Importance and Role of Radioisotopes to the Medical Community

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Radionuclides Used in Clinical Nuclear Medicine (Diagnostic)

- Single Photon
  - $^{99}$Mo/$^{99m}$Tc generator, $^{201}$Tl, $^{111}$In, $^{67}$Ga, *I
- Positron Emitting
  - $^{18}$F 2-fluoro-2-deoxy-glucose
### Increase in Nuclear Medicine Procedures

<table>
<thead>
<tr>
<th>Year</th>
<th>Procedures (millions)</th>
<th>Annual % + or -</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>12.9</td>
<td></td>
</tr>
<tr>
<td>1998</td>
<td>13.6</td>
<td>5.4%</td>
</tr>
<tr>
<td>1999</td>
<td>14.7</td>
<td>8.1%</td>
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<tr>
<td>2000</td>
<td>16.2</td>
<td>10.2%</td>
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<td>2001</td>
<td>16.8</td>
<td>3.7%</td>
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<tr>
<td>2002</td>
<td>18.4</td>
<td>9.5%</td>
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<tr>
<td>2005</td>
<td>19.7</td>
<td>7.1%</td>
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<tr>
<td>2006</td>
<td>17.7</td>
<td>-10.2%</td>
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</table>

*From IMV 2007 Nuclear Medicine Market Summary Report*
# Types of Procedures

<table>
<thead>
<tr>
<th>Type</th>
<th>2002</th>
<th>2005</th>
<th>2006</th>
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<tbody>
<tr>
<td>Cardiovascular</td>
<td>54%</td>
<td>57%</td>
<td>56%</td>
</tr>
<tr>
<td>Bone</td>
<td>23%</td>
<td>20%</td>
<td>17%</td>
</tr>
<tr>
<td>Liver/Hepatobiliary</td>
<td>6%</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Respiratory</td>
<td>6%</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Renal</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Infection/Abcesses</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Tumor</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Other</td>
<td>4%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Thyroid/Parathyroid</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
</tr>
</tbody>
</table>

*From IMV 2007 Nuclear Medicine Market Summary Report*
## Nuclear Medicine Procedure Volume (Millions)

<table>
<thead>
<tr>
<th>Type</th>
<th>1999</th>
<th>2001</th>
<th>2002</th>
<th>2005</th>
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<tbody>
<tr>
<td>Cardiovascular</td>
<td>7.1</td>
<td>8.4</td>
<td>9.9</td>
<td>9.8</td>
</tr>
<tr>
<td>Bone</td>
<td>3.7</td>
<td>4.2</td>
<td>4.2</td>
<td>3.4</td>
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<tr>
<td>Liver/Hepatobiliary</td>
<td>1.4</td>
<td>1.7</td>
<td>1.7</td>
<td>1.2</td>
</tr>
<tr>
<td>Respiratory</td>
<td>1.1</td>
<td>1.1</td>
<td>1.0</td>
<td>0.7</td>
</tr>
<tr>
<td>Thyroid/Parathyroid</td>
<td>0.4</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Infection/Abcesses</td>
<td>0.4</td>
<td>0.4</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Tumor</td>
<td>0.3</td>
<td>0.3</td>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Other</td>
<td>0.2</td>
<td>0.2</td>
<td>0.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Renal</td>
<td></td>
<td></td>
<td></td>
<td>0.5</td>
</tr>
</tbody>
</table>

*From IMV 2007 Nuclear Medicine Market Summary Report*
# Increase in Total PET Patient Studies

<table>
<thead>
<tr>
<th>Year</th>
<th>Procedures (Thousands)</th>
<th>Annual Increase</th>
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<tbody>
<tr>
<td>2001</td>
<td>248.3</td>
<td></td>
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<tr>
<td>2002</td>
<td>447.2</td>
<td>80%</td>
</tr>
<tr>
<td>2003</td>
<td>706.1</td>
<td>58%</td>
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<tr>
<td>2005</td>
<td>1129.9</td>
<td>60%</td>
</tr>
</tbody>
</table>

*From Bio-Tech Systems*
## Increase in PET and PET/CT Studies (Thousands)

<table>
<thead>
<tr>
<th>Studies</th>
<th>2001</th>
<th>2002</th>
<th>Annual Increase</th>
<th>2003</th>
<th>Annual Increase</th>
<th>2005</th>
<th>Annual Increase</th>
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<tr>
<td>Oncology</td>
<td>182.6</td>
<td>385.7</td>
<td>111%</td>
<td>638.8</td>
<td>66%</td>
<td>1045.4</td>
<td>64%</td>
</tr>
<tr>
<td>Cardiac</td>
<td>18.9</td>
<td>16.7</td>
<td>-12%</td>
<td>22.3</td>
<td>34%</td>
<td>35.9</td>
<td>61%</td>
</tr>
<tr>
<td>Neurologic</td>
<td>10.1</td>
<td>15.5</td>
<td>53%</td>
<td>24.9</td>
<td>61%</td>
<td>39.8</td>
<td>60%</td>
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</tbody>
</table>

*From Bio-Tech Systems*
## Historic and Forecast PET Procedure Volume for Cardiology, Neurology and Oncology

<table>
<thead>
<tr>
<th>Year</th>
<th>Myocardial % of total</th>
<th>Neurology % of total</th>
<th>Oncology % of total</th>
<th>Total PET Procedures % of total</th>
<th>% growth</th>
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</thead>
<tbody>
<tr>
<td>2000</td>
<td>8,000 60.0 7.3</td>
<td>6,000 20.0 5.5</td>
<td>38,000 126.2 71.7</td>
<td>52,000 109.6</td>
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<tr>
<td>2001</td>
<td>20,000 150.0 11.8</td>
<td>10,000 66.7 5.9</td>
<td>140,000 268.4 82.8</td>
<td>170,000 226.9</td>
<td></td>
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<tr>
<td>2002</td>
<td>36,000 80.0 14.1</td>
<td>18,000 80.0 7.0</td>
<td>206,000 47.1 80.5</td>
<td>260,000 52.9</td>
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<tr>
<td>2003</td>
<td>57,000 58.3 8.3</td>
<td>28,000 55.6 4.1</td>
<td>600,000 191.3 87.6</td>
<td>685,000 163.5</td>
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<tr>
<td>2004</td>
<td>85,000 49.1 8.5</td>
<td>42,000 50.0 4.2</td>
<td>875,000 45.8 87.3</td>
<td>1,002,000 46.3</td>
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<tr>
<td>2005</td>
<td>115,000 35.3 8.4</td>
<td>60,000 42.9 4.4</td>
<td>1,200,000 37.1 87.3</td>
<td>1,375,000 37.2</td>
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<td>2006</td>
<td>145,000 26.1 8.4</td>
<td>85,000 41.7 4.9</td>
<td>1,500,000 25.0 86.7</td>
<td>1,730,000 25.8</td>
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<tr>
<td>2007</td>
<td>180,000 24.1 8.6</td>
<td>115,000 35.3 5.5</td>
<td>1,800,000 20.0 85.9</td>
<td>2,095,000 21.1</td>
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<tr>
<td>2008</td>
<td>215,000 19.4 8.7</td>
<td>145,000 26.1 5.9</td>
<td>2,100,000 16.7 85.4</td>
<td>2,460,000 17.4</td>
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<tr>
<td>2009</td>
<td>245,000 14.0 8.7</td>
<td>180,000 24.1 6.4</td>
<td>2,400,000 14.3 85.0</td>
<td>2,825,000 14.8</td>
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<tr>
<td>2010</td>
<td>270,000 10.2 8.5</td>
<td>210,000 16.7 6.6</td>
<td>2,700,000 12.5 84.9</td>
<td>3,180,000 12.6</td>
<td></td>
</tr>
</tbody>
</table>

*From Bio-Tech Systems*
Treatment Assessment with FDG-PET

- Residual mass: post-treatment effect or tumor?
- Prediction and early monitoring of treatment effectiveness
Hypothetical Relationship of Tumor FDG Uptake to Clinical Outcome

STI571 Trial in GIST
Dana-Farber Cancer Institute

Baseline  24 hours  7 days  2 months  5.5 months
Major Areas of Research

*Development of agents to image:*

- Amyloid plaques in Alzheimer’s Disease
- Cellular proliferation
- Tissue hypoxia in tumors, heart disease and stroke
- Receptors – Neurological, tumor and cardiac
- Cell trafficking
- Monitoring gene therapy
### Standard Nuclides Produced at Washington University

<table>
<thead>
<tr>
<th></th>
<th>Reaction</th>
<th>$T_{1/2}$ (min)</th>
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<tbody>
<tr>
<td>$^{15}\text{O}$</td>
<td>$^{14}\text{N}(d, n)^{15}\text{O}$</td>
<td>2.04</td>
</tr>
<tr>
<td>$^{13}\text{N}$</td>
<td>$^{16}\text{O}(p, \alpha)^{13}\text{N}$</td>
<td>9.97</td>
</tr>
<tr>
<td>$^{11}\text{C}$</td>
<td>$^{14}\text{N}(p, \alpha)^{11}\text{C}$</td>
<td>20.3</td>
</tr>
<tr>
<td>$^{18}\text{F}$</td>
<td>$^{18}\text{O}(p, n)^{18}\text{F}$</td>
<td>109.7</td>
</tr>
</tbody>
</table>
Non Standard Nuclides Selected for Production

- Cu-60, Cu-61, Cu-64 - wide range of $t_{1/2}$
  
  Cu-64 has the potential for diagnosis and therapy

- I-124, Br-76, Br-77 - PET and therapeutic isotopes nuclides applicable to a wide range of compounds

- Tc-94m - PET Tc-nuclide

- Ga-66 - $t_{1/2}$ between Ga-68 and Ga-67

- Y-86 - potentially useful for dosimetry prior to Y-90 therapy
Benzothiazole Analog, $[^{11}\text{C}]\text{PIB}$, is a PET Tracer for \textit{in vivo} Imaging of $\beta$-Amyloid Plaques

$N-[^{11}\text{C}]\text{methyl-6-OH-BTA-1}$

Courtesy of William E. Klunk, MD, PhD and Chet Mathis, PhD
In vivo Amyloid Binding of $[^{11}C]PIB$: Mild AD Patient vs. Normal Control

Courtesy of William E. Klunk, MD, PhD and Chet Mathis, PhD
PIB Uptake

A.
Subj. 18
DAT

B.
Subj. 14
Old Cntrl
Imaging with FLT

- $^{18}$F-FLT is taken up by cells and phosphorylated by TK1, which leads to intracellular trapping within the cell.
- The retention of FLT within the cell provides a measure of cellular TK activity, an enzyme which is closely tied to cellular proliferation.

![Chemical Diagram of FLT Phosphorylation](image)
Imaging Breast Cancer with FLT

Pre-Treatment

FLT Coronal Images

Post-Treatment

A. Shields et al.
Imaging Hypoxia
## Copper Radionuclides

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Half-life</th>
<th>Decay modes ( % )</th>
<th>Maximum ( \beta^+ ) energy (MeV)</th>
<th>Reaction</th>
<th>Natural abundance of target isotope</th>
</tr>
</thead>
<tbody>
<tr>
<td>(^{60}\text{Cu})</td>
<td>23.7 m</td>
<td>( \beta^+/93.0 ) ( \text{EC}/7.0 )</td>
<td>3.92</td>
<td>(^{60}\text{Ni}(p,n))</td>
<td>26.1%</td>
</tr>
<tr>
<td>(^{61}\text{Cu})</td>
<td>3.32 h</td>
<td>( \beta^+/60.0 ) ( \text{EC}/7.0 )</td>
<td>1.22</td>
<td>(^{61}\text{Ni}(p,n))</td>
<td>1.25%</td>
</tr>
<tr>
<td>(^{64}\text{Cu})</td>
<td>12.7 h</td>
<td>( \beta^+/19.0 ) ( \text{EC}/43.0 ) ( \beta^-/38 )</td>
<td>0.66</td>
<td>(^{64}\text{Ni}(p,n))</td>
<td>1.16%</td>
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</tbody>
</table>
$^{60}\text{Cu(ATSM)}$ – Chemistry and Engineering

Production technology developed with Newton Scientific, Inc with NIH Small Business Grants

DW McCarthy et al., Nucl Med Biol 1999;26:351-358
PET Imaging Agents – Cu(ATSM)

Theory:

Hypoxic cell (-O₂)

Normal cell (+O₂)
Overall Survival Based on $^{60}$Cu-ATSM Uptake (T/M) in NSCLC (n=14)

Disease-Free Survival Based on $^{60}$Cu-ATSM Uptake in Cervical Cancer (n = 14)

Dehdashti et al., IJORBP 55(5):1233-1238, 2003
Survival Based on $^{60}\text{Cu-ATSM}$ Uptake in Rectal Cancer ($n=17$)

Unpublished data
Comparison of $^{60}$Cu-ATSM and $^{64}$Cu-ATSM (IND 62,675)

- Assessed quality of $^{60}$Cu- and $^{64}$Cu-ATSM PET images
- Crossover study of 10 patients with Ib2-IVa cervical CA
  - Subjective – comparable; but, $^{64}$Cu-ATSM images less noisy
    - Similar quality in 8 patients
    - $^{64}$Cu-ATSM better than $^{60}$Cu-ATSM in 2 patients
  - T/M evaluation
    - Generally better target to background ratio (tumors seen more clearly on $^{64}$Cu-ATSM-PET in most cases)
CT

FDG-PET

$^{60}$Cu-ATSM-PET

$^{64}$Cu-ATSM-PET

T/M = 5.0

T/M = 5.8
Comparison of $^{60}$Cu-ATSM and $^{64}$Cu-ATSM (IND 62,675)

- Correlation of T/M for $^{60}$Cu-ATSM and $^{64}$Cu-ATSM

![Graph showing correlation between T/M Ratio $^{64}$Cu-ATSM and T/M Ratio $^{60}$Cu-ATSM.](image)

- $R = 0.9$
- $P < 0.0001$
Tumor Detection and Treatment Using Bavituximab Labeled with Arsenic Radionuclides

Guiyang Hao, Xiankai Sun, Philip E. Thorpe, and Ralph P. Mason

Departments of Radiology and Pharmacology
University of Texas Southwestern Medical Center at Dallas, Texas
**Bavituximab**: A chimeric antibody targeting exposed vascular phosphatidylserine. It is composed of the Fv regions of the mouse antibody 3G4 and the constant regions of human IgG1.

**Bavituximab** binds to human β2-glycoprotein I with an affinity of $1.7 \times 10^{-8}$ mol/L (monovalent interaction) and an avidity of $\sim 10^{-10}$ mol/L.

**Rituximab** (monoclonal antibody Thera, CD20): a negative control in this project.

Localization of Bavituximab to Tumor Vessels

A: stained with biotinylated goat anti-human IgG followed by Cy2-streptavidin (green) to detect localized bavituximab; B: stained with mouse anti-rat CD31 followed by Cy3-labeled goat anti-mouse IgG (red) to detect vascular endothelium; C: a merged image of bavituximab localized on CD31-positive endothelium. D: a merged image of blood vessels in the tumor of a rat injected with rituximab (negative control). E-F, higher magnification merged images of blood vessels in tumors from rats injected with rituximab (E) or bavituximab (F). Bars, 100 µm. (Dunning prostate R3227-AT1 tumor)
## Decay Data of Arsenic Radioisotopes

<table>
<thead>
<tr>
<th>Property</th>
<th>$^{71}\text{As}$</th>
<th>$^{72}\text{As}$</th>
<th>$^{73}\text{As}$</th>
<th>$^{74}\text{As}$</th>
<th>$^{76}\text{As}$</th>
<th>$^{77}\text{As}$</th>
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<tbody>
<tr>
<td>$T_{1/2}$ [d]</td>
<td>2.7</td>
<td>1.1</td>
<td>80.3</td>
<td>17.8</td>
<td>1.1</td>
<td>1.6</td>
</tr>
<tr>
<td>Mode of decay (%)</td>
<td>EC (70)</td>
<td>EC (12.2)</td>
<td>EC (100)</td>
<td>EC (66)</td>
<td>$\beta^-$ (100)</td>
<td>$\beta^-$ (100)</td>
</tr>
<tr>
<td>$\beta^+$ (%)</td>
<td>(30)</td>
<td>(87.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\beta^+$ (%)</td>
<td>(29)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most abundant γ-lines [kev]</td>
<td>175.0 (82.0%)</td>
<td>834.0 (79.5%)</td>
<td>53.4 (10.0%)</td>
<td>595.8 (59.0%)</td>
<td>559.1 (45.0%)</td>
<td>239.0 (1.6%)</td>
</tr>
<tr>
<td></td>
<td>629.9 (7.9%)</td>
<td>634.8 (15.4%)</td>
<td>657.1 (6.2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean positron energy [kev]</td>
<td>350</td>
<td>1170</td>
<td>440</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Whole-body Planar Scintigraphy

A: Image of rat injected with 5MBq $[^{74}\text{As}]$bavituximab 72h p.i.; B: uptake ratio of $[^{74}\text{As}]$bavituximab in tumor versus upper organs (liver, lung, heart) at various time points after injection (outer tumor regions; entire tumor); C-D: scintigraphy of rats injected with 3MBq $[^{77}\text{As}]$bavituximab or $[^{77}\text{As}]$rituximab (negative control).
Small Animal

A-B: small animal PET images obtained from a Dunning prostate R3227-AT1 tumor-bearing rat 48 h after injection of 10MBq of $^{74}$As]bavituximab coronal (A) and transaxial (B). PET intensity is overlaid on slices obtained by 3-D MRI.

C: images of 1-mm sequential tumor slices from the 3-D data sets.

Conclusion

Radioarsenic-labeled bavituximab has shown potential as a new agent for imaging (\textsuperscript{74}As) the vasculature and radiotherapy (\textsuperscript{77}As) of solid tumors.

Acknowledgements

DOD IDEA awards
W81XWH-06-1-0149 and W81XWH-06-1-0050

National Cancer Institute Pre-ICMIC P20
CA086334 and SAIRP U24 CA126608
The first $^{68}$Ge/$^{68}$Ga Generator


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**A Positron Cow**

G.I. Gleason

Abbott Laboratories, Oak Ridge, Tennessee, U.S.A.

*(Received 6 January 1960)*

Short-lived Ga$^{68}$ can be prepared from its long-lived parent, Ge$^{68}$, thus providing a convenient source of positron-emitting activity for medical or other applications. Solvent extraction is used for the rapid separation of the gallium daughter and a method for the production of the germanium parent is given. A review of the usable positron emitters serves to underscore the advantages of the Ge-Ga$^{68}$ system.

**INTRODUCTION**

One of the more sophisticated techniques to emerge from the wide variety of medical applications of radioisotopes in recent years is the localization of certain intercranial lesions and tumors by the so-called positron scan.$^{11}$ This procedure, which we refer to as annihiscopy, is based on the 180° correlation of the 511 keV radiation arising from the annihilation of positrons with detection by means of two opposing counters recording only coincident events. Thus, concentrations of positron emitters offer a type of “beamed” signal to search out which may offer advantages over similar concentrations of isotopes emitting only isotropic γ-radiation.

The limited availability and/or expense of suitable positron-emitting isotopes has, unfortunately, proven a serious handicap in this otherwise promising technique. This, coupled with a high initial outlay for instrumentation has limited clinical evaluation to relatively few institutions. Commercial preparations of two of the more important isotopes, As$^{74}$ and Cu$^{64}$, have been of some encouragement, but continuing supply problems still exist. In an effort to find some solution, the latest nuclear data have been searched for more ideal source materials.
PRELIMINARY PROGRESS NOTE

Localization of Brain Tumors with the Positron Scintillation Camera

Hal O. Anger, B.S., and Alexander Gottschalk, M.D.

Fig. 1. A 10-minute positron scintiphoto taken with Ga"EDTA. This frontal view shows a large midline meningioma.

Fig. 2. A 10-minute lateral positron scintiphoto demonstrating an area of abnormal uptake posterior to the eye marker in a patient with a chromophobe adenoma of the pituitary.
Image of the month

$^{68}$Ga-DOTANOC: a first compound for PET imaging with high affinity for somatostatin receptor subtypes 2 and 5

Damian Wild$^1$, Helmut R. Mäcke$^4$, Beatrice Waser$^2$, Jean Claude Reubi$^2$, Mihaela Ginj$^1$, Helmut Rasch$^1$, Jan Müller-Brand$^1$, Michael Hofmann$^2$

Translation of PET agents to the Clinic

95% of studies involve FDG

WHY?
Barriers to Translation (PET agents)

- Nuclide Availability
- Intellectual property
- Radiochemical yields
- Variable Specific Activity
- Approval process
Emerging Trends in Radiotherapy

#1 Better match radiation field to tumor dimensions
#2 More potent radiation to increase effectiveness

External Beam | Targeted Radionuclide

Advantages of Targeted Radiotherapy

- Potentially can be applied to:
  - Tumor sites not detectable by imaging
  - Multi-focal disease
  - Simultaneous application to primary and metastatic disease

Short range, high LET $\alpha$-particles
## Selected α-Particle Emitting Radionuclides

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Daughters</th>
<th>Half-life</th>
<th>α-particle Energy (MeV)</th>
<th>Yield per 100 decays</th>
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<tbody>
<tr>
<td>$^{149}$Tb</td>
<td></td>
<td>4.15 h</td>
<td>3.97</td>
<td>17</td>
</tr>
<tr>
<td>$^{211}$At</td>
<td>$^{211}$Po</td>
<td>7.21 h</td>
<td>5.87</td>
<td>42</td>
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<td></td>
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<td>516 msec</td>
<td>7.44</td>
<td>58</td>
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<tr>
<td>$^{212}$Bi</td>
<td>$^{212}$Po</td>
<td>61 min</td>
<td>6.05</td>
<td>36</td>
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<td></td>
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<td>298 nsec</td>
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<td>64</td>
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<tr>
<td>$^{213}$Bi</td>
<td>$^{213}$Po</td>
<td>45.6 min</td>
<td>5.84</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.2 μsec</td>
<td>8.38</td>
<td>64</td>
</tr>
<tr>
<td>$^{225}$Ac</td>
<td>$^{221}$Fr</td>
<td>10 days</td>
<td>5.75</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>$^{217}$At</td>
<td>4.9 min</td>
<td>6.36</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>$^{213}$Bi</td>
<td>32 msec</td>
<td>7.07</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>$^{213}$Po</td>
<td>45.6 min</td>
<td>5.84</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.2 μsec</td>
<td>8.38</td>
<td>98</td>
</tr>
</tbody>
</table>
Bismuth-213

\[
\begin{align*}
\text{\textsuperscript{225}Ac} & \rightarrow \text{\textsuperscript{221}Fr} \quad & \text{10 d} \\
\text{\textsuperscript{221}Fr} & \rightarrow \text{\textsuperscript{217}At} \quad & \text{4.8 m} \\
\text{\textsuperscript{217}At} & \rightarrow \text{\textsuperscript{213}Bi} \quad & \text{0.032 s} \\
\text{\textsuperscript{213}Bi} & \rightarrow \text{\textsuperscript{213}Po} \quad & \text{46 m} \\
\text{\textsuperscript{213}Po} & \rightarrow \text{\textsuperscript{209}Pb} \quad & \text{0.004 ms} \\
\text{\textsuperscript{209}Pb} & \rightarrow \text{\textsuperscript{209}Bi} \quad & \text{3.3 h}
\end{align*}
\]
Bi-213-Labeled Hu195

- Reacts with CD33 antigen over expressed on acute myelogenous leukemia
- CHX-A-DTPA chelate

Jurcic and Scheinberg, MSKCC
Phase I Trial of $^{213}$Bi-HuM195

- Patients were treated with 16-95 mCi in 3-7 fractions.
- HuM195 doses were adjusted to a specific activity of 12-15 mCi/mg.

- Myelosuppression lasted 12-41 days (median, 22 days).
- Transient, low-grade liver function abnormalities were seen in 6 patients.
- Maximum tolerated dose was not reached.
- 14/18 patients had reductions in bone marrow blasts.

## Comparison of $^{131}\text{I}$, $^{90}\text{Y}$, and $^{213}\text{Bi}$ Dosimetry for HuM195

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Mean Absorbed Dose (mSv/MBq)</th>
<th>Marrow/Whole Body Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Marrow</td>
<td>Liver</td>
</tr>
<tr>
<td>$^{131}\text{I}$</td>
<td>2.7</td>
<td>0.8</td>
</tr>
<tr>
<td>$^{90}\text{Y}$</td>
<td>6.8</td>
<td>4.0</td>
</tr>
<tr>
<td>$^{213}\text{Bi}$</td>
<td>9.8</td>
<td>5.8</td>
</tr>
</tbody>
</table>

Jurcic JG et al. Blood 2002; 100:1233-1239
Rationale for α-Particle Emitters in Cytoreduced Disease

• The short range and high LET of α-particles make them best-suited for treatment of small-volume disease.

• In patients with overt AML, there are $10^{16}$ CD33 binding sites, making it difficult to target 1-2 $^{213}\text{Bi}$ atoms to each leukemia cell.

• Hypothesis: Cytoreduction with cytarabine should decrease tumor burden by 1-2 logs and increase the ratio of $^{213}\text{Bi}$ atoms to target cells.
**Astatine-211**

**Rationale for Targeted Radiotherapy**

- 7.2 hr half-life compatible with MRT pharmacokinetics
- α-emission with each decay
- No long-lived daughter radionuclides
- Cyclotron produced at reasonable cost
- Can be imaged providing safety margin
Rationale for Initiating Clinical Trials of $^{211}$At Targeted $\alpha$-Particle Therapy with $^{211}$At-labeled Chimeric 81C6 in Glioma Patients

- **Clinical need**
  - Poor prognosis for conventional XRT even with TMZ
  - $>90\%$ local recurrence
- **Non-intravenous setting** minimizes risk and maximizes tumor delivery
- **Wealth of experience** in patients with $^{131}$I-labeled mAb in this setting
Tenascin Expression in Brain Tumors

- Extracellular matrix glycoprotein
- Expressed on >95% of GBM
- Hexamer with 200-300 kDa arms
Chimeric 81C6 IgG₂

- Higher retention in tumor and many normal tissues
- Less generation of 75 kD metabolite in vivo
- Slower SCRC clearance in patients

Uptake in D54 MG Glioma xenografts

SDS-PAGE Tumor 144 h
At-211 Labeled Chimeric 81C6: Clinical Protocol

- Thyroid blocking with SSKI and Cytomel beginning 48 hr prior to therapy
- Dose administration via indwelling catheter
- Patients injected via the SCRC with 10 mg of mAb labeled with 2 (n=5), 4 (n=7), 6.7 (n=5) or 10 mCi (n=1) mCi $^{211}$At
- Blood sampling at 1, 2, 4, 8, 12, 18 and 24 hr
- SPECT of head and whole body imaging at 2, 4, 8, 18 and 24 hr
Whole Body Images after SCRC Injection of $^{211}\text{At}$-Labeled 81C6

1% window; i.e. upper threshold set to 0.01X maximum pixel count
Phase 1 $^{211}$At-Labeled Chimeric 81C6 in Recurrent Brain Tumor Patients: Outcome

Historical Control: GBM 31 weeks Brem et al. 1995
Survival: Recurrent Patients

- 8 of 14 GBM patients survived for 1 year
- Two GBM patients survived for nearly 3 years (151 and 152 weeks)
- All patients with lower grade tumors survived for more than 71 weeks (71, 78, 116, 235 weeks)
Radionuclide Availability

- Most crucial need for those emitting “short range” radiation:

<table>
<thead>
<tr>
<th>Short</th>
<th>Low Energy $\beta$</th>
<th>$^{67}$Cu</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shorter</td>
<td>$\alpha$-emitter</td>
<td>$^{225}$Ac, $^{211}$At</td>
</tr>
<tr>
<td>Shortest</td>
<td>Auger</td>
<td>$^{77}$Br</td>
</tr>
</tbody>
</table>
Specific Activity

• Challenge is greater for therapy than imaging (acceptable contrast vs. homogeneous delivery of effective level of radionuclide)

• Competition of cold and hot molecule for receptor
  – Some molecular targets expressed at low levels ($\alpha$-MSH receptor)
  – Many molecular targets expressed with high degree of heterogeneity within tumor

• Cross fire can compensate in part for this but at the expense of specificity
Regulatory Affairs

- Requirement for evaluating late radiation effects without adequate guidance (endpoints, species, time frame)
- Guidelines for radiotoxicity of high-LET emitters
- Handling of patient-specific treatment plans (cocktails of radionuclides and carriers, variations in dosing schemes)
Consequences of Heterogeneity for Radionuclide Needs

- **Macro**: Need to administer multiple radionuclides to compensate for range of tumor sizes in a particular patient
- **Micro**: Need to balance advantages of longer range radiation (cross fire of receptor negative populations) with disadvantages (irradiation of normal tissue)
- **Normal tissue**: Need to distribute uptake of labeled catabolites among organs through use of different radionuclides and labeling methods