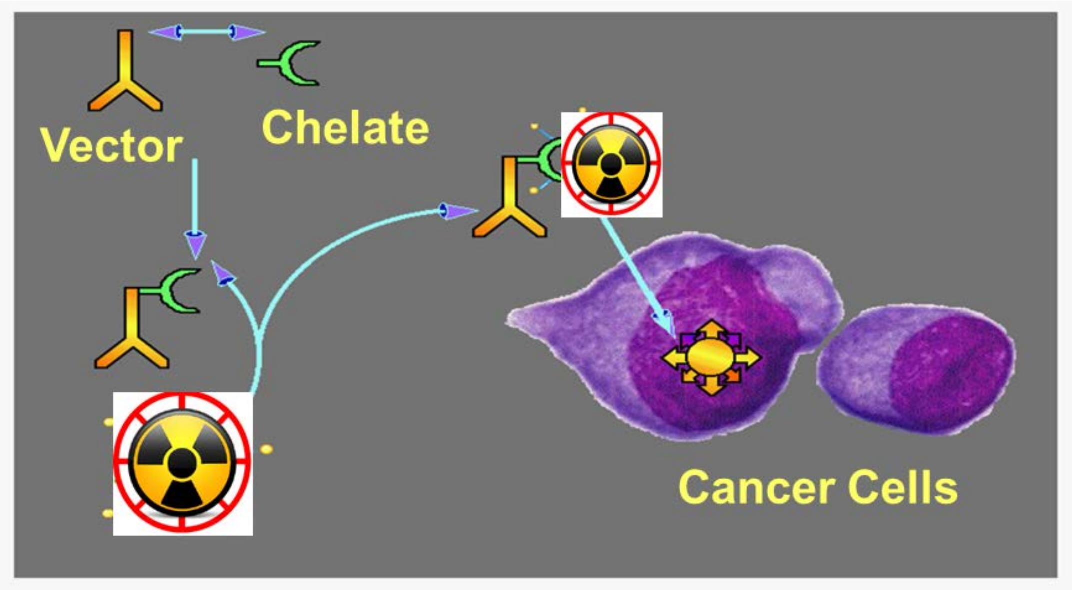
on behalf of the REPARE collaboration

Radionuclides production for nuclear medicine

In Nuclear medicine, radionuclides are used:

- for **imaging and diagnosis** (X-ray, γ , β+)
- for **therapy (**α**,** β**-,** Auger-e**)**

In most cases, **a vector molecule is needed** to target the cells of interest.

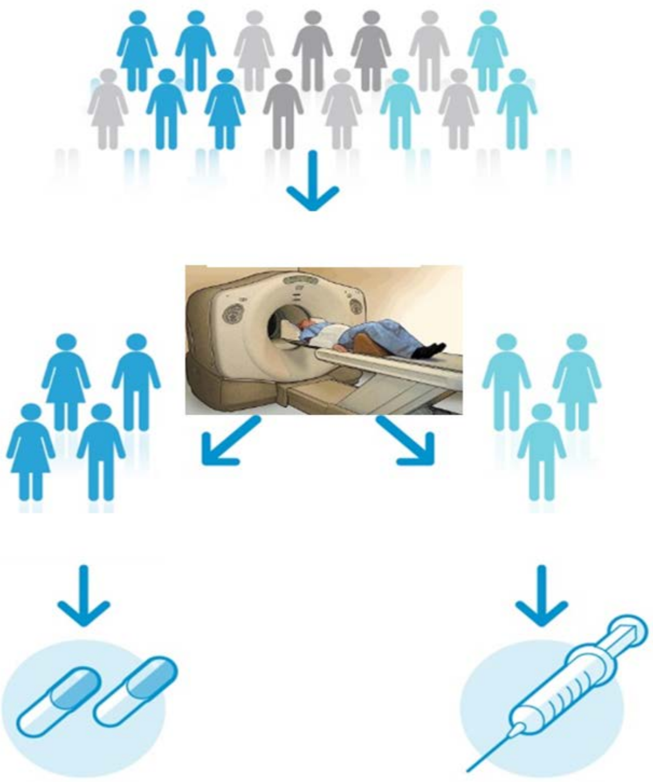


We need to **adapt** $\mathbf{T_{1/2}}$ to the distribution time of the vector molecule

Theranostics

It is a **treatment strategy** that combines **thera**peutics with diag**nostics**.

- Localized lesions
- Define the **biodistribution** of a therapeutic agent to anticipate its effect
- **Select patients which are expected to response to the therapeutic agent**
- Calculate the optimal activity to be injected
- Evaluate the response after treatment



The Right Drug To The Right Patient For The Right Disease At The Right Time With The Right Dosage

One example of treatment

^{225}Ac – PSMA-617 :

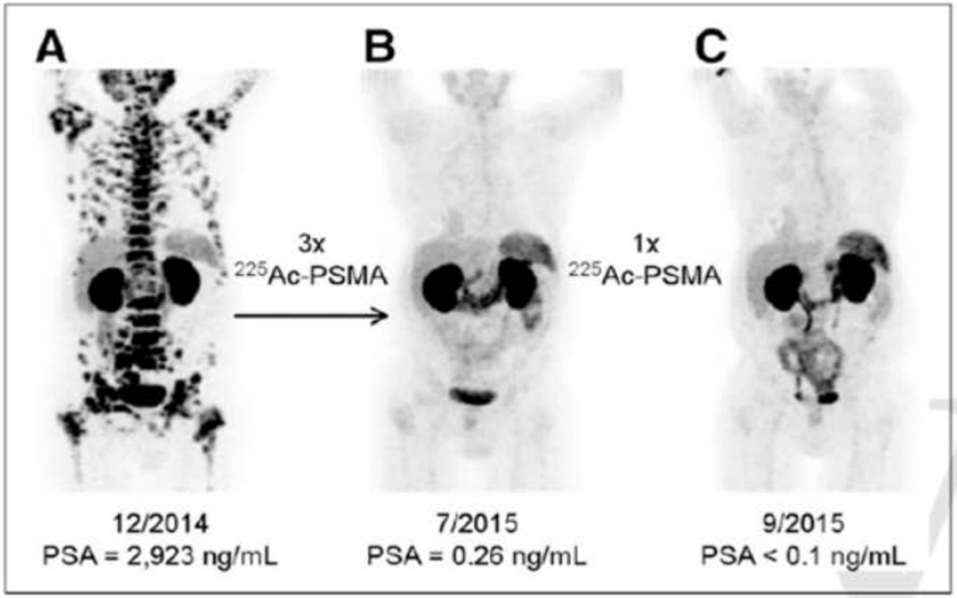


FIGURE 1. ^{68}Ga-PSMA-11 PET/CT scans of patient A. Pretherapeutic tumor spread (A), restaging 2 mo after third cycle of ^{225}Ac-PSMA-617(B), and restaging 2 mo after one additional consolidation therapy (C).

Kratochwil et al. J Nucl Med 2016

Kratochwil et al. J Nucl Med 2016; 57:1-4
http://www.c-ad.bnl.gov/esfd/Particle%20Post/MIRP.htm

There is a demand for new radionuclides

- with different **decay radiations** (imaging / therapy – High LET vs Low LET)
- with different **Chemical properties**
- with different **Half-lives:** to match with vector distribution time in targeted therapy
- To be used for the **Theranostics approach**

Over the last years, several radionuclides have emerged:

- **β^+**: ^{64}Cu, ^{68}Ga, ^{89}Zr …
- **γ**: ^{203}Pb …
- **β^-**: ^{166}Ho, ^{177}Lu …
- **α**: ^{211}At, ^{212}Bi, ^{213}Bi, ^{223}Ra, ^{225}Ac ...
- **Auger**: ^{117m}Sn, ^{155}Tb
- **Theranostic**: ^{44}Sc/^{47}Sc, ^{64}Cu/^{67}Cu, ^{68}Ga/^{177}Lu …

- Diagnosis (γ, β^+)
  - SPECT, TEP — ^{99m}Tc, ^{18}F, ^{64}Cu — ***Detecnet (^{64}Cu)***
- Therapy (β^-, α, e_{Auger})
  - RIV — ^{117}Lu, ^{225}Ac — ***Pluvicto, Lutathera (^{177}Lu)***

Courtesy of A. Guetin

How can nuclear physics help?

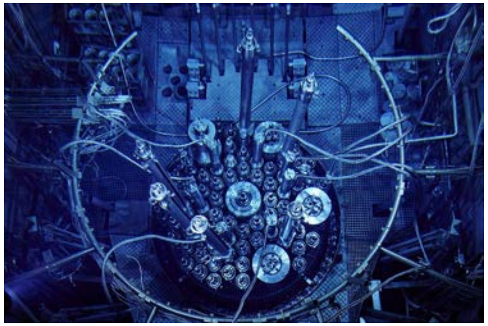
1. **Identify production route**

2. **Generate data to optimize production route**

3. **Proof of new concepts**

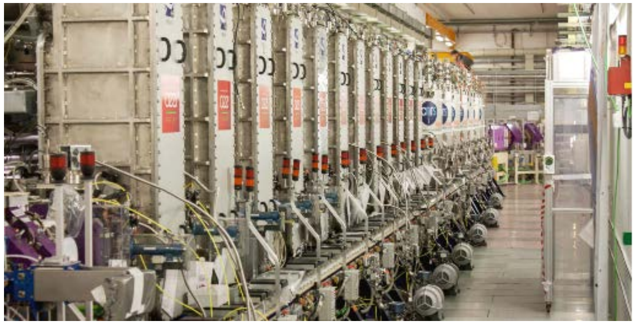
4. **Accompany preclinical and early phase clinical research**

5. **Generate Accurate and reliable sets of data to constrains Nuclear codes**



BR2 reactor @ SCK•CEN

C70XP @ ARRONAX



SPIRAL 2 @ GANIL

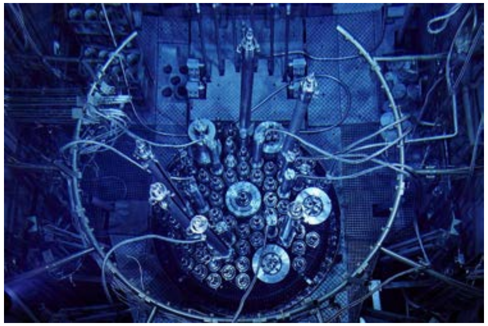
Astatine-211 as an example

Thanks to all REPARE collaborators : GANIL, Subatech, Arronax, LDM-TEP and CERN

and our Czech colleagues: J. Mrazek, E. Simeckova, V. Glagolev and R. Behal

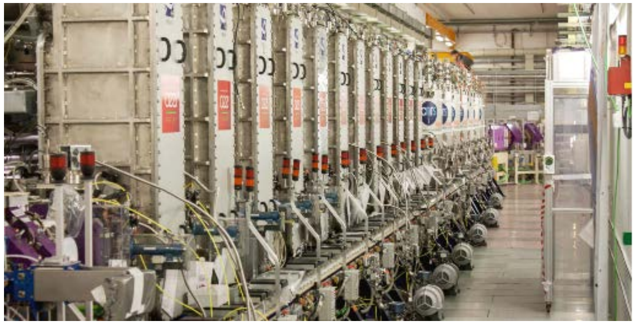
How can nuclear physics help?

1. **Identify production route**
2. **Generate data to optimize production route**
3. **Proof of new concepts**
4. **Accompany preclinical and early phase clinical research**
5. **Generate Accurate and reliable sets of data to constrains Nuclear codes**



BR2 reactor @ SCK•CEN

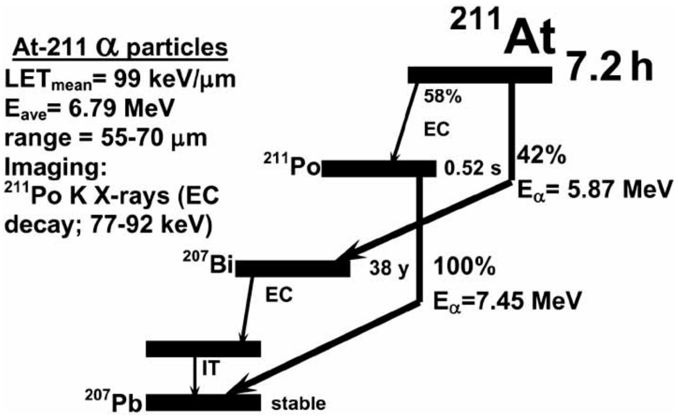
C70XP @ ARRONAX



SPIRAL 2 @ GANIL

Subatech ARRONAX afaq ISO 9001 Qualité AFNOR CERTIFICATION

^{211}At for α-targeted internal radiotherapy



1 alpha emitted by decay

$T_{1/2}$ = 7.2 h convenient for labeling

Direct production with alpha beam impinging a ^{209}Bi

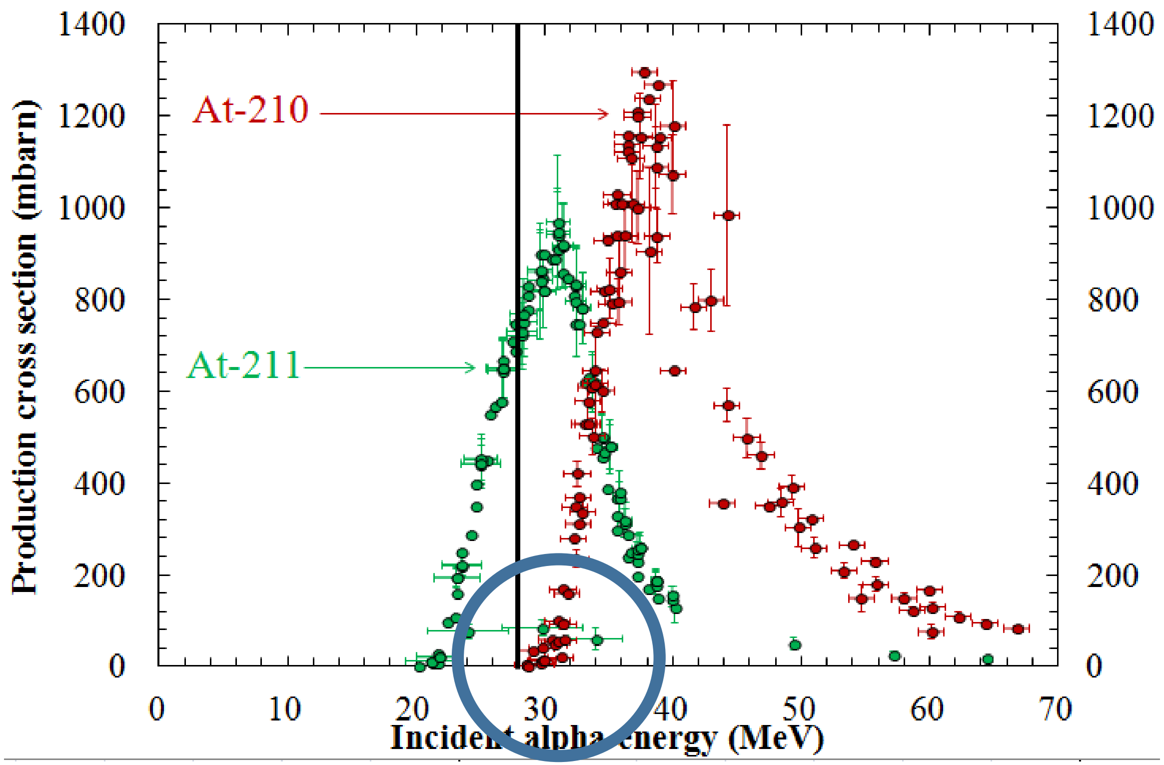
Bi-209(α,2n)At-211, 20.7 MeV

Potential co-production ^{210}At :

Bi-209(α,3n)At-210, 28.6 MeV ⚠

At-210, $T_{1/2}$ 8.1 h decays at 99.8% by EC to **Po-210** (138.4 days), a bone seeker

^{211}At: Direct production with alpha particles



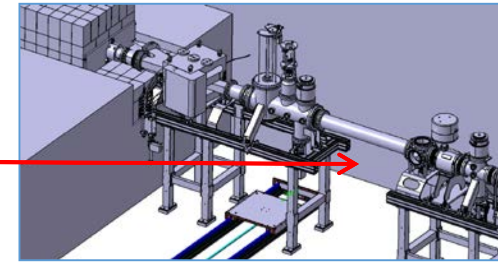
It is very important to have a good knowledge of the ^{210}At production cross section to optimize ^{211}At yield and limit contamination of ^{210}At

→ New measurements at NFS thanks to very precise beam energy and the activation station developed by our Czech colleagues

Measurement by activation technique

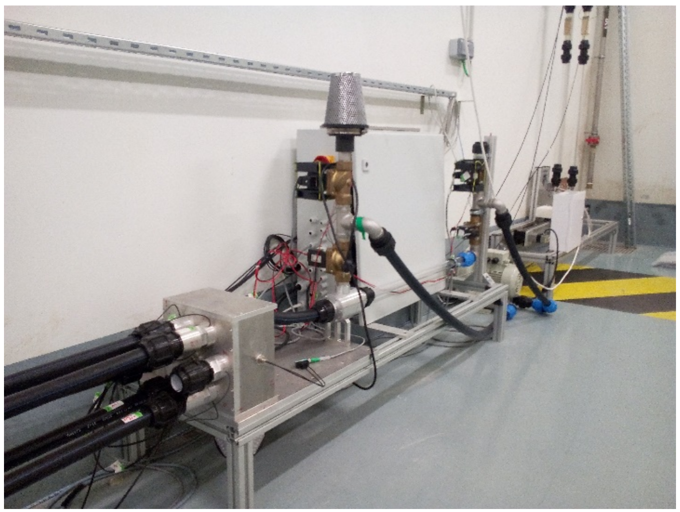
1- Irradiation of a sample in the converter room of NFS :

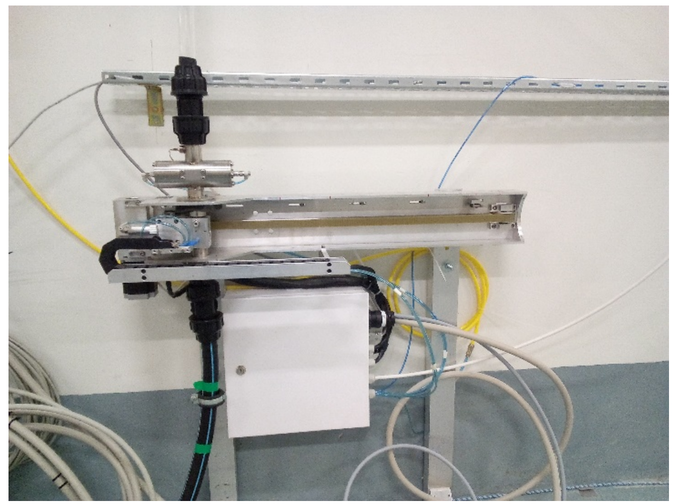
-with ions (in the irradiation station)

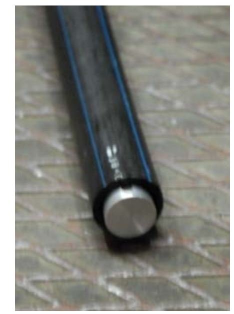


2- Transfer of the sample to the TOF room for activity measurement

Pneumatic transfer system





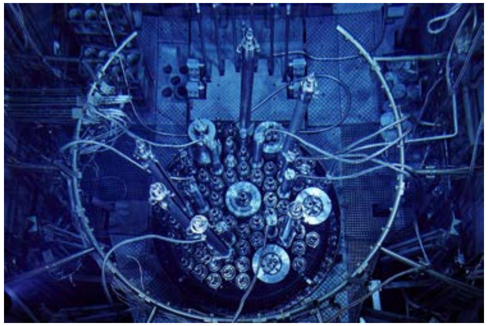


First experiment performed last September 2022
Energy beam step: 0.5 MeV
Measurements using Ge detectors on-line and then off line

Courtesy X. Ledoux

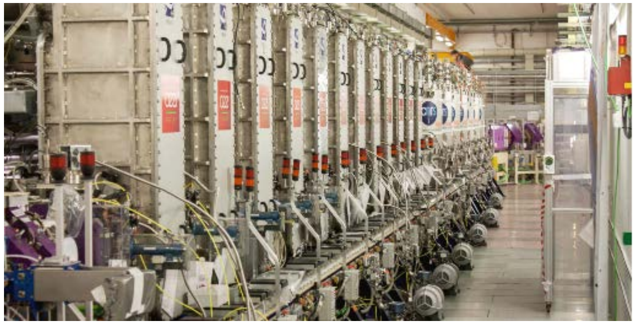
How can nuclear physics help?

1. **Identify production route**
2. **Generate data to optimize production route**
3. **Proof of new concepts**
4. **Accompany preclinical and early phase clinical research**
5. **Generate Accurate and reliable sets of data to constrains Nuclear codes**



BR2 reactor @ SCK•CEN

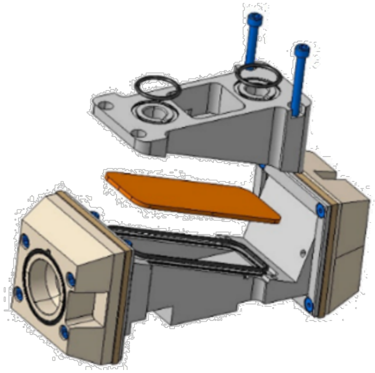
C70XP @ ARRONAX



SPIRAL 2 @ GANIL

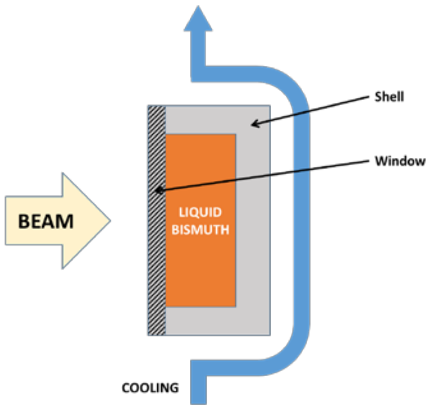
Proof of Concept

Current production uses solid targets :

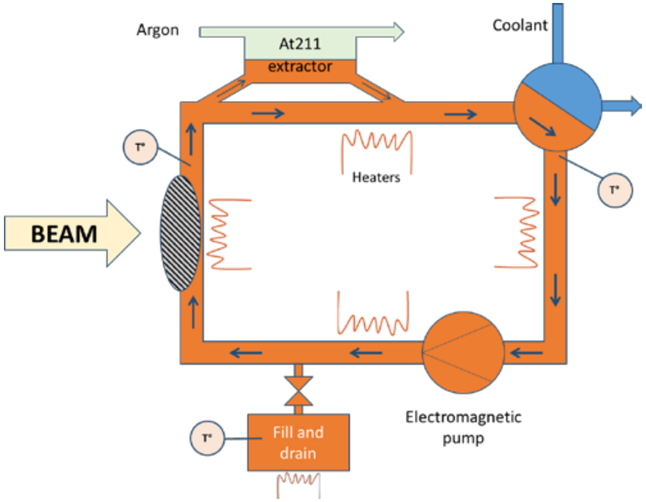


Bismuth has a low melting point (271°C) and astatine a low evaporation temperature (312°C). Possibility to use LBE (123.5°C)

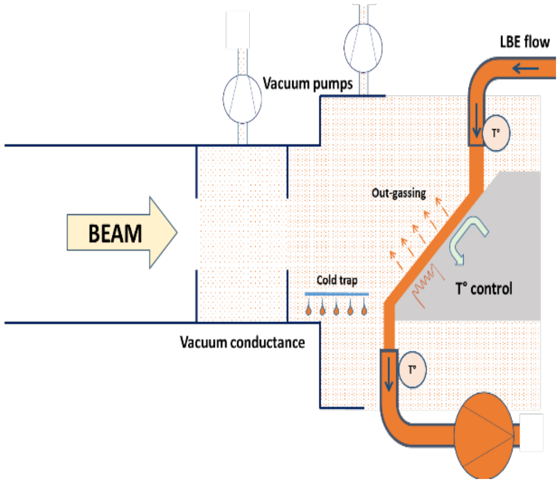
→ can we go for a liquid target? For on-line extraction?



Bismuth Capsule



LBE loop



Windowless LBE loop

Courtesy T. Bigourdan

Conclusion and way forward

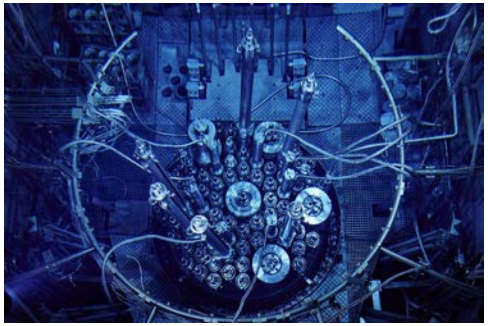
- **Physical limits** to At211 production through liquid bismuth target
  - **Windows** strongly limit the production rate: beam absorption and mechanical stress
  - **Window removal** compromises At211 retrieval (adsorption on metallic surface)
  - Bismuth **metallic loops** compromise At211 retrieval (?)
- **High power liquid target** dedicated installation?
  - Current concepts are showing physical limits
  - Only **30%** (loop) **to 2%** (flat capsule) of SPIRAL II's **3mAe** are used
  - Smaller local production units more adequate?
- Small scale **experiment** (capsule) will be conducted to:
  - Study At211 migration risks
  - Crosscheck computation
  - Demonstrate capsule concept's feasibility

Criteria	Bismuth Capsule	LBE loop	Windowless LBE loop	ARRONAX
Production	**	*	***	*
Maturity	***	**	*	*****
Exploitation	***	**	*	***
Cost	****	**	*	****
Integration	****	**	*	****

Courtesy T. Bigourdan

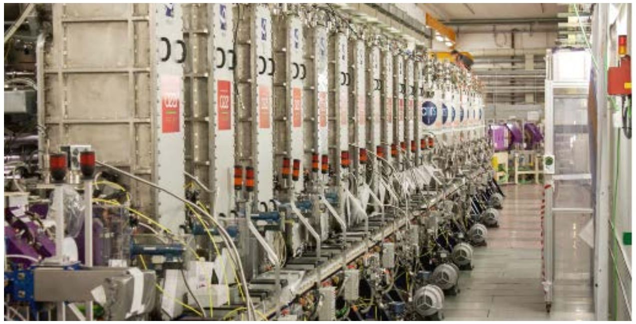
How can nuclear physics help?

1. **Identify production route**
2. **Generate data to optimize production route**
3. **Proof of new concepts**
4. **Accompany preclinical and early phase clinical research**
5. **Generate Accurate and reliable sets of data to constrains Nuclear codes**



BR2 reactor @ SCK•CEN

C70XP @ ARRONAX



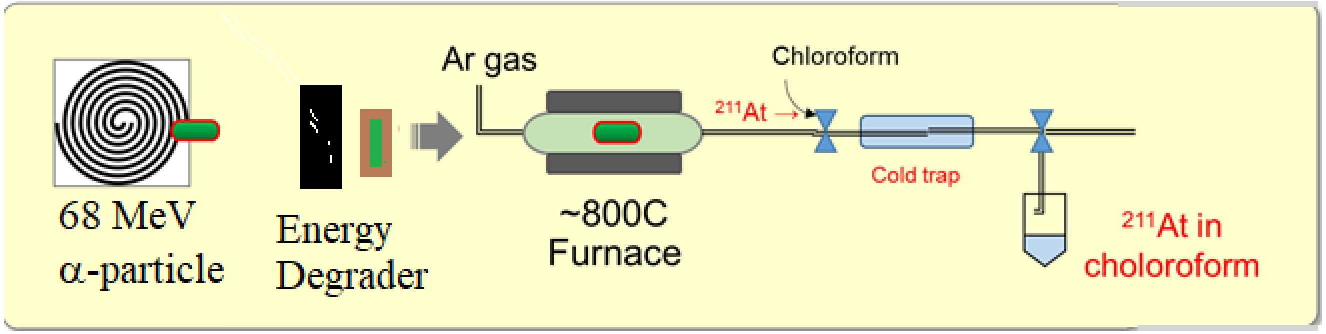
SPIRAL 2 @ GANIL

Basic and translational research

Astatine-211 production route used @Arronax:

$^{209}Bi + \alpha \rightarrow {}^{211}At + 2n$

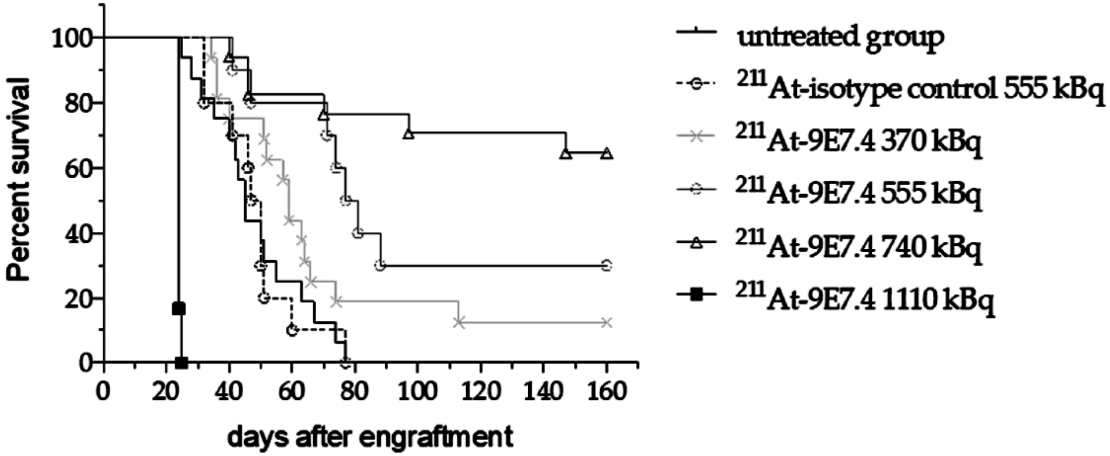
Production scheme:



We are producing 3-4 times a month At-211 (600 MBq-1.2GBq EOB)

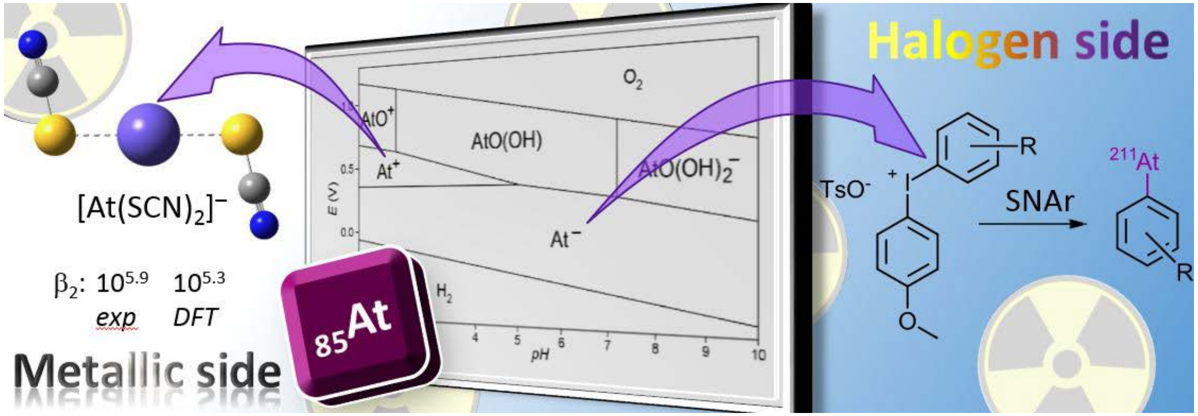
Astatine-211-labeled anti-mCD138 in mouse syngeneic multiple myeloma

Gouard S et al. Cancers (Basel). 2020 Sep 22;12(9):2721



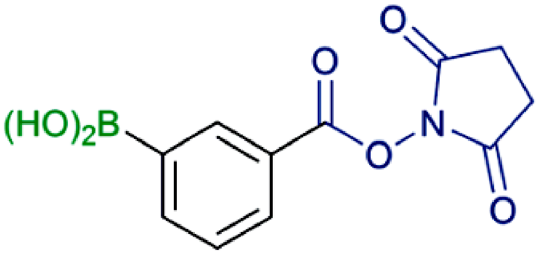
Subatech ARRONAX afaq ISO 9001 Qualité AFNOR CERTIFICATION

Basic and translational research



Chemical properties and quantum chemistry of astatine-211

Review: Guérard F et al. Acc Chem Res. 2021, 54, 16: 3264–3275

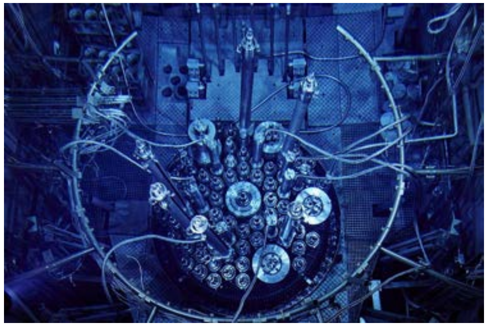


A new astatine-211 radiolabeling method based on boronic acids

Berdal M et al. Chem Sci. 2020 Nov 23;12(4):1458-1468

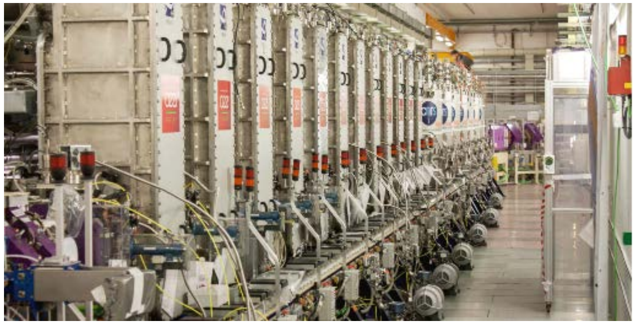
How can nuclear physics help?

1. **Identify production route**
2. **Generate data to optimize production route**
3. **Proof of new concepts**
4. **Accompany preclinical and early phase clinical research**
5. **Generate Accurate and reliable sets of data to constrains Nuclear codes**



BR2 reactor @ SCK•CEN

C70XP @ ARRONAX



SPIRAL 2 @ GANIL

Generate a coherent and accurate data sets

Proton induced reactions:

Ac-225 from Th-232(p,x)
Ra-223 from Th-232(p,x)
Fission fragment distribution from Th-232(p,x)
Cu-67, Ga-67, Ga-66 from Zn-68(p,x),
Cu-67 and Cu-64, Ga-67, Ga-66, Zn-65 and Zn-69m, from Zn-70(p,x)
Tb-149 ,Tb150, Tb151, Tb152, Tb153, Tb154, Tb154m2, Tb155, Tb156 from Gd-nat(p,x)
Monitor reactions on Ti, Ni and Cu
Sc-47,44mSc,44ScSc-48,46,43, K43,42 ,V-48, Cr-51,49,48 from V-nat(p,x)
Sc-47,44mSc,44Sc from Ti-48(p,x)

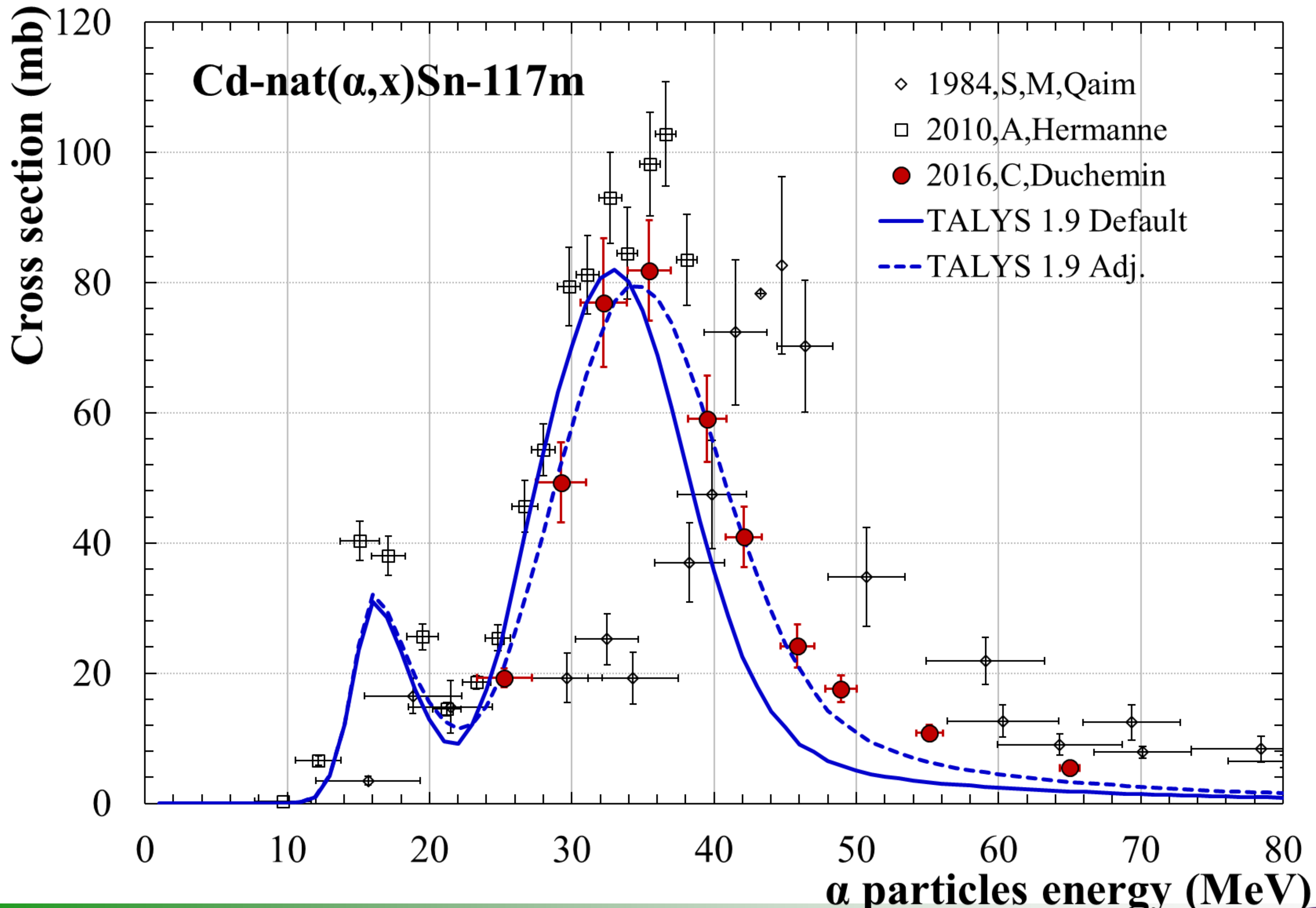
Alpha induced reactions:

Mo-99 New data set from Zr-96(α,n)
Sn-117m New data set from Cd-116(α,x)
Monitor reactions on Cu, Ti, Ni
Ru-97 New data set from Mo-nat(α,x)

Deuteron induced reactions:

Sc-44 New data set for Ca-44(d,x)
Tb-155 New data set for Gd-nat(d,x)
Re-186g New data set for W-186(d,x)
Th-226 New data set for Th-232(d,x)
Fission fragment distribution from Th-232(d,x)
Monitor reactions on Ti, Ni
Rh-105 New data set for Ru-104(d,x)
Hg-197m New data set for Au-197(d,x)
Cu-67 New data set for Zn-70(d,x)

Novel therapeutic and imaging nuclide



C. Duchemin et al, Appl Radiat Isot **115** (2016) **113-124**

Conclusions

Nuclear Physics can have an impact on translational research in Nuclear medicine by

- Defining proper production route to get high purity products
- Optimizing production
- Developing new targetry systems to help scale-up production
- Producing radionuclides to allow research at the preclinical and clinical level
- Collecting new data on different mechanisms (isomer states, fission, activation …) that will help constrain nuclear code (PHITS, Talys …)

Conclusions

For that purpose, it will be necessary to have :

- Access to ion beams: d, ^{3}He, ^{4}He and Li

Here some opportunities with alpha particle beams

- ✓ **Avoid** radioactive target material
  ^{211}At, ^{97}Ru
- ✓ **Access** to a higher cross section
  ^{43}Sc
- ✓ **Reuse** an existing process : targetry, chemistry
  ^{67}Cu
- ✓ **Facilitate** target manufacturing
  ^{117m}Sn
- ✓ **Use** a monoisotopic target
  ^{135}La

Conclusions

For that purpose, it will be necessary to have :

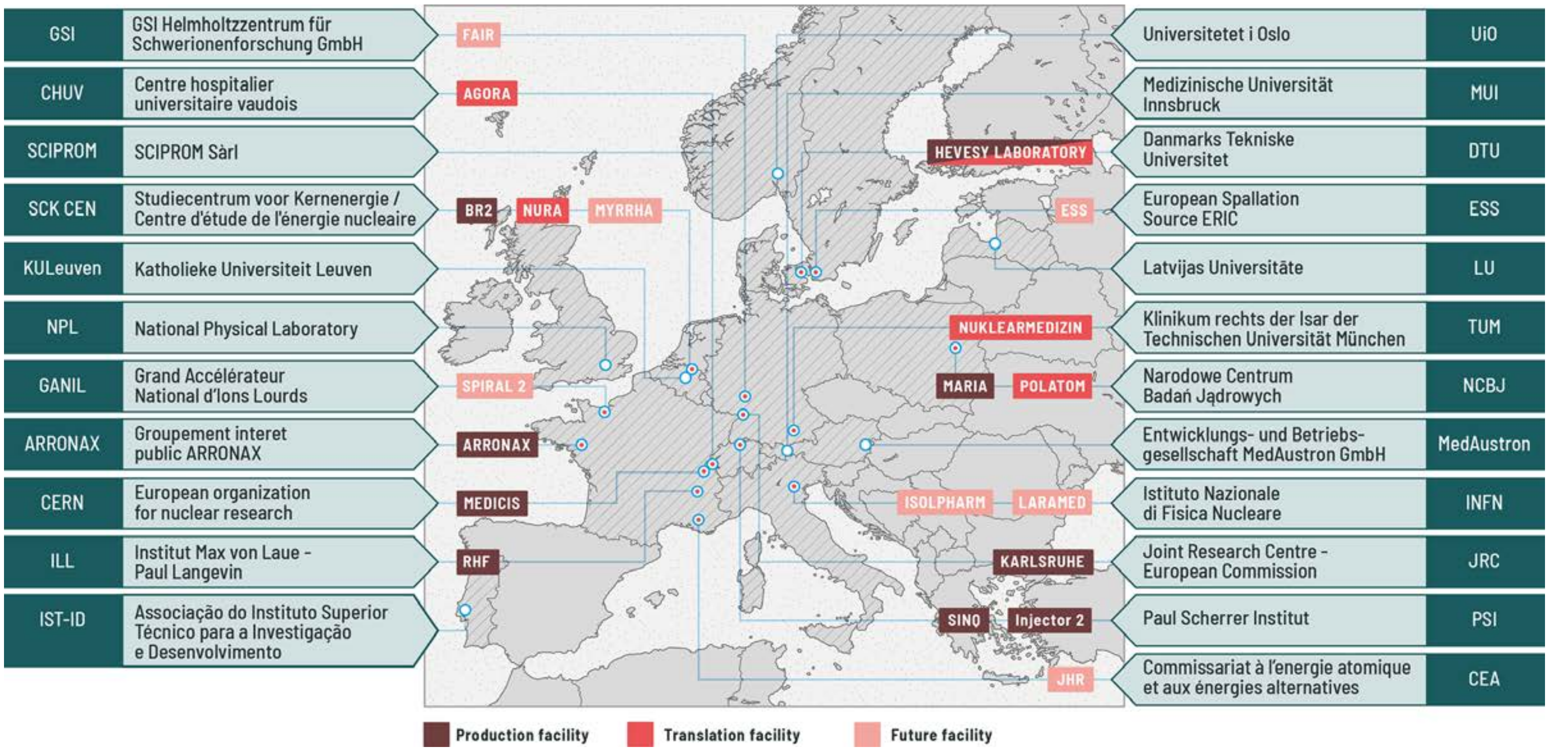
- Access to ion beams: **d, ^{3}He, ^{4}He and Li**
- Access to beam time for **cross section** measurements (Intensity of the order of 100nA), time depends on the desired uncertainties on energy
- Access, from time to time, to beam time to **test new concepts**
- Access to **regular beam time** to provide radionuclides to researcher for **translational research** (tens of µA for few hours regularly)

- Secondary intense neutron source may be interesting to look at

Projet INFRAIA PRISMAP (2021-2025)

Objectives (Leader : CERN)

- Provide access to new radionuclides and new purity grades for the medical research
- Create a common entry port and web interface to the starting research community
- Enhance clarity and regulatory procedures to enhance research with radiopharmaceuticals
- Improve the delivered radionuclide data and regulation, along with biomedical research capacity
- Ensure sustainability of PRISMAP on the long term



Sept 2022, our first call for projects

Isotope for free. Only cost for transportation to be paid

Stay in touch https://www.prismap.eu/

Thank you for your attention

The **ARRONAX** project is supported by:

the **Regional Council of Pays de la Loire**

the **Université de Nantes**

the **French government** (CNRS, INSERM)

the **European Union**.

This work has been, in part, supported by the FEDER EU program and grants from the French National Agency for Research noANR-11-EQPX-0004 and noANR-11-LABX-18-01 and noANR-16-IDEX-0007. Part of this work was performed within the ANR REPARE.