MOLECULAR TARGETING WITH RADIOISOTOPES: APPLICATION OF LASER-DRIVEN ISOTOPIC PRODUCTION

Dana Niculae, PhD
Horia Hulubei National Institute for Physics and Nuclear Engineering, IFIN-HH, Romania
overview

- (Some) statistics about use of radioisotopes in nuclear medicine
- What are the needs of modern medicine?
- Examples of the use of medical radioisotopes
- Emerging radioisotopes and production routes
- Estimates of the production of radioisotopes at ELI-NP
The number of requests by both patients and doctors for state-of-the-art nuclear medical imaging procedures has increased seven fold in the last 25 years.

Computed X-ray tomography (CT) scans and nuclear medicine contribute 36% of the total radiation exposure and 75% of the medical exposure to the US population, average total yearly radiation exposure had increased from 3.6 mSv to 6.2 mSv per year since the early 1980s due to medical-related procedures. (Report of the National Council on Radiation Protection and Measurements, 2009)
• Over 10,000 hospitals worldwide use radioisotopes in medicine, and about 90% of the procedures are for diagnosis.

• The most common radioisotope used in diagnosis is Tc-99m, accounting for about 80% of all nuclear medicine procedures.

• Over 40 million nuclear medicine procedures are performed each year, and demand for radioisotopes is increasing at up to 5% annually.

• In developed countries (26% of world population) the frequency of diagnostic nuclear medicine is 1.9% per year. In the USA there are over 20 million nuclear medicine procedures per year among 311 million people, and in Europe about 10 million among 500 million people.

• The global radioisotope market was valued at $4.8 billion in 2012, with medical radioisotopes accounting for about 80% of this, and is poised to reach about $8 billion by 2017. North America is the dominant market for diagnostic radioisotopes with close to half of the market share, while Europe accounts for about 20%.

Estimates of worldwide use (per 100,000 people) of nuclear cardiology procedures.


(c) Copyright 2014 SNMMI; all rights reserved
Breakdown of diagnostic imaging procedures

Composition of Nuclear Medical procedures where Tc-99m is predominant

Source: http://www.arpansa.gov.au

Source: Natural Resources Canada, 2009.
What are the needs of modern medicine?

What is the major challenge in medical research?

- Cancer: One person in three will have cancer
- Heart Disease: 50% die after 1st heart attack
- Brain Disorders: 20% aged 75-84 suffer from Alzheimer’s disease

Personalized Medicine

Predictability ⟷ Diagnosis ⟷ Information ⟷ Treatment
What are the needs of modern nuclear medicine?

• Imaging
  • Early diagnosis
  • Therapy follow-up

High quality images
Low radiation dose

Unlike other tests/procedures, nuclear medicine provides information about the function of virtually every major organ system within the body.

Advances in technology, including hybrid imaging,
Introduction of new radiopharmaceuticals for diagnosis/therapy
Development of molecular imaging based on the tracer principle
What are the needs of modern nuclear medicine?

- **Targeted therapy**
  - **Targeting** high specificity
  - **Efficacy** high selectivity
  - **Therapy follow-up**

High amount of energy imparted to the target tissue (to destroy cancer cells) relative to critical normal organs and tissues (to prevent radiation damage and side-effects)
Due to the **crossfire effect** more complex (heterogeneous) tumors may benefit from targeted radionuclide therapy

The **bystander effect** in should be investigated as it contribute to the total therapeutic effect

**Induced radioresistance** and **radiosensitivity**

D. Niculae, seminar at UCIrvine October 2016
Targeting moieties on cell surface/inside cell

Molecular Imaging Targets/Probes

- MAb, Fragments
- Hormones
- Drugs and Ligands
- Peptides

- Enzyme Activity: Inhibition, Conc., Synthesis
- Accumulation via DNA-Synthesis
- Oligonucleotides mRNA Binding

- DNA
- mRNA
- Reporter Gene
- Reporter Probe

- Accumulation via AA Transport or Protein Synthesis
- Accumulation via Phosphorylation [18F]FDG
- glut 4
- Hexokinase

D. Niculae, seminar at UCIrvine October 2016
SCHEMATIC REPRESENTATION OF A DRUG FOR IMAGING AND TARGETED THERAPY

**Target**
- Antigens (CD20, HER2)
- GPCRs
- Transporters

**Molecular Address**
- Antibodies, their fragments and modifications
- Regulatory peptides and analogs thereof
- Amino Acids

**Reporting Unit**
- $^{99m}\text{Tc}$, $^{111}\text{In}$, $^{67}\text{Ga}$
- $^{64}\text{Cu}$, $^{68}\text{Ga}$
- $\text{Gd}^{3+}$

**Cytotoxic Unit**
- $^{90}\text{Y}$, $^{177}\text{Lu}$, $^{213}\text{Bi}$
- $^{105}\text{Rh}$, $^{67}\text{Cu}$, $^{186,188}\text{Re}$

*Courtesy prof H. Maecke, Basel*

D. Niculae, seminar at UCIrvine October 2016
Examples - use of medical radioisotopes

**Neurologic Applications:**
Stroke
Alzheimer's Disease
Demonstrate Changes in AIDS Dementia
Evaluate Patients for Carotid Surgery Localize Seizure Foci
Evaluate Post Concussion Syndrome Diagnose Multi-Infarct Dementia

**Cardiac Applications:**
Coronary Artery Disease
Measure Effectiveness of Bypass Surgery Measure Effectiveness of Therapy for Heart Failure
Detect Heart Transplant Rejection
Select Patients for Bypass or Angioplasty
Identify Surgical Patients at High Risk for Heart Attacks
Measure Chemotherapy Cardiac Toxicity
Evaluate Valvular Heart Disease
Identify Shunts and Quantify Them
Diagnose and Localize Acute Heart Attacks before Enzyme Changes

**Orthopedic Applications:**
Identify Occult Bone Trauma (Sports Injuries)
Diagnose Osteomyelitis
Evaluate Arthritic Changes and Extent
Localize Sites for Tumor Biopsy
Measure Extent of Certain Tumors
Identify Bone Infarcts in Sickle Cell Disease

**Renal Applications:**
Detect Urinary Tract Obstruction
Diagnose Renovascular Hypertension
Measure Differential Renal Function
Detect Renal Transplant Rejection
Detect Pyelonephritis
Detect Renal Scars

**Oncology Applications:**
Tumor Localization
Tumor Staging
Identify Metastatic Sites
Judge Response to Therapy
Relieve Bone Pain Caused by Cancer

**Pulmonary Applications:**
Diagnose Pulmonary Emboli
Detect Pulmonary Complications of AIDS Quantify Lung Ventilation and Perfusion
Detect Lung Transplant Rejection
Detect Inhalation Injury in Burn Patients

**Other Applications:**
Detect Occult Infections
Diagnose and Treat Blood Cell Disorders
Diagnose and Treat Hyperthyroidism (Graves’ Disease)
Detect Acute Cholecystitis
Chronic Biliary Tract Disfunction
Detect Acute Gastrointestinal Bleeding
Detect Testicular Torsion
Cancer therapy demonstrated with $^{90}$Y–ibritumomab tiuxetan (Zevalin)
Peter Conti, University of Southern California – NCI Report 2008
Brain tumor

Neuroinflammation

D. Niculae, seminar at UCIrvine October 2016
[$^{18}\text{F}]\text{CHOLINE}$

$[^{18}\text{F}]\text{Fluoromethylcholine}$  $[^{18}\text{F}]\text{Fluoroethylcholine}$
Prostate cancer
$(^{11}\text{C})\text{Tracers}$

$[^{11}\text{C}]\text{Choline}$

Synthesis of cell membrane phospholipids

$[^{11}\text{C}]\text{Methionine}$

Protein synthesis

$[^{11}\text{C}]\text{Acetate}$

Fatty-acid metabolism
Astrocytoma (no response)
(courtesy by PET Centre St. Orsola Hospital, Bologna)

Before therapy
After therapy

D. Niculae, seminar at UC Irvine October 2016
Emerging radioisotopes and (alternative) production routes

All medical radioisotopes now produced in reactors can be produced alternatively or can be replaced by isotopes which can be produced other than in a nuclear reactor.

Particle Accelerators
Linear
- Ge-68/Ga-68, and Sr-82/Rb-82, Zn-65, Mg-28, Fe-52, Rb-83 (200 MeV proton beam, 150 uA)
- Cyclotrons (10-100 MeV, up to 2 mA)
- F-18, Sr-82, Cu-64, O-15, C-11, Br-77, I-124, Y-86, Ga-66/68, Cu-60/61, Zr-89, Tc-99m

New routes
Compact systems (Bench-scale electronic devices for achieving various high-energy nuclear reactions):
  - proton accelerator: production of F-18, In-111, I-123, C-11, N-13, O-15
  - alpha linac: Sn-117m, Ac-225, As-73, Fe-55, At-211, Cd-109, Y-88, Se-75, Po-210
  - neutron sources

Electron-beam accelerator
- Bremsstrahlung 10-25 MeV electrons proposed for isotope production through:
  - Photo-fission of heavy elements
  - (γ,n) reactions
  - Photo-neutron activation and (n,2n) reactions
## Emerging radioisotopes and (alternative) production routes

Emerging medical radioisotopes: $\beta$-emitters and theragnostic agents – *in preclinical and clinical research*: Lu-177, Ho-166, Re-186/188, Cu-67, Pm-149, Au-199, Y-90

<table>
<thead>
<tr>
<th>Radio nuclide</th>
<th>Emission</th>
<th>Half-life (hrs)</th>
<th>Production Mechanism</th>
<th>Particle/gamma Energy (MeV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{67}$Cu</td>
<td>$\beta$ (0.14 MeV) $\gamma$ (0.18 MeV)</td>
<td>62</td>
<td>$^{68}$Zn(p, 2p) $^{70}$Zn(p,α) $^{67}$Zn(n,p) $^{68}$Zn(γ,p)</td>
<td>Ep (&gt;&gt; 30) Ep (&gt;&gt; 30) Reactor $E_\gamma$ (&gt;19) $\sigma$ = 0.03 barn</td>
</tr>
<tr>
<td>$^{47}$Sc</td>
<td>$\beta$ (0.16 MeV) $\gamma$ (0.16 MeV)</td>
<td>3.35 d</td>
<td>$^{48}$Ti(γ,p)</td>
<td>$E_\gamma$ (&gt;27) $\sigma$ = 0.01 barn</td>
</tr>
<tr>
<td>$^{186}$Re</td>
<td>$\beta$ (0.35 MeV) $\gamma$ (0.14 MeV)</td>
<td>3.7 d</td>
<td>$^{187}$Re(γ,n)</td>
<td>$E_\gamma$ (&gt;15) $\sigma$ = 0.6 barn</td>
</tr>
<tr>
<td>$^{149}$Pm</td>
<td>$\beta$ (1.072 MeV)</td>
<td>53.08</td>
<td>$^{150}$Nd(γ,n)$^{149}$Nd</td>
<td>$E_\gamma$ (&gt;12.5) $\sigma$ =0.22 barn</td>
</tr>
<tr>
<td>$^{152/155/161}$Tb</td>
<td>$\beta^+$ (1.08 MeV) EC (0.86, 0.10 MeV) $\beta^-$ (0.154 MeV), Auger</td>
<td>17.5/127.2/165.3</td>
<td>$^{152}$Tb/$^{155}$Tb proton-induced spallation $^{160}$Gd(γ,$^{161}$Gd</td>
<td>Neutron source Reactor</td>
</tr>
</tbody>
</table>

D. Niculae, seminar at UCIrvine October 2016  
22
Emerging radioisotopes and (alternative) production routes

Emerging medical radioisotopes: $\alpha$-emitters and Auger-electrons emitters

<table>
<thead>
<tr>
<th>Radio nuclide</th>
<th>Emission</th>
<th>Half-life (hrs)</th>
<th>Production Mechanism</th>
<th>Particle Energy (MeV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{211}$At</td>
<td>$\alpha$</td>
<td>7.2</td>
<td>$^{210}$Bi($\alpha,2n$)</td>
<td>$E\alpha$ (30)</td>
</tr>
<tr>
<td>$^{225}$Ac</td>
<td>$\alpha$ (5.8 MeV), $\beta$ (0.1 MeV)</td>
<td>240</td>
<td>$^{229}$Thorium generator ion exchange from $^{225}$Ra $^{226}$Ra($p,2n$) $^{226}$Ra($\gamma,p$)</td>
<td>Reactor $Ep$ (25–8) $E\gamma$ (&gt;19) $\sigma$ = 0.02 barn</td>
</tr>
<tr>
<td>$^{224}$Ra/$^{212}$Pb/$^{212}$Bi</td>
<td>$\alpha$ (5.7 MeV)/$\beta^-$ (0.1 MeV)/$\alpha$ (6.0 MeV), $\beta$ (0.77 MeV)</td>
<td>3.7/10.64 h/60.6 m</td>
<td>$^{226}$Ra($\gamma,2n$)</td>
<td>$E\gamma$ (&gt;16) $\sigma$ = 0.1 barn</td>
</tr>
<tr>
<td>$^{165}$Er</td>
<td>$\alpha$ (0.038 MeV)/$\gamma$ (0.05 MeV)</td>
<td>10.3</td>
<td>$^{166}$Er($\gamma,n$)</td>
<td>$E\gamma$ (&gt;13) $\sigma$ = 0.3 barn</td>
</tr>
<tr>
<td>$^{149}$Tb</td>
<td>$\alpha$ (3.967 MeV), $\beta$ (0.7 MeV)</td>
<td>4.12</td>
<td>$^{152}$Gd($p,4n$)$^{149}$Tb, Ta($p,X$)$^{149}$Tb</td>
<td></td>
</tr>
</tbody>
</table>
ELI–NP GBS Layout

- Low Energy Gamma Beam < 3.5 MeV
- Photo-gun e⁻ source
- Interaction Laser Low Energy
- e⁻ RF LINAC Low Energy 300 MeV
- Photo-gun Laser

D. Niculae, seminar at UCIrvine October 2016
ELI–NP GBS Layout

High Energy Gamma Beam
< 19.5 MeV

Interaction Laser
High Energy

e⁻ RF LINAC
High Energy
720 MeV

Interaction Laser
Low Energy

Photo–gun

e⁻ source

Photo–gun Laser

e⁻ RF LINAC
Low Energy
300 MeV
## ELI–NP GBS Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy (MeV)</td>
<td>0.2 – 19.5</td>
</tr>
<tr>
<td>Spectral Density (ph/s·eV)</td>
<td>&gt; 0.5·10⁴</td>
</tr>
<tr>
<td>Bandwidth rms (%)</td>
<td>≤ 0.5</td>
</tr>
<tr>
<td># photons per pulse within FWHM bdw.</td>
<td>~10⁵</td>
</tr>
<tr>
<td># photons/s within FWHM bdw.</td>
<td>10⁸ – 10⁹</td>
</tr>
<tr>
<td>Source rms size (µm)</td>
<td>10 – 30</td>
</tr>
<tr>
<td>Source rms divergence (µrad)</td>
<td>25 – 200</td>
</tr>
<tr>
<td>Peak brilliance (N(_{ph}/s\cdot m^2\cdot mrad^2\cdot 0.1%))</td>
<td>10(^{20}) – 10(^{23})</td>
</tr>
<tr>
<td>Radiation pulse length rms (ps)</td>
<td>0.7 – 1.5</td>
</tr>
<tr>
<td>Linear polarization (%)</td>
<td>&gt; 95</td>
</tr>
<tr>
<td>Macro repetition rate (Hz)</td>
<td>100</td>
</tr>
<tr>
<td># pulses per macropulse</td>
<td>32</td>
</tr>
<tr>
<td>Pulse–to–pulse separation (nsec)</td>
<td>16</td>
</tr>
</tbody>
</table>

\[ E_L = 2.3 \text{ eV} \]

D. Niculăe, seminar at UCIrvine October 2016
Potential radioisotopes produced in $(\gamma,n)$, $(\gamma,p)$ or $(\gamma,2n)$ reactions


<table>
<thead>
<tr>
<th>Product isotope</th>
<th>$T_{1/2}$</th>
<th>Emission energy (MeV)</th>
<th>Target isotope</th>
<th>Reaction type</th>
<th>$E_\gamma$ MeV</th>
<th>$\sigma$ (barn)</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{47}$Ca</td>
<td>4.5 d</td>
<td>0.4 ($\beta$) 1.3 ($\gamma$)</td>
<td>$^{48}$Ca</td>
<td>$(\gamma,n)$</td>
<td>19</td>
<td>0.09</td>
<td>Targeted radiotherapy, SPECT</td>
</tr>
<tr>
<td>$^{64}$Cu</td>
<td>12.7 h</td>
<td>0.28 ($\beta^+$) 0.191 ($\beta$) 0.511 ($\gamma$)</td>
<td>$^{65}$Cu</td>
<td>$(\gamma,n)$</td>
<td>17</td>
<td>0.09</td>
<td>PET, Various other applications</td>
</tr>
<tr>
<td>$^{99}$Mo/$^{99m}$Tc</td>
<td>2.8 d /0.25</td>
<td>0.39 ($\beta^+$)/ 0.14 ($\gamma$)</td>
<td>$^{100}$Mo</td>
<td>$(\gamma,n)$</td>
<td>14</td>
<td>0.16</td>
<td>SPECT</td>
</tr>
<tr>
<td>$^{103}$Pd</td>
<td>17 d</td>
<td>0.036 (CE) 0.02 ($\gamma$)</td>
<td>$^{104}$Pd</td>
<td>$(\gamma,n)$</td>
<td>17</td>
<td>0.05*</td>
<td>Targeted radiotherapy, Brachytherapy</td>
</tr>
<tr>
<td>$^{165}$Er</td>
<td>10.36 h</td>
<td>0.005, 0.038 (Auger) 0.05 ($\gamma$)</td>
<td>$^{166}$Er</td>
<td>$(\gamma,n)$</td>
<td>13</td>
<td>0.3</td>
<td>Tumor therapy</td>
</tr>
<tr>
<td>$^{169}$Er</td>
<td>9.4 d</td>
<td>0.1 ($\beta$)</td>
<td>$^{170}$Er</td>
<td>$(\gamma,n)$</td>
<td>12</td>
<td>0.3*</td>
<td>Targeted radiotherapy</td>
</tr>
</tbody>
</table>
Potential radioisotopes produced in $(\gamma,n)$, $(\gamma,p)$ or $(\gamma,2n)$ reactions -cont


<table>
<thead>
<tr>
<th>Product isotope</th>
<th>$T_{1/2}$</th>
<th>Emission energy (MeV)</th>
<th>Target isotope</th>
<th>Reaction type</th>
<th>$E_\gamma$ MeV</th>
<th>$\sigma$ (barn)</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{186}\text{Re}$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.7</td>
<td>0.35 ($\beta$) 0.14 ($\gamma$)</td>
<td>$^{187}\text{Re}$</td>
<td>$(\gamma,n)$</td>
<td>15</td>
<td>0.6</td>
<td>Bone pain palliation, radiosynovectomy, and targeted radionuclide therapy</td>
<td></td>
</tr>
<tr>
<td>$^{225}\text{Ra}/^{225}\text{Ac}$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14.8</td>
<td>0.10 ($\beta$)/ 5.8 ($\alpha$)</td>
<td>$^{226}\text{Ra}$</td>
<td>$(\gamma,n)$</td>
<td>12</td>
<td>0.2*</td>
<td>Targeted alpha therapy</td>
<td></td>
</tr>
<tr>
<td>$^{47}\text{Sc}$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.35</td>
<td>0.16 ($\beta$) 0.16 ($\gamma$)</td>
<td>$^{48}\text{Ti}$</td>
<td>$(\gamma,p)$</td>
<td>19</td>
<td>0.02*</td>
<td>Targeted radiotherapy, SPECT or $\gamma$-camera</td>
<td></td>
</tr>
<tr>
<td>$^{67}\text{Cu}$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.6</td>
<td>0.14 ($\beta$) 0.18 ($\gamma$)</td>
<td>$^{68}\text{Zn}$</td>
<td>$(\gamma,p)$</td>
<td>19</td>
<td>0.03*</td>
<td>Targeted radiotherapy, SPECT or $\gamma$-camera</td>
<td></td>
</tr>
<tr>
<td>$^{44}\text{Ti}/^{44}\text{Sc}$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>59.1 y 3.97 h</td>
<td>0.07 ($\gamma$)/ 632 keV ($\beta^+$), 511, 1157 keV ($\gamma$)</td>
<td>$^{46}\text{Ti}$</td>
<td>$(\gamma,2n)$</td>
<td>27</td>
<td>0.01*</td>
<td>PET, Compton telescope</td>
<td></td>
</tr>
</tbody>
</table>
Potential radioisotopes produced in (γ,n), (γ,p) or (γ,2n) reactions -cont


<table>
<thead>
<tr>
<th>Product isotope</th>
<th>$T_{1/2}$</th>
<th>Emission energy (MeV)</th>
<th>Target isotope</th>
<th>Reaction type</th>
<th>$E_γ$ MeV</th>
<th>$σ$ (barn)</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{224}$Ra/$^{212}$Pb/$^{212}$Bi</td>
<td>3.7/10.64h/60.6m</td>
<td>5.7 ($α$)/0.1 ($β^−$)/6.0 ($α$), 0.77 ($β$)</td>
<td>$^{226}$Ra</td>
<td>(γ,2n)</td>
<td>16</td>
<td>0.1*</td>
<td>Targeted alpha therapy</td>
</tr>
</tbody>
</table>

For $β$ and $ε$ decay mode, the emission energy is the mean energy. *Estimated cross sections are marked in italics.
170Er

Stable

Abundance: 14.9%

169Er

T1 = 9.4 d

β-, 100 keV

169Tm

Stable

- Due to the low 168Er(nth, γ) cross section, it cannot be produced with higher specific activity\[^1\] by neutron capture.

166Er

Stable

Abundance: 33.5%

165Er

T1 = 10.4 h

ε, 5 and 38.4 keV

165Ho

Stable

γ, 0.05 MeV

- Today, 64Cu is mainly produced with small cyclotrons by the 64Ni(p,n) reactions, which require the rare and expense 64Ni targets and saves the chemical separation step.

65Cu

Stable

Abundance: 30.85%

64Cu

T1 = 12.7 h

β-, 191 keV

64Ni

Stable

ε, 278 keV

64Zn

T2 > 7.620 y

γ, 0.511

D. Niculae, seminar at UCIrvine October 2016
The $^{47}$Sc could be chemically separated from the irradiated Ca or Ti element. The Sc/Ti separation schemes were established. The alternative production via $^{46}$Ca($n,\gamma$)$^{47}$Ca→$^{47}$Sc is uneconomic due to the extremely low natural abundance of $^{46}$Ca, 0.004%.

• $^{44}$Sc has very favorable properties, but not yet used in clinical routine, since the generator isotopes $^{44}$Ti is difficult to produce and therefore prohibitively expensive. Exposing enriched $^{46}$Ti to an intense $\gamma$-beam allows producing $^{44}$Ti by $(\gamma, 2n)$ reactions.
Alike $^{47}$Sc, $^{67}$Cu has a sufficiently long half-life for accumulation in the tumor cells when bound to antibodies and its 185 keV gamma-ray allows imaging with SPECT or gamma cameras.

The usual production routes $^{68}$Zn(p,2p), $^{70}$Zn(p,α), or $^{64}$Ni(α,p), are all characterized by low yields. The former requires energetic protons (>30 MeV from larger cyclotrons) and the latter two methods use expensive enriched targets with low natural abundances, of the order of 0.5%.

Production via $^{68}$Zn(γ,p) reactions, more abundant and hence cheaper $^{68}$Zn targets could be used. An established Cu/Zn separation schemes.
• The noble gas $^{220}\text{Rn}$ isotope can be extracted easily. The $\alpha$ emitter $^{212}\text{Bi}$ and its mother isotopes $^{212}\text{Pb}$ are also considered for targeted alpha therapy, e.g., for malignant melanoma metastases. A competing reaction $^{226}\text{Ra}(\gamma,n)^{225}\text{Ra}$ could be used for $^{225}\text{Ac}/^{213}\text{Bi}$ generator also for targeted alpha therapy.
Conclusions

- Are there “ideal” radioisotopes for imaging/therapy (physical, chemical and biological properties)?
- What emerging radioisotopes can improve in any of these views?
- What are the limitations for both “traditional” and “emerging” radioisotopes in term of production routes, availability, processing, to access into clinical practice?
- Can radioisotopes address functionality / early diagnosis / personalized medicine?
Photonuclear reactions with $\gamma$ beams allow to produce certain radioisotopes, $^{47}$Sc, $^{44}$Ti, $^{67}$Cu/$^{64}$Cu, $^{103}$Pd, $^{117m}$Sn, $^{169}$Er, $^{195m}$Pt, $^{225}$Ac, $^{99}$Mo ($^{99m}$Tc), $^{111}$In with higher specific activity and/or more economically than with classical methods.

New clinical applications of radioisotopes:

Monitoring of the response to therapy (in real-time)
Theragnostic agents $^{64/67}$Cu used as reporting and therapeutical

Increased availability of very promising radioisotopes innovative isotopes like $^{47}$Sc, $^{67}$Cu and $^{225}$Ac could be produced for the first time in sufficient quantities for large-scale application in targeted radionuclide therapy.

Development of alternative methods for producing well established radioisotopes in clinical practice
Thank you for attention!