From Isotopes to Images: Accelerator Production of Radionuclides for Nuclear Medicine

Suzanne Lapi, Associate Professor of Radiology
Director, UAB Cyclotron facility
What are isotopes used for?
The tracer principle

- In Nuclear Medicine and many areas of basic science, radioactive atoms are used tracers.
- Tracer behaves in a similar way to the components of the system to be probed.
- Tracer does not alter the system in any measurable fashion.
- Tracer concentration can be measured.
The first tracer experiment?

- George de Hevesy was a pioneer in radiochemistry
- While in Manchester in the early 1910’s working with Rutherford, he suspected his landlady was serving recycled food

Sunday night roast  Radium  Wednesday hash
Radiopharmaceuticals

- A **radiopharmaceutical** is a drug labeled with a radionuclide to image a biological process or to deliver therapy to a specific disease site.
  - the overall chemical structure determines biological properties.
  - the radionuclide determines imaging or therapeutic properties.

 ![Diagram of Radiopharmaceuticals](image)
Radiopharmaceuticals

- A **radiopharmaceutical** is a drug labeled with a radionuclide to image a biological process or to deliver therapy to a specific disease site.
- The overall chemical structure determines biological properties.
- The radionuclide determines imaging or therapeutic properties.

D-glucose

2-[\(^{18}\text{F}\)]fluoro-2-deoxy-D-glucose (FDG)
Radiopharmaceuticals

- Radiolabel compound of interest
- Use the radioisotope as a beacon to determine distribution over time
PET imaging is a very sensitive tool capable of providing quantitative information about biochemical and physiological processes in a non-invasive manner.
59 year old woman with T-cell lymphoma

Initial study

4 months later, after chemotherapy
Why develop new imaging agents?

• Imaging more than detection of cancer.
• Imaging can provide more information: detection, prediction of treatment response, receptor status, oxygenation, microenvironment............
Different information can be obtained using different tracers.

$^{[18F]}$FDG

$^{[68Ga]}$DOTATOC
How to pick a radioisotope?

• Chemistry
• Half-life
• Decay Properties
• Availability
• Purity
“Standard” PET Isotopes

\[ ^{14}\text{N}(p,\alpha)^{11}\text{C} \quad t_{1/2} = 20.3 \text{ min.} \]

\[ ^{18}\text{O}(p,n)^{18}\text{F} \quad t_{1/2} = 109.7 \text{ min.} \]

\[ ^{16}\text{O}(p,\alpha)^{13}\text{N} \quad t_{1/2} = 9.97 \text{ min} \]

\[ ^{14}\text{N}(d,n)^{15}\text{O} \quad t_{1/2} = 2.0 \text{ min} \]
Radiometals

- Often have longer half-lives to probe longer biological processes.
- Variety of half-lives and decay characteristics available (can be used for imaging or therapy).
- Co-ordination chemistry varies, thus stable chelates are the key.
~3000 known isotopes
Radiometals?

<table>
<thead>
<tr>
<th>Z</th>
<th>62Ga</th>
<th>63Ga</th>
<th>64Ga</th>
<th>65Ga</th>
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<td>25.7 M</td>
<td>3.333 H</td>
<td>9.673 M</td>
<td>STABLE 69.17%</td>
<td>12.701 H</td>
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<td>5.120 M</td>
<td>61.83 H</td>
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<td></td>
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<td>STABLE</td>
<td>100.1 Y</td>
<td>926%</td>
<td>2.517 H</td>
<td>STABLE 54.6 H</td>
<td>STABLE 100.00%</td>
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<tr>
<td>28</td>
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<tr>
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<td>7.64+4 Y</td>
<td>STABLE 26.223%</td>
<td>STABLE 1.140%</td>
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<td>100.00%</td>
<td>STABLE 0.926%</td>
<td>2.517 H</td>
<td>STABLE 54.6 H</td>
</tr>
<tr>
<td></td>
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<td>STABLE</td>
<td>STABLE</td>
<td>β−: 100.00%</td>
<td>β−: 100.00%</td>
<td>β−: 100.00%</td>
<td>STABLE 100.00%</td>
<td>STABLE 100.00%</td>
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Radiometals?

Second row:

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<tr>
<th>86Nb</th>
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<td>86 S</td>
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<td>14.55 M</td>
<td>2.03 H</td>
<td>14.60 H</td>
<td>6.3E+2 Y</td>
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<td>ε: 100.00%</td>
<td>ε: 100.00%</td>
<td>ε: 100.00%</td>
<td>ε: 100.00%</td>
<td>ε: 100.00%</td>
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<tr>
<th>85Zr</th>
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<th>88Zr</th>
<th>89Zr</th>
<th>90Zr</th>
<th>91Zr</th>
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<tbody>
<tr>
<td>7.96 M</td>
<td>16.5 H</td>
<td>1.68 H</td>
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<td>78.41 H</td>
<td>STABLE</td>
<td>51.45%</td>
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<td>ε: 100.00%</td>
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<td>ε: 100.00%</td>
<td>ε: 100.00%</td>
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<table>
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<th>89Y</th>
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<tr>
<td>4.6 s</td>
<td>2.66 H</td>
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<td>ε: 100.00%</td>
<td>ε: 100.00%</td>
<td>ε: 100.00%</td>
<td>ε: 100.00%</td>
<td>ε: 100.00%</td>
<td>β−: 100.00%</td>
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<table>
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<th>84Sr</th>
<th>85Sr</th>
<th>86Sr</th>
<th>87Sr</th>
<th>88Sr</th>
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</thead>
<tbody>
<tr>
<td>32.41 H</td>
<td>64.84 D</td>
<td>STABLE</td>
<td>9.88%</td>
<td>STABLE</td>
<td>7.00%</td>
<td>50.53 D</td>
</tr>
<tr>
<td>ε: 100.00%</td>
<td>ε: 100.00%</td>
<td>β−: 100.00%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Current Research

• Isotope production and separation chemistry
• Radiochemistry for new imaging agents
• Characterization of new radiopharmaceuticals
• Translation into clinical trials
Cyclotron Production of Radionuclides
University of Alabama: Wallace Tumor Institute
Cyclotrons

Magnetic field bends path of charged particle

Alternating electric field accelerates charged particle at each gap crossing

vacuum chamber
ion source
electric field region

beam
target

dees
magnetic field
## Cyclotrons (University of Alabama at Birmingham)

<table>
<thead>
<tr>
<th>Model</th>
<th>Manufacturer</th>
<th>Energy</th>
<th>Current</th>
<th>Targets</th>
<th>Beamlines</th>
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<tr>
<td>TR 24</td>
<td>Advanced Cyclotron Systems, Inc. (ACSI)</td>
<td>15-24 MeV protons; variable energy</td>
<td>300 μA (total)</td>
<td>2 extraction ports</td>
<td>Solid, liquid, and gas targets</td>
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</tbody>
</table>
Cyclotrons (University of Alabama at Birmingham)

<table>
<thead>
<tr>
<th>TR 24</th>
</tr>
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<tr>
<td><strong>Advanced Cyclotron Systems, Inc. (ACSI)</strong></td>
</tr>
<tr>
<td>15-24 MeV protons; variable energy</td>
</tr>
<tr>
<td>300 µA (total)</td>
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<tr>
<td>2 extraction ports</td>
</tr>
<tr>
<td>Solid, liquid, and gas targets</td>
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<tr>
<td>4 beamlines</td>
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</table>
Targetry Systems (University of Alabama at Birmingham)
<table>
<thead>
<tr>
<th>Isotope</th>
<th>Half-Life</th>
<th>Target Material</th>
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</thead>
<tbody>
<tr>
<td>$^{52}$Mn</td>
<td>5.6 d</td>
<td>$^{52}$Cr</td>
</tr>
<tr>
<td>$^{55}$Co</td>
<td>17.5 h</td>
<td>$^{58}$Ni</td>
</tr>
<tr>
<td>$^{64}$Cu</td>
<td>12.7 h</td>
<td>$^{64}$Ni</td>
</tr>
<tr>
<td>$^{86}$Y</td>
<td>14.7 h</td>
<td>$^{86}$Sr</td>
</tr>
<tr>
<td>$^{89}$Zr</td>
<td>3.27 d</td>
<td>$^{89}$Y</td>
</tr>
</tbody>
</table>
Zirconium-89

- Half-life of 3.27 d – well suited for study of pharmacokinetics of antibodies (achieve optimal biodistribution ~4-5 d)
- Scouting in preparation for immunotherapy, confirming tumor targeting, and estimating dosimetry
- Generally inert to biological systems
- Decay properties
  - EC = 76.6%
  - $\beta^+ = 22.3\%$
  - $R_{\text{ave}}(\beta^+)$ = 1.18 mm
Zr-89 production and purification

- $^{89}\text{Y}(p,n)^{89}\text{Zr}$
Zr-89 production

- $^{89}\text{Y}(p,n)^{89}\text{Zr}$
$^{89}$Zr purification

- Purified by hydroxamate resin
  - Modified Accell Plus resin (Waters)
- Weak cation exchange resin

Verel et al J Nuc Med 2003
Scale Up and Automated Separation
Imaging with Antibodies:

Specificity

Sensitivity

Antigen binding sites
Variable region on heavy chain
Light chain
Disulfide bridges
Heavy chain
Variable region on light chain
Constant region on light chain
Constant region on heavy chain

511 keV Gamma Ray

511 keV Gamma Ray
Why Antibodies?

- Antibodies (and/or fragments) are very selective targeting agents.
- A wide variety of antibody based therapeutics have been developed in the last 2 decades.
- Antibody imaging offers the potential of:
  - Stratifying patients that may benefit from antibody therapy
  - Monitoring the course of therapy
  - Paving the way for next generation targeted radiotherapeutics
Human Epidermal Growth Factor Receptor 2 (HER2)

- Transmembrane receptor
- No known natural ligands
- Amplified in approximately 20% of invasive breast cancers
- Associated with increased tumor aggressiveness, resistance to therapies, and increased mortality
Anti-HER2 Antibodies

Trastuzumab
- Binds to domain IV
- Suppresses HER2 signaling activity

Pertuzumab
- Binds to domain II
- Inhibit HER2 dimerization by sterically preventing HER2 pairing with other growth factor receptors

Marks tumor cells for immunological attack through antibody-dependent cell-mediated cytotoxicity

Trastuzumab

- Clinically approved antibody

- Trastuzumab imaging agent may be useful for determining dosing strategies and for predicting response to Trastuzumab therapy
89Zr: Conjugation and Labeling

(a) mAb conjugation to DFO-Bz-NCS

(b) Radiolabeling of DFO-Bz-NCS-Trastuzumab
$^{89}$Zr-DFO-Trastuzumab

Her2+  Her2-  24 h

Her2+  Her2-  96 h

Chang et al, Pharmaceuticals, 2012
\(^{89}\text{Zr}-\text{DFO-Trastuzumab Imaging Metastasis}\)

Bioluminescent Imaging

Axial

Sagittal

Coronal

Chang et al, Pharmaceuticals, 2012
**89Zr-DFO-Trastuzumab**  
Washington University Clinical Trial

Assessment of HER2 Receptors in Breast Carcinoma by Positron Emission Tomography (PET) Using $^{89}$Zr-Trastuzumab  
PI: Farrokh Dehdashti

<table>
<thead>
<tr>
<th>Arms</th>
<th>Assigned Interventions</th>
</tr>
</thead>
</table>
| Experimental: Cohort 1  
$^{89}$Zr-Trastuzumab Human Dosimetry and Safety | Drug: $^{89}$Zr-Trastuzumab Human Dosimetry and Safety PET Imaging following administration of $^{89}$Zr labeled Trastuzumab for calculation of human dosimetry and overall safety  
Drug: HER2 Positive Lesion Detection and Safety Detection of HER2 Positive Breast Cancer with $^{89}$Zr Labeled Trastuzumab and PET imaging |
| Experimental: Cohort 2:  
Lesion Detection and Safety HER2 Positive Lesion Detection and Safety | Drug: $^{89}$Zr-Trastuzumab Human Dosimetry and Safety PET Imaging following administration of $^{89}$Zr labeled Trastuzumab for calculation of human dosimetry and overall safety  
Drug: HER2 Positive Lesion Detection and Safety Detection of HER2 Positive Breast Cancer with $^{89}$Zr Labeled Trastuzumab and PET imaging |
$^{89}$Zr-Trastuzumab Clinical Trial: Day 2
Zr-Trastuzumab Clinical Trial: Day 5
What’s Next?
Expanding the Toolbox.
Development of Novel Radionuclides

Examples: $^{52}$Mn

- PET analogue for Mn MRI agents.
- Biological roles in plants and animals
- Mechanism of Manganese toxicity (manganism)
### 52Mn Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Production</th>
<th>Positron Emission</th>
<th>Gamma Radiation</th>
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<tbody>
<tr>
<td></td>
<td>Half-Life</td>
<td>Most Common Target</td>
<td>Target Natural Abundance</td>
</tr>
<tr>
<td>52Mn</td>
<td>5.6 d</td>
<td>54Cr(p,ν) (S)</td>
<td>83.8%</td>
</tr>
<tr>
<td>124I</td>
<td>4.2 d</td>
<td>124Te(p,ν) (S)</td>
<td>4.7%</td>
</tr>
<tr>
<td>89Zr</td>
<td>3.3 d</td>
<td>89Y(p,ν) (S)</td>
<td>100.0%</td>
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<tr>
<td>88Y</td>
<td>14.7 h</td>
<td>86Sr(p,ν) (S)</td>
<td>9.9%</td>
</tr>
<tr>
<td>64Cu</td>
<td>12.7 h</td>
<td>60Ni(p,ν) (S)</td>
<td>0.9%</td>
</tr>
<tr>
<td>18F</td>
<td>110 m</td>
<td>18O(p,ν) (L)</td>
<td>0.2%</td>
</tr>
<tr>
<td>66Ga</td>
<td>9.5 h</td>
<td>60Zn(p,ν) (S)</td>
<td>69.2%</td>
</tr>
<tr>
<td>68Ga</td>
<td>68 m</td>
<td>68Ge (Gen)</td>
<td>-</td>
</tr>
<tr>
<td>11C</td>
<td>20 m</td>
<td>14N(p,α) (G)</td>
<td>99.6%</td>
</tr>
</tbody>
</table>

Targets: (S)=solid; (L)=liquid; (G)=gas; (Gen)=generator.

Data in table take from or accessed via: BNL/NNDC; IAEA; Smith, D.S.; Stabin, M.G. *Health Phys.* 2012.

![Image](image_url)

Image courtesy: Richard Laforest (WUSM/MIR).
$^{52}$Mn Production

- Produced via $^{52}$Cr(p,n)$^{52}$Mn reaction
- Targetry using natural composition Cr foils
$^{52}$Mn Targets, Bombardment and Purification

- Cross section and yield measurements using thin foils
- Separation via ion chromatography

Wooten et al. Appl Rad Isot 2015
$^{52}$Mn Characterization

- Imaging characteristics and preliminary animal studies
Cyclotron Production of Isotopes:

- Similar machines in many hospitals and academic centers.
- Small number of accessible nuclear reactions:
  - $(p,n)$, $(p2n)$, $(p,\alpha)$
  - Produce high purity isotopes in high yield
  - Some desirable isotopes are inaccessible – other routes?
Other Isotopes?

~3000 known isotopes

Half-life Range
- Unknown
- <0.1 s
- 0.1 - 5 s
- 5 - 100 s
- 100 s - 1 h
- 1 h - 1 y
- 1 y - 1 Gy
- Stable
Production of Radionuclides by Heavy Ion Fragmentation

Incoming Beam
Beryllium Target

Assortment of isotopes formed from the break up of atoms in the incoming beam
## Potential Isotopes of Interest

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Decay Mode</th>
<th>Half-life</th>
<th>Application</th>
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</thead>
<tbody>
<tr>
<td>$^{32}$Si</td>
<td>$\beta^-, 221$keV no $\gamma$</td>
<td>162y</td>
<td>Tracer, geology, botany</td>
</tr>
<tr>
<td>$^{44}$Ti</td>
<td>$\varepsilon, \gamma$-78.3, 67.8keV</td>
<td>59.2y</td>
<td>Medicine, astrophysics, Nuclear Structure</td>
</tr>
<tr>
<td>$^{48}$V</td>
<td>$\beta^+, 694$keV $\gamma$-983.5, 1312.1keV</td>
<td>15.98d</td>
<td>Stockpile Stewardship, Medicine</td>
</tr>
<tr>
<td>$^{67}$Cu</td>
<td>$\beta^-, 390, 480, 580$keV $\gamma$-184.6keV</td>
<td>2.6d</td>
<td>Medicine</td>
</tr>
<tr>
<td>$^{85}$Kr</td>
<td>$\beta^-, 687$keV $\gamma$-514.0keV</td>
<td>10.76y</td>
<td>Astrophysics, Stockpile Stewardship</td>
</tr>
<tr>
<td>Eu*</td>
<td>$\gamma$-674.1, 1363.0, 678.4keV $\alpha$-5.784, 5.851MeV</td>
<td>24d-37y</td>
<td>Stockpile Stewardship</td>
</tr>
<tr>
<td>$^{211}$Rn</td>
<td>$\gamma$-1363.0, 1363.4keV $\alpha$-1364.2, 1365.8MeV</td>
<td>14.6h</td>
<td>Medicine</td>
</tr>
<tr>
<td>$^{225}$Ra</td>
<td>$\beta^-, 320$keV $\gamma$-40.3keV</td>
<td>14.9d</td>
<td>Medicine, Electric Dipole Moment</td>
</tr>
<tr>
<td>$^{225}$Ac</td>
<td>$\alpha$-5.829, 5.793, 5.731MeV</td>
<td>10.0d</td>
<td>Medicine</td>
</tr>
</tbody>
</table>

*A range of Eu isotopes are of interest, A~147 – 154.*
National Superconducting Cyclotron Laboratory (NSCL)

Located at Michigan State University
Upgrade of NSCL to FRIB

(Facility for Rare Isotope Beams)
Schematic of Proposed Secondary Beam Separator and Beam Dump at FRIB
Why is Isotope Harvesting Important?

Half-lives greater than 1 minute
Preliminary experiments performed at the national superconducting cyclotron laboratory (NSCL)

- End station that serves as a mock beam dump
- Effectively collect isotopes to show that we can collect beam in our end station
- Chemistry!

End Station Design (Hope College)

- Water Cell w/ 8µm kapton window
- Multiple containers of water purged with He
- Gas exit manifold
- Collection Bottles on rotating carousel
- Beam

*Pen, A., et al, NIM A, 2014*
$^{76}$Ge Beam Fragmentation Products without Wedge

2.6% $^{67}$Cu
Separation Schematic

a) Initial
- Cu^{2+}, Ni^{2+}, Zn^{2+}, Ga^{3+}, Ge(OH)_4, Sc^{3+},
- Sc(OH)_2 and Sc(OH)_3, H_2VO_4, Mn^{2+}
- and MnO, Cr_2O_7 and [Cr(H_2O)_6]^{3-},
- H_3AsO_4 and H_2AsO_4, Co^{2+}, Fe^{2/3+}, Ca(OH)
- and Cu^{2+}, K(OH) and K^{+}, BeO, TiO,
- HSeO_3 in 1.25M NH_4OAc pH 5

Bound to Chelation Disk
- Cu^{2+}, Ni^{2+}, Zn^{2+}, Ga^{3+},
- Co^{2+}, Fe^{2/3+},
- Sc^{3+} (~63%), Cr^{3+} (~8%),

Extracted from Disk
- Cu^{2+}, Co^{2+}, Ni^{2+},
- Zn^{2+}, Sc^{3+} (~51%), Fe^{2+} (~10%)

b) Passed through Chelation Disk
- Ge(OH)_4, H_2AsO_4 and
- H_2AsO_4, H_2VO_4, MnO,
- K(OH), Ca(OH), HSeO_3,
- BeO, TiO, Cr_2O_7 (~92%),
- Sc(OH)_3, (~37%)

c) Remained on Chelation Disk
- Ga^{3+} (~99%),
- Fe^{3+} (~90%),
- Sc^{3+} (~12%),
- Cr^{3+} (~8%)

Anion Exchange Chromatography

d) 6M HCl Fraction 1
- Ni^{2+},
- Sc^{3+} (~24%),
- Co^{2+} (~17%),

e) 6M HCl Fraction 2
- Co^{2+} (~35%),
- Sc^{3+} (~16%),
- Cu^{2+} (~2%)  
g) 2.5M HCl Fraction
- Cu^{2+} (~74%),
- Co^{2+} (~30%),
- Sc^{3+} (~2%)
h) 0.5M HCl Fraction
- Fe^{2+} (~5%),
- Cu^{2+} (~5%),
- Sc^{3+} (~0.1%)
i) Remained on Column
- Zn^{2+},
- Trace (Ga^{3+}, Sc^{3+}, Fe^{2+}, Cu^{2+})

Mastren et al, Scientific Reports, 2014
HPGe Spectra of Different Points Throughout the Separation

Mastren et al, Scientific Reports, 2014
Separation Results

<table>
<thead>
<tr>
<th>Contaminating Element</th>
<th>Identifying Isotopes</th>
<th>Initial Contaminant to $^{67}\text{Cu}$ Ratio</th>
<th>Final Contaminant to $^{67}\text{Cu}$ Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ge</td>
<td>$^{69}\text{Ge}$</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>As</td>
<td>$^{74}\text{As}$</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>Ga</td>
<td>$^{72}\text{Ga}$</td>
<td>5.48</td>
<td>0.1096</td>
</tr>
<tr>
<td>Zn</td>
<td>$^{69m}\text{Zn}$</td>
<td>5.48</td>
<td>0</td>
</tr>
<tr>
<td>Ni</td>
<td>$^{57}\text{Ni}$</td>
<td>3.55</td>
<td>0</td>
</tr>
<tr>
<td>Fe</td>
<td>$^{59}\text{Fe}$</td>
<td>2.58</td>
<td>0</td>
</tr>
<tr>
<td>Cu</td>
<td>$^{67}\text{Cu}$</td>
<td>1.87</td>
<td>1.87</td>
</tr>
<tr>
<td>Cr</td>
<td>$^{51}\text{Cr}$</td>
<td>1.13</td>
<td>0</td>
</tr>
<tr>
<td>K</td>
<td>$^{43}\text{K}$</td>
<td>0.81</td>
<td>0</td>
</tr>
<tr>
<td>Ca</td>
<td>$^{47}\text{Ca}$</td>
<td>0.81</td>
<td>0</td>
</tr>
<tr>
<td>V</td>
<td>$^{48}\text{V}$</td>
<td>0.42</td>
<td>0</td>
</tr>
<tr>
<td>Sc</td>
<td>$^{46}\text{Sc}$, $^{47}\text{Sc}$, $^{48}\text{Sc}$</td>
<td>0.39</td>
<td>0.0078</td>
</tr>
<tr>
<td>Mn</td>
<td>$^{52}\text{Mn}$</td>
<td>0.32</td>
<td>0</td>
</tr>
<tr>
<td>Se</td>
<td>$^{75}\text{Se}$</td>
<td>0.13</td>
<td>0</td>
</tr>
<tr>
<td>Co</td>
<td>$^{58}\text{Co}$</td>
<td>0.06</td>
<td>0.018</td>
</tr>
</tbody>
</table>

$74 \pm 4\%$ of the $^{67}\text{Cu}$ was obtained in the 2.5M fractions with a radiochemical purity of $>99\%$. The other contaminants present in the $^{67}\text{Cu}$ fractions measured by HPGe for 12 hours and decay corrected to end of bombardment were $^{58}\text{Co}$ ($0.07\%$), $^{48}\text{Sc}$ ($0.06\%$), $^{47}\text{Sc}$ ($0.06\%$), and $^{72}\text{Ga}$ ($0.30\%$).
Biodistribution of $^{67}\text{Cu}$-NOTA-Bz-Panitumumab

The %ID/g of the tumor was measured to be $12.5 \pm 0.7\%$. 

Mastren et al, Scientific Reports, 2014
Summary

• Radioisotopes continue to play an important role in medicine.
• A wide variety of half-lives, imaging characteristics and chemistries leads to a unique toolbox for the development of new nuclear medicine imaging and therapeutic agents.
• Development and increased use of these agents will require collaborations between chemists, physicists, biologists and physicians.
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