Isotope production for medical applications: what can be done?

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on behalf of the Arronax team
and Prisma@subatech
Radionuclides production for nuclear medicine

Nuclear medicine is a medical specialty which deals with radionuclide used as open sources (30 Millions procedures per year - 2013).

- *Highly penetrating* radiation are used for imaging and diagnosis (X, $\gamma$, $\beta^+$)
- *Low penetrating* radiation are used for therapy ($\alpha$, $\beta^-$, e-Auger)

In some cases, the radionuclide can be injected directly:

- Iodine-131 goes directly to the thyroid
- Rubidium-82 is accumulating in the heart
- Radium-223 goes to the bones.

In most cases, a vector molecule is needed to target the cells of interest.
Peptides and Antibodies can be used as vector for either imaging and therapy

There is often a limited number of receptor sites on a cell
Targeting allows to find the right guy in a complex environment

antibody anti-« red and white strips »
Targeting allows to find the right guy in a complex environment
Targeting allows to find the right guy in a complex environment

Changing vector, we can be more specific
Every patient is unique

There is differences between each person:

- Some are straightforward: Age, Sex, Size, Weight, ...

- Some others are less simple as biological and biochemical constants, genetic characteristics, ...

There is a need for personalized treatment
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 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**
Which radionuclides?

- **Radionuclides of the same element** (\(^{44}\text{Sc}/^{47}\text{Sc}, {^{64}}\text{Cu}/^{67}\text{Cu}, {^{124}}\text{I}/^{131}\text{I}, \text{Tb} \ldots \))
- **Radionuclides** with comparable properties (\(^{68}\text{Ga}/^{177}\text{Lu}, {^{99m}}\text{Tc}/^{188}\text{Re}\))
- **Radionuclide** with radiations for both imaging and therapy (\(^{117m}\text{Sn}\))
$^{177}$Lu-radioligand therapy
of advanced prostate cancer

Nuclear medicine needs radionuclides

- with different **decay radiations**:
  - imaging / therapy
  - short range High LET vs long range 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
  - pair of isotopes
- With an appropriate purity

Nuclear Physics can help by developing **efficient large scale** production of **high purity** radionuclides (innovative or not)
Its unique characteristics

Main characteristics:
- Multi-particles
- High energy
- High intensity

<table>
<thead>
<tr>
<th>Beam</th>
<th>Accelerated particles</th>
<th>Energy range (MeV)</th>
<th>Intensity (eµA)</th>
<th>Dual beam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proton</td>
<td>H-</td>
<td>30-70</td>
<td>&lt;375</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>HH+</td>
<td>17</td>
<td>&lt;50</td>
<td>No</td>
</tr>
<tr>
<td>Deuteron</td>
<td>D-</td>
<td>15-35</td>
<td>&lt;50</td>
<td>Yes</td>
</tr>
<tr>
<td>Alpha</td>
<td>He++</td>
<td>68</td>
<td>&lt;70</td>
<td>No</td>
</tr>
</tbody>
</table>
What can we do?

High purity:
- Nuclear data
- Allow to estimate production yield
- Allow to define level of contaminants
- Allow to adjust energy range of interest

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

Energy range of interest:
[ 20 MeV - 28.3 MeV ]
Cu-67 production

It is a β- emitter with 185 keV γ-line

$T_{1/2} = 61.83$ h

It has a β+ emitter partner: $^{64}_{28}$Cu $- T_{1/2} = 12.7$ h

Targeted therapy with β-, SPECT imaging

Central production + continental delivery

Theranostic pair: $^{64}_{28}$Cu/$^{67}_{28}$Cu

Production routes with charged particles:

- $^{68}_{30}$Zn(p,2p)
  used at BNL to make $^{67}_{28}$Cu available part of the year
  used at PSI in the past
- $^{70}_{30}$Zn(p,α)
- $^{68}_{30}$Zn(d,x)
- $^{70}_{30}$Zn(d,x)
- $^{64}_{28}$Ni(α,p)
  Used in the USA

Looking to cross section will allow to determine the best ones

IAEA current CRP on Cu-67
Cu-67 production

New cross section dataset for $^{70}\text{Zn}(d,x)^{67}\text{Cu}$

Cross section is 2 more important than with the proton route
Code calculations fail to reproduce the data
→ Our data help improve predictions
What can we do?

High purity:
- Nuclear data
- Mass separation technique to get high purity products

Laser resonance ionization coupled to mass separation will increase product purity

Arronax is part of the MEDICIS collaboration (CERN)
Resonant laser ionization & mass separation: cold experiments

Experiments performed for Tb and lanthanides

Experiments performed at JGU Mainz (LARISSA team)

High efficiency obtained for lanthanides using resonant laser ionization

Proof of principle should be performed as soon as MELISSA laboratory@CERN will be ready
Radionuclides production as part of the MEDICIS@CERN project
How to survive the CERN long shutdown?

**Target**

**Projectile**

Mass Separation

Er-169 produced @ILL
Terbium produced @Arronax

Experiment already performed without laser ionization (2018 and 2019)
Soon laser ON

**R. Formento et al, NIMB (2019)**
https://doi.org/10.1016/j.nimb.2019.04.022
What can we do?

High purity:
- Nuclear data
- Mass separation technique to get high purity products

Innovative radionuclides
- New isotopes for new concept (44Sc, Tb quadruplet, $\alpha$ emitters, …)


$\alpha$-emitters are giving good results
Main α-emitters of medical interest

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Half-life (h)</th>
<th># of alpha particles / decay</th>
<th>$E_\gamma$ (keV)</th>
<th>Branching Ratio (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tb-149</td>
<td>4.1 h</td>
<td>0.17 (β and ε)</td>
<td>165</td>
<td>26</td>
</tr>
<tr>
<td>At-211</td>
<td>7.2 h</td>
<td>1</td>
<td>79</td>
<td>21</td>
</tr>
<tr>
<td>Bi-212</td>
<td>1 h</td>
<td>1 (β)</td>
<td>727</td>
<td>7</td>
</tr>
<tr>
<td>Bi-213</td>
<td>45 m</td>
<td>1 (2β)</td>
<td>440</td>
<td>26</td>
</tr>
<tr>
<td>Ra-223</td>
<td>11.4 d</td>
<td>4 (2β)</td>
<td>269</td>
<td>14</td>
</tr>
<tr>
<td>Ac-225</td>
<td>10 d</td>
<td>4 (2β)</td>
<td>100</td>
<td>1</td>
</tr>
<tr>
<td>Th-226</td>
<td>31 m</td>
<td>4</td>
<td>111</td>
<td>3</td>
</tr>
<tr>
<td>Th-227</td>
<td>18.7 d</td>
<td>5 (2β)</td>
<td>256</td>
<td>7</td>
</tr>
</tbody>
</table>

A limited number of potential candidates

Astatine-211 is our choice
At-211 characteristics

Nearly ideal alpha emitter:

- $T_{1/2}$: not too short nor too long (7.2 h) → suitable for targeting biomolecules
- 2 decay branches leading to the emission of one alpha particle
- Available from accelerator production (28 MeV) → easy to scale-up
Use of high LET particles: Astine-211

Production route: $^{209}\text{Bi} + \alpha \rightarrow ^{211}\text{At} + 2n$

Target preparation (deposition under vacuum)

Dry extraction method

Astatine output: few minutes – extraction time around $\approx 2$ h – Extraction yield: $>80\%$
What can we do?

High purity:
- Nuclear data
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Innovative radionuclides
- New isotopes for new concept (44Sc, Tb quadruplet, α emitters, …)

Large scale
- Highly intense beams: Targetry, beam diagnostics, activation and maintenance issues
ANR Repare (granted July 2019)

REPARE: research and developments for the Production of innovative radioelements

Partners: GANIL (Leader), Subatech, GIP Arronax, LDM-TEP, CERN

Duration: 4 years

Production of Astatine-211

• Cross section measurements of alpha and lithium induced reaction on Bi and Pb
• Solid target technology
• Liquid target with on line extraction
• Indirect production $^{211}\text{Rn} \rightarrow ^{211}\text{At}$ using Li beam
The principle of the liquid target with on-line extraction

- Niobium beam window
- Beam tube
- Beam collimators
- Condensers (mitigate leak propagation)

Gaz plenum

Neutral gaz

Flacon final

Astatine Condenser -60°C

Bismuth target, 300 to 600°C. Buoyancy flow induce by beam and may be assisted by heaters. Long live target, with a At extraction in target, several options are possible and will be explored during design.

Temperature control. (up to 600°C) Overall pre heating and heat removal during beam. Design based on heat losses / heaters equilibrium. May be conduction/convection external drain.
What can we do?

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**Innovative radionuclides**
- New isotopes for new concept (44Sc, Tb quadruplet, α emitters, …)

**Large scale**
- Highly intense beams: Targetry, beam diagnostics, activation and maintenance issues
- New developments in accelerator: electron Linac and photoreaction
Isotopes of interest:

$^{99}$Mo, $^{67}$Cu, $^{225}$Ac, …
What can we do?

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Large scale
- Highly intense beams: Targetry, beam diagnostics, activation and maintenance issues
- New developments in accelerator: linac or compact cyclotrons

Efficient
- Neutron production without reactor
A Neutron source with industrial capabilities @ Arronax

Partnership: AAA, Nanoh, ARRONAX, SUBATECH, vetAgro, INSA Lyon,

350µA, 70 MeV protons $\rightarrow 10^{12}$ n/s
Our neutron Activator

Loading/unloading station

Partnership: AAA, Nanoh, ARRONAX, SUBATECH, vetAgro, INSA Lyon,
What can we do?

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- New isotopes for new concept (44Sc, Tb quadruplet, α emitters, …)

Large scale
- Highly intense beams: Targetry, beam diagnostics, activation and maintenance issues
- New developments in accelerator: linac or compact cyclotrons

Efficient
- Neutron production without reactor
- Alternative production route for established radionuclides
Re-186 ($T_{1/2} = 3.7 \text{ d} - \beta$- emitter)

Deuteron is 3 times more efficient than proton

C. Duchemin et al, Appl. Rad. And Isot. 97 (2015) 52
Conclusions

Nuclear Physics can do a lot for radionuclide production

However, **producing the radionuclide is just the first step**, someone has to use it. For that you need:

1. Produce it on a **regular basis** with the appropriate **quality** and **quantity**

2. Insure that this production capability will stay **available for several years** (small animals studies and clinical trials take time)

3. Produce it as an **Active Pharmaceutical Ingredient**
   - A quality assurance program helps
Thank you for your attention

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