From Antimatter to Images: The Use of Radioisotopes in Medical Imaging

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Diagnostic Medicine: Past

Rembrandt - anatomy lesson

Lapi, NNPSS, July 2012
How can we probe the human body without a knife?
Basics of Nuclear Medicine

- Nuclear medicine encompasses most of the medical uses of radioactive substances
  - diagnostic tests
  - imaging studies
  - therapy for certain diseases
Radiotracer

- A substance that is radioactive used as a tracer.
- The radioactivity makes it possible to determine where it is and how much is present, an extremely sensitive tool.
Tracer Principle

• 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
  - the overall chemical structure determines biological properties
  - the radionuclide determines imaging properties

D-glucose \[\rightarrow\text{linker} \rightarrow \text{Pharmacophore} \rightarrow 2-[^{18}\text{F}]\text{fluoro-2-deoxy-D-glucose (FDG)}\]
Nuclear Imaging

**SPECT**: Single Photon Emission Computed Tomography

**PET**: Positron Emission Tomography
In planar imaging, the camera records an image from one perspective.

In SPECT imaging, the camera rotates around the patient, recording multiple images that are then reconstructed into a three-dimensional data set by a computer.
Gamma cameras are used for planar and SPECT imaging. $^{99m}$Tc-radiopharmaceuticals are imaged with gamma cameras.
Tc - Background

• Tc discovered in 1937 by Perrier and Segré, who separated it from a Mo deflector plate after years of deuteron irradiation in the Berkeley cyclotron

• 17 known isotopes of Tc - all radioactive
  • $^{99m}$Tc ($T_{1/2} = 6.03$ h) is most widely used in Nuclear Medicine - discovered in 1938 by Seaborg and Segré
  • $^{99}$Tc ($T_{1/2} = 2.1 \times 10^5$ y) is produced by U fission; used to establish chemistry of the element under conventional chemical concentrations
A device that separates a daughter radionuclide from a parent radionuclide

- Typically a chromatographic separation based on the different chemical properties of the parent and daughter radionuclides
- The daughter radionuclide is the desired radionuclide used for nuclear medicine applications
$^{99}$Mo Decay

$^{98}$Mo (n, $\gamma$) → $^{99}$Mo

$^{235}$U (n, fission) → $^{99}$Mo

87%

$^{99}$Mo → $^{99m}$Tc

13%

$^{99m}$Tc → $^{99}$Tc

$^{99}$Tc → $^{99}$Ru

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99\textsuperscript{Mo}/99m\textsuperscript{Tc} Generator

• Comments on patent application of Green, Richards and Tucker in 1958 for 99\textsuperscript{Mo}/99m\textsuperscript{Tc} generator:
  • “While this method is probably novel, it appears the product will probably be used mostly for experimental purposes in the laboratory. On this basis no further patent action is believed warranted…” Atomic Energy Commission
  • “We are not aware of a potential market for 99m\textsuperscript{Tc}… We would recommend against filing…” Research Corporation for Associated Universities, Inc.

• First injection of 99m\textsuperscript{TcO}_4\textsuperscript{-} into a human was made in 1961, following development of the BNL generator

• By 1970, it was estimated that more than 2000 daily diagnostic procedures were carried out in the U.S.

• By 1985 market for 99m\textsuperscript{Tc} was >$30 million

• Diagnostic radiopharmaceutical market was $1.69 billion in 2005 ($259 million for FDG)
Example: Skeletal imaging

- Used to detect osseous metastases, fractures and infection
- Often called a bone scan
- Common radiopharmaceuticals:
  - $^{99m}$Tc-MDP binds to calcium matrix
  - $^{18}$F-fluoride can be used for PET skeletal imaging
- Non-specific marker of increased bone matrix turnover
Normal $^{99m}$Tc-MDP bone scan

Images acquired about 3 hours after injection
58 year old man with prostate cancer
Looming Isotope Shortage Has Clinicians Worried

By Michael Smith, North American Correspondent, MedPage Today
Published: February 16, 2010

Medical isotope shortage reduces tests

| Last Updated: Wednesday, June 16, 2010 | 6:58 PM ET CBC News |

Isotope shortage to get worse with closing of more reactors

GLORIA GALLOWAY
Ottawa— From Thursday's Globe and Mail
Published Wednesday, Feb. 17, 2010 10:57PM EST

Worldwide Shortage of Isotopes for Medical Imaging Could Threaten Quality of Patient Care

ScienceDaily (Aug. 22, 2010) — Twenty million medical scans and treatments are done each year that require radioactive isotopes and scientists are now describing a global shortage of these life-saving materials that could jeopardize patient care and drive-up health care costs.

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99m Tc Availability Issues: “The Isotope Crisis”

- Tc-99m is most widely used radionuclide for nuclear medicine procedures in the world and accounts for >80% of all procedures.

- Many radiopharmaceuticals to assess
  - Cardiac function
  - Blood flow
  - Bone metastases

- Half life & chemical properties of Mo-99 and Tc-99m are exploited to separate them in generator
  - Mo-99/Tc-99m generator invented at Brookhaven National Laboratory
  - Mo-99 half life is 66 hours, Tc-99m has a half life of 6 hours

- Generators sent around the world
The simplicity of the $^{99}\text{Mo}/^{99m}\text{Tc}$ generator

Developed at BNL in 1958 it was never patented.
## Where does the $^{99}$Mo come from? → Fission

<table>
<thead>
<tr>
<th>Reactor</th>
<th>In-service date</th>
<th>Target uranium enrichment type</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRU (Canada)</td>
<td>1957</td>
<td>HEU</td>
</tr>
<tr>
<td>BR2 (Belgium)</td>
<td>1961</td>
<td>HEU</td>
</tr>
<tr>
<td>HFR (Netherlands)</td>
<td>1963</td>
<td>HEU</td>
</tr>
<tr>
<td>SAFARI (South Africa)</td>
<td>1965</td>
<td>HEU</td>
</tr>
</tbody>
</table>

Notes:
- Other smaller suppliers: RA-3 (Argentina) is a domestic supplier and OSIRIS (France) provides some back-up to BR2 and HFR.
Issues

• Chemistry is performed on targets resulting in a Mo-99 solution
• Solution shipped to companies for purification and placement into column
• Mo-99 is eluted (extracted with a solvent) from the column
• Produced eluate is conditioned and $^{99}$Mo re-extracted
• Meeting US demand requires about 34,000–46,000 Curies/week at the reactor
Other Issues

• US production was halted in 1989
  – Foreign subsidies were claimed to be the cause for lower costs abroad
  – Deemed “not worth it” to continue in US

• US demand shared by Canada + The Netherlands

• HEU has significant security issues; future will likely require use of something else

• Stay tuned....
Positron Emission Tomography (PET)

PET imaging is a very sensitive tool capable of providing quantitative information about biochemical and physiological processes in a non-invasive manner.
Principles of Positron Emission Tomography (PET)

• Based on tracer principle
• Tracer labeled with positron emitting radioisotope
• Positron decay
• Coincidence detection of annihilation radiation
Principles of PET Imaging

Positron-emitting isotopes produced on cyclotrons or generators

Injection of a tracer compound labeled with a positron-emitting radionuclide

The radionuclide in the radiotracer decays and the resulting positrons subsequently annihilate on contact with electrons after traveling a short distance (~1-10 mm) within the body.
Each annihilation produces two 511 keV photons traveling in opposite directions (180°) which are detected by the detectors surrounding the subject.
Early PET Imaging

1951: Gordon L. Brownell and colleagues at the Massachusetts General Hospital

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Preclinical Imaging
PET Radiopharmaceutical: FDG

Glucose

Fluorodeoxyglucose (FDG)
FDG Uptake and Retention

Blood  |  Cells
--- | ---
Glucose  |  Glucose  |  Glucose-6P  |  Glycolysis
FDG  |  FDG  |  FDG-6P  |  \(\times\)
Diagnostic Medicine: Present
59 year old woman with T-cell lymphoma

Initial study

4 months later, after chemotherapy
$^{18}$FDG - micro PET/CT
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

\[ ^{18}\text{F}-\text{DOPA} \]

\[ ^{18}\text{F}-\text{FDG} \]

\[ ^{18}\text{F}-\text{FDA} \]


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Octreotide and DOTATOC

Targets somatostatin receptors (sstr) overexpressed on neuroendocrine tumors
A 61-year-old man presented with the sudden onset of vision problems of the right eye. Ophthalmoscopy and MRI were suspicious for a choroidal melanoma. A subsequent FDG PET showed no FDG accumulation.
FDG

\( ^{68}\text{Ga-DOTATOC} \)
PET in Oncology

• **diagnosis**
  – location and extent of disease
  – general (FDG) or tumour-specific probes

• **prognosis**
  – size, stage, grade of disease
  – proliferation (FLT) and/or hypoxia (EF5, etc)

• **“real-time” therapy evaluation**
  – customizing treatment could increase efficacy, decrease toxicity, and improve economics
How to pick a radioisotope?

• Chemistry
• Half-life
• Decay Properties
• Availability
• Purity
• Specific Activity (amount of radioactivity per mass)
Common PET isotopes

\[ ^{14}\text{N}(p,\alpha)^{11}\text{C} \quad t_{\frac{1}{2}} = 20.3 \text{ min.} \]
\[ ^{18}\text{O}(p,n)^{18}\text{F} \quad t_{\frac{1}{2}} = 109.7 \text{ min.} \]
\[ ^{16}\text{O}(p,\alpha)^{13}\text{N} \quad t_{\frac{1}{2}} = 9.97 \text{ min} \]
\[ ^{14}\text{N}(d,n)^{15}\text{O} \quad t_{\frac{1}{2}} = 2.0 \text{ min} \]
The Toolbox

~3000 known isotopes
### Radiometsals?

<table>
<thead>
<tr>
<th>Z</th>
<th>62Ga 116.12 MS</th>
<th>63Ga 32.4 S</th>
<th>64Ga 2.627 M</th>
<th>65Ga 15.2 M</th>
<th>66Ga 9.49 H</th>
<th>67Ga 3.2617 D</th>
<th>68Ga 67.71 M</th>
<th>69Ga STABLE 60.108%</th>
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<tr>
<td>30</td>
<td>61Zn 89.1 S</td>
<td>62Zn 9.186 H</td>
<td>63Zn 38.47 M</td>
<td>64Zn STABLE 48.63%</td>
<td>65Zn 243.66 D</td>
<td>66Zn STABLE 27.90%</td>
<td>67Zn STABLE 4.10%</td>
<td>68Zn STABLE 18.75%</td>
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<tr>
<td>29</td>
<td>60Cu 23.7 M</td>
<td>61Cu 3.353 H</td>
<td>62Cu 9.673 M</td>
<td>63Cu STABLE 69.17%</td>
<td>64Cu 12.701 H</td>
<td>65Cu STABLE 30.83%</td>
<td>66Cu 5.120 M</td>
<td>67Cu 61.83 H</td>
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<tr>
<td>28</td>
<td>59Ni 7.6E+4 Y</td>
<td>60Ni STABLE 26.223%</td>
<td>61Ni STABLE 1.140%</td>
<td>62Ni STABLE 3.634%</td>
<td>63Ni 100.1 Y</td>
<td>64Ni STABLE 0.926%</td>
<td>65Ni 2.5172 H</td>
<td>66Ni 54.6 H</td>
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First row:
Radiometals?

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<td>88 S</td>
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<td>85Zr</td>
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<td>7.86 M</td>
<td>16.5 H</td>
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<td>84Y</td>
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<td>14.74 H</td>
<td>79.8 H</td>
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<td>32.41 H</td>
<td>64.84 D</td>
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<td>0.56%</td>
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</table>

- **89Zr**: 78.41 H, Stable
- **90Zr**: Stable, 51.45%
- **91Zr**: Stable, 11.22%
- **92Zr**: 6.8E+2 Y, Stable
- **93Zr**: 3.47E+7 Y, Stable
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.
## Metal radionuclides discussed

<table>
<thead>
<tr>
<th>Radionuclides</th>
<th>Half-life</th>
<th>Decay</th>
<th>Production Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copper-64</td>
<td>12.7 h</td>
<td>EC/β⁻/β⁺</td>
<td>Cyclotron</td>
</tr>
<tr>
<td>Zirconium-89</td>
<td>3.27 d</td>
<td>EC/β⁺</td>
<td>Cyclotron</td>
</tr>
</tbody>
</table>
Assessing Image quality: Derenzo Phantom

2.0 mm
1.5 mm
1.25 mm
2.5 mm
1.0 mm
Assessing Image quality: Derenzo Phantom

F-18
Cu-64
Ga-66
Br-76

Y-86
Zr-89
Tc-94m
I-124
Cyclotron Production of Radionuclides
Production of PET isotopes

- β+ isotopes are proton rich
- For use in imaging we typically would like short lived isotopes (minutes to hours)
- Produced by proton induced reactions: (p,n), (p,α), (p,2n)......
The CS-15
Production
Copper-64

- $T_{1/2}$ 12.7 hours,
- $\beta^+ (17.8\%)$ $\beta^- (38.4\%)$
- Used for imaging distribution of molecules with biological half-lives of hours-days
- Also potential for targeted radiotherapy
- Produced by $^{64}\text{Ni}(p,n)$ reaction with CS-15
Zirconium-89

- Half-life of 3.17 d – well suited for study of pharmacokinetics of antibodies (achieve optimal biodistribution ~4-5 d)
- Immuno-PET - Scouting in preparation for radioimmununotherapy, confirming tumor targeting, and estimating dosimetry
- Generally inert to biological systems
- Decay properties
  - EC = 76.6%
  - $\beta^+ = 22.3\%$
  - $R_{ave.}(\beta^+) = 1.18$ mm

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Zr-89 production and purification

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

<table>
<thead>
<tr>
<th>Element</th>
<th>Mass</th>
<th>Half-life</th>
<th>Stability</th>
<th>Decay</th>
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<tbody>
<tr>
<td>$^{87}Zr$</td>
<td>1.68 H</td>
<td>100.00%</td>
<td>Stable</td>
<td>β- 100.00%</td>
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<tr>
<td>$^{88}Zr$</td>
<td>83.4 D</td>
<td>100.00%</td>
<td>Stable</td>
<td>β- 100.00%</td>
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<tr>
<td>$^{89}Zr$</td>
<td>78.41 H</td>
<td>100.00%</td>
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<td></td>
<td>β- 100.00%</td>
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<tr>
<td>$^{93}Zr$</td>
<td>1.53E+6 Y</td>
<td></td>
<td></td>
<td>β- 100.00%</td>
</tr>
</tbody>
</table>

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

![Chemical structure](image)

**Accell resin**  
**Hydroxamate resin**
Zr-89 purification

Zr-89 recovery (uCi)

- Loading
- 2M HCl
- H₂O
- 1M Oxalic Acid
Copper-64 Imaging Agents
Hypoxia: lack of oxygen in tissue
In cancer: Hypoxia influences response to treatment:

- Radiotherapy - hypoxic cells are protected from lethal effects of conventional ionizing radiation therapy
- Chemotherapy - effect of hypoxia on special genes and drug delivery

 Imaging of hypoxia is required in order to predict response to traditional therapies
 Imaging of hypoxia in the brain, heart and cancer have been explored
[\textsuperscript{64}Cu]ATSM: Proposed Mechanism

TRAPPED

Hypoxic cell (-O\textsubscript{2})

NOT TRAPPED

Normal cell (+O\textsubscript{2})

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[\textsuperscript{64}Cu]ATSM: Clinical Studies

- Presence of tumor was confirmed in all patients on pretherapy CT and/or FDG-PET

- Treatment
  - Radiotherapy alone (11 NSCLC and 1 cervical cancer)
  - Radiation and chemotherapy (5 NSCLC and 13 cervical cancer)
  - Chemotherapy alone (3 NSCLC)

- Follow-up after therapy
  - Clinical evaluation at 4-6 weeks after completion of therapy and every 3 months thereafter for 2 years
[\textsuperscript{64}Cu]ATSM: Cervical Cancer

**Responder**

- CT
- FDG-PET
- \textsuperscript{64}Cu-ATSM-PET
  
  \( \text{T/M} = 4.4 \)

**Non-Responder**

- Fused PET/CT
- FDG-PET
- \textsuperscript{64}Cu-ATSM-PET
  
  \( \text{T/M} = 10.3 \)
Clinical Prediction: Cervical Cancer

Fig. 2. Progression-free survival and overall survival based on $^{60}$Cu-ATSM uptake using Kaplan-Meier method. Patient survival has an inverse relationship with tumor uptake of $^{60}$Cu-ATSM assessed by tumor-to-muscle activity ratio ($P = 0.0005$ and $p = 0.015$, respectively).

- 5/14 pt’s tumors were characterized as hypoxic
- All pts with hypoxic tumors developed recurrent disease
- 6/9 pts with normoxic tumors disease free at end of study


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Summary of $[^{64}\text{Cu}]\text{ATSM}$

- It is feasible to study human tumors with $^{64}\text{Cu}$-ATSM-PET
- The T/M activity ratio is a simple reliable semiquantitative method for evaluation of tumor uptake of $^{64}\text{Cu}$-ATSM
- Pre-therapy $^{64}\text{Cu}$-ATSM-PET
  - Predictive of response to therapy
  - Predictive of disease-free survival
- $^{64}\text{Cu}$-ATSM-PET may direct radiation therapy
- $^{64}\text{Cu}$-ATSM-PET can be used to monitor the effect of therapeutic strategies known to overcome hypoxia
Zirconium-89 ImmunoPET
<table>
<thead>
<tr>
<th>Antibody</th>
<th>Target</th>
<th>FDA-approved indication</th>
<th>Approval in Europe*</th>
<th>Mechanisms of action</th>
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<tbody>
<tr>
<td><strong>Naked antibodies: solid malignancies</strong></td>
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<tr>
<td>Trastuzumab (Herceptin; Genentech): humanized IgG1</td>
<td>ERBB2</td>
<td>ERBB2-positive breast cancer, as a single agent or in combination with chemotherapy for adjuvant or palliative treatment</td>
<td>Similar</td>
<td>Inhibition of ERBB2 signalling and ADCC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ERBB2-positive gastric or gastro-oesophageal junction carcinoma as first-line treatment in combination with cisplatin and capecitabine or 5-fluorouracil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bevacizumab (Avastin; Genentech/Roche): humanized IgG1</td>
<td>VEGF</td>
<td>For first-line and second-line treatment of metastatic colon cancer, in conjunction with 5-fluorouracil-based chemotherapy; for first-line treatment of advanced NSCLC. In combination with carboplatin and paclitaxel, in patients who have not yet received chemotherapy; as a single agent in adult patients with glioblastoma whose tumour has progressed after initial treatment; and in conjunction with IFNα to treat metastatic kidney cancer</td>
<td>Similar</td>
<td>Inhibition of VEGF signalling</td>
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<tr>
<td>Cetuximab (Erbitux; Bristol-Myers Squibb): humanized EGFR</td>
<td>EGFR</td>
<td>In combination with radiation therapy for the initial treatment of locally or regionally advanced SCC-CHN as a single agent for patients with SCC-CHN for whom prior platinum-based therapy has failed; and palliative treatment of pretreated metastatic EGFR-positive colorectal cancer</td>
<td>Similar</td>
<td>Inhibition of EGFR signalling and ADCC</td>
</tr>
<tr>
<td>Panitumumab (Vectibix; Amgen): human IgG2</td>
<td>EGFR</td>
<td>As a single agent for the treatment of pretreated EGFR-expressing, metastatic colorectal carcinoma</td>
<td>Similar</td>
<td>Inhibition of EGFR signalling</td>
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<tr>
<td>Ipilimumab (Yervoy; Bristol-Myers Squibb): IgG1</td>
<td>CTLA4</td>
<td>For the treatment of unresectable or metastatic melanoma</td>
<td>Similar</td>
<td>Inhibition of CTLA4 signalling</td>
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<tr>
<td><strong>Naked antibodies: haematological malignancies</strong></td>
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</tr>
<tr>
<td>Rituximab (Mabthera; Roche): humanized IgG1</td>
<td>CD20</td>
<td>For the treatment of CD20-positive B cell NHL and CLL, and for maintenance therapy for untreated follicular CD20-positive NHL</td>
<td>Similar</td>
<td>ADCC, direct induction of apoptosis and CDC</td>
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<tr>
<td>Alectinumab (Campath; Genzyme): humanized IgG1</td>
<td>CD52</td>
<td>As a single agent for the treatment of B cell chronic lymphocytic leukaemia</td>
<td>Similar</td>
<td>Direct induction of apoptosis and CDC</td>
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<td>Ofatumumab (Arzerra; Genentech): human IgG1</td>
<td>CD20</td>
<td>Treatment of patients with CLL refractory to fludarabine and alemtuzumab</td>
<td>Similar</td>
<td>ADCC and CDC</td>
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<tr>
<td><strong>Conjugated antibodies: haematological malignancies</strong></td>
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<td>Gemtuzumab ozogamicin (Mylotarg; Wyeth): humanized IgG4</td>
<td>CD33</td>
<td>For the treatment of patients with CD33-positive acute myeloid leukaemia in first relapse who are 60 years of age or older and who are not considered candidates for other cytotoxic chemotherapy; withdrawn from use in June 2010</td>
<td>Not approved in the European Union</td>
<td>Delivery of toxic payload, calicheamicin toxin</td>
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<tr>
<td>Brentuximab vedotin (Ad cetris; Seattle Genetics): humanized IgG1</td>
<td>CD30</td>
<td>For the treatment of relapsed or refractory Hodgkin’s lymphoma and systemic anaplastic lymphoma</td>
<td>Not approved in the European Union</td>
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</tr>
<tr>
<td>131I-Labeled Ibritumomab tuxetan (Zevalin; IDEC Pharmaceuticals): murine IgG1</td>
<td>CD20</td>
<td>Treatment of relapsed or refractory, low-grade or follicular B cell NHL previously untreated follicular NHL in patients who achieve a partial or complete response to first-line chemotherapy</td>
<td>Similar</td>
<td>Delivery of the radiolabel</td>
</tr>
<tr>
<td>131I-Labeled tositumomab (Bexxar; GlaxoSmithKline): murine IgG2</td>
<td>CD20</td>
<td>Treatment of patients with CD20 antigen-expressing relapsed or refractory, low-grade, follicular or transformed NHL</td>
<td>Granted orphan status drug in 2003 in the European Union</td>
<td>Delivery of the radiolabel</td>
</tr>
</tbody>
</table>

ADCC, antibody-dependent cellular cytotoxicity; CDC, complement-dependent cytotoxicity; CLL, chronic lymphocytic leukaemia; CTLA4, cytotoxic T lymphocyte-associated antigen 4; EGFR, epidermal growth factor receptor; FDA, US Food and Drug Administration; IgG, immunoglobulin G; IFNα, interferon α; NHL, non-Hodgkin’s lymphoma; NSCLC, non-small-cell lung cancer; SCC-CHN, squamous cell carcinoma of the head and neck; VEGF, vascular endothelial growth factor.

*Based on information from the European Medicines Agency. **Not recommended for patients with colorectal cancer whose tumours express mutated KRAS.
**89Zr: Herceptin**

- Well characterized antibody

**INDICATIONS AND USAGE**

HERCEPTIN as a single agent is indicated for the treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have received one or more chemotherapy regimens for their metastatic disease. HERCEPTIN in combination with paclitaxel is indicated for treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have not received chemotherapy for their metastatic disease. HERCEPTIN should be used in patients whose tumors have been evaluated with an assay validated to predict HER2 protein overexpression (see PRECAUTIONS: HER2 Testing and CLINICAL STUDIES: HER2 Detection).

- Herceptin imaging agent may be useful for predicting response
- Conjugation with DFO-Bz-NCS
$^{89}\text{Zr}$: Conjugation and Labeling
Examples of fusion images from HER2 PET and MRI scans. (a) In a vertebral metastasis seen on MRI but unapproachable for biopsy, HER2 status was revealed by 89Zr-trastuzumab uptake on PET imaging. (b) Example of HER2-positive brain lesion undetected by conventional scans, revealed by 89Zr-trastuzumab PET imaging, and subsequently confirmed by MRI.

Dijkers et al Clinical Pharm and Therapeutics May 2010
In this study, $^{89}$Zr-trastuzumab allowed the researchers to distinguish between lesions with HER2 overexpression and those without.

The PET images produced with $^{89}$Zr-trastuzumab showed high spatial resolution and good signal-to-noise ratio, resulting in an image quality unapproachable by our previous $^{111}$In-trastuzumab SPECT scans.

Dijkers et al *Clinical Pharm and Therapeutics* May 2010
$^{89}$Zr-Panitumumab for ImmunoPET Imaging of the Epidermal Growth Factor Receptor
EGFR activation mediates multiple processes

Lapi, NNPSS, July 2012
EGFR Expression in Solid Tumors

EGFR is expressed in a variety of solid tumors

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Expression Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal cancer</td>
<td>72-82%</td>
</tr>
<tr>
<td>Head &amp; neck cancer</td>
<td>95-100%</td>
</tr>
<tr>
<td>Lung cancer (NSCLC)</td>
<td>40-80%</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>14-91%</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>35-70%</td>
</tr>
<tr>
<td>Renal cell cancer</td>
<td>50-90%</td>
</tr>
</tbody>
</table>

Lapi, NNPSS, July 2012
EGFR-Targeted Monoclonal Antibodies

- **Cetuximab**
  - Human-mouse chimeric IgG\(_1\) mAb
  - For advanced colon cancer

- **Panitumumab**
  - Fully humanized IgG\(_2\) mAb
  - For advanced colon cancer, non-small cell lung cancer, esophageal cancer, and pancreatic cancer
EGFR Expression on Different Cancer Cell Lines: Flow Cytometry Data

- **A431 (lung)**: ~98%
- **HCT116 (colorectal)**: ~44%
- **T47D (breast)**: 0%
- **MDA-MB-435 (breast)**: 0%
Labeling of Panitumumab with $^{89}$Zr

(a) mAb conjugation to DFO-Bz-NCS

(b) Radiolabeling of DFO-Bz-NCS-Panitumumab
Cell Uptake Studies

% Administered Activity vs Cell Number (1 x 10^6)

- A431
- HCT116
- HCT116 + block
- T47D
- MDA-MB435

Lapi, NNPSS, July 2012
microPET and BioD studies

- Athymic nude mice, 6-8 weeks of age
- $4 \times 10^6$ cells injected into right flank
- Tumor size $\sim 200 \text{ mm}^3$
- $\sim 15 \mu\text{Ci}$ for BioD and $\sim 85 \mu\text{Ci}$ for microPET

- Blocking Studies
  HCT116 tumor cell line with moderate EGFR expression
  1 mg of unlabeled panitumumab was injected 2h before injection of activity
Imaging EGFR Expression with $[^{89}\text{Zr}]\text{DFO-Bn-NCS-Panitumumab}$ at 24 h Post Injection
Biodistribution Studies at 24 h Post Injection

![Graph showing biodistribution studies at 24 h post injection for A431 and HCT116.]
Imaging EGFR Expression with $[^{89}\text{Zr}]\text{DFO-Bn-NCS-Panitumumab}$ at 120 h Post Injection

- **A431**
- **HCT116**
- **MDA-MB435**
- **T47D**

Lapi, NNPSS, July 2012
Biodistribution Studies at 120 h Post Injection

<table>
<thead>
<tr>
<th></th>
<th>A431</th>
<th>HCT116</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 h post</td>
<td>5.2</td>
<td>4.6</td>
</tr>
<tr>
<td>120 h post</td>
<td>16.4</td>
<td>12.8</td>
</tr>
</tbody>
</table>
Immunofluorescent Staining of Tumors

A431  HCT116  MDA-MB435  T47D

- DAPI (nucleus)
- Anti-EGFR
$SUV_{\text{max}}$ of Tumors

![Diagram showing SUV max for different cell lines at 24h and 120h](image)

- A431
- HCT116
- T47D
- MDA-MB435

Lapi, NNPSS, July 2012
Outlook

-Nuclear medicine offers very sensitive techniques to non-invasively investigate biological phenomena

-New isotopes and new imaging agents can aid in the future of “personalized medicine”
Isotope Harvesting?

• FRIB (facility for rare isotope beams)
  – Broadens the energy range and types of rare isotope beams currently available.
  – Rare isotope beams come from primary beams of different types that are fragmented. In the process of fragmentation lots of other isotopes will be simultaneously created and available for harvest in the beam dump.
  – Some of these “orphan” isotopes are relevant for many scientific applications.
    • Medicine, Nuclear Power, Homeland Security, Stockpile Stewardship, Industrial and Environmental Tracers
Schematic of FRIB
Schematic of Proposed Secondary Beam Separator at FRIB
Separated Isotopes from FRIB

Half-life limit set at 1 minute

Activity after 12 hours of collection:
- $0.1 \text{ mCi} < 1 \text{ mCi}$
- $1 \text{ mCi} < 10 \text{ mCi}$
- $10 \text{ mCi} < 100 \text{ mCi}$
- $100 \text{ mCi} < 1,000 \text{ mCi}$
- $1,000 \text{ mCi} < 10,000 \text{ mCi}$
- $10,000 \text{ mCi} <$
Acknowledgements

• Lapi Lab
  – Tayo Ikotun, Efrem Mebrahtu, Bernadette Marquez, Tolu Aweda, Nilnatya Bandara, Alex Zheleznyak, Mai Lin, Tara Mastren, Albert Chang, Ravi DeSilva,

• Isotope Production Team
  – Tom Voller, Evelyn Madrid, Paul Eisenbeis, Bill Margenau, Greg Gaehle, Pat Margenau

• Funding
  • DOE DESC0004038
  • NIH HHSN268201000046C
  • DOE DESC0002114