Production of non standard medical radionuclides

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on behalf of the REPARE collaboration
Radionuclides production for nuclear medicine

In Nuclear medicine, radionuclides are used:

- for **imaging and diagnosis** (X-ray, $\gamma$, $\beta^+$)
- for **therapy** ($\alpha$, $\beta^-$, Auger-e)

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

We need to adapt $T_{1/2}$ to the distribution time of the vector molecule.
Theranostics

It is a **treatment strategy** that combines **therapeutics** with **diagnostics**.

- **Localized lesions**
- Define the **biodistribution** of a therapeutic agent to anticipate its effect
- **Select patients which are expected to respond 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

\[ ^{225} \text{Ac} - \text{PSMA-617} : \]

\begin{figure}
\centering
\includegraphics[width=\textwidth]{image.png}
\caption{\textsuperscript{68}Ga-PSMA-11 PET/CT scans of patient A. Pretherapeutic tumor spread (A), restaging 2 mo after third cycle of \textsuperscript{225}Ac-PSMA-617 (B), and restaging 2 mo after one additional consolidation therapy (C).}
\end{figure}

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:**

- $\beta^+$: $^{64}$Cu, $^{68}$Ga, $^{89}$Zr …
- $\gamma$: $^{203}$Pb …
- $\beta^-$: $^{166}$Ho, $^{177}$Lu …
- $\alpha$: $^{211}$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 ($\gamma$, $\beta^+$) SPECT, TEP $^{99m}$Tc, $^{18}$F, $^{64}$Cu **Detecnet ($^{64}$Cu)**
- Therapy ($\beta^-$, $\alpha$, $e_{\text{Auger}}$) RIV $^{117}$Lu, $^{225}$Ac **Pluvicto, Lutathera ($^{177}$Lu)**
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
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$^{211}\text{At}$ for $\alpha$-targeted internal radiotherapy

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

$\text{Bi-209}(\alpha,2n)\text{At-211}$, 20.7 MeV

Potential co-production $^{210}\text{At}$:

$\text{Bi-209}(\alpha,3n)\text{At-210}$, 28.6 MeV

1 alpha emitted by decay

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

$\text{At-210}$, $T_{1/2}$ 8.1 h decays at 99.8% by EC to $\text{Po-210}$ (138.4 days), a bone seeker
It is very important to have a good knowledge of the $^{210}\text{At}$ production cross section to optimize $^{211}\text{At}$ yield and limit contamination of $^{210}\text{At}$.

➔ 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
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BR2 reactor @ SCK•CEN  C70XP @ ARRONAX  SPIRAL 2 @ GANIL
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?
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

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Bismuth Capsule</th>
<th>LBE loop</th>
<th>Windowless LBE loop</th>
<th>ARRONAX</th>
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<tbody>
<tr>
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<td>Integration</td>
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*Courtesy T. Bigourdan*
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BR2 reactor @ SCK•CEN
C70XP @ ARRONAX
SPIRAL 2 @ GANIL
Basic and translational research

Astatine-211 production route used @Arronax:

\[ ^{209}\text{Bi} + \alpha \rightarrow ^{211}\text{At} + 2n \]

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
Basic and translational research

Chemical properties and quantum chemistry of astatine-211


A new astatine-211 radiolabeling method based on boronic acids

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, 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

Cd-nat(α,x)Sn-117m

Cross section (mb)

α particles energy (MeV)
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 \(\mu\)A 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/](https://www.prismap.eu/)
Thank you for your attention

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