Neutron capture produced radioisotopes for diagnostics and therapy - opportunities and challenges

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Forschungsneutronenquelle Heinz Maier-Leibnitz & ITG
OUTLINE

Radio isotopes for diagnostic and therapy by neutron capture

Lu-177, a combination of therapy by high LET $\beta$-irradiation and diagnostic by low energy $\gamma$-emission

Ho-166 microspheres for the radioembolization of liver tumors

New ideas for the working horse in nuclear medicine Mo-99/Tc-99m

Even higher LET by $\alpha$-emitter – an outlook
Radioisotopes for diagnostic and therapy

Activation by n-capture reaction

\[ A = N \sigma_{\text{abs}} \phi (1-e^{-t/\tau}) \]

\[ \sigma_{\text{abs}} \propto \lambda \]

\[ \phi = \text{high because small } \tau \]

saturation for \( t \geq 6 \tau \)

\[ \tau = \text{short for application, long for breeding} \]
Top view into the reactor pool

Future Mo-99 production

Rabbit system (Ho-166)

Capsule irradiation (Lu-177 n.c.a.)
## Capsule Irradiation

<table>
<thead>
<tr>
<th>Position</th>
<th>Flux$_{\text{thermal}}$ [cm$^{-2}$s$^{-1}$]</th>
<th>Flux$_{\text{epithermal}}$ [cm$^{-2}$s$^{-1}$]</th>
<th>Flux$_{\text{fast}}$ [cm$^{-2}$s$^{-1}$]</th>
</tr>
</thead>
<tbody>
<tr>
<td>KBA 1-1</td>
<td>1.3*10$^{14}$</td>
<td>2.6*10$^{11}$</td>
<td>3.9*10$^{11}$</td>
</tr>
<tr>
<td>KBA 1-2</td>
<td>9.9*10$^{13}$</td>
<td>9.9*10$^{10}$</td>
<td>2.0*10$^{11}$</td>
</tr>
<tr>
<td>KBA 2-1</td>
<td>1.1*10$^{14}$</td>
<td>7.5*10$^{10}$</td>
<td>2.1*10$^{11}$</td>
</tr>
<tr>
<td>KBA 2-2</td>
<td>7.7*10$^{13}$</td>
<td>3.9*10$^{10}$</td>
<td>1.0*10$^{11}$</td>
</tr>
</tbody>
</table>

## Rabbit System

<table>
<thead>
<tr>
<th>Position</th>
<th>Flux$_{\text{thermal}}$ [cm$^{-2}$s$^{-1}$]</th>
<th>Flux$_{\text{epithermal}}$ [cm$^{-2}$s$^{-1}$]</th>
<th>Flux$_{\text{fast}}$ [cm$^{-2}$s$^{-1}$]</th>
</tr>
</thead>
<tbody>
<tr>
<td>RPA-1</td>
<td>3.6*10$^{13}$</td>
<td>6.7*10$^{9}$</td>
<td>2.0*10$^{9}$</td>
</tr>
<tr>
<td>RPA-2</td>
<td>1.5*10$^{13}$</td>
<td>3.2*10$^{9}$</td>
<td>4.1*10$^{8}$</td>
</tr>
<tr>
<td>RPA-3</td>
<td>4.8*10$^{12}$</td>
<td>7.6*10$^{8}$</td>
<td>7.2*10$^{7}$</td>
</tr>
<tr>
<td>RPA-4</td>
<td>7.3*10$^{13}$</td>
<td>2.4*10$^{10}$</td>
<td>5.6*10$^{10}$</td>
</tr>
<tr>
<td>RPA-5</td>
<td>3.9*10$^{13}$</td>
<td>1.2*10$^{10}$</td>
<td>5.9*10$^{9}$</td>
</tr>
<tr>
<td>RPA-6</td>
<td>7.1*10$^{12}$</td>
<td>1.2*10$^{9}$</td>
<td>1.5*10$^{8}$</td>
</tr>
</tbody>
</table>

## Mo-99 Production Process (max 16 Targets)

<table>
<thead>
<tr>
<th>Position</th>
<th>Flux$_{\text{thermal}}$ [cm$^{-2}$s$^{-1}$]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>Ca. 2.0*10$^{14}$</td>
</tr>
</tbody>
</table>
# Comparison of Different Therapeutic Radioisotopes

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Max. Particle Energy</th>
<th>Range in Tissue</th>
<th>Interaction</th>
<th>Nuclide Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>High energy β</td>
<td>~2</td>
<td>~12.000</td>
<td>Cross</td>
<td>166Ho 90Y</td>
</tr>
<tr>
<td>Low energy β</td>
<td>~0.5</td>
<td>~2.000</td>
<td></td>
<td>177Lu 47Sc</td>
</tr>
<tr>
<td>Auger electrons</td>
<td>~0.02</td>
<td>&lt;1</td>
<td>Single cell</td>
<td>161Tb</td>
</tr>
<tr>
<td>Alpha particles</td>
<td>~5</td>
<td>~45</td>
<td></td>
<td>225Ac 213Bi</td>
</tr>
</tbody>
</table>

Produced at FRM II
Ways to produce Lu-177

<table>
<thead>
<tr>
<th>Hf 176 5.206</th>
<th>Hf 177 18.60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lu 175 97.41</td>
<td>Lu 176 2.59</td>
</tr>
<tr>
<td>Yb 174 31.8</td>
<td>Yb 175 4.2 d</td>
</tr>
</tbody>
</table>

- Lu-177 is a low energy
  - $\beta^-$-emitter (0.5 MeV $\rightarrow$ therapy) &
  - $\gamma$-emitter (0.2 MeV $\rightarrow$ molecular imaging)
with short live time (6.7 days)
- Together, FRM II, the company ITM & Radiochemistry TUM succeeded in producing ultrapure Lu-177 in a **unique** process,
- This so called **no carrier added** Lu-177 (n.c.a.). is completely free of impurities by other Lu isotopes
- **Strict avoidance of long-living** Lu-177m allows less waste disposal

production
desired side reactiontherapeutic use
Decay Scheme of Lu-177

Emission of electron (100%, $E_{\text{max}} \approx 0.5$ MeV):
- Range in tissue short (few mm)
- High LET
- Suited for radio nuclide therapy

Emission of $\gamma$'s ($\approx 10\%$, $E=208$ keV):
- Penetrates tissue
- Leave the body and can be detected from outside by means of szintigraphy and SPECT
- Suited for therapy-monitoring (incl. dosimetry)
Key – lock principle of targeted radiotherapy

Example: Radionuclide therapy
(Lu-177-PSMA)
Lu-177-DOTATATE therapy of neuroendocrine tumor (NET)

Pre-therapeutic PET/CT with $^{68}$Ga-DOTATATE

Post-therapeutic PET/CT with $^{68}$Ga-DOTATATE

Patient, 60 y, with metastatic pancreatic NET

Therapy with $^{177}$Lu-DOTATATE (2 cycles à 7400 MBq)
Lu-177-DOTATATE Therapy of neuroendocrine tumors (NET)

Phase 3 Study of Lu-177-DOTATATE (NETTER1-trial, N=229)
Patient with metastatic from prostate cancer (mCRPC)

4 therapy cycles; 6 Gbq Lu-177-PSMA/cycle

8/2015
Ga-68-PSMA PETCT
Prior to
Lu-177-PSMA therapy
PSA: 453 ng/ml

2/2016
Ga-68-PSMA PETCT
Two therapy cycles completed:
Lu-177-PSMA
PSA: 1,77 ng/ml

7/2016
Ga-68-PSMA PETCT
Four therapy cycles completed:
Lu-177-PSMA
PSA: 0,85 ng/ml
Patient with metastatic prostate cancer (mCRPC)

- Therapy of a patient with prostate cancer with Lu-177 n.c.a. linked with
  - Bisphosphonate
    → Imaging
    Bone metastases
  - Specific molecule for the prostate specific membrane antigen (PSMA)
    → Imaging
    Metastases of tissue

- Diagnosis (PET/CT)
  with Ga-68

- 2 Treatments with Lu-177 n.c.a.
  with 4 – 5 GBq/Dos each

→ Lu-177-PSMA as a new option for therapy with huge success
Patient with metastasias from Prostatacarzinoma (mCRPC)

male, 77 years, 4 therapy cycles à 6 GBq Lu-177-PSMA
### Ho-166 microspheres for the radioembolization of liver tumors

<table>
<thead>
<tr>
<th>Production route</th>
<th>Ho-165(100%) (n,γ) → Ho-166</th>
</tr>
</thead>
<tbody>
<tr>
<td>Material</td>
<td>PLLA microspheres with Holmium-166</td>
</tr>
<tr>
<td>Mean diameter (µm)</td>
<td>30 (equal to diameter of the hepatic artery)</td>
</tr>
<tr>
<td>Therapeutic β-emission</td>
<td>1850 keV (50.0%) 1770 keV (48.7%)</td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>26.8</td>
</tr>
<tr>
<td>Patient dose (GBq)</td>
<td>2-12</td>
</tr>
</tbody>
</table>
Irradiation using the Rabbit System

Requirements to be met:

- High accuracy with respect to Ho-166 target activity
- Low heat load to microspheres
- Low fast neutron flux density to guarantee mechanical integrity of microspheres.
- Just-in-time delivery is crucial
Blood source for liver:
- 70% portal vein
- 30% hepatic artery

Blood source for tumor:
- 99% hepatic artery
Diagnostics: Most common used isotope Mo-99/Tc-99m

- Sustainable supply with Mo-99 is mandatory for millions of patients worldwide
  - → 30 mio examinations per year
    - Investigation of thyroid function
    - Diagnosis of diseases of
      - lungs
      - heart
      - liver,
      - skeletal apparatus, etc.

Bone scintigraphy of an ankle joint by means of Tc-99m
- bright areas show an abnormally increased bone metabolism indicating an inflammation

- Most efficient and mostly used method to produce Molybdenum-99 is by irradiation of U-235 targets

\[ ^{235}\text{U} \xrightarrow{(n,f)} ^{99}\text{Mo} \xrightarrow{66\text{~h}} ^{99\text{m}}\text{Tc} \xrightarrow{6\text{~h}} ^{99}\text{Tc} \]

Major organ systems imaged with Tc-99m-based radiopharmaceuticals
Conversion from HEU to LEU targets increases liquid radioactive waste volume by 200% and decreases Mo-99 production efficiency to 50%.

**Solution: Dry-chemical separation process**

Irradiated target 0.1 wt% Mo-99 → Cladding separation → Fluorination → Physical pre-separation → Chemical separation → MoO$_4^{2-}$

Fluorine radicals from NF$_3$ plasma
Chemical Separation Step – liquid SO$_2$ or supercritical CO

Mixture of UF$_6$ and MoF$_6$ in SO$_2$ solution

Solid UF$_6$ (green) precipitate; MoF$_6$ still in SO$_2$ solution

Distilled mixture of MoF$_6$ and SO$_2$

**Ratios before separation**

<table>
<thead>
<tr>
<th>Mo</th>
<th>U</th>
</tr>
</thead>
<tbody>
<tr>
<td>62.1%</td>
<td>37.9%</td>
</tr>
</tbody>
</table>

**Ratios after separation**

<table>
<thead>
<tr>
<th>Mo</th>
<th>U</th>
</tr>
</thead>
<tbody>
<tr>
<td>100.0%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

**Ratios before separation**

<table>
<thead>
<tr>
<th>Mo</th>
<th>U</th>
</tr>
</thead>
<tbody>
<tr>
<td>21.9%</td>
<td>78.1%</td>
</tr>
</tbody>
</table>

**Ratios after separation**

<table>
<thead>
<tr>
<th>Mo</th>
<th>U</th>
</tr>
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<tbody>
<tr>
<td>71.1%</td>
<td>28.9%</td>
</tr>
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</table>

Increased separation efficiency by cascading
Even higher LET by Ac-225 α-emitter – an outlook

α-particle, highest LET

\[ E_\alpha = 5 \ E_\beta, \ m_\alpha = 8000 \ m_\beta, \]
penetration depth in tissue = 50 \( \mu \text{m} \) = cell diameter

possible production:
Th-232(100%)(n,\gamma) \rightarrow \text{Th-232} \rightarrow \text{Th(233)} \rightarrow \text{Th(229)} \rightarrow \text{Ac(225)}

available from wapon production

→ Similar targeted Therapy like Lu-77,
→ only the cancerous cell is irradiated,
→ today, several clinical studies
Neutrons for Medicine at FRM II

- Tumor therapy with fast neutrons
- Production of radioisotopes:
  - Lu-177,
  - Ho-166,
  - Tb-161,
  - Re-188,
  - in future: Mo-99/Tc-99m
- For therapy and diagnostics of tumors
- Radiopharmaceutical industry (ITM/ITG) on-site FRM II